

HETEROCYCLYLALKYNYL SUBSTITUTED AMIDE DERIVATIVE, AND PREPARATION METHOD THEREFOR AND USE THEREOF

TECHNICAL FIELD

The present disclosure relates to the field of pharmaceutical chemistry, and in particular, to a heterocycloalkynyl-substituted amide derivative, a preparation method therefor and use thereof.

BACKGROUND

Epigenetic regulation of gene expression plays an important biological role in protein maturation and cell differentiation, and plays an important role in many human diseases. Arginine guanido methylation catalyzed by protein arginine methyltransferase (PRMT) is a common post-translational modification in eukaryotic cells. It affects various biological processes such as cell signaling, gene transcription, mRNA translation, and DNA recombination and repair (*Cell Mol. Life Sci.* 2015. 72(11): 2041-2059).

PRMT5 is one of the members of the PRMT family, and its mediated methylation plays a crucial role in maintaining normal intracellular environmental balance. However, an increasing number of studies have shown that the abnormal expression of PRMT5 is associated with the development of various tumors. PRMT5 is overexpressed in a variety of tumors, and the pathogenesis varies in different tumors (*Cell Mol. Life Sci.* 2015. 72(11): 2041-2059).

Homozygous deletion of cancer suppressor genes is a key driver of tumorigenesis. The deletion of the cancer suppressor gene CDKN2A located on human chromosome 9p21 is one of the genes with the highest mutation frequency in tumors, and the incidence rate is 15%. Due to its close proximity to CDKN2A, the methylthioadenosine phosphorylase gene (MTAP) is often concomitantly deleted in tumors, and it plays an important role in the methionine and adenine salvage pathways (*Cell Reports*, 2016, 15: 574-587). The deletion of MTAP may lead to the accumulation of its substrate methylthioadenosine (MTA). Since MTA is structurally similar to S-adenosylmethionine (SAM), it can selectively compete with SAM for binding to PRMT5, inhibit part of the activity of PRMT5, and sensitize further inhibition of PRMT5, i.e., synthetic lethality (*Science*, 2016, VOL 351 ISSUE 6278: 1214-1217).

However, PRMT5 is a known and necessary gene. The knockout or siRNA silencing of PRMT5 in normal tissues will lead to abnormal physiological functions, such as hematocytopenia, infertility, skeletal muscle loss, and cardiac hypertrophy (*Journal of Clinical Investigation*, 2015, 125(9): 3532-44). At present, none of the PRMT5 inhibitors in clinical stage can cause synthetic lethality in the context of MTAP deletion. Thus, new strategies are needed to exploit the metabolic fragility caused by MTAP deletion.

The development of small-molecule inhibitors targeting PRMT5·MTA enables preferential targeting of MTAP-deficient tumor cells. Because normal cells exhibit no deletion of MTAP and maintain a relatively low MTA concentration, these inhibitors do not show significant inhibitory effect on normal cells, thereby increasing the therapeutic index (AACR Annual Meeting, 2021, Abstract LB003) and providing a new strategy for tumor treatment.

SUMMARY

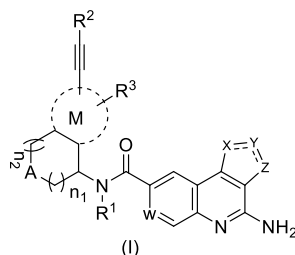
Problems to be Solved by the Present Disclosure:

Although patent applications related to some PRMT5 inhibitors have been disclosed, new compounds still need to be further developed, considering the large market demand for MTAP-/-cancer patients and the insufficient clinical effects of existing PRMT5 inhibitors. Through continuous efforts, the inventors of the present application have designed compounds having a structure represented by general formula (I) and found that the compounds having such a structure exhibit an excellent inhibitory effect and action on PRMT5, demonstrating great application prospects.

Solutions to Problems:

To solve the above problems, the inventors of the present application have carried out intensive research and found that a class of heterocycloalkynyl-substituted amide derivatives can achieve the desired objective, thus resulting in the present disclosure. To achieve the above objective, the present disclosure provides the following technical solutions:

A compound represented by formula I or a tautomer, a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



wherein

$\equiv$ is selected from a single bond and a double bond, or $\equiv$ is absent;

when $\equiv$ is a single bond or a double bond, X, Y, and Z are independently selected from CR^4R^5 , NR^6 , O, N, S, and CR^4 ;

when $\equiv$ is absent, Y is absent, X is hydrogen, and Z is CR^4R^5 ;

W is selected from CR^7 and N;

A is selected from CR^8R^9 , NR^8 , and O;

ring M is selected from 5-10 membered aryl and 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl contains 1-4 heteroatoms selected from N, O, and S;

R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen, deuterium, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{3-6} cycloalkoxy, wherein the C_{1-6} alkyl and C_{1-6} alkoxy are unsubstituted or substituted with one or more R_i , and the C_{3-6} cycloalkyl and C_{3-6} cycloalkoxy are unsubstituted or substituted with one or more R_j ;

R^1 is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl- $(\text{C}_{1-6} \text{ alkyl})_m$ -, 4-10 membered heterocyclyl- $(\text{C}_{1-6} \text{ alkyl})_n$ -, 5-10 membered heteroaryl- $(\text{C}_{1-6} \text{ alkyl})_p$ -, and 5-10 membered aryl- $(\text{C}_{1-6} \text{ alkyl})_q$ -, wherein $n = 0$ or 1 , $m = 0$ or 1 , $p = 0$ or 1 , and $q = 0$ or 1 ; the heterocyclyl and heteroaryl each independently contain 1-4 ring heteroatoms selected from O, N, and S, wherein the C_{1-6} alkyl is unsubstituted or substituted with one or more R_i , the C_{3-10} cycloalkyl is unsubstituted or substituted with one or more R_j , the 4-10 membered heterocyclyl is unsubstituted or substituted with one or more R_k , and the 5-10 membered aryl and 5-10 membered heteroaryl are unsubstituted or are each independently substituted with one or more R_l ;

R^2 is selected from 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the 5-10 membered heteroaryl and 4-10 membered heterocyclyl each

independently contain 1-4 heteroatoms selected from N, O, and S, and the 5-10 membered heteroaryl and 4-10 membered heterocyclyl are unsubstituted or substituted with one or more identical or different R^b;

n₁ and n₂ are each independently 0, 1, or 2;

each R_i, R_j, R_k, and R_l is independently selected from hydroxy, deuterium, halogen, cyano, C₁₋₆ alkyl optionally substituted with one or more groups selected from halogen, cyano, and hydroxy, C₁₋₆ alkoxy optionally substituted with one or more groups selected from halogen, cyano, hydroxy, -NR'R'', and C₁₋₆ alkoxy, C₃₋₁₀ cycloalkyl, and 5-10 membered heteroaryl optionally substituted with one or more C₁₋₆ alkyl, the 5-10 membered heteroaryl containing 1-4 heteroatoms selected from N, O, and S, wherein R' and R'' are each independently selected from H, C₁₋₆ alkyl, and halogenated C₁₋₆ alkyl, or R' and R'', together with the nitrogen atom linked thereto, form 4-8 membered heterocyclyl, the 4-8 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S;

each R^b is independently selected from hydroxy, deuterium, cyano, halogen, -NR'R'', C_{1-C6} alkyl, C₁₋₆ alkoxy, and C_{3-C6} cycloalkyl, wherein the C_{1-C6} alkyl, C_{1-C6} alkoxy, and C_{3-C6} cycloalkyl are unsubstituted or are each independently substituted with one or more substituents selected from halogen, hydroxy, cyano, and C_{1-C6} alkoxy; in -NR'R'', R' and R'' are each independently selected from hydrogen, C₁₋₆ alkyl, and halogenated C₁₋₆ alkyl, or R' and R'', together with the nitrogen atom linked thereto, form 4-8 membered heterocyclyl, the 4-8 membered heterocyclyl containing 1-4 heteroatoms selected from N, O, and S.

In some specific embodiments, ring M is selected from 5-6 membered aryl and 5-6 membered heteroaryl.

In the present disclosure, unless otherwise specified, each occurrence of the 5-10 membered heteroaryl preferably means that each 5-10 membered heteroaryl contains 1-4 heteroatoms selected from N, O, and S; each occurrence of the 5-6 membered heteroaryl preferably means that each 5-6 membered heteroaryl contains 1-3 heteroatoms selected from N, O, and S.

In some specific embodiments, ring M is selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, furanyl, oxazolyl,

isoxazolyl, and thiazolyl.

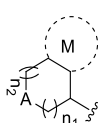
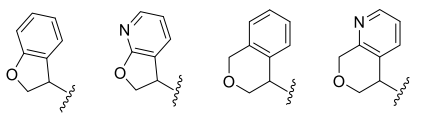
In some specific embodiments, ring M is selected from phenyl and pyridyl.

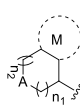
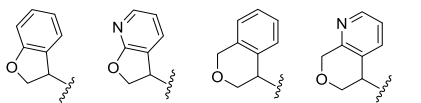
In some specific embodiments, when --- is a single bond or a double bond, X, Y, and Z are independently selected from CR^4R^5 , NR^6 , O, N, S, and CR^4 .

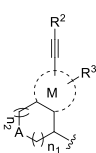
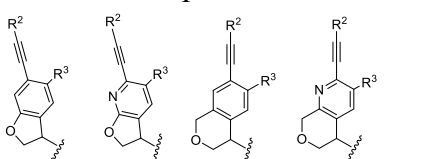
In some specific embodiments, when --- is absent, Y is absent, X is hydrogen, and Z is CR^4R^5 .

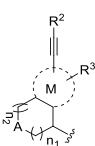
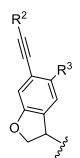
In some specific embodiments, A is selected from O.

In some specific embodiments, n_1 and n_2 are each independently 0 or 1.

In some specific embodiments, the group  is selected from .

In some specific embodiments, the group  is selected from .

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In some specific embodiments, the group  is selected from .

In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl and 4-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl and 4-6 membered heterocyclyl each independently contain 1-3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl and 4-6 membered heterocyclyl are unsubstituted or are each independently substituted with one or more identical or different R^b .

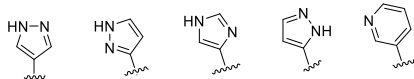
In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 heteroatoms selected from N, O, and S, the 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl are unsubstituted or are each independently substituted with one or more identical or different R^b .

In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl contains 1-3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl is unsubstituted or substituted with one or more identical or different R^b .

In some specific embodiments, R^2 is selected from pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b .

In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl contains 1, 2, or 3 N heteroatoms, and the 5-6 membered heteroaryl is unsubstituted or substituted with one or more identical or different R^b .

In some specific embodiments, R^2 is selected from pyrazolyl, imidazolyl, and pyridyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b .

In some specific embodiments, R^2 is selected from , which are unsubstituted or independently substituted with 1, 2, or 3 R^b .

In some specific embodiments, R^2 is selected from 5-membered heteroaryl, wherein the 5-membered heteroaryl contains 1-3 heteroatoms selected from N, O, and S, and the 5-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^b .

In some specific embodiments, R^2 is selected from pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, and isoxazolyl, which are unsubstituted or substituted with 1, 2, or 3 R^b .

In some specific embodiments, R^2 is selected from 5-membered heteroaryl, wherein the 5-membered heteroaryl contains 1-2 heteroatoms selected from N and S, and the

5-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^b.

In some specific embodiments, R² is selected from pyrazolyl, imidazolyl, thiazolyl, and isothiazolyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b.

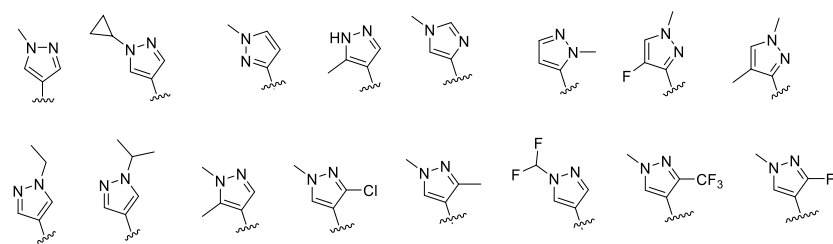
In some specific embodiments, R² is selected from 5-membered heteroaryl, wherein the 5-membered heteroaryl contains 1, 2, or 3 N heteroatoms, and the 5-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b.

In some specific embodiments, R² is selected from pyrazolyl and imidazolyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b.

In some specific embodiments, R² is selected from pyrazolyl, wherein the pyrazolyl is unsubstituted or independently substituted with 1, 2, or 3 R^b.

In some specific embodiments, R² is selected from , wherein the  is unsubstituted or independently substituted with 1, 2, or 3 R^b.

In some specific embodiments, R² is selected from



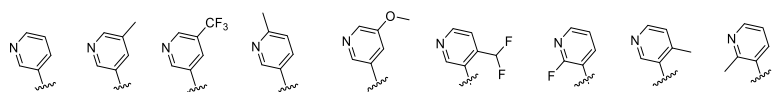
In some specific embodiments, R² is selected from 6-membered heteroaryl, wherein the 6-membered heteroaryl contains 1, 2, or 3 heteroatoms selected from N, O, and S, and the 6-membered heteroaryl is unsubstituted or substituted with one or more identical or different R^b.

In some specific embodiments, R² is selected from 6-membered heteroaryl, wherein the 6-membered heteroaryl contains 1, 2, or 3 N heteroatoms, and the 6-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b.

In some specific embodiments, R² is selected from pyridyl, wherein the pyridyl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b.

In some specific embodiments, R² is selected from , wherein the  is unsubstituted or substituted with 1, 2, or 3 identical or different R^b.

In some specific embodiments, R^2 is selected from

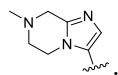


In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl is unsubstituted or substituted with one or more identical or different R^b .

In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 N heteroatoms, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl is unsubstituted or substituted with one or more identical or different R^b .

In some specific embodiments, R^2 is selected from 5-membered heteroaryl-fused 6-membered heterocyclyl, wherein the 5-membered heteroaryl and 6-membered heterocyclyl each independently contain 1, 2, or 3 N heteroatoms, and the 5-membered heteroaryl-fused 6-membered heterocyclyl is unsubstituted or substituted with one or more identical or different R^b .

In some specific embodiments, R^2 is selected from imidazolyl-fused piperazinyl, wherein the imidazolyl-fused piperazinyl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b .



In some specific embodiments, R^2 is selected from

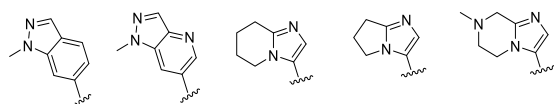
In some specific embodiments, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl, wherein the 5-6 membered heteroaryl and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl are unsubstituted or substituted with one or more

identical or different R^b.

In some specific embodiments, R² is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl, wherein the 5-6 membered heteroaryl is selected from imidazolyl, pyrazolyl, and pyridyl, the 5-6 membered heterocyclyl is selected from pyrrolidinyl, piperidinyl, and piperazinyl, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl are unsubstituted or substituted with one or more identical or different R^b.

In some specific embodiments, R² is selected from imidazopyrrolidinyl, imidazopiperidinyl, imidazopiperazinyl, pyrazolophenyl, and pyrazolopyridyl, wherein the imidazopyrrolidinyl, imidazopiperidinyl, imidazopiperazinyl, pyrazolophenyl, and pyrazolopyridyl are unsubstituted or substituted with one or more identical or different R^b.

In some specific embodiments, R² is selected from



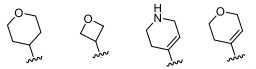
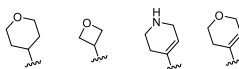
In some specific embodiments, R² is selected from 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl contains 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b.

In some specific embodiments, R² is selected from 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b.

In some specific embodiments, R² is selected from 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-2 heteroatoms

selected from N and O, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, R^2 is selected from tetrahydro-2H-pyranyl, oxetanyl, 1,2,3,6-tetrahydropyridyl, and 3,6-dihydro-2H-pyranyl, wherein the tetrahydro-2H-pyranyl, oxetanyl, 1,2,3,6-tetrahydropyridyl, and 3,6-dihydro-2H-pyranyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, R^2 is selected from , wherein the  is unsubstituted or independently substituted with 1, 2, or 3 identical or different R^b .

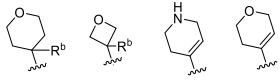
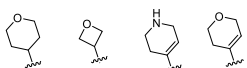
In some specific embodiments, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom linked thereto, form 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl contains 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocyclyl is unsubstituted or independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom linked thereto, form 4-6 membered heterocycloalkyl or 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom linked thereto, form 4-6 membered heterocycloalkyl or 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-2 heteroatoms selected from N and O, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are

each independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom linked thereto, form tetrahydro-2H-pyranyl, oxetanyl, 1,2,3,6-tetrahydropyridyl, and 3,6-dihydro-2H-pyranyl, wherein the tetrahydro-2H-pyranyl, oxetanyl, 1,2,3,6-tetrahydropyridyl, and 3,6-dihydro-2H-pyranyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, R^2 is selected from , wherein the group  is unsubstituted or independently substituted with 1, 2, or 3 identical or different R^b .

In some specific embodiments, each R^b is independently selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl, wherein the C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 halogens.

In some specific embodiments, each R^b is independently selected from H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, and C_3 - C_5 cycloalkyl, wherein the C_1 - C_3 alkyl, C_1 - C_3 alkoxy, and C_3 - C_5 cycloalkyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 substituents selected from F, Cl, and Br.

In some specific embodiments, each R^b is independently selected from H, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

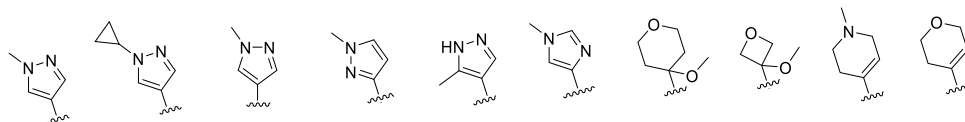
In some specific embodiments, each R^b is independently selected from methyl, methoxy, and cyclopropyl.

In some specific embodiments, each R^b is independently selected from cyclopropyl.

In some specific embodiments, each R^b is independently selected from methoxy.

In some specific embodiments, each R^b is independently selected from methyl.

In some specific embodiments, R^2 is selected from



In some specific embodiments, R^2 is selected from .

In some specific embodiments, each R^b is independently selected from H, deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl, wherein the C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 halogens.

In some specific embodiments, each R^b is independently selected from H, deuterium, halogen, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, and C_3 - C_5 cycloalkyl, wherein the C_1 - C_3 alkyl, C_1 - C_3 alkoxy, and C_3 - C_5 cycloalkyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 halogens.

In some specific embodiments, each R^b is independently selected from H, deuterium, F, Cl, Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, wherein the methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 substituents selected from F, Cl, and Br.

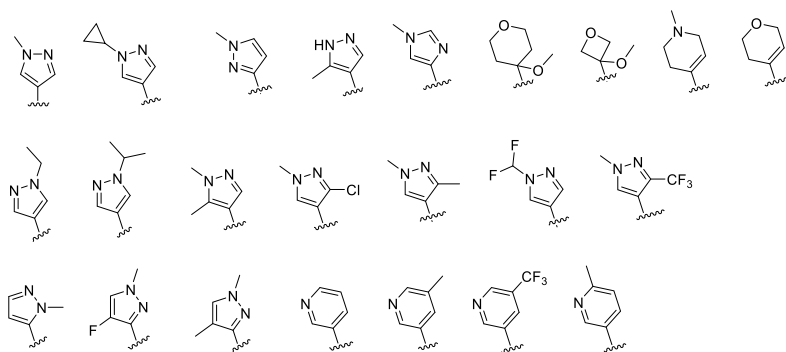
In some specific embodiments, each R^b is independently selected from H, deuterium, F, Cl, Br, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CHF_2$, and $-CF_3$.

In some specific embodiments, each R^b is independently selected from H, deuterium, F, Cl, methyl, ethyl, isopropyl, methoxy, cyclopropyl, $-CHF_2$, and $-CF_3$.

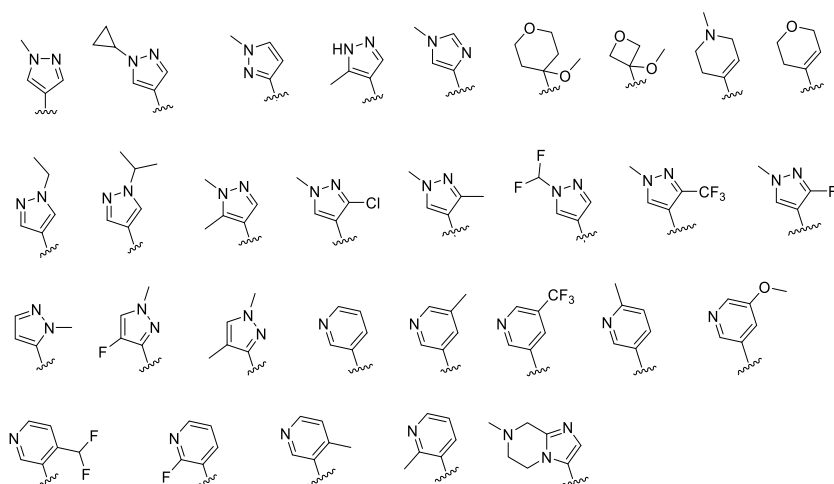
In some specific embodiments, R^b described herein may be further deuterated.

In some specific embodiments, each R^b is independently selected from H, deuterium, F, Cl, methyl, ethyl, isopropyl, methoxy, cyclopropyl, $-CHF_2$, $-CF_3$, and $-CD_3$.

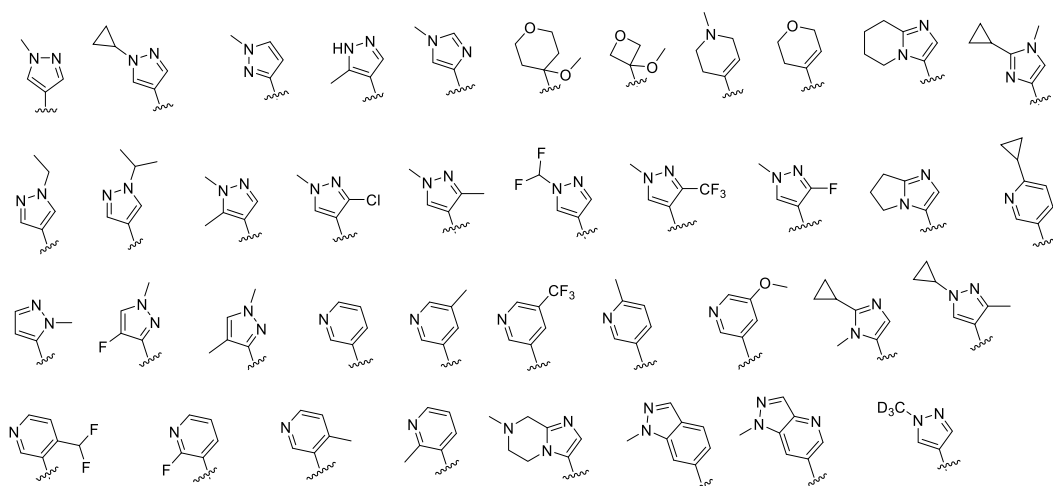
In some specific embodiments, R^2 is selected from



In some specific embodiments, R^2 is selected from



In some specific embodiments, R^2 is selected from



In some specific embodiments, R^3 is selected from hydrogen, halogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

In some specific embodiments, R^3 is selected from hydrogen, F, Cl, Br, C_{1-4} alkyl, C_{5-6} alkyl, and C_{3-5} cycloalkyl.

In some specific embodiments, R^3 is selected from hydrogen, F, Cl, Br, C_{1-4} alkyl, and C_{3-5} cycloalkyl.

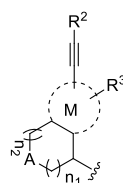
In some specific embodiments, R^3 is selected from hydrogen, F, Cl, Br, methyl, ethyl, propyl, isopropyl, butyl, cyclopropyl, cyclobutyl, and cyclopentyl.

In some specific embodiments, R^3 is selected from hydrogen, F, Cl, methyl, ethyl, and cyclopropyl.

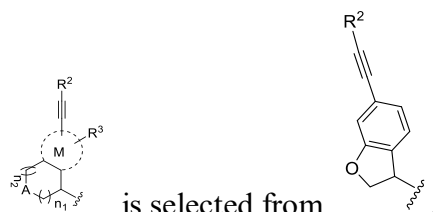
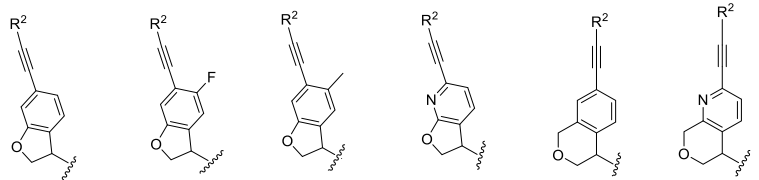
In some specific embodiments, R^3 is selected from hydrogen, F, Cl, Br, and C_{1-4} alkyl.

In some specific embodiments, R^3 is selected from hydrogen, F, Cl, methyl, and ethyl.

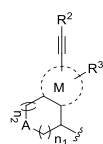
In some specific embodiments, R^3 is selected from hydrogen, F, and methyl.



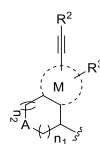
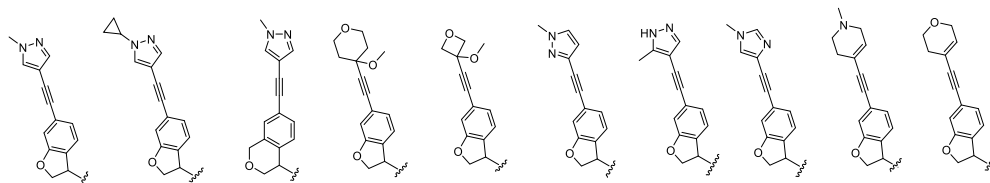
In some specific embodiments, the group



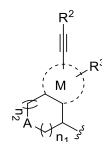
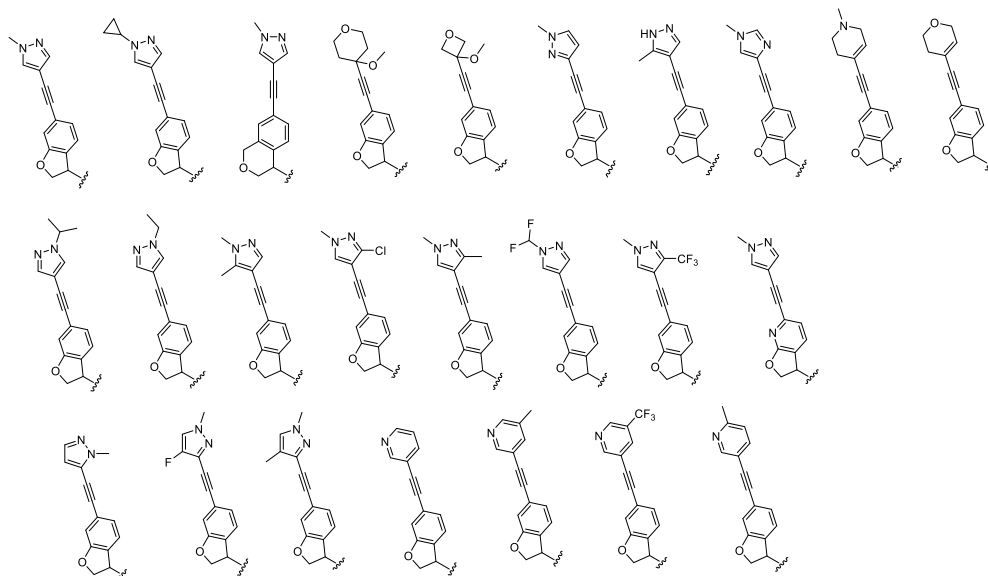
In some specific embodiments, the group



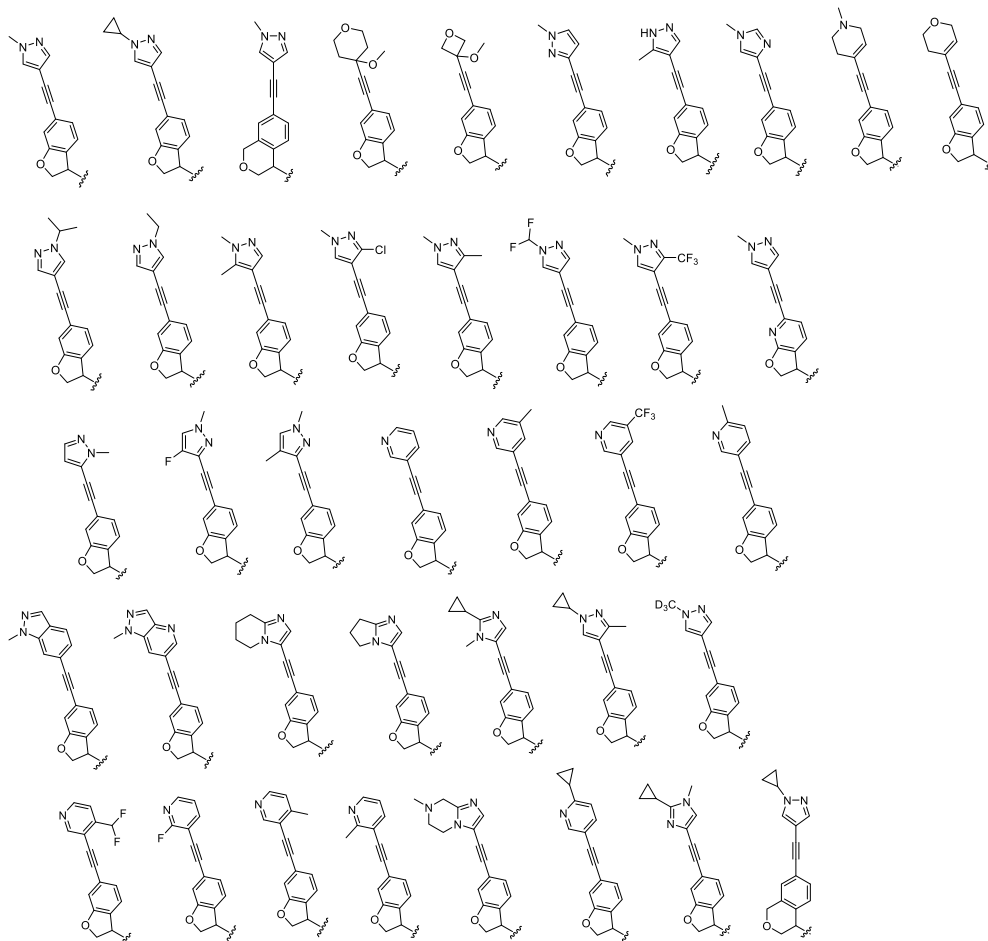
In some specific embodiments, the group



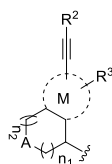
In some specific embodiments, the group



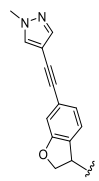
In some specific embodiments, the group is selected from



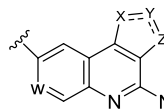
In some specific embodiments, the group



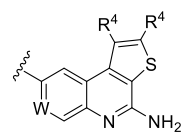
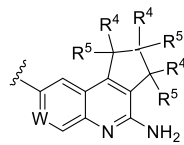
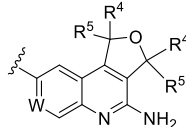
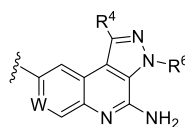
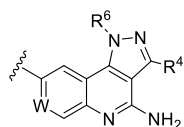
is selected from



In some specific embodiments, the group



is selected from



wherein W is selected from N and CR⁷.

In some specific embodiments, W is selected from CR⁷.

In some specific embodiments, W is selected from N.

In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, and C₁₋₆ alkyl.

In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, C₁₋₄ alkyl, and C₅₋₆ alkyl.

In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, and C₁₋₄ alkyl.

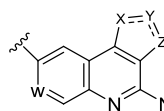
In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, F, Cl, Br, methyl, ethyl, propyl, and isopropyl.

In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, F, Cl, and methyl.

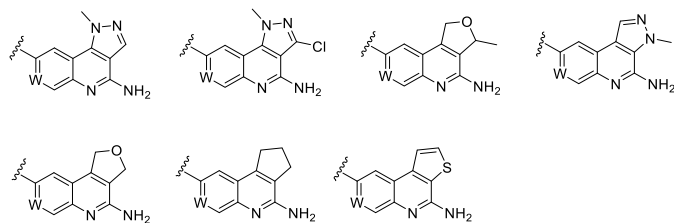
In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ described herein may be further deuterated.

In some specific embodiments, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, F, Cl, methyl, and -CD₃.

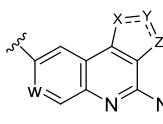
In some specific embodiments, the group

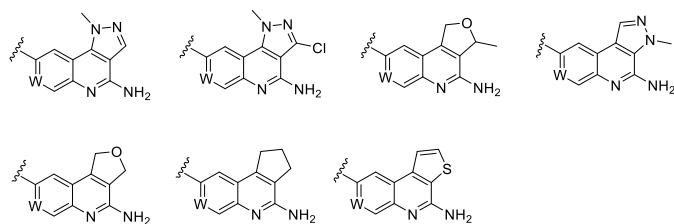


is selected from

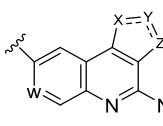


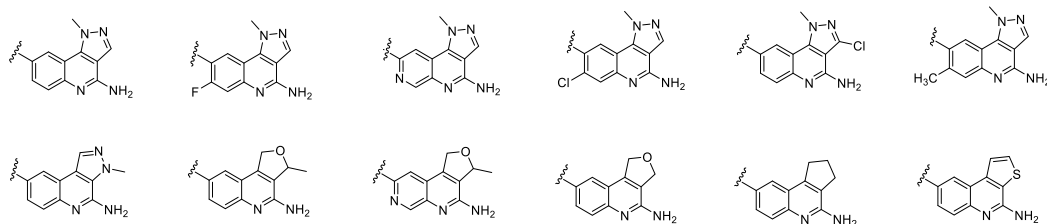
, wherein W is selected from N and CR⁷.

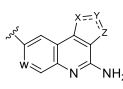
In some specific embodiments, the group  is selected from

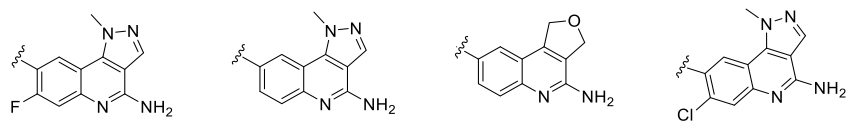


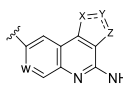
, wherein W is selected from N and CR⁷, and R⁷ is selected from H, F, Cl, and methyl.

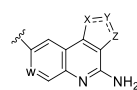
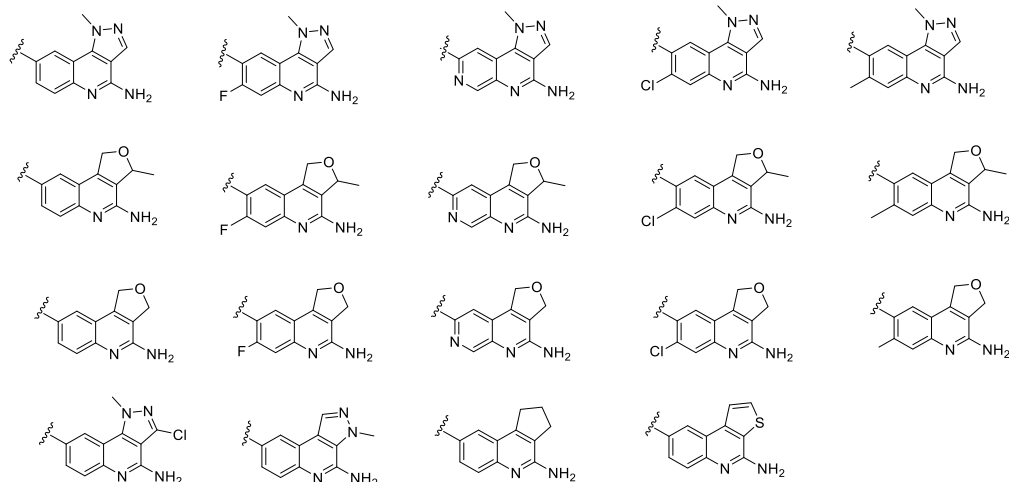
In some specific embodiments, the group  is selected from:



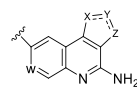
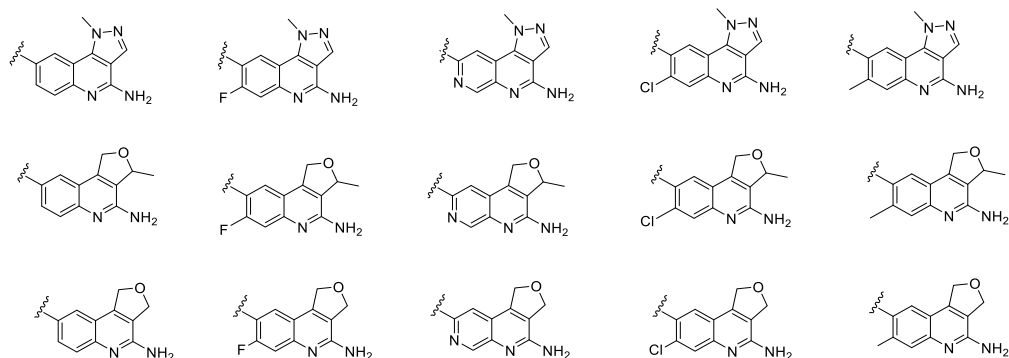
In some specific embodiments, the group  is selected from



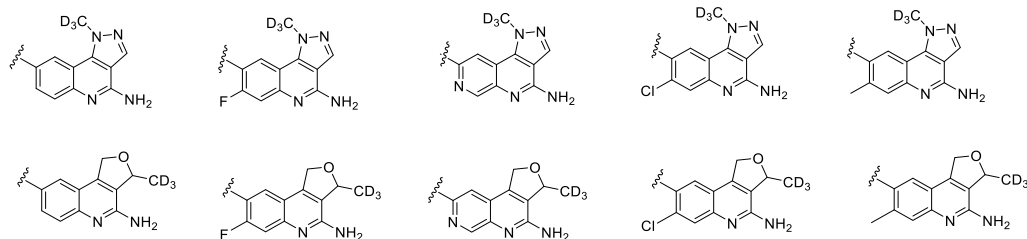
In some specific embodiments, the group  is selected from



In some specific embodiments, the group is selected from



In some specific embodiments, the group is selected from

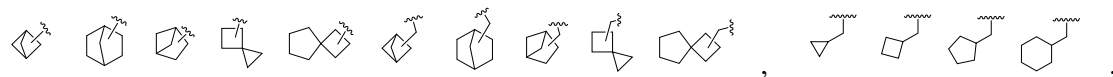


In some specific embodiments, R^1 is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl-, and 5-10 membered heteroaryl, wherein the C_{1-6} alkyl is unsubstituted or substituted with one or more R_i , the C_{3-10} cycloalkyl is unsubstituted or substituted with one or more R_j , and the 5-10 membered heteroaryl is unsubstituted or substituted with one or more R_l .

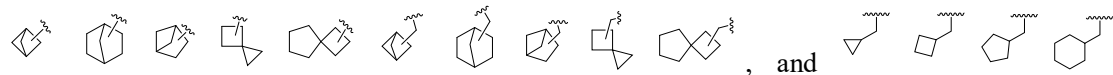
In some specific embodiments, R^1 is selected from C_{1-4} alkyl, C_{3-6} monocycloalkyl, C_{5-8} bridged cycloalkyl, C_{5-8} spirocycloalkyl, C_{3-6} monocycloalkyl- C_{1-4} alkyl-, C_{5-8} bridged cycloalkyl- C_{1-4} alkyl-, C_{5-8} spirocycloalkyl- C_{1-4} alkyl-, and 5-6 membered

heteroaryl, wherein the C₁₋₄ alkyl is unsubstituted or substituted with one or more R_i, the C₃₋₆ monocycloalkyl, C₅₋₈ bridged cycloalkyl, and C₅₋₈ spirocycloalkyl are unsubstituted or substituted with one or more R_j, and the 5-10 membered heteroaryl is unsubstituted or substituted with one or more R_l.

In some specific embodiments, R¹ is selected from methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

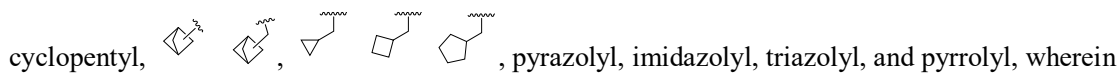


pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, and thiazolyl, wherein the methyl, ethyl, propyl, and butyl are unsubstituted or substituted with one or more R_i, the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

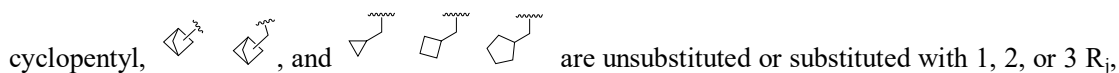


are unsubstituted or substituted with one or more R_j, and the pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, and thiazolyl are unsubstituted or substituted with one or more R_l.

In some specific embodiments, R¹ is selected from methyl, ethyl, cyclopropyl, cyclobutyl,

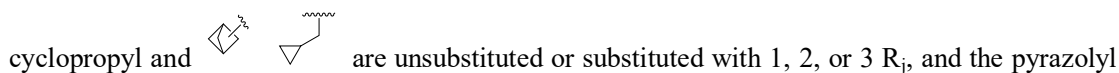


cyclopentyl, pyrazolyl, imidazolyl, triazolyl, and pyrrolyl, wherein the methyl and ethyl are unsubstituted or substituted with 1, 2, or 3 R_i, the cyclopropyl, cyclobutyl,



cyclopentyl, and are unsubstituted or substituted with 1, 2, or 3 R_j, and the pyrazolyl, imidazolyl, triazolyl, and pyrrolyl are unsubstituted or substituted with 1, 2, or 3 R_l.

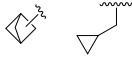
In some specific embodiments, R¹ is selected from methyl, ethyl, cyclopropyl, and pyrazolyl, wherein the methyl and ethyl are unsubstituted or substituted with 1, 2, or 3 R_i, the



cyclopropyl and are unsubstituted or substituted with 1, 2, or 3 R_j, and the pyrazolyl is unsubstituted or substituted with 1, 2, or 3 R_l.

It should be understood that in the definition of substituent R¹ in the present disclosure, the substitution with R_i is always performed on alkyl or alkylene, the substitution with R_j is always performed on cycloalkyl, including monocycloalkyl, bridged cycloalkyl, and spirocycloalkyl, the substitution with R_k is always performed

on heterocyclyl, and the substitution with R_l is always performed on aryl or heteroaryl.

For example, in , if the substituent R_j appears, the substitution position for R_j is located on cyclopropyl or .

In some specific embodiments, R^1 is selected from methyl, ethyl, cyclopropyl, , , and pyrazolyl, wherein the methyl, ethyl, cyclopropyl, and  are unsubstituted, and the pyrazolyl is unsubstituted or substituted with 1, 2, or 3 R_l .

In some specific embodiments, each R_i , R_j , R_k , and R_l is independently selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

In some specific embodiments, each R_i , R_j , R_k , and R_l is independently selected from halogen, halogenated C_{1-4} alkyl, C_{1-4} alkyl, and C_{3-6} cycloalkyl.

In some specific embodiments, each R_i , R_j , R_k , and R_l is independently selected from halogen, C_{1-4} alkyl, and C_{3-6} cycloalkyl.

In some specific embodiments, each R_i , R_j , R_k , and R_l is independently selected from F, Cl, Br, methyl, ethyl, propyl, isopropyl, cyclopropyl, and cyclobutyl.

In some specific embodiments, each R_i , R_j , R_k , and R_l is independently selected from F, Cl, methyl, and ethyl.

In some specific embodiments, each R_i , R_j , R_k , and R_l is independently selected from methyl.

In some specific embodiments, each R_l is independently selected from halogen, halogenated C_{1-6} alkyl, C_{1-6} alkyl, and C_{3-6} cycloalkyl.

In some specific embodiments, each R_l is independently selected from halogen, halogenated C_{1-4} alkyl, C_{1-4} alkyl, and C_{3-6} cycloalkyl.

In some specific embodiments, each R_l is independently selected from halogen, C_{1-4} alkyl, and C_{3-6} cycloalkyl.

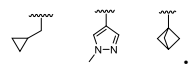
In some specific embodiments, each R_l is independently selected from F, Cl, Br, methyl, ethyl, propyl, isopropyl, cyclopropyl, and cyclobutyl.

In some specific embodiments, each R_l is independently selected from F, Cl, methyl, and ethyl.

In some specific embodiments, each R_1 is independently selected from methyl.

In some specific embodiments, each R_1 is independently selected from D, F, Cl, methyl, and ethyl.

In some specific embodiments, R^1 is selected from methyl, ethyl, cyclopropyl, and

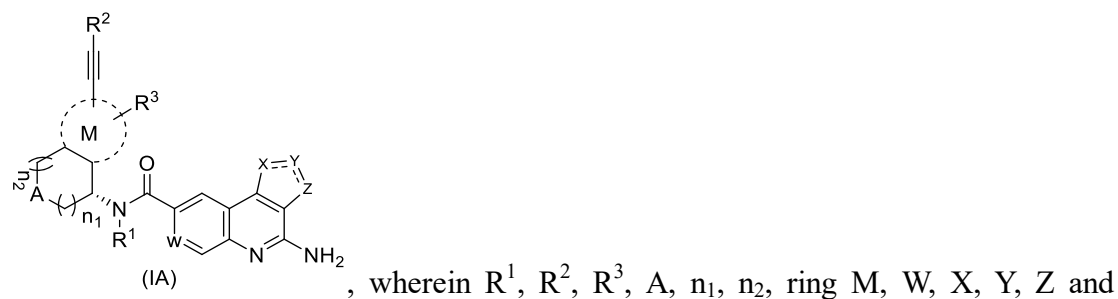


In some specific embodiments, R^1 is selected from methyl, ethyl, and cyclopropyl.

In some specific embodiments, R^1 is selected from methyl.

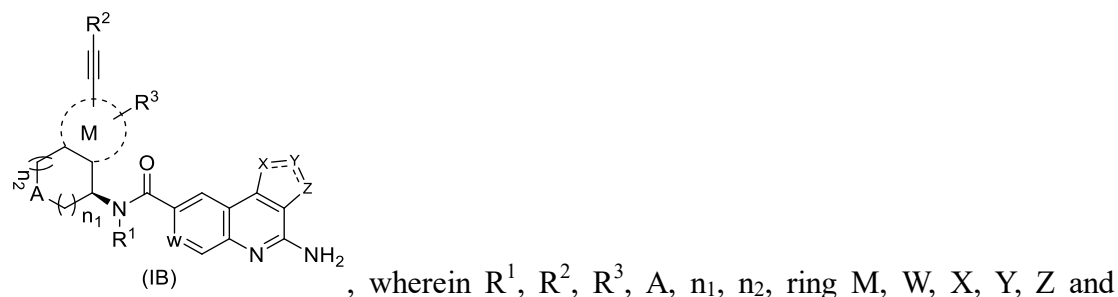
In some specific embodiments, R^1 is selected from $-CD_3$.

In some specific embodiments, formula (I) has a structure shown as formula IA:



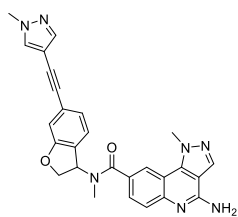
--- are each as defined above.

formula (I) has a structure shown as formula IB:

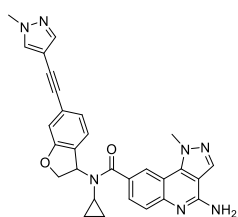


--- are each as defined above.

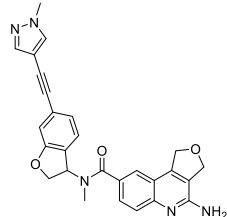
As an exemplary compound of the present disclosure, the compound represented by formula (I) is selected from any of the following specific compounds:



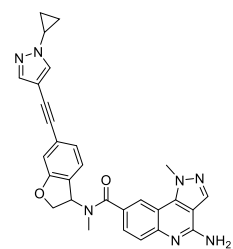
Compound 1



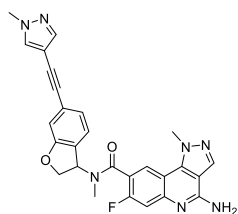
Compound 2



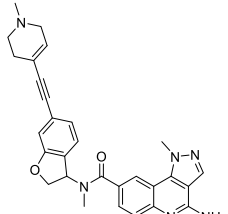
Compound 3



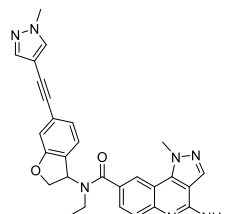
Compound 4



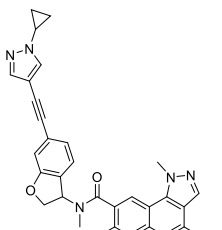
Compound 5



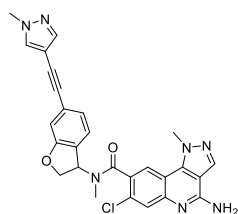
Compound 6



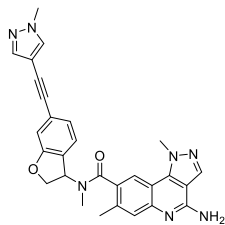
Compound 7



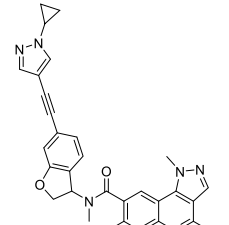
Compound 8



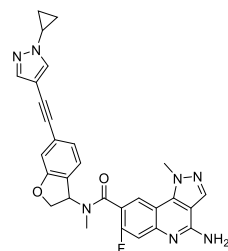
Compound 9



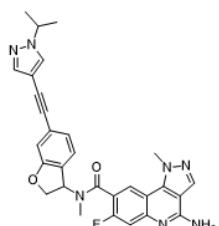
Compound 10



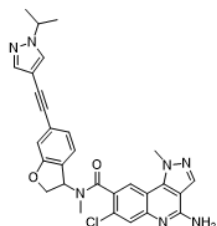
Compound 11



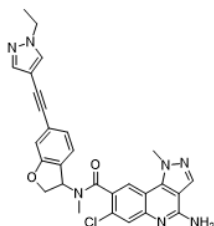
Compound 12



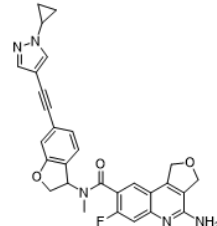
Compound 13



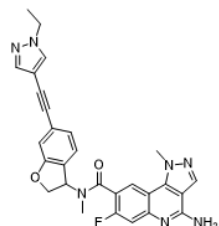
Compound 14



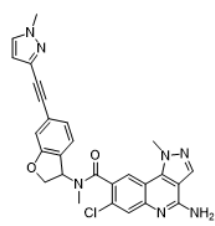
Compound 15



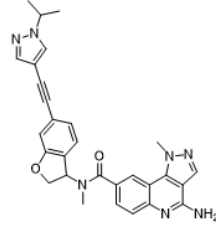
Compound 16



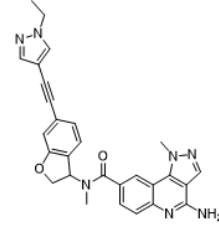
Compound 17



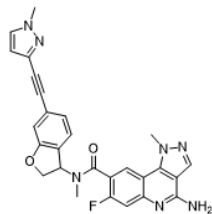
Compound 18



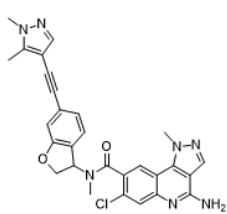
Compound 19



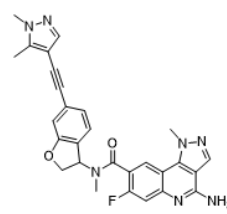
Compound 20



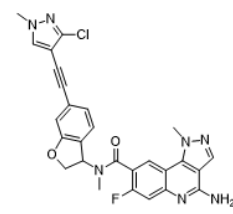
Compound 21



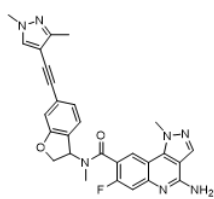
Compound 22



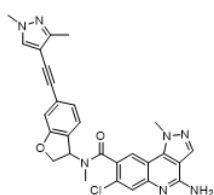
Compound 23



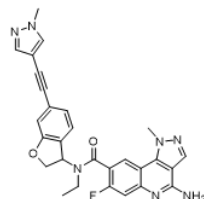
Compound 24



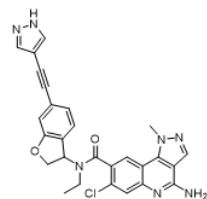
Compound 25



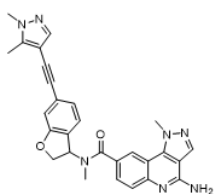
Compound 26



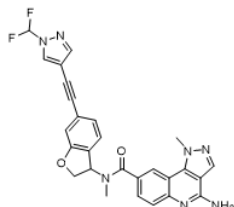
Compound 27



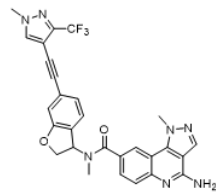
Compound 28



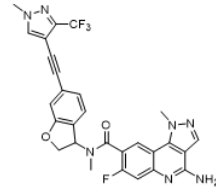
Compound 29



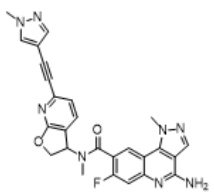
Compound 30



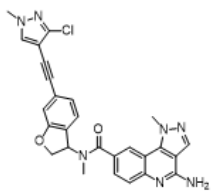
Compound 31



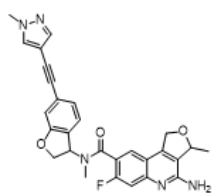
Compound 32



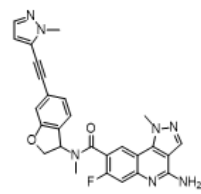
Compound 33



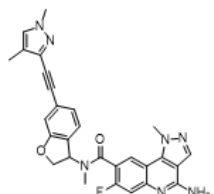
Compound 34



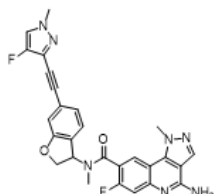
Compound 35



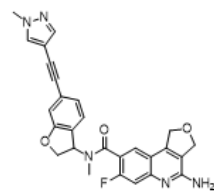
Compound 36



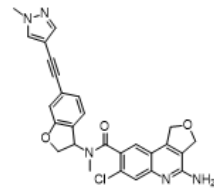
Compound 37



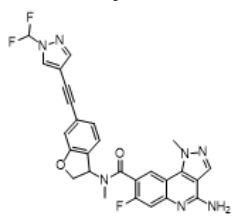
Compound 38



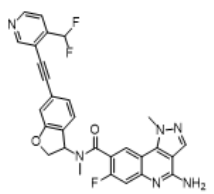
Compound 39



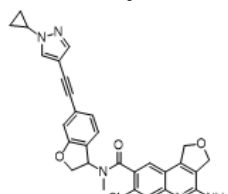
Compound 40



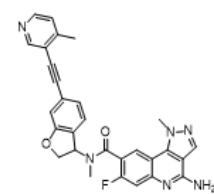
Compound 41



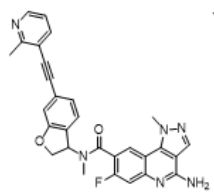
Compound 42



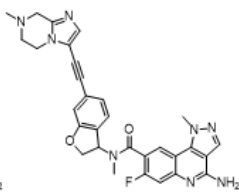
Compound 43



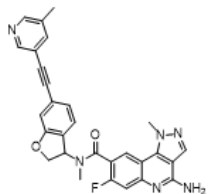
Compound 44



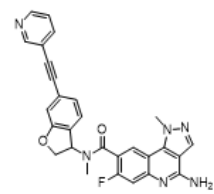
Compound 45



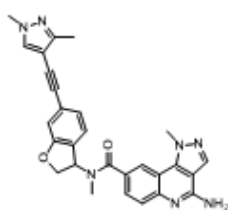
Compound 46



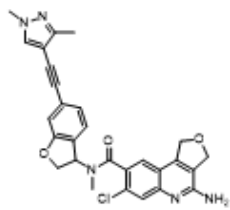
Compound 47



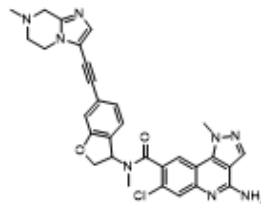
Compound 48



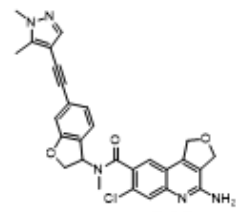
Compound 49



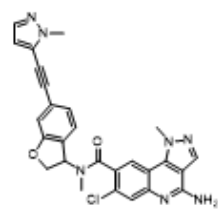
Compound 50



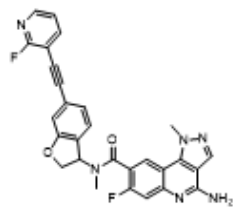
Compound 51



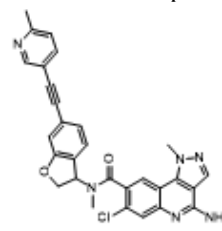
Compound 52



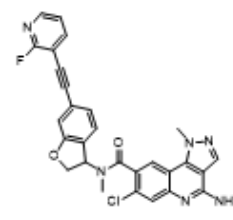
Compound 53



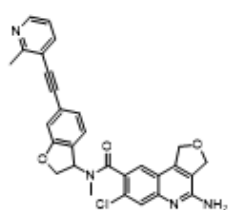
Compound 54



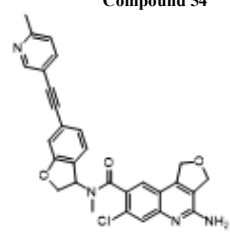
Compound 55



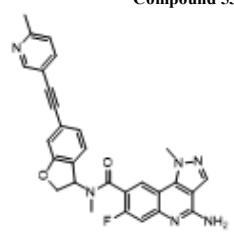
Compound 56



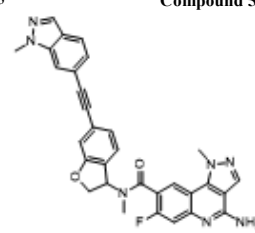
Compound 57



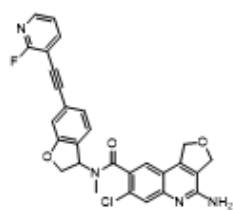
Compound 58



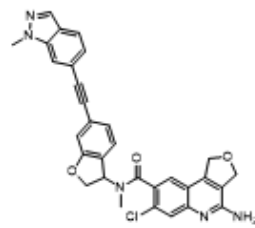
Compound 59



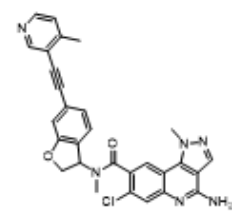
Compound 60



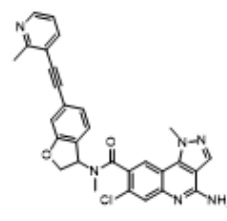
Compound 61



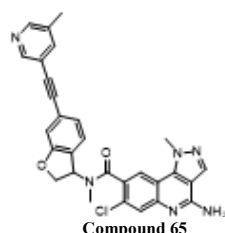
Compound 62



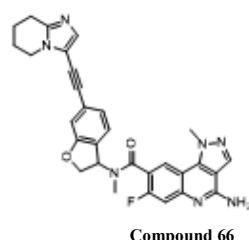
Compound 63



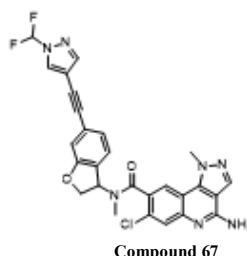
Compound 64



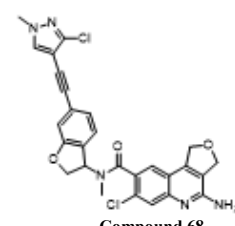
Compound 65



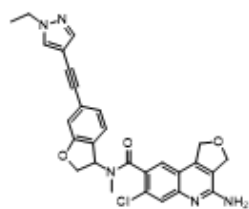
Compound 66



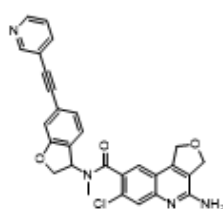
Compound 67



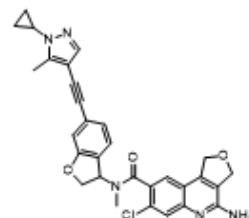
Compound 68



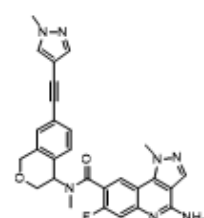
Compound 69



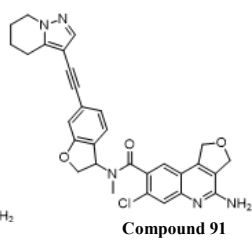
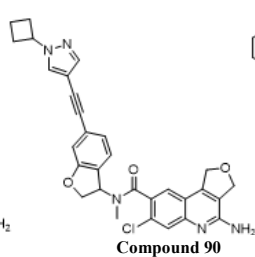
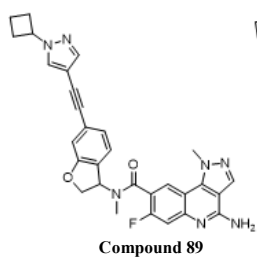
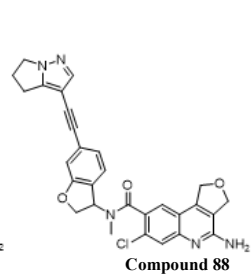
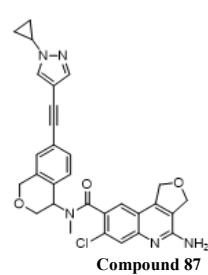
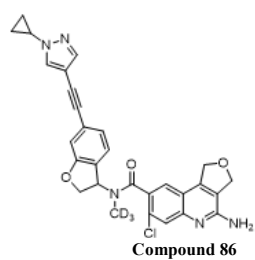
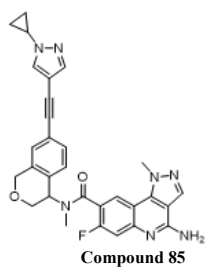
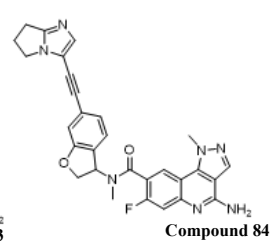
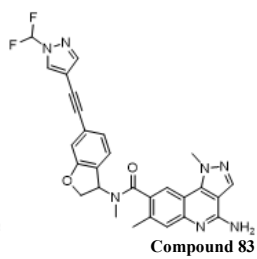
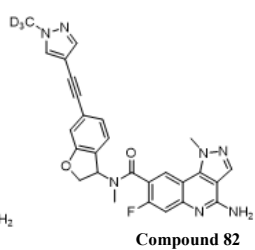
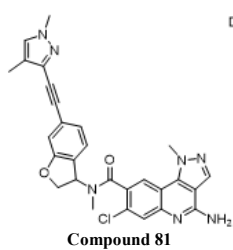
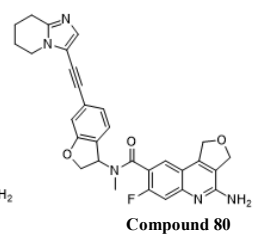
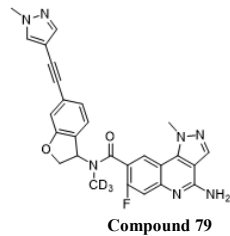
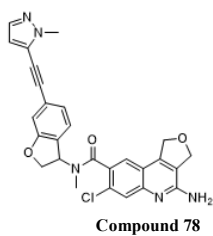
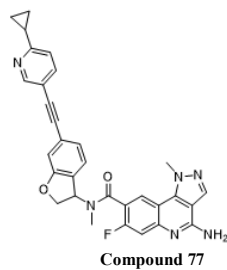
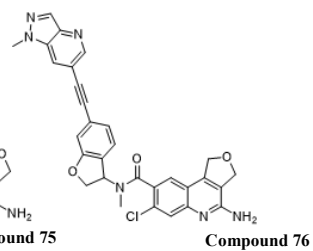
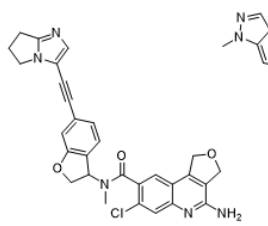
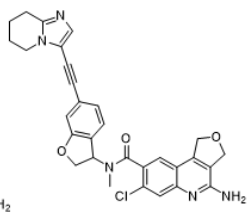
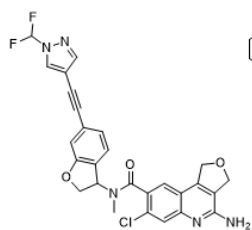
Compound 70

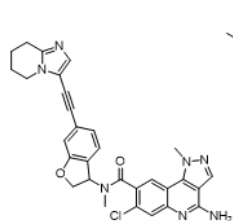


Compound 71

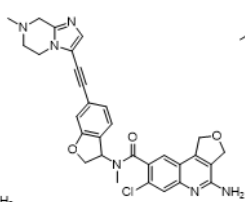


Compound 72

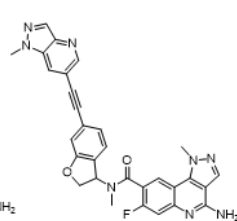




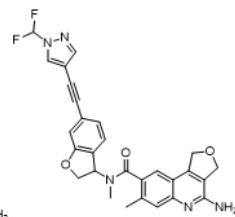
Compound 93



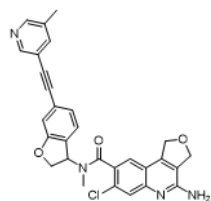
Compound 94



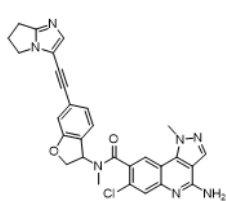
Compound 95



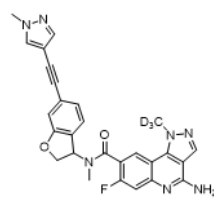
Compound 98



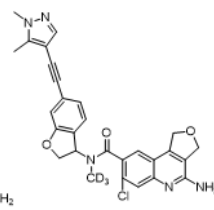
Compound 100



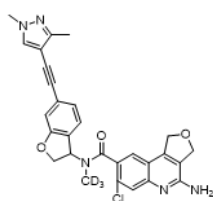
Compound 101



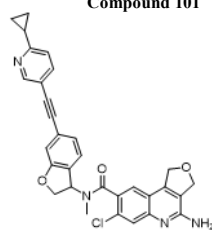
Compound 103



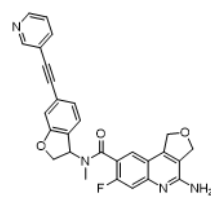
Compound 104



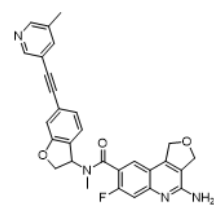
Compound 105



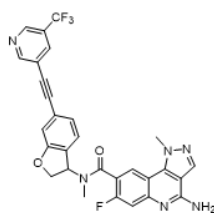
Compound 106



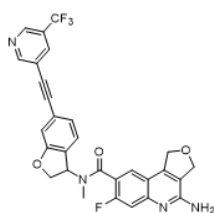
Compound 107



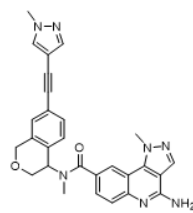
Compound 108



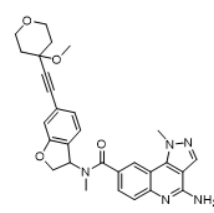
Compound 113



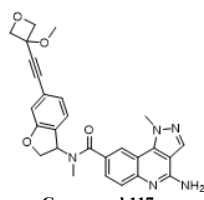
Compound 114



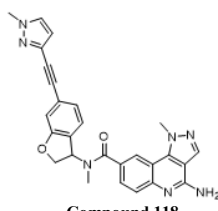
Compound 115



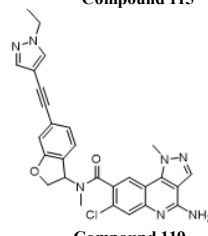
Compound 116



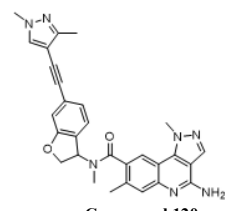
Compound 117



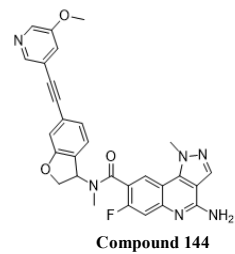
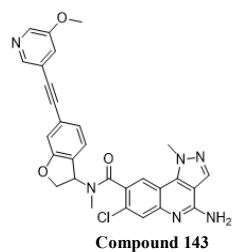
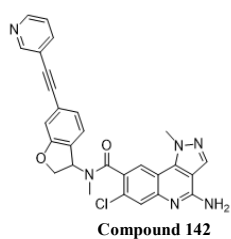
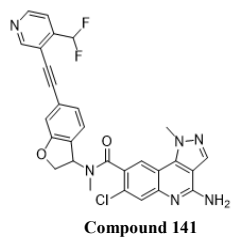
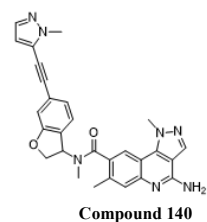
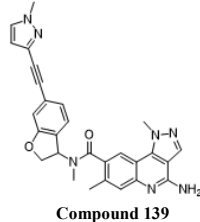
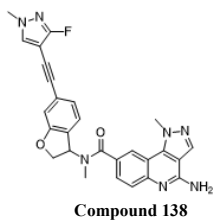
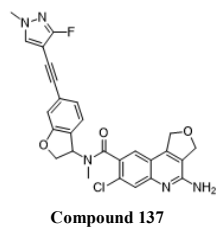
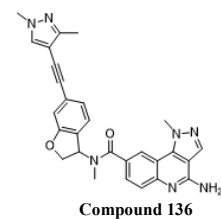
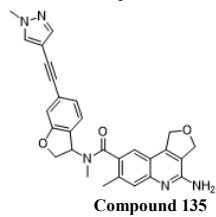
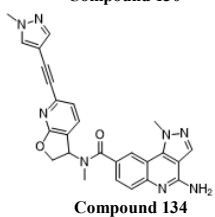
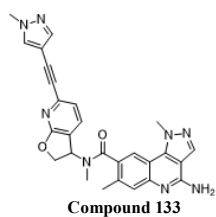
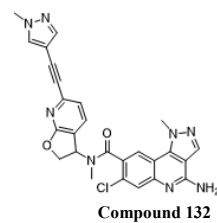
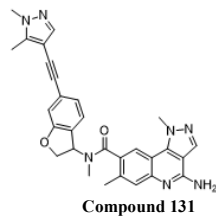
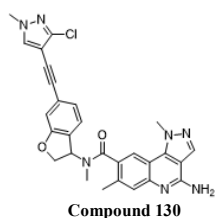
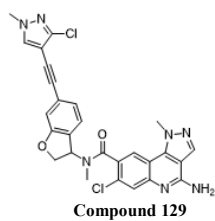
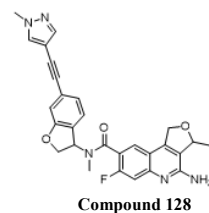
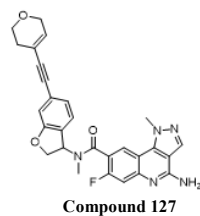
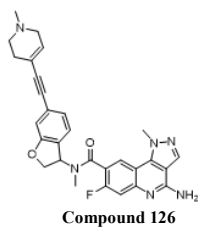
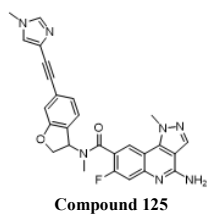
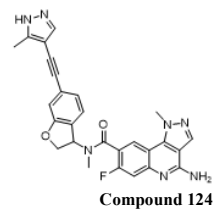
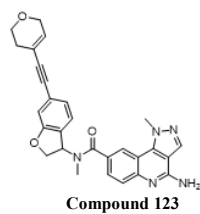
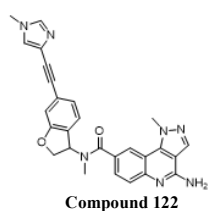
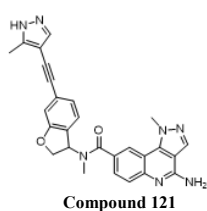
Compound 118

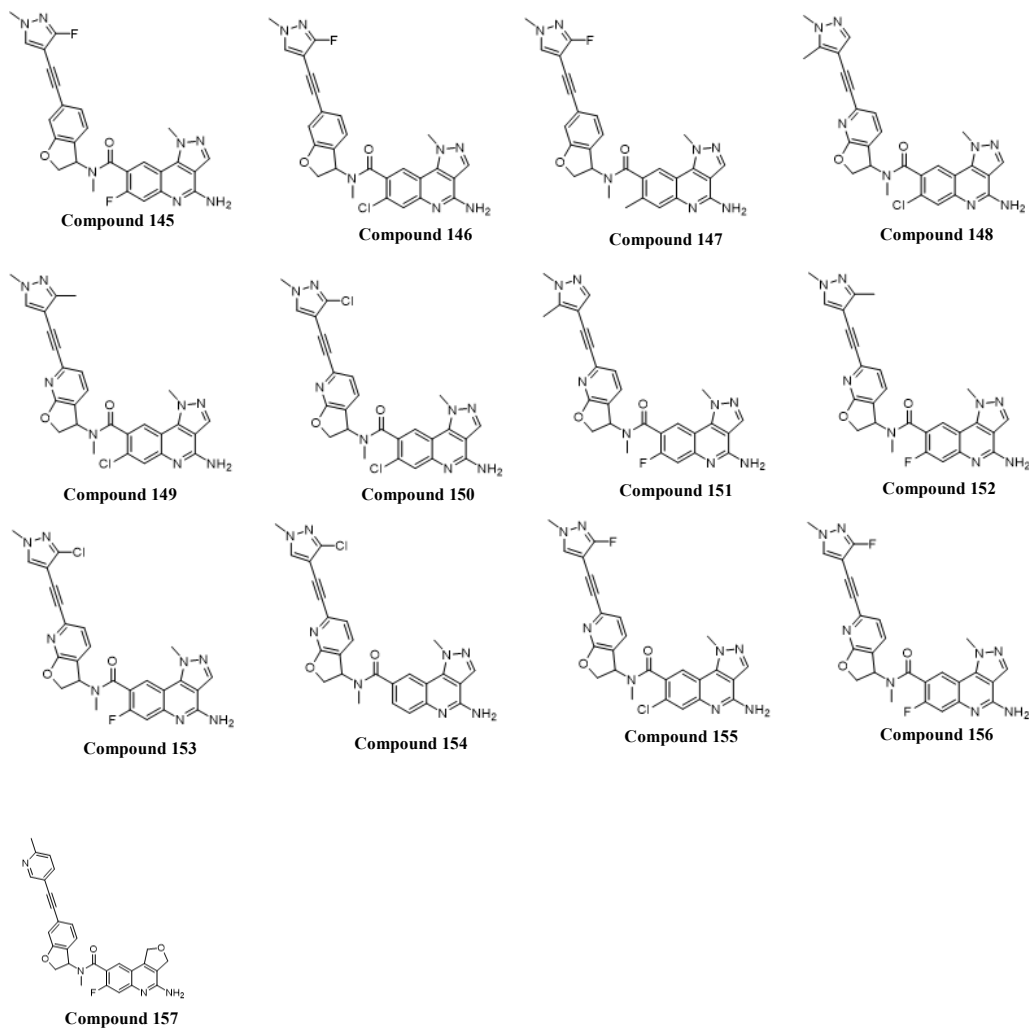


Compound 119

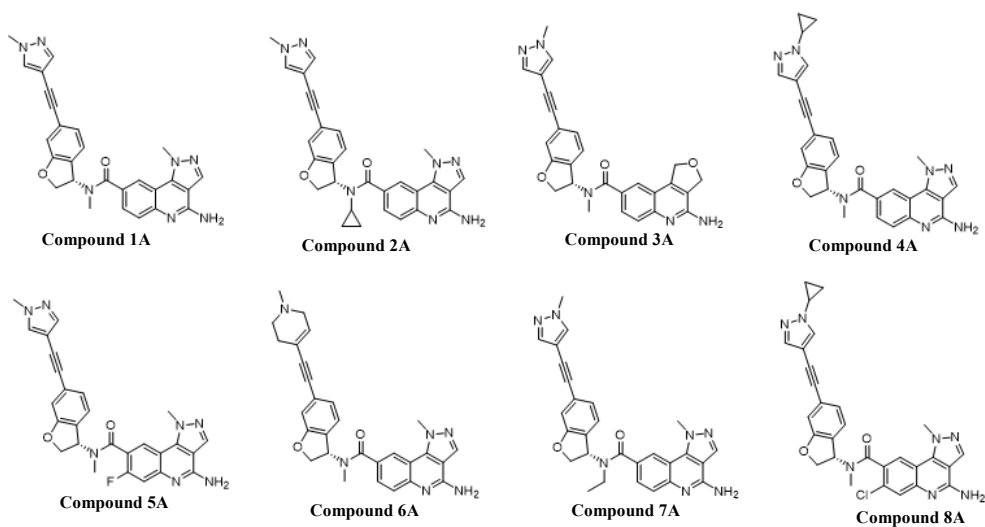


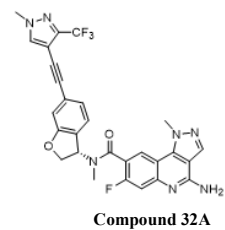
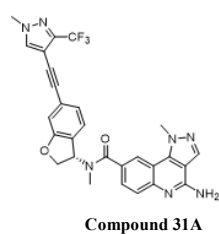
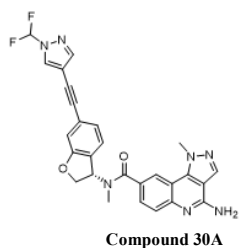
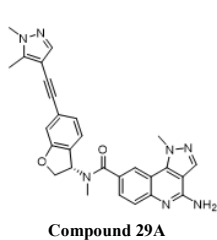
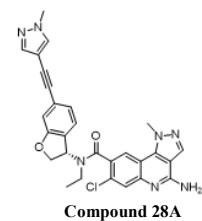
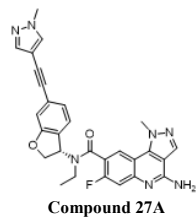
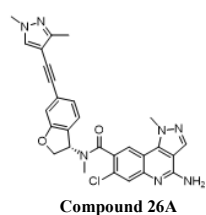
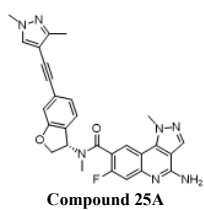
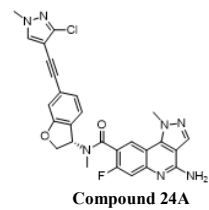
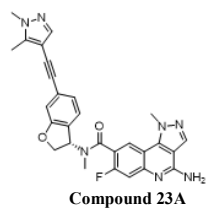
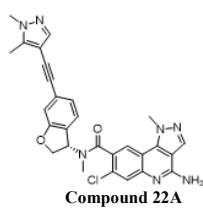
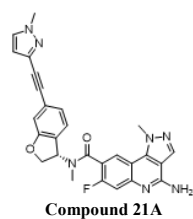
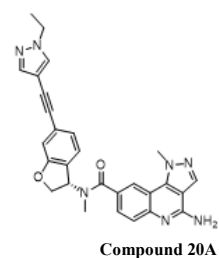
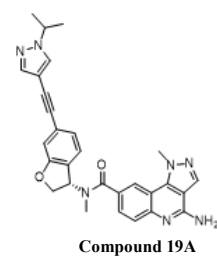
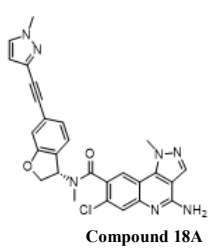
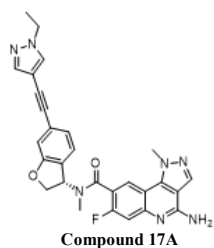
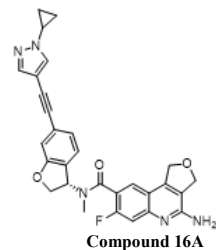
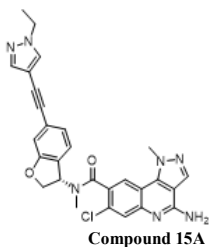
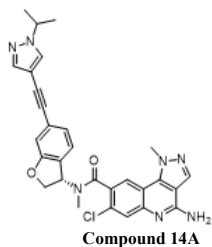
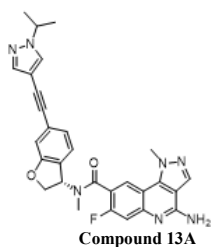
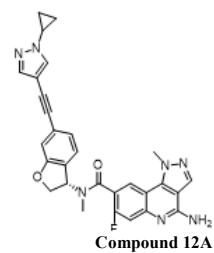
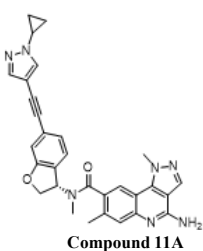
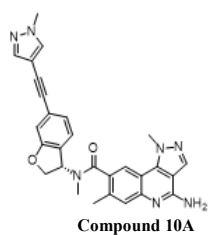
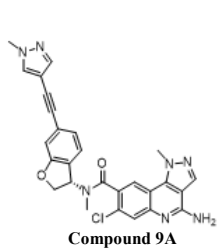
Compound 120

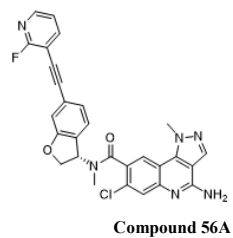
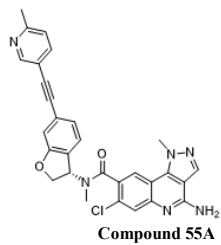
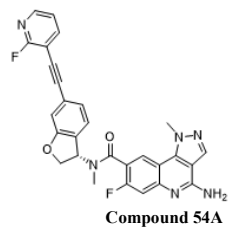
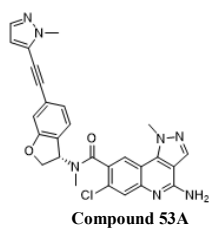
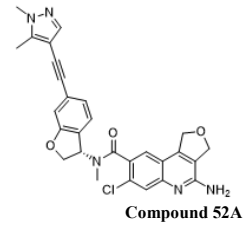
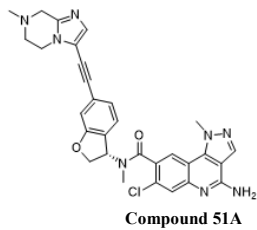
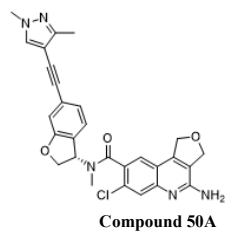
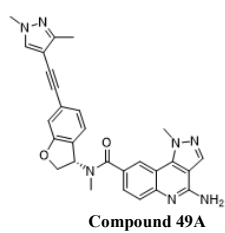
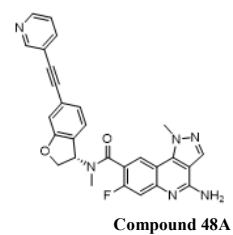
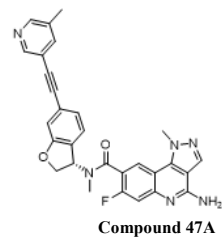
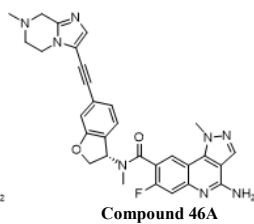
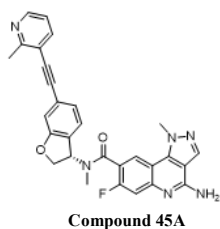
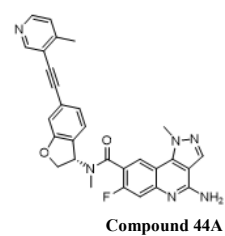
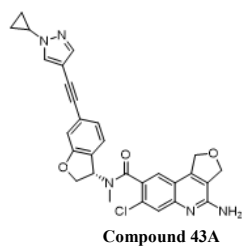
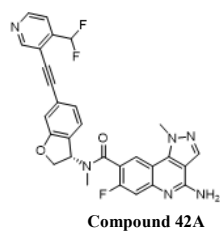
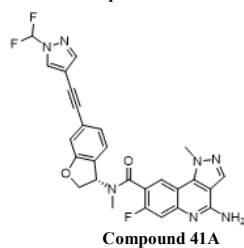
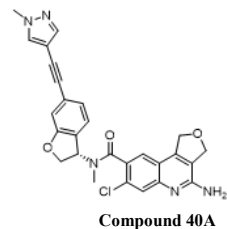
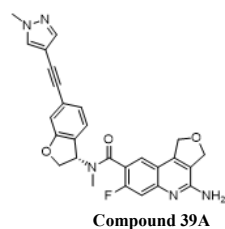
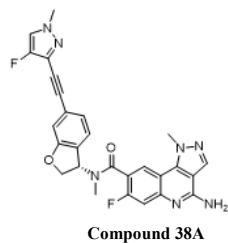
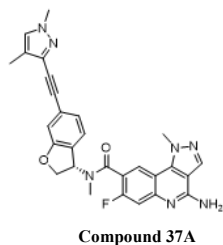
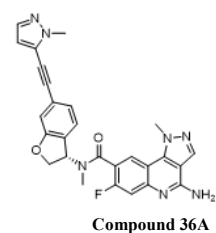
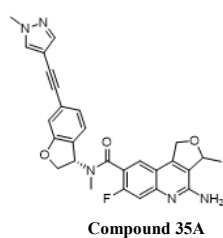
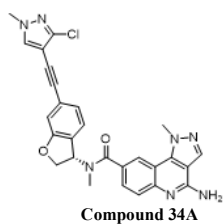
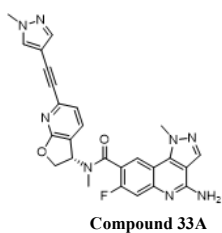


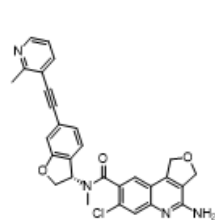


Further, the present disclosure also provides the S configurations of the exemplary compounds described above:

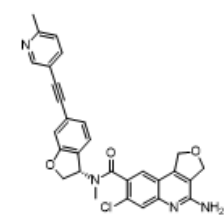




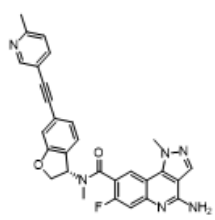




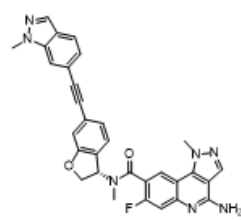
Compound 57A



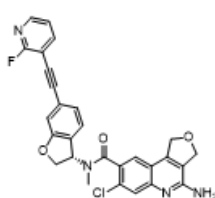
Compound 58A



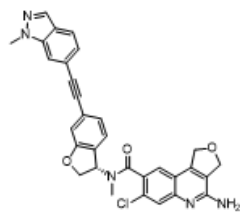
Compound 59A



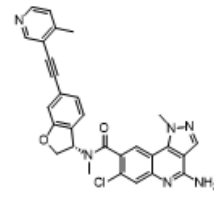
Compound 60A



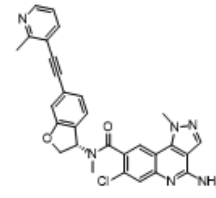
Compound 61A



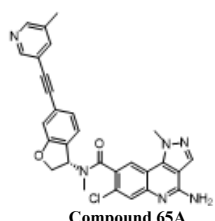
Compound 62A



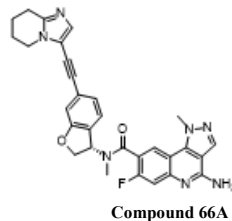
Compound 63A



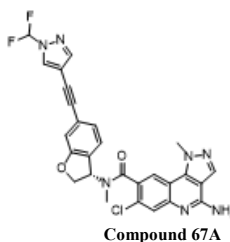
Compound 64A



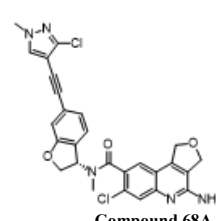
Compound 65A



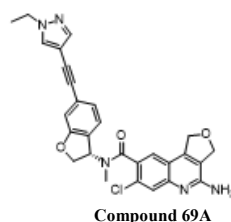
Compound 66A



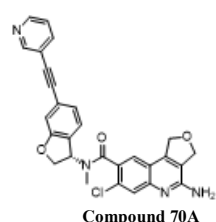
Compound 67A



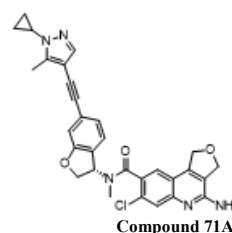
Compound 68A



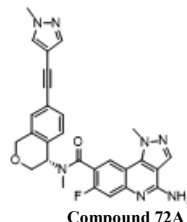
Compound 69A



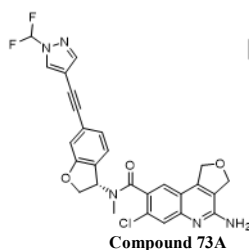
Compound 70A



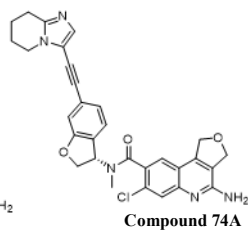
Compound 71A



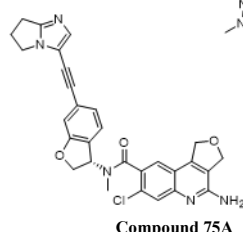
Compound 72A



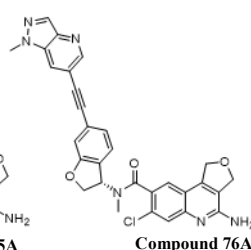
Compound 73A



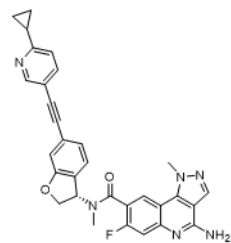
Compound 74A



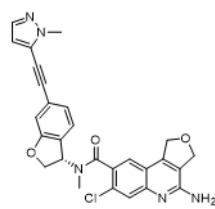
Compound 75A



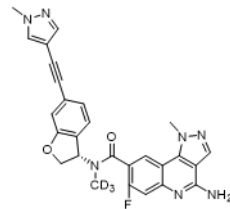
Compound 76A



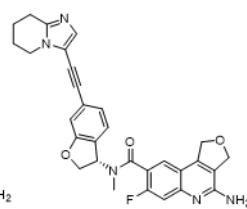
Compound 77A



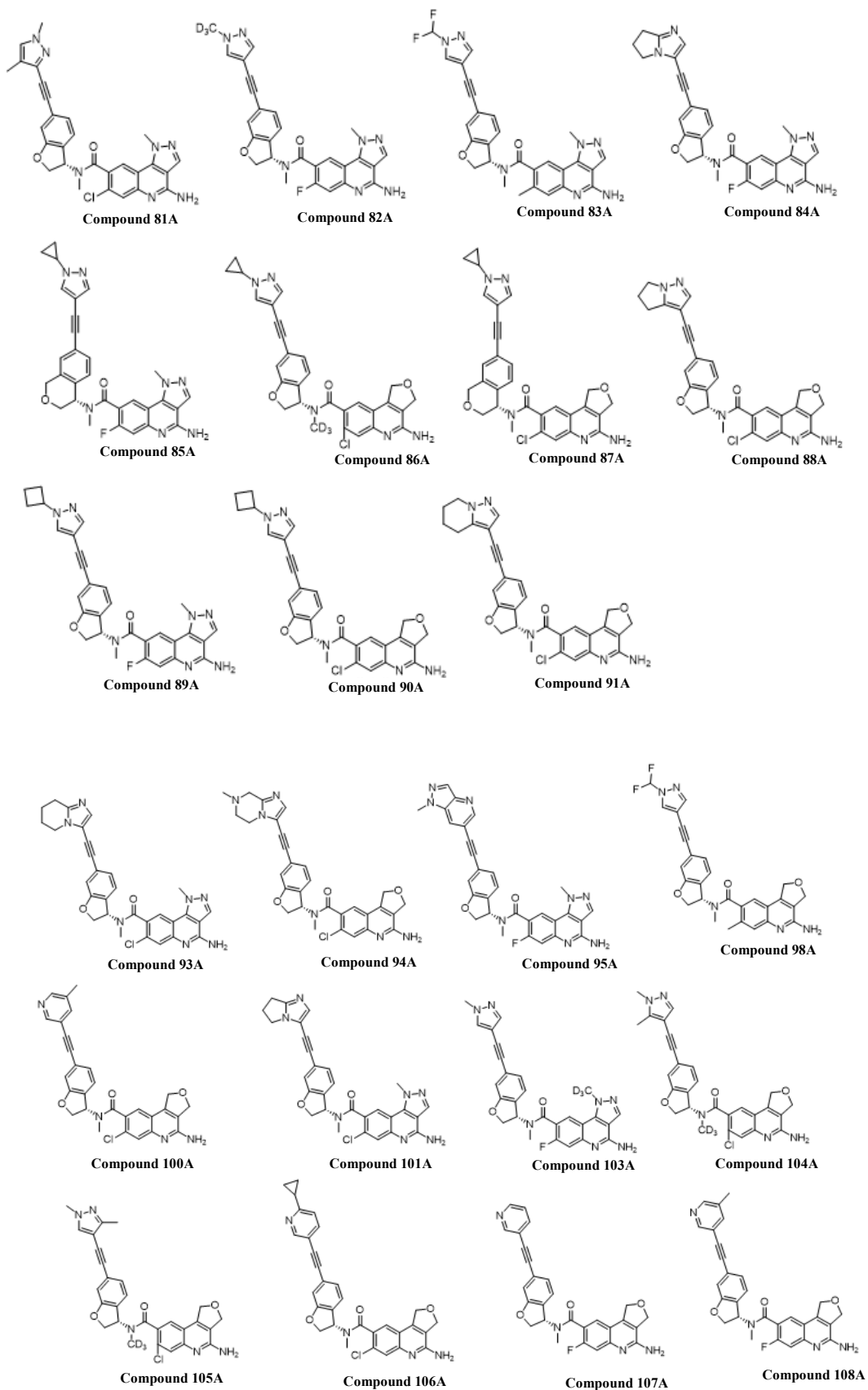
Compound 78A

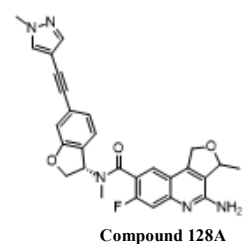
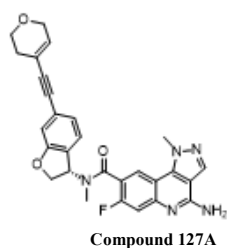
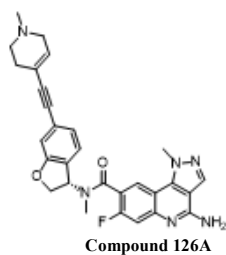
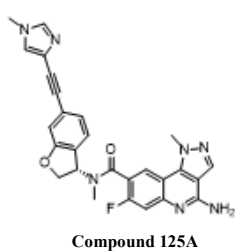
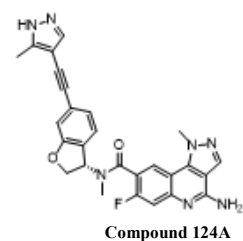
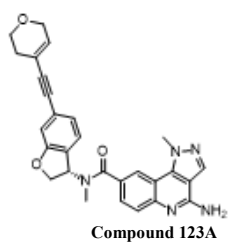
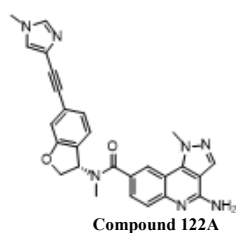
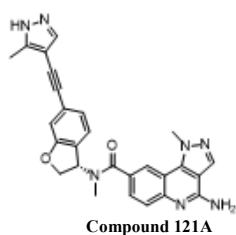
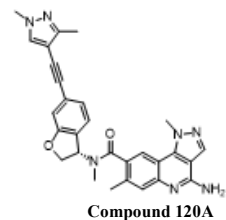
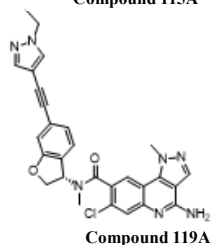
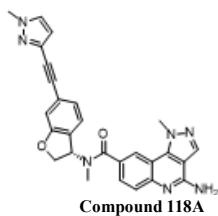
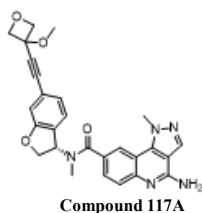
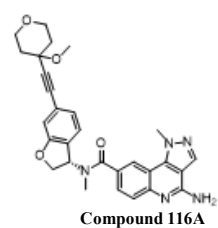
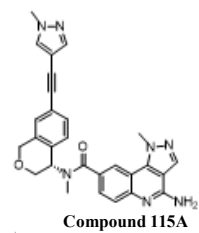
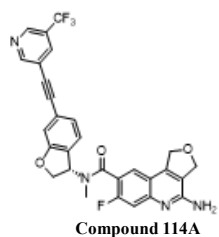
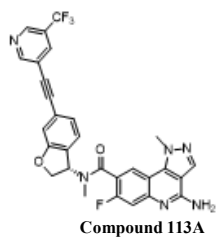


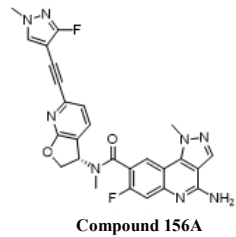
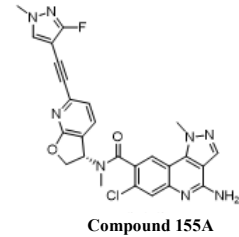
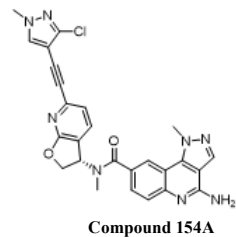
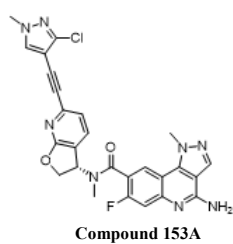
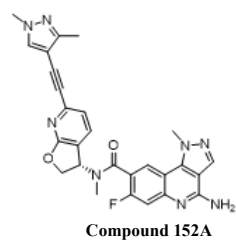
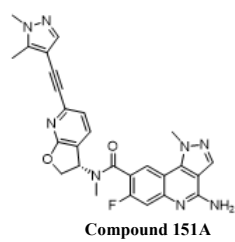
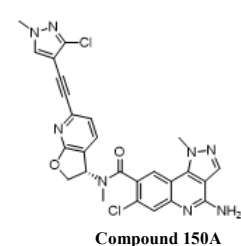
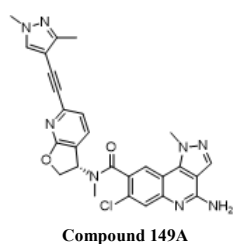
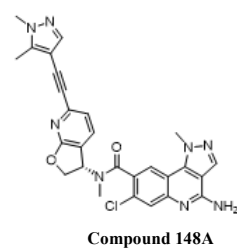
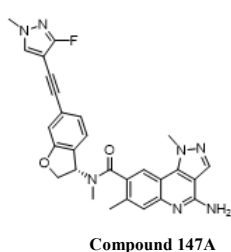
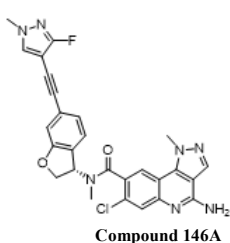
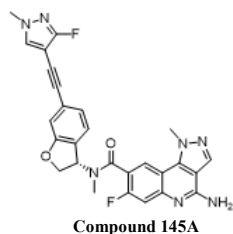
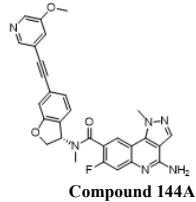
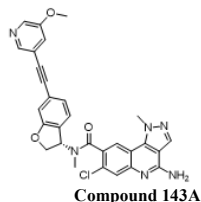
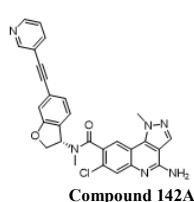
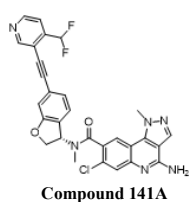
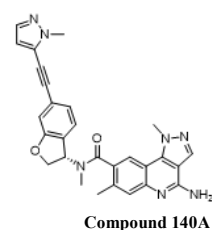
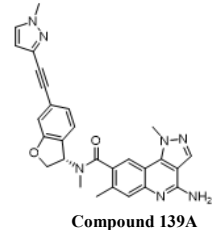
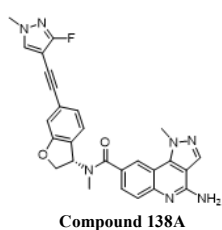
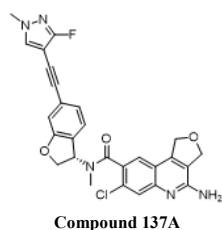
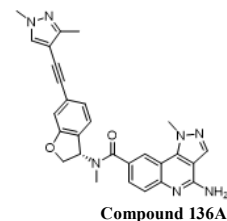
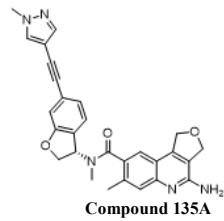
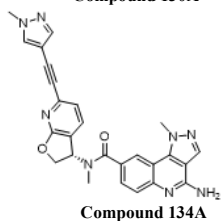
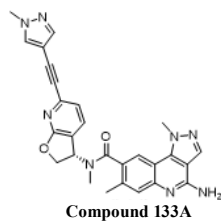
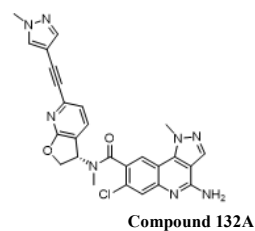
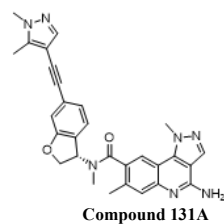
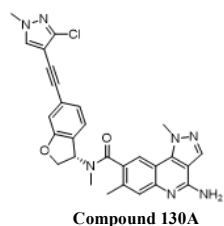
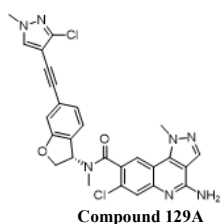
Compound 79A

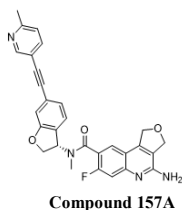


Compound 80A









The term “pharmaceutically acceptable salt” refers to a salt of the compound of the present disclosure prepared from the compound with specific substituents discovered in the present disclosure and a relatively non-toxic acid or base. When the compound of the present disclosure comprises a relatively acidic functional group, a base addition salt may be obtained by contacting a sufficient amount of base with the compound in a pure solution or a suitable inert solvent. When the compound of the present disclosure comprises a relatively basic functional group, an acid addition salt may be obtained by contacting a sufficient amount of acid with the compound in a pure solution or a suitable inert solvent.

The term “deuterated compound” means that the compound of the present disclosure comprises at least one deuterium atom, and specifically means that one or more hydrogen atoms in the compound of the present disclosure can be replaced or substituted by deuterium atoms. In some embodiments, the compound comprises two or more deuterium atoms. In some embodiments, the compound comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 deuterium atoms. Synthetic methods for including an isotope in an organic compound are known in the art.

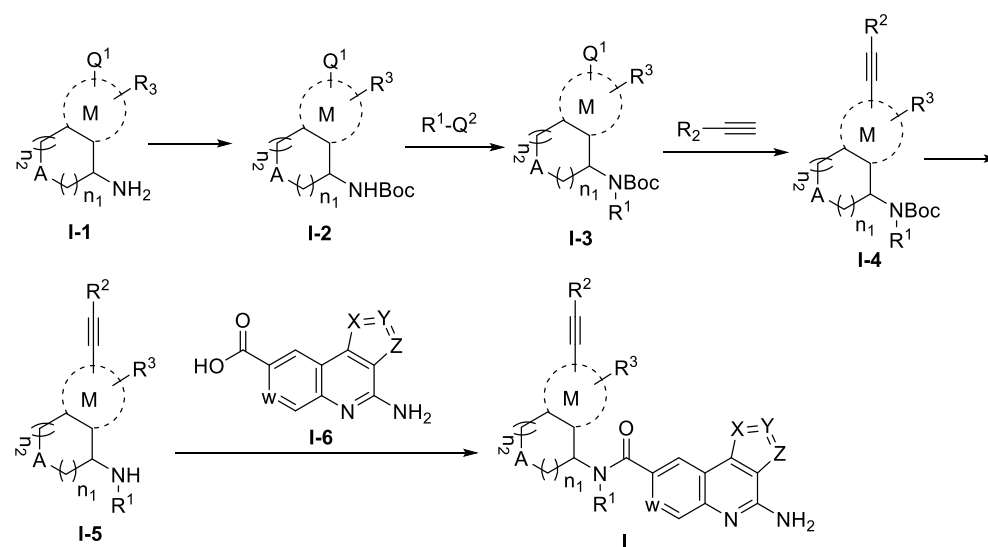
Preparation Method:

The present disclosure further provides a method for preparing the compound. The compound of formula (I) of the present disclosure may be prepared by the following exemplary methods and examples; however, these methods and examples are not construed in any way as limiting the scope of the present disclosure. The compound of the present disclosure may also be synthesized by synthetic techniques known to those skilled in the art, or comprehensively using synthetic methods known in the art and the method of the present disclosure. The product from each reaction step is obtained by separation techniques known in the art, including but not limited to extraction, filtration, distillation, crystallization, chromatography separation, etc. The

starting materials and chemical reagents required for the synthesis may be conventionally synthesized according to literature (as provided by Scifinder) or purchased.

Synthetic process route:

Route I:



Step 1: Reacting a compound represented by formula I-1 with di-tert-butyl dicarbonate to yield a compound represented by formula I-2;

Step 2: Reacting the compound represented by formula I-2 with a compound represented by R^1-Q^2 under alkaline conditions well known in the art to yield a compound represented by formula I-3;

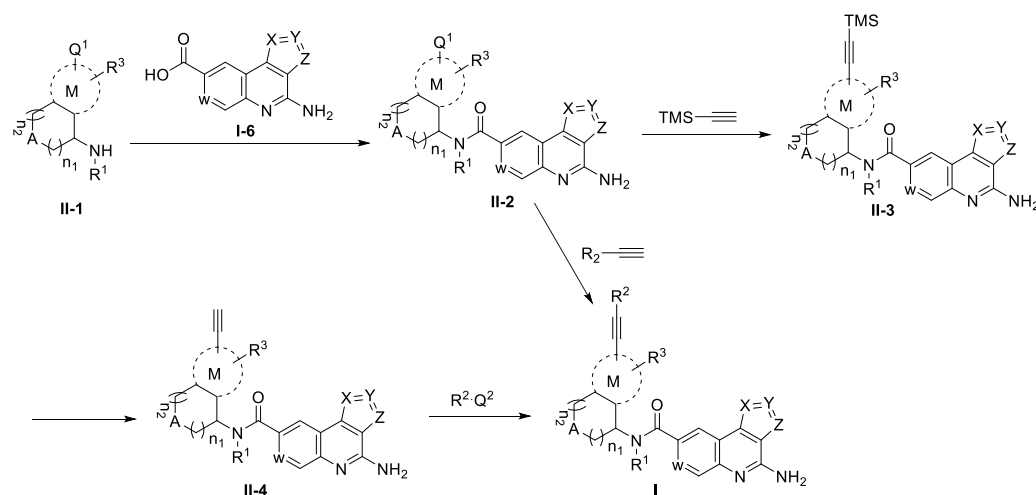
Step 3: Reacting the compound represented by formula I-3 with a compound represented by $R_2-C\equiv C-$ under coupling conditions well known in the art to yield a compound represented by formula I-4;

Step 4: removing a Boc protecting group of the compound represented by formula I-4 under acidic conditions to yield a compound represented by formula I-5;

Step 5: Reacting the compound represented by formula I-5 with a compound represented by formula I-6 under condensation conditions well known in the art to yield the compound represented by formula I;

wherein, Q^1 and Q^2 are halogens, and X, Y, Z, W, A, R^1 , R^2 , R^3 , n_1 , n_2 , and ring M are as defined in the formula (I) herein.

Route II:



Step 1: Reacting a compound represented by formula II-1 with a compound represented by formula I-6 under condensation conditions well known in the art to yield a compound represented by formula II-2;

Step 2: Reacting the compound represented by formula II-2 with a compound represented by $\text{TMS}-\text{C}\equiv\text{CH}$ under coupling conditions well known in the art to yield a compound represented by formula II-3;

Step 3: Reacting the compound represented by formula II-3 with tetrabutylammonium fluoride to yield a compound represented by formula II-4;

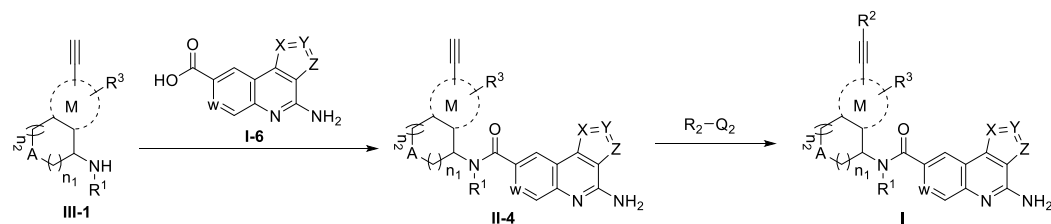
Step 4: Reacting the compound represented by formula II-4 with a compound represented by R_2-Q_2 under coupling conditions well known in the art to yield the compound represented by formula I;

or,

Step 2: Reacting the compound represented by formula II-2 with a compound represented by $\text{R}_2-\text{C}\equiv\text{CH}$ under coupling conditions well known in the art to yield the compound represented by formula I;

wherein, Q^1 and Q^2 are halogens, and X, Y, Z, W, A, R^1 , R^2 , R^3 , n_1 , n_2 , and ring M are as defined in the formula (I) herein.

Route III:



Step 1: Reacting a compound represented by formula III-1 with a compound

represented by formula I-6 under condensation conditions well known in the art to yield a compound represented by formula II-4;

Step 2: Reacting the compound represented by formula II-4 with a compound represented by R_2-Q_2 under coupling conditions well known in the art to yield the compound represented by formula I;

wherein, Q^2 is halogen, and X, Y, Z, W, A, R^1 , R^2 , R^3 , n_1 , n_2 , and ring M are as defined in the formula (I) herein.

Pharmaceutical Composition:

The present disclosure further provides a pharmaceutical composition for treating and/or preventing a disease associated with abnormal PRMT5 expression, which comprises a therapeutically and/or prophylactically effective amount of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above, and optionally a pharmaceutical auxiliary material.

In some embodiments, the disease associated with abnormal PRMT5 expression is a tumor or cancer.

In some embodiments, the disease associated with abnormal PRMT5 expression is a disease associated with abnormal PRMT5 expression and characterized by MTAP deletion.

In some embodiments, the disease associated with abnormal PRMT5 expression is a tumor or cancer characterized by MTAP deletion.

Methods for preparing various pharmaceutical compositions comprising certain amounts of active ingredients are known or, according to the content of the present disclosure, apparent to those skilled in the art. Methods for preparing the pharmaceutical composition comprise incorporating a suitable pharmaceutical excipient, carrier, diluent, etc., as described in *REMINGTON'S PHARMACEUTICAL SCIENCES*, Martin, E.W., ed., Mack Publishing Company, 19th ed. (1995).

The present disclosure further provides a PRMT5 inhibitor, which comprises a therapeutically and/or prophylactically effective amount of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above.

Pharmaceutical Use:

The present disclosure further provides use of the compound or the tautomer, the

stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above, or the pharmaceutical composition as described above in preparing a PRMT5 inhibitor.

The present disclosure further provides use of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above, or the pharmaceutical composition as described above in preparing a medicament for treating and/or preventing a disease associated with abnormal PRMT5 expression.

The present disclosure further provides use of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above, or the pharmaceutical composition as described above in treating and/or preventing a disease associated with abnormal PRMT5 expression.

The present disclosure further provides the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above, or the pharmaceutical composition as described above for use in treating and/or preventing a disease associated with abnormal PRMT5 expression.

In some embodiments, the disease associated with abnormal PRMT5 expression is a tumor or cancer.

In some embodiments, the disease associated with abnormal PRMT5 expression is a disease associated with abnormal PRMT5 expression and characterized by MTAP deletion.

In some embodiments, the disease associated with abnormal PRMT5 expression is a tumor or cancer characterized by MTAP deletion.

The present disclosure further provides a method for treating and/or preventing a disease associated with abnormal PRMT5 expression, which comprises administering to an individual in need thereof a therapeutically and/or prophylactically effective amount of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof as described above, or the pharmaceutical composition as described above.

In some embodiments, the disease associated with abnormal PRMT5 expression is a tumor or cancer.

In some embodiments, the disease associated with abnormal PRMT5 expression is a disease associated with abnormal PRMT5 expression and characterized by MTAP

deletion.

In some embodiments, the disease associated with abnormal PRMT5 expression is a tumor or cancer characterized by MTAP deletion.

In the present disclosure, “treating” or “treatment” usually refers to acquiring desired pharmacological and/or physiological effects. The effect may be prophylactic in terms of completely or partially preventing the disease or symptoms thereof, and/or therapeutic in terms of partially or completely stabilizing or curing the disease and/or side effects caused by the disease. As used herein, “treating” or “treatment” encompasses any treatment of a disease in a patient, including: (a) preventing a disease or symptom in a patient who is susceptible to the disease or symptom but has not yet been diagnosed as having the disease; (b) inhibiting symptoms of the disease, that is, preventing its progression; or (c) alleviating symptoms of the disease, that is, causing regression of the disease or symptom.

In the present disclosure, “subject” or “individual in need” refers to a vertebrate. In certain embodiments, the vertebrate refers to a mammal. The mammal includes, but is not limited to, livestock (such as cattle), pets (such as cats, dogs, and horses), primates, mice, and rats. In certain embodiments, the mammal refers to a human.

In the present disclosure, “effective amount” refers to an amount effective, at doses and for periods of time necessary, in achieving a desired therapeutic or prophylactic effect. The “therapeutically effective amount” of a substance/molecule of the present disclosure may vary depending on factors such as the disease state, age, sex, and body weight of the individual, as well as the ability of the substance/molecule to elicit a desired response in the individual. A therapeutically effective amount also encompasses an amount in which any toxic or detrimental consequence of the substance/molecule is outweighed by its therapeutically beneficial effects. “Prophylactically effective amount” refers to an amount effective, at doses and for periods of time necessary, in achieving a desired prophylactic effect. Typically but not necessarily, the prophylactically effective amount will be less than the therapeutically effective amount as the prophylactic dose is used in the subject prior to the onset of the disease or at an early stage of the disease. In the case of cancer, the therapeutically effective amount of the drug can reduce the number of cancer cells, reduce the tumor

volume, inhibit (that is, slow to some extent, preferably stop) the infiltration of cancer cells into peripheral organs, inhibit (that is, slow to some extent, preferably stop) tumor metastasis, inhibit tumor growth to some extent, and/or palliate one or more cancer-associated symptoms to some extent.

Definitions of Terms:

According to a convention in the art,  is used in the structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or main structure.

A dash “-” that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, C₃₋₆ cycloalkyl-(C₁₋₆ alkyl)_r- means being linked to the remainder of the molecule via (C₁₋₆ alkyl)_r-.

The term “substituted” as used herein means that any one or more hydrogen atoms on a specified atom or group are replaced with a selection from a specified group, provided that the normal valence of the specified atom is not exceeded.

In each part of the specification, the substituents of the compound of the present disclosure are disclosed according to the group types or ranges. It is specifically noted that the present disclosure includes every individual subcombination of the members of these group types and ranges. For example, the term “C₁₋₆ alkyl” specifically refers to individually disclosed methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl, or individually disclosed “C₁₋₄ alkyl”, or individually disclosed “C₁₋₃ alkyl”.

The term “alkyl” is meant to include branched and linear saturated aliphatic hydrocarbon groups with a specified number of carbon atoms. For example, “C₁₋₆ alkyl” refers to C₁, C₂, C₃, C₄, C₅, and C₆. In addition, for example, “C₁₋₆ alkyl” refers to alkyl having 1 to 6 carbon atoms. Alkyl may be unsubstituted or substituted such that one or more hydrogen atoms thereof are replaced with another chemical group. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, and tert-butyl), pentyl (e.g., n-pentyl, isopentyl, and neopentyl), etc. It should be understood by those skilled in the art that C₁₋₆ alkyl herein includes monovalent C₁₋₆ alkyl and divalent C₁₋₆ alkylene. For example, C₁-C₆ alkyl in C₃-C₆ cycloalkyl-(C₁-C₆ alkyl)_r- refers to C₁ -C₆ alkylene.

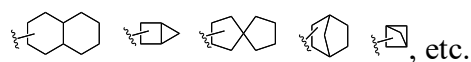
The term “alkoxy” refers to any of the above alkyl groups (e.g., C₁₋₆ alkyl, C₁₋₄ alkyl, C₁₋₃ alkyl, etc.) attached to the remainder of the molecule via an oxygen atom (-O-).

The term “halogenated C₁₋₆ alkyl” or “halogenated C₁₋₆ alkoxy” means that one or

more (e.g., 2 or 3) hydrogen atoms in the alkyl or alkoxy are substituted with halogen atoms, such as fluorine, chlorine, or bromine. The alkyl or alkoxy is as defined above. In some embodiments, the term “halogenated C₁₋₆ alkyl” preferably refers to fluoro-substituted C₁₋₆ alkyl, and may be, for example, -CF₃, -CHF₂, -CH₂F, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, or the like. In some embodiments, the term “halogenated C₁₋₆ alkoxy” preferably refers to fluoro-substituted C₁₋₆ alkoxy, and may be, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCH₂CH₂F, -OCH₂CHF₂, -OCH₂CF₃, or the like.

The term “hydroxy-substituted C₁₋₆ alkyl” means that one hydrogen atom in the alkyl is substituted with hydroxy, and the alkyl is as defined above. As an example, the “hydroxy-substituted C₁₋₆ alkyl” may be hydroxymethyl.

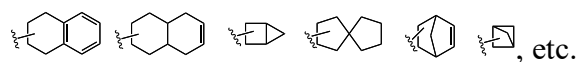
The term “cycloalkyl” refers to a cyclized alkyl group, including monocyclic, bicyclic, or polycyclic ring systems. When a cycloalkyl group is bicyclic or polycyclic, each ring thereof should be a saturated carbocycle or carbocyclic residue. Every two rings of a bicyclic or polycyclic cycloalkyl group may be connected in manners including bridging, fusion, or spiro-linkage. For example, C₃₋₁₀ cycloalkyl is meant to include C₃, C₄, C₅, C₆, C₇, C₈, C₉, and C₁₀ cycloalkyl. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,



The term “cycloalkenyl” refers to cycloalkyl having at least one carbon-carbon double bond in the cycloalkyl as defined above, e.g., .

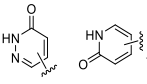
The term “cycloalkoxy” refers to any of the cycloalkyl groups described above (e.g., C₃₋₆ cycloalkyl) attached to the remainder of the molecule via an oxygen atom (-O-).

The term “carbocycle” or “carbocyclic residue” refers to any stable 3-, 4-, 5-, 6-, or 7-membered monocyclic ring or 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered bicyclic or polycyclic ring, wherein any one ring may be saturated, partially saturated, unsaturated, or aromatic. Every two rings of a bicyclic or polycyclic carbocycle may be connected in manners including bridging, fusion, or spiro-linkage. Examples of these carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptenyl, cycloheptyl, adamantyl, cyclooctyl, phenyl, naphthyl, [2,2,2]bicyclooctane,



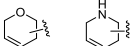
The term “aryl” refers to a monocyclic, bicyclic, or tricyclic aromatic hydrocarbon group having 5-14 carbon atoms in the ring moiety. When the “aryl” is bicyclic or tricyclic, each ring thereof is an aromatic ring. Every two rings of a bicyclic or tricyclic aryl group may be connected in manners including bridging, fusion, or spiro-linkage. Examples include phenyl and naphthyl, each of which may be optionally substituted.

The terms “heterocycle”, “heterocyclic”, and “heterocyclyl” are used interchangeably and refer to substituted and unsubstituted 4-8 membered monocyclic or bicyclic groups, 8-10 membered bicyclic or tricyclic groups, and 10-14 membered tricyclic or polycyclic groups, wherein at least one ring has at least one heteroatom (O, S, or N), and the ring containing the heteroatom preferably has 1, 2, or 3 heteroatoms selected from O, S, and N. In these groups, each heteroatom-containing ring may contain 1 to 2 oxygen or sulfur atoms and/or 1-4 nitrogen atoms, provided that the total number of heteroatoms in each ring is 4 or less, and further provided that the ring contains at least one carbon atom. In some preferred embodiments, the heteroatom refers only to N or O, and the total number thereof does not exceed 3; preferably, only 1-2 heteroatoms are contained. Carbon and sulfur atoms are optionally oxidized, and nitrogen atoms are optionally quaternized. Where the valence permits, a ring atom on

a heterocycle is optionally substituted with =O (oxo) (e.g., ). The rings completing bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, fully unsaturated, aromatic, or non-aromatic. A heterocyclyl group may be attached to any available nitrogen or carbon atom. As described above, heterocyclyl includes “spiroheterocyclyl”, “heterobridged ring group”, “heterocycloalkenyl”, and the like as described below. Exemplary heterocyclyl includes, but is not limited to, azetidiny, oxetanyl, pyrrolidiny, imidazoliny, oxazolidiny, isoxazoliny, thiazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, 2-oxopiperaziny, 2-oxopiperidiny, 2-oxopyrrolidiny, 2-oxoazepiny, 1-pyridony, 4-piperidony, tetrahydropyranyl, morpholiny, 1,3-dioxolany, quinuclidiny, and the like.

The term “saturated heterocyclyl” refers to the aforementioned “heterocyclyl” in which the monocyclic, bicyclic, or tricyclic group is in a fully saturated state. The “heterocyclyl” is as described above. As an example, the saturated heterocyclyl may

be morpholinyl (e.g., ) , piperidinyl (e.g., ) , piperazinyl () , or the like.

The term “heterocycloalkenyl” refers to heterocyclyl having at least one carbon-carbon double bond in the heterocycle as defined above, e.g., .

The term “heteroaryl” refers to substituted and unsubstituted aryl described above having at least one heteroatom (O, N, or S) in at least one ring, including aromatic 5-8 membered monocyclic groups, 8-10 membered bicyclic groups, and 10-14 membered tricyclic groups; the heteroatom-containing ring preferably has 1, 2, or 3 ring heteroatoms selected from O, N, and S. Each heteroatom-containing ring of heteroaryl may contain 1 or 2 oxygen or sulfur atoms and/or 1-4 nitrogen atoms, provided that the total number of heteroatoms in each ring is 4 or less and each ring has at least one carbon atom. Each ring of a bicyclic or tricyclic heteroaryl group is an aromatic ring.

The term “spiro ring group” refers to a bicyclic ring structure having one common ring atom, and each monocyclic ring is a saturated or unsaturated, aromatic or non-aromatic carbocycle having 3-7 carbon atoms. Exemplary spirocycloalkyl includes, but is not limited to: spiro[4.5]decane, spiro[3.4]octane, spiro[2.3]hexane,



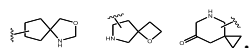
, and the like. Herein, the spiro ring group does not include aryl as defined above.

The terms “saturated spiro ring group” and “spirocycloalkyl” refer to “spiro ring group” as defined above in which each monocyclic ring is in a fully saturated state. Exemplary spirocycloalkyl includes, but is not limited to, spiro[4.5]decane, spiro[3.4]octane, and spiro[2.3]hexane.

The term “spiroheterocyclyl” refers to a bicyclic ring structure having one common ring atom or a tricyclic ring structure having two independent common ring atoms, and each monocyclic ring is a saturated or unsaturated monocyclic group having 3-8 ring atoms, wherein at least one ring has 1 or 2 ring atoms selected from N, O, and S(O)_n, wherein n is an integer from 0 to 2, and the remaining ring atoms are C. In addition, 1 or 2 ring carbon atoms in the heterocyclyl ring are optionally replaced by a -CO- group. Exemplary spiroheterocyclyl includes, but is not limited to: 5-azaspiro[2.3]hexane and 6-oxaspiro[3.4]-7-octanone. Herein, the spiroheterocyclyl does not include the heteroaryl as defined above.

The terms “saturated spiroheterocyclyl” and “spiroheterocycloalkyl” refer to the “spiroheterocyclyl” as defined above in which each monocyclic ring is in a fully

saturated state. Exemplary spirocycloalkyl includes, but is not limited to,



The term “bridged ring group” refers to a saturated or unsaturated, aromatic or non-aromatic 3-8 membered monocyclic carbocyclic group, wherein two non-adjacent ring atoms are linked by a (CRR)_n group, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or a bond, wherein n is an integer from 1 to 3, and each R is independently H or methyl (wherein the (CRR)_n group, the C₂₋₆ alkenyl, the C₂₋₆ alkynyl, or the bond is also referred to herein as a bridging group). The bridged ring group is optionally substituted with one or two substituents independently selected from alkyl, halogen, alkoxy, hydroxy, and cyano, wherein the alkyl, alkoxy, alkenyl, and alkynyl are each as defined above. Examples of the bridged ring group include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and the like. It should be understood herein that when two non-adjacent ring atoms of a monocyclic 4-7 membered hydrocarbon group are linked by a bond, the “bridged ring group” may be referred to as a “fused ring group” or a “condensed ring group”. Herein, the bridged ring group does not include aryl as defined above.

The terms “saturated bridged ring group” and “bridged cycloalkyl” refer to “bridged ring group” as defined above in which each ring is in a saturated state. Herein, the saturated should be interpreted as meaning that each ring carbon atom in the bridged ring group is in a saturated state (including the carbon atoms in the bridging group).

The term “heterobridged ring group” refers to the “bridged ring group” as defined above in which 1, 2, 3, or 4 ring carbon atoms (including carbon atoms in the bridging group) are replaced with heteroatoms selected from N, O, and S(O)_n, wherein n is an integer from 0 to 2. Examples of “heterobridged ring group” include, but are not limited to, 2-azabicyclo[2.2.2]octane, quinuclidine, 7-oxabicyclo[2.2.1]heptane, and the like. Herein, the heterobridged ring group does not include the heteroaryl as defined above.

The terms “saturated heterobridged ring group” and “heterobridged cycloalkyl” refer to the “heterobridged ring group” as defined above in which each ring is in a saturated state, wherein the saturated should be interpreted as meaning that each ring atom in the bridged ring group is in a saturated state (including carbon atoms/heteroatoms in the bridging group).

Unless indicated otherwise, when an explicitly named aryl (e.g., phenyl), cycloalkyl

(e.g., cyclohexyl), heterocycle (e.g., pyrrolidinyl, piperidinyl, or morpholinyl), or heteroaryl (e.g., imidazolyl, pyrazolyl, or triazolyl) is mentioned, it means that a ring having 0-3, preferably 0-2, substituents is mentioned, and the substituents are selected from the substituents described above for aryl, cycloalkyl, heterocycle, and/or heteroaryl as appropriate.

The term “heteroatom” shall include oxygen, sulfur, and nitrogen.

The term “halogen” shall include “F, Cl, Br, and I”.

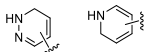
When the term “unsaturated” is used herein to described a ring or a group, the ring or the group may be fully unsaturated or partially unsaturated.

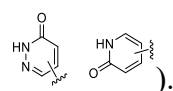
When the term “saturated” is used herein to described a ring or a group, the ring or the group should be fully saturated, unless otherwise specified.

From all the above description, it will be apparent to those skilled in the art that any group whose name is a composite name, e.g., “C₃₋₁₀ cycloalkyl-C(O)-”, shall refer to a moiety conventionally derived therefrom, e.g., constructed from carbonyl substituted with C₃₋₁₀ cycloalkyl, wherein the cycloalkyl is as defined above. Other similar composite names may be understood with reference to the foregoing content.

The term “optionally” means that it may or may not occur. For example, “C₁₋₆ alkyl optionally substituted with 1-3 R^d” means that the C₁₋₆ alkyl may or may not be substituted with 1-3 R^d. Other similar definitions may be understood with reference to the foregoing content.

The term “the ring atom of heterocyclyl is optionally oxo-substituted” means that the ring atom on the heterocycle is optionally substituted with =O (oxo) (for example, the

ring atom CH₂ of , after oxo-substitution, results in the group



Throughout the specification, groups and substituents thereof may be chosen by one skilled in the art to provide stable moieties and compounds and compounds useful as pharmaceutically acceptable compounds and/or intermediate compounds useful in preparing pharmaceutically acceptable compounds.

Herein, unless otherwise explicitly indicated, the descriptive phrase “... be each independently selected from” used throughout the present disclosure may mean that specific items expressed by the same or different symbols in different groups do not affect each other, or that specific items expressed by the same or different symbols in

the same group do not affect each other.

The term “XXX is substituted at any substitutable position with one or more substituents selected from YYY” means that XXX may be substituted at any substitutable position with one or more substituents and the substituents are selected from YYY. When XXX is substituted with a plurality of substituents selected from YYY at any substitutable positions, the plurality of substituents may be identical or different. “Plurality of” means 2 or more, preferably 2, 3, or 4, and more preferably 2 or 3. For example, C₁₋₆ alkyl substituted at any substitutable positions with one or more substituents selected from cyano and hydroxy means that C₁₋₆ alkyl may be substituted with one or more cyano at any substitutable positions, may also be substituted with one or more hydroxy at any substitutable positions, or may further be substituted with one or more cyano and hydroxy (e.g., one cyano and one hydroxy, or two cyano and one hydroxy, or two cyano and two hydroxy) at any substitutable positions.

Herein, when the structure does not accord with the chemical name, the structure prevails.

Effects of the Present Disclosure:

The compounds of the present disclosure exhibit excellent inhibitory activity against PRMT5. The compounds of the present disclosure demonstrate excellent selective inhibition against the human MTAP-deficient HCT-116 cell line over the MTAP wild-type (WT) HCT-116 cell line. The compounds can be used in the development of small-molecule drugs targeting PRMT5·MTA and preferentially act on MTAP-deficient tumor cells.

Further, it can be found from experiments that the compounds of the present disclosure exhibit different degrees of advantages in terms of human liver microsome stability, mouse pK, rat pK, and *in vivo* anti-tumor efficacy in an established mouse tumor model.

Further, compared with existing compounds, the compounds of the present disclosure possess a higher safety window, and are significantly superior to the prior art in terms of safety (e.g., toxicity from inhibition of hERG, CYP, etc.).

DETAILED DESCRIPTION

It should also be understood that the terms used herein are for the purpose of

describing specific embodiments only, and are not intended to be limiting. In addition, although any methods, apparatus, and materials similar or equivalent to those described herein may be used for practicing or testing the present disclosure, the preferred methods, apparatus, and materials are now described.

The structures of the compounds were determined by nuclear magnetic resonance (NMR) or mass spectrometry (MS). The NMR analysis was performed using a Bruker ASCENA-400 nuclear magnetic resonance instrument, with deuterated dimethyl sulfoxide (DMSO-d₆), deuterated chloroform (CDCl₃), and deuterated methanol (CD₃OD) as solvents and tetramethylsilane (TMS) as an internal standard. The chemical shifts were given in 10⁻⁶ (ppm).

The reaction monitoring and MS analysis were performed using a Thermofisher ESQ (ESI) mass spectrometer.

The HPLC analysis was performed using a Thermo Fisher U3000 DAD high pressure liquid chromatograph (with a GL Sciences ODS-HL HP 3 μm 3.0 × 100 mm chromatography column).

The thin-layer chromatography silica gel plates used were Qingdao Haiyang GF254 silica gel plates. The silica gel plates used in the thin-layer chromatography (TLC) analysis were 0.15-0.2 mm silica gel plates, and the plates used in the thin-layer chromatography separation and purification of the products were 0.9-1.0 mm preparative high-performance thin-layer chromatography plates. A Qingdao Haiyang 200-300 mesh silica gel was used as a carrier in the column chromatography. The developing solvent systems used included A: a dichloromethane and methanol system; B: a petroleum ether and ethyl acetate system. The volume ratio of the solvents was adjusted depending on the polarity of the compound. The preparative intermediate-pressure liquid chromatography purification was performed using a biotage isera one preparative liquid chromatography system.

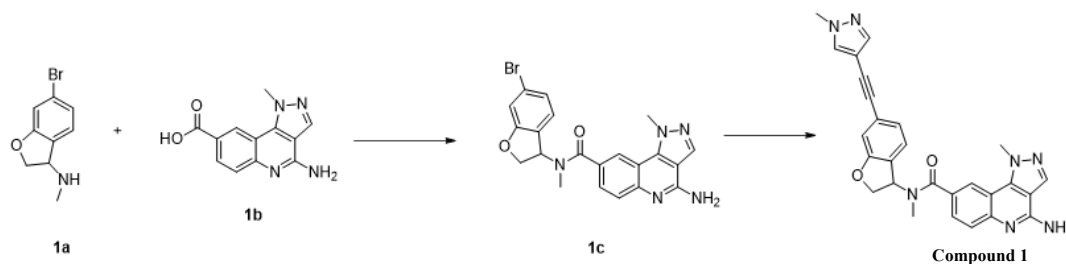
In the following examples, unless otherwise specified, all reaction starting materials were commercially available from suppliers in the scifinder database. For example, some of the reagents in the examples of the present disclosure were commercially available from manufacturers such as Sun Chemical Technology (Shanghai) Co., Ltd., Shanghai Accela ChemBio Co., Ltd., Nanjing PharmaBlock Sciences Inc., Jiangsu Aikon Biopharmaceutical R&D Co., Ltd., and Shanghai Bide Pharmatech Co., Ltd. Further, unless otherwise specified, the starting materials used in the examples of the present disclosure were all analytically pure. Unless otherwise specified, the ratios of

two liquid substances involved herein were all volume ratios, and the percentages of the substances involved were mass percentages.

Example

1:

4-amino-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 1)



Preparation of compound 1c

Compound **1a** (86 mg, 0.38 mmol) was dissolved in *N,N*-dimethylacetamide (3 mL), and compound **1b** (94.2 mg, 0.39 mmol, see WO2022169948A1 for the preparation method), *N,N*-diisopropylethylamine (205.17 μ L, 1.24 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (235.5 mg, 0.62 mmol) were added. After completion of the addition, the mixture was stirred at 25 $^{\circ}$ C for 3 h, water was added to quench the reaction, and the reaction solution was extracted with ethyl acetate (15 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated, and the residue was purified by normal phase silica gel column chromatography (dichloromethane:methanol = 10:1) to give compound **1c** (60 mg, 0.13 mmol), ESI-MS(*m/z*): 452.3 [*M*+*H*]⁺.

Preparation of compound 1

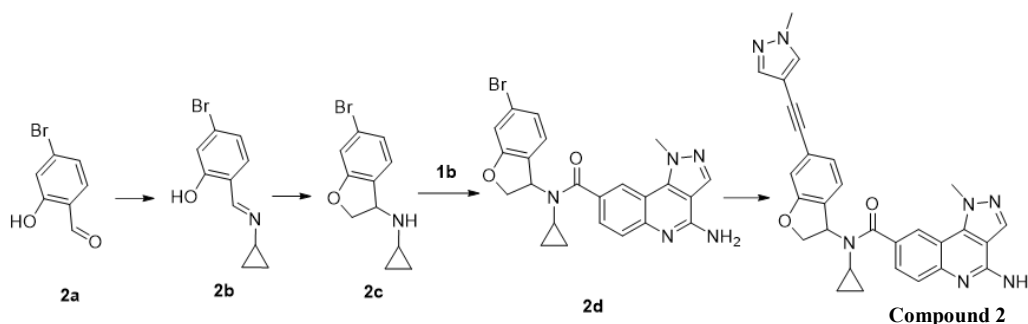
To a solution of compound **1c** (66 mg, 0.15 mmol) in *N*-methylpyrrolidone (1 mL) were sequentially added 4-ethynyl-1-methyl-1*H*-pyrazole (32 mg, 0.3 mmol), cuprous iodide (6 mg, 0.03 mmol), *N,N*-diisopropylethylamine (39 mg, 0.3 mmol), and tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 70 $^{\circ}$ C for 3 h. After the reaction was completed, water (10 mL) was added, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases

were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was purified by reversed phase column chromatography (acetonitrile:0.05% aqueous ammonium bicarbonate solution = 0:100% - 50%:50%) to give compound **1** (19 mg). ESI-MS (m/z): 478.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.33 (s, 1H), 8.28 (s, 1H), 8.08 (s, 1H), 7.69 (s, 1H), 7.65 – 7.63 (m 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.16 (s, 2H), 7.10 (d, J = 8.0 Hz, 1H), 6.99 (s, 1H), 4.81 – 4.68 (m, 2H), 4.44 (s, 3H), 3.87 (s, 3H), 2.70 (s, 3H).

Example

2:

4-amino-*N*-cyclopropyl-1-methyl-*N*-{6-[(1-methylpyrazol-4-yl)ethynyl]-2,3-dihydro-1-benzofuran-3-yl}pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 2)



Preparation of compound 2b

To a solution of compound **2a** (1.0 g, 4.98 mmol) in dichloromethane (10 mL) were added cyclopropylamine (0.38 mL, 5.48 mmol) and acetic acid (0.09 mL, 1.49 mmol), and the mixture was allowed to react at 25 °C overnight. After the reaction was completed, the reaction solution was concentrated to give compound **2b** (1.0 g). ESI-MS (m/z): 240.0 $[M+H]^+$.

Preparation of compound 2c

To a solution of trimethylsulfoxonium iodide (2.3 g, 10.41 mmol) in tetrahydrofuran (10 mL) was added potassium tert-butoxide (1.16 g, 10.41 mmol), and the mixture was stirred at 25 °C for 30 min. Compound **2b** (1.0 g, 4.16 mmol) was dissolved in tetrahydrofuran (5 mL), and the resulting solution was then added dropwise to the system. The mixture was allowed to react at room temperature for 1 h, then heated to 50 °C, and then allowed to react for 3 h. Potassium tert-butoxide (4.16 mmol, 467 mg)

was then added, and the mixture was allowed to react at 25 °C overnight. After the reaction was completed, water (15 mL) was added to quench the reaction, and the reaction solution was extracted with ethyl acetate (20 mL × 3). The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (ethyl acetate/petroleum ether = 0:100% - 50%:50%) to give compound **2c** (200.0 mg). ESI-MS (m/z): 254.2 [M+H]⁺.

Preparation of compound **2d**

To a solution of compound **2c** (100 mg, 0.39 mmol) in *N,N*-dimethylacetamide (5 mL) were added compound **1b** (114.4 mg, 0.47 mmol), *O*-(*1H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethylisouronium tetrafluoride (189.6 mg, 0.59 mmol), and *N,N*-diisopropylethylamine (0.20 mL, 1.18 mmol), and the mixture was allowed to react at 25 °C for 3 h. Water (20 mL) was added, and the reaction solution was extracted with ethyl acetate (20 mL × 3). The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (methanol/dichloromethane = 0:100% - 10%:90%) to give compound **2d** (130.0 mg). ESI-MS (m/z): 478.2 [M+H]⁺.

Preparation of compound **2**

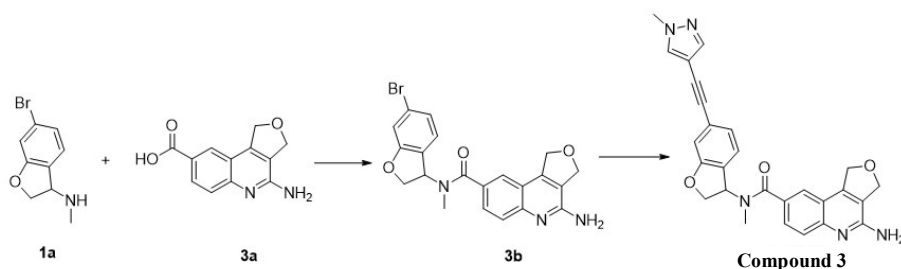
To a solution of compound **2d** (48 mg, 0.1 mmol) in *N*-methylpyrrolidone (1 mL) were sequentially added 4-ethynyl-1-methyl-1*H*-pyrazole (21 mg, 0.2 mmol), cuprous iodide (4 mg, 0.02 mmol), *N,N*-diisopropylethylamine (26 mg, 0.2 mmol), and tetrakis(triphenylphosphine)palladium (12 mg, 0.01 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 70 °C for 3 h. After the reaction was completed, water (10 mL) was added, and the reaction solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was purified by reversed phase column chromatography (acetonitrile:0.05% aqueous ammonium bicarbonate solution = 0:100% - 40%:60%) to give compound **2** (23 mg).

ESI-MS (m/z): 503.7 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (d, J = 2.0 Hz, 1H), 8.28 (s, 1H), 8.08 (s, 1H), 7.77 (dd, J = 8.0, 2.0 Hz, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.16 (s, 2H), 7.09 (dd, J = 7.6, 1.2 Hz, 1H), 6.98 (d, J = 1.2 Hz, 1H), 5.96 (dd, J = 9.2, 4.0 Hz, 1H), 4.85 – 4.67 (m, 2H), 4.42 (s, 3H), 3.87 (s, 3H), 2.88 – 2.79 (m, 1H), 0.46 – 0.06 (m, 4H).

Example

3:

4-amino-*N*-methyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuran[3,4-*c*]quinoline-8-carboxamide (Compound 3)



Preparation of compound 3b

To a solution of compound **1a** (50 mg, 0.22 mmol) in *N,N*-dimethylformamide (2 mL) were added compound **3a** (50.6 mg, 0.22 mmol, see WO2022169948 A1 for the preparation method), *N,N*-diisopropylethylamine (108.93 μ L, 0.66 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (208.4 mg, 0.55 mmol). The mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 10:1) to give compound **3b** (50 mg). ESI-MS (m/z): 439.92 $[M+H]^+$.

Preparation of compound 3

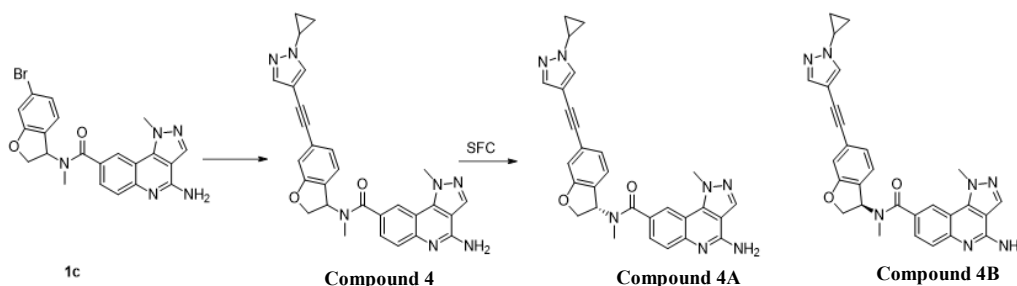
To a solution of **3b** (50 mg, 0.11 mmol) in *N*-methylpyrrolidone (2 mL) were added cuprous iodide (4.3 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium (13.1 mg,

0.01 mmol), *N,N*-diisopropylethylamine (56.43 μ L, 0.34 mmol), and 4-ethynyl-1-methylpyrazole (155.8 mg, 1.59 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 70 $^{\circ}$ C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 10:1) to give a crude compound. The crude compound was then subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 40%:60%) to give compound **3** (16 mg). ESI-MS (*m/z*): 466.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (s, 1H), 7.68 – 7.57 (m, 2H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.69 (s, 2H), 6.30 – 5.64 (m, 1H), 5.40 – 5.33 (m, 2H), 5.06 – 4.97 (m, 2H), 4.72 – 4.60 (m, 2H), 3.85 (s, 3H), 2.62 (s, 3H).

Example

4:

4-amino-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound **4**)



To a solution of **1c** (63 mg, 0.14 mmol) in *N*-methylpyrrolidone (2 mL) were added cuprous iodide (4 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium (32 mg, 0.03 mmol), *N,N*-diisopropylethylamine (90 mg, 0.7 mmol), and 1-cyclopropyl-4-ethynyl-1*H*-pyrazole (55 mg, 0.42 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 80 $^{\circ}$ C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (15 mL) was added, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3).

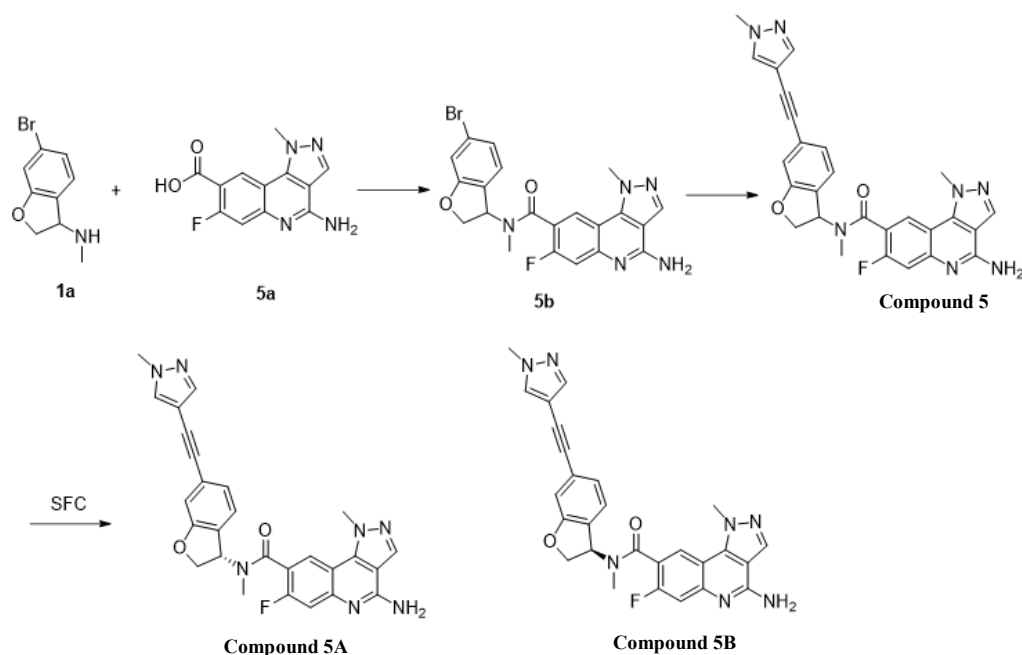
The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 50%:50%) to give compound **4** (15 mg). ESI-MS (m/z): 504.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.33 (s, 1H), 8.28 (s, 1H), 8.18 (s, 1H), 7.71 – 7.62 (m, 3H), 7.45 (d, J = 7.6 Hz, 1H), 7.16 – 7.06 (m, 3H), 6.97 (s, 1H), 6.39 – 5.84 (m, 1H), 4.79 – 4.69 (m, 2H), 4.44 (s, 3H), 3.79 – 3.74 (m, 1H), 2.70 (s, 3H), 1.11 – 0.97 (m, 4H).

Compound **4** was separated by SFC (instrument: Waters 150 Prep-SFC; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.1% NH₃•H₂O); B%: 35%) to give compounds **4A** and **4B**.

Compound **4A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.176 min, ee = 100%.

Compound **4B**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.565 min, ee = 100%.

Example 5:
4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound **5**)



Preparation of compound **5b**

To a solution of compound **1a** (50 mg, 0.22 mmol) in *N,N*-dimethylformamide (2 mL) were added compound **5a** (57.2 mg, 0.22 mmol, see WO2022169948 A1 for the preparation method), *N,N*-diisopropylethylamine (108.93 μ L, 0.66 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (208.4 mg, 0.55 mmol). After completion of the addition, the mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 10:1) to give compound **5b** (55 mg). ESI-MS (*m/z*): 469.95 [*M*+*H*]⁺.

Preparation of compound **5**

To a solution of compound **5b** (55 mg, 0.12 mmol) in *N*-methylpyrrolidone (2 mL) were added cuprous iodide (4.5 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium (13.5 mg, 0.01 mmol), *N,N*-diisopropylethylamine (58.11 μ L, 0.35 mmol), and 4-ethynyl-1-methylpyrazole (62.0 mg, 0.58 mmol). After completion of the addition, the mixture was reacted in a

microwave reactor at 70 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (methanol/dichloromethane = 10:1) to give a crude compound. The crude compound was then subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 45%:55%) to give compound **5** (18 mg). ESI-MS (*m/z*): 496.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 – 8.22 (m, 2H), 8.05 (s, 1H), 7.67 (s, 1H), 7.39 – 7.27 (m, 4H), 7.12 – 7.06 (m, 1H), 6.99 – 6.92 (m, 1H), 6.48 – 5.56 (m, 1H), 4.83 – 4.64 (m, 2H), 4.41 – 4.39 (m, 3H), 3.85 (s, 3H), 2.69 – 2.57 (m, 3H).

Compound **5** was separated by SFC (instrument: Waters 150 Prep-SFC; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.1% NH₃•H₂O); B%: 35%) to give compounds **5A** and **5B**.

Compound **5A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 1.997 min, ee = 99.7%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.29 – 8.24 (m, 2H), 8.07 (s, 1H), 7.67 (s, 1H), 7.40 – 7.29 (m, 4H), 7.12 – 7.07 (m, 1H), 6.99 – 6.94 (m, 1H), 6.48 – 5.56 (m, 1H), 4.83 – 4.64 (m, 2H), 4.41 – 4.39 (m, 3H), 3.85 (s, 3H), 2.69 – 2.58 (m, 3H). ¹H NMR (400 MHz, DMSO-*d*₆, 90 °C) δ 8.25 – 8.23 (m, 2H), 7.96 (s, 1H), 7.60 (s, 1H), 7.34 – 7.30 (m, 2H), 7.07 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.98 (s, 2H), 6.92 (s, 1H), 4.69 – 4.58 (m, 2H), 4.38 (s, 3H), 3.84 (s, 3H), 2.65 (s, 3H). [α]₂₅^D +201.4 (c 1mg/mL, DMF).

Compound **5B**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.237 min, ee = 100%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 – 8.22 (m, 2H), 8.05 (s, 1H), 7.67 (s, 1H), 7.40 – 7.27 (m, 4H), 7.12 – 7.06 (m, 1H), 6.99 – 6.95 (m, 1H), 6.46 – 5.56 (m,

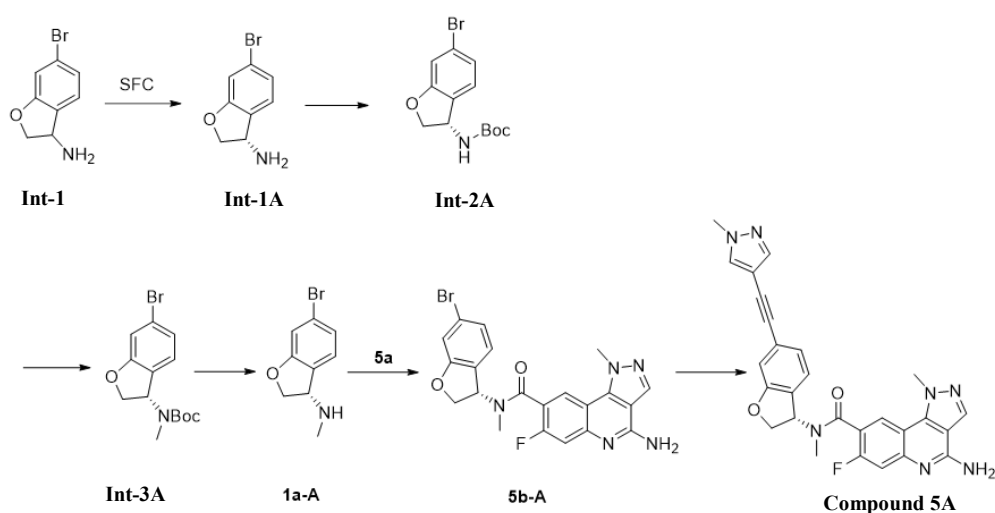
1H), 4.83 – 4.63 (m, 2H), 4.41 – 4.39 (m, 3H), 3.85 (s, 3H), 2.69 – 2.57 (m, 3H). ¹H NMR (400 MHz, DMSO-*d*₆, 90 °C) δ 8.25 – 8.23 (m, 2H), 7.96 (s, 1H), 7.60 (s, 1H), 7.34 – 7.31 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 2H), 6.92 (s, 1H), 4.70 – 4.58 (m, 2H), 4.38 (s, 3H), 3.84 (s, 3H), 2.65 (s, 3H). [α]₂₅^D -215.6 (c 1mg/mL, DMF).

Example

5A:

(*S*)-4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide

(Compound 5A)



Compound Int-1 was separated by SFC (instrument: Shimadzu Prep-SFC; chromatographic column: Opti-Chiral A1 column (20 × 250 mm, 5 μm); mobile phase A: CO₂, mobile phase B: ethanol (containing 0.1% NH₃•H₂O); B%: 35%) to give two fractions.

Compound **Int-1A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Opti-Chiral A1-3 column (100 × 4.6 mm, 3 μm); mobile phase A: CO₂, mobile phase B: ethanol (containing 0.05% diethylamine); B%: 30%; retention time: 1.924 min, ee = 100%.

Reference was made to WO2024131901 A1 for the preparation process of compound **Int-3A**.

Confirmation of absolute configuration of compound **Int-2A**: the crystal structure of **Int-2A** was determined by MicroED. The crystal structure belongs to a triclinic

crystal system with a P1 (No. 1) space group. The unit cell constants measured by MicroED are that $a = 5.160(18) \text{ \AA}$, $b = 5.599(12) \text{ \AA}$, $c = 11.582(9) \text{ \AA}$, $\alpha = 97.51(12)^\circ$, $\beta = 89.49(15)^\circ$, $\gamma = 99.60(18)^\circ$, and the unit cell volume $V = 327.1(14) \text{ \AA}^3$. Z' of the system is 1, and the asymmetric unit of the crystal consists of one API molecule.

Preparation of compound 1a-A

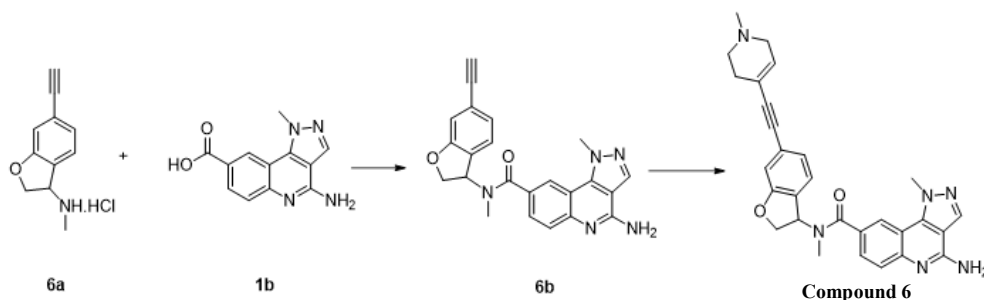
Compound **Int-3A** (310 mg, 0.95 mmol) was dissolved in tetrahydrofuran (2 mL), and a 4 M dioxane solution of hydrochloric acid (2 mL) was added. The reaction solution was stirred at 25 °C for 1 h. The reaction solution was then concentrated to dryness by rotary evaporation, slurried with methyl tert-butyl ether (5 mL), and filtered to give **1a-A** (180 mg). ESI-MS (m/z): 227.96 $[M+H]^+$.

Preparation of compound 5A: For the synthesis process of preparing compound **5A** from compound **1a-A**, reference was made to the synthesis process of preparing compound **5** from compound **1a**. ESI-MS (m/z): 496.0 $[M+H]^+$. $[\alpha]_D^{25} +213.4$ (c 1mg/mL, DMF).

Example

6:

4-amino-*N*,1-dimethyl-*N*-(6-((1-methyl-1,2,3,6-tetrahydropyridin-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide
(Compound 6)



Preparation of compound 6b

To a solution of compound **6a** (41.9 mg, 0.20 mmol, see WO2024131901 A1 for the preparation method) in *N,N*-dimethylacetamide (3 mL) were added compound **1b**

(48.4 mg, 0.20 mmol), triethylamine (0.07 mL, 0.50 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (156.0 mg, 0.30 mmol). After completion of the addition, the mixture was allowed to react at 25 °C for 18 h. The reaction solution was diluted with ethyl acetate (10 mL) and water (10 mL), followed by liquid separation. The organic phase was concentrated and purified by high-pressure liquid chromatography to give compound **6b** (5 mg). ESI-MS (*m/z*): 398.17 [M+H]⁺.

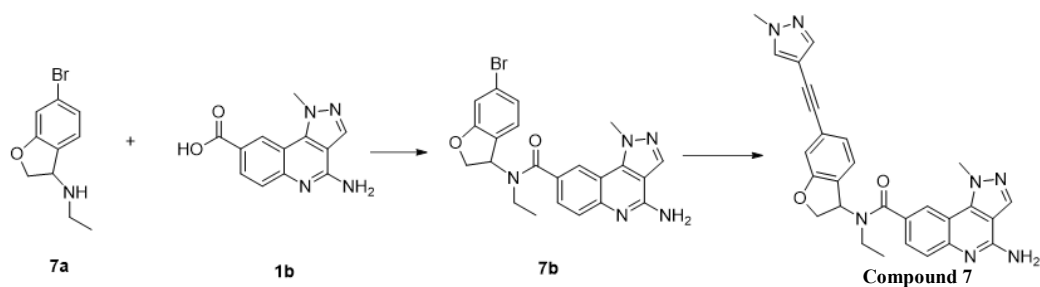
Preparation of compound 6

To a solution of compound **6b** (50 mg, 0.13 mmol) in *N,N*-dimethylformamide (2 mL) were sequentially added 1-methyl-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (64 mg, 0.26 mmol), cuprous iodide (9.90 mg, 0.05 mmol), *N,N*-diisopropylethylamine (134.16 mg, 1.04 mmol), and tetrakis(triphenylphosphine)palladium (30.1 mg, 0.03 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react at 25 °C for 3 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was subjected to reversed phase chromatography (acetonitrile/0.05% aqueous ammonia bicarbonate solution = 0:100% - 40%:60%) to give compound **6** (15 mg). ESI-MS (*m/z*): 493.38 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 8.28 (s, 1H), 7.67 – 7.62 (m, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.94 (s, 1H), 6.43 – 5.80 (m, 2H), 4.75 – 4.70 (m, 2H), 4.44 (s, 3H), 2.99 – 2.96 (m, 2H), 2.69 (s, 3H), 2.50 – 2.47 (m, 2H), 2.31 – 2.26 (m, 3H).

Example

7:

4-amino-*N*-ethyl-1-methyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 7)



Preparation of compound 7b

Compound **1b** (100 mg, 0.41 mmol) was dissolved in *N,N*-dimethylformamide (10 mL), and *N,N*-diisopropylethylamine (0.36 mL, 2.1 mmol) was added. The mixture was stirred for 5 min under an ice bath, and then *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (236 mg, 0.62 mmol) was added. The mixture was allowed to react for another 5 min, and finally, **7a** (110 mg, 0.45 mmol) was added. The mixture was allowed to react for another hour, water (30 mL) was then added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **7b** (120 mg). ESI-MS (*m/z*): 465.91 [*M*+*H*]⁺.

Preparation of compound 7

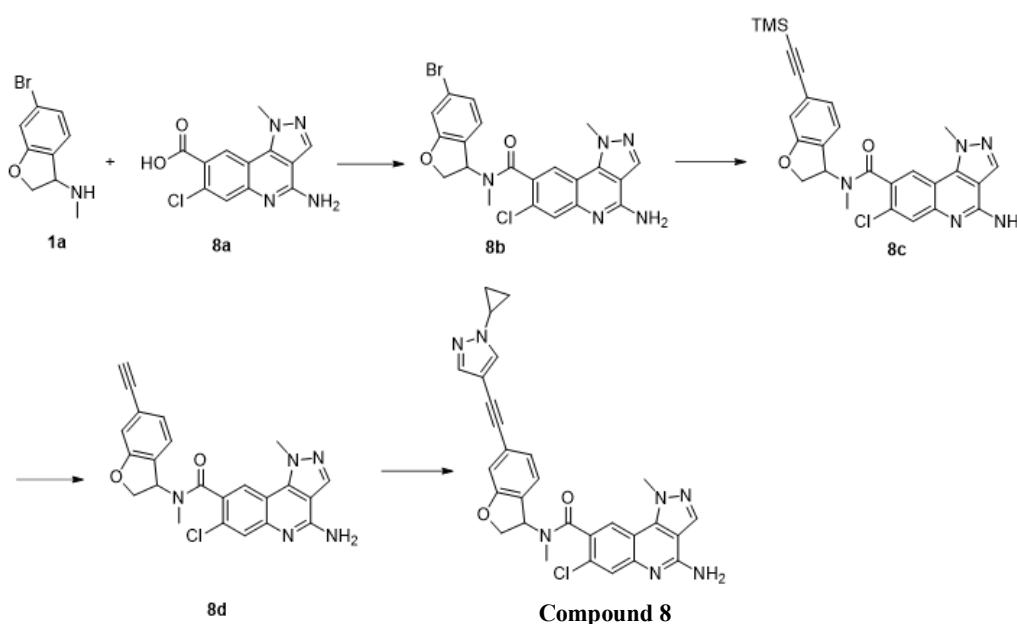
To a solution of compound **7b** (120 mg, 0.26 mmol) in *N*-methylpyrrolidone (3 mL) were sequentially added 4-ethynyl-1-methyl-1*H*-pyrazole (54.7 mg, 0.52 mmol), cuprous iodide (9.8 mg, 0.05 mmol), *N,N*-diisopropylethylamine (0.18 mL, 1.03 mmol), and tetrakis(triphenylphosphine)palladium (29.8 mg, 0.026 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 70 °C for 3 h. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give

compound **7** (60 mg). ESI-MS (m/z): 492.22 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.28 (s, 2H), 8.08 (s, 1H), 7.69 – 7.59 (m, 3H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.16 (s, 2H), 7.08 (dd, $J = 7.6$ 1.2 Hz, 1H), 6.99 (s, 1H), 5.92 (s, 1H), 4.80 – 4.63 (m, 2H), 4.44 (s, 3H), 3.87 (s, 3H), 3.30 – 3.22 (m, 2H), 0.99 – 0.89 (m, 3H).

Example

8:

4-amino-7-chloro-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound **8**)



Preparation of compound **8b**

To a solution of compound **1a** (230 mg, 1.01 mmol) in *N,N*-dimethylformamide (10 mL) were added compound **8a** (279 mg, 1.01 mmol, see WO2022169948 A1 for the preparation method), triethylamine (255.1 mg, 2.52 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (576.3 mg, 1.51 mmol), and the mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column

chromatography (dichloromethane/methanol = 50:1) to give compound **8b** (280 mg). ESI-MS (m/z): 487.89 $[M+H]^+$.

Preparation of compound **8c**

To a solution of compound **8b** (280 mg, 0.58 mmol) in *N*-methylpyrrolidone (3 mL) were added cuprous iodide (21.9 mg, 0.12 mmol), tetrakis(triphenylphosphine)palladium (66.5 mg, 0.06 mmol), *N,N*-diisopropylethylamine (371.52 mg, 2.88 mmol), and trimethylsilylacetylene (113 mg, 1.15 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 70 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 20:1) to give compound **8c** (220 mg). ESI-MS (m/z): 504.3 $[M+H]^+$.

Preparation of compound **8d**

Tetrabutylammonium fluoride (870 μ L, 0.87 mmol) was added to a solution of compound **8c** (220 mg, 0.44 mmol) in tetrahydrofuran (5 mL), and the mixture was allowed to react at 25 °C for 1 h. Water (15 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was separated and purified by a preparative plate (dichloromethane/methanol = 10:1) to give compound **8d** (160 mg). ESI-MS (m/z): 432.03 $[M+H]^+$.

Preparation of compound **8**

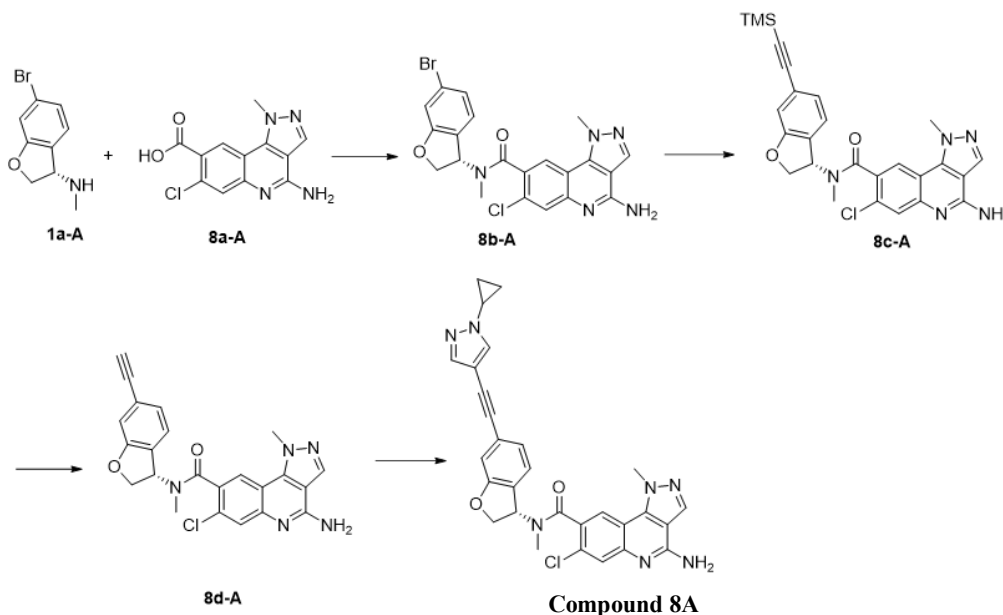
To a solution of compound **8d** (43 mg, 0.10 mmol) in *N,N*-dimethylformamide (2 mL) were sequentially added 1-cyclopropyl-4-iodopyrazole (46.6 mg, 0.20 mmol), cuprous iodide (7.60 mg, 0.04 mmol), *N,N*-diisopropylethylamine (51.6 mg, 0.4 mmol), and tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react at 25 °C for 3 h.

Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was then subjected to reversed phase chromatography (acetonitrile/0.05% aqueous ammonia bicarbonate solution = 0:100% - 40%:60%) to give compound **8** (28 mg). ESI-MS (m/z): 538.15 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.41 – 8.21 (m, 2H), 8.19 – 8.15 (m, 1H), 7.72 – 7.61 (m, 2H), 7.54 – 7.30 (m, 3H), 7.15 – 6.94 (m, 2H), 6.53 – 6.48 and 5.46 – 5.42 (m, 1H), 4.91 – 4.53 (m, 2H), 4.48 – 4.38 (m, 3H), 3.79 – 3.74 (m, 1H), 2.73 – 2.50 (m, 3H), 1.11 – 1.04 (m, 2H), 1.03 – 0.97 (m, 2H).

Example

8A:

(*S*)-4-amino-7-chloro-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 8A)



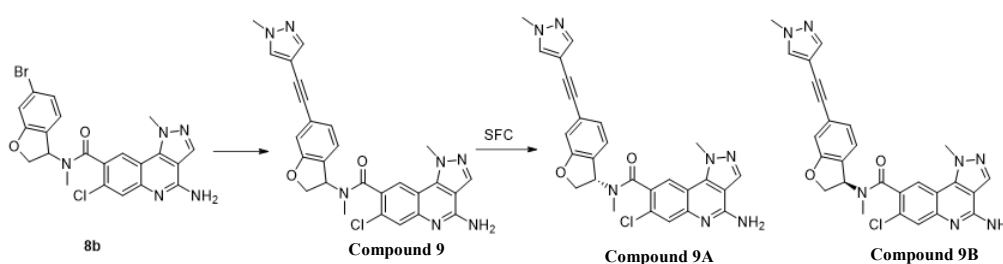
For the synthesis process of preparing compound **8A** from compound **1a-A**, reference was made to the synthesis process of preparing compound **8** from compound **1a**.

ESI-MS (m/z): 538.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.41 – 8.21 (m, 2H), 8.19 – 8.15 (m, 1H), 7.72 – 7.61 (m, 2H), 7.54 – 7.38 (m, 1H), 7.32 – 7.30 (m, 2H), 7.15 – 6.94 (m, 2H), 6.53 – 5.42 (m, 1H), 4.91 – 4.53 (m, 2H), 4.48 – 4.38 (m, 3H), 3.79 – 3.74 (m, 1H), 2.73 – 2.50 (m, 3H), 1.11 – 0.97 (m, 4H).

Example

9:

4-amino-7-chloro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 9)



To a 10 mL microwave tube were added reactant **8b** (48.6 mg, 0.10 mmol), cuprous iodide (3.8 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium (11.5 mg, 0.01 mmol), and *N*-methylpyrrolidone (2 mL). After nitrogen bubbling for 3 min, *N,N*-diisopropylethylamine (52.94 μ L, 0.32 mmol) and *N*-methyl-4-alkynylpyrazole (21.2 mg, 0.20 mmol) were added. The reaction solution was reacted in a microwave reactor at 70 °C and stirred for 3 h. After the reaction was completed, water was added to quench the reaction, and the reaction solution was extracted three times with ethyl acetate (30 mL). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was separated by preparative reversed-phase column chromatography (acetonitrile:0.05% aqueous ammonium bicarbonate solution = 0:100% - 35%:65%) to give compound **9** (15 mg). ESI-MS (m/z): 511.90 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.41 – 8.21 (m, 2H), 8.10 – 8.05 (m, 1H), 7.72 – 7.61 (m, 2H), 7.54 – 7.30 (m, 3H), 7.15 – 6.91 (m, 2H), 6.54 – 6.48 and 5.47 – 5.42 (m, 1H), 4.87 – 4.56 (m, 2H), 4.47 – 4.41 (m, 3H), 3.87 – 3.86

(m, 3H), 2.73 – 2.50 (m, 3H).

Compound **9** was separated by SFC (instrument: Waters 150 Prep-SFC; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.1% NH₃•H₂O); B%: 45%) to give compounds **9A** and **9B**.

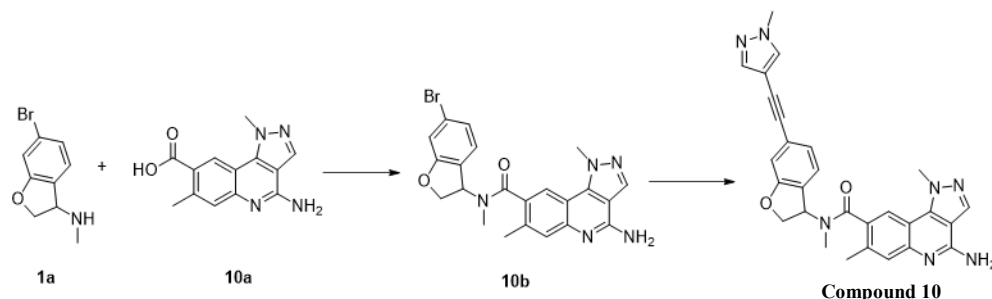
Compound **9A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.187 min, ee = 100%. ESI-MS (m/z): 512.2 [M+H]⁺.

Compound **9B**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.376 min, ee = 100%. ESI-MS (m/z): 512.3 [M+H]⁺.

Example

10:

4-amino-*N*,1,7-trimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 10)



Preparation of compound 10b

To a solution of compound **1a** (210 mg, 0.92 mmol) in *N,N*-dimethylformamide (10 mL) were added compound **10a** (256.3 mg, 0.92 mmol, see WO2022169948 A1 for the preparation method), triethylamine (232.9 mg, 2.30 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (526.2 mg, 1.38 mmol), and the mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL × 2). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered.

The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 50:1) to give compound **10b** (360 mg). ESI-MS (*m/z*): 468.07 [M+H]⁺.

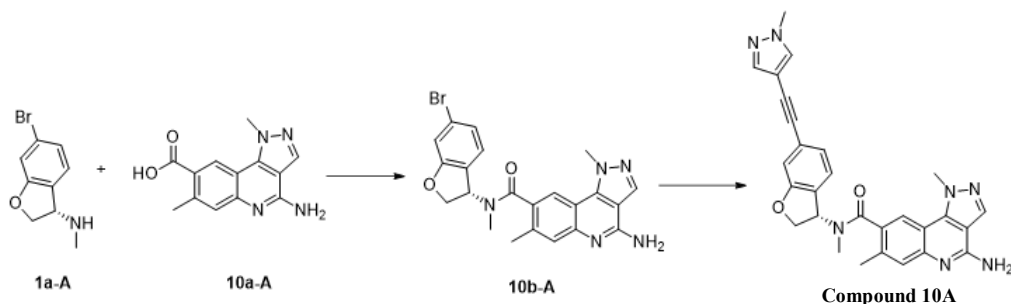
Preparation of compound 10

To a 10 mL microwave tube were added reactant **10b** (46.6 mg, 0.10 mmol), cuprous iodide (3.8 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium (11.5 mg, 0.01 mmol), and a solvent *N*-methylpyrrolidone (2 mL). After nitrogen bubbling for 3 min, *N,N*-diisopropylethylamine (52.94 μ L, 0.32 mmol) and *N*-methyl-4-alkynylpyrazole (21.2 mg, 0.20 mmol) were added. The reaction solution was reacted in a microwave reactor at 70 °C and stirred for 3 h. After the reaction was completed, water was added to quench the reaction, and the reaction solution was extracted three times with ethyl acetate (30 mL). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was separated by preparative reversed-phase column chromatography (acetonitrile:0.05% aqueous ammonium bicarbonate solution = 0:100% - 35%:65%) to give compound **10** (15 mg). ESI-MS (*m/z*): 491.96 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 (s, 1H), 8.07 – 8.04 (m, 2H), 7.69 (s, 1H), 7.52 – 7.43 (m, 2H), 7.17 – 6.95 (m, 4H), 6.55 – 6.48 and 5.54 – 5.45 (m, 1H), 4.91 – 4.54 (m, 2H), 4.39 (s, 3H), 3.87 (s, 3H), 3.30 (s, 3H), 2.72 – 2.37 (m, 3H).

Example

10A:

(*S*)-4-amino-*N*,1,7-trimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound **10A**)



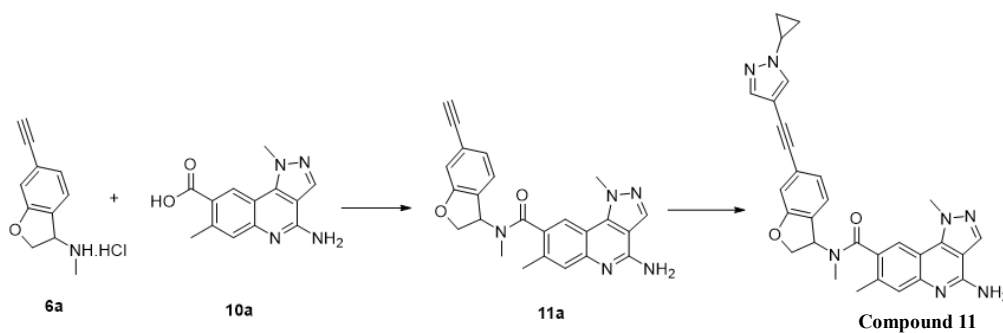
For the synthesis process of preparing compound **10A** from compound **1a-A**, reference was made to the synthesis process of preparing compound **10** from compound **1a**.

Compound 10A: ESI-MS (m/z): 492.01 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.24 (s, 1H), 8.07 – 8.04 (s, 1H), 7.69 (s, 1H), 7.52 – 7.44 (m, 2H), 7.14 – 6.95 (m, 4H), 6.55 – 5.45 (m, 1H), 4.91 – 4.54 (m, 2H), 4.39 (s, 3H), 3.87 (s, 3H), 3.30 (s, 3H), 2.72 – 2.37 (s, 3H).

Example

11:

4-amino-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1,7-trimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 11)



Preparation of compound 11b

To a solution of compound **10a** (30.8 mg, 0.12 mmol) in *N,N*-dimethylacetamide (5 mL) were added compound **6a** (25 mg, 0.12 mmol), triethylamine (0.05 mL, 0.36 mmol), and *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethylisouronium tetrafluoroborate (57.8 mg, 0.18 mmol), and the mixture was allowed to react at 25 °C overnight. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (3 mL $\times$ 10). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and

filtered. The filtrate was concentrated, and the residue was subjected to reversed phase column chromatography (acetonitrile/0.05% aqueous ammonium bicarbonate solution = 0:100% - 50%:50%) to give compound **11a** (7.0 mg). ESI-MS (*m/z*): 412.15.

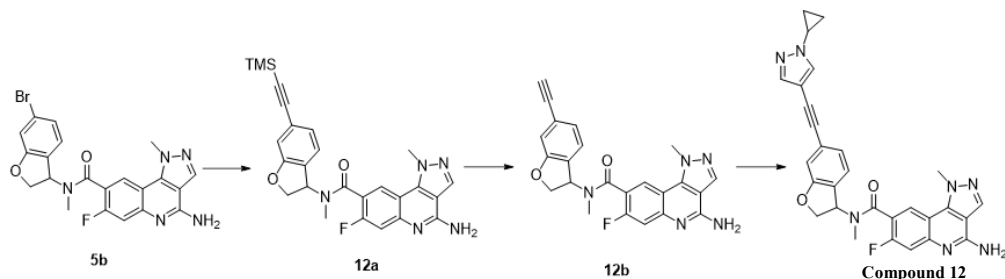
Preparation of compound 11

To a solution of compound **11a** (50 mg, 0.12 mmol) in *N,N*-dimethylformamide (2 mL) were sequentially added 1-cyclopropyl-4-iodopyrazole (56.9 mg, 0.24 mmol), cuprous iodide (9.90 mg, 0.05 mmol), *N,N*-diisopropylethylamine (134.16 mg, 1.04 mmol), and tetrakis(triphenylphosphine)palladium (30.1 mg, 0.03 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react at 25 °C for 3 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was then subjected to reversed phase chromatography (acetonitrile/0.05% aqueous ammonia bicarbonate solution = 0:100% - 40%:60%) to give compound **11** (20 mg). ESI-MS (*m/z*): 518.22 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 8.30 – 8.10 (m, 2H), 7.95 – 7.38 (m, 4H), 7.26 – 6.94 (m, 3H), 6.52 – 6.50 and 5.50 – 5.42 (m, 1H), 4.89 – 4.42 (m, 5H), 3.80 – 3.74 (m, 1H), 2.73 and 2.49 (s, 3H), 2.56 and 2.39 (s, 3H), 1.14 – 1.05 (m, 2H), 1.05 – 0.95 (m, 2H).

Example

12:

4-amino-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide
(Compound 12)



Preparation of compound 12a

To a solution of compound **5b** (808 mg, 1.72 mmol) in *N*-methylpyrrolidone (10 mL) were sequentially added trimethylsilylacetylene (338.5 mg, 3.45 mmol), cuprous iodide (65.6 mg, 0.34 mmol), *N,N*-diisopropylethylamine (890.9 mg, 6.89 mmol), and tetrakis(triphenylphosphine)palladium (199.1 mg, 0.17 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 100 °C for 3 h. Water (200 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **12a** (595 mg). ESI-MS (m/z): 488.18 $[M+H]^+$.

Preparation of compound 12b

To a solution of compound **12a** (595 mg, 1.22 mmol) in tetrahydrofuran (10 mL) was added a solution of tetrabutylammonium fluoride (2.44 mL, 1 M). After completion of the addition, the mixture was allowed to react at room temperature for 1 h. Water was added, and the reaction solution was extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **12b** (470 mg). ESI-MS (m/z): 416.12 $[M+H]^+$.

Preparation of compound 12

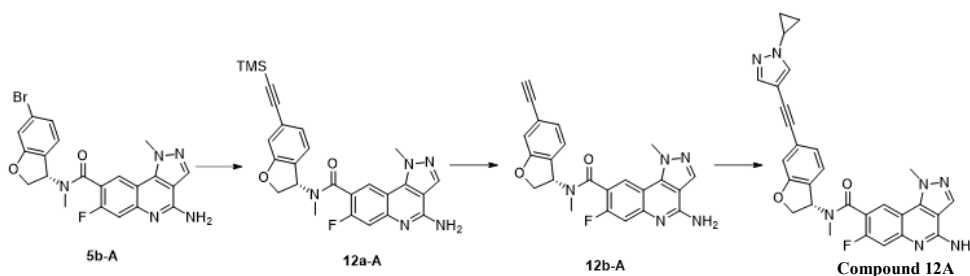
To a solution of compound **12b** (62.3 mg, 0.15 mmol) in *N*-methylpyrrolidone (1.5 mL) were sequentially added 1-cyclopropyl-4-iodo-1*H*-pyrazole (70.2 mg, 0.3 mmol),

cuprous iodide (5.7 mg, 0.03 mmol), *N,N*-diisopropylethylamine (77.5 mg, 0.6 mmol), and tetrakis(triphenylphosphine)palladium (17.3 mg, 0.015 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react under an oil bath at 50 °C for 3 h. Water (100 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **12** (25 mg). ESI-MS (*m/z*): 521.97 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.32 – 8.24 (m, 2H), 8.18 (s, 1H), 7.68 (s, 1H), 7.42 – 7.28 (m, 4H), 7.14 – 7.05 (m, 1H), 7.02 – 6.92 (m, 1H), 6.51 – 5.58 (m, 1H), 4.88 – 4.66 (m, 2H), 4.44 – 4.40 (m, 3H), 3.81 – 3.73 (m, 1H), 2.71 – 2.59 (m, 3H), 1.09 – 0.95 (m, 4H).

Example

12A:

(*S*)-4-amino-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound **12A)**



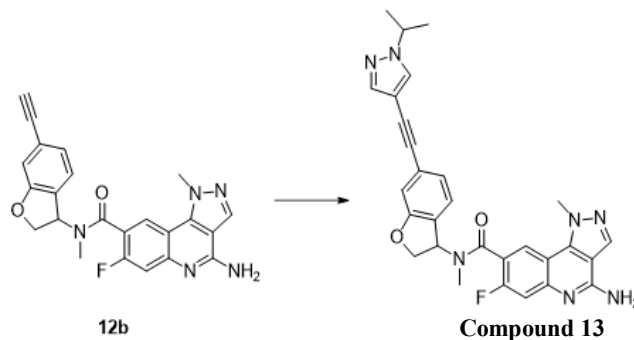
For the synthesis process of preparing compound **12A** from compound **5b-A**, reference was made to the synthesis process of preparing compound **12** from compound **5b**.

Compound **12A**: ESI-MS (*m/z*): 521.94 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.34 – 8.23 (m, 2H), 8.18 (s, 1H), 7.69 (s, 1H), 7.45 – 7.29 (m, 4H), 7.16 – 7.05 (m, 1H), 7.02 – 6.92 (m, 1H), 6.50 – 5.56 (m, 1H), 4.87 – 4.65 (m, 1H), 4.44 – 4.40 (m, 3H), 3.84 – 3.70 (m, 1H), 2.71 – 2.60 (m, 1H), 1.11 – 0.96 (m, 4H).

Example

13:

4-amino-7-fluoro-*N*-(6-((1-isopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide
(Compound 13)

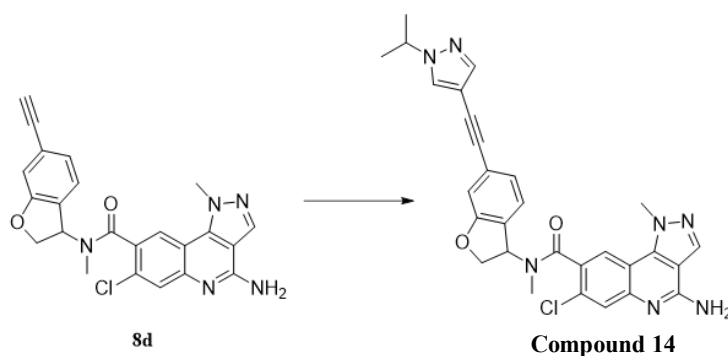


Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 4-iodo-1-isopropyl-1*H*-pyrazole (70.8 mg, 0.3 mmol), and the mixture was reacted at 50 °C for 3 h under nitrogen atmosphere to give compound **13** (28 mg). ESI-MS (*m/z*): 524.05 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.39 – 8.22 (m, 2H), 8.17 (s, 1H), 7.70 (s, 1H), 7.44 – 7.28 (m, 4H), 7.17 – 7.05 (m, 1H), 7.02 – 6.93 (m, 1H), 6.51 – 5.52 (m, 1H), 4.87 – 4.66 (m, 2H), 4.57 – 4.48 (m, 1H), 4.44 – 4.40 (m, 3H), 2.71 – 2.60 (m, 3H), 1.45 – 1.42 (m, 6H).

Example

14:

4-amino-7-chloro-*N*-(6-((1-isopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide
(Compound 14)



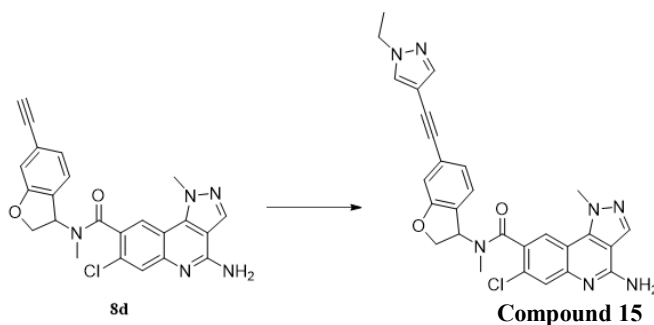
Referring to the preparation process of compound **8**, compound

1-cyclopropyl-4-iodopyrazole was replaced with compound 4-iodo-1-(propan-2-yl)pyrazole (21.9 mg, 0.09 mmol), and the mixture was reacted at 50 °C for 3 h under nitrogen atmosphere to give compound **14** (12 mg). ESI-MS (m/z): 540.17 $[M+H]^+$. 1H NMR (400 MHz, DMSO- D_2O) δ 8.41 – 8.19 (m, 2H), 8.14 – 8.08 (m, 1H), 7.77 – 7.64 (m, 2H), 7.49 – 7.25 (m, 1H), 7.12 – 6.88 (m, 2H), 6.51 – 6.42 and 5.42 – 5.34 (m, 1H), 4.84 – 4.46 (m, 3H), 4.44 and 4.38 (s, 3H), 2.7 – 2.47 (m, 3H), 1.45 – 1.34 (m, 6H).

Example

15:

4-amino-7-chloro-*N*-(6-((1-ethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 15)

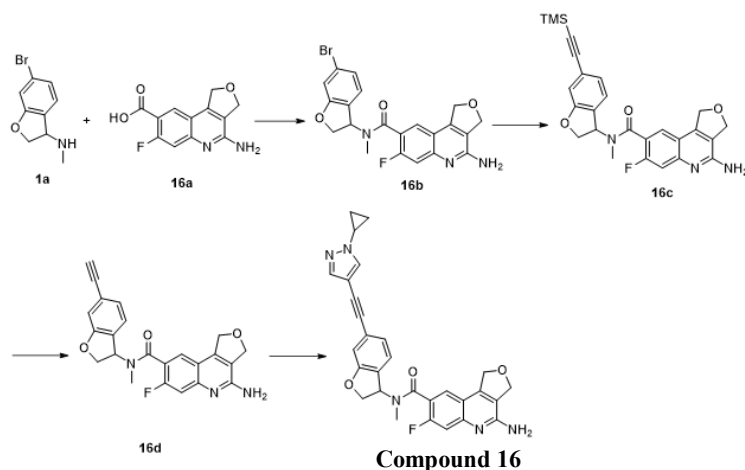


Referring to the preparation process of compound **8**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 1-ethyl-4-iodopyrazole (30.8 mg, 0.14 mmol), and the mixture was reacted at 50 °C for 3 h under nitrogen atmosphere to give compound **15** (16.4 mg). ESI-MS (m/z): 526.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.43 – 8.11 (m, 3H), 7.72 – 7.61 (m, 2H), 7.54 – 7.29 (m, 3H), 7.17 – 7.04 (m, 1H), 7.04 – 6.91 (m, 1H), 6.55 – 6.48 and 5.48 – 5.38 (m, 1H), 4.86 – 4.55 (m, 2H), 4.47 and 4.41 (s, 3H), 4.21 – 4.09 (m, 2H), 2.73 – 2.50 (m, 3H), 1.44 – 1.34 (m, 3H).

Example

16:

4-amino-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 16)



Preparation of compound 16b

To a solution of compound **1a** (100 mg, 0.44 mmol) in *N,N*-dimethylformamide (10 mL) were added compound **16a** (109 mg, 0.44 mmol, see WO2022169948 A1 for the preparation method), triethylamine (110.9 mg, 1.10 mmol), and *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (250.5 mg, 0.66 mmol), and the mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 50:1) to give compound **16b** (118 mg). ESI-MS (*m/z*): 459.85 [*M*+*H*]⁺.

Preparation of compound 16c

To a solution of **16b** (118 mg, 0.26 mmol) in *N*-methylpyrrolidone (3 mL) were added cuprous iodide (9.8 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium (29.8 mg, 0.03 mmol), triethylamine (104.2 mg, 2.88 mmol), and trimethylsilylacetylene (50.6 mg, 0.51 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 70 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were combined, washed

with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 20:1) to give compound **16c** (105 mg). ESI-MS (m/z): 476.2 [M+H]⁺.

Preparation of compound 16d

Tetrabutylammonium fluoride (440 μ L, 0.44 mmol) was added to a solution of compound **16c** (105 mg, 0.22 mmol) in tetrahydrofuran (5 mL), and the mixture was allowed to react at 25 °C for 1 h. Water (15 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was separated and purified by a preparative plate (dichloromethane/methanol = 15:1) to give compound **16d** (89.1 mg). ESI-MS (m/z): 404.09 [M+H]⁺.

Preparation of compound 16

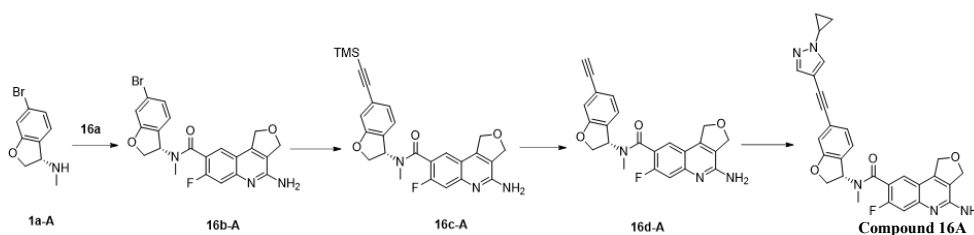
To a solution of compound **16d** (43 mg, 0.11 mmol) in *N,N*-dimethylformamide (2 mL) were sequentially added 1-cyclopropyl-4-iodopyrazole (49.9 mg, 0.22 mmol), cuprous iodide (8.10 mg, 0.04 mmol), triethylamine (43.1 mg, 0.43 mmol), and tetrakis(triphenylphosphine)palladium (24.6 mg, 0.02 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react at 25 °C for 3 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was then subjected to preparative reversed-phase column chromatography (acetonitrile/0.05% aqueous ammonia bicarbonate solution = 0:100% - 40%:60%) to give compound **16** (18 mg). ESI-MS (m/z): 510.18 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 – 8.18 (m, 1H), 7.69 – 7.65 (m, 2H), 7.38 – 7.31 (m, 2H), 7.13 – 7.07 (m, 1H), 7.00 – 6.95 (m, 1H), 6.85 (s, 2H), 6.45 – 6.42 and 5.52 – 5.49 (m, 1H), 5.38 – 5.32 (m, 2H), 5.04 – 5.00 (m, 2H), 4.82 – 4.59 (m, 2H),

3.80 – 3.74 (m, 1H), 2.68 and 2.55 (s, 3H), 1.11 – 0.97 (m, 4H).

Example

16A:

(S)-4-amino-N-(6-((1-cyclopropyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 16A)



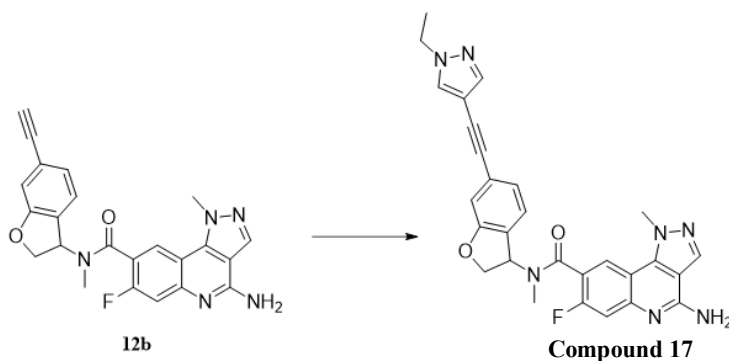
For the synthesis process of preparing compound **16A** from compound **1a-A**, reference was made to the synthesis process of preparing compound **16** from compound **1a**.

Compound **16A**: ESI-MS (m/z): 510.08 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.20 – 8.17 (m, 1H), 7.71 – 7.62 (m, 2H), 7.40 – 7.26 (m, 2H), 7.14 – 7.05 (m, 1H), 7.01 – 6.94 (m, 1H), 6.85 (s, 2H), 6.47 – 6.38 and 5.53 – 5.46 (m, 1H), 5.40 – 5.32 (m, 2H), 5.04 – 5.00 (m, 2H), 4.83 – 4.56 (m, 2H), 3.82 – 3.72 (m, 1H), 2.68 and 2.55 (s, 3H), 1.10 – 1.05 (m, 2H), 1.02 – 0.97 (m, 2H).

Example

17:

4-amino-N-(6-((1-ethyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 17)



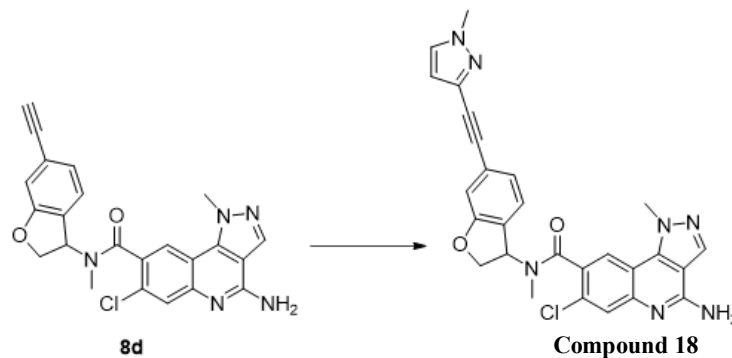
Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1H-pyrazole was replaced with compound

1-ethyl-4-iodo-1*H*-pyrazole (66.6 mg, 0.3 mmol) to give compound **17** (30 mg). ESI-MS (*m/z*): 510.05 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.36 – 8.21 (m, 2H), 8.13 (s, 1H), 7.70 (s, 1H), 7.43 – 7.28 (m, 4H), 7.16 – 7.05 (m, 1H), 7.03 – 6.94 (m, 1H), 6.50 – 5.54 (m, 1H), 4.87 – 4.61 (m, 2H), 4.45 – 4.40 (m, 3H), 4.20 – 4.13 (m, 2H), 2.71 – 2.60 (m, 3H), 1.42 – 1.37 (m, 3H).

Example

18:

4-amino-7-chloro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 18)

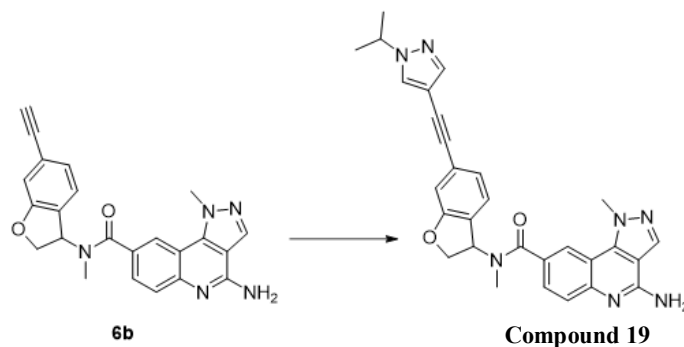


Referring to the preparation process of compound **8**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-iodo-1-methylpyrazole (41.6 mg, 0.20 mmol) to give compound **18** (21 mg). ESI-MS (*m/z*): 511.97 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 – 8.21 (m, 2H), 7.79 – 7.78 (m, 1H), 7.71 – 7.61 (m, 1H), 7.57 – 7.28 (m, 3H), 7.20 – 6.96 (m, 2H), 6.53 – 5.43 (m, 2H), 4.87 – 4.55 (m, 2H), 4.46 and 4.41 (s, 3H), 3.88 – 3.87 (m, 3H), 2.74 – 2.53 (m, 3H).

Example

19:

4-amino-*N*-(6-((1-isopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 19)

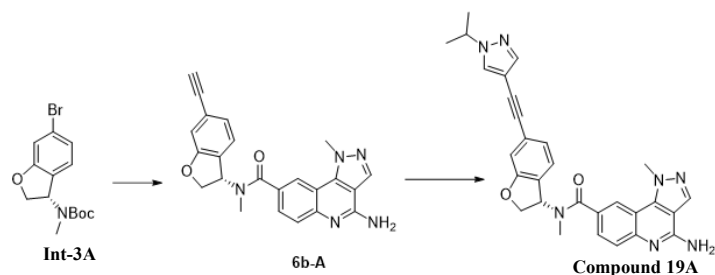


To a solution of compound **6b** (49.6 mg, 0.125 mmol) in *N*-methylpyrrolidone (1.5 mL) were sequentially added 4-iodo-1-isopropyl-1*H*-pyrazole (59.0 mg, 0.25 mmol), cuprous iodide (4.8 mg, 0.025 mmol), *N,N*-diisopropylethylamine (64.6 mg, 0.5 mmol), and tetrakis(triphenylphosphine)palladium (14.5 mg, 0.0125 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react under an oil bath at 50 °C for 3 h. Water (100 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **19** (30 mg). ESI-MS (*m/z*): 506.05 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.34 (s, 1H), 8.28 (s, 1H), 8.17 (s, 1H), 7.70 (s, 1H), 7.68 – 7.62 (m, 2H), 7.48 – 7.42 (m, 1H), 7.18 (s, 2H), 7.12 – 7.07 (m, 1H), 6.98 (s, 1H), 6.30 – 5.87 (m, 1H), 4.79 – 4.70 (m, 2H), 4.57 – 4.49 (m, 1H), 4.44 (s, 3H), 2.70 (s, 3H), 1.46 – 1.43 (m, 6H).

Example

19A:

(*S*)-4-amino-*N*-(6-((1-isopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound **19A**)



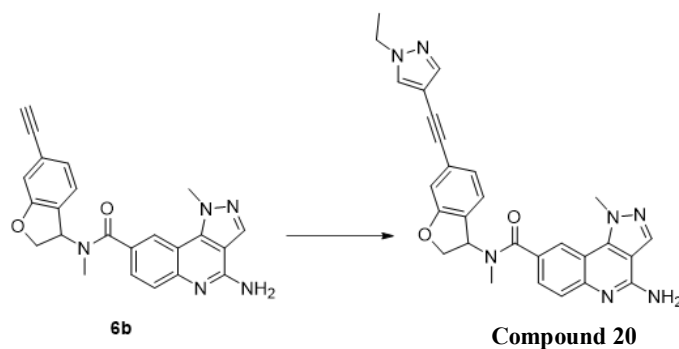
Reference was made to WO2024131901 A1 for the preparation process of compound **6b-A**. For the synthesis process of preparing compound **19A** from compound **6b-A**, reference was made to the synthesis process of preparing compound **19** from compound **6b**.

Compound 19A: ESI-MS (m/z): 506.13 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 8.28 (s, 1H), 8.17 (s, 1H), 7.70 (s, 1H), 7.67 – 7.62 (m, 2H), 7.48 – 7.42 (m, 1H), 7.16 (s, 2H), 7.11 – 7.06 (m, 1H), 6.97 (s, 1H), 4.80 – 4.67 (m, 2H), 4.57 – 4.48 (m, 1H), 4.44 (s, 3H), 2.69 (s, 3H), 1.45 – 1.42 (m, 6H).

Example

20:

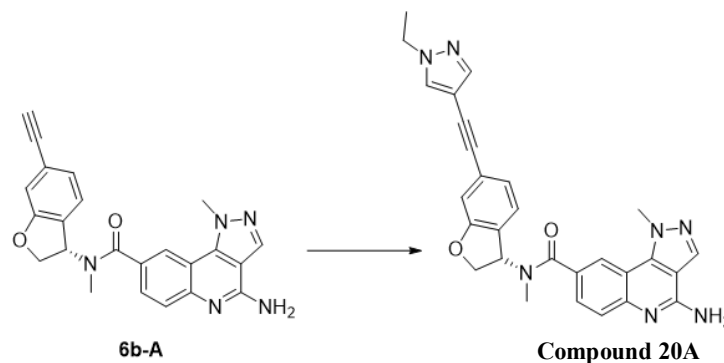
4-amino-*N*-(6-((1-ethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 20)



Referring to the preparation process of compound **19**, compound 4-iodo-1-isopropyl-1*H*-pyrazole was replaced with compound 1-ethyl-4-iodo-1*H*-pyrazole (55.5 mg, 0.25 mmol) to give compound **20** (15 mg). ESI-MS (m/z): 492.02 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.36 (s, 2H), 8.14 (s, 1H), 7.70 – 7.39 (m, 6H), 7.14 – 7.07 (m, 1H), 6.99 (s, 1H), 6.36 – 5.82 (m, 1H), 4.82 – 4.68 (m, 2H), 4.45 (s, 3H), 4.20 – 4.13 (m, 2H), 2.70 (s, 3H), 1.43 – 1.36 (m, 3H).

Example**20A:**

(S)-4-amino-N-(6-((1-ethyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 20A)

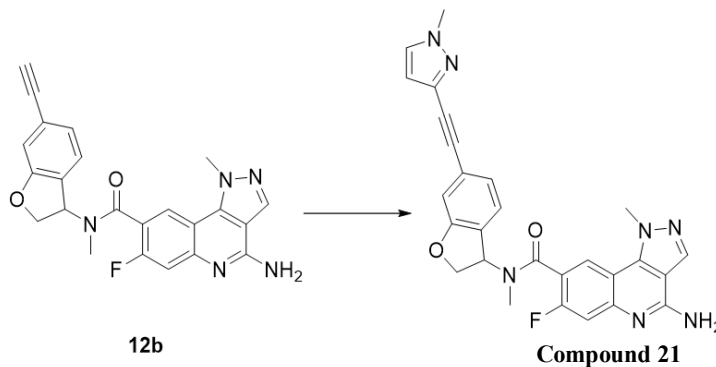


For the synthesis process of preparing compound **20A** from compound **6b-A**, reference was made to the synthesis process of preparing compound **20** from compound **6b**.

Compound **20A**: ESI-MS (m/z): 492.02 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.34 (s, 1H), 8.28 (s, 1H), 8.13 (s, 1H), 7.70 (s, 1H), 7.68 – 7.61 (m, 2H), 7.48 – 7.42 (m, 1H), 7.19 (s, 2H), 7.12 – 7.07 (m, 1H), 6.98 (s, 1H), 4.80 – 4.68 (m, 2H), 4.44 (s, 3H), 4.22 – 4.11 (m, 2H), 2.69 (s, 3H), 1.41 – 1.37 (m, 3H).

Example**21:**

4-amino-7-fluoro-N,1-dimethyl-N-(6-((1-methyl-1H-pyrazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 21)



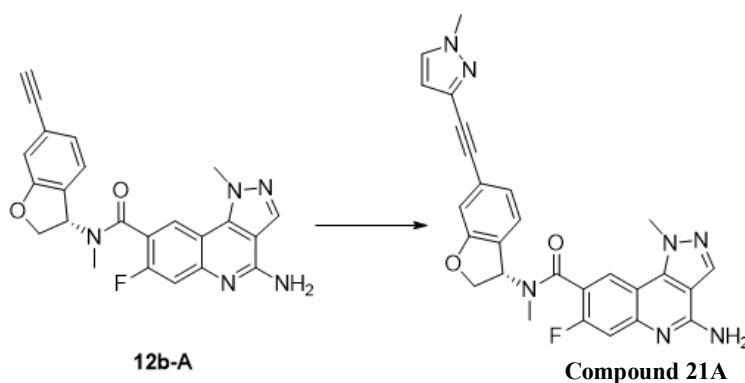
Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1H-pyrazole was replaced with compound

3-iodo-1-methylpyrazole (21 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **21** (20 mg). ESI-MS (m/z): 495.74 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.40 – 8.24 (m, 2H), 7.81 – 7.78 (m, 1H), 7.51 – 7.26 (m, 4H), 7.21 – 7.12 (m, 1H), 7.09 – 7.01 (m, 1H), 6.55 – 6.51 (m, 1H), 6.50 – 6.45 and 5.64 – 5.57 (m, 1H), 4.86 – 4.65 (m, 2H), 4.44 – 4.41 (m, 3H), 3.89 (s, 3H), 2.72 and 2.61 (s, 3H).

Example

21A:

(S)-4-amino-7-fluoro-N,1-dimethyl-N-(6-((1-methyl-1H-pyrazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide
(Compound 21A)



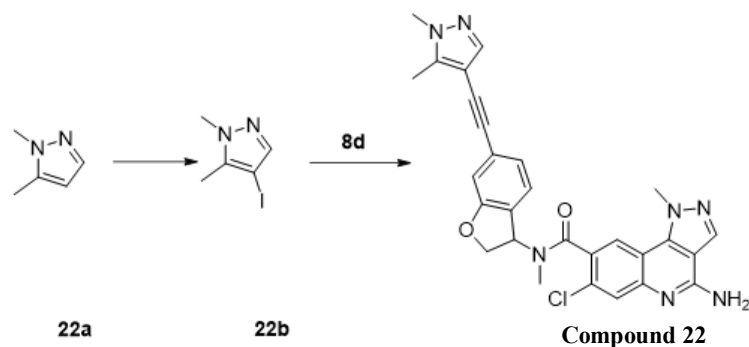
For the synthesis process of preparing compound **21A** from compound **12b-A**, reference was made to the synthesis process of preparing compound **21** from compound **12b**.

Compound 21A: ESI-MS (m/z): 496.08 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.40 – 8.24 (m, 2H), 7.81 – 7.78 (m, 1H), 7.51 – 7.26 (m, 4H), 7.21 – 7.12 (m, 1H), 7.09 – 7.01 (m, 1H), 6.55 – 6.51 (m, 1H), 6.51 – 5.57 (m, 1H), 4.90 – 4.62 (m, 2H), 4.44 – 4.41 (s, 3H), 3.89 (s, 3H), 2.72 and 2.61 (s, 3H).

Example

22:

4-amino-7-chloro-N-(6-((1,5-dimethyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide
(Compound 22)



Preparation of compound 22b

To a solution of compound **22a** (1.0 g, 10.41 mmol) in *N,N*-dimethylformamide (10 mL) was added *N*-iodosuccinimide (2.5 g, 10.93 mmol). After completion of the addition, the mixture was allowed to react at 25 °C for 1 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (petroleum ether:ethyl acetate = 6:1) to give **22b** (1.75 g).

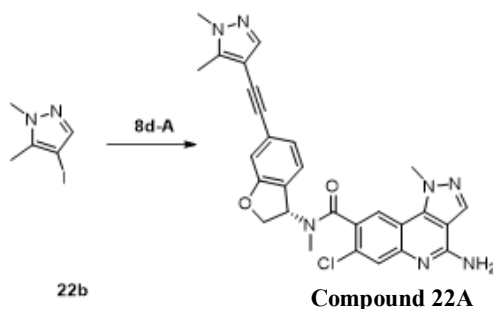
Preparation of compound 22

Referring to the preparation process of compound **8**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound **22b** (41.1 mg, 0.19 mmol) to give compound **22** (15 mg). ESI-MS (*m/z*): 526.07 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 – 8.21 (m, 2H), 7.72 – 7.26 (m, 5H), 7.15 – 6.93 (m, 2H), 6.55 – 6.48 and 5.48 – 5.40 (m, 1H), 4.86 – 4.57 (m, 2H), 4.47 and 4.41 (s, 3H), 3.78 – 3.77 (m, 3H), 2.76 – 2.41 (m, 3H), 2.38 – 2.36 (m, 3H).

Example

22A:

(*S*)-4-amino-7-chloro-*N*-(6-((1,5-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 22A)



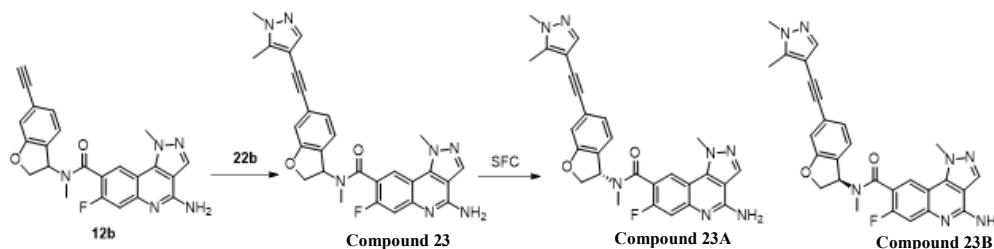
For the synthesis process of preparing compound **22A** from compound **22b** and compound **8d-A**, reference was made to the synthesis process of preparing compound **22** from compound **22b** and compound **8d**.

Compound **22A**: ESI-MS (m/z): 525.95 $[M+H]^+$.

Example

23:

4-amino-N-(6-((1,5-dimethyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide
(Compound **23**)



Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1H-pyrazole was replaced with compound **22b** (44.4 mg, 0.20 mmol), and the mixture was reacted at room temperature for 3 h to give compound **23** (15 mg). ESI-MS (m/z): 510.38 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.41 – 8.21 (m, 2H), 7.59 (s, 1H), 7.47 – 7.20 (m, 4H), 7.17 – 7.05 (m, 1H), 7.04 – 6.96 (m, 1H), 6.49 – 6.43 and 5.62 – 5.54 (m, 1H), 4.87 – 4.65 (m, 2H), 4.43 – 4.41 (m, 3H), 3.78 (s, 3H), 2.72 and 2.60 (s, 3H), 2.37 (s, 3H).

Compound **23** was separated by SFC (instrument: Waters 150 Prep-SFC; chromatographic column: Chiral AS column; mobile phase A: CO_2 , mobile phase B: methanol (containing 0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$); B%: 40%) to give compounds **23A** and **23B**.

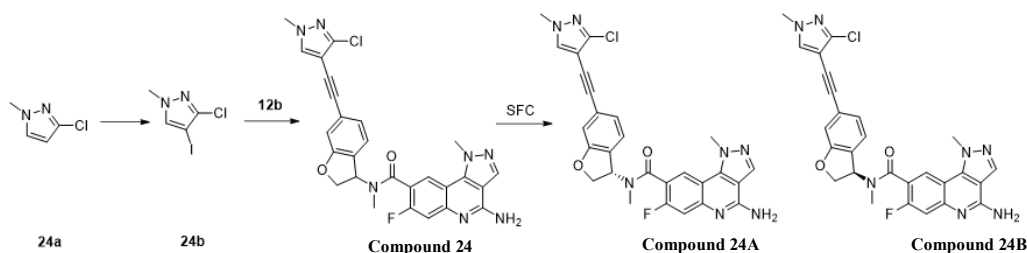
Compound **23A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 1.948 min, ee = 100%. [α]_D²⁵ +247 (c 1mg/mL, DMF).

Compound **23B**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.155 min, ee = 100%. [α]_D²⁵ -271 (c 1mg/mL, DMF).

Example

24:

4-amino-*N*-(6-((3-chloro-1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 24)



Preparation of compound 24b

To a solution of 3-chloro-1-methylpyrazole (116 mg, 1.0 mmol) in acetonitrile (3 mL) was added *N*-iodosuccinimide (235.2 mg, 1.05 mmol). After completion of the addition, the mixture was reacted at 25 °C for 1 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (petroleum ether:ethyl acetate = 6:1) to give compound **24b** (210 mg). ESI-MS (*m/z*): 242.89 [$M+H$]⁺.

Preparation of compound 24

Referring to the preparation process of compound **12**, compound

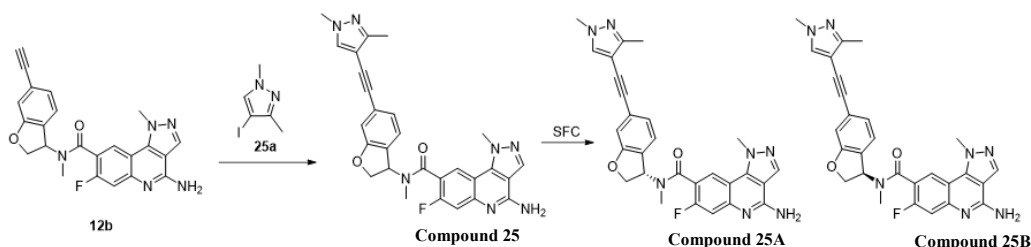
1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound **24b** (24.2 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **24** (20 mg). ESI-MS (*m/z*): 530.17 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 – 8.15 (m, 2H), 7.97 – 7.73 (m, 1H), 7.49 – 7.28 (m, 4H), 7.20 – 7.12 (m, 1H), 7.04 – 6.97 (m, 1H), 6.51 – 6.39 and 5.63 – 5.52 (m, 1H), 4.86 – 4.62 (m, 2H), 4.43 – 4.41 (s, 3H), 3.85 (s, 3H), 2.71 and 2.60 (s, 3H).

Compound **24** was separated by SFC (instrument: Waters 150 Prep-SFC; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.1% NH₃•H₂O); B%: 40%) to give compounds **24A** and **24B**.

Compound **24A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 0.789 min, ee = 99.71%.

Compound **24B**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 1.213 min, ee = 99.83%.

Example 25: 4-amino-*N*-(6-((1,3-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 25)



Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound **25a** (22.2 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **25** (20 mg). ESI-MS (*m/z*): 510.16 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 – 8.25 (m,

2H), 7.94 (s, 1H), 7.41 – 7.30 (m, 2H), 7.15 – 7.06 (m, 1H), 7.03 – 6.95 (m, 1H), 6.49 – 6.43 and 5.62 – 5.55 (m, 1H), 4.87 – 4.60 (m, 2H), 4.43 – 4.41 (m, 3H), 3.78 (s, 3H), 2.71 and 2.60 (s, 3H), 2.24 (s, 3H).

Compound **25** was separated by SFC (instrument: Waters 150 Prep-SFC; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.1% NH₃•H₂O); B%: 40%) to give compounds **25A** and **25B**.

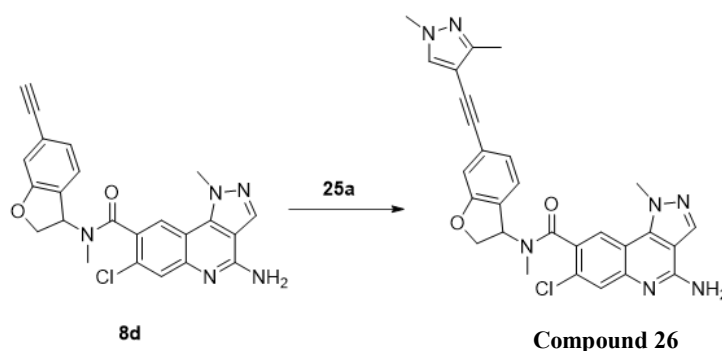
Compound **25A**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 1.832 min, ee = 99.94%. $[\alpha]_{25}^D +231.4$ (c 1mg/mL, DMF).

Compound **25B**: SFC analytical method: instrument: SHIMADZU LC-20AD; chromatographic column: Chiral AS column; mobile phase A: CO₂, mobile phase B: methanol (containing 0.05% diethylamine); B%: 5-40%; retention time: 2.019 min, ee = 100%. $[\alpha]_{25}^D -253$ (c 1mg/mL, DMF).

Example

26:

4-amino-7-chloro-N-(6-((1,3-dimethyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 26)



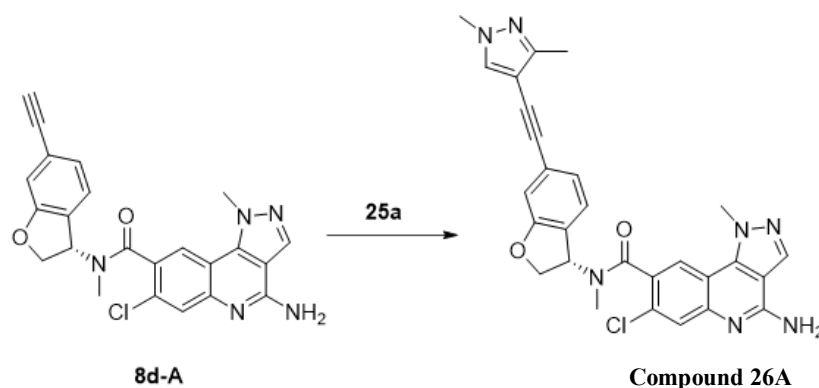
Referring to the preparation process of compound **8**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound **25a** (22.2 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **26** (20 mg). ESI-MS (m/z): 525.98 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.44 – 8.21 (m,

2H), 7.95 – 7.93 (m, 1H), 7.70 – 7.63 (m, 1H), 7.52 – 7.27 (m, 3H), 7.14 – 6.95 (m, 2H), 6.52 – 6.50 and 5.47 – 5.42 (m, 1H), 4.89 – 4.55 (m, 2H), 4.47 – 4.41 (m, 3H), 3.79 and 3.78 (s, 3H), 2.74 – 2.51 (m, 3H), 2.25 – 2.23 (m, 3H).

Example

26A:

(*S*)-4-amino-7-chloro-*N*-(6-((1,3-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 26A)



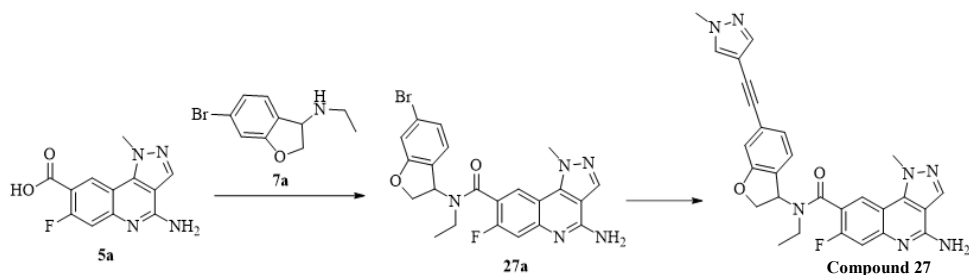
For the synthesis process of preparing compound **26A** from compound **8d-A**, reference was made to the synthesis process of preparing compound **26** from compound **8d**.

Compound **26A**: ESI-MS (*m/z*): 525.97 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.44 – 8.21 (m, 2H), 7.95 – 7.93 (m, 1H), 7.70 – 7.63 (m, 1H), 7.52 – 7.27 (m, 3H), 7.14 – 6.95 (m, 2H), 6.52 – 5.42 (m, 1H), 4.89 – 4.55 (m, 2H), 4.47 – 4.41 (m, 3H), 3.79 – 3.78 (m, 3H), 2.74 – 2.51 (m, 3H), 2.25 – 2.23 (m, 3H).

Example

27:

4-amino-*N*-ethyl-7-fluoro-1-methyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 27)



Preparation of compound 27a

Compound **5a** (106 mg, 0.41 mol) was dissolved in *N,N*-dimethylformamide (10 mL), and *N,N*-diisopropylethylamine (0.36 mL, 2.04 mol) was added. The mixture was stirred for 5 min under an ice bath, and then *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (232.53 mg, 0.61 mol) was added. The mixture was allowed to react for another 5 min, and finally, **7a** (113.54 mg, 0.41 mol) was added. The mixture was allowed to react for another hour. Water (100 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **27a** (120 mg). ESI-MS (*m/z*): 484.11 [*M*+*H*]⁺.

Preparation of compound 27

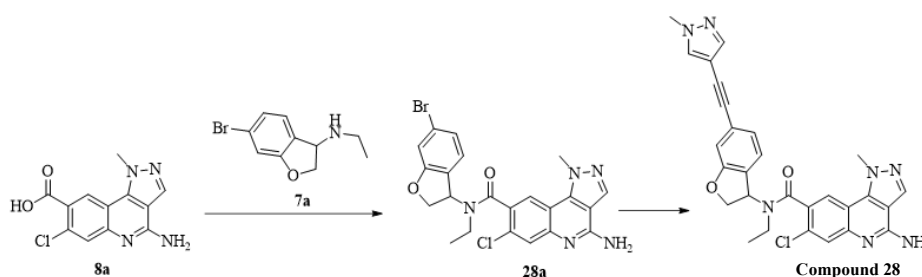
To a solution of compound **27a** (120 mg, 0.25 mmol) in *N*-methylpyrrolidone (3 mL) were sequentially added 4-ethynyl-1-methyl-1*H*-pyrazole (53.0 mg, 0.50 mmol), cuprous iodide (9.5 mg, 0.05 mmol), *N,N*-diisopropylethylamine (0.17 mL, 0.99 mmol), and tetrakis(triphenylphosphine)palladium (28.7 mg, 0.025 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 100 °C for 3 h. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20)

to give compound **27** (15 mg). ESI-MS (m/z): 510.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.38 – 8.17 (m, 2H), 8.07 (s, 1H), 7.69 (s, 1H), 7.50 – 7.26 (m, 4H), 7.14 – 6.95 (m, 2H), 6.20 – 5.53 (m, 1H), 4.91 – 4.53 (m, 2H), 4.42 (s, 3H), 3.87 (s, 3H), 3.25 – 3.05 (m, 2H), 1.10 – 0.72 (m, 3H).

Example

28:

4-amino-7-chloro-*N*-ethyl-1-methyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 28)



Preparation of compound 28a

Referring to the preparation process of compound **27a**, compound **5a** was replaced with compound **8a** (120 mg, 0.43 mmol) to give compound **28a** (160 mg). ESI-MS (m/z): 499.94 $[M+H]^+$.

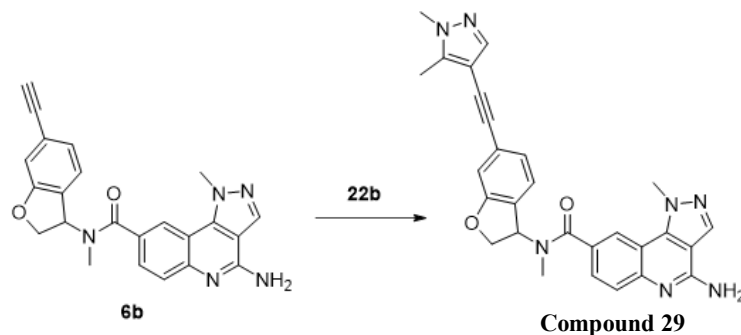
Preparation of compound 28

Referring to the preparation process of compound **27**, compound **27a** was replaced with compound **28a** (100 mg, 0.2 mmol) to give compound **28** (20 mg). ESI-MS (m/z): 526.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.40 – 8.15 (m, 2H), 8.11 – 8.04 (m, 1H), 7.72 – 7.62 (m, 2H), 7.55 – 7.36 (m, 1H), 7.30 (s, 2H), 7.16 – 6.93 (m, 2H), 6.22 – 5.31 (m, 1H), 4.91 – 4.57 (m, 2H), 4.51 – 4.37 (m, 3H), 3.87 (s, 3H), 3.32 – 2.91 (m, 2H), 1.14 – 0.75 (m, 3H).

Example

29:

4-amino-*N*-(6-((1,5-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 29)

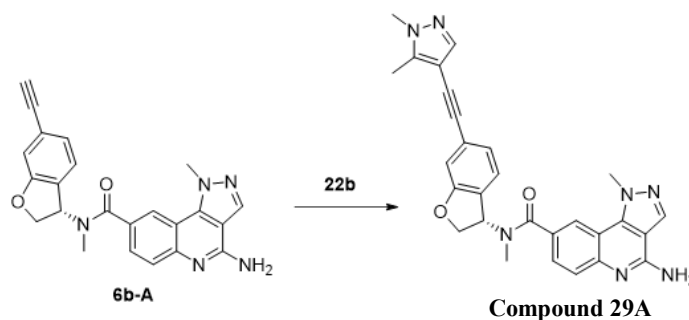


Referring to the preparation process of compound **19**, compound 4-iodo-1-isopropyl-1*H*-pyrazole was replaced with compound **22b** (22.2 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **29** (15 mg). ESI-MS (*m/z*): 492.14 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 8.28 (s, 1H), 7.68 – 7.61 (m, 2H), 7.58 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.64 – 5.80 (m, 1H), 4.82 – 4.66 (m, 2H), 4.44 (s, 3H), 3.77 (s, 3H), 2.70 (s, 3H), 2.37 (s, 3H).

Example

29A:

(*S*)-4-amino-*N*-(6-((1,5-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 29A)



For the synthesis process of preparing compound **29A** from compound **6b-A**, reference was made to the synthesis process of preparing compound **29** from compound **6b**.

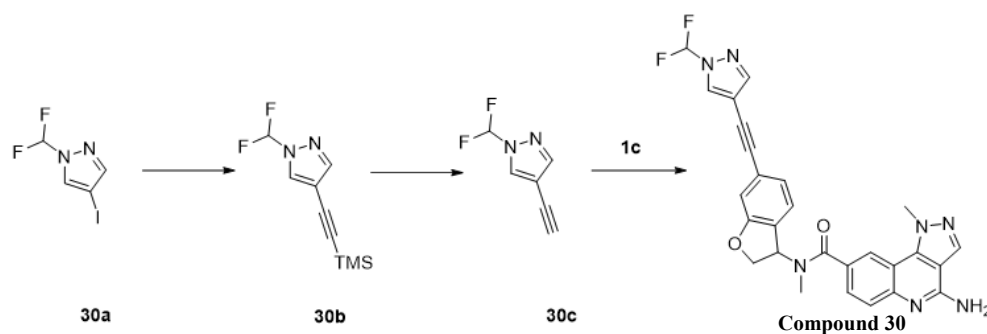
Compound 29A: ESI-MS (*m/z*): 492.16 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 8.28 (s, 1H), 7.68 – 7.61 (m, 2H), 7.58 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.18 (s, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.64 – 5.80 (m, 1H), 4.80 – 4.69

(m, 2H), 4.44 (s, 3H), 3.77 (s, 3H), 2.70 (s, 3H), 2.37 (s, 3H).

Example

30:

4-amino-*N*-(6-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 30)



Preparation of compound 30b

To a solution of compound **30a** (300 mg, 1.23 mmol) in *N*-methylpyrrolidone (5 mL) were added cuprous iodide (36 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (288 mg, 0.25 mmol), *N,N*-diisopropylethylamine (476 mg, 3.69 mmol), and trimethylsilylacetylene (242 mg, 2.46 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 80 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (50 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (methanol/dichloromethane = 1:20) to give compound **30b** (178 mg). ESI-MS (*m/z*): 215.1 [*M*+*H*]⁺.

Preparation of compound 30c

Tetrabutylammonium fluoride (434 mg, 1.66 mmol) was added to a solution of compound **30b** (178 mg, 0.83 mmol) in tetrahydrofuran (5 mL), and the mixture was allowed to react at 25 °C for 0.5 h. Water (30 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (30 mL $\times$ 3). The organic

phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (methanol/dichloromethane = 1:15) to give compound **30c** (89 mg). ESI-MS (m/z): 143.1 $[M+H]^+$.

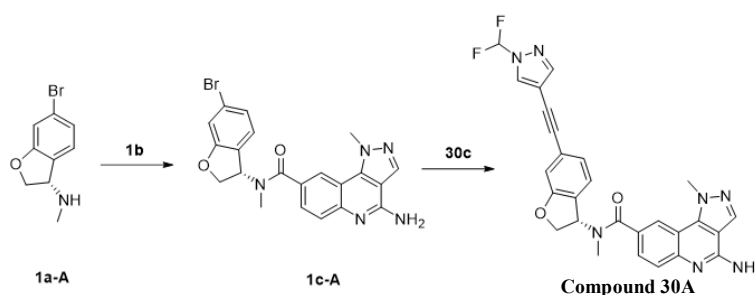
Preparation of compound 30

To a solution of **1c** (45 mg, 0.1 mmol) in *N*-methylpyrrolidone (2 mL) were added cuprous iodide (4 mg, 0.02 mmol), tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol), *N,N*-diisopropylethylamine (39 mg, 0.3 mmol), and **30c** (29 mg, 0.2 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 80 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (20 mL) was added, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 50%:50%) to give compound **30** (15 mg). ESI-MS (m/z): 513.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.67 (s, 1H), 8.34 (s, 1H), 8.28 (s, 1H), 8.08 (s, 1H), 7.86 (t, J = 58.8 Hz, 1H), 7.65 (s, 2H), 7.53 – 7.42 (m, 1H), 7.17 (s, 3H), 7.04 (s, 1H), 6.57 – 5.50 (m, 1H), 4.83 – 4.69 (m, 2H), 4.44 (s, 3H), 2.71 (s, 3H).

Example

30A:

(*S*)-4-amino-*N*-(6-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 30A)



For the preparation process of compound **1c-A**, reference was made to the preparation

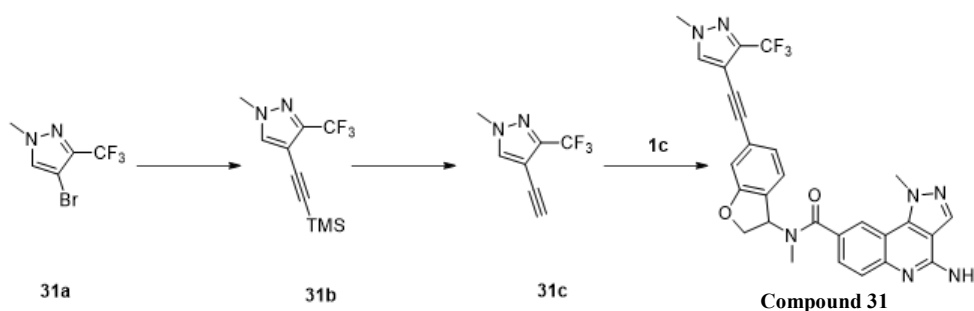
process of compound **1c**. For the synthesis process of preparing compound **30A** from compound **1c-A**, reference was made to the synthesis process of preparing compound **30** from compound **1c**.

Compound **30A**: ESI-MS (m/z): 513.98 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.65 (s, 1H), 8.34 – 8.24 (m, 2H), 8.05 (s, 1H), 7.83 (t, $J = 59$ Hz, 1H), 7.66 – 7.59 (m, 2H), 7.51 – 7.41 (m, 1H), 7.14 – 7.12 (m, 3H), 7.02 (s, 1H), 6.63 – 5.60 (m, 1H), 4.84 – 4.61 (m, 2H), 4.42 (s, 3H), 2.68 (s, 3H).

Example

31:

4-amino-*N*,1-dimethyl-*N*-(6-((1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 31)



Preparation of compound 31b

To a solution of compound **31a** (500 mg, 2.19 mmol) in *N*-methylpyrrolidone (10 mL) were added cuprous iodide (63 mg, 0.33 mmol), tetrakis(triphenylphosphine)palladium (508 mg, 0.44 mmol), *N,N*-diisopropylethylamine (848 mg, 6.57 mmol), and trimethylsilylacetylene (430 mg, 4.38 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 80 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (50 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (methanol/dichloromethane = 1:20) to give compound **31b** (350 mg). ESI-MS (m/z): 247.1 $[M+H]^+$.

Preparation of compound 31c

Tetrabutylammonium fluoride (741 mg, 2.84 mmol) was added to a solution of compound **31b** (350 mg, 1.42 mmol) in tetrahydrofuran (10 mL), and the mixture was allowed to react at 25 °C for 0.5 h. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (50 mL × 3). The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (methanol/dichloromethane = 1:15) to give compound **31c** (165 mg). ESI-MS (m/z): 175.1 $[M+H]^+$.

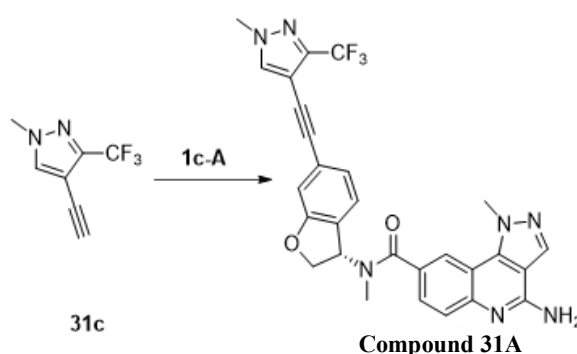
Preparation of compound 31

Referring to the preparation process of compound **30**, compound **30c** was replaced with compound **31c** (35 mg, 0.2 mmol) to give compound **31** (15 mg). ESI-MS (m/z): 546.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.33 (s, 2H), 8.28 (s, 1H), 7.64 (s, 2H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.16 (s, 2H), 7.11 (d, $J = 7.6$ Hz, 1H), 6.98 (s, 1H), 6.47 – 5.70 (m, 1H), 4.82 – 4.68 (m, 2H), 4.43 (s, 3H), 3.96 (s, 3H), 2.70 (s, 3H).

Example

31A:

(S)-4-amino-N,1-dimethyl-N-(6-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 31A)



For the synthesis process of preparing compound **31A** from compound 31c and compound **1c-A**, reference was made to the synthesis process of preparing compound **31** from compound **1c**.

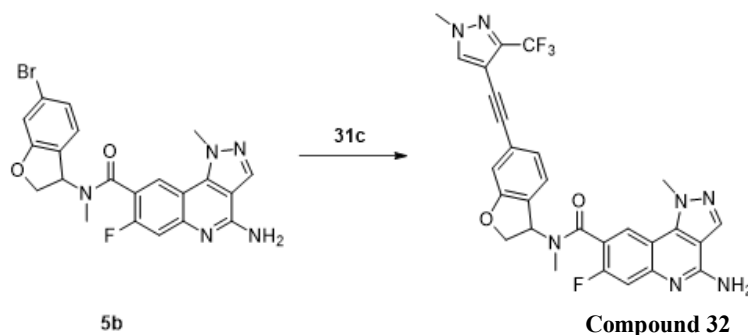
Compound **31A**: ESI-MS (m/z): 546.17 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.31

(s, 2H), 8.26 (s, 1H), 7.67 – 7.60 (m, 2H), 7.50 – 7.43 (m, 1H), 7.14 (s, 2H), 7.11 – 7.06 (m, 1H), 6.97 (s, 1H), 6.44 – 5.74 (m, 1H), 4.82 – 4.70 (m, 2H), 4.42 (s, 3H), 3.94 (s, 3H), 2.68 (s, 3H).

Example

32:

4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 32)

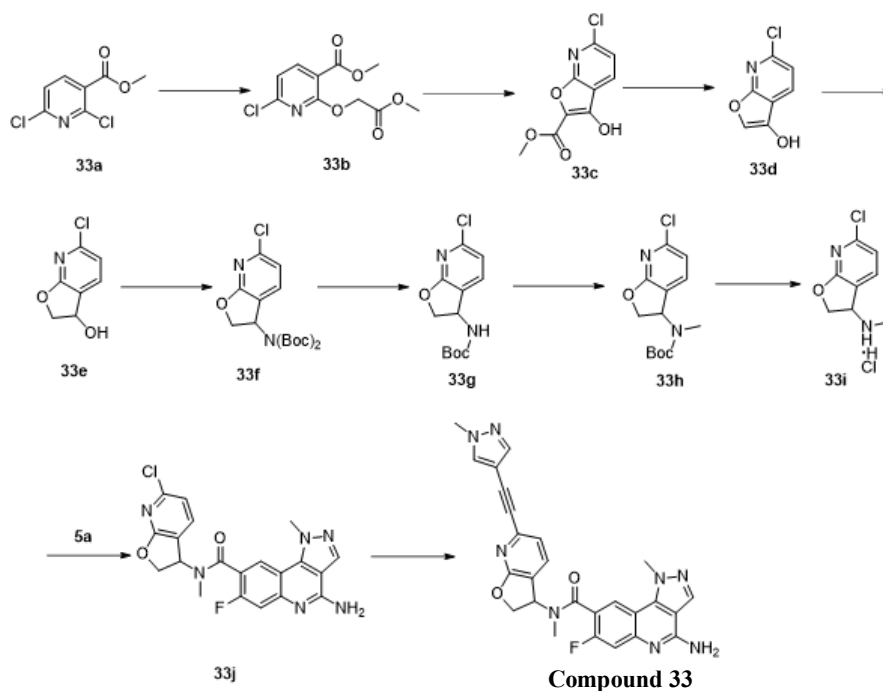


Referring to the preparation process of compound **5**, compound 4-ethynyl-1-methylpyrazole was replaced with compound **31c** (35 mg, 0.2 mmol), and the mixture was reacted in a microwave reactor at 80 °C for 3 h under nitrogen atmosphere to give compound **32** (15 mg). ESI-MS (*m/z*): 563.6 [*M*+*H*]⁺. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.48 – 8.16 (m, 3H), 7.55 – 7.19 (m, 4H), 7.18 – 6.96 (m, 2H), 6.48 – 5.60 (m, 1H), 4.87 – 4.61 (m, 2H), 4.43 – 4.40 (m, 3H), 3.96 (s, 3H), 2.72 – 2.60 (m, 3H).

Example

33:

4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrofuro[2,3-*b*]pyridin-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 33)



Preparation of compound 33b

Compound methyl glycolate (450 mg, 5.00 mmol) was dissolved in ethylene glycol dimethyl ether (10 mL). The mixture was cooled to 0 °C, and sodium hydride (210 mg, 5.25 mmol, 60% purity) was added. After the reaction solution was reacted at 0 °C for 30 min, compound **33a** (1.03 g, 5.00 mmol) was added. Then the reaction solution was stirred at 25 °C for 2 h. Water (5 mL) was added to the reaction solution to quench the reaction, and the reaction solution was extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined and concentrated to give a crude product **33b** (1.15 g). MS (m/z): 259.95 [$M+H$]⁺.

Preparation of compound 33c

Compound **33b** (416 mg, 1.60 mmol) was dissolved in tetrahydrofuran (20 mL), and potassium tert-butoxide (215 mg, 1.92 mmol) was added. After the reaction solution was reacted at 25 °C for 1 h, water (20 mL) was added to the reaction solution to quench the reaction, and the reaction solution was extracted with ethyl acetate (5 mL $\times$ 3). The organic phases were combined and concentrated to give a crude product.

The crude product was then subjected to column chromatography (petroleum ether:ethyl acetate = 2:1) to give **33c** (240 mg). ESI-MS (m/z): 228.08 $[M+H]^+$.

Preparation of compound 33d

Compound **33c** (228 mg, 1.00 mmol) was dissolved in methanol (20 mL), and a 6 M hydrochloric acid solution (5 mL) was added. The reaction solution was heated to 100 °C and stirred for 16 h, then diluted with ethyl acetate (50 mL) and water (50 mL), and extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined and concentrated to give a crude product. The crude product was subjected to column chromatography (petroleum ether:ethyl acetate = 5:1) to give **33d** (140 mg). ESI-MS (m/z): 170.01 $[M+H]^+$.

Preparation of compound 33e

Compound **33d** (138 mg, 0.81 mmol) was dissolved in methanol (5 mL), and sodium borohydride (46 mg, 1.22 mmol) was added. The reaction solution was stirred at 25 °C for 1 h, then diluted with ethyl acetate (20 mL) and water (20 mL), and extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined and concentrated to give a crude product. The crude product was subjected to column chromatography (petroleum ether:ethyl acetate = 2:1) to give **33e** (98 mg). ESI-MS (m/z): 172.04 $[M+H]^+$.

Preparation of compound 33f

To a solution of compound **33e** (700 mg, 4.08 mmol) in tetrahydrofuran (20 mL) were added bis(tert-butoxycarbonyl)amine (1.06 g, 4.90 mmol), triphenylphosphine (1.60 g, 6.12 mmol), and diisopropyl azodicarboxylate (1.24 g, 6.12 mmol), and the mixture was reacted at 25 °C for 2 h under nitrogen atmosphere. The reaction solution was directly concentrated to give a crude product. The crude product was subjected to normal phase column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **33f** (1.10 g). ESI-MS (m/z): 371.15 $[M+H]^+$.

Preparation of compound 33g

Compound **33f** (1.10 g, 2.97 mmol) was dissolved in acetonitrile (20 mL), and lithium bromide (0.80 g, 8.90 mmol, 60% purity) was added. The reaction solution was reacted at 65 °C for 16 h. Water (5 mL) was added to the reaction solution to quench

the reaction, and the reaction solution was extracted with ethyl acetate (5 mL $\times$ 3). The organic phases were combined and concentrated to give a crude product. The crude product was subjected to column chromatography (petroleum ether:ethyl acetate = 3:1) to give **33g** (610 mg). ESI-MS (m/z): 271.05 $[M+H]^+$.

Preparation of compound **33h**

Compound **33g** (271 mg, 1.00 mmol) was dissolved in tetrahydrofuran (5 mL), and the mixture was cooled to 0 °C. Sodium hydride (80.0 mg, 2.00 mmol, 60% purity) was added. After the reaction solution was reacted at 0 °C for 1 h, iodomethane (0.10 mg, 1.20 mmol) was added. Then the reaction solution was stirred at 25 °C for 12 h. Water (5 mL) was added to the reaction solution to quench the reaction, and the reaction solution was extracted with ethyl acetate (5 mL $\times$ 3). The organic phases were combined and concentrated to give a crude product. The crude product was then purified by preparative thin-layer chromatography (petroleum ether:ethyl acetate = 20:1) to give **33h** (110 mg).

Preparation of compound **33i**

Compound **33h** (70 mg, 0.25 mmol) was dissolved in tetrahydrofuran (2 mL), and a 4 M dioxane solution of hydrochloric acid (0.5 mL) was added. The reaction solution was stirred at 25 °C for 1 h and then concentrated to dryness by rotary evaporation to give compound **33i** (40 mg). ESI-MS (m/z): 184.96 $[M+H]^+$.

Preparation of compound **33j**

To a solution of compound **5a** (51.9 mg, 0.20 mmol) in *N,N*-dimethylformamide (3 mL) were added compound **33i** (44.22 mg, 0.20 mmol), triethylamine (80.7 mg, 0.80 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (113.7 mg, 0.30 mmol), and the mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 10:1) to give compound **33j** (40 mg). ESI-MS (m/z): 426.95 $[M+H]^+$.

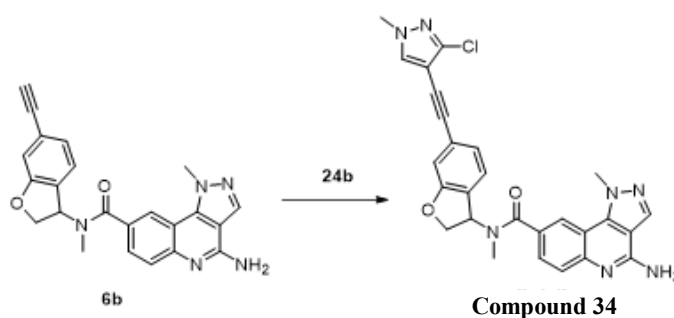
Preparation of compound 33

To a solution of compound **33j** (40 mg, 0.09 mmol) in *N,N*-dimethylformamide (2 mL) were sequentially added 4-ethynyl-1-methylpyrazole (9.9 mg, 0.09 mmol), XPhos Pd G3 95% (15.9 mg, 0.02 mmol), and triethylamine (37.9 mg, 0.37 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was heated to 80 °C in a microwave reactor and reacted for 3 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was subjected to reversed phase column chromatography (acetonitrile/0.05% aqueous ammonia bicarbonate solution = 0:100% - 40%:60%) to give compound **33** (5 mg). ESI-MS (*m/z*): 496.96 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 – 8.23 (m, 2H), 8.16 (s, 1H), 7.93 – 7.81 (m, 1H), 7.76 (s, 1H), 7.40 – 7.17 (m, 4H), 6.46 – 5.60 (m, 1H), 4.97 – 4.59 (m, 2H), 4.46 – 4.40 (m, 3H), 3.89 (s, 3H), 2.77 – 2.65 (m, 3H).

Example

34:

4-amino-*N*-(6-((3-chloro-1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 34)



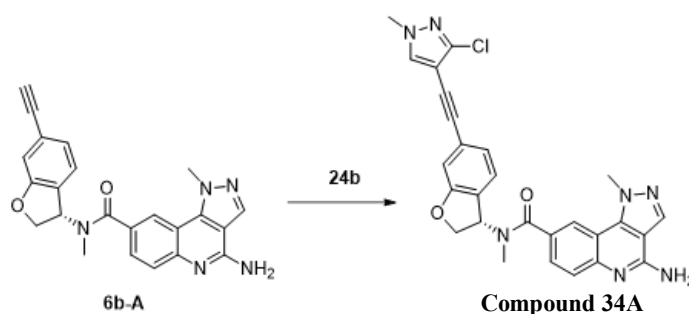
Referring to the preparation process of compound **19**, compound 4-iodo-1-isopropyl-1*H*-pyrazole was replaced with compound 3-chloro-4-iodo-1-methylpyrazole (**24b**, 24.2 mg, 0.10 mmol), and the mixture was

reacted at 25 °C for 3 h to give compound **34** (22 mg). ESI-MS (m/z): 511.92 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.34 (s, 1H), 8.28 (s, 1H), 8.18 (s, 1H), 7.68 – 7.62 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.18 (s, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.57 – 5.70 (m, 1H), 4.83 – 4.70 (m, 2H), 4.44 (s, 3H), 3.85 (s, 3H), 2.70 (s, 3H).

Example

34A:

(S)-4-amino-N-(6-((3-chloro-1-methyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 34A)



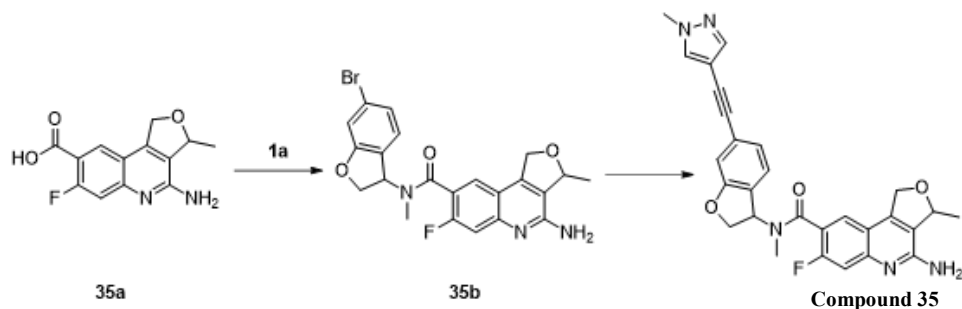
For the synthesis process of preparing compound **34A** from compound **6b-A**, reference was made to the synthesis process of preparing compound **34** from compound **6b**.

Compound 34A: ESI-MS (m/z): 512.02 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.34 (s, 1H), 8.28 (s, 1H), 8.18 (s, 1H), 7.68 – 7.62 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.18 (s, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.57 – 5.70 (m, 1H), 4.83 – 4.70 (m, 2H), 4.44 (s, 3H), 3.85 (s, 3H), 2.70 (s, 3H).

Example

35:

4-amino-7-fluoro-N,3-dimethyl-N-(6-((1-methyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 35)



Preparation of compound 35b

To a solution of compound **35a** (321.9 mg, 1.23 mmol) in *N,N*-dimethylformamide (10 mL) were added compound **1a** (325.33 mg, 1.23 mmol), triethylamine (310.6 mg, 3.07 mmol), and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (701.5 mg, 1.84 mmol), and the mixture was allowed to react at 25 °C overnight. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 10:1) to give compound **35b** (510 mg). ESI-MS (*m/z*): 472.02 [*M*+*H*]⁺.

Preparation of compound 35

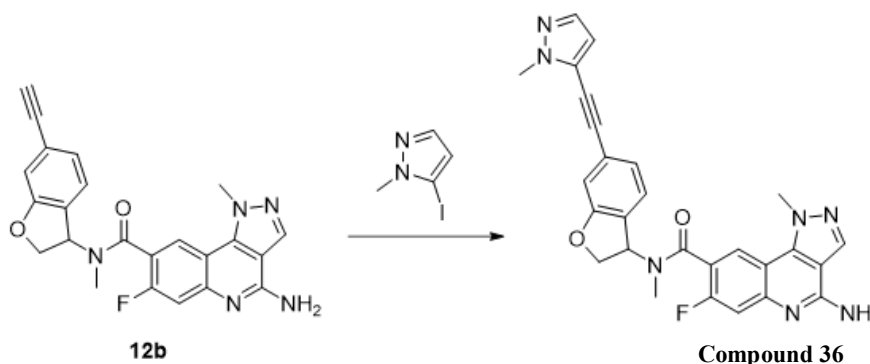
To a solution of compound **35b** (47.2 mg, 0.10 mmol) in *N,N*-dimethylformamide (2 mL) were sequentially added 4-ethynyl-1-methylpyrazole (21.2 mg, 0.20 mmol), cuprous iodide (7.7 mg, 0.04 mmol), triethylamine (40.9 mg, 0.40 mmol), and tetrakis(triphenylphosphine)palladium (23.4 mg, 0.02 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was heated to 100 °C in a microwave reactor and reacted for 3 h. Water (10 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give a crude product. The crude product was then subjected to reversed phase column chromatography (acetonitrile/0.05% aqueous ammonia bicarbonate solution =

0:100% - 40%:60%) to give compound **35** (21 mg). ESI-MS (m/z): 497.95 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.08 – 8.06 (m, 1H), 7.90 – 7.60 (m, 2H), 7.40 – 7.27 (m, 2H), 7.15 – 7.06 (m, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.76 (s, 2H), 6.45 – 6.41 and 5.54 – 5.48 (m, 1H), 5.48 – 5.23 (m, 3H), 4.83 – 4.53 (m, 2H), 3.87 (s, 3H), 2.68 – 2.55 (m, 3H), 1.43 – 1.41 (m, 3H).

Example

36:

4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-5-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 36)

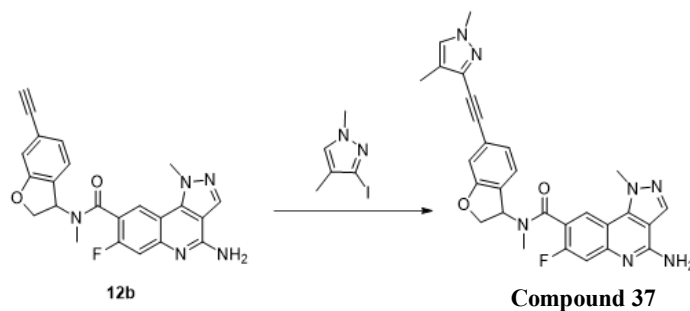


Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 5-iodo-1-methylpyrazole (49.9 mg, 0.24 mmol), and the mixture was reacted at 50 °C for 3 h under nitrogen atmosphere to give compound **36** (18 mg). ESI-MS (m/z): 496.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.44 – 8.18 (m, 2H), 7.51 (s, 1H), 7.48 – 7.08 (m, 6H), 6.61 (s, 1H), 6.51 – 6.40 and 5.69 – 5.54 (m, 1H), 4.87 – 4.61 (m, 2H), 4.41 and 4.39 (s, 3H), 3.93 (s, 3H), 2.70 – 2.59 (m, 3H).

Example

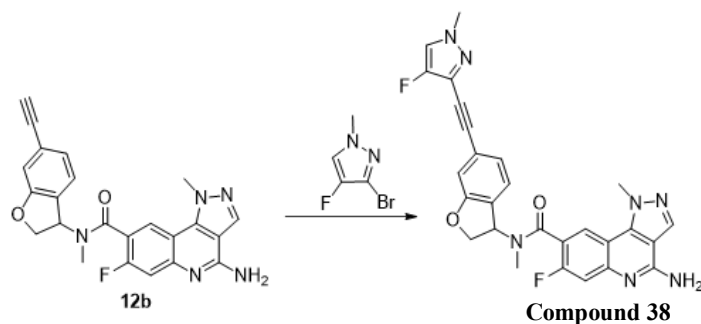
37:

4-amino-*N*-(6-((1,4-dimethyl-1*H*-pyrazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 37)



Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 3-iodo-1,4-dimethylpyrazole (22.2 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **37** (5 mg). ESI-MS (*m/z*): 510.14 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 – 8.23 (m, 2H), 7.58 (s, 1H), 7.49 – 7.30 (m, 4H), 7.22 – 7.11 (m, 1H), 7.09 – 7.00 (m, 1H), 6.50 – 6.44 and 5.62 – 5.57 (m, 1H), 4.88 – 4.60 (m, 2H), 4.43 – 4.41 (m, 3H), 3.81 (s, 3H), 2.72 – 2.61 (m, 3H), 2.09 (s, 3H).

Example 38:
4-amino-7-fluoro-*N*-(6-((4-fluoro-1-methyl-1*H*-pyrazol-3-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 38)



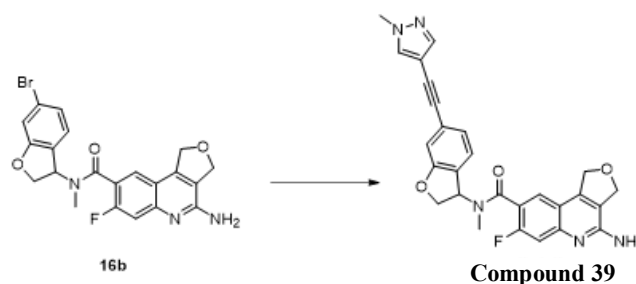
Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 3-bromo-4-fluoro-1-methylpyrazole (17.9 mg, 0.10 mmol), and the mixture was reacted in a microwave reactor at 80 °C for 3 h to give compound **38** (5 mg). ESI-MS (*m/z*): 514.21 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 – 8.22 (m, 2H), 8.00 (d, *J* = 4.8 Hz, 1H), 7.54 – 7.27 (m, 4H), 7.23 – 7.14 (m, 1H), 7.12 – 7.03 (m, 1H),

6.51 – 6.44 and 5.63 – 5.58 (m, 1H), 4.90 – 4.61 (m, 2H), 4.43 – 4.41 (m, 3H), 3.83 (s, 3H), 2.72 – 2.61 (m, 3H).

Example

39:

4-amino-7-fluoro-*N*-methyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 39)

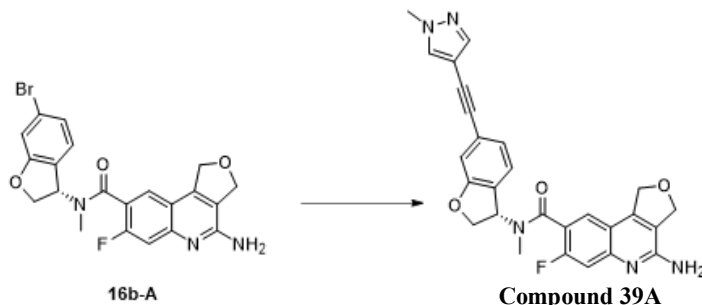


To a solution of **16b** (90 mg, 0.20 mmol) in *N*-methylpyrrolidone (3 mL) were added cuprous iodide (7.6 mg, 0.04 mmol), tetrakis(triphenylphosphine)palladium (23.1 mg, 0.02 mmol), *N,N*-diisopropylethylamine (99.38 μ L, 0.60 mmol), and 4-ethynyl-1-methylpyrazole (63.7 mg, 0.60 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 100 °C for 4 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by a preparative plate (dichloromethane/methanol = 10:1) to give a crude compound. The crude compound was then subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 45%:55%) to give compound **39** (22 mg). ESI-MS (m/z): 483.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.08 – 8.05 (m, 1H), 7.75 – 7.60 (m, 2H), 7.39 – 7.27 (m, 2H), 7.14 – 7.04 (m, 1H), 6.96 (d, J = 17.2 Hz, 1H), 6.82 (s, 2H), 6.45 – 6.36 and 5.54 – 5.44 (m, 1H), 5.37 – 5.31 (m, 2H), 5.00 (s, 2H), 4.83 – 4.51 (m, 2H), 3.85 (s, 3H), 2.66 – 2.53 (m, 3H).

Example

39A:

(S)-4-amino-7-fluoro-N-methyl-N-(6-((1-methyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide
(Compound 39A)



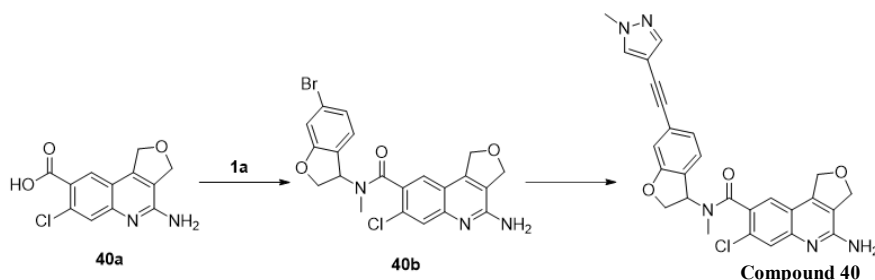
For the synthesis process of preparing compound **39A** from compound **16b-A**, reference was made to the synthesis process of preparing compound **39** from compound **16b**.

Compound **39A**: ESI-MS (m/z): 484.00 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.10 – 8.07 (m, 1H), 7.74 – 7.62 (m, 2H), 7.42 – 7.28 (m, 2H), 7.15 – 7.06 (m, 1H), 7.05 – 6.95 (m, 1H), 6.85 (s, 2H), 6.48 – 6.39 and 5.55 – 5.46 (m, 1H), 5.42 – 5.33 (m, 2H), 5.03 (s, 2H), 4.85 – 4.57 (m, 2H), 3.88 (s, 3H), 2.69 – 2.56 (m, 3H).

Example

40:

4-amino-7-chloro-N-methyl-N-(6-((1-methyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound **40**)



Preparation of compound 40b

To a solution of compound **40a** (150 mg, 0.57 mmol, see WO2022169948 A1 for the preparation method) in *N,N*-dimethylformamide (5 mL) were added compound **1a** (149.9 mg, 0.57 mmol), *N,N*-diisopropylethylamine (366.1 mg, 2.83 mmol), and

O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (323.2 mg, 0.85 mmol), and the mixture was allowed to react at 25 °C for 16 h. After the reaction was completed, the reaction solution was cooled to room temperature. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL × 2). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 20:1) to give compound **40b** (200 mg). ESI-MS (*m/z*): 473.96 [*M*+*H*]⁺.

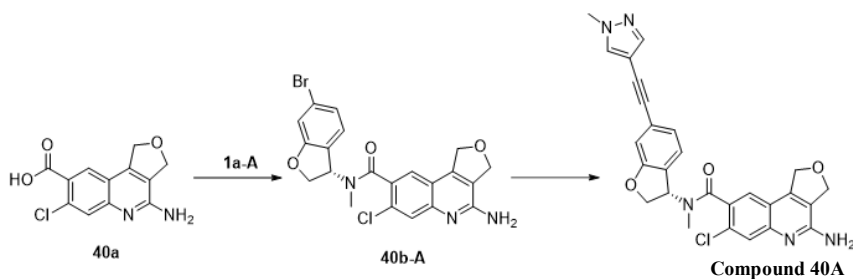
Preparation of compound 40

Referring to the preparation method for compound **39**, compound **16b** was replaced with compound **40b** (100 mg, 0.21 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h under nitrogen atmosphere to give compound **40** (40 mg). ESI-MS (*m/z*): 500.1 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.07 – 8.03 (m, 1H), 7.86 – 7.56 (m, 3H), 7.44 – 7.28 (m, 1H), 7.13 – 7.02 (m, 1H), 7.00 – 6.91 (m, 1H), 6.83 (s, 2H), 6.50 – 5.27 (m, 3H), 5.07 – 4.94 (m, 2H), 4.83 – 4.44 (m, 2H), 3.88 – 3.81 (m, 3H), 2.67 and 2.45 (s, 3H).

Example

40A:

(*S*)-4-amino-7-chloro-*N*-methyl-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide
(Compound **40A**)



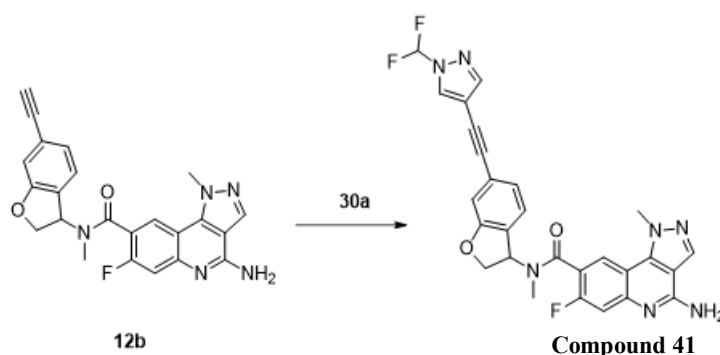
For the synthesis process of preparing compound **40A** from compound **1a-A**, reference was made to the synthesis process of preparing compound **40** from compound **1a**.

Compound **40A**: ESI-MS (m/z): 499.95 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.08 – 8.03 (m, 1H), 7.85 – 7.56 (m, 3H), 7.44 – 7.26 (m, 1H), 7.12 – 7.02 (m, 1H), 7.00 – 6.91 (m, 1H), 6.83 (s, 2H), 6.52 – 5.28 (m, 3H), 5.07 – 4.94 (m, 2H), 4.84 – 4.45 (m, 2H), 3.85 – 3.84 (s, 3H), 2.67 and 2.45 (s, 3H).

Example

41:

4-amino-*N*-(6-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 41)

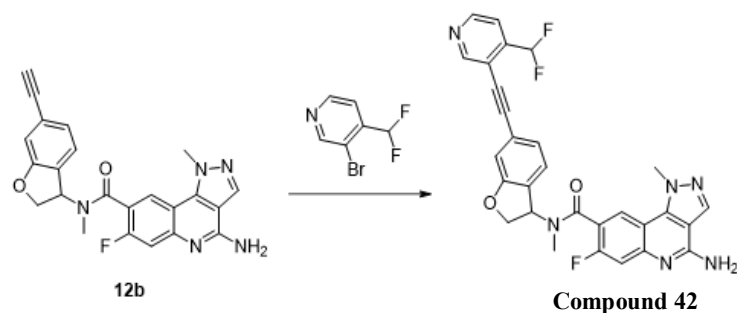


Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound **30a** (24.4 mg, 0.10 mmol), and the mixture was reacted in a microwave reactor at 80 °C for 3 h to give compound **41** (35 mg). ESI-MS (m/z): 531.98 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.66 (s, 1H), 8.40 – 8.22 (m, 2H), 8.07 (s, 1H), 7.86 (t, $J = 58.8$ Hz, 1H), 7.56 – 7.27 (m, 4H), 7.21 – 7.10 (m, 1H), 7.08 – 7.00 (m, 1H), 6.50 – 6.42 and 5.63 – 5.56 (m, 1H), 4.91 – 4.58 (m, 2H), 4.43 – 4.41 (m, 3H), 2.71 – 2.60 (m, 3H).

Example

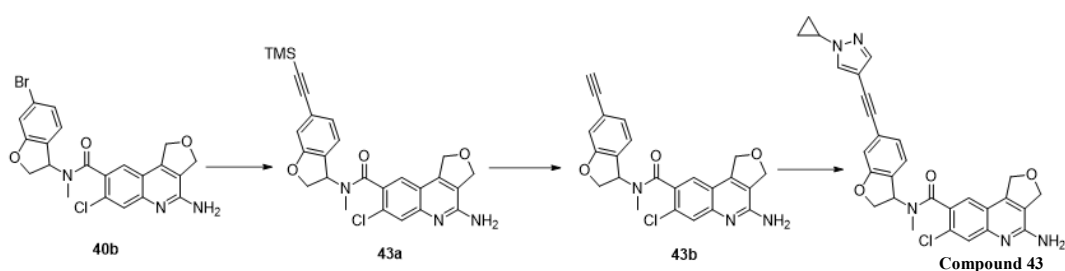
42:

4-amino-*N*-(6-((4-(difluoromethyl)pyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 42)



Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 3-bromo-4-(difluoromethyl)pyridine (50.1 mg, 0.24 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **42** (8 mg). ESI-MS (*m/z*): 543.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.90 (s, 1H), 8.76 (d, J = 5.2 Hz, 1H), 8.41 – 8.21 (m, 2H), 7.69 (d, J = 5.2 Hz, 1H), 7.48 – 7.12 (m, 7H), 6.53 – 6.41 and 5.68 – 5.55 (m, 1H), 4.90 – 4.60 (m, 2H), 4.42 – 4.39 (m, 3H), 2.71 – 2.59 m, 3H).

Example 43:
4-amino-7-chloro-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 43)



Preparation of compound 43a

To a solution of **40b** (298 mg, 0.63 mmol) in *N*-methylpyrrolidone (3 mL) were added cuprous iodide (24.1 mg, 0.13 mmol), tetrakis(triphenylphosphine)palladium (73.0 mg, 0.06 mmol), *N,N*-diisopropylethylamine (314.04 μL , 1.90 mmol), and trimethylsilylacetylene (446.48 μL , 3.16 mmol). After completion of the addition, the mixture was reacted in a microwave reactor at 80 °C for 4 h under nitrogen

atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 10:1) to give compound **43a** (300 mg). ESI-MS (m/z): 492.0 $[M+H]^+$.

Preparation of compound 43b

Tetrabutylammonium fluoride (1.5 mL, 1.52 mmol) was added to a solution of compound **43a** (300 mg, 0.61 mmol) in tetrahydrofuran (3 mL), and the mixture was allowed to react at 25 °C for 1 h. Water (15 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was separated and purified by a preparative plate (dichloromethane/methanol = 10:1) to give a crude product. The crude product was then subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 40%:60%) to give compound **43b** (210 mg). ESI-MS (m/z): 419.94 $[M+H]^+$.

Preparation of compound 43

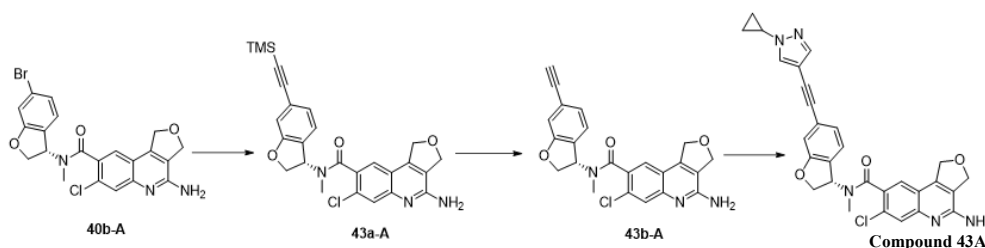
To a solution of compound **43b** (100 mg, 0.24 mmol) in *N*-methylpyrrolidone (2 mL) were added cuprous iodide (9.1 mg, 0.05 mmol), tetrakis(triphenylphosphine)palladium (27.5 mg, 0.02 mmol), triethylamine (99.05 μ L, 0.71 mmol), and 1-cyclopropyl-4-iodopyrazole (112 mg, 0.48 mmol). After completion of the addition, the mixture was allowed to react at 25 °C for 16 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to normal phase column chromatography (dichloromethane/methanol = 20:1) to give a crude compound. The crude compound was then subjected to reversed phase column chromatography (acetonitrile/0.05% ammonium bicarbonate solution = 0:100% - 40%:60%) to give compound **43** (36 mg). ESI-MS (m/z): 526.1 $[M+H]^+$. 1H

NMR (400 MHz, DMSO) δ 8.18 – 8.13 (m, 1H), 7.86 – 7.56 (m, 3H), 7.44 – 7.27 (m, 1H), 7.12 – 7.01 (m, 1H), 6.99 – 6.91 (m, 1H), 6.83 (s, 2H), 6.51 – 5.33 (m, 3H), 5.03 – 4.96 (m, 2H), 4.84 – 4.45 (m, 2H), 3.79 – 3.71 (m, 1H), 2.67 and 2.45 (s, 3H), 1.10 – 0.93 (m, 4H).

Example

43A:

(S)-4-amino-7-chloro-N-(6-((1-cyclopropyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 43A)



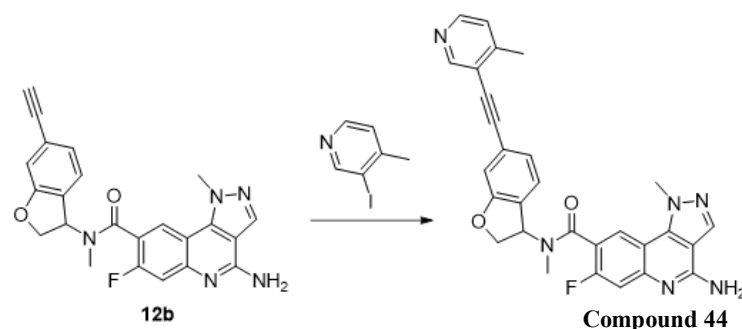
For the synthesis process of preparing compound **43A** from compound **40b-A**, reference was made to the synthesis process of preparing compound **43** from compound **40b**.

Compound **43A**: ESI-MS (m/z): 526.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.16 – 8.13 (m, 1H), 7.84 – 7.58 (m, 3H), 7.42 – 7.29 (m, 1H), 7.10 – 7.01 (m, 1H), 6.99 – 6.91 (m, 1H), 6.83 (s, 2H), 6.49 – 5.32 (m, 3H), 5.01 – 4.98 (m, 2H), 4.84 – 4.45 (m, 2H), 3.79 – 3.71 (m, 1H), 2.67 and 2.45 (s, 3H), 1.09 – 0.96 (m, 4H). 1H NMR (400 MHz, DMSO- d_6 , 90 °C) δ 8.05 (s, 1H), 7.62 – 7.53 (m, 3H), 7.34 (d, J = 2.8 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.90 (s, 1H), 6.53 (s, 2H), 6.44 – 5.32 (m, 3H), 5.01 (s, 2H), 4.77 – 4.58 (m, 2H), 3.75 – 3.70 (m, 1H), 2.68 – 2.49 (m, 3H), 1.06 – 0.94 (m, 4H). $[\alpha]_D^{25}$ 179.6 (c 1 mg/mL, DMF).

Example

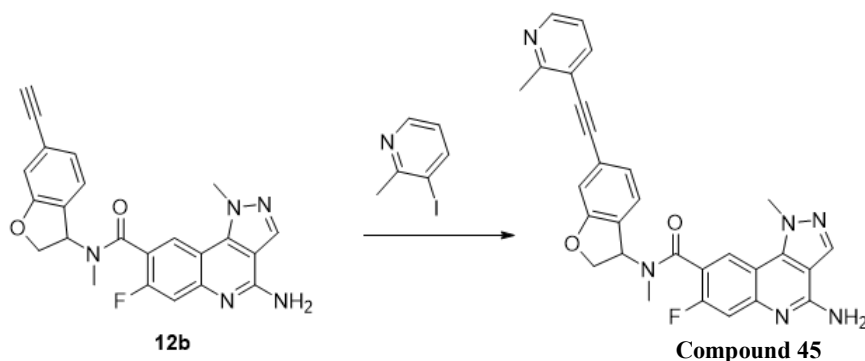
44:

4-amino-7-fluoro-N,1-dimethyl-N-(6-((4-methylpyridin-3-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 44)



Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 3-iodo-4-methylpyridine (22.0 mg, 0.1 mmol), and the mixture was reacted under an oil bath at 40 °C for 3 h to give compound **44** (15 mg). ESI-MS (*m/z*): 506.95 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.66 (s, 1H), 8.49 – 8.41 (m, 1H), 8.36 – 8.24 (m, 2H), 7.56 – 7.32 (m, 5H), 7.29 – 7.09 (m, 2H), 6.52 – 5.56 (m, 1H), 4.92 – 4.65 (m, 2H), 4.48 – 4.33 (m, 3H), 2.77 – 2.56 (m, 3H), 2.48 (s, 3H).

Example **45:**
4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((2-methylpyridin-3-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 45)



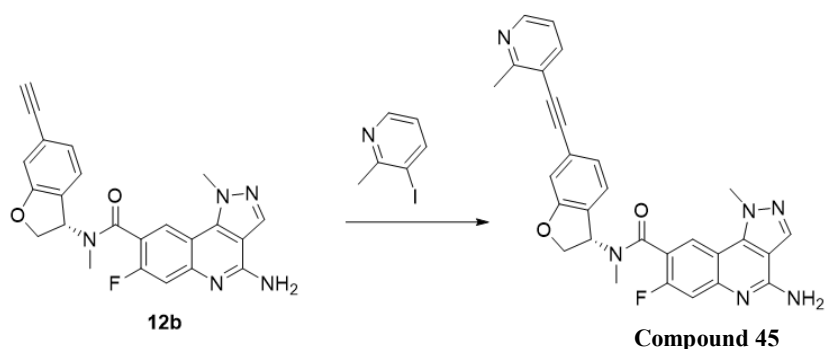
Referring to the preparation process of compound **12**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 3-iodo-2-methylpyridine (43.8 mg, 0.2 mmol), and the mixture was reacted at 40 °C for 3 h to give compound **45** (20 mg). ESI-MS (*m/z*): 507.02 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.51 – 8.42 (m, 1H), 8.35 – 8.22 (m, 2H), 7.96 – 7.85 (m, 1H), 7.54 – 7.05 (m, 7H), 6.53 – 5.55 (m, 1H), 4.91 – 4.62 (m, 2H), 4.48 – 4.34 (m, 3H), 2.74 –

2.62 (m, 6H).

Example

45A:

(S)-4-amino-7-fluoro-N,1-dimethyl-N-(6-((2-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 45A)



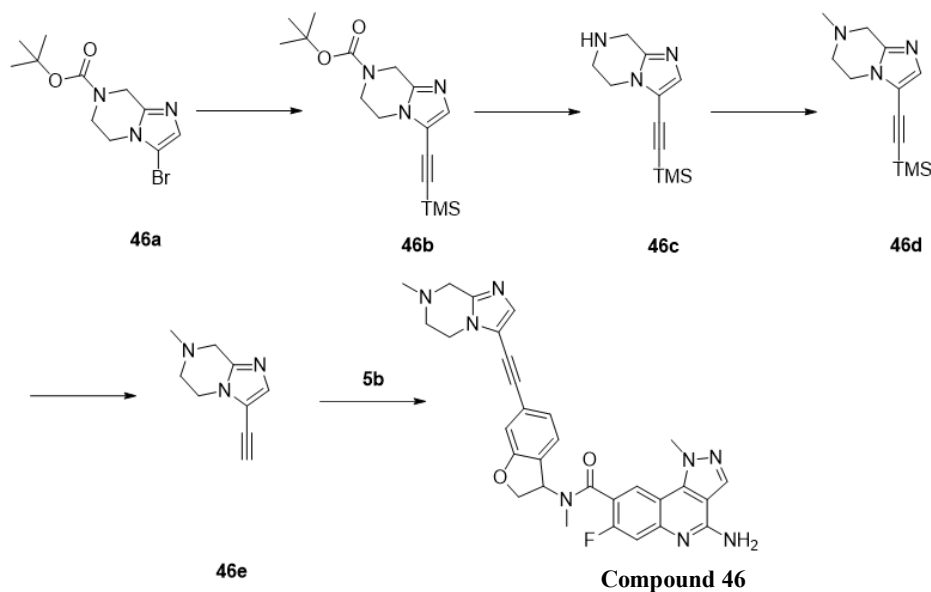
For the synthesis process of preparing compound **45A** from compound **12b-A**, reference was made to the synthesis process of preparing compound **45** from compound **12b**.

Compound 45A: ESI-MS (m/z): 506.99 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.51 – 8.45 (m, 1H), 8.39 – 8.20 (m, 2H), 7.94 – 7.86 (m, 1H), 7.54 – 7.07 (m, 7H), 6.54 – 6.44 and 5.67 – 5.57 (m, 1H), 4.92 – 4.79 and 4.74 – 4.61 (m, 2H), 4.43 (s, 3H), 2.75 – 2.60 (m, 6H).

Example

46:

4-amino-7-fluoro-N,1-dimethyl-N-(6-((7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 46)



Preparation of compound 46b

To a solution of **46a** (3000 mg, 9.93 mmol) in *N,N*-dimethylacetamide (5 mL) were added

methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (565.2 mg, 0.66 mmol), triethylamine (4.13 mL, 29.78 mmol), and trimethylsilyl (4.21 mL, 29.78 mmol). The reaction solution was purged three times with nitrogen and reacted in a microwave reactor at 70 °C for 3 h. The reaction solution was filtered through celite. Water (100 mL) was added, and the reaction solution was extracted with ethyl acetate (100 mL × 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by normal phase column chromatography (dichloromethane/methanol = 20:1) to give compound **46b** (2700 mg). ESI-MS (*m/z*): 320.11 [*M*+*H*]⁺.

Preparation of compound 46c

To a solution of compound **46b** (2700 mg, 8.45 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (6.47 mL, 84.50 mmol). After completion of the addition, the mixture was allowed to react at 25 °C for 16 h. After the reaction was completed, the reaction solution was concentrated to give a crude product **46c** (1800

mg), which was directly used in the next step. ESI-MS (m/z): 220.11 $[M+H]^+$.

Preparation of compound 46d

To a solution of **46c** (1800 mg, 8.20 mmol) in formic acid (5 mL) was added a formaldehyde solution (2400.0 mg, 29.60 mmol). After completion of the addition, the mixture was allowed to react at 100 °C for 1 h. Ammonium bicarbonate was added to quench the reaction. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (50 mL $\times$ 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by normal phase column chromatography (dichloromethane/methanol = 20:1) to give compound **46d** (1000 mg). ESI-MS (m/z): 234.13 $[M+H]^+$.

Preparation of compound 46e

Cesium fluoride (2603.3 mg, 17.14 mmol) was added to a solution of **46d** (1000 mg, 4.28 mmol) in *N,N*-dimethylformamide (5 mL). After completion of the addition, the mixture was reacted at 25 °C for 30 min. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (50 mL $\times$ 2). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was purified by normal phase column chromatography (dichloromethane/methanol = 20:1) to give compound **46e** (450 mg). ESI-MS (m/z): 162.12 $[M+H]^+$.

Preparation of compound 46

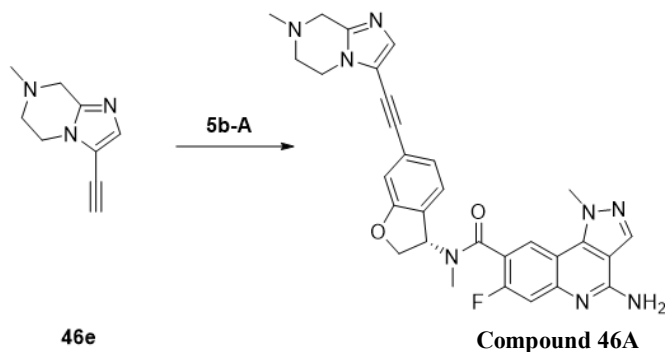
Referring to the preparation process of compound **5**, compound 4-ethynyl-1-methylpyrazole was replaced with compound **46e** (102.8 mg, 0.64 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 3 h to give compound **46** (7.3 mg). ESI-MS (m/z): 550.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.37 – 8.20 (m, 2H), 7.47 – 7.04 (m, 7H), 6.51 – 5.53 (m, 1H), 4.87 – 4.56 (m, 2H), 4.45 – 4.33 (m, 3H), 3.99 (s, 2H), 3.56 (s, 2H), 2.86 – 2.79 (m, 2H), 2.69 – 2.58 m, 3H), 2.39 (s, 3H).

Example

46A:

(S)-4-amino-7-fluoro-N,1-dimethyl-N-(6-((7-methyl-5,6,7,8-tetrahydroimidazo[1,

2-*a*[pyrazin-3-yl]ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 46A)



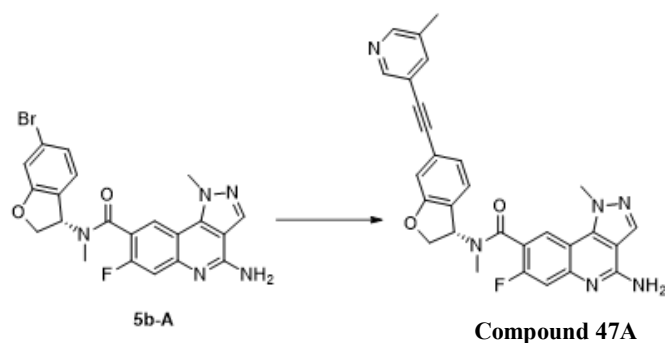
For the synthesis process of preparing compound **46A** from compound 46e and compound **5b-A**, reference was made to the synthesis process of preparing compound **46** from compound 46e and compound **5b**.

Compound **46A**: ESI-MS (*m/z*): 551.0 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.36 – 8.19 (m, 2H), 7.46 – 7.28 (m, 5H), 7.19 – 6.99 (m, 2H), 6.49 – 5.54 (m, 1H), 4.85 – 4.61 (m, 2H), 4.45 – 4.37 (m, 3H), 4.02 – 3.97 (m, 2H), 3.54 (s, 2H), 2.86 – 2.81 (m, 2H), 2.70 and 2.58 (s, 3H), 2.40 (s, 3H).

Example

47A:

(*S*)-4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((5-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 47A)



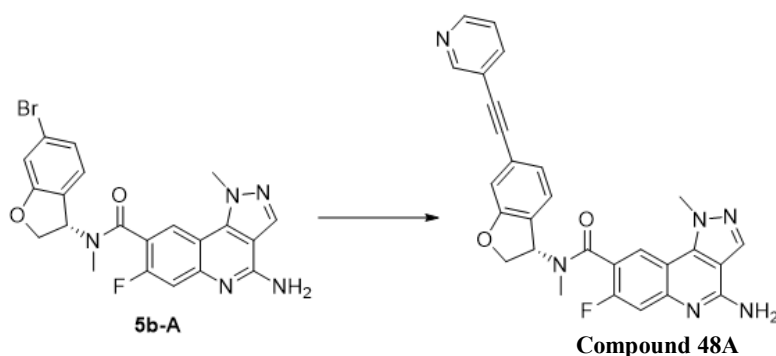
Referring to the preparation process of compound **5A**, compound

4-ethynyl-1-methylpyrazole was replaced with compound 3-ethynyl-5-methylpyridine (23.4 mg, 0.2 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **47A** (25 mg). ESI-MS (m/z): 507.27 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.73 – 8.23 (m, 4H), 7.83 (s, 1H), 7.60 – 7.03 (m, 6H), 6.54 – 5.57 (m, 1H), 4.91 – 4.60 (m, 2H), 4.51 – 4.35 (m, 3H), 2.77 – 2.58 (m, 3H), 2.34 (s, 3H).

Example

48A:

(*S*)-4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-(pyridin-3-ylethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 48A)

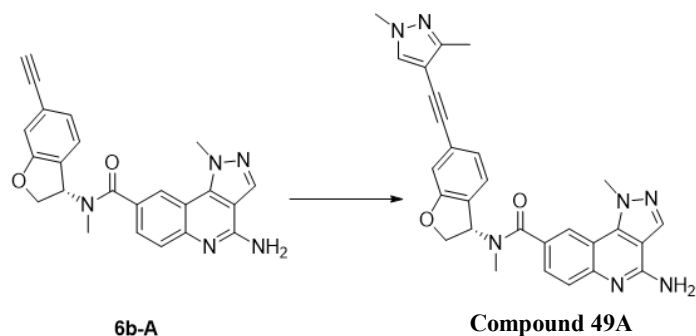


Referring to the preparation process of compound **5A**, compound 4-ethynyl-1-methylpyrazole was replaced with compound 3-ethynylpyridine (52.6 mg, 0.51 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **48A** (40 mg). ESI-MS (m/z): 493.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.75 (s, 1H), 8.60 – 8.59 (m, 1H), 8.39 – 8.22 (m, 2H), 8.00 – 7.94 (m, 1H), 7.52 – 7.16 (m, 6H), 7.15 – 7.05 (m, 1H), 6.54 – 5.53 (m, 1H), 4.88 – 4.61 (m, 2H), 4.41 – 4.39 (m, 3H), 2.70 – 2.59 (m, 3H).

Example

49A:

(*S*)-4-amino-*N*-(6-((1,3-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 49A)

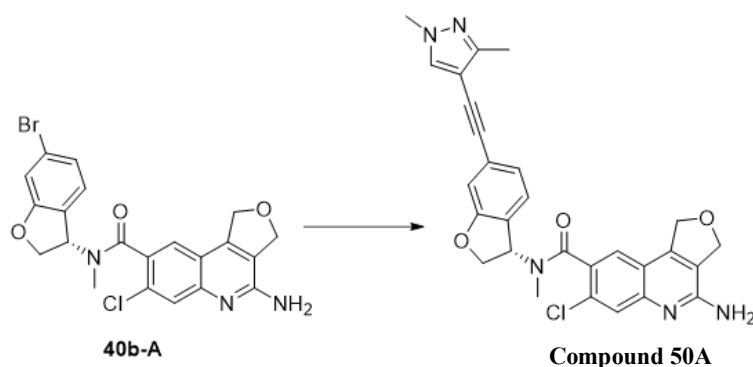


Referring to the preparation process of compound **19**, compound 4-iodo-1-isopropyl-1*H*-pyrazole was replaced with compound 4-iodo-1,3-dimethylpyrazole (22.2 mg, 0.1 mmol), and compound **6b** was replaced with compound **6b-A** (39.7 mg, 0.12 mmol). The mixture was reacted at 25 °C for 3 h to give compound **49A** (23 mg). ESI-MS (*m/z*): 492.19 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 – 8.33 (m, 1H), 8.28 (s, 1H), 7.95 (s, 1H), 7.67 – 7.62 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.19 (s, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 6.40 – 5.56 (m, 1H), 4.88 – 4.60 (m, 2H), 4.44 (s, 3H), 3.78 (s, 3H), 2.70 (s, 3H), 2.24 (s, 3H).

Example

50A:

(*S*)-4-amino-7-chloro-*N*-(6-((1,3-dimethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 50A)



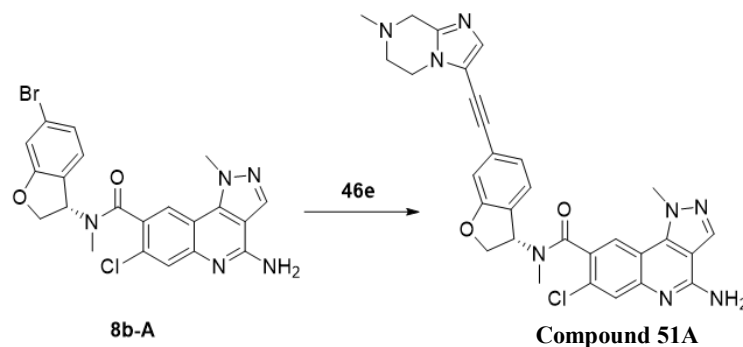
Referring to the preparation process of compound **40A**, compound 4-ethynyl-1-methylpyrazole was replaced with compound 4-ethynyl-1,3-dimethylpyrazole (75.7 mg, 0.63 mmol), and the mixture was reacted in

a microwave reactor at 100 °C for 3 h under nitrogen atmosphere to give compound **50A** (50 mg). ESI-MS (m/z): 513.96 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 7.95 – 7.88 (m, 1H), 7.86 – 7.55 (m, 2H), 7.44 – 7.26 (m, 1H), 7.13 – 7.02 (m, 1H), 7.01 – 6.91 (m, 1H), 6.83 (s, 2H), 6.52 – 5.28 (m, 3H), 5.06 – 4.92 (m, 2H), 4.84 – 4.44 (m, 2H), 3.76 – 3.75 (m, 3H), 2.67 and 2.45 (s, 3H), 2.22 – 2.21 (s, 3H).

Example

51A:

(S)-4-amino-7-chloro-N,1-dimethyl-N-(6-((7-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 51A)

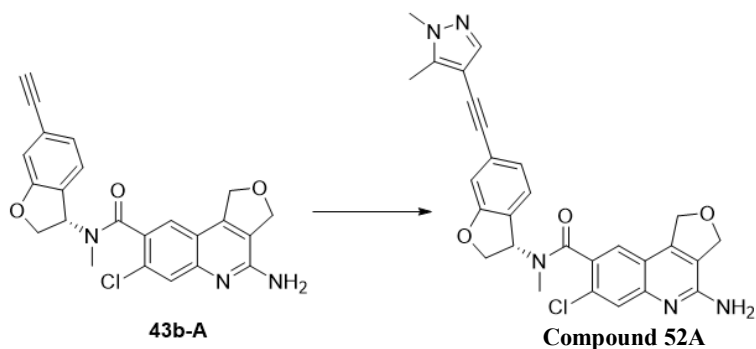


Referring to the preparation process of compound **46A**, compound **5b-A** was replaced with compound **8b-A** (100 mg, 0.21 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 3 h under nitrogen atmosphere to give compound **51A** (41 mg). ESI-MS (m/z): 566.97 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.43 – 8.19 (m, 2H), 7.72 – 7.62 (m, 1H), 7.58 – 7.29 (m, 4H), 7.22 – 7.01 (m, 2H), 6.60 – 5.40 (m, 1H), 4.90 – 4.56 (m, 2H), 4.46 – 4.41 (m, 3H), 4.05 – 3.97 (m, 2H), 3.58 – 3.57 (m, 2H), 2.88 – 2.81 (m, 2H), 2.73 – 2.51 (m, 3H), 2.42 – 2.41 (m, 3H).

Example

52A:

(S)-4-amino-7-chloro-N-(6-((1,5-dimethyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 52A)

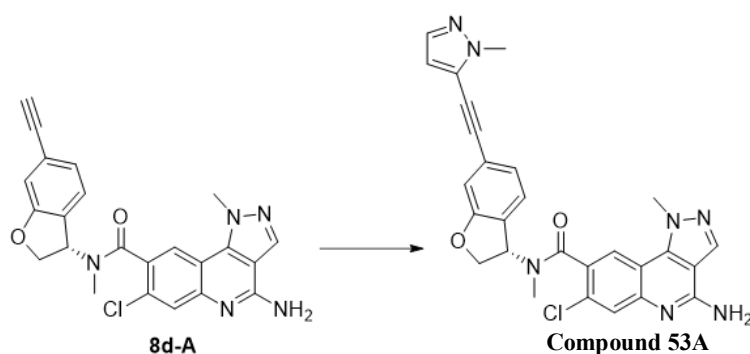


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 4-iodo-1,5-dimethylpyrazole (66.2 mg, 0.30 mmol), and the mixture was reacted at room temperature for 16 h under nitrogen atmosphere to give compound **52A** (51 mg). ESI-MS (m/z): 513.96 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 7.85 – 7.55 (m, 3H), 7.45 – 7.25 (m, 1H), 7.14 – 7.03 (m, 1H), 7.02 – 6.93 (m, 1H), 6.83 (s, 2H), 6.50 – 5.27 (m, 3H), 5.08 – 4.95 (m, 2H), 4.88 – 4.40 (m, 2H), 3.75 (s, 3H), 2.67 and 2.45 (s, 2H), 2.35 – 2.34 (s, 3H).

Example

53A:

(*S*)-4-amino-7-chloro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-pyrazol-5-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 53A)



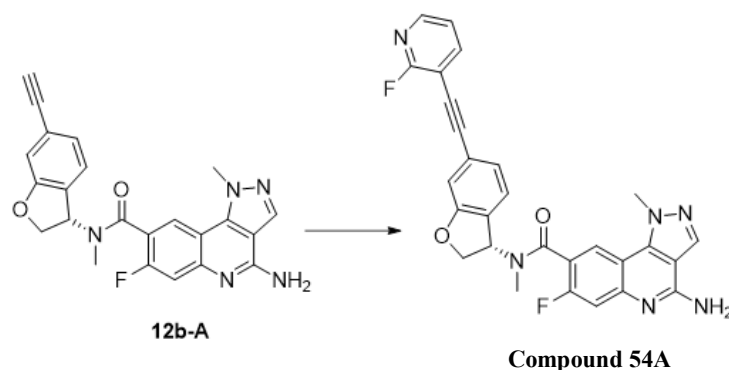
Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 5-iodo-1-methylpyrazole (105.7 mg, 0.51 mmol), and the mixture was reacted at room temperature for 16 h under nitrogen atmosphere to give compound **53A** (55 mg). ESI-MS (m/z): 511.99

$[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.44 – 8.17 (m, 2H), 7.70 – 7.59 (m, 1H), 7.58 – 7.33 (m, 2H), 7.27 – 7.08 (m, 4H), 6.65 – 6.58 (m, 1H), 6.55 – 5.41 (m, 1H), 4.88 – 4.55 (m, 2H), 4.45 – 4.39 (s, 3H), 3.94 – 3.92 (m, 3H), 2.72 – 2.47 (m, 3H).

Example

54A:

(*S*)-4-amino-7-fluoro-*N*-(6-((2-fluoropyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 54A)

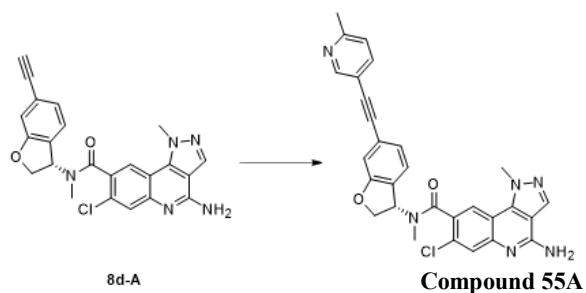


Referring to the preparation process of compound **12A**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 2-fluoro-3-iodopyridine (22.3 mg, 0.1 mmol), and the mixture was reacted at 40 °C for 3 h to give compound **54A** (15 mg). ESI-MS (m/z): 511.07 $[M+H]^+$. ^1H NMR (400 MHz, DMSO) δ 8.44 – 8.17 (m, 4H), 7.57 – 7.43 (m, 2H), 7.43 – 7.19 (m, 4H), 7.18 – 7.07 (m, 1H), 6.56 – 5.57 (m, 1H), 4.92 – 4.63 (m, 2H), 4.49 – 4.33 (m, 3H), 2.78 – 2.57 (m, 3H).

Example

55A:

(*S*)-4-amino-7-chloro-*N*,1-dimethyl-*N*-(6-((6-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 55A)

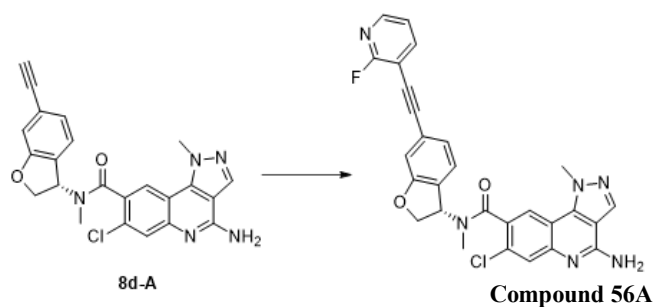


Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 5-iodo-2-methylpyridine (21.9 mg, 0.10 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **55A** (15 mg). ESI-MS (m/z): 522.91 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.69 – 8.59 (m, 1H), 8.44 – 8.20 (m, 2H), 7.90 – 7.84 (m, 1H), 7.72 – 7.63 (m, 1H), 7.59 – 7.05 (m, 6H), 6.57 – 5.44 (m, 1H), 4.91 – 4.57 (m, 2H), 4.48 – 4.42 (s, 3H), 3.34 (s, 3H), 2.76 – 2.54 (m, 3H).

Example

56A:

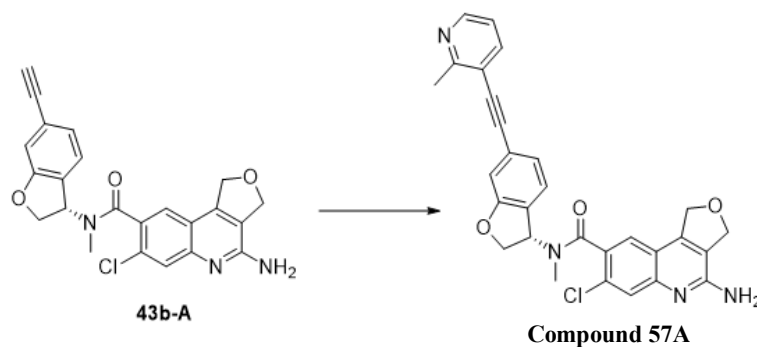
(S)-4-amino-7-chloro-N-(6-((2-fluoropyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 56A)



Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 2-fluoro-3-iodopyridine (44.6 mg, 0.20 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **56A** (10 mg). ESI-MS (m/z): 526.73 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.45 – 8.17 (m, 4H), 7.72 – 7.64 (m, 1H), 7.62 – 7.35 (m, 2H), 7.34 – 7.07 (m, 1H), 6.57 – 5.45 (m, 1H), 4.94 – 4.57 (m, 2H), 4.47 – 4.41 (s, 3H), 2.76 – 2.53 (m, 3H).

Example**57A:**

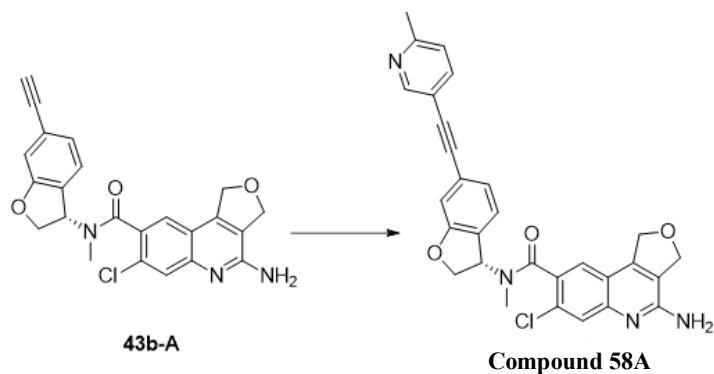
(S)-4-amino-7-chloro-N-methyl-N-(6-((2-methylpyridin-3-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 57A)



Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-iodo-2-methylpyridine (31.3 mg, 0.14 mmol), and the mixture was reacted at room temperature for 3 h under nitrogen atmosphere to give compound **57A** (13 mg). ESI-MS (m/z): 510.92 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.50 – 8.46 (m, 1H), 7.93 – 7.87 (m, 1H), 7.70 – 7.57 (m, 2H), 7.52 – 7.17 (m, 3H), 7.17 – 7.07 (m, 1H), 6.86 (s, 2H), 6.55 – 5.32 (m, 3H), 5.05 – 4.98 (m, 2H), 4.89 – 4.49 (m, 2H), 2.71 – 2.68 (m, 3H), 2.66 – 2.67 (m, 3H).

Example**58A:**

(S)-4-amino-7-chloro-N-methyl-N-(6-((6-methylpyridin-3-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 58A)

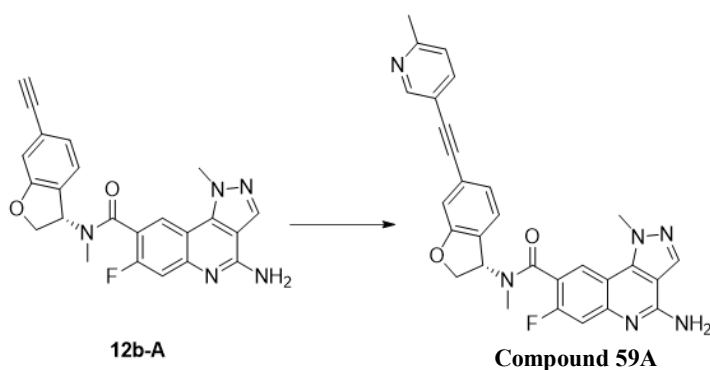


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 5-iodo-2-methylpyridine (30.7 mg, 0.14 mmol), and the mixture was reacted at room temperature for 3 h under nitrogen atmosphere to give compound **58A** (15 mg). ESI-MS (m/z): 510.93 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.66 – 8.61 (m, 1H), 7.89 – 7.58 (m, 3H), 7.52 – 7.32 (m, 2H), 7.25 – 7.15 (m, 1H), 7.13 – 7.06 (m, 1H), 6.86 (s, 2H), 6.53 – 5.30 (m, 3H), 5.05 – 4.98 (m, 2H), 4.89 – 4.48 (m, 2H), 2.72 – 2.47 (m, 6H).

Example

59A:

(S)-4-amino-7-fluoro-N,1-dimethyl-N-(6-((6-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 59A)



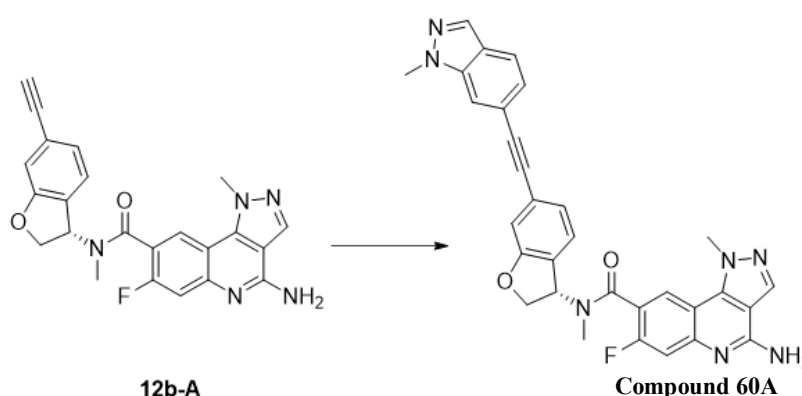
Referring to the preparation process of compound **12A**, compound 1-cyclopropyl-4-iodo-1H-pyrazole was replaced with compound 5-iodo-2-methylpyridine (36.9 mg, 0.17 mmol), and the mixture was reacted at 25 °C

for 3 h to give compound **59A** (15 mg). ESI-MS (m/z): 507.21 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.64 (s, 1H), 8.29 – 8.24 (m, 2H), 7.89 – 7.84 (m, 1H), 7.69 – 7.07 (m, 6H), 6.52 – 5.57 (m, 1H), 4.92 – 4.64 (m, 2H), 4.43 – 4.41 (s, 3H), 3.33 – 3.24 (m, 3H), 2.72 – 2.61 (m, 3H).

Example

60A:

(*S*)-4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-methyl-1*H*-indazol-6-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 60A)

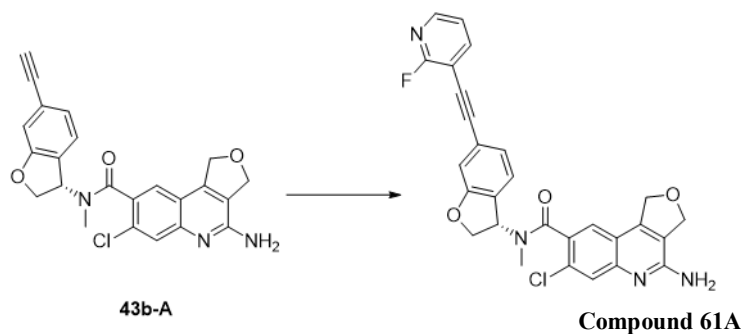


Referring to the preparation process of compound **12A**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound 6-iodo-1-methylindazole (41.3 mg, 0.16 mmol), and the mixture was reacted at 25 °C for 3 h to give compound **60A** (8 mg). ESI-MS (m/z): 546.08 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.39 – 8.24 (m, 2H), 8.12 (s, 1H), 8.02 (s, 1H), 7.75 – 7.70 (m, 1H), 7.58 – 7.52 (m, 1H), 7.47 – 7.31 (m, 4H), 7.26 – 7.14 (m, 1H), 7.13 – 7.05 (m, 1H), 6.52 – 5.56 (m, 1H), 4.92 – 4.60 (m, 2H), 4.44 – 4.41 (m, 3H), 4.08 (s, 3H), 2.73 – 2.61 (m, 3H).

Example

61A:

(*S*)-4-amino-7-chloro-*N*-(6-((2-fluoropyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 61A)

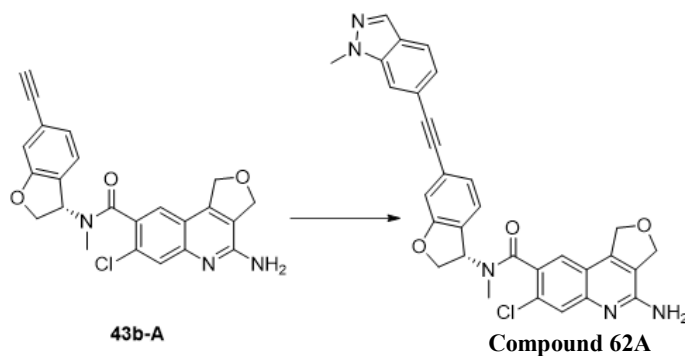


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 2-fluoro-3-iodopyridine (31.2 mg, 0.14 mmol), and the mixture was reacted at room temperature for 3 h to give compound **61A** (20 mg). ESI-MS (m/z): 515.13 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.32 – 8.28 (m, 1H), 8.26 – 8.18 (m, 1H), 7.70 – 7.56 (m, 2H), 7.52 – 7.36 (m, 2H), 7.28 – 7.17 (m, 1H), 7.15 – 7.07 (m, 1H), 6.86 (s, 2H), 6.56 – 5.28 (m, 3H), 5.07 – 4.97 (m, 2H), 4.92 – 4.44 (m, 2H), 2.70 and 2.48 (s, 3H).

Example

62A:

(S)-4-amino-7-chloro-N-methyl-N-(6-((1-methyl-1*H*-indazol-6-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 62A)



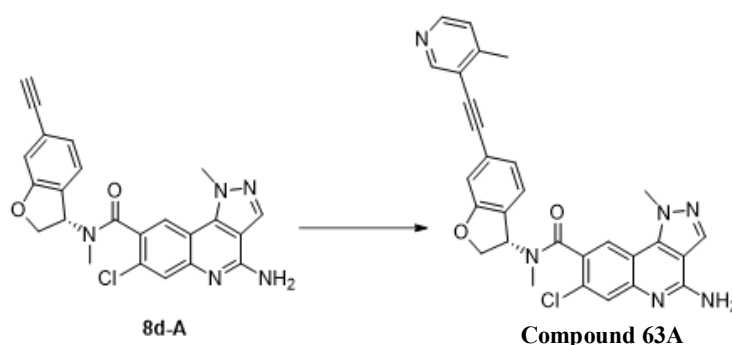
Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 6-iodo-1-methylindazole (36.1 mg, 0.14 mmol), and the mixture was reacted at room temperature for 3 h to give compound **62A** (13 mg). ESI-MS (m/z): 549.92 $[M+H]^+$. 1H NMR (400 MHz,

DMSO-d₆) δ 8.12 – 8.08 (m, 1H), 7.96 – 7.92 (m, 1H), 7.88 – 7.59 (m, 3H), 7.52 – 7.34 (m, 1H), 7.30 – 7.17 (m, 2H), 7.14 – 7.07 (m, 1H), 6.86 (s, 2H), 6.54 – 6.46 and 5.43 – 5.40 (m, 1H), 5.39 – 5.29 (m, 2H), 5.06 – 4.98 (m, 2H), 4.89 – 4.48 (m, 2H), 4.09 – 4.08 (m, 3H), 2.71 and 2.49 (s, 3H).

Example

63A:

(S)-4-amino-7-chloro-N,1-dimethyl-N-(6-((4-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 63A)

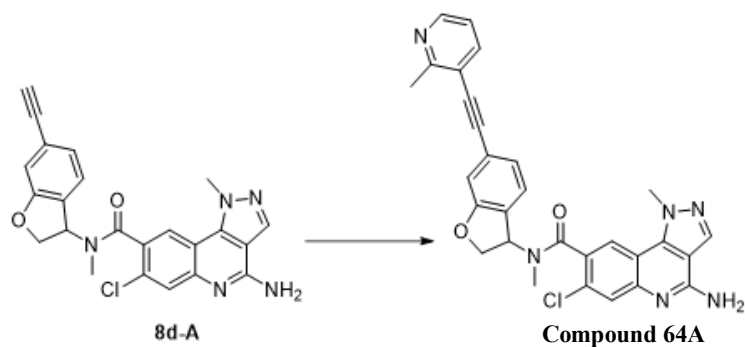


Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-iodo-4-methylpyridine (43.8 mg, 0.2 mmol), and the mixture was reacted at 40 °C for 3 h to give compound **63A** (15 mg). ESI-MS (m/z): 522.89 $[M+H]^+$. ¹H NMR (400 MHz, DMSO) δ 8.69 – 8.64 (m, 1H), 8.48 – 8.21 (m, 3H), 7.71 – 7.63 (m, 1H), 7.41 – 7.24 (m, 6H), 6.59 – 5.42 (m, 1H), 4.89 – 4.62 (m, 2H), 4.47 – 4.40 (m, 3H), 2.77 – 2.47 (m, 6H).

Example

64A:

(S)-4-amino-7-chloro-N,1-dimethyl-N-(6-((2-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 64A)

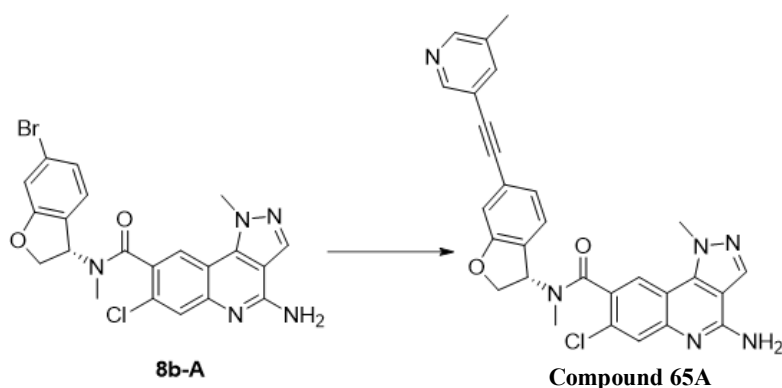


Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-iodo-2-methylpyridine (43.8 mg, 0.2 mmol), and the mixture was reacted at 40 °C for 3 h to give compound **64A** (15 mg). ESI-MS (m/z): 522.92 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.51 – 8.45 (m, 1H), 8.42 – 8.19 (m, 2H), 7.93 – 7.86 (m, 1H), 7.70 – 7.61 (m, 1H), 7.58 – 7.07 (m, 6H), 6.57 – 5.43 (m, 1H), 4.88 – 4.64 (m, 2H), 4.47 – 4.40 (m, 3H), 2.74 – 2.66 (m, 6H).

Example

65A:

(S)-4-amino-7-chloro-N,1-dimethyl-N-(6-((5-methylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 65A)



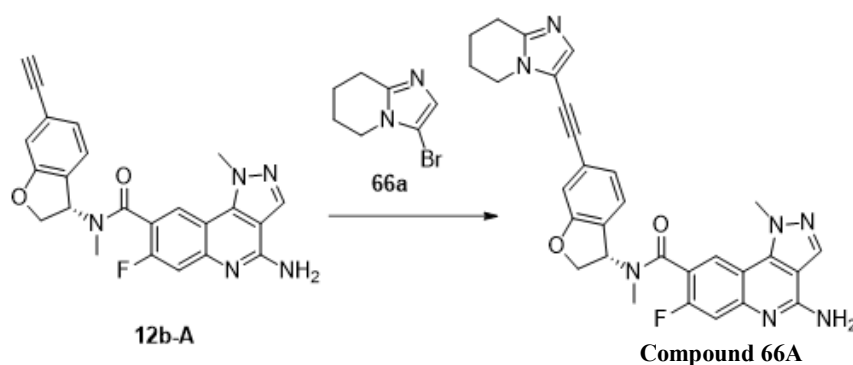
Referring to the preparation process of compound **51A**, compound **46e** was replaced with compound 3-ethynyl-5-methylpyridine (23.4 mg, 0.2 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h under nitrogen atmosphere to give compound **65A** (12 mg). ESI-MS (m/z): 522.96 $[M+H]^+$. 1H NMR (400 MHz,

DMSO) δ 8.59 – 8.55 (m, 1H), 8.48 – 8.21 (m, 3H), 7.84 – 7.81 (m, 1H), 7.71 – 7.64 (m, 1H), 7.60 – 7.08 (m, 5H), 6.58 – 5.42 (m, 1H), 4.88 – 4.54 (m, 2H), 4.47 – 4.41 (m, 3H), 2.75 – 2.33 (m, 6H).

Example

66A:

(*S*)-4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 66A)

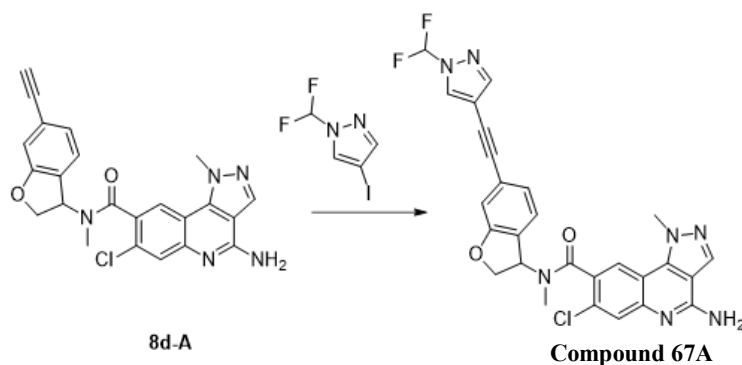


Referring to the preparation process of compound **12A**, compound 1-cyclopropyl-4-iodo-1*H*-pyrazole was replaced with compound **66a** (50.5 mg, 0.20 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 3 h to give compound **66A** (18 mg). ESI-MS (*m/z*): 536.39 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 – 8.22 (m, 2H), 7.47 – 7.26 (m, 5H), 7.22 – 7.13 (m, 1H), 7.10 – 7.03 (m, 1H), 6.51 – 5.56 (m, 1H), 4.90 – 4.67 (m, 2H), 4.43 – 4.41 (s, 3H), 4.01 – 3.95 (m, 2H), 2.82 – 2.75 (m, 2H), 2.72 – 2.60 (m, 3H), 2.01 – 1.94 (m, 2H), 1.91 – 1.83 (m, 2H).

Example

67A:

(*S*)-4-amino-7-chloro-*N*-(6-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 67A)

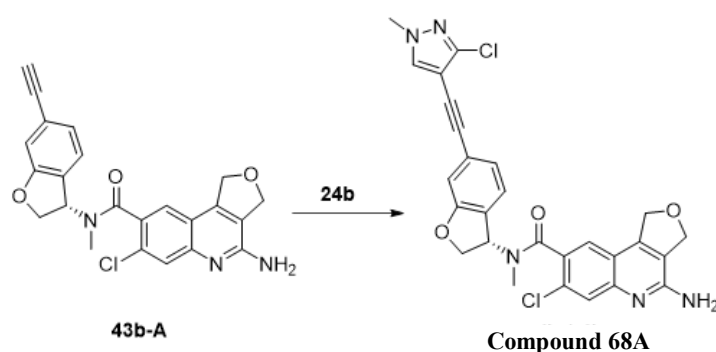


Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 1-(difluoromethyl)-4-iodopyrazole (46.4 mg, 0.19 mmol), and the mixture was reacted at room temperature of 25 °C for 3 h to give compound **67A** (8 mg). ESI-MS (m/z): 547.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.69 – 8.63 (m, 1H), 8.42 – 8.18 (m, 2H), 8.10 – 8.04 (m, 1H), 7.99 – 7.62 (m, 2H), 7.58 – 7.29 (m, 3H), 7.20 – 6.96 (m, 2H), 6.55 – 5.41 (m, 1H), 4.86 – 4.55 (m, 2H), 4.46 – 4.40 (m, 3H), 2.74 – 2.47 (m, 3H).

Example

68A:

(S)-4-amino-7-chloro-N-(6-((3-chloro-1-methyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 68A)



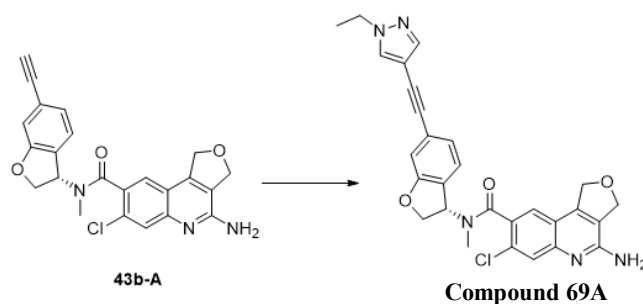
Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound **24b** (38.8 mg, 0.16 mmol), and the mixture was reacted at room temperature for 3 h to give compound **68A** (10 mg). ESI-MS (m/z): 533.89 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.20

– 8.17 (m, 1H), 7.89 – 7.61 (m, 2H), 7.54 – 7.32 (m, 1H), 7.18 – 7.06 (m, 1H), 7.04 – 6.97 (m, 1H), 6.86 (s, 2H), 6.53 – 5.31 (m, 3H), 5.05 – 4.98 (m, 2H), 4.86 – 4.48 (m, 2H), 4.19 – 4.11 (m, 2H), 3.85 – 3.84 (s, 3H), 2.69 and 2.47 (s, 3H).

Example

69A:

(*S*)-4-amino-7-chloro-*N*-(6-((1-ethyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 69A)

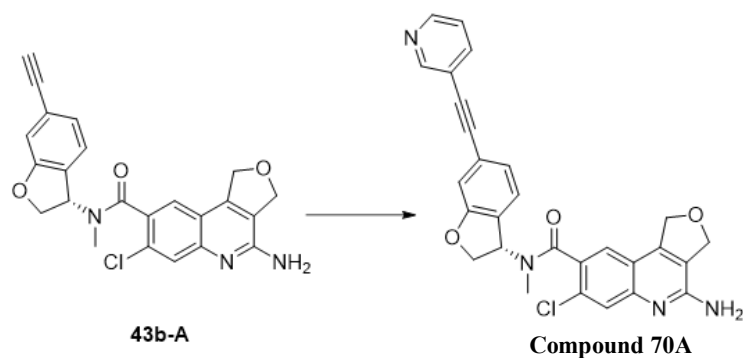


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 1-ethyl-4-iodo-1*H*-pyrazole (52.9 mg, 0.24 mmol), and the mixture was reacted at room temperature for 3 h to give compound **69A** (10 mg). (13 mg) ESI-MS (*m/z*): 514.0 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15 – 8.11 (m, 1H), 7.89 – 7.61 (m, 3H), 7.47 – 7.26 (m, 1H), 7.14 – 7.03 (m, 1H), 7.02 – 6.92 (m, 1H), 6.85 (s, 2H), 6.51 – 5.30 (m, 3H), 5.05 – 4.97 (m, 2H), 4.84 – 4.44 (m, 2H), 4.19 – 4.11 (m, 2H), 2.69 and 2.46 (s, 3H), 1.42 – 1.34 (m, 3H).

Example

70A:

(*S*)-4-amino-7-chloro-*N*-methyl-*N*-(6-(pyridin-3-ylethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 70A)

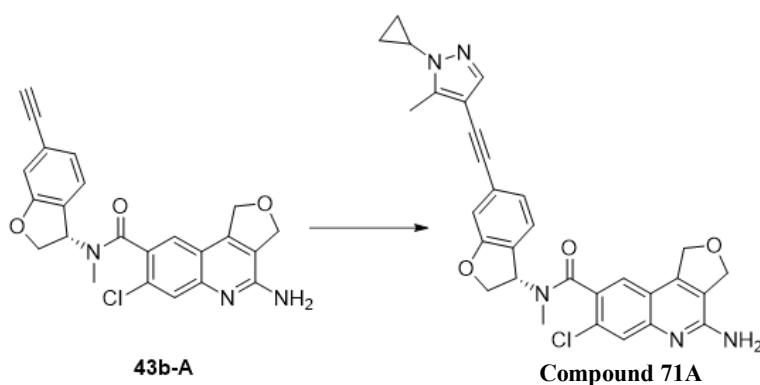


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-iodopyridine (48.8 mg, 0.24 mmol), and the mixture was reacted at room temperature for 3 h to give compound **70A** (24 mg). ESI-MS (m/z): 497.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.79 – 8.74 (m, 1H), 8.63 – 8.58 (m, 1H), 8.02 – 7.96 (m, 1H), 7.90 – 7.57 (m, 2H), 7.54 – 7.34 (m, 2H), 7.28 – 7.07 (m, 2H), 6.86 (s, 2H), 6.54 – 5.33 (m, 3H), 5.08 – 4.97 (m, 2H), 4.89 – 4.48 (m, 2H), 2.70 and 2.48 (s, 3H).

Example

71A:

(S)-4-amino-7-chloro-N-(6-((1-cyclopropyl-5-methyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 71A)



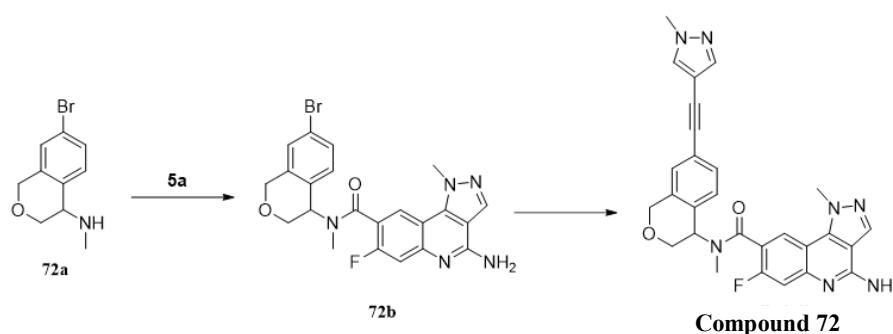
Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 1-cyclopropyl-4-iodo-5-methyl-1H-pyrazole (59.52 mg, 0.24 mmol, see WO2023044171 A1 for the preparation method), and the mixture was reacted at room

temperature for 3 h to give compound **71A** (8 mg). ESI-MS (m/z): 540.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.90 – 7.60 (m, 2H), 7.57 – 7.52 (m, 1H), 7.48 – 7.28 (m, 1H), 7.16 – 7.05 (m, 1H), 7.04 – 6.95 (m, 1H), 6.86 (s, 2H), 6.52 – 5.28 (m, 3H), 5.07 – 4.97 (m, 2H), 4.86 – 4.46 (m, 2H), 3.60 – 3.53 (m, 1H), 2.69 and 2.47 (s, 3H), 2.45 – 2.44(m, 3H), 1.08 – 1.01 (m, 4H).

Example

72:

4-amino-7-fluoro-*N*,1-dimethyl-*N*-(7-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)isochroman-4-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 72)

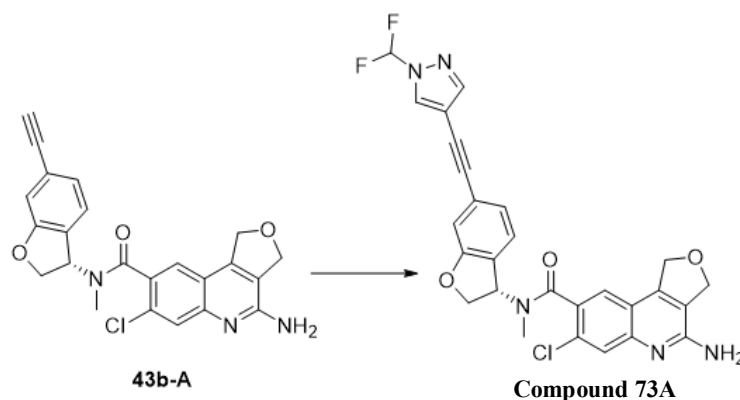


Referring to the preparation method for compound 9c in WO2024131901 A1, compound **72a** was condensed with compound **5c** to give compound **72b**.

To a solution of compound **72a** (48.4 mg, 0.1 mmol) in *N,N*-dimethylacetamide (2 mL) were sequentially added 4-ethynyl-1-methyl-1*H*-pyrazole (21.2 mg, 0.2 mmol), Xphos Pd G3 (8.5 mg, 0.01 mmol), and triethylamine (40.5 mg, 0.4 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 90 °C for 4 h. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **72** (25 mg). ESI-MS (m/z): 510.01 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.40 – 8.26 (m, 2H), 8.10 – 8.05 (m, 1H), 7.72 – 7.67 (m, 1H), 7.49 – 7.23 (m, 6H), 5.84 – 4.52 (m, 3H), 4.44 – 4.39 (m, 3H), 4.23 – 3.97 (m, 2H), 3.89 – 3.86 (m, 3H), 2.85 – 2.65 (m, 3H).

Example**73A:**

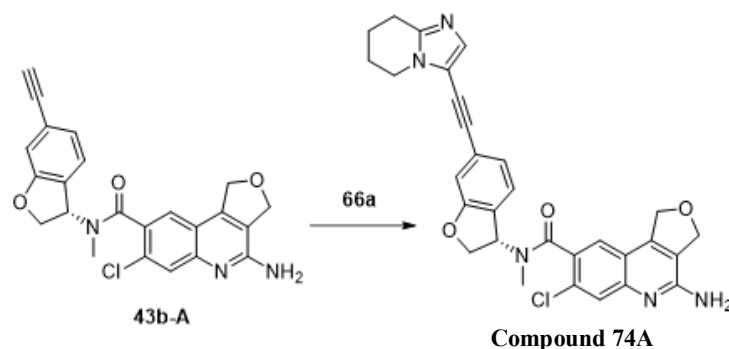
(S)-4-amino-7-chloro-N-(6-((1-(difluoromethyl)-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 73A)



Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 1-difluoromethyl-4-iodo-1H-pyrazole (48.8 mg, 0.2 mmol), and the mixture was reacted at 40 °C for 3 h to give compound **73A** (20 mg). ESI-MS (m/z): 536.12 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.71 – 8.64 (m, 1H), 8.12 – 8.04 (m, 1H), 8.02 – 7.82 (m, 1H), 7.73 – 7.58 (m, 2H), 7.51 – 7.31 (m, 1H), 7.20 – 6.99 (m, 2H), 6.86 (s, 2H), 6.55 – 5.29 (m, 3H), 5.08 – 4.99 (m, 2H), 4.88 – 4.45 (m, 2H), 2.71 and 2.46 (s, 1H).

Example**74A:**

(S)-4-amino-7-chloro-N-methyl-N-(6-((5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 74A)

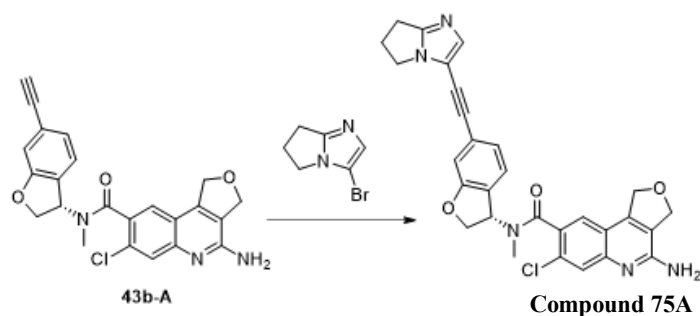


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound **66b** (40.2 mg, 0.2 mmol), and the mixture was reacted at 100 °C for 3 h to give compound **74A** (25 mg). ESI-MS (m/z): 540.25 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 7.90 – 7.58 (m, 2H), 7.47 – 7.32 (m, 1H), 7.29 – 7.23 (m, 1H), 7.21 – 7.00 (m, 2H), 6.86 (s, 2H), 6.54 – 6.42 (m, 1H), 6.51 – 5.28 (m, 3H), 5.07 – 4.97 (m, 2H), 4.86 – 4.48 (m, 2H), 4.03 – 3.93 (m, 2H), 2.82 – 2.73 (m, 2H), 2.71 and 2.46 (s, 3H), 2.01 – 1.93 (m, 2H), 1.90 – 1.82 (m, 2H).

Example

75A:

(S)-4-amino-7-chloro-N-(6-((6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 75A)



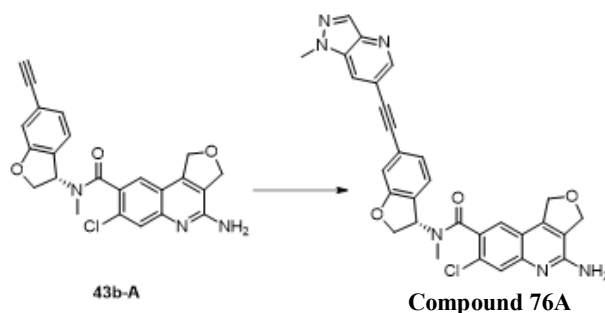
Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-bromo-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (37.4 mg, 0.2 mmol), and the mixture was reacted at 100 °C for 4 h to give compound **75A** (25 mg). ESI-MS (m/z):

526.08 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 7.87 – 7.58 (m, 2H), 7.49 – 7.26 (m, 2H), 7.18 – 6.97 (m, H), 6.85 (s, 2H), 6.53 – 5.29 (m, 3H), 5.06 – 4.97 (m, 2H), 4.86 – 4.46 (m, 2H), 4.09 – 3.96 (m, 2H), 2.86 – 2.75 (m, 2H), 2.72 – 2.45 (m, 5H).

Example

76A:

(S)-4-amino-7-chloro-N-methyl-N-(6-((1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide (Compound 76A)

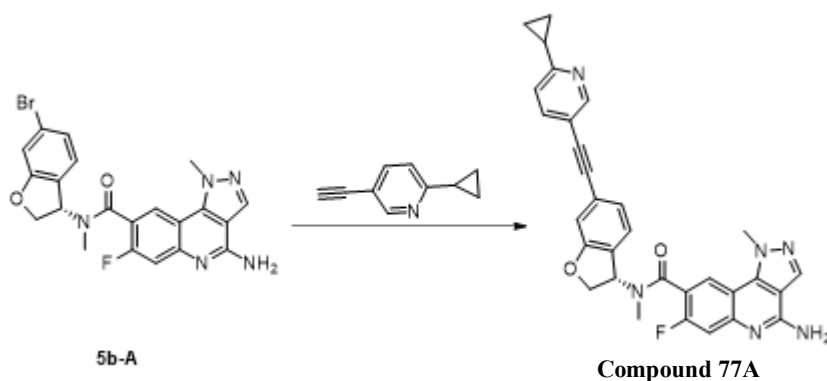


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 6-bromo-1-methylpyrazolo[4,3-*b*]pyridine (50.5 mg, 0.24 mmol), and the mixture was reacted at 100 °C for 4 h to give compound **76A** (18 mg). ESI-MS (*m/z*): 551.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.69 – 8.64 (m, 1H), 8.51 – 8.43 (m, 1H), 8.36 – 8.31 (m, 1H), 7.90 – 7.36 (m, 3H), 7.30 – 7.09 (m, 2H), 6.85 (s, 2H), 6.56 – 5.30 (m, 3H), 5.07 – 4.97 (m, 2H), 4.89 – 4.50 (m, 2H), 4.12 – 4.11 (m, 3H), 2.71 and 2.50 (s, 3H).

Example

77A:

(S)-4-amino-N-(6-((6-cyclopropylpyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-N,1-dimethyl-1H-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 77A)

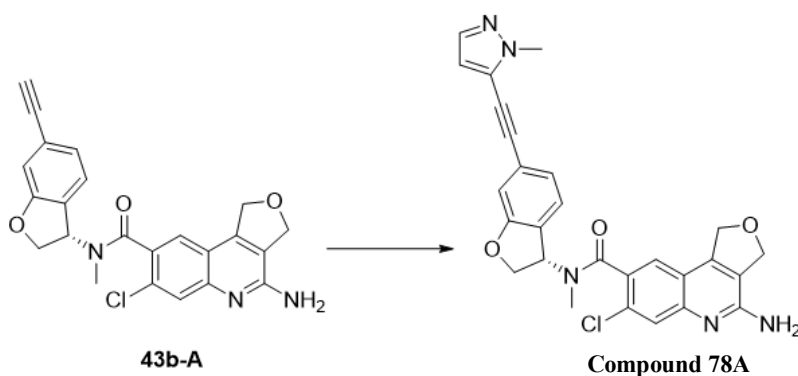


Referring to the preparation process of compound **5A**, compound 4-ethynyl-1-methylpyrazole was replaced with compound 2-cyclopropyl-5-ethynylpyridine (70 mg, 0.49 mmol), and the mixture was reacted in a microwave reactor at 80 °C for 4 h to give compound **77A** (33 mg). ESI-MS (m/z): 533.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.58 (s, 1H), 8.31 – 8.23 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.49 – 7.05 (m, 7H), 6.53 – 5.55 (m, 1H), 4.89 – 4.61 (m, 2H), 4.50 – 4.30 (m, 3H), 2.72 and 2.60 (s, 3H), 2.21 – 2.12 (m, 1H), 1.07 – 0.93 (m, 4H).

Example

78A:

(S)-4-amino-7-chloro-N-methyl-N-(6-((1-methyl-1*H*-pyrazol-5-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 78A)



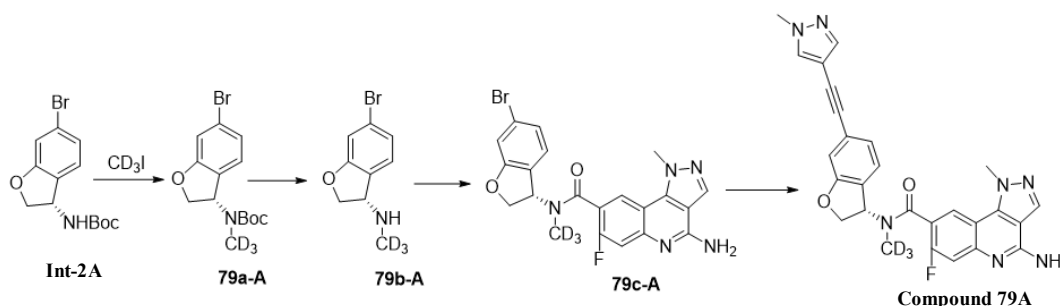
Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 5-iodo-1-methylpyrazole (59.4 mg, 0.29 mmol), and the mixture was reacted at room temperature for 3 h under

nitrogen atmosphere to give compound **78A** (23 mg). ESI-MS (m/z): 499.91 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 7.88 – 7.62 (m, 1H), 7.62 – 7.59 (m, 1H), 7.55 – 7.50 (m, 1H), 7.49 – 7.33 (m, 1H), 7.27 – 7.07 (m, 2H), 6.84 (s, 2H), 6.65 – 6.59 (m, 1H), 6.57 – 5.27 (m, 3H), 5.05 – 4.96 (m, 2H), 4.85 – 4.47 (m, 2H), 3.94 and 3.93 (s, 3H), 2.68 and 2.46 (s, 3H).

Example

79A:

(*S*)-4-amino-7-fluoro-1-methyl-*N*-(methyl-*D*3)-*N*-(6-((1-methyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 79A)

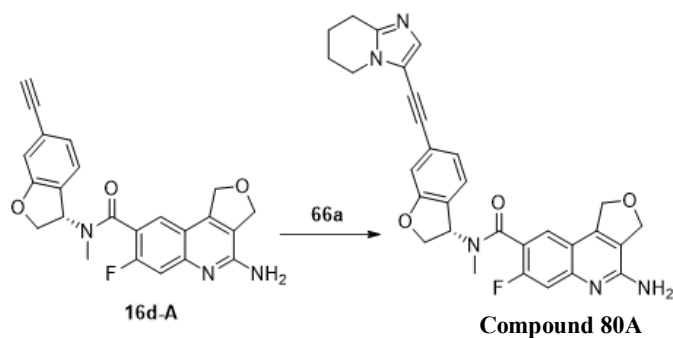


For the synthesis process of preparing compound **79A** from compound **Int-2A**, reference was made to the synthesis process of preparing compound **5A** from compound **Int-2A**. Compound **79A** (25 mg). ESI-MS (m/z): 499.00 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.38 – 8.20 (m, 2H), 8.08 (s, 1H), 7.69 (s, 1H), 7.45 – 7.25 (m, 4H), 7.17 – 6.93 (m, 2H), 6.50 – 5.54 (m, 1H), 4.87 – 4.61 (m, 2H), 4.46 – 4.37 (m, 3H), 3.87 (s, 3H).

Example

80A:

(*S*)-4-amino-7-fluoro-*N*-methyl-*N*-(6-((5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 80A)

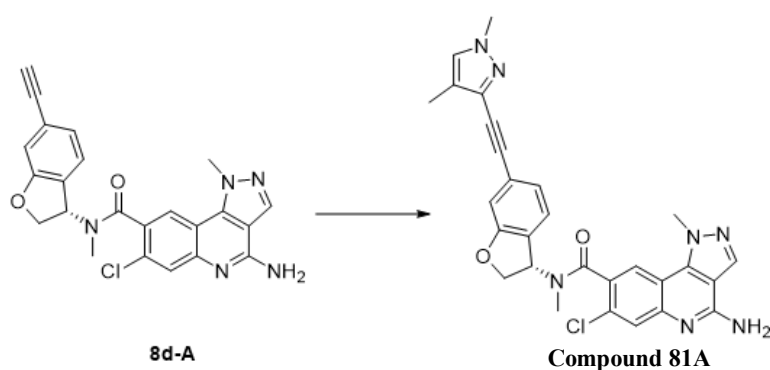


Referring to the preparation process of compound **16A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound **66a** (40.2 mg, 0.2 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **80A** (15 mg). ESI-MS (m/z): 524.32 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 7.68 – 7.62 (m, 1H), 7.42 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.21 – 7.11 (m, 1H), 7.09 – 7.02 (m, 1H), 6.85 (s, 2H), 6.49 – 5.50 (m, 1H), 5.43 – 5.30 (m, 2H), 5.06 – 4.98 (m, 2H), 4.85 – 4.57 (m, 2H), 4.02 – 3.93 (m, 2H), 2.81 – 2.74 (m, 2H), 2.70 and – 2.55 (s, 3H), 2.01 – 1.94 (m, 2H), 1.90 – 1.82 (m, 2H).

Example

81A:

(S)-4-amino-7-chloro-N-(6-((1,4-dimethyl-1H-pyrazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide (Compound 81A)



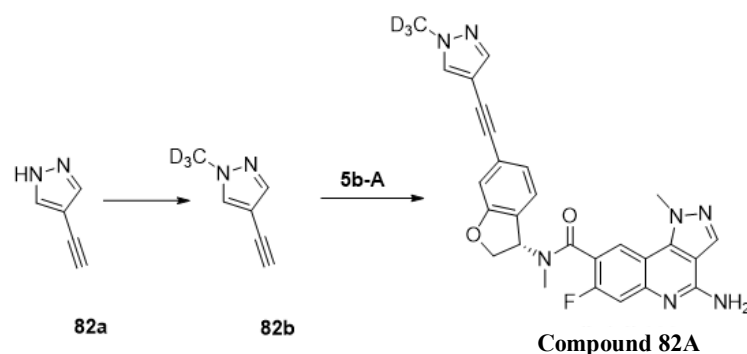
Referring to the preparation process of compound **8A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound

3-iodo-1,4-dimethylpyrazole (35.5 mg, 0.16 mmol), and the mixture was reacted at room temperature for 16 h under nitrogen atmosphere to give compound **81A** (15 mg). ESI-MS (m/z): 526.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.42 – 8.21 (m, 2H), 7.72 – 7.26 (m, 5H), 7.21 – 7.10 (m, 1H), 7.10 – 6.99 (m, 1H), 6.55 – 5.43 (m, 1H), 4.89 – 4.57 (m, 2H), 4.47 and 4.41 (s, 3H), 3.82 – 3.81 (m, 3H), 2.75 – 2.51 (m, 3H), 2.10 – 2.08 (m, 3H).

Example

82A:

(*S*)-4-amino-7-fluoro-*N*,1-dimethyl-*N*-(6-((1-(methyl-*D*3)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide
(Compound **82A**)



Preparation of compound **82b**

Compound **82a** (236.7 mg, 2.57 mmol) was dissolved in *N,N*-dimethylformamide (10 mL). The reaction solution was cooled to 0 °C, and sodium hydride (205.6 mg, 5.14 mmol, 60% purity) was added. After the reaction solution was reacted at 0 °C for 1 h, deuterated iodomethane (745.1 mg, 5.14 mmol) was added. Then the reaction solution was stirred at 25 °C for 12 h, water (5 mL) was added to the reaction solution to quench the reaction, and the reaction solution was extracted with ethyl acetate (25 mL $\times$ 3). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (ethyl acetate:petroleum ether = 1:10) to give compound **82b** (250 mg). ESI-MS (m/z): 110.02 $[M+H]^+$.

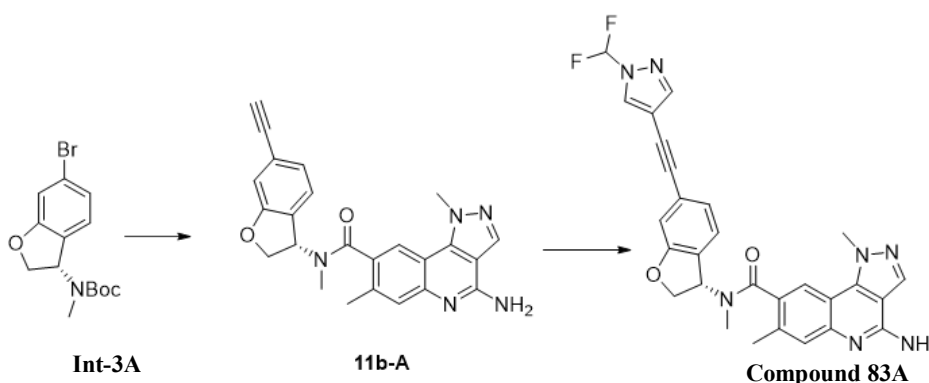
Preparation of compound **82A**

Referring to the preparation process of compound **5A**, compound 4-ethynyl-1-methylpyrazole was replaced with compound **82b** (21.8 mg, 0.2 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **82A** (25 mg). ESI-MS (*m/z*): 498.98 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.40 – 8.22 (m, 2H), 8.07 (s, 1H), 7.69 (s, 1H), 7.46 – 7.24 (m, 4H), 7.17 – 7.06 (m, 1H), 7.05 – 6.93 (m, 1H), 6.50 – 5.52 (m, 1H), 4.88 – 4.64 (m, 2H), 4.48 – 4.35 (m, 3H), 2.74 – 2.57 (m, 3H).

Example

83A:

(*S*)-4-amino-*N*-(6-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 83A)

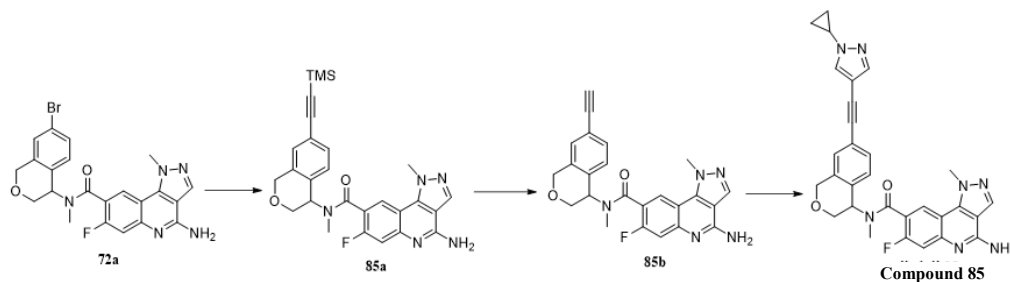


Reference was made to WO2024131901 A1 for the preparation process of compound **11b-A**.

Preparation of compound 83A

To a solution of compound **11b-A** (60 mg, 0.15 mmol) in *N*-methylpyrrolidone (2 mL) were added cuprous iodide (5.6 mg, 0.03 mmol), tetrakis(triphenylphosphine)palladium (16.8 mg, 0.01 mmol), triethylamine (60.64 µL, 0.44 mmol), and 1-(difluoromethyl)-4-iodopyrazole (106.7 mg, 0.44 mmol). After completion of the addition, the mixture was reacted at 25 °C for 3 h under nitrogen atmosphere. The reaction solution was filtered through celite. Water (50 mL) was added, and the reaction solution was extracted with ethyl acetate (25 mL × 2). The organic phases were combined, washed with saturated brine, dried over anhydrous

-*N*,1-dimethyl-1*H*-pyrazolo[4,3-*c*]quinoline-8-carboxamide (Compound 85)



Preparation of compound 85a

To a solution of compound **72a** (214 mg, 0.44 mmol) in *N,N*-dimethylacetamide (5 mL) were sequentially added trimethylsilylacetylene (86.9 mg, 0.88 mmol), Xphos Pd G3 (37.4 mg, 0.044 mmol), and triethylamine (179 mg, 1.77 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 90 °C for 4 h. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **85a** (224 mg). ESI-MS (*m/z*): 501.7 [*M*+*H*]⁺.

Preparation of compound 85b

To a solution of compound **85a** (224 mg, 0.45 mmol) in tetrahydrofuran (5 mL) was added a solution of tetrabutylammonium fluoride (0.9 mL, 1 M). After completion of the addition, the mixture was allowed to react at room temperature for 1 h. Water was added, and the reaction solution was extracted with ethyl acetate (30 mL $\times$ 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **85b** (140 mg). ESI-MS (*m/z*): 430.2 [*M*+*H*]⁺.

Preparation of compound 85

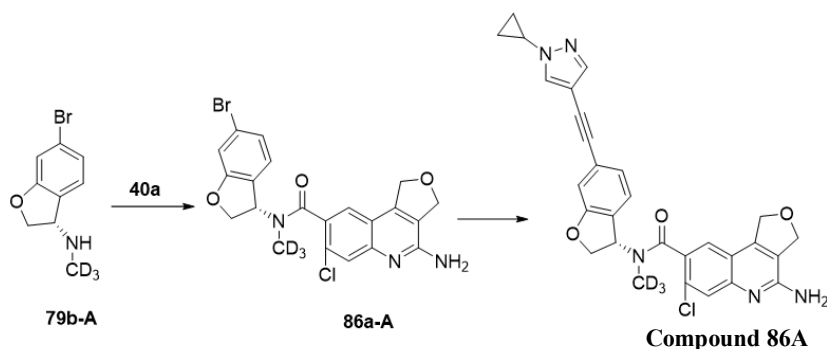
To a solution of compound **85b** (43 mg, 0.1 mmol) in *N*-methylpyrrolidone (2 mL) were sequentially added 1-cyclopropyl-4-iodo-1*H*-pyrazole (46.8 mg, 0.2 mmol),

cuprous iodide (3.8 mg, 0.02 mmol), *N,N*-diisopropylethylamine (51.7 mg, 0.4 mmol), and tetrakis(triphenylphosphine)palladium (11.6 mg, 0.01 mmol) under nitrogen atmosphere. After completion of the addition, the mixture was allowed to react under an oil bath at 40 °C for 3 h. Water (100 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **85** (20 mg). ESI-MS (*m/z*): 535.84 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.40 – 8.25 (m, 2H), 8.23 – 8.16 (m, 1H), 7.71 – 7.67 (m, 1H), 7.47 – 7.26 (m, 6H), 5.82 – 4.51 (m, 3H), 4.42 (s, 3H), 4.23 – 3.96 (m, 2H), 3.83 – 3.72 (m, 1H), 2.82 and 2.69 (s, 3H), 1.13 – 0.97 (m, 4H).

Example

86A:

(*S*)-4-amino-7-chloro-*N*-(6-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)-2,3-dihydro benzofuran-3-yl)-*N*-(methyl-*D*3)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 86A)



Referring to the preparation process of compound **40b-A**, compound **1a-A** was replaced with compound **79b-A** to give compound **86a-A**.

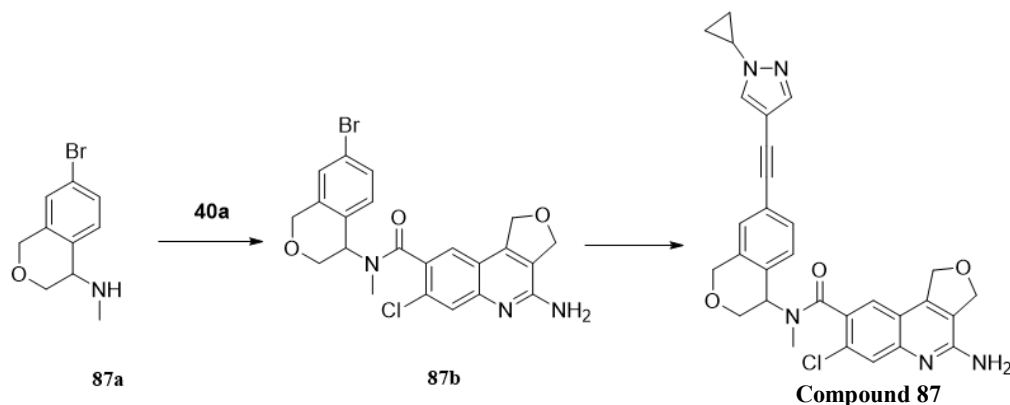
Referring to the preparation process of compound **43A**, compound **40b-A** was replaced with compound **86a-A** to give compound **86A** (30 mg). ESI-MS (*m/z*): 528.96 [*M*+*H*]⁺. ¹H NMR (400 MHz, DMSO) δ 8.20 – 8.15 (m, 1H), 7.87 – 7.57 (m, 3H), 7.47 – 7.29 (m, 1H), 7.15 – 7.03 (m, 1H), 7.02 – 6.92 (m, 1H), 6.85 (s, 2H), 6.54 – 5.28 (m, 3H), 5.08 – 4.96 (m, 2H), 4.85 – 4.43 (m, 2H), 3.81 – 3.71 (m, 1H), 1.10 –

0.97 (m, 4H).

Example

87:

4-amino-7-chloro-*N*-(7-((1-cyclopropyl-1*H*-pyrazol-4-yl)ethynyl)isochroman-4-yl)-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 87)



Preparation of compound 87b

Compound **40a** (193 mg, 0.73 mmol) was dissolved in *N,N*-dimethylformamide (10 mL), and *N,N*-diisopropylethylamine (0.63 mL, 3.64 mmol) was added. The mixture was stirred for 5 min under an ice bath, and *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (415 mg, 1.09 mmol) was then added, followed by addition of **87a** (176.2 mg, 0.73 mmol, see WO2024131901 A1 for the preparation method). The mixture was allowed to react for another hour. Water (100 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL $\times$ 3). The organic phases were washed three times with saturated brine, combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **87b** (212 mg). ESI-MS (*m/z*): 488.0[M+H]⁺.

Preparation of compound 87

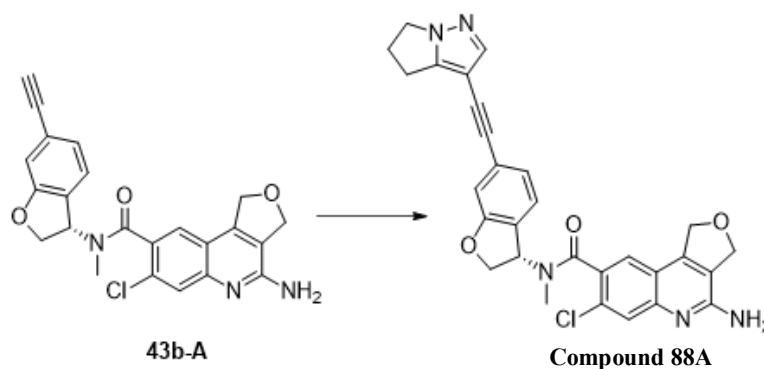
To a solution of compound **87b** (48.8 mg, 0.1 mmol) in *N,N*-dimethylacetamide (2 mL) were sequentially added 1-cyclopropyl-4-ethynyl-1*H*-pyrazole (26.4 mg, 0.2 mmol), cuprous iodide (3.8 mg, 0.02 mmol), *N,N*-diisopropylethylamine (0.07 mL, 0.4 mmol), and tetrakis(triphenylphosphine)palladium (11.6 mg, 0.01 mmol) under

nitrogen atmosphere. After completion of the addition, the mixture was reacted in a microwave reactor at 100 °C for 4 h. Water (50 mL) was added to the reaction solution, and the reaction solution was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was subjected to column chromatography (methanol:dichloromethane = 1:20) to give compound **87** (30 mg). ESI-MS (m/z): 539.96 $[M+H]^+$. 1H NMR (400 MHz, DMSO) δ 8.21 – 8.17 (m, 1H), 7.76 – 7.63 (m, 3H), 7.51 – 7.38 (m, 2H), 7.34 – 7.24 (m, 1H), 6.85 (s, 2H), 5.84 – 5.76 (m, 1H), 5.40 – 5.31 (m, 2H), 5.07 – 4.98 (m, 2H), 4.89 – 4.51 (m, 2H), 4.22 – 3.91 (m, 2H), 3.84 – 3.73 (m, 1H), 2.79 – 2.57 (m, 3H), 1.12 – 0.98 (m, 4H).

Example

88A:

(*S*)-4-amino-7-chloro-*N*-(6-((5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazol-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-*N*-methyl-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 88A)



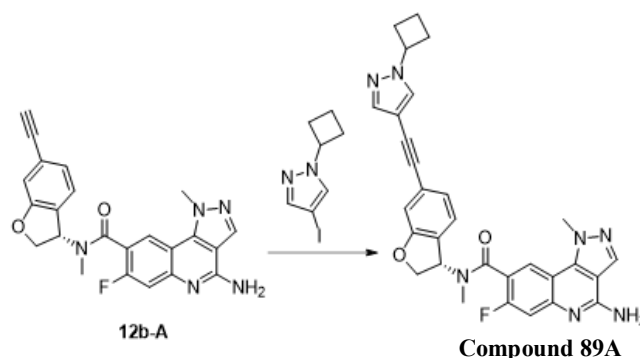
Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 3-bromo-5,6-dihydro-4*H*-pyrrolo[2,1-*e*]pyrazole (44.5 mg, 0.24 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **88A** (10 mg). ESI-MS (m/z): 525.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.90 – 7.58 (m, 3H), 7.45 – 7.27 (m, 1H), 7.15 – 7.02 (m, 1H), 6.99 – 6.93 (m, 1H), 6.85 (s, 2H), 6.50 – 5.28 (m, 3H), 5.06 – 4.99 (m, 2H), 4.87 – 4.45 (m, 2H), 4.16 – 4.08 (m, 2H),

2.98 – 2.90 (m, 2H), 2.69 – 2.46 (m, 5H).

Example

89A:

(S)-4-amino-N-(6-((1-cyclobutyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-7-fluoro-N,1-dimethyl-1H-pyrazolo[4,3-c]quinoline-8-carboxamide
(Compound 89A)

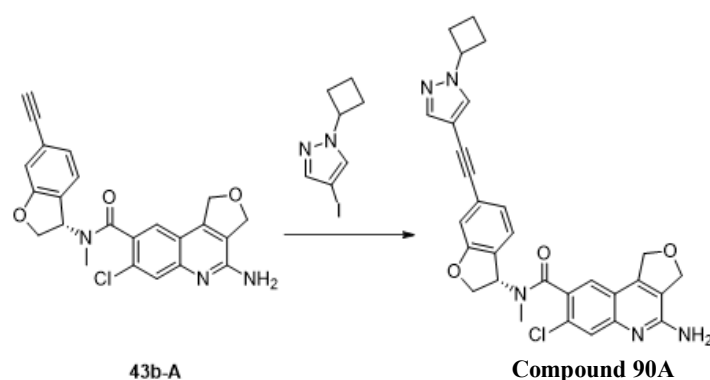


Referring to the preparation process of compound **12A**, compound 1-cyclopropyl-4-iodo-1H-pyrazole was replaced with compound 1-cyclobutyl-4-iodopyrazole (25 mg, 0.1 mmol), and the mixture was reacted at 25 °C for 2 h under nitrogen atmosphere to give compound **89A** (32 mg). ESI-MS (m/z): 536.02 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.42 – 8.20 (m, 3H), 7.73 (s, 1H), 7.47 – 7.31 (m, 4H), 7.15 – 7.05 (m, 1H), 7.03 – 6.94 (m, 1H), 6.50 – 5.54 (m, 1H), 4.92 – 4.56 (m, 3H), 4.53 – 4.29 (m, 3H), 2.75 – 2.56 (m, 3H), 2.50 – 2.29 (m, 4H), 1.86 – 1.74 (m, 2H).

Example

90A:

(S)-4-amino-7-chloro-N-(6-((1-cyclobutyl-1H-pyrazol-4-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-N-methyl-1,3-dihydrofuro[3,4-c]quinoline-8-carboxamide
(Compound 90A)

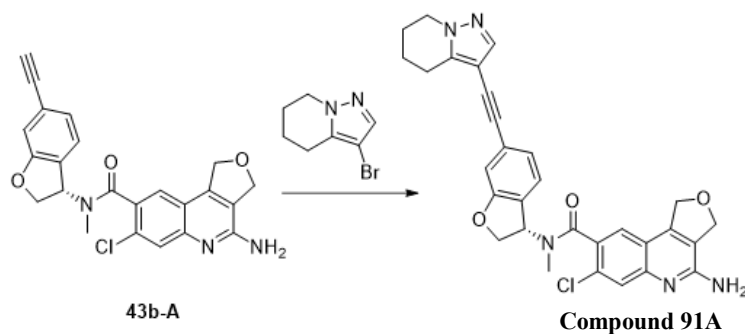


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound 1-cyclobutyl-4-iodopyrazole (50 mg, 0.20 mmol), and the mixture was reacted at room temperature for 2 h under nitrogen atmosphere to give compound **90A** (24 mg). ESI-MS (m/z): 540.00 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.24 – 8.20 (m, 1H), 7.88 – 7.58 (m, 3H), 7.47 – 7.29 (m, 1H), 7.15 – 7.03 (m, 1H), 7.02 – 6.93 (m, 1H), 6.86 (s, 2H), 6.52 – 5.29 (m, 3H), 5.07 – 4.98 (m, 2H), 4.93 – 4.46 (m, 3H), 2.69 – 2.35 (m, 7H), 1.87 – 1.74 (m, 2H).

Example

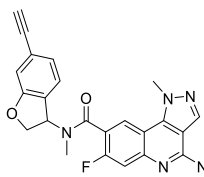
91A:

(S)-4-amino-7-chloro-N-methyl-N-((6-((4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridin-3-yl)ethynyl)-2,3-dihydrobenzofuran-3-yl)-1,3-dihydrofuro[3,4-*c*]quinoline-8-carboxamide (Compound 91A)

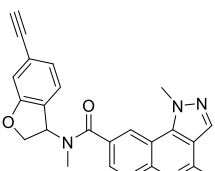


Referring to the preparation process of compound **43A**, compound 1-cyclopropyl-4-iodopyrazole was replaced with compound

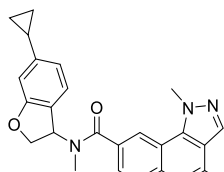
3-bromo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine (47.8 mg, 0.24 mmol), and the mixture was reacted in a microwave reactor at 100 °C for 4 h to give compound **91A** (8 mg). ESI-MS (m/z): 539.87 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.93 – 7.54 (m, 3H), 7.47 – 7.31 (m, 1H), 7.14 – 6.88 (m, 4H), 6.52 – 5.29 (m, 3H), 5.06 – 4.98 (m, 2H), 4.85 – 4.45 (m, 2H), 4.12 – 4.04 (m, 2H), 2.85 – 2.81 (m, 2H), 2.69 and 2.47 (s, 3H), 2.04 – 1.94 (m, 2H), 1.88 – 1.80 (m, 2H).



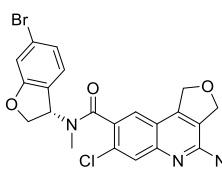
Reference Example 1:
which was prepared with reference to the method in WO2024131901A1.



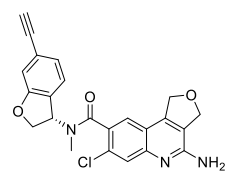
Reference Example 2:
which was prepared with reference to the method in WO2024131901A1.



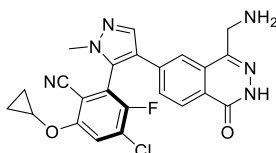
Reference Example 3:
which was prepared with reference to the method in WO2022169948 A1.



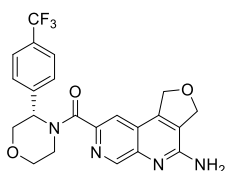
Reference Example 4:



Reference Example 5:



Reference Example 6:
MRTX1719, which was prepared with reference to the method in *J. Med. Chem.* 2022, 65(3), 1749-1766.



Reference Example 7: **AMG-193**, which was prepared with reference to the method in WO2022132914 A1.

Experimental Example 1: Inhibitory Activity of Compounds of the Present Disclosure Against Proliferation of Human Colon Cancer Cells

1. Construction of MTAP^{-/-} HCT-116 cell strain

The colon cancer cell strain HCT-116 (purchased from Nanjing Cobioer) was co-transfected with the gene editing tool CRISPR/Cas9 and sgRNA, and the MTAP^{-/-} HCT-116 cell strain with biallelic inactivation of MTAP was obtained by assays such as Western Blotting and Sanger sequencing. The MTAP^{-/-} HCT-116 cell strain was used for compound selectivity screening and evaluation based on the synergistic mechanism of MTAP deletion and PRMT5, including a symmetric dimethylarginine (SDMA) level test, a cell proliferation test, and the like.

2. Cell proliferation

MTAP^{-/-} HCT-116 and wild-type HCT-116 cell strains were cultured in complete medium McCoy's 5A (Gibco, 16600082)/10% FBS (Gibco, 10099141C)/1% p/s (Gibco, 15140122) to evaluate the enhanced inhibitory effect of the compounds against the proliferation selectivity of MTAP^{-/-} HCT-116 cells. On day 0, MTAP^{-/-} HCT-116 cells or wild-type HCT-116 cells were added to a 96-well cell culture plate (Corning, 3599) at 100 cells/well, and the plate was incubated in an incubator at 37 °C with 5% CO₂. The compound was diluted in a 3-fold gradient with DMSO (Sigma, D5879) (initial concentration: 20 μM, 3-fold dilution, 8 concentration points in total). On day 1, the compound was diluted to multiple concentration points, and the cells were treated separately and incubated in the incubator at 37 °C with 5% CO₂ for another 10 days. On Day 11, 20 μL of MTS (CellTiter 96® Aqueous One Solution Cell Proliferation Assay) (Promega, G3581) was added to each well. After the plate was incubated in the incubator at 37 °C with 5% CO₂ for another 2 h, readings (OD = 490 nm) were taken on Tecan Spark, and the data were then analyzed using the data

analysis software GraphPad Prism 8 and using the equation “log(inhibitor) vs. normalized response -- variable slope” (formula $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogIC}_{50} - X) \times \text{HillSlope}))})$) to give IC_{50} values of the compound. In the formula, Y represents the inhibition rate, X represents the logarithm of the compound concentration, Top represents the maximum response (the inhibition rate at the maximum compound concentration), Bottom represents the baseline response (the inhibition rate where the compound concentration was 0), Hill Slope represents the slope of the IC_{50} curve, and IC_{50} represents the half maximal inhibitory concentration. The experimental results are shown in Table 1.

Table 1. IC_{50} (μM)

Compound	HCT116 WT	HCT116 MTAP-/-	Selectivity	Compound	HCT116 WT	HCT116 MTAP-/-	Selectivity
1	1.802	0.0129	140	2	1.026	0.0139	74
3	4.312	0.027	160	4	1.322	0.008	165
4A	0.872	0.0045	194	5	0.584	0.006	97
5A	0.170	0.0017	100	6	2.777	0.0108	257
7	0.593	0.0054	110	8	0.141	0.003	47
9	0.0977	0.0009	109	9A	0.06	0.0012	50
10	0.162	0.002	81	10A	0.028	0.0005	56
11	0.185	0.003	62	12	0.650	0.008	81
12A	0.426	0.0037	115	13	0.607	0.011	55
14	-	0.009	-	15	-	0.0048	-
/	/	/	/	16A	1.165	0.0139	84
17	0.405	0.007	58	18	0.159	0.003	53
19	0.986	0.0097	102	19A	1.295	0.0087	149
20	0.948	0.0098	97	20A	1.039	0.0061	170
21	0.365	0.007	52	22	0.095	0.0019	50
21A	0.233	0.0027	86.3	22A	0.055	0.001	55
23	0.307	0.004	77	24	0.115	0.0019	61
23A	0.507	0.0031	164	24A	0.214	0.0027	79
25	0.471	0.0047	100	26	-	0.0028	-
25A	0.249	0.0018	138	26A	-	0.0009	-
27	0.185	0.0032	58	28	-	0.0023	-
29	1.498	0.0098	153	30	1.753	0.0087	201
29A	0.480	0.0036	133	30A	0.240	0.0029	83

31	1.455	0.0142	102	32	2.271	0.022	103
31A	0.192	0.0033	58	33	0.567	0.0044	129
34	1.14	0.0076	150	34A	0.266	0.002	133
36	1.73	0.0137	126	37	2.04	0.022	93
39	2.965	0.020	148	40	1.461	0.0058	252
39A	-	0.011	-	40A	0.483	0.0046	105
41	1.782	0.0138	129	42	0.785	0.0185	42
43A	0.646	0.0038	170	44	0.736	0.011	67
45	0.654	0.0059	111	45A	0.213	0.004	53
46	0.467	0.003	156	46A	0.158	0.0011	144
47	0.56	0.0074	76	47A	0.598	0.0052	115
48A	0.141	0.002	71	49A	0.378	0.0018	210
50A	0.431	0.0024	180	51A	-	0.001	-
52A	0.487	0.0032	152	53A	0.045	0.001	45
54A	-	0.0055	-	55A	0.217	0.005	43
56A	0.16	0.003	53	57A	1.002	0.008	125
58A	2.222	0.0095	234	59A	0.305	0.0046	66
60A	0.486	0.008	61	61A	0.64	0.007	91
62A	1.264	0.0159	79	63A	0.085	0.002	43
64A	-	0.003	-	65A	0.141	0.002	71
66A	0.299	0.002	150	67A	0.085	0.002	43
68A	0.312	0.0066	47	69A	0.864	0.005	173
70A	0.475	0.0036	132	71A	0.674	0.014	48
72	-	0.006	-	73A	-	0.011	-
74A	0.472	0.0027	175	75A	0.424	0.004	106
76A	0.167	0.003	56	77A	-	0.011	-
78A	0.512	0.0039	131	79A	0.304	0.002	152
80A	1.506	0.006	251	81A	0.122	0.0027	45
82A	0.196	0.0026	75	83A	0.062	0.001	62
84A	0.143	0.0026	55	85	0.165	0.003	55
86A	1.077	0.0087	124	87	0.504	0.009	56
88A	0.777	0.0045	173	89A	0.263	0.003	88
90A	1.181	0.012	98	91A	1.388	0.0071	195
Reference Example 7	2.009	0.0974	21				

The results show that the specific compounds and isomers thereof exemplified herein have strong inhibitory activity against the proliferation of the human MTAP-deleted

HCT-116 cell strain, and most of the exemplified compounds have IC₅₀ values less than 0.01 μ M for the human MTAP-deleted HCT-116 cell strain. In terms of selectivity, each of the specific compounds and isomers thereof exemplified herein has relatively good selective inhibition on the human MTAP-deleted HCT-116 cell strain relative to the HCT-116 cell strain with wild-type (WT) MTAP, and the selective inhibition of most compounds is more than 90 times.

Experimental Example 2: Human Liver Microsome Stability Experiment

Experimental materials: human liver microsomes (purchased from BIOIVT);

Preparation of reagents:

PBS: 0.1 M KH₂PO₄ and K₂HPO₄ buffers, pH 7.4.

MgCl₂: a certain amount of MgCl₂ was weighed out and prepared into a 16 mM MgCl₂ solution with PBS.

NADPH (Chinese name: reduced nicotinamide adenine dinucleotide phosphate, purchased from Sigma, Cat. No.: 481973-500 mg): a certain amount of NADPH was weighed out and a 4 mM solution of NADPH was prepared with a 16 mM MgCl₂ solution, and the final incubation concentration was 1 mM.

Compounds: 4 μ M solutions of the test compounds and positive compounds were prepared with PBS, and the final incubation concentration was 1 μ M.

Liver microsomes (purchased from BIOIVT, Cat. No.: X008070): the liver microsomes were diluted to 1 mg/mL with PBS, and the final incubation concentration was 0.5 mg/mL.

Experimental procedures:

The prepared test compound or positive compound was added to a test tube, and then the prepared NADPH was added. The mixture was mixed well. The mixture was pre-incubated in a thermostat incubator at 220 rpm at 37 °C for 5 min, and the prepared liver microsomes were added to start the reaction. All steps were performed in replicate wells. At 0 min, 15 min, 30 min, 45 min, and 60 min, a certain volume of glacial acetonitrile solution containing an internal standard was added to the corresponding tube to precipitate the protein. The mixture was vortexed for 5 min with shaking, and then centrifuged at 4000 rpm for 10 min. The supernatant was

collected and added to a 96-well plate. The samples were analyzed by LC-MS/MS. The concentrations (peak area ratios) of the example compounds were determined by LC-MS/MS. Rate constants were obtained by plotting “Ln (residual amount of compound %)” versus “incubation time” in Excel, thereby calculating the half-lives and intrinsic clearances of the drugs and providing a basis for the prediction of the in-vivo clearance. The experimental results are shown in Table 2.

Data analysis:

$$CL_{int} = (0.693/t_{1/2, \text{ microsome}}) \times [\text{incubation solution volume (mL)/microsome protein mass (mg)}] \times [\text{microsome protein mass (mg)/liver mass (g)}] \times [\text{liver mass (g)/body weight (kg)}]^{[1]}$$

$$CL_H = CL_{int} \times f_u \times Q_h / (CL_{int} \times f_u + Q_h)$$

In the formula,

CL_{int} --Intrinsic clearance (mL/min/kg)

CL_H --Hepatic clearance (mL/min/kg)

f_u --Plasma protein unbound fraction of 1

Q_h --Hepatic blood flow

Table 2. Stability in human liver microsomes

Compound	T1/2 (min)	Compound	T1/2 (min)
Reference Example 1	16.6	Example 4	169
Reference Example 2	33.6	Compound 5A	66.5
Reference Example 5	25.6	Compound 25A	68.9
Reference Example 7	28.9	Compound 40A	62.9
Compound 50A	49.9	Compound 43A	122
		Compound 91A	47.2

Table 2 shows that the compounds of the present disclosure have excellent stability in human liver microsomes.

Experimental Example 3: hERG Test

Experimental reagents:

Predictor™ hERG Fluorescence Polarization Assay Kit (ThermoFisher Scientific, PV5365).

Experimental procedures:

The procedures in the kit instructions were followed: 4× Predictor™ hERG Tracer Red, 4× E-4031, and 4× test substance solutions (final assay concentration: 10 μM) were prepared in advance. 5 μL Predictor™ hERG FP Assay Buffer and 5 μL Predictor™ hERG Membrane were added sequentially to the Assay Blank group in a 384-well plate. 2.5 μL Predictor™ hERG FP Assay Buffer, 2.5 μL of 4× E-4031, and 2.5 μL of 4× test substance were added to the negative control group, the positive control group, and the test substance group, respectively, and then 5 μL Predictor™ hERG Membrane and 2.5 μL of 4× Predictor™ hERG Tracer Red were sequentially added. The total volume of the experimental system was 10 μL, and three duplicate wells were set for each group. After loading, the plate was gently tapped to mix well and incubated at room temperature (25 °C) in the dark for 3.5 h. After the incubation was completed, the fluorescence polarization value mP was measured on a microplate reader, and G Factor was 2.14.

Data analysis:

The inhibition rate of the test substance was calculated using the following formula:

Inhibition rate % = (mP negative control – mP test substance)/(mP negative control – mP positive control) × 100%.

Using the experimental method described above, the experimental results of hERG inhibition of some compounds of the present disclosure are shown in Table 3 below.

Table 3. hERG test

Compound	Inhibition (10 μM)	IC ₅₀ (μM)	Compound	Inhibition (10 μM)	IC ₅₀ (μM)
Reference Example 6	77.39%±23.77%	< 10	Compound 43A	30.33±29.9%	> 10

Compound 5A	27.67%±11.38%	> 10	Compound 45	20.97%±14.19%	> 10
Compound 9A	35.70%±3.15%	> 10	Compound 46A	43.93±18.76%	> 10
Compound 12A	22.42±1.73%	> 10	Compound 50A	22.42±25.47%	> 10
Compound 23A	39.48%±13.86%	> 10	Compound 52A	10.4±49.06%	> 10
Compound 25A	32.97%±23.29%	> 10	Compound 57A	14.15±18%	> 10
Compound 39	23.78%±11.14%	> 10	Compound 66A	14.22±13.96%	> 10
Compound 40	22.04%±1.45%	> 10			

Table 3 shows that the compounds of the present disclosure have lower hERG inhibition toxicity than the prior art (e.g., Reference Example 6).

Experimental Example 4: CYP Inhibition Test

Experimental materials: human liver microsomes (purchased from BIOIVT);

Preparation of reagents:

PBS: 0.1 M KH₂PO₄ and K₂HPO₄ buffers, pH 7.4.

MgCl₂: a certain amount of MgCl₂ was weighed out and prepared into a 20 mM MgCl₂ solution with PBS.

NADPH (Chinese name: reduced nicotinamide adenine dinucleotide phosphate, purchased from Sigma, Cat. No.: 481973-500 mg): a certain amount of NADPH was weighed out and a 5 mM solution of NADPH was prepared with a 20 mM MgCl₂ solution, and the final incubation concentration was 1 mM.

Compounds: 3 mM, 1 mM, 0.3 mM, 0.1 mM, 0.03 mM, 0.01 mM, and 0 mM solutions of the test compounds were prepared with a DMSO-methanol (v:v = 1:9) solution, and the final incubation concentrations were 30 μM, 10 μM, 3 μM, 1 μM,

0.3 μ M, 0.1 μ M, and 0 μ M. 30 μ M, 10 μ M, 3 μ M, 1 μ M, 0.3 μ M, and 0 μ M solutions of the positive compound (ketoconazole) were prepared with a DMSO-methanol (v:v = 1:9) solution, and the final incubation concentrations were 0.3 μ M, 0.1 μ M, 0.03 μ M, 0.01 μ M, 0.003 μ M, and 0 μ M.

Substrate working solutions: 200 μ M and 15 μ M solutions of substrate working solutions (testosterone and midazolam) were prepared with PBS, separately, and the final incubation concentrations were 40 μ M and 3 μ M.

Liver microsomes (purchased from BIOIVT, Cat. No.: X008070): the liver microsomes were diluted to 0.17 mg/mL with PBS, and the final incubation concentration was 0.1 mg/mL.

Experimental procedures:

The prepared test compounds or positive compounds were added to a 96-well plate, and then the prepared human liver microsome working solution and substrate working solution were added. The mixture was mixed well. The mixture was pre-incubated in a thermostat incubator at 37 °C for 5 min, and then the prepared NADPH was added to start the reaction. The mixture was incubated for 5 min or 10 min. After the incubation was completed, a pre-cooled acetonitrile solution containing an internal standard was added to terminate the reaction. After protein precipitation, the mixture was vortexed for 5 min with shaking and then centrifuged at 4000 rpm for 10 min. The supernatant was collected and added to the 96-well plate. The content (peak concentration ratio) of the metabolites of the substrate was determined by an LC-MS/MS method. The residual activity and the half maximal inhibitory concentration (IC_{50}) of the enzyme were calculated based on the detected content.

Data analysis:

Percentage of remaining enzyme activity:

The activity of each subtype of CYP450 enzyme was expressed as the amount of metabolite produced, and the percentage of remaining enzyme activity was calculated as follows:

Remaining activity (%) = (activity of the CYP450 enzyme subtype in the presence of the test substance $\div$ activity of the solvent control group) $\times$ 100%, and the activity of

the solvent control group (0 μ M) was set as 100%.

IC₅₀:

The concentrations of the test substances and the corresponding residual activity percentages were fitted using a nonlinear model of Excel software, and the concentration of the test substances at which 50% inhibition of metabolite production was achieved was the IC₅₀ value. The experimental results are shown in Table 4.

Table 4

Compound	IC ₅₀ (μ M)	
	3A4-Midazolam	3A4-Testosterone
Reference Example 6	2.13	1.95
Compound 5A	>30	>30
Compound 23A	>30	>30
Compound 25A	>30	>30
Compound 40A	>30	>30
Compound 43A	>30	>30
Compound 50A	>30	>30

Table 4 shows that the compounds of the present disclosure have lower CYP inhibitory toxicity than the prior art (e.g., Reference Example 6).

Experimental Example 5: PK Experiment in Mice

Experimental materials: the experimental animals were healthy adult female BALB/c mice (provided by Sichuan Vital River Laboratory Animal Technology Co., Ltd.).

Procedures:

Administration mode and sample collection in mice: BALB/c female mice received oral intragastrical administration (10 mg/kg, vehicle: 0.5% methylcellulose/0.2% Tween 80), and 60 μ L of whole blood from the venous plexus of the fundus of the mice at different time points was collected at 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, and 24 h after administration and centrifuged at 4000 rpm for 6 min to collect plasma.

Sample analysis:

10 μ L of mouse plasma sample was added to 190 μ L of acetonitrile solution containing an internal standard to precipitate protein. The mixture was vortexed for 10 min and centrifuged at 4000 rpm for 10 min. The supernatant was collected and added to a 96-well plate. The samples were analyzed by LC-MS/MS. The drug concentrations in the plasma of mice at different time points after intragastric administration of the example compounds were measured by an LC-MS/MS method, and the related pharmacokinetic parameters were calculated, such that the pharmacokinetic behavior of the compounds in the mice was studied, and the pharmacokinetic characteristics were evaluated. The experimental results are shown in Table 5.

Table 5. Pharmacokinetic parameters of the compounds of the present disclosure for mice

Compound¹	<i>C_{max}</i> (ng/mL)	AUC_{last} (h*ng/mL)	Compound¹	<i>C_{max}</i> (ng/mL)	AUC_{last} (h*ng/mL)
Reference Example 3	741±601	5131±2925	Compound 39	2667±180	20888±8399
Reference Example 4	649±45	3268±588	Compound 40A	793±28	10070±3504
Reference Example 5	1400±165	9083±2788	Compound 43A	3420±913	32339±3341
Reference Example 6 ²	428±220	1970±316	Compound 52A	1503±313	14200±2432
Reference Example 7	1923±76	12626±1915	Compound 57A	1810±195	10534±2400
Compound 4	634±71	9154±2244	Compound 61A	2077±299	22184±2713
Compound 5A	2223±230	15699±1601	Compound 66A	3827±533	23153±3387
Compound 9A	4500±147	24341±3342	Compound 74A	2807±780	14527±1756
Compound 12A	2673±421	26904±7453	Compound 75A	5013±846	26976±4260

Compound 16A	1600±352	23324±5524	Compound 82A	1433±195	14072±4741
Compound 23A	1967±508	19401±7262	Compound 86A	1480±187	15339±2935
Compound 30	984±123	12607±1363			

Note: 1. The vehicle was 0.5% MC/0.2% Tween 80, with PO administration.

2. Reference was made to *J. Med. Chem.* 2022, 65(3), 1749-1766 for the test method of PK in MRTX1719 mice.

Table 5 shows that the compounds provided herein have excellent pharmacokinetic properties in mice.

Experimental Example 6: PK Experiment in Rats

Experimental materials: the experimental animals were healthy adult SD male rats (provided by Sichuan Vital River Laboratory Animal Technology Co., Ltd.).

Procedures:

Administration mode and sample collection in rats: SD male rats received oral intragastrical administration (10 mg/kg, vehicle: 0.5% methylcellulose/0.2% Tween 80), and 200 µL of whole blood from the venous plexus of the fundus of the rats at different time points was collected at 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, and 24 h after administration and centrifuged at 4000 rpm for 6 min to collect plasma.

Sample analysis:

10 µL of rat plasma sample was added to 190 µL of acetonitrile solution containing an internal standard to precipitate protein. The mixture was vortexed for 10 min and centrifuged at 4000 rpm for 10 min. The supernatant was collected and added to a 96-well plate. The samples were analyzed by LC-MS/MS. The drug concentrations in the plasma of rats at different time points after intragastric administration of the example compounds were measured by an LC-MS/MS method, and the related pharmacokinetic parameters were calculated, such that the pharmacokinetic behavior of the compounds in the rats was studied, and the pharmacokinetic characteristics were evaluated. The experimental results are shown in Table 6.

Table 6. Pharmacokinetic parameters for rats

Compound ¹	C _{max}	AUC _{last}	Compound ¹	C _{max}	AUC _{last}
-----------------------	------------------	---------------------	-----------------------	------------------	---------------------

	(ng/mL)	(h*ng/mL)		(ng/mL)	(h*ng/mL)
Reference Example 2	131±17	784±595	Compound 5A	2177±777	15583±4638
Reference Example 5	549±139	2940±438	Compound 16A	1280±270	13731±2775
Reference Example 6	107±149	100±103	Compound 23A	1163±181	6330±2495
Reference Example 7	477±110	853±79	Compound 43A	1221±417	9653±1169

Note: 1. The vehicle was 0.5% MC/0.2% Tween 80, with PO administration.

Table 6 shows that the compounds provided herein have excellent pharmacokinetic properties in rats.

Experimental Example 7: Efficacy Evaluation in Gene-Editing MTAP^{-/-} Human Colon Cancer Cell Strain HCT116 Subcutaneous Xenograft Mouse Model

Experimental materials:

The gene-editing MTAP^{-/-} human colon cancer cell strain HCT116 (purchased from Nanjing Cobioer) was cultured with a McCoy's 5A medium (Invitrogen) containing 10% fetal bovine serum (Gibco);

the administration was performed after the test substances were prepared into suspensions at concentrations of 0.3 mg/mL and 1 mg/mL using a 0.5% MC + 0.2% Tween 80 aqueous solution. The administration was performed after Reference Example 6 (MRTX1719) was prepared into a 5 mg/mL clear solution using 40% PEG400 normal saline containing 2% DMSO. The blank group contained 40% PEG400 normal saline with 2% DMSO.

Experimental method:

HCT116 MTAP^{-/-} cells in the logarithmic growth phase were digested, collected, and counted, and the cell density was adjusted to 1×10^8 cells/mL using a serum-free medium. 20-22 g of Balb/c nude mice (Beijing Huafukang Biotechnology Co., Ltd.) were inoculated subcutaneously with 100 μ L of cell suspension per mouse. On day 10

after inoculation, animals with tumor volumes of 100-150 mm³ were randomly grouped, with 8 animals in each group, according to the body weight and the tumor volume. The test substance was intragastrically administered at 10 mg/kg once daily, and MRTX1719 was intragastrically administered at 50 mg/kg once daily. Model control: The vehicle (2% DMSO + 40% PEG400 + 58% normal saline) was intragastrically administered at a dose of 10 mL/kg once daily. Administration was performed for 28 days in total.

After the animals were inoculated with HCT116 MTAP^{-/-} cells, the body weight and tumor volume of the mice were measured 2-3 times a week, and the tumor volume was calculated based on $\text{length} \times \text{width}^2 \times 0.5$. The mice were euthanized on the day when the last administration was completed.

The tumor growth inhibition TGI of each administration group was calculated based on the following formula:

TGI (tumor volume) was calculated as follows: $\text{TGI}_{\text{TV}} = 1 - ((V_{\text{Tt}} - V_{\text{T0}})/(V_{\text{Ct}} - V_{\text{C0}})) \times 100\%$. In the formula, V_{Tt} represents the tumor volume of the treatment group at each measurement, and V_{T0} represents the tumor volume measured when the treatment group is grouped; V_{Ct} represents the tumor volume of the vehicle group at each measurement (same as V_{Tt}), and V_{C0} represents the tumor volume measured when the vehicle group is grouped.

Data were analyzed using GraphPad Prism 9.0 software and expressed as Mean $\pm$ SEM (standard error). Pairwise comparisons between each administration group and the control group were performed using one-way analysis of variance (ANOVA). Variance homogeneity was determined using the Brown-Forsythe method, and variance heterogeneity was determined using the Dunnett's T3 method.

Table 7. Efficacy evaluation in HCT116 subcutaneous xenograft mouse model

Test substance	Dose of administration	Tumor volume (mm ³)	TGI
Blank	-	1580.00	-
MRTX1719	50 mg/kg, PO, qd	525.74	72.21%

Compound 5A	10 mg/kg, PO, qd	378.72	82.25%
Compound 23A	10 mg/kg, PO, qd	423.62	79.22%
Compound 25A	10 mg/kg, PO, qd	534.36	71.59%

As shown in Table 7, the in-vivo anti-tumor effect of the compound of the present disclosure in the HCT116 subcutaneous xenograft mouse model is significantly better than that of the clinical molecule MRTX1719.

Experimental Example 8: Efficacy Evaluation in Xenograft Mouse Model of Human Large Cell Lung Cancer LU99

Experimental materials:

The human large cell lung cancer cell line LU99 was purchased from Nanjing Cobioer Biosciences Co., Ltd. (CBP61512) and cultured in RPMI-1640 medium (Gibco) containing 10% fetal bovine serum (Gibco);

the test substances were prepared into suspensions at concentrations of 0.3 mg/mL, 1 mg/mL, and 5 mg/mL using a 0.5% aqueous MC solution containing 0.2% Tween 80. Reference Example 6 (MRTX1719) was prepared into a 5 mg/mL clear solution using 40% PEG400 normal saline containing 2% DMSO.

Experimental method:

LU99 cells in the logarithmic growth phase were digested, collected, and counted, and the cell density was adjusted to 2×10^7 cells/mL using a 1:1 serum-free medium and matrigel (Corning). 18-20 g of Balb/c nude mice (Beijing Huafukang Biotechnology Co., Ltd.) were inoculated subcutaneously with 100 μ L of cell suspension per mouse. On day 12 after inoculation, animals with a mean tumor volume of 116 mm³ were randomly grouped, with 7 animals in each group. The test substances were intragastrically administered at 3 mg/kg, 10 mg/kg, and 50 mg/kg once daily, and MRTX1719 was intragastrically administered at 50 mg/kg once daily. A vehicle (2% DMSO + 40% PEG400 + 58% normal saline) was intragastrically administered to the blank group at a dose of 10 mL/kg once daily. Administration was performed for 28 days in total.

After the animals were inoculated with LU99 cells, the tumor volume was measured

2-3 times a week, and the tumor volume was calculated based on $\text{length} \times \text{width}^2 \times 0.5$. On the day when the last administration was completed, except for the mice with tumor regression, which were subjected to discontinuation observation, the remaining mice were euthanized.

The tumor growth inhibition TGI of each administration group was calculated based on the following formula:

TGI (tumor volume) was calculated as follows: $\text{TGI}_{\text{TV}} = 1 - ((V_{\text{Tt}} - V_{\text{T0}})/(V_{\text{Ct}} - V_{\text{C0}})) \times 100\%$. In the formula, V_{Tt} represents the tumor volume of the treatment group at each measurement, and V_{T0} represents the tumor volume measured when the treatment group is grouped; V_{Ct} represents the tumor volume of the model control group at each measurement, and V_{C0} represents the tumor volume measured when the model control group is grouped.

Data were analyzed using GraphPad Prism 9.0 software and expressed as Mean $\pm$ SEM (standard error). Pairwise comparisons between each administration group and the model control group were performed using one-way analysis of variance (ANOVA). Variance homogeneity was determined using the Brown-Forsythe method, and variance heterogeneity was determined using the Dunnett's T3 method.

Table 8. Efficacy evaluation in LU99 xenograft mouse model

Test substance	Dose of administration	Tumor volume (mm ³)	TGI
Blank	-	1911.67	-
MRTX1719	50 mg/kg, PO, qd	279.68	90.96%
Compound 5A	3 mg/kg, PO, qd	438.73	81.96%
	10 mg/kg, PO, qd	202.05	95.20%
	50 mg/kg, PO, qd	60.72	103.12%
Compound 43A	3 mg/kg, PO, qd	415.58	83.27%
	10 mg/kg, PO, qd	210.31	94.77%
	50 mg/kg, PO, qd	28.13	104.92%

Results and analysis:

The experimental results are shown in Table 8. The compounds of the present disclosure can significantly reduce the tumor volume at 3 mg/kg, 10 mg/kg, and 50 mg/kg ($P < 0.0001$). The anti-tumor effect of the test substances at 10 mg/kg and 50 mg/kg is significantly better than that of MRTX1719 at 50 mg/kg, and the test substances at 50 mg/kg can cause tumor regression.

In conclusion, the experimental results show that, in the human large cell lung cancer LU99 CDX model, the test substances of the present disclosure have a relatively good anti-tumor effect, and the anti-tumor efficacy is significantly superior to that of the positive control at a relatively low dose.

Industrial applicability

The compounds of the present disclosure exhibit excellent inhibitory activity against PRMT5. The compounds of the present disclosure demonstrate excellent selective inhibition against the human MTAP-deficient HCT-116 cell line over the MTAP wild-type (WT) HCT-116 cell line. The compounds can be used in the development of small-molecule drugs targeting PRMT5·MTA and preferentially act on MTAP-deficient tumor cells.

Furthermore, through tests such as human liver microsome stability, mouse pK, rat pK, and in-vivo anti-tumor efficacy evaluation in mice, it can be found that the compounds of the present disclosure have excellent anti-tumor application prospects.

Further, compared with existing compounds, the compounds of the present disclosure possess a higher safety window, and are significantly superior to the prior art in terms of safety (e.g., toxicity from inhibition of hERG, CYP, etc.).

In conclusion, compared with the prior art, the compounds of the present disclosure have achieved unexpected technical effects in the aspects of druggability and safety, and have great development potential.

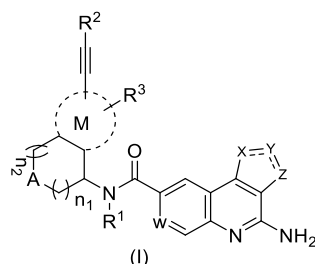
The above description merely represents preferred embodiments of the present disclosure. It should be noted that those of ordinary skill in the art can make several improvements and modifications without departing from the principles of the present disclosure, and these improvements and modifications shall fall within the protection scope of the present disclosure.

Reference

- [1] Davies B, Morris T. Physiological parameters in laboratory animals and humans. Pharm Res. 1993; 10: 1093-5

CLAIMS

1. A compound represented by formula I or a tautomer, a stereoisomer, a pharmaceutically acceptable salt, or a deuterated compound thereof:



wherein

$\equiv$ is selected from a single bond and a double bond, or $\equiv$ is absent;

when $\equiv$ is a single bond or a double bond, X, Y, and Z are independently selected from CR^4R^5 , NR^6 , O, N, S, and CR^4 ;

when $\equiv$ is absent, Y is absent, X is hydrogen, and Z is CR^4R^5 ;

W is selected from CR^7 and N;

A is selected from CR^8R^9 , NR^8 , and O;

ring M is selected from 5-10 membered aryl and 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl contains 1-4 heteroatoms selected from N, O, and S;

R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen, deuterium, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, and C_{3-6} cycloalkoxy, wherein the C_{1-6} alkyl and C_{1-6} alkoxy are unsubstituted or substituted with one or more R_i , and the C_{3-6} cycloalkyl and C_{3-6} cycloalkoxy are unsubstituted or substituted with one or more R_j ;

R^1 is selected from C_{1-6} alkyl, C_{3-10} cycloalkyl- $(\text{C}_{1-6} \text{ alkyl})_m$ -, 4-10 membered heterocyclyl- $(\text{C}_{1-6} \text{ alkyl})_n$ -, 5-10 membered heteroaryl- $(\text{C}_{1-6} \text{ alkyl})_p$ -, and 5-10 membered aryl- $(\text{C}_{1-6} \text{ alkyl})_q$ -, wherein $n = 0$ or 1 , $m = 0$ or 1 , $p = 0$ or 1 , and $q = 0$ or 1 ; the heterocyclyl and heteroaryl each independently contain 1-4 ring heteroatoms selected from O, N, and S, wherein the C_{1-6} alkyl is unsubstituted or substituted with one or more R_i , the C_{3-10} cycloalkyl is unsubstituted or substituted with one or more R_j , the 4-10

membered heterocyclyl is unsubstituted or substituted with one or more R_k , and the 5-10 membered aryl and 5-10 membered heteroaryl are unsubstituted or are each independently substituted with one or more R_l ;

R^2 is selected from 5-10 membered heteroaryl and 4-10 membered heterocyclyl, wherein the 5-10 membered heteroaryl and 4-10 membered heterocyclyl each independently contain 1-4 heteroatoms selected from N, O, and S, and the 5-10 membered heteroaryl and 4-10 membered heterocyclyl are unsubstituted or substituted with one or more identical or different R^b ;

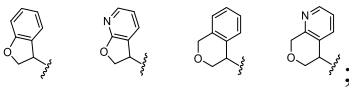
n_1 and n_2 are each independently 0, 1, or 2;

each R_i , R_j , R_k , and R_l is independently selected from hydroxy, deuterium, halogen, cyano, C_{1-6} alkyl optionally substituted with one or more groups selected from halogen, cyano, and hydroxy, C_{1-6} alkoxy optionally substituted with one or more groups selected from halogen, cyano, hydroxy, $-NR'R''$, and C_{1-6} alkoxy, C_{3-10} cycloalkyl, and 5-10 membered heteroaryl optionally substituted with one or more C_{1-6} alkyl, the 5-10 membered heteroaryl contains 1-4 heteroatoms selected from N, O, and S, wherein R' and R'' are each independently selected from H, C_{1-6} alkyl, and halogenated C_{1-6} alkyl, or R' and R'' , together with the nitrogen atom attached thereto, form a 4-8 membered heterocyclyl, wherein the 4-8 membered heterocyclyl contains 1-4 heteroatoms selected from N, O, and S;

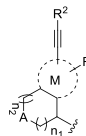
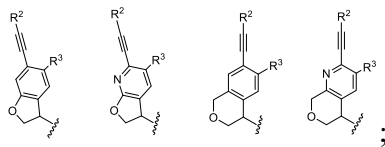
each R^b is independently selected from hydroxy, deuterium, cyano, halogen, $-NR'R''$, C_{1-6} alkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl, wherein the C_{1-6} alkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl are unsubstituted or are each independently substituted with one or more substituents selected from halogen, hydroxy, cyano, and C_{1-6} alkoxy; in $-NR'R''$, R' and R'' are each independently selected from hydrogen, C_{1-6} alkyl, and halogenated C_{1-6} alkyl, or R' and R'' , together with the nitrogen atom attached thereto, form a 4-8 membered heterocyclyl, wherein the 4-8 membered heterocyclyl contains 1-4 heteroatoms selected from N, O, and S.

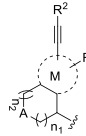
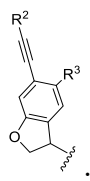
2. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to claim 1, wherein

ring M is selected from 5-6 membered aryl and 5-6 membered heteroaryl;
preferably, ring M is selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, and thiazolyl;
further preferably, ring M is selected from phenyl and pyridyl;
preferably, ring A is selected from O;
preferably, n_1 and n_2 are each independently 0 or 1;

preferably, the group  is selected from ;

preferably, the group  is selected from ;

preferably, the group  is selected from ;

preferably, the group  is selected from .

3. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to claim 1, wherein

R^2 is selected from 5-6 membered heteroaryl and 4-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl and 4-6 membered heterocyclyl each independently contain 1-3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl and 4-6 membered heterocyclyl are unsubstituted or are each independently substituted with one or more identical or different R^b ; or

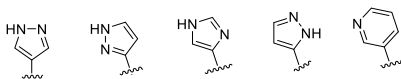
R^2 is selected from 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl, 4-6 membered heterocyclyl, and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 heteroatoms selected from N, O, and S, the 5-6

membered heteroaryl, 4-6 membered heterocyclyl, and 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl are unsubstituted or are each independently substituted with one or more identical or different R^b ;

preferably, R^2 is selected from 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl contains 1-3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl is unsubstituted or substituted with one or more identical or different R^b ;
preferably, R^2 is selected from pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b ; or

preferably, R^2 is selected from 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl contains 1, 2, or 3 N heteroatoms, and the 5-6 membered heteroaryl is unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from pyrazolyl, imidazolyl, and pyridyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b ;

preferably, R^2 is selected from , which are unsubstituted or independently substituted with 1, 2, or 3 R^b ; or

preferably, R^2 is selected from 5-membered heteroaryl, wherein the 5-membered heteroaryl contains 1-3 heteroatoms selected from N, O, and S, and the 5-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^b ;

preferably, R^2 is selected from pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, and isoxazolyl, which are unsubstituted or substituted with 1, 2, or 3 R^b ; or

preferably, R^2 is selected from 5-membered heteroaryl, wherein the 5-membered heteroaryl contains 1-2 heteroatoms selected from N and S, and the 5-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 R^b ;

preferably, R^2 is selected from pyrazolyl, imidazolyl, thiazolyl, and isothiazolyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b ; or

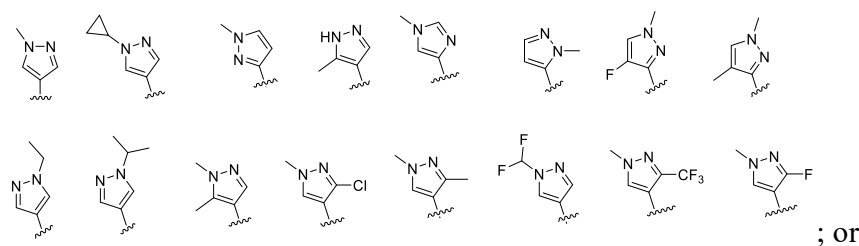
preferably, R^2 is selected from 5-membered heteroaryl, wherein the 5-membered heteroaryl contains 1, 2, or 3 N heteroatoms, and the 5-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from pyrazolyl and imidazolyl, which are unsubstituted or are each independently substituted with 1, 2, or 3 R^b ;

preferably, R^2 is selected from pyrazolyl, wherein the pyrazolyl is independently unsubstituted or substituted with 1, 2, or 3 R^b ;

preferably, R^2 is selected from , wherein the  is unsubstituted or independently substituted with 1, 2, or 3 R^b ;

preferably, R^2 is selected from



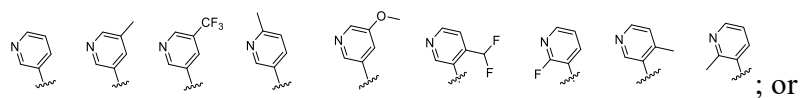
preferably, R^2 is selected from 6-membered heteroaryl, wherein the 6-membered heteroaryl contains 1, 2, or 3 heteroatoms selected from N, O, and S, and the 6-membered heteroaryl is unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from 6-membered heteroaryl, wherein the 6-membered heteroaryl contains 1, 2, or 3 N heteroatoms, and the 6-membered heteroaryl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from pyridyl, wherein the pyridyl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from , wherein the  is unsubstituted or substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from



preferably, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl is unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, wherein the 5-6 membered heteroaryl and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 N heteroatoms, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl is unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from 5-membered heteroaryl-fused 6-membered heterocyclyl, wherein the 5-membered heteroaryl and 6-membered heterocyclyl each independently contain 1, 2, or 3 N heteroatoms, and the 5-membered heteroaryl-fused 6-membered heterocyclyl is unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from imidazolyl-fused piperazinyl, wherein the imidazolyl-fused piperazinyl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b ;

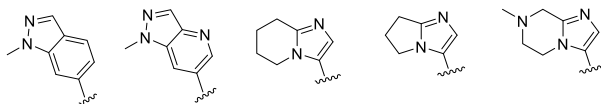
preferably, R^2 is selected from ; or

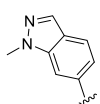
preferably, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl, wherein the 5-6 membered heteroaryl and 5-6 membered heterocyclyl each independently contain 1, 2, or 3 heteroatoms selected from N, O, and S, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl are unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from 5-6 membered heteroaryl-fused 5-6 membered

heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl, wherein the 5-6 membered heteroaryl is selected from imidazolyl, pyrazolyl, and pyridyl, the 5-6 membered heterocyclyl is selected from pyrrolidinyl, piperidinyl, and piperazinyl, and the 5-6 membered heteroaryl-fused 5-6 membered heterocyclyl, 5-6 membered heteroaryl-fused 5-6 membered heteroaryl, and 5-6 membered heteroaryl-fused phenyl are unsubstituted or substituted with one or more identical or different R^b ;

preferably, R^2 is selected from imidazopyrrolidinyl, imidazopiperidinyl, imidazopiperazinyl, pyrazolophenyl, and pyrazolopyridyl, wherein the imidazopyrrolidinyl, imidazopiperidinyl, imidazopiperazinyl, pyrazolophenyl, and pyrazolopyridyl are unsubstituted or substituted with one or more identical or different R^b ;



preferably, R^2 is selected from ; or

preferably, R^2 is selected from 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl contains 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocyclyl is unsubstituted or substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-2 heteroatoms selected from N and O, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are

unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from tetrahydro-2H-pyran-2-yl, oxetanyl, 1,2,3,6-tetrahydropyrid-2-yl, and 3,6-dihydro-2H-pyran-2-yl, wherein the tetrahydro-2H-pyran-2-yl, oxetanyl, 1,2,3,6-tetrahydropyrid-2-yl, and 3,6-dihydro-2H-pyran-2-yl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from , wherein the  is unsubstituted or independently substituted with 1, 2, or 3 identical or different R^b ; or

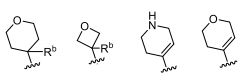
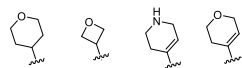
preferably, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom attached thereto, form a 4-6 membered heterocyclyl, wherein the 4-6 membered heterocyclyl contains 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocyclyl is unsubstituted or independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom attached thereto, form a 4-6 membered heterocycloalkyl or 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-3 heteroatoms selected from N, O, and S, and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom attached thereto, form a 4-6 membered heterocycloalkyl or 4-6 membered heterocycloalkenyl, wherein the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl each independently contain 1-2 heteroatoms selected from N and O,

and the 4-6 membered heterocycloalkyl and 4-6 membered heterocycloalkenyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from , wherein R^{2a} and R^{2b} , together with the carbon atom attached thereto, form tetrahydro-2H-pyranyl, oxetanyl, 1,2,3,6-tetrahydropyridyl, and 3,6-dihydro-2H-pyranyl, wherein the tetrahydro-2H-pyranyl, oxetanyl, 1,2,3,6-tetrahydropyridyl, and 3,6-dihydro-2H-pyranyl are unsubstituted or are each independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, R^2 is selected from , wherein the group  is unsubstituted or independently substituted with 1, 2, or 3 identical or different R^b ;

preferably, each R^b is independently selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl, wherein the C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and C_3 - C_6 cycloalkyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 halogens;

preferably, each R^b is independently selected from H, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, and C_3 - C_5 cycloalkyl, wherein the C_1 - C_3 alkyl, C_1 - C_3 alkoxy, and C_3 - C_5 cycloalkyl are unsubstituted or are each independently substituted with 1, 2, 3, or 4 substituents selected from F, Cl, and Br;

preferably, each R^b is independently selected from H, methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

preferably, each R^b is independently selected from methyl, methoxy, and cyclopropyl;

preferably, each R^b is independently selected from cyclopropyl;

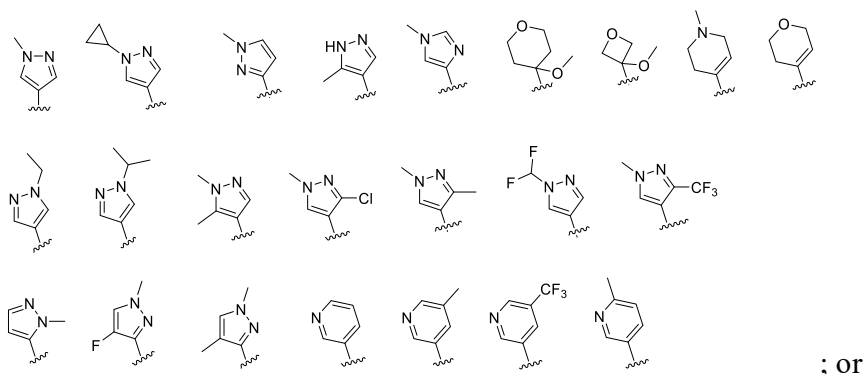
preferably, each R^b is independently selected from methoxy;

preferably, each R^b is independently selected from methyl;

Chemical structures of various heterocyclic compounds, including pyridine, pyrrole, imidazole, and others, with wavy lines indicating attachment points.

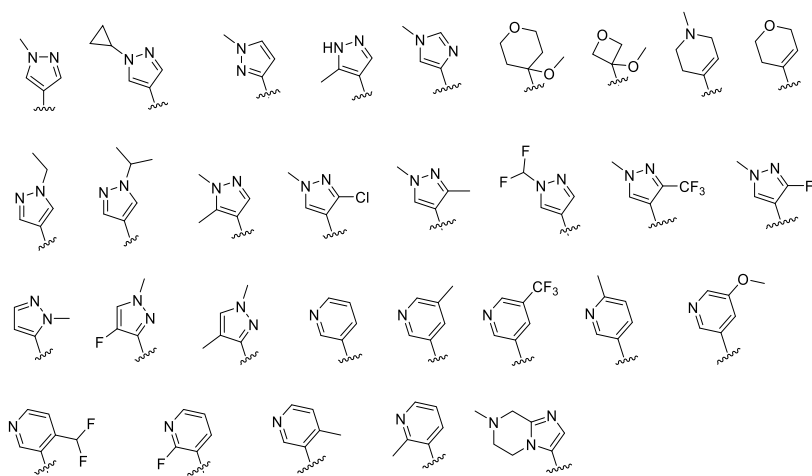
; or

further preferably, R^2 is selected from



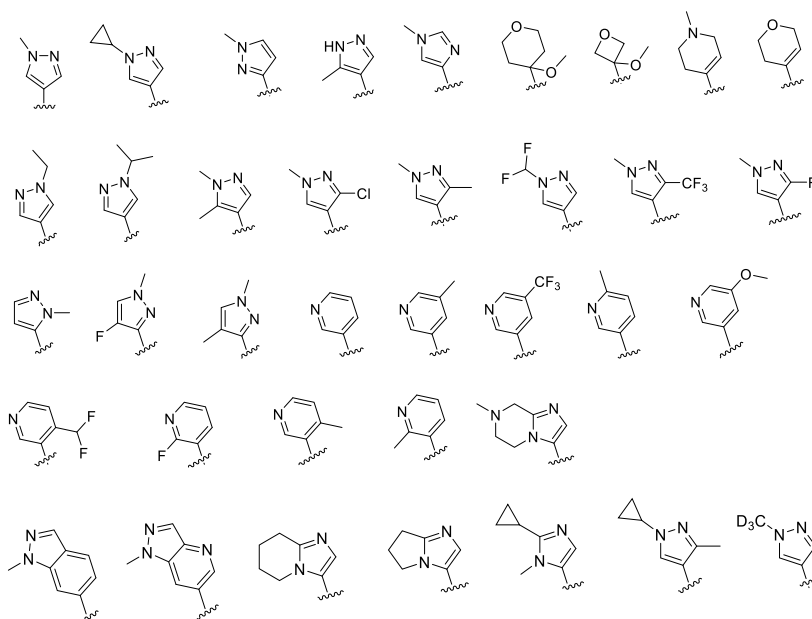
; or

preferably, R^2 is selected from

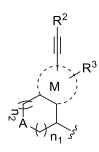


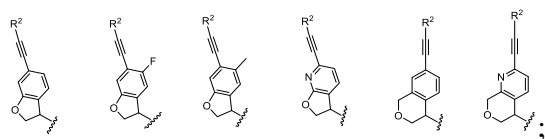
; or

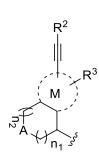
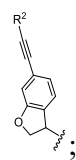
preferably, R^2 is selected from

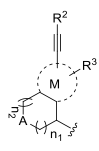


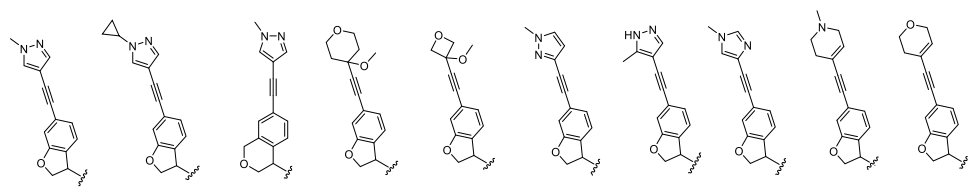
4. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to any one of claims 1 to 3, wherein R^3 is selected from hydrogen, halogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl; preferably, R^3 is selected from hydrogen, F, Cl, Br, C_{1-4} alkyl, C_{5-6} alkyl, and C_{3-5} cycloalkyl; preferably, R^3 is selected from hydrogen, F, Cl, Br, C_{1-4} alkyl, and C_{3-5} cycloalkyl; preferably, R^3 is selected from hydrogen, F, Cl, Br, methyl, ethyl, propyl, isopropyl, butyl, cyclopropyl, cyclobutyl, and cyclopentyl; preferably, R^3 is selected from hydrogen, F, Cl, methyl, ethyl, and cyclopropyl; or preferably, R^3 is selected from hydrogen, F, Cl, Br, and C_{1-4} alkyl; preferably, R^3 is selected from hydrogen, F, Cl, methyl, and ethyl; preferably, R^3 is selected from hydrogen, F, and methyl;

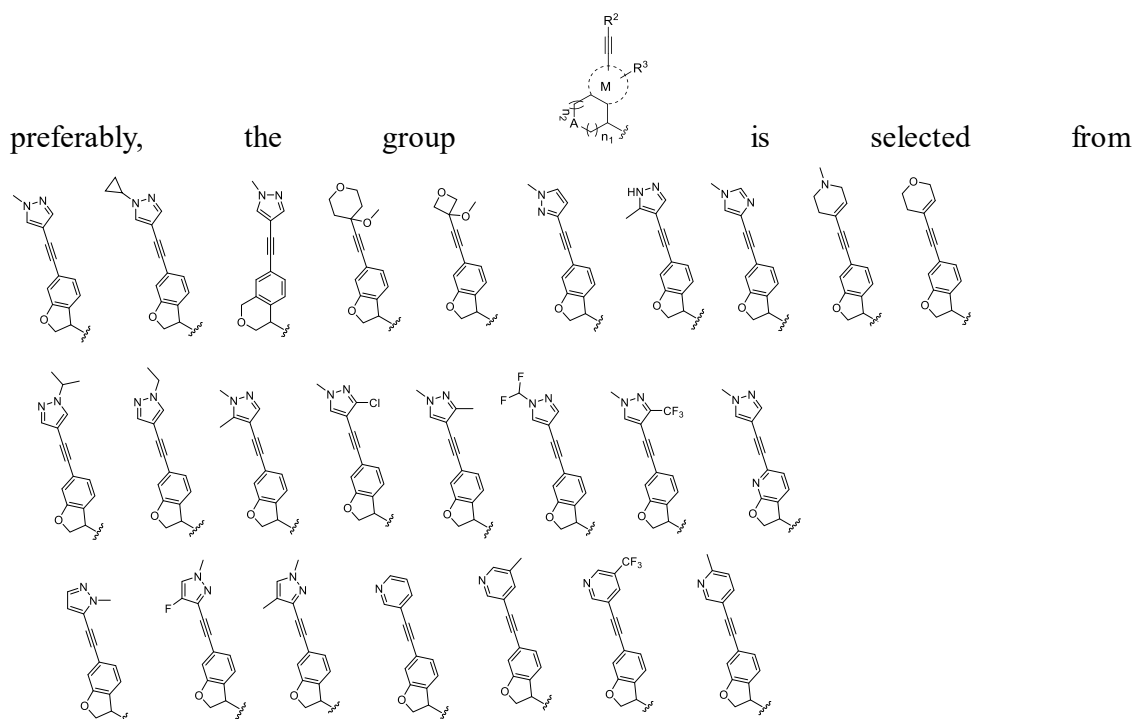
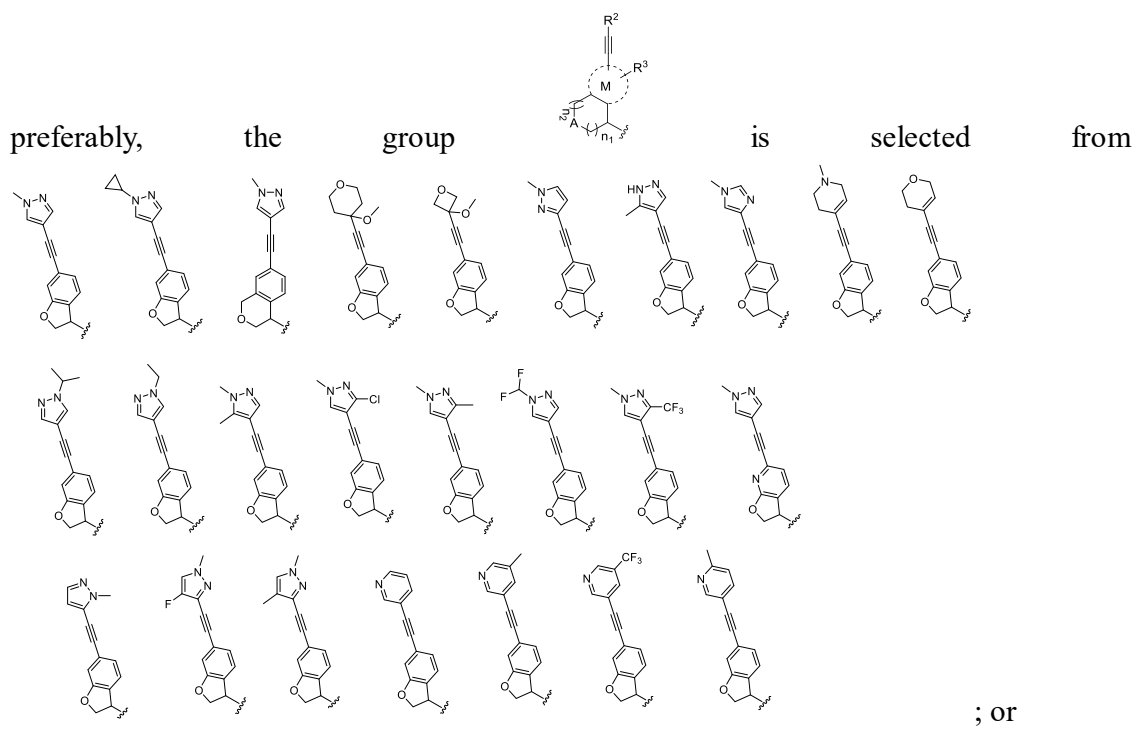
preferably, the group  is selected from

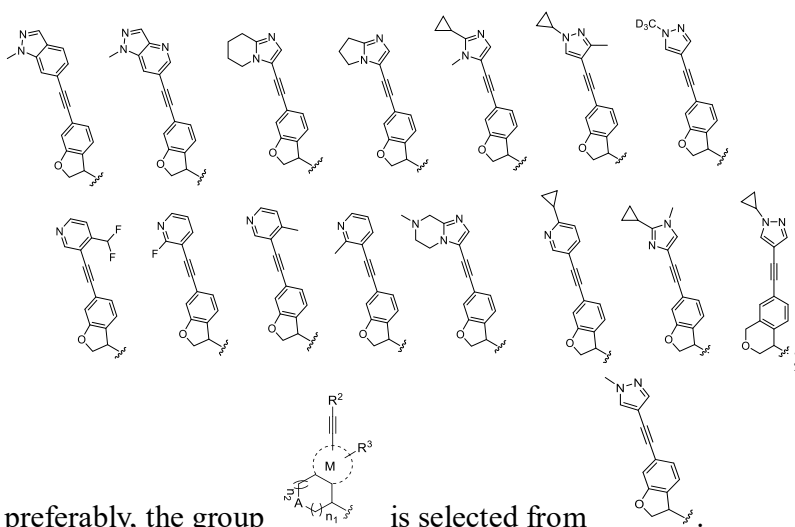


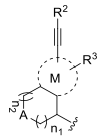
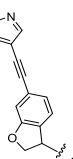
preferably, the group  is selected from ;

preferably, the group  is selected from

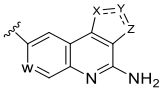


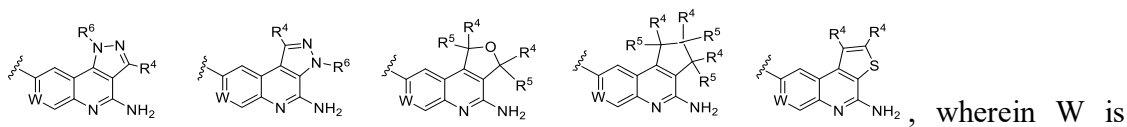




preferably, the group  is selected from .

5. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to claim 1, wherein

the group  is selected from



selected from N and CR⁷;

preferably, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, and C₁₋₆ alkyl;

preferably, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, C₁₋₄ alkyl, and C₅₋₆ alkyl;

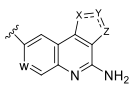
preferably, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, halogen, and C₁₋₄ alkyl;

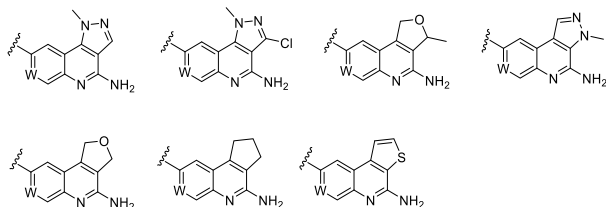
preferably, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, F, Cl, Br, methyl, ethyl, propyl, and isopropyl;

preferably, R⁴, R⁵, R⁶, and R⁷ are each independently selected from hydrogen, F, Cl, and methyl;

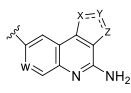
further preferably, R⁴, R⁵, R⁶, and R⁷ described above may be further deuterated;

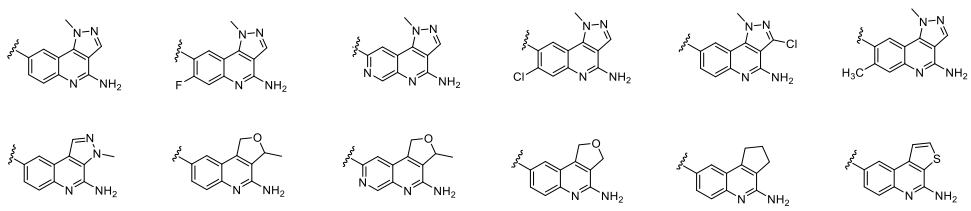
preferably, R^4 , R^5 , R^6 , and R^7 are each independently selected from hydrogen, F, Cl, methyl, and $-CD_3$;

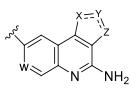
preferably, the group  is selected from

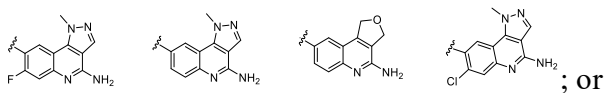


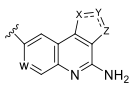
, wherein W is selected from N and CR^7 , and R^7 is selected from H, F, Cl, and methyl;

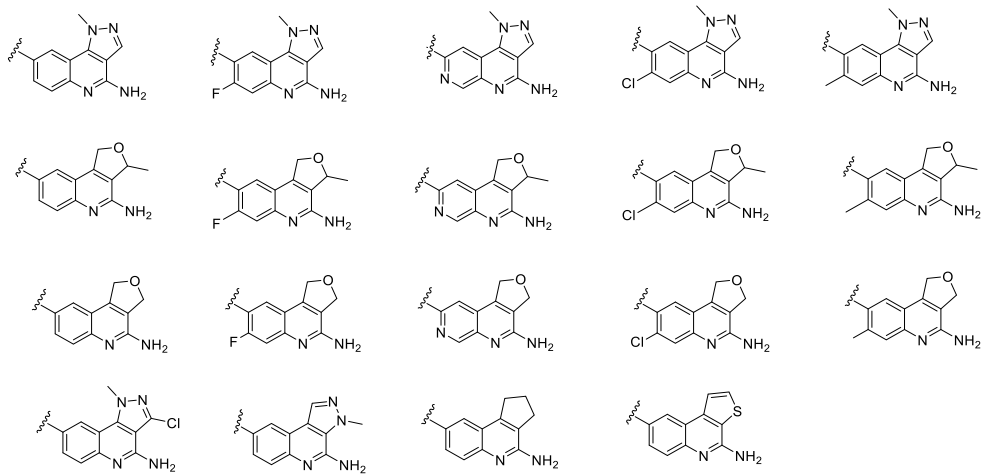
preferably, the group  is selected from:



preferably, the group  is selected from



preferably, the group  is selected from

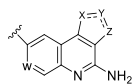


;

preferably,

the

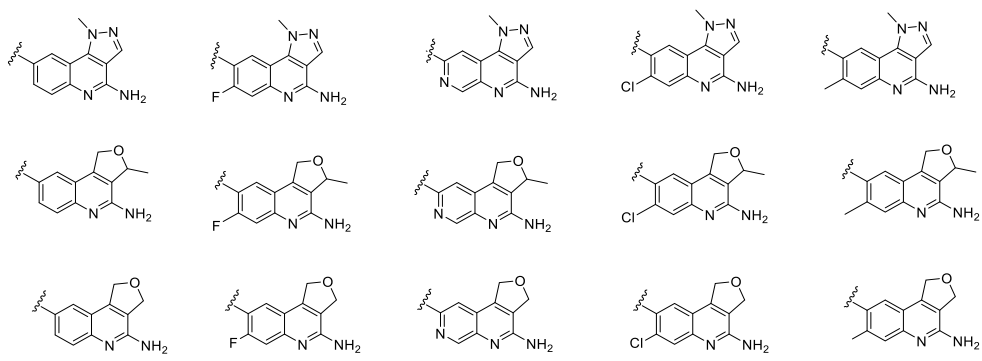
group



is

selected

from

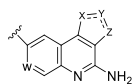


;

preferably,

the

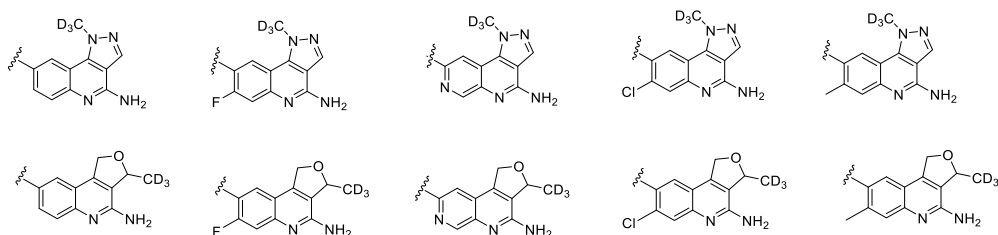
group



is

selected

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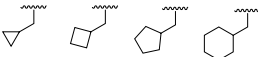


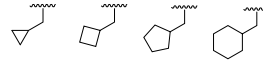
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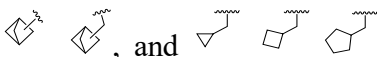
6. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to claim 1, wherein

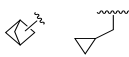
R¹ is selected from C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkyl-C₁₋₆ alkyl-, and 5-10 membered heteroaryl-, wherein the C₁₋₆ alkyl is unsubstituted or substituted with one or more R_i, the C₃₋₁₀ cycloalkyl is unsubstituted or substituted with one or more R_j, and

the 5-10 membered heteroaryl is unsubstituted or substituted with one or more R_i ;
preferably, R^1 is selected from C_{1-4} alkyl, C_{3-6} monocycloalkyl, C_{5-8} bridged cycloalkyl, C_{5-8} spirocycloalkyl, C_{3-6} monocycloalkyl- C_{1-4} alkyl-, C_{5-8} bridged cycloalkyl- C_{1-4} alkyl-, C_{5-8} spirocycloalkyl- C_{1-4} alkyl-, and 5-6 membered heteroaryl, wherein the C_{1-4} alkyl is unsubstituted or substituted with one or more R_i , the C_{3-6} monocycloalkyl, C_{5-8} bridged cycloalkyl, and C_{5-8} spirocycloalkyl are unsubstituted or substituted with one or more R_j , and the 5-10 membered heteroaryl is unsubstituted or substituted with one or more R_i ;

preferably, R^1 is selected from methyl, ethyl, propyl, butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, , , pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, and thiazolyl, wherein the methyl, ethyl, propyl, and butyl are unsubstituted or substituted with one or more R_i , the cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl, , and  are unsubstituted or substituted with one or more R_j , and the pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, imidazolyl, triazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, and thiazolyl are unsubstituted or substituted with one or more R_i ;

preferably, R^1 is selected from methyl, ethyl, cyclopropyl, cyclobutyl, cyclopentyl, , pyrazolyl, imidazolyl, triazolyl, and pyrrolyl, wherein the methyl and ethyl are unsubstituted or substituted with 1, 2, or 3 R_i , the cyclopropyl, cyclobutyl, cyclopentyl, , and  are unsubstituted or substituted with 1, 2, or 3 R_j , and the pyrazolyl, imidazolyl, triazolyl, and pyrrolyl are unsubstituted or substituted with 1, 2, or 3 R_i ;

preferably, R^1 is selected from methyl, ethyl, cyclopropyl, , and pyrazolyl, wherein the methyl and ethyl are unsubstituted or substituted with 1, 2, or 3 R_i , the

cyclopropyl and   are unsubstituted or substituted with 1, 2, or 3 R_j, and the pyrazolyl is unsubstituted or substituted with 1, 2, or 3 R_i;

preferably, R¹ is selected from methyl, ethyl, cyclopropyl,  , and pyrazolyl, wherein the methyl, ethyl, cyclopropyl, and   are unsubstituted, and the pyrazolyl is unsubstituted or substituted with 1, 2, or 3 R_i;

preferably, each R_i is independently selected from halogen, halogenated C₁₋₆ alkyl, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

preferably, each R_i is independently selected from halogen, halogenated C₁₋₄ alkyl, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

preferably, each R_i is independently selected from halogen, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

preferably, each R_i is independently selected from F, Cl, Br, methyl, ethyl, propyl, isopropyl, cyclopropyl, and cyclobutyl;

preferably, each R_i is independently selected from F, Cl, methyl, and ethyl;

preferably, each R_i is independently selected from methyl;

preferably, each R_i is independently selected from D, F, Cl, methyl, and ethyl;

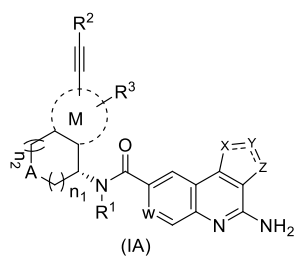
preferably, R¹ is selected from methyl, ethyl, cyclopropyl, and   .

preferably, R¹ is selected from methyl, ethyl, and cyclopropyl;

preferably, R¹ is selected from methyl;

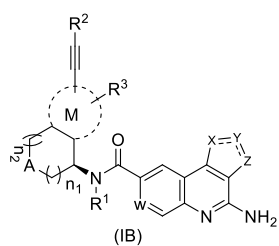
preferably, R¹ is selected from -CD₃.

7. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to any one of claims 1 to 6, wherein formula (I) has a structure shown as formula IA:



, wherein R^1 , R^2 , R^3 , A, n_1 , n_2 , ring M, W, X, Y, Z, and --- are each as defined in formula I; or

formula (I) has a structure shown as formula IB:



, wherein R^1 , R^2 , R^3 , A, n_1 , n_2 , ring M, W, X, Y, Z and --- are each as defined in formula I.

8. The compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to any one of claims 1 to 7, wherein the compound represented by formula (I) is selected from:

compound 1, compound 2, compound 3, compound 4, compound 5, compound 6, compound 7, compound 8, compound 9, compound 10, compound 11, compound 12, compound 13, compound 14, compound 15, compound 16, compound 17, compound 18, compound 19, compound 20, compound 21, compound 22, compound 23, compound 24, compound 25, compound 26, compound 27, compound 28, compound 29, compound 30, compound 31, compound 32, compound 33, compound 34, compound 35, compound 36, compound 37, compound 38, compound 39, compound 40, compound 41, compound 42, compound 43, compound 44, compound 45, compound 46, compound 47, compound 48, compound 49, compound 50, compound 51, compound 52, compound 53, compound 54, compound 55, compound 56, compound 57, compound 58, compound 59, compound 60, compound 61, compound 62, compound 63, compound 64, compound 65, compound 66, compound 67, compound 68, compound 69, compound 70, compound 71, compound 72,

compound 73, compound 74, compound 75, compound 76, compound 77, compound 78, compound 79, compound 80, compound 81, compound 82, compound 83, compound 84, compound 85, compound 86, compound 87, compound 88, compound 89, compound 90, compound 91, compound 93, compound 94, compound 95, compound 98, compound 100, compound 101, compound 103, compound 104, compound 105, compound 106, compound 107, compound 108, compound 113, compound 114, compound 115, compound 116, compound 117, compound 118, compound 119, compound 120, compound 121, compound 122, compound 123, compound 124, compound 125, compound 126, compound 127, compound 128, compound 129, compound 130, compound 131, compound 132, compound 133, compound 134, compound 135, compound 136, compound 137, compound 138, compound 139, compound 140, compound 141, compound 142, compound 143, compound 144, compound 145, compound 146, compound 147, compound 148, compound 149, compound 150, compound 151, compound 152, compound 153, compound 154, compound 155, compound 156, compound 157, and an S-configuration of any of the compounds described above.

9. A pharmaceutical composition for treating and/or preventing a disease associated with abnormal PRMT5 expression, comprising a therapeutically and/or prophylactically effective amount of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to any one of claims 1 to 8, and an optional pharmaceutically acceptable excipient;

preferably, the disease associated with abnormal PRMT5 expression is a tumor or cancer;
preferably, the disease associated with abnormal PRMT5 expression is a disease associated with abnormal PRMT5 expression and characterized by MTAP deletion;
preferably, the disease associated with abnormal PRMT5 expression is a tumor or cancer characterized by MTAP deletion.

10. Use of the compound or the tautomer, the stereoisomer, the pharmaceutically acceptable salt, or the deuterated compound thereof according to any one of claims 1 to 8, or the pharmaceutical composition according to claim 9 in manufacture of a medicament

for treating and/or preventing a disease associated with abnormal PRMT5 expression and/or in treating and/or preventing a disease associated with abnormal PRMT5 expression;

preferably, the disease associated with abnormal PRMT5 expression is a tumor or cancer;

preferably, the disease associated with abnormal PRMT5 expression is a disease associated with abnormal PRMT5 expression and characterized by MTAP deletion;

preferably, the disease associated with abnormal PRMT5 expression is a tumor or cancer characterized by MTAP deletion.