

PYRIDAZINONE PARP INHIBITOR, AND PREPARATION METHOD THEREFOR, AND PHARMACEUTICAL COMPOSITION AND USE THEREOF

TECHNICAL FIELD

5 The present disclosure relates to the field of pharmaceuticals, and particularly, to a pyridazinone derivative, a method for preparing same, a pharmaceutical composition thereof, and use thereof.

BACKGROUND OF THE INVENTION

10 Poly(ADP-ribose)polymerase-1 (PARP1) is present in eukaryotic cells and catalyzes the poly-ADP-ribosylation, among other family members. PARP1 is the first known nuclear enzyme with the functionality of catalyzing poly(ADP-ribosyl)phosphate, and other subtypes, such as PARP2, PARP3, PARP4 (VPARP), PARP5a (tankyrase1), PARP5b (tankyrase2), PARP7 (TiPARP), PARP1, were then subsequently isolated.

15 PARP7 is a gene regulated by AHR and an important member of the PARP family. PARP7 can transfer only one mono-ADP-ribose (MAR), belonging to MonoPARPs. The PARP catalytic domain of PARP7 contains a zinc finger motif that can confer DNA binding capacity and a WWE domain that can mediate protein interactions. The mediated mono-ADP-ribosylation is a reversible
20 post-translational modification involved in a variety of important biological processes, such as immune cell functions, transcriptional regulation, protein expression, and DNA repair.

 Furthermore, PARP7 is part of a negative feedback loop that regulates the activity of AHR, which can regulate the immune functions, inflammation and stem differentiation, and play a role
25 in cancers. PARP7 has been demonstrated to be overactive in tumors and plays a key role in cancer cell survival. More importantly, many cancer cells rely on PARP7 for intrinsic cell survival, and studies have shown that PARP7 allows cancer cells to “hide” from the immune system; the inhibition of PARP7 can effectively inhibit the growth of cancer cells, restore interferon signaling, and inhibit the “brakes” of innate and adaptive immune mechanisms. In several cancer models,
30 PARP7 inhibitors exhibited durable tumor growth inhibition, potent anti-proliferative activity, and restoration of interferon signaling.

Stroke is mainly divided into hemorrhagic stroke and ischemic stroke. The former mainly includes

cerebral hemorrhage, subarachnoid hemorrhage, and the like; the latter mainly includes transient ischemic attack, cerebral thrombosis, cerebral embolism, and the like. Studies have shown that circular RNAs (circRNAs) are highly expressed in the central nervous system and are involved in the regulation of physiological and pathophysiological processes. Using circRNA microarrays, a significant increase in the circRNA Hect1 (circHect1) level in an ischemic brain tissue was found in a transient middle cerebral artery occlusion (tMCAO) mouse stroke model, and this finding was further validated in acute ischemic stroke (AIS) patient plasma samples. The reduction in circHect1 expression significantly reduced the infarct area, alleviated neuronal defects, and improved the activation of astrocytes in tMCAO mice. Mechanistically, circHect1 acts as an endogenous MIR142 (microRNA 142) sponge to inhibit MIR142 activity, thereby inhibiting PARP7 expression and subsequently inhibiting astrocyte activation through macroautophagy/autophagy. It can be seen from the results that circHect1 and its coupling mechanism are involved in cerebral ischemia, and the inhibition of PARP7 expression can also be used to treat stroke.

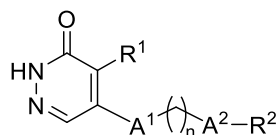
Stroke is a common disease in middle-aged and elderly populations, and some survivors may have disability to various extents, even severe disability. Existing drugs are intended to block the neuronal necrosis caused by ischemia, prolong the ischemic tolerance and treatment time window, enhance the neuronal viability, reverse the ischemic semi-dark zone, reduce the infarct volume, and promote the recovery of nerve function in the treatment of stroke, but none of the drugs has yet achieved an accepted therapeutic effect.

RBN-2397 is the first compound with potent inhibitory activity and selectivity for PARP7. However, the compound is only suitable for anti-tumor applications, and the large molecular weight makes it difficult to permeate the blood-brain barrier and thus difficult to apply to central nervous system diseases such as stroke.

SUMMARY

Objectives: The first objective of the present disclosure is to provide a pyridazinone derivative having inhibitory activity against PARP, the second objective is to provide a method for preparing the compound, the third objective is to provide a pharmaceutical composition comprising the compound, and the fourth objective is to provide use of the compound and the pharmaceutical composition thereof.

Technical solution: In order to solve the technical problems in the prior art, the present disclosure provides a compound of formula (I), or a racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof:

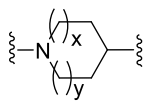


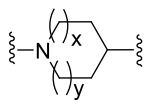
(I)

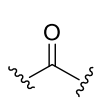
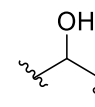
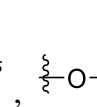
wherein:

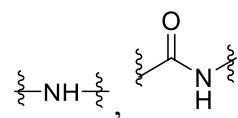
n is selected from 0, 1, 2, 3, and 4;

R¹ is selected from hydrogen, deuterium, halogen, cyano, nitro, C₁-C₁₂ haloalkyl, C₁-C₁₂ alkyl, C₁-C₁₂ alkyloxy, C₁-C₁₂ alkylthio, C₁-C₁₂ alkylsulfonyl, and -C(O)N(R¹¹)(R¹²); R¹¹ and R¹² are identical or different, and are each independently selected from H, deuterium, and C₁-C₆ alkyl;

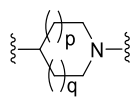


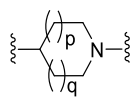
A¹ is selected from -O-, -S-, , and -N(R³)-, wherein x and y are each independently selected from 0, 1, and 2; R³ is selected from H, deuterium, C₁-C₁₂ alkyl, and C₃-C₁₄ cycloalkyl;

A² is absent or selected from methylene, vinylene, ethynylene, , , ,



, and the following groups unsubstituted or optionally substituted with one, two,



or more (preferably, one) R_{a2}: , C₆-C₁₄ aryl, and 5- to 14-membered heteroaryl (preferably, 5- to 14-membered heteroaryl containing one nitrogen atom), wherein p and q are each independently selected from 0, 1, and 2; the R_{a2} groups are identical or different, and are each independently selected from hydrogen, deuterium, halogen, cyano, hydroxy, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ alkyloxy, C₁-C₁₂ haloalkyl, C₁-C₁₂ haloalkyloxy, -C(O)OR_{a21}, -C(O)R_{a22}, -N(R_{a23})(R_{a24}), -S(O)₂R_{a25}, and -S(O)R_{a26}; the R_{a21}, R_{a22}, R_{a23}, R_{a24}, R_{a25}, and R_{a26} groups are identical or different and are each independently selected from H, deuterium, C₁-C₁₂ alkyl, and C₁-C₁₂ alkyl-C(O)-;

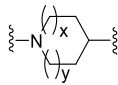
R² is selected from the following groups unsubstituted or optionally substituted with one, two, or more (preferably, one or two) R²¹: C₆-C₁₄ aryl, 5- to 14-membered heteroaryl (preferably, 5- to 14-membered heteroaryl containing one or two nitrogen or sulfur atoms), 3- to 8-membered heterocyclyl (preferably, 3- to 8-membered heterocyclyl containing one nitrogen atom), C₁-C₁₂ alkyl, -S(O)₂-NH-, -C(O)NH₂, and NH₂-S(O)₂-NH-; the R²¹ groups are identical or different, and

are each independently selected from hydrogen, deuterium, halogen, cyano, hydroxy, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ haloalkyl, C₆-C₁₄ aryl, 5- to 14-membered heteroaryl (preferably, 5- to 14-membered heteroaryl containing one or two nitrogen or sulfur atoms), 3- to 8-membered heterocyclyl (preferably, 3- to 8-membered heterocyclyl containing one nitrogen atom), R₂₁-O-, -C(O)OR₂₂, -C(O)R₂₃, -N(R₂₄)(R₂₅), -S(O)₂R₂₆, and -S(O)R₂₇; the R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, and R₂₇ groups are identical or different, and are each independently selected from H, deuterium, C₁-C₆ alkyl, C₁-C₆ haloalkyl, 3- to 14-membered cycloalkyl, 3- to 14-membered cycloalkyl-C₁-C₆ alkyl, C₆-C₁₄ aryl, 5- to 14-membered heteroaryl, and 3- to 8-membered heterocyclyl.

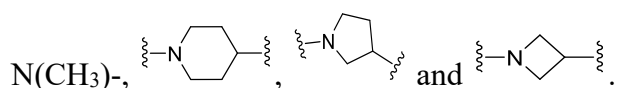
According to the embodiments of the present disclosure, n is selected from 0, 1, and 2.

According to the embodiments of the present disclosure, R¹ is selected from halogen, cyano, and trifluoromethyl.

According to the embodiments of the present disclosure, R¹ is trifluoromethyl.

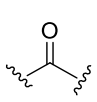
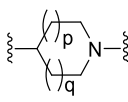
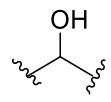
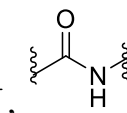
According to the embodiments of the present disclosure, A¹ is selected from  and -N(R³)-, wherein x and y are each independently selected from 0, 1, and 2; R³ is selected from H and C₁-C₆ alkyl.

According to the embodiments of the present disclosure, A¹ is selected from -NH-, -

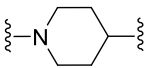
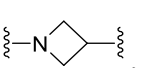
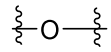
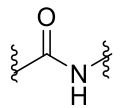
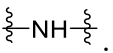


According to the embodiments of the present disclosure, A¹ is selected from -NH-.

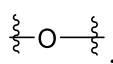
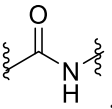
According to the embodiments of the present disclosure, A² is absent or selected from

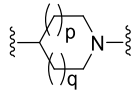
vinylene, ethynylene, , , , , , , C₆-C₁₀ arylene, and 5- to 10-membered heteroarylene (preferably, 5- to 10-membered heteroarylene containing one nitrogen atom), wherein p and q are each independently selected from 0, 1, and 2.

According to the embodiments of the present disclosure, A² is absent or selected from

vinylene, ethynylene, phenylene, , , , , , , and .

According to the embodiments of the present disclosure, A² is selected from ethynylene,

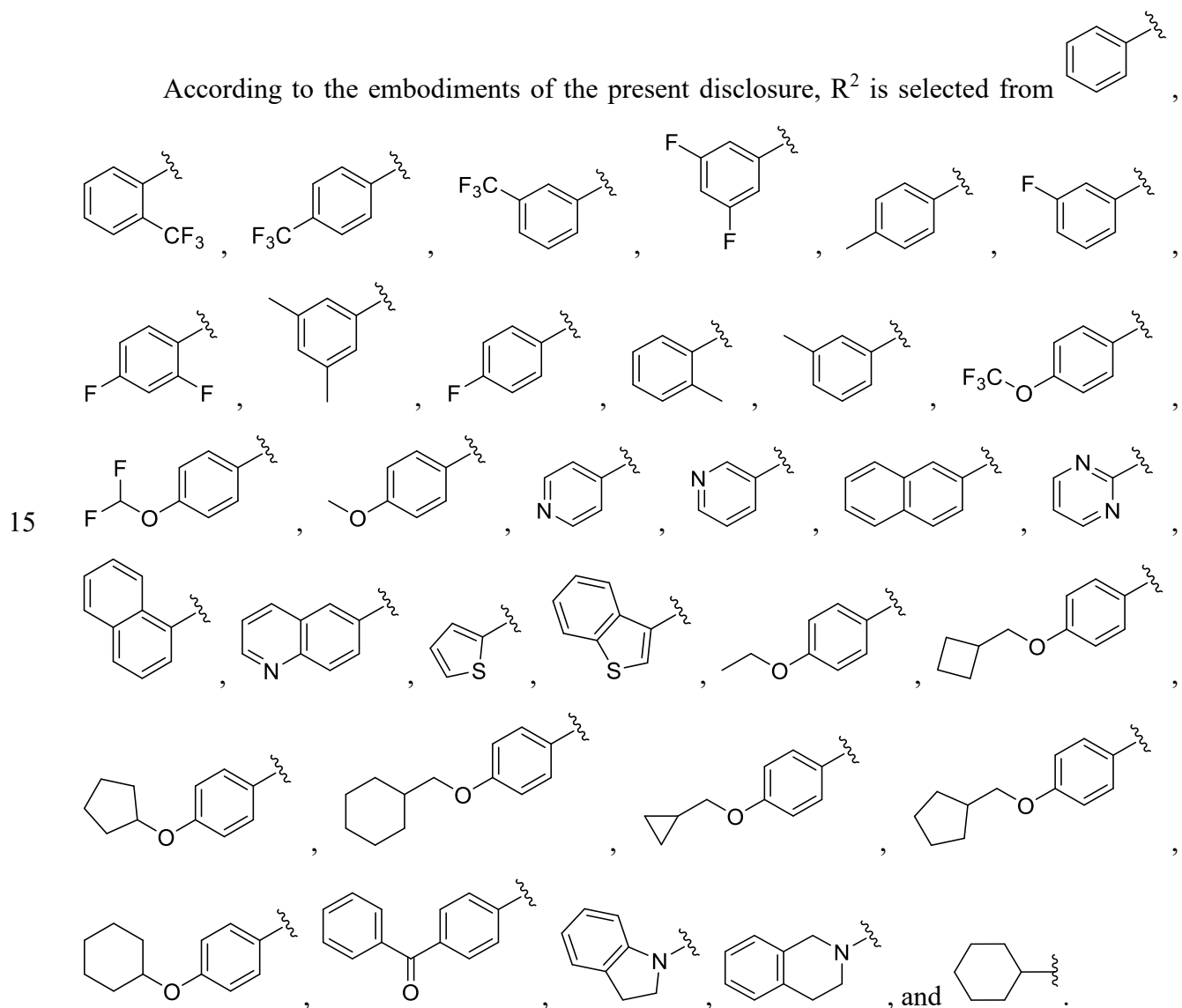
5 , , , , and .

According to the embodiments of the present disclosure,  is unsubstituted or optionally substituted with one, two, or more (preferably, one) R_{a2}, and the R_{a2} groups are identical or different, and are each independently selected from C₁-C₆ alkyl, C₁-C₆ alkyloxy, trifluoromethyl, 2,2-difluoroethyl, methoxy, hydroxy, amino, methylamino, dimethylamino, 10 acetylamino, carboxyl, methoxycarbonyl, methanesulfonyl, and nitro.

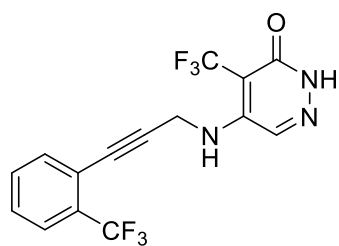
According to the embodiments of the present disclosure, R² is selected from the following groups unsubstituted or optionally substituted with one, two, or more (preferably, one) R²¹: C₆-C₁₀ aryl, 5- to 10-membered heteroaryl (preferably, 5- to 10-membered heteroaryl containing one or 15 two nitrogen or sulfur atoms), and 3- to 8-membered heterocyclyl (preferably, 3- to 8-membered heterocyclyl containing one nitrogen atom); the R²¹ groups are identical or different and are each independently selected from hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkyloxy, C₁-C₆ haloalkyloxy, 3- to 8-membered cycloalkyloxy, 3- to 8-membered cycloalkyl-C₁-C₆ alkyloxy, and C₆-C₁₀ aryl-C(O)-.

20 According to the embodiments of the present disclosure, R² is selected from substituted C₆-C₁₄ aryl and substituted 5- to 14-membered heteroaryl (preferably, 5- to 14-membered heteroaryl containing one or two nitrogen or sulfur atoms); the C₆-C₁₄ aryl or 5- to 14-membered heteroaryl is a monocyclyl or fused rings; the substituent is selected from hydrogen, halogen, cyano, trifluoromethyl, 2,2-difluoroethyl, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkyloxy, amino, 25 methylamino, ethylamino, dimethylamino, diethylamino, C₃-C₆ azacycloalkyl (preferably C₃-C₆ azacycloalkyl containing one nitrogen atom), formyl, acetyl, acetylamino, carbamoyl, and sulfamoyl; the substituent is monosubstituted or disubstituted.

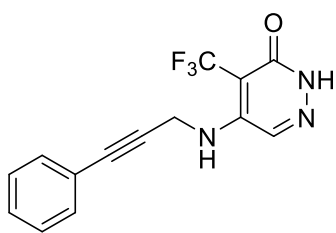
According to the embodiments of the present disclosure, R^2 is selected from substituted C_6 - C_{10} aryl and substituted 5- to 10-membered heteroaryl (preferably, 5- to 10-membered heteroaryl containing one or two nitrogen or sulfur atoms), wherein the C_6 - C_{10} aryl is phenyl, naphthyl, anthryl, indanyl, indenyl, or 1,2,3,4-tetrahydronaphthyl, and the 5- to 10-membered heteroaryl is selected from pyridinyl, thienyl, pyrrolyl, furanyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, indolinyl, quinolyl, isoquinolyl, tetrahydroisoquinolyl, indazolyl, benzothienyl, benzofuranyl, and benzimidazolyl; the substituent is selected from hydrogen, halogen, cyano, trifluoromethyl, 2,2-difluoroethyl, methyl, ethyl, hydroxy, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, azetidiny, tetrahydropyrrol-1-yl, piperidin-1-yl, morpholinyl, piperazinyl, N-methylpiperazinyl, acetyl, acetylamino, carbamoyl, and sulfamoyl; the substituent is monosubstituted or disubstituted.



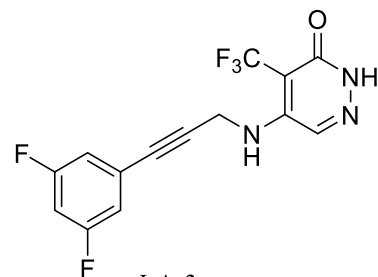
According to the embodiments of the present disclosure, the compound of formula (I) is selected from the following compounds:



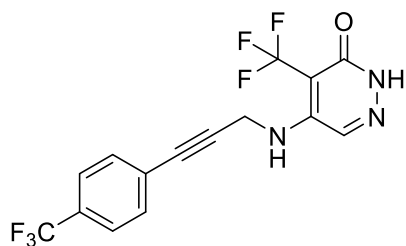
I-A-1



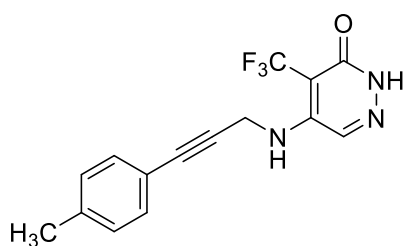
I-A-2



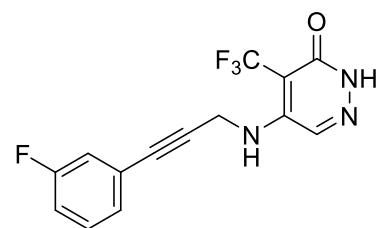
I-A-3



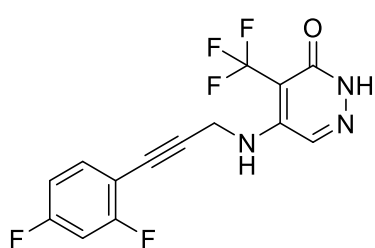
I-A-4



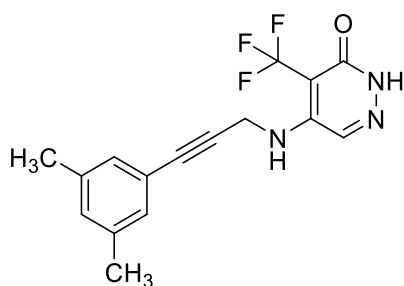
I-A-5



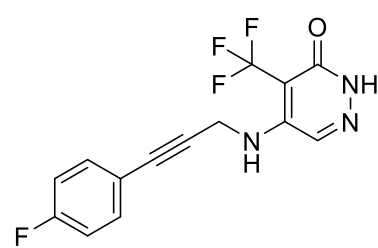
I-A-6



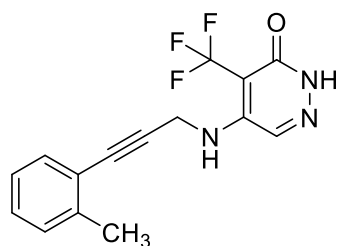
I-A-7



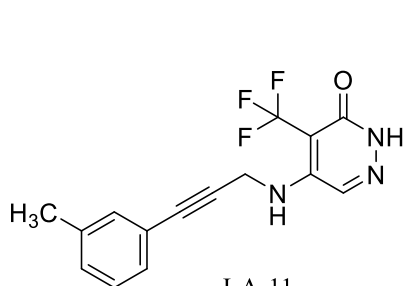
I-A-8



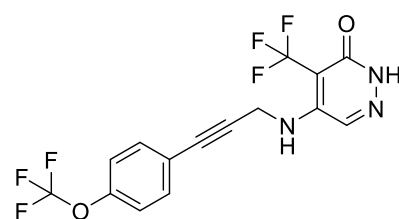
I-A-9



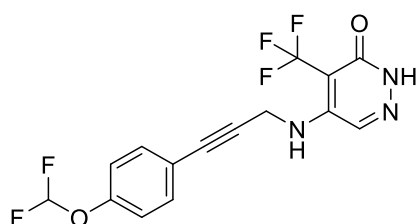
I-A-10



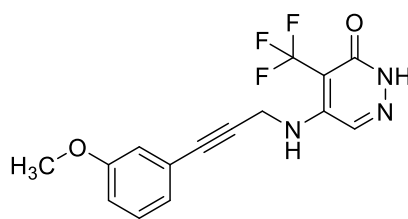
I-A-11



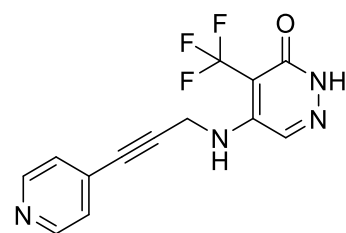
I-A-12



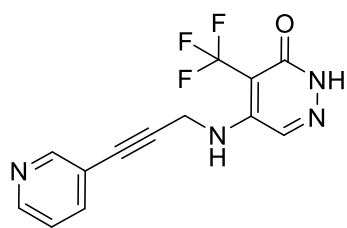
I-A-13



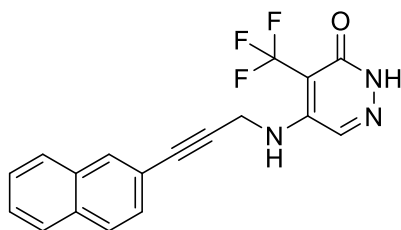
I-A-14



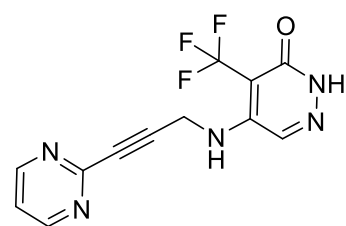
I-A-15



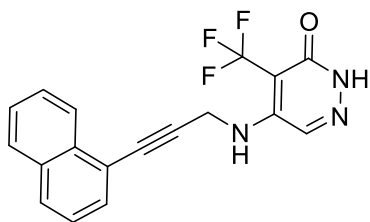
I-A-16



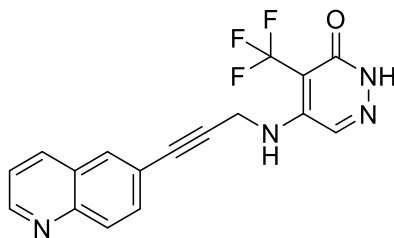
I-A-17



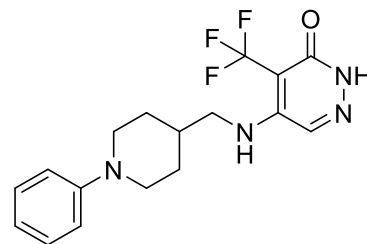
I-A-18



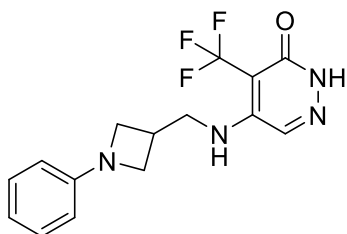
I-A-19



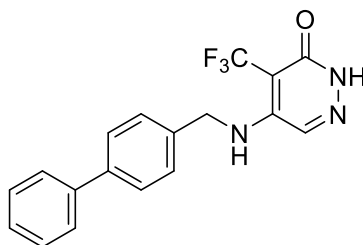
I-A-20



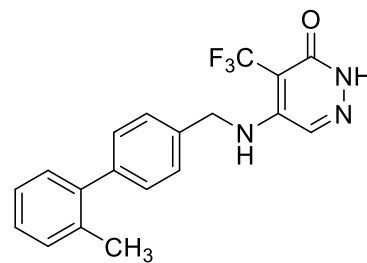
I-B-1



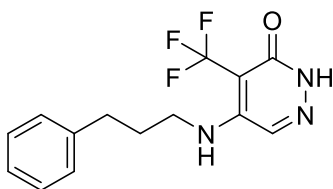
I-B-2



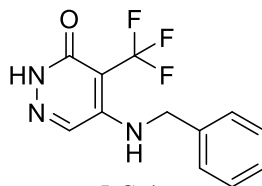
I-C-1



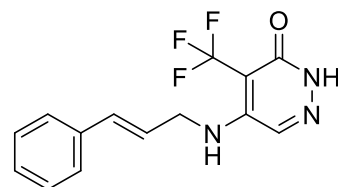
I-C-2



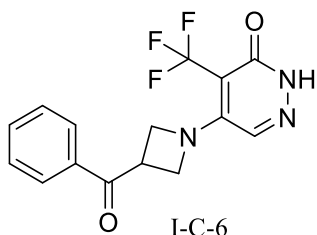
I-C-3



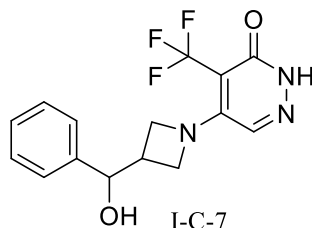
I-C-4



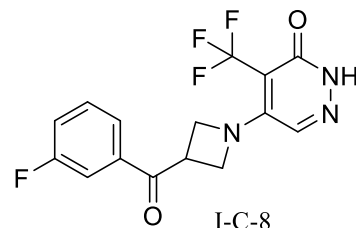
I-C-5



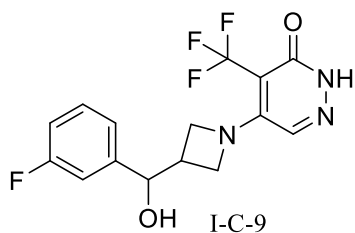
I-C-6



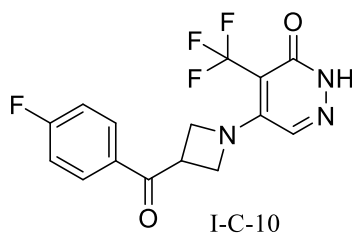
I-C-7



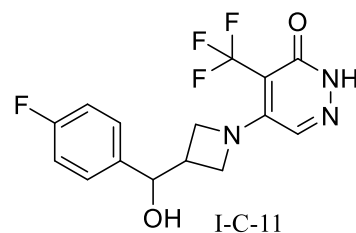
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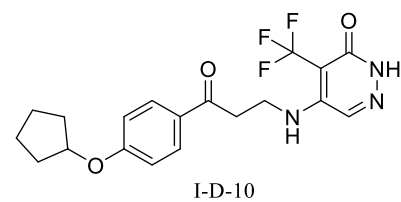
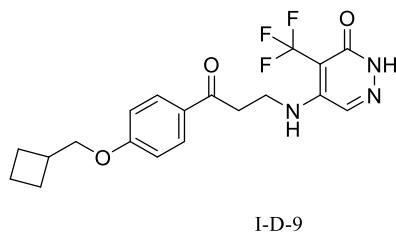
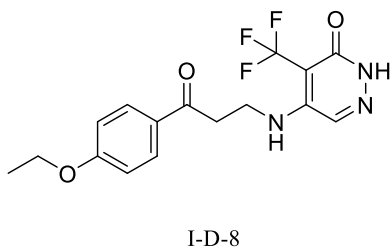
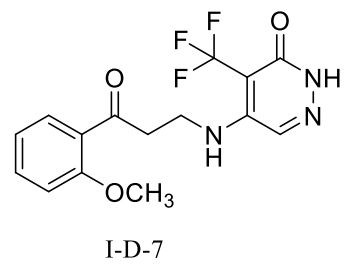
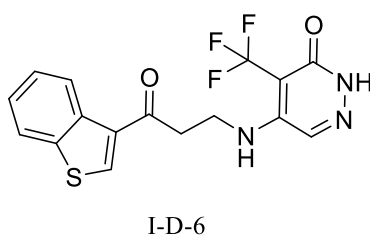
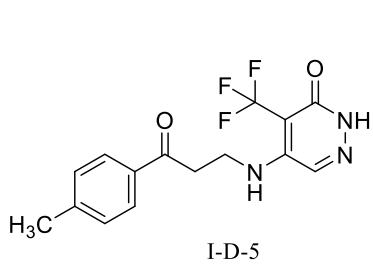
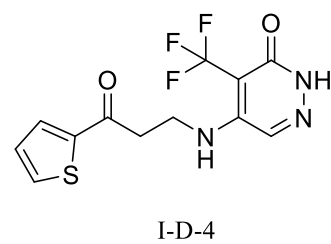
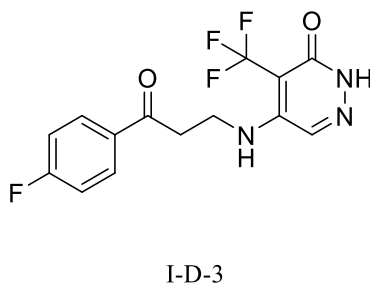
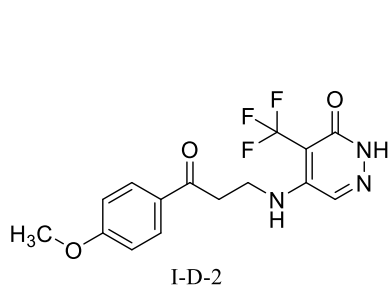
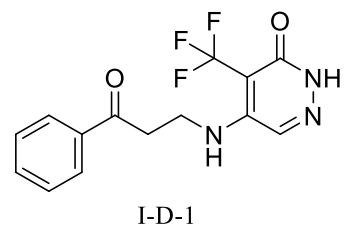
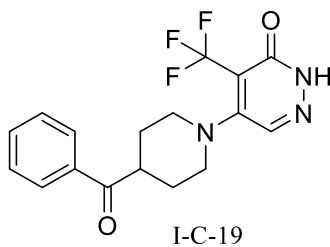
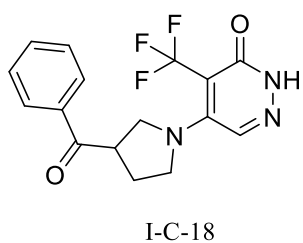
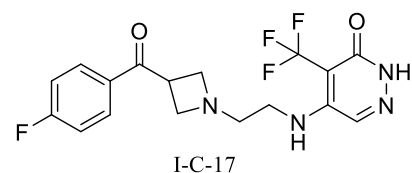
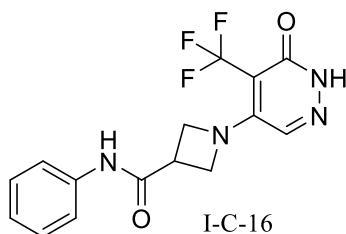
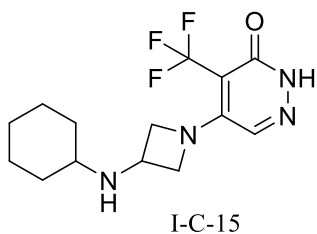
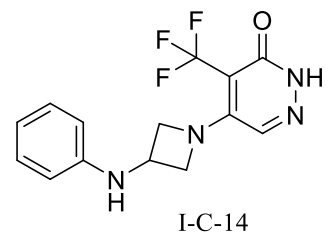
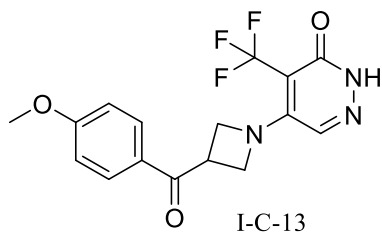
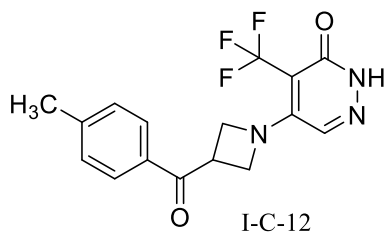
I-C-9

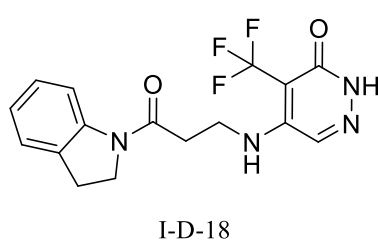
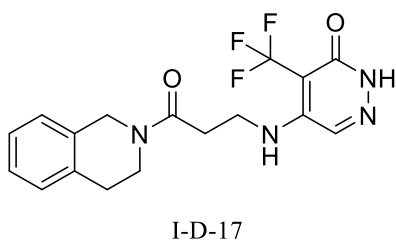
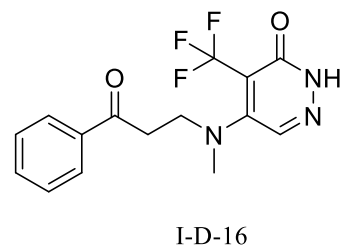
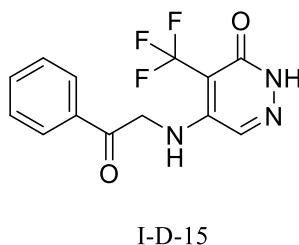
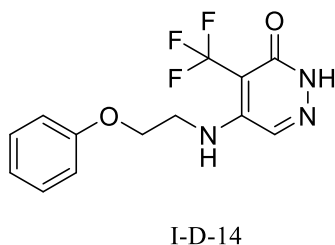
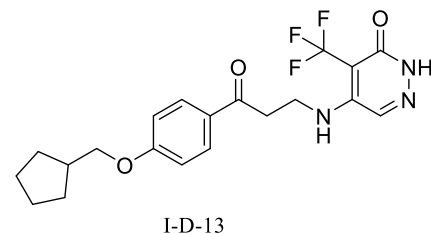
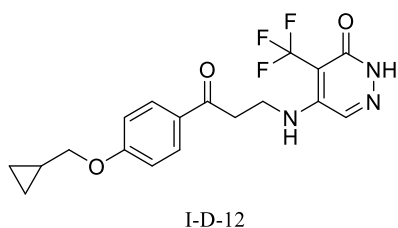
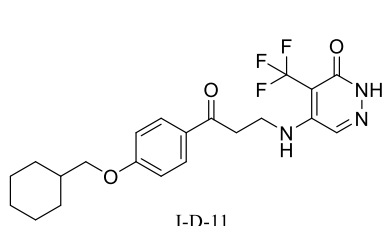


I-C-10



I-C-11



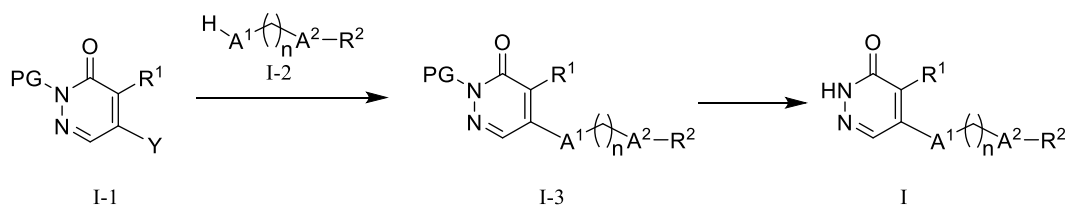


According to the embodiments of the present disclosure, the pharmaceutically acceptable salt is a salt formed by the compound and an acid, and the acid is selected from at least one of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, carbonic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, citric acid, malic acid, tartaric acid, lactic acid, pyruvic acid, acetic acid, maleic acid, succinic acid, fumaric acid, salicylic acid, phenylacetic acid, mandelic acid, and ferulic acid.

According to the embodiments of the present disclosure, the isotopic label is preferably a substitution of deuterium (D or ^2H) for hydrogen (^1H).

The present disclosure further provides a method for preparing the compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, comprising:

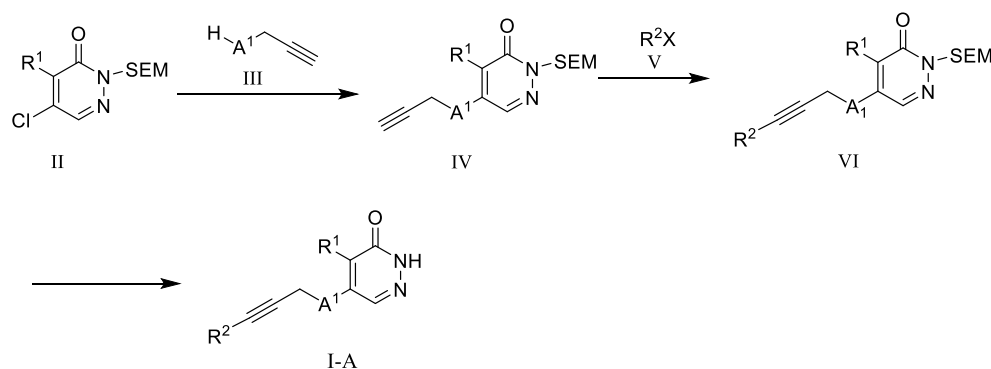
- (1) reacting compound I-1 with compound I-2 to give compound I-3; and
- (2) removing PG from compound I-3 to give the compound of formula (I);



wherein Y is selected from a leaving group, for example, halogen, such as Cl and Br; PG is selected from a protecting group, e.g., (trimethylsilyl)ethoxymethyl (SEM) and p-methoxybenzyl (PMB).

5 According to the embodiments of the present disclosure, the method further comprises at least one of the following schemes:

Scheme I: when R¹ is selected from trifluoromethyl, cyano, and halogen, A¹ denotes -NH- or -N(CH₃)-, A² is ethynylene, and n = 1, the compound of formula (I) has a structure of formula (I-A), and the method comprises:



10 wherein the groups have the definitions as described herein, X is Cl, Br, or I, and SEM is (trimethylsilyl)ethoxymethyl.

(1-1) reacting compound II with compound III to give compound IV

15 According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is ethanol, *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide, tetrahydrofuran (THF), 1,4-dioxane, glycol dimethyl ether, or acetonitrile, preferably 1,4-dioxane or ethanol.

20 According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid-binding agent, wherein the acid-binding agent is sodium carbonate, potassium carbonate, triethylamine, or *N,N*-diisopropylethylamine (DIPEA), preferably DIPEA or triethylamine.

(1-2) reacting compound IV with compound V to give compound VI

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is DMF, *N,N*-dimethylacetamide, THF, 1,4-dioxane, glycol dimethyl ether, or acetonitrile, preferably THF.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid-binding agent, wherein the acid-binding agent is sodium carbonate, potassium carbonate, triethylamine, or DIPEA, preferably triethylamine.

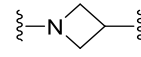
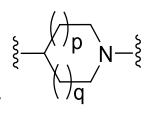
According to the embodiments of the present disclosure, the reaction may be performed in the presence of a catalyst, wherein the catalyst may be selected from a copper-based catalyst and a palladium-based catalyst; the copper-based catalyst is cuprous iodide or cuprous bromide, preferably cuprous iodide; the palladium-based catalyst is palladium acetate, bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium(0), or 1,1'-bis(diphenylphosphino)ferrocenepalladium dichloride, preferably bis(triphenylphosphine)palladium dichloride.

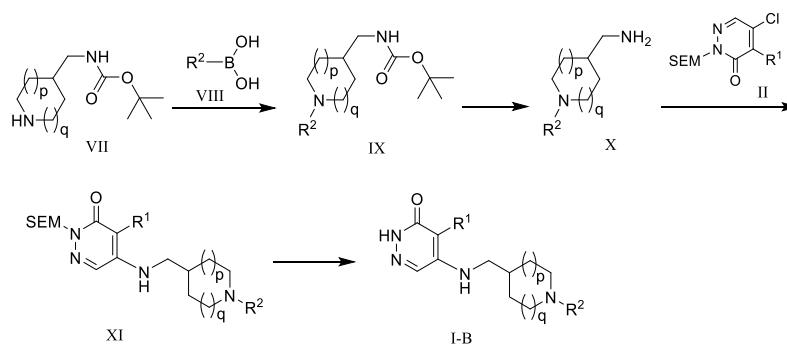
(1-3) removing a protecting group from compound VI and performing an SEM reaction to give compound I-A

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF, acetonitrile, or dichloromethane, preferably dichloromethane.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid, wherein the acid is hydrochloric acid, trifluoroacetic acid, or trifluoromethanesulfonic acid, preferably trifluoroacetic acid or trifluoromethanesulfonic acid.

Scheme II: when R^1 is selected from trifluoromethyl, cyano, and halogen, A^1 denotes -NH-,

, or -N(CH₃)-, $n = 1$ or 0 , A^2 is -NH- or , and p and q are each independently selected from 0, 1, and 2, the compound of formula (I) has a structure of formula (I-B), and the method comprises:



wherein the groups have the definitions as described herein, and SEM is (trimethylsilyl)ethoxymethyl.

5 (2-1) reacting compound VII with compound VIII to give compound IX

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is dichloromethane, toluene, DMF, *N,N*-dimethylacetamide, THF, 1,4-dioxane, glycol dimethyl ether, or acetonitrile, preferably
10 dichloromethane.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid-binding agent, wherein the acid-binding agent is sodium carbonate, potassium carbonate, triethylamine, or DIPEA, preferably triethylamine.
15

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a catalyst, wherein the catalyst may be selected from a copper-based catalyst, such as copper acetate.

20 (2-2) subjecting compound IX to a tert-butoxycarbonyl removal reaction to give compound X

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF, acetonitrile, or dichloromethane, preferably dichloromethane.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid, wherein the acid is hydrochloric acid, trifluoroacetic acid, or trifluoromethanesulfonic acid, preferably trifluoroacetic acid.
25

(2-3) reacting compound X with compound II to give compound XI

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is ethanol, DMF, *N,N*-dimethylacetamide, THF, 1,4-dioxane, glycol dimethyl ether, or acetonitrile, preferably 1,4-dioxane or ethanol.

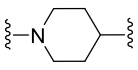
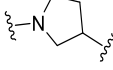
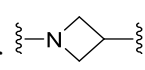
According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid-binding agent, wherein the acid-binding agent is sodium carbonate, potassium carbonate, triethylamine, or DIPEA, preferably DIPEA or triethylamine.

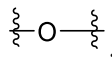
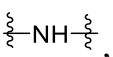
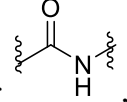
(2-4) removing a protecting group from compound XI and performing an SEM reaction to give compound I-B

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF, acetonitrile, or dichloromethane, preferably dichloromethane.

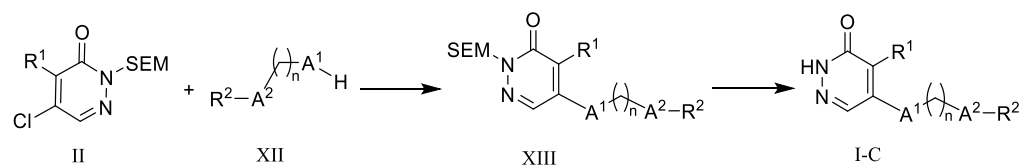
According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid, wherein the acid is hydrochloric acid, trifluoroacetic acid, or trifluoromethanesulfonic acid, preferably trifluoroacetic acid.

Scheme III: when R^1 is selected from trifluoromethyl, cyano, and halogen, A^1 denotes -NH-, -

$N(CH_3)-$, , , or ,

A^2 is -CH=CH-, a benzene ring, -CH₂-, , , , , or , and n is 0,

1, or 2, the compound of formula (I) has a structure of formula (I-C), and the method comprises:



wherein the groups have the definitions as described herein, and SEM is (trimethylsilyl)ethoxymethyl.

(3-1) reacting compound II with compound XII to give compound XIII

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is ethanol, DMF, *N,N*-dimethylacetamide, THF, 1,4-dioxane, glycol dimethyl ether, or acetonitrile, preferably 1,4-dioxane or ethanol.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid-binding agent, wherein the acid-binding agent is sodium carbonate, potassium carbonate, triethylamine, or DIPEA, preferably DIPEA or triethylamine.

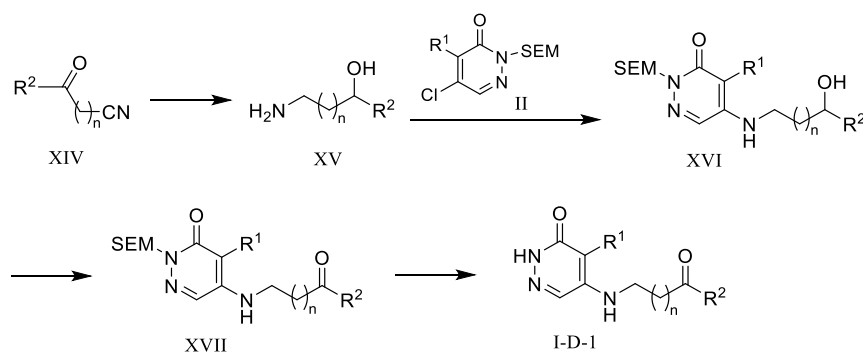
(3-2) removing a protecting group from compound XIII and performing an SEM reaction to give compound I-C

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF, acetonitrile, or dichloromethane, preferably dichloromethane.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid, wherein the acid is hydrochloric acid, trifluoroacetic acid, or trifluoromethanesulfonic acid, preferably trifluoroacetic acid.

Scheme IV: when R^1 is selected from trifluoromethyl, cyano, and halogen, A^1 denotes -NH- or -

$N(CH_3)-$, A^2 is $\text{---}\overset{\text{O}}{\parallel}\text{---}$, and n is 1 or 2, the compound of formula (I) has a structure of formula (I-D), and the method comprises:



wherein the groups have the definitions as described herein, and SEM is (trimethylsilyl)ethoxymethyl.

(4-1) subjecting compound XIV to a reduction reaction in a hydrogen atmosphere to give compound XV

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF, ethanol, or methanol, preferably methanol.

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a catalyst, wherein the catalyst is palladium on carbon or palladium hydroxide, preferably palladium on carbon.

10

(4-2) reacting compound XV with compound II to give compound XVI

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is ethanol, DMF, *N,N*-dimethylacetamide, THF, 1,4-dioxane, glycol dimethyl ether, or acetonitrile, preferably 1,4-dioxane or ethanol.

15

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid-binding agent, wherein the acid-binding agent is sodium carbonate, potassium carbonate, triethylamine, or DIPEA, preferably DIPEA or triethylamine.

20

(4-3) subjecting compound XVI to an oxidation reaction to give compound XVII

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF or dichloromethane, preferably dichloromethane.

25

According to the embodiments of the present disclosure, the reaction may be performed in the presence of an oxidant, wherein the oxidant is Dess-Martin periodinane, hydrogen peroxide, or pyridinium chlorochromate (PCC), preferably PCC.

30

(4-4) removing a protecting group from compound XVII and performing an SEM reaction to give compound I-D

According to the embodiments of the present disclosure, the reaction may be performed in the presence of a solvent, wherein the solvent is THF, acetonitrile, or dichloromethane, preferably dichloromethane.

5 According to the embodiments of the present disclosure, the reaction may be performed in the presence of an acid, wherein the acid is hydrochloric acid, trifluoroacetic acid, or trifluoromethanesulfonic acid, preferably trifluoroacetic acid or trifluoromethanesulfonic acid.

10 According to the embodiments of the present disclosure, a corresponding acid is salified with the compound of formula (I) to give the pharmaceutically acceptable salt of the compound of formula (I).

15 The present disclosure further provides a pharmaceutical composition, comprising a therapeutically effective amount of at least one of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

20 According to the embodiments of the present disclosure, a pharmaceutically acceptable carrier may be added to the pharmaceutical composition to prepare a common pharmaceutical formulation, such as a tablet, a capsule, a syrup, a suspension, or an injection, or a common pharmaceutically acceptable excipient, such as a flavorant, a sweetener, a liquid/solid filler, or a diluent, may be added to the formulation.

25 The present disclosure further provides use of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, or the pharmaceutical composition in preparing a medicament for preventing and/or treating a PARP-mediated disease, for example, in preparing a PARP inhibitor medicament.

30 According to the embodiments of the present disclosure, the subtype of PARP may be selected from PARP2, PARP3, PARP4 (VPARP), PARP5a (tankyrase1), PARP5b (tankyrase2), PARP7 (TiPARP), and/or sPARP1, preferably PARP7.

According to the embodiments of the present disclosure, the PARP-mediated disease may be a central nervous system disease, a cancer, an infection, an immune disease, a cardiovascular disease, or a metabolic disease; the central nervous system disease is, for example, stroke, such as ischemic stroke; the cancer is selected from lung cancer, pancreatic cancer, colorectal cancer, leukemia, Ewing's sarcoma, breast cancer, prostate cancer, T-cell lymphoma, B-cell lymphoma, malignant rhabdomyoma, synovial sarcoma, endometrioma, gastric cancer, liver cancer, renal cancer, melanoma, ovarian cancer, cerebral glioma, cholangiocarcinoma, nasopharyngeal cancer, cervical cancer, head and neck cancer, esophageal cancer, thyroid cancer, and bladder cancer.

The present disclosure further provides use of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, or the pharmaceutical composition in preparing a medicament for preventing and/or treating a central nervous system disease, a cerebral ischemia-associated disease, a cancer, an infection, an immune disease, a cardiovascular disease, or a metabolic disease.

According to the embodiments of the present disclosure, the central nervous system disease is, for example, stroke, such as ischemic stroke; the cerebral ischemia-associated disease may be transient ischemic attack, cerebral thrombosis, or cerebral embolism; the cancer is selected from lung cancer, pancreatic cancer, colorectal cancer, leukemia, Ewing's sarcoma, breast cancer, prostate cancer, T-cell lymphoma, B-cell lymphoma, malignant rhabdomyoma, synovial sarcoma, endometrioma, gastric cancer, liver cancer, renal cancer, melanoma, ovarian cancer, cerebral glioma, cholangiocarcinoma, nasopharyngeal cancer, cervical cancer, head and neck cancer, esophageal cancer, thyroid cancer, and bladder cancer.

The present disclosure further provides a method for preventing and/or treating a PARP-mediated disease, comprising administering to a patient a prophylactically or therapeutically effective amount of at least one of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, or a prophylactically or therapeutically effective amount of the pharmaceutical composition described above.

The present disclosure further provides at least one of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically

acceptable salt thereof, or the pharmaceutical composition thereof, for use in preventing and/or treating a PARP-mediated disease.

5 According to the embodiments of the present disclosure, the disease may be a central nervous system disease, a cancer, an infection, an immune disease, a cardiovascular disease, or a metabolic disease; the central nervous system disease is, for example, stroke, such as ischemic stroke; the cancer is selected from lung cancer, pancreatic cancer, colorectal cancer, leukemia, Ewing's sarcoma, breast cancer, prostate cancer, T-cell lymphoma, B-cell lymphoma, malignant rhabdomyoma, synovial sarcoma, endometrioma, gastric cancer, liver cancer, renal cancer, 10 melanoma, ovarian cancer, cerebral glioma, cholangiocarcinoma, nasopharyngeal cancer, cervical cancer, head and neck cancer, esophageal cancer, thyroid cancer, and bladder cancer.

The present disclosure further provides a method for preventing and/or treating a cerebral ischemia-associated disease, comprising administering to a patient a prophylactically or 15 therapeutically effective amount of at least one of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, or a prophylactically or therapeutically effective amount of the pharmaceutical composition described above.

20 The present disclosure further provides at least one of the compound of formula (I), or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof, for use in preventing and/or treating a cerebral ischemia-associated disease.

25 According to the embodiments of the present disclosure, the cerebral ischemia-associated disease may be transient ischemic attack, cerebral thrombosis, or cerebral embolism.

Beneficial Effects: The present disclosure has the following remarkable advantages compared with the prior art:

30 (1) The compound described herein has good membrane infiltration capacity, and the physicochemical parameters acquired by calculation meet the Clark-Lobell rules (the physicochemical property principles of a drug penetrating the blood-brain barrier: the total number of nitrogen atoms and oxygen atoms (N+O) is less than 6, the polar surface area (PSA) is less than

60-70, and the molecular weight is less than 450);

(2) The compound and the pharmaceutical composition thereof described herein also demonstrate an anti-tumor effect, good efficacy at the molecular level, and a nanomolar inhibitory level against the PARP7 enzyme;

5 (3) The method for preparing the compound features ease to operate.

Definitions and Description

Unless otherwise stated, the terms used in the specification and claims have the following meanings.

10

The term “alkyl” refers to a saturated aliphatic hydrocarbon group, which is a linear or branched group containing 1 to 20 carbon atoms, preferably an alkyl containing 1 to 12 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12) carbon atoms, and more preferably an alkyl containing 1 to 6 carbon atoms (C₁₋₆ alkyl). Non-limiting examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, various branched isomers thereof, and the like. The alkyl may be substituted or
20 unsubstituted.

The term “alkyloxy” refers to -O-(alkyl), wherein the alkyl is as defined herein. Preferably, the term refers to an alkyloxy containing 1 to 12 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12) carbon atoms (C₁₋₁₂ alkyloxy), and more preferably an alkyloxy containing 1 to 6 carbon atoms (C₁₋₆ alkyloxy). Non-limiting examples of alkyloxy include: methoxy, ethoxy, propoxy, and butoxy. The
25 alkyloxy may be substituted or unsubstituted.

The term “alkylene” refers to a saturated divalent hydrocarbyl group obtained by removing two H from a saturated linear or branched hydrocarbyl, which may contain 1-12 carbon atoms. Non-limiting examples include methylene (-CH₂-), ethylene (-CH₂CH₂-), and the like. The
30 alkylene may be substituted or unsubstituted.

The term “alkenyl” should be interpreted as preferably a linear or branched hydrocarbyl

containing one or more double bonds and having 2-12 carbon atoms, preferably “C₂₋₁₀ alkenyl”. The “C₂₋₁₀ alkenyl” should be interpreted as preferably a linear or branched monovalent hydrocarbyl group, which contains one or more double bonds and has 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, for example, 2, 3, 4, 5, or 6 carbon atoms (i.e., C₂₋₆ alkenyl) or 2 or 3 carbon atoms (i.e., C₂₋₃ alkenyl). It will be appreciated that when the alkenyl contains more than one double bond, the double bonds may be separated or conjugated. The alkenyl is, for example, vinyl, allyl, (E)-2-methylvinyl, (Z)-2-methylvinyl, (E)-but-2-enyl, (Z)-but-2-enyl, (E)-but-1-enyl, (Z)-but-1-enyl, pent-4-enyl, (E)-pent-3-enyl, (Z)-pent-3-enyl, (E)-pent-2-enyl, (Z)-pent-2-enyl, (E)-pent-1-enyl, (Z)-pent-1-enyl, hex-5-enyl, (E)-hex-4-enyl, (Z)-hex-4-enyl, (E)-hex-3-enyl, (Z)-hex-3-enyl, (E)-hex-2-enyl, (Z)-hex-2-enyl, (E)-hex-1-enyl, (Z)-hex-1-enyl, isopropenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (E)-1-methylprop-1-enyl, (Z)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (E)-2-methylbut-2-enyl, (Z)-2-methylbut-2-enyl, (E)-1-methylbut-2-enyl, (Z)-1-methylbut-2-enyl, (E)-3-methylbut-1-enyl, (Z)-3-methylbut-1-enyl, (E)-2-methylbut-1-enyl, (Z)-2-methylbut-1-enyl, (E)-1-methylbut-1-enyl, (Z)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, or 1-isopropylvinyl. The alkenyl may be substituted or unsubstituted.

The term “alkynyl” should be interpreted as a linear or branched monovalent hydrocarbyl containing one or more triple bonds and having 2-12 carbon atoms, preferably “C₂₋₁₀ alkynyl”. The term “C₂₋₁₀ alkynyl” should be interpreted as preferably a linear or branched monovalent hydrocarbyl group, which contains one or more triple bonds and has 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, for example, 2, 3, 4, 5, or 6 carbon atoms (i.e., “C₂₋₆ alkynyl”) or 2 or 3 carbon atoms (“C₂₋₃ alkynyl”). The alkynyl is, for example, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl, pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl, hex-3-ynyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl, 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl, 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methylpent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl. In particular, the alkynyl is ethynyl, prop-1-ynyl, or prop-2-ynyl. The alkynyl may be substituted or unsubstituted.

The term “cycloalkyl” refers to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbon substituent. The cycloalkyl ring contains 3 to 14 carbon atoms, preferably 3 to 8 (e.g., 3, 4, 5, 6, 7, and 8) carbon atoms, and more preferably 3 to 6 carbon atoms. The ring atoms may optionally be substituted with oxo, and the oxo (=O) on the ring belongs to a part of the ring. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl, and the like. The polycyclic cycloalkyl includes spiro, fused, and bridged cycloalkyl.

The term “heterocyclyl” refers to a saturated or unsaturated non-aromatic ring or ring system having 3 to 14 members, which, for example, is a 3-, 4-, 5-, 6-, or 7-membered monocyclic ring system, a 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic (e.g., fused, bridged, or spiro) ring system, or a 10-, 11-, 12-, 13-, or 14-membered tricyclic ring system, and contains at least one, e.g., 1, 2, 3, 4, 5, or more, heteroatoms selected from O, S, and N, wherein N and S may also be optionally oxidized to various oxidized forms to form nitrogen oxides, -S(O)-, or -S(O)₂-. Unless otherwise stated, the heterocyclyl may be carbon- or nitrogen-based, and the -CH₂- group may be optionally substituted with -C(=O)-. The sulfur atom of the ring may be optionally oxidized to a S-oxide. The nitrogen atom of the ring may be optionally oxidized to a N-oxide. In some embodiments, the heterocyclyl is a heterocyclyl consisting of 5 to 12 atoms. In some other embodiments, the heterocyclyl is a heterocyclyl consisting of 5 to 8 atoms. In still some other embodiments, the heterocyclyl is a heterocyclyl consisting of 5 to 7 atoms. In yet some other embodiments, the heterocyclyl is a heterocyclyl consisting of 5 to 6 atoms. The heterocyclyl may also be a bicyclic heterocyclyl; in some embodiments, the heterocyclyl is a bicyclic heterocyclyl consisting of 7-12 atoms; in some other embodiments, the heterocyclyl is a bicyclic heterocyclyl consisting of 7-10 atoms; in still other embodiments, the heterocyclyl is a bicyclic heterocyclyl consisting of 8-10 atoms.

The term “aryl” should be interpreted as preferably an aromatic or partially aromatic monovalent monocyclic, bicyclic, or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms (“C₆₋₁₄ aryl”), in particular a ring having 6 carbon atoms (“C₆ aryl”), such as phenyl; or biphenyl, a ring having 9 carbon atoms (“C₉ aryl”), such as indanyl or indenyl, a ring having 10 carbon atoms (“C₁₀ aryl”), such as tetrahydronaphthyl, dihydronaphthyl or naphthyl, a ring having 13 carbon atoms (“C₁₃ aryl”), such as fluorenyl, or a ring having 14 carbon atoms (“C₁₄

aryl”), such as anthryl. When the C₆₋₂₀ aryl is substituted, it may be monosubstituted or polysubstituted. In addition, the substitution site is not limited, and may be, for example, ortho-substitution, para-substitution, or meta-substitution. The aryl group includes a ring system formed by fusing an aromatic ring and another aromatic ring, or an aromatic ring and a non-aromatic carbon ring. Examples of the aryl group may include phenyl, naphthyl, anthryl, 1,2,3,4-tetrahydronaphthyl, 2,3-dihydro-1*H*-indenyl, and bicyclo[4,2,0]octa-1(6),2,4-trienyl. The aryl group may be substituted or unsubstituted, wherein the substituents include, but are not limited to, fluorine, chlorine, bromine, oxo (=O), cyano, nitro, carboxyl, hydroxy, amino, aminomethyl, aminoacyl, methylamino, phenylamino, hydroxymethyl, methylsulfonyl, aminosulfonyl, acetyl, methoxy, phenoxy, trifluoromethoxy, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, cyclopropyl, cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyrrolyl, imidazolyl, imidazoliny, piperidiny, piperaziny, morpholiny, thienyl, thiazolyl, furanyl, pyrrolyl, phenyl, pyridiny, pyrimidiny, -C(=NH)NH₂, trifluoromethyl, or the like.

The term “heteroaryl” should be interpreted as a monovalent monocyclic, bicyclic (e.g., fused, bridged or spiro) or tricyclic ring system containing 5 to 14 ring atoms. The heteroaryl has 5 to 14 ring atoms, including 1 to 5 heteroatoms independently selected from N, O, and S, wherein at least one ring (or the whole ring) is aromatic. The heteroaryl has one or more attachment points connected to the rest of the molecule. The term “heteroaryl” may be used interchangeably with the term “heteroaromatic ring” or “heteroaromatic compound”. The heteroaryl includes a ring system formed by fusing a heteroaromatic ring and an aromatic ring, a heteroaromatic ring and another heteroaromatic ring, or a heteroaromatic ring and a non-aromatic carbon ring or heterocyclic ring. In some embodiments, the heteroaryl consisting of 5 to 10 atoms contains 1, 2, 3, or 4 heteroatoms independently selected from oxygen, sulfur, and nitrogen. In some embodiments, the heteroaryl is a heteroaryl consisting of 7 to 12 atoms, including 1, 2, 3, or 4 heteroatoms independently selected from O, S, and N; the heteroaryl consisting of 7 to 12 atoms may be a monocyclic ring system or a bicyclic ring system containing two rings. In some other embodiments, the heteroaryl is a heteroaryl consisting of 7 to 10 atoms, including 1, 2, 3, or 4 heteroatoms independently selected from oxygen, sulfur, and nitrogen; the heteroaryl consisting of 7 to 10 atoms may be a monocyclic ring system or a bicyclic ring system containing two rings.

The term “halogen” refers to F, Cl, Br, or I.

The term “hydroxy” refers to -OH.

The term “amino” refers to -NH₂.

5 The term “cyano” refers to -CN.

The term “nitro” refers to -NO₂.

The term “oxo” refers to “=O”.

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The term “carbonyl” refers to C=O.

The term “carboxyl” refers to -C(O)OH.

15 The term “patient” refers to any animal including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, pigs, cattle, sheep, horses, or primates, and most preferably humans.

The term “therapeutically effective amount” refers to the amount of the active compound or drug that induces a biological or medical response pursued by researchers, veterinarians, physicians, or other clinicians in tissues, systems, animals, individuals, or humans, including one or more of the following effects: (1) disease prevention: for example, the prevention of a disease, disorder, or condition in an individual who is susceptible to the disease, disorder, or condition but has not yet experienced or exhibited the pathology or symptoms of the disease; (2) disease inhibition: for example, the inhibition of a disease, disorder, or condition in an individual who is experiencing or exhibiting the pathology or symptoms of the disease, disorder, or condition (i.e., the prevention of the further progression of the pathology and/or symptoms); (3) disease alleviation: for example, the alleviation of a disease, disorder, or condition in an individual who is experiencing or exhibiting the pathology or symptoms of the disease, disorder, or condition (i.e., the reverse of the pathology and/or symptoms).

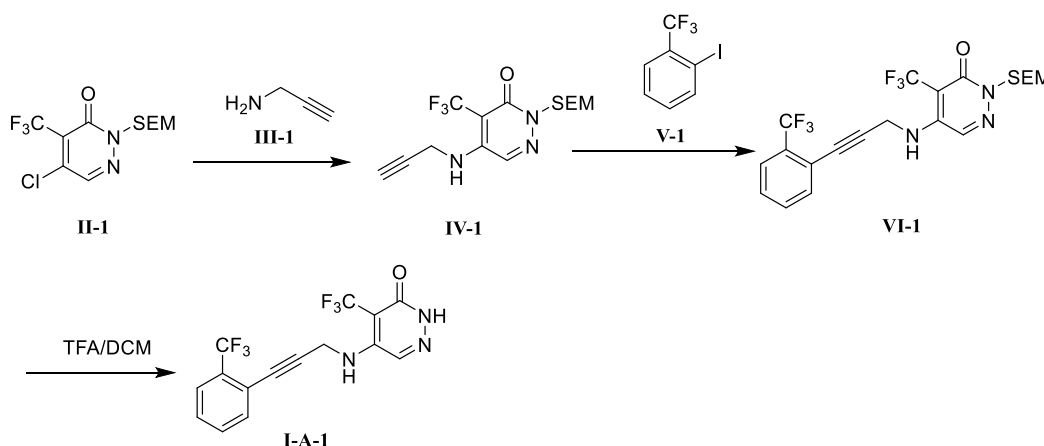
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DETAILED DESCRIPTION OF EMBODIMENTS

The technical schemes of the present disclosure will be further illustrated in detail with reference to the following specific examples. It will be appreciated that the following examples are merely exemplary illustration and explanation of the present disclosure, and should not be construed as limiting the claimed scope of the present disclosure. All techniques implemented on the basis of the above content of the present disclosure are encompassed within the claimed scope of the present disclosure.

Unless otherwise stated, the starting materials and reagents used in the following examples are all commercially available products or can be prepared by known methods.

Example 1: Synthesis of 4-trifluoromethyl-5-((3-(2-(trifluoromethyl)phenyl)prop-2-yn-1-yl)amino)pyridazin-3(2 *H*)-one (**I-A-1**)



Synthesis of 5-(prop-2-yn-1-ylamino)-4-trifluoromethyl-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2 *H*)-one (**IV-1**)

The compound 5-chloro-4-trifluoromethyl-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2 *H*)-one (**II-1**) (7.0 g, 22.0 mmol) was dissolved in 20 mL of 1,4-dioxane, and propargylamine (**III-1**) (1.3 g, 24.2 mmol) and DIPEA (8.5 g, 66.0 mmol) were added. The mixture was heated to 70 °C and incubated for 0.5 h. The reaction was monitored by thin-layer chromatography (*V*petroleum ether:*V*ethyl acetate = 4:1) until completion. 15 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered in vacuum, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography

(*V*petroleum ether:*V*ethyl acetate = 8:1). The crude product was purified to give a brown oily substance (**IV-1**, 4.1 g, 53.7% yield). ESI-MS [*M*+*H*]⁺348.1.

Synthesis of 4-trifluoromethyl-5-((3-(2-(trifluoromethyl)phenyl)prop-2-yn-1-yl)amino)-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2*H*)-one (**VI-1**)

Compound **IV-1** (365.4 mg, 1.0 mmol) was dissolved in 3 mL of anhydrous tetrahydrofuran, and o-iodobenzotrifluoride (**V-1**) (299.2 mg, 1.1 mmol) was added, followed by the addition of cuprous iodide (38.1 mg, 0.2 mmol), bis(triphenylphosphine)palladium dichloride (70.2 mg, 0.1 mmol), and triethylamine (303.0 mg, 3.0 mmol). The mixture was purged with nitrogen, heated to 70 °C, and incubated for 0.5 h. The reaction was monitored by thin-layer chromatography (*V*petroleum ether:*V*ethyl acetate = 2:1) until completion. 10 mL of water was added, and the mixture was extracted with ethyl acetate (5 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered in vacuum, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (*V*petroleum ether:*V*ethyl acetate = 8:1). The crude product was purified to give a yellow solid (**VI-1**, 0.4 g, 81.5% yield). ESI-MS [*M*+*H*]⁺492.1.

Synthesis of 4-trifluoromethyl-5-((3-(2-(trifluoromethyl)phenyl)prop-2-yn-1-yl)amino)pyridazin-3(2*H*)-one (**I-A-1**)

Compound **VI-1** (245.5 mg, 0.5 mmol) was dissolved in 3 mL of dichloromethane before 3 mL of trifluoroacetic acid was added. The system was incubated at room temperature for 3 h. The reaction was monitored by thin-layer chromatography (*V*dichloromethane:*V*methanol = 15:1) until completion. The reaction mixture was concentrated by rotary evaporation at reduced pressure to remove the solvent, and the mixture was adjusted to pH 8 by adding a saturated aqueous sodium bicarbonate solution. 10 mL of water was added, and the resultant mixture was extracted with dichloromethane (10 mL × 3). The organic phases were combined, washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and filtered in vacuum, and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (*V*dichloromethane:*V*methanol = 50:1) to give a white solid (**I-A-1**, 124.0 mg, 68.9% yield). ESI-MS [*M*+*H*]⁺362.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.64 (s, 1H), 7.94 (s,

1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.69-7.65 (m, 2H), 7.63-7.56 (m, 1H), 7.56-7.52 (m, 1H), 4.50 (d, $J = 5.9$ Hz, 2H).

The following compounds were prepared with reference to the method for preparing compound

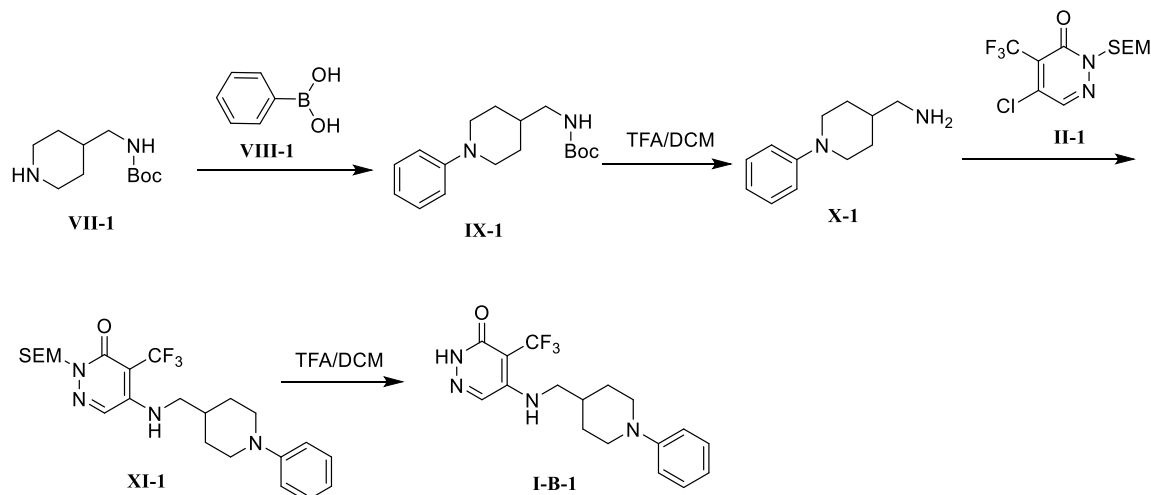
5 **I-A-1:**

Compound No.	¹ H-NMR	MS
Example 2 (I-A-2)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.67 (s, 1H), 7.99 (s, 1H), 7.59-7.52 (m, 1H), 7.45-7.40 (m, 2H), 7.39-7.34 (m, 3H), 4.45 (d, $J = 5.7$ Hz, 2H).	ESI-MS: [M+H] ⁺ 294.1
Example 3 (I-A-3)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.68 (s, 1H), 7.96 (s, 1H), 7.61-7.49 (m, 1H), 7.38-7.30 (m, 1H), 7.24-7.17 (m, 2H), 4.47 (d, $J = 5.7$ Hz, 2H).	ESI-MS: [M+H] ⁺ 330.1
Example 4 (I-A-4)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.70 (s, 1H), 8.00 (s, 1H), 7.73 (d, $J = 8.2$ Hz, 2H), 7.64 (d, $J = 8.2$ Hz, 2H), 7.60-7.56 (m, 1H), 4.49 (d, $J = 5.8$ Hz, 2H).	ESI-MS: [M+H] ⁺ 362.1
Example 5 (I-A-5)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.66 (s, 1H), 7.98 (s, 1H), 7.60-7.50 (m, 1H), 7.30 (d, $J = 7.8$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 4.43 (d, $J = 5.8$ Hz, 2H), 2.30 (s, 3H).	ESI-MS: [M+H] ⁺ 308.1
Example 6 (I-A-6)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.68 (s, 1H), 7.98 (s, 1H), 7.59-7.52 (m, 1H), 7.46-7.38 (m, 1H), 7.32-7.21 (m, 3H), 4.46 (d, $J = 5.7$ Hz, 2H).	ESI-MS: [M+H] ⁺ 312.2
Example 7 (I-A-7)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.68 (s, 1H), 7.97 (s, 1H), 7.62-7.59 (m, 1H), 7.60-7.50 (m, 1H), 7.42-7.35 (m, 1H), 7.15-7.09 (m, 1H), 4.48 (d, $J = 5.8$ Hz, 2H).	ESI-MS: [M+H] ⁺ 330.1
Example 8 (I-A-8)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.66 (s, 1H), 7.96 (s, 1H), 7.58-7.52 (m, 1H), 7.02 (s, 3H), 4.43 (d, $J = 5.8$ Hz, 2H), 2.23 (s, 6H).	ESI-MS: [M+H] ⁺ 322.1
Example 9 (I-A-9)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.67 (s, 1H), 7.98 (s, 1H), 7.59-7.54 (m, 1H), 7.50-7.44 (m, 2H), 7.25-7.18 (m, 2H), 4.43 (d, $J = 5.8$ Hz, 2H).	ESI-MS: [M+H] ⁺ 312.2

Example 10 (I-A-10)	^1H NMR (300 MHz, DMSO- d_6) δ 12.64 (s, 1H), 8.02 (s, 1H), 7.59-7.54 (m, 1H), 7.37-7.34 (m, 1H), 7.28-7.26 (m, 2H), 7.20-7.14 (m, 1H), 4.49 (d, J = 5.9 Hz, 2H), 2.30 (s, 3H).	ESI-MS: [M+H] $^+$ 308.1
Example 11 (I-A-11)	^1H NMR (300 MHz, DMSO- d_6) δ 12.65 (s, 1H), 7.97 (s, 1H), 7.55-7.52 (m, 1H), 7.28-7.18 (m, 4H), 4.44 (d, J = 5.8 Hz, 2H), 2.28 (s, 3H).	ESI-MS: [M+H] $^+$ 308.1
Example 12 (I-A-12)	^1H NMR (300 MHz, DMSO- d_6) δ 12.68 (s, 1H), 7.98 (s, 1H), 7.59-7.57 (m, 1H), 7.56-7.54 (m, 2H), 7.39 (d, J = 8.3 Hz, 2H), 4.47 (d, J = 5.7 Hz, 2H).	ESI-MS: [M+H] $^+$ 378.1
Example 13 (I-A-13)	^1H NMR (300 MHz, DMSO- d_6) δ 12.48 (s, 1H), 7.97 (s, 1H), 7.60-7.45 (m, 3H), 7.30-7.00 (m, 3H), 4.45-4.43 (m, 2H).	ESI-MS: [M+H] $^+$ 360.1
Example 14 (I-A-14)	^1H NMR (300 MHz, DMSO- d_6) δ 12.65 (s, 1H), 7.98 (s, 1H), 7.55-7.51 (m, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.00-6.94 (m, 3H), 4.44 (d, J = 5.7 Hz, 2H), 3.75 (s, 3H).	ESI-MS: [M+H] $^+$ 324.1
Example 15 (I-A-15)	^1H NMR (300 MHz, DMSO- d_6) δ 12.68 (s, 1H), 8.57 (s, 2H), 7.98 (s, 1H), 7.55 (s, 1H), 7.39 (s, 2H), 4.51 (s, 2H).	ESI-MS: [M+H] $^+$ 295.1
Example 16 (I-A-16)	^1H NMR (300 MHz, DMSO- d_6) δ 12.68 (s, 1H), 8.62 (s, 1H), 8.56 (d, J = 5.7 Hz, 1H), 7.99 (s, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.56 (s, 1H), 7.41 (t, J = 6.5 Hz, 1H), 4.49 (d, J = 5.8 Hz, 2H).	ESI-MS: [M+H] $^+$ 295.1
Example 17 (I-A-17)	^1H NMR (300 Hz, DMSO- d_6) δ 12.69 (s, 1H), 8.05 (d, J = 6.0 Hz, 2H), 7.95-7.88 (m, 3H), 7.63-7.52 (m, 3H), 7.47 (d, J = 8.3 Hz, 1H), 4.51 (d, J = 4.7 Hz, 2H).	ESI-MS: [M+H] $^+$ 344.1
Example 18 (I-A-18)	^1H NMR (300 Hz, DMSO- d_6) δ 12.72 (s, 1H), 8.80 (d, J = 4.9 Hz, 2H), 8.00 (s, 1H), 7.65-7.56 (m, 1H), 7.51 (t, J = 5.0 Hz, 1H), 4.53 (d, J = 5.6 Hz, 2H).	ESI-MS: [M+H] $^+$ 296.1
Example 19 (I-A-19)	^1H NMR (300 Hz, DMSO- d_6) δ 12.69 (s, 1H), 8.20-8.17 (m, 1H), 8.16 (s, 1H), 7.99-7.96 (m, 2H), 7.68 (d, J = 6.9 Hz, 2H), 7.61-7.58 (m, 2H), 7.50 (t, J = 7.7 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H).	ESI-MS: [M+H] $^+$ 344.1
Example 20 (I-A-20)	^1H NMR (300 Hz, DMSO- d_6) δ 12.69 (s, 1H), 8.94-8.89 (m, 1H), 8.37 (d, J = 7.9 Hz, 1H), 8.47-8.10 (m, 1H), 8.04 (s, 1H), 7.99 (d,	ESI-MS: [M+H] $^+$ 345.1

$J = 8.7$ Hz, 1H), 7.73-7.70 (m, 1H), 7.62-7.59 (m, 1H), 7.57-7.54 (m, 1H), 4.52 (d, $J = 5.7$ Hz, 2H).

Example 21: Synthesis of 5-(((1-phenylpiperidin-4-yl)methyl)amino)-4-trifluoromethylpyridazin-3(2*H*)-one (**I-B-1**)



5 Synthesis of tert-butyl ((1-phenylpiperidin-4-yl)methyl)carbamate (**IX-1**)

4-tert-Butyloxycarbonylaminoethyl piperidine (**VII-1**) (500.0 mg, 2.5 mmol) was added to a 25 mL eggplant-shaped flask and dissolved in 10 mL of dichloromethane. Phenylboronic acid (**VIII-1**) (1.5 g, 12.2 mmol), Cu(AcO)₂ (978.0 mg, 4.9 mmol), and Et₃N (2.5 g, 24.5 mmol) were added, and the system was incubated at room temperature for 48 h. 10 mL of water was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (10 mL × 3). The organic phases were combined, washed three times with saturated brine (10 mL × 3), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (*V*_{petroleum ether}:*V*_{ethyl acetate} = 8:1) to give a yellow oily substance (**IX-1**, 638 mg, 90% yield). ESI-MS: [M+H]⁺291.2.

Synthesis of (1-phenylpiperidin-4-yl)methanamine (**X-1**)

Compound **IX-1** (520.0 mg, 1.8 mmol) was added to a 50 mL eggplant-shaped flask and dissolved in 5 mL of dichloromethane. 4 mL of trifluoroacetic acid was added, and the system was incubated at room temperature for 10 min. The reaction was monitored by thin-layer chromatography (*V*_{petroleum ether}:*V*_{ethyl acetate} = 4:1) until completion. The reaction mixture was concentrated by rotary evaporation at reduced pressure to remove the solvent and the

remaining trifluoroacetic acid. 10 mL of water was added, and the mixture was back-extracted with DCM (5 mL $\times$ 3). The aqueous layer was adjusted to pH 9-10 with a NaOH solution, extracted with dichloromethane (10 mL $\times$ 3), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent and give a yellow oily substance (**X-1**, 265 mg, 78% yield). ESI-MS: $[M+H]^+$ 191.2.

Synthesis of 5-(((1-phenylpiperidin-4-yl)methyl)amino)-4-trifluoromethyl-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2*H*)-one (**XI-1**)

Compound **X-1** (234.0 mg, 1.23 mmol) was added to a 25 mL eggplant-shaped flask and dissolved in 6 mL of 1,4-dioxane, and DIPEA (477.0 mg, 3.7 mmol) and compound **II-1** (470.0 mg, 1.5 mmol) were sequentially added. The system was incubated at room temperature for 40 min. The reaction was monitored by thin-layer chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 2:1$) until completion. 20 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL $\times$ 4). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent. The crude product was purified by silica gel column chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 5:1$) to give a yellow solid (**XI-1**, 230 mg, 40% yield). ESI-MS: $[M+H]^+$ 483.2.

Synthesis of 5-(((1-phenylpiperidin-4-yl)methyl)amino)-4-trifluoromethylpyridazin-3(2 *H*)-one (**I-B-1**)

Compound **XI-1** (110.0 mg, 0.23 mmol) was added to a 25 mL eggplant-shaped flask and dissolved in 4 mL of dichloromethane. 3 mL of trifluoroacetic acid was added. After the addition, the system was incubated at room temperature for 15 min. The reaction was monitored by thin-layer chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 1:1$) until completion. The mixture was concentrated by rotary evaporation at reduced pressure to remove the solvent and the remaining trifluoroacetic acid, and adjusted to pH 8 with a saturated sodium bicarbonate solution. 10 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent. The crude product was purified by silica gel column chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 1.5:1$) to

give a yellow solid (**I-B-1**, 40 mg, 57% yield). ESI-MS $[M+H]^+$:353.2; 1H NMR (300 MHz, DMSO- d_6) δ 12.55 (s, 1H), 7.96 (s, 1H), 7.05 (t, $J = 7.7$ Hz, 2H), 6.56 (d, $J = 7.9$ Hz, 2H), 6.49 (t, $J = 7.2$ Hz, 1H), 5.66 (s, 1H), 3.70-3.61 (m, 2H), 3.20-3.10 (m, 2H), 2.94-2.89 (m, 2H), 2.78 (s, 1H), 1.85-1.79 (m, 2H), 1.27-1.22 (m, 2H).

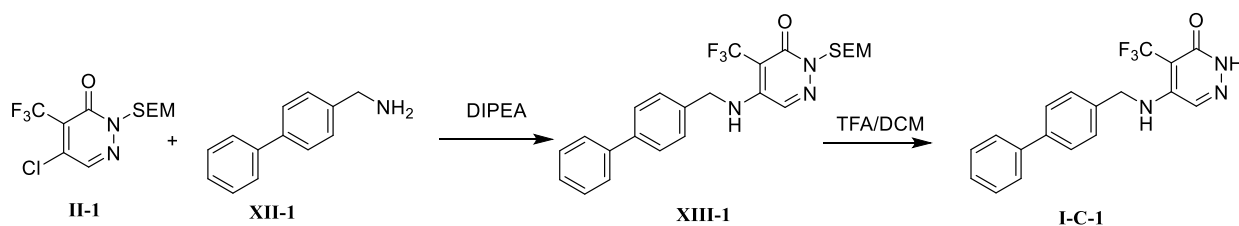
5

The following compound was prepared with reference to the method for preparing compound **I-B-1**:

Compound No.	1H -NMR	MS
Example 22 (I-B-2)	1H NMR (300 MHz, DMSO- d_6) δ 12.48 (s, 1H), 7.96 (s, 1H), 7.30-7.21 (m, 1H), 7.15 (t, $J = 7.9$ Hz, 2H), 6.66 (t, $J = 7.3$ Hz, 1H), 6.42 (d, $J = 7.9$ Hz, 2H), 3.82 (t, $J = 7.5$ Hz, 2H), 3.70-3.63 (m, 2H), 3.58-3.53 (m, 2H), 2.99-2.86 (m, 1H).	ESI-MS: $[M+H]^+$ 325.1

Example 23: Synthesis of 5-(((1,1'-biphenyl-4-yl)methyl)amino)-4-trifluoromethylpyridazin-3(2H)-one (**I-C-1**)

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Synthesis of 5-(((1,1'-biphenyl-4-yl)methyl)amino)-4-trifluoromethyl-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2H)-one (**XIII-1**)

15

The compound (1,1'-biphenyl-4-yl)methylamine (**XII-1**, 155.0 mg, 0.85 mmol) was added to a 25 mL eggplant-shaped flask and dissolved in 10 mL of 1,4-dioxane. DIPEA (219.0 mg, 1.7 mmol) was added, and the system was stirred at room temperature for 15 min. Compound II-1 (404.0 mg, 1.3 mmol) was then added, and the system was incubated at room temperature for 2 h. The reaction was monitored by thin-layer chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 4:1$) until completion. 20 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL $\times$ 4). The organic phases were combined, washed three times with saturated brine (15 mL $\times$ 3), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent. The residue was purified by column

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chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 10:1$) to give a pale yellow solid (**XIII-1**, 165 mg, 41% yield). ESI-MS: $[M+H]^+ 184.3$.

Synthesis of 5-(((1,1'-biphenyl-4-yl)methyl)amino)-4-trifluoromethylpyridazin-3(2 *H*)-one (**I-C-1**)

Compound **XIII-1** (150.0 mg, 0.3 mmol) was added to a 25 mL eggplant-shaped flask and dissolved in 4 mL of dichloromethane. 3 mL of trifluoroacetic acid was added. The system was incubated at room temperature for 15 min. The reaction was monitored by thin-layer chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 2:1$) until completion. The mixture was concentrated by rotary evaporation at reduced pressure to remove the solvent and the remaining trifluoroacetic acid, and adjusted to pH 8 with a saturated sodium bicarbonate solution. 10 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent. The crude product was purified by silica gel column chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 2:1$) to give a yellow solid (**I-C-1**, 110 mg, 99% yield). ESI-MS: $[M+H]^+ 346.1$; ^1H NMR (300 MHz, DMSO- d_6) δ 12.52 (s, 1H), 7.86-7.78 (m, 1H), 7.73 (s, 1H), 7.70-7.61 (m, 4H), 7.50-7.29 (m, 5H), 4.66 (d, $J = 6.3$ Hz, 2H).

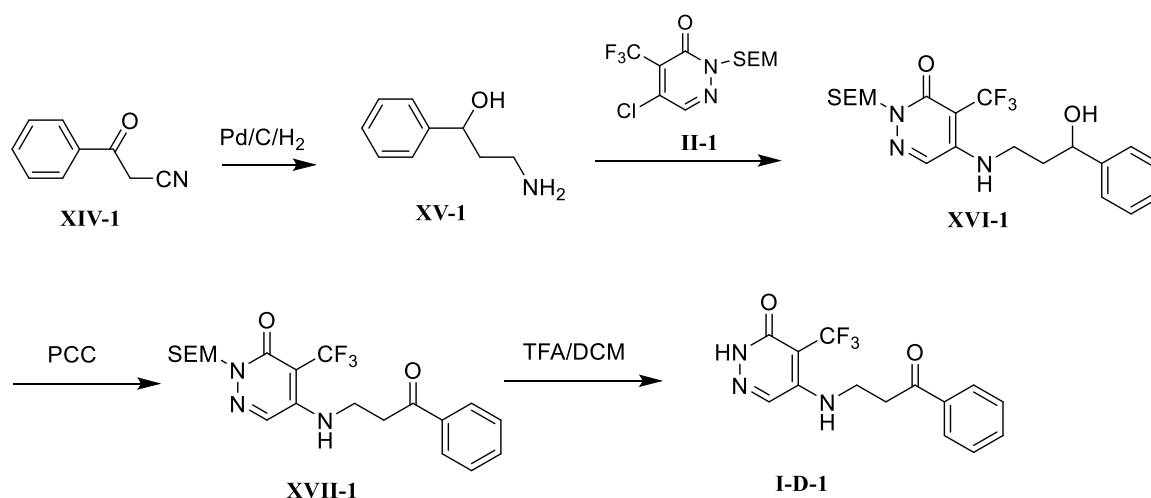
The following compounds were prepared with reference to the method for preparing compound **I-C-1**:

Compound No.	^1H -NMR	MS
Example 24 (I-C-2)	^1H NMR (300 MHz, DMSO- d_6) δ 12.64 (s, 1H), 7.85-7.77 (m, 1H), 7.77 (s, 1H), 7.40-7.30 (m, 4H), 7.29-7.21 (m, 3H), 7.20-7.13 (m, 1H), 4.68 (d, $J = 5.9$ Hz, 2H), 2.21 (s, 3H).	ESI-MS: $[M+H]^+$ 360.1
Example 25 (I-C-3)	^1H NMR (300 MHz, DMSO- d_6) δ 12.45 (s, 1H), 7.83 (s, 1H), 7.31-7.24 (m, 2H), 7.23-7.17 (m, 3H), 7.15-7.09 (m, 1H), 3.42-3.33 (m, 2H), 2.61 (t, $J = 7.7$ Hz, 2H), 1.87-1.76 (m, 2H).	ESI-MS: $[M+H]^+$ 298.1
Example 26 (I-C-4)	^1H NMR (300 MHz, DMSO- d_6) δ 12.49 (s, 1H), 7.80-7.70 (m, 1H), 7.67 (s, 1H), 7.40-7.20 (m, 5H), 4.62 (d, $J = 6.3$ Hz, 2H).	ESI-MS: $[M+H]^+$ 270.1

Example 27 (I-C-5)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.50 (s, 1H), 7.81 (s, 1H), 7.46-7.41 (m, 3H), 7.35-7.21(m, 3H), 6.53 (d, <i>J</i> = 16.1 Hz, 1H), 6.37-6.28 (m, 1H), 4.18 (t, <i>J</i> = 5.7 Hz, 2H).	ESI-MS: [M+H] ⁺ 296.1
Example 28 (I-C-6)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.41 (s, 1H), 7.91 (d, <i>J</i> = 7.3 Hz, 2H), 7.69 (t, <i>J</i> = 7.3 Hz, 1H), 7.57 (t, <i>J</i> = 7.5 Hz, 2H), 7.51 (s, 1H), 4.66-4.52 (m, 3H), 4.48-4.38 (m, 2H).	ESI-MS: [M+H] ⁺ 324.1
Example 29 (I-C-7)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.32 (s, 1H), 7.46 (s, 1H), 7.39-7.22 (m, 5H), 5.78-5.69 (m, 1H), 4.80-4.66 (m, 1H), 4.25-4.08 (m, 4H), 3.03-2.86 (m, 1H).	ESI-MS: [M+H] ⁺ 326.1
Example 30 (I-C-8)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.41 (s, 1H), 7.78-7.74 (m, 1H), 7.72-7.68 (m, 1H), 7.66-7.60 (m, 1H), 7.58-7.53 (m, 1H), 7.51 (s, 1H), 4.63-4.52 (m, 3H), 4.46-4.40 (m, 2H).	ESI-MS: [M+H] ⁺ 342.1
Example 31 (I-C-9)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.32 (s, 1H), 7.46 (s, 1H), 7.42-7.34 (m, 1H), 7.22-7.16 (m, 2H), 7.11-7.03 (m, 1H), 5.88(d, <i>J</i> = 4.8 Hz, 1H), 4.81-4.75 (m, 1H), 4.22-4.08 (m, 4H), 3.03-2.92 (m, 1H).	ESI-MS: [M+H] ⁺ 344.1
Example 32 (I-C-10)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.40 (s, 1H), 8.02-7.97 (m, 2H), 7.51 (s, 1H), 7.43-7.37 (m, 2H), 4.63-4.53 (m, 3H), 4.46-4.39 (m, 2H).	ESI-MS: [M+H] ⁺ 342.1
Example 33 (I-C-11)	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ 12.31 (s, 1H), 7.45 (s, 1H), 7.42-7.37 (m, 2H), 7.16 (t, <i>J</i> = 8.9 Hz, 2H), 5.78 (d, <i>J</i> = 4.8 Hz, 1H), 4.78-4.74 (m, 1H), 4.23-4.13 (m, 3H), 4.10-4.03 (m, 1H), 2.99-2.89 (m, 1H).	ESI-MS: [M+H] ⁺ 344.1
Example 34 (I-C-12)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.43 (s, 1H), 7.81 (d, <i>J</i> = 8.0 Hz, 2H), 7.51 (s, 1H), 7.37 (d, <i>J</i> = 7.9 Hz, 2H), 4.63-4.48 (m, 3H), 4.45-4.36 (m, 2H), 2.39 (s, 3H).	ESI-MS: [M+H] ⁺ 338.1
Example 35 (I-C-13)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.41 (s, 1H), 7.89 (d, <i>J</i> = 8.9 Hz, 2H), 7.51 (s, 1H), 7.08 (d, <i>J</i> = 8.9 Hz, 2H), 4.63-4.54 (m, 2H), 4.53-4.45 (m, 1H), 4.45-4.36 (m, 2H), 3.85 (s, 3H).	ESI-MS: [M+H] ⁺ 354.1
Example 36 (I-C-14)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.39 (s, 1H), 7.52 (s, 1H), 7.15-7.09 (m, 2H), 6.66-6.59 (m, 1H), 6.54-6.49 (m, 2H), 6.36 (d, <i>J</i> = 6.6 Hz, 1H), 4.68-4.59 (m, 2H), 4.34-4.23 (m, 1H), 4.09-4.01 (m, 2H).	ESI-MS: [M+H] ⁺ 311.1

Example 37 (I-C-15)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.32 (s, 1H), 7.44 (s, 1H), 4.40 (t, <i>J</i> = 8.2 Hz, 2H), 3.95-3.86 (m, 2H), 3.75-3.66 (m, 1H), 2.40-2.29 (m, 1H), 1.75-1.61 (m, 4H), 1.57-1.47 (m, 1H), 1.30-0.88 (m, 6H).	ESI-MS: [M+H] ⁺ 317.2
Example 38 (I-C-16)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.41 (s, 1H), 10.15 (s, 1H), 7.61 (d, <i>J</i> = 8.0 Hz, 2H), 7.51 (s, 1H), 7.32 (t, <i>J</i> = 7.8 Hz, 2H), 7.06 (t, <i>J</i> = 7.4 Hz, 1H), 4.50-4.34 (m, 4H), 3.71-3.60 (m, 1H).	ESI-MS: [M+H] ⁺ 339.1
Example 39 (I-C-17)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 7.99-7.91 (m, 2H), 7.85 (s, 1H), 7.35 (t, <i>J</i> = 8.8 Hz, 2H), 6.92-6.80 (m, 1H), 4.31-4.17 (m, 1H), 3.60 (t, <i>J</i> = 7.7 Hz, 2H), 3.34-3.29 (m, 2H), 3.25 (t, <i>J</i> = 7.1 Hz, 2H), 2.56 (t, <i>J</i> = 5.8 Hz, 2H).	ESI-MS: [M+H] ⁺ 385.1
Example 40 (I-C-18)	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ 12.48 (s, 1H), 8.06-8.03 (m, 2H), 7.91 (s, 1H), 7.71-7.66 (m, 1H), 7.59-7.54 (m, 2H), 4.34-4.27 (m, 1H), 3.77 (d, <i>J</i> = 6.5 Hz, 2H), 3.71-3.64 (m, 1H), 3.59-3.52 (m, 1H), 2.37-2.29 (m, 1H), 2.08-1.99 (m, 1H).	ESI-MS: [M+H] ⁺ 338.1
Example 41 (I-C-19)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.60 (s, 1H), 8.03 (s, 1H), 8.01-7.99 (m, 2H), 7.66 (t, <i>J</i> = 7.3 Hz, 1H), 7.55 (t, <i>J</i> = 7.4 Hz, 2H), 3.82-3.64 (m, 3H), 3.45-3.35 (m, 2H), 1.91-1.82 (m, 2H), 1.73-1.58 (m, 2H).	ESI-MS: [M+H] ⁺ 352.1

Example 42: Synthesis of 5-((3-oxo-3-phenylpropyl)amino)-4-(trifluoromethyl)pyridazin-3(2*H*)-one (**I-D-1**)



5 Synthesis of 3-amino-1-phenylpropan-1-ol (**XV-1**)

3-Oxo-3-phenylpropanenitrile (**XIV-1**, 1.0 g, 6.89 mmol) was added to a 100 mL three-necked flask and dissolved in 12 mL of methanol, and 10% palladium on carbon (100 mg) was added. The reaction system was purged with hydrogen 3 times and hydrogenated for 8 h. The reaction was monitored by TLC ($V_{\text{dichloromethane}}:V_{\text{methanol}} = 10:1$) until completion. The reaction mixture was filtered in vacuum, and the filter cake was washed 4 times with methanol, and the filtrate and the washings were combined and concentrated by rotary evaporation at reduced pressure to remove the solvent and give a yellow oily substance (0.9 g, **XV-1**), which was directly used in the next step without purification.

10 Synthesis of 5-((3-hydroxy-3-phenylpropyl)amino)-4-trifluoromethyl-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2 *H*)-one (**XVI-1**)

15 **XV-1** (0.9 g, 5.96 mmol) was added to a 100 mL eggplant-shaped flask and dissolved in 16 mL of ethanol, and Et₃N (1.8 g, 18.00 mmol) and **II-1** (2.0 g, 6.55 mmol) were added. The system was incubated at room temperature for 1 h. The reaction was monitored by TLC ($V_{\text{dichloromethane}}:V_{\text{methanol}} = 10:1$) until completion. The reaction mixture was concentrated by rotary evaporation at reduced pressure to remove the solvent, and 20 mL of water was added to the residue. The mixture was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent. The crude product was purified by silica gel column chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 100:1$) to give a pale yellow solid (**XVI-1**, 900 mg, 78% yield). ESI-MS: $[M+H]^+ 434.2$.

25 Synthesis of 5-((3-oxo-3-phenylpropyl)amino)-4-(trifluoromethyl)-2-((2-(trimethylsilyl)ethoxy)methyl)pyridazin-3(2 *H*)-one (**XVII-1**)

30 **XVI-1** (0.9 g, 2.08 mmol) was added to a 100 mL eggplant-shaped flask and dissolved in 10 mL of DCM, and PCC (1.3 g, 6.23 mmol) was added. The system was incubated at room temperature for 1 h. The reaction was monitored by thin-layer chromatography ($V_{\text{dichloromethane}}:V_{\text{methanol}} = 10:1$) until completion. 20 mL of water was added. The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate

was concentrated by rotary evaporation at reduced pressure to remove the solvent. The crude product was purified by silica gel column chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 5:1$) to give a yellow oily substance (**XVII-1**, 643 mg, 72% yield). ESI-MS: $[M+H]^+ 432.2$.

5 Synthesis of 5-(3-oxo-3-phenylpropylamino)-4-trifluoromethylpyridazin-3(2H)-one (**I-D-1**)

XVII-1 (0.6 g, 1.49 mmol) was added to a 50 mL eggplant-shaped flask. Dichloromethane (5 mL) and trifluoroacetic acid (5 mL) were added. The system was incubated at room temperature for 30 min. The reaction was monitored by thin-layer chromatography ($V_{\text{dichloromethane}}:V_{\text{methanol}} = 1:1$) until completion. The mixture was concentrated by rotary evaporation at reduced pressure to remove the solvent and the remaining trifluoroacetic acid, and adjusted to pH 8 with a saturated sodium bicarbonate solution. 10 mL of water was added, and the mixture was extracted with ethyl acetate (10 mL $\times$ 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated by rotary evaporation at reduced pressure to remove the solvent. The crude product was purified by silica gel column chromatography ($V_{\text{petroleum ether}}:V_{\text{ethyl acetate}} = 2:1$) to give a yellow solid (**I-D-1**, 343 mg, 74% yield). ESI-MS: $[M+H]^+ 312.1$; ^1H NMR (300 MHz, DMSO- d_6) δ 12.48 (s, 1H), 7.99 (s, 1H), 7.98-7.96 (m, 2H), 7.67-7.62 (m, 1H), 7.55-7.49 (m, 2H), 7.04-6.97 (m, 1H), 3.74 (q, $J = 6.6$ Hz, 2H), 3.39 (t, $J = 6.8$ Hz, 2H).

The following compounds were prepared with reference to the method for preparing compound **I-D-1**:

Compound No.	^1H -NMR	MS
Example 43 (I-D-2)	^1H NMR (400 MHz, DMSO- d_6) δ 12.46 (s, 1H), 7.97-7.94 (m, 3H), 7.06-7.02 (m, 2H), 6.99-6.95 (m, 1H), 3.84 (s, 3H), 3.72 (q, $J = 6.6$ Hz, 2H), 3.31 (t, $J = 6.9$ Hz, 2H).	ESI-MS: $[M+H]^+ 324.1$
Example 44 (I-D-3)	^1H NMR (300 Hz, DMSO- d_6) δ 12.48 (s, 1H), 8.09-8.04 (m, 1H), 7.99-7.97 (m, 1H), 7.68-7.62 (m, 1H), 7.55-7.50 (m, 1H), 7.39-7.32 (m, 1H), 7.02-7.00 (m, 1H), 3.77-3.70 (m, 2H), 3.41-3.36 (m, 2H).	ESI-MS: $[M+H]^+ 330.1$

Example 45 (I-D-4)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.48 (s, 1H), 8.03-8.01 (m, 1H), 7.99-7.98 (m, 1H), 7.96 (s, 1H), 7.26-7.23 (m, 1H), 7.05-7.02 (m, 1H), 3.73 (q, <i>J</i> = 6.6 Hz, 2H), 3.31 (t, <i>J</i> = 6.8 Hz, 2H).	ESI-MS: [M+H] ⁺ 300.0
Example 46 (I-D-5)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.48 (s, 1H), 7.97 (s, 1H), 7.88 (d, <i>J</i> = 8.2 Hz, 2H), 7.33 (d, <i>J</i> = 8.0 Hz, 2H), 7.03-6.98 (m, 1H), 3.73 (q, <i>J</i> = 6.6 Hz, 2H), 3.35-3.32 (m, 2H), 2.37 (s, 3H).	ESI-MS: [M+H] ⁺ 326.1
Example 47 (I-D-6)	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 9.00 (s, 1H), 8.62 (d, <i>J</i> = 7.7 Hz, 1H), 8.09 (d, <i>J</i> = 7.8 Hz, 1H), 8.00 (s, 1H), 7.54-7.44 (m, 2H), 7.09-7.02 (m, 1H), 3.79 (q, <i>J</i> = 6.7 Hz, 2H), 3.41 (t, <i>J</i> = 6.9 Hz, 2H).	ESI-MS: [M+H] ⁺ 368.1
Example 48 (I-D-7)	¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ 12.46 (s, 1H), 7.94 (s, 1H), 7.63-7.51 (m, 2H), 7.17-7.16 (m, 1H), 7.07-7.00 (m, 1H), 7.00-6.92 (m, 1H), 3.87 (s, 3H), 3.75-3.66 (m, 2H), 3.42-3.20 (m, 2H).	ESI-MS: [M+H] ⁺ 324.1
Example 49 (I-D-8)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 7.96 (s, 2H), 7.93 (s, 1H), 7.04-6.97 (m, 3H), 4.11 (q, <i>J</i> = 6.9 Hz, 2H), 3.72 (q, <i>J</i> = 6.4 Hz, 2H), 3.31 (t, <i>J</i> = 6.8 Hz, 2H), 1.31 (t, <i>J</i> = 7.0 Hz, 3H).	ESI-MS: [M+H] ⁺ 356.1
Example 50 (I-D-9)	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ 12.45 (s, 1H), 7.95 (s, 1H), 7.94 (d, <i>J</i> = 9.2 Hz, 2H), 7.03 (d, <i>J</i> = 8.8 Hz, 2H), 7.00-6.94 (m, 1H), 4.04 (d, <i>J</i> = 6.7 Hz, 2H), 3.72 (q, <i>J</i> = 6.1 Hz, 2H), 3.31 (t, <i>J</i> = 6.8 Hz, 2H), 2.78-2.66 (m, 1H), 2.11-2.03 (m, 2H), 1.95-1.77 (m, 4H).	ESI-MS: [M+H] ⁺ 396.1
Example 51 (I-D-10)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 7.95 (s, 1H), 7.92 (d, <i>J</i> = 8.8 Hz, 2H), 7.02-6.97 (m, 3H), 4.96-4.89 (m, 1H), 3.72 (q, <i>J</i> = 6.4 Hz, 2H), 3.30 (t, <i>J</i> = 6.7 Hz, 2H), 1.98-1.86 (m, 2H), 1.77-1.60 (m, 6H).	ESI-MS: [M+H] ⁺ 356.1
Example 52 (I-D-11)	¹ H NMR (300 MHz, Chloroform- <i>d</i>) δ 12.47 (s, 1H), 7.95 (s, 1H), 7.93 (d, <i>J</i> = 8.0 Hz, 2H), 7.02 (d, <i>J</i> = 8.5 Hz, 2H), 7.00-6.92 (m, 1H), 3.86 (d, <i>J</i> = 5.6 Hz, 2H), 3.72 (q, <i>J</i> = 7.5 Hz, 2H), 3.30 (t, <i>J</i> = 6.4 Hz, 2H), 1.85-1.64 (m, 5H), 1.33-1.12 (m, 4H), 1.10-0.95 (m, 2H).	ESI-MS: [M+H] ⁺ 424.2

Example 53 (I-D-12)	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ 12.45 (s, 1H), 7.95 (s, 1H), 7.93 (d, <i>J</i> = 8.7 Hz, 2H), 7.02 (d, <i>J</i> = 8.4 Hz, 2H), 6.99-6.93 (m, 1H), 3.91 (d, <i>J</i> = 7.0 Hz, 2H), 3.72 (q, <i>J</i> = 6.5 Hz, 2H), 3.30 (t, <i>J</i> = 6.6 Hz, 2H), 1.28-1.20 (m, 1H), 0.58 (q, <i>J</i> = 5.7 Hz, 2H), 0.34 (q, <i>J</i> = 5.4 Hz, 2H).	ESI-MS: [M+H] ⁺ 382.1
Example 54 (I-D-13)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 7.95 (s, 1H), 7.93 (d, <i>J</i> = 8.9 Hz, 2H), 7.03 (d, <i>J</i> = 8.9 Hz, 2H), 7.00-6.94 (m, 1H), 3.93 (d, <i>J</i> = 7.0 Hz, 2H), 3.72 (q, <i>J</i> = 6.6 Hz, 2H), 3.30 (t, <i>J</i> = 6.8 Hz, 2H), 2.36-2.26 (m, 1H), 1.82-1.71 (m, 2H), 1.62-1.51 (m, 4H), 1.38-1.28 (m, 2H).	ESI-MS: [M+H] ⁺ 410.2
Example 55 (I-D-14)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 8.00 (s, 1H), 7.28 (t, <i>J</i> = 7.8 Hz, 2H), 7.20-7.07 (m, 1H), 6.97-6.87 (m, 3H), 4.11 (t, <i>J</i> = 5.0 Hz, 2H), 3.79 (t, <i>J</i> = 6.1 Hz, 2H).	ESI-MS: [M+H] ⁺ 300.1
Example 56 (I-D-15)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.57 (s, 1H), 8.05 (d, <i>J</i> = 7.0 Hz, 2H), 7.85 (s, 1H), 7.71 (t, <i>J</i> = 7.4 Hz, 1H), 7.59 (t, <i>J</i> = 7.6 Hz, 2H), 7.11-7.02 (m, 1H), 5.09 (d, <i>J</i> = 5.3 Hz, 2H).	ESI-MS: [M+H] ⁺ 298.1
Example 57 (I-D-16)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.48 (s, 1H), 8.00 (s, 1H), 7.97 (d, <i>J</i> = 7.2 Hz, 2H), 7.64 (t, <i>J</i> = 7.3 Hz, 1H), 7.52 (t, <i>J</i> = 7.5 Hz, 2H), 3.79 (t, <i>J</i> = 6.7 Hz, 2H), 3.46 (t, <i>J</i> = 6.5 Hz, 2H), 3.02 (s, 3H).	ESI-MS: [M+H] ⁺ 326.1
Example 58 (I-D-17)	¹ H NMR (300 Hz, DMSO- <i>d</i> ₆) δ 12.47 (s, 1H), 7.93 (s, 1H), 7.20-7.15 (m, 4H), 7.12-7.04 (m, 1H), 4.62 (d, <i>J</i> = 9.6 Hz, 2H), 3.69-3.59 (m, 4H), 2.85 (t, <i>J</i> = 6.0 Hz, 1H), 2.78-2.70 (m, 3H).	ESI-MS: [M+H] ⁺ 367.1
Example 59 (I-D-18)	¹ H NMR (400 Hz, DMSO- <i>d</i> ₆) δ 12.48 (s, 1H), 8.07 (d, <i>J</i> = 8.7 Hz, 1H), 7.98 (s, 1H), 7.23 (d, <i>J</i> = 7.4 Hz, 1H), 7.15 (t, <i>J</i> = 7.7 Hz, 1H), 7.08-7.02 (m, 1H), 6.99 (t, <i>J</i> = 7.4 Hz, 1H), 4.07 (d, <i>J</i> = 8.5 Hz, 2H), 3.70 (q, <i>J</i> = 6.5 Hz, 2H), 3.13 (t, <i>J</i> = 8.5 Hz, 2H), 2.79 (t, <i>J</i> = 6.6 Hz, 2H).	ESI-MS: [M+H] ⁺ 353.1

Example 60: Inhibitory activity of compounds against PARP7 enzyme

Materials: PARP7 Chemiluminescent Assay Kit, BPS Bioscience; DMSO, Sinopharm, Nivo, PerkinElmer.

Procedures:

(1) Preparation of solutions and buffers

Preparation of 10× PBS: 720 mg of KH_2PO_4 , 45 g of NaCl, and 5.311 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ were dissolved in 500 mL of deionized water. The system was adjusted to pH 7.4, sterilized at 121 °C for 30 min, and cooled, and then preserved at 4 °C for later use.

Preparation of 1× PBS: 10× PBS was diluted 10-fold with deionized water, i.e., 1 part of 10× PBS was diluted with 9 parts of deionized water.

Preparation of wash buffer: 1× PBS containing 0.05% Tween-20.

Preparation of 1× PARP buffer: (prepared right before use) 10× PARP buffer was diluted 10-fold with deionized water and placed on ice for later use.

(2) Preparation of compound working solution of different concentrations

According to the study requirements, the test compound was diluted to the desired concentration with 100% DMSO, and then diluted 10-fold with 1× PARP buffer to give a 10× compound working solution.

(3) Procedures

a. 5× histone mixture was thawed on ice the day before the study;

b. 1× histone mixture was prepared by diluting 5× histone mixture into 1× histone mixture with 1× PBS; 25 µL of 1× histone mixture was added to each well of the test plate and incubated overnight at 4 °C;

c. 100 µL of the blocking buffer was taken per well and added to the test plate, and the plate was incubated at 25 °C for 90 min;

d. After the incubation was completed, the liquid in the test plate was discarded, and the plate was washed 3 times;

e. 2.5 µL of compound working solution was taken from each well and added to the test plate according to the experimental layout; a corresponding volume of 1× PARP buffer containing 10% DMSO was added to the positive control wells (Positive control), and a corresponding volume of

1× PARP buffer was added to the blank control wells (Blank);

f. After the enzyme was completely dissolved, the enzyme stock solution was diluted to 6 ng/µL with 1× PARP buffer;

g. The enzyme solution was added to a test well plate at 10 μ L/well, and a corresponding volume of 1 $\times$ PARP buffer was added to the blank control wells, where the enzyme amount was 60 ng/well.

Note: this procedure should be performed on ice;

h. Master mixture (12.5 μ L of master mixture containing 1.25 μ L of 10 $\times$ PARP buffer, 1.25 μ L of Opti-PARP 10 $\times$ Assay mixture, and 10 μ L of water) was added to the test plate at 12.5 μ L/well; the test plate was sealed with a film and incubated at 25 $^{\circ}$ C for 60 min;

i. After the incubation, the liquid in the test plate was discarded, and the plate was washed 3 times;

j. Streptavidin-HRP in the kit was 50-fold diluted with the Blocking buffer, and added to the test plate at 25 μ L/well, and the plate was incubated at 25 $^{\circ}$ C for 30 min;

k. After the incubation, the liquid in the test plate was discarded, and the plate was washed 3 times;

l. ELISA ECL Substrate A and ELISA ECL Substrate B in the kit were mixed in a ratio of 1:1, the mixed solution was added to the test plate at 50 μ L/well, luminescence detection was immediately performed using Nivo, and the luminescence value (RLU) was read;

m. Calculation of enzyme inhibition:

% Enzyme Activity = (RLU(Sample) - RLU(Blank)) / (RLU(Pos.Ctrl) - RLU(Blank)) $\times$ 100%;

Enzyme inhibition = 1 - % Enzyme Activity; the IC₅₀ was calculated using GraphPad Prism 8.

The specific results are shown in Tables 1 and 2 below.

Table 1. Inhibitory activity of test compounds against PARP7 at 100 nM

Compound No.	Inhibition at 100 nM	Compound No.	Inhibition at 100 nM
I-A-1	+++	I-C-14	+++
I-A-2	+++	I-C-17	++
I-A-3	++	I-C-18	+++
I-A-5	+++	I-C-19	++
I-A-6	++	I-D-1	+++
I-A-9	++	I-D-2	+++
I-A-18	++	I-D-3	+++
I-A-20	+++	I-D-5	+++
I-C-3	++	I-D-6	+++
I-C-6	+++	I-D-7	+++
I-C-7	+++	I-D-8	+++

I-C-8	+++	I-D-9	++
I-C-9	+++	I-D-10	+++
I-C-10	+++	I-D-11	+++
I-C-11	+++	I-D-12	++
I-C-12	+++	I-D-13	+++
I-C-13	+++	I-D-14	+++

Note: “+++” denotes that inhibition at 100 nM $\geq$ 50%; “++” indicates that 50% > inhibition at 100 nM $\geq$ 25%.

Table 2. Inhibitory activity of test compounds against PARP7 enzyme (IC₅₀)

Compound No.	IC ₅₀	Compound No.	IC ₅₀
I-A-1	+++	I-C-14	+++
I-A-2	+++	I-C-18	+++
I-A-3	++	I-D-1	+++
I-A-5	++	I-C-12	+++
I-A-6	++	I-C-13	+++
I-A-9	++	I-D-2	+++
I-A-18	++	I-D-3	+++
I-A-20	+++	I-D-5	+++
I-C-3	++	I-D-6	+++
I-C-6	+++	I-D-7	+++
I-C-7	+++	I-D-8	+++
I-C-8	+++	I-D-10	+++
I-C-9	+++	I-D-11	+++
I-C-10	+++	I-D-13	+++
I-C-11	+++	I-D-14	+++

5 Note: “+++” denotes that IC₅₀ < 0.1 μ M; “++” denotes that 0.1 μ M $\leq$ IC₅₀ < 0.5 μ M.

As shown in Tables 1 and 2, all the test compounds of the present disclosure exhibited good enzyme inhibitory activity against PARP7, and the IC₅₀ values of a number of compounds were less than 100 nM.

Example 61: Physicochemical properties of compounds (see Table 3; tPSA was calculated using ChemDraw Professional 17 software).

Materials: test compounds I-A-1, I-A-2, and RBN-2397.

5

Procedures:

(1) Caco-2 cell plating

1. 600 μL of cell culture medium and 100 μL of cell culture medium were added to the wells of a Transwell insert and a reservoir, respectively;
- 10 2. Before cell inoculation, Transwell was pre-incubated at 37 °C and 5% CO_2 for 1 h;
3. 100 μL of cell suspension (4×10^5 cells/mL) was seeded into the culture medium and cultured at 37 °C, 5% CO_2 , and 95% relative humidity for 14-21 days;
4. The cell culture medium was replaced once every other day in the first 7 days, and once every day after day 7;
- 15 5. The transepithelial electrical resistance (TEER) of the monolayer membrane was measured using EVOM3.

(2) ABBA process

- 20 1. The plate was washed twice with pre-heated HBSS (10 mM HEPES, pH 7.4) and then incubated at 37 °C for 30 min.
2. Test compounds were prepared in 1 mM DMSO and diluted 200-fold to 5 μM with HBSS (10 mM HEPES, pH 7.4) and HBSS (100 μM Lucifer Yellow, 10 mM HEPES, pH 7.4).
3. Apical to basal direction: 200 μL of 5 μM working solution (100 μM Lucifer Yellow) was added to the apical compartment, and 600 μL of HBSS (10 mM HEPES, pH 7.4) was added to the basal compartment.
- 25 4. Basal to apical direction: 600 μL of 5 μM working solution was added to the basal compartment, and 200 μL of HBSS (100 μM Lucifer Yellow, 10 mM HEPES, pH 7.4) was added to the apical compartment.
5. 100 μL of 5 μM working solution was transferred to a sample plate containing 400 μL of cold methanol, and IS* was C_0 .
- 30 6. The cell plate was incubated at 37 °C, 5% CO_2 , and 95% relative humidity for 2 h.

7. 5 μ L of the working solution was transferred from the apical compartment and the basal compartment to the plate. After 0.5 h of incubation, the 427 nM excitation values and 536 nM emission values were read by the Lucifer Yellow leakage detector.

8. After 2 h of incubation, 100 μ L of the solution was transferred from the apical and basal compartments with IS* to a sample plate containing 400 μ L of cold methanol.

9. The sample plate was centrifuged at 3220 g for 40 min.

10. 100 μ L of the supernatant was transferred to an assay plate containing an appropriate volume of water for LC-MS/MS analysis.

(3) Calculation

The apparent permeability coefficient (P_{app} , cm/s) and the efflux ratio were calculated using Microsoft Excel.

$$P_{app} = \frac{V_A \times C_{acceptor} \times 100}{Area \times Time \times C_{initial,donor}}$$

$$Efflux\ Ratio = \frac{P_{app(B-A)}}{P_{app(A-B)}}$$

Table 3. Physicochemical properties of test compounds

Compound No.	$P_{app\ A \rightarrow B}$ (1E-6 cm/s)	$P_{app\ B \rightarrow A}$ (1E-6 cm/s)	Efflux Ratio	Number of N + O	Molecular weight	tPSA
RBN-2397	4.1	24	5.9	10	523.4	110.99
I-A-1	39.86	20.92	0.52	4	361.2	53.49
I-A-2	39.27	25.16	0.64	4	293.2	53.49

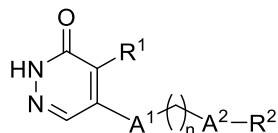
Note: tPSA is a predicted value.

As shown in Table 3, compounds I-A-1 and I-A-2 of the present disclosure exhibited better membrane permeability and lower efflux ratio, conforming to the Clark-Lobell rules, suggesting that the two compounds theoretically can well penetrate the blood-brain barrier and treat stroke; whereas, the existing compound RBN-2397 exhibited poor membrane permeability that failed to conform to the Clark-Lobell rules, indicating difficulties in penetrating the blood-brain barrier.

The embodiments of the technical schemes of the present disclosure have been described above by way of example. It will be appreciated that the claimed scope of the present disclosure is not limited to the embodiments described above. Any modification, equivalent replacement, improvement, and the like made by those skilled in the art without departing from the spirit and
5 principle of the present disclosure shall fall within the claimed scope of the present application.

CLAIMS

1. A compound of formula (I), or a racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof:

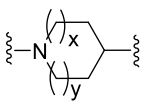


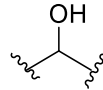
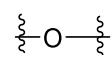
5 (I)

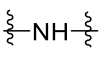
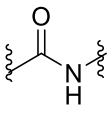
wherein:

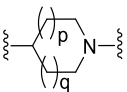
n is selected from 0, 1, 2, 3, and 4;

10 R^1 is selected from hydrogen, halogen, cyano, nitro, C_1 - C_{12} haloalkyl, C_1 - C_{12} alkyl, C_1 - C_{12} alkyloxy, C_1 - C_{12} alkylthio, C_1 - C_{12} alkylsulfonyl, and $-C(O)N(R^{11})(R^{12})$; R^{11} and R^{12} are identical or different, and are each independently selected from H and C_1 - C_6 alkyl;

A^1 is selected from -O-, -S-, , and $-N(R^3)-$, wherein x and y are each independently selected from 0, 1, and 2; R^3 is selected from H, C_1 - C_{12} alkyl, and C_3 - C_{14} cycloalkyl;

15 A^2 is absent or selected from methylene, vinylene, ethynylene, , , ,

, , and the following groups unsubstituted or optionally substituted with one, two,

or more R_{a2} : , C_6 - C_{14} aryl, and 5- to 14-membered heteroaryl, wherein p and q are each independently selected from 0, 1, and 2; the R_{a2} groups are identical or different, and are each independently selected from hydrogen, halogen, cyano, hydroxy, nitro, C_1 - C_{12} alkyl, C_1 - C_{12} alkyloxy, C_1 - C_{12} haloalkyl, C_1 - C_{12} haloalkyloxy, $-C(O)OR_{a21}$, $-C(O)R_{a22}$, $-N(R_{a23})(R_{a24})$, $-S(O)_2R_{a25}$, and $-S(O)R_{a26}$; the R_{a21} , R_{a22} , R_{a23} , R_{a24} , R_{a25} , and R_{a26} groups are identical or different and are each independently selected from H, C_1 - C_{12} alkyl, and C_1 - C_{12} alkyl- $C(O)-$;

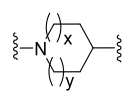
25 R^2 is selected from the following groups unsubstituted or optionally substituted with one, two, or more R^{21} : C_6 - C_{14} aryl, 5- to 14-membered heteroaryl, 3- to 8-membered heterocyclyl, C_1 - C_{12} alkyl, $-S(O)_2-NH-$, $-C(O)NH_2$, and $NH_2-S(O)_2-NH-$; the R^{21} groups are identical or different, and are

each independently selected from hydrogen, halogen, cyano, hydroxy, nitro, C₁-C₁₂ alkyl, C₁-C₁₂ haloalkyl, C₆-C₁₄ aryl, 5- to 14-membered heteroaryl, 3- to 8-membered heterocyclyl, R₂₁-O-, -C(O)OR₂₂, -C(O)R₂₃, -N(R₂₄)(R₂₅), -S(O)₂R₂₆, and -S(O)R₂₇; the R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, R₂₆, and R₂₇ groups are identical or different, and are each independently selected from H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, 3- to 14-membered cycloalkyl, 3- to 14-membered cycloalkyl-C₁-C₆ alkyl, C₆-C₁₄ aryl, 5- to 14-membered heteroaryl, and 3- to 8-membered heterocyclyl.

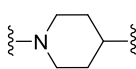
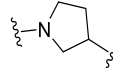
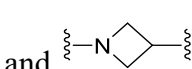
2. The compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to claim 1, wherein n is selected from 0, 1, and 2;

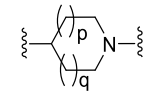
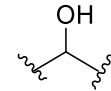
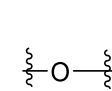
R¹ is selected from halogen, cyano, and trifluoromethyl.

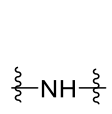
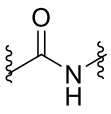
3. The compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to claim 1, wherein A¹ is selected from

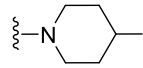
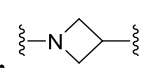


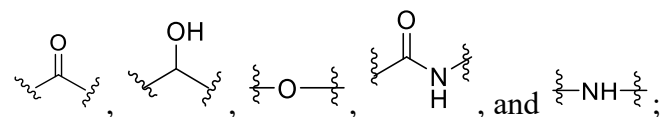
and -N(R³)-, wherein x and y are each independently selected from 0, 1, and 2; R³ is selected from H and C₁-C₆ alkyl;

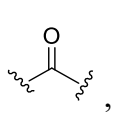
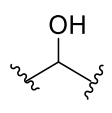
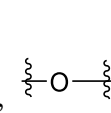
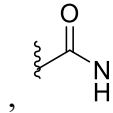
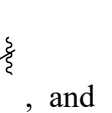
A¹ is selected from -NH-, -N(CH₃)-, , , and ; preferably, A¹ is selected from -NH-;

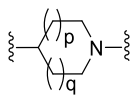
A² is absent or selected from vinylene, ethynylene, , , , ,

, , C₆-C₁₀ arylene, and 5- to 10-membered heteroarylene, wherein p and q are each independently selected from 0, 1, and 2;

preferably, A² is absent or selected from vinylene, ethynylene, phenylene, , ,



more preferably, A² is selected from ethynylene, , , , , and ;



is unsubstituted or optionally substituted with one, two, or more R_{a2} , and the R_{a2} groups are identical or different, and are each independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, trifluoromethyl, 2,2-difluoroethyl, methoxy, hydroxy, amino, methylamino, dimethylamino, acetylamino, carboxyl, methoxycarbonyl, methanesulfonyl, and nitro.

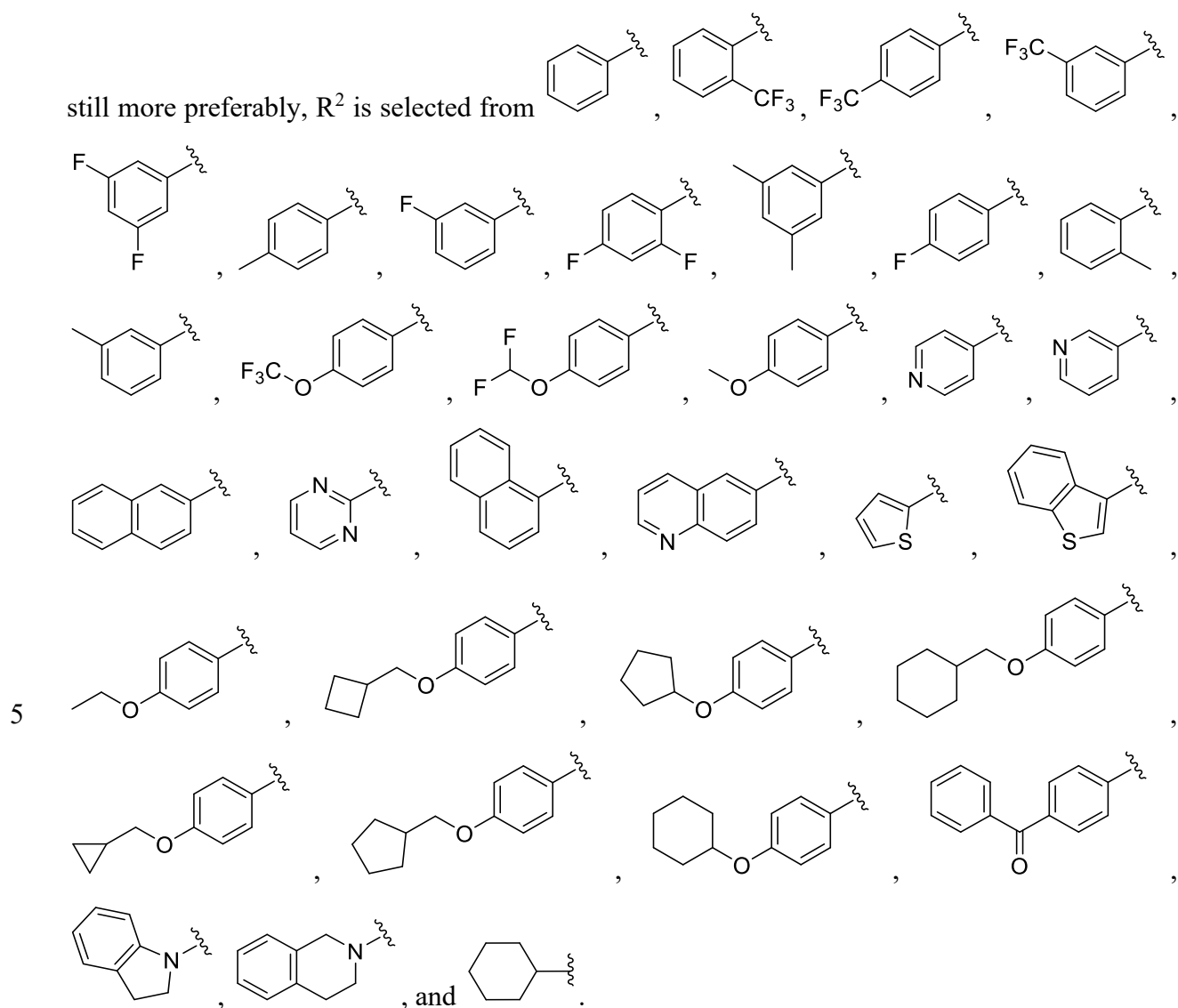
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4. The compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to claim 1, wherein R^2 is selected from the following groups unsubstituted or optionally substituted with one, two, or more R^{21} : C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, and 3- to 8-membered heterocyclyl; the R^{21} groups are identical or
10 different and are each independently selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkyloxy, C_1 - C_6 haloalkyloxy, 3- to 8-membered cycloalkyloxy, 3- to 8-membered cycloalkyl- C_1 - C_6 alkyloxy, and C_6 - C_{10} aryl- $C(O)-$;

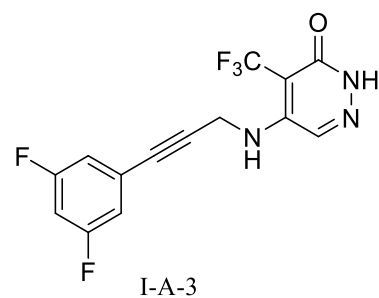
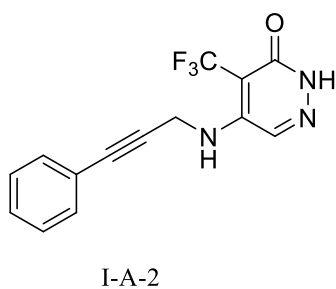
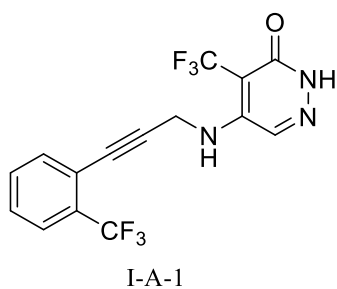
more preferably, R^2 is selected from substituted C_6 - C_{14} aryl and substituted 5- to 14-membered
15 heteroaryl; the substituent is selected from hydrogen, halogen, cyano, trifluoromethyl, 2,2-difluoroethyl, C_1 - C_6 alkyl, hydroxy, C_1 - C_6 alkyloxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, C_3 - C_6 azacycloalkyl, formyl, acetyl, acetylamino, carbamoyl, and sulfamoyl; the substituent is monosubstituted or disubstituted;

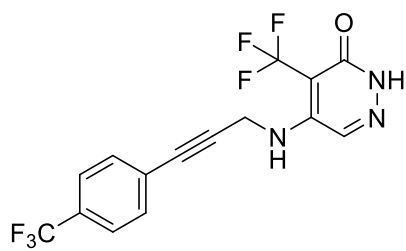
20 even more preferably, R^2 is selected from substituted C_6 - C_{10} aryl and substituted 5- to 10-membered heteroaryl, wherein the C_6 - C_{10} aryl is phenyl or naphthyl, and the 5- to 10-membered heteroaryl is selected from pyridinyl, thienyl, pyrrolyl, furanyl, imidazolyl, pyrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolyl, isoquinolyl, indazolyl, benzothienyl, benzofuranyl, and benzimidazolyl; the substituent is selected from hydrogen, halogen, cyano, trifluoromethyl, 2,2-
25 difluoroethyl, methyl, ethyl, hydroxy, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, azetidiny, tetrahydropyrrol-1-yl, piperidin-1-yl, morpholinyl, piperazinyl, N-methylpiperazinyl, acetyl, acetylamino, carbamoyl, and sulfamoyl; the substituent is monosubstituted or disubstituted;

still more preferably, R^2 is selected from

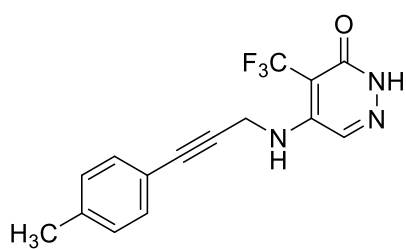


5. The compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to any one of claims 1-4, wherein the compound of formula (I) is selected from the following compounds:

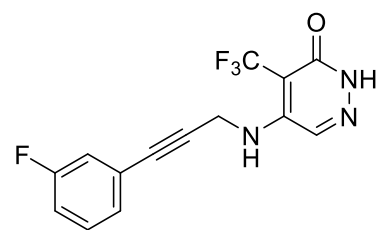




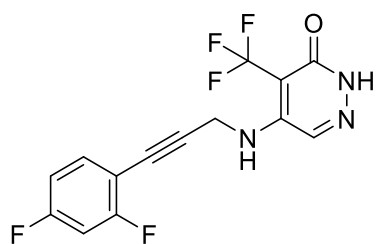
I-A-4



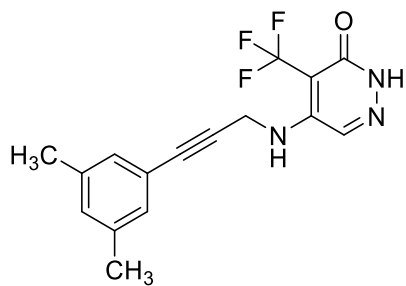
I-A-5



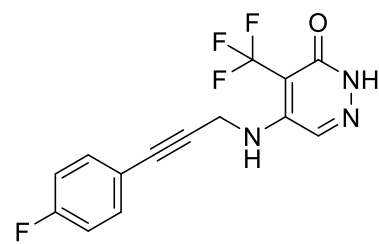
I-A-6



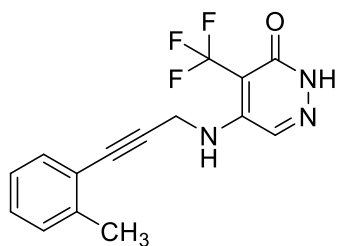
I-A-7



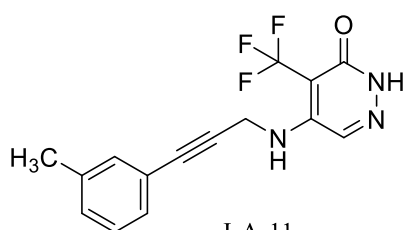
I-A-8



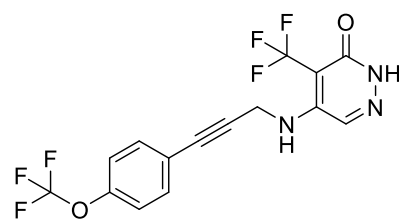
I-A-9



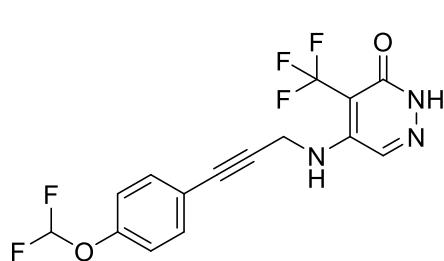
I-A-10



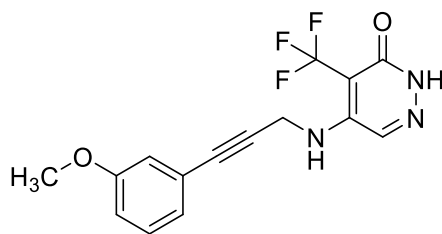
I-A-11



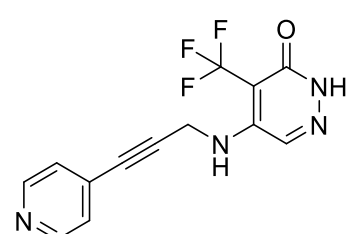
I-A-12



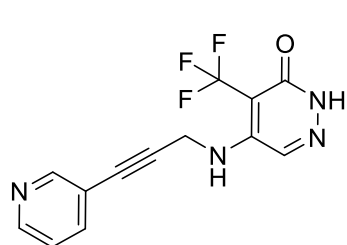
I-A-13



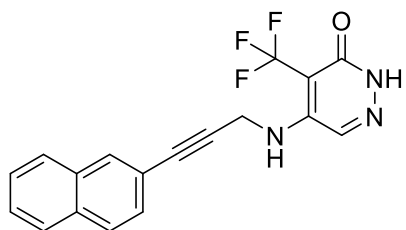
I-A-14



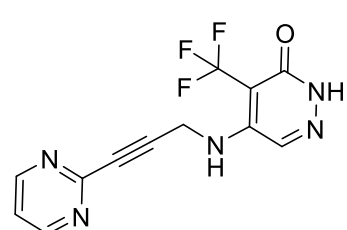
I-A-15



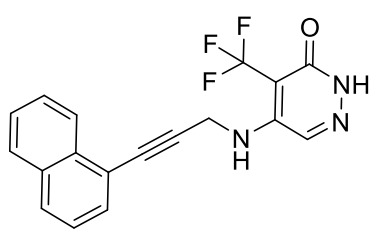
I-A-16



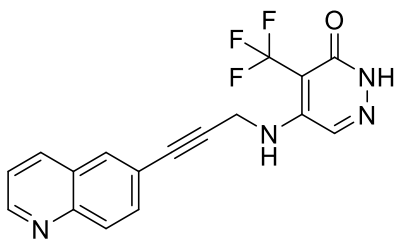
I-A-17



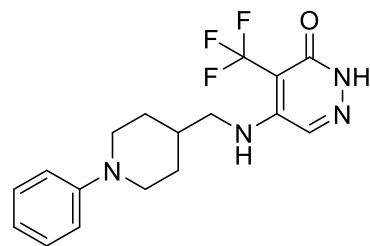
I-A-18



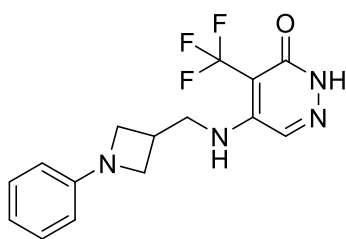
I-A-19



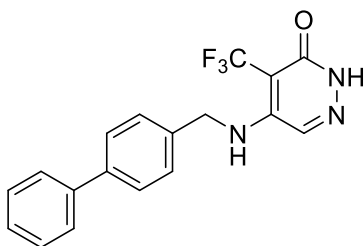
I-A-20



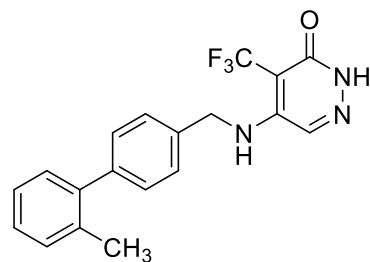
I-B-1



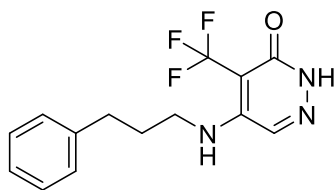
I-B-2



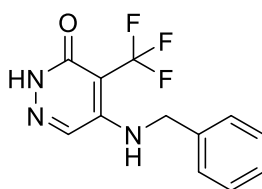
I-C-1



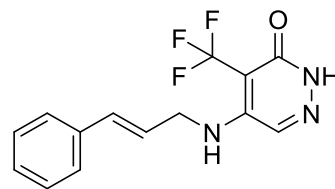
I-C-2



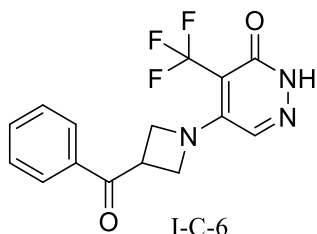
I-C-3



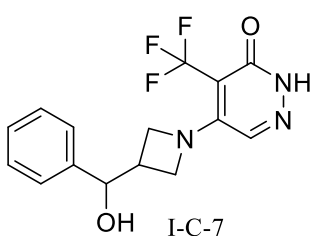
I-C-4



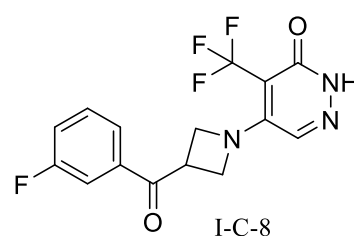
I-C-5



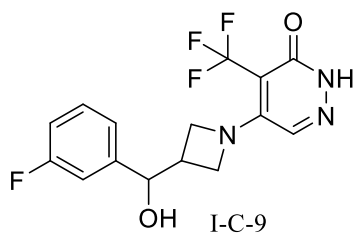
I-C-6



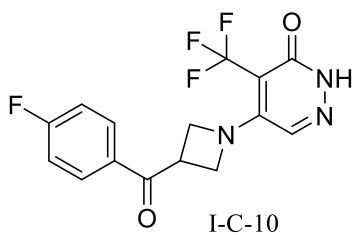
I-C-7



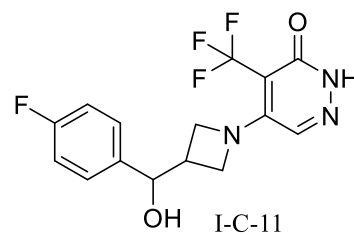
I-C-8



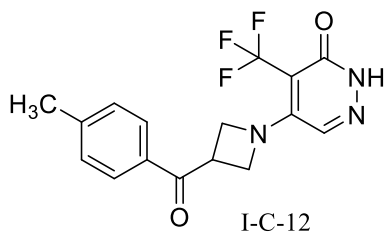
I-C-9



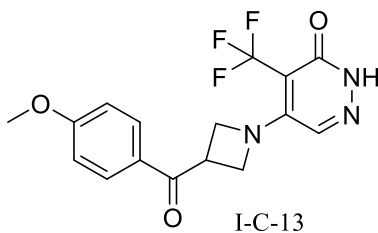
I-C-10



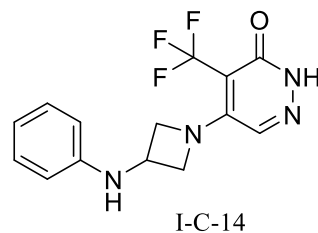
I-C-11



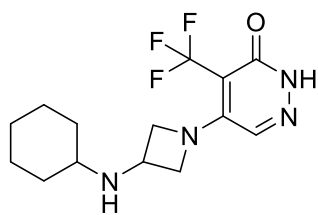
I-C-12



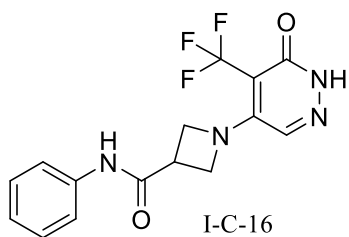
I-C-13



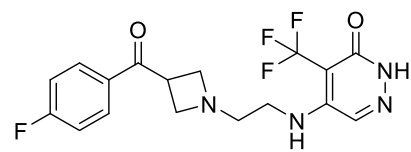
I-C-14



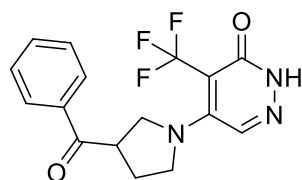
I-C-15



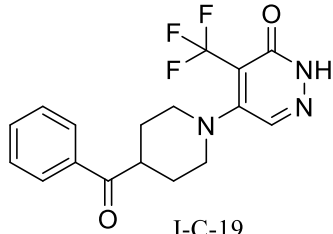
I-C-16



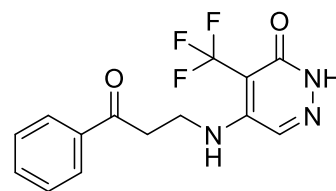
I-C-17



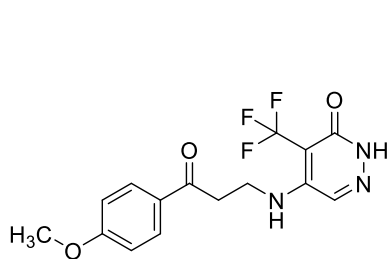
I-C-18



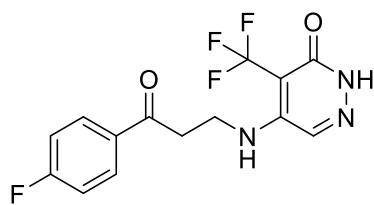
I-C-19



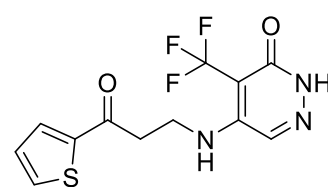
I-D-1



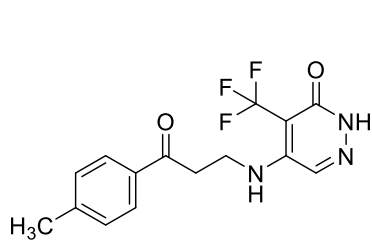
I-D-2



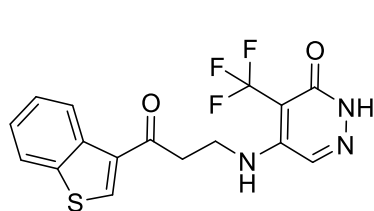
I-D-3



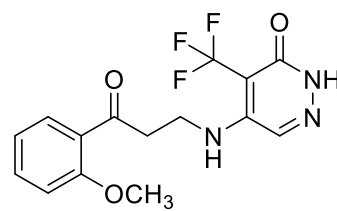
I-D-4



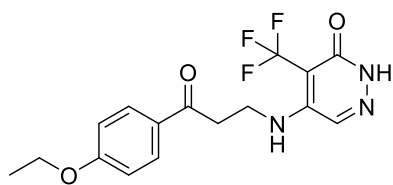
I-D-5



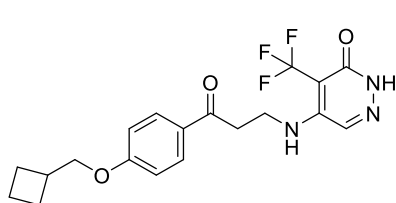
I-D-6



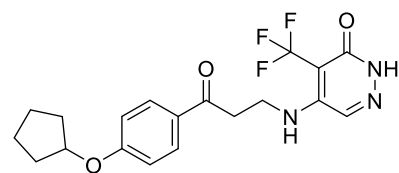
I-D-7



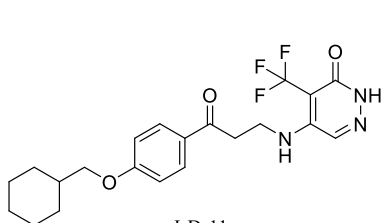
I-D-8



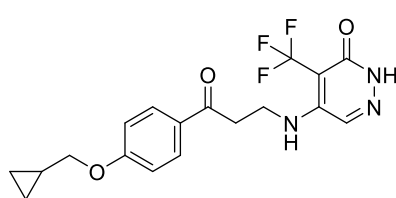
I-D-9



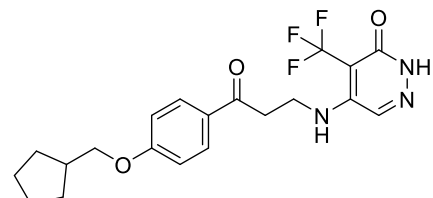
I-D-10



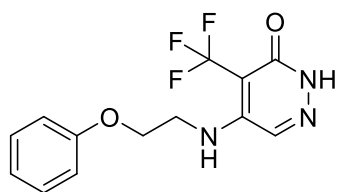
I-D-11



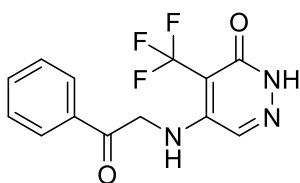
I-D-12



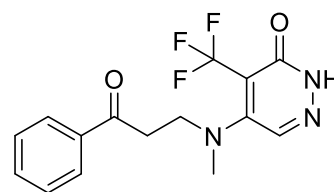
I-D-13



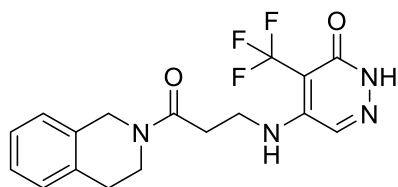
I-D-14



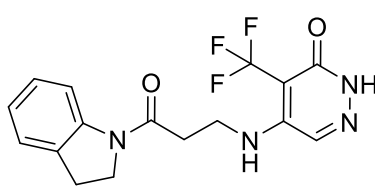
I-D-15



I-D-16



I-D-17



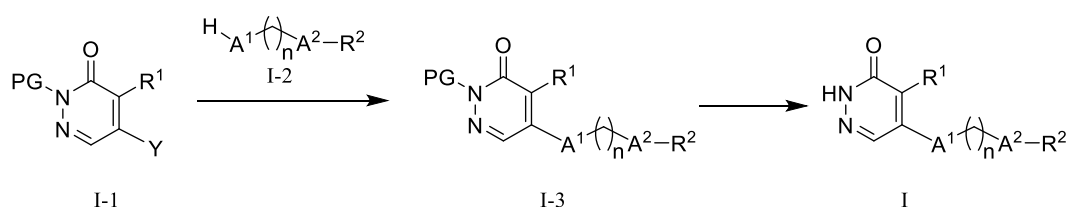
I-D-18

6. The compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to claim 1, wherein the pharmaceutically acceptable salt is a salt formed by the compound and an acid, and the acid is selected from at least one of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, carbonic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, citric acid, malic acid, tartaric acid, lactic acid, pyruvic acid, acetic acid, maleic acid, succinic acid, fumaric acid, salicylic acid, phenylacetic acid, mandelic acid, and ferulic acid.

7. A method for preparing the compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to any one of claims 1-6, comprising:

(1) reacting compound I-1 with compound I-2 to give compound I-3; and

(2) removing PG from compound I-3 to give the compound of formula (I);



wherein Y is selected from a leaving group, preferably halogen, and more preferably Cl and Br; PG is selected from a protecting group, preferably (trimethylsilyl)ethoxymethyl (SEM) and p-methoxybenzyl (PMB).

8. A pharmaceutical composition, comprising a therapeutically effective amount of at least one of the compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to any one of claims 1-6, and one or more pharmaceutically acceptable excipients.

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9. Use of the compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to any one of claims 1-6, or the pharmaceutical composition according to claim 8 in preparing a medicament for preventing and/or treating a PARP-mediated disease, preferably in preparing a PARP inhibitor medicament, wherein

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more preferably, the subtype of PARP is selected from PARP2, PARP3, PARP4, PARP5a, PARP5b, PARP7, and/or PARP1.

10. Use of the compound, or the racemate, stereoisomer, tautomer, isotopically labeled form, solvate or pharmaceutically acceptable salt thereof according to any one of claims 1-6, or the pharmaceutical composition according to claim 8 in preparing a medicament for preventing and/or treating a central nervous system disease, a cerebral ischemia-associated disease, a cancer, an infection, an immune disease, a cardiovascular disease, or a metabolic disease, wherein the central nervous system disease is selected from stroke, preferably ischemic stroke; the cerebral ischemia-associated disease is selected from transient ischemic attack, cerebral thrombosis, and cerebral embolism; the cancer is selected from lung cancer, pancreatic cancer, colorectal cancer, leukemia, Ewing's sarcoma, breast cancer, prostate cancer, T-cell lymphoma, B-cell lymphoma, malignant rhabdomyoma, synovial sarcoma, endometrioma, gastric cancer, liver cancer, renal cancer, melanoma, ovarian cancer, cerebral glioma, cholangiocarcinoma, nasopharyngeal cancer, cervical cancer, head and neck cancer, esophageal cancer, thyroid cancer, and bladder cancer.

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