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Application No.: 202311372605.9

Application Type: Patent of Invention

Title of the invention: BENZO NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVE MODULATOR, AND PREPARATION METHOD THEREFOR AND USE THEREOF

Application Date: October 20, 2023

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July 09, 2024

Description

BENZO NITROGEN-CONTAINING HETEROCYCLIC DERIVATIVE MODULATOR, AND PREPARATION METHOD THEREFOR AND USE THEREOF

Technical Field

The present disclosure belongs to the field of drug synthesis and specifically relates to a benzo nitrogen-containing heterocyclic derivative modulator, and a preparation method therefor and the use thereof.

Background Art

Diabetes mellitus is a prevalent endocrine and metabolic disease, which is caused by metabolic disorders due to various reasons and leads to damage of multiple systems and organs. Diabetes mellitus exhibits a high incidence rate, with approximately 425 million diabetic patients worldwide. The incidence rate of diabetes mellitus in China is about 10%, among which type II diabetes accounts for 90% of all diabetes cases, with an increasing prevalence trend and a notable shift towards younger ages.

Currently, there are many types of drugs on the market for the treatment of type II diabetes, including insulin, biguanides, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase IV (DPP-IV) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, α -glycosidase inhibitors, etc., among which GLP-1 receptor agonists are of greatest concern.

GLP-1 is a peptide hormone secreted by human intestinal L cells. Its receptors are distributed across pancreas islet cells, various gastrointestinal cells, and neurons of the central nervous system and peripheral nervous system. After activation, GLP-1 receptors have physiological effects such as promoting insulin secretion, inhibiting glucagon secretion, suppressing appetite and delaying gastric emptying. Clinical evidence demonstrates that compared with other hypoglycemic drugs, GLP-1 receptor agonists have better glucose-lowering effects and are less likely to cause side effects such as hypoglycemia. In addition, it has additional cardiovascular benefits and may be conducive to weight control by reducing food intake and delaying gastric emptying.

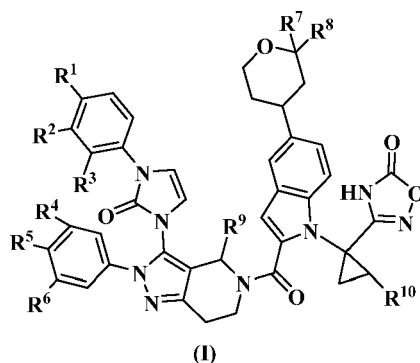
Currently, the GLP-1 receptor agonists available on the market are all polypeptide drugs, most of which require subcutaneous administration, leading to suboptimal patient compliance. Furthermore, oral polypeptides exhibit an extremely low bioavailability. Therefore, there is a substantial clinical need for the development of small molecule GLP-1 receptor agonists for oral administration.

There are currently no approved small molecule GLP-1 receptor agonists. Three small molecule GLP-1 receptor agonists, PF-06882961 and PF-07081532 developed by Pfizer, and TTP273 developed by vTv, have been included in clinical research. They are currently in phase I/II clinical trials. Among them, PF-06882961 has demonstrated significant effects on lowering blood glucose and reducing body weight in early clinical trials, with a similar safety to polypeptide-based GLP-1 receptor agonists. It is expected that PF-06882961 will provide more treatment options for patients with diabetes, obesity, and NASH in the future.

There is a huge clinical need for GLP-1 receptor agonists. Oral small molecule GLP-1 receptor agonists with lower cost and better compliance have the potential to treat a variety of metabolic diseases and have broad market prospects.

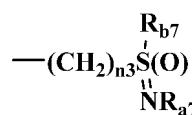
Summary of the Invention

An objective of the present disclosure is to provide a compound represented by general formula (I), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

- 5 each R^1 , R^2 or R^3 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, -



- (CH_2) $_{n1}$ $C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$, $-(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}$, wherein the
 10 amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl
 15 or 5- to 10-membered heteroaryl;

- each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -
 20 $NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy,

C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a6} and R_{b6} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

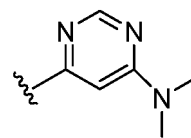
each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

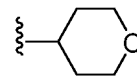
n₁ to n₄ are integers from 0 to 5;

when R⁴, R⁶, R⁹ and R¹⁰ are methyl, R⁷ and R⁸ are hydrogen, R⁵ is fluorine, R¹ is methoxy, and R² is fluorine, R³ cannot be hydrogen;

when R⁴, R⁶, R⁹ and R¹⁰ are methyl, R⁷ and R⁸ are hydrogen, R⁵ is fluorine, R¹ is , and R² is methyl, R³ cannot be hydrogen;



when R^4 , R^6 , R^9 and R^{10} are methyl, R^7 and R^8 are hydrogen, R^5 is fluorine, R^1 is R^2 is methyl, R^3 cannot be hydrogen;



when R^4 , R^6 , R^9 and R^{10} are methyl, R^7 and R^8 are hydrogen, R^5 is fluorine, and R^1 is and R^3 cannot both be hydrogen.

5 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R^1 , R^2 or R^3 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, -

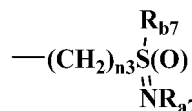
10 $-(CH_2)_{n3}S(O)NR_{a7}$ or $-(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

preferably, each R^1 , R^2 or R^3 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, -

20 $-(CH_2)_{n3}S(O)NR_{a7}$ or $-(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl or C_{2-4} alkynyl is optionally further substituted with one or more substituents selected from halogen, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl or C_{3-6} cycloalkyl;

25 further preferably, each R^1 , R^2 or R^3 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl,

C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₂₋₄ alkynyl, C₃₋₈ bridged cycloalkyl, C₃₋₈ spirocycloalkyl, 3- to 8-membered spiroheterocyclyl containing 1 to 3 heteroatoms, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -(CH₂)_{n1}C(O)NR_{a6}R_{b6}, -



(CH₂)_{n1}P(O)R_{a3}R_{b3}, or -(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}, wherein the amino, C₁₋₃ alkyl, C₁₋₃

5 deuterioalkyl, C₁₋₃ haloalkyl or C₂₋₄ alkynyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl or C₃₋₆ cycloalkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

10 each R¹, R² or R³ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is
15 optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl.

20 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

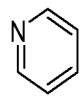
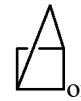
each R¹, R² or R³ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl and 5- to 8-membered heteroaryl are
25 optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered
30 heteroaryl;

preferably, each R^1 , R^2 or R^3 is independently hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl is optionally further substituted with one or more substituents selected from halogen, $-NS(O)R_{a1}R_{b1}$ or C_{1-3} alkyl.

5 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{3-6} bridged cycloalkyl, C_{3-6} spirocycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C_{6-10} aryl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{3-6} bridged cycloalkyl, C_{3-6} spirocycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C_{6-10} aryl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S is optionally further substituted with one or more substituents selected from halogen or C_{1-3} alkyl;

15 preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is

independently selected from hydrogen, deuterium, halogen, methyl, cyclopropyl, , ,  or



, which is optionally further substituted with fluorine.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

20 R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a6} and R_{b6} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

preferably, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a6} and R_{b6} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C_{3-6} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

25 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl,

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C₆₋₁₀ aryl or 5- to 10-membered heteroaryl; alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen or methyl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} are each independently attached to adjacent atom(s) to form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

preferably, each R⁴, R⁵ or R⁶ is independently fluorine or methyl.

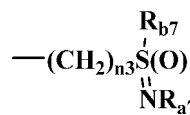
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

preferably, R⁷, R⁸, R⁹ or R¹⁰ is methyl.

In another embodiment of the present disclosure, in the compound represented by general formula (I),

each R¹, R² or R³ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4},



5 $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, $-(CH_2)_{n1}C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$ or
 C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

10 R^1 and R^2 together with adjacent atom(s) to which they are attached form C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-12} aryl or 5- to 12-membered heteroaryl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

15 each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{a6} , R_{b6} , R_{a7} or R_{b7} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

25 R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R^1 , R^2 or R^3 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, -

$-(CH_2)_{n1}C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$ or $-(CH_2)_{n3}\overset{\overset{R_{b7}}{|}}{\underset{\underset{NR_{a7}}{||}}{S(O)}}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy,

C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, each R¹, R² or R³ is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

5
$$-(CH_2)_{n3} \overset{\overset{R_{b7}}{|}}{\underset{\underset{NR_{a7}}{||}}{S(O)}}$$
 (CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3} or
$$-(CH_2)_{n3} \overset{\overset{R_{b7}}{|}}{\underset{\underset{NR_{a7}}{||}}{S(O)}}$$
, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl or C₂₋₄ alkynyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl or C₃₋₆ cycloalkyl;

further preferably, each R¹, R² or R³ is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₂₋₄ alkynyl, C₃₋₈ bridged cycloalkyl, C₃₋₈ spirocycloalkyl, 3- to 8-membered spiroheterocyclyl containing 1 to 3 heteroatoms, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -

10 (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -(CH₂)_{n1}C(O)NR_{a6}R_{b6}, -
$$-(CH_2)_{n3} \overset{\overset{R_{b7}}{|}}{\underset{\underset{NR_{a7}}{||}}{S(O)}}$$
 (CH₂)_{n1}P(O)R_{a3}R_{b3} or
$$-(CH_2)_{n3} \overset{\overset{R_{b7}}{|}}{\underset{\underset{NR_{a7}}{||}}{S(O)}}$$
, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl or C₂₋₄ alkynyl is optionally further substituted with one or more substituents selected from halogen, -

15 NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl or C₃₋₆ cycloalkyl.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

R¹ and R² together with adjacent atom(s) to which they are attached form 3- to 10-membered fused heterocyclyl containing 1 to 4 heteroatoms;

20 preferably, R¹ and R² together with adjacent atom(s) to which they are attached form 9-membered fused heterocyclyl containing 1 to 4 N atoms.

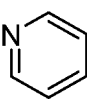
In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{a6}, R_{b6}, R_{a7} or R_{b7} is independently selected from

25 hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₃₋₆ bridged cycloalkyl, C₃₋₆ spirocycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms, C₆₋₁₀ aryl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₃₋₆ bridged cycloalkyl, C₃₋₆ spirocycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms, C₆₋₁₀ aryl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms is optionally further

30 substituted with halogen or C₁₋₃ alkyl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{a6}, R_{b6}, R_{a7} or R_{b7} is independently hydrogen,

deuterium, halogen, methyl, cyclopropyl, , ,  or , which is optionally further substituted with fluorine.

In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

5 R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl; preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} are each independently attached to adjacent atom(s) to form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

10 In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

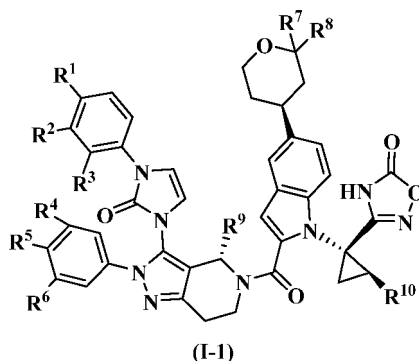
each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

preferably, each R^4 , R^5 or R^6 is independently fluorine or methyl.

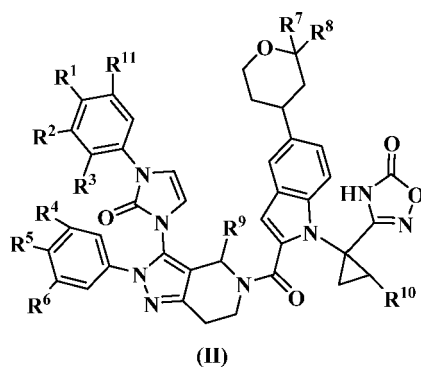
15 In another further preferred embodiment of the present disclosure, in the compound represented by general formula (I),

each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

20 preferably, each R^7 , R^8 , R^9 or R^{10} is independently methyl. In a further preferred embodiment of the present disclosure, the compound represented by general formula (I) is further as represented by general formula (I-1):



An objective of the present disclosure is to provide a compound represented by general formula (II), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl, wherein the C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

R^1 , R^2 , R^3 or R^{11} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -NS(O) $R_{a1}R_{b1}$, -(CH₂)_nS(O)NR_{a2}R_{b2}, -P(O) $R_{a3}R_{b3}$ or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O) $R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl,

3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

5 each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

10 each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

20 n1 is an integer from 0 to 5.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

25 R¹ and R², and R¹ and R¹¹ together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl.

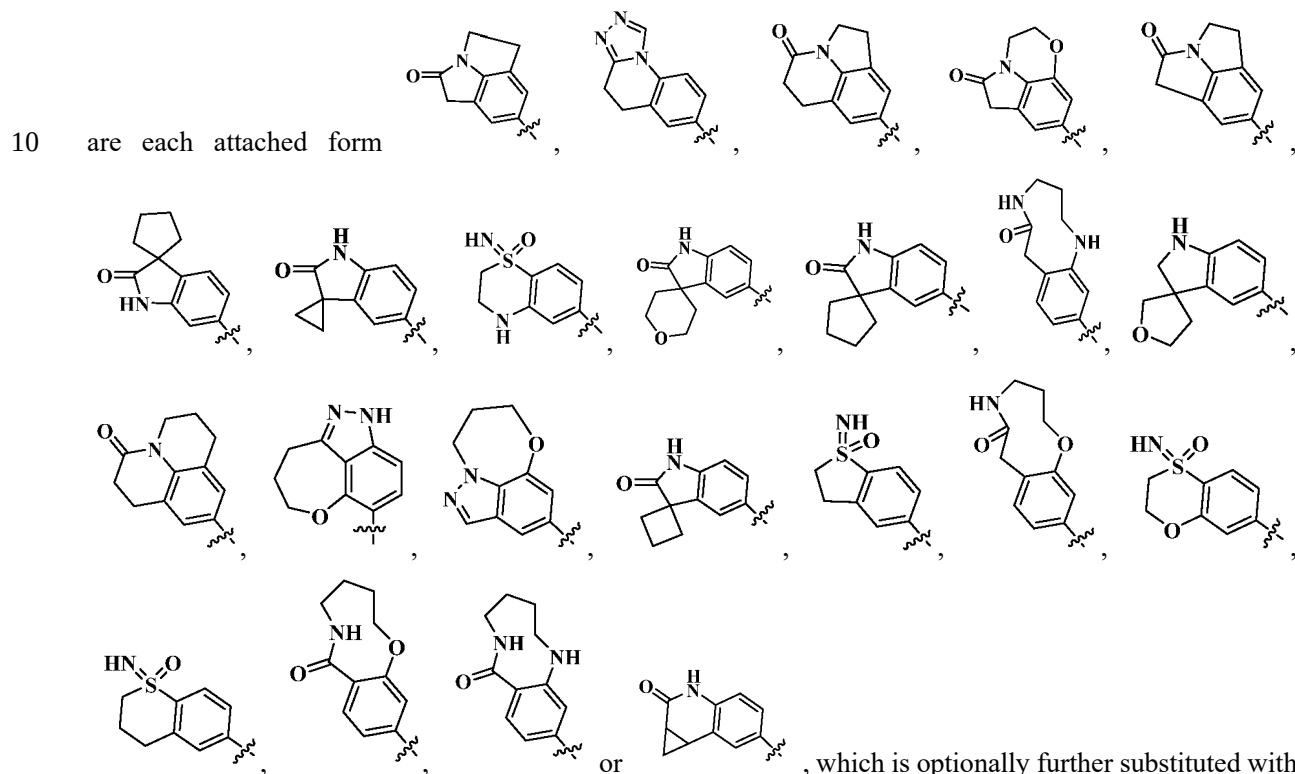
30 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, C_{1-3} alkyl, amino or oxo;

preferably, R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with oxo.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

even further preferably, R^1 and R^2 , and R^1 and R^{11} together with adjacent phenyl groups to which they



one or more substituents selected from halogen, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{3-6} cycloalkyl, amino or oxo.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino or oxo;

preferably, R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with oxo.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl,

C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, R¹, R², R³ or R¹¹ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl,

C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

5 more preferably, R¹, R², R³ or R¹¹ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

10 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

15 alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

20 preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

25 preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

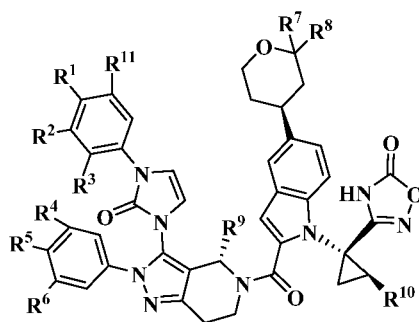
further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

30 preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

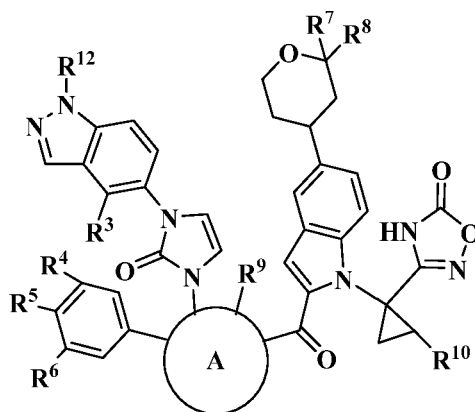
further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (II) is further as represented by general formula (II-1):



(II-1)

An objective of the present disclosure is to provide a compound represented by general formula (III), or a stereoisomer or a pharmaceutically acceptable salt thereof:

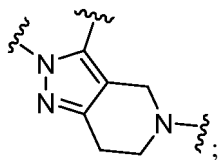


(III)

5 wherein

ring A is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

10 R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;



wherein ring A cannot be

15 R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl,

C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

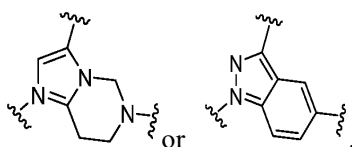
each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl,

C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5.

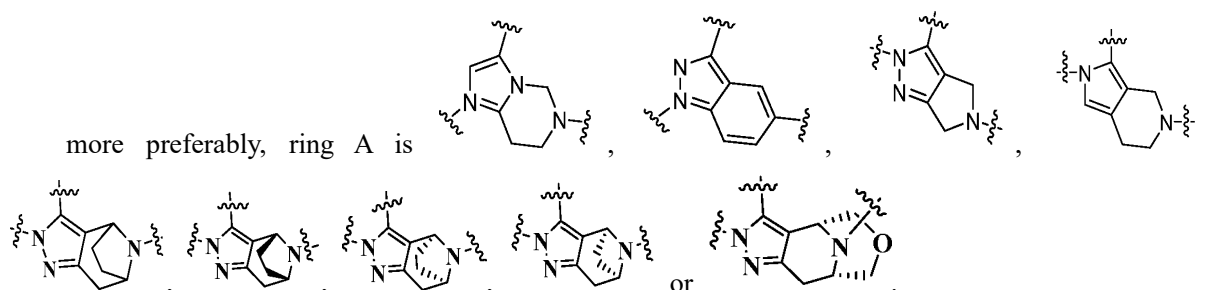
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (III),

ring A is selected from C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;



further preferably, ring A is

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (III),



In a further preferred embodiment of the present disclosure, in the compound represented by general formula (III),

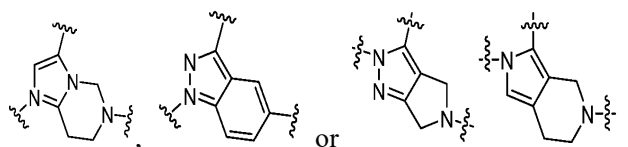
R¹² is selected from C₁₋₃ alkyl;

further preferably, R¹² is methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (III),

ring A is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

preferably, ring A is C₃₋₈ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;



more preferably, ring A is

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1},

$-(CH_2)_nS(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

more preferably, R^3 is hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_nS(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl is optionally further substituted with one or more substituents selected from halogen, $-NS(O)R_{a1}R_{b1}$ or C_{1-3} alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

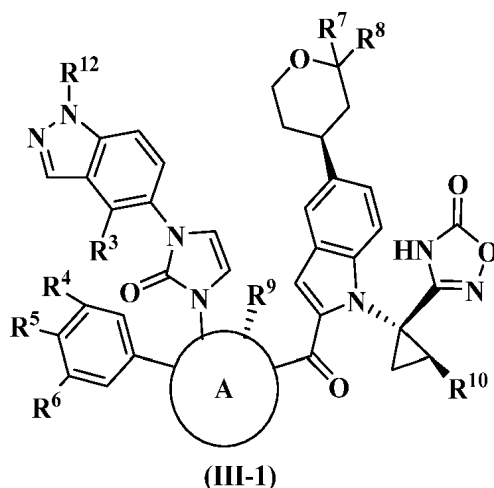
further preferably, each R^4 , R^5 or R^6 is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

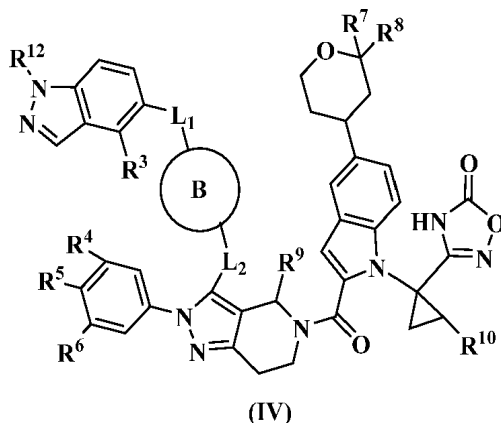
preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (III) is further as represented by general formula (III-1):



An objective of the present disclosure is to provide a compound represented by general formula (IV), or a stereoisomer or a pharmaceutically acceptable salt thereof:



5 wherein

L_1 and L_2 are each independently selected from a bond, C_{2-4} alkenylene, C_{2-4} alkynylene, $-(CH_2)_{n2}-$ or $-(CH_2)_{n3}NR_{b5}$;

10 ring B is selected from C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, mercapto, thio, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy or C_{1-6} haloalkoxy;

R_{b5} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

15 R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl,

C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl,

C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5;

n2 is an integer from 0 to 5;

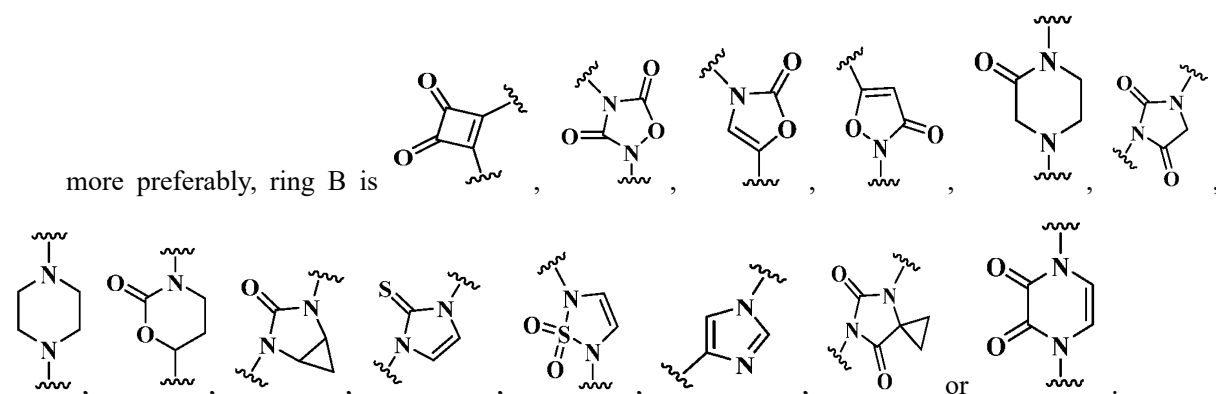
n3 is an integer from 0 to 5.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IV),

L₁ and L₂ are each independently selected from a bond or -(CH₂)_{n3}NR_{b5}.

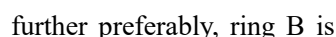
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IV),

preferably, ring B is C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S or 5- to 8-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, amino, oxo, thio or C₁₋₃ alkyl;

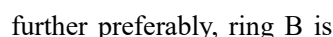


In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IV),

ring B is selected from C₃₋₆ cycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, amino, oxo, thio or C₁₋₃ alkyl;



5 ring B is selected from C₃₋₆ cycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, amino, oxo, thio or C₁₋₃ alkyl;



preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -
 15 (CH₂)_nS(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl,
 20 C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl,

-NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

5 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

10 alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

15 preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

20 preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (II),

25 preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

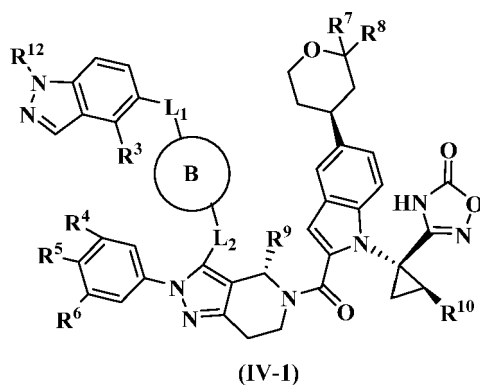
further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (III),

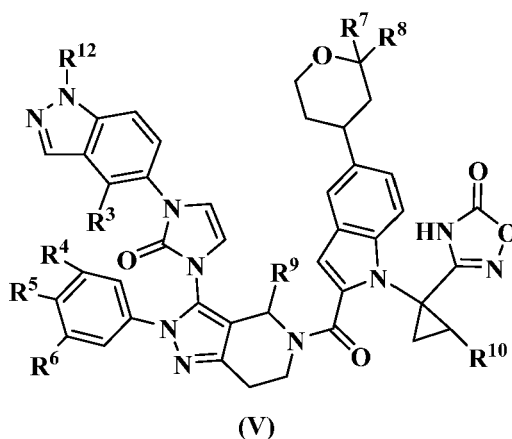
R¹² is selected from C₁₋₃ alkyl;

30 further preferably, R¹² is methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (IV) is further as represented by general formula (IV-1):



An objective of the present disclosure is to provide a compound represented by general formula (V), or a stereoisomer or a pharmaceutically acceptable salt thereof:



5 wherein

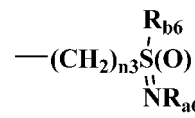
each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

15 alternatively, R^5 and R^6 together with adjacent atom(s) to which they are attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy,

20

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -



(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n2}R_{a5}R_{b5} or

, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, R_{a4} and R_{b4}, R_{a5} and R_{b5}, and R_{a6} and R_{b6} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl,

C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -

$$\text{---}(\text{CH}_2)_{n_3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}$$
 (CH₂)_{n₂}R_{a5}R_{b5} or

which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n₁ is an integer from 0 to 5;

wherein when R⁷ and R⁸ are hydrogen, R⁹, R¹⁰ and R¹² are methyl, and R³ and R⁵ are fluorine, R⁴ and R⁶ are not both methyl;

when R⁷ and R⁸ are hydrogen, R⁹, R¹⁰ and R¹² are methyl, R³ is hydrogen, and R⁵ is halogen, R⁴ and R⁶ are not both methyl;

when R⁷, R⁸, R⁹, R¹⁰ and R¹² are methyl, R⁵ is fluorine, and R⁴ is halogen, trifluoromethyl or cyclopropyl, R⁶ is not hydrogen;

when R⁷, R⁸, R⁹ and R¹⁰ are methyl, R¹² is deuterated methyl, R³ is fluorine, R⁵ is halogen, and R⁴ is deuterated methyl, R⁶ is not deuterated methyl;

when R⁴, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are methyl, and R³ and R⁵ are fluorine, R¹² is not deuterated methyl;

when R⁷, R⁸, R⁹, R¹⁰ and R¹² are methyl, R³ is fluorine, R⁵ is halogen, and R⁴ is methyl, R⁶ is not methyl;

when R⁷, R⁵, R⁹ and R¹⁰ are methyl, R¹² is deuterated methyl, R³ is fluorine, R⁵ is halogen, and R⁴ is deuterated methyl, R⁶ is not deuterated methyl;

when R⁴, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are methyl, and R³ and R⁵ are fluorine, R¹² is not deuterated methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

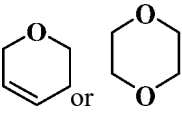
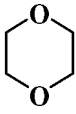
each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, cyano, C₁₋₃ alkyl, C₁₋₃ thioalkyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ alkoxy;

further preferably, each R⁴, R⁵ or R⁶ is independently fluorine, methyl, cyano, ethynyl, methylthio, amino, cyclopropyl or oxetane, which is optionally further substituted with halogen, methoxy or deuterated methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

R^5 and R^6 together with adjacent atom(s) to which they are attached form C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, C_{1-3} alkyl or oxo;

preferably, R^5 and R^6 together with adjacent atom(s) to which they are attached form 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, amino, C_{1-3} alkyl or oxo;

further preferably, R^5 and R^6 together with adjacent atom(s) to which they are attached form ,  or , which is optionally further substituted with one or more substituents selected from halogen, amino, C_{1-3} alkyl or oxo.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

R^7 and R^8 are each independently selected from deuterium or C_{1-6} deuterioalkyl;

preferably, R^7 and R^8 are deuterium or C_{1-3} deuterioalkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

R^9 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, R^9 is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-8} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, R^9 is cyano or cyclopropyl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl,

C₆₋₁₀ aryl or 5- to 8-membered heteroaryl.

In another embodiment of the present disclosure, in the compound represented by general formula (V),

R⁹ and the carbon atom connected thereto form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

5 preferably, R⁹ and the carbon atom connected thereto form C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R⁹ and the carbon atom connected thereto form cyclopropyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

10 preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -

(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n2}R_{a5}R_{b5} or
$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}$$
, wherein the

15 amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

20 more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl,

$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}$$
, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n2}R_{a5}R_{b5} or
wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

25 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

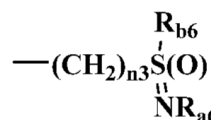
R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1},

-(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

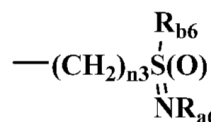
preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, - (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),



preferably, R¹² is C₁₋₃ alkyl, C₃₋₆ cycloalkyl, -(CH₂)_{n2}R_{a5}R_{b5} or further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;



more preferably, R¹² is methyl, cyclopropyl, -(CH₂)_{n2}R_{a5}R_{b5} or further substituted with one or more substituents selected from halogen,

amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, R_{a4} and R_{b4}, R_{a5} and R_{b5}, and R_{a6} and R_{b6} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

5 alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

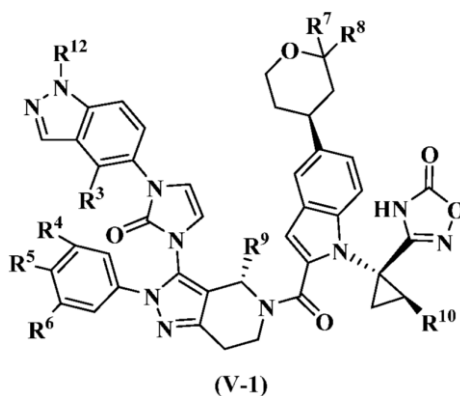
R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl; preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached
15 form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (V),

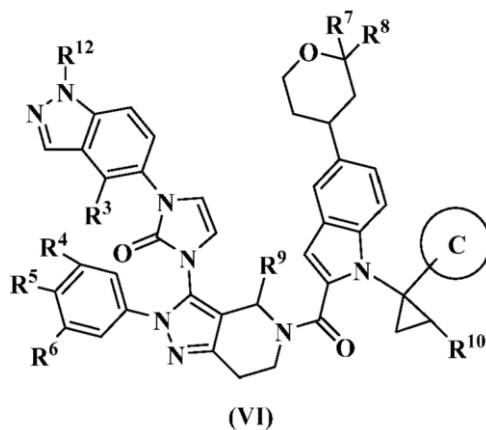
preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

20 further preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (V) is further as represented by general formula (V-1):



An objective of the present disclosure is to provide a compound represented by general formula (VI),
25 or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

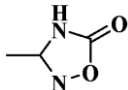
ring C is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, mercapto, thio, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy or -NR_{a6}S(O)₂R_{b6};

R¹⁰ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

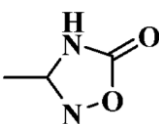
alternatively, R¹⁰ and the C atom connected thereto form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ thioalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R_{a6} and R_{b6} are each independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

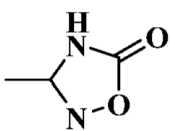
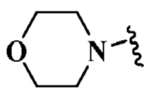
wherein when R³ is fluorine, R⁴ and R⁶ are methyl, R⁵ is fluorine, R⁷ and R⁸ are hydrogen or methyl,

R¹² is methyl, and ring C is , R¹⁰ cannot be methyl;

when R³ is fluorine, R⁴ and R⁶ are methyl, R⁵ is fluorine, R⁷ and R⁸ are hydrogen, R¹² is methyl, and

ring C is , R¹⁰ cannot be hydroxymethyl;

when R³ is fluorine, R⁴ and R⁶ are methyl, R⁵ is fluorine, R⁷ and R⁸ are hydrogen, R¹² is methyl, and

ring C is , R¹⁰ cannot be ;

5 R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, - (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3-
10 to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen,
15 amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to
20 which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

25 each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸ or R⁹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

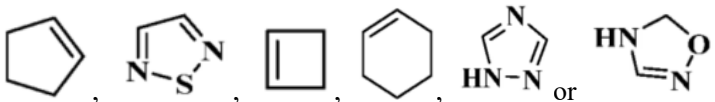
R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

ring C is selected from C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, mercapto, thio, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy or -NR_{a6}S(O)₂R_{b6};

preferably, ring C is C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S or 5- to 8-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from hydroxyl, oxo or -NR_{a6}S(O)₂R_{b6};

further preferably, ring C is , which is optionally further substituted with one or more substituents selected from hydroxyl, oxo or $\text{-NR}_{a6}\text{S(O)}_2\text{R}_{b6}$.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

- 5 preferably, R^{10} is hydrogen, deuterium, halogen or C_{1-3} alkyl;
 preferably, R^{10} is methyl;
 alternatively, R^{10} and the C atom connected thereto form C_{3-6} cycloalkyl;
 preferably, R^{10} and the C atom connected thereto form cyclopropyl.

10 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

R_{a6} and R_{b6} are each independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{3-8} cycloalkyl, 5- to 7-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

- 15 preferably, R_{a6} and R_{b6} are hydrogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

- 20 preferably, R^3 is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $\text{-NS(O)R}_{a1}\text{R}_{b1}$, $\text{-(CH}_2\text{)}_n\text{S(O)NR}_{a2}\text{R}_{b2}$, $\text{-P(O)R}_{a3}\text{R}_{b3}$ or $\text{-NR}_{a5}\text{S(O)NR}_{a4}\text{R}_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $\text{-NS(O)R}_{a1}\text{R}_{b1}$, C_{1-3} alkyl,
- 25 C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

- 30 more preferably, R^3 is hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, $\text{-NS(O)R}_{a1}\text{R}_{b1}$, $\text{-(CH}_2\text{)}_n\text{S(O)NR}_{a2}\text{R}_{b2}$, $\text{-P(O)R}_{a3}\text{R}_{b3}$ or $\text{-NR}_{a5}\text{S(O)NR}_{a4}\text{R}_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl is optionally further substituted with one or more substituents selected from halogen, $\text{-NS(O)R}_{a1}\text{R}_{b1}$ or C_{1-3} alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen,

amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

more preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

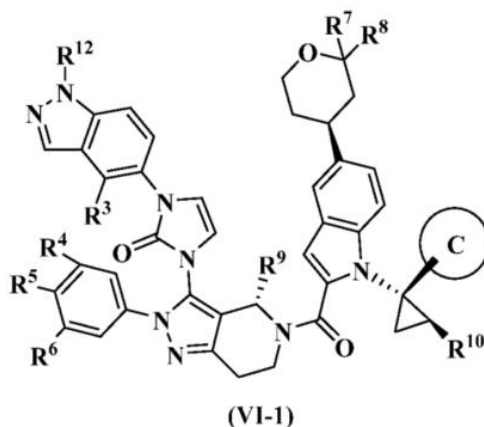
preferably, R⁷, R⁸ and R⁹ are each independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, R⁷, R⁸ and R⁹ are each independently selected from methyl.

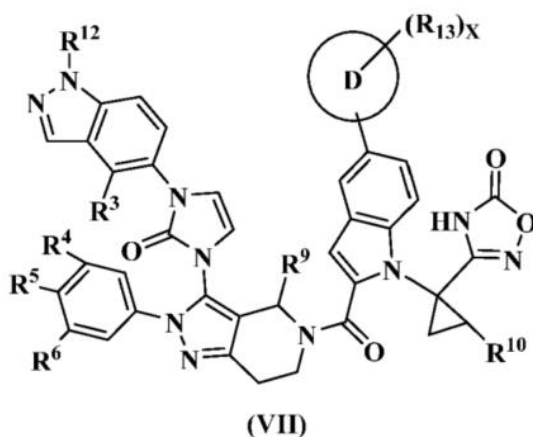
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VI),

preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (VI) is further as represented by general formula (VI-1):



An objective of the present disclosure is to provide a compound represented by general formula (VII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

ring D is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

5 R¹³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋
 10 6 alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

 R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -
 15 (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

20 each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

 alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to
 25 which they are each attached form C₃₋₈ cycloalkyl,

3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

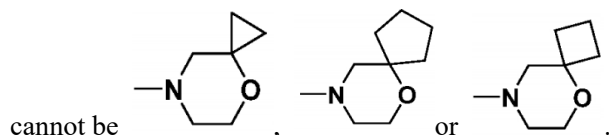
each R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5;

x is an integer from 0 to 5;

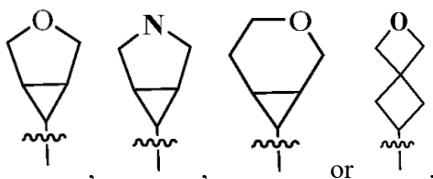
wherein when R^3 is hydrogen, R^4 and R^6 are methyl, R^5 is fluorine, and R^9 , R^{10} and R^{12} are methyl, R^{10}



In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VII),

5 ring D is selected from 5- to 12-membered bicyclic fused heterocyclyl, 5- to 12-membered bicyclic spiroheterocyclyl or 5- to 12-membered bicyclic bridged heterocyclyl;

further preferably, ring D is 5- to 8-membered bicyclic fused heterocyclyl, 5- to 8-membered bicyclic spiroheterocyclyl or 5- to 8-membered bicyclic bridged heterocyclyl;



10 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (VII),

R^{13} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally
15 further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl; further preferably, R^{13} is methyl.

In another embodiment of the present disclosure, in the compound represented by general formula (VII),
20 ring D is selected from C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl;

R^{13} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally
25 further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$,
30

-(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

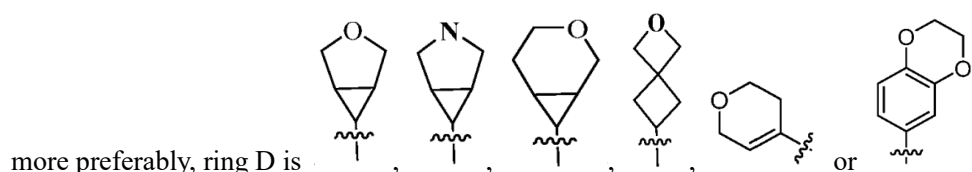
R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5;

x is an integer from 0 to 5.

In another embodiment of the present disclosure, in the compound represented by general formula (VII), preferably, ring D is 3- to 8-membered monocyclic heterocyclyl, 5- to 12-membered bicyclic fused heterocyclyl, 5- to 12-membered bicyclic spiroheterocyclyl or 5- to 12-membered bicyclic bridged heterocyclyl;

further preferably, ring D is 5- to 6-membered monocyclic heterocyclyl, 5- to 10-membered bicyclic fused heterocyclyl, 5- to 10-membered bicyclic spiroheterocyclyl or 5- to 8-membered bicyclic bridged heterocyclyl;



In another embodiment of the present disclosure, in the compound represented by general formula (VII), preferably, R¹³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R¹³ is methyl.

In another embodiment of the present disclosure, in the compound represented by general formula (VII),

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -
5 (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl,
10 C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from
15 halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

In another embodiment of the present disclosure, in the compound represented by general formula (VII),

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

more preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium,
20 halogen or methyl.

In another embodiment of the present disclosure, in the compound represented by general formula (VII),

more preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} are each independently attached to adjacent atom(s) to form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In another embodiment of the present disclosure, in the compound represented by general formula (VII),

preferably, each R⁴, R⁵ or R⁶ is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;
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more preferably, each R⁴, R⁵ or R⁶ is independently fluorine or methyl.

In another embodiment of the present disclosure, in the compound represented by general formula (VII),

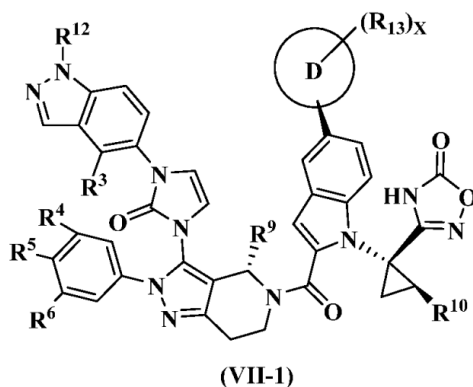
preferably, each R⁹ or R¹⁰ is independently hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl
30 or C₁₋₃ haloalkyl;

more preferably, R^9 or R^{10} is methyl.

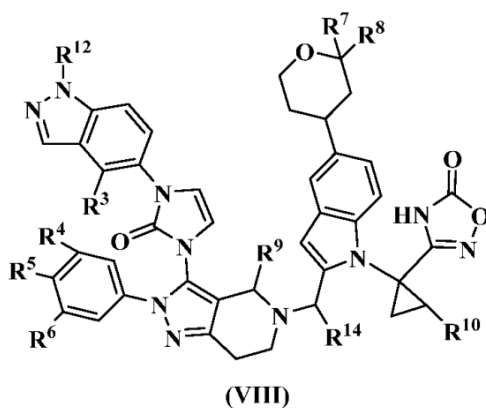
In another embodiment of the present disclosure, in the compound represented by general formula (VII), preferably, R^{12} is C_{1-3} alkyl;

more preferably, R^{12} is methyl.

5 In a further preferred embodiment of the present disclosure, the compound represented by general formula (VII) is further as represented by general formula (VII-1):



An objective of the present disclosure is to provide a compound represented by general formula (VIII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



10

wherein

R^{14} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, thio, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally
 15 further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl,

20

C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy,

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

R¹⁴ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, thio, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R¹⁴ is thio or trifluoromethyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl,

C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from
5 halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

10 further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to
15 which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2} or R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general
20 formula (IX),

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general
25 formula (IX),

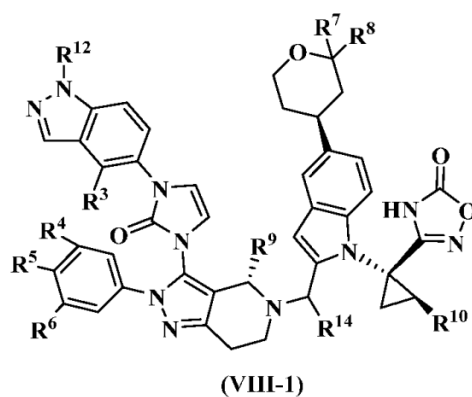
preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl.

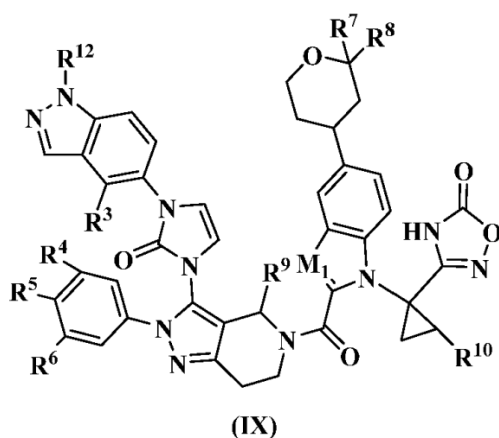
In a further preferred embodiment of the present disclosure, in the compound represented by general
30 formula (IX),

preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (VIII) is further as represented by general formula (VIII-1):



An objective of the present disclosure is to provide a compound represented by general formula (IX), or a stereoisomer or a pharmaceutically acceptable salt thereof:



5 wherein

M_1 is S or N;

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$,

$-(CH_2)_nS(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl,

C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl or C_{1-3} haloalkyl;

further preferably, each R^4 , R^5 or R^6 is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

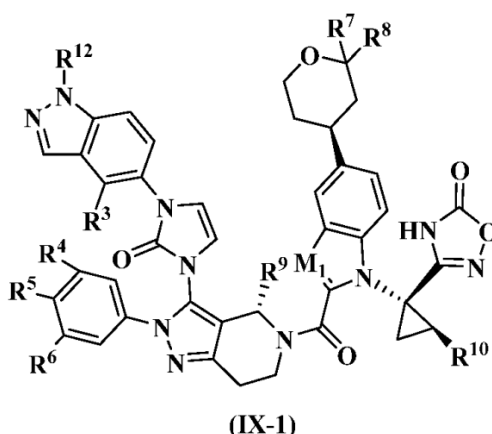
preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deuterioalkyl or C_{1-3} haloalkyl;

further preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from methyl.

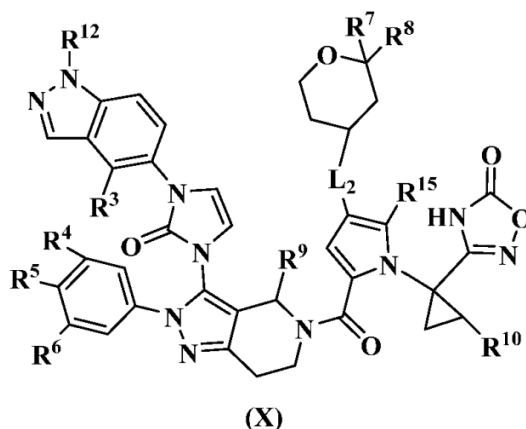
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (IX),

preferably, R^{12} is C_{1-3} alkyl; more preferably, R^{12} is methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (IX) is further as represented by general formula (IX-1):



An objective of the present disclosure is to provide a compound represented by general formula (X), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

L_2 is selected from a bond, $-(CH_2)_{n4}-$, C_{2-4} alkenylene or C_{2-4} alkynylene;

R^{15} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl,

3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

5 each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

15 each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

20 R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5;

n4 is an integer from 0 to 5.

25 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

R^{15} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, R^{15} is methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

preferably, R^3 is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

more preferably, R^3 is hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl is optionally further substituted with one or more substituents selected from halogen, $-NS(O)R_{a1}R_{b1}$ or C_{1-3} alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

preferably, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

5 preferably, each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R^4 , R^5 or R^6 is independently selected from fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

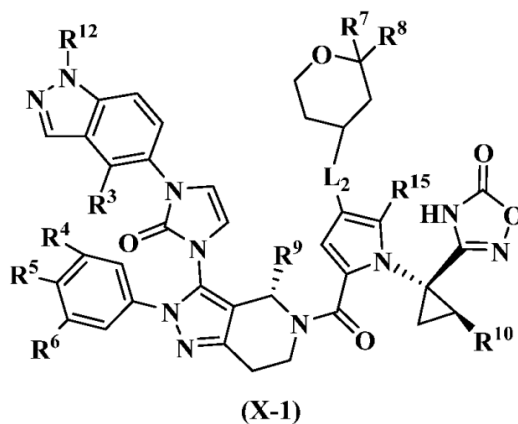
10 preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from methyl.

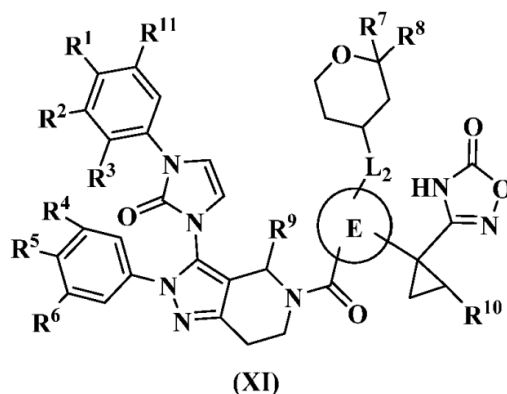
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (X),

15 preferably, R^{12} is C_{1-3} alkyl; more preferably, R^{12} is methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (X) is further as represented by general formula (X-1):



20 An objective of the present disclosure is to provide a compound represented by general formula (XI), or a stereoisomer or a pharmaceutically acceptable salt thereof:

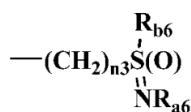


wherein

ring E is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

5 L₂ is selected from a bond, -(CH₂)_{n4}-, C₂₋₄ alkenylene or C₂₋₄ alkynylene;

each R¹, R², R³ or R¹¹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -



10 (CH₂)_{n1}S(O)₂R_{a5}, -(CH₂)_{n1}O(CH₂)_{n2}R_{b5}, , -(CH₂)_nP(O)R_{a7}R_{b7} or -(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9},

wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆

15 hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl; each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy,

20

C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8}, R_{b8}, R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a7} and R_{b7} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from

5 halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to

10 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

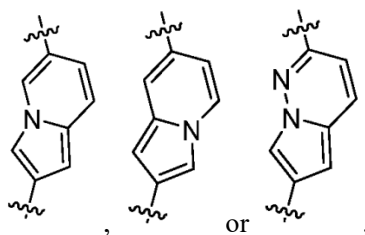
alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{a4} or R_{a7} and R_{b7} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-

15 membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

$n1$ to $n4$ are integers from 0 to 5.

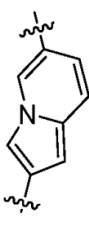
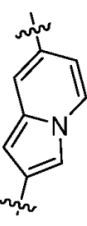
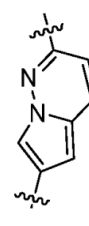
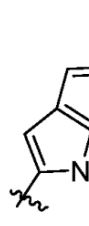
20 In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

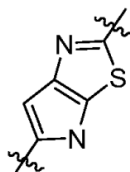
preferably, ring E is C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C_{6-10} aryl or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;



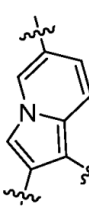
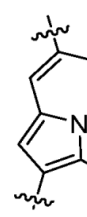
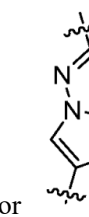
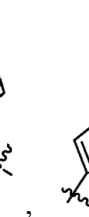
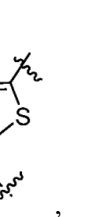
25 further preferably, ring E is , or .

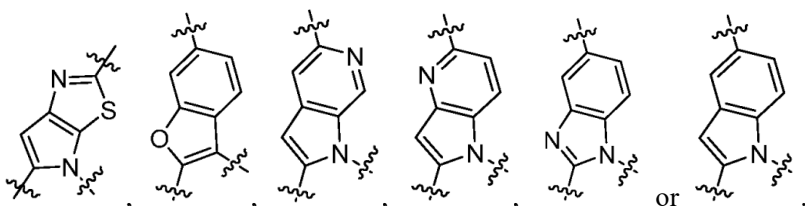
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

further preferably, ring E is ,  or , ,  or



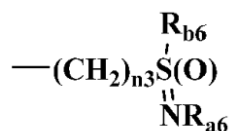
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

5 further preferably, ring E is ,  or , , ,



In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

10 each R^1 , R^2 , R^3 or R^{11} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, -



15 $(CH_2)_{n1}S(O)_2R_{a5}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{b5}$ or $-(CH_2)_{n1}S(O)NR_{a6}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, each R^1 , R^2 , R^3 or R^{11} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, -

$-(CH_2)_{n3}S(O)R_{b6}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{b5}$, $-(CH_2)_nS(O)R_{a5}$, $-(CH_2)_nO(CH_2)_{n2}R_{b5}$, $-(CH_2)_nS(O)NR_{a6}$, $-(CH_2)_nP(O)R_{a7}R_{b7}$ or $-(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}$,

wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, each R^1 , R^2 , R^3 or R^{11} is independently hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}S(O)_2R_{a5}$, -

$-(CH_2)_{n3}S(O)R_{b6}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{b5}$ or $-(CH_2)_nS(O)NR_{a6}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

R^1 and R^2 or R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -NS(O) $R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}S(O)_2R_{a5}$, -

10 $-(CH_2)_{n1}O(CH_2)_{n2}R_{b5}$ or $-(CH_2)_{n3}S(O)NR_{a6}$. In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, R^1 and R^2 or R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -NS(O) $R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}S(O)_2R_{a5}$, -

$-(CH_2)_{n1}O(CH_2)_{n2}R_{b5}$ or $-(CH_2)_{n3}S(O)NR_{a6}$;

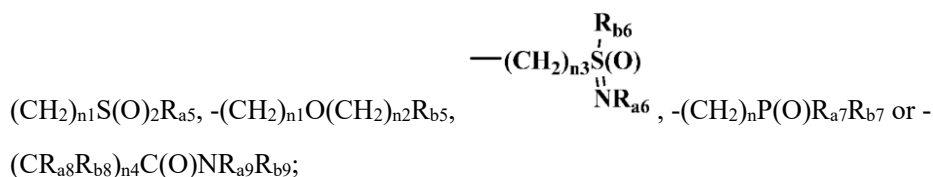
more preferably, R^1 and R^2 or R^1 and R^{11} together with adjacent atom(s) to which they are each attached form phenyl or 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with oxo, -NS(O) $R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, -

$NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}S(O)_2R_{a5}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{b5}$ or $-(CH_2)_{n3}S(O)NR_{a6}$.

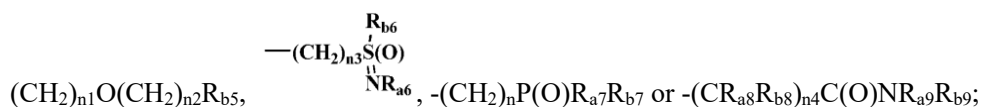
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

25 preferably, R^1 and R^2 or R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy,

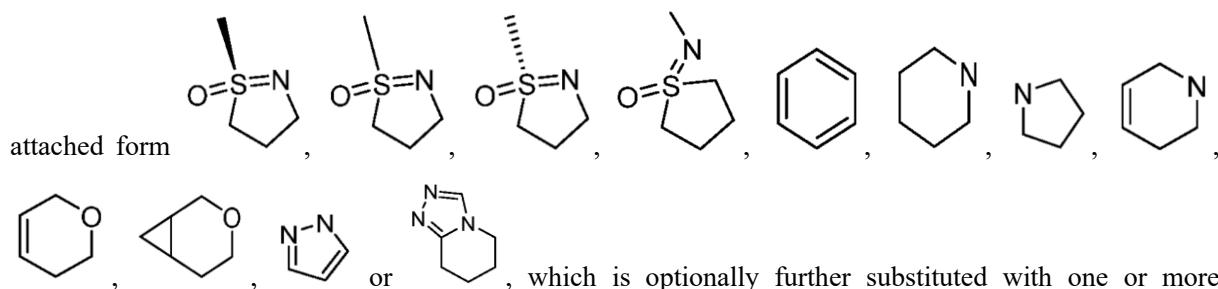
C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -



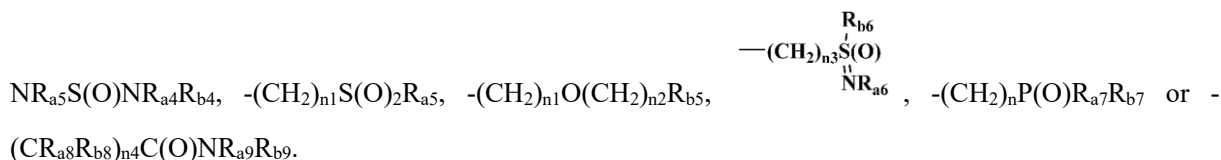
- 5 further preferably, R¹ and R² or R¹ and R¹¹ together with adjacent atom(s) to which they are each attached form phenyl or 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from methyl, halogen, oxo, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}S(O)₂R_{a5}, -



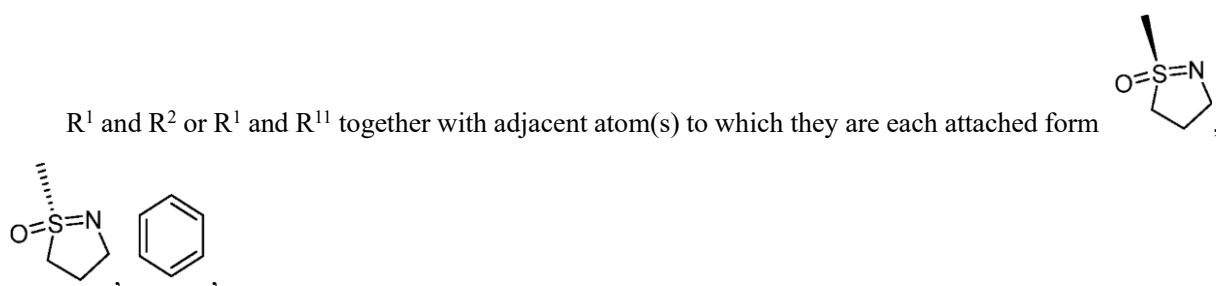
- 10 even further preferably, R¹ and R² or R¹ and R¹¹ together with adjacent atom(s) to which they are each

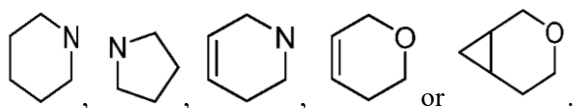


substituents selected from methyl, halogen, oxo, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -



In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),





In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, each R^4 , R^5 or R^6 is independently hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{3-6} cycloalkyl or C_{1-3} haloalkyl;

more preferably, each R^4 , R^5 or R^6 is independently fluorine, methyl or cyclopropyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, each R^7 , R^8 , R^9 or R^{10} is independently hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

more preferably, each R^7 , R^8 , R^9 or R^{10} is independently hydrogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl; alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl. In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI).

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, cyano, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, cyano, cyclopropyl,

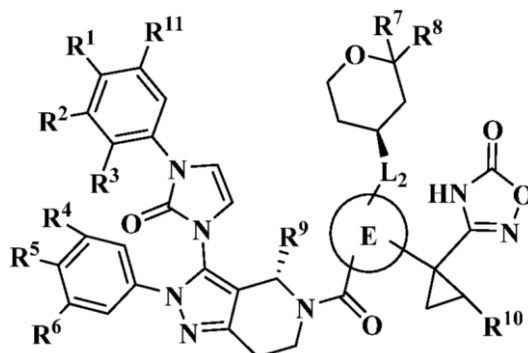
cyclopentyl, methyl, ethyl, phenyl or .

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XI),

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} or R_{b6} is independently hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

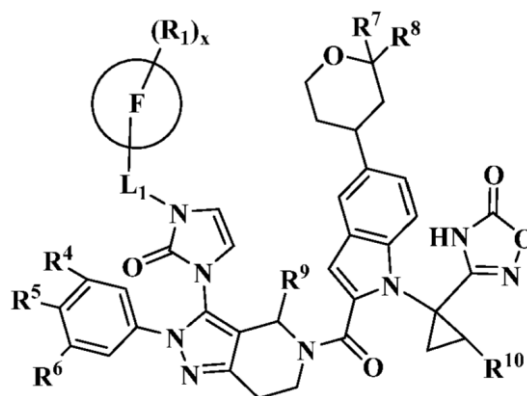
further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} or R_{b6} is independently hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (XI) is further as represented by general formula (XI-1):



(XI-1).

An objective of the present disclosure is to provide a compound represented by general formula (XII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



(XII)

wherein L_1 is selected from a bond, C_{2-4} alkenylene, C_{2-4} alkynylene, $-(CH_2)_{n4}-$ or $-(CH_2)_{n5}NR_{b5}$, wherein the C_{2-4} alkenylene, C_{2-4} alkynylene, $-(CH_2)_{n4}-$ or $-(CH_2)_{n5}NR_{b5}$ is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

ring F is selected from C₃₋₂ cycloalkyl, 3- to 14-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

each R¹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b7}}{\underset{\text{NR}_{a7}}{\text{S}(\text{O})}}(\text{CH}_2)_{n1}\text{C}(\text{O})\text{NR}_{a6}\text{R}_{b6}, \text{---}(\text{CH}_2)_{n1}\text{P}(\text{O})\text{R}_{a3}\text{R}_{b3}, \text{---}(\text{CH}_2)_{n4}\text{NR}_{a8}\text{C}(\text{O})\text{R}_{b8},$$
 wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively,

R¹ and the C atom connected thereto form C₃₋₁₀ cycloalkyl, 3- to 10-membered heterocyclyl, C₆₋₁₂ aryl or 5- to 12-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl,

C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8}, R_{b8} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n₁ to n₅ are integers from 0 to 5.

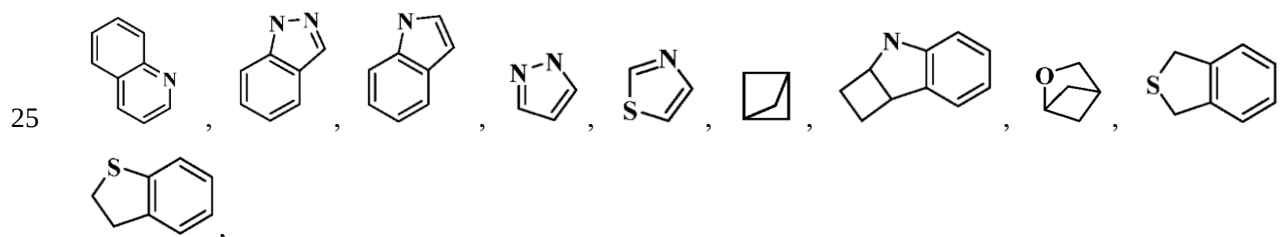
In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

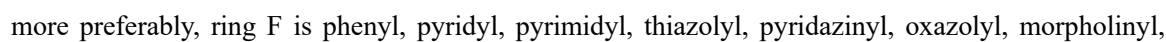
ring F is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl. In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

further preferably, ring F is C₃₋₁₀ cycloalkyl, 5- to 14-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, ring F is C₃₋₆ bridged cycloalkyl, 8- to 14-membered tricyclic fused heterocyclyl containing 1 to 5 heteroatoms, 3- to 8-membered bridged heterocyclyl containing 1 to 3 heteroatoms, fused heterocyclyl containing 1 to 3 heteroatoms, bridged heterocyclyl containing 1 to 3 heteroatoms, C₆₋₁₀ aryl or 5- to 10-membered fused heteroaryl containing 1 to 3 heteroatoms;

more preferably, ring F is phenyl, pyridyl, pyrimidyl, thiazolyl, pyridazinyl, oxazolyl, morpholinyl,



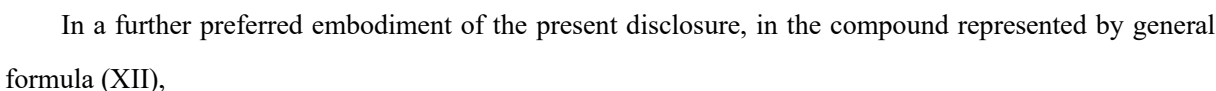


10 membered heteroaryl;

10

more preferably, ring F is phenyl, pyridyl, pyrimidyl, thiazolyl, pyridazinyl, oxazolyl, morpholinyl,





In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b7}}{\underset{\text{NR}_{a7}}{\text{S}(\text{O})}}\text{---}$$

wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R¹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

5 (CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3}, $\begin{array}{c} \text{R}_{b7} \\ | \\ \text{---}(\text{CH}_2)_{n3}\text{S}(\text{O}) \\ || \\ \text{NR}_{a7} \end{array}$, -(CH₂)_{n1}NR_{a8}C(O)R_{b8} or -(CH₂)_{n1}S(O)₂R_{b5},

wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, each R¹ is independently selected from amino, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

15 (CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3}, $\begin{array}{c} \text{R}_{b7} \\ | \\ \text{---}(\text{CH}_2)_{n3}\text{S}(\text{O}) \\ || \\ \text{NR}_{a7} \end{array}$, -(CH₂)_{n1}NR_{a8}C(O)R_{b8} or -(CH₂)_{n1}S(O)₂R_{b5}, wherein the amino or C₁₋₃ alkyl is optionally further substituted with cyano or C₁₋₃ alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

preferably, each R¹ is independently hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

20 (CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3}, $\begin{array}{c} \text{R}_{b7} \\ | \\ \text{---}(\text{CH}_2)_{n3}\text{S}(\text{O}) \\ || \\ \text{NR}_{a7} \end{array}$ or -(CH₂)_{n1}NR_{a8}C(O)R_{b8}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl,

C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, each R¹ is independently amino, oxo, C₁₋₃ alkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -(CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3},

$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b7}}{\underset{\text{NR}_{a7}}{\text{S}(\text{O})}}$$
or -(CH₂)_{n1}NR_{a8}C(O)R_{b8}, wherein the amino or C₁₋₃ alkyl is optionally further substituted with cyano or C₁₋₃ alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

preferably, R¹ and the C atom connected thereto form C₃₋₆ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R¹ and the C atom connected thereto form C₃₋₄ cycloalkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

preferably, each R⁴, R⁵ or R⁶ is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl

is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

5 preferably, R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;

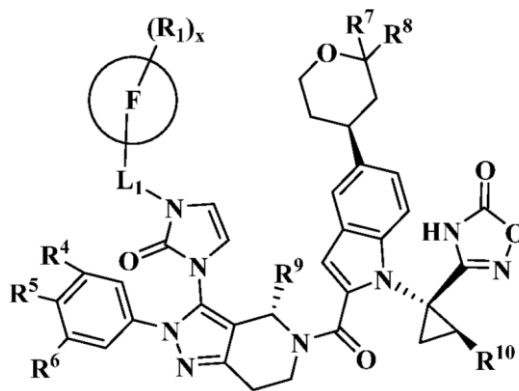
10 further preferably, R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently selected from hydrogen, deuterium, halogen, phenyl or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XII),

preferably, R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

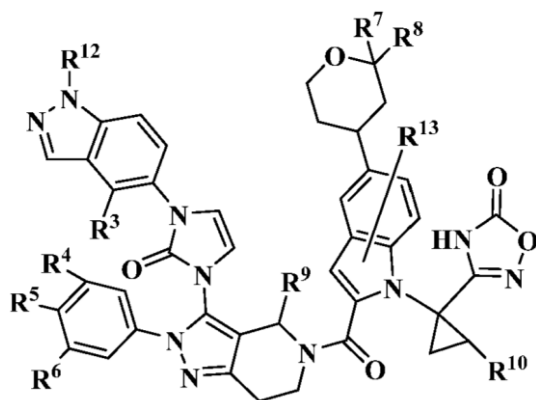
15 further preferably, R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (XII) is further as represented by general formula (XII-1):



(XII-1).

An objective of the present disclosure is to provide a compound represented by general formula (XIII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



(XIII)

wherein

each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl,

C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹³ is selected from deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n₁ is an integer from 0 to 5.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

preferably, each R⁴, R⁵ or R⁶ is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently fluorine or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

preferably, R^3 is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

more preferably, R^3 is hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl is optionally further substituted with one or more substituents selected from halogen, $-NS(O)R_{a1}R_{b1}$ or C_{1-3} alkyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

more preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen or methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

more preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} are each independently attached to adjacent atom(s) to form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

preferably, each R^7 , R^8 , R^9 or R^{10} is independently hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R^7 , R^8 , R^9 or R^{10} is independently methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

preferably, R^{12} is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl,

C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

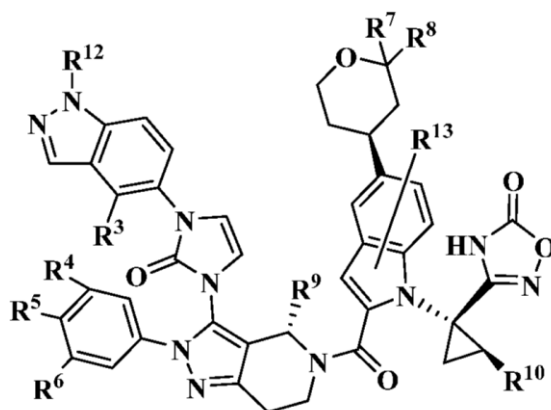
further preferably, R¹² is methyl.

In a further preferred embodiment of the present disclosure, in the compound represented by general formula (XIII),

preferably, R¹³ is deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R¹³ is methoxy or cyclopropyl.

In a further preferred embodiment of the present disclosure, the compound represented by general formula (XIII) is further as represented by general formula (XIII-1):



(XIII-1).

The present disclosure further relates to a pharmaceutical composition comprising a therapeutically effective dose of any of the compound represented by general formula, or the stereoisomer or the pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents or excipients.

In certain embodiments of the present disclosure, the weight percentage of the compound, or the stereoisomer or the pharmaceutically acceptable salt thereof in the pharmaceutical composition is 0.1-95%, preferably 5-70%, e.g., 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% on a free base basis.

In certain embodiments of the present disclosure, the pharmaceutical composition is selected from a tablet, a capsule, a liquid preparation or an injection, and the pharmaceutical composition preferably further comprises a filler, optionally further comprises a disintegrant, or further comprises one or more of a glidant or a lubricant.

5 In certain embodiments of the present disclosure, the pharmaceutical composition is an immediate release preparation or a sustained release preparation.

In certain embodiments of the present disclosure, the unit dose of the compound, or the stereoisomer or the pharmaceutically acceptable salt thereof in the pharmaceutical composition is 1-1000 mg, preferably 1-500 mg, or preferably 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 20 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200
10 mg, 300 mg, 400 mg or 500 mg on a free base basis.

In certain embodiments of the present disclosure, the compound, or the stereoisomer or the pharmaceutically acceptable salt thereof can be administered by any convenient method, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, intrathecal or transdermal administration, and the pharmaceutical composition can be adjusted accordingly.

15 In certain embodiments of the present disclosure, the compound, or the stereoisomer or the pharmaceutically acceptable salt thereof can be formulated into a liquid or solid preparation, such as a syrup, suspension, emulsion, tablet, capsule, powder, granule or lozenge.

The present disclosure further relates to the use of any of the compound represented by general formula, or the stereoisomer or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition in the
20 preparation of a GLP-1 receptor agonist drug.

The present disclosure further relates to the use of the compound represented by general formula, or the stereoisomer or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a drug for treating a metabolic-related disease, wherein the disease is selected from diabetes, obesity or non-alcoholic steatohepatitis related diseases or other related diseases caused by diabetes, obesity
25 or non-alcoholic steatohepatitis.

The present disclosure further relates to a method of using the compound represented by general formula, or the stereoisomer or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a drug for treating a metabolic disease and related diseases.

The present disclosure further relates to a method for preventing and/or treating a metabolic-related
30 disease, comprising administering to a patient a therapeutically effective dose of the compound represented by general formula, or the stereoisomer or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof.

The present disclosure further provides a method for treating a disease condition with the compound or the pharmaceutical composition of the present disclosure, wherein the disease condition includes, but is not
35 limited to, conditions related to GLP-1 receptor modulators.

The present disclosure further relates to a method for treating metabolic disease-related diseases in a mammal, comprising administering to the mammal a therapeutically effective amount of the compound of the present disclosure, or the pharmaceutically acceptable salt, ester, prodrug,

solvate, hydrate or derivative thereof.

Detailed Description of the Invention

Unless stated to the contrary, the terms used in the description and claims have the following meanings.

5 The term "alkyl" refers to a saturated aliphatic hydrocarbon group, which is a linear or branched group containing 1 to 20 carbon atoms, preferably alkyl containing 1 to 8 carbon atoms, more preferably alkyl containing 1 to 6 carbon atoms, and most preferably alkyl containing 1 to 3 carbon atoms. Non-limiting examples 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-
10 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, n-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, n-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-
15 dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, n-nonyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2,2-diethylpentyl, n-decyl, 3,3-diethylhexyl, 2,2-diethylhexyl, and various branched isomers thereof, etc. More preferably, the alkyl is a lower alkyl group containing 1 to 6 carbon atoms, and non-limiting examples 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-
20 dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,3-dimethylbutyl, etc. Alkyl can be substituted or unsubstituted, and when substituted, the substituent can be substituted at any available connection point, and the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, oxo, carboxyl or a carboxylate group. In the present disclosure, alkyl is preferably methyl, ethyl, isopropyl, tert-butyl, haloalkyl, deuterioalkyl, alkoxy-substituted alkyl and hydroxyl-substituted alkyl.

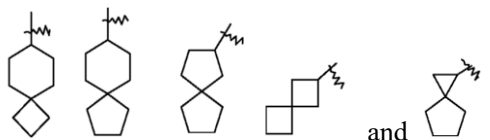
The term "alkylene" refers to one hydrogen atom of alkyl being further substituted, for example:
30 "methylene" refers to $-\text{CH}_2-$, "ethylene" refers to $-(\text{CH}_2)_2-$, "propylene" refers to $-(\text{CH}_2)_3-$, and "butylene" refers to $-(\text{CH}_2)_4-$, etc.

The term "alkenyl" refers to an alkyl group as defined above consisting of at least two carbon atoms and at least one carbon-carbon double bond, such as ethenyl, 1-propenyl, 2-propenyl, 1-, 2- or 3 -butenyl, etc. Alkenyl can be substituted or unsubstituted. When the alkenyl is substituted, the substituent is preferably one
35 or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro,

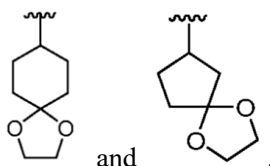
cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio or heterocycloalkylthio.

The term “alkenylene” refers to an alkenyl group in which one hydrogen atom is further substituted. For example, “vinylidene” refers to $-\text{CH}_2=\text{CH}_2-$, and “propenylidene” refers to $-\text{CH}_2=\text{CH}_2-\text{CH}_2-$. Alkenylene can be substituted or unsubstituted. When the alkenylene is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, or heterocycloalkylthio. The term “cycloalkyl” refers to a saturated or partially unsaturated monocyclic or polycyclic cyclic hydrocarbon substituent, and the cycloalkyl ring comprises 3 to 20 carbon atoms, preferably 3 to 12 carbon atoms, more preferably 3 to 8 carbon atoms, and further preferably 3 to 6 carbon atoms. Non-limiting examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, cycloheptyl, cycloheptatrienyl, cyclooctyl, etc.; and polycyclic cycloalkyl includes spiro, fused and bridged cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term “spirocycloalkyl” refers to a polycyclic group with 5- to 20-membered monocyclic rings sharing one carbon atom (called a spiro atom). It may contain one or more double bonds, but no ring has a fully conjugated π electron system. Preferably, the spirocycloalkyl is 6- to 14-membered, and more preferably 7- to 10-membered. According to the number of shared spiro atoms between the rings, the spirocycloalkyl is divided into monospirocycloalkyl, bispilocycloalkyl or polyspirocycloalkyl, preferably monospirocycloalkyl and bispilocycloalkyl, and more preferably 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered or 5-membered/6-membered monospirocycloalkyl. Non-limiting examples of spirocycloalkyl include:



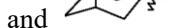
Also included are spirocycloalkyl in which monospirocycloalkyl and heterocycloalkyl share a spiro atom, and non-limiting examples include:



The term “fused cycloalkyl” refers to a 5- to 20-membered all-carbon polycyclic group, in which each ring in the system shares an adjacent pair of carbon atoms with other rings in the system, one or more ring of which may contain one or more double bonds, but no ring has a fully conjugated π electron system. Preferably, the fused cycloalkyl is 6- to 14-membered, and more preferably 7- to 10-membered. According to the number of constituent rings, it can be divided into bicyclic, tricyclic, tetracyclic or polycyclic fused cycloalkyl, preferably bicyclic or tricyclic, and more preferably 5-membered/5-membered or 5-membered/6-membered bicyclic cycloalkyl. Non-limiting examples of fused cycloalkyl include:



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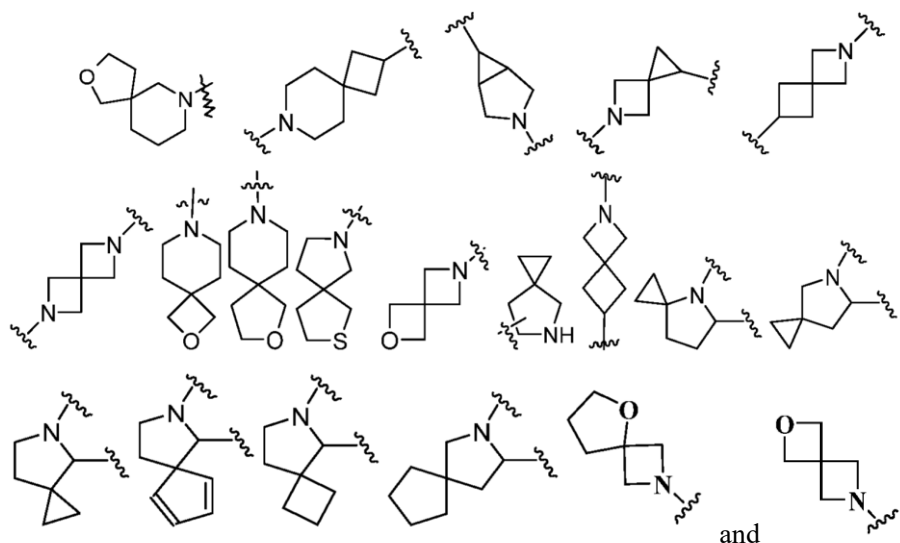


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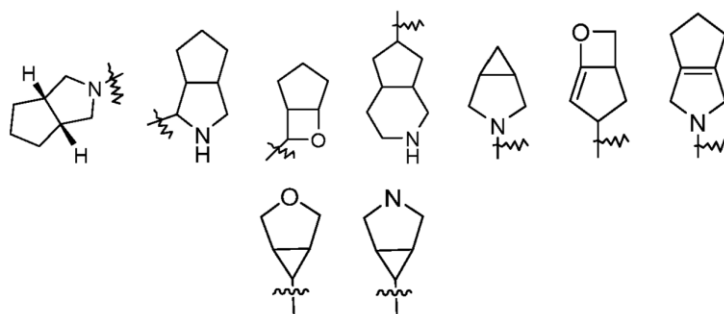
The term “spiroheterocyclyl” refers to a 5- to 20-membered polycyclic heterocyclyl with monocyclic rings sharing one atom (called a spiro atom), wherein one or more ring atoms are heteroatoms selected from nitrogen, oxygen, or S(O)_m (wherein m is an integer of 0 to 2), and the remaining ring atoms are carbon. Spiroheterocyclyl may contain one or more double bonds, but no ring has a fully conjugated π electron system.

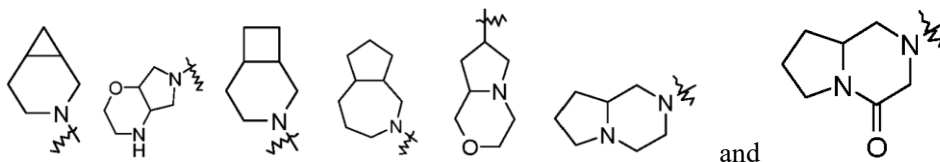
5 Preferably, the spiroheterocyclyl is 6- to 14-membered, and more preferably 7- to 10-membered. According to the number of shared spiro atoms between the rings, the spiroheterocyclyl is divided into monospiroheterocyclyl, bispiroheterocyclyl or polyspiroheterocyclyl, preferably monospiroheterocyclyl and bispiroheterocyclyl, and more preferably 4-membered/4-membered, 4-membered/5-membered, 4-membered/6-membered, 5-membered/5-membered or 5-membered/6-membered monospiroheterocyclyl.

10 Non-limiting examples of spiroheterocyclyl include:

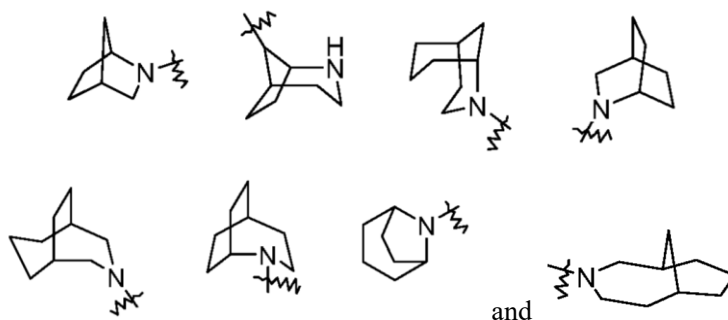


The term “fused heterocyclyl” refers to a 5- to 20-membered polycyclic heterocyclyl, in which each ring in the system shares an adjacent pair of atoms with other rings in the system, and one or more rings may contain one or more double bonds, but no ring has a fully conjugated π electron system, wherein one or more ring atoms are heteroatoms selected from nitrogen, oxygen, or S(O)_m (wherein m is an integer of 0 to 2), and the remaining ring atoms are carbon. Preferably, the fused heterocyclyl is 6- to 14-membered, and more preferably 7- to 10-membered. According to the number of constituent rings, it can be divided into bicyclic, tricyclic, tetracyclic or polycyclic fused heterocyclyl, preferably bicyclic or tricyclic, more preferably 5-membered/5-membered or 5-membered/6-membered bicyclic fused heterocyclyl. Non-limiting examples of fused heterocyclyl include:

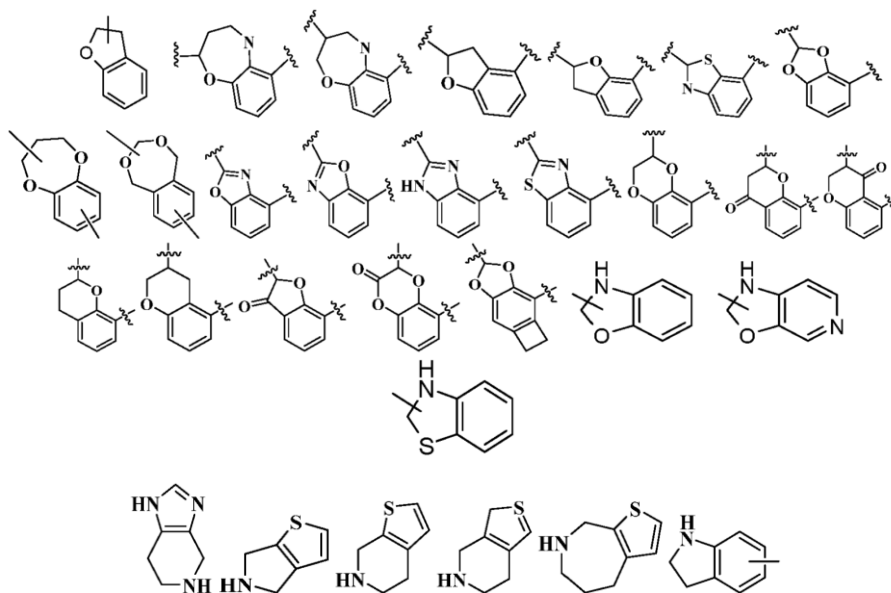




The term “bridged heterocyclyl” refers to a 5- to 14-membered polycyclic heterocyclyl with any two rings sharing two atoms that are not directly connected. It may contain one or more double bonds, but no ring has a fully conjugated π electron system, wherein one or more ring atoms are heteroatoms selected from nitrogen, oxygen, or $S(O)_m$ (wherein m is an integer of 0 to 2), and the remaining ring atoms are carbon. Preferably, the bridged heterocyclyl is 6- to 14-membered, and more preferably 7- to 10-membered. According to the number of constituent rings, it can be divided into bicyclic, tricyclic, tetracyclic or polycyclic bridged heterocyclyl, preferably bicyclic, tricyclic or tetracyclic, and more preferably bicyclic or tricyclic. Non-limiting examples of bridged heterocyclyl include:



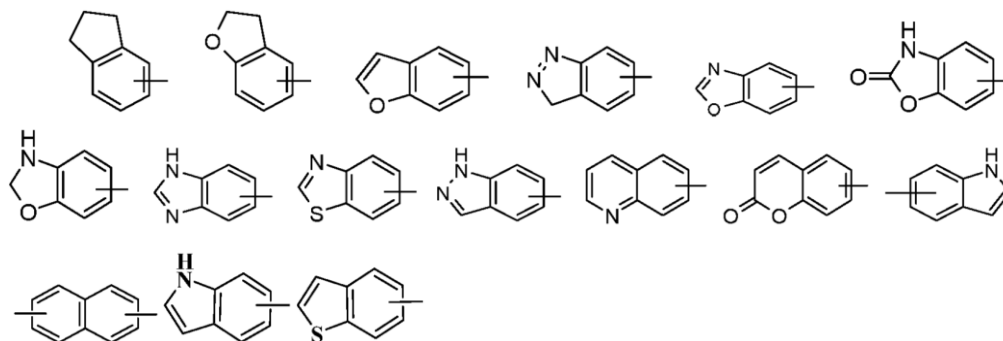
The heterocyclyl ring can be fused to an aryl, heteroaryl or cycloalkyl ring, wherein the ring connected to the parent structure is heterocyclyl, and the non-limiting examples thereof include:



Heterocyclyl can be optionally substituted or unsubstituted. When the heterocyclyl is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy,

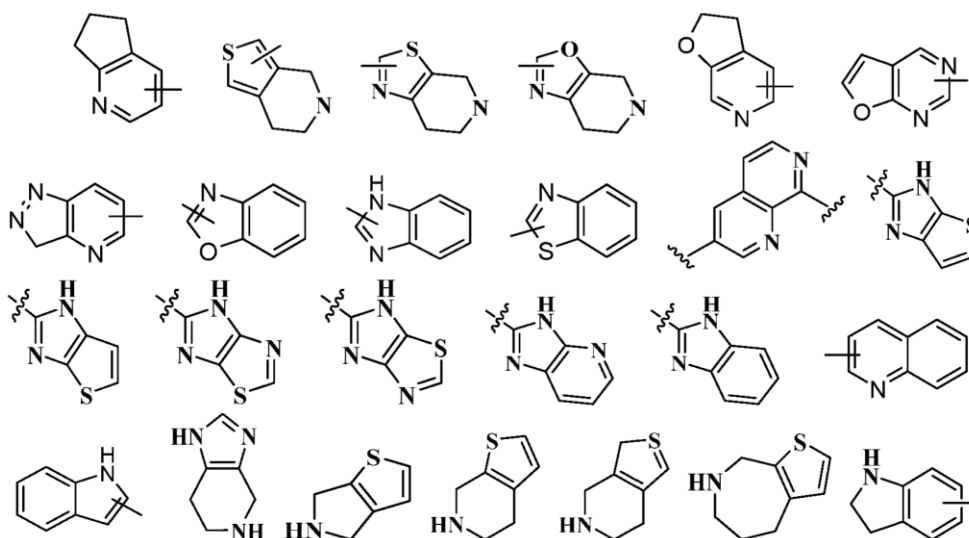
heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, oxo, carboxyl or a carboxylate group.

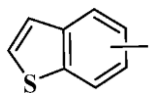
The term “aryl” refers to a 6- to 14-membered all-carbon monocyclic or fused polycyclic (*i.e.*, rings sharing adjacent pairs of carbon atoms) group having a conjugated π electron system, preferably 6- to 10-membered aryl, more preferably 6- to 8-membered aryl, such as phenyl and naphthyl, and more preferably phenyl. The aryl ring can be fused to a heteroaryl, heterocyclyl or cycloalkyl ring, wherein the ring connected to the parent structure is an aryl ring, and the non-limiting examples thereof include:



Aryl can be substituted or unsubstituted. When the aryl is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, carboxyl or a carboxylate group.

The term “heteroaryl” refers to a heteroaromatic system containing 1 to 4 heteroatoms and 5 to 14 ring atoms, wherein the heteroatoms are selected from oxygen, sulfur and nitrogen. The heteroaryl is preferably 5- to 10-membered, more preferably 5- to 8-membered, most preferably 5-membered or 6-membered, such as imidazolyl, furyl, thienyl, thiazolyl, pyrazolyl, oxazolyl, pyrrolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, thiadiazole, pyrazinyl, etc., preferably triazolyl, thienyl, imidazolyl, pyrazolyl, pyrimidinyl or thiazolyl; more preferably triazolyl, pyrrolyl, thienyl, thiazolyl and pyrimidinyl. The heteroaryl ring can be fused to an aryl, heterocyclyl or cycloalkyl ring, wherein the ring connected to the parent structure is heteroaryl ring, and the non-limiting examples thereof include:





Heteroaryl can be optionally substituted or unsubstituted. When the heteroaryl is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, carboxyl or a carboxylate group.

The term “alkoxy” refers to -O- (alkyl) and -O- (unsubstituted cycloalkyl), where alkyl is as defined above, preferably alkyl containing 1 to 8 carbon atoms, more preferably alkyl containing 1 to 6 carbon atoms, and most preferably alkyl containing 1 to 3 carbon atoms. Non-limiting examples of alkoxy include: methoxy, ethoxy, propoxy, butoxy, cyclopropoxy, cyclobutoxy, cyclopentoxy, and cyclohexoxy. Alkoxy can be optionally substituted or unsubstituted. When the alkoxy is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, carboxyl or a carboxylate group.

“Haloalkyl” refers to alkyl substituted with one or more halogen, wherein alkyl is defined as above.

“Haloalkoxy” refers to alkoxy substituted with one or more halogen, wherein alkoxy is defined as above.

“Hydroxyalkyl” refers to alkyl substituted with hydroxyl, wherein alkyl is defined as above.

“Alkenyl” refers to a chain alkenyl group, also known as an alkene group, preferably alkyl containing 2 to 8 carbon atoms, more preferably alkyl containing 2 to 6 carbon atoms, and most preferably alkyl containing 2 to 3 carbon atoms. Moreover, the alkenyl can be further substituted with other related groups, such as: alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, carboxyl or a carboxylate group.

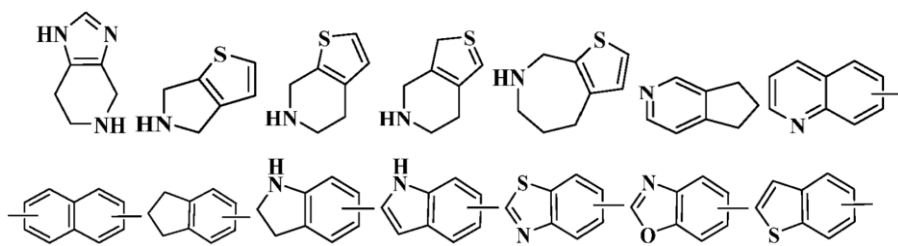
“Alkynyl” refers to $\text{CH}\equiv\text{C}-$, preferably alkyl containing 2 to 8 carbon atoms, more preferably alkyl containing 2 to 6 carbon atoms, and most preferably alkyl containing 2 to 3 carbon atoms. Moreover, the alkynyl can be further substituted with other related groups, such as: alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, carboxyl or a carboxylate group.

The term “alkynylene” refers to an alkynyl group in which one hydrogen atom is further substituted. For example, “ethynylene” refers to $-\text{C}\equiv\text{C}-$, and “propenylidene” refers to $-\text{C}\equiv\text{C}-\text{CH}_2-$. Alkynylene (containing more than three carbon atoms) can be substituted or unsubstituted. When the alkynylene is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, or heterocycloalkylthio.

The term “fused-ring group” refers to a polycyclic group formed by two or more carbocyclic or heterocyclic rings sharing ring edges, including fused cycloalkyl, fused heteroaryl, fused aryl, and fused heteroaryl, wherein the fused cycloalkyl refers to a polycyclic group formed by cycloalkyl sharing ring edges with heterocyclyl, aryl or heteroaryl;

the fused heterocyclyl refers to a polycyclic group formed by heterocyclyl sharing ring edges with cycloalkyl, aryl or heteroaryl; the fused aryl refers to a polycyclic group formed by aryl sharing ring edges with cycloalkyl, heterocyclyl or heteroaryl; and the fused heteroaryl refers to a polycyclic group formed by heteroaryl sharing ring edges with cycloalkyl, heterocyclyl or aryl; for example,

5



“Haloalkyl” refers to alkyl substituted with one or more halogen, wherein alkyl is defined as above.

“Haloalkoxy” refers to alkoxy substituted with one or more halogen, wherein alkoxy is defined as above.

“Hydroxyalkyl” refers to alkyl substituted with hydroxyl, wherein alkyl is defined as above.

10

“Hydroxyl” refers to an -OH group.

“Halogen” refers to fluorine, chlorine, bromine or iodine.

“Amino” refers to -NH₂.

“Cyano” refers to -CN.

“Nitro” refers to -NO₂.

15

“Carboxylic acid” refers to -C(O)OH.

“THF” refers to tetrahydrofuran.

“EtOAc” refers to ethyl acetate.

“MeOH” refers to methanol.

“DMF” refers to N,N-dimethylformamide.

20

“DIPEA” refers to diisopropylethylamine.

“TFA” refers to trifluoroacetic acid.

“MeCN” refers to acetonitrile.

“DMA” refers to N,N-dimethylacetamide.

“Et₂O” refers to diethyl ether.

25

“DCE” refers to 1,2-dichloroethane.

“DIPEA” refers to N,N-diisopropylethylamine.

“NBS” refers to N-bromosuccinimide.

“NIS” refers to N-iodosuccinimide.

“Cbz-Cl” refers to benzyl chloroformate.

30

“Pd₂(dba)₃” refers to tris(dibenzylideneacetone)dipalladium.

“Dppf” refers to 1,1'-bis(diphenylphosphine)ferrocene.

“HATU” refers to 2-(7-azabenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate.

“KHMDs” refers to potassium hexamethyldisilamide.

“LiHMDs” refers to lithium bistrimethylsilylamide.

“MeLi” refers to methyllithium.

“n-BuLi” refers to n-butyl lithium.

5 “NaBH(OAc)₃” refers to sodium triacetoxymethylborohydride.

Different expressions such as “X is selected from A, B, or C”, “X is selected from A, B and C”, “X is A, B or C”, and “X is A, B and C” all express the same meaning, i.e., X can be any one or more of A, B, and C.

10 The hydrogen atoms of the present disclosure can be substituted with its isotope deuterium, and any hydrogen atom in the example compounds involved in the present disclosure can also be substituted with a deuterium atom.

“Optional” or “optionally” means that the event or circumstance subsequently described may but need not to occur, and the description includes the occasion where the event or circumstance occurs or does not occur. For example, “heterocyclic group optionally substituted with alkyl” means that the alkyl may but need not be present, and the description includes the case where the heterocyclic group is substituted with alkyl and the case where the heterocyclic group is not substituted with alkyl.

“Substituted” means that one or more hydrogen atoms, preferably at most 5, more preferably 1-3 hydrogen atoms in the group are each independently substituted with a corresponding number of substituents. It goes without saying, the substituents may be only in their possible chemical positions, a person skilled in the art can determine the possible or impossible substitutions (by experiment or theory) without paying too much effort. For example, amino or hydroxyl having a free hydrogen may be unstable when combined with carbon atoms having unsaturated bonds (e.g., olefinic).

20 “Pharmaceutical composition” denotes a mixture containing one or more compounds described herein or physiologically/pharmaceutically acceptable salts or prodrugs thereof and other chemical components, as well as other components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of pharmaceutical compositions is to facilitate administration to living organisms and facilitate the absorption of active ingredients to exert biological activity.

“Pharmaceutically acceptable salts” refer to salts of the compounds of the present disclosure, which are safe and effective when used in mammals, and have appropriate biological activity.

30

Detailed Description of Embodiments

The present disclosure will be further described below in conjunction with examples, but these examples are not meant to limit the scope of the present disclosure.

Example

35 The structure of the compound of the present disclosure is determined by nuclear magnetic resonance (NMR) and/or liquid chromatography-mass spectrometry (LC-MS). NMR chemical shift (δ) is given in parts per million (ppm). NMR is determined with Bruker AVANCE-400 nuclear magnetic resonance instrument; the solvents for determination are deuterated dimethyl sulfoxide (DMSO-*d*₆), deuterated methanol (CD₃OD) and deuterated chloroform (CDCl₃); and the internal standard is tetramethylsilane (TMS).

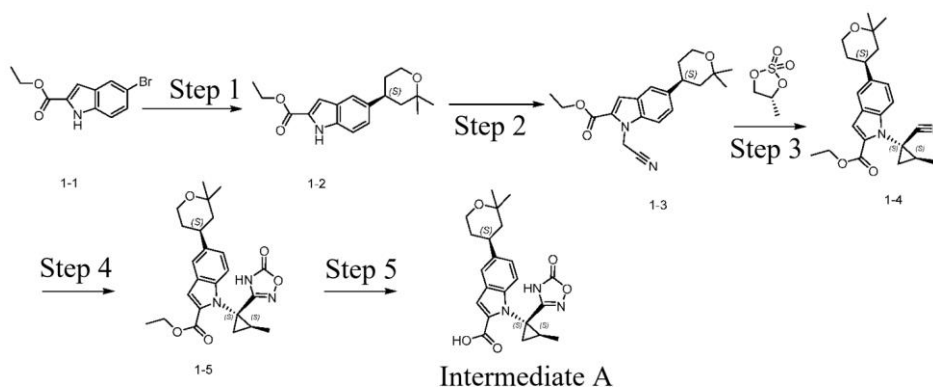
40 Agilent 1200 Infinity Series mass spectrometer is used for measurement by liquid chromatography-mass chromatography (LC-MS). HPLC determination was carried out using Agilent 1200DAD high-pressure liquid chromatograph instrument (Sunfire C18 150 × 4.6 mm chromatographic column) and Waters 2695-2996 high-pressure liquid chromatograph instrument (Gimini C18 150 × 4.6 mm chromatographic column).

Yantai Huanghai HSGF254 or Qingdao GF254 silica gel plate is used as a thin layer chromatography silica plate, and TLC is of the specification of 0.15-0.20 mm, and the specification when separating and purifying a product by thin layer chromatography is 0.4-0.5 mm. For the column chromatography, Yantai Huanghai silica gel of 200-300 mesh silica gel was generally used as a carrier.

The starting materials in the examples of the present disclosure are known and can be purchased on the market, or can be synthesized using or according to methods known in the art.

Unless otherwise specified, all reactions in the present disclosure are carried out under continuous magnetic stirring in a dry nitrogen or argon atmosphere, the solvent is a dry solvent, and the reaction temperature unit is degrees Celsius.

Intermediate A



Step 1: ethyl (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate

A zinc powder (4.88 g, 74.6 mmol) was suspended in DMF (20 mL), and the suspension was protected by nitrogen replacement. Chlorotrimethylsilane (1.01 g, 9.32 mmol) and 1,2-dibromoethane (1.75 g, 9.32 mmol) were added, and the resulting mixture was stirred at room temperature for 5 minutes. To the mixture was added dropwise a solution of 4-iodo-2,2-dimethyltetrahydropyran (13.43 g, 55.95 mmol) in DMF (25 mL), and the mixture was stirred at room temperature for 20 minutes. To the above solution were added palladium acetate (209 mg, 0.93 mmol), 4-(N,N-dimethylamino)phenyl]di-tert-butylphosphine (494 mg, 1.86 mmol), and ethyl 5-bromoindole-2-carboxylate (5.0 g, 18.65 mmol), and nitrogen gas was introduced into the container. The mixture was stirred at an external temperature of 50°C for 1 hour, and then the external temperature was reduced to 0°C and 5 N hydrochloric acid (6 mL) was added for neutralization. A 30% aqueous sodium chloride solution (50 mL) and ethyl acetate (300 mL) were added, and the insoluble matter was removed with diatomaceous earth. The filtrate was extracted with ethyl acetate, and the organic layer was washed with a 30% aqueous sodium chloride solution. Then, the material was dried over magnesium sulfate and passed through a filter, and the solvent was removed by evaporation under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 1) to obtain the product, and the product was subjected to chiral separation to obtain the product compound ethyl (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (1.96 g, yield 35%).

MS m/z (ESI): 302.2[M+1].

Step 2: ethyl (S)-1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate

At room temperature, the ethyl (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (1.96 g, 6.5 mmol) was dissolved in acetonitrile (30 mL), and to the solution was added potassium carbonate (2.70 g, 19.51 mmol). At an external temperature of 10°C, to the resulting solution was added 2-chloroacetonitrile (736 mg, 9.75 mmol), and the solution was stirred for 12 hours. To the reaction solution were added saturated brine (50 mL) and ethyl acetate (100 mL) for extraction, and the aqueous layer was extracted a second time using ethyl acetate (20 mL). The combined organic layer was washed with saturated brine (50 mL), followed by concentration under reduced pressure at an external temperature 40°C to obtain ethyl (S)-1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (2 g), which was used in the subsequent step without purification.

MS m/z (ESI): 341.2[M+1].

Step 3: ethyl 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate

Ethyl (S)-1-(cyanomethyl)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (2 g, 5.88 mmol) and (4R)-4-methyl-1,3,2-dioxathiolane 2,2-dioxide (2.43 g, 17.6 mmol) were dissolved in tetrahydrofuran (15 mL), and the mixture was cooled to 0°C. Under a nitrogen atmosphere, a solution of potassium bis(trimethylsilyl)amide in THF (23.5 mL, 23.5 mmol, 1M) was slowly added dropwise. The reaction mixture was stirred at 0°C for 2.5 hours, and then formic acid (3 mL) was added and the mixture was extracted with ethyl acetate (40 mL). The organic layer was washed three times with water, washed twice with a saturated aqueous solution of sodium bicarbonate, and once with brine, and then dried over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 4), to obtain ethyl 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (1.20 g, yield 54%).

MS m/z (ESI): 381.2[M+1].

Step 4: ethyl 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylate

To a solution of ethyl 1-((1S,2S)-1-cyano-2-methylcyclopropyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (1.20 g, 3.15 mmol) in dimethyl sulfoxide (DMSO) (10 mL) was added a 50% aqueous hydroxylamine solution (2.08 g, 31.5 mmol), and the mixture was stirred at room temperature for 17 hours. Ethyl acetate (50 mL) was added, and the mixture was washed with water (50 mL) and brine (50 mL), and then dried over magnesium sulfate.

The mixture was filtered, then the filtrate was concentrated under reduced pressure, and the resulting residue was dissolved in DMSO (10 mL). Then, carbonyldiimidazole (1.02 g, 6.31 mmol) and 1,8-diazabicycloundec-7-ene (1.20, 7.88 mmol) were added, and the resulting mixture was stirred at room temperature for 0.5 hours. To the mixture was added formic acid for purification by reverse phase chromatography (acetonitrile/water, 0.1% formic acid), to obtain ethyl 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylate (0.96 g, yield 69%).

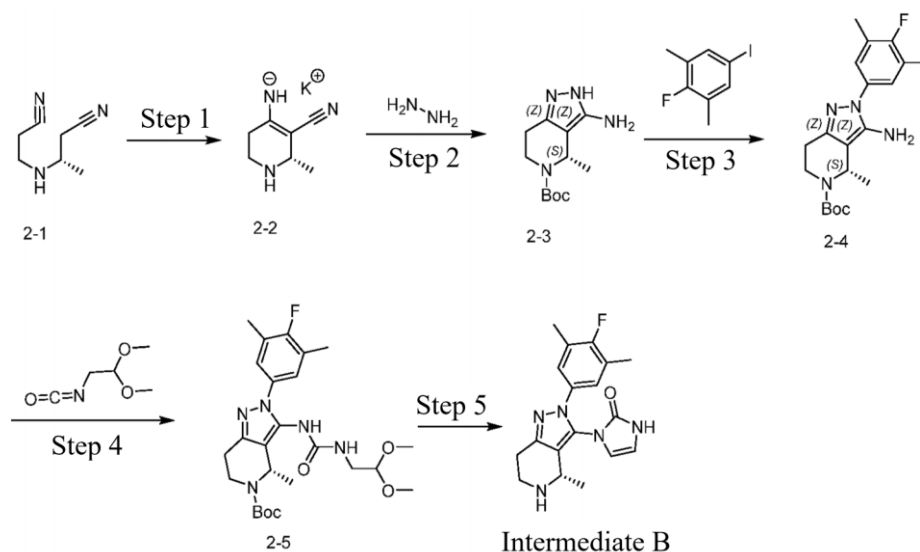
MS m/z (ESI): 440.2[M+1].

Step 5: 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid

To a solution of ethyl 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylate (0.96 g, 2.18 mmol) in DMSO (8 mL) was added a 2M aqueous sodium hydroxide solution (3.28 mL, 6.55 mmol), and the mixture was stirred at room temperature for 1.5 hours. To the mixture was added formic acid for purification by reverse phase chromatography (acetonitrile/water, 0.1% formic acid), to obtain 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid (0.65 g, yield 72%).

MS m/z (ESI): 412.2[M+1].

Intermediate B



Step 1: potassium (S)-(5-cyano-6-methyl-1,2,3,6-tetrahydropyridin-4-yl)amide

To a solution of (S)-3-((2-cyanoethyl)amino)butyronitrile (2.4 g, 17.9 mmol) in tetrahydrofuran (THF) (20 mL) was added a solution of 1M potassium tert-butoxide in THF (17.9 mL), and the mixture was stirred at room temperature for 1 hour.

The reaction mixture was filtered, washed with THF (50 mL), and then the filtrate was dried under reduced pressure to obtain potassium (S)-(5-cyano-6-methyl-1,2,3,6-tetrahydropyridin-4-yl)amide (2.7 g, yield 88%).

MS m/z (ESI): 138.1[M+1].

Step 2: tert-butyl (S)-3-amino-4-methyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate

To a solution of hydrazine hydrochloride (1.06 g, 15.4 mmol) and potassium (S)-(5-cyano-6-methyl-1,2,3,6-tetrahydropyridin-4-yl)amide (2.7 g, 15.4 mmol) in ethanol (30 mL) was added 2N hydrochloric acid (11.5 mL, 23.1 mmol), and the mixture was stirred at 50°C for 1 hour. The reaction mixture was cooled to 0°C, then a 5M aqueous sodium hydroxide solution (4.62 mL, 23.1 mmol) and di-tert-butyl dicarbonate (3.36g, 15.4mmol) were added, and the mixture was stirred at 0°C for 1 hour. To the reaction mixture, water was added, the mixture was extracted with ethyl acetate, and then the organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (dichloromethane : methanol = 20:1), to obtain tert-butyl (S)-3-amino-4-methyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (2.5 g, yield 65%).

MS m/z (ESI): 253.1[M+1].

Step 3: tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

Tert-butyl (S)-3-amino-4-methyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (2.5 g, 9.91 mmol), 2-fluoro-5-iodo-1,3-dimethylbenzene (2.48 g, 9.91 mmol), and L-proline (342.23 mg, 2.97 mmol) were dissolved in dimethyl sulfoxide (30 mL), and under nitrogen protection, cuprous iodide (754.82 mg, 3.96 mmol) and potassium carbonate (1.10 g, 7.93 mmol) were added. The mixture was reacted under stirring at 120°C for 19 hours. To the mixture, saturated brine (150 mL) was added to quench the reaction, the mixture was extracted with ethyl acetate (50 mL × 3), and the organic phases were combined, washed with saturated brine (50 mL × 5), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the target product tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.9 g, yield 78%).

MS m/z (ESI): 375.2[M+1].

Step 4: tert-butyl (S)-3-(3-(2,2-dimethoxyethyl)ureido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

To a solution of tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.9 g, 7.4 mmol) in pyridine (10 mL)

was added 2-isocyanato-1,1-dimethoxyethane (2.03 g, 15.49 mmol), and the mixture was stirred at room temperature. After 3 hours, diethylamine (1.13 g, 15.49 mmol) was added, and the mixture was stirred at room temperature for 5 minutes, and then water (50 mL) was added and the resulting mixture was stirred at room temperature for 20 minutes. The reaction mixture which had become a suspension was filtered, and the resulting solid was washed with water (20 mL) and then dried under reduced pressure, to obtain tert-butyl (S)-3-(3-(2,2-dimethoxyethyl)ureido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (3.6 g, yield 92%).

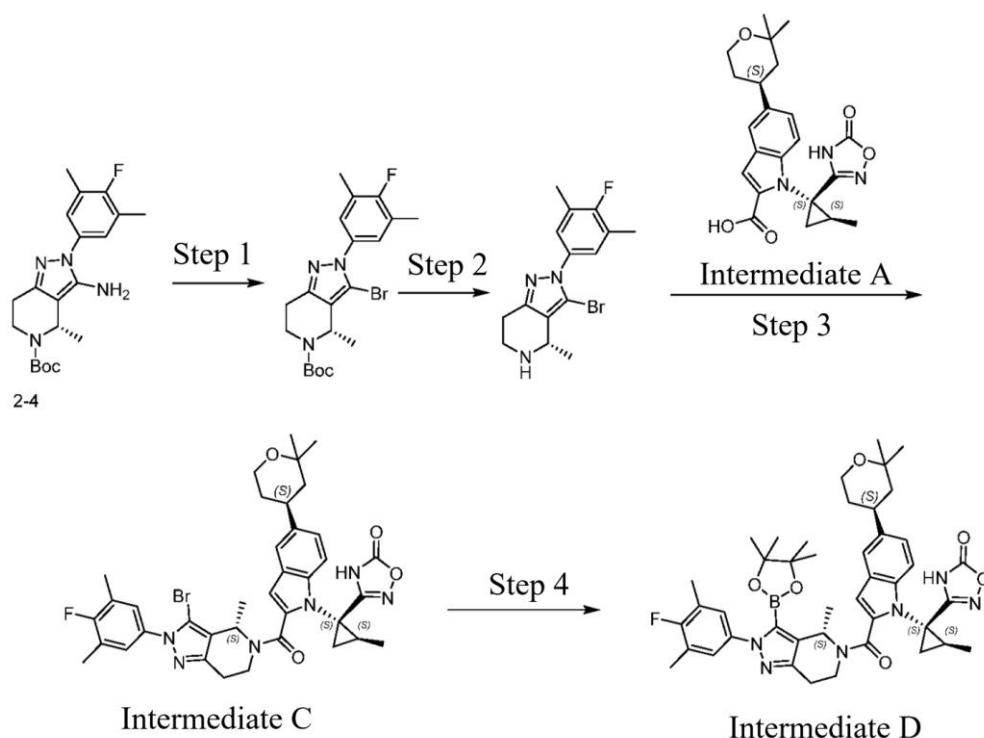
MS m/z (ESI): 506.3[M+1].

Step 5: (S)-1-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

To tert-butyl (S)-3-(3-(2,2-dimethoxyethyl)ureido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (3.6 g, 7.12 mmol) was added formic acid (40 mL), and the mixture was stirred at room temperature for 21 hours. The reaction mixture was concentrated under reduced pressure, and toluene was added, and the solvent was removed by evaporation under reduced pressure. The residue was dissolved with dichloromethane (10 mL), and then at room temperature, hydrogen chloride (a 4 M dioxane solution, 10 mL) was added and stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. Toluene was added, and the solvent was removed by evaporation under reduced pressure, to obtain the crude product (S)-1-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one (3.6 g).

MS m/z (ESI): 342.2[M+1].

Intermediate C and Intermediate D



Step 1: tert-butyl (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

5 Tert-butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.5 g, 6.68 mmol) was dissolved in bromoform (8 mL), and under nitrogen protection, isoamyl nitrite (2.07 g, 20.03 mmol) was added. The mixture was reacted under stirring at 60°C for 2 hours. The mixture was concentrated under reduced pressure, and saturated brine (30 mL) was added to quench the reaction; and the mixture was extracted with ethyl acetate (50 mL), washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively.

10 The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the target product tert-butyl (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.1 g, yield 72%).

MS m/z (ESI): 438.1, 440.1[M+1].

15 Step 2: (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine

tert-Butyl (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.1 g, 4.79 mmol) was added to hydrogen chloride (a 4M dioxane solution, 20 mL) at room temperature and stirred at room temperature for 2 hours. The resulting crude product (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (1.7 g) was

20 concentrated under reduced pressure, and the crude product was used directly in the next step.

MS m/z (ESI): 338.0, 340.0[M+1].

Step 3: 3-((1S,2S)-1-(2-((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5 (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine hydrochloride (1.7 g, 4.54 mmol), intermediate A (526.84 mg, 4.54 mmol) and diisopropylethylamine (1.76 g, 13.61 mmol, 2.37 mL) were dissolved in N,N'-dimethylformamide (15 mL), and under nitrogen protection, 2-(7-azobenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.59 g, 6.81 mmol) was added. The mixture was reacted under stirring at 25°C for 12 hours. The crude reaction solution was separated by
10 preparative high-performance liquid chromatography to give the product 3-((1S,2S)-1-(2-((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (2 g, yield 60%).

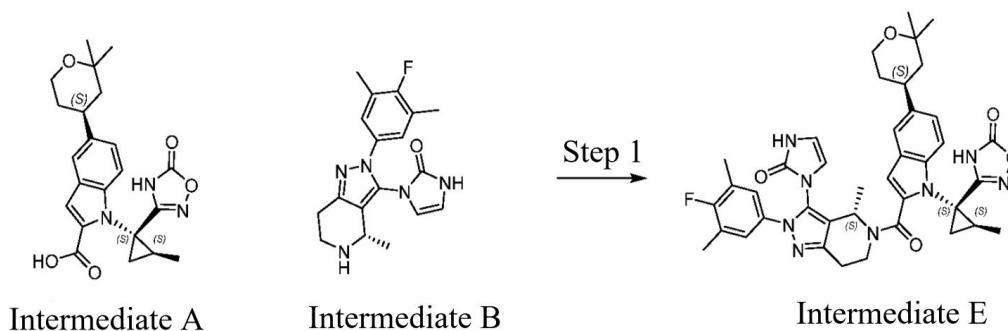
MS m/z (ESI): 731.2, 733.2[M+1].

15 Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

3-((1S,2S)-1-(2-((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (1 g, 1.37 mmol), bis(pinacolato)diboron (0.52 g, 2.05
20 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium dichloromethane complex (100 mg, 137 µmol) were dissolved in 1,4-dioxane (30 mL), and under nitrogen protection, potassium acetate (335 mg, 3.42 mmol) was added. The mixture was reacted under stirring at 90°C for 12 hours. The mixture was concentrated under reduced pressure. The crude product was added into saturated brine (50 mL) to quench
25 the reaction, and extracted with ethyl acetate (50 mL × 2), and the organic phases were combined, washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, concentrated under reduced pressure, successively. The crude reaction solution was separated by preparative high-performance liquid chromatography to give the product (0.6 g, yield 56%).

MS m/z (ESI): 779.4[M+1].

30 **Intermediate E**

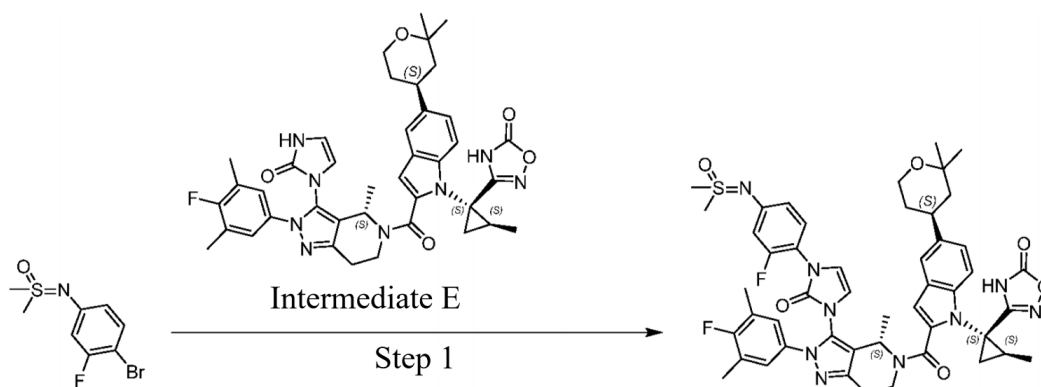


Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5 The product was obtained by following the step 3 for intermediate C and intermediate D.

MS m/z (ESI): 735.3[M+1].

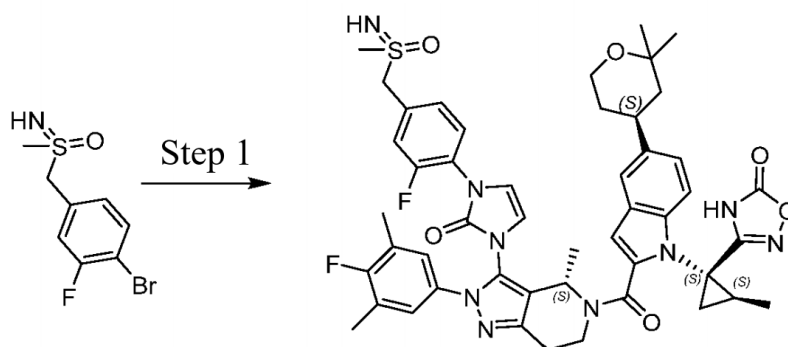
Example 1



Step 1: 3-((1S,2S)-1-(2-((S)-3-(3-(4-((dimethyl(carbonyl)-l6-sulfaneylidene)amino)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

At room temperature, to a suspension of intermediate E (20 mg, 0.027 mmol), ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione (14.5 mg, 0.054 mmol), (1S,2S)-1-N,2-N-dimethylcyclohexane-1,2-diamine (1.9 mg, 0.013 mmol) and potassium carbonate (11.3 mg, 0.082 mmol) in N-methylpyrrolidone (0.5 mL) was added cuprous iodide(I) (1.0 mg, 0.0054 mmol), and the mixture was stirred at 130°C for 3 hours under a nitrogen atmosphere. The reaction mixture was purified by reverse phase silica gel chromatography (acetonitrile/water, 0.1% formic acid) to obtain the target compound (10 mg, yield 40%).

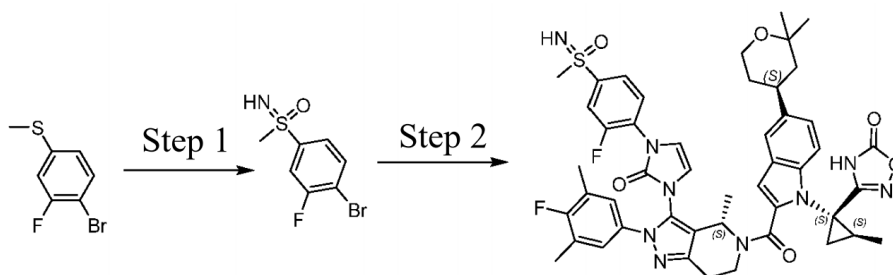
MS m/z (ESI): 920.3[M+1].

Example 2

Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(2-fluoro-4-((S-methylsulfonylimino)methyl)phenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-3-fluorobenzyl)(imino)(methyl)-16aminosulfanone was used as a raw material, following Example 1 to obtain the target product.

MS m/z (ESI): 920.4[M+1].

Example 3

Step 1: (4-bromo-3-fluorophenyl)(imino)(methyl)-16aminosulfanone

1-thiomethyl-4-bromo-3-fluorobenzene was used as a raw material, following European Journal of Organic Chemistry, 2017, vol. 2017, # 44, p. 6486 - 6490, to obtain the target product.

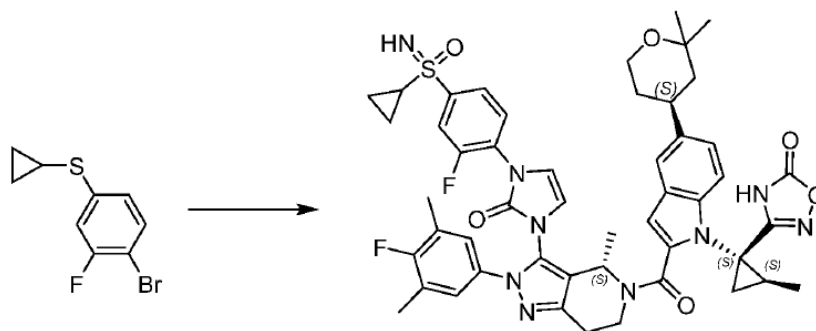
MS m/z (ESI): 251.9, 253.9[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(2-(2-fluoro-4-(S-methylsulfonylimino)phenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 1, the target product was obtained.

MS m/z (ESI): 906.4[M+1].

Example 4

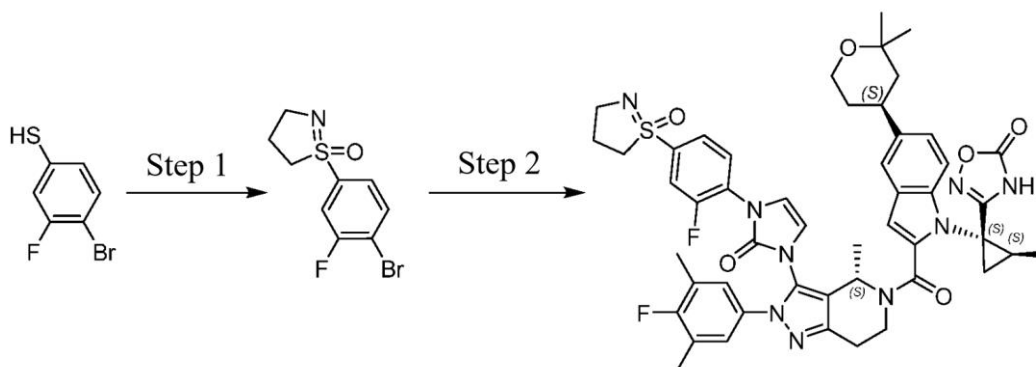


Step 1: 3-((1S,2S)-1-(2-((4S)-3-(3-(4-(cyclopanesulfonyl)-2-fluorophenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-3-fluorophenyl)(cyclopropyl)sulfone was used as a raw material, following Example 1 to obtain the target product.

MS m/z (ESI): 932.4[M+1].

Example 5



Step 1: 1-(4-bromo-3-fluorophenyl)-4,5-dihydro-3H-isothiazole 1-oxide

4-bromo-3-fluorobenzenethiol was used as a raw material, following Angewandte Chemie - International Edition, 2018, vol. 57, # 37, p. 12053 - 12056 to obtain the target product.

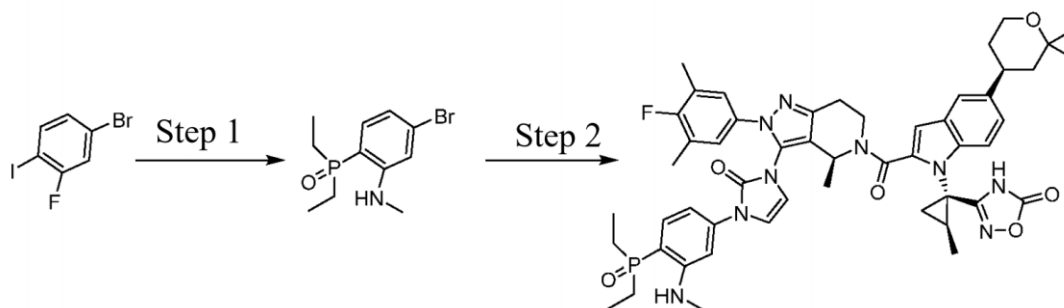
MS m/z (ESI): 278.0, 280.0[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(1-oxide-4,5-dihydro-3H-116-isothiazol-1-yl)phenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 1, the target product was obtained.

MS m/z (ESI): 932.4[M+1].

Example 6



Step 1: (4-bromo-2-(methylamino)phenyl)diethylphosphine oxide

4-bromo-2-fluoro-1-iodobenzene was used as a raw material, following WO2023/16546, 2023, A1 Page/Page column 160-162 to obtain the target product.

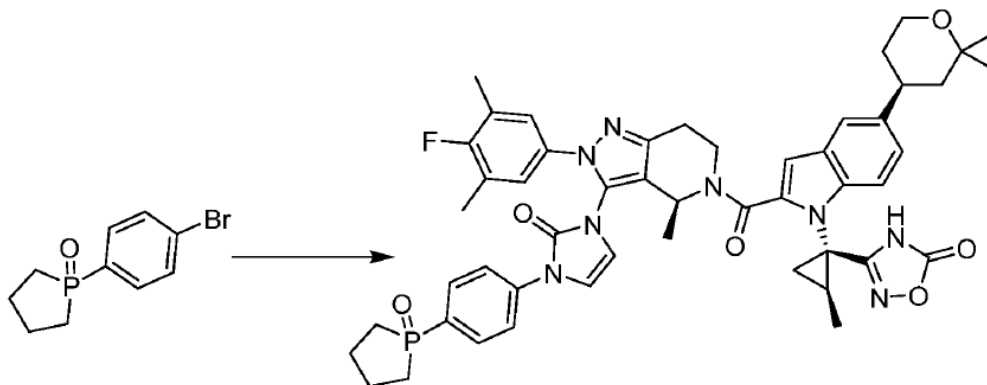
MS m/z (ESI): 290.0, 292.0[M+1].

Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(4-(diethylphosphoryl)-3-(methylamino)phenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 1, the target product was obtained.

MS m/z (ESI): 944.4[M+1].

Example 7

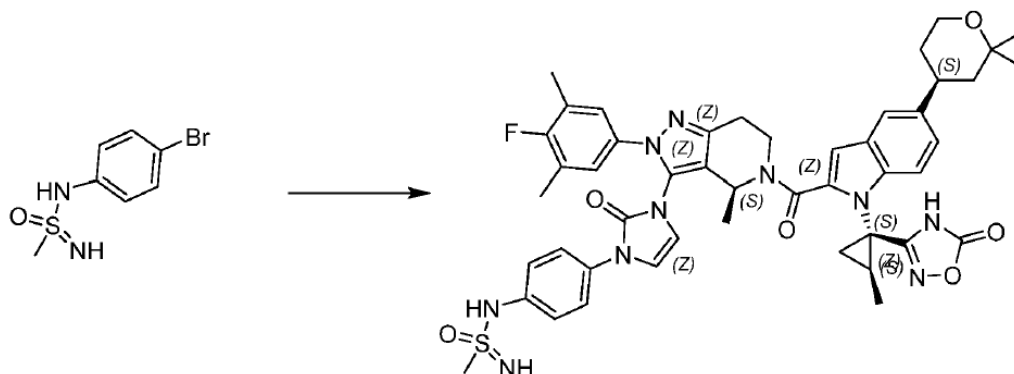


Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(4-(1-phosphine oxide-1-yl)phenyl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-(4-bromophenyl)cyclopentylphosphine1-oxide was used as a raw material, following Example 1 to obtain the target product.

MS m/z (ESI): 913.4[M+1].

Example 8



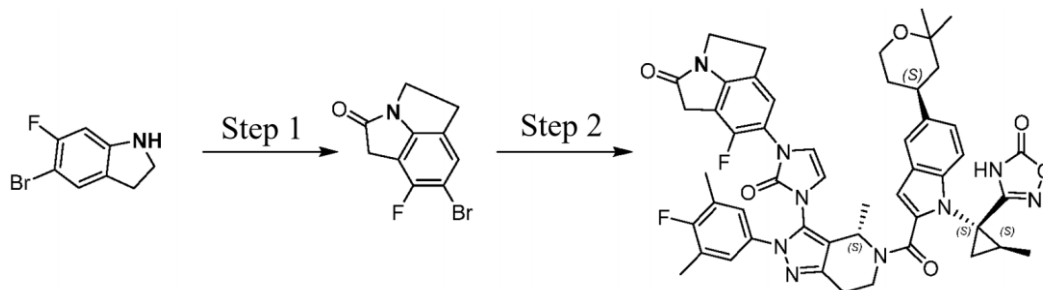
5

Step 1: N-(4-(3-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrano[4,3]pyridin-3-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)phenyl)methanesulfonamide

10 N-(4-bromophenyl)methanesulfonamide was used as a raw material, following Example 1 to obtain the target product.

MS m/z (ESI): 903.4[M+1].

Example 9



15 Step 1: 7-bromo-8-fluoro-4,5-dihydropyrrolo[3,2,1-hi]indole-2(1H)-one

5-bromo-6-fluoroindoline was used as a raw material, according to Journal of Organic Chemistry, 1992, vol. 57, # 8, p. 2508 - 2511 to obtain the target product.

MS m/z (ESI): 256.0, 258.0[M+1].

20 Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(8-fluoro-2-oxo-1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indol-7-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)

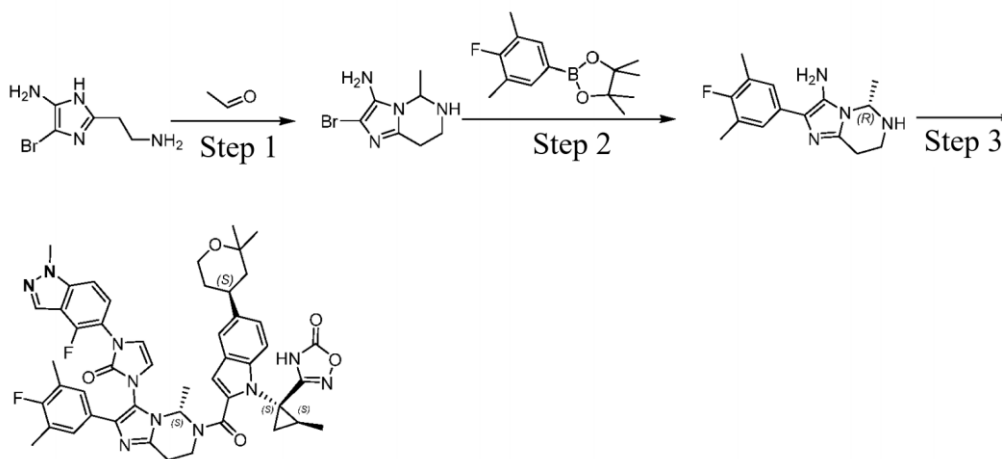
2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 1, the target product was obtained.

MS m/z (ESI): 910.4[M+1].

5

Example 10



Step 1: 2-bromo-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-c]pyrimidin-3-amine

2-(2-aminoethyl)-4-bromo-1H-imidazol-5-amine (0.2 g, 0.97 mmol) was dissolved in 1,2-dichloroethane (10 mL), then an aqueous acetaldehyde solution (859 mg, 4.88 mmol, 25% aqueous solution) was added, and the reaction solution was stirred at room temperature for 1 hour and then heated to reflux for 5 hours. The reaction solution was evaporated to dryness, washed with water, and dried to obtain a crude product (0.2 g), which was used directly in the next step.

MS m/z (ESI): 231.0, 233.0[M+1].

Step 2: (R)-2-(4-fluoro-3,5-dimethylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-c]pyrimidin-3-amine

2-bromo-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-c]pyrimidin-3-amine (0.2 g, 0.87 mmol), 2-(4-fluoro-3,5-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (216 mg, 0.87 mmol), and sodium carbonate (273.77 mg, 2.58 mmol) were dissolved in 1,4-dioxane (8 mL) and water (2 mL), and under nitrogen protection, bis(triphenyl)palladium dichloride (30.22 mg, 43.05 μ mol) was added. The mixture was reacted under stirring at 90°C for 5 hours. The reaction solution was cooled, and saturated brine (5 mL) was added to quench the reaction, followed by extraction with ethyl acetate (30 mL $\times$ 2). The mixture was subjected to liquid-liquid separation, and the organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a crude product. The crude product was separated by preparative high-performance liquid chromatography and chirally resolved to obtain the product (45 mg, yield 19%).

25

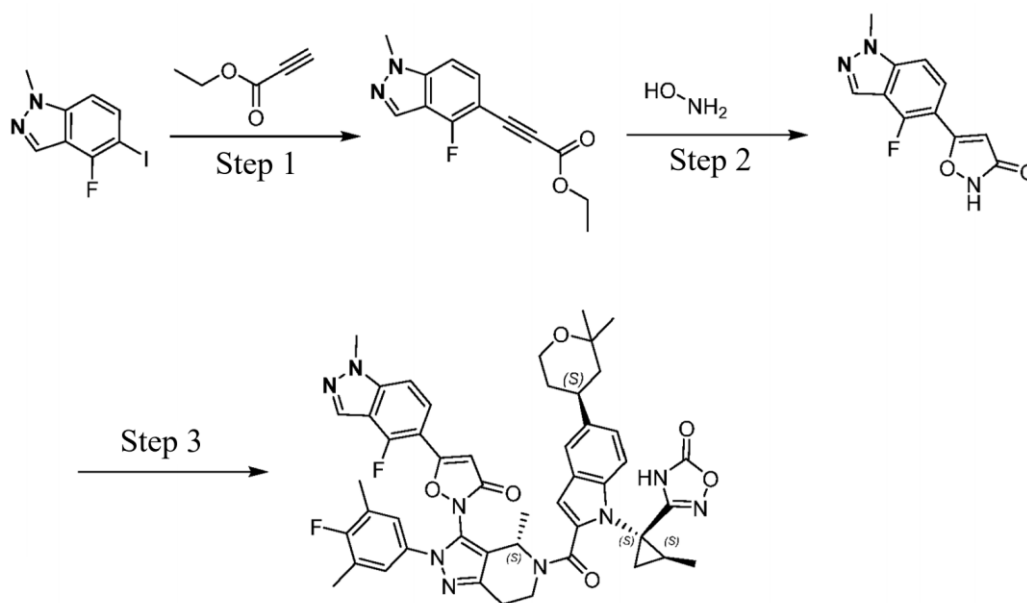
MS m/z (ESI): 275.2[M+1].

Step 3: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-c]pyrimidin-6-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following step 4 and step 5 for intermediate B and step 1 for intermediate E, Example 1, (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione) and the target product was synthesized.

MS m/z (ESI): 883.4[M+1].

Example 11



Step 1: ethyl 3-(4-fluoro-1-methyl-1H-indazol-5-yl)propionate

4-fluoro-5-iodo-1-methyl-1H-indazole was used as a raw material, following Organic and Biomolecular Chemistry, 2018, vol. 16, # 34, p. 6341 - 6349, to obtain the target product.

MS m/z (ESI): 247.1[M+1].

Step 2: 5-(4-fluoro-1-methyl-1H-indazol-5-yl)isoxazol-3(2H)-one

Ethyl 3-(4-fluoro-1-methyl-1H-indazol-5-yl)propionate (1.43 g, 5.8 mmol) was dissolved in ethanol (15 mL), then a solution of 10% hydroxylamine hydrochloride (1.2 g, 17.5 mmol) in sodium hydroxide (17 mL) was added dropwise, and the reaction solution was stirred overnight at room temperature. The reaction solution was adjusted to PH = 2 with concentrated hydrochloric acid, stirred for 30 minutes, filtered, and washed with water to obtain a solid product (0.6 g, yield 44%),

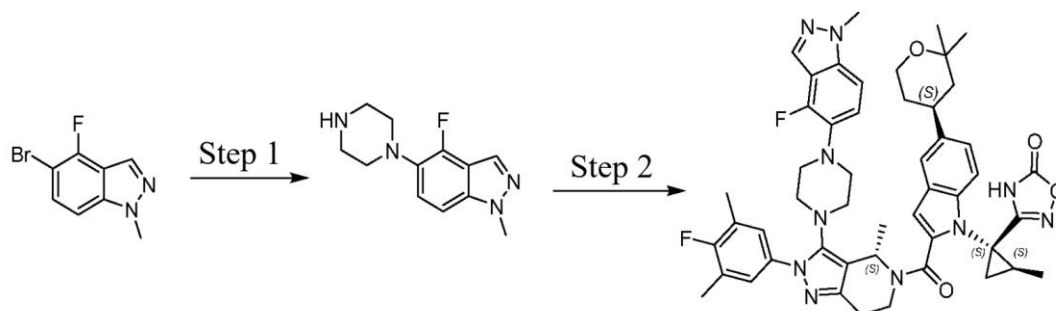
MS m/z (ESI): 234.1[M+1].

Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(5-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-oxoisoxazol-2(3H)-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrano[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5 Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 884.4[M+1].

Example 12



Step 1: 4-fluoro-1-methyl-5-(piperazin-1-yl)-1H-indazole

10 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Bioorganic and Medicinal Chemistry Letters, 2010, vol. 20, # 13, p. 3941 - 3945, to obtain the target product.

MS m/z (ESI): 235.1[M+1].

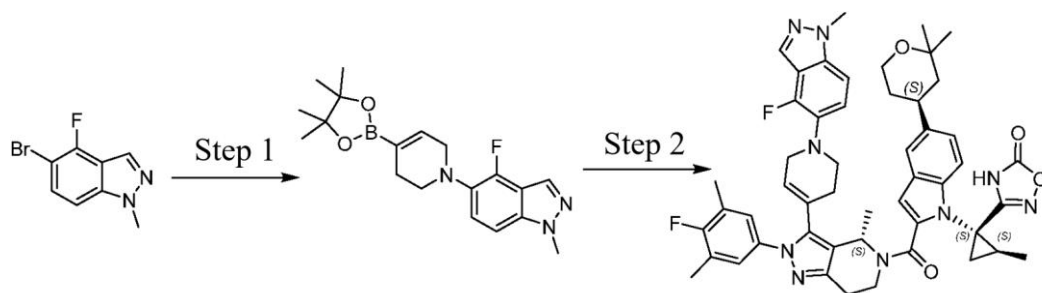
Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)piperazin-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

15

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 885.4[M+1].

Example 13



20

Step 1: 4-fluoro-1-methyl-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridin-1(2H)-yl)-1H-indazole

5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following ACS Medicinal Chemistry Letters, 2021, vol. 12, # 7, p. 1108 - 1115, to obtain the target product.

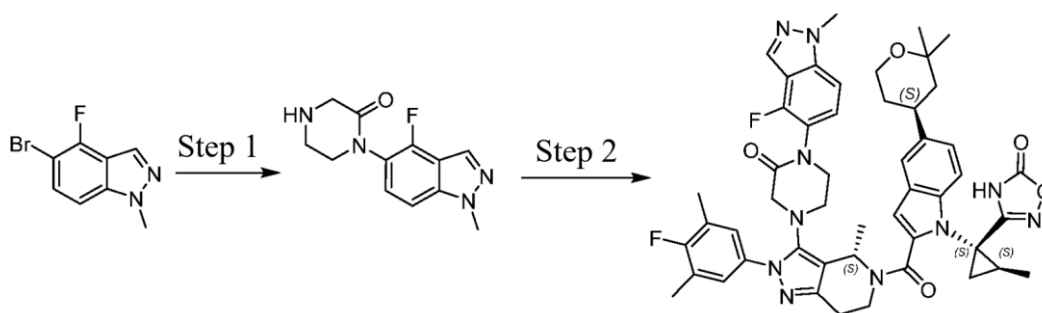
MS m/z (ESI): 358.2[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(1-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,2,3,6-tetrahydropyridin-4-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate C was used as a raw material, following Example 10, Step 2, to obtain the target product.

MS m/z (ESI): 882.4[M+1].

Example 14



Step 1: 1-(4-fluoro-1-methyl-1H-indazol-5-yl)piperazin-2-one

5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Bioorganic and Medicinal Chemistry Letters, 2010, vol. 20, # 13, p. 3941 - 3945 to obtain the target product.

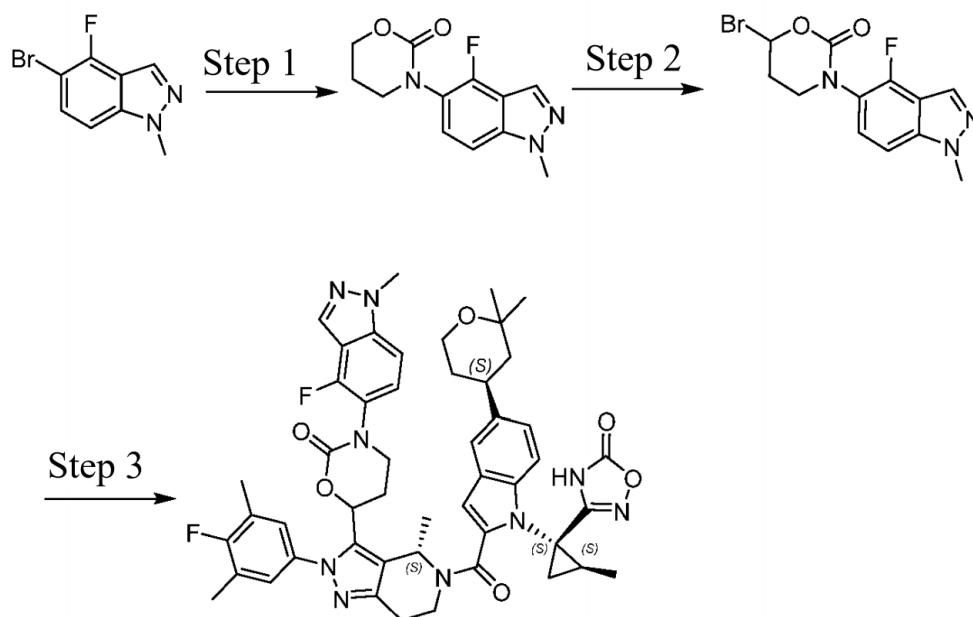
MS m/z (ESI): 249.1[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-oxopiperazin-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 899.4[M+1].

Example 15



Step 1: 3-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-oxazin-2-one

5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product.

5 MS m/z (ESI): 250.1[M+1].

Step 2: 6-bromo-3-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-oxazin-2-one

3-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-oxazin-2-one (50 mg, 0.20 mmol) was dissolved in dichloromethane (4 mL), then N-bromosuccinimide (NBS) (35 mg, 0.20 mmol) was added, and the reaction solution was stirred at room temperature for 1 hour. The separation by TCL (petroleum ether : ethyl acetate = 1 : 1) was followed, to obtain the target product (10 mg, yield 15%).

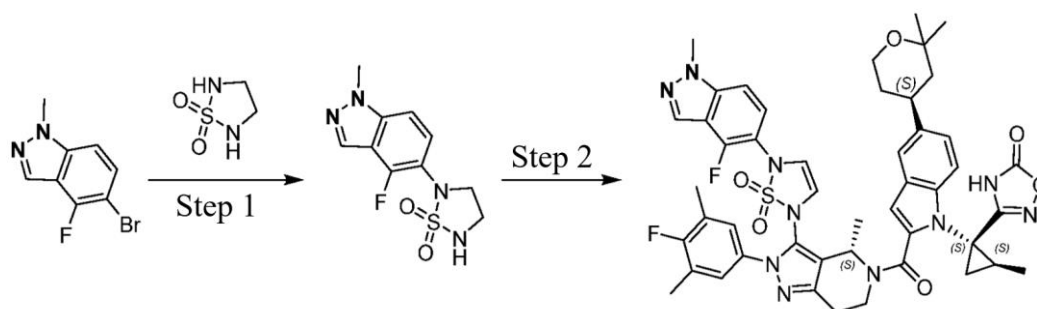
MS m/z (ESI): 328.0, 330.0[M+1].

Step 3: 6-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-oxazin-2-one

Intermediate D was used as a raw material, following Example 10, Step 2, to obtain the target product.

MS m/z (ESI): 900.4[M+1].

Example 16



Step 1: 2-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,2,5-thiadiazolidine 1,1-dioxide

5-bromo-4-fluoro-1-methyl-1H-indazole and 1,2,5-thiadiazolidine 1,1-dioxide were used as raw materials, following Example 1, to obtain the target product.

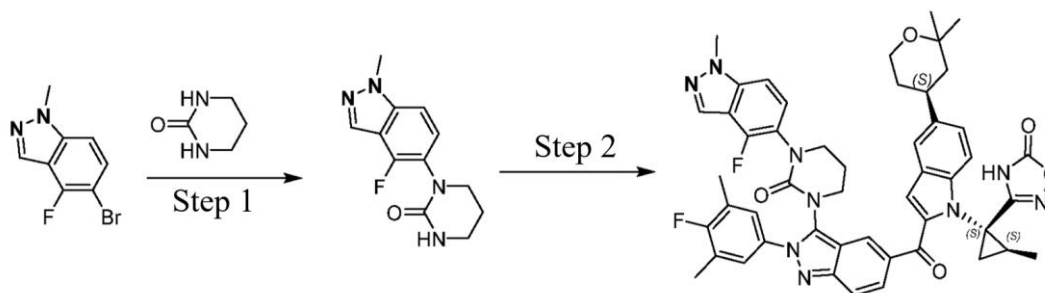
5 MS m/z (ESI): 271.1[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(5-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,1-dioxide-1,2,5-thiadiazol-2(5H)-yl)-2--(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrano[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10 Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 919.3[M+1].

Example 17



Step 1: 1-(4-fluoro-1-methyl-1H-indazol-5-yl)tetrahydropyrimidin-2(1H)-one

15 5-bromo-4-fluoro-1-methyl-1H-indazole and tetrahydropyrimidin-2(1H)-one were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 249.1[M+1].

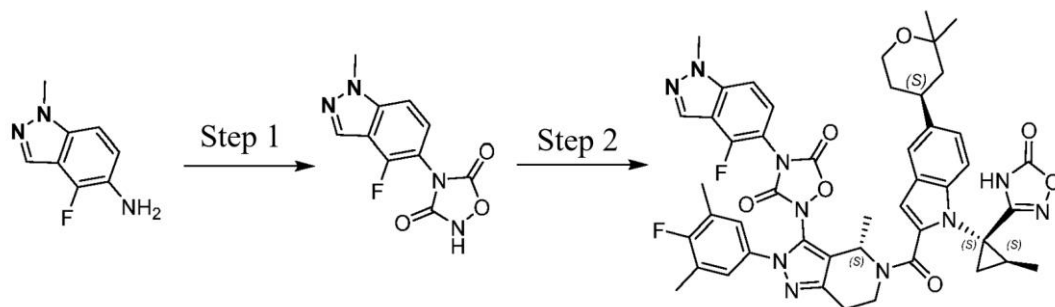
Step 2: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxotetrahydropyrimidin-1(2H)-yl)-2--(4-fluoro-3,5-dimethylphenyl)-2H-imidazol-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

20

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 880.4[M+1].

Example 18



Step 1: 4-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,2,4-oxadiazolidin-3,5-dione

4-fluoro-1-methyl-1H-indazol-5-amine was used as a raw material, following Archiv der Pharmazie, 1981, vol. 314, # 4, p. 294 - 302, to obtain the target product.

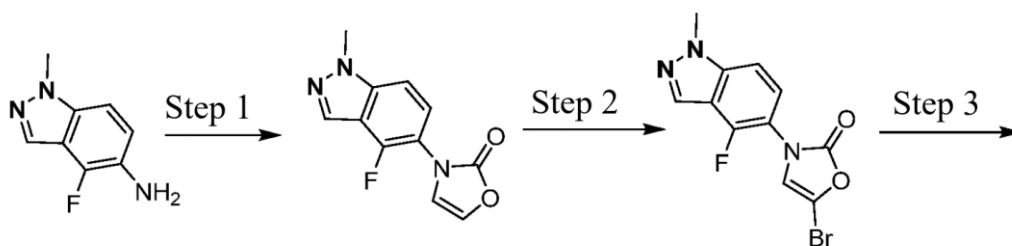
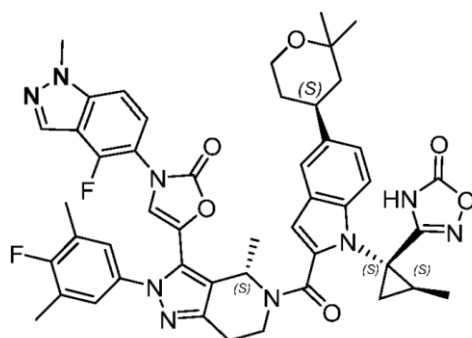
MS m/z (ESI): 251.1[M+1].

Step 2: 2-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridin-3-yl)-4-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,2,4-oxadiazolidin-3,5-one

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 901.4[M+1].

Example 19



Step 1: 3-(4-fluoro-1-methyl-1H-indazol-5-yl)oxazol-2(3H)-one

4-fluoro-1-methyl-1H-indazol-5-amine was used as a raw material, following Organic Letters, 2008, vol. 10, # 5, p. 925 - 928, to obtain the target product.

5 MS m/z (ESI): 234.1[M+1].

Step 2: 5-bromo-3-(4-fluoro-1-methyl-1H-indazol-5-yl)oxazol-2(3H)-one

Following Example 15 Step 2, the target product was obtained.

MS m/z (ESI): 312.0, 314.0 [M+1].

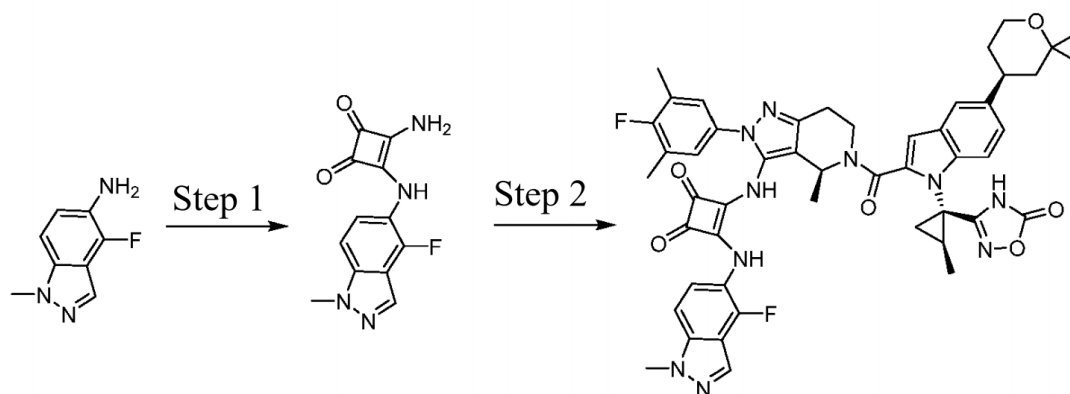
10 Step 3: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydrooxazol-5-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate D was used as a raw material, following Example 10, Step 2, to obtain the target product.

MS m/z (ESI): 884.4[M+1].

15

Example 20



Step 1: 3-ethoxy-4-((4-fluoro-1-methyl-1H-indazol-5-yl)amino)cyclobut-3-ene-1,2-dione

4-fluoro-1-methyl-1H-indazol-5-amine was used as a raw material, following Journal of Organic Chemistry, 2010, vol. 75, # 12, p. 3983 - 3992, to obtain the target product.

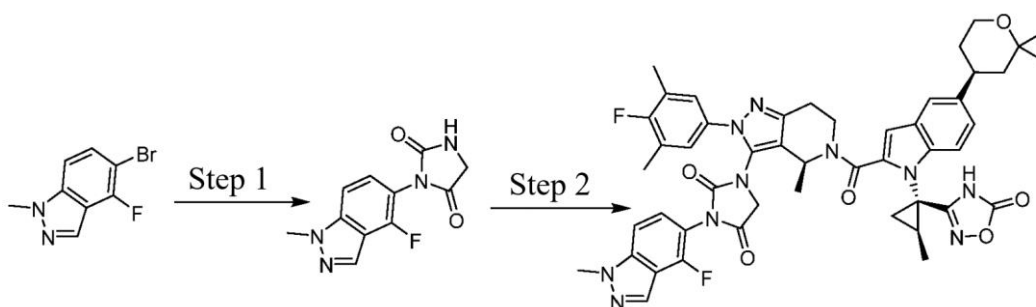
MS m/z (ESI): 261.0[M+1].

5 Step 2: 3-(((S)-5-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridin-3-yl)amino)-4-((4-fluoro-1-methyl-1H-indazol-5-yl)amino)-cyclobut-3-ene-1,2-one

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

10 MS m/z (ESI): 911.4[M+1].

Example 21



Step 1: 3-(4-fluoro-1-methyl-1H-indazol-5-yl)imidazolidin-2,4-dione

15 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Journal of Medicinal Chemistry, 2012, vol. 55, # 7, p. 2945 - 2959, to obtain the target product.

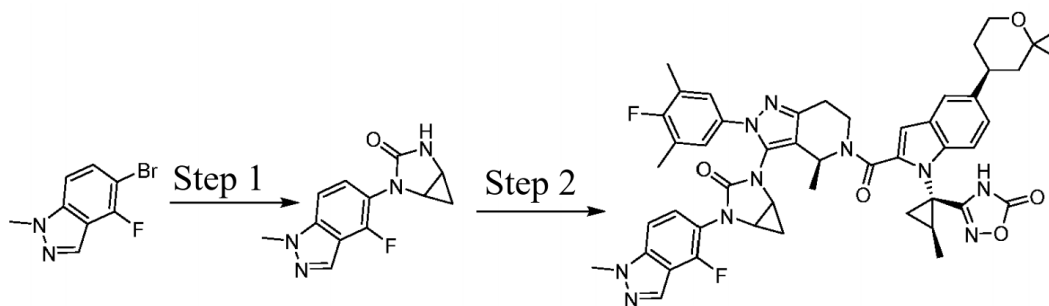
MS m/z (ESI): 249.1[M+1].

20 Step 2: 1-(((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)imidazolidin-2,4-dione

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 899.4[M+1].

Example 22



Step 1: 2-(4-fluoro-1-methyl-1H-indazol-5-yl)-2,4-diazabicyclo[3.1.0]hexan-3-one

5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product.

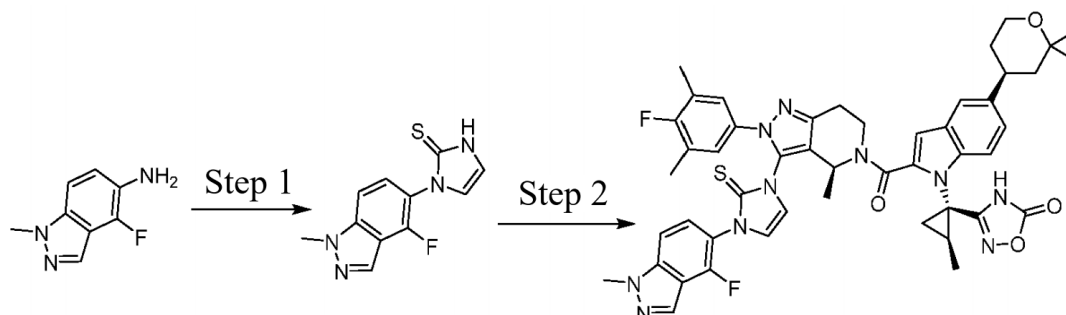
5 MS m/z (ESI): 247.1[M+1].

Step 2: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-oxo-2,4-diazabicyclo[3.1.0]hexan-2-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10 Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 897.4[M+1].

Example 23



Step 1: 1-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-thione

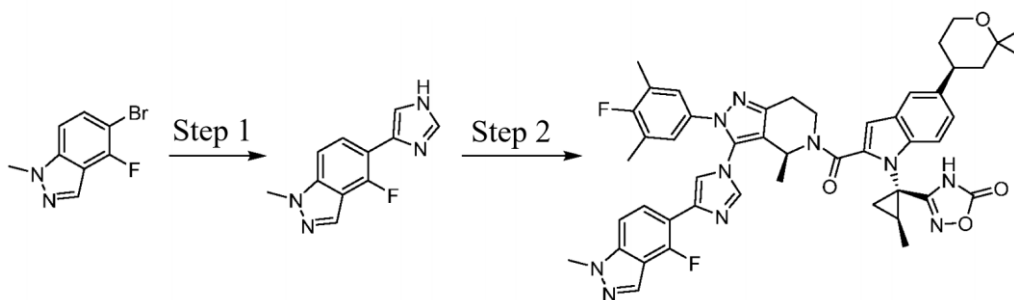
15 4-fluoro-1-methyl-1H-indazol-5-amine was used as a raw material, following New Journal of Chemistry, 2014, vol. 38, # 9, p. 4071-4082, to obtain the target product.

MS m/z (ESI): 249.1[M+1].

Step 2: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-thio-2,3-dihydro-1H-imidazol-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 899.4[M+1].

Example 24

Step 1: 4-fluoro-5-(1H-imidazol-4-yl)-1-methyl-1H-indazole

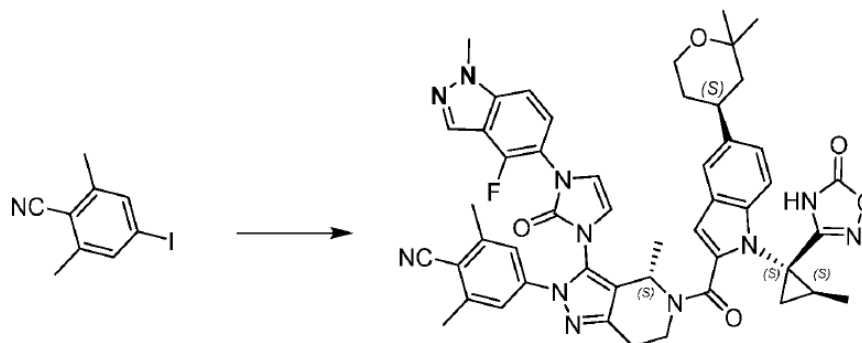
5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Bioorganic and Medicinal Chemistry Letters, 2001, vol. 11, # 16, p. 2061 - 2065, to obtain the target product.

MS m/z (ESI): 217.1[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 867.4[M+1].

Example 25

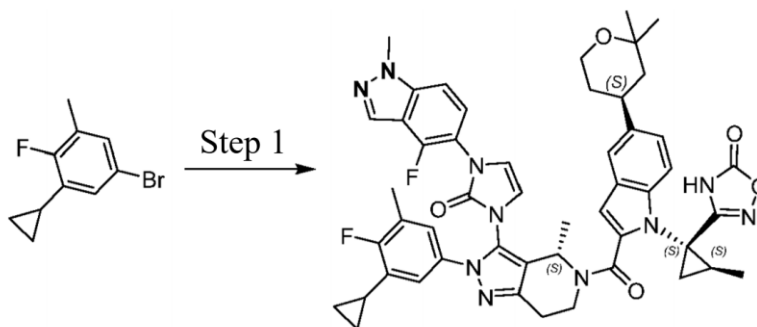
Step 1: 4-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridin-2-yl)-2,6-dimethylbenzonitrile

Following intermediate B Step 3, 4-iodo-2,6-dimethylbenzonitrile was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate,

then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione) to synthesize the target product.

MS m/z (ESI): 890.4[M+1].

Example 26

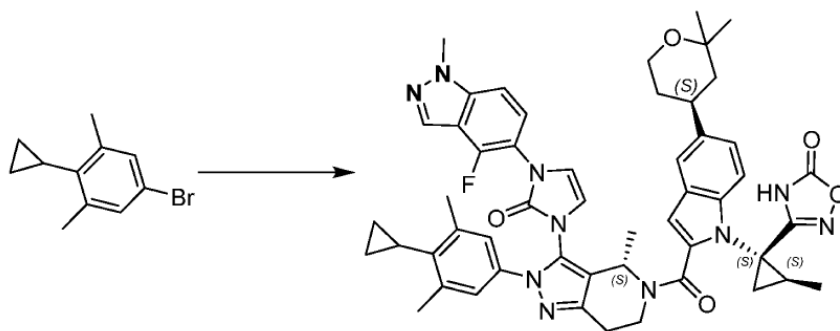


Step 1: 3-((1S,2S)-1-(2-(((S)-2-(3-cyclopropyl-4-fluoro-5-methylphenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 5-bromo-1-cyclopropyl-2-fluoro-3-toluene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 909.4[M+1].

Example 27

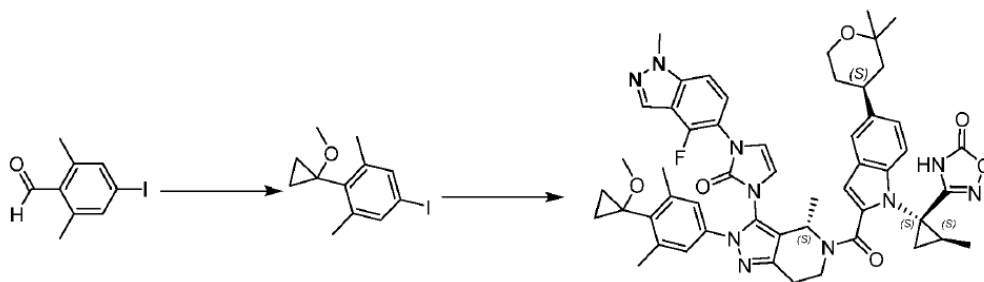


Step 1: 3-((1S,2S)-1-(2-(((S)-2-(4-cyclopropyl-3,5-dimethylphenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 5-bromo-2-cyclopropyl-1,3-dimethylbenzene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 905.4[M+1].

Example 28



Step 1: 5-iodo-2-(1-methoxycyclopropyl)-1,3-dimethylbenzene

4-iodo-2,6-dimethylbenzenecarbaldehyde was used as a raw material, following WO2020/201079, to synthesize the target product.

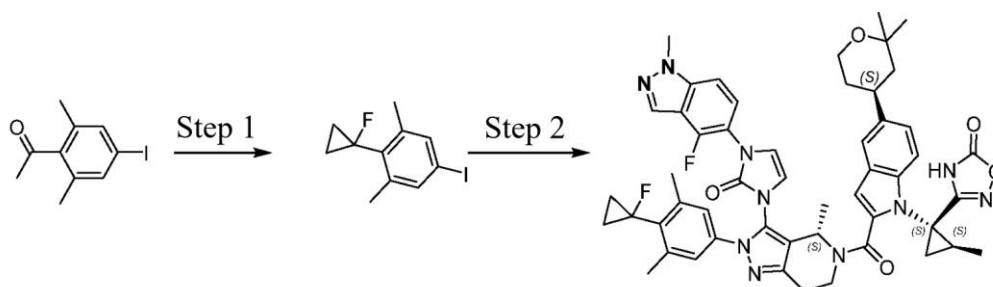
MS m/z (ESI): 303.0[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-(1-methoxycyclopropyl)-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 5-iodo-2-(1-methoxycyclopropyl)-1,3-dimethylbenzene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 935.4[M+1].

Example 29



Step 1: 2-(1-fluorocyclopropyl)-5-iodo-1,3-dimethylbenzene

1-(4-iodo-2,6-dimethylphenyl)ethan-1-one was used as a raw material, following Chemical Communications, 1996, # 10, p. 1103 - 1104, to obtain the target product.

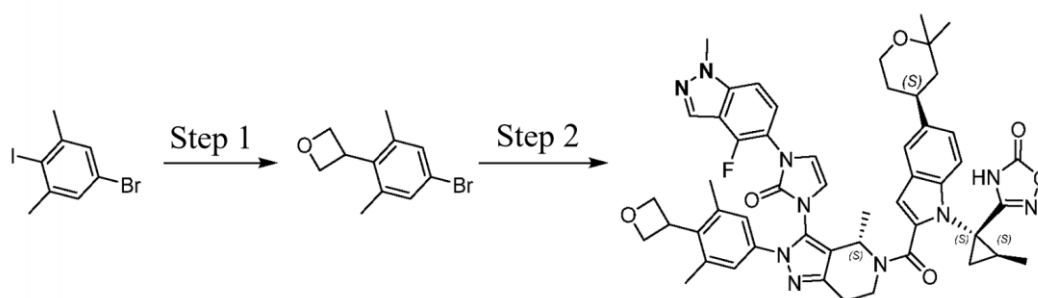
MS m/z (ESI): 291.0[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-(1-fluorocyclopropyl)-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 2-(1-fluorocyclopropyl)-5-iodo-1,3-dimethylbenzene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 923.4[M+1].

Example 30



Step 1: 3-(4-bromo-2,6-dimethylphenyl)oxetane

5-bromo-2-iodo-1,3-dimethylbenzene was used as a raw material, following WO 2021/155320, 2021, A1 Page/Page column 71; 115-116, to obtain the target product.

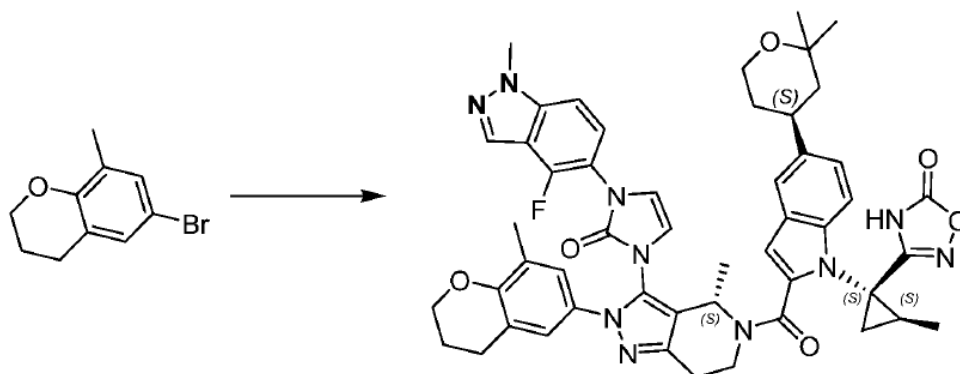
MS m/z (ESI): 241.0[M+1].

Step 2: 3-((1S,2S)-1-(2-(((S)-2-(3,5-dimethyl-4-(oxetan-3-yl)phenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 3-(4-bromo-2,6-dimethylphenyl)oxetane was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 921.4[M+1].

Example 31

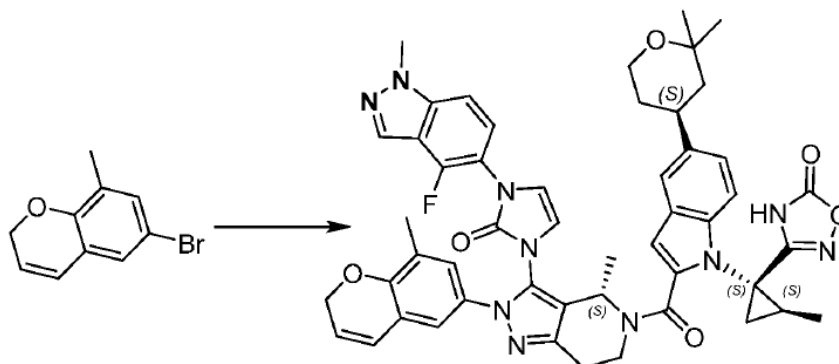


Step 1: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2-(8-methylchroman-6-yl)-4,5,6,7-tetrahydro-2H pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 6-bromo-8-methyl-chromene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzenesynthesizedintermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 907.4[M+1].

Example 32

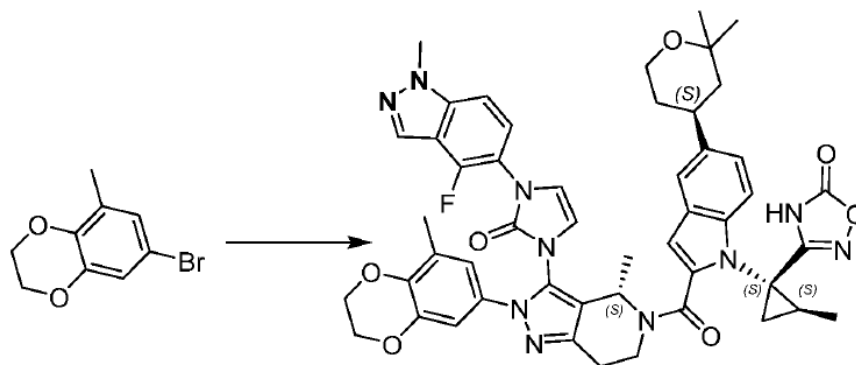


Step 1: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2-(8-methyl-2H-methylene-6-yl)-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 6-bromo-8-methyl-2H-chromene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 905.4[M+1].

Example 33

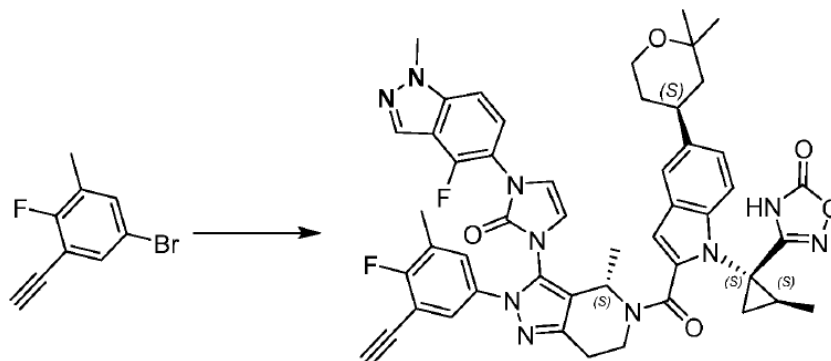


Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2-(8-methyl-2,3-dihydrobenzo[b][1,4]dioxan-6-yl)-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 7-bromo-5-methyl-2,3-dihydrobenzo[b][1,4]dioxazine was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 909.4[M+1].

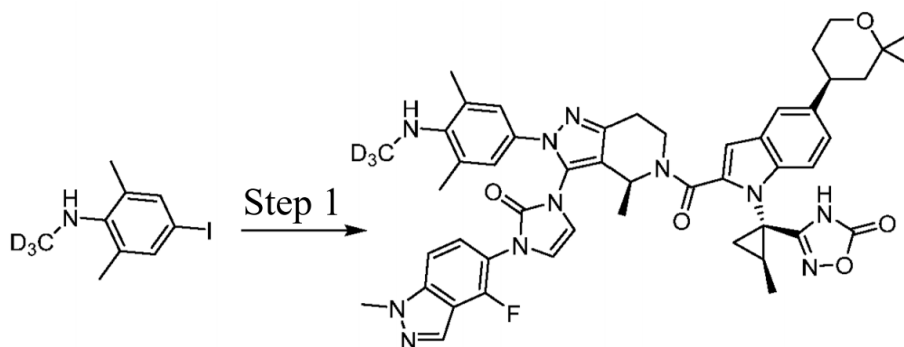
Example 34



Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-2-(3-ethynyl-4-fluoro-5-methylphenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 5-bromo-1-ethynyl-2-fluoro-3-toluene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize a target product.

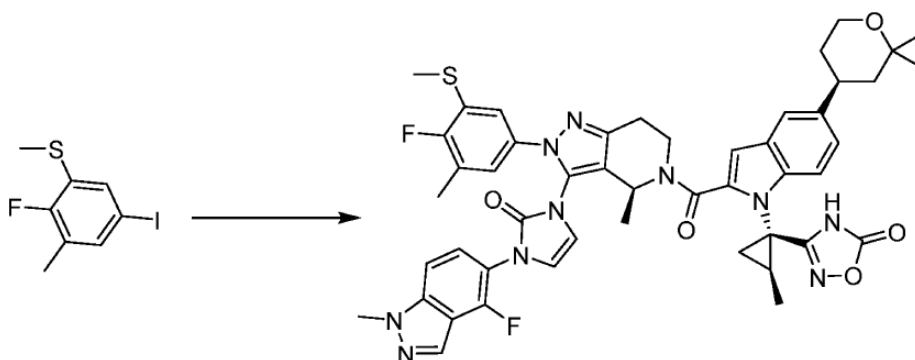
MS m/z (ESI): 893.4[M+1].

Example 35

Step 1: 3-((1S,2S)-1-(2-((S)-2-(3,5-dimethyl-4-((methyl-d3)amino)phenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-5-((S-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 4-iodo-2,6-dimethyl-N-(methyl-d3)benzenamine was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

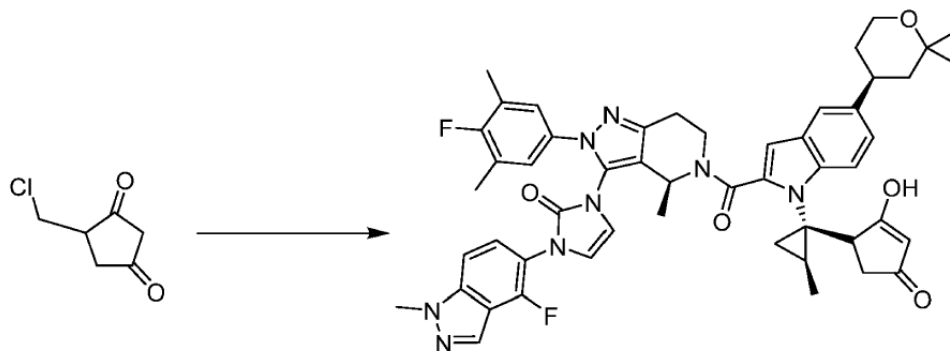
MS m/z (ESI): 897.4[M+1].

Example 36

Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3-methyl-5-(methylthio)phenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 3, 2-fluoro-5-iodo-3-methyl(thiomethyl)benzene was used instead of 2-fluoro-5-iodo-1,3-dimethylbenzene to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

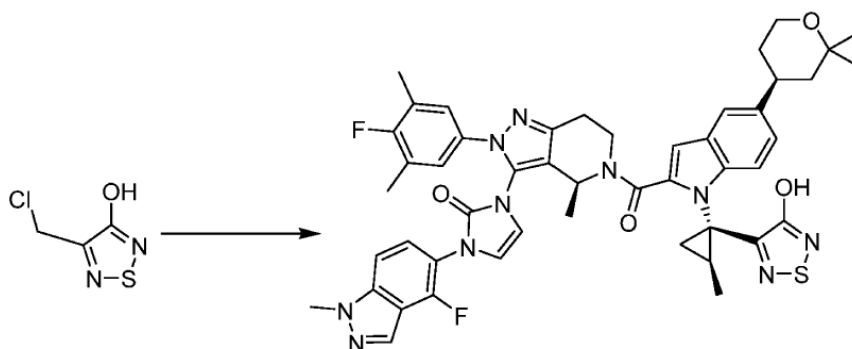
MS m/z (ESI): 915.4[M+1].

Example 37

Step 1: 1-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-(1S,2S)-1-((R)-2-hydroxyl-4-oxocyclopent-2-ene-1-yl)-2-methylcyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-one

Following intermediate A Step 2, 4-(chloromethyl)cyclopentane-1,3-dione was used instead of 2-chloroacetonitrile to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 895.4[M+1].

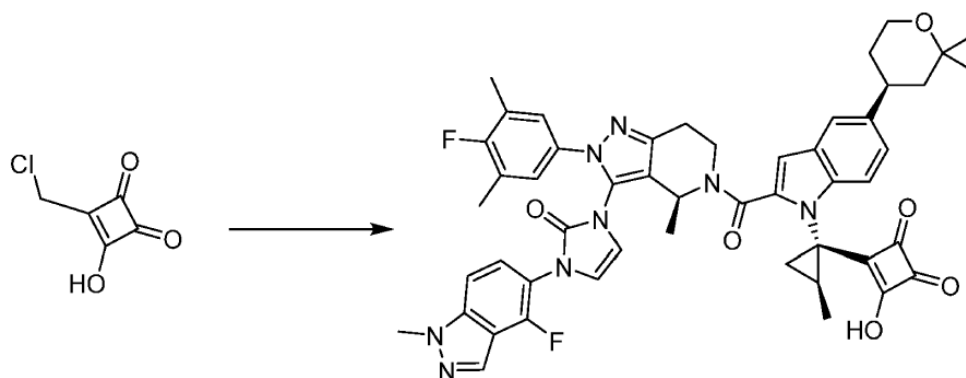
Example 38

Step 1: 1-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-(1S,2S)-1-(4-hydroxyl-1,2,5-thiadiazol-3-yl)-2-methylcyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrano[4,3-c]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-one

Following intermediate A Step 2, 4-(chloromethyl)-1,2,5-thiadiazol-3-ol was used instead of 2-chloroacetonitrile to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 899.4[M+1].

Example 39

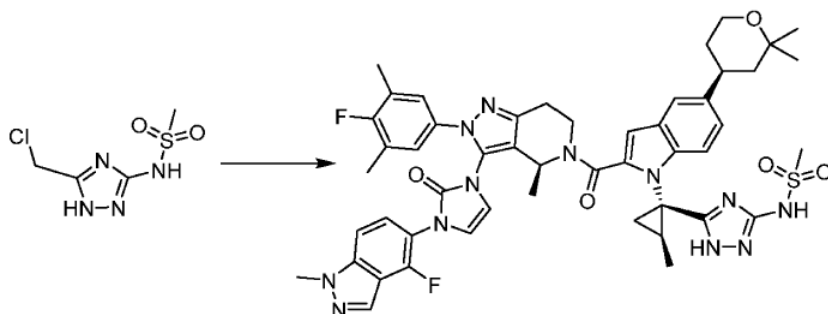


Step 1: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-4-hydroxycyclobut-3-ene-1,2-dione

Following intermediate A Step 2, 3-(chloromethyl)-4-hydroxycyclobut-3-ene-1,2-dione was used instead of 2-chloroacetonitrile to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-one), to synthesize the target product.

MS m/z (ESI): 895.4[M+1].

Example 40



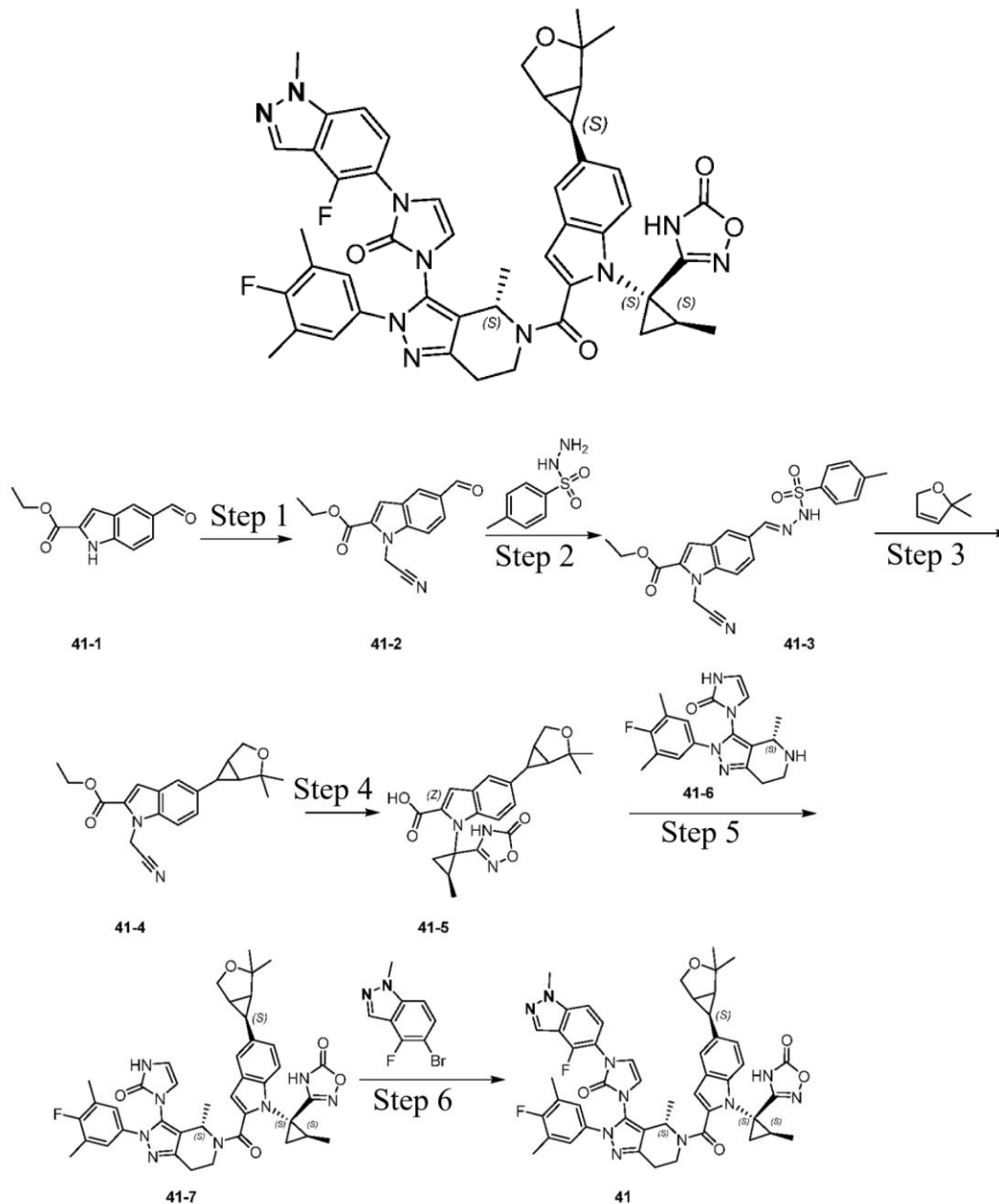
Step 1: N-(5-((1S,2S)-1-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1H-1,2,4-triazol-3-yl)methanesulfonamide

Following intermediate A Step 2, N-(5-(chloromethyl)-1H-1,2,4-triazol-3-yl)methanesulfonamide was used instead of 2-chloroacetonitrile to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 959.4[M+1].

Example 41

3-((1S,2S)-1-(5-(((6S)-2,2-dimethyl-3-oxabicyclo[3.1.0]hexan-6-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazole



Step 1

Ethyl 1-(cyanomethyl)-5-formyl-1H-indole-2-carboxylate

Following the synthesis conditions for intermediate **A** Step 2, the title product ethyl 1-(cyanomethyl)-5-formyl-1H-indole-2-carboxylate **41-2** was obtained,

MS m/z(ESI):257.1 [M+1].

Step 2

Ethyl (E)-1-(cyanomethyl)-5-((2-toluenesulfonylhydrazono)methyl)-1H-indole-2-carboxylate

A mixture of ethyl 1-(cyanomethyl)-5-formyl-1H-indole-2-carboxylate **41-2** (3.2 g, 12.5 mmol), 4-methylbenzenesulfonhydrazide (2.33 g, 12.5 mmol), and tetrahydrofuran (50 mL) were stirred at room temperature for 12 hours, and concentrated under reduced pressure to dryness after the completion of reaction, and the crude product was used directly in the next step, to obtain the title product ethyl (E)-1-(cyanomethyl)-

5-((2-toluenesulfonylhydrazono)methyl)-1H-indole-2-carboxylate **41-3** (5.7 g, crude)

MS m/z(ESI):425.1 [M+1].

Step 3

Ethyl 1-(cyanomethyl)-5-(2,2-dimethyl-3-oxabicyclo[3.1.0]hexan-6-yl)-1H-indole-2-carboxylate

To a solution of ethyl (E)-1-(cyanomethyl)-5-((2-toluenesulfonylhydrazono)methyl)-1H-indole-2-carboxylate **41-3** (5.7 g, 13.44 mmol) in tetrahydrofuran (50 mL), sodium hydride (60%, 538 mg, 13.44 mmol) was added, stirred at 60°C for 1 hour, cooled, and filtered, and the filtrate was concentrated under reduced pressure to dryness to obtain a residue. The residue was dissolved using dichloromethane (20 mL), then added dropwise to a solution of 2,5-dihydro-2,2-dimethylfuran (1.32 g, 13.44 mmol) and zinc iodide (41 mg, 0.13 mmol) in dichloromethane (15 mL), and stirred at room temperature for 1 hour, and water was added, followed by extraction with dichloromethane (50 mL * 3). The resulting organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and then separated by column chromatography to obtain the title product ethyl 1-(cyanomethyl)-5-(2,2-dimethyl-3-oxabicyclo[3.1.0]hexan-6-yl)-1H-indole-2-carboxylate **41-4** (900 mg), yield: 19.8%

MS m/z (ESI): 339.2 [M+1].

Step 4

5-(2,2-dimethyl-3-oxabicyclo[3.1.0]hexan-6-yl)-1-((2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid

Following the synthesis conditions for intermediate **A**, the title product 5-(2,2-dimethyl-3-oxabicyclo[3.1.0]

hexan-6-yl)-1-((2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid **41-5**, was obtained,

MS m/z (ESI):410.1 [M+1].

Step 5

5 3-(((1S,2S)-1-(5-(((6S)-2,2-dimethyl-3-dimethyl-3-oxabicyclo3.1.1.0]hexan-6-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1-imidazol-1-yl)-4,5,6,6,7-tetrahydro-2-pyrazolyl-4,3-c]pyridine-5-carbonyl-1-benzyl-1-yl-4,3-pyridine-5-carbonyl)-1-1-1-ethenyl-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10 Following the synthesis conditions for intermediate E, the title product 3-(((1S,2S)-1-(5-(((6S)-2,2-dimethyl-3-dimethyl-3-oxabicyclo3.1.1.0]hexan-6-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1-imidazol-1-yl)-4,5,6,6,7-tetrahydro-2-pyrazolyl-4,3-c]pyridine-5-carbonyl-1-benzyl-1-yl-4,3-pyridine-5-carbonyl)-1-1-1-ethenyl-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one **41-6** was obtained,

MS m/z (ESI):733.3 [M+1].

15 Step 6

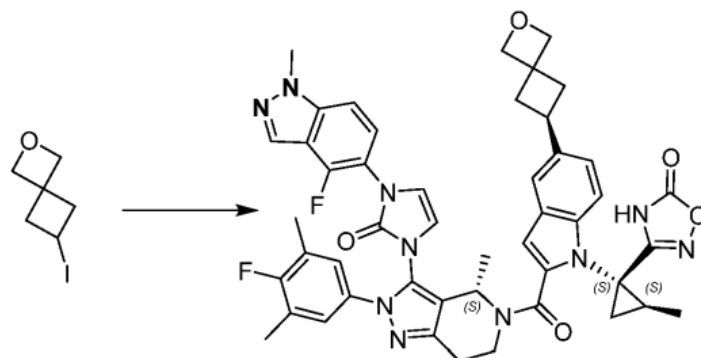
3-(((1S,2S)-1-(5-(((6S)-2,2-dimethyl-3-oxabicyclo[3.1.0]hexan-6-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazole

20 Following the synthesis conditions for Example 1, followed by chiral resolution, the title product 3-(((1S,2S)-1-(5-(((6S)-2,2-dimethyl-3-oxabicyclo[3.1.0]hexan-6-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazole **41** was obtained

MS m/z (ESI):881.4 [M+1].

25

Example 42

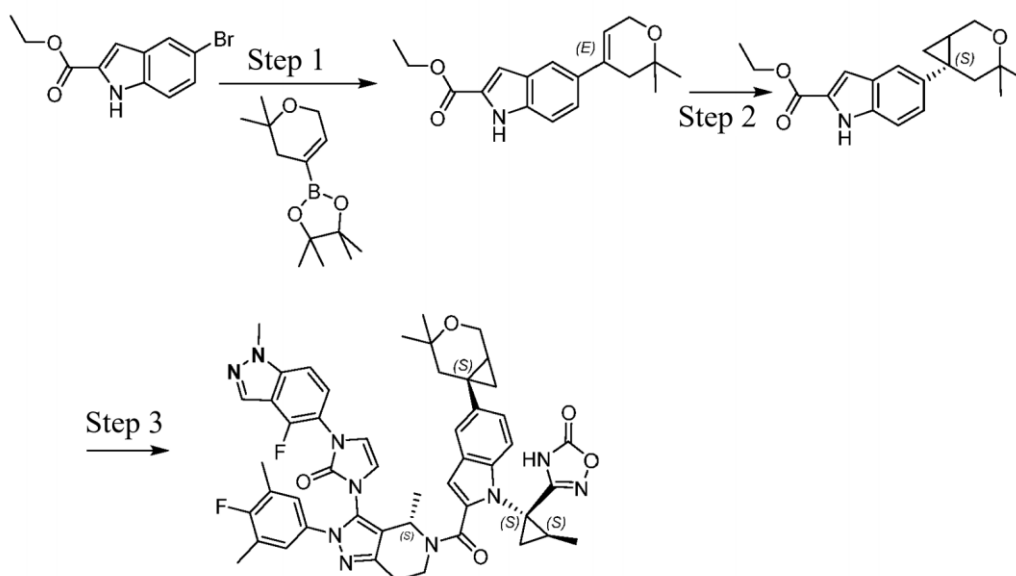


Step 1: 3-((1S,2S)-1-(2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-5-(2-oxaspiro[3.3]heptan-6-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate A Step 1, 6-iodo-2-oxaspiro[3.3]heptane was used instead of 4-iodo-2,2-dimethyltetrahydropyran to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 867.4[M+1].

Example 43



Step 1: ethyl 5-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-1H-indole-2-carboxylate

Ethyl 5-bromo-1H-indole-2-carboxylate (0.3 g, 1.12 mmol), 2-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (266.46 mg, 1.12 mmol) and sodium carbonate (355.79 mg, 3.36 mmol) were dissolved in 1,4-dioxane (12 mL) and water (4 mL),

and under nitrogen protection, bis(triphenyl)palladium dichloride (39.27 mg, 55.95 μmol) was added. The mixture was reacted under stirring at 90°C for 5 hours. To the mixture, saturated brine (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (30 mL $\times$ 2). The organic phases were combined, washed with saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the target product (0.28 g, yield 84%).

MS m/z(ESI): 300.2[M+1].

Step 2: ethyl 5-((6S)-4,4-dimethyl-3-oxabicyclo[4.1.0]heptan-6-yl)-1H-indole-2-carboxylate

Trimethylsulfoxonium iodide (617.51 mg, 2.81 mmol) was dissolved in dimethyl sulfoxide (10 mL), and under nitrogen protection, sodium hydride (112.23 mg, 2.81 mmol, 60%w/w) was added. The mixture was reacted under stirring at 25°C for 1 hours. Then, at 0°C, ethyl 5-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (0.28 g, 935.32 μmol) was added. The mixture was reacted under stirring at 25°C for 12 hours. To the mixture, saturated brine (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (30 mL $\times$ 2). The organic phases were combined, washed with saturated brine (30 mL $\times$ 5), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the target product (0.13 g, yield 44%). The product was chirally separated to obtain ethyl 5-((6S)-4,4-dimethyl-3-oxabicyclo[4.1.0]heptan-6-yl)-1H-indole-2-carboxylate (46 mg)

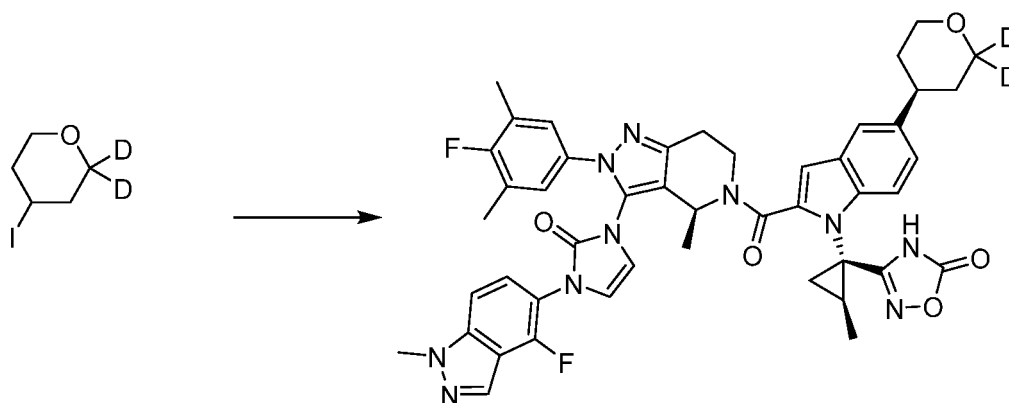
MS m/z(ESI): 314.2[M+1].

Step 3: 3-((1S,2S)-1-(5-((6S)-4,4-dimethyl-3-oxabicyclo[4.1.0]heptan-6-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate A Step 2, ethyl 5-((6S)-4,4-dimethyl-3-oxabicyclo[4.1.0]heptan-6-yl)-1H-indole-2-carboxylate was used instead of ethyl (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 895.4[M+1].

Example 44

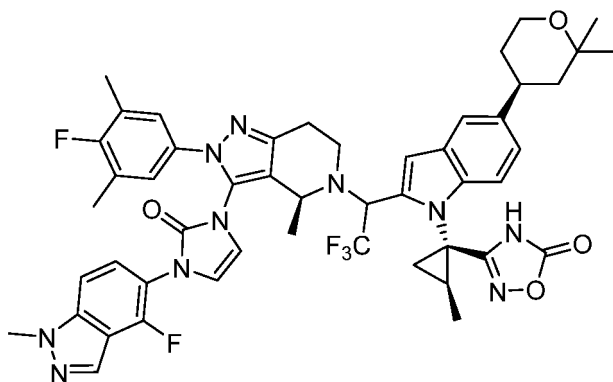


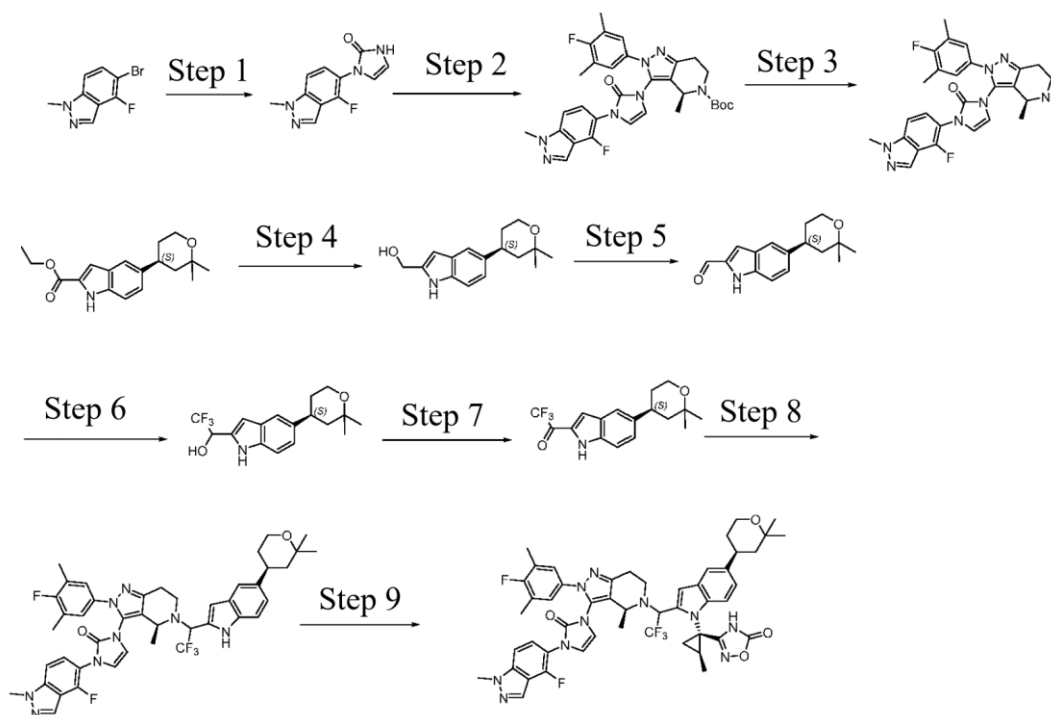
Step 1: 3-((1S,2S)-1-(2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S-tetrahydro-2H-pyran-4-yl-2,2-d₂)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate A Step 1, 4-iodotetrahydro-2H-pyran-2,2-d₂ was used instead of 4-iodo-2,2-dimethyltetrahydropyran to synthesize an intermediate, then following intermediate E and Example 1, (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 857.4[M+1].

Example 45





Step 1: 1-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-one

At room temperature, 5-bromo-4-fluoro-1-methyl-1H-indazole (2.29 g, 10 mmol), 1,3-dihydro-2H-imidazol-2-one (0.84 g, 10 mmol), cuprous iodide (1.91 g, 10 mmol), potassium phosphate (3.92 g, 20 mmol) and N,N,N',N'-tetramethylethylenediamine (1.16 g, 10 mmol) were dissolved in toluene (30 mL), subjected to nitrogen replacement, heated to reflux for 24 hours, cooled to room temperature, and filtered, the filter residue was washed with ethyl acetate (30 mL), the organic phase was washed with saturated brine (20 mL × 2), dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified with Flash column (dichloromethane : methanol = 20 : 1), to obtain 1-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-one (1.28 g, yield: 55%)

MS m/z (ESI): 233.1[M+H]⁺.

Step 2: tert-butyl (S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

At room temperature, 1-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-one (1.28 g, 5.5 mmol), tert-butyl (S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (2.41 g, 5.5 mmol), cuprous iodide (1.05 g, 5.5 mmol), potassium phosphate (2.16 g, 11 mmol), and N,N,N',N'-tetramethylethylenediamine (0.64 g, 5.5 mmol) were dissolved in toluene (30 mL),

subjected to nitrogen replacement, heated to reflux for 24 hours, cooled to room temperature, and filtered, the filter residue was washed with ethyl acetate (20 mL), the organic phase was washed with saturated brine (20 mL × 2), organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified by Flash column (dichloromethane : methanol = 20 : 1), to obtain tert-butyl (S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.26 g, yield:39%)

MS m/z(ESI): 590.2[M+H]⁺.

Step 3: (S)-1-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

At room temperature, tert-butyl (S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (1.26 g, 2.15 mmol) was dissolved in dichloromethane (25 mL), and then trifluoroacetic acid (6 mL) was added, and stirred for 2 hours at room temperature, with LCMS indicating the completion of the reaction, followed by spin-drying; the residue was dissolved in ethyl acetate (30 mL), then washed with a saturated sodium bicarbonate solution (15 mL × 2) and saturated brine (20 mL × 2), successively; and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, to obtain (S)-1-(4-fluoro-1-methyl-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one (1.0 g, yield:95%)

MS m/z (ESI): 490.2[M+H]⁺.

Step 4: (S)-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanol

Under an ice bath, ethyl (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (3.01 g, 10 mmol) was dissolved in tetrahydrofuran (30 mL), followed by nitrogen replacement; then lithium aluminum hydride (0.76 g, 20 mmol) was slowly added, and stirred in the ice bath for 2 hours, with LCMS indicating the completion of the reaction; the reaction solution was quenched with ethyl acetate (50 mL) and then washed with saturated brine; the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified with Flash column (eluting with petroleum ether : ethyl acetate = 10 : 1 - 3 : 1), to obtain (S)-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanol (2.07 g, yield: 80%)

MS m/z(ESI): 260.2[M+H]⁺.

Step 5: (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carbaldehyde

At room temperature, (S)-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanol (2.07 g, 8 mmol) was dissolved in dichloromethane (30 mL),

then Dess-Martin (6.78 g, 16 mmol) was added and stirred at room temperature for 2 hours, with LCMS indicating the completion of the reaction; the reaction solution was quenched with a saturated sodium bicarbonate solution (30 mL), then extracted with dichloromethane (25 mL × 3); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified with Flash column (eluting with petroleum ether : ethyl acetate = 10 : 1 - 5 : 1), to obtain (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carbaldehyde (1.64 g, yield: 80%)

MS m/z (ESI): 258.2[M+H]⁺.

Step 6: 1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethan-1-ol

At room temperature, (S)-5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indole-2-carbaldehyde (1.64 g, 6.4 mmol) was dissolved in N,N-dimethylformamide (20 mL), and then potassium carbonate (1.77 g, 12.8 mmol) and trifluoromethyltrimethylsilane (1.82 g, 12.8 mmol) were added and stirred overnight at room temperature, with LCMS indicating the completion of the reaction; the reaction solution was quenched with water (20 mL), and then extracted with ethyl acetate (15 mL × 3); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and spin-dried to obtain 1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethan-1-ol (1.51 g, yield: 72%)

MS m/z (ESI): 328.1[M+H]⁺.

Step 7: (S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethan-1-one

At room temperature, 1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethan-1-ol (1.51 g, 4.61 mmol) was dissolved in dichloromethane (30 mL), and then Dess-Martin (2.93 g, 6.92 mmol) was added and stirred at room temperature for 3 hours, with LCMS indicating the completion of the reaction; the reaction solution was quenched with a saturated sodium bicarbonate solution (30 mL) and then extracted with dichloromethane (25 mL × 3); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered and spin-dried, and the residue was purified with Flash column (eluting with petroleum ether : ethyl acetate = 10 : 1 - 5 : 1), to obtain (S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethan-1-one (1.23 g, yield: 82%).

MS m/z (ESI): 326.1[M+H]⁺.

Step 8: 1-((4S)-5-(1-(5-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethoxy)-2-(4-fluoro-3,5,3-dimethylphenyl)-4-methyl-4,5,5,6,6,7-tetrahydro-2-dihydro-4-pyrazolyl-4,3-c)pyridin-3-yl)-3-yl)-3-(4-fluoro-1-methyl-1,1-dihydro-3-dihydro-1,1,1,1-tetrahydro-3-dihydro-1,1,1,1,2H-imidazol-2-one

At room temperature, (S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-trifluoroethan-1-one (1.23 g, 3.78 mmol) and (S)-1-(4-fluoro-1-methyl-1H-indol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one (2.03 g, 4.16 mmol) were dissolved in tetrahydrofuran (20 mL); then tetraisopropyl titanate (2.15 g, 7.56 mmol) was added, heated to 60°C and reacted for 2 hours, and cooled to 0°C; then sodium borohydride (0.29 g, 7.56 mmol) was added and stirred at room temperature for 2 hours; then the reaction solution was poured into ammonia water, with a solid precipitating out, and filtered; the filter residue was washed with ethyl acetate and subjected to liquid-liquid separation; the organic phase was washed with a saturated sodium bicarbonate solution and saturated brine, successively; and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified with Flash column (eluting with petroleum ether : ethyl acetate = 10 : 1 - 1 : 1), to obtain 1-((4S)-5-(1-(5-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-fluorofluorofluoroethyl)-2-(4-fluoro-3,5,3-dimethylphenyl)-4-methyl-4,5,5,6,6,7-tetrahydro-2-dihydro-4-pyrazolyl-4,3-c]pyridin-3-yl)-3-(4-fluoro-1-methyl-1,1-dihydro-3-dihydro-1,1,1,1,4-dihydro-3-dihydro-1,1,1,1,2H-imidazol-2-one (1.27 g, yield: 42%).

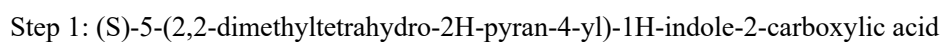
MS m/z (ESI): 799.3[M+H]⁺.

Step 9: 3-(((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(2,2,2-trifluoro-1-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3]pyridin-5-yl)ethyl)-1H-indolyl)-1-yl)-2-yl)-2-methylcyclopropyl)-1,1,2,4-oxadiazol-5(4H)-one

1-((4S)-5-(1-(5-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)-2,2,2-fluorofluorofluoroethyl)-2-(4-fluoro-3,5,3-dimethylphenyl)-4-methyl-4,5,5,6,6,7-tetrahydro-2-dihydro-4-pyrazolyl-4,3-c]pyridin-3-yl)-3-(4-fluoro-1-methyl-1,1-dihydro-3-dihydro-1,1,1,1,4-dihydro-3-dihydro-1,1,1,1,2H-imidazol-2-one was used as a raw material, following intermediate A Steps 2, 3, and 4, to obtain 3-(((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(2,2,2-trifluoro-1-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3]pyridin-5-yl)ethyl)-1H-indolyl)-1-yl)-2-yl)-2-methylcyclopropyl)-1,1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 937.4[M+H]⁺.

Example 46



5

Step 2: ((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-
ridin-5-yl(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indazol-2-yl)methanone

10

following Example intermediate D Step 3, ((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanone was obtained.

MS m/z(ESI): 593.2[M+H]⁺.

Step 3: ((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanethione

At room temperature, ((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanone (2.97 g, 5 mmol) was dissolved in toluene (30 mL), and then a Lawesson reagent (1.01 g, 2.5 mmol) was added, heated to reflux for 14 hours, cooled to room temperature and filtered; the filter residue was washed with ethyl acetate; the organic phase was washed with a saturated sodium bicarbonate solution and saturated brine, successively, dried over anhydrous sodium sulfate, filtered, and spin-dried; and the residue was separated by Flash column chromatography (PE : EA = 2 : 1), to obtain ((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanethione (1.52 g, yield: 42%).

MS m/z(ESI): 609.2[M+H]⁺.

Step 4: 2-(2-(((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-0]pyridine-5-thiocarbonyl)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)acetonitrile

((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-2-yl)methanethione was used as a raw material, following Example intermediate A Step 2, to obtain 2-(2-(((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-thiocarbonyl)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)acetonitrile.

MS m/z(ESI): 648.2[M+H]⁺.

Step 5: 2-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2Hpyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)acetonitrile

1-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,3-dihydro-2H-imidazol-2-one and 2-(2-(((S)-3-bromo-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-thiocarbonyl)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)acetonitrile were used as raw materials,

Following Example 45 Step 1, 2-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazole[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)acetonitrile was obtained.

MS m/z (ESI): 800.3[M+H]⁺.

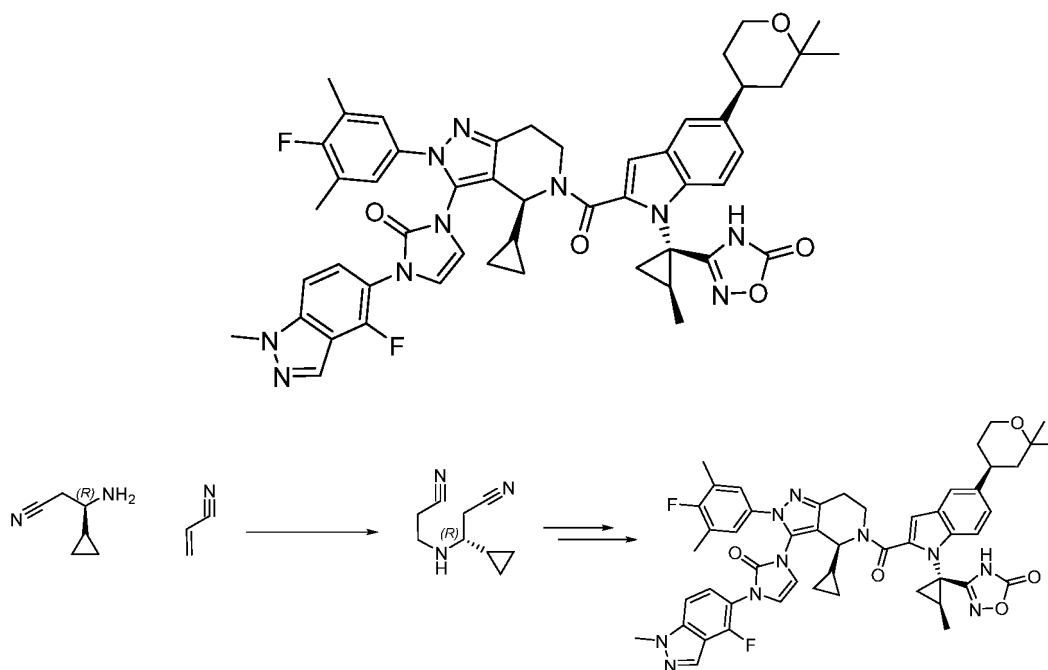
5 Step 6: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyran[4,3]pyridine-5-carbonyl)-1H-indol)-2-methylcyclopropyl)-1,2,2,4-oxadiazol-5(4H)-one

2-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)acetonitrile was used as a raw material, following intermediate A Step 3 and Step 4, to obtain 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyran[4,3]pyridine-5-carbonyl)-1H-indol)-2-methylcyclopropyl)-1,2,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 899.4[M+H]⁺.

Example 47

3-((1S,2S)-1-(2-(((S)-4-cyclopropyl-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2-dimethylphenol-3,3-pyridine-5-carbonyl)-5-5-5-5-(S)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: (R)-3-((2-cyanoethyl)amino)-3-cyclopropylpropanenitrile

In a 250 mL reaction bottle, (R)-3-amino-3-cyclopropylpropanenitrile (10.0 g, 90.78 mmol) was dissolved in ethanol (50.0 mL), and then triethylamine (11.02 g, 108.93 mmol) and acrylonitrile (5.78 g, 108.93 mmol) were added, and the reaction solution was stirred at 70°C for 3 hours. The reaction was stopped, cooled to room temperature, and concentrated to obtain the title product (R)-3-((2-cyanoethyl)amino)-3-cyclopropylpropanenitrile (21.0 g), yield: 87.8%.

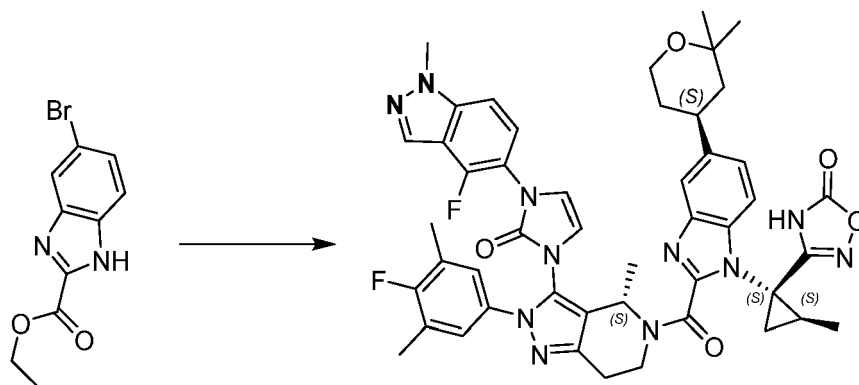
MS *m/z* (ESI): 164.1[M+1].

Step 2: 3-((1S,2S)-1-(2-(((S)-4-cyclopropyl-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydrodihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2-dimethylphenol-3,3-pyridine-5-carbonyl-5-5-5-(S)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(R)-3-((2-cyanoethyl)amino)-3-cyclopropylpropanenitrile was used as a raw material, following Example 1, to obtain the product 3-((1S,2S)-1-(2-(((S)-4-cyclopropyl-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydrodihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2-dimethylphenol-3,3-pyridine-5-carbonyl-5-5-5-(S)-5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

MS *m/z* (ESI): 909.3[M+1].

Example 48



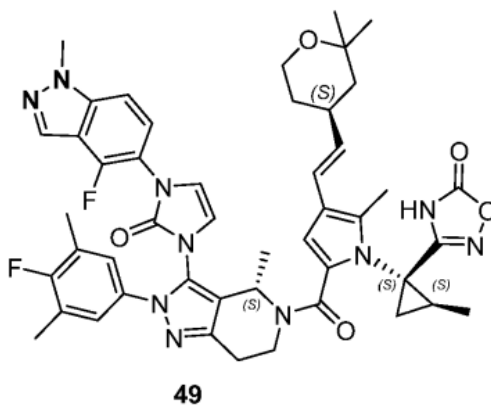
Step 1: 3-((1S,2S)-1-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-benzo[d]imidazol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

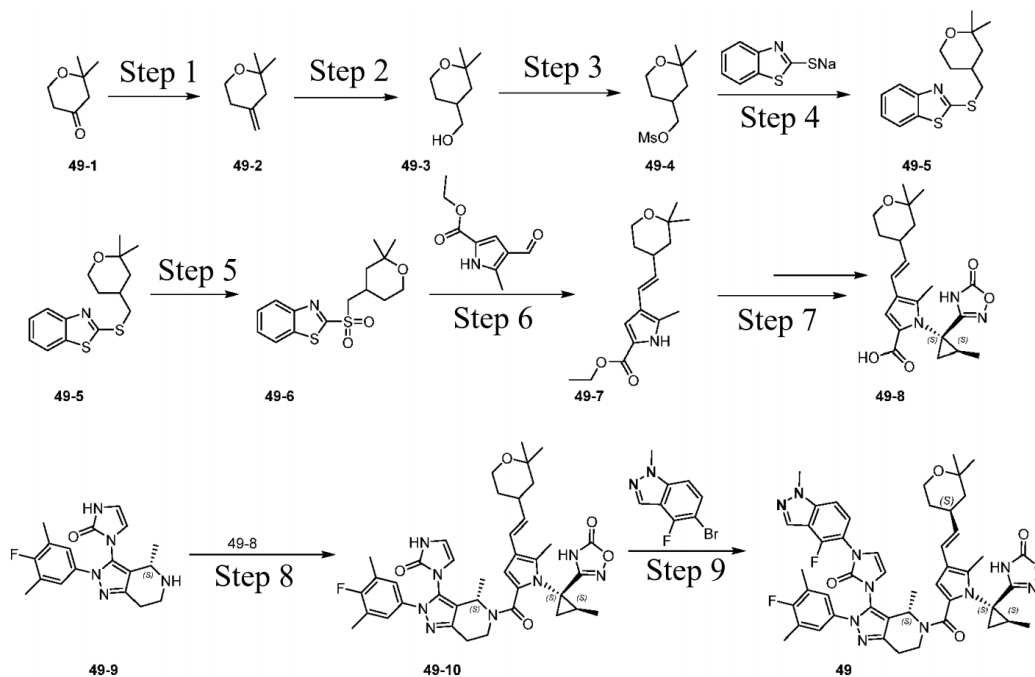
Following intermediate A Step 1, ethyl 5-bromo-1H-benzo[d]imidazol-2-carboxylate was used instead of ethyl 5-bromoindole-2-carboxylate to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 884.4[M+1].

Example 49

3-((1S,2S)-1-(3-((E)-2-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-2-methyl-1H-pyrrole-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one





Step 1

2,2-dimethyl-4-methylenetetrahydro-2H-pyran

To a solution of methyltriphenylphosphonium bromide (27.9 g, 78.13 mmol) in dimethyl sulfoxide (300 mL) was added potassium tert-butoxide (8.75 g, 78.13 mmol) and stirred at room temperature for 1 hour, and then 2,2-dimethyltetrahydro-4H-pyran-4-one **49-1** (5 g, 39.06 mmol) was added at 80°C, stirred for 12 hours, added with water, and extracted with dichloromethane; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and then separated by column chromatography, to obtain the title product 2,2-dimethyl-4-methylenetetrahydro-2H-pyran **49-2** (3.5 g), yield: 71%

MS m/z (ESI): 127.1[M+1].

Step 2

(2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol

To a solution of 2,2-dimethyl-4-methylenetetrahydro-2H-pyran **49-2** (3.5 g, 27.78 mmol) in tetrahydrofuran (50 mL), borane-tetrahydrofuran solution (55.6 mL, 55.6 mmol, 1M) was added dropwise, then stirred at 70°C for 1 hour, cooled, and fed with methanol for quenching; then an aqueous sodium hydroxide solution (2N, 27.8 mL) and a hydrogen peroxide solution (30%, 12 mL) were added dropwise, stirred at room temperature for 2 hours, fed with water, and extracted with dichloromethane; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and then separated by column chromatography, to obtain the title product (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol **49-3** (2.7 g), yield: 67%

MS m/z (ESI): 145.1[M+1].

Step 3

(2,2-dimethyltetrahydro-2H-pyran-4-yl)methylmethanesulfonate

In a 25 mL reaction bottle, (2,2-dimethyltetrahydro-2H-pyran-4-yl)methanol **49-3** (2.7 g, 18.75 mmol), and triethylamine (3.8 g, 37.5 mmol) were dissolved in dichloromethane (50 mL), and then methanesulfonyl chloride (3.2 g, 28.13 mmol) was added dropwise, and the reaction solution was stirred at room temperature for 3 hours. The reaction was stopped, and water (50 mL) was added to quench the reaction, followed by extraction with dichloromethane (50 mL × 3); and the organic phases were combined, washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to dryness, to obtain the title product (2,2-dimethyltetrahydro-2H-pyran-4-yl)methylmethanesulfonate **49-4** (3 g, crude).

MS m/z (ESI): 223.1 [M+1].

Step 4

2-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)thio)benzo[d]thiazole

A mixture of 2,2-dimethyltetrahydro-2H-pyran-4-yl)methylmethanesulfonate **49-4** (3 g, 13.51 mmol), sodium mercaptobenzo[thiazole (5.1 g, 27.02 mmol), toluene (50 mL), and water (20 mL) were stirred at 80°C for 12 hours, cooled, fed with water, and extracted with dichloromethane; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and then separated by column chromatography, to obtain the title product 2-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)thio)benzo[d]thiazole **49-5** (1.4 g), yield: 35%

MS m/z (ESI): 294.1 [M+1].

Step 5

2-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)sulfonyl)benzo[d]thiazole

To a solution of 2-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)thio)benzo[d]thiazole **49-5** (1.4 g, 4.77 mmol) in dichloromethane (15 mL) was added m-chloro benzoyl hydroperoxide (1.6 g, 9.56 mmol), then stirred at room temperature overnight, fed with an aqueous saturated sodium hydroxide solution and extracted with dichloromethane; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and then separated by column chromatography, to obtain the title product 2-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)sulfonyl)benzo[d]thiazole **49-6** (1.1 g), yield: 71%

MS m/z (ESI): 326.1 [M+1].

Step 6

Ethyl (E)-4-(2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-methyl-1H-pyrrole-2-carboxylate

To a solution of 2-(((2,2-dimethyltetrahydro-2H-pyran-4-yl)methyl)sulfonyl)benzo[d]thiazole **49-6** (1.1 g, 3.38 mmol) in tetrahydrofuran (15 mL) at -40°C, lithium bis(trimethylsilyl)amide (6.8 mL, 6.8 mmol, 1M) was added dropwise, and

stirred for 0.5 hours, then ethyl 4-formyl-5-methyl-1H-pyrrole-2-carboxylate (612 mg, 3.38 mmol) was added and continued to stir for 2 hours; then aqueous saturated ammonium chloride solution was added for quenching, and extracted with dichloromethane; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and then separated by column chromatography, to obtain the title product ethyl (E)-4-(2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-methyl-1H-pyrrole-2-carboxylate **49-7** (400 mg), yield: 41%

MS m/z (ESI): 292.2 [M+1].

Step 7

4-((E)-2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-methyl-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-pyrrole-2-carboxylic acid

Following the synthesis conditions for intermediate A, the title product 4-((E)-2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-methyl-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-pyrrole-2-carboxylic acid **49-8** was obtained

MS m/z (ESI): 402.2[M+1].

Step 8

3-((1S,2S)-1-(3-((E)-2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-2-methyl-1H-pyrrole-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following the synthesis conditions for intermediate E, the title product 3-((1S,2S)-1-(3-((E)-2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-2-methyl-1H-pyrrole-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one **49-10** was obtained

MS m/z (ESI): 725.3[M+1].

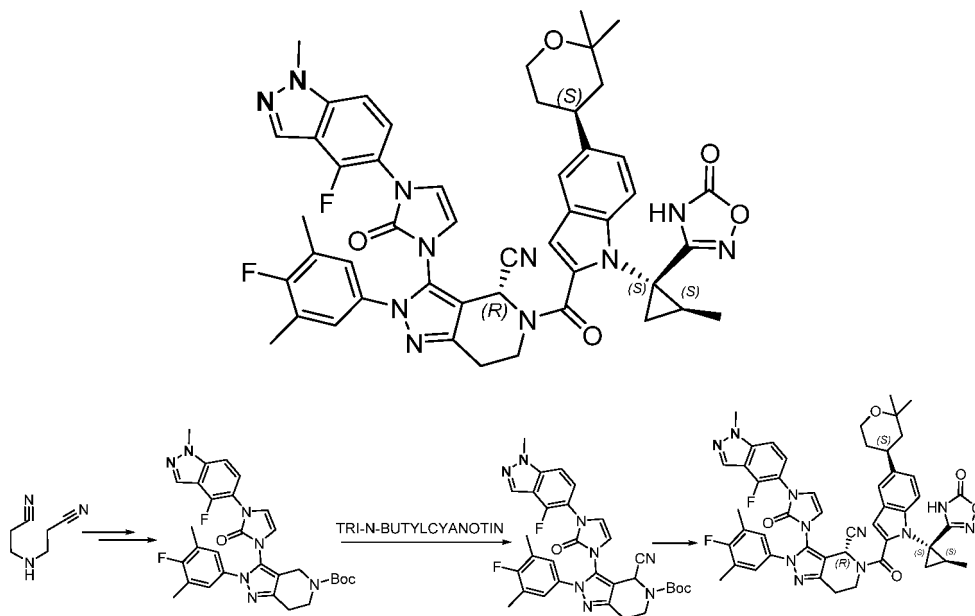
Step 9

3-((1S,2S)-1-(3-((E)-2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-2-methyl-1H-pyrrole-1-yl)2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following the synthesis conditions for Example 1, followed by chiral resolution, the title product 3-((1S,2S)-1-(3-((E)-2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)ethenyl)-5-(S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-2-methyl-1H-pyrrole-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one **49** was obtained

MS m/z (ESI): 873.4[M+1].

Example 50



Step 1: tert-butyl 3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

3,3'-iminodipropenenitrile was used as a raw material, following Example 1, to obtain the product tert-butyl 3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

MS m/z (ESI): 576.2[M+1].

Step 2: tert-butyl 4-cyano-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

In a 50 mL reaction bottle, tert-butyl 3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (100 mg, 173.73 μ mol), and 4 Å MS (molecular sieves, 120 mg) were dissolved in dichloromethane (2 mL), and

then 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (43.38 mg, 191.10 μmol) was added batchwise, and the reaction solution was stirred at 25°C for 1 hour. Then tributyltin cyanide ((n-Bu)₃SnCN) (137.28 mg, 434.31 μmol) was added dropwise, and the reaction solution was stirred at 25°C for 1 hour. The reaction was stopped, an aqueous sodium bicarbonate solution (2 mL) was added to quench the reaction, followed by extraction with dichloromethane (2 mL $\times$ 2); and the organic phases were combined, washed with saturated sodium chloride (2 mL), dried over anhydrous sodium sulfate, and filtered, and the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate, and then resolved to obtain the title product tert-butyl 4-cyano-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (60 mg), yield: 57.5%.

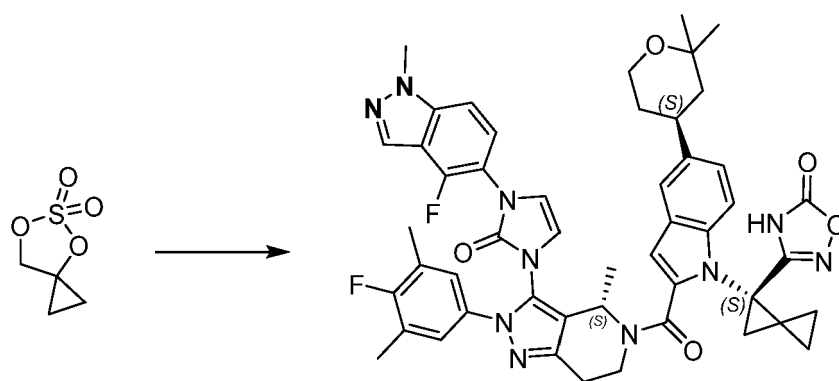
MS m/z (ESI): 601.2 [M+1].

Step 3: (R)-5-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-3-(3-(3-fluoro-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,6,7-tetrahydro-2Hpyrazolo[4,3-pyrazole]

tert-butyl 4-cyano-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate was used as a raw material, following Example 1, to obtain the product (R) 5-(5-(((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-3-(3-(3-fluoro-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,6,7-tetrahydro-2Hpyrazolo[4,3-pyrazole].

MS m/z (ESI): 894.3 [M+1].

Example 51



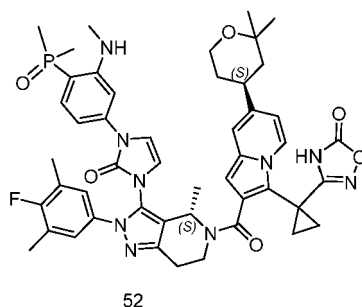
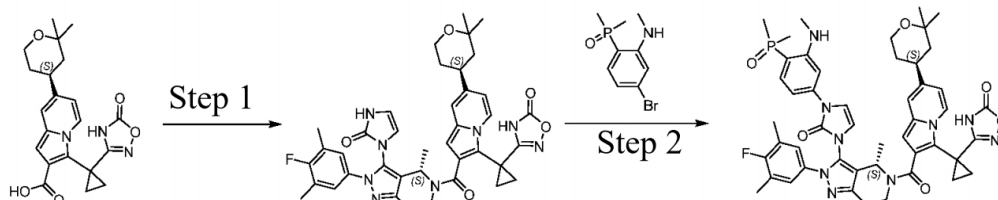
Step 1: 3-((S)-1-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-3-(3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-1H-indol-1-yl)spiro[2.2]pentan-1-yl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate A Step 3, 4,6-dioxa-5-thiaspiro[2.4]heptane-5,5-dioxide was used instead of (4R)-4-methyl-1,3,2-dioxathiolane-2,2-dioxide to synthesize an intermediate, then following intermediate E and Example 1 (5-bromo-4-fluoro-1-methyl-1H-indazole was used instead of ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione), to synthesize the target product.

MS m/z (ESI): 895.4[M+1].

Example 52

3-(1-(2-((S)-3-(3-(4-(dimethylphospholano)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid was used as a raw material, following the step 3 for intermediate C and intermediate D to obtain the product.

MS m/z (ESI): 721.3 [M+1].

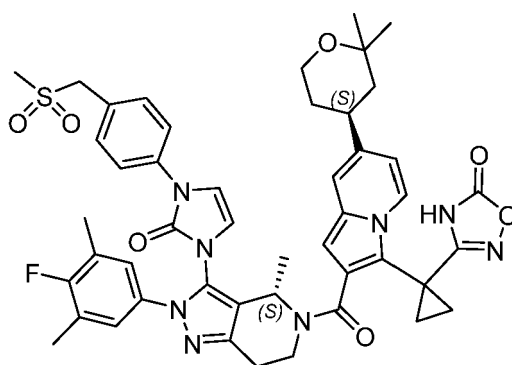
Step 2: 3-(1-(2-((S)-3-(3-(4-(dimethylphospholano)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-2-(methylamino)phenyl)dimethylphosphine oxide was used, following Example 1, to obtain the target product.

MS m/z (ESI): 902.4[M+1].

Example 53

3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(4-((methylsulfonyl)methyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

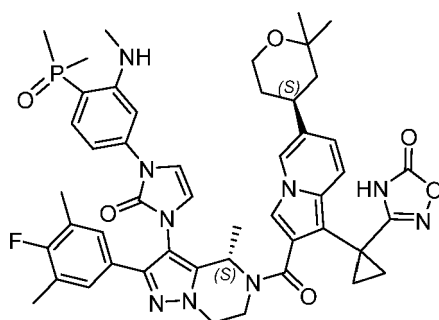


53

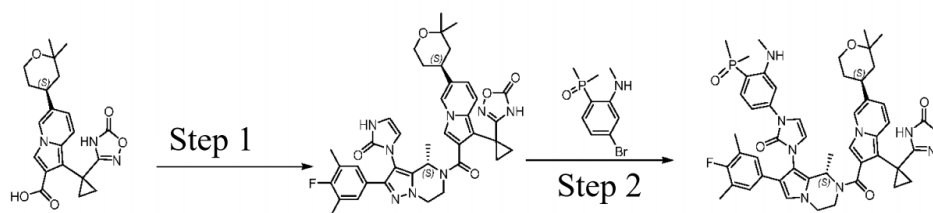
1-Bromo-4-((methylsulfonyl)methyl)benzene and 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 889.4 [M+1].

Example 54



54



Step 1: 3-(1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-5-carbonyl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(S)-6-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid was used as a raw material, following step 3 for intermediate C and intermediate D to obtain the product.

MS m/z (ESI): 721.3[M+1].

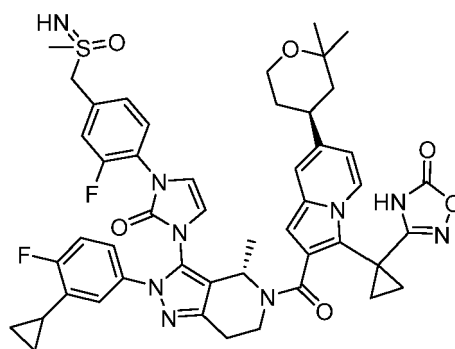
Step 2: 3-(1-(2-((S)-8-(3-(4-(dimethylphospholano)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-7-(4-fluoro-3,5-dimethylphenyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-2-carbonyl)-6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 1, the target product was obtained

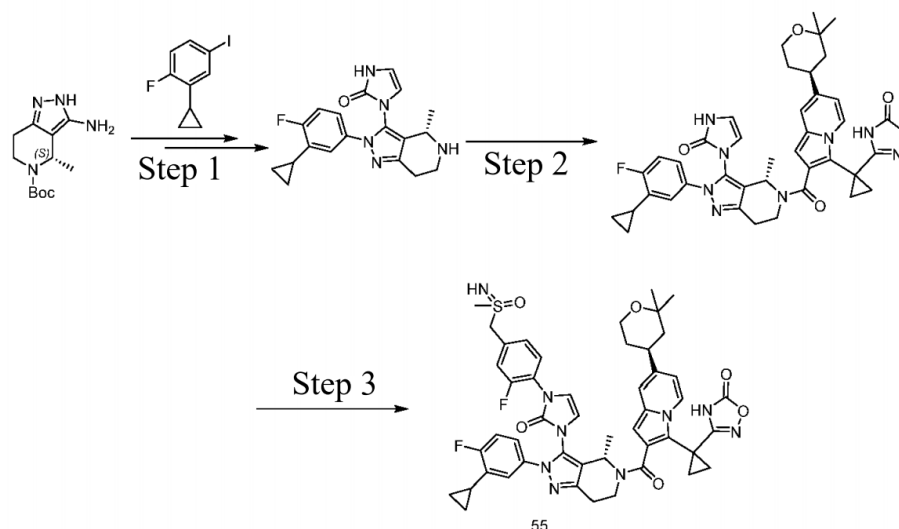
MS m/z (ESI): 902.3 [M+1].

Example 55

3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-4-((S-methylsulfonimidoyl)methyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



55



Step 1: (S)-1-(2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

tert-Butyl (S)-3-amino-4-methyl-6,7-dihydro-2H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate and 2-cyclopropyl-1-fluoro-4-iodobenzene were used as raw materials, following intermediate B, to obtain the product.

MS m/z (ESI): 354.2 [M+1].

Step 2: 3-(1-(2-((S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

The product was obtained by following the step 3 for intermediate C and intermediate D.

MS m/z (ESI): 733.3 [M+1].

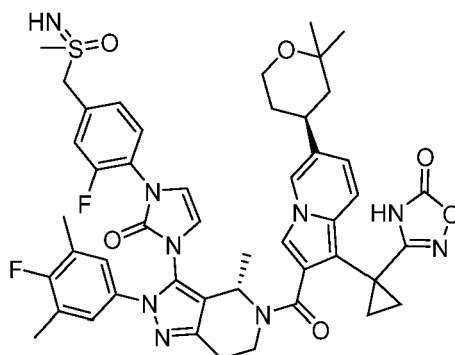
Step 3: 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-4-((S-methylsulfonimidoyl)methyl)phenyl)-2-carboxyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-3-fluorobenzyl)(imino)(methyl)-16aminosulfanone was used as a raw material, following Example 1 to obtain the target product.

MS m/z (ESI): 918.4 [M+1].

Example 56

3-(1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-((S-methylsulfonimidoyl)methyl)phenyl)-2-carboxyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



56

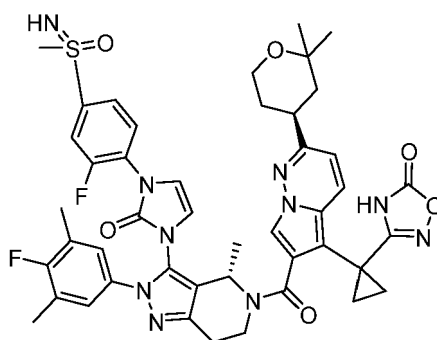
(4-bromo-3-fluorobenzyl)(imino)(methyl)-16aminosulfanone was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI):906.3 [M+1].

5

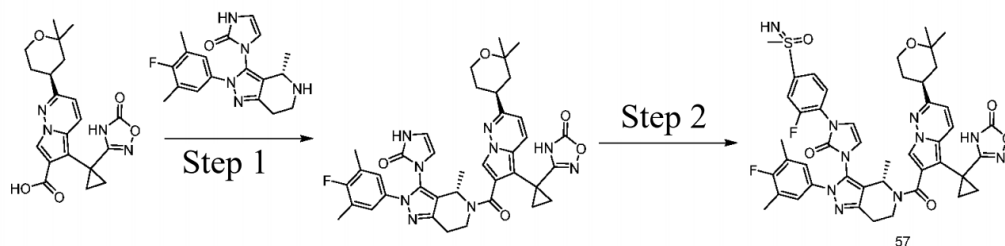
Example 57

3-(1-(2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-6-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(2-fluoro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)pyrrolo[1,2-b]pyridazin-5-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



57

10



Step 1: 3-(1-(2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-6-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)pyrrolo[1,2-b]pyridazin-5-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

15

(S)-2-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-5-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)pyrrolo[1,2-b]pyridazine-6-carboxylic acid was used as a raw material, following the step 3 for intermediate C and intermediate D, to obtain the product.

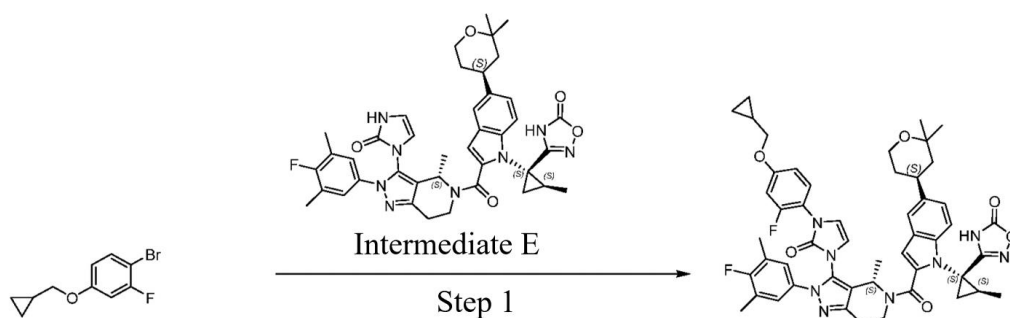
MS m/z (ESI): 722.3 [M+1].

Step 2: 3-(1-(2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-6-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)pyrrolo[1,2-b]pyridazin-5-yl)cyclopropyl-1,2,4-oxadiazol-5(4H)-one

4-bromo-3-fluorophenyl(imino)(methyl)-l-6aminosulfanone was used as a raw material, following Example 3, to obtain the target product.

MS m/z (ESI): 893.3[M+1].

Example 58

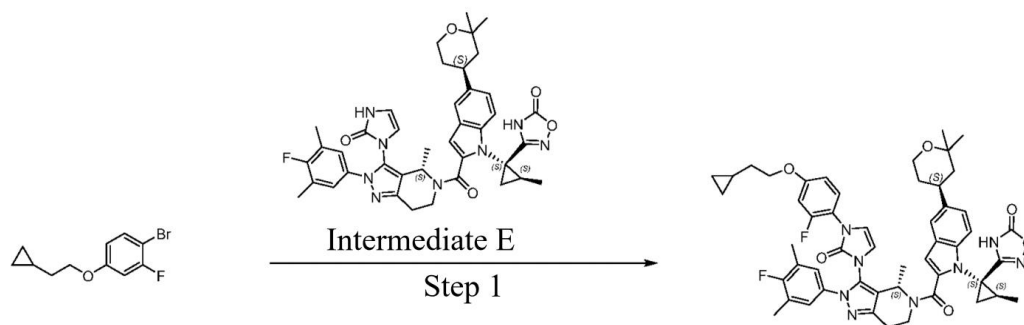


Step 1: 3-((1S,2S)-1-(2-((S)-3-(3-(4-(cyclopropylmethoxy)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-bromo-4-(cyclopropylmethoxy)-2-fluorobenzene and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 899.4[M+H]⁺.

Example 59

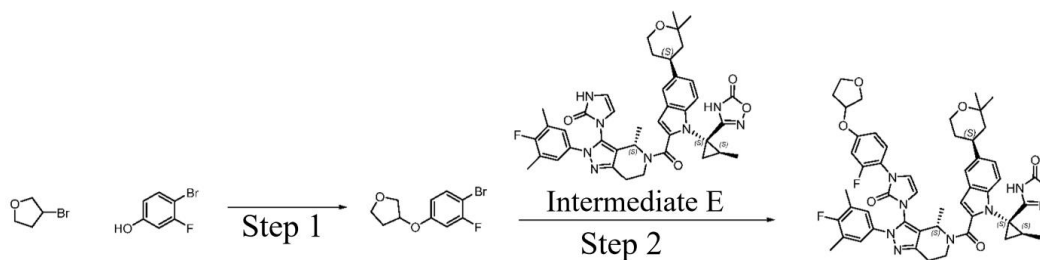


Step 1: 3-((1S,2S)-1-(2-((S)-3-(3-(4-(2-cyclopropylethoxy)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-bromo-4-(2-cyclopropylethoxy)-2-fluorobenzene and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 913.4[M+H]⁺.

Example 60



Step 1: 3-(4-bromo-3-fluorophenoxy)tetrahydrofuran

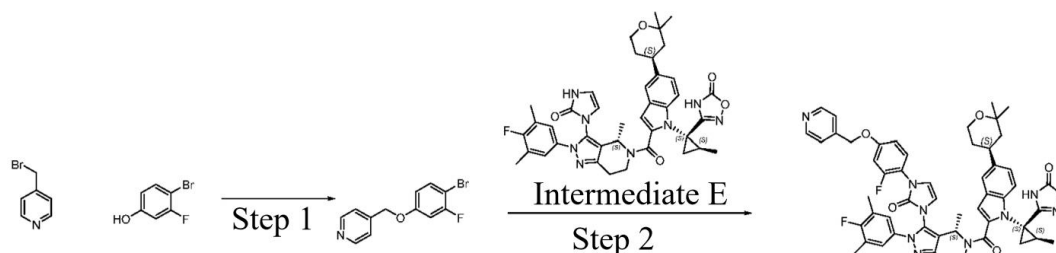
At room temperature, 4-bromo-3-fluorophenol (1.91 g, 10 mmol) was dissolved in acetonitrile (30mL), then potassium carbonate (4.15 g, 30 mmol) and 3-bromotetrahydrofuran (3.02 g, 20 mmol) were added, heated to 85°C, reacted for 24 hours, and cooled to room temperature; the reaction solution was diluted with ethyl acetate (30 mL), then washed with saturated brine (25 mL × 2); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph (PE:EA = 2 : 1), to obtain the target product, as a yellow oil (2.09 g, yield 80%).

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-((tetrahydrofuran-3-yl)oxo)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

3-(4-bromo-3-fluorophenoxy)tetrahydrofuran and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 915.4[M+H]⁺.

Example 61



5

Step 1: 4-((4-bromo-3-fluorophenoxy)methyl)pyridine

At room temperature, 4-bromo-3-fluorophenol (1.91 g, 10 mmol) was dissolved in N,N-dimethylformamide (30 mL), then potassium carbonate (2.76 g, 20 mmol) and 4-bromomethylpyridine (2.06 g, 12 mmol) were added, and the mixture was reacted at room temperature for 12 hours, with LCMS indicating the completion of the reaction; the reaction solution was diluted with ethyl acetate (60 mL), then washed with saturated brine (25 mL × 3); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph (PE : EA = 2 : 1), to obtain the target product as a yellow solid (0.28 g, yield 10%).

10

MS m/z (ESI): 282.1, 284.1[M+H]⁺.

15

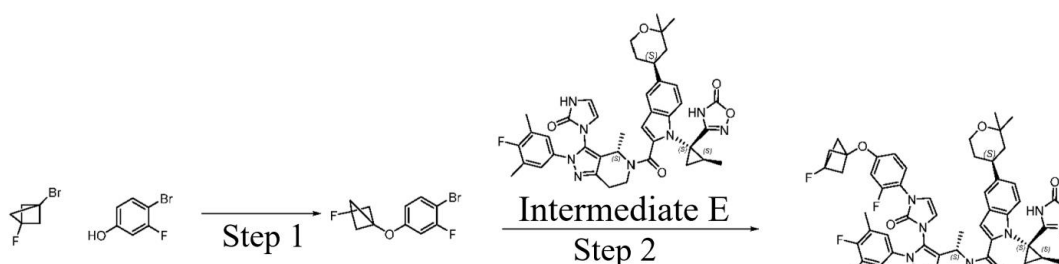
Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(pyridin-4-ylmethoxy)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

4-((4-bromo-3-fluorophenoxy)methyl)pyridine and intermediate E were used as raw materials, following Example 1, to obtain the target product.

20

MS m/z (ESI): 936.4[M+H]⁺.

Example 62



Step 1: 1-(4-bromo-3-fluorophenoxy)-3-fluorobicyclo[1.1.1]pentane

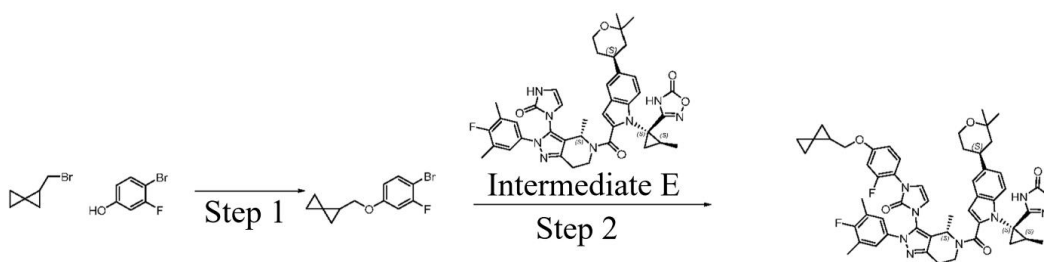
At room temperature, 4-bromo-3-fluorophenol (1.91 g, 10 mmol) was dissolved in acetonitrile (30 mL), and then potassium carbonate (4.15 g, 30 mmol) and 1-bromo-3-fluorobicyclo[1.1.1]pentane (3.3 g, 20 mmol) were added, heated to 85°C for reaction for 24 hours, cooled to room temperature; the reaction solution was diluted with ethyl acetate (30 mL), then washed with saturated brine (25 mL×2); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph (PE:EA = 3 : 1), to obtain the target product, as a yellow oil (1.93 g, yield 70%).

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-((3-fluorobicyclo[1.1.1]pentan-1-yl)oxo)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-(4-bromo-3-fluorophenoxy)-3-fluorobicyclo[1.1.1]pentane and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 929.4[M+H]⁺.

Example 63



Step 1: 1-((4-bromo-3-fluorophenoxy)methyl)spiro[2.2]pentane

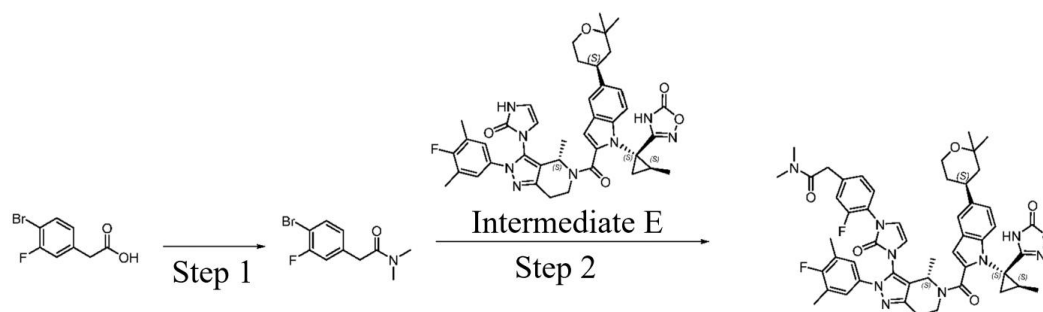
At room temperature, 4-bromo-3-fluorophenol (1.91 g, 10 mmol) was dissolved in acetonitrile (30 mL), then potassium carbonate (4.15 g, 30 mmol) and 1-(bromomethyl)spiro[2.2]pentane (3.22 g, 20 mmol) were added, heated to 85°C for reaction for 24 hours, and cooled to room temperature; the reaction solution was diluted with ethyl acetate (30 mL), and then washed with saturated brine (25 mL × 2); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, the residue was separated by Flash column chromatograph (PE:EA = 3 : 1), to obtain the target product, as a yellow oil (2.03 g, yield 75%).

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(spiro[2.2]pentan-1-ylmethoxy)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-((4-bromo-3-fluorophenoxy)methyl)spiro[2.2]pentane and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 925.4[M+H]⁺.

Example 64



Step 1: 2-(4-bromo-3-fluorophenyl)-N,N-dimethylacetamide

At room temperature, 2-(4-bromo-3-fluorophenyl)acetic acid (2.33 g, 10 mmol) was dissolved in N,N-dimethylformamide (30 mL), and then dimethanamine hydrochloride (0.98 g, 12 mmol) and triethylamine (4.05 g, 40 mmol), were added, followed by 2-(7-azobenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (5.7 g, 15 mmol); the mixture was stirred at room temperature overnight, with LCMS indicating the completion of the reaction; the reaction solution was diluted with ethyl acetate (60 mL), and then washed with saturated brine (15 mL×4); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatography (PE : EA = 1 : 1), to obtain the target product as a white solid (1.30 g, yield 50%).

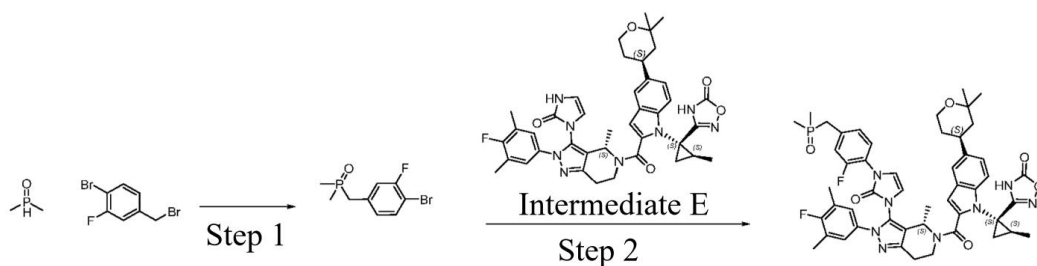
MS m/z (ESI): 260.0, 262.0[M+H]⁺.

Step 2: 2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylacetamide

2-(4-bromo-3-fluorophenyl)-N,N-dimethylacetamide and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 914.4[M+H]⁺.

Example 65



Step 1: (4-bromo-3-fluorophenylmethyl)dimethylphosphine oxide

At room temperature, dimethylphosphine oxide (0.78 g, 10 mmol) was dissolved in tetrahydrofuran (10 mL), followed by nitrogen replacement; then sodium hexamethyldisilazide (12 mL, 1.0 M in THF) was added, stirred at room temperature for 30 minutes; then a solution of 3-fluoro-4-bromobenzyl bromide (2.41 g, 9 mmol) in tetrahydrofuran (20 mL) was added dropwise to the reaction system and stirred overnight at room temperature; the reaction solution was quenched with a saturated ammonium chloride solution and subjected to liquid-liquid separation, and then the aqueous phase was extracted with an ethyl acetate solution (15 mL × 2); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph (PE : EA = 1 : 1), to obtain the target product as a white solid (1.59 g, yield 60%).

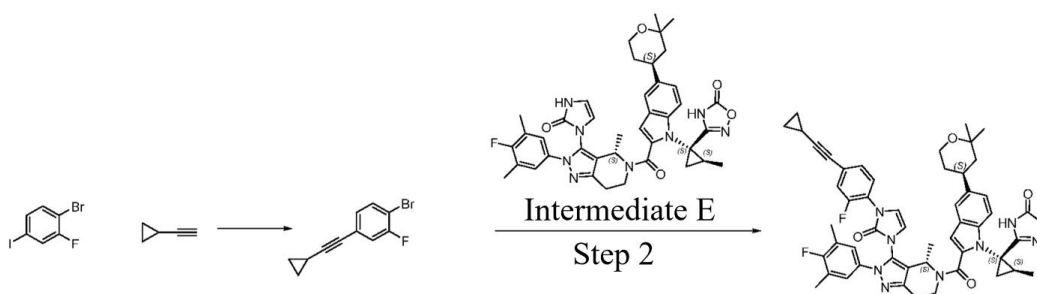
MS m/z (ESI): 265.0, 267.0[M+H]⁺.

Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(4-((dimethylphospholano)methyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-3-fluorophenylmethyl)dimethylphosphine oxide and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 919.4[M+H]⁺.

Example 66



Step 1: 1-bromo-4-(cyclopropylethynyl)-2-fluorobenzene

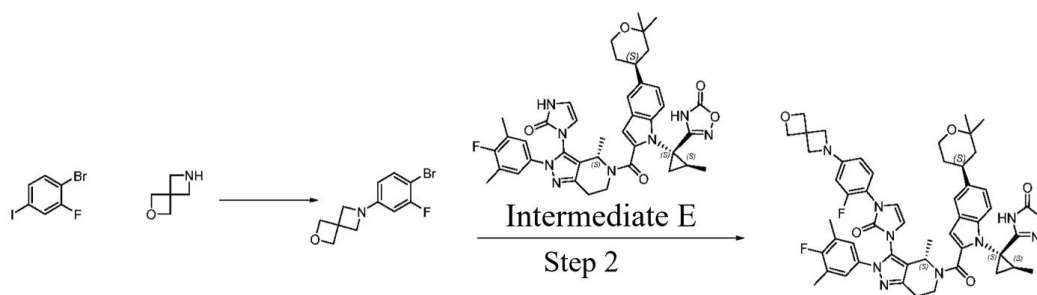
At room temperature, 3-fluoro-4-bromoiodobenzene (3.01 g, 10 mmol), cyclopropylethyne (6.61 g, 100 mmol), cuprous iodide (0.38 g, 2 mol), and bis(triphenylphosphine)dichloropalladium (0.75 g, 1 mmol) were dissolved in triethylamine (40 mL), followed by nitrogen replacement; the mixture was heated to 100°C for reaction for 14 hours, cooled to room temperature, with LCMS indicating the completion of the reaction, and spin-dried; the residue was dissolved with ethyl acetate (40 mL), then washed with saturated brine (15 mL × 2); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph (PE : EA = 10 : 1), to obtain the target product, as a yellow oil (0.91 g, yield 38%).

Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(4-(cyclopropylethynyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-bromo-4-(cyclopropylethynyl)-2-fluorobenzene and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 893.4[M+H]⁺.

Example 67



Step 1: 6-(4-bromo-3-fluorophenyl)-2-oxa-6-azaspiro[3.3]heptane

At room temperature, 3-fluoro-4-bromoiodobenzene (0.30 g, 1 mmol), 2-oxa-6-aza-spiro[3,3]heptane (0.09 g, 0.9 mmol), tris(dibenzylideneacetone)dipalladium (0.09 g, 0.1 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.12 g, 0.2 mmol), and sodium tert-butoxide (0.14 g, 1.5 mmol) were dissolved in 1,4-dioxane (3 mL), subjected to nitrogen replacement, heated to 100°C, reacted for 14 hours, and cooled to room temperature; the reaction solution was diluted with ethyl acetate (15 mL), and filtered; and the organic phase was washed with saturated brine (15 mL × 2), dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph (PE : EA = 3 : 1), to obtain the target product, as a yellow oil (0.095 g, yield 35%).

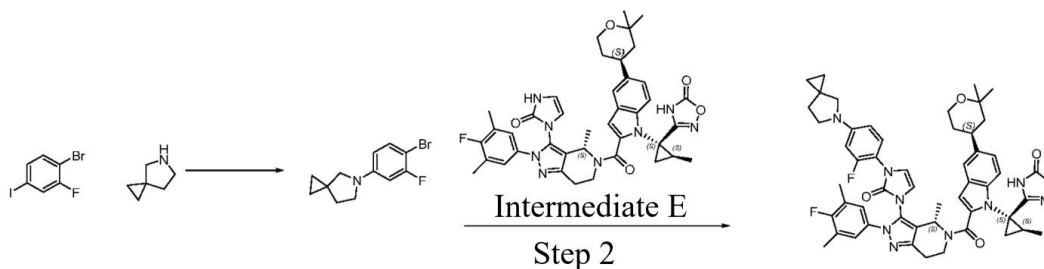
MS m/z (ESI): 272.1, 274.1[M+H]⁺.

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

6-(4-bromo-3-fluorophenyl)-2-oxa-6-azaspiro[3.3]heptane and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 926.4[M+H]⁺.

Example 68



Step 1: 5-(4-bromo-3-fluorophenyl)-5-azaspiro[2.4]heptane

3-fluoro-4-bromiodobenzene and 5-azaspiro[2.4]heptane were used as raw materials, following Example 67 Step 1, to obtain the target product 5-(4-bromo-3-fluorophenyl)-5-azaspiro[2.4]heptane.

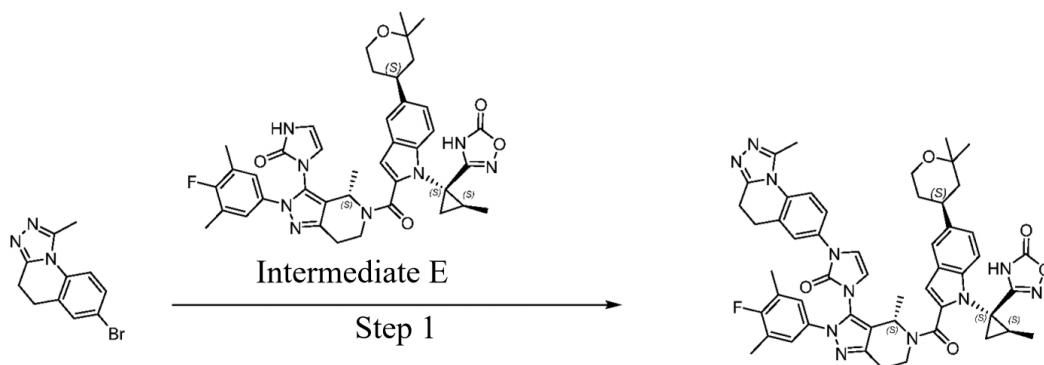
MS m/z (ESI): 270.1, 272.1[M+H]⁺.

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(5-azaspiro[2.4]heptan-5-yl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5-(4-bromo-3-fluorophenyl)-5-azaspiro[2.4]heptane and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 924.4[M+H]⁺.

Example 69



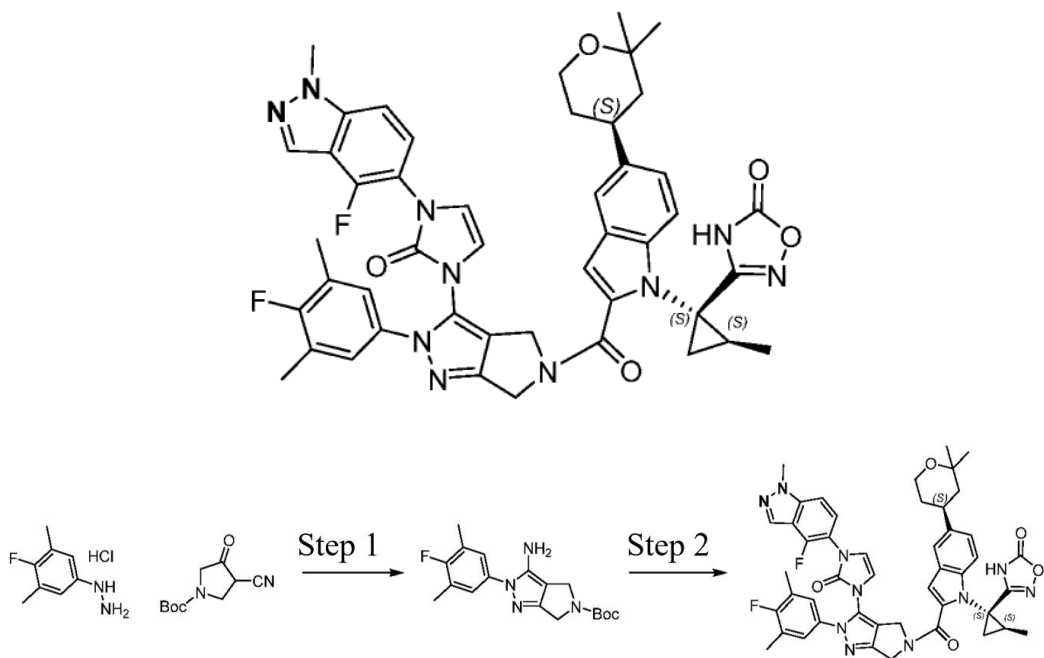
Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

7-bromo-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 918.4[M+H]⁺.

Example 70

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: tert-butyl 3-amino-2-(4-fluoro-3,5-dimethylphenyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate

4-fluoro-3,5-dimethylphenyl)hydrazine hydrochloride (10 g, 52.45 mmol) and tert-butyl 3-cyano-4-carboxylpyrrolidine-1-carboxylate (11.03 g, 52.45 mmol) were dissolved in ethanol (120 mL) and acetic acid (30 mL), and under nitrogen protection, the mixture was reacted at 50°C under stirring for 12 hours. In the mixture, most of the solvent was removed under reduced pressure, and a 1N aqueous sodium hydroxide solution was added to adjust PH = 8, and the mixture was extracted with ethyl acetate (100 mL × 2); and the organic phases were combined, washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluted with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the target product tert-butyl 3-amino-2-(4-fluoro-3,5-dimethylphenyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5(4H)-carboxylate (9.1 g, yield 50.08%).

MS m/z (ESI): 347.2[M+1].

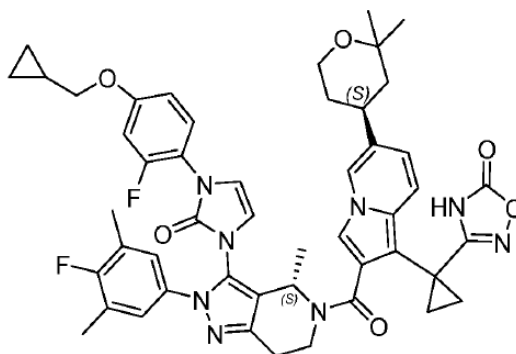
Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Step 4 and Step 5, intermediate E and Example 1, 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was synthesized.

MS m/z (ESI): 855.4[M+1].

Example 71

3-(1-(2-((S)-3-(3-(4-(cyclopropylmethoxy)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



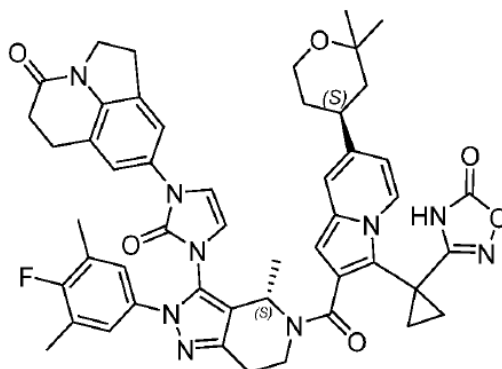
71

1-bromo-4-cyclopropylmethoxy-2-fluorobenzene and 3-(1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine-5-carbonyl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one were used as raw materials, following Example 1, to obtain the target product

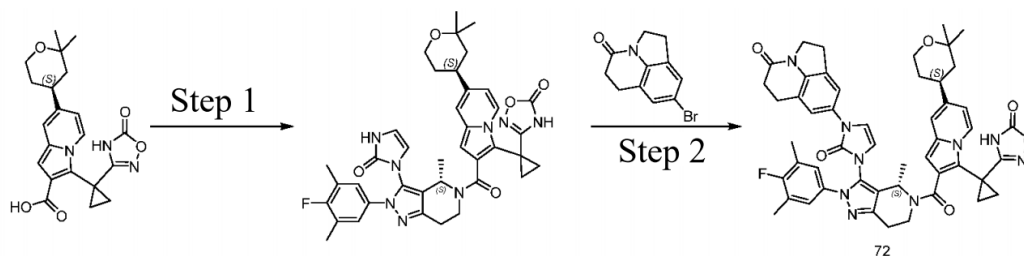
MS m/z (ESI):885.4[M+1].

Example 72

3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(4-carbonyl-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-8-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



72



72

Step 1: 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

The product was obtained by following the step 3 for intermediate C and intermediate D.

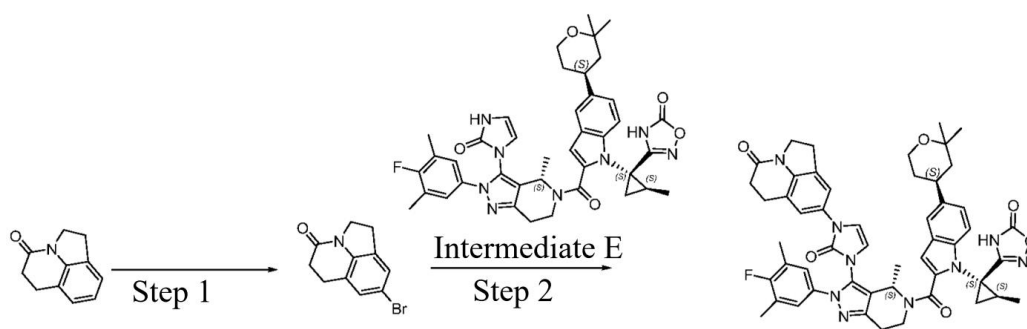
MS m/z (ESI): 721.3 [M+1].

Step 2: 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(4-carbonyl-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-8-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

8-bromo-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinoline-4(2H)-one was used as a raw material, following Example 1. to obtain the target product

MS m/z (ESI): 892.4[M+1].

Example 73



Step 1: 8-bromo-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinoline-4-one

At 0°C, 1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinoline-4-one (1.73 g, 10 mmol) was dissolved in N,N-dimethylformamide (12 mL), and then N-bromosuccinimide (1.96 g, 11 mmol) in N,N-dimethylformamide (20 mL) was added dropwise, followed by stirring at room temperature for 2 hours; the reaction solution was quenched with water (60 mL), then extracted with ethyl acetate (25 mL × 3); and the organic phases were combined, washed with saturated brine (25 mL × 2), dried over anhydrous sodium sulfate, filtered, and spin-dried, and the crude product was crystallized with acetone/water, to obtain the target product, as a yellow solid (1.89 g, yield 75%).

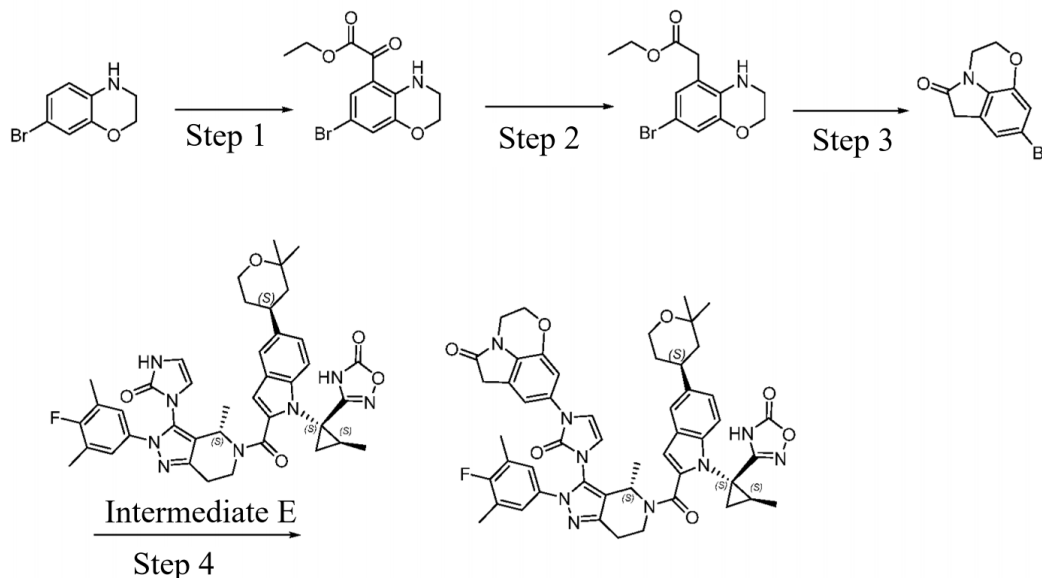
MS m/z (ESI): 252.1, 254.1[M+H]⁺.

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(4-carbonyl-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ij]quinolin-8-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

8-bromo-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-ii]quinoline-4-one and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI) : 906.4[M+H]⁺.

Example 74



5

Step 1: ethyl 2-(7-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)-2-carboxylate

Under an ice bath, ethyl oxalyl chloride (1.64 g, 12 mmol) was dissolved in dichloromethane (20 mL), and then aluminum trichloride (8.0 g, 60 mmol) was added and stirred for 30 minutes under the ice bath; then 7-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazine (2.14 g, 10 mmol) was added and stirred at room temperature for 2 hours, with LCMS indicating the generation of the target product; the reaction solution was quenched with a 10% aqueous sodium hydroxide solution, and filtered; the filter residue was washed with dichloromethane, and the organic phase was washed with a saturated sodium bicarbonate solution (25 mL × 2) and saturated brine (25 mL × 2), successively; and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph, to obtain the target product ethyl 2-(7-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)-2-carboxylate (0.31 g, yield 10%).

MS m/z (ESI): 314.1, 316.1[M+H]⁺.

Step 2: ethyl 2-(7-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)acetate

At room temperature, ethyl 2-(7-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)-2-carboxylate (0.31 g, 1 mmol) was dissolved in trifluoroacetic acid (5 mL),

20

and then triethylsilane (0.23 g, 2 mmol) was added, heated to 60°C reacted for 2 hours, with LCMS indicating completed reaction, cooled to room temperature, and spin-dried; the residue was diluted with ethyl acetate (20 mL), and then washed with a saturated sodium bicarbonate solution (25 mL × 2) and saturated brine (25 mL × 2) successively; and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue used directly in the next step.

MS m/z (ESI): 300.1, 302.1[M+H]⁺.

Step 3: 8-bromo-2,3-dihydro-[1,4]oxaazino[2,3,4-hi]indole-5(6H)-one

At room temperature, ethyl 2-(7-bromo-3,4-dihydro-2H-benzo[b][1,4]oxazin-5-yl)acetate (0.30 g, 1 mmol) was dissolved in ethanol (5 mL), and then acetic acid (0.2 mL) was added, heated to 80°C, reacted for 2 hours, cooled to room temperature, with LCMS indicating the generation of the target product, and spin-dried; the residue was dissolved with ethyl acetate (20 mL), then washed with a saturated sodium bicarbonate solution (25 mL × 2) and saturated brine (25 mL × 2), successively; and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph, to obtain the target product 8-bromo-2,3-dihydro-[1,4]oxaazino[2,3,4-hi]indole-5(6H)-one (0.05 g, yield 20%).

MS m/z (ESI): 254.1, 256.1[M+H]⁺.

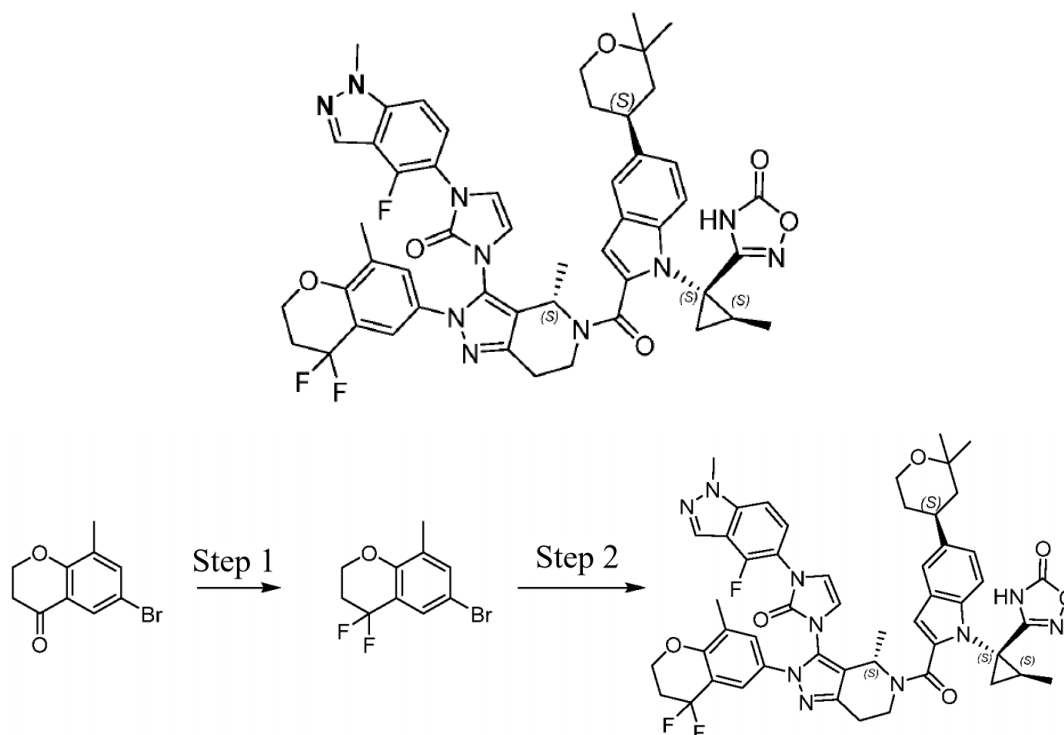
Step 4: 8-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,3-dihydro-[1,4]oxaazino[2,3,4-hi]indole-5(6H)-one

8-bromo-2,3-dihydro-[1,4]oxaazino[2,3,4-hi]indole-5(6H)-one and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 908.4[M+H]⁺.

Example 75

3-((1S,2S)-1-(2-((S)-2-(4,4-difluoro-8-methylchroman-6-yl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 6-bromo-4,4-difluoro-8-methylchromane

6-Bromo-8-methylchroman-4-one (5 g, 20.57 mmol) was dissolved in dichloromethane (50 mL) and ethanol (1 mL), and under nitrogen protection and cooling in an ice water bath, bis(2-methoxyethyl)aminosulfur trifluoride (45.50 g, 205.68 mmol, 37.92 mL) was added. The mixture was reacted under stirring at 50°C for 36 hours. The mixture was cooled, and a saturated sodium bicarbonate aqueous solution (150 mL) was added dropwise to quench the reaction, followed by extraction with dichloromethane (50 mL × 3); and the organic phases were combined, washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluted with petroleum ether : ethyl acetate = 100 : 0 to 95 : 5), to obtain the target product 6-bromo-4,4-difluoro-8-methylchromane (2.1 g, yield 38.51%).

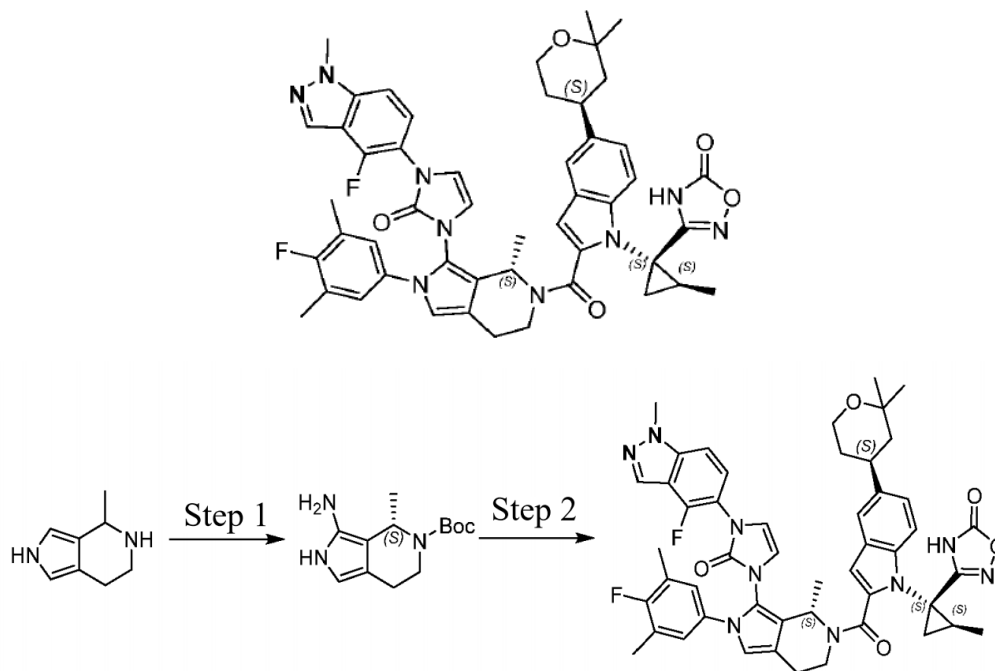
Step 2: 3-((1S,2S)-1-(2-((S)-2-(4,4-difluoro-8-methylchroman-6-yl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Steps 3, 4 and 5, intermediate E and Example 1, 3-((1S,2S)-1-(2-((S)-2-(4,4-difluoro-8-methylchroman-6-yl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was synthesized.

MS m/z (ESI): 943.4[M+1].

Example 76

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: tert-butyl (S)-3-amino-4-methyl-2,4,6,7-tetrahydro-5H-pyrrolo[3,4-c]pyridine-5-carboxylate
4-methyl-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine was used as a raw material, following
Tetrahedron Letters, 2005, vol. 46, # 42, p. 7101 - 7105, to obtain the target product.

MS m/z (ESI): 252.2[M+1].

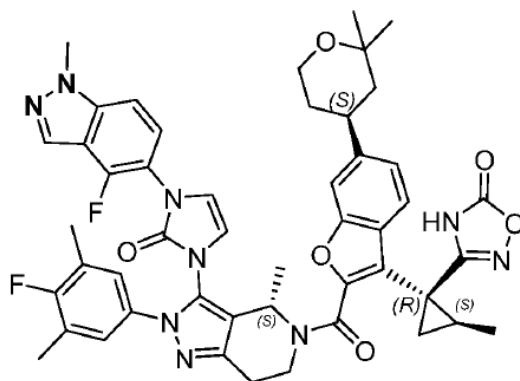
Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following intermediate B Steps 3, 4 and 5, intermediate E and Example 1, 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was synthesized.

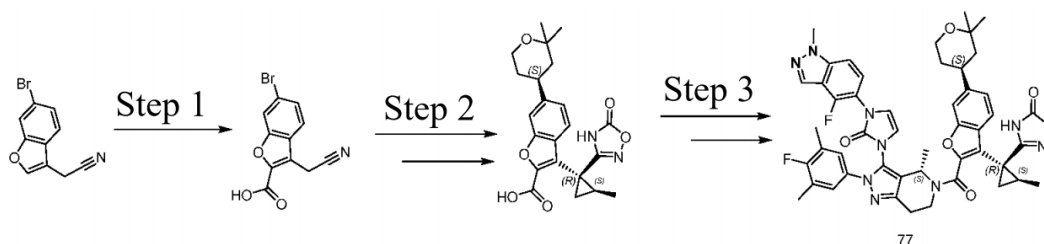
MS m/z (ESI): 882.4[M+1].

Example 77

3-((1R,2S)-1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)benzofuran-3-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



77



Step 1: 6-bromo-3-(cyanomethyl)benzofuran-2-carboxylic acid

2-(6-bromo-1-benzofuran-3-yl)acetonitrile was used as a raw material, following reference [Chemistry - An Asian Journal, 2015, vol. 10, # 4, p. 1010 - 1016], to obtain the target product

MS m/z (ESI): 279.9 [M+1].

Step 2: 6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-((1R,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)benzofuran-2-carboxylic acid

Following intermediate A, the target product was obtained

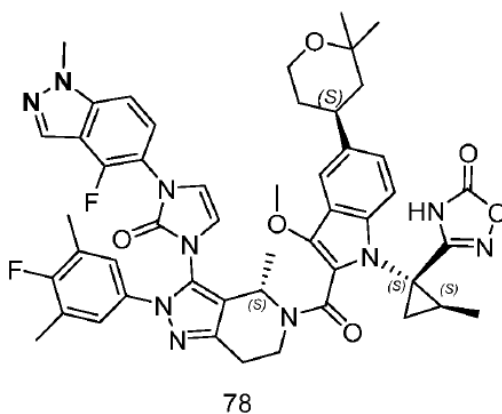
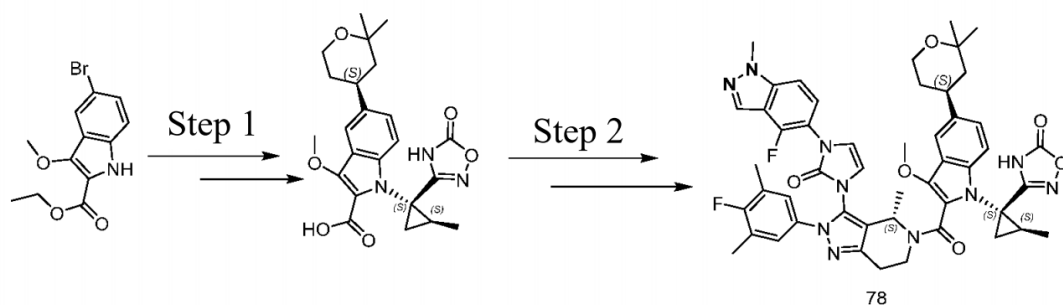
MS m/z (ESI): 413.1[M+1].

Step 3: 3-((1R,2S)-1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)benzofuran-3-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following step 3 for intermediate C and intermediate D, the product was obtained, and then 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product MS m/z (ESI):884.4 [M+1].

Example 78

5 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-3-methoxy-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10

Step 1: 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-methoxy-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid

Ethyl 5-bromo-3-methoxyindole-2-carboxylate was used as a raw material, following intermediate A, to obtain the target product

15

MS m/z (ESI):442.2 [M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-3-methoxy-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

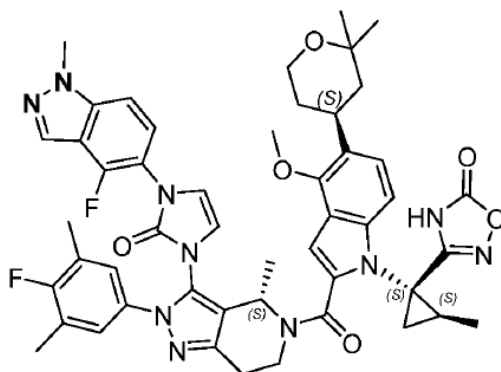
20

Following step 3 for intermediate C and intermediate D, the product was obtained, and then 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI):913.4 [M+1].

Example 79

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-methoxy-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



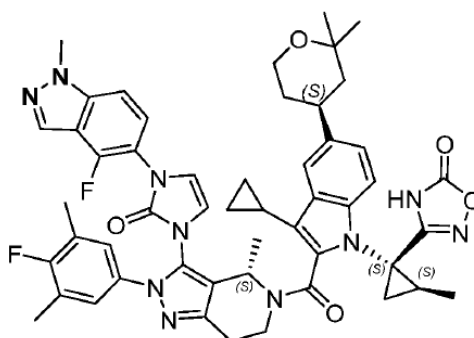
79

Ethyl 5-bromo-4-methoxy-1H-indole-2-carboxylate was used as a raw material, following Example 78, to obtain the target product

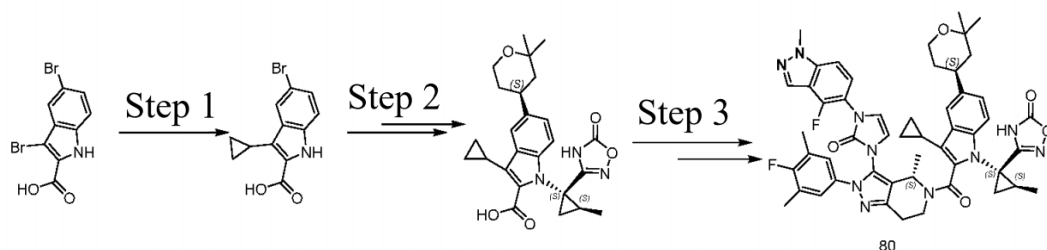
MS m/z (ESI):913.4 [M+1].

Example 80

3-((1S,2S)-1-(3-cyclopropyl-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



80



Step 1: 5-bromo-3-cyclopropyl-1H-indole-2-carboxylic acid

3,5-dibromo-indole-2-carboxylic acid and cyclopropylboronic acid were used as raw materials, following Example 10 Step 2, to obtain the target product.

MS m/z (ESI): 279.9 [M+1].

Step 2: 3-cyclopropyl-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid

Following intermediate A, the target product was obtained

MS m/z (ESI): 452.2[M+1].

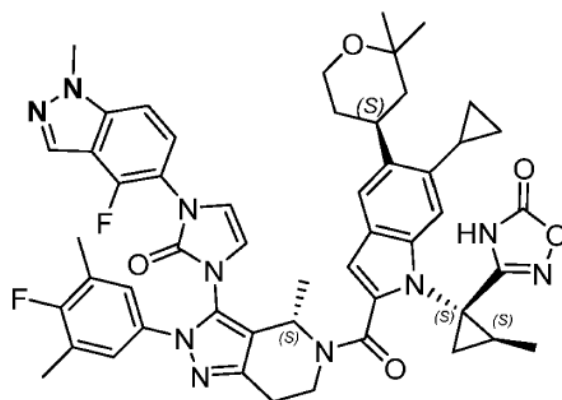
Step 3: 3-((1S,2S)-1-(3-cyclopropyl-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following step 3 for intermediate C and intermediate D, the product was obtained, and then 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product

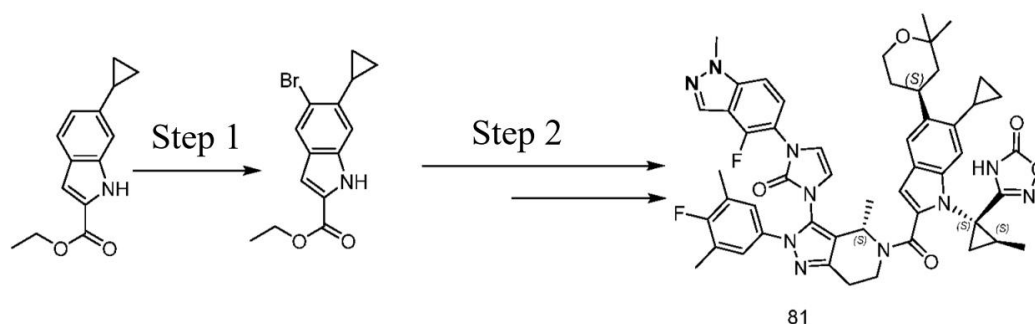
MS m/z (ESI): 923.4 [M+1].

Example 81

3-((1S,2S)-1-(6-cyclopropyl-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



81



Step 1: Ethyl 5-bromo-6-cyclopropyl-1H-indole-2-carboxylate

Ethyl 6-cyclopropyl-1H-indole-2-carboxylate was used as a raw material, following reference
5 [Heterocycles, 1992, vol. 34, # 12, p. 2349 - 2362], to obtain the target product

MS m/z (ESI): 308.0[M+1].

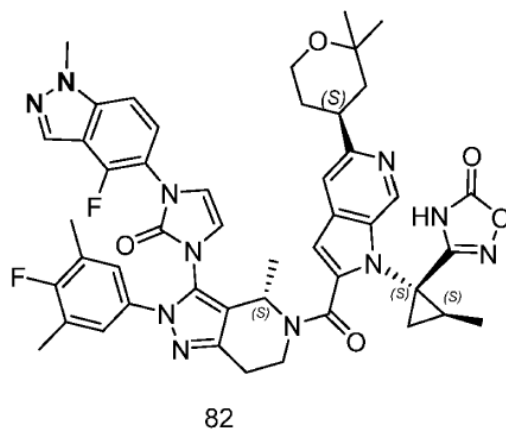
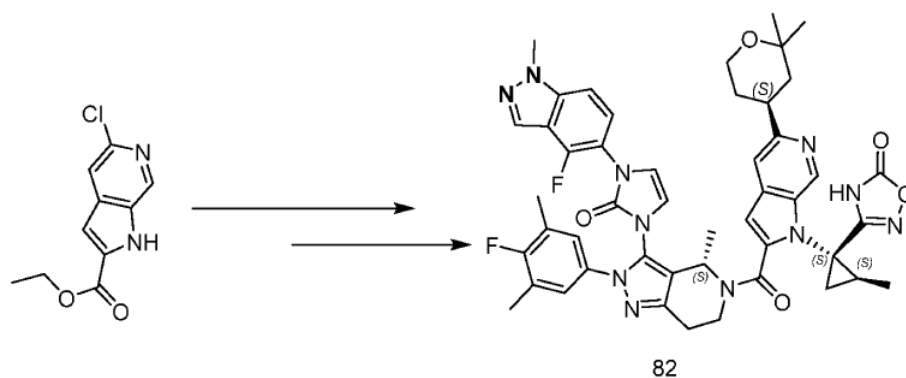
Step 2: 3-((1S,2S)-1-(6-cyclopropyl-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-
fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-
dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-
10 methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 80, the target product was obtained.

MS m/z (ESI): 923.4[M+1].

Example 82

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-
15 yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-
tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-pyrrolo[2,3-c]pyridin-1-yl)-2-methylcyclopropyl)-
1,2,4-oxadiazol-5(4H)-one



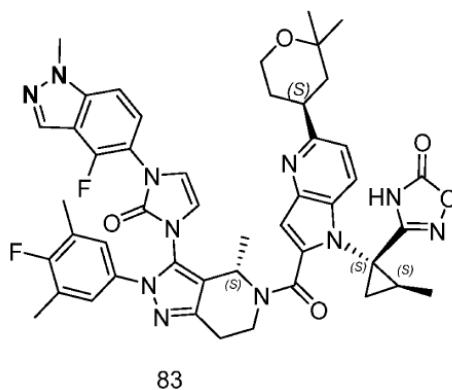
Ethyl 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate was used as a raw material, following Example 78, to obtain the target product

5 MS m/z (ESI):884.4 [M+1].

Example 83

3-((1S,2S)-1-(2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((4S)-2-methyltetrahydro-2H-pyran-4-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

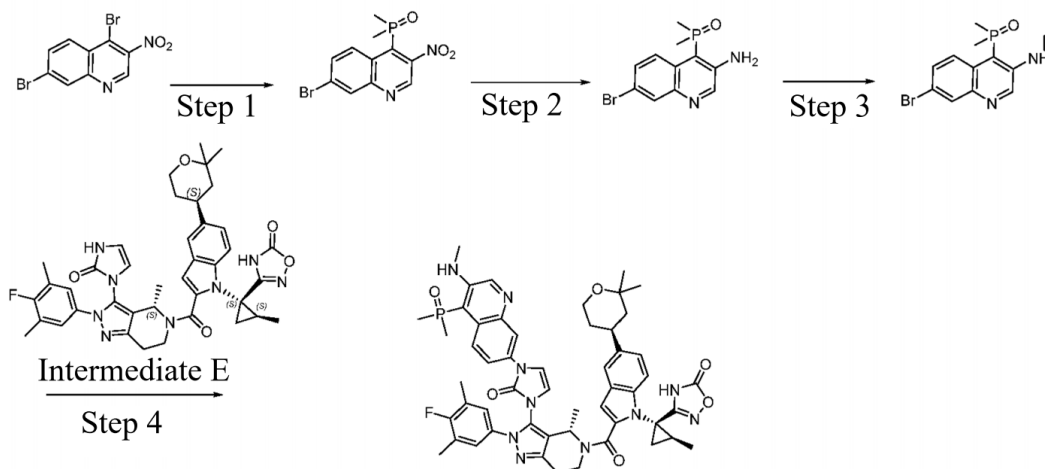
10



Methyl 5-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylate was used as a raw material, following Example 78, to obtain the target product

MS m/z (ESI): 884.4[M+1].

Example 84



Step 1: (7-bromo-3-nitroquinolin-4-yl)dimethylphosphine oxide

5 At room temperature, 4,7-dibromo-3-nitroquinoline (0.99 g, 3 mmol), dimethylphosphine oxide (0.36 g, 4.5 mmol), palladium acetate (0.07 g, 0.3 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.36 g, 0.6 mmol), and potassium phosphate (1.27 g, 6 mmol) were dissolved in dioxane (15 mL), followed by nitrogen replacement; the mixture was heated to 100°C, reacted for 18 hours, and cooled to room temperature; the reaction solution was diluted with ethyl acetate (20 mL), and filtered; the filter residue was washed with ethyl acetate; and the organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph, to obtain (7-bromo-3-nitroquinolin-4-yl)dimethylphosphine oxide (0.49 g, yield 50%).

MS m/z (ESI): 329.1, 331.1[M+H]⁺.

Step 2: (3-amino-7-bromoquinolin-4-yl)dimethylphosphine oxide

15 At room temperature, (7-bromo-3-nitroquinolin-4-yl) dimethylphosphine oxide (0.49 g, 1.5 mmol) was dissolved in ethanol (10 mL), then a zinc powder (0.49 g, 7.5 mmol) and an aqueous saturated ammonium chloride solution (50 mL) were added, heated to 60°C, reacted for 2 hours, with LCMS indicating the completion of the reaction, cooled to room temperature, and filtered; the filter residue was washed with ethanol (10 mL), and ethanol was removed by rotary evaporation; the aqueous phase was extracted with ethyl acetate (15 mL×3); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was used directly in the next step.

MS m/z (ESI): 299.1, 301.1[M+H]⁺.

Step 3: (7-bromo-3-(methylamino)quinolin-4-yl)dimethylphosphine oxide

25 At room temperature, (3-amino-7-bromoquinolin-4-yl)dimethylphosphine oxide (0.45 g, 1.5 mmol) was dissolved in tetrahydrofuran (10 mL),

then an aqueous carbaldehyde solution (3 mL) was added and stirred at room temperature for 20 minutes, and then sodium borohydride acetate (0.38 g, 18 mmol) was added and stirred at room temperature for 14 hours, with LCMS indicating the completion of the reaction; the reaction solution was quenched with water, then extracted with ethyl acetate (15 mL $\times$ 2); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph, to obtain the target product (7-bromo-3-(methylamino)quinoline-4-yl)dimethylphosphine oxide (0.23 g, yield 50%).

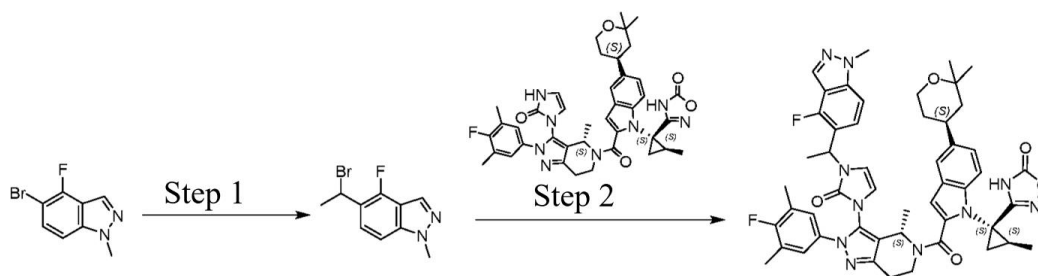
MS m/z (ESI): 313.1, 315.1[M+H]⁺.

Step 4: 3-((1S,2S)-1-(2-((S)-3-(3-(4-(dimethylphospholano)-3-(methylamino)quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(7-bromo-3-(methylamino)quinolin-4-yl)dimethylphosphine oxide and intermediate E were used as raw materials, following Example 1 to obtain the target product.

MS m/z (ESI): 967.4[M+H]⁺.

Example 85



Step 1: 5-(1-bromoethyl)-4-fluoro-1-methyl-1H-indazole

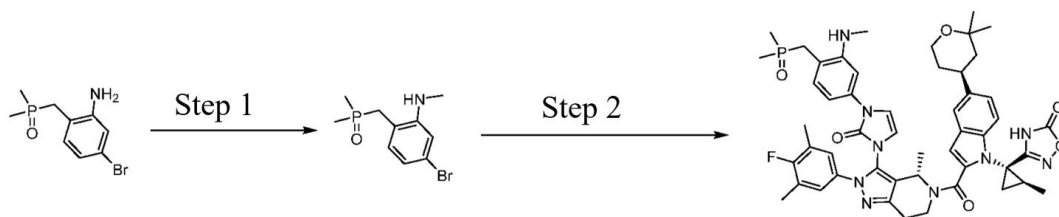
5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following BRISTOL-MYERS SQUIBB CO - WO2020/6018, 2020, A1, to obtain the target product.

MS m/z (ESI): 257.0[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(1-(4-fluoro-1-methyl-1H-indazol-5-yl)ethyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate E was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 911.4[M+1].

Example 86

Step 1: (4-bromo-2-(methylamino)phenylmethyl)dimethylphosphine oxide

(2-amino-4-bromophenylmethyl)dimethylphosphine oxide was used as a raw material, following

5 Organic and Biomolecular Chemistry, 2018, vol. 16, # 25, p. 4701 - 4714, to obtain the target product.

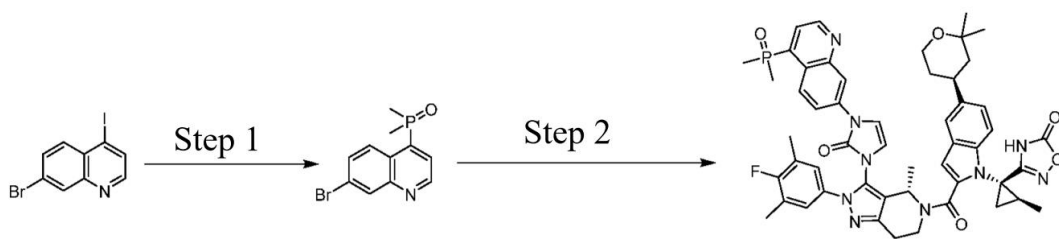
MS m/z (ESI): 276.0[M+1].

Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(4-((dimethylphospholano)methyl)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10

Intermediate E was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 930.4[M+1].

Example 87

Step 1: (7-bromoquinolin-4-yl)dimethylphosphine oxide

15

7-bromo-4-iodoquinoline was used as a raw material, following Journal of Organic Chemistry, 2021, vol. 86, # 18, p. 12783 - 12801, to obtain the target product.

MS m/z (ESI): 283.9 [M+1].

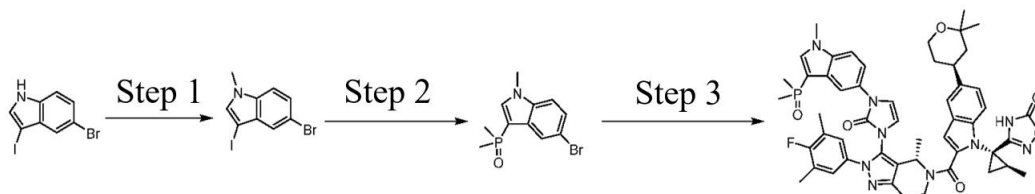
Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(4-(dimethylphospholano)quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

20

Intermediate E was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 938.3 [M+1].

Example 88



Step 1: 5-bromo-3-iodo-1-methyl-1H-indole

5-bromo-3-iodo-1H-indole was used as a raw material, following European Journal of Medicinal Chemistry, 2020, vol. 190, to obtain the target product.

MS m/z (ESI): 335.8 [M+1].

Step 2: (5-bromo-1-methyl-1H-indol-3-yl)dimethylphosphine oxide

5-bromo-3-iodo-1-methyl-1H-indole was used as a raw material, following Journal of Organic Chemistry, 2021, vol. 86, # 18, p. 12783 - 12801, to obtain the target product.

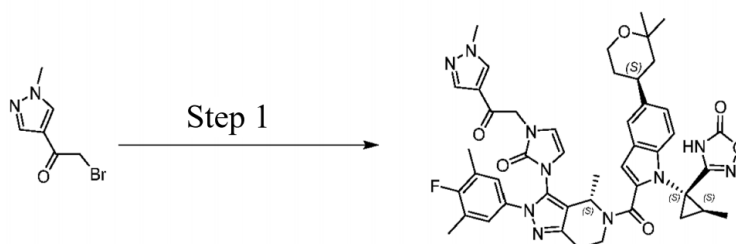
MS m/z (ESI): 318.0 [M+1].

Step 3: 3-((1S,2S)-1-(2-((S)-3-(3-(3-(dimethylphospholano)-1-methyl-1H-indol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate E was used as a raw material, following Example 1, to obtain the target product.

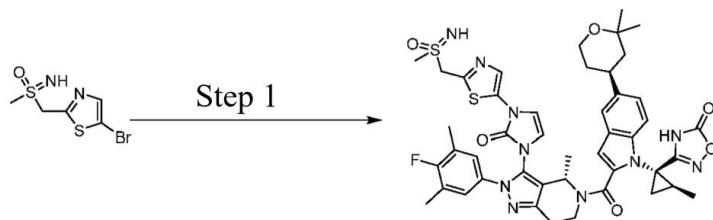
MS m/z (ESI): 940.4 [M+1].

Example 89

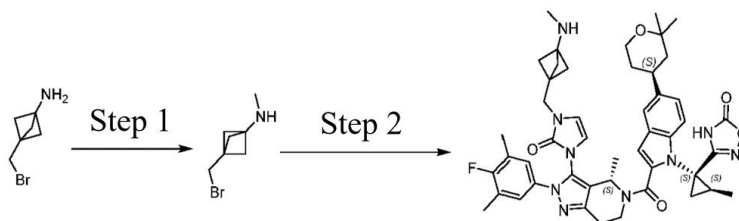


Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(2-(1-methyl-1H-pyrazol-4-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

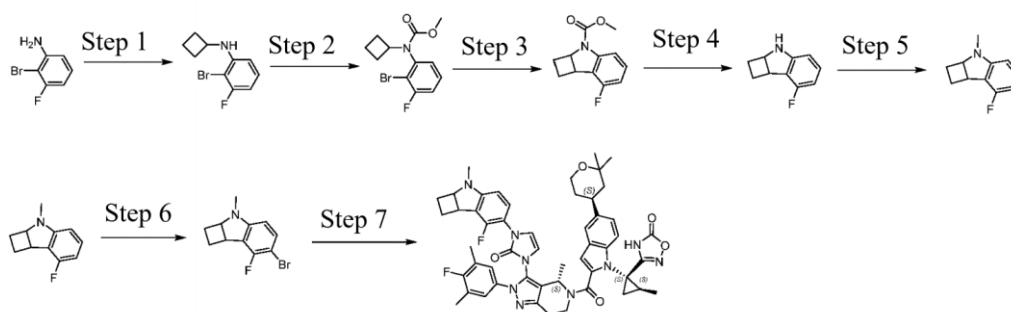
MS m/z (ESI): 857.3 [M+1].



MS m/z (ESI): 909.4 [M+1].



MS m/z (ESI): 844.4 [M+1].

Example 92

Step 1: 2-bromo-N-cyclobutyl-3-fluoroaniline

2-bromo-3-fluoroaniline was used as a raw material, following MERCK & CO INC - WO 2020/96871, 2020, A1, to obtain the target product.

MS m/z (ESI): 244.0 [M+1].

Step 2: Methyl (2-bromo-3-fluorophenyl)(cyclobutyl)carbamate

2-bromo-N-cyclobutyl-3-fluoroaniline was used as a raw material, following MERCK & CO INC - WO 2020/96871, 2020, A1, to obtain the target product.

MS m/z (ESI): 302.0 [M+1].

Step 3: Methyl 7-fluoro-1,2,2a,7b-tetrahydro-3H-cyclobut[b]indole-3-carboxylate

Methyl (2-bromo-3-fluorophenyl)(cyclobutyl)carbamate was used as a raw material, following Bioorganic and Medicinal Chemistry Letters, 2021, vol. 47, to obtain the target product.

MS m/z (ESI): 222.0 [M+1].

Step 4: 7-fluoro-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indole

Methyl 7-fluoro-1,2,2a,7b-tetrahydro-3H-cyclobut[b]indole-3-carboxylate was used as a raw material, following Tetrahedron, 2015, vol. 71, # 37, art. no. 26568, p. 6499 - 6505, to obtain the target product.

MS m/z (ESI): 164.0 [M+1].

Step 5: 7-fluoro-3-methyl-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indole

7-fluoro-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indole was used as a raw material, following European Journal of Medicinal Chemistry, 2020, vol. 190, to obtain the target product.

MS m/z (ESI): 178.1 [M+1].

Step 6: 6-bromo-7-fluoro-3-methyl-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indole

7-fluoro-3-methyl-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indole was used as a raw material, following Chemistry - A European Journal, 2022, vol. 28, # 2, art. no. E202103135, to obtain the target product.

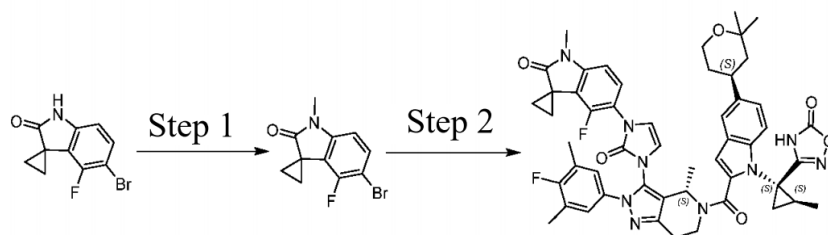
MS m/z (ESI): 256.0 [M+1].

Step 7: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(7-fluoro-3-methyl-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indol-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

6-bromo-7-fluoro-3-methyl-2,2a,3,7b-tetrahydro-1H-cyclobut[b]indole and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 910.4 [M+1].

Example 93



Step 1: 5'-bromo-4'-fluoro-1'-methylspiro[cycloprop-1,3'-dihydroindol]-2'-one

5'-bromo-4'-fluorospiro[cycloprop-1,3'-dihydroindol]-2'-one was used as a raw material, following European Journal of Medicinal Chemistry, 2020, vol. 190, to obtain the target product.

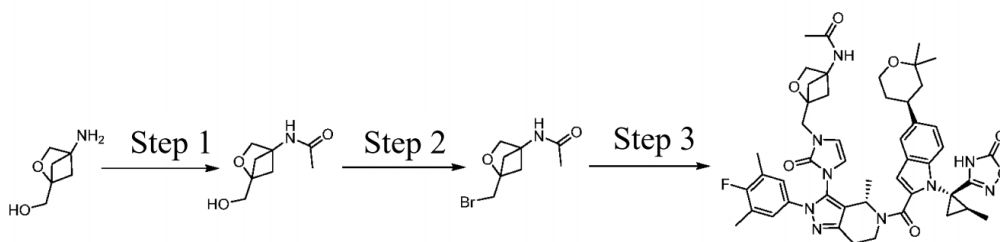
MS m/z (ESI): 269.9 [M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4'-fluoro-1'-methyl-2'-carbonylspiro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Intermediate E was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 924.3 [M+1].

Example 94



Step 1: N-(1-(hydroxymethyl)-2-oxabicyclo[2.1.1]hexan-4-yl)acetamide

(4-amino-2-oxabicyclo[2.1.1]hexan-1-yl)methanol was used as a raw material, following BAYER AG - US 3960945, 1976, A, to obtain the target product.

MS m/z (ESI): 172.0 [M+1].

5 Step 2: N-(1-(bromomethyl)-2-oxabicyclo[2.1.1]hexan-4-yl)acetamide

N-(1-(hydroxymethyl)-2-oxabicyclo[2.1.1]hexan-4-yl)acetamide was used as a raw material, following Tetrahedron Letters, 2015, vol. 56, # 24, p. 3758 - 3761, to obtain the target product.

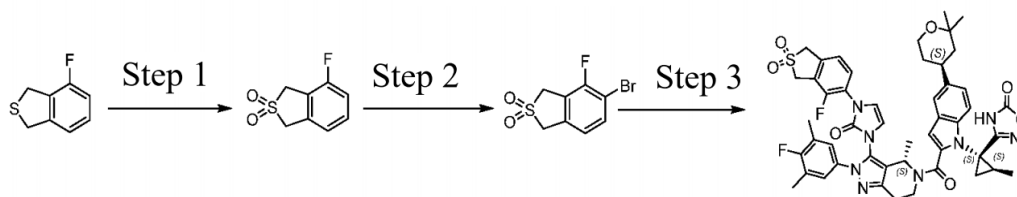
MS m/z (ESI): 234.0 [M+1].

10 Step 3: N-(1-((3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)methyl)-2-oxabicyclo[2.1.1]hexan-4-yl)acetamide

N-(1-(bromomethyl)-2-oxabicyclo[2.1.1]hexan-4-yl)acetamide and intermediate E were used as raw materials, following Example 1, to obtain the target product.

15 MS m/z (ESI): 888.4 [M+1].

Example 95



Step 1: 4-fluoro-1,3-dihydrobenzo[c]thiophene-2,2-dioxide

4-fluoro-1,3-dihydro-benzothiophene was used as a raw material, following Catalysis Communications, 2014, vol. 56, p. 68 - 71, to obtain the target product.

MS m/z (ESI): 187.0 [M+1].

Step 2: 5-bromo-4-fluoro-1,3-dihydrobenzo[c]thiophene-2,2-dioxide

4-fluoro-1,3-dihydrobenzo[c]thiophene-2,2-dioxide was used as a raw material, following [Chemistry - A European Journal, 2022, vol. 28, # 2, art. no. E202103135], to obtain the target product.

25 MS m/z (ESI): 264.9 [M+1].

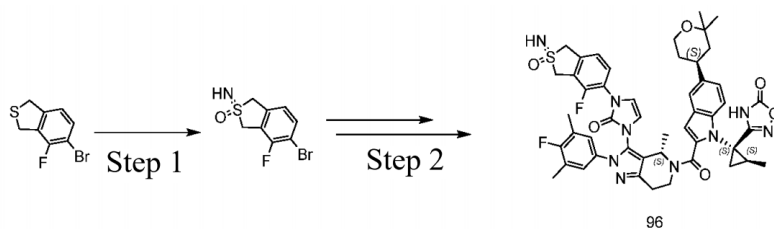
Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-2,2-dihydroxyl-1,3-dihydrobenzo[c]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

30

5-Bromo-4-fluoro-1,3-dihydrobenzo[c]thiophene2,2-dioxide and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 919.3 [M+1].

Example 96



Step 1: 5-bromo-4-fluoro-2-imino-2,3-dihydro-1H-2l4-benzo[c]thiophene2-oxide

5-bromo-4-fluoro-1,3-dihydrobenzo[c]thiophene was used as a raw material, following Example 3 Step 1, to obtain the title product 5-bromo-4-fluoro-2-imino-2,3-dihydro-1H-2l4-benzo[c]thiophene2-oxide.

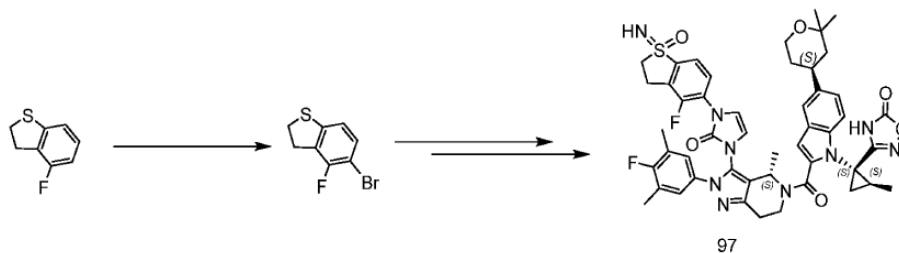
MS m/z (ESI): 263.9, 265.9 [M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-2-imino-2-hydroxyl-2,3-dihydro-1H-2l4-benzo[c]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5-bromo-4-fluoro-2-imino-2,3-dihydro-1H-2l4-benzo[c]thiophene2-oxide was used as a raw material, following Example 1, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-2-imino-2-hydroxyl-2,3-dihydro-1H-2l4-benzo[c]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 918.3[M+1].

Example 97



Step 1: 5-bromo-4-fluoro-2,3-dihydrobenzo[b]thiophene

4-fluoro-2,3-dihydrobenzo[b]thiophene was used as a raw material, following Example 95 Step 1, to obtain the title product 5-bromo-4-fluoro-2,3-dihydrobenzo[b]thiophene.

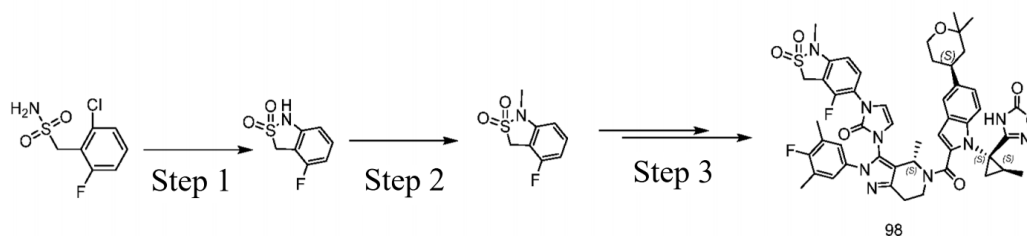
5 MS m/z (ESI): 232.9, 234.9 [M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-1-imino-1-hydroxyl-2,3-dihydro-1H-114-benzo[b]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10 5-bromo-4-fluoro-2,3-dihydrobenzo[b]thiophene was used as a raw material, following Example 96, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-1-imino-1-hydroxyl-2,3-dihydro-1H-114-benzo[b]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

15 MS m/z (ESI): 918.3[M+1].

Example 98



Step 1: 4-fluoro-1,3-dihydrobenzo[c]isothiazole-2,2-dioxide

20 In a 50 mL reaction bottle, (2-chloro-6-fluorophenyl)methanesulfonamide (1 g, 4.47 mmol), tris(dibenzylideneacetone)dipalladium (204.73 mg, 223.57 μmol), 2-di-tert-butylphosphino-2',4',6'-triisopropylidiphenyl (189.88 mg, 447.13 μmol), and potassium carbonate (1.24 g, 8.94 mmol) were dissolved in tetrahydrofuran (10.0 mL), and the reaction solution was stirred at 80°C for 10 hours under nitrogen protection. The reaction was stopped, and an aqueous solution (10 mL) was added to quench the reaction,

the mixture was extracted with dichloromethane (10 mL × 2), and the organic phases were combined, washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, and filtered, and the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product 4-fluoro-1,3-dihydrobenzo[c]isothiazole2,2-dioxide (410 mg, a yellow solid), yield: 49.0%.

MS m/z (ESI): 188.0 [M+1].

Step 2: 4-fluoro-1-methyl-1,3-dihydrobenzo[c]isothiazole2,2-dioxide

In a 50 mL reaction bottle, 4-fluoro-1,3-dihydrobenzo[c]isothiazole2,2-dioxide (410 mg, 2.19 mmol), iodomethane (466.34 mg, 3.29 mmol), and potassium carbonate (605.42 g, 4.38 mmol) were dissolved in DMF (5.0 mL), and the reaction solution was stirred at 25°C for 10 hours under nitrogen protection. The reaction was stopped, quenched by adding an aqueous solution (10 mL), extracted with dichloromethane (10 mL × 2); and the organic phases were combined, washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, filtered, and the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product 4-fluoro-1-methyl-1,3-dihydrobenzo[c]isothiazole2,2-dioxide (400 mg, yellow solid), yield: 90.7%.

MS m/z (ESI): 202.0 [M+1].

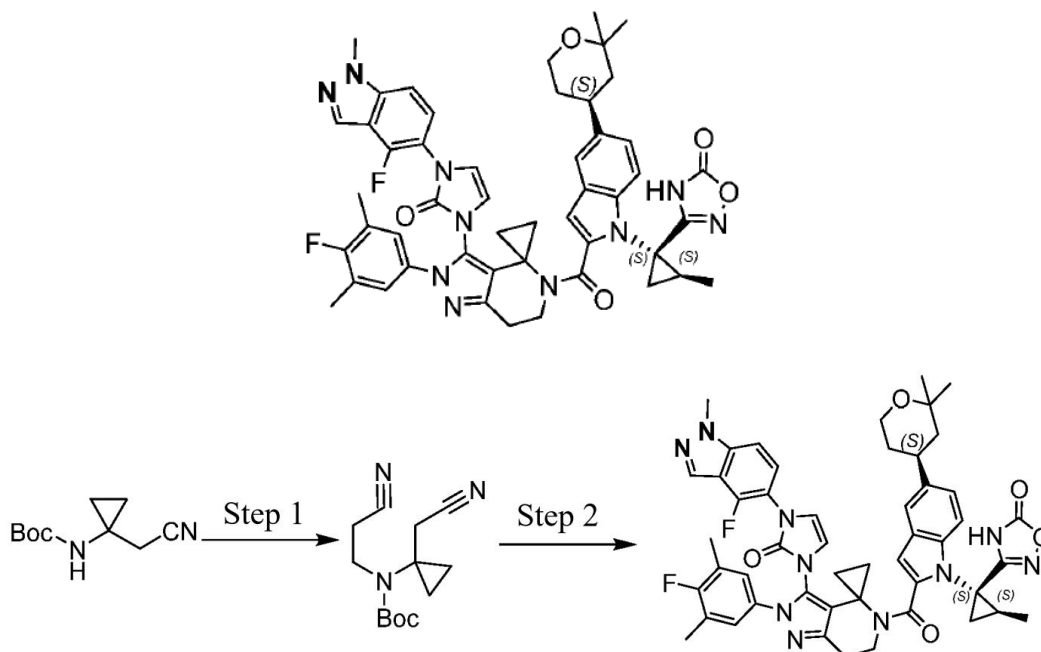
Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-2,2-dihydroxyl-1,3-dihydrobenzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

4-fluoro-1-methyl-1,3-dihydrobenzo[c]isothiazole2,2-dioxide was used as a raw material, following Example 95 Step 1 and Example 1, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-2,2-dihydroxyl-1,3-dihydrobenzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 934.3[M+1].

Example 99

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3'-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2'-(4-fluoro-3,5-dimethylphenyl)-2',5',6',7'-tetrahydrospiro[cyclopropan-1,4'-pyrazolo[4,3-c]pyridine]-5'-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: tert-butyl (2-cyanoethyl)(1-(cyanomethyl)cyclopropyl)carbamate

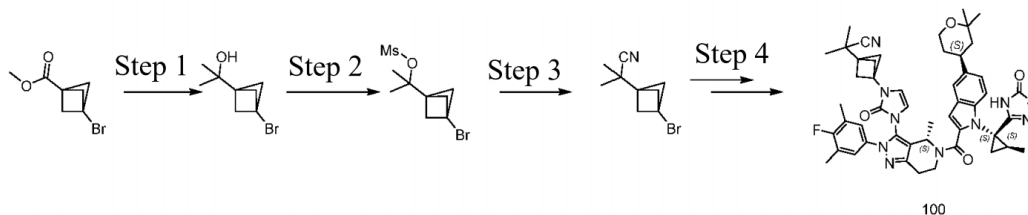
tert-Butyl (1-(cyanomethyl)cyclopropyl)carbamate (5 g, 25.48 mmol) and 3-bromopropanenitrile (3.41 g, 25.48 mmol) were dissolved in acetonitrile (100 mL), and potassium carbonate (10.56 g, 76.43 mmol) was added under nitrogen protection. The mixture was reacted under stirring at 25°C for 12 hours. The reaction solution was evaporated to dryness, and to the crude product was added saturated brine (130 mL), followed by extraction with ethyl acetate (80 mL × 2); and the organic phases were combined, washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain tert-butyl (2-cyanoethyl)(1-(cyanomethyl)cyclopropyl)carbamate (6 g, yield: 94.46%).

MS m/z (ESI): 250.2[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3'-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2'-(4-fluoro-3,5-dimethylphenyl)-2',5',6',7'-tetrahydrospiro[cyclopropan-1,4'-pyrazolo[4,3-c]pyridine]-5'-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

tert-Butyl (1-(cyanomethyl)cyclopropyl)carbamate was used as a raw material, following intermediate B, intermediate E and Example 1, to synthesize 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 895.4[M+1].

Example 100

Step 1: 2-(3-bromobicyclo[1.1.1]pentan-1-yl)propan-2-ol

Methyl 3-bromobicyclo[1.1.1]pentan-1-carboxylate was used as a raw material, following [Chemical Communications, 2022, vol. 58, # 71, p. 9886 - 9889], to obtain the target product 2-(3-bromobicyclo[1.1.1]pentan-1-yl)propan-2-ol.

MS m/z (ESI): 205.0[M+1].

Step 2: 2-(3-bromobicyclo[1.1.1]pentan-1-yl)propan-2-ylmethanesulfonate

2-(3-bromobicyclo[1.1.1]pentan-1-yl)propan-2-ol was used as a raw material, following Chemistry - A European Journal, 2019, vol. 25, # 25, p. 6290 - 6294, to obtain the target product 2-(3-bromobicyclo[1.1.1]pentan-1-yl)propan-2-ylmethanesulfonate.

MS m/z (ESI): 282.9[M+1].

Step 3: 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2-methylpropionitrile

2-(3-bromobicyclo[1.1.1]pentan-1-yl)propan-2-ylmethanesulfonate was used as a raw material, following [Bioorganic and Medicinal Chemistry Letters, 2007, vol. 17, # 8, p. 2150 - 2155], to obtain the target product 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2-methylpropionitrile.

MS m/z (ESI): 214.0[M+1].

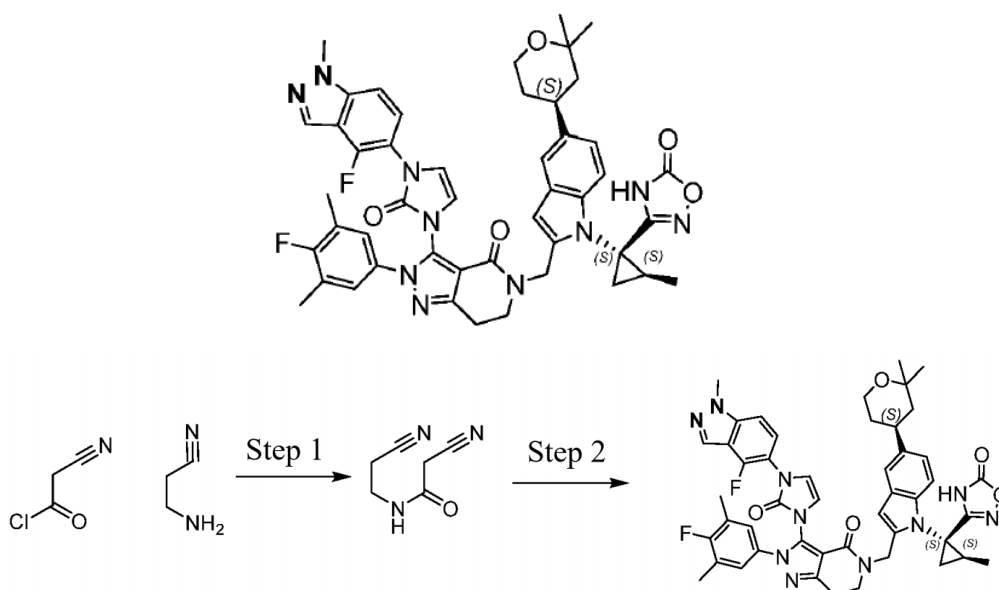
Step 4: 2-(3-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)bicyclo[1.1.1]pentan-1-yl)-2-methylpropionitrile

2-(3-Bromobicyclo[1.1.1]pentan-1-yl)-2-methylpropionitrile and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 868.4[M+1].

Example 101

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-carbonyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)methyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



5

Step 1: 2-cyano-N-(2-cyanoethyl)acetamide

3-aminopropanenitrile (2.71 g, 38.64 mmol) and triethylamine (11.73 g, 115.93 mmol, 16.16 mL) were dissolved in dichloromethane (80 mL), and 2-cyanoacetyl chloride (4 g, 38.64 mmol) was added under cooling in an ice water bath and nitrogen protection. The mixture was reacted under stirring at 0°C for 1
10 hours. To the reaction solution, saturated brine (130 mL) was added, and extracted with dichloromethane (40 mL × 2); and the organic phases were combined, washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain 2-cyano-N-(2-cyanoethyl)acetamide (5 g, yield: 94.34%).

MS m/z (ESI): 138.1[M+1].

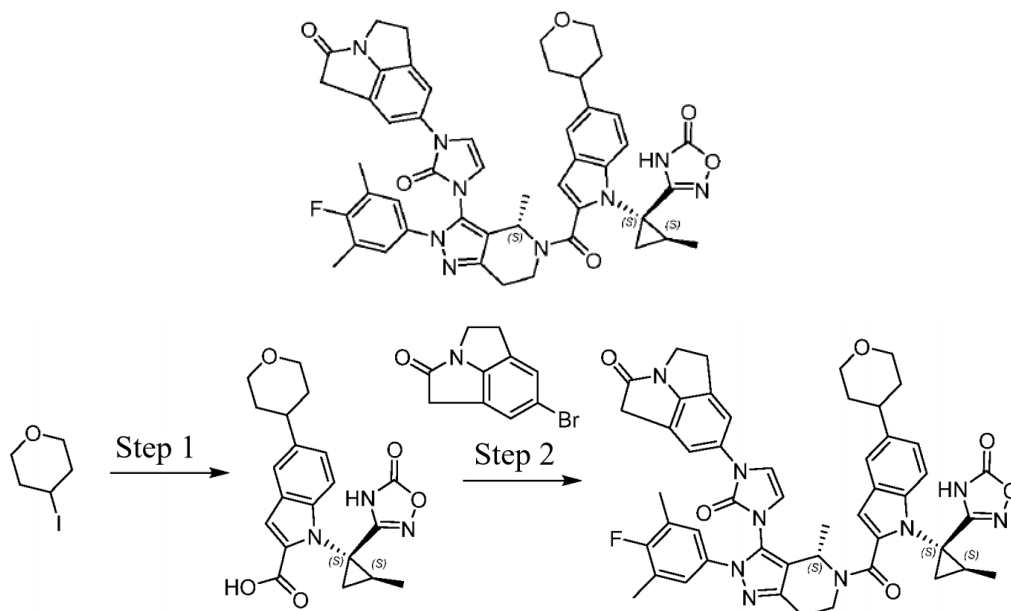
15 Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-carbonyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridin-5-yl)methyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

2-cyano-N-(2-cyanoethyl)acetamide was used as a raw material, following intermediate B, intermediate
20 E and Example 1, to synthesize 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-carbonyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-yl)methyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 869.4[M+1].

Example 102

3-((1S,2S)-1-(2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(2-carbonyl-1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indol-7-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 1-((1S,2S)-2-methyl-1-(5-carboxyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylic acid

4-iodotetrahydro-2H-pyran was used as a raw material, following intermediate A, to synthesize 1-((1S,2S)-2-methyl-1-(5-carboxyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indole-2-carboxylic acid.

MS m/z (ESI): 384.2[M+1].

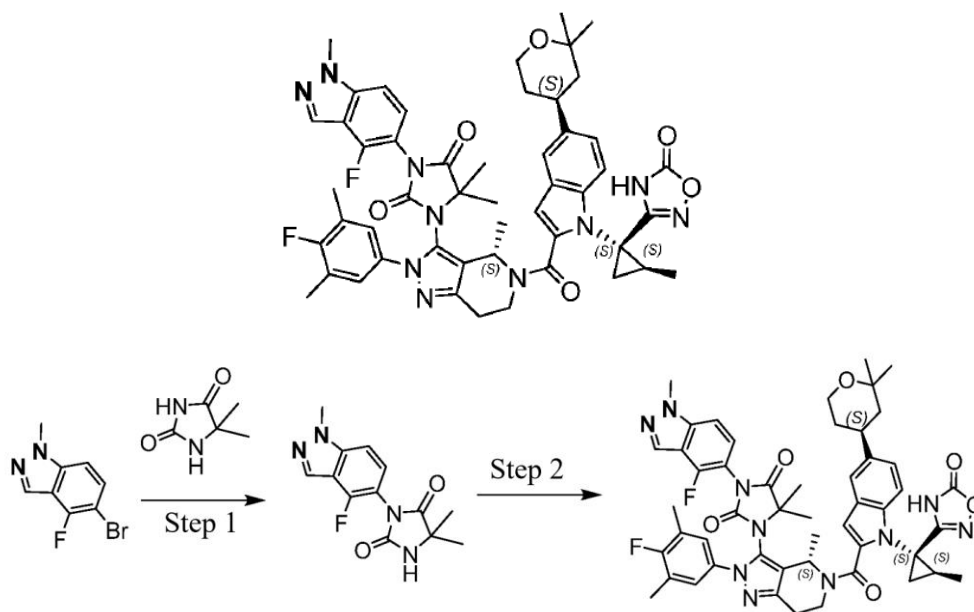
Step 2: 3-((1S,2S)-1-(2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(2-carbonyl-1,2,4,5-tetrahydropyrrolo[3,2,1-hi]indol-7-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

7-bromo-4,5-dihydropyrrolo[3,2,1-hi]indole-2(1H)-one was used as a raw material, following Example 1, to synthesize the target compound.

MS m/z (ESI): 864.4[M+1].

Example 103

1-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)-5,5-dimethylimidazolidin-2,4-dione



Step 1: 3-(4-fluoro-1-methyl-1H-indazol-5-yl)-5,5-dimethylimidazolidin-2,4-dione

5-bromo-4-fluoro-1-methyl-1H-indazole and 5,5-dimethylimidazolidin-2,4-dione were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 277.1[M+1].

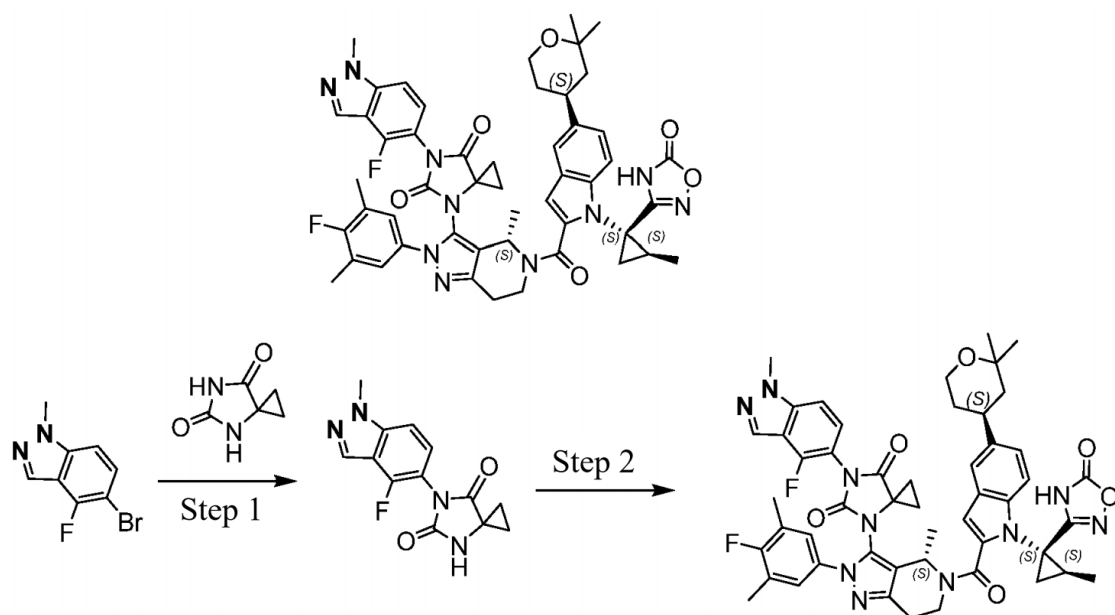
Step 2: 1-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(4-fluoro-1-methyl-1H-indazol-5-yl)-5,5-dimethylimidazolidin-2,4-dione

Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 927.4[M+1].

Example 104

4-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-6-(4-fluoro-1-methyl-1H-indazol-5-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione



Step 1: 6-(4-fluoro-1-methyl-1H-indazol-5-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione

5-bromo-4-fluoro-1-methyl-1H-indazole and 4,6-diazaspiro[2.4]heptan-5,7-dione were used as raw materials, following Example 1, to obtain the target product.

5 MS m/z (ESI): 275.1[M+1].

Step 2: 4-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-6-(4-fluoro-1-methyl-1H-indazol-5-yl)-4,6-diazaspiro[2.4]heptane-5,7-dione

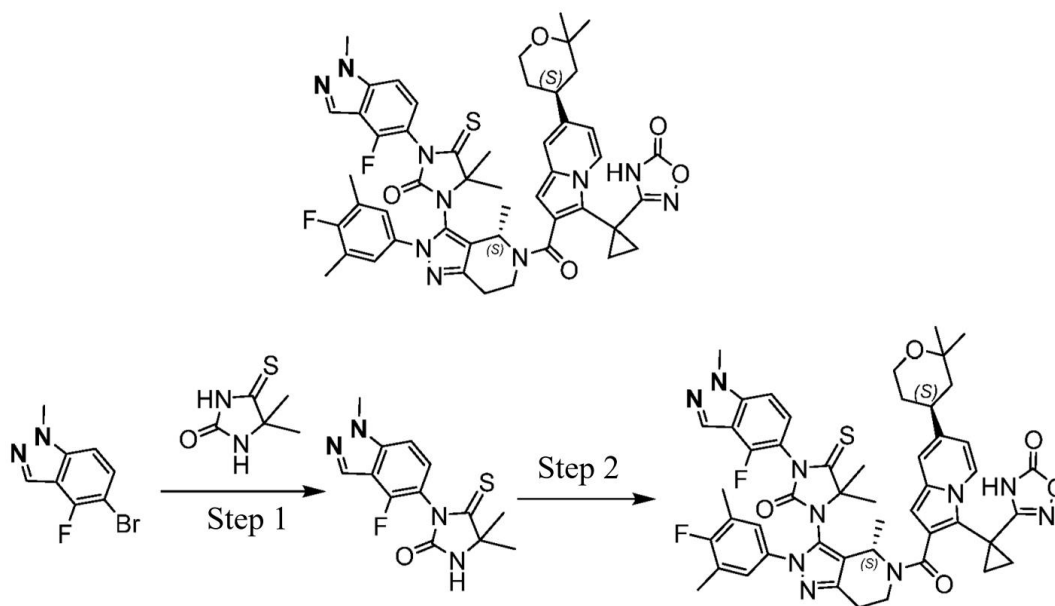
10 Intermediate C was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 925.4[M+1].

Example 105

3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-5,5-dimethyl-2-carbonyl-4-thioimidazolidin-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-

15 tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 1-(4-fluoro-1-methyl-1H-indazol-5-yl)-4,4-dimethyl-5-thioimidazolidin-2-one

5-bromo-4-fluoro-1-methyl-1H-indazole and 4,4-dimethyl-5-thioimidazolidin-2-one were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 293.1[M+1].

Step 2: 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-5,5-dimethyl-2-carbonyl-4-thioimidazolidin-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

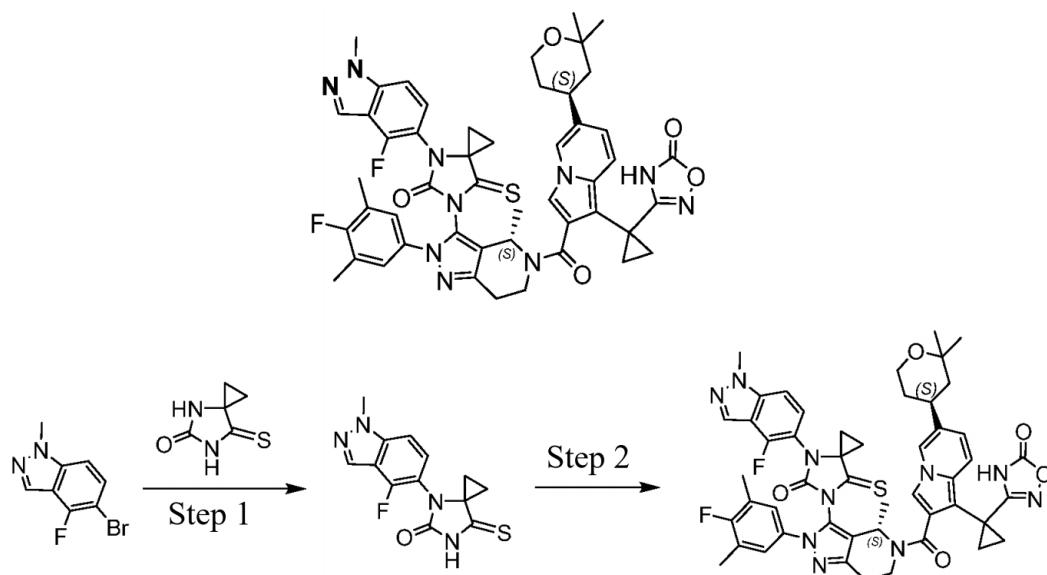
Example 52 Step 2 was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 929.4[M+1].

Example 106

3-(1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-5-carbonyl-7-thio-4,6-diazaspiro[2.4]heptan-6-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-

15 tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 4-(4-fluoro-1-methyl-1H-indazol-5-yl)-7-thio-4,6-diazaspiro[2.4]heptan-5-one

5-bromo-4-fluoro-1-methyl-1H-indazole and 7-thio-4,6-diazaspiro[2.4]heptan-5-one were used as raw materials, following Example 1, to obtain the target product.

5 MS m/z (ESI): 291.1[M+1].

Step 2: 3-(1-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(4-(4-fluoro-1-methyl-1H-indazol-5-yl)-5-carbonyl-7-thio-4,6-diazaspiro[2.4]heptan-6-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

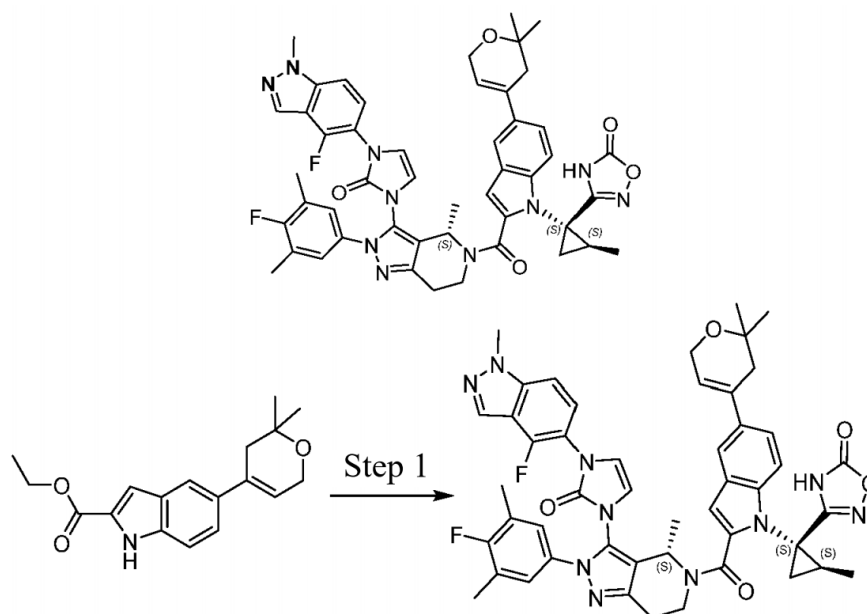
10 Following Example 1, the target product was obtained.

MS m/z (ESI): 927.4[M+1].

Example 107

3-((1S,2S)-1-(5-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

15



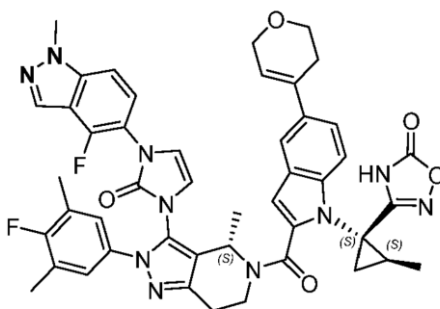
Step 1: 3-((1S,2S)-1-(5-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

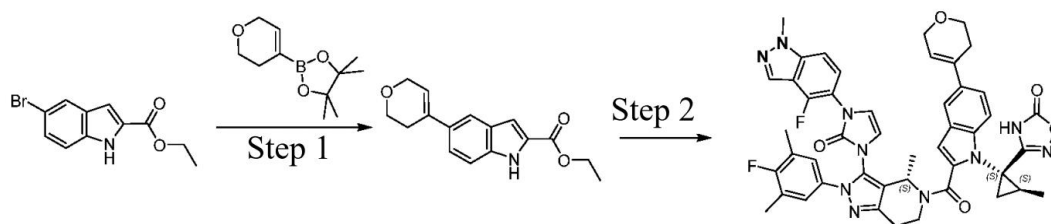
Ethyl 5-(2,2-dimethyl-3,6-dihydro-2H-pyran-4-yl)-1H-indole-2-carboxylate was used as a raw material, following intermediate A, intermediate B, intermediate E and Example 1, to synthesize the target product.

MS m/z (ESI): 881.4[M+1].

Example 108

3-((1S,2S)-1-(5-(3,6-dihydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one





Step 1: ethyl 5-(3,6-dihydro-2H-pyran-4-yl)-1H-indole-2-carboxylate

Ethyl 5-bromo-1H-indole-2-carboxylate (3 g, 11.19 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.35 g, 11.19 mmol), and potassium carbonate (3.09 g, 22.38 mmol) were dissolved in dioxane (30 mL), and under nitrogen protection, (409.37 mg, 559.48 μ mol) was added. The mixture was reacted under stirring at 90°C for 4 hours. The mixture was added saturated brine (50 mL) to quench the reaction, and extracted with ethyl acetate (50 mL $\times$ 2); and the organic phases were combined, washed with saturated brine (50 mL $\times$ 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluted with petroleum ether : ethyl acetate = 100 : 0 to 90 : 10), to obtain the target product ethyl 5-(3,6-dihydro-2H-pyran-4-yl)-1H-indole-2-carboxylate (1.3 g, yield: 42.82%).

MS m/z (ESI): 272.1[M+1].

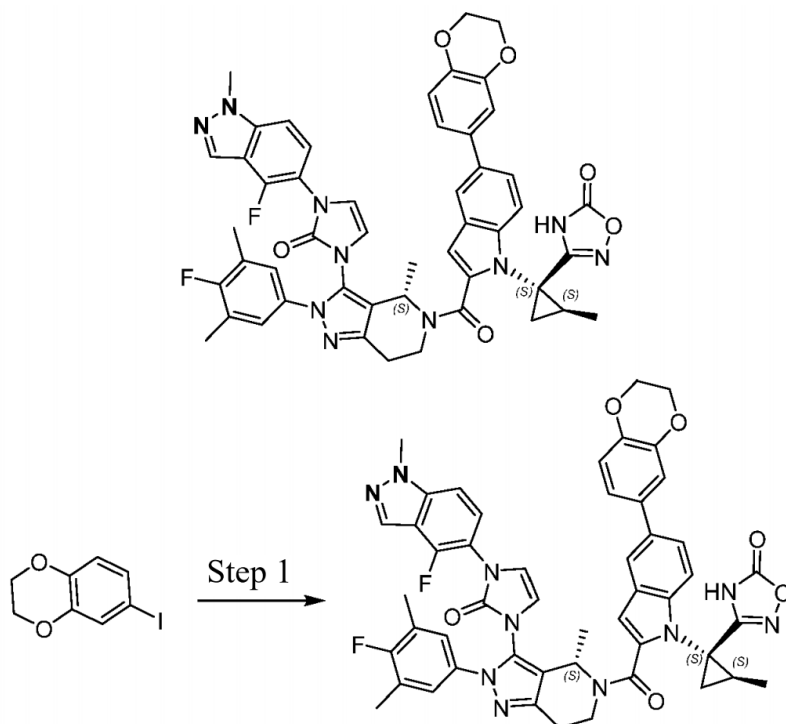
Step 2: 3-((1S,2S)-1-(5-(3,6-dihydro-2H-pyran-4-yl)-2((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Ethyl 5-(3,6-dihydro-2H-pyran-4-yl)-1H-indole-2-carboxylate was used as a raw material, following intermediate A, intermediate B, intermediate E and Example 1, to synthesize the target product.

MS m/z (ESI): 853.3[M+1].

Example 109

3-((1S,2S)-1-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

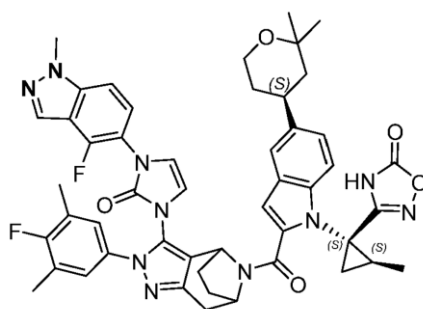


Step 1: 3-((1S,2S)-1-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

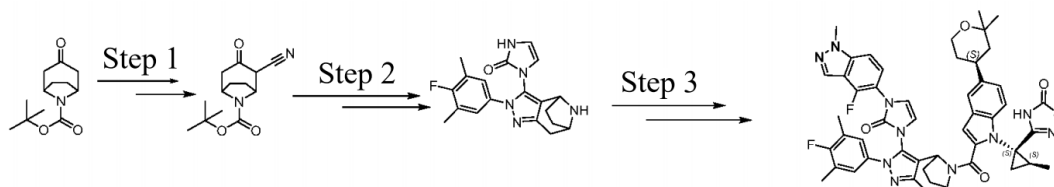
6-iodo-2,3-dihydrobenzo[b][1,4]dioxin was used as a raw material, following intermediate A, intermediate B, intermediate E and Example 1, to synthesize the target product.

MS m/z (ESI): 905.3 [M+1].

Example 110



110



Step 1: tert-butyl (1S,5R)-2cyano-3-carbonyl-8-azabicyclo[3.2.1]octane-8-carboxylate

N-tertbutoxycarbonyl-nortropaone was used as a raw material, following reference [*Eur. J. Org. Chem.* 2015, 6679-6686], to obtain the target product

5 MS m/z (ESI): 251.1[M+1].

Step 2: 1-(2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohept[c]pyrazol-3-yl)-1,3-dihydro-2H-imidazol-2-one

Following the synthesis for intermediate B, the target product was obtained

MS m/z (ESI): 354.2[M+1].

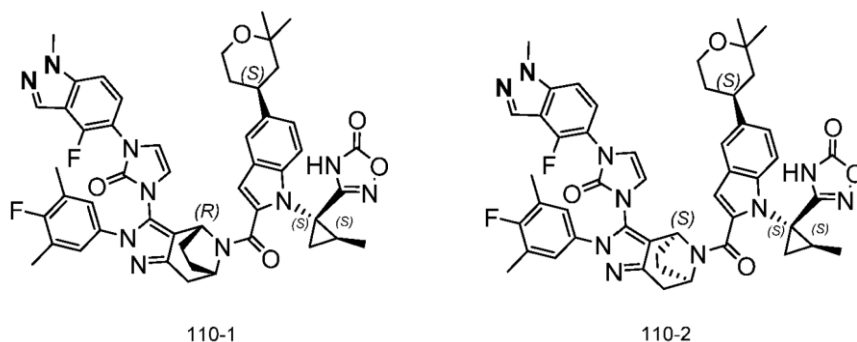
10 Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohept[c]pyrazole-9-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

15 Following step 3 for intermediate C and intermediate D, the product was obtained, and then 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 895.4[M+1].

Example 110-1 and Example 110-2

20 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4R,7S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,6,7,8-hexahydro-4,7-epiminocyclohept[c]pyrazole-9-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Example 110 was chirally resolved to obtain the target products 110-1 and 110-2

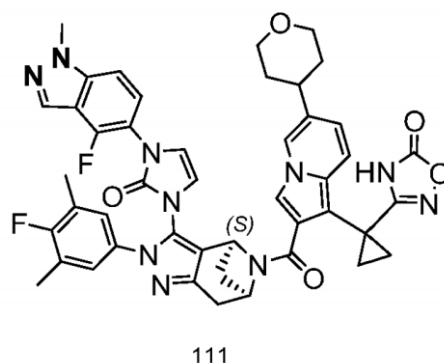
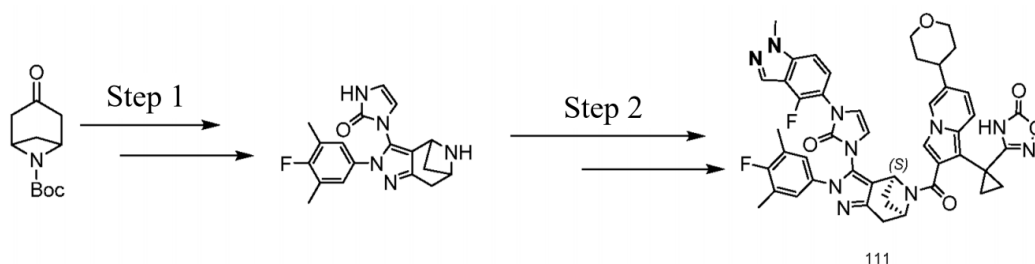
110-1 MS m/z (ESI): 895.4[M+1].

110-2 MS m/z (ESI): 895.4[M+1].

5

Example 111

3-(1-(2-((4S,6R)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-4,6-epiminoindazole-8-carbonyl)-6-(tetrahydro-2H-pyran-4-yl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10

Step 1: 1-(2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-4,6-epiminoindazol-3-yl)-1,3-dihydro-2H-imidazol-2-one--methane (1/1)

tert-Butyl 3-carbonyl-6-azabicyclo[3.1.1]heptan-6-carboxylate was used as a raw material, following

Example 110, to obtain the target product

15

MS m/z (ESI): 356.2[M+1].

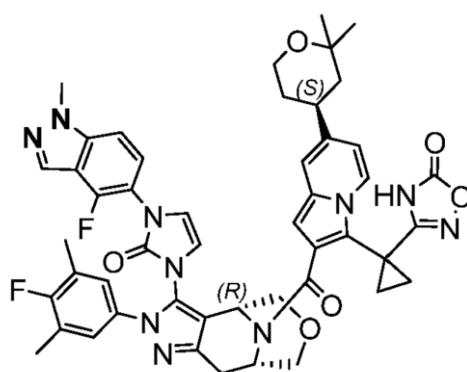
Step 2: 3-(1-(2-((4S,6R)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-4,6-epiminindazole-8-carbonyl)-6-(tetrahydro-2H-pyran-4-yl)indolizin-1-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Intermediate C and Intermediate D Step 3, the product was obtained, and then 5-bromo-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, the product was obtained, followed by chiral resolution, to obtain the target product

MS m/z (ESI): 839.3[M+1].

Example 112

3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4R,8S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-2,4,5,7,8,9-hexahydro-4,8-epiminooxocino[5,4-c]pyrazole-10-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

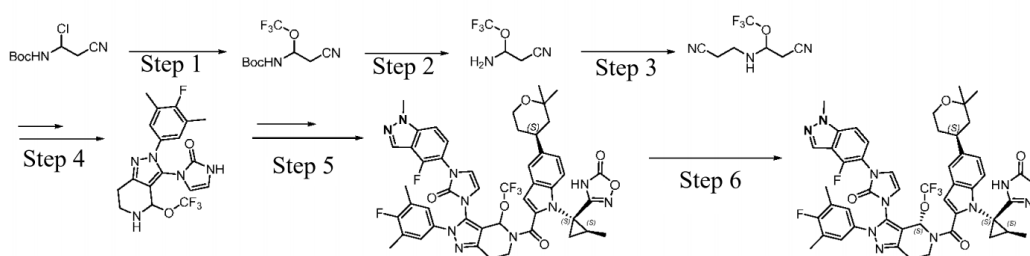


112

tert-Butyl 7-carbonyl-3-oxa-9-azabicyclo[3.3.1]nonan-9-carboxylate was used as a raw material, following the synthesis method in Example 110, to obtain the target product

MS m/z (ESI): 897.4[M+1].

Example 113



Step 1: tert-butyl (2-cyano-1-(trifluoromethoxy)ethyl)carbamate

At room temperature, tert-butyl(1-chloro-2-cyanoethyl)carbamate (2.04 g, 10 mmol) was dissolved in N,N-dimethylformamide (50mL), and then (E)-4-(tert-butyl)benzaldehydeoxy-trifluoromethyloxime (12.25 g, 50 mmol) and cesium carbonate (11.41 g, 35 mmol) were added,

followed by nitrogen replacement; the mixture was heated to 90°C, reacted for 14 hours, and cooled to room temperature, and then N-methylmorpholine (1.01 g, 10 mmol) was added, heated to 50°C, and reacted for 2 hours, cooled to room temperature, and filtered; the reaction solution was diluted with ethyl acetate (200 mL), then washed with saturated brine (35 mL × 4); and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph, to obtain tert-butyl (2-cyano-1-(trifluoromethoxy)ethyl)carbamate (1.52 g, yield 60%).

MS m/z (ESI): 255.1[M+H]⁺.

Step 2: 3-amino-3-(trifluoromethoxy)propanenitrile

At room temperature, tert-butyl (2-cyano-1-(trifluoromethoxy)ethyl)carbamate (1.52 g, 6 mmol) was dissolved in dichloromethane (15 mL), then trifluoroacetic acid (5 mL) was added, and the mixture was stirred at room temperature for 2 hours, with LCMS indicating the completion of the reaction, followed by spin-drying; and the residue was used directly in the next step.

MS m/z (ESI): 155.1[M+H]⁺.

Step 3: 3-((2-cyanoethyl)amino)-3-(trifluoromethoxy)propanenitrile

At room temperature, 3-amino-3-(trifluoromethoxy)propanenitrile (0.92 g, 6 mmol) was dissolved in acetonitrile (15 mL), and then bromopropanenitrile (2.01 g, 15 mmol) and potassium iodide (0.1 g, 0.6 mmol) were added, heated to reflux for 14 hours, and cooled to room temperature; the reaction solution was diluted with ethyl acetate (20 mL), and then washed with saturated brine (10 mL × 3; and the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatograph, to obtain 3-((2-cyanoethyl)amino)-3-(trifluoromethoxy)propanenitrile (0.49 g, yield 40%).

MS m/z (ESI): 208.1[M+H]⁺.

Step 4: 1-(2-(4-fluoro-3,5-dimethylphenyl)-4-(trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

3-((2-cyanoethyl)amino)-3-(trifluoromethoxy)propanenitrile was used as a raw material, following the synthesis step for intermediate B, to obtain 1-(2-(4-fluoro-3,5-dimethylphenyl)-4-(trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one.

MS m/z (ESI): 412.1[M+H]⁺.

Step 5: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-(2-(4-fluoro-3,5-dimethylphenyl)-4-(trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one was used as a raw material, following the synthesis step for intermediate E and Example 1, to obtain 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-

5 dimethylphenyl)-4-(trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 953.3[M+H]⁺.

Step 6: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-

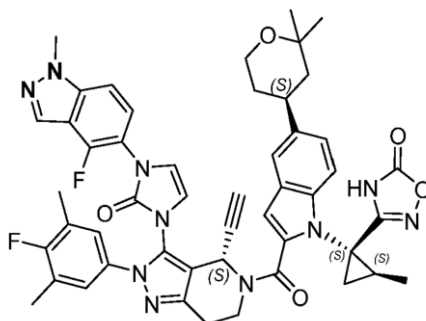
10 (trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(trifluoromethoxy)-

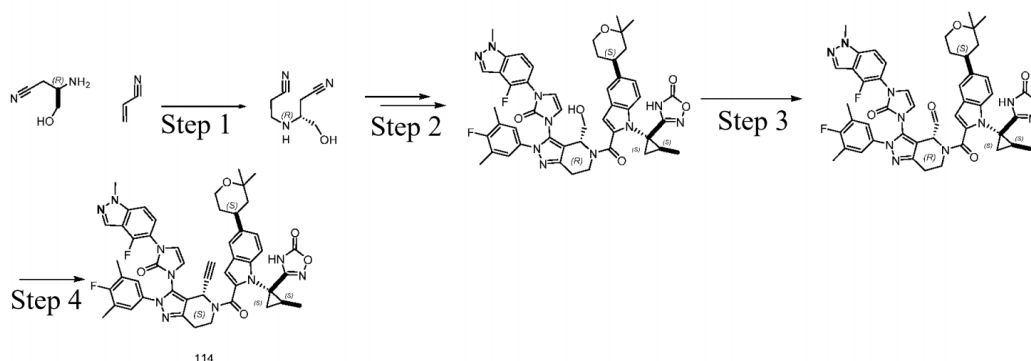
15 4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was chirally resolved to obtain 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(trifluoromethoxy)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 953.3[M+H]⁺.

Example 114



114



Step 1: (R)-3-((2-cyanoethyl)amino)-4-hydroxybutyronitrile

(R)-3-amino-4-hydroxybutyronitrile was used as a raw material, following Example 47 Step 1, to obtain the title product (R)-3-((2-cyanoethyl)amino)-4-hydroxybutyronitrile.

5 MS m/z (ESI): 154.1[M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((R)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(hydroxymethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10 (R)-3-((2-cyanoethyl)amino)-4-hydroxybutyronitrile was used as a raw material, following the synthesis method in Example 1, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((R)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(hydroxymethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

15 MS m/z (ESI): 899.3 [M+1].

Step 3: (R)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-4-carbaldehyde

20 In a 50 mL reaction bottle, 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((R)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(hydroxymethyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (100 mg, 111.24 μ mol) was dissolved in dichloromethane (5.0 mL),

25

then manganese dioxide (96.71 mg, 1.11 mmol) was added, and the reaction solution was stirred under nitrogen protection at 25°C for 10 hours. The reaction was stopped and filtered, and an aqueous solution (10 mL) was added to quench the reaction, followed by extraction with dichloromethane (10 mL × 2); and the organic phases were combined, washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, and filtered, and the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product (R)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-4-carbaldehyde (60 mg, a yellow solid), yield: 60.1%.

MS m/z (ESI): 897.3 [M+1].

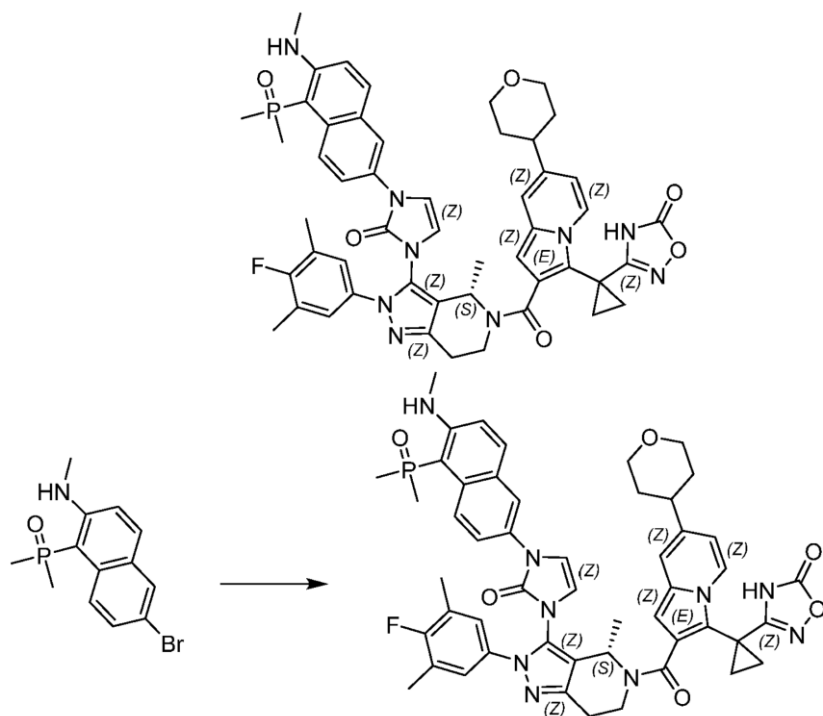
Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-4-ethynyl-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

In a 50 mL reaction bottle, (R)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-4-carbaldehyde (60 mg, 66.89 μmol) and 1-diazo-2-carbonylpropylphosphonate (19.28 mg, 100.34 μmol) were dissolved in methanol (5.0 mL), then potassium carbonate (18.49 mg, 133.79 μmol) was added, and the reaction solution was stirred under nitrogen at 25°C for 10 hours. The reaction was stopped and filtered, and aqueous solution (10 mL) was added to quench the reaction, followed by extraction with dichloromethane (10 mL × 2); and the organic phases were combined, washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, and filtered, and the resulting residue was subjected to prep-hplc, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-4-ethynyl-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one (16 mg), yield: 26.8%.

MS m/z (ESI): 893.3 [M+1].

Example 115

(S)-3-(1-(2-(3-(3-(5-(dimethylphosphoryl)-6-(methylamino)naphthalen-2-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3]pyridine-5-carbonyl)-7-(tetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



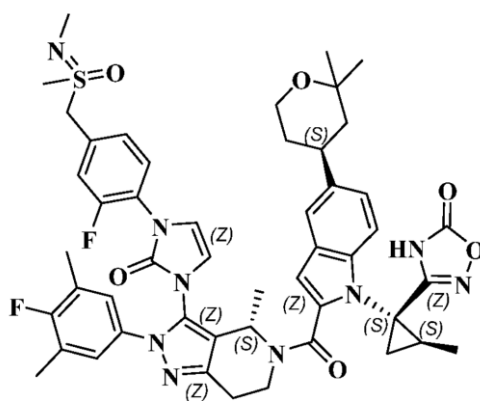
(6-bromo-2-(methylamino)naphthalen-1-yl)dimethylphosphine oxide was used as a raw material, following Example 52, to synthesize the target product.

MS m/z (ESI): 924.4 $[M+1]$.

5

Example 116

3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)methyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



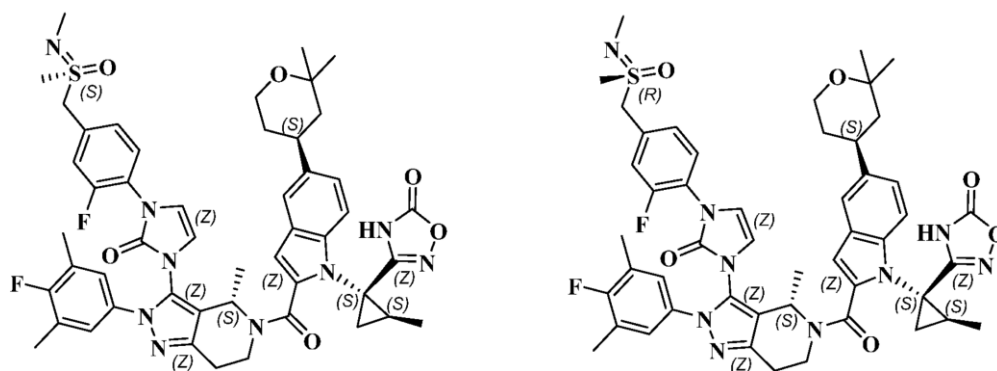
10

(4-bromo-3-fluorobenzenemethyl)(methyl)(methylimino)-16-sulfanone was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 934.4 [M+1].

Examples 116-1 and 116-2

- 5 3-((1S,2S)-1-(2-((S)-3-(3-(4-(((S)-N,S-dimethylsulfonimidoyl)methyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one and 3-((1S,2S)-1-(2-((S)-3-(3-(4-(((R)-N,S-dimethylsulfonimidoyl)methyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one
- 10

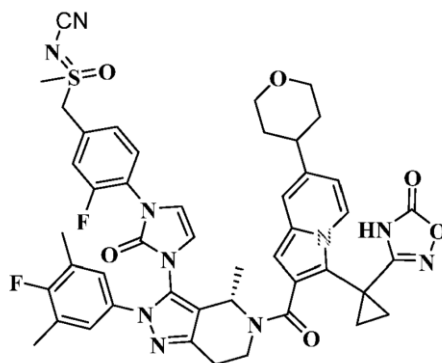


- Example 116 product 3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)methyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was chirally resolved to obtain the target product.
- 15

MS m/z (ESI): 934.4[M+1].

Example 117

- 20 N-((3-fluoro-4-(3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-5-(3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-7-(tetrahydro-2H-pyran-4-yl)indolizine-2-carbonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)phenylmethyl)(methyl)(carbonyl)-16-sulfaneylidene)cycanoamide

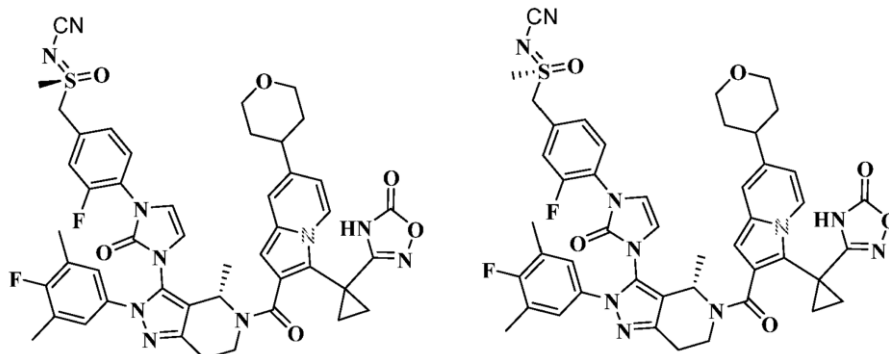


N-((4-bromo-3-fluorophenylmethyl)(methyl)(carbonyl)-l6-sulfaneylidene)cyanoamide was used as a raw material, following Example 52, to obtain the target product.

MS m/z (ESI): 903.3[M+1].

5 Examples 117-1 and 117-2

N-((R)-(3-fluoro-4-(3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-5-(3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-7-(tetrahydro-2H-pyran-4-yl)indolizine-2-carbonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)phenylmethyl)(methyl)(carbonyl)-l6-sulfaneylidene)cyanoamide and N-((S)-(3-fluoro-4-(3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-5-(3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-7-(tetrahydro-2H-pyran-4-yl)indolizine-2-carbonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)phenylmethyl)(methyl)(carbonyl)-l6-sulfaneylidene)cyanoamide

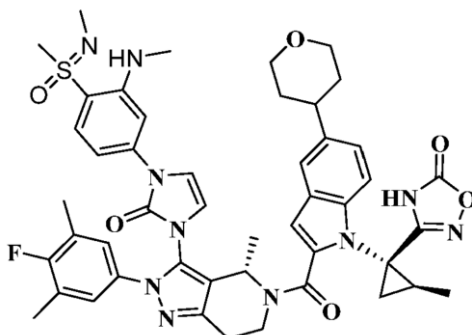


15 Example 117 product N-((3-fluoro-4-(3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-5-(3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-7-(tetrahydro-2H-pyran-4-yl)indolizine-2-carbonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)phenylmethyl)(methyl)(carbonyl)-l6-sulfaneylidene)cyanoamide was chirally resolved, to obtain the target product.

MS m/z (ESI): 903.3[M+1].

Example 118

3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

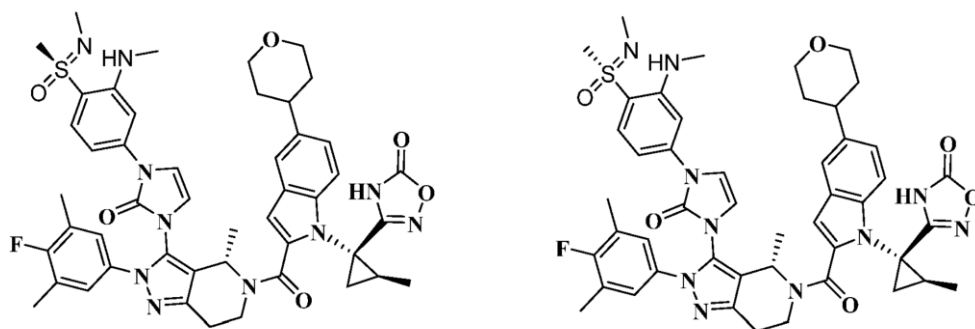


(4-bromo-2-(methylamino)phenyl)(methyl)(methylimino)-l6-sulfanone was used as a raw material, following Example 52, to obtain the target product.

MS m/z (ESI): 903.4[M+1].

Examples 118-1 and 118-2

3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one and 3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-(tetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

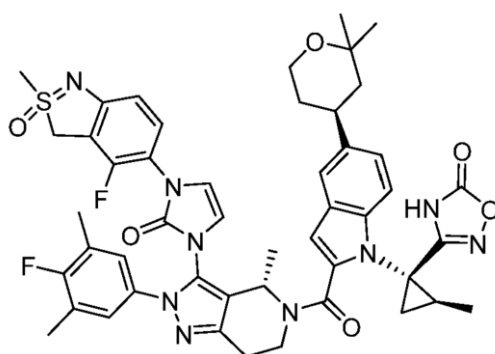


Example 118 product was chirally resolved to obtain the target product.

MS m/z (ESI): 903.4[M+1].

Example 119

- 5 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-2-methyl-2-hydroxyl-3H-214-benzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

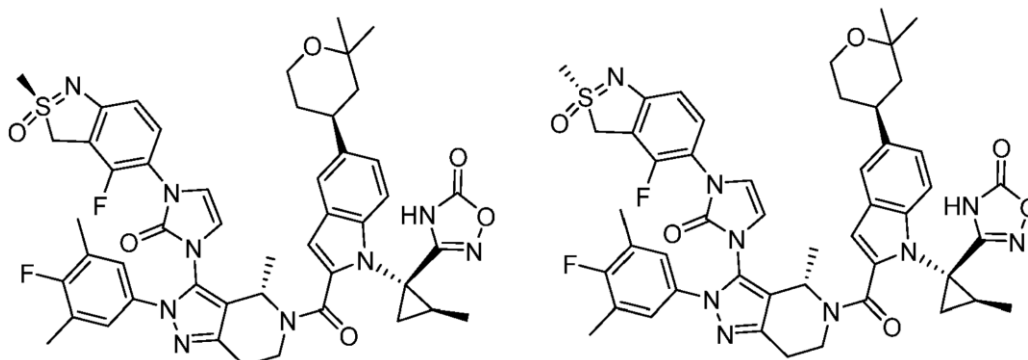


- 10 5-bromo-4-fluoro-2-methyl-3H-214-benzo[c]isothiazole2-oxide was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 918.4 [M+1].

Example 119-1 and 119-2

- 15 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-((S)-4-fluoro-2-methyl-2-hydroxyl-3H-214-benzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one and 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-((R)-4-fluoro-2-methyl-2-hydroxyl-3H-214-benzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one
- 20

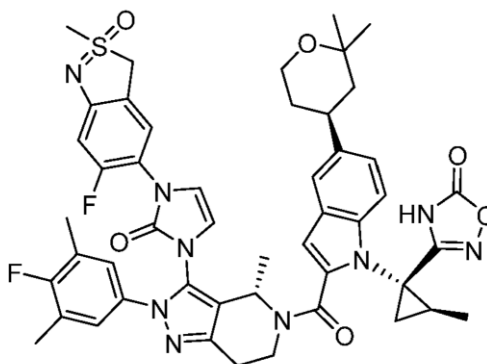


Example 119 product was chirally resolved to obtain the target product.

MS m/z (ESI): 918.4[M+1].

Example 120

- 5 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(6-fluoro-2-methyl-2-hydroxyl-3H-214-benzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

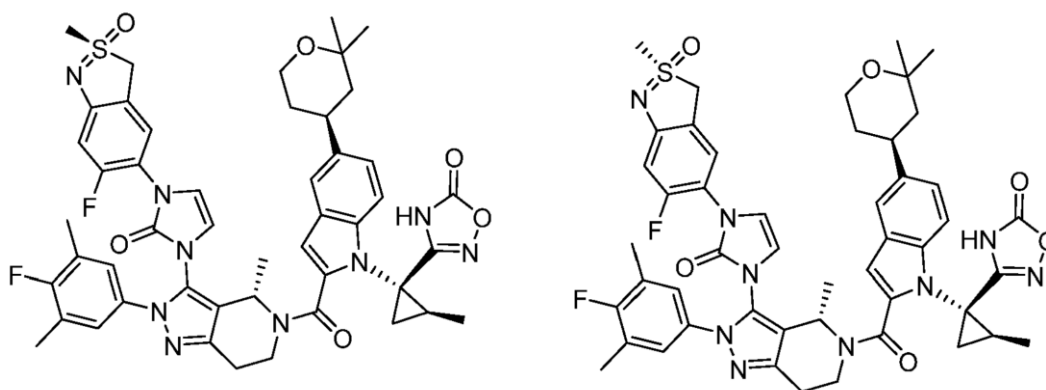


- 10 5-bromo-6-fluoro-2-methyl-3H-214-benzo[c]isothiazole2-oxide was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 918.4[M+1].

Examples 120-1 and 120-2

- 15 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-((R)-6-fluoro-2-methyl-2-hydroxyl-3H-214-benzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one and 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-((S)-6-fluoro-2-methyl-2-hydroxyl-3H-214-benzo[c]isothiazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one
- 20

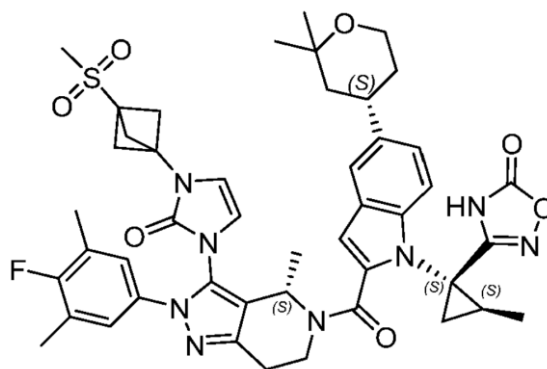


Example 120 product was chirally resolved to obtain the target product.

MS m/z (ESI): 918.4 [M+1].

Example 121

- 5 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylsulfonyl)bicyclo[1.1.1]pentan-1-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

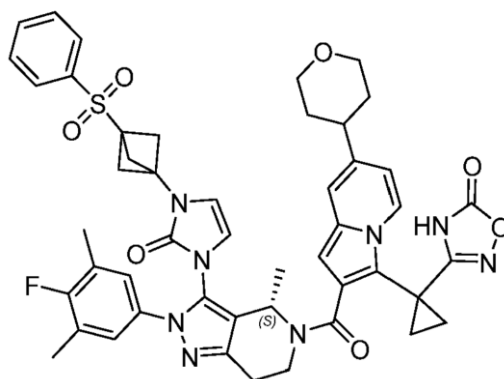


- 10 1-bromo-3-(methylsulfonyl)bicyclo[1.1.1]pentane was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 879.4[M+1].

Example 122

- 15 (S)-3-(1-(2-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(3-(benzenesulfonyl)bicyclo[1.1.1]pentan-1-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-(tetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one



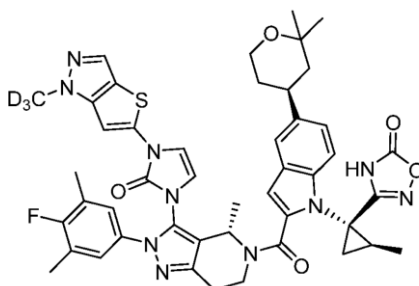
1-bromo-3-(benzenesulfonyl)bicyclo[1.1.1]pentane was used as a raw material, following Example 52, to obtain the target product.

MS m/z (ES): 899.3 [M+1].

5

Example 123

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(methyl-d3)-1H-thieno[3,2-c]pyrazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



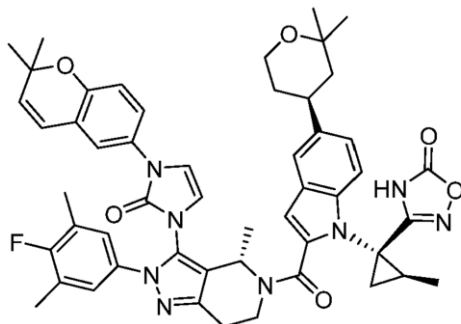
10

5-bromo-1-(methyl-d3)-1H-thieno[3,2-c]pyrazole was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 874.4[M+1].

Example 124

3-((1S,2S)-1-(2-((S)-3-(3-(2,2-dimethyl-2H-chromene-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



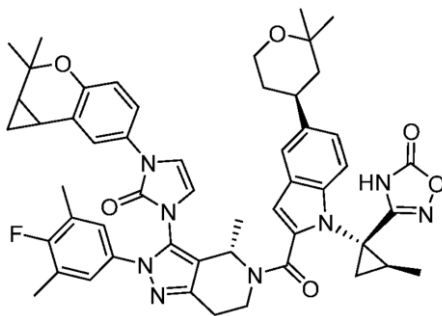
6-bromo-2,2-dimethyl-2H-chromene was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 893.4[M+1].

5

Example 125

3-((1S,2S)-1-(2-((4S)-3-(3-(2,2-dimethyl-1,1a,2,7b-tetrahydrocyclopropeno[c]chromen-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10

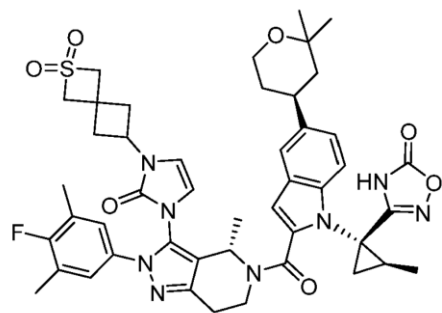
6-bromo-2,2-dimethyl-1,1a,2,7b-tetrahydrocyclopropeno[c]chromene was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 907.4[M+1].

Example 126

15

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(2,2-dihydroxyl-2-thiaspiro[3.3]heptan-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



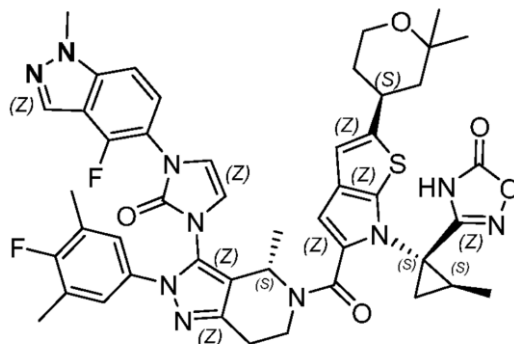
20

6-bromo-2-thiaspiro[3.3]heptane2,2-dioxide was used as a raw material, following Example 53, to obtain the target product.

MS m/z (ESI): 879.4[M+1].

Example 127

- 5 3-((1S,2S)-1-(2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-5-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-6H-thieno[2,3-b]pyrrole-6-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

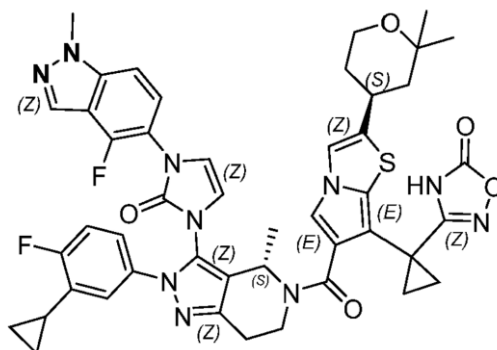


- 10 Ethyl 2-bromo-6H-thieno[2,3-b]pyrrole-5-carboxylate was used as a raw material, following intermediate A, intermediate E and Example 1, to obtain the target product.

MS m/z (ESI): 889.3[M+1].

Example 128

- 15 3-(1-(6-((S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)pyrrolo[2,1-b]thiazol-7-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

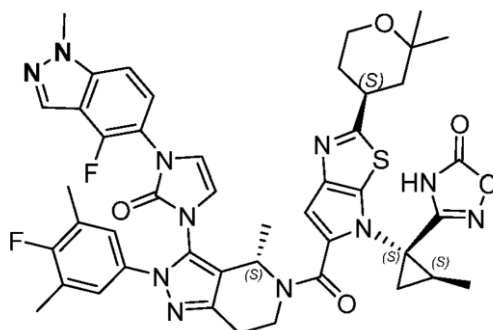


3-(5-bromothiazol-2-yl)propanenitrile was used as a raw material, following ECCOGENE-WO 2022/17338, 2022, A1, to obtain the target product.

- 20 MS m/z (ESI): 887.3[M+1].

Example 129

3-((1S,2S)-1-(2-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-5-((S)-3-(3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-4H-pyrrolo[3,2-d]thiazol-4-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



5

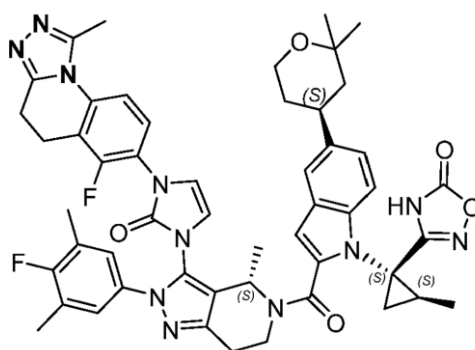
Following the synthesis method in Example 127, the product was obtained.

MS m/z (ESI): 890.3[M+1].

Example 130

10

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(6-fluoro-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



130

15

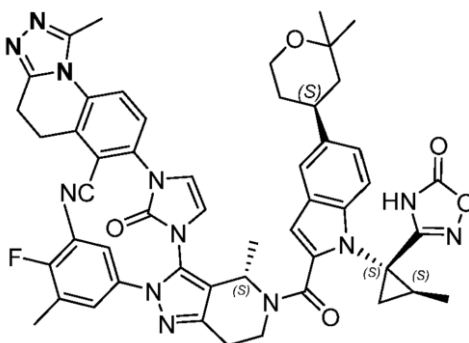
7-bromo-6-fluoro-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 936.4[M+1].

Example 131

20

7-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-6-carbonitrile



131

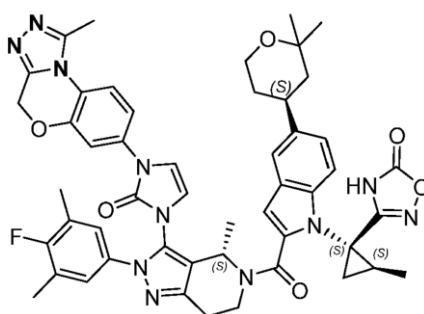
7-bromo-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-6-carbonitrile was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 943.4[M+1].

5

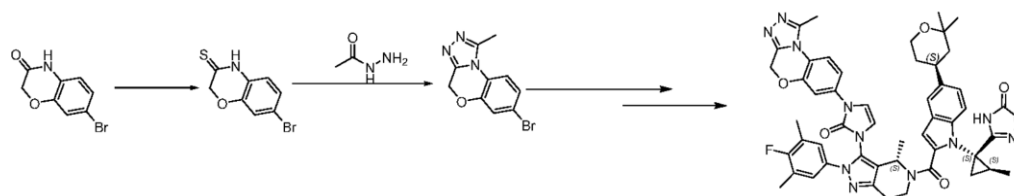
Example 132

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



132

10



Step 1: 7-bromo-2H-benzo[b][1,4]oxazine-3(4H)-thione

A mixture of 7-bromo-2H-benzo[b][1,4]oxazin-3(4H)-one (3g, 13.16 mmol), a Lawesson reagent (3.19 g, 7.89 mmol), and toluene (100 mL) was stirred at 110°C for 1 hour, cooled, directly concentrated with silica gel, and separated by column chromatography (PE/EtOAc = 10 : 1), to obtain 7-bromo-2H-benzo[b][1,4]oxazine-3(4H)-thione as a light yellow solid (600 mg, yield: 18%)

15

MS m/z (ESI): 244.0 246.0 [M+1].

Step 2: 7-bromo-1-methyl-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazine

A mixture of 7-bromo-2H-benzo[b][1,4]oxazin-3(4H)-thione (300 mg, 1.23mmol), acetylhydrazine (109 mg, 1.47 mmol), and n-butanol (10mL) was stirred at 120°C for 24 hours, cooled, directly concentrated with silica gel, and separated by column chromatography (DCM/MeOH = 10 : 1), to obtain 7-bromo-1-methyl-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazine (190 mg, yield: 58%)

MS m/z (ESI): 266.0 268.0[M+1].

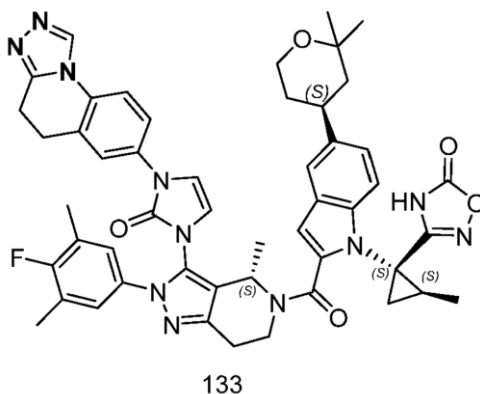
Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

7-bromo-1-methyl-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]oxazine was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 920.4[M+1].

Example 133

3-((1S,2S)-1-(2-((S)-3-(3-(4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

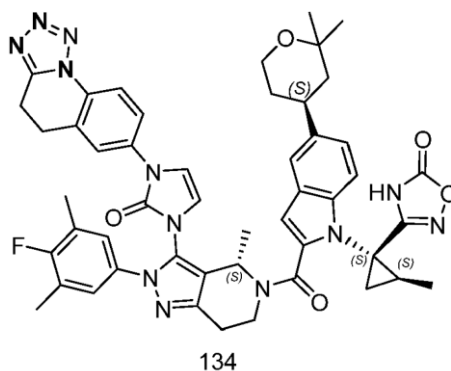


7-bromo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 904.4[M+1].

Example 134

3-((1S,2S)-1-(2-((S)-3-(3-(4,5-dihydro-1,2,4-triazolo[4,3-a]quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



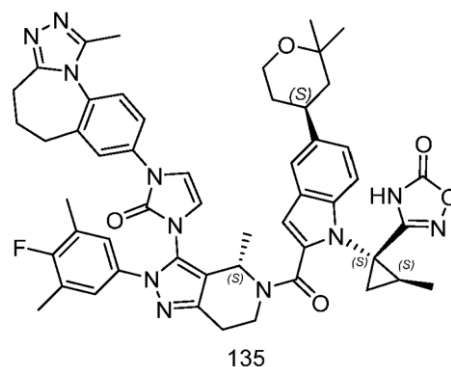
7-bromo-4,5-dihydro-1,2,4-oxadiazolo[1,5-a]quinoline was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 905.4[M+1].

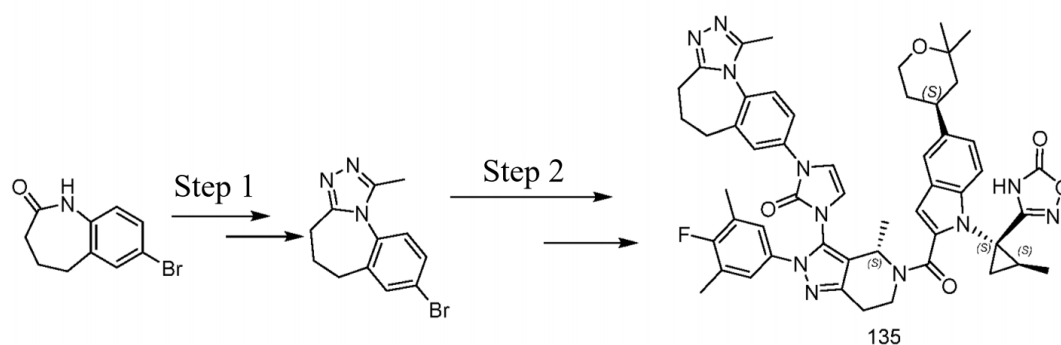
5

Example 135

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepin-8-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10



Step 1: 8-bromo-1-methyl-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine

7-bromo-1,3,4,5-tetrahydro-2H-1-benzazepine-2-one was used as a raw material, following Example 132 Step 1 and Step 2, to obtain 8-bromo-1-methyl-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine

15

MS m/z (ESI): 278.0 280.0[M+1].

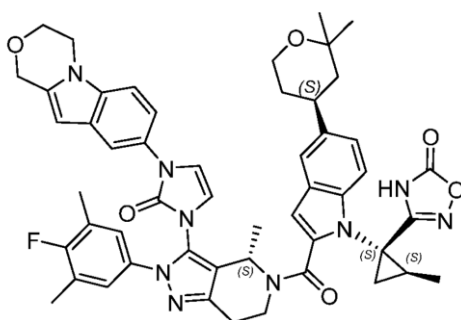
Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepin-8-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

8-bromo-1-methyl-5,6-dihydro-4H-benzo[f][1,2,4]triazolo[4,3-a]azepine was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 932.4[M+1].

Example 136

10 3-((1S,2S)-1-(2-((S)-3-(3-(3,4-dihydro-1H-[1,4]oxahydrazino[4,3-a]indol-8-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



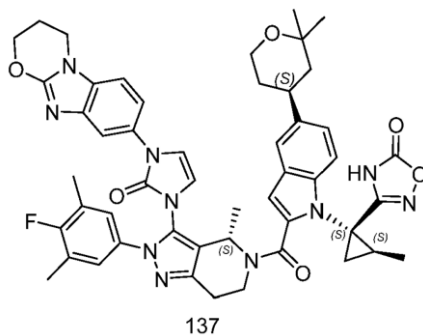
136

15 8-bromo-3,4-dihydro-1H-[1,4]oxahydrazino[4,3-a]indole was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 906.4[M+1].

Example 137

20 3-((1S,2S)-1-(2-((S)-3-(3-(3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]oxazin-8-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



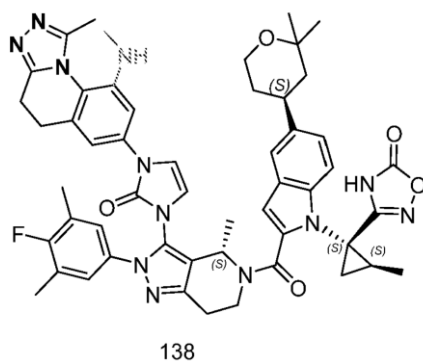
8-bromo-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]oxazine was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 907.4[M+1].

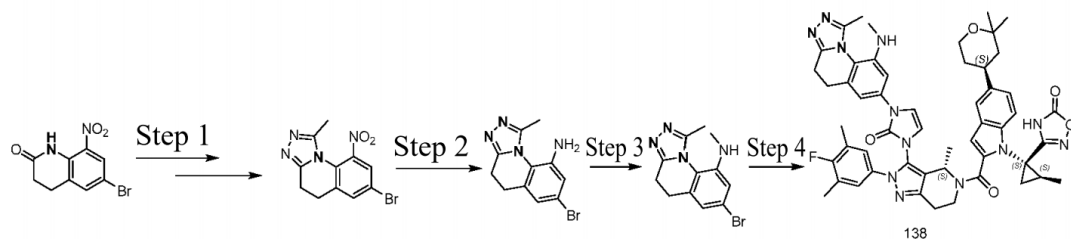
5

Example 138

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-9-(methylamino)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10



Step 1: 7-bromo-1-methyl-9-nitro-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline

6-bromo-8-nitro-3,4-dihydroquinoline-2(1H)-one was used as a raw material, following Example 1, to obtain the target product

15

MS m/z (ESI): 309.0 311.0 [M+1].

Step 2: 7-bromo-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-9-amine

To a solution of 7-bromo-1-methyl-9-nitro-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline (2 g, 6.49 mmol) in ethanol (20 mL) and water (15 mL) was added sodium dithionite (9.03 g, 51.92 mmol), and the mixture was stirred at room temperature for 12 hours, and filtered; the filter cake was washed with EtOH, and water was added to filtrate, followed by extraction with EtOAc; and the organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to dryness, to obtain 7-bromo-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-9-amine (1.5 g, yield: 83.1%)

MS m/z (ESI): 279.0 281.0 [M+1].

Step 3: 7-bromo-N,1-dimethyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-9-amine

To a solution of 7-bromo-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-9-amine (600 mg, 2.16 mmol) in DMF (10 mL), NaH (130 mg, 3.24 mmol, 60% purity) was added and stirred at room temperature for 30 minutes, and then iodomethane (457 mg, 3.24 mmol) was added dropwise and stirred at room temperature for 1 hour; water was added, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; the filtrate was concentrated under reduced pressure to dryness and separated by column chromatography, to obtain 7-bromo-N,1-dimethyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-9-amine as a light yellow oil (300 mg, yield: 47.6%)

MS m/z (ESI): 293.0 295.0 [M+1].

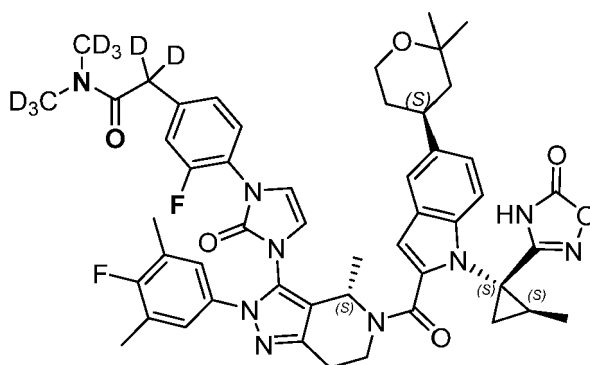
Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-9-(methylamino)-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

7-bromo-N,1-dimethyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline-9-amine was used as a raw material, following Example 1, to obtain the target product

MS m/z (ESI): 947.4 [M+1].

Example 139

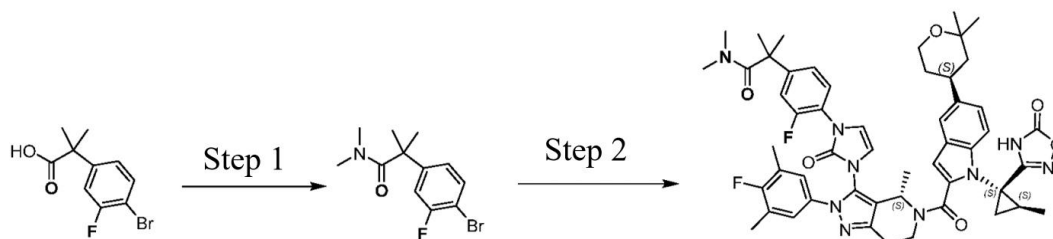
2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-di(methyl-d3)acetamide-d2



Following the synthesis for Example 64, the target product was obtained

MS m/z (ESI): 922.4 $[M+1]$.

Example 140



5

Step 1: 2-(4-bromo-3-fluorophenyl)-N,N,2-trimethylpropionamide

2-(4-Bromo-3-fluorophenyl)-2-methylpropanoic acid was used as a raw material, following Example 139 Step 1, to obtain the target product.

MS m/z (ESI): 288.0, 290.0 $[M+1]$.

10

Step 2 2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S, 2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N,2-trimethylpropionamide

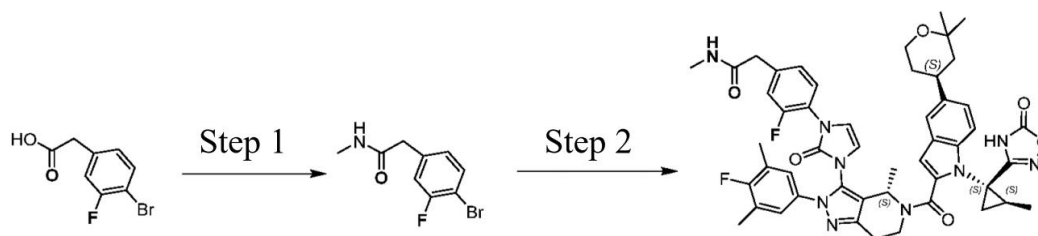
2-(4-bromo-3-fluorophenyl)-N,N,2-trimethylpropionamide was used as a raw material, following

15

Example 1, finally to obtain the target product.

MS m/z (ESI): 942.4 $[M+1]$.

Example 141



Step 1: 2-(4-bromo-3-fluorophenyl)-N-methylacetamide

20

2-(4-bromo-3-fluorophenyl)acetic acid was used as a raw material, following Example 139, Step 1 reaction, to obtain the target product.

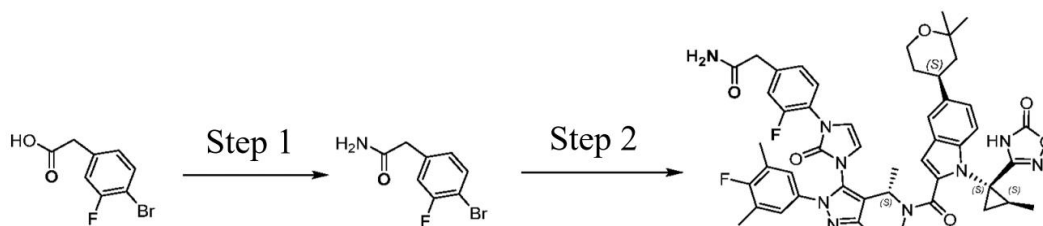
MS m/z (ESI): 246.0, 248.0 [M+1].

Step 2 2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S, 2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4, 3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N-methylacetamide

2-(4-bromo-3-fluorophenyl)-N-methylacetamide was used as a raw material, following Example 1, finally to obtain the target product.

MS m/z (ESI): 900.4 [M+1].

Example 142



Step 1: 2-(4-bromo-3-fluorophenyl)acetamide

2-(4-bromo-3-fluorophenyl)acetic acid was used as a raw material, following Example 139, Step 1 reaction, to obtain the target product.

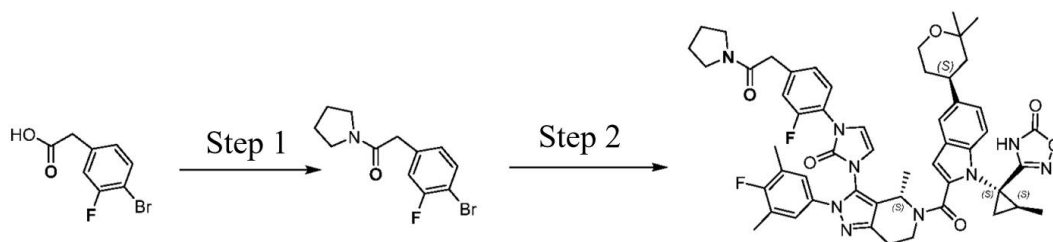
MS m/z (ESI): 232.0, 234.0 [M+1].

Step 2 2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4, 3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)acetamide

2-(4-bromo-3-fluorophenyl)acetamide was used as a raw material, following Example 1, finally to obtain the target product.

MS m/z (ESI): 886.4 [M+1].

Example 143



Step 1: 2-(4-bromo-3-fluorophenyl)-1-(pyrrolidin-1-yl)ethan-1-one

2-(4-bromo-3-fluorophenyl)acetic acid was used as a raw material, following Example 139, Step 1 reaction, to obtain the target product.

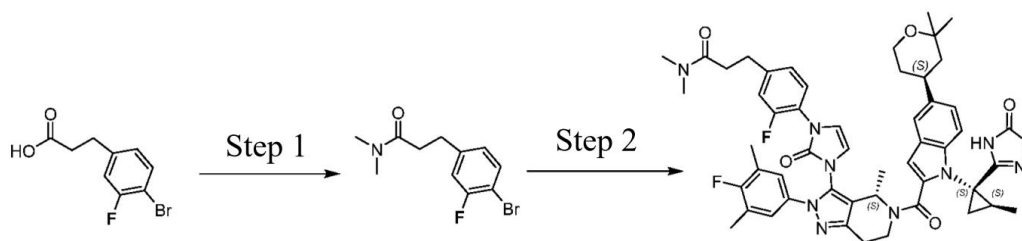
MS m/z (ESI): 286.0, 288.0 [M+1].

Step 2 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(2-carbonyl-2-(pyrrolidin-1-yl)ethyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

2-(4-bromo-3-fluorophenyl)-1-(pyrrolidin-1-yl)ethan-1-one was used as a raw material, following Example 1, finally to obtain the target product.

MS m/z (ESI): 940.4 [M+1].

Example 144



Step 1: 3-(4-bromo-3-fluorophenyl)-N,N-dimethylpropionamide

3-(4-bromo-3-fluorophenyl)propanoic acid was used as a raw material, following Example 139, Step 1 reaction, to obtain the target product.

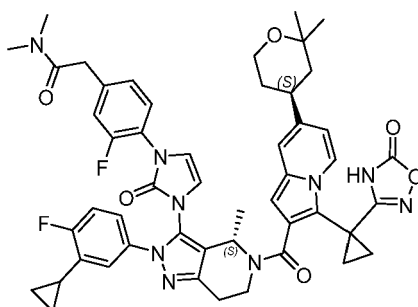
MS m/z (ESI): 274.0, 276.0 [M+1].

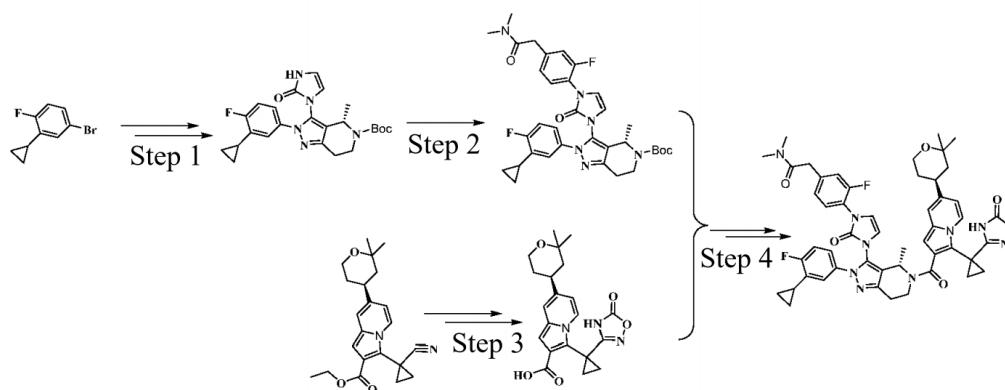
Step 2 3-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylpropionamide

3-(4-bromo-3-fluorophenyl)-N,N-dimethylpropionamide was used as a raw material, following Example 1, finally to obtain the target product.

MS m/z (ESI): 928.4 [M+1].

Example 145





Step 1: tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl 4-bromo-2-cyclopropyl-1-fluorophenyl was used as a raw material, following the synthesis in intermediate B Step 3 to Step 5, to obtain the title product (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

MS m/z (ESI): 454.2 [M+1].

Step 2: tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(4-(2-(dimethylamino)-2-carbonylethyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and 2-(4-bromo-3-fluorophenyl)-N,N-dimethylacetamide were used as raw materials, following the synthesis steps in Example 1, to obtain the title product tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(4-(2-(dimethylamino)-2-carbonylethyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

MS m/z (ESI): 633.3 [M+1].

Step 3: (S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid

Ethyl (S)-3-(1-cyanocyclopropyl)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizine-2-carboxylate was used as a raw material, following the synthesis steps in intermediate A Step 4 and Step 5, to obtain the title product (S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid.

MS m/z (ESI): 398.2 [M+1].

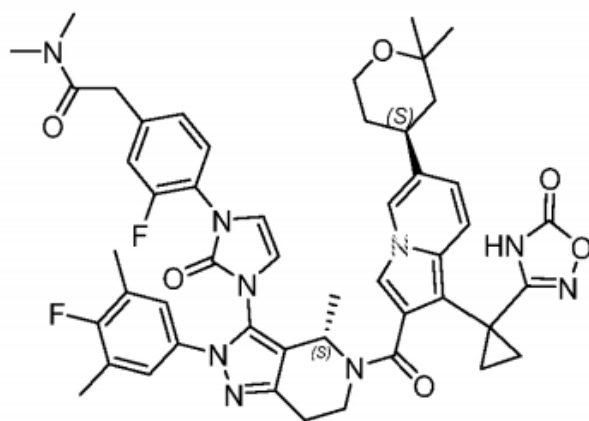
Step 4: 2-(4-(3-((S)-2-(3-cyclopropyl-4-fluorophenyl)-5-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carbonyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylacetamide

tert-Butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(4-(2-(dimethylamino)-2-carbonylethyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and (S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid were used as raw materials, following the synthesis for intermediate C Step 2 and Step 3, to obtain the title product 2-(4-(3-((S)-2-(3-cyclopropyl-4-fluorophenyl)-5-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carbonyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylacetamide.

MS m/z (ESI): 912.4 [M+1].

Example 146

2-(4-(3-((S)-5-(6-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylacetamide

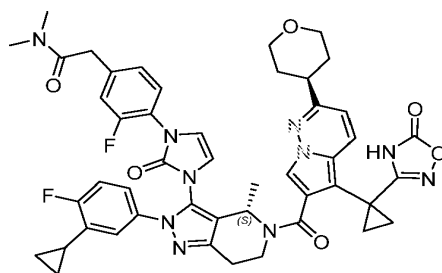


5-bromo-2-fluoro-1,3-dimethylbenzene was used as a raw material, following the synthesis in Example 145, to obtain the target product.

MS m/z (ESI): 900.4 [M+1].

Example 147

(S)-2-(4-(3-(2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-5-(5-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-2-(tetrahydro-2H-pyran-4-yl)pyrrolo[1,2-b]pyridazine-6-carbonyl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylacetamide

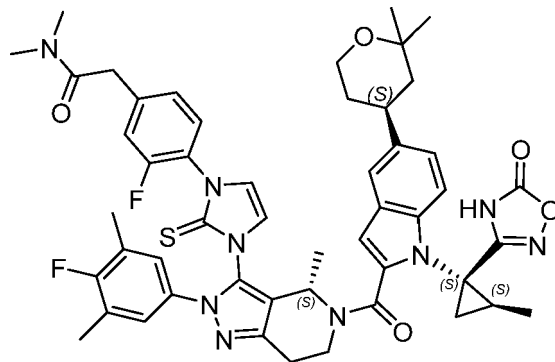


Following the synthesis in Example 145, the target product was obtained.

MS m/z (ESI): 885.4 [M+1].

Example 148

2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S, 2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-thio-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylacetamide

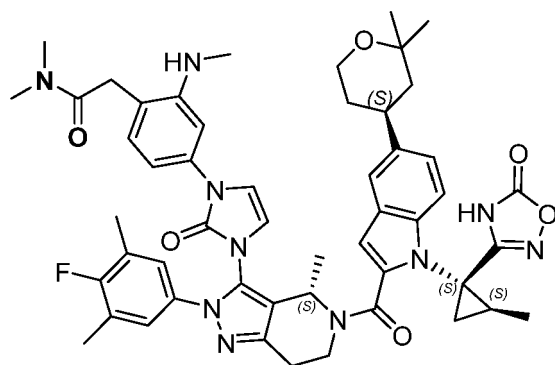


2-(4-bromo-3-fluorophenyl)-N,N-dimethylacetamide was used, following the synthesis in Example 23, to obtain the target product.

MS m/z (ESI): 930.4 [M+1].

Example 149

2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S, 2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(methylamino)phenyl)-N,N-dimethylacetamide

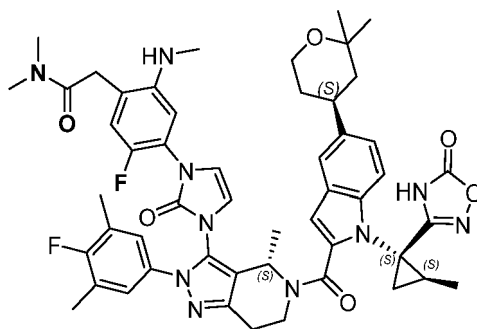


2-(4-bromo-2-(methylamino)phenyl)acetic acid was used as a raw material, following the synthesis in Example 31, to obtain the target product.

MS m/z (ESI): 925.4 [M+1].

Example 150

2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S, 2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-5-fluoro-2-(methylamino)phenyl)-N,N-dimethylacetamide

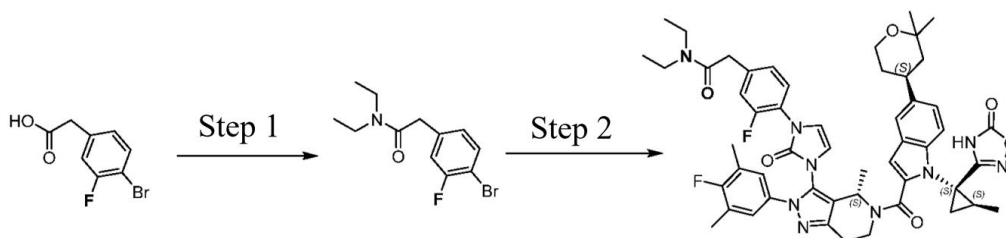


2-(4-bromo-5-fluoro-2-(methylamino)phenyl)acetic acid was used, following the synthesis for Example 64, to obtain the target product.

MS m/z (ESI): 943.4 [M+1].

5

Example 151



Step 1: 2-(4-bromo-3-fluorophenyl)-N,N-diethylacetamide

2-(4-bromo-3-fluorophenyl)acetic acid was used as a raw material, following Example 139, Step 1 reaction, to obtain the target product.

10

MS m/z (ESI): 288.0, 290.0 [M+1].

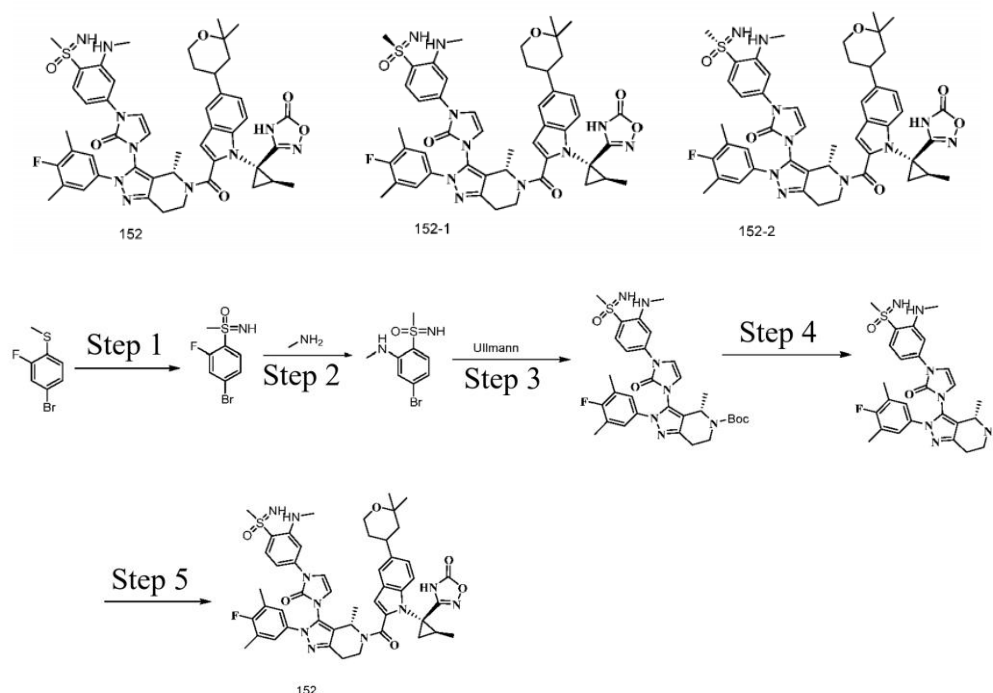
Step 2 2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-diethylacetamide

15

3-(4-bromo-3-fluorophenyl)-N,N-dimethylpropionamide was used as a raw material, following Example 1, finally to obtain the target product.

MS m/z (ESI): 942.4 [M+1].

Example 152



Step 1: (4-bromo-2-fluorophenyl)(imino)(methyl)-l6-sulfanone

To a solution of 4-bromo-2-fluoro-1-methylsulfanyl-phenyl (2 g, 9.05 mmol) in methanol (100 mL) were added successively ammonium carbamate (2.82 g, 36.18 mmol) and [di(acetoxy)iodo]phenyl (8.74 g, 27.14 mmol), and the mixture was then stirred at room temperature for half an hour, and water was added, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered; and the filtrate was concentrated under reduced pressure to dryness, and separated by column chromatography (DCM/MeOH = 10 : 1), to obtain (4-bromo-2-fluorophenyl)(imino)(methyl)-l6-sulfanone (2 g, yield: 87.7%) as a light yellow oil

MS m/z (ESI): 252.0, 254.0[M+H]⁺.

Step 2: (4-bromo-2-(methylamino)phenyl)(imino)(methyl)-l6-sulfanone

A mixture of (4-bromo-2-fluorophenyl)(imino)(methyl)-l6-sulfanone (400 mg, 1.59 mmol) methanaminehydrochloride (214 mg, 3.17 mmol), potassium carbonate (657 mg, 4.76 mmol) and DMF (10 mL) was stirred at 120°C for 3 hours, and water was added, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; and the filtrate was concentrated under reduced pressure to dryness, and separated by column chromatography (DCM/MeOH = 10 : 1), to obtain (4-bromo-2-(methylamino)phenyl)(imino)(methyl)-l6-sulfanone, as a light yellow oil (200 mg, yield: 47.9%)

MS m/z (ESI): 263.0 265.0 [M+H]⁺

Step 3: tert-butyl (4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

(4-bromo-2-(methylamino)phenyl)(imino)(methyl)-l6-sulfanone was used as a raw material, following Example 1, to obtain the product

MS m/z (ESI): 624.3 [M+H]⁺

Step 4: 1-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-1,3-dihydro-2H-imidazol-2-one

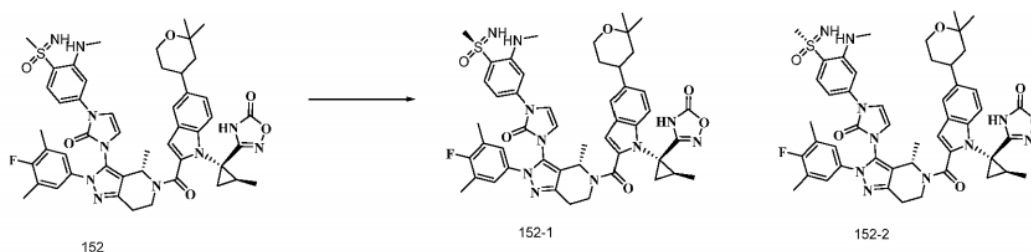
To a solution of tert-butyl (4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (60 mg, 96.19 μmol) in DCM (3 mL), TFA (1 mL) was added dropwise, and the mixture was stirred at room temperature for 0.5 hours and spin-dried; saturated NaHCO₃ was added to adjust pH = 10, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; and the filtrate was concentrated under reduced pressure to dryness, to obtain 1-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-1,3-dihydro-2H-imidazol-2-one as a light yellow oil (50 mg, crude)

MS m/z (ESI): 524.2 [M+H]⁺

Step 5: 3-((1S,2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

To a solution of 1-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-1,3-dihydro-2H-imidazol-2-one (23.57 mg, 57.29 μmol) and intermediate A (30 mg, 57.29 μmol) in DMF (3 mL), HATU (43.23 mg, 114.59 μmol) and DIEA (22 mg, 171.88 μmol) were added and stirred at room temperature for 16 hours, and water was added, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; and the filtrate was concentrated under reduced pressure to dryness, to obtain light yellow oil, which was separated by preparative chromatography (acid), to obtain 3-((1S,2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one⁵² as a white solid (9 mg, yield: 16.7%)

MS m/z (ESI): 917.4 [M+H]⁺

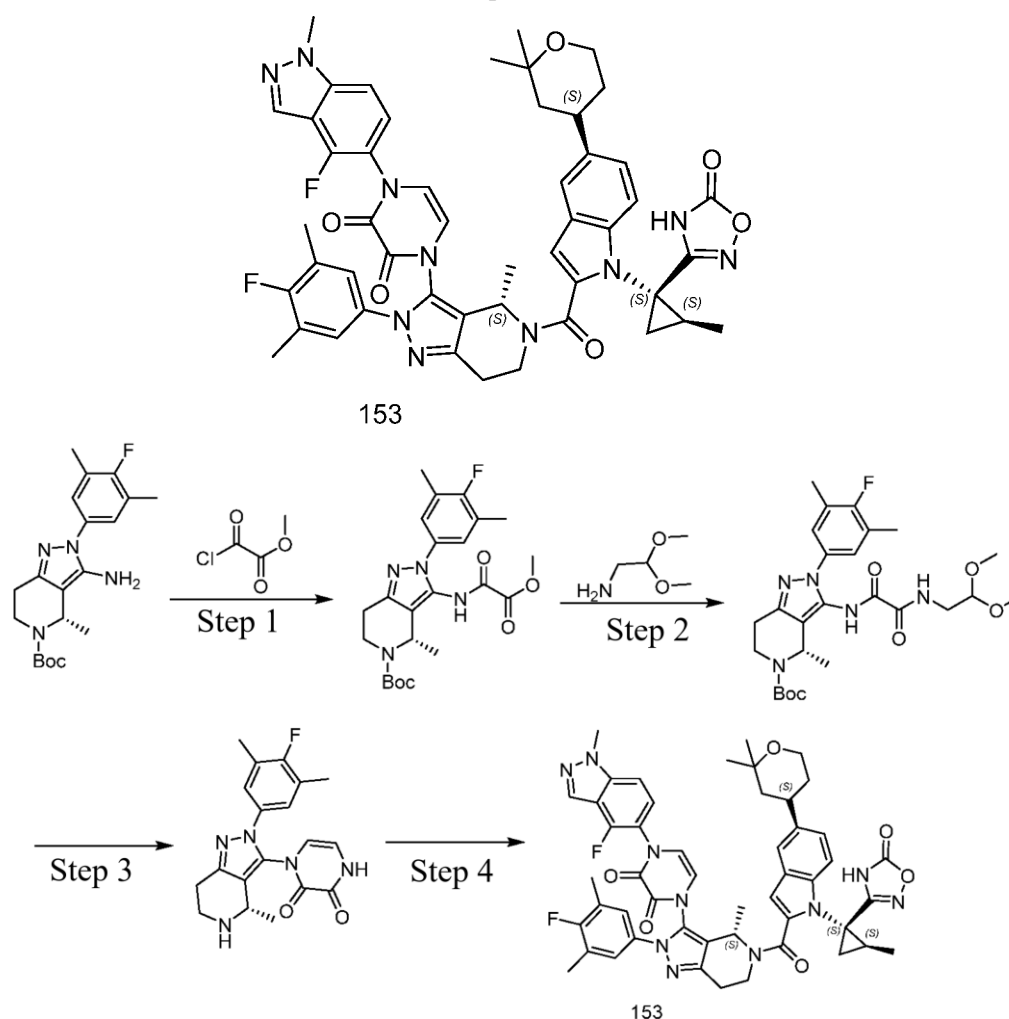


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By chiral resolution, the target product 3-((1S,2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one 152-1 and 3-((1S,2S)-1-(5-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one 151-2 were obtained

MS m/z (ESI): 917.4 [M+H]⁺

Example 153



Step 1: tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(2-methoxy-2-carboxylacetamido)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl(S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (0.5 g, 1.34 mmol) and triethylamine (405.35 mg, 4.01 mmol, 558.72 μ L) were dissolved in DCM (15 mL), and under nitrogen protection, methyl oxalyl chloride (212.66 mg, 1.74 mmol) was added.

The mixture was reacted under stirring at 25°C for 2 hours. The reaction solution was quenched with saturated brine (30 mL); the organic phase was separated; the aqueous phase was extracted with dichloromethane (30 mL); the organic phases were combined, washed with saturated brine (30 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain crude tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(2-methoxy-2-carboxylacetamido)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (0.61 g). The crude product was directly used for the next step.

MS m/z (ESI): 461.2 [M+1].

Step 2: tert-butyl (S)-3-(2-((2,2-dimethoxyethyl)amino)-2-carboxylacetamido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(2-methoxy-2-carboxylacetamido)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (0.61 g, 1.32 mmol) was dissolved in methanol (20 mL), and under nitrogen protection, 2,2-dimethoxyethanamine (417.80 mg, 3.97 mmol) was added. The mixture was reacted under stirring at 80°C for 12 hours. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 30 : 70), to obtain the target product tert-butyl (S)-3-(2-((2,2-dimethoxyethyl)amino)-2-carboxylacetamido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (0.6 g, yield: 84.89%), as a white solid.

MS m/z (ESI): 534.3 [M+1].

Step 3: (S)-1-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,4-dihydropyrazine-2,3-dione

tert-butyl (S)-3-(2-((2,2-dimethoxyethyl)amino)-2-carboxylacetamido)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (0.7 g, 1.31 mmol) was dissolved in glacial acetic acid (10 mL), and under nitrogen protection, methanesulfonic acid (1 mL) was added. The mixture was reacted under stirring at 130°C for 2 hours. The reaction solution was evaporated to dryness; the crude product and triethylamine (3 mL) were dissolved in dichloromethane (20 mL), and under nitrogen protection, di-tert-butyl dicarbonate (567.19 mg, 2.60 mmol) was added. The mixture was reacted under stirring at 25°C for 1 hours. To the mixture, saturated brine (50 mL) was added to quench the reaction, and the organic phase was separated, washed with saturated brine (50 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the product, and the product was dissolved in 4M hydrochloric acid dioxane (7 mL); and the reaction solution was stirred at room temperature for 1 hour, and evaporated to dryness to obtain the product (S)-1-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,4-dihydropyrazine-2,3-dione (0.12 g, yield: 22.54%).

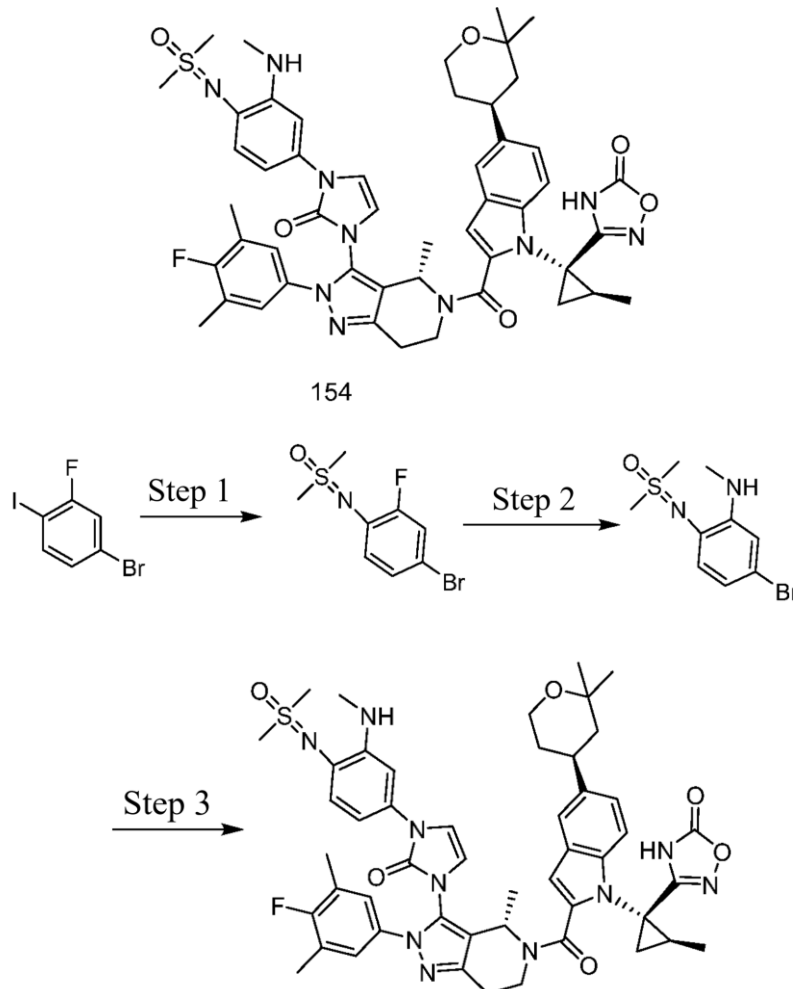
MS m/z (ESI): 370.2 [M+1].

Step 4: 1-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S, 2S)-2-methyl-1-(5-carboxyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-4-(4-fluoro-1-methyl-1H-indazol-5-yl)-1,4-dihydropyrazine-2,3-dione

Following intermediate E and Example 1, the target product was synthesized.

MS m/z (ESI): 911.4 $[M+1]$.

Example 154



5

Step 1: ((4-bromo-2-fluorophenyl)imino)dimethyl- λ 6-sulfanone

4-bromo-2-fluoro-1-iodobenzene (0.5 g, 1.66 mmol), dimethylsulfonylimide (154.78 mg, 1.66 mmol) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (96.15 mg, 166.17 μ mol) were dissolved in 1,4-dioxane (10 mL), and under nitrogen protection, tris(dibenzylideneacetone)dipalladium (47.77 mg, 83.09 μ mol) and cesium carbonate (1.08 g, 3.32 mmol) were added. The mixture was reacted under stirring at 100°C for 12 hours. To the mixture, saturated brine (50 mL) was added to quench the reaction, followed by extraction with ethyl acetate (30 mL $\times$ 2). The organic phases were combined, washed with saturated brine (30 mL $\times$ 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively.

10

The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 50 : 50), to obtain the target product ((4-bromo-2-fluorophenyl)imino)dimethyl- λ 6-sulfanone (0.35 g, yield: 79.14%).

MS m/z (ESI): 266.0, 268.0 [M+1].

5 Step 2: ((4-bromo-2-(methylamino)phenyl)imino)dimethyl- λ 6-sulfanone

((4-Bromo-2-fluorophenyl)imino)dimethyl- λ 6-sulfanone (0.35 g, 1.32 mmol) was dissolved in methanaminemethanol solution (4 M, 10 mL), and under nitrogen protection, the mixture was reacted under stirring at 80°C for 12 hours. The reaction solution was evaporated to dryness, and the crude product ((4-bromo-2-(methylamino)phenyl)imino)dimethyl- λ 6-sulfanone (0.36 g) was used directly in the next step.

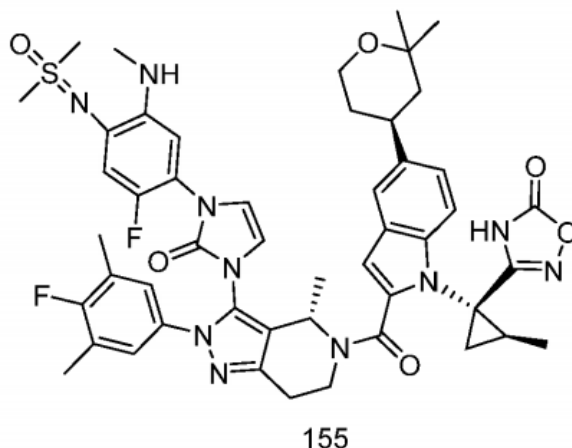
10 MS m/z (ESI): 277.0, 279.0 [M+1].

Step 3: 3-((1S,2S)-1-(2-((S)-3-(3-(4-((dimethyl(carbonyl)-l6-sulfaneylidene)amino)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

15 Following Example 1, the target product was synthesized.

MS m/z (ESI): 931.4 [M+1].

Example 155

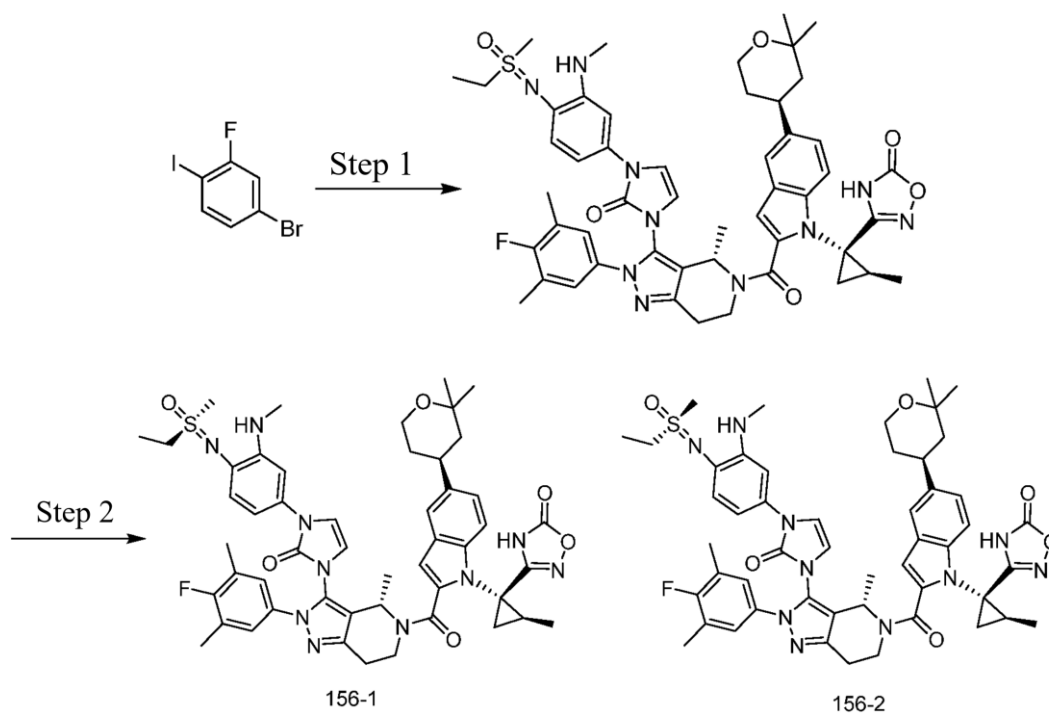


20 Step 1: 3-((1S,2S)-1-(2-((S)-3-(3-(4-((dimethyl(carbonyl)-l6-sulfaneylidene)amino)-2-fluoro-5-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-bromo-2,5-difluoro-4-iodobenzene was used as a raw material, following Example 154, to synthesize the target product.

25 MS m/z (ESI): 949.4 [M+1].

Example 156



Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-
 5 ((ethyl(methyl)(carbonyl)-l6-sulfaneylidene)amino)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-
 imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-
 carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

4-bromo-2-fluoro-1-iodobenzene and S-ethyl-S-methylsulfoximine were used as raw materials,
 following Example 154, to synthesize the target product.

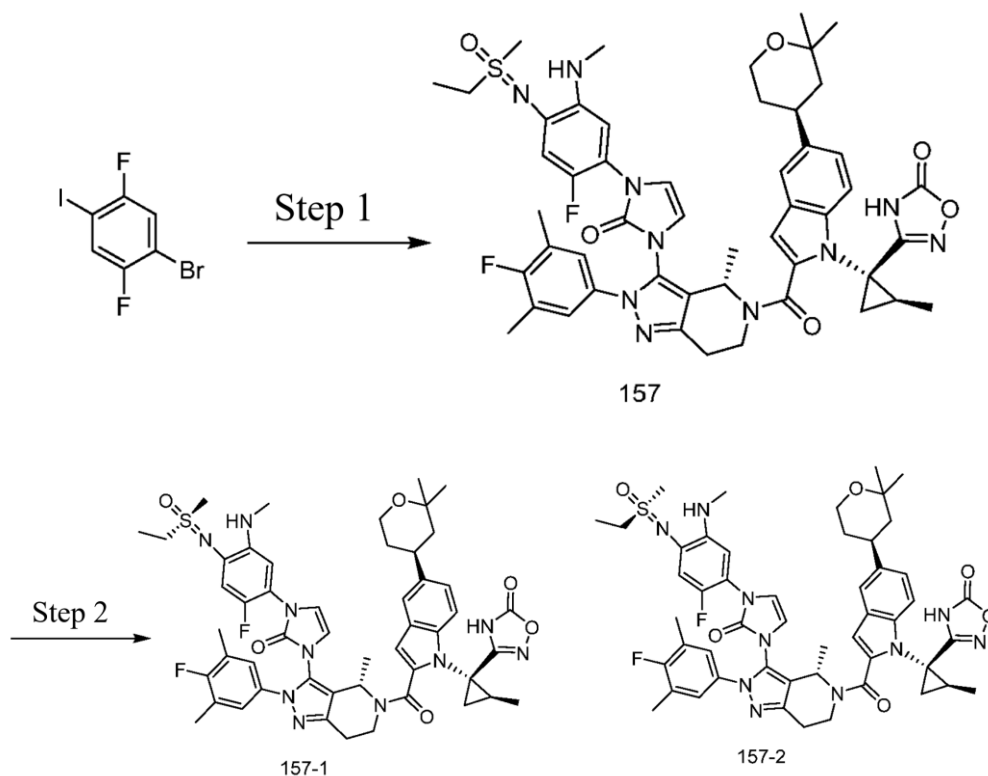
MS m/z (ESI): 945.4 [M+1].

Step 2:

By chiral resolution, 156-1 and 156-2 were obtained.

MS m/z (ESI): 945.4 [M+1].

Example 157



Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-
 5 ((ethyl(methyl)(carbonyl)-l6-sulfaneylidene)amino)-2-fluoro-5-(methylamino)phenyl)-2-carbonyl-2,3-
 dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-
 c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-bromo-2,5-difluoro-4-iodobenzene and S-ethyl-S-methylsulfoximine were used as raw materials, following Example 154, to synthesize the target product.

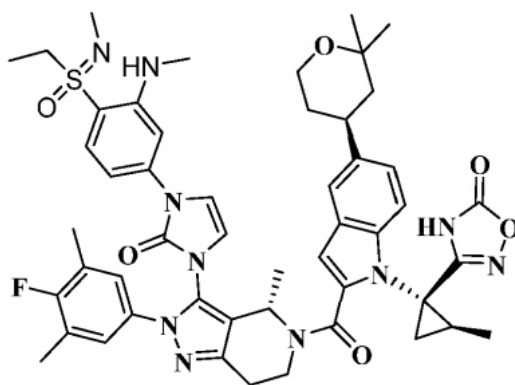
MS m/z (ESI): 963.4 [M+1].

Step 2:

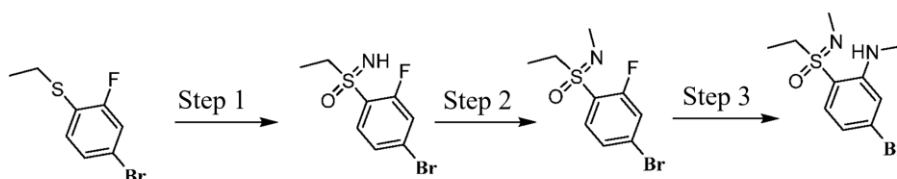
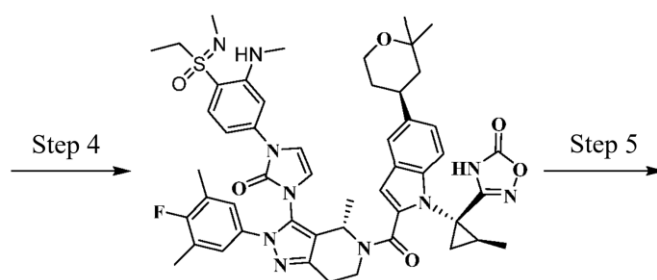
By chiral resolution, 157-1 and 157-2 were obtained.

MS m/z (ESI): 963.4 [M+1].

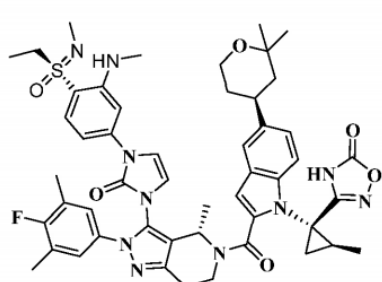
Example 158



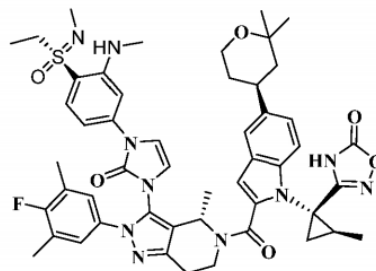
158



158



158-1



158-2

Step 1: (4-bromo-2-fluorophenyl)(ethyl)(imino)-λ6-sulfanone

- 5 (4-bromo-3-fluorophenyl)(ethyl)sulfane (0.5 g, 2.13 mmol) and ammonium carbamate (664.10 mg, 8.51 mmol) were dissolved in methanol (15 mL), and under nitrogen protection, iodobenzenediacetic acid (2.05 g, 6.38 mmol) was added. The mixture was reacted under stirring at 25°C for 12 hours. The mixture was evaporated to dryness under reduced pressure, and the reaction was quenched by adding saturated brine (100 mL), followed by extraction with ethyl acetate (30 mL × 2); and the organic phases were combined, and
- 10 washed with saturated brine (50 mL × 2),

dried over anhydrous sodium sulfate, and concentrated under reduced pressure, successively. The residue was purified by flash silica gel chromatography (eluting with petroleum ether : ethyl acetate = 100 : 0 to 0 : 100), to obtain the target product (4-bromo-2-fluorophenyl)(ethyl)(imino)- λ 6-sulfanone (0.46 g, yield: 81.28%), as a white solid.

5 MS m/z (ESI): 266.0, 268.0 [M+1].

Step 2: (4-bromo-2-fluorophenyl)(ethyl)(methylimino)-6-sulfanone

(4-Bromo-2-fluorophenyl)(ethyl)(imino)- λ 6-sulfanone (0.46 g, 1.73 mmol) was dissolved in tetrahydrofuran (20 mL), and under nitrogen protection, sodium hydride (82.96 mg, 2.07 mmol, 60%w/w) was added. The mixture was reacted under stirring at 25°C for 0.5 hours. Under nitrogen protection,
10 iodomethane (368.01 mg, 2.59 mmol) was added. The mixture was reacted under stirring at 25°C for 12 hours. The reaction solution was added saturated brine (50 mL) to quench the reaction, and the mixture was subjected to liquid-liquid separated; the organic phase was dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure to obtain a crude product, which was purified by flash silica gel chromatographic column (petroleum ether : ethyl acetate = 1 : 1), to obtain the target product (4-bromo-
15 2-fluorophenyl)(ethyl)(methylimino)- λ 6-sulfanone (0.21 g, yield: 43.37%), as a white solid.

MS m/z (ESI): 280.0, 282.0 [M+1].

Step 3: (4-bromo-2-(methylamino)phenyl)(ethyl)(methylimino)- λ 6-sulfanone

Following Example 154 Step 2, the target product was obtained.

MS m/z (ESI): 291.0, 293.0 [M+1].

20 Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(N-methylethylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 1, the target product was obtained.

25 MS m/z (ESI): 945.4 [M+1].

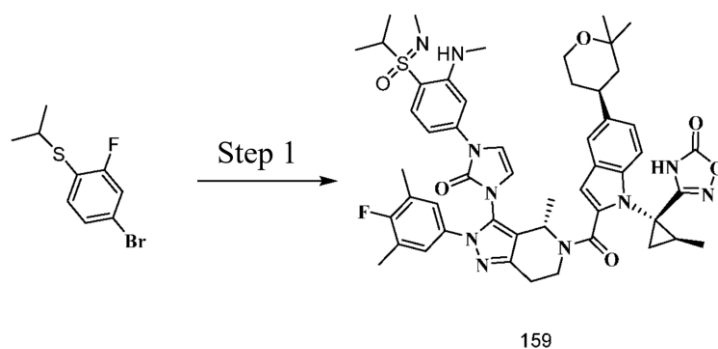
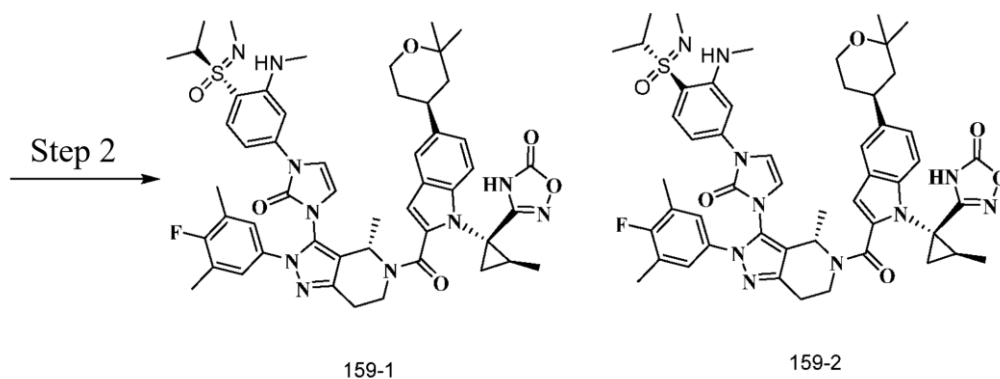
Step 5:

By chiral resolution, 158-1 and 158-2 were obtained.

MS m/z (ESI): 945.4 [M+1].

Example 159

30



Step 1: 3-(((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(N-methylpropan-2-ylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-2-fluorophenyl)(isopropyl)sulfane was used as a raw material, following Example 158, to synthesize the target product.

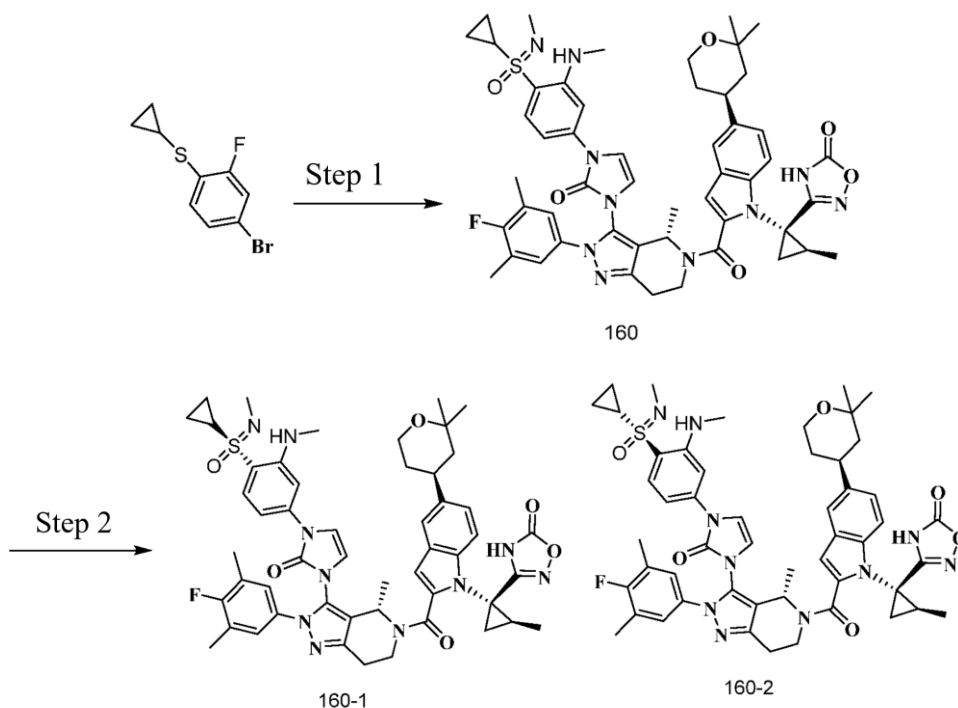
MS m/z (ESI): 959.4 [M+1].

Step 2:

By chiral resolution, 159-1 and 159-2 were obtained.

MS m/z (ESI): 959.4 [M+1].

Example 160



Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-2-fluorophenyl)(cyclopropyl)sulfane was used as a raw material, following Example 158, to synthesize the target product.

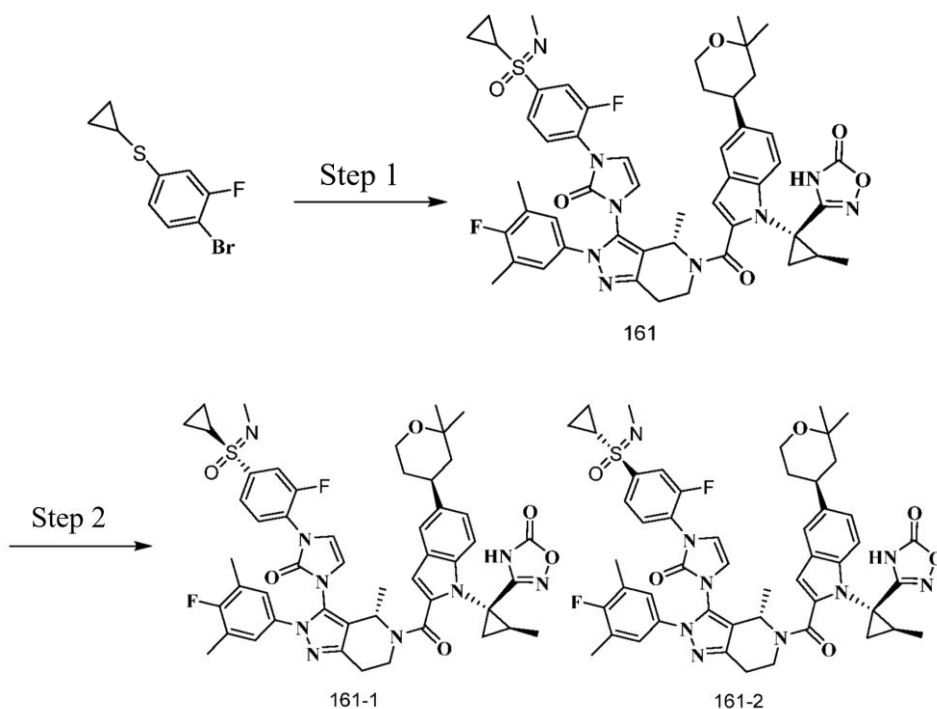
MS m/z (ESI): 957.4 [M+1].

Step 2:

By chiral resolution, 160-1 and 160-2 were obtained.

MS m/z (ESI): 957.4 [M+1].

Example 161



Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-3-fluorophenyl)(cyclopropyl)sulfane was used as a raw material, following Example 158, to synthesize the target product.

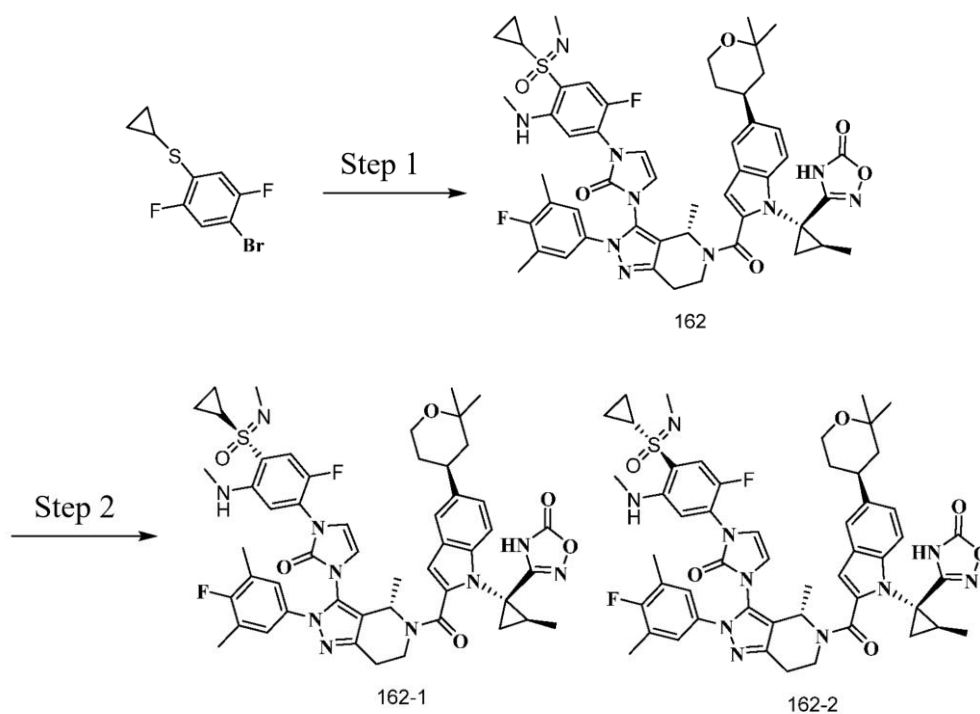
MS m/z (ESI): 946.4 [M+1].

Step 2:

By chiral resolution, 161-1 and 161-2 were obtained.

MS m/z (ESI): 946.4 [M+1].

Example 162



Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-2,5-difluorophenyl)(cyclopropyl)sulfane was used as a raw material, following Example 154, to synthesize the target product.

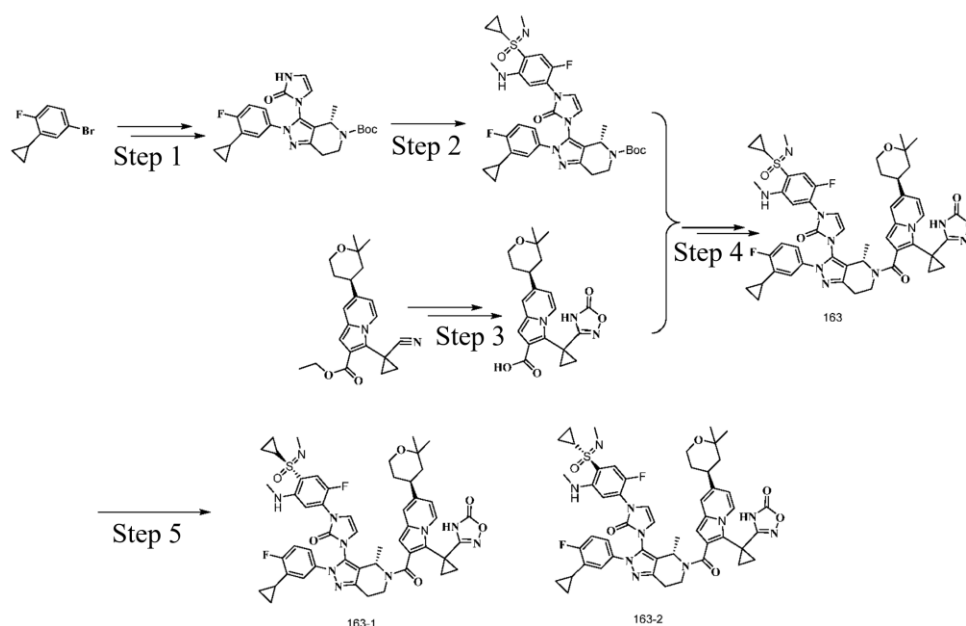
MS m/z (ESI): 975.4 [M+1].

Step 2:

By chiral resolution, 162-1 and 162-2 were obtained.

MS m/z (ESI): 975.4 [M+1].

Example 163



Step 1: tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl 4-bromo-2-cyclopropyl-1-fluorophenyl was used as a raw material, following the synthesis in intermediate B Step 3 to Step 5, to obtain the title product (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

MS m/z (ESI): 454.2 [M+1].

Step 2: tert-butyl (4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and (4-bromo-5-fluoro-2-(methylamino)phenyl)(cyclopropyl)(methylimino)-1,6-sulfanone were used as raw materials, following the synthesis step in Example 1, to obtain the title product tert-butyl (4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

MS m/z (ESI): 694.3 [M+1].

Step 3: (S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid

Ethyl (S)-3-(1-cyanocyclopropyl)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizine-2-carboxylate was used as a raw material, following the synthesis steps in intermediate A Step 4 and Step 5, to obtain the title product (S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid.

MS m/z (ESI): 398.4 [M+1].

Step 4: 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizine-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

tert-Butyl

(4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and (S)-7-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-3-(1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)indolizine-2-carboxylic acid were used as raw materials, following the synthesis in intermediate C Step 2 and Step 3, to obtain the title product 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizine-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

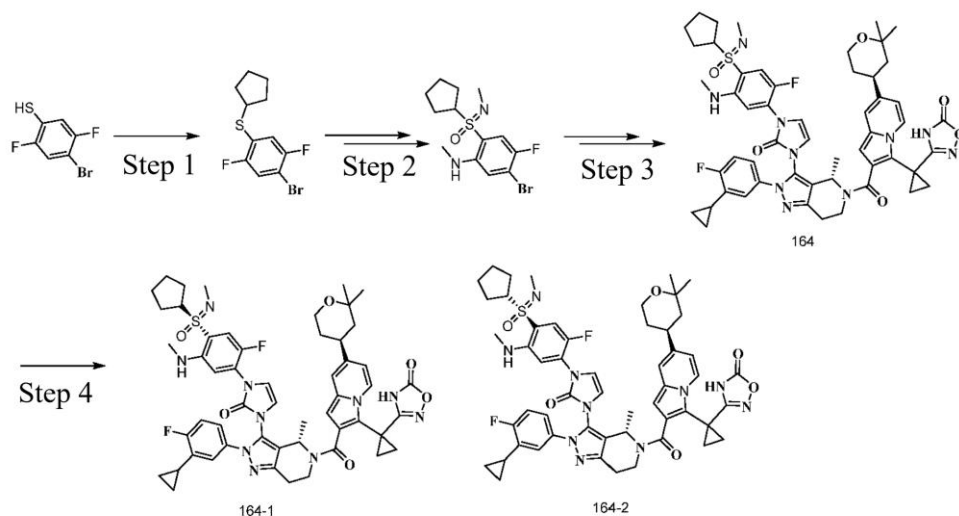
MS m/z (ESI): 973.4 [M+1].

Step 5:

By chiral resolution, 163-1 and 163-2 were obtained.

MS m/z (ESI): 973.4 [M+1].

Example 164



Step 1: (4-bromo-2,5-difluorophenyl)(cyclopentyl)sulfane

In a 100 mL reaction bottle, potassium tert-butoxide (997.23 mg, 8.89 mmol) was dissolved in DMSO (25.0 mL), and then under nitrogen protection, 4-bromo-2,5-difluorobenzenethiol (2 g, 8.89 mmol) was added to reaction solution; then the reaction solution was stirred at 25°C for 30 minutes; and then bromocyclopentane (1.82 g, 17.77 mmol) was added, and the reaction solution was stirred at 80°C for 10 hours. The reaction was stopped, and quenched by adding an aqueous solution (60 mL), followed by extraction with ethyl acetate (60 mL × 2); and the organic phases were combined, washed with saturated sodium chloride (60 mL × 3), dried over anhydrous sodium sulfate, and filtered, and

the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product (4-bromo-2,5-difluorophenyl)(cyclopentyl)sulfane (1.1 g, yellow solid), yield: 42.2%.

MS m/z (ESI): 293.0, 295.0 [M+1].

Step 2: (4-bromo-5-fluoro-2-(methylamino)phenyl)(cyclopentyl)(methylimino)-l6-sulfanone

(4-bromo-2,5-difluorophenyl)(cyclopentyl)sulfane was used as a raw material, following the synthesis in Example 158 Step 1 to Step 3, to obtain the title product (4-bromo-5-fluoro-2-(methylamino)phenyl)(cyclopentyl)(methylimino)-l6-sulfanone.

MS m/z (ESI): 349.0, 351.0 [M+1].

Step 3: 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopentsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-5-fluoro-2-(methylamino)phenyl)(cyclopentyl)(methylimino)-l6-sulfanone was used as a raw material, following the synthesis step in Example 163 Step 2 to Step 4, to obtain the title product 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-5-(methylamino)-4-(N-methylcyclopentsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

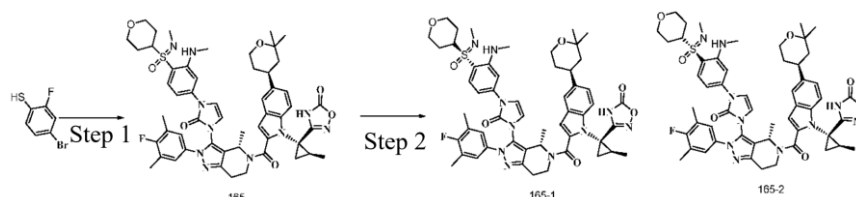
MS m/z (ESI): 1001.4 [M+1].

Step 4:

By chiral resolution, 164-1 and 164-2 were obtained.

MS m/z (ESI): 1001.4 [M+1].

Example 165



Step 1: 3-((1S, 2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(N-methyltetrahydro-2H-pyran-4-sulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

4-bromo-2-fluorobenzenethiol and 4-bromotetrahydro-2H-pyran were used as raw materials, following the synthesis in Example 164 Step 1 and Example 158 Step 1 to Step 3, to obtain the title product 3-((1S, 2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(3-(methylamino)-4-(N-methyltetrahydro-2H-pyran-4-sulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 1001.4 [M+1].

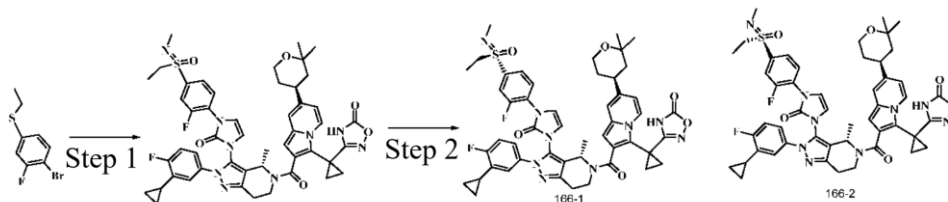
Step 2:

By chiral resolution, 165-1 and 165-2 were obtained.

MS m/z (ESI): 1001.4 [M+1].

5

Example 166



Step 1: 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-4-(N-methylethylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10

(4-bromo-3-fluorophenyl)(ethyl)sulfane was used as a raw material, following the synthesis in Example 158 Step 1 to Step 2 and 163 Step 2 to Step 4, to obtain the title product 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-4-(N-methylethylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

15

MS m/z (ESI): 932.4 [M+1].

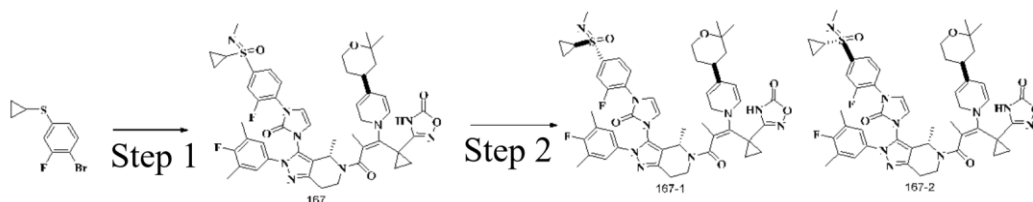
Step 2:

By chiral resolution, 166-1 and 166-2 were obtained.

MS m/z (ESI): 932.4 [M+1].

20

Example 167



Step 1: 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

25

(4-bromo-3-fluorophenyl)(cyclopropyl)sulfane was used as a raw material, following the synthesis in Example 158 Step 1 to Step 2 and 163 Step 2 to Step 4, with tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate in Example 163 being replaced with tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate, to obtain the title product 3-(1-(7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(2-fluoro-4-(N-methylcyclopropanesulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)indolizine-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

30

35

MS m/z (ESI): 936.4 [M+1].

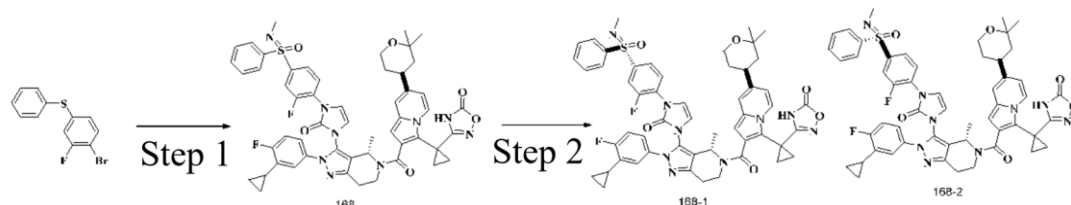
Step 2:

By chiral resolution, 167-1 and 167-2 were obtained.

MS m/z (ESI): 936.4 [M+1].

5

Example 168



Step 1: 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-4-(N-methylphenylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10

4-bromo-3-fluoro-1-phenyl-thiophenyl was used as a raw material, following the synthesis in Example 158 Step 1 to Step 2 and 163 Step 2 to Step 4, to obtain the title product 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(2-fluoro-4-(N-methylphenylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

15

MS m/z (ESI): 980.4 [M+1].

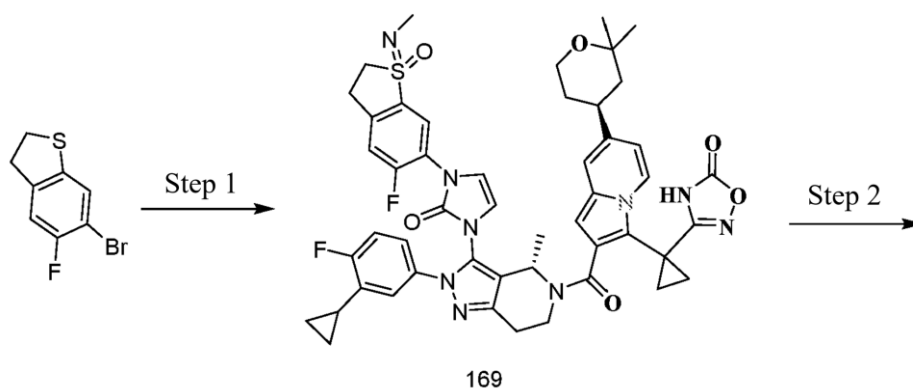
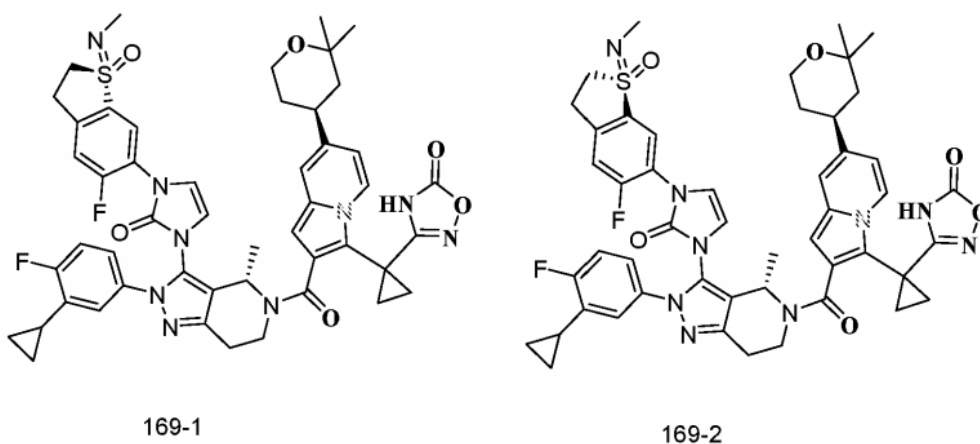
Step 2:

By chiral resolution, 168-1 and 168-2 were obtained.

MS m/z (ESI): 980.4 [M+1].

20

Example 169



Step 1: 3-(1-(2-((4S)-2-(3-cyclopropyl-4-fluorophenyl)-3-(3-(5-fluoro-1-(methylimino)-1-hydroxyl-2,3-dihydro-1H-114-benzo[b]thiophen-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-7-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)indolizin-3-yl)cyclopropyl)-1,2,4-oxadiazol-5(4H)-one

6-bromo-5-fluoro-2,3-dihydrobenzo[b]thiophene was used as a raw material, following Example 158 Step 1 and Step 2 and Example 52, to synthesize the target product.

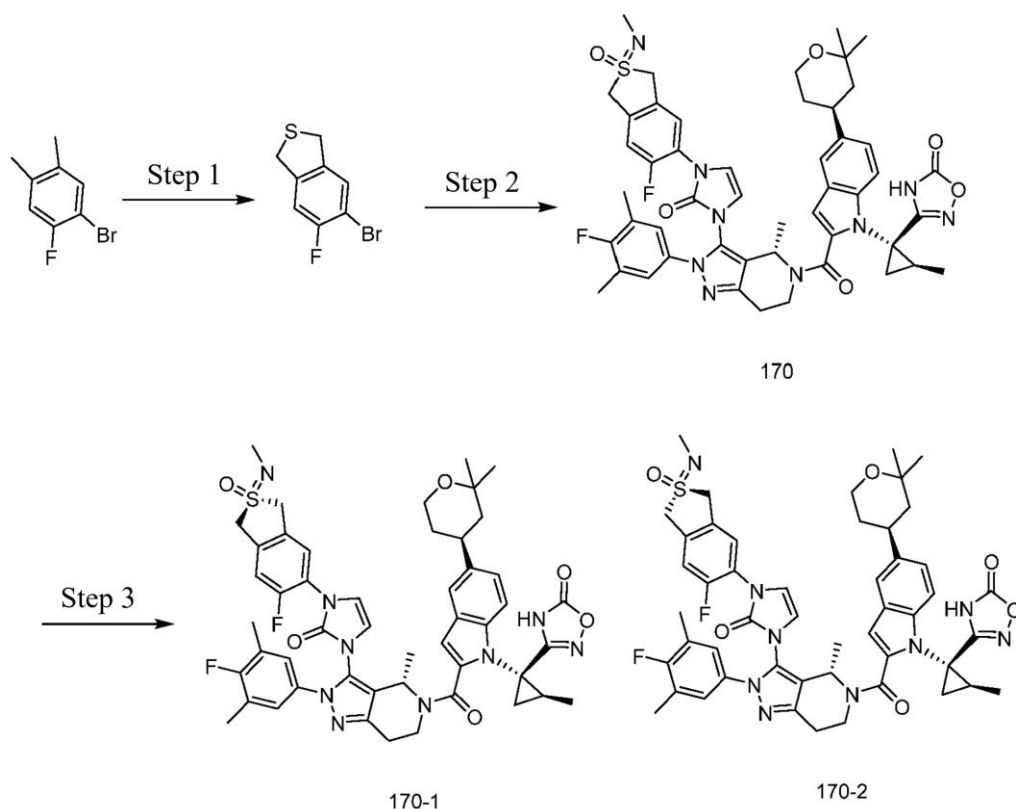
MS m/z (ESI): 930.4 [M+1].

Step 2:

By chiral resolution, 169-1 and 169-2 were obtained.

MS m/z (ESI): 930.4 [M+1].

Example 170



Step 1: 5-bromo-6-fluoro-1,3-dihydrobenzo[c]thiophene

1-bromo-2-fluoro-4,5-dimethylbenzene was used as a raw material, following [Journal of Organic Chemistry, 1985, vol. 50, # 24, p. 4969 - 4971], to synthesize the target compound.

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(6-fluoro-2-(methylimino)-2-hydroxyl-2,3-dihydro-1H-214-benzo[c]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

Following Example 158 Step 1 and Step 2 and Example 1, the target product was synthesized.

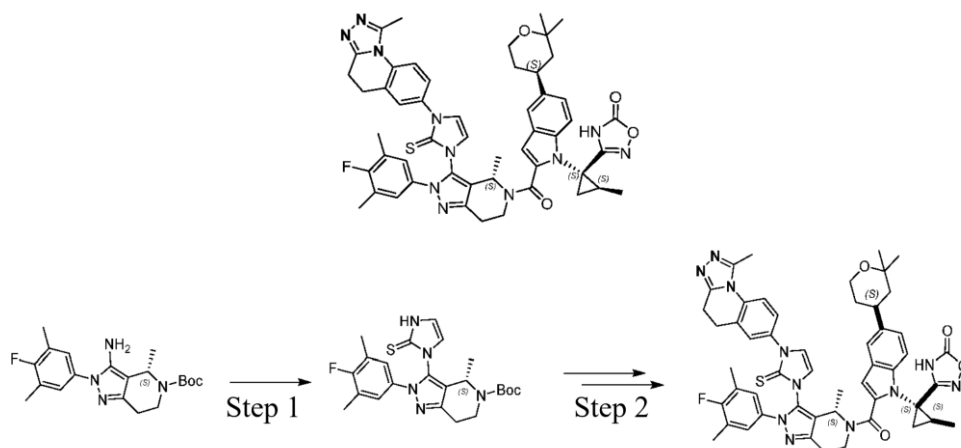
MS m/z (ESI): 932.4 [M+1].

Step 3:

By chiral resolution, 170-1 and 170-2 were obtained.

MS m/z (ESI): 932.4 [M+1].

Example 171



Step 1: tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-thio-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl (S)-3-amino-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate was used as a raw material, following the synthesis step in Example 23 Step 1, to obtain the title product tert-butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-thio-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

MS m/z (ESI): 458.2 [M+1].

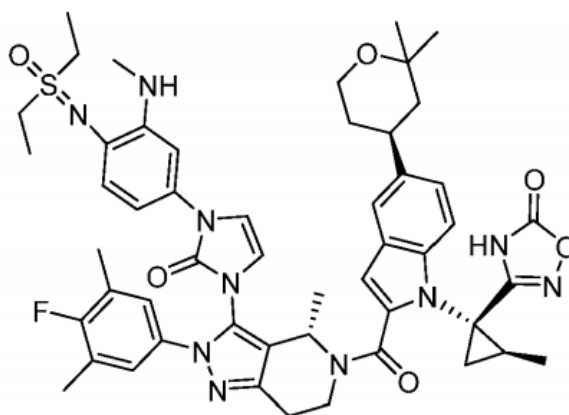
Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-thio-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

tert-Butyl (S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-thio-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate was used as a raw material, following the synthesis step for intermediate E and Example 1, with ((4-bromo-3-fluorophenyl)imino)dimethyl-6-thione in Example 1 being replaced with 7-bromo-1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinoline, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-methyl-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-7-yl)-2-thio-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 934.4 [M+1].

Example 172

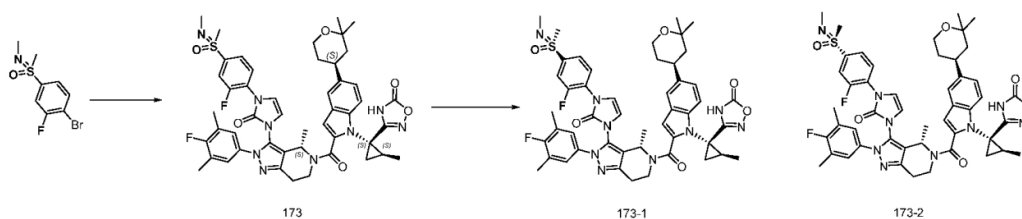
3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-l6-sulfaneylidene)amino)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Following the synthesis in Example 154, the target product was obtained

MS m/z (ESI): 959.4 [M+1].

Example 173



5

Following the synthesis in Example 116, the target product 3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-2-fluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazole(5H)-one was obtained

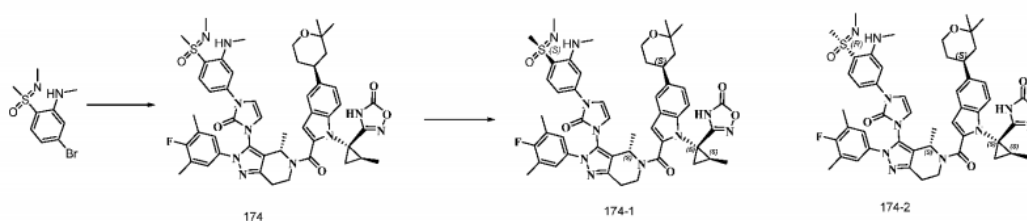
10

MS m/z (ESI): 920.3 [M+1].

173 was chirally resolved to obtain 173-1 and 173-2

MS m/z (ESI): 920.3 [M+1].

Example 174



15

Following the synthesis in Example 118, the target product 3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was obtained

20

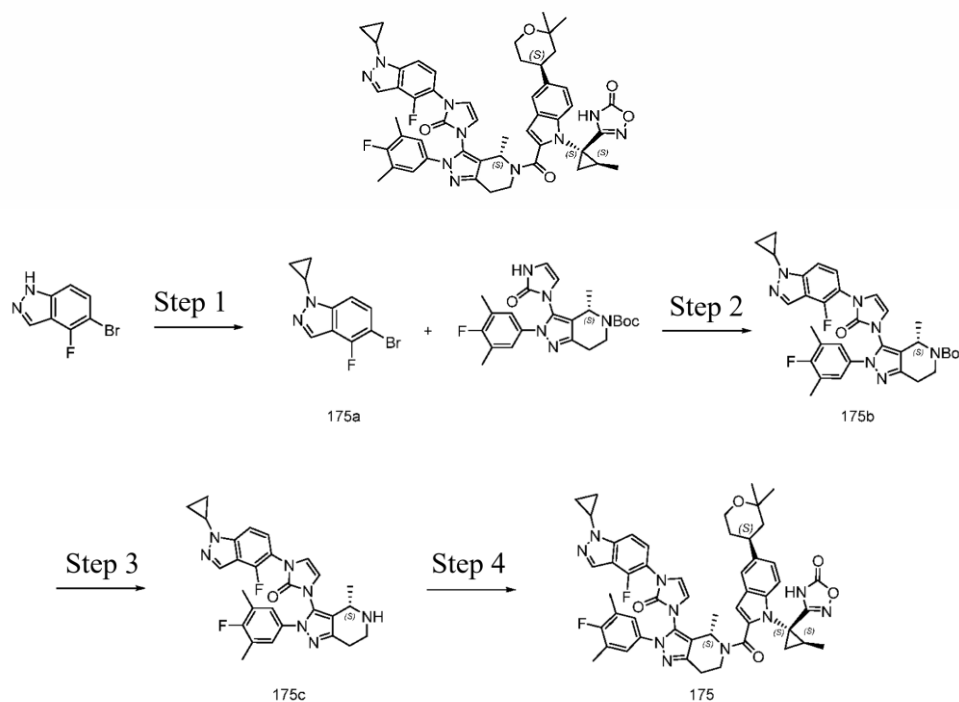
MS m/z (ESI): 931.4 [M+1].

174 was chirally resolved to obtain 174-1 and 174-2

MS m/z (ESI): 931.4 [M+1].

Example 175

5 3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carbonyl)-5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)one



10 Step 1

5-bromo-1-cyclopropyl-4-fluoroindazole

15 5-bromo-4-fluoro-1H-indazole (200 mg, 0.93 mmol), cyclopropylboronic acid (160 mg, 1.86 mmol), copper acetate (169 mg, 0.93 mmol), 2,2'-bipyridine (146 mg, 0.93 mmol), and sodium carbonate (197 mg, 1.86 mmol) were dispersed in acetonitrile (6 mL), and the reaction solution was heated to 70°C and reacted under stirring for 4 hours. The reaction solution was cooled to room temperature and concentrated under reduced pressure reaction, and the residue was purified by silica gel column chromatography, to obtain the target product 5-bromo-1-cyclopropyl-4-fluoroindazole (204 mg, yield 86%).

MS m/z (ESI): 255.0, 257.0 [M+1].

Step 2

(S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

5 5-Bromo-1-cyclopropyl-4-fluorindazole (52 mg, 0.20 mmol), tert-butyl 4(S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-oxo-1H-imidazol-3-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (60 mg, 0.14 mmol), (1S, 2S)-1-N,2-N-dimethylcyclohexane-1,2-diamine (19 mg, 0.14 mmol), potassium carbonate (19 mg, 0.14 mmol), and cuprous iodide (26 mg, 0.14 mmol) were dispersed in N-methylpyrrolidone (2 mL), and the reaction solution was heated to 130°C and reacted under stirring for 4
10 hours. The reaction solution was cooled to room temperature, and the reaction was quenched by adding saturated brine (5 mL), followed by extraction with ethyl acetate (5 mL × 3); and the organic phases were combined, washed with saturated brine (20 mL × 5), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography, to obtain the target product (S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-
15 fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate (55 mg, yield: 62%).

MS m/z (ESI): 616.3[M+1].

Step 3

(S)-1-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

20 175b (55 mg, 89.33 μmol) and trifluoroacetic acid (0.5 mL) were dissolved in dichloromethane (2 mL) and reacted under stirring at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure to obtain the target product (S)-1-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-
25 imidazol-2-one (42 mg, yield: 91%)

MS m/z (ESI): 516.2[M+1].

Step 4

3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carbonyl)-5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)one

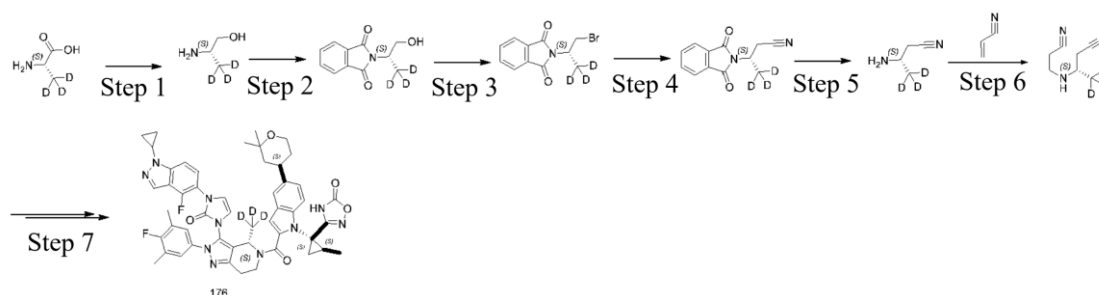
30 dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)one

175c (42 mg, 81.5 μ mol), intermediate A (51 mg, 0.122 mmol), HATU (46 mg, 0.122 mmol), and DIEA (53 mg, 0.407 mmol) were dissolved in DMF (3 mL), and stirred at room temperature and reacted for 3 hours. To the reaction solution, a saturated ammonium chloride solution was added for quenching, followed by extraction with ethyl acetate (5 mL $\times$ 3); and the organic phases were combined, washed with a saturated sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure, and then the resulting residue was purified by silica gel column chromatography, to obtain the title product 3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydropyrazolo[4,3-c]pyridine-5-carbonyl)-5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)one (62 mg, yield: 84%).

MS m/z (ESI): 909.4[M+1].

Example 176

3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(methyl-d₃)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: (S)-2-aminopropane-3,3,3-d₃-1-ol

In a 500 mL reaction bottle, L-alanine-3,3,3-d₃ (10 g, 108.56 mmol) was dissolved in tetrahydrofuran (200 mL), then lithium aluminum hydride (4.12 g, 108.56 mmol) was added batchwise at 0°C, and then the reaction solution was stirred at 0°C for 2 hours under nitrogen protection. The reaction was stopped, quenched by slowly adding an aqueous sodium hydroxide solution (1M, 15 mL), filtered, and concentrated to obtain the title product (S)-2-aminopropane-3,3,3-d₃-1-ol (8 g, a yellow oil), yield: 94.3%.

Step 2: (S)-2-(1-hydroxypropylpropan-2-yl-3,3,3-d₃)isodihydroindole-1,3-dione

In a 500 mL reaction bottle, (S)-2-aminopropane-3,3,3-d₃-1-ol (8 g, 102.39 mmol), phthalic anhydride (15.17 g, 102.39 mmol), and triethylamine (10.36 g, 102.39 mmol) were dissolved in toluene (200 mL),

Then the reaction solution was placed under nitrogen protection and added into a water separator and stirred at 110°C for 12 hours. The reaction was stopped, concentrated and recrystallized from diethyl ether to obtain the title product (S)-2-(1-hydroxypropan-2-yl-3,3,3-d3)isodihydroindole-1,3-dione (17 g, a yellow oil), yield: 79.7%.

5 MS m/z (ESI): 209.0[M+1].

Step 3: (S)-2-(1-bromopropan-2-yl-3,3,3-d3)isodihydroindole-1,3-dione

In a 500 mL reaction bottle, (S)-2-(1-hydroxypropan-2-yl-3,3,3-d3)isodihydroindole-1,3-dione (17 g, 81.64 mmol) was dissolved in dichloromethane (200 mL), and at 25°C phosphorus tribromide (22.1 g, 81.64 mmol) was added, and then the reaction solution was stirred at 25°C for 1 hour under nitrogen protection.

10 The reaction was stopped, and quenched by adding an aqueous solution (100 mL), followed by extraction with dichloromethane (100 mL × 2); the organic phases were combined, washed with saturated sodium chloride (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated, to obtain the title product (S)-2-(1-bromopropane-2-yl-3,3,3-d3)isodihydroindole-1,3-dione (19 g, yellow solid), yield: 85.8%.

MS m/z (ESI): 271.0[M+1].

15 Step 4: (S)-3-(1,3-dicarbonylisodihydroindol-2-yl)butyronitrile-4,4,4-d3

In a 500 mL reaction bottle, (S)-2-(1-bromopropan-2-yl-3,3,3-d3)isodihydroindole-1,3-dione (19 g, 70.08 mmol) was dissolved in DMSO (200 mL), and at 25°C sodium cyanide (3.43 g, 70.08 mmol) and potassium iodide (1.16 g, 7.01 mmol) were added, and then the reaction solution was stirred at 25°C for 12 hours under nitrogen protection. The reaction was stopped and quenched by adding an aqueous solution (200 mL), followed by extraction with dichloromethane (200mL × 2); and the organic phases were combined, washed with saturated sodium chloride (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated, and the resulting residue was then purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product (S)-3-(1,3-dicarbonylisodihydroindol-2-yl)butyronitrile-4,4,4-d3 (11 g, yellow solid), yield: 72.2%.

25 MS m/z (ESI): 218.0[M+1].

Step 5: (S)-3-aminobutyronitrile-4,4,4-d3

In a 250 mL reaction bottle, (S)-3-(1,3-dicarbonylisodihydroindol-2-yl)butyronitrile-4,4,4-d3 (11 g, 50.63 mmol) was dissolved in ethanol (100 mL), and at 25°C hydrazine hydrate (2.53 g, 50.63 mmol) was added, and then the reaction solution was stirred at 50°C for 2 hours under nitrogen protection. The reaction was stopped and cooled to room temperature, with a white solid precipitating, and filtered; the filtrate was concentrated and treated by adding 20 mL ethanol, with a solid precipitating, and further filtered; and the filtrate was concentrated, to obtain the title product (S)-3-aminobutyronitrile-4,4,4-d3 (4 g, yellow oil), yield: 90.6%.

Step 6: (S)-3-((2-cyanoethyl)amino)butyronitrile-4,4,4-d3

35 (S)-3-aminobutyronitrile-4,4,4-d3 was used as a raw material, following the synthesis in Example 47 Step 1, to obtain the title product (S)-3-((2cyanoethyl)amino)butyronitrile-4,4,4-d3.

MS m/z (ESI): 141.0[M+1].

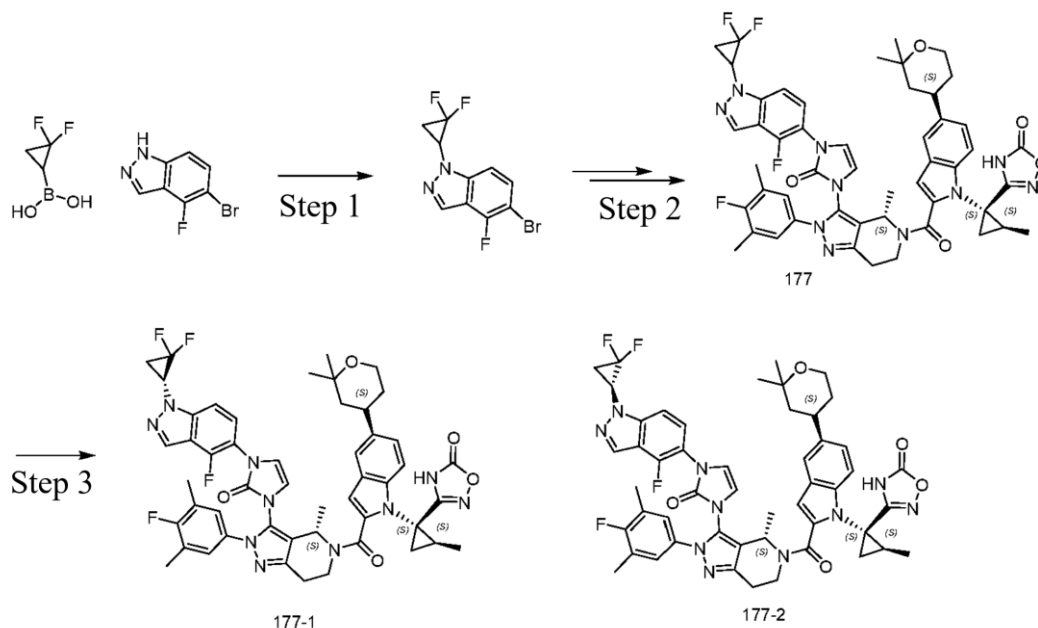
Step 7: 3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(methyl-d3)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(S)-3-((2-cyanoethyl)amino)butyronitrile-4,4,4-d3 was used as a raw material, following the synthesis for intermediate B, intermediate E and Example 1, to obtain the title product 3-((1S,2S)-1-(2-((S)-3-(3-(1-cyclopropyl-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-(methyl-d3)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 912.4[M+1].

Example 177

3-((1S,2S)-1-(2-((4S)-3-(3-(1-(2,2-difluorocyclopropyl)-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 5-bromo-1-(2,2-difluorocyclopropyl)-4-fluoro-1H-indazole

In a 100 mL reaction bottle, 5-bromo-4-fluoro-1H-indazole (1 g, 4.65 mmol), (2,2-difluorocyclopropyl)boronic acid (1.13 g, 9.30 mmol),

copper acetate monohydrate (928.37 mg, 4.65 mmol), sodium carbonate (985.81 mg, 9.30 mmol), and 2,2'-bipyridine (726.37 mg, 4.65mmol) were dissolved in 1,2-dichloroethane (25.0 mL), and then the reaction solution was stirred at 25°C for 4 hours under nitrogen protection. The reaction was stopped, and saturated aqueous ammonium chloride solution (60 mL) was added to quench the reaction, followed by extraction with dichloromethane (60 mL × 2); and the organic phases were combined, washed with saturated sodium chloride (60 mL × 1), dried over anhydrous sodium sulfate, and filtered, and the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product 5-bromo-1-(2,2-difluorocyclopropyl)-4-fluoro-1H-indazole (700 mg, yellow solid), yield: 51.7%.

MS m/z (ESI): 291.0, 293.0[M+1].

Step 2: 3-((1S,2S)-1-(2-((4S)-3-(3-(1-(2,2-difluorocyclopropyl)-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5-bromo-1-(2,2-difluorocyclopropyl)-4-fluoro-1H-indazole was used as a raw material, following the synthesis step in Example 1, to obtain the title product 3-((1S,2S)-1-(2-((4S)-3-(3-(1-(2,2-difluorocyclopropyl)-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 945.3[M+1].

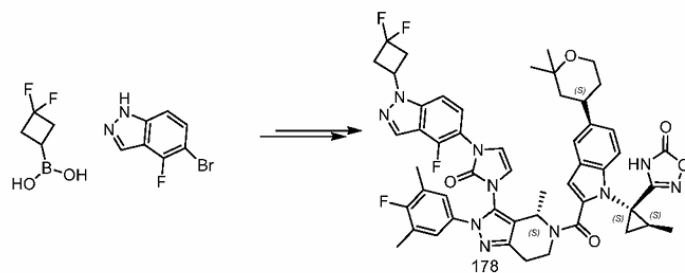
Step 3:

By chiral resolution, 177-1 and 177-2 were obtained.

MS m/z (ESI):945.3[M+1].

Example 178

3-((1S,2S)-1-(2-((S)-3-(3-(1-(3,3-difluorocyclobutyl)-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

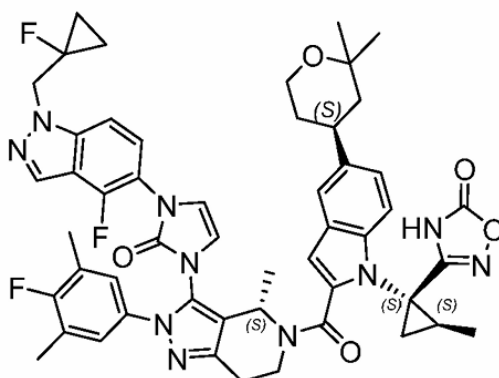


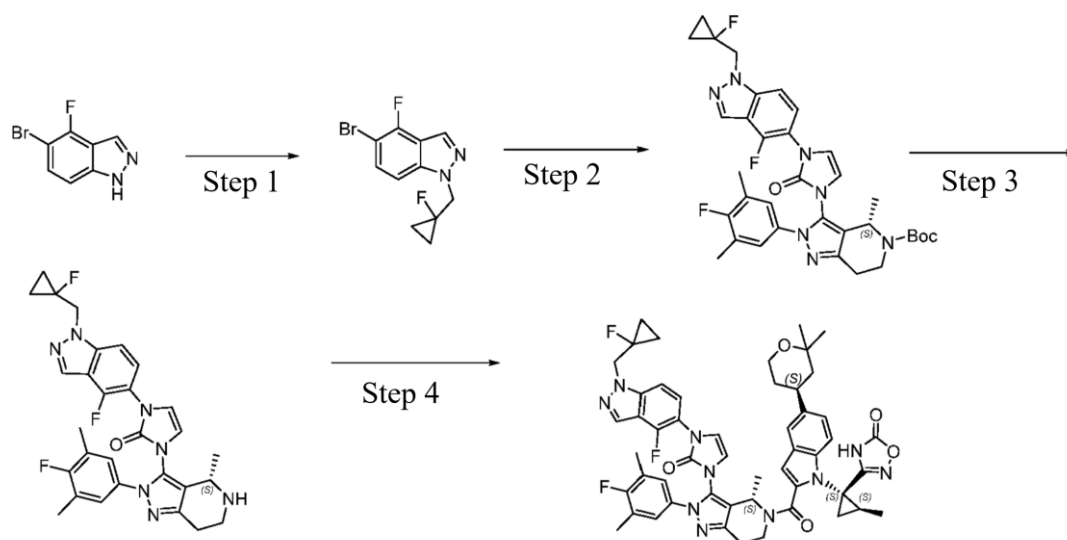
5-bromo-4-fluoro-1H-indazole and (3,3-difluorocyclobutyl)boronic acid were used as raw materials, following the synthesis step in Example 177, to obtain the title product 3-((1S,2S)-1-(2-((S)-3-(3-(1-(3,3-difluorocyclobutyl)-4-fluoro-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 959.3[M+1].

Example 179

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one





Step 1: 5-bromo-4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazole

Under an ice bath, 5-bromo-4-fluoro-1H-indazole (0.43 g, 2 mmol) was dissolved in tetrahydrofuran (6 mL), followed by nitrogen replacement; then triphenylphosphine (0.79 g, 3 mmol) and diisopropyl azodicarboxylate (0.61 g, 3 mmol) were added, successively and stirred for 30 minutes under the ice bath, and finally (1-fluorocyclopropyl)methanol was added, and stirred for 2 hours at room temperature, with LCMS indicating the completion of the reaction; the reaction solution was quenched with a saturated ammonium chloride solution (10 mL), and then extracted with ethyl acetate (15 mL $\times$ 2); and the organic phases were combined, dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was separated by Flash column chromatography, to obtain the target product 5-bromo-4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazole (0.29 g, yield 50%).

MS m/z (ESI): 287.0, 289.0[M+1].

Step 2: tert-butyl (S)-3-(3-(4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

At room temperature, tert-butyl (4S)-2-(4-fluoro-3,5-dimethyl-phenyl)-4-methyl-3-(2-carbonyl-1H-imidazol-3-yl)-6,7-dihydro-4H-pyrazolo[4,3-c]pyridine-5-carboxylate (50 mg, 0.11 mmol), 5-bromo-4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazole (37 mg, 0.13 mmol), cuprous iodide (11 mg, 0.06 mmol), potassium carbonate (47 mg, 0.33 mmol) and (1S,2S)-N,N'-dimethyl-1,2-diaminocyclohexane (8 mg, 0.06 mmol) were dissolved in N-methylpyrrolidone (2 mL), subjected to nitrogen replacement, heated to 130°C for reaction for 5 hours, and cooled to room temperature, with LCMS indicating the completion of the reaction; the reaction solution was diluted with ethyl acetate (15 mL) and filtered; the filter residue was washed with ethyl acetate (10 mL); and the organic phases were combined, washed with saturated brine (15 mL $\times$ 2),

dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified by thin-layer preparative chromatography (dichloromethane : methanol = 20 : 1), to obtain the target product, as a yellow oil (0.043 g, yield 60%).

MS m/z (ESI): 648.2[M+1].

5 Step 3: (S)-1-(4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

At room temperature, tert-butyl (S)-3-(3-(4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-10 5H-pyrazolo[4,3-c]pyridine-5-carboxylate (43 mg, 0.07 mmol) was dissolved in dichloromethane (2 mL), and then a hydrochloric acid/dioxane solution (4.0 M, 1 mL) was added and stirred at room temperature for 1 hour, with LCMS indicating the completion of the reaction, followed by spin-drying; and the residue was used directly in the next step (40 mg, crude product, yellow oil).

MS m/z (ESI): 548.2[M+1].

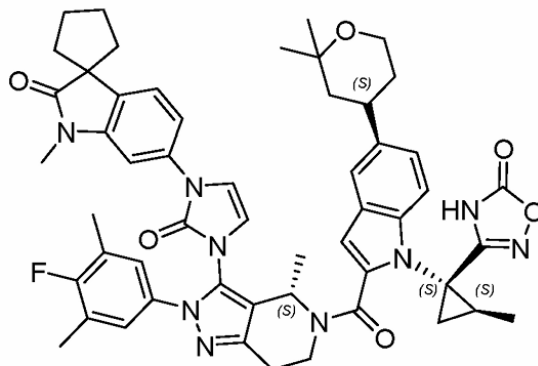
15 Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-3-(3-(4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

At room temperature, (S)-1-(4-fluoro-1-((1-fluorocyclopropyl)methyl)-1H-indazol-5-yl)-3-(2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one hydrochloride (40 mg, 0.07 mmol) was dissolved in N,N-dimethylformamide (3 mL), and then N,N-diisopropylethylamine (0.5 mL), 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid (29 mg, 0.07 mmol) and 2-(7-azobenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (38 mg, 0.1 25 mmol) were added successively, and stirred at room temperature for 14 hours, with LCMS indicating the completion of the reaction; the reaction solution was diluted with ethyl acetate (15 mL), and then washed with saturated brine (15 mL × 2); the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried, and the residue was purified by reverse phase preparative chromatography and lyophilized, to obtain the target compound as a white solid (10 mg, yield 15.6%).

30 MS m/z (ESI): 941.3[M+1].

Example 180

3-((1S,2S-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspiro[cyclopenta-1,3'-dihydroindole]-6'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



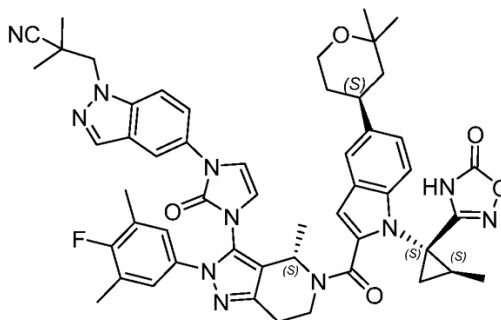
5

6'-bromospiro[cyclopenta-1,3'-dihydroindol]-2'-one was used as a raw material, following Example 93 Step 1 and Example 175 Step 2 to Step 4, to obtain the product.

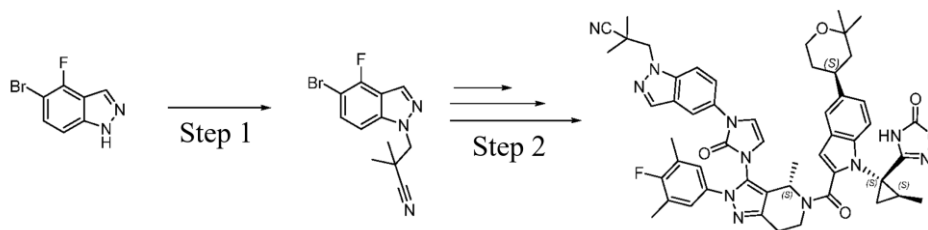
MS m/z (ESI): 934.4[M+1].

Example 181

10 3-(5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-1H-indazol-1-yl)-2,2-dimethylpropionitrile



15



Step 1: 3-(5-bromo-4-fluoro-1H-indazol-1-yl)-2,2-dimethylpropionitrile

3-hydroxyl-2,2-dimethylpropionitrile was used as a raw material, following Example 179 Step 1, to obtain 3-(5-bromo-4-fluoro-1H-indazol-1-yl)-2,2-dimethylpropionitrile.

5 MS m/z (ESI): 296.0, 298.0[M+1].

Step 2: 3-(5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-1H-indazol-1-yl)-2,2-dimethylpropionitrile

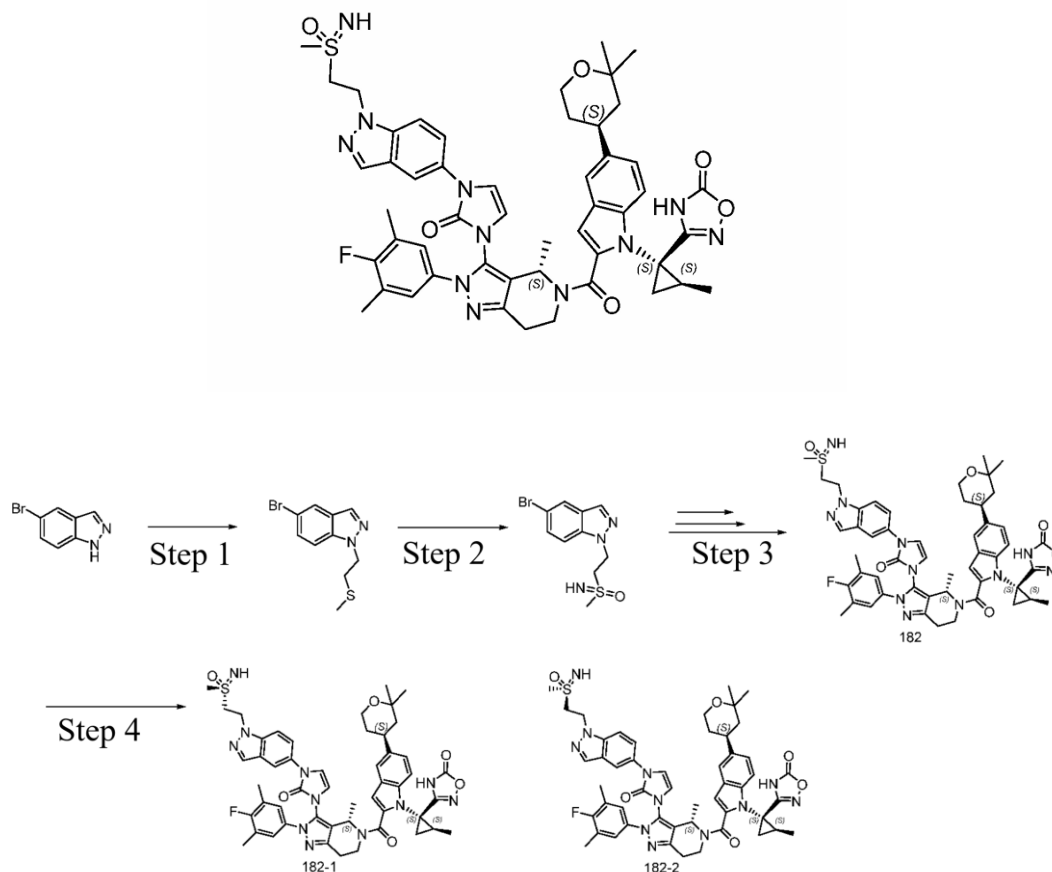
10 3-(5-bromo-4-fluoro-1H-indazol-1-yl)-2,2-dimethylpropionitrile was used as a raw material, following Example 179 Steps 2, 3 and 4, to obtain 3-(5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-1H-indazol-1-yl)-2,2-dimethylpropionitrile.

15 MS m/z (ESI): 932.4[M+1].

Example 182

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(2-(S-methylsulfonimidoyl)ethyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

20



Step 1: 5-bromo-1-(2-(methylthio)ethyl)-1H-indazole

5-bromo-1H-indazole and (2-bromoethyl)(methyl)sulfane were used as raw materials, following Example 180 Step 1, to obtain 5-bromo-1-(2-(methylthio)ethyl)-1H-indazole.

MS m/z (ESI): 271.0, 273.0[M+1].

Step 2: (2-(5-bromo-1H-indazol-1-yl)ethyl)(imino)(methyl)-l6-sulfanone

At room temperature, 5-bromo-1-(2-(methylthio)ethyl)-1H-indazole (0.54 g, 2 mmol) was dissolved in methanol (20 mL), and then [di(acetoxy)iodo]phenyl (1.93 g, 6 mmol) and ammonium carbamate (0.62 g, 8 mmol) were added successively; and the mixture was stirred at room temperature for 2 hours, with LCMS indicating the completion of the reaction, and spin-dried, and the residue was separated by Flash column chromatography (eluting with DCM : MeOH = 10 : 1), to obtain the target product as a colorless solid (0.24 g, yield: 40%).

MS m/z (ESI): 302.0, 304.0[M+1].

Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(2-(S-methylsulfonimidoyl)ethyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(2-(5-bromo-1H-indazol-1-yl)ethyl)(imino)(methyl)-l6-sulfanone was used as a raw material, following Example 179 Steps 2, 3 and 4, to obtain 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(2-(S-methylsulfonimidoyl)ethyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

MS m/z (ESI): 956.3[M+1].

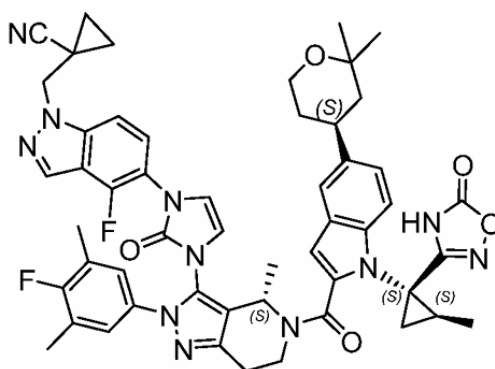
Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-(S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(2-((S)-S-methylsulfonimidoyl)ethyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one and 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(2-((R)-S-methylsulfonimidoyl)ethyl)-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

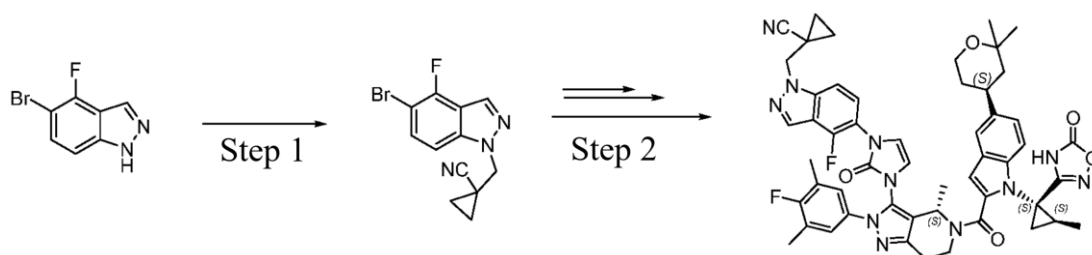
By chiral resolution, 182-1 and 182-2 were obtained.

MS m/z (ESI):956.3[M+1]

Example 183

1-((5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-fluoro-1H-indazol-1-yl)methyl)cyclopropane-1-carbonitrile





Step 1: 1-((5-bromo-4-fluoro-1H-indazol-1-yl)methyl)cyclopropane-1-carbonitrile

1-(Hydroxymethyl)cyclopropane-1-carbonitrile and 5-bromo-4-fluoro-1H-indazole were used as raw materials, following Example 179 Step 1, to obtain 1-((5-bromo-4-fluoro-1H-indazol-1-yl)methyl)cyclopropane-1-carbonitrile.

MS m/z (ESI):294.0, 296.0[M+1].

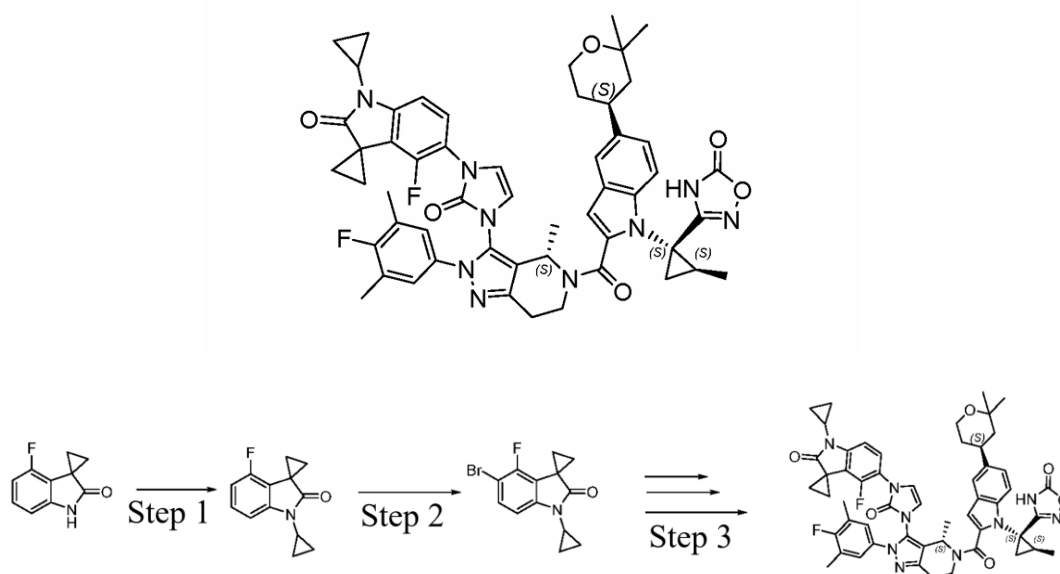
Step 2: 1-((5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-fluoro-1H-indazol-1-yl)methyl)cyclopropane-1-carbonitrile

1-((5-bromo-4-fluoro-1H-indazol-1-yl)methyl)cyclopropane-1-carbonitrile was used as a raw material, following Example 179 Steps 2, 3 and 4, to obtain 1-((5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-fluoro-1H-indazol-1-yl)methyl)cyclopropane-1-carbonitrile.

MS m/z (ESI):948.3[M+1].

Example 184

3-((1S,2S)-1-(2-((S)-3-(3-(1'-cyclopropyl-4'-fluoro-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 1'-cyclopropyl-4'-fluorospiro[cycloprop-1,3'-dihydroindole]-2'-one

At room temperature, 4'-fluorospiro[cycloprop-1,3'-dihydroindole]-2'-one (0.35 g, 2 mmol), 2-(2-pyridyl)pyridine (0.47 g, 3 mmol), cyclopropylboronic acid (0.52 g, 6 mmol), copper acetate (0.54 g, 3 mmol) and sodium carbonate (0.64 g, 6 mmol) were dissolved in 1,2-dichloroethane (10 mL), subjected to oxygen replacement, heated to 80°C for reaction for 14 hours, and cooled to room temperature, with LCMS indicating the completion of the reaction, followed by filtration and spin-drying; and the residue was separated by Flash column chromatograph (PE : EA = 10 : 1), to obtain 1'-cyclopropyl-4'-fluorospiro[cycloprop-1,3'-dihydroindole]-2'-one (0.15 g, yield: 35%).

MS m/z (ESI):218.1[M+1].

Step 2: 5'-bromo-1'-cyclopropyl-4'-fluorospiro[cycloprop-1,3'-dihydroindole]-2'-one

At room temperature, 1'-cyclopropyl-4'-fluorospiro[cycloprop-1,3'-dihydroindole]-2'-one (0.15 g, 0.7 mmol) was dissolved in N,N-dimethylformamide (5 mL), and then N-bromosuccinimide (0.12 g, 0.7 mmol) was added and stirred at room temperature for 1 hour, with LCMS indicating the completion of the reaction; the reaction solution was diluted with ethyl acetate (20 mL), and then washed with saturated brine (15 mL × 2); the organic phase was dried over anhydrous sodium sulfate, filtered, and spin-dried; and the residue was separated by Flash column chromatography (PE : EA = 10 : 1), to obtain 5'-bromo-1'-cyclopropyl-4'-fluorospiro[cycloprop-1,3'-dihydroindole]-2'-one (0.10 g, yield: 50%).

MS m/z (ESI):296.0, 298.0[M+1].

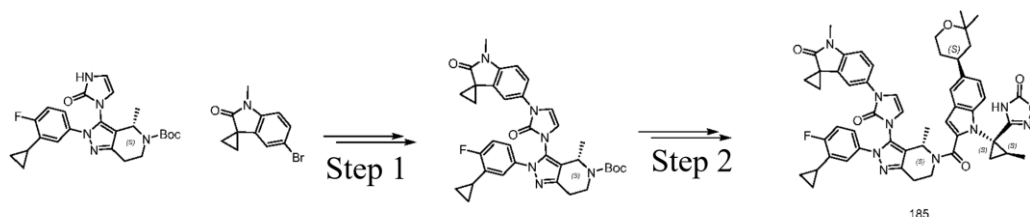
Step 3: 3-((1S,2S)-1-(2-((S)-3-(3-(1'-cyclopropyl-4'-fluoro-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5'-bromo-1'-cyclopropyl-4'-fluorospiro[cycloprop-1,3'-dihydroindol]-2'-one was used as a raw material, following Example 179 Steps 2, 3 and 4, to obtain 3-((1S,2S)-1-(2-((S)-3-(3-(1'-cyclopropyl-4'-fluoro-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 950.3[M+1].

Example 185

3-((1S,2S)-1-(2-((S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

tert-Butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(2-carboxyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate and 5'-bromo-1'-methylspiro[cycloprop-1,3'-dihydroindol]-2'-one were used as raw materials, following the synthesis step in Example 1, to obtain the title product tert-butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

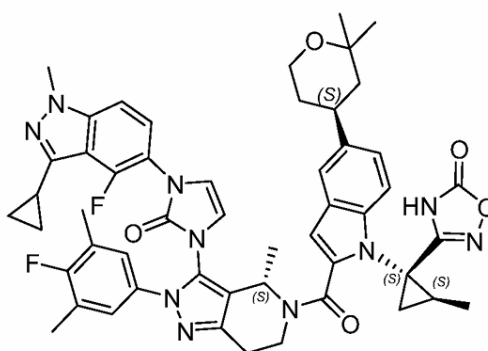
MS m/z (ESI): 625.2[M+1].

Step 2: 3-((1S,2S)-1-(2-((S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

tert-Butyl (S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspiro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate was used as a raw material, following the synthesis steps in intermediate C Step 2 to Step 3, to obtain the title product 3-((1S,2S)-1-(2-((S)-2-(3-cyclopropyl-4-fluorophenyl)-4-methyl-3-(3-(1'-methyl-2'-carbonylspiro[cycloprop-1,3'-dihydroindol]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

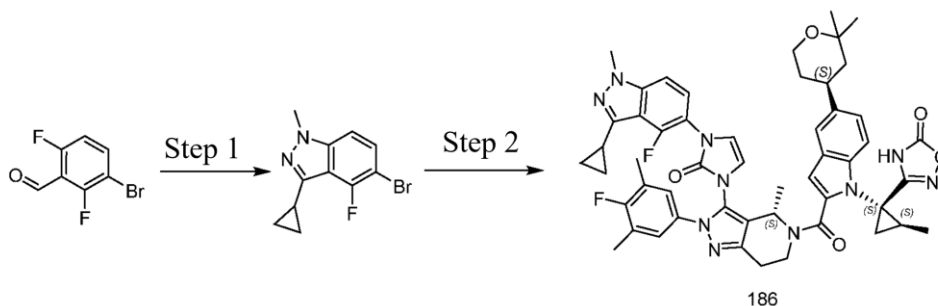
MS m/z (ESI): 918.4 [M+1].

Example 186



186

10



186

Step 1: 5-bromo-3-cyclopropyl-4-fluoro-1-methyl-1H-indazole

3-bromo-2,6-difluorobenzaldehyde was used as a raw material, following ROCHE HOLDING AG; WUXI APPTEC CO., LTD.; MORPHOSYS AG-WO 2016/55028, 2016, A1, Page/Page column 141, to obtain the target product.

15

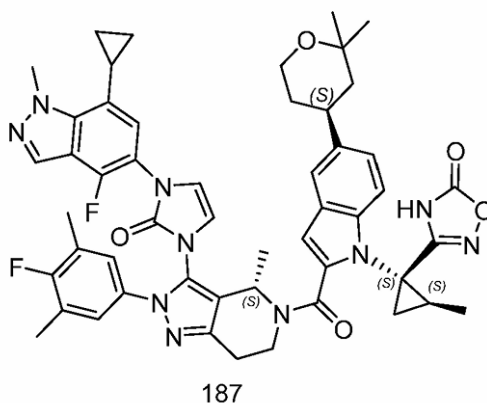
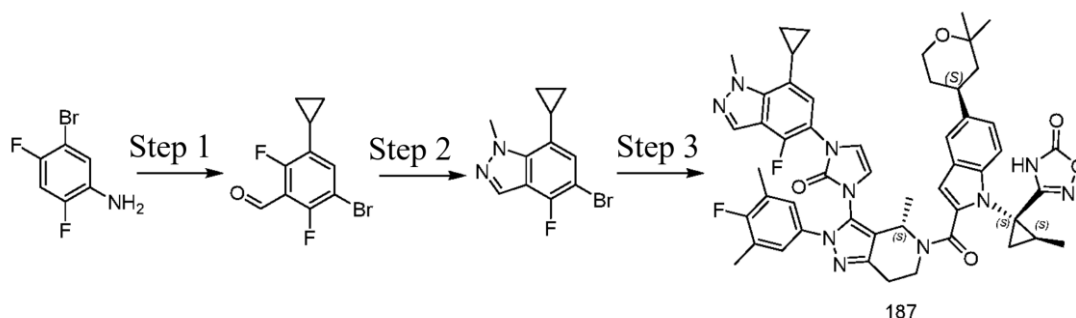
MS m/z (ESI): 269.0, 271.0 [M+1].

Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(3-cyclopropyl-4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5 5-bromo-3-cyclopropyl-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product.

MS-m/z-(ESI): 923.4[M+1].

Example 187



10

Step 1: 3-bromo-5-cyclopropyl-2,6-difluorobenzaldehyde

5-bromo-2,4-difluoroaniline was used as a raw material, following WO 2021/76890, 2021, A1, Page/Page column 163, to obtain the target product.

MS m/z(ESI): 261.0, 263.0[M+1].

15

Step 2: 5-bromo-7-cyclopropyl-4-fluoro-1-methyl-1H-indazole

3-bromo-5-cyclopropyl-2,6-difluorobenzaldehyde was used as a raw material, following [Organic Letters, 2007, vol.9, #3, p.525-528], to obtain the target product.

MS m/z (ESI): 269.0, 271.0[M+1].

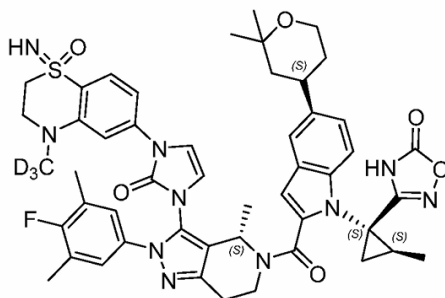
20

Step 3: 3-((1S,2S)-1-(2-((S)-3-(3-(7-cyclopropyl-4-fluoro-1-methyl-1H-indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5-bromo-7-cyclopropyl-4-fluoro-1-methyl-1H-indazole was used as a raw material, following Example 1, to obtain the target product.

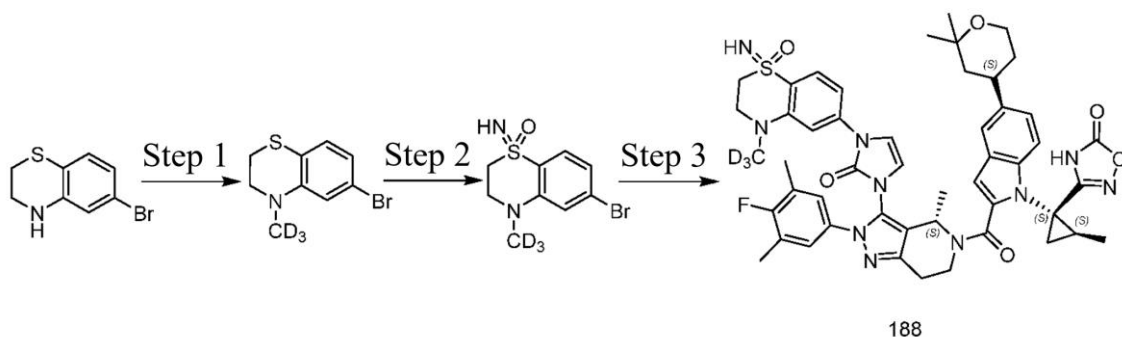
MS m/z (ESI): 923.4[M+1],

Example 188



188

5



188

Step 1: 6-bromo-4-(methyl-d3)-3,4-dihydro-2H-benzo[b][1,4]thiazide

6-bromo-3,4-dihydro-2H-benzo[b][1,4]thiazide was used as a raw material, following Example 88 Step 1, to obtain the target product.

10 MS m/z (ESI): 247.0, 249.0[M+1].

Step 2: 6-bromo-1-imino-4-(methyl-d3)-1,2,3,4-tetrahydro-114-benzo[b][1,4]thiazide 1-oxide

6-bromo-4-(methyl-d3)-3,4-dihydro-2H-benzo[b][1,4]thiazide was used as a raw material, following US 2018/170869, 2018, to obtain the target product.

MS m/z (ESI): 278.0, 280.0[M+1].

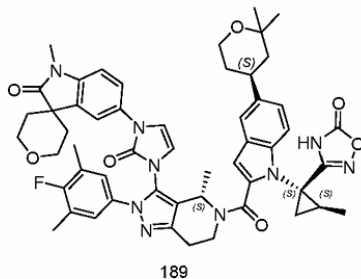
15 Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(1-imino-4-(methyl-d3)-1-hydroxyl-1,2,3,4-tetrahydro-114-benzo[b][1,4]thiazid-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

6-bromo-1-imino-4-(methyl-d3)-1,2,3,4-tetrahydro-1H-benzo[b][1,4]thiazide 1-oxide was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 932.4[M+1].

Example 189

- 5 5-(3-(S)-5-(5-(S)-2,2-dimethyltetrahydropyran-4-yl)-1-(1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-1-methyl-2,3,5,6-tetrahydrospiroindoline-3,4-pyran-2-one

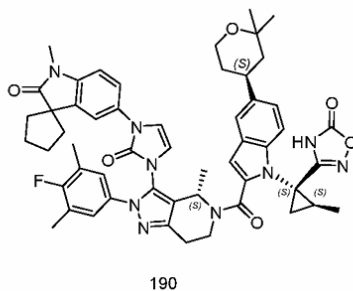


- 10 5-bromo-1-methyl-2,3,5,6-tetrahydrospiroindolin-3,4-pyran-2-one was used as a raw material, following Example 175, to obtain the target product.

MS m/z (ESI): 950.4[M+1].

Example 190

- 15 3-(1S,2S)-1-(5-(S)-2,2-dimethyltetrahydropyran-4-yl)-2-(S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1'-methyl-2'-oxospirocyclopentan-1,3'-indolin)-5'-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)one

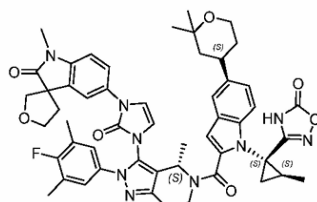


5-bromo-1-methylspirocyclopentan-1,3-indolin-2-one was used as a raw material, following Example 175, to obtain the target product.

MS m/z (ESI): 934.4[M+1].

Example 191

5-((5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-(1S,2S)-2-methyl-1-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl)-1'-methyl-4,5-dihydro-2H-spiro[furan-3,3'-indoline]-2'-one



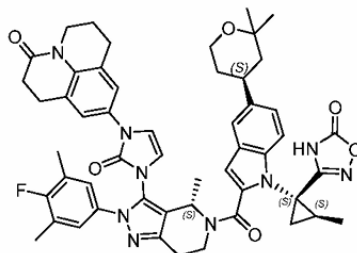
191

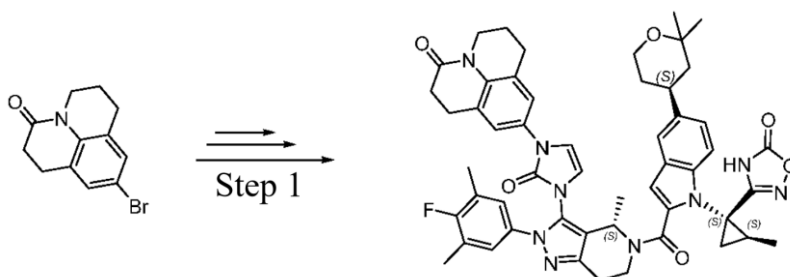
5-bromo-1-methyl-4,5-dihydro-2H-spirofuran-3,3-indolin-2-one was used as a raw material, following Example 175, to obtain the target product.

MS m/z (ESI): 936.4[M+1].

Example 192

3-(((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(3-carbonyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one





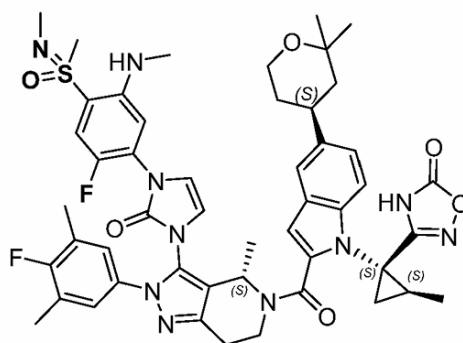
Step 1: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(3-carbonyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

9-bromo-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-5-one was used as a raw material, following Example 179 Steps 2, 3 and 4, to obtain 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(3-carbonyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

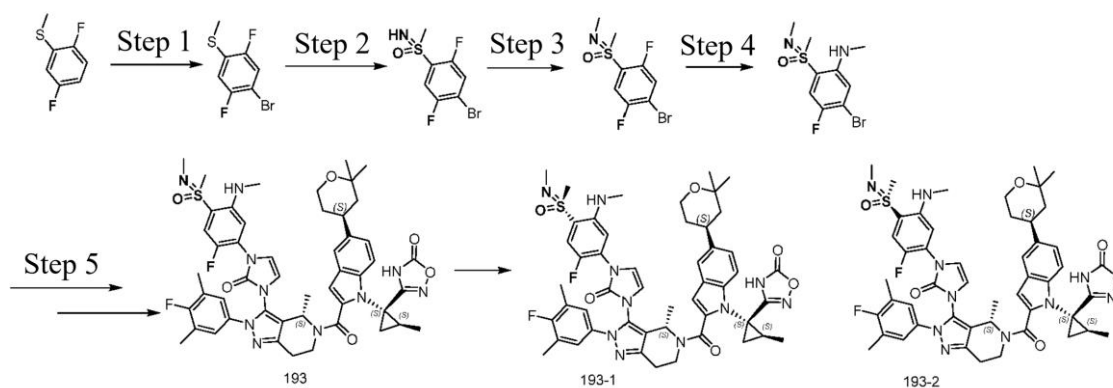
MS m/z (ESI):920.3[M+1].

Example 193

3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-2-fluoro-5-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



193



Step 1: (4-bromo-2,5-difluorophenyl)(methyl)sulfane

Following Example 15 Step 2, the target product (4-bromo-2,5-difluorophenyl)(methyl)sulfane was obtained.

5 MS m/z (ESI): 239.0 241.0[M+1].

Step 2: (4-bromo-2,5-difluorophenyl)(imino)(methyl)-l6-sulfanone

Following Example 3 Step 1, the target product (4-bromo-2,5-difluorophenyl)(imino)(methyl)-l6-sulfanone was obtained.

MS m/z (ESI): 270.0 272.0[M+1].

10 Step 3: (4-bromo-2,5-difluorophenyl)(methyl)(methyylimino)-l6-sulfanone

To a solution of (4-bromo-2,5-difluorophenyl)(imino)(methyl)-l6-sulfanone(600 mg, 2.22 mmol) in DCM(10 mL) was added trimethyloxonium tetrafluoroborate (329 mg, 2.22 mmol) and stirred at room temperature for 15 minutes, then sodium carbonate (1.12 g, 11.1 mmol) was added and stirred at room temperature for 1 hour, and then water was added, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; the filtrate was concentrated under reduced pressure to dryness, separated by column chromatography (PE/EA = 1 : 1), to obtain a light yellow oil (4-bromo-2,5-difluorophenyl)(methyl)(methyylimino)-l6-sulfanone (500 mg, yield: 84%)

MS m/z (ESI):284.0 286.0[M+1].

20 Step 4: (4-bromo-5-fluoro-2-(methylamino)phenyl)(methyl)(methyylimino)-l6-sulfanone

A mixture of (4-bromo-2,5-difluorophenyl)(methyl)(methyylimino)-l6-sulfanone (500 mg, 1.86 mmol), methanamine hydrochloride (253 mg, 3.71 mmol), potassium carbonate (770 mg, 5.58 mmol) and DMF (10 mL) was stirred at 120°C for 3 hours and cooled, and then water was added, followed by extraction with DCM three times; the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; and the filtrate was concentrated under reduced pressure to dryness and separated by column chromatography (DCM/MeOH = 10 : 1), to obtain a light yellow oil (200 mg, yield: 36%)

MS m/z (ESI): 295.0 297.0[M+1].

Step 5: 3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-2-fluoro-5-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

(4-bromo-5-fluoro-2-(methylamino)phenyl)(methyl)(methylimino)-l6-sulfanone was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 949.4[M+1].

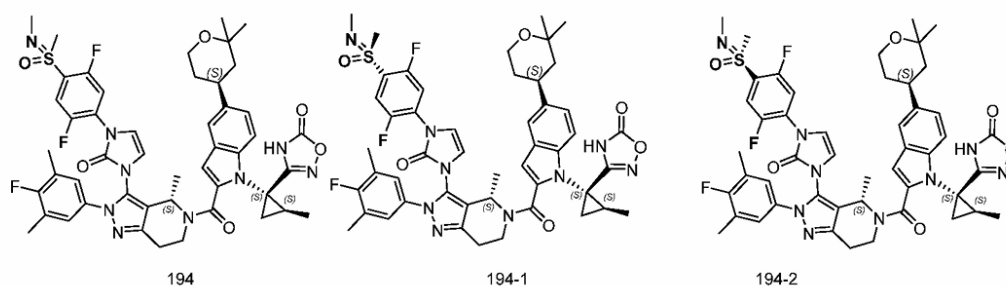
Step 6:

By chiral resolution, 193-1 and 193-2 were obtained.

MS m/z (ESI): 949.4[M+1].

Example 194

3-((1S,2S)-1-(2-((4S)-3-(3-(4-(N,S-dimethylsulfonimidoyl)-2,5-difluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

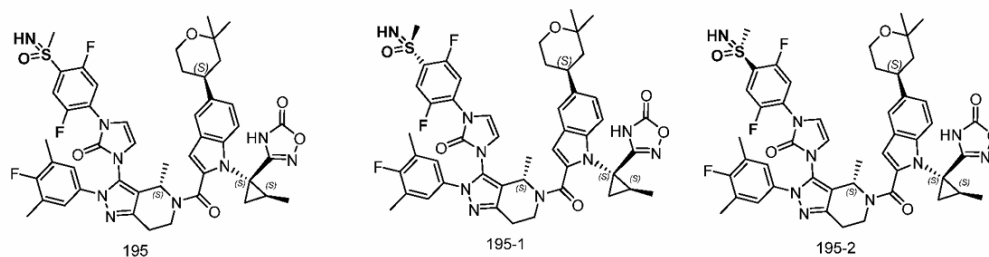


(4-bromo-2,5-difluorophenyl)(methyl)(methylimino)-l6-sulfanone was used as a raw material, following Example 1, to obtain the target product. Then chiral resolution was performed to obtain 194-1 and 194-2

MS m/z (ESI): 938.4[M+1].

Example 195

3-((1S,2S)-1-(2-((4S)-3-(3-(2,5-difluoro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



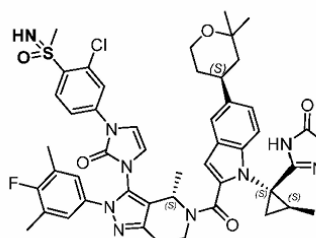
(4-bromo-2,5-difluorophenyl)(imino)(methyl-l6-sulfanone) was used as a raw material, following Example 1, to obtain the target product. Then chiral resolution was performed to obtain 195-1 and 195-2.

MS m/z (ESI):924.3[M+1].

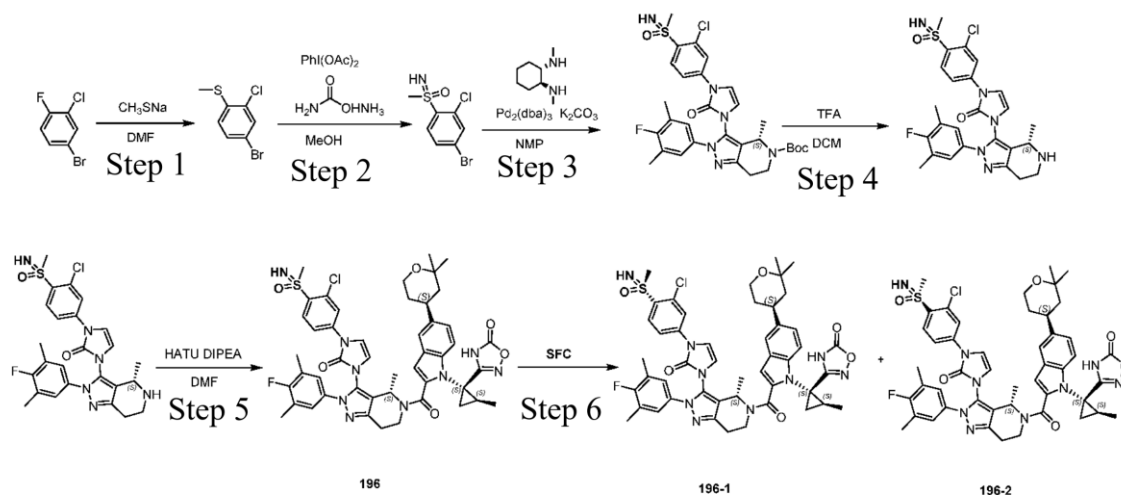
5

Example 196

3-((1S,2S)-1-(2-((4S)-3-(3-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10



Step 1: (4-bromo-2-chlorophenyl)(methyl)sulfane

4-bromo-2-chloro-1-fluorophenyl was used as a raw material, following IPSEN SA-WO 2015/100617, 2015, A1 Page/Page column 39, to obtain the target product (4-bromo-2-chlorophenyl)(methyl)sulfane.

MS m/z (ESI): 236.9, 238.9[M+1].

Step 2: (4-bromo-2-chlorophenyl)(imino)(methyl)-I6-sulfanone

5 (4-bromo-2-chlorophenyl)(methyl)sulfane was used as a raw material, following [Journal of Medicinal Chemistry, 2022, vol. 65, # 18, p. 12256-12272], to obtain the target product (4-bromo-2-chlorophenyl)(imino)(methyl)-I6-sulfanone.

MS m/z (ESI): 267.9, 269.9[M+1].

10 Step 3: tert-butyl (4S)-3-(3-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate

(4-bromo-2-chlorophenyl)(imino)(methyl)-I6-sulfanone was used as a raw material, following Example 1, to obtain the target product tert-butyl (4S)-3-(3-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate.

MS m/z (ESI): 629.2[M+1].

Step 4 1-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one

20 tert-Butyl (4S)-3-(3-(3-chloro-4(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carboxylate was used as a raw material, following intermediate C Step 2 reaction, to obtain the target product 1-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one.

MS m/z (ESI): 529.2[M+1].

25 Step 5 3-((1S,2S)-1-(2-((4S)-3-(3-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

1-(3-chloro-4-(S-methylsulfonimidoyl)phenyl)-3-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-1,3-dihydro-2H-imidazol-2-one and 5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carboxylic acid were used as raw materials, following the synthesis for intermediate E, finally to obtain the target product.

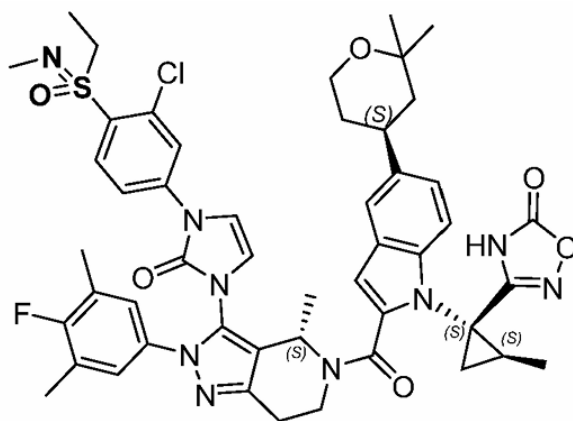
MS m/z (ESI): 922.3[M+1].

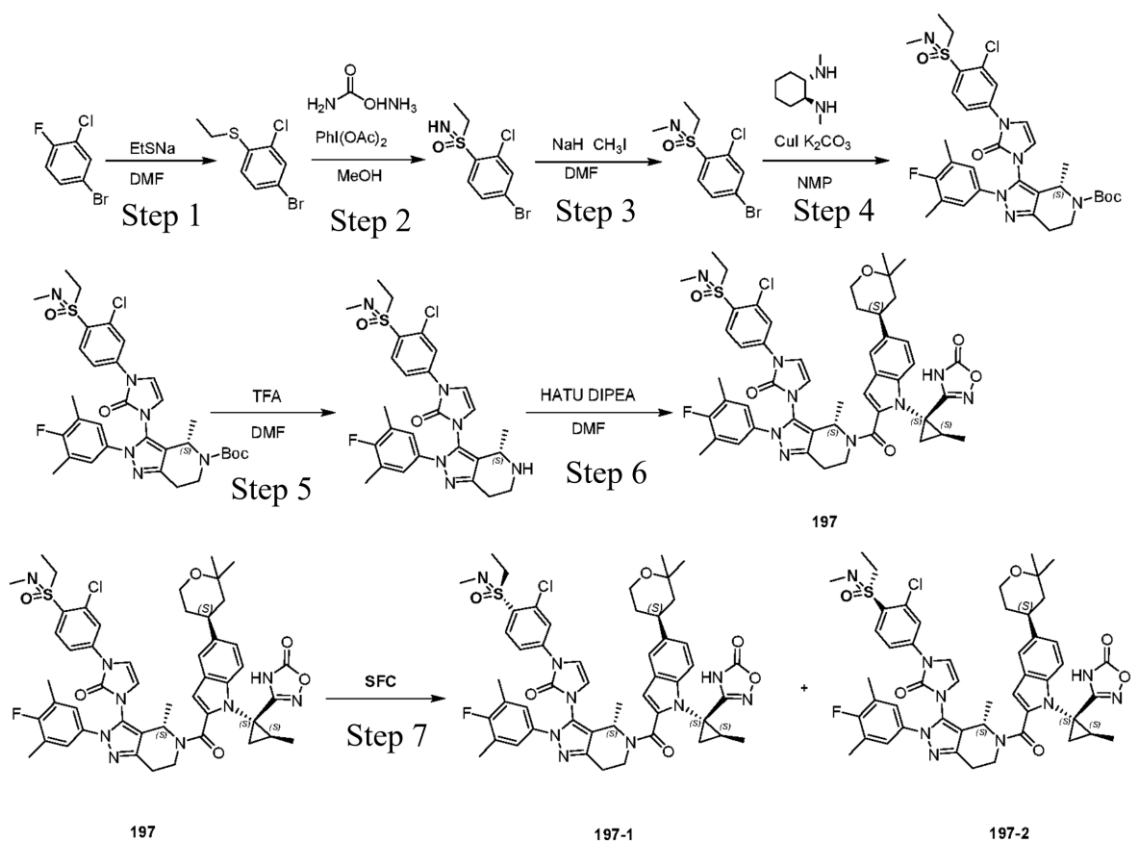
Step 6 chiral resolution was performed, to obtain **196-1** and **196-2**

MS m/z (ESI):922.3[M+1].

Example 197

3-((1S,2S)-1-(2-((4S)-3-(3-(3-chloro-4-(N-methylethylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



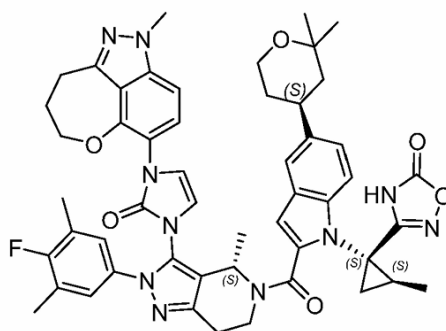


4-Bromo-2-chloro-1-fluorophenyl was used as a raw material, following respectively Example **196** and Example **158** Step 2 reaction, to obtain the target product 3-((1S,2S)-1-(2-((4S)-3-(3-chloro-4-(N-methylethylsulfonimidoyl)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

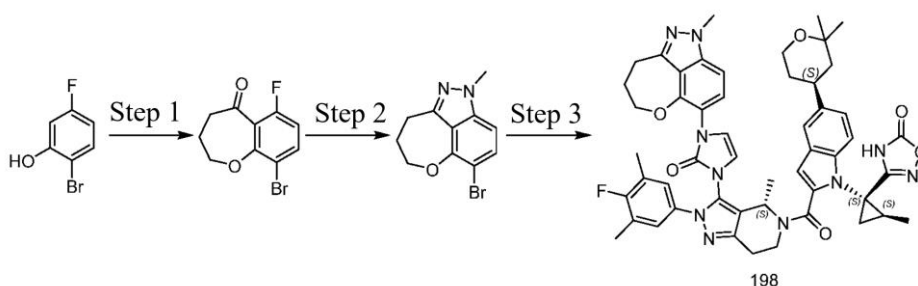
MS m/z (ESI): 950.3[M+1].

Step 7 chiral resolution was performed, to obtain **197-1** and **197-2**

MS m/z (ESI): 950.3[M+1].



198



198

Step 1: 9-bromo-6-fluoro-3,4-dihydrobenzo[b]oxepin-5(2H)-one

2-bromo-5-fluorophenol was used as a raw material, following Bioorganic and Medicinal Chemistry Letters, 2004, vol. 14, # 10, p. 2451-2457, to obtain the target product.

MS m/z (ESI): 259.0, 261.0[M+1].

Step 2: 5-bromo-2-methyl-2,7,8,9-tetrahydrooxepino[4,3,2-cd]indazole

9-bromo-6-fluoro-3,4-dihydrobenzo[b]oxepin-5(2H)-one was used as a raw material, following Example 187 Step 2, to obtain the target product.

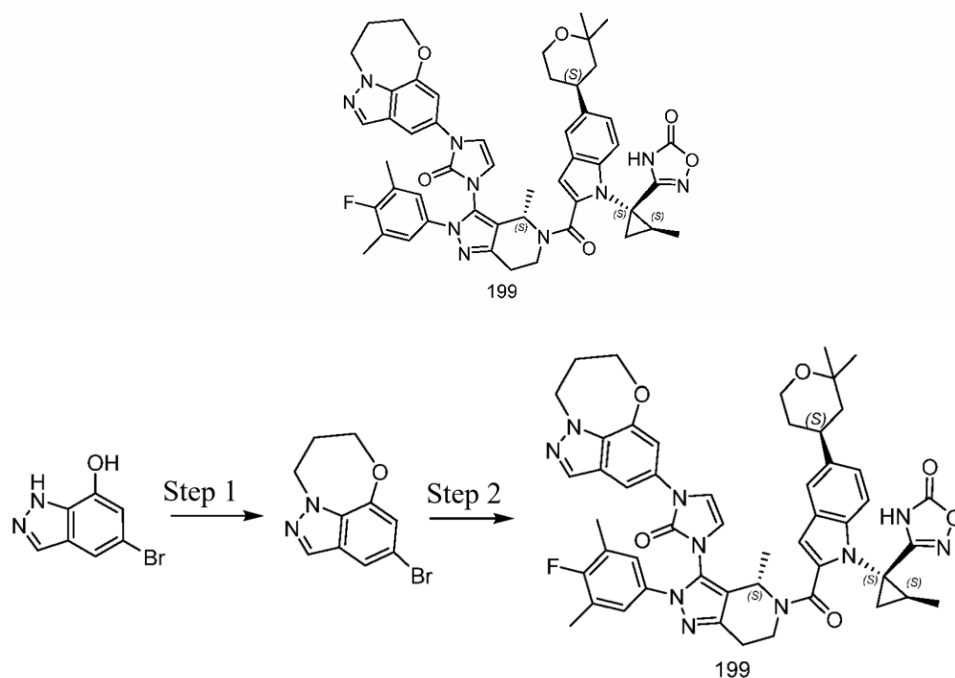
MS m/z (ESI): 267.0, 269.0[M+1].

Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(2-methyl-2,7,8,9-tetrahydrooxepino[4,3,2-cd]indazol-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5-bromo-2-methyl-2,7,8,9-tetrahydrooxepino[4,3,2-cd]indole was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 921.4[M+1].

Example 199



Step 1: 9-bromo-3,4-dihydro-2H-[1,4]oxazepino[2,3,4-hi]indazole

5-bromo-1H-indazol-7-ol was used as a raw material, following NANJING SANHOME INVESTMENT GROUP CO LTD - EP 3290419, 2018, A1, Paragraph 0592; 0593; 0594, to obtain the target product.

MS m/z (ESI): 253.0, 255.0[M+1].

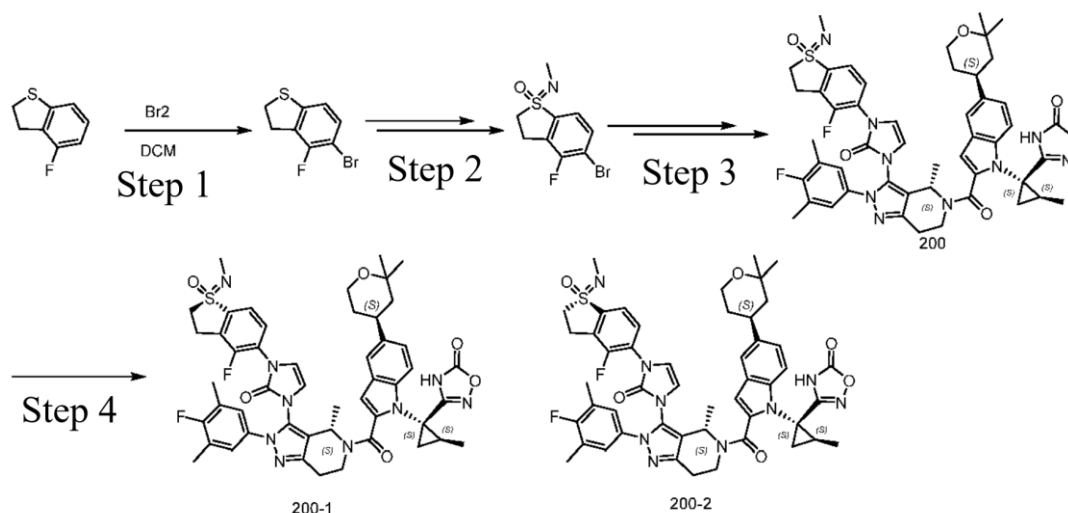
Step 2: 3-((1S,2S)-1-(2-((S)-3-(3-(3,4-dihydro-2H-[1,4]oxazepino[2,3,4-hi]indazol-9-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

9-bromo-3,4-dihydro-2H-[1,4]oxazepino[2,3,4-hi]indazole was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 907.4[M+1].

Example 200

3-((1S,2S)-1-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-1-(methylimino)-1-hydroxyl-2,3-dihydro-1H-114-benzo[b]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Step 1: 5-bromo-4-fluoro-2,3-dihydrobenzothiophene

In a 50 mL reaction bottle, 4-fluoro-2,3-dihydrobenzothiophene (300 mg, 1.95 mmol) was dissolved in dichloromethane (5 mL), and to the reaction solution was added Br₂ (310.90 mg, 1.95 mmol) at 25°C under nitrogen protection. The reaction solution was stirred at 25°C for 0.5 hours. The reaction was stopped, and an aqueous sodium bicarbonate solution (5 mL) was added to quench the reaction, followed by extraction with dichloromethane (5 mL x 2); and the organic phases were combined, washed with saturated sodium chloride (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the resulting residue was purified by silica gel column chromatography with an eluent system of petroleum ether and ethyl acetate to obtain the title product 5-bromo-4-fluoro-2,3-dihydrobenzothiophene (400 mg, yellow solid), yield: 88.2%.

MS m/z (ESI): 232.9, 234.9 [M+1].

Step 2: 5-bromo-4-fluoro-1-(methylimino)-2,3-dihydro-1H-114-benzo[b]thiophene 1-oxide

5-bromo-4-fluoro-2,3-dihydrobenzothiophene was used as a raw material, following the synthesis step in Example 158 Step 1 to Step 2, to obtain the title product 5-bromo-4-fluoro-1-(methylimino)-2,3-dihydro-1H-114-benzo[b]thiophene 1-oxide.

MS m/z (ESI): 277.9, 279.9 [M+1].

Step 3: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-1-(methylimino)-1-hydroxyl-2,3-dihydro-1H-114-benzo[b]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

5-bromo-4-fluoro-1-(methylimino)-2,3-dihydro-1H-114-benzo[b]thiophene 1-oxide was used as a raw material, following the synthesis step in Example 1, to obtain the title product 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-3-(3-(4-fluoro-1-(methylimino)-1-hydroxyl-2,3-dihydro-1H-114-benzo[b]thiophen-5-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI):932.3 [M+1].

Step 4:

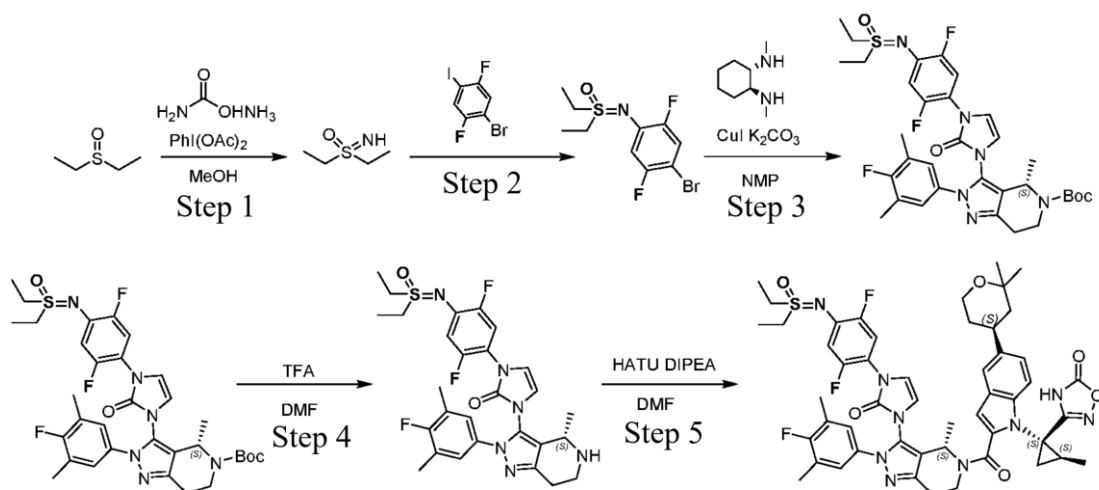
By chiral resolution, 200-1 and 200-2 were obtained.

MS m/z (ESI): 932.3 [M+1].

5

Example 201

3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-I6-sulfaneylidene)amino)-2,5-difluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



201

10

Ethanesulfinylethane and 1-bromo-2,5-difluoro-4-iodobenzene were used as raw materials, following Example 196 and Example 157 Step 1 reaction respectively, finally to obtain the target product 3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-I6-sulfaneylidene)amino)-2,5-difluorophenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

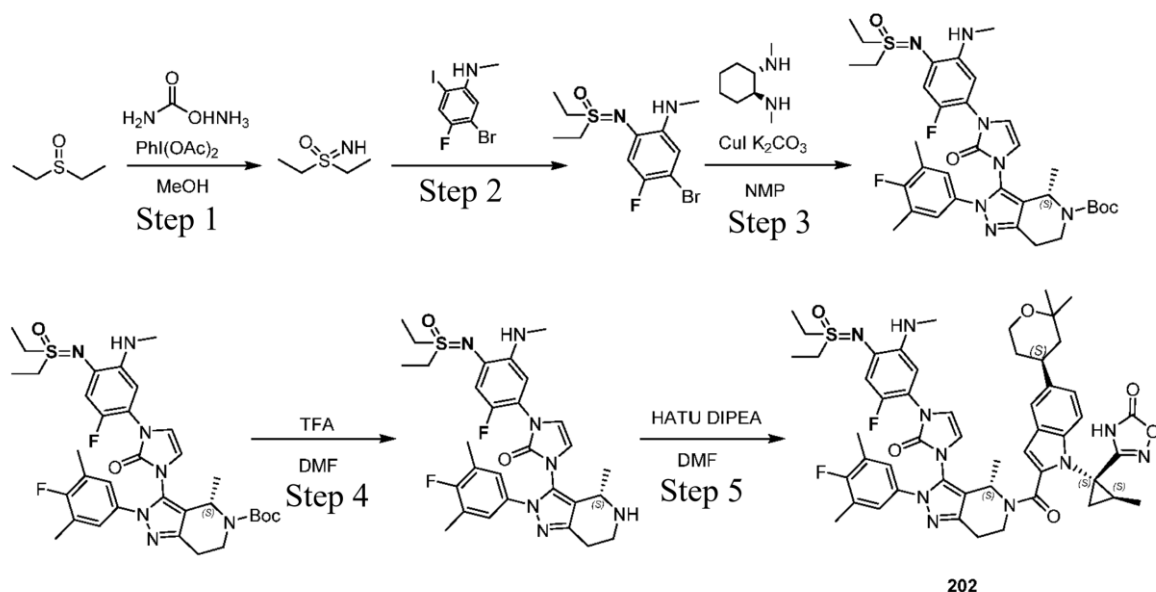
MS m/z (ESI): 966.4[M+1].

Example 202

3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-I6-sulfaneylidene)amino)-2-fluoro-5-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

20

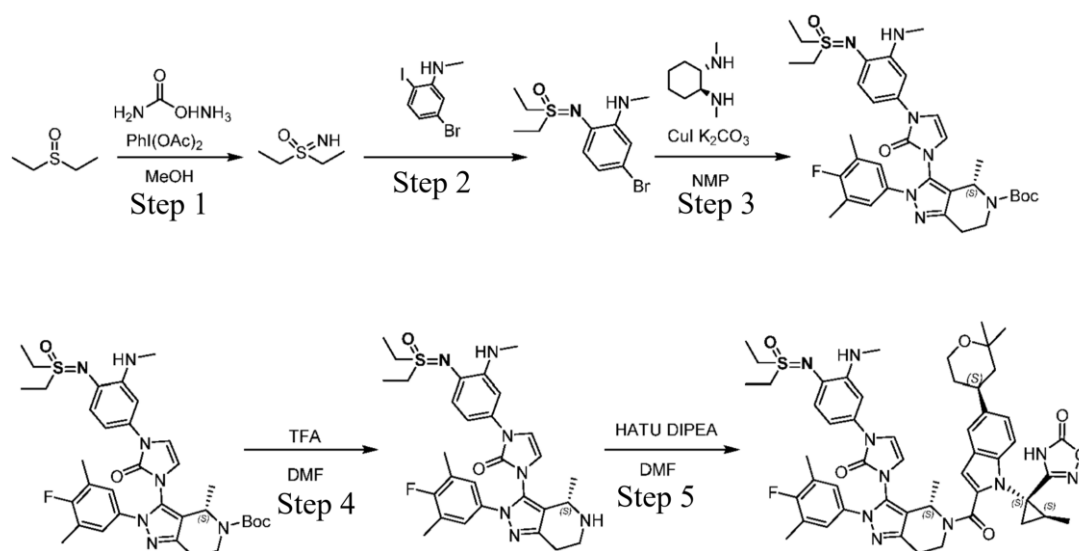
-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



Ethanesulfinylethane and 5-bromo-4-fluoro-2-iodo-N-methylbenzenamine were used as raw materials, following Example **201**, finally to obtain the target product 3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-I6-sulfaneylidene)amino)-2-fluoro-5-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one MS m/z (ESI): 977.4 [M+1].

Example 203

3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-I6-sulfaneylidene)amino)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



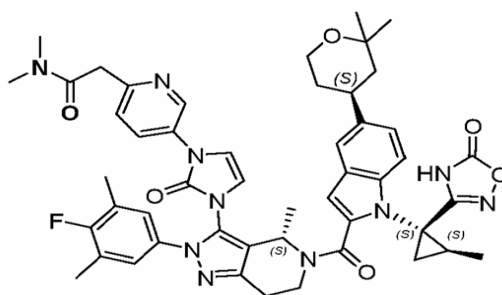
203

Ethanesulfinylethane and 5-bromo-2-iodo-N-methylbenzenamine were used as raw materials, following Example **202**, finally to obtain the target product 3-((1S,2S)-1-(2-((S)-3-(3-(4-((diethyl(carbonyl)-I6-sulfaneylidene)amino)-3-(methylamino)phenyl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one.

MS m/z (ESI): 959.4[M+1].

Example 204

2-(5-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)pyridin-2-yl)-N,N-dimethylacetamide



2-(5-bromopyridin-2-yl)acetic acid was used as a raw material, following the method for Example 64, to synthesize the target compound.

MS m/z (ESI): 897.4[M+1].

5

5(4H)-one



10

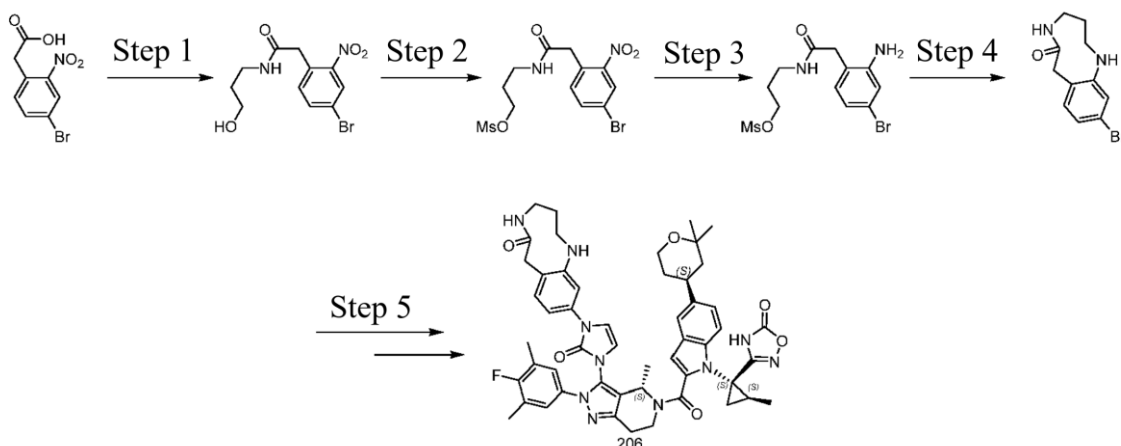
205 was chirally resolved to obtain 205-1 and 205-2.

15

15

methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one





Step 1: 2-(4-bromo-2-nitrophenyl)-N-(3-hydroxypropyl)acetamide

2-(4-bromo-2-nitrophenyl)acetic acid and 3-aminopropanol were used as raw materials, following intermediate C and intermediate D Step 3, to obtain the target product.

5 MS m/z (ESI): 317.0 319.0 [M+1].

Step 2: 3-(2-(4-bromo-2-nitrophenyl)acetamido)propylmethanesulfonate

2-(4-bromo-2-nitrophenyl)-N-(3-hydroxypropyl)acetamide was used as a raw material, following Example 49 Step 3, to obtain the target product.

MS m/z (ESI): 395.0 397.0 [M+1].

10 Step 3: 3-(2-(2-amino-4-bromophenyl)acetamido)propylmethanesulfonate

To a solution of 3-(2-(4-bromo-2-nitrophenyl)acetamido)propylmethanesulfonate (500 mg, 1.26 mmol) and 4,4'-bipyridine (20 mg, 0.13 mmol) in DMF (10 mL) was added tetrahydroxydiboron (449 mg, 5 mmol); the mixture was stirred at room temperature for 10 minutes, and water was added, followed by extraction with DCM; and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered, spin-dried, and separated by column chromatography (PE/EA = 1 : 1), to obtain a light yellow oil (300 mg, yield: 65%)

MS m/z (ESI): 365.0 367.0 [M+1].

Step 4: 10-bromo-1,2,3,4,5,7-hexahydro-6H-benzo[f][1,5]diazonine-6-one

a mixture of 3-(2-(4-bromo-2-nitrophenyl)acetamido)propylmethanesulfonate (300 mg, 0.82 mmol), potassium carbonate (340 mg, 2.46 mmol) and DMF (10 mL) was stirred under microwave conditions at 80°C for 5 hours, and water was added, followed by extraction with DCM three times, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and filtered; the filtrate was concentrated under reduced pressure to dryness, and separated by column chromatography (PE/EA = 1 : 1), to obtain 10-bromo-1,2,3,4,5,7-hexahydro-6H-benzo[f][1,5]diazonin-6-one (100 mg, yield: 45 %) as a light yellow oil

25 MS m/z (ESI): 269.0 271.0 [M+1].

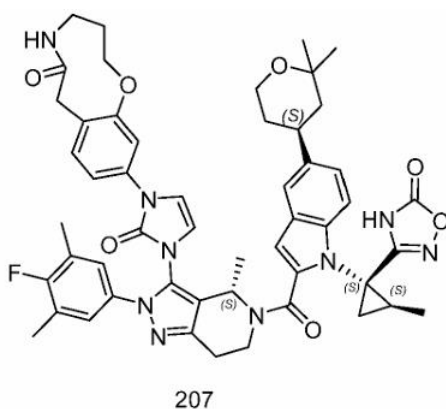
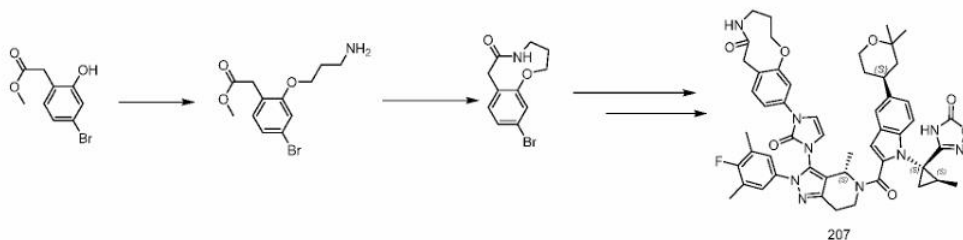
Step 5: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(2-carbonyl-3-(6-carbonyl-2,3,4,5,6,7-hexahydro-1H-benzo[f][1,5]diazonin-10-yl)-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

10-bromo-1,2,3,4,5,7-hexahydro-6H-benzo[f][1,5]diazonin-6-one was used as a raw material, following Example 1, to obtain the target product.

MS m/z(ESI):923.4[M+1].

Example 207

10-((3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indole-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,3,4,5-tetrahydrobenzo[h][1,5]oxazonin-6(7H)-one



Step 1: methyl 2-(2-(3-aminopropoxy)-4-bromophenyl)acetate

methyl 2-(4-bromo-2-hydroxyphenyl)acetate was used as a raw material, following reference [European-Journal of Medicinal Chemistry, 1993, vol.28, #7-8, p.625-632] to obtain method, to obtain the target product methyl 2-(2-(3-aminopropoxy)-4-bromophenyl)acetate.

MS m/z (ESI):302.0 304.0 [M+1].

Step 2: 10-bromo-2,3,4,5-tetrahydrobenzo[h][1,5]oxazonin-6(7H)-one

To a solution of methyl 2-(2-(3-aminopropoxy)-4-bromophenyl)acetate (400 mg, 1.32 mmol) in THF was added dropwise LiHMDS (2.64 mL, 2.64 mmol, 1M), then reacted at room temperature for 2 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate, and the organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and spin-dried. The residue was purified by flash silica gel chromatography (petroleum ether : ethyl acetate = 5 : 1), to obtain the target product 10-bromo-2,3,4,5-tetrahydrobenzo[h][1,5]oxazonin-6(7H)-one (150 mg, yield: 42%).

MS m/z (ESI): 270.0 272.0 [M+1].

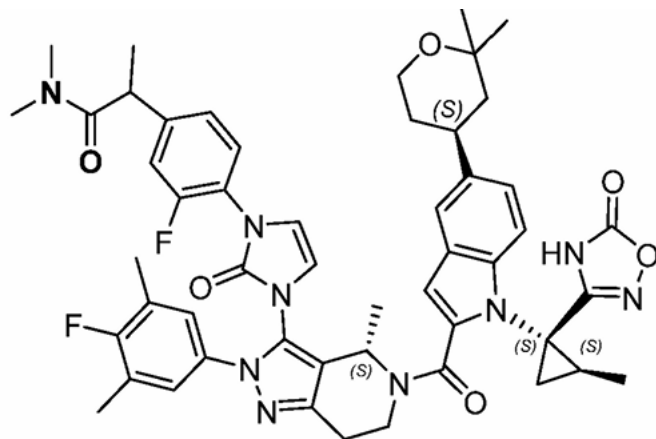
Step 3: 10-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2,3,4,5-tetrahydrobenzo[h][1,5]oxazonin-6(7H)-one

10-bromo-2,3,4,5-tetrahydrobenzo[h][1,5]oxazonin-6(7H)-one was used as a raw material, following Example 1, to obtain the target product.

MS m/z (ESI): 924.4[M+1].

Example 208

2-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3-fluorophenyl)-N,N-dimethylpropionamide

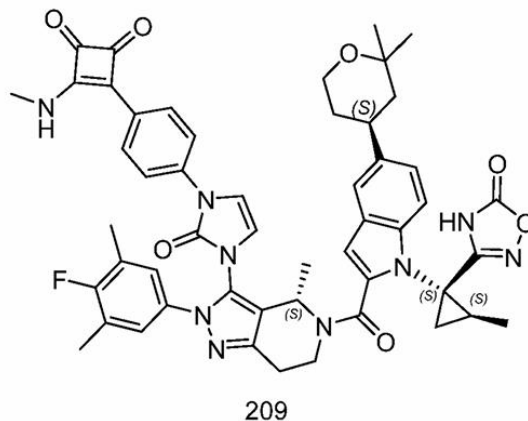
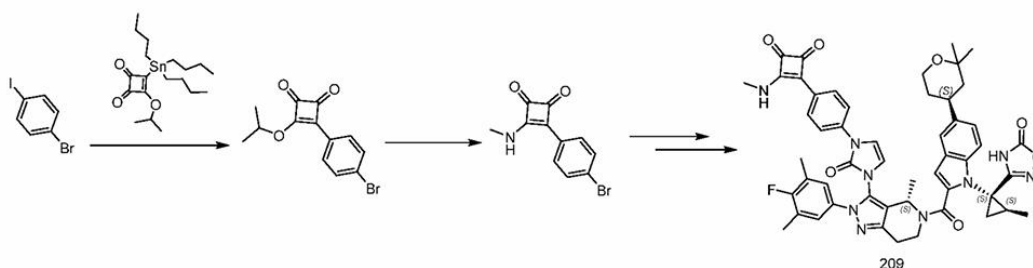


5 2-(4-bromo-3-fluorophenyl)propanoic acid was used as a raw material, following the method for Example 64, to synthesize the target compound.

MS m/z (ESI): 928.4[M+1].

Example 209

3-(4-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)phenyl)-4-(methylamino)cyclobut-3-ene-1,2-dione



Step 1: 3-(4-bromophenyl)-4-isopropoxycyclobut-3-ene-1,2-dione

1-Bromo-4-iodobenzene (1 g, 3.55 mmol), 3-isopropoxy-4-(tri-n-butyltin)-3-cyclobutene-1,2-dione (1.5 g, 3.55 mmol) and cuprous chloride (36 mg, 0.35 mmol) were dissolved in DMF (12 mL), and tris(dibenzylideneacetone)palladium (146 mg, 0.16 mmol) was added under nitrogen protection. The mixture was reacted at 50°C for 2 hours. Water was added to the reaction solution, followed by extraction with ethyl acetate, and the organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate, filtered, and spin-dried. The residue was purified by flash silica gel chromatography (petroleum ether : ethyl acetate = 5 : 1), to obtain the target product 3-(4-bromophenyl)-4-isopropoxycyclobut-3-ene-1,2-dione (300 mg, yield 28%).

MS m/z (ESI): 295.0 297.0 $[M+1]$.

Step 2: 3-(4-bromophenyl)-4-(methylamino)cyclobut-3-ene-1,2-dione

A mixture of 3-(4-bromophenyl)-4-isopropoxycyclobut-3-ene-1,2-dione (300 mg, 1.02 mmol),

and methanamineethanol solution (10 mL) was stirred at room temperature for 12 hours, and, after the completion of the reaction, concentrated under reduced pressure to dryness, and the crude product was directly used in the next step, to obtain the title product 3-(4-bromophenyl)-4-(methylamino)cyclobut-3-ene-1,2-dione (5.7 g, crude)

5 MS m/z (ESI): 266.0 268.0 [M+1].

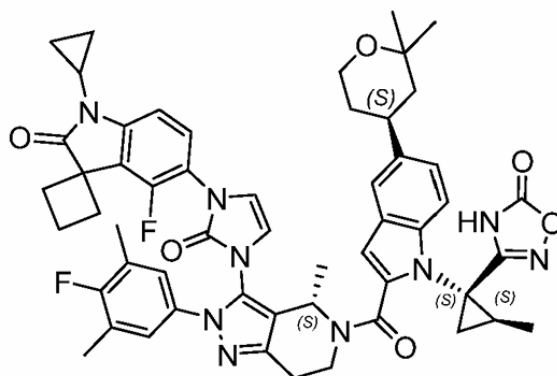
Step 3: 3-(4-(3-((S)-5-(5-(S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)phenyl)-4-(methylamino)cyclobut-3-ene-1,2-dione

10 3-(4-bromophenyl)-4-(methylamino)cyclobut-3-ene-1,2-dione and intermediate E were used as raw materials, following Example 1, to obtain the target product.

MS m/z (ESI): 920.4[M+1].

Example 210

15 3-((1S,2S)-1-(2-((S)-3-(3-(1'-cyclopropyl-4'-fluoro-2'-carbonylspro [cyclobuta-1,3'-dihydroindole]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

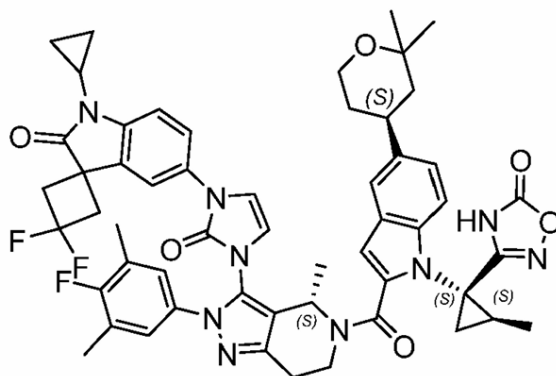


20 4'-fluorospiro [cyclobuta-1,3'-dihydroindole]-2-one, following the synthesis method for Example 184, to obtain the target product.

MS m/z (ESI): 964.4 [M+1].

Example 211

25 3-((1S,2S)-1-(2-((S)-3-(3-(1'-cyclopropyl-3,3-difluoro-2'-carbonylspro [cyclobuta-1,3'-dihydroindole]-5'-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

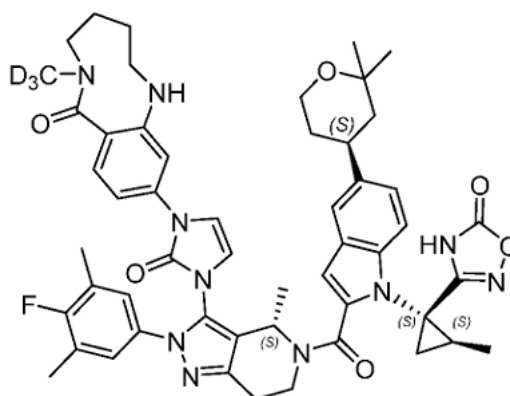


5'-bromo-3,3-difluorospiro [cyclobuta-1,3'-dihydroindol]-2'-one was used as a raw material, following Example 184, to obtain the target product.

MS m/z (ESI): 982.4 [M+1].

Example 212

3-((1S,2S-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(6-(methyl-d3)-7-carbonyl-2,3,4,5,6,7-hexahydro-1H-benzo[b][1,5]diazonin-10-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

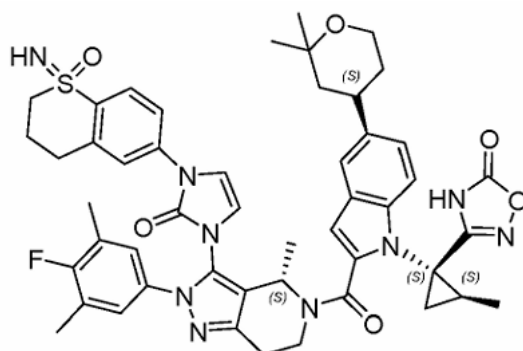


2-amino-4-bromobenzoic acid was used as a raw material, following Example 207, to obtain the target product.

MS m/z (ESI): 940.4[M+1].

Example 213

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(1-imino-1-hydroxyl-114-thiochroman-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



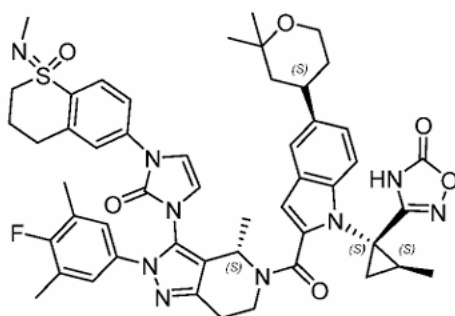
6-bromothiochromane was used as a raw material, following Example 3 Step 1, and Example 175 Step 2 to Step 4, to obtain the target product.

MS m/z (ESI): 914.3 [M+1].

5

Example 214

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(1-(methylimino)-1-hydroxyl-114-thiochroman-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



10

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(1-imino-1-hydroxyl-114-thiochroman-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one was used as a raw material, following Example 193 Step 3, to obtain the target product.

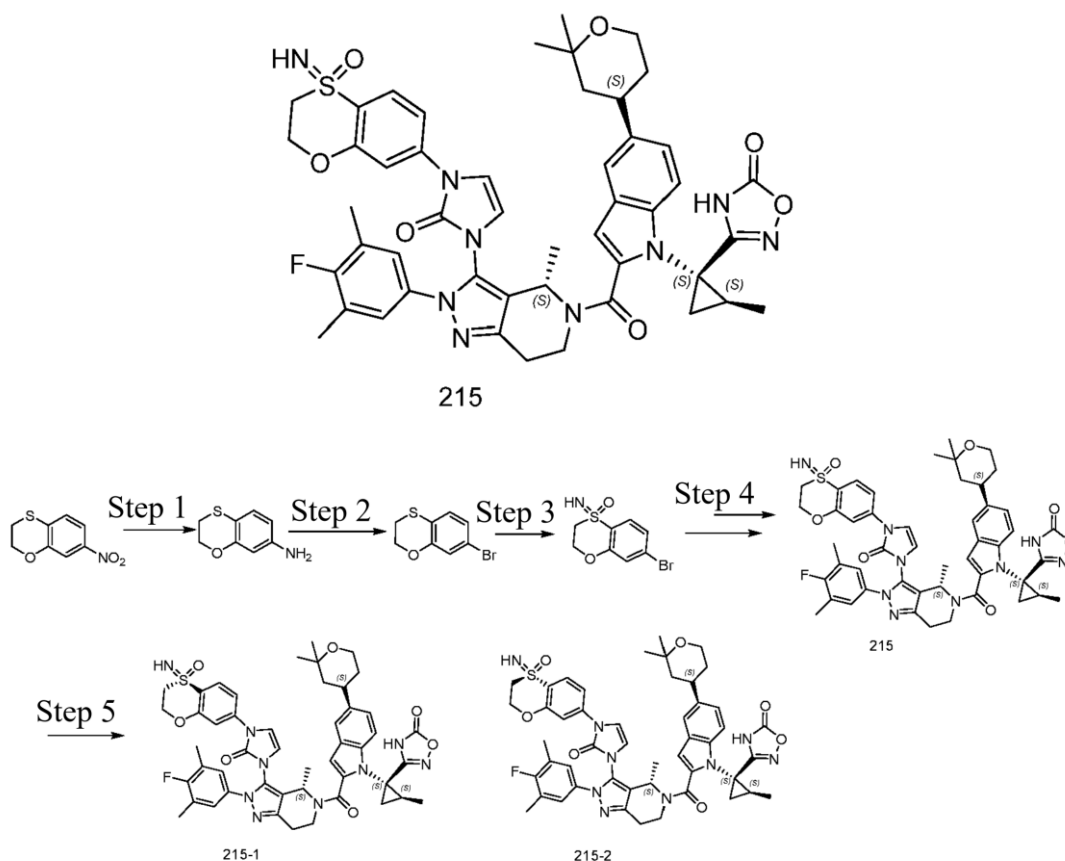
15

MS m/z (ESI): 928.3 [M+1].

Example 215

3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(4-imino-4-hydroxyl-3,4-dihydro-2H-414-benzo[b][1,4]oxathiin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

20



Step 1: 2,3-dihydrobenzo[b][1,4]oxathiin-7-amine

Following Example 206 Step 3, the target product was obtained.

MS m/z (ESI): 168.0 [M+1].

5 Step 2: 7-bromo-2,3-dihydrobenzo[b][1,4]oxathiin

Following intermediate C and intermediate D Step 1, the target product was obtained.

MS m/z (ESI): 231.0 233.0[M+1].

Step 3: 7-bromo-4-imino-3,4-dihydro-2H-4H-benzo[b][1,4]oxathiin-4-oxide

Following Example 182 Step 2, the target product was obtained

10 MS m/z (ESI):262.0 264.0 [M+1].

Step 4: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-(3-(4-imino-4-hydroxyl-3,4-dihydro-2H-4H-benzo[b][1,4]oxathiin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

15 Following Example 175, the target product was obtained.

MS m/z (ESI): 916.4[M+1].

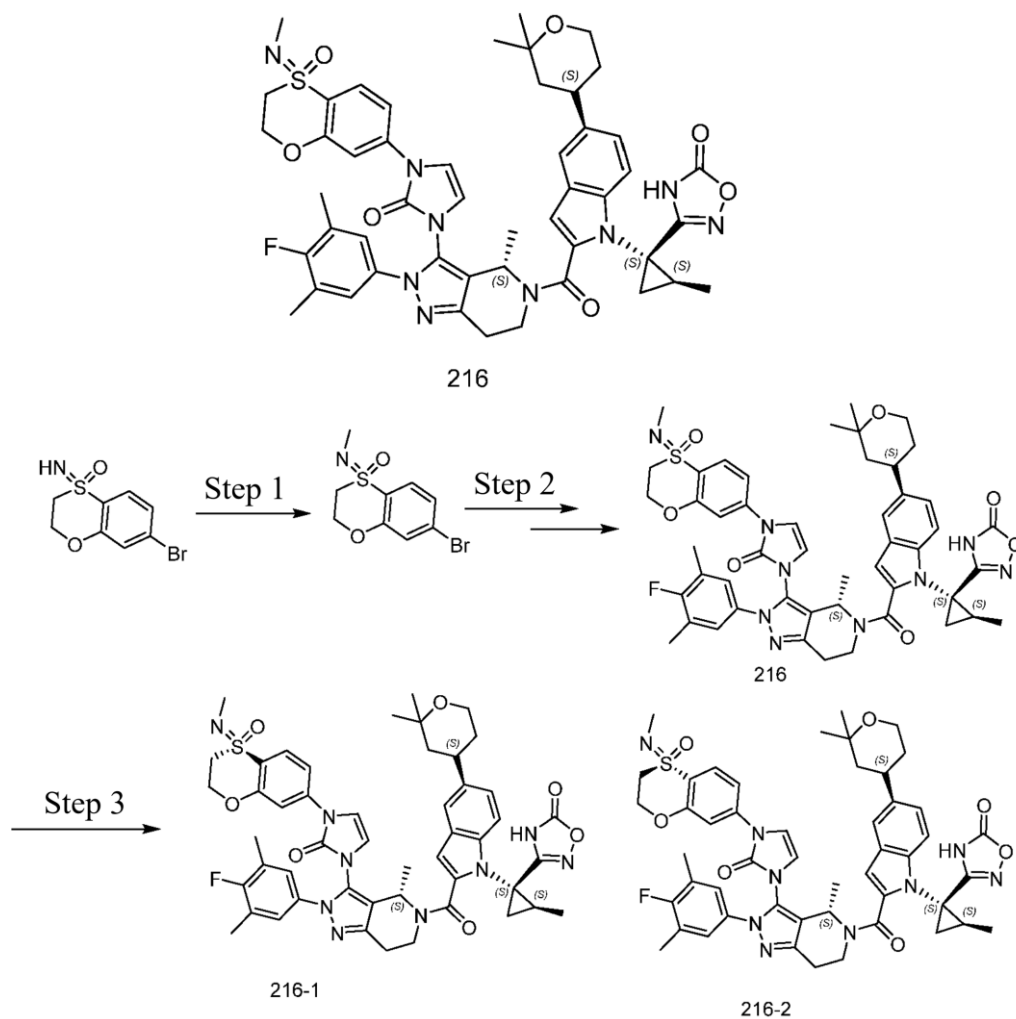
Step 5:

215 was chirally resolved, to obtain 215-1 and 215-2.

MS m/z(ESI):916.4 [M+1].

Example 216

- 5 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(4-(methylimino)-4-hydroxyl-3,4-dihydro-2H-4H-benzo[b][1,4]oxathiin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



- 10 Step 1: 7-bromo-4-(methylimino)-3,4-dihydro-2H-4H-benzo[b][1,4]oxathiin-4-oxide

Following Example 193 Step 3, the target product was obtained

MS m/z (ESI): 276.0 278.0 [M+1].

Step 2: 3-((1S,2S)-1-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2-((4S)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-3-(3-(4-(methylimino)-4-hydroxyl-3,4-dihydro-2H-4H-benzo[b][1,4]oxathiin-7-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4)-one

5 Following Example 175, the target product was obtained.

MS m/z (ESI): 930.4 [M+1].

Step 3:

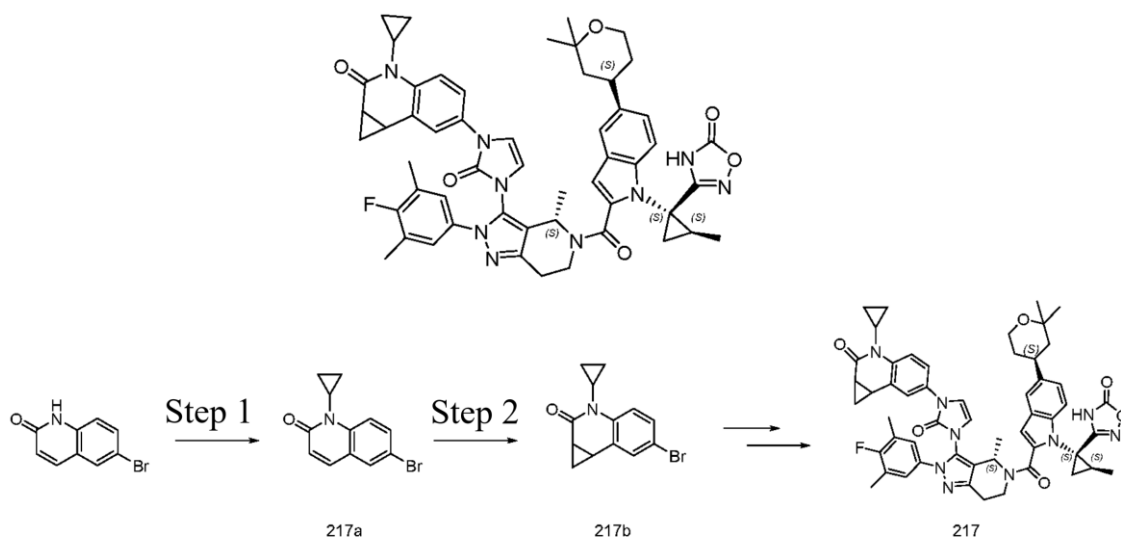
216 was chirally resolved, to obtain 216-1 and 216-2

MS m/z (ESI): 930.4 [M+1].

10

Example 217

3-((1S,2S)-1-(2-((4S)-3-(3-(3-cyclopropyl-2-carbonyl-1a,2,3,7b-tetrahydro-1H-cyclopropeno[c]quinolin-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one



15

Step 1: 6-bromo-1-cyclopropylquinoline-2(1H)-one

Following Example 184 Step 1, the target product was obtained

MS m/z (ESI): 264.0, 266.0[M+1].

Step 2: 6-bromo-3-cyclopropyl-1,1a,3,7b-tetrahydro-2H-cyclopropeno[c]quinoline-2-one

20

Trimethylsulfoxonium iodide (94 mg, 0.43 mmol), and NaH (20 mg, 0.84 mmol) were dispersed in DMSO (5 mL), and reacted under stirring at room temperature for 30 minutes. Subsequently, 6-bromo-1-cyclopropylquinoline-2(1H)-one (66 mg, 0.25 mmol) was added thereto, and the reaction solution was heated to a temperature of 80°C, and reacted under stirring for 18 hours.

The reaction solution, was quenched by adding a saturated ammonium chloride solution, and extracted with ethyl acetate (10 mL × 3); the organic phases were combined, washed with a saturated sodium chloride solution (30 mL), dried over anhydrous sodium sulfate, and filtered; the filtrate was concentrated under reduced pressure, and then the resulting residue was purified by silica gel column chromatography, to obtain the title product 6-bromo-3-cyclopropyl-1,1a,3,7b-tetrahydro-2H-cyclopropeno[c]quinoline-2-one (42 mg, yield: 60%).

MS m/z (ESI): 278.0, 280.0[M+1]

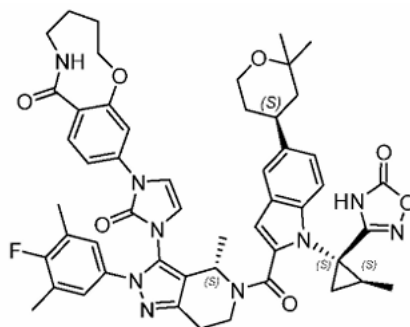
Step 3: 3-((1S,2S)-1-(2-((4S)-3-(3-(3-cyclopropyl-2-carbonyl-1a,2,3,7b-tetrahydro-1H-cyclopropeno[c]quinoline-6-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine-5-carbonyl)-5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1H-indol-1-yl)-2-methylcyclopropyl)-1,2,4-oxadiazol-5(4H)-one

6-bromo-3-cyclopropyl-1,1a,3,7b-tetrahydro-2H-cyclopropeno[c]quinoline-2-one was used as a raw material, following Example 175, to obtain the target product.

MS m/z (ESI): 932.4[M+1].

Example 218

10-(3-((S)-5-(5-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-1-((1S,2S)-2-methyl-1-(5-carbonyl-4,5-dihydro-1,2,4-oxadiazol-3-yl)cyclopropyl)-1H-indol-2-carbonyl)-2-(4-fluoro-3,5-dimethylphenyl)-4-methyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-yl)-2-carbonyl-2,3-dihydro-1H-imidazol-1-yl)-3,4,5,6-tetrahydrobenzo[b][1,5]oxazonin-7(2H)-one



2-hydroxyl-4-bromobenzoic acid was used as a raw material, following Example 207, to obtain the target product

MS m/z (ESI): 924.4[M+1].

Biological test and evaluation

The present disclosure will be further described and explained below in conjunction with test examples, but these examples are not meant to limit the scope of the present disclosure.

I. Determination of ability of compounds of the present disclosure to stimulate cAMP production in cell lines stably transfected with human GLP1 receptors

1. Experimental objective:

The objective of the test example is to test the ability of the compound to activate human GLP-1 receptors on the cell surface. The ability of the compound to activate human GLP-1 receptors is characterized by the EC₅₀ for the agonist-stimulated AMP production.

2. Experimental reagents and instruments:

2.1 Experimental instruments:

Microplate reader (BioTek Synergy H1);

Pipette (Eppendorf & Rainin).

2.2 Experimental reagents:

DMEM/F12 medium, purchased from Gibco with a catalog number of 11330032;

Casein, purchased from Sigma with a catalog number of C3400;

384-well plate, purchased from Sigma with a catalog number of CLS4514;

IBMX, purchased from Sigma with a catalog number of I7018;

Cisbio cAMP - Gs Dynamic kit, purchased from Cisbio with a catalog number of 62AM4PEC.

3. Experimental method:

The cryopreserved cell line CHO-K1/GLP-1R/CRE-luc stably transfected with human GLP1 receptors was taken from a liquid nitrogen tank, quickly thawed in a water bath kettle at 37°C and resuspended in a DMEM/F12 medium. After centrifugation, the cells were washed once and resuspended in a DMEM/F12 medium containing 0.1% casein as a test buffer. The cell density was adjusted using the test buffer, and the cells were plated in a 384-well plate at a density of 2500 cells/5 µL/well. Then 2.5 µL of an IBMX working solution formulated with the buffer (final concentration of IBMX: 0.5 mM) was added to each well, followed by the addition of 2.5 µL of the compound sample diluted in gradients (starting from 1000 nM, 3-fold dilution, 11 concentrations in total). The mixture was centrifuged at 1000 rpm for 1 min, shaken and mixed homogeneously for 30 seconds, and left to stand and incubated at room temperature for 30 minutes. The Cisbio cAMP-GS Dynamic kit was used for detection, and cAMP-d2 and Anti-cAMP-Eu³⁺-Cryptate were respectively diluted 20-fold with cAMP Lysis & Detection Buffer and then mixed homogeneously. To each well was added 5 µL of the diluted cAMP-d2 solution, followed by 5 µL of the diluted Anti-cAMP-Eu³⁺-Cryptate solution, and the mixture was shaken and mixed homogeneously for 30 seconds, and incubated at room temperature in the dark for 1 hour. The HTRF signal was read using a Biotek Synergy H1 microplate reader with an excitation wavelength of 320 nm and emission wavelengths of 620 nm and 665 nm.

4. Experimental data processing method:

The signal ratio (665 nm/620 nm*10,000) was calculated, and the nonlinear fitting of the signal ratio and sample concentration was performed using a four-parameter equation in GraphPad Prism 6 to obtain the EC₅₀ value.

In some embodiments, the example compounds of the present disclosure show good biological activity in the experiment of stimulating cAMP production in cell lines stably transfected with human GLP1 receptors. The EC₅₀ of the experiment of the compounds of the present disclosure for stimulating cAMP production in cell lines stably transfected with hGLP1R is less than about 100 nM, preferably less than about 50 nM, further preferably less than about 10 nM, more preferably less than about 5 nM, more preferably less than about 1 nM, and most preferably less than 0.1 nM among the compounds listed in the present disclosure.

II. Effect of single administration of compounds of the present disclosure on intraperitoneal glucose tolerance of GLP-1R humanized mice

1. Experimental objective:

The objective is to evaluate the effect of a single administration of the compounds of the present disclosure on blood glucose changes in an intraperitoneal glucose tolerance test (*ip*GTT) of GLP-1R humanized C57BL/6 mice.

2. Experiment materials:

C57BL/6 *hGLP-1R*, male, 5-8 weeks; Ultra-clean workbench; Electronic balance; Active blood glucose monitoring meter; Glucose.

3. Experimental operations and data processing:

3.1 One day before the experiment, the animals were randomly divided into groups according to their body weights, with 5 animals in each group. Before administration, all animals underwent overnight fasting with food withdrawn for at least 16 h.

3.2 A 0.2 g/mL glucose solution was formulated with pure water and filtered through a 0.22 μm membrane for later use.

3.3 On the day of the test, before drug administration, blood glucose levels were sequentially measured in each animal by the tail-clipping method and recorded as baseline values.

The method for testing blood glucose involves: placing the mice in a restrainer, disinfecting the tail tip with an alcohol swab, cutting a small portion from the tail tip with scissors, discarding the first drop of blood, and taking the second drop to a prepared glucose test strip for blood glucose measurement.

3.4 The animals were administered according to their body weights, and the administration time for each animal was recorded. Blood glucose levels were sequentially measured in each animal 1 h after the administration and recorded as 0 min blood glucose levels.

3.5 Subsequently, depending on the body weight on that day, either pure water or glucose solution (volume: 10 mL/kg; glucose dose: 2 g/kg) was immediately administered via intraperitoneal injection.

3.6 Blood glucose levels were measured in each mouse at 15, 30, 60, 90, and 120 minutes following the injection of pure water or glucose solution, and the time points and the corresponding data were recorded.

3.7 After the test was completed, all animals were allowed to resume feeding.

3.8 Data processing:

The blood glucose (BG)-time curve was plotted and the area under the blood glucose-time curve was calculated according to the formula:

$$\text{AUC (mmol/L.hr)} = (\text{BG0} + \text{BG15}) \times 0.25/2 + (\text{BG15} + \text{BG30}) \times 0.25/2 + (\text{BG30} + \text{BG60}) \times 0.5/2 + (\text{BG60} + \text{BG90}) \times 0.5/2 + (\text{BG90} + \text{BG120}) \times 0.5/2.$$

Note: BG0, BG15, BG30, BG60, BG90, and BG120 represent blood glucose levels before glucose administration (0 min), and 15, 30, 60, 90, and 120 min after glucose administration, respectively.

The blood glucose decline rate of each time point and the AUC was calculated based on the average blood glucose level and the blood glucose AUC at each time point according to the formula: blood glucose decline rate = (blood glucose of administration group/AUC — blood glucose of model control group/AUC)/blood glucose of model control group/AUC × 100%.

The example compounds of the present disclosure can effectively reduce blood glucose levels in mice with a blood glucose decline rate of greater than 20%; preferably, the compounds achieved a blood glucose decline rate of greater than 40%, and more preferably, the compounds achieved a blood lipid decline rate of greater than 60%.

III. Effect of long-term administration of compounds of the present disclosure on body weight and food intake of GLP-1R humanized mice fed with high-fat diet

1. Experimental objective:

The test objective is to evaluate the effect of the long-term administration of the compounds on the body weight and food intake of GLP-1R humanized C57BL/6 mice fed with a high-fat diet.

2. Experimental reagents and instruments

C57BL/6 *hGLP-1R*, male, 5-8 weeks, purchased from Biocytogen Pharmaceuticals (Beijing) Co., Ltd. 60% high-fat diet (HFD), purchased from Shanghai Bopai Biosciences Co., Ltd. (D12492, Research Diet)

Ultra-clean workbench (CJ-2F, Suzhou Fengshi Experimental Animal Equipment Co., Ltd.)

Electronic balance (BSA2202S-CW, Sartorius)

3. Experimental method

3.1 On the starting day of high-fat diet feeding, C57BL/6 mice were randomly divided into two groups according to their body weights, wherein the first group was used as a blank group (7 mice) and received normal control feed, and the remaining animals were fed with the high-fat diet until the end of the experiment to establish a modeling group.

3.2 On week 8 of HFD feeding, the animals in the modeling group were randomly divided into groups (7 mice per group) according to their body weights, wherein the first group was used as a vehicle group administered with the vehicle (0.5% CMC-Na- + 1% Tween 80), and the remaining groups were used as administration groups. The administration regimen involves: orally administering the corresponding compounds once daily for an administration period of 14 days (administration dose: 10 mg/kg; administration volume: 10 mL/kg). The blank group still received normal feed, and no drug administration procedures were carried out.

3.3 The day of the administration was defined as Day 0.

3.4 At each administration, the animals were first weighed and the data were recorded. The compounds were then orally administered at an administration volume of 10 mL/kg based on the body weight.

3.5 Commencing on day 0 of the experiment, food intake measurement was conducted every three days for the mice in all groups. Specifically, after each weighing and administration, the feed was changed, and the addition amount and the remaining amount were recorded.

3.6 On day 14 (the last day), all mice were euthanized sequentially according to the group assignment, followed by necropsy with liver excision and gravimetric analysis.

4. Experimental data processing and statistical analysis

Body weights and body weight change rates of mice after administration were collected and subjected to statistical analysis. The weight change rate was calculated according to the formula: $(BW_t - BW_0)/BW_0 \times 100\%$. BW_t denotes the body weight of the mouse on day t of the experiment, and BW_0 denotes the body weight of the mouse on day 0 of the experiment.

The food intake was calculated using the formula: $(\text{addition amount (g)} - \text{remaining amount (g)})/\text{animal number in each cage}$, and the cumulative food intake was the aggregated daily food intake per animal during the administration period.

Experimental data was analyzed and plotted with GraphPad Prism software. The intergroup comparison between two groups was performed using a t-test. The comparison among three or more groups was performed using one-way ANOVA. $p < 0.05$ was defined as a statistically significant difference.

The long-term administration of the example compounds of the present disclosure exhibited good effects on reducing body weight in GLP-1R humanized C57BL/6 mice fed with a high-fat diet, with a body weight reduction rate of greater than 5%, further preferably greater than 10%.

IV. Pharmacokinetic evaluation test in mice

1. Research objective:

Balb/c mice were used as test animals to study the pharmacokinetic behavior of the compounds of the present disclosure in mice (plasma) after oral administration at a dose of 5 mg/kg and intravenous administration at a dose of 1 mg/kg.

2. Experimental scheme:

2.1 Experimental drugs:

The example compounds of the present disclosure, made in house.

2.2 Experimental animals:

Balb/c mice (3 mice per group), male, from Shanghai Bk Lab Animal Co., Ltd., with animal production license number (SCXK (Shanghai) 2013-0006 N0.311620400001794).

2.3 Formulation prescription:

Formulation of a drug for oral administration: 10% PEG400/10% PG/80% glycine buffer (100 mM glycine, 64 Mm NaOH, pH 10) buffer.

10 ml of PEG400, 10 ml of PG, and 80 ml of (100 mM glycine, 64 Mm NaOH, pH 10) were weighed to a 100-ml volumetric flask, and the mixture was homogeneously mixed by vortex and subjected to ultrasound treatment to afford a clear solution.

The example compound was weighed and added to a 4-mL glass bottle, the solution was added and the mixture was subjected to ultrasound treatment for 10 minutes to afford a colorless clear solution with a concentration of 0.5 mg/mL.

Formulation of a drug for intravenous administration: 5% DMSO + 10% Solutol HS15 + 85% PBS

The compounds of Example 1 and Example 2 were weighed, and 5% DMSO was added on the basis of the proportion relative to the total administration volume. The mixture was vortexed and subjected to ultrasound treatment for 2 min

to achieve complete dissolution. Then, 10% Solutol HS15 was added, and the mixture was vortexed and subjected to ultrasound treatment for 2 min to achieve complete dissolution. Finally, 85% PBS was added, and the mixture was vortexed and subjected to ultrasound treatment for 5 min; the obtained mixture was filtered through a 0.22 μ m membrane to obtain a colorless, transparent and clear solution with a concentration of 0.2 mg/mL.

2.4 Administration:

After overnight fasting, 3 male Balb/c mice were respectively administered p.o. with the solution at a dose of 5 mg/kg and an administration volume of 10 mL/kg.

After overnight fasting, 3 male Balb/c mice were respectively administered IV with the solution at a dose of 1 mg/kg and an administration volume of 5 mL/kg.

2.5 Sample collection:

Blood collection: 0.04 mL of blood was collected from the orbit of mice before administration and at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after administration, placed in EDTA-K₂ anticoagulation tubes, and centrifuged at 6000 rpm at 4°C for 6 min to separate plasma, which was stored at -80°C; and the animals were fed 4 h after administration.

2.6 Sample treatment:

1) 160 μ L of acetonitrile was added to 40 μ L of plasma sample for precipitation, and same was mixed and centrifuged at $3500 \times g$ for 5 to 20 min.

2) The treated supernatant solution was taken and subjected to LC/MS/MS to analyze the concentrations of the compounds to be tested. LC/MS/MS analysis instrument: AB Sciex API 4000 Qtrap.

2.7 Liquid phase analysis:

- Liquid phase conditions: Shimadzu LC-20AD pump
- Chromatographic column: Agilent ZORBAX XDB-C18 (50 $\times$ 2.1 mm, 3.5 μ m), mobile phase:

liquid A: 0.1% aqueous formic acid solution, and liquid B: acetonitrile

- Flow rate: 0.4 mL/min
- Elution time: 0-4.0 min, the eluent was as follows:

Time/min	Liquid A	Liquid B
0.01	90%	10%
0.5	90%	10%
0.8	5%	95%
2.4	5%	95%
2.5	90%	10%
4.0	Stop	

3. Experimental results and analysis

The main pharmacokinetic parameters were calculated using WinNonlin 6.1. The results of pharmacokinetic experiments in mice are as shown in Table 3 below:

Table 3: Pharmacokinetic parameters of oral administration of compounds of the present disclosure in rats

Parameters	Example 1	Example 3	Example 64	Example 173	Example 174
t _{max} (h)	0.5	0.5	0.5	0.5	1.0
C _{max} (ng/mL)	1377	1897	2970	2610	1135

AUC 0-t (ng/mL*h)	5360	4416	10324	8179	5793
AUC 0-∞ (ng/mL*h)	5425	4429	10768	8448	5837
t _{1/2} (h)	1.0	0.8	1.6	1.4	3.8
MRT 0-∞ (h)	2.5	1.9	2.8	2.7	4.3

3.4 Experimental conclusion:

The experimental results show that the example compounds of the present disclosure exhibit good metabolic properties, and perform well in both exposure (AUC) and maximum blood drug concentration C_{max} .

5 V. Pharmacokinetic determination in SD rats

1. Research objective

SD rats were used as test animals to study the pharmacokinetic behavior of the following example compounds in the plasma of rats after administration at a dose of 50 mg/kg.

2. Test scheme

10 2.1 Test drugs

Vehicle formula: 0.5% CMC-Na (1% Tween 80);

the examples of the present disclosure, made in house.

2.2 Test animals

3 SD rats per group, male.

15 2.3 Administration:

After overnight fasting, 3 male SD rats per group were respectively administered PO with the solution at a dose of 50 mg/kg and an administration volume of 10 mL/kg.

2.4 Sample collection:

20 0.2 mL of blood was collected from the jugular vein of rats before administration and at 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after administration, and placed in EDTA- K_2 test tubes, and centrifuged at 6000 rpm at 4°C for 6 min to separate plasma, which was stored at -80°C. The rats were fed 4 h after administration.

2.5 Sample treatment:

1) 160 uL of acetonitrile was added to 40 uL of plasma sample for precipitation, and same was mixed and centrifuged at 3500 x g for 5 to 20 min.

25 2) 100 uL of the treated supernatant solution was taken and subjected to LC/MS/MS to analyze the concentrations of the compounds to be tested.

2.6 Liquid phase analysis

- Liquid phase conditions: Shimadzu LC-20AD pump
- Mass spectrometry conditions: AB Sciex API 4000 mass spectrometer
- 30 • Chromatographic column: Phenomenex Gemu 5 um C18 50 × 4.6 mm

- Mobile phase: liquid A: 0.1% aqueous formic acid solution, and liquid B: methanol
- Flow rate: 1.0 mL/min
- Elution time: 0-4.0 min, the eluent was as follows:

Time/min	Liquid A	Liquid B
0.01	90%	10%
0.5	90%	10%
0.8	5%	95%
2.4	5%	95%
2.5	90%	10%
4.0	Stop	

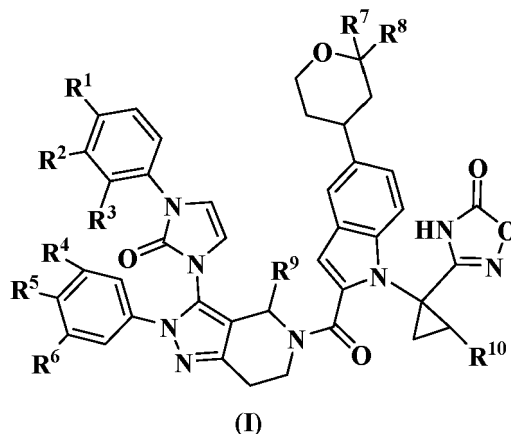
5 3. Experimental results and analysis

The main pharmacokinetic parameters were calculated using WinNonlin 8.2.

The example compounds of the present disclosure exhibit good metabolic properties, and perform well in both exposure (AUC) and maximum blood drug concentration $C_{\max}$.

Claims

1. A compound represented by general formula (I), or a stereoisomer or a pharmaceutically acceptable salt thereof:



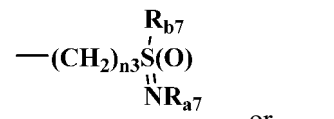
wherein

each R^1 , R^2 or R^3 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, $-(CH_2)_{n1}C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$, $-(CH_2)_{n1}C(O)NR_{a9}R_{b9}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

alternatively,

R^1 and R^2 together with adjacent atom(s) to which they are attached form C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-12} aryl or 5- to 12-membered heteroaryl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy,



C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a6} and R_{b6} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

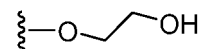
each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 to n4 are integers from 0 to 5;

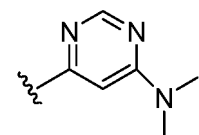
when R⁴, R⁶, R⁹ and R¹⁰ are methyl, R⁷ and R⁸ are hydrogen, R⁵ is fluorine, R¹ is methoxy, and R² is fluorine, R³ cannot be hydrogen;

when R⁴, R⁶, R⁹ and R¹⁰ are methyl, R⁷ and R⁸ are hydrogen, R⁵ is fluorine, R¹ is



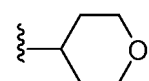
and R² is methyl, R³ cannot be hydrogen;

when R⁴, R⁶, R⁹ and R¹⁰ are methyl, R⁷ and R⁸ are hydrogen, R⁵ is fluorine, R¹ is



and R² is methyl, R³ cannot be hydrogen;

when R⁴, R⁶, R⁹ and R¹⁰ are methyl, R⁷ and R⁸ are hydrogen, R⁵ is fluorine, and R¹ is

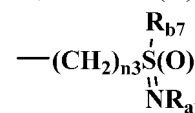


R² and R³ cannot both be hydrogen.

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

each R¹, R² or R³ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -

(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -(CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3}, or -



(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, each R¹, R² or R³ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, 5- to 8-membered heteroaryl,

-NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

(CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3}, $\begin{array}{c} \text{R}_{b7} \\ | \\ \text{---}(\text{CH}_2)_{n3}\text{S}(\text{O}) \\ || \\ \text{NR}_{a7} \end{array}$ or -(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl or C₂₋₄ alkynyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl or C₃₋₆ cycloalkyl;

5 further preferably, each R¹, R² or R³ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₂₋₄ alkynyl, C₃₋₈ bridged cycloalkyl, C₃₋₈ spirocycloalkyl, 3- to 8-membered spiroheterocyclyl containing 1 to 3 heteroatoms, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}O(CH₂)_{n2}R_{a5}, -

(CH₂)_{n1}C(O)NR_{a6}R_{b6}, -(CH₂)_{n1}P(O)R_{a3}R_{b3}, $\begin{array}{c} \text{R}_{b7} \\ | \\ \text{---}(\text{CH}_2)_{n3}\text{S}(\text{O}) \\ || \\ \text{NR}_{a7} \end{array}$ or -(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl or C₂₋₄ alkynyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl or C₃₋₆ cycloalkyl;

alternatively,

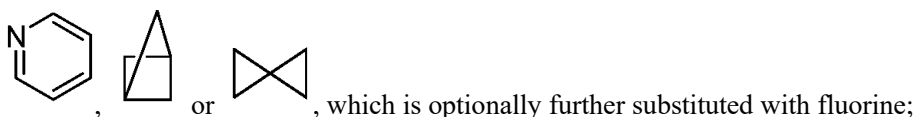
R¹ and R² together with adjacent atom(s) to which they are attached form 3- to 10-membered fused heterocyclyl containing 1 to 4 heteroatoms;

15 preferably, R¹ and R² together with adjacent atom(s) to which they are attached form 9-membered fused heterocyclyl containing 1 to 4 N atoms;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8}, R_{b8}, R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₃₋₆ bridged cycloalkyl, C₃₋₆ spirocycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₃₋₆ bridged cycloalkyl, C₃₋₆ spirocycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S is optionally further substituted with one or more substituents selected from halogen or C₁₋₃ alkyl;

25 preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8}, R_{b8}, R_{a9} or R_{b9} is

independently selected from hydrogen, deuterium, halogen, methyl, cyclopropyl, ,



alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a6} and R_{b6} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

5 preferably, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a6} and R_{b6} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C₃₋₆ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

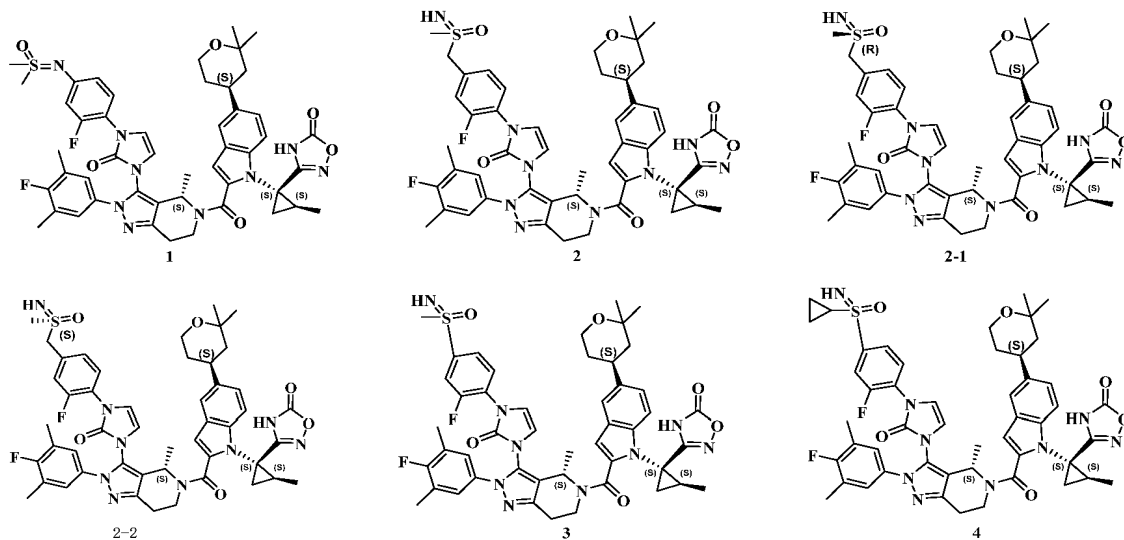
each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

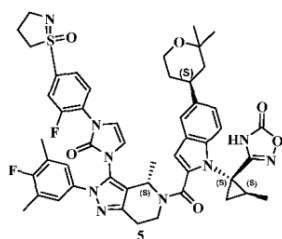
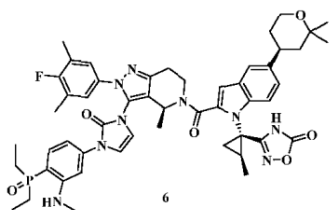
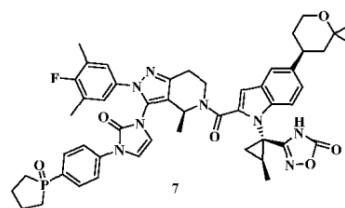
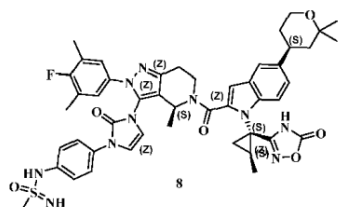
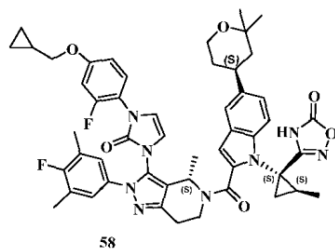
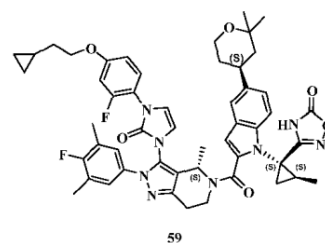
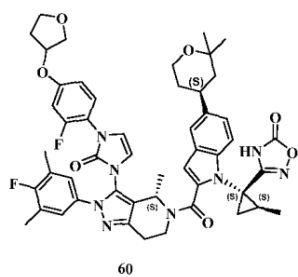
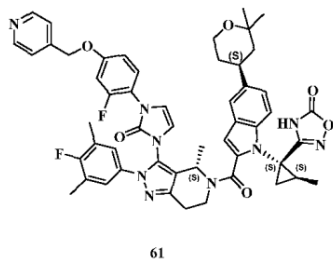
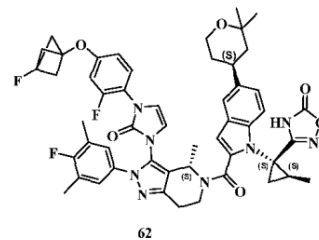
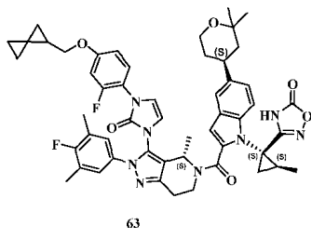
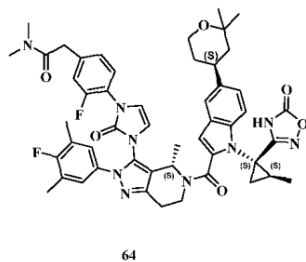
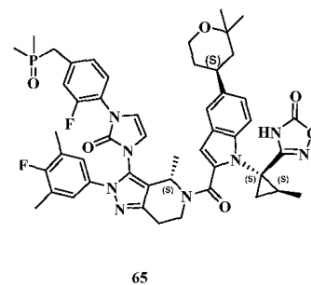
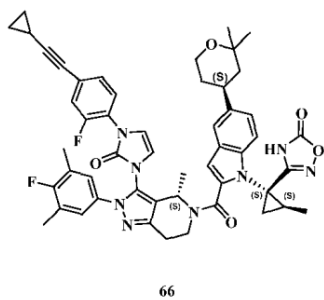
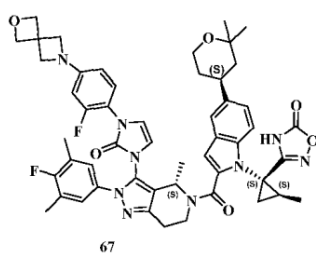
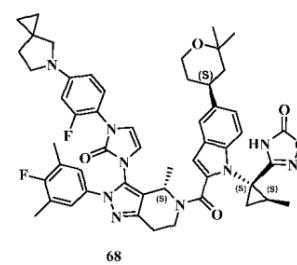
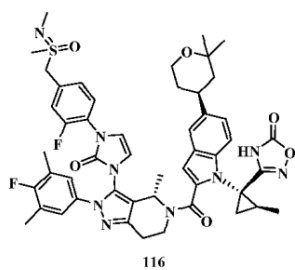
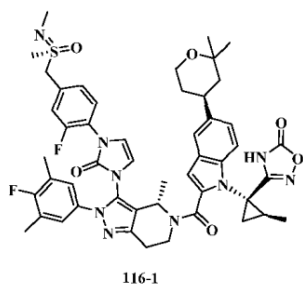
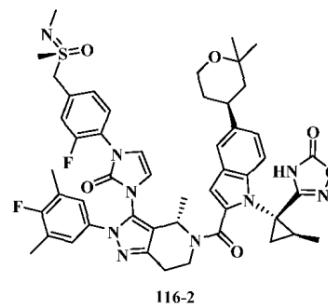
10 preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

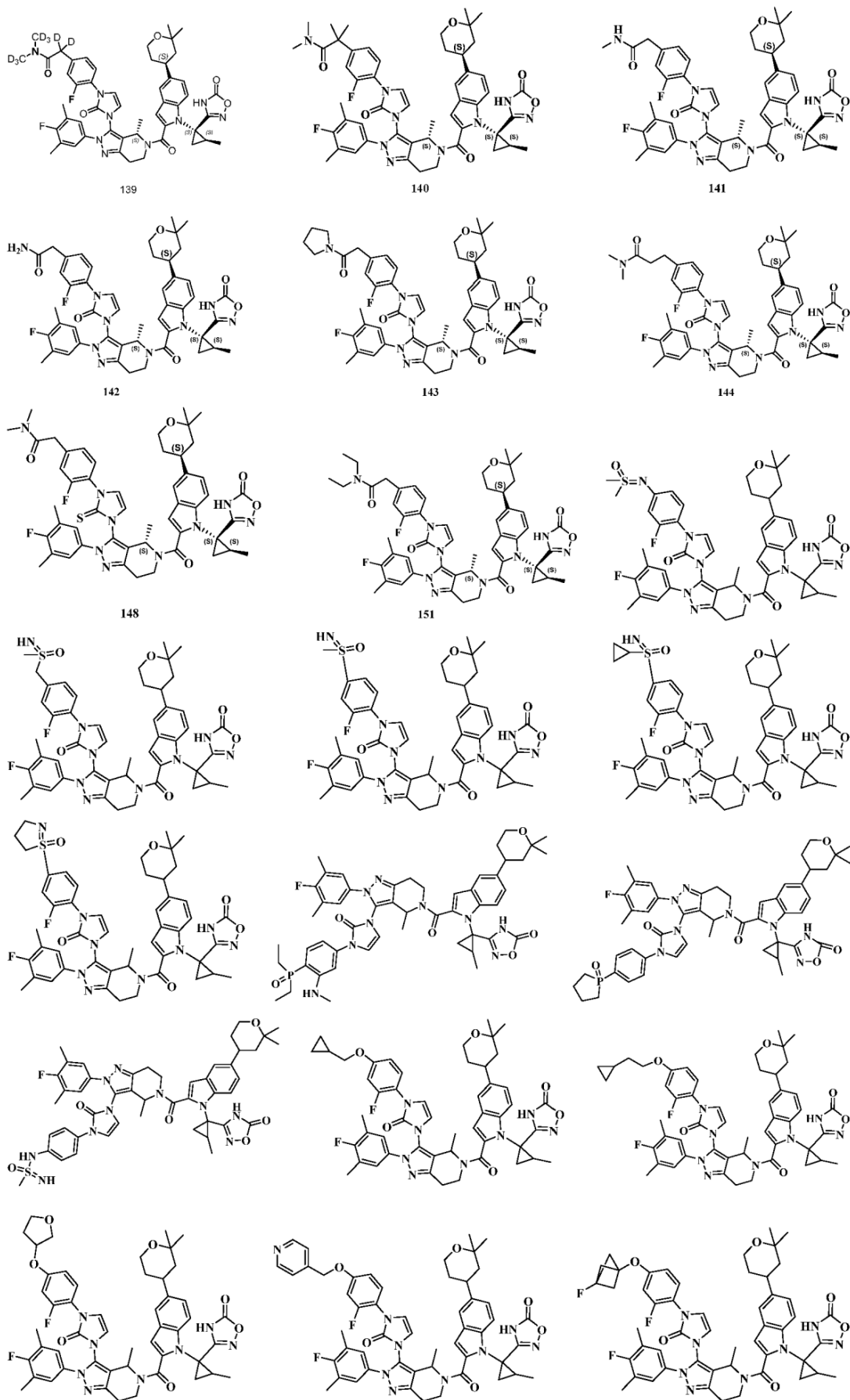
each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

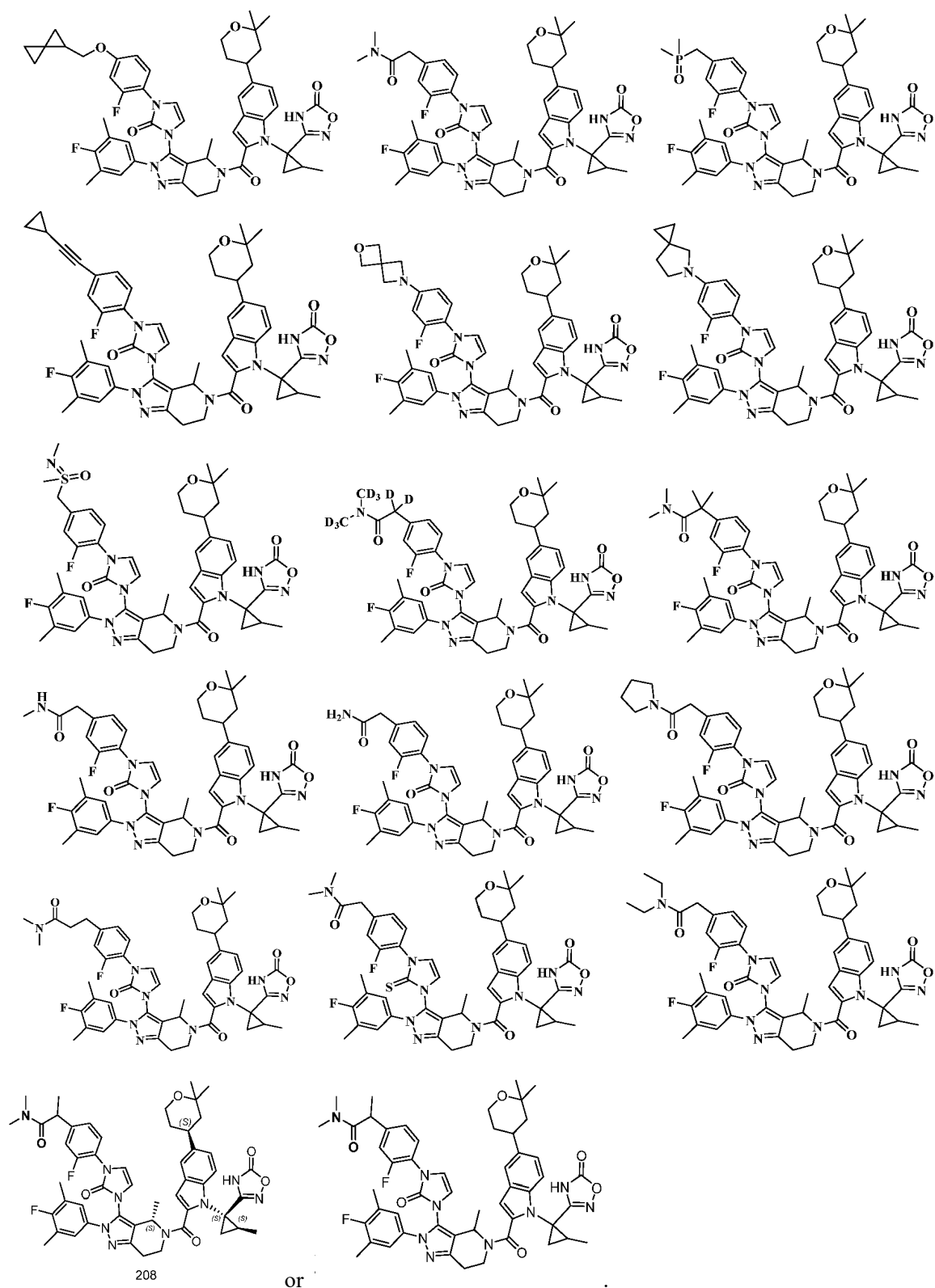
preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl.

15 3. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 1, wherein the compound has the following structure:

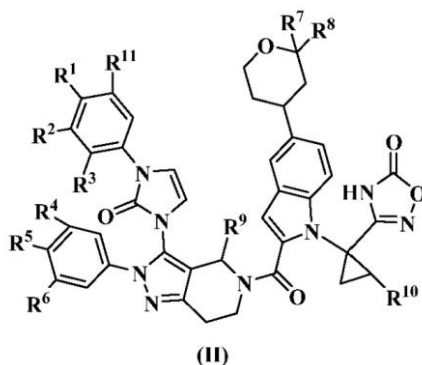








4. A compound represented by general formula (II), or a stereoisomer or a pharmaceutically
5 acceptable salt thereof:



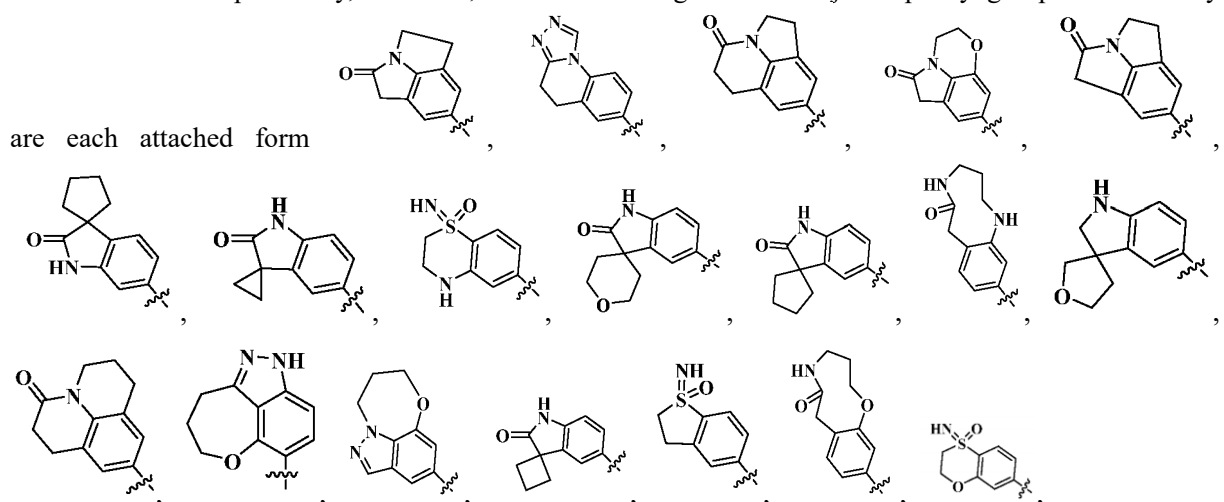
wherein

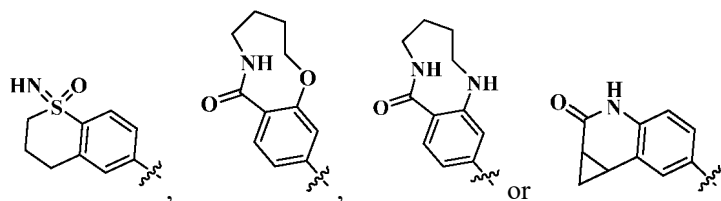
R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl, wherein the C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form C_{3-6} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, C_{1-3} alkyl, amino or oxo;

further preferably, R^1 and R^2 , and R^1 and R^{11} together with adjacent atom(s) to which they are each attached form 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with oxo;

even further preferably, R^1 and R^2 , and R^1 and R^{11} together with adjacent phenyl groups to which they





, which is optionally further substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₃₋₆ cycloalkyl, amino or oxo;

R¹, R², R³ or R¹¹ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹, R², R³ or R¹¹ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R¹, R², R³ or R¹¹ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen,

amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano,

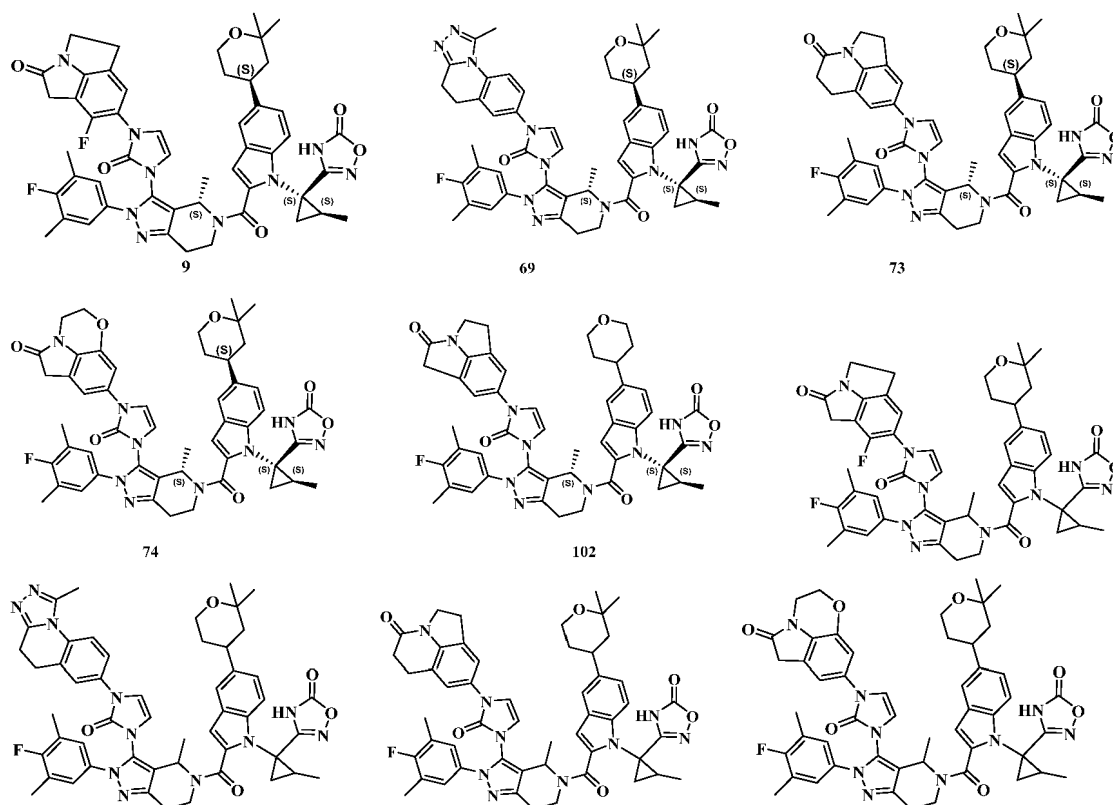
oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

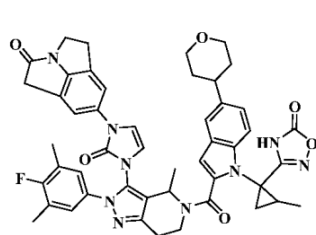
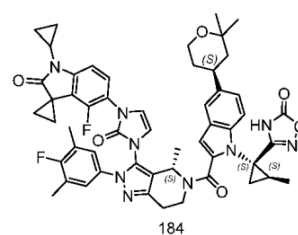
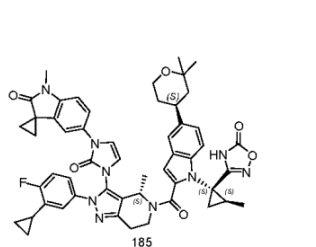
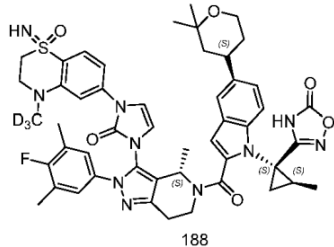
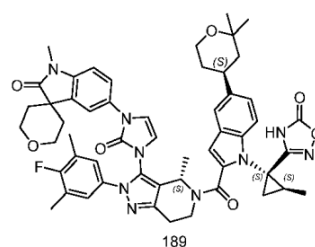
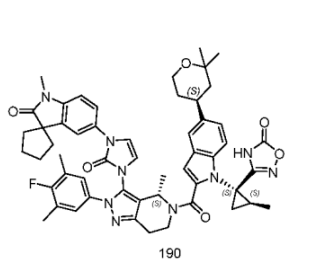
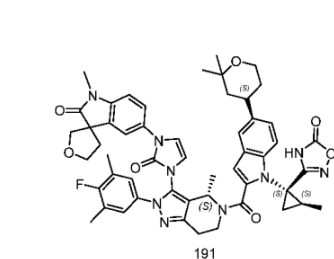
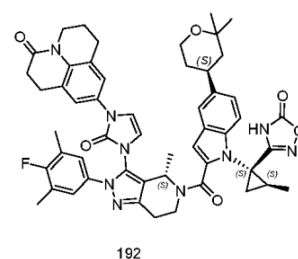
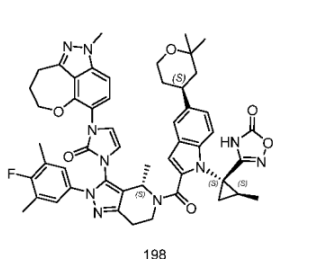
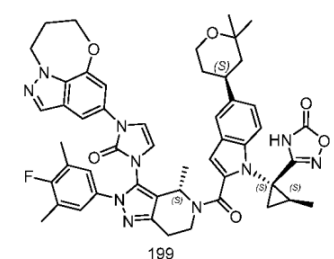
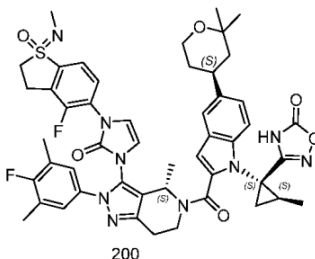
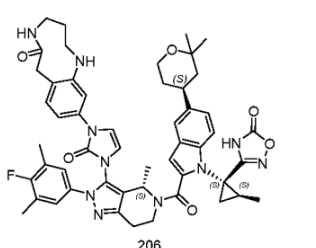
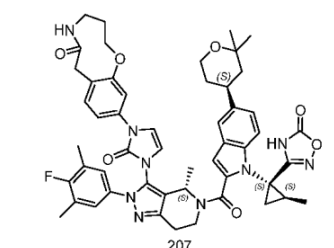
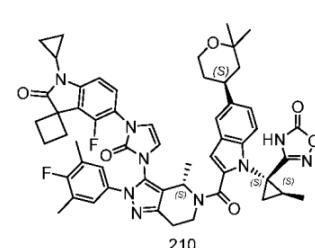
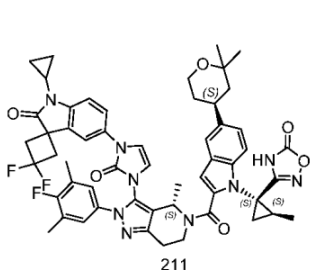
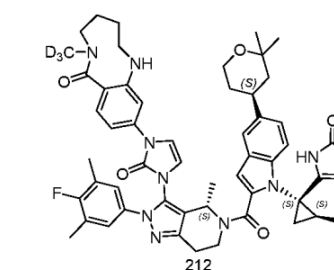
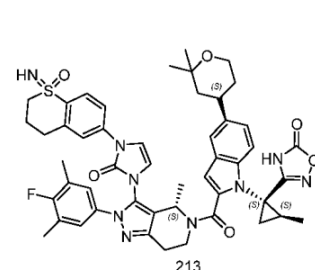
preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

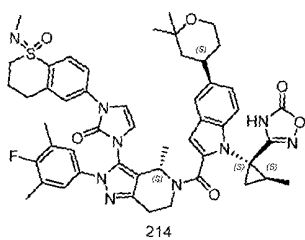
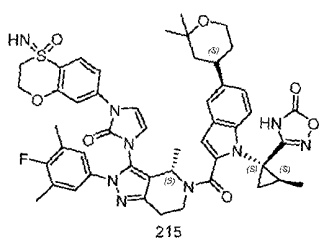
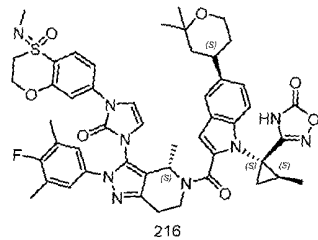
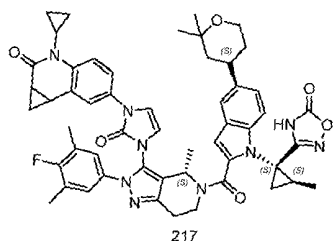
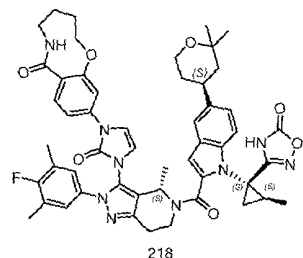
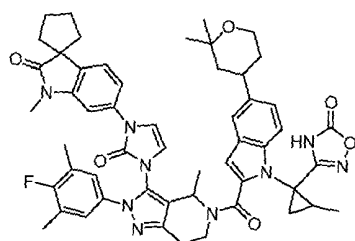
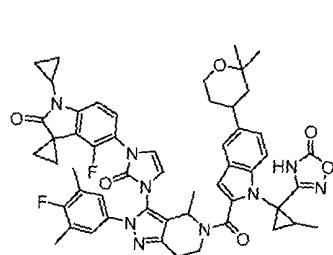
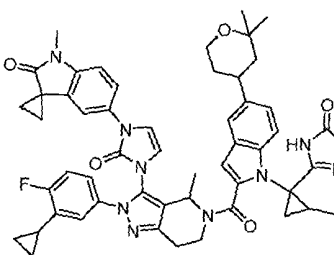
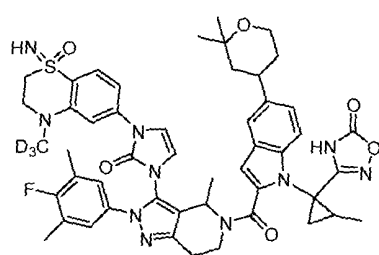
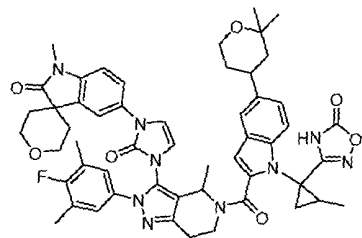
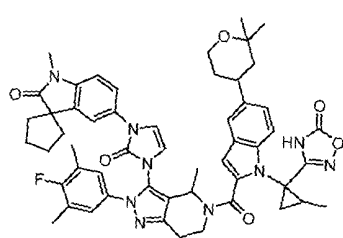
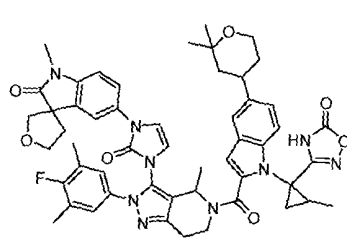
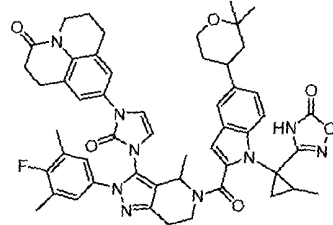
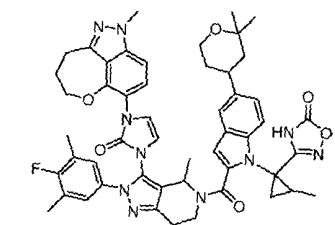
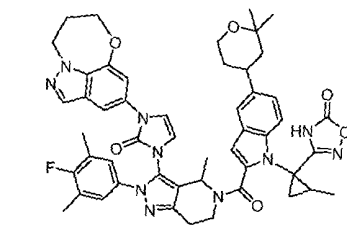
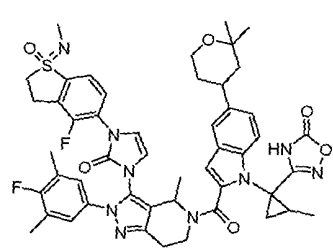
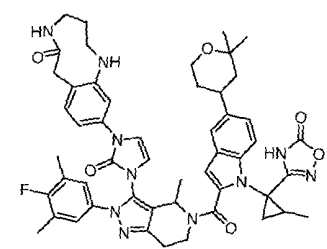
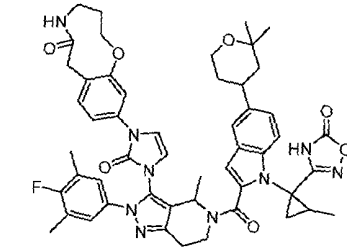
further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

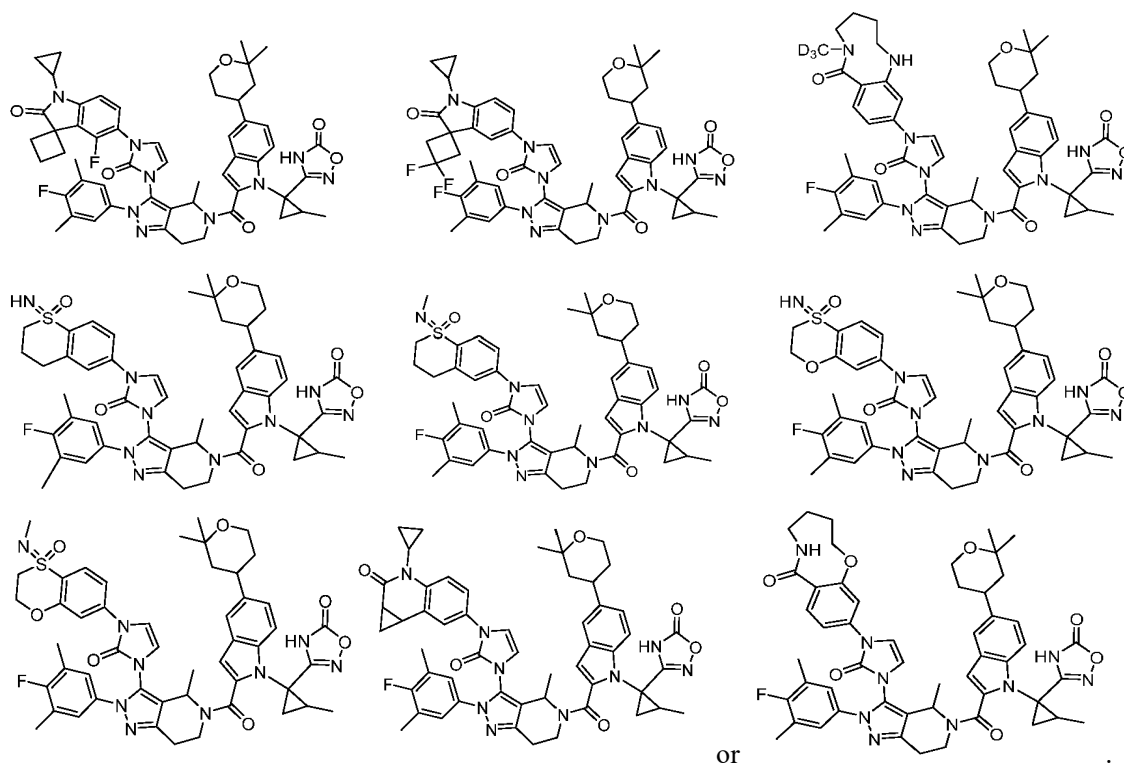
n1 is an integer from 0 to 5.

5. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 4, wherein the compound has the following structure:

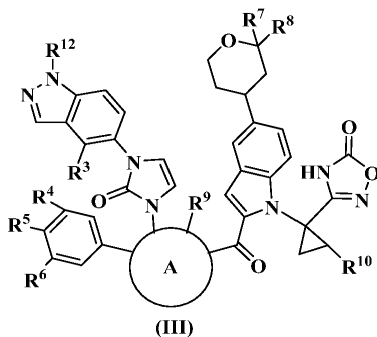








6. A compound represented by general formula (III), or a stereoisomer or a pharmaceutically acceptable salt thereof:

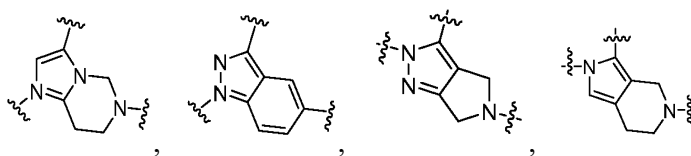


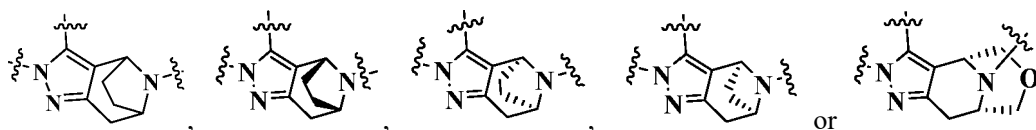
wherein

ring A is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

10 preferably, ring A is C₃₋₈ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;

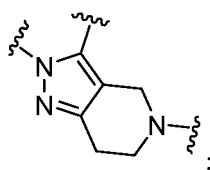
more preferably, ring A is





R^{12} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, R^{12} is C_{1-3} alkyl; more preferably, R^{12} is methyl;



wherein ring A cannot be

R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_nS(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, R^3 is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_nS(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl,

C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl,

C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

5 preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

15 preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

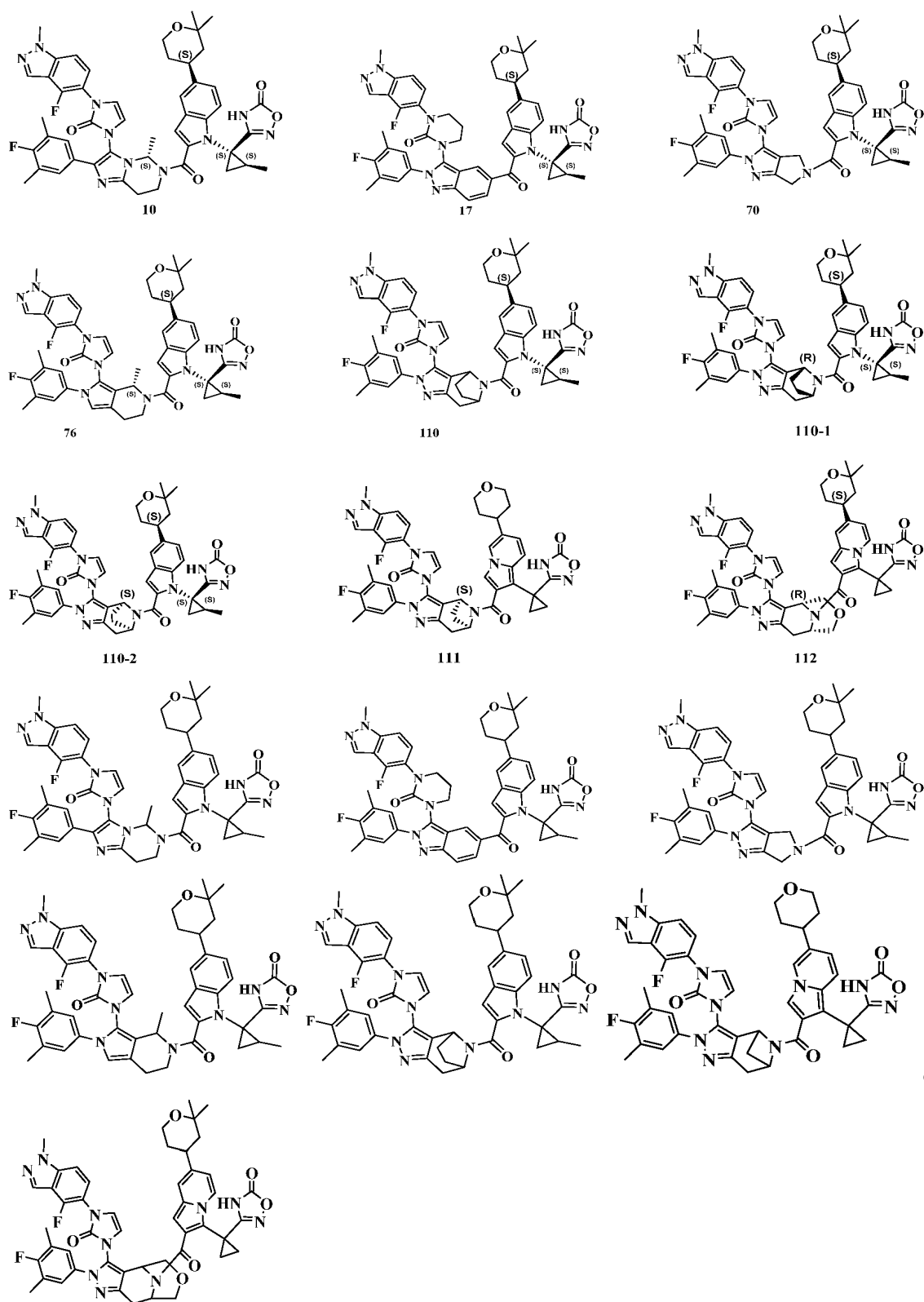
further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

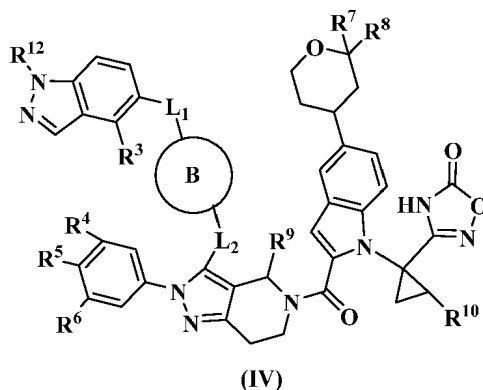
preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl;

25 n1 is an integer from 0 to 5.

7. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 6, wherein the compound has the following structure:



5 8. A compound represented by general formula (IV), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

L₁ and L₂ are each independently selected from a bond, C₂₋₄ alkenylene, C₂₋₄ alkynylene, -(CH₂)_{n2} or -(CH₂)_{n3}NR_{b5};

ring B is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, mercapto, thio, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy or C₁₋₆ haloalkoxy;

R_{b5} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclcyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

n1 is an integer from 0 to 5;

n2 is an integer from 0 to 5;

n3 is an integer from 0 to 5.

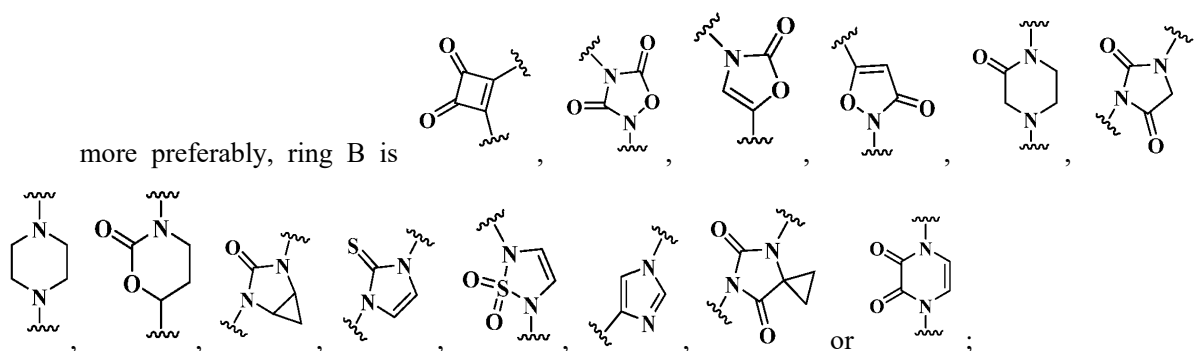
9. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 8, wherein

L₁ and L₂ are each independently selected from a bond or $-(CH_2)_{n3}NR_{b5}$;

ring B is selected from C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, oxo, mercapto, thio or C₁₋₆ alkyl;

preferably, ring B is C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S or 5- to 8-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, amino, oxo, thio or C₁₋₃ alkyl;

more preferably, ring B is



R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino,

C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

5 preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

10 preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

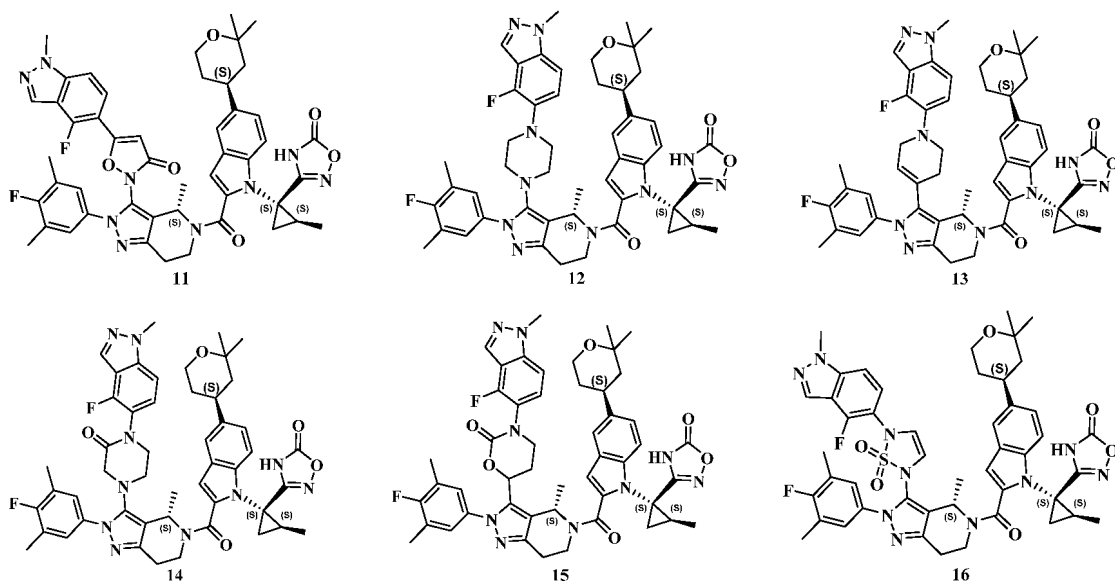
preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

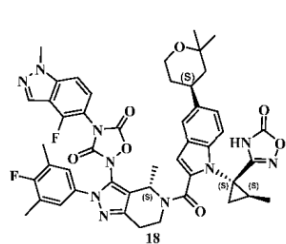
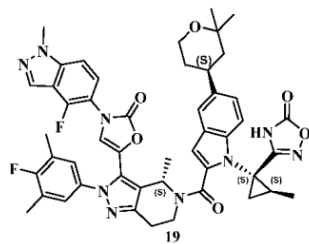
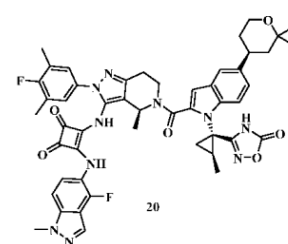
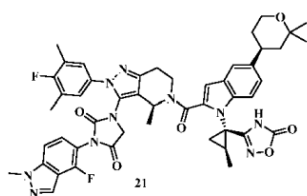
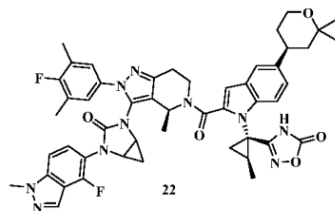
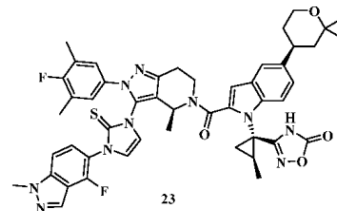
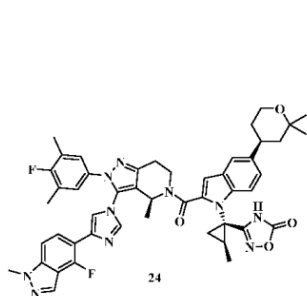
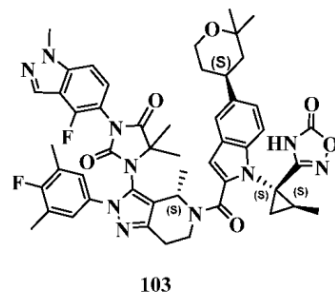
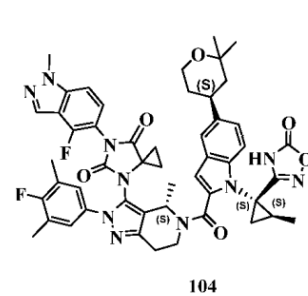
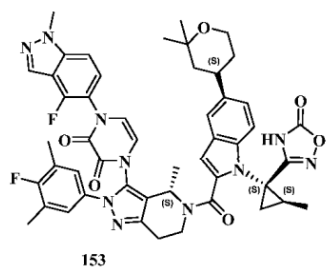
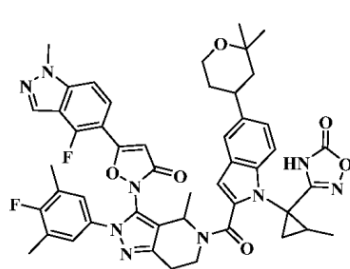
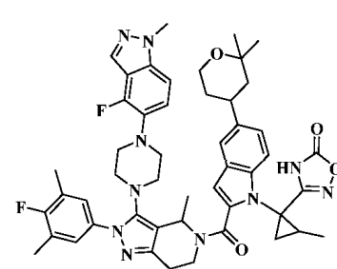
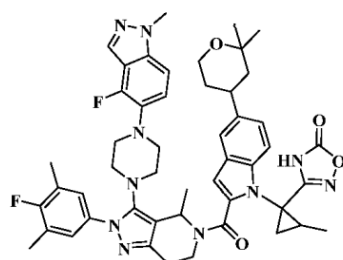
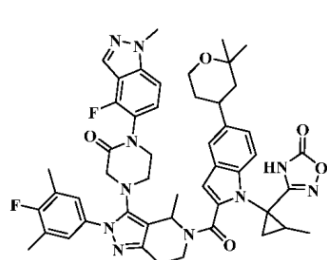
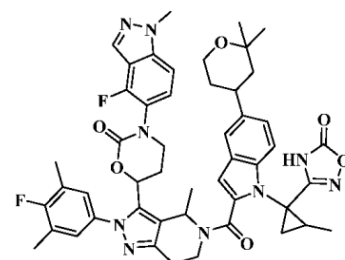
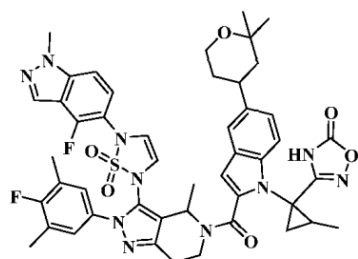
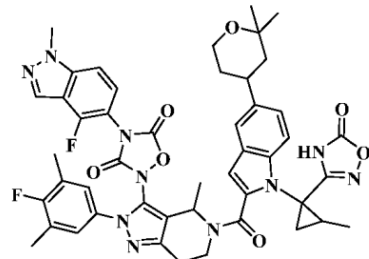
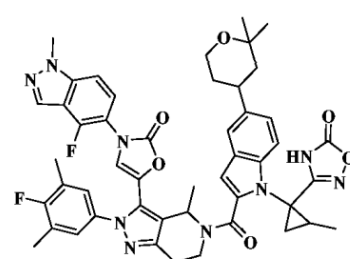
15 each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

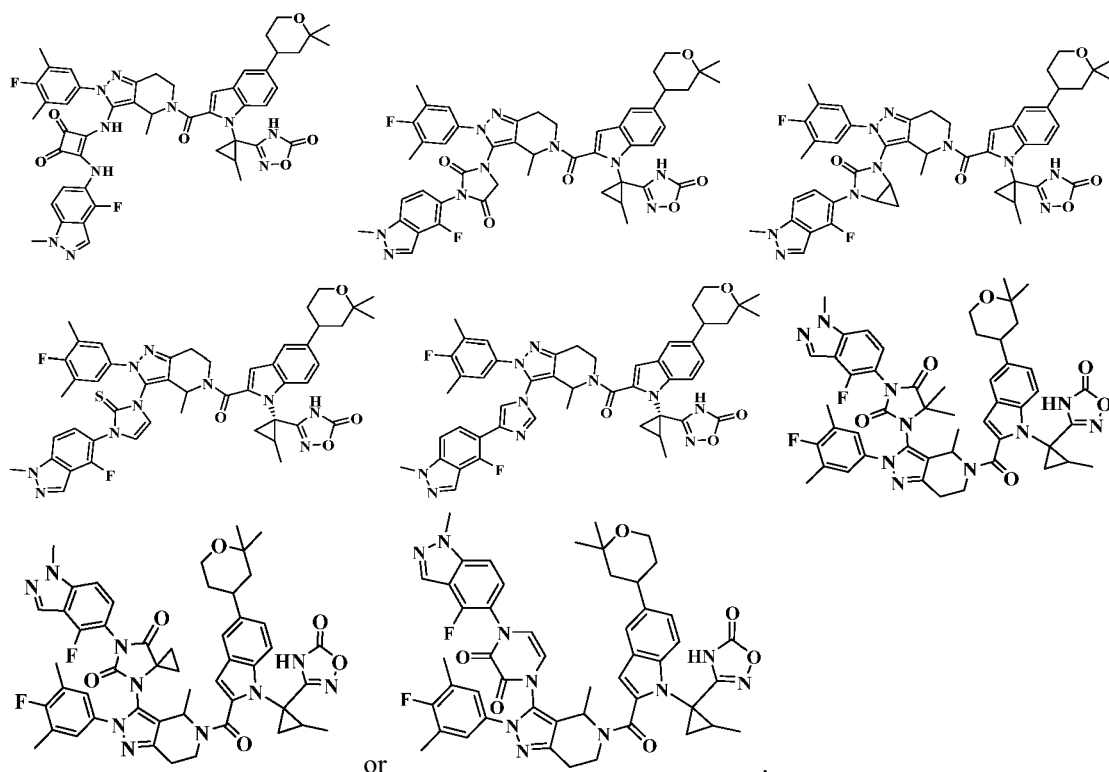
preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl.

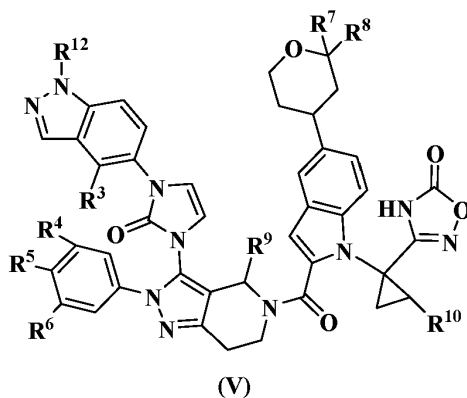
20 10. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 8, wherein the compound has the following structure:







11. A compound represented by general formula (V), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} thioalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino,

nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R⁴, R⁵ or R⁶ is hydrogen, deuterium, halogen, amino, cyano, C₁₋₃ alkyl, C₁₋₃ thioalkyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ alkoxy;

more preferably, R⁴, R⁵ or R⁶ is fluorine, methyl, cyano, ethynyl, methylthio, amino, cyclopropyl or oxetane, which is optionally further substituted with halogen, methoxy or deuterated methyl;

alternatively, R⁵ and R⁶ together with adjacent atom(s) to which they are attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ thioalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R⁵ and R⁶ together with adjacent atom(s) to which they are attached form C₃₋₆ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, C₁₋₃ alkyl or oxo;

further preferably, R⁵ and R⁶ together with adjacent atom(s) to which they are attached form 5- to 7-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from halogen, amino, C₁₋₃ alkyl or oxo;

more preferably, R⁵ and R⁶ together with adjacent atom(s) to which they are attached form ,  or , which is optionally further substituted with one or more substituents selected from halogen, amino, C₁₋₃ alkyl or oxo;

wherein when R⁷ and R⁸ are hydrogen, R⁹, R¹⁰ and R¹² are methyl, and R³ and R⁵ are fluorine, R⁴ and R⁶ are not both methyl;

when R⁷ and R⁸ are hydrogen, R⁹, R¹⁰ and R¹² are methyl, R³ is hydrogen, and R⁵ is halogen, R⁴ and R⁶ are not both methyl;

when R⁷, R⁸, R⁹, R¹⁰ and R¹² are methyl, R⁵ is fluorine, and R⁴ is halogen, trifluoromethyl or cyclopropyl, R⁶ is not hydrogen;

when R⁷, R⁸, R⁹ and R¹⁰ are methyl, R¹² is deuterated methyl, R³ is fluorine, R⁵ is halogen, and R⁴ is deuterated methyl, R⁶ is not deuterated methyl;

when R⁴, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are methyl, and R³ and R⁵ are fluorine, R¹² is not deuterated methyl;

when R⁷, R⁸, R⁹, R¹⁰ and R¹² are methyl, R³ is fluorine, R⁵ is halogen, and R⁴ is methyl, R⁶ is not methyl;

when R⁷, R⁸, R⁹ and R¹⁰ are methyl, R¹² is deuterated methyl, R³ is fluorine, R⁵ is halogen, and R⁴ is deuterated methyl, R⁶ is not deuterated methyl;

when R⁴, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are methyl, and R³ and R⁵ are fluorine, R¹² is not deuterated methyl;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -

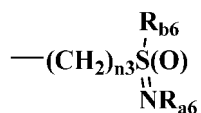
(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n2}R_{a5}R_{b5} or $\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}$, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -

(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n2}R_{a5}R_{b5} or $\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}$, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl,

cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n2}R_{a5}R_{b5} or



, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, R_{a4} and R_{b4}, R_{a5} and R_{b5}, and R_{a6} and R_{b6} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6} or R_{b6} is independently selected from hydrogen, deuterium, halogen or methyl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, R_{a4} and R_{b4}, R_{a5} and R_{b5}, and R_{a6} and R_{b6} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R_{a2} and R_{b2}, R_{a3} and R_{b3}, R_{a4} and R_{b4}, R_{a5} and R_{b5}, and R_{a6} and R_{b6} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy,

C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R⁷, R⁸, R⁹ and R¹⁰ are each independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, $-(CH_2)_{n_2}R_{a5}R_{b5}$ or $-(CH_2)_{n_3}\overset{\overset{R_{b6}}{|}}{\underset{\underset{NR_{a6}}{||}}{S}}(O)$, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹² is C₁₋₃ alkyl, C₃₋₆ cycloalkyl, $-(CH_2)_{n_2}R_{a5}R_{b5}$ or $-(CH_2)_{n_3}\overset{\overset{R_{b6}}{|}}{\underset{\underset{NR_{a6}}{||}}{S}}(O)$, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R¹² is methyl, cyclopropyl, $-(CH_2)_{n_2}R_{a5}R_{b5}$ or $-(CH_2)_{n_3}\overset{\overset{R_{b6}}{|}}{\underset{\underset{NR_{a6}}{||}}{S}}(O)$, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

alternatively,

R⁷ and R⁸ are each independently selected from deuterium or C₁₋₆ deuterioalkyl;

preferably, R⁷ and R⁸ are deuterium or C₁₋₃ deuterioalkyl;

alternatively,

preferably, R⁹ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₈ aryl or 5- to 8-membered heteroaryl, which is optionally
 5 further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R⁹ is cyano or cyclopropyl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃
 10 haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

alternatively,

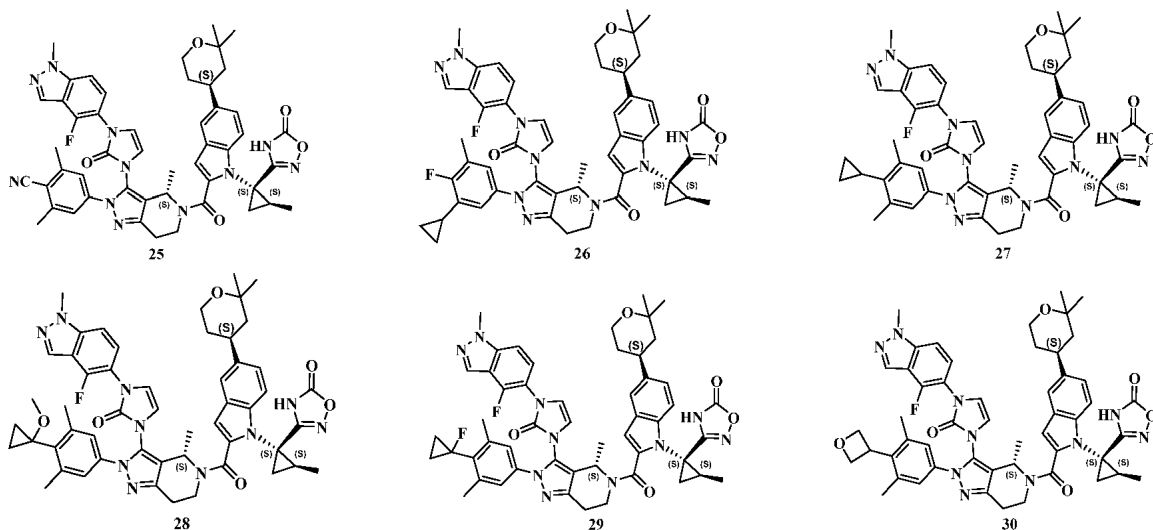
R⁹ and the carbon atom connected thereto form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

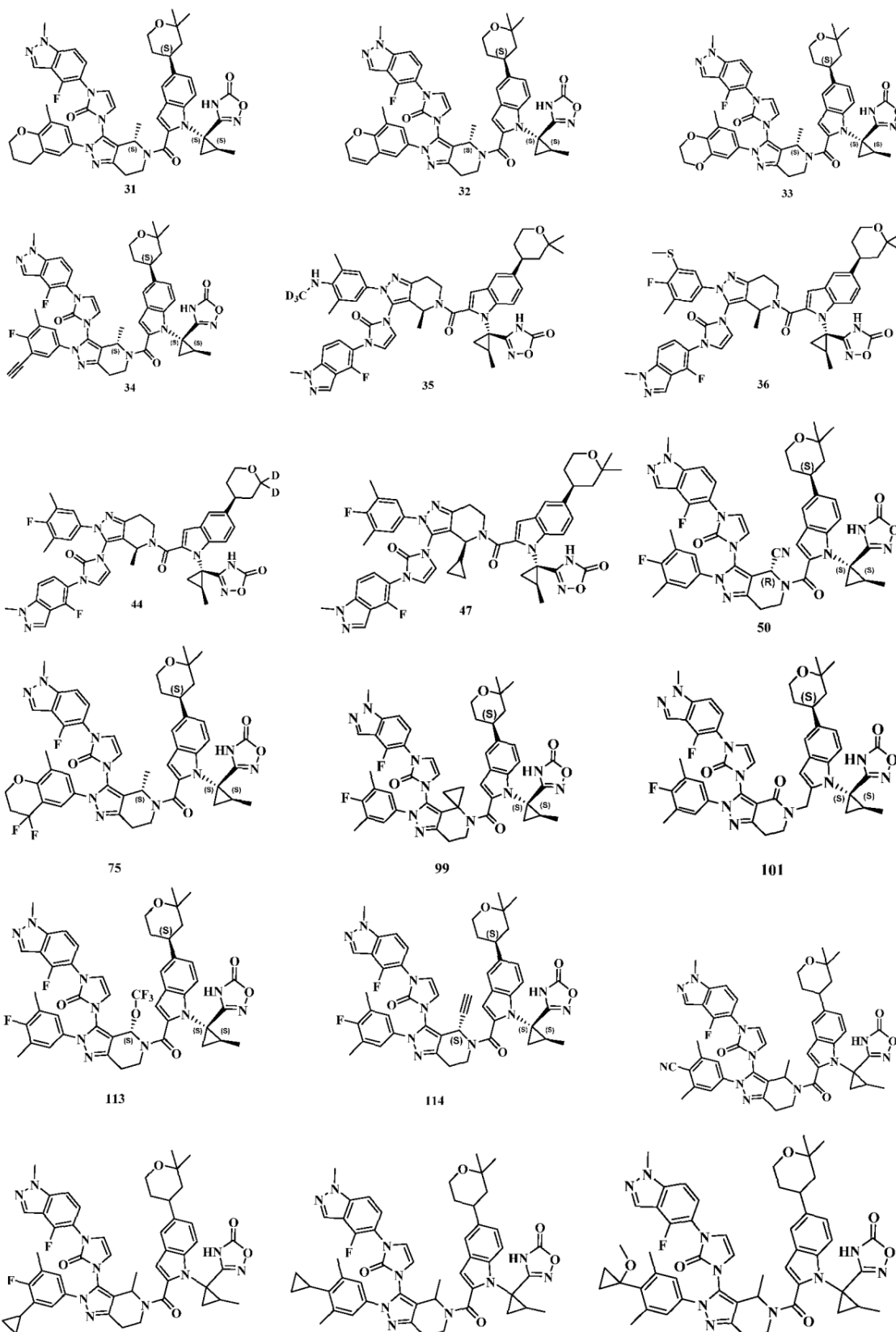
preferably, R⁹ and the carbon atom connected thereto form C₃₋₆ cycloalkyl, 3- to 6-membered
 15 heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

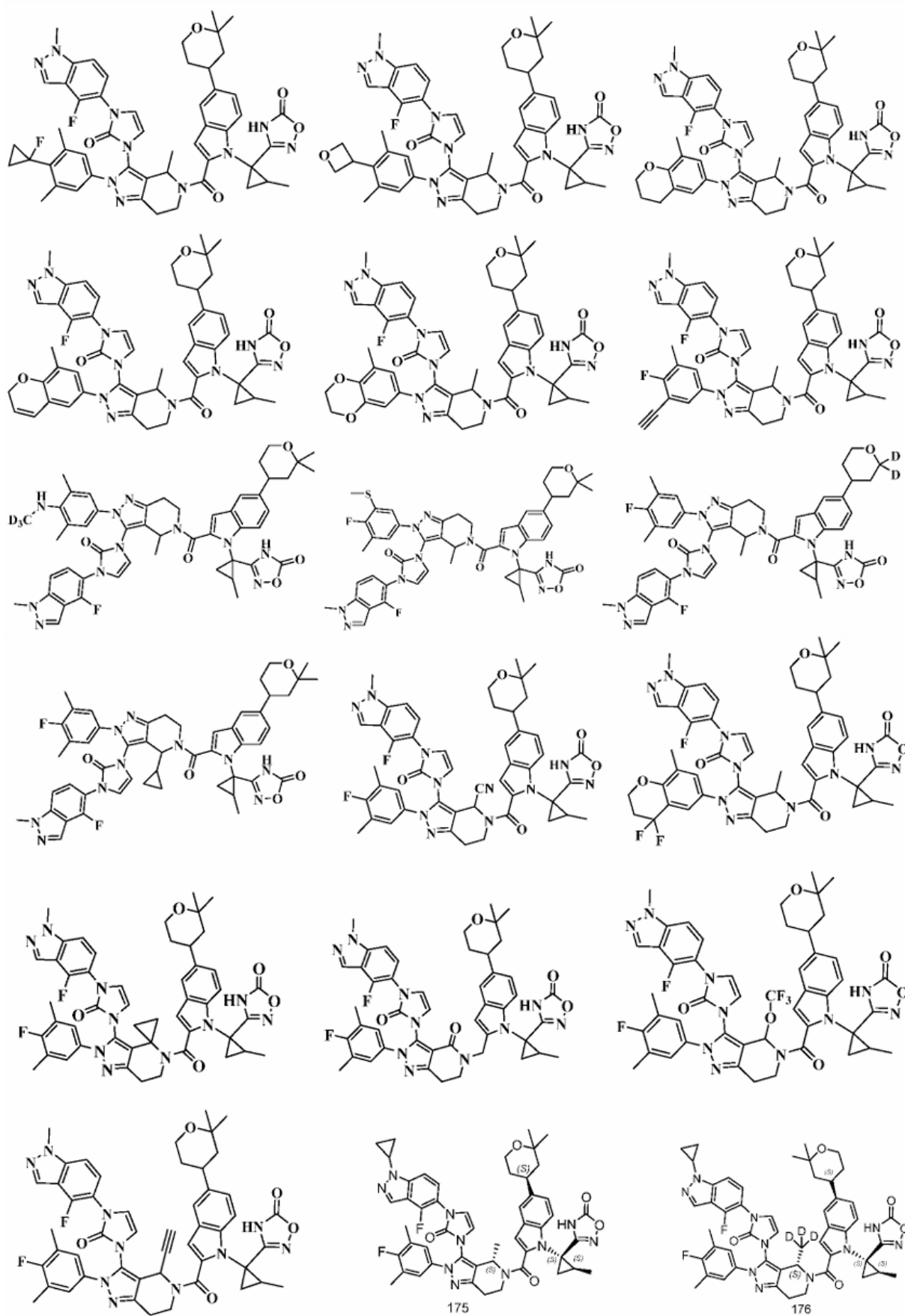
further preferably, R⁹ and the carbon atom connected thereto form cyclopropyl;

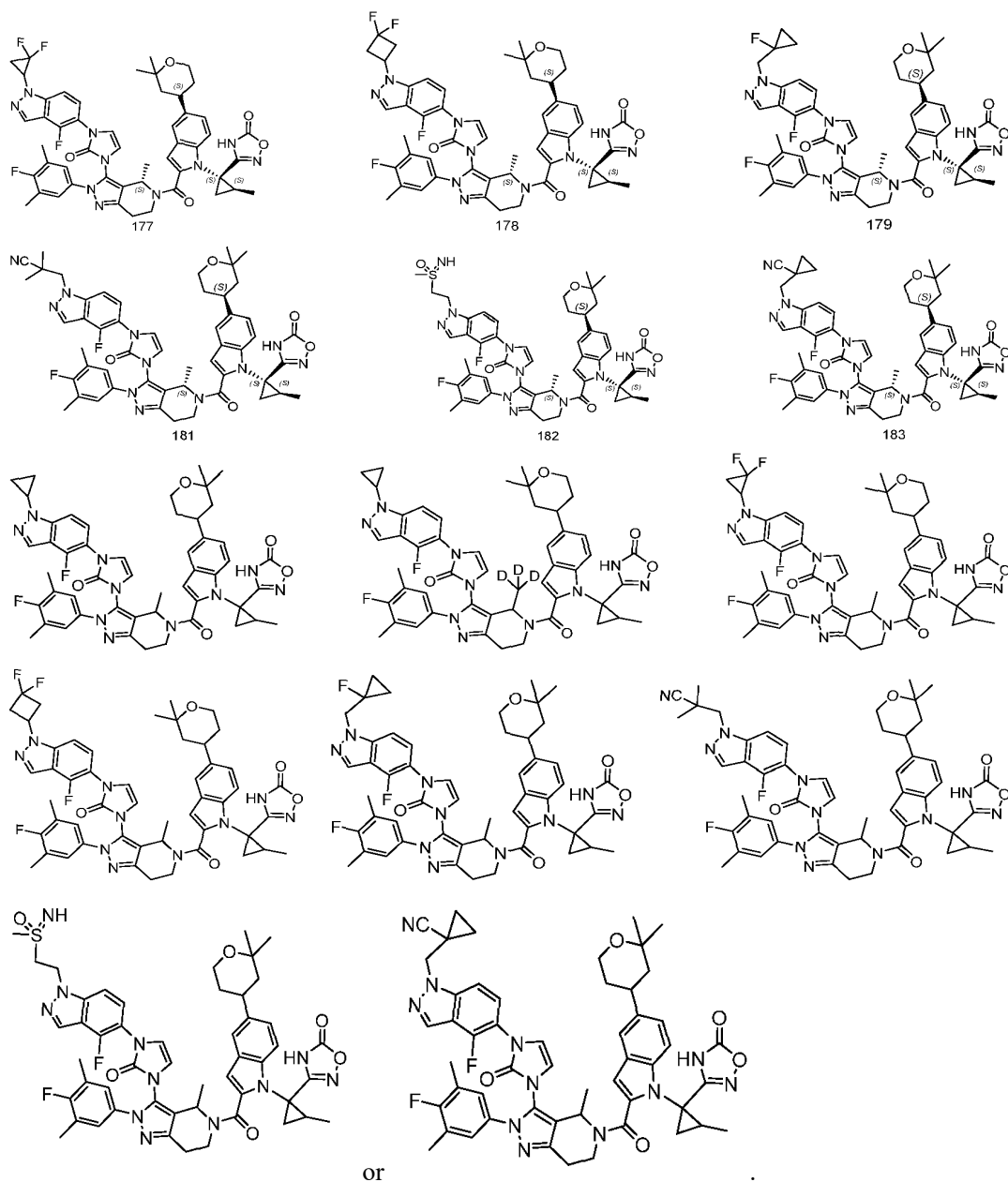
n1 is an integer from 0 to 5.

12. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according
 20 to claim 11, wherein the compound has the following structure:

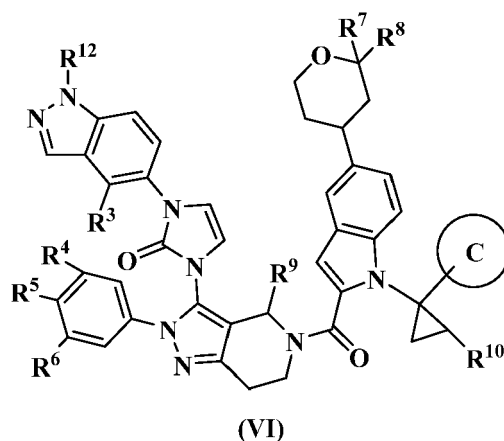








13. A compound represented by general formula (VI), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

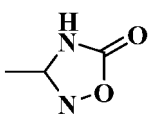
ring C is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl, which is optionally further substituted with one or more substituents selected from
 5 halogen, amino, nitro, hydroxyl, cyano, oxo, mercapto, thio, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy or -NR_{a6}S(O)₂R_{b6};

R¹⁰ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally
 10 further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

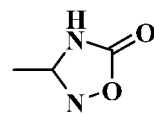
alternatively, R¹⁰ and the C atom connected thereto form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered
 15 heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ thioalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R_{a6} and R_{b6} are each independently selected from hydrogen, deuterium, halogen, amino, nitro,
 20 hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

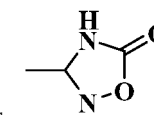
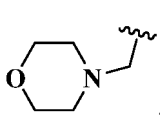
wherein when R³ is fluorine, R⁴ and R⁶ are methyl, R⁵ is fluorine, R⁷ and R⁸ are hydrogen or methyl, R¹² is methyl, and

ring C is , R¹⁰ cannot be methyl;

when R³ is fluorine, R⁴ and R⁶ are methyl, R⁵ is fluorine, R⁷ and R⁸ are hydrogen, R¹² is methyl, and

ring C is , R¹⁰ cannot be hydroxymethyl;

when R³ is fluorine, R⁴ and R⁶ are methyl, R⁵ is fluorine, R⁷ and R⁸ are hydrogen, R¹² is methyl, and

5 ring C is , R¹⁰ cannot be  ;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

15 preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

25 more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino,

C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

more preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen or methyl;

alternatively,

preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

each R⁷, R⁸ or R⁹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R⁷, R⁸ and R⁹ are each independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, R⁷, R⁸ and R⁹ are each independently selected from methyl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

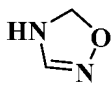
preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl;

n₁ is an integer from 0 to 5.

14. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 13, wherein

ring C is selected from C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, mercapto, thio, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy or -NR_{a6}S(O)₂R_{b6};

preferably, ring C is C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S or 5- to 8-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S, which is optionally further substituted with one or more substituents selected from hydroxyl, oxo or -NR_{a6}S(O)₂R_{b6};

further preferably, ring C is , , , ,  or , which is optionally further substituted with one or more substituents selected from hydroxyl, oxo or -NR_{a6}S(O)₂R_{b6};

R¹⁰ is selected from hydrogen, deuterium, halogen or C₁₋₃ alkyl;

preferably, R¹⁰ is methyl;

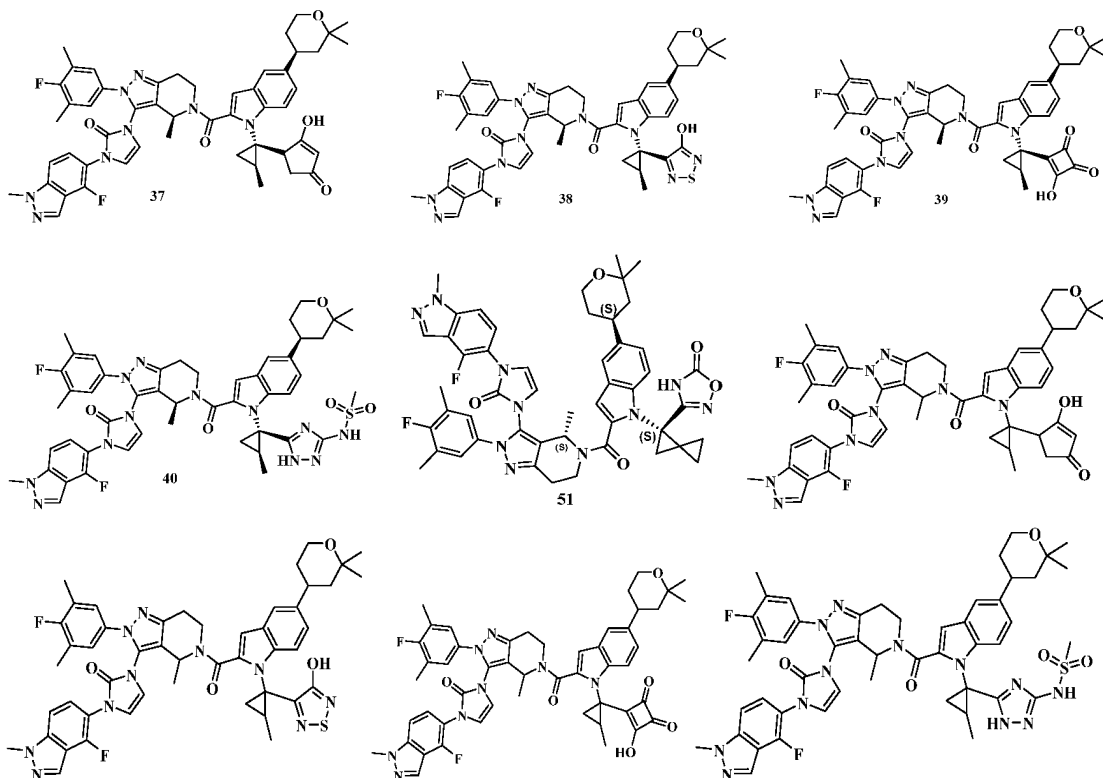
5 alternatively, R¹⁰ and the C atom connected thereto together with adjacent atom(s) to which they are attached form C₃₋₆ cycloalkyl;

preferably, R¹⁰ and the C atom connected thereto together with adjacent atom(s) to which they are attached form cyclopropyl;

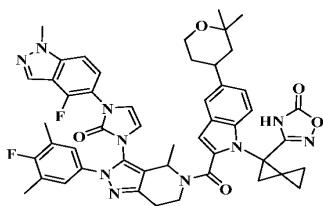
R_{a6} and R_{b6} are each independently selected from hydrogen, deuterium, halogen, amino, nitro,
10 hydroxyl, cyano, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₃₋₈ cycloalkyl, 5- to 7-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

preferably, R_{a6} and R_{b6} are each independently hydrogen or methyl.

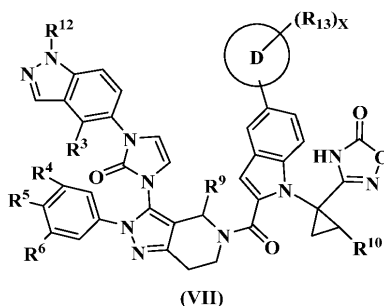
15 15. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 13, wherein the compound has the following structure:



or



16. A compound represented by general formula (VII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



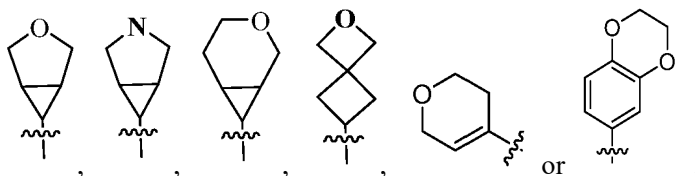
5

wherein

ring D is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

preferably, ring D is 3- to 8-membered monocyclic heterocyclyl, 5- to 12-membered bicyclic fused heterocyclyl, 5- to 12-membered bicyclic spiroheterocyclyl or 5- to 12-membered bicyclic bridged heterocyclyl;

further preferably, ring D is 5- to 6-membered monocyclic heterocyclyl, 5- to 10-membered bicyclic fused heterocyclyl, 5- to 10-membered bicyclic spiroheterocyclyl or 5- to 8-membered bicyclic bridged heterocyclyl;



15

more preferably, ring D is , , , , or ;

R¹³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

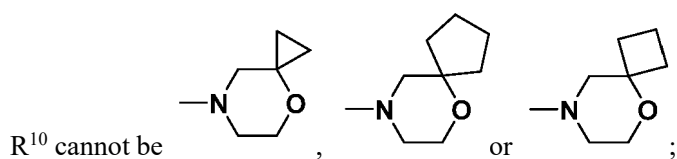
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preferably, R^{13} is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo,

5 C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, R^{13} is methyl;

wherein when R^3 is hydrogen, R^4 and R^6 are methyl, R^5 is fluorine, and R^9 , R^{10} and R^{12} are methyl,



10 R^3 is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3-

15 to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, R^3 is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3}

20 deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 8-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl is optionally further substituted with

25 one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl,

C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents
5 selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;
10
15

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

more preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently hydrogen, deuterium, halogen or methyl;
20

alternatively, preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;
25

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano,
30

oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

5 further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

each R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, 10 nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

15 further preferably, each R⁹ or R¹⁰ is independently selected from methyl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, 20 C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹² is C₁₋₃ alkyl;

more preferably, R¹² is methyl;

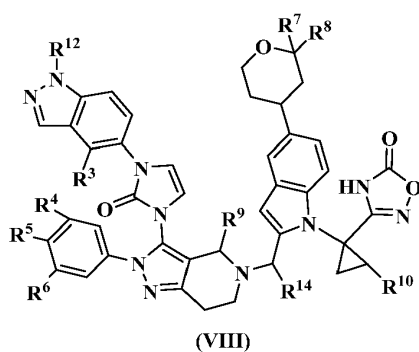
n₁ is an integer from 0 to 5;

25 X is an integer from 0 to 5.

17. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 16, wherein the compound has the following structure:



5 acceptable salt thereof:



R¹⁴ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, thio, C₁₋₆ alkyl, C₆ deutoalkyl,

C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹⁴ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, thio, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R¹⁴ is thio or trifluoromethyl;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl,

C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents
5 selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;
10
15

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;
20

alternatively, preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2} or R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;
25

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano,
30

oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

5 further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from
10 halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

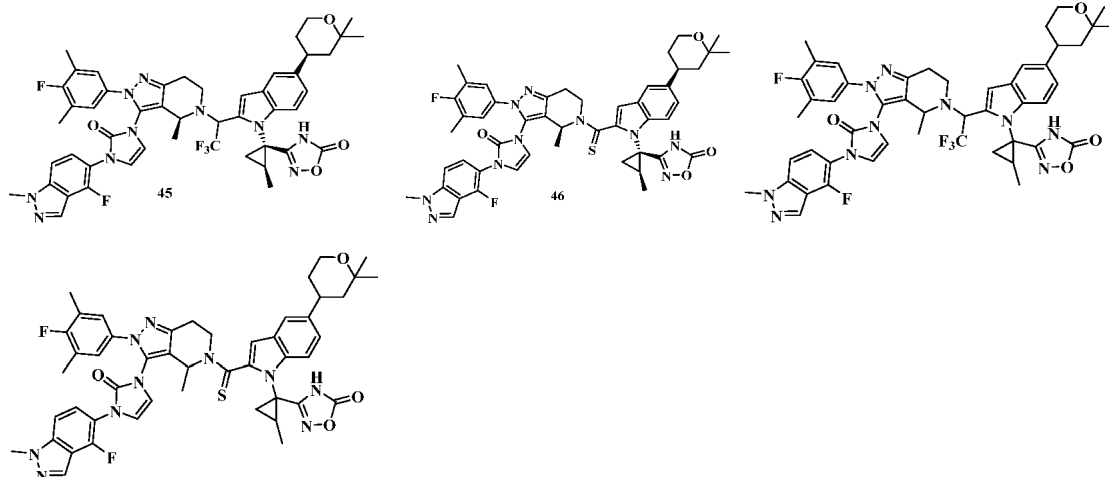
15 further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo,
20 C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

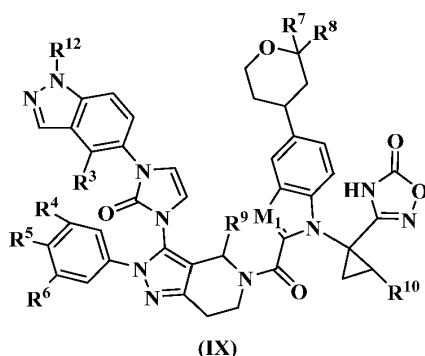
preferably, R¹² is C₁₋₃ alkyl; more preferably, R¹² is methyl;

n₁ is an integer from 0 to 5.

25 19. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 18, wherein the compound has the following structure:



20. A compound represented by general formula (IX), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

M₁ is S or N;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen,

amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl,

C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -
 5 (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl,
 10 C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents
 15 selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

alternatively, preferably, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2}, and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently selected from fluorine or methyl;

preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

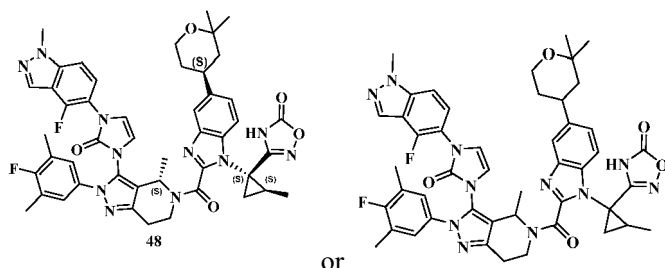
further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

preferably, R^{12} is C_{1-3} alkyl; more preferably, R^{12} is methyl;

$n1$ is an integer from 0 to 5.

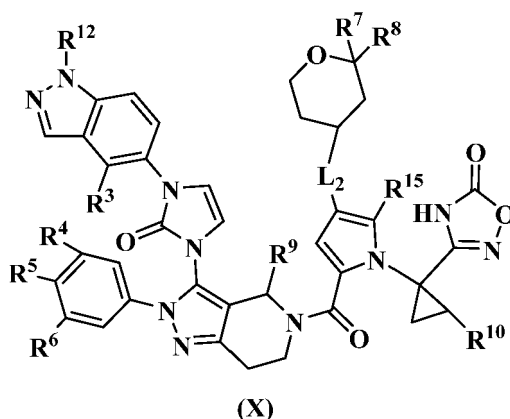
21. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according

5 to claim 20, wherein the compound has the following structure:



OR

22. A compound represented by general formula (X), or a stereoisomer or a pharmaceutically acceptable salt thereof:



(X)

wherein

L_2 is selected from a bond, $-(CH_2)_{n4}-$, C_{2-4} alkenylene or C_{2-4} alkynylene;

R^{15} is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, R^{15} is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl,

which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

5 further preferably, R¹⁵ is methyl;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -
 10 (CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

15 each R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1}, R_{a2} and R_{b2}, R_{a3} and R_{b3}, and R_{a4} and R_{b4} together with adjacent atom(s) to
 20 which they are each attached form C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl
 25 or 5- to 10-membered heteroaryl;

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl,
 30

C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

5 each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

10 R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

15 preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

25 more preferably, R³ is hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl is optionally further substituted with one or more substituents selected from halogen, -NS(O)R_{a1}R_{b1} or C₁₋₃ alkyl;

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

5 alternatively, preferably, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

further preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

10 preferably, each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R^4 , R^5 or R^6 is independently selected from fluorine or methyl;

preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

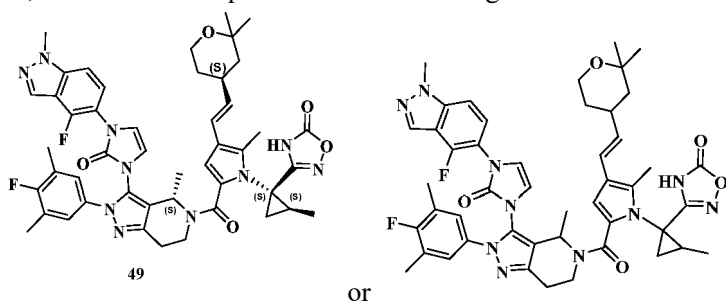
15 further preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from methyl;

preferably, R^{12} is C_{1-3} alkyl; more preferably, R^{12} is methyl;

n_1 is an integer from 0 to 5;

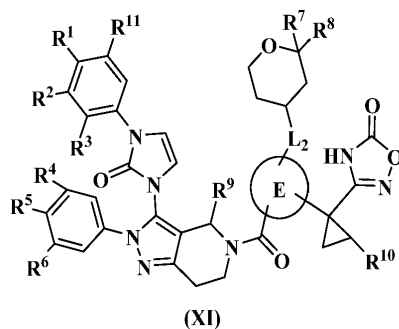
n_4 is an integer from 0 to 5.

20 23. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 22, wherein the compound has the following structure:



24. A compound represented by general formula (XI), or a stereoisomer or a pharmaceutically acceptable salt thereof:

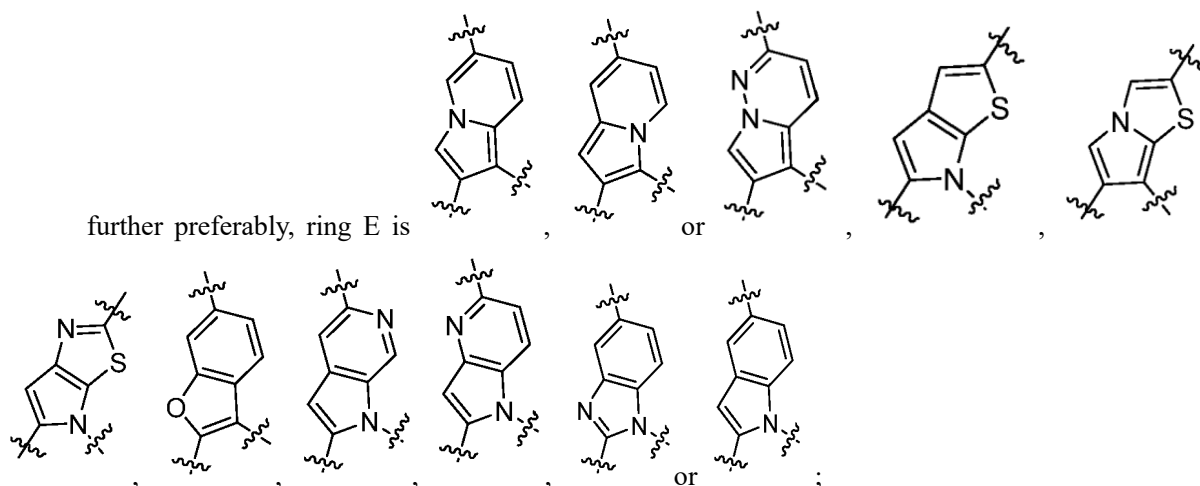
25



wherein

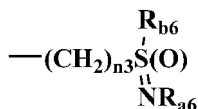
ring E is selected from C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl;

- 5 preferably, ring E is C₃₋₈ cycloalkyl, 3- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;



- 10 L₂ is selected from a bond, -(CH₂)_{n4}-, C₂₋₄ alkenylene or C₂₋₄ alkynylene;

each R¹, R², R³ or R¹¹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -



- 15 (CH₂)_{n1}S(O)₂R_{a5}, -(CH₂)_{n1}O(CH₂)_{n2}R_{b5}, -(CH₂)_{n4}P(O)R_{a7}R_{b7} or - (CR_{a8}R_{b8})_{n5}C(O)NR_{a9}R_{b9}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl,

C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R¹, R², R³ or R¹¹ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -

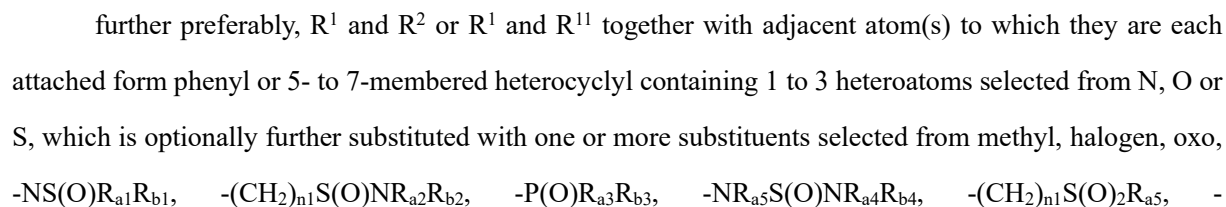
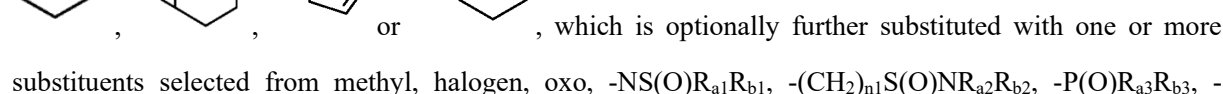
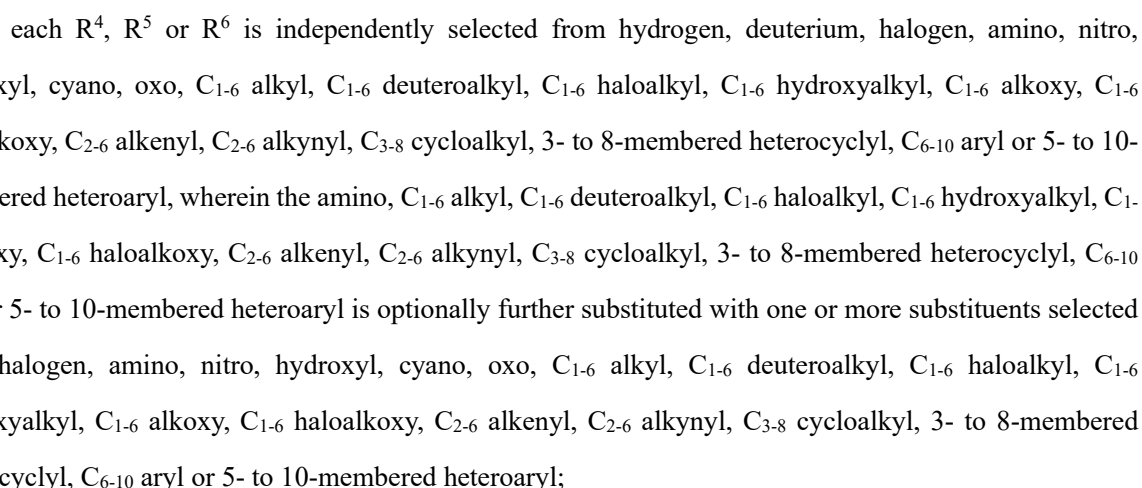
(CH₂)_{n1}S(O)₂R_{a5}, -(CH₂)_{n1}O(CH₂)_{n2}R_{b5},
$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}\text{---}$$
, -(CH₂)_nP(O)R_{a7}R_{b7} or -

(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

alternatively, R¹ and R² or R¹ and R¹¹ together with adjacent atom(s) to which they are each attached form C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl, wherein the C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, C₆₋₁₄ aryl or 5- to 14-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3}, -NR_{a5}S(O)NR_{a4}R_{b4}, -(CH₂)_{n1}S(O)₂R_{a5}, -

(CH₂)_{n1}O(CH₂)_{n2}R_{b5},
$$\text{---}(\text{CH}_2)_{n3}\overset{\text{R}_{b6}}{\underset{\text{NR}_{a6}}{\text{S}(\text{O})}}\text{---}$$
, -(CH₂)_{n1}P(O)R_{a7}R_{b7} or -(CR_{a8}R_{b8})_{n4}C(O)NR_{a9}R_{b9};

preferably, R¹ and R² or R¹ and R¹¹ together with adjacent atom(s) to which they are each attached form C₃₋₈ cycloalkyl, 3- to 10-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3},



preferably, each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{3-6} cycloalkyl or C_{1-3} haloalkyl;

further preferably, each R^4 , R^5 or R^6 is independently selected from fluorine, methyl or cyclopropyl;

each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deutoalkyl or C_{1-3} haloalkyl;

further preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen or methyl;

each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} or R_{a2} and R_{b2} or R_{a3} and R_{b3} or R_{a4} and R_{b4} or R_{a7} and R_{b7} or R_{a8} and R_{b8} or R_{a9} and R_{b9} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} , R_{b6} , R_{a7} , R_{b7} , R_{a8} , R_{b8} , R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, amino, cyano, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

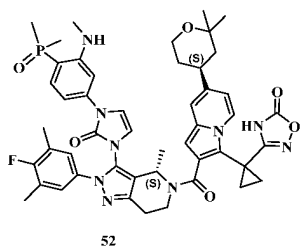
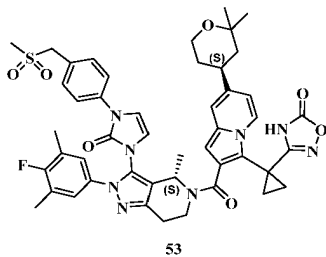
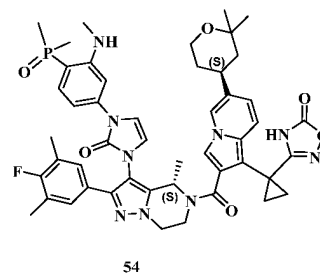
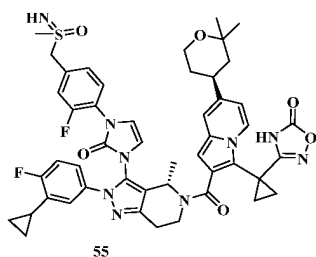
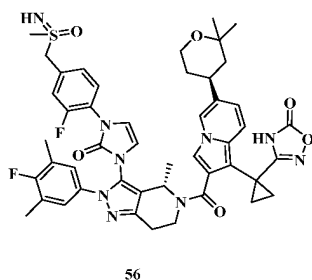
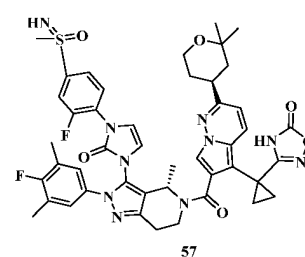
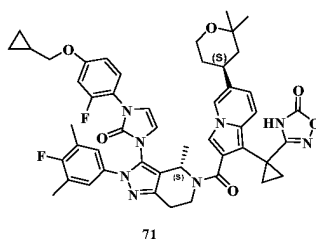
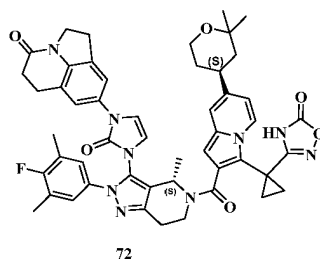
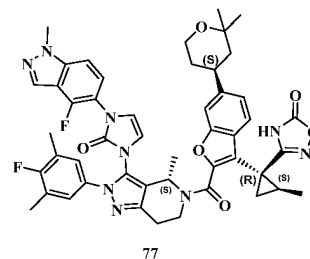
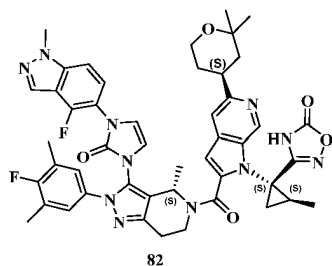
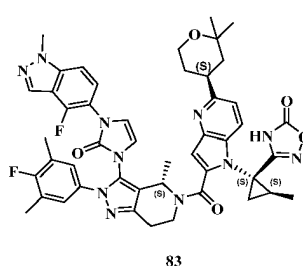
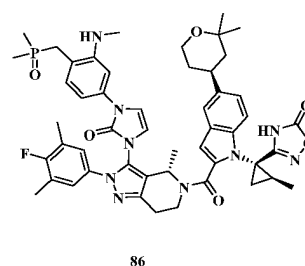
further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} , R_{b4} , R_{a5} , R_{b5} , R_{a6} ,

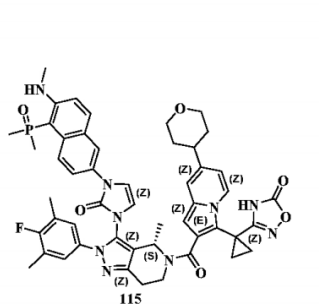
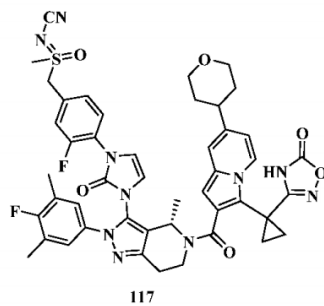
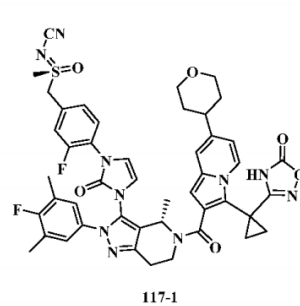
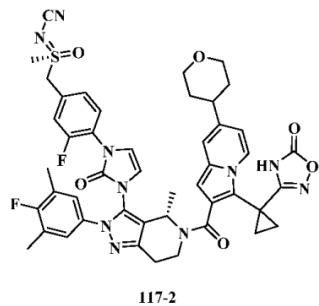
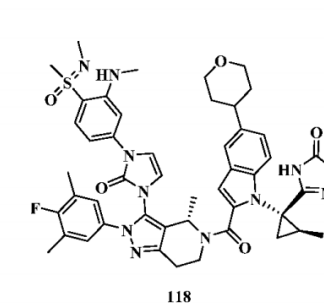
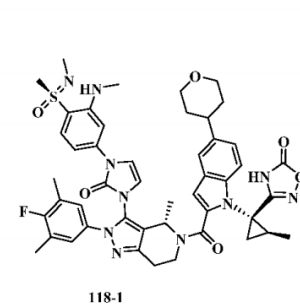
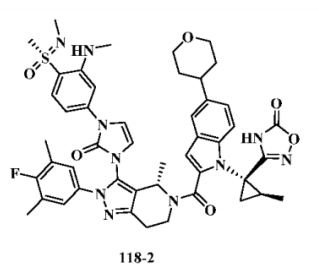
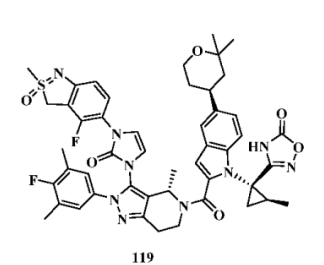
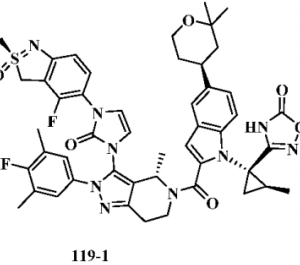
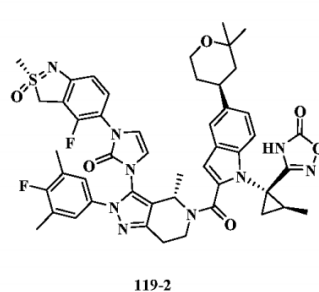
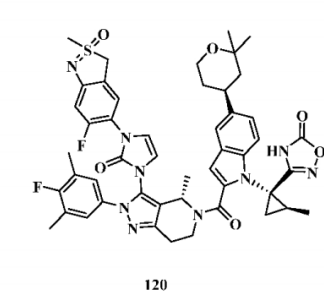
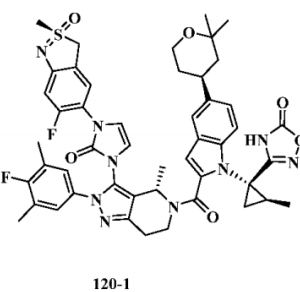
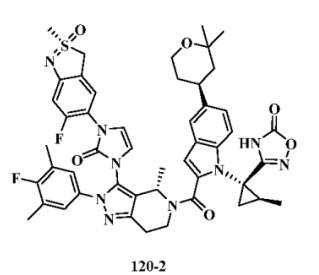
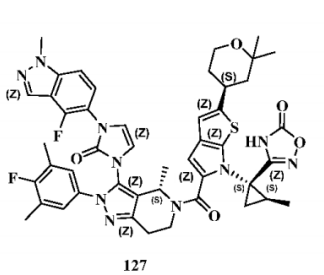
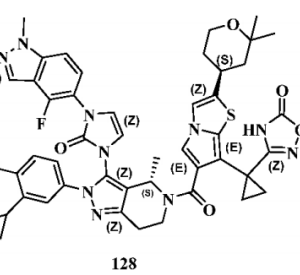
R_{b6}, R_{a7}, R_{b7}, R_{a8}, R_{b8}, R_{a9} or R_{b9} is independently selected from hydrogen, deuterium, halogen, cyano,

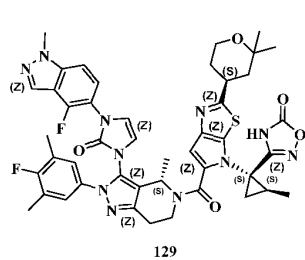
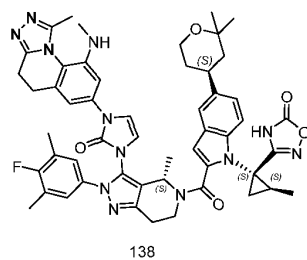
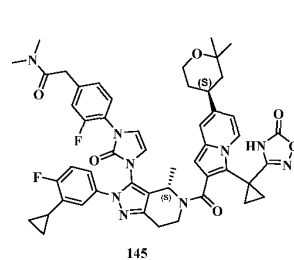
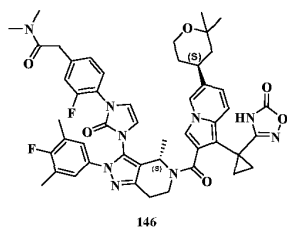
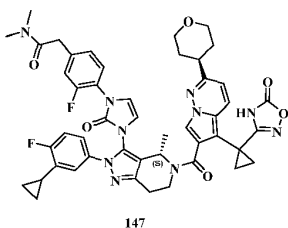
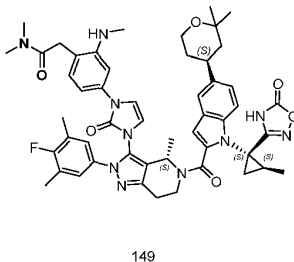
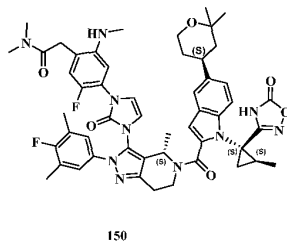
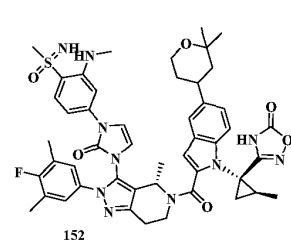
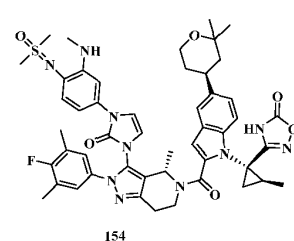
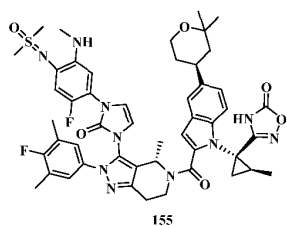
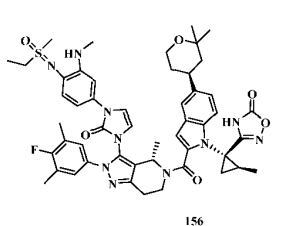
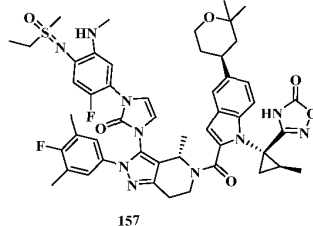
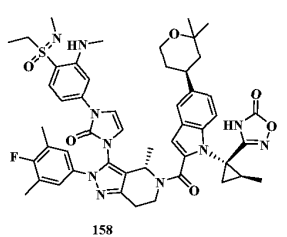
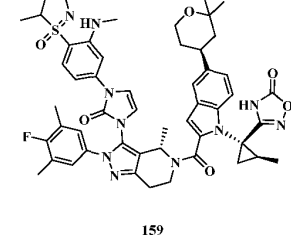
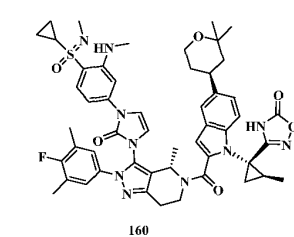
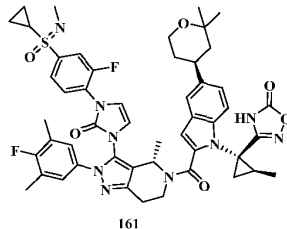
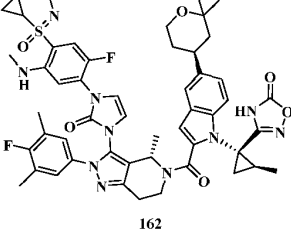
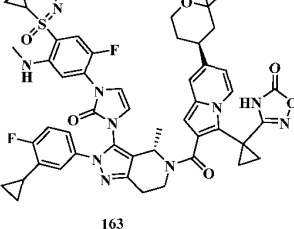
cyclopropyl, cyclopentyl, methyl, ethyl, phenyl or  ;

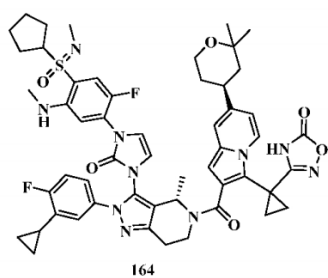
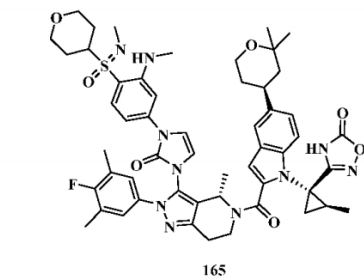
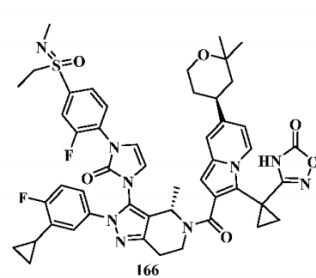
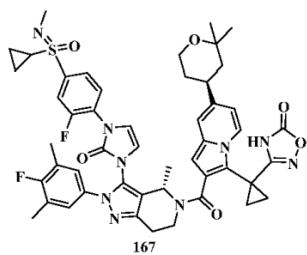
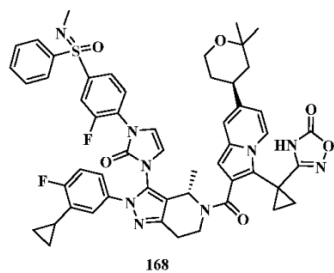
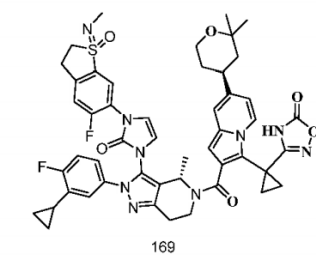
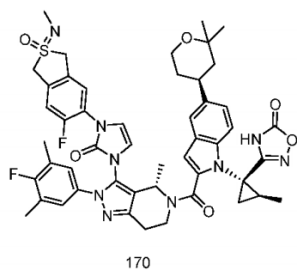
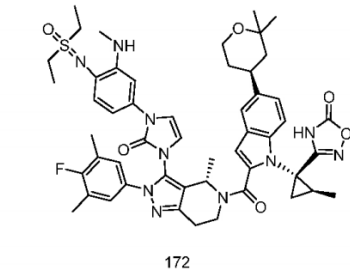
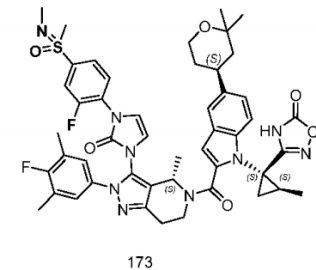
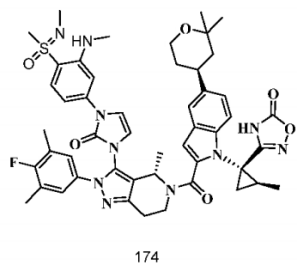
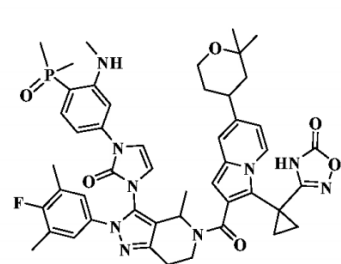
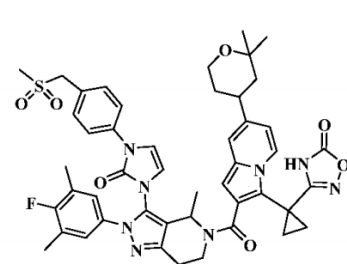
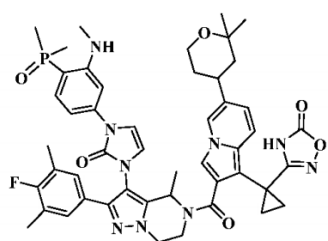
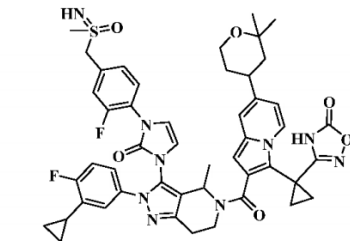
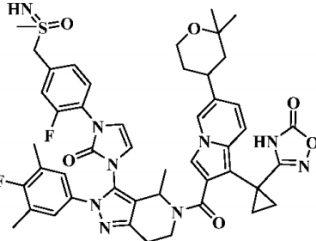
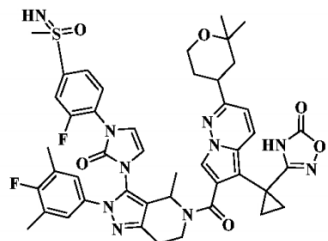
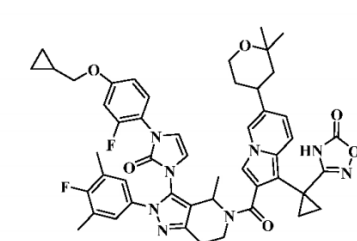
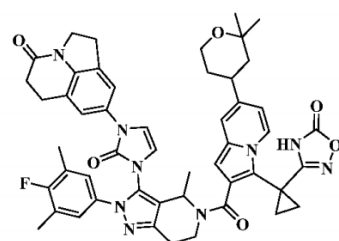
n₁ to n₄ are integers from 0 to 5.

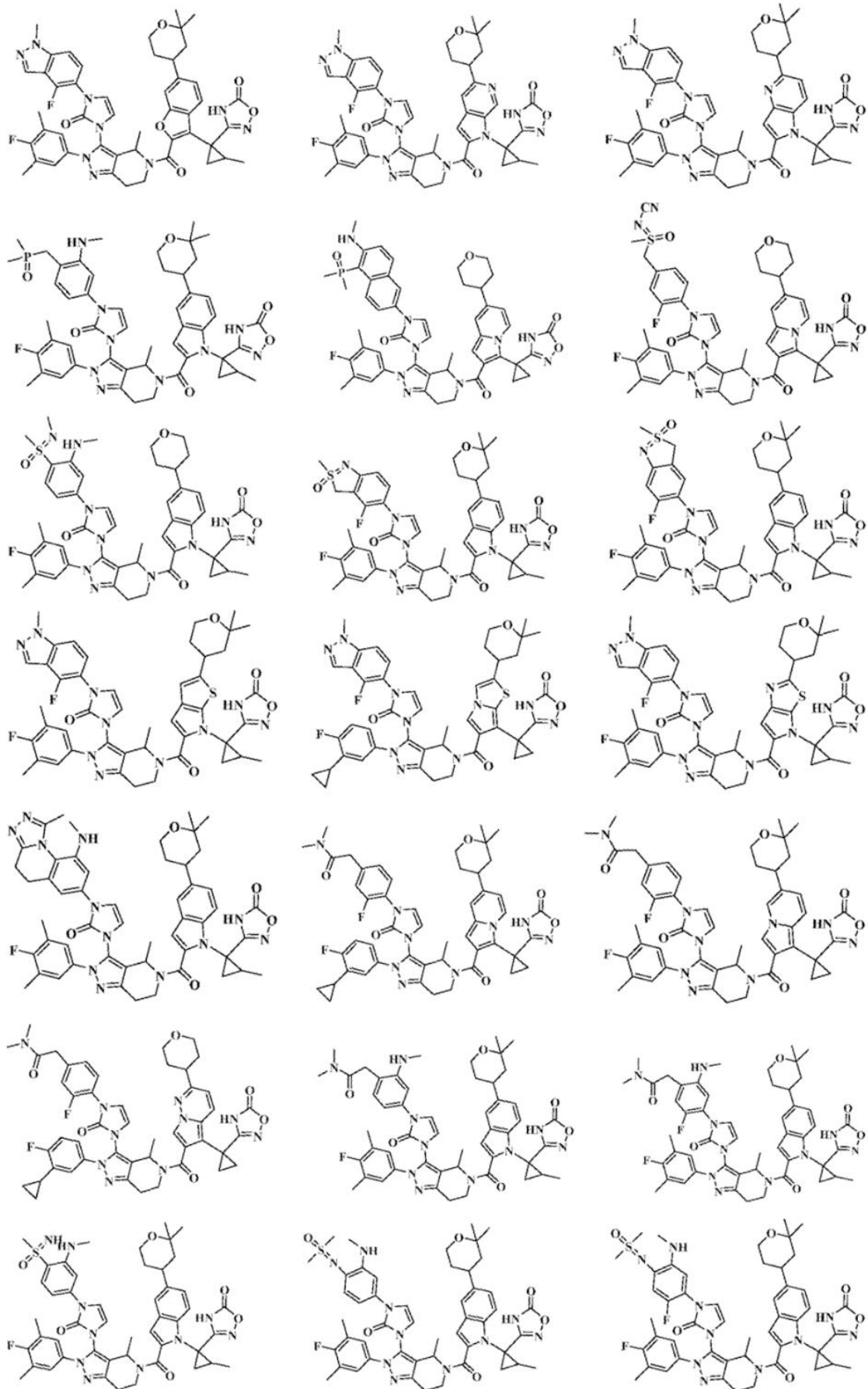
5 25. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 24, wherein the compound has the following structure:

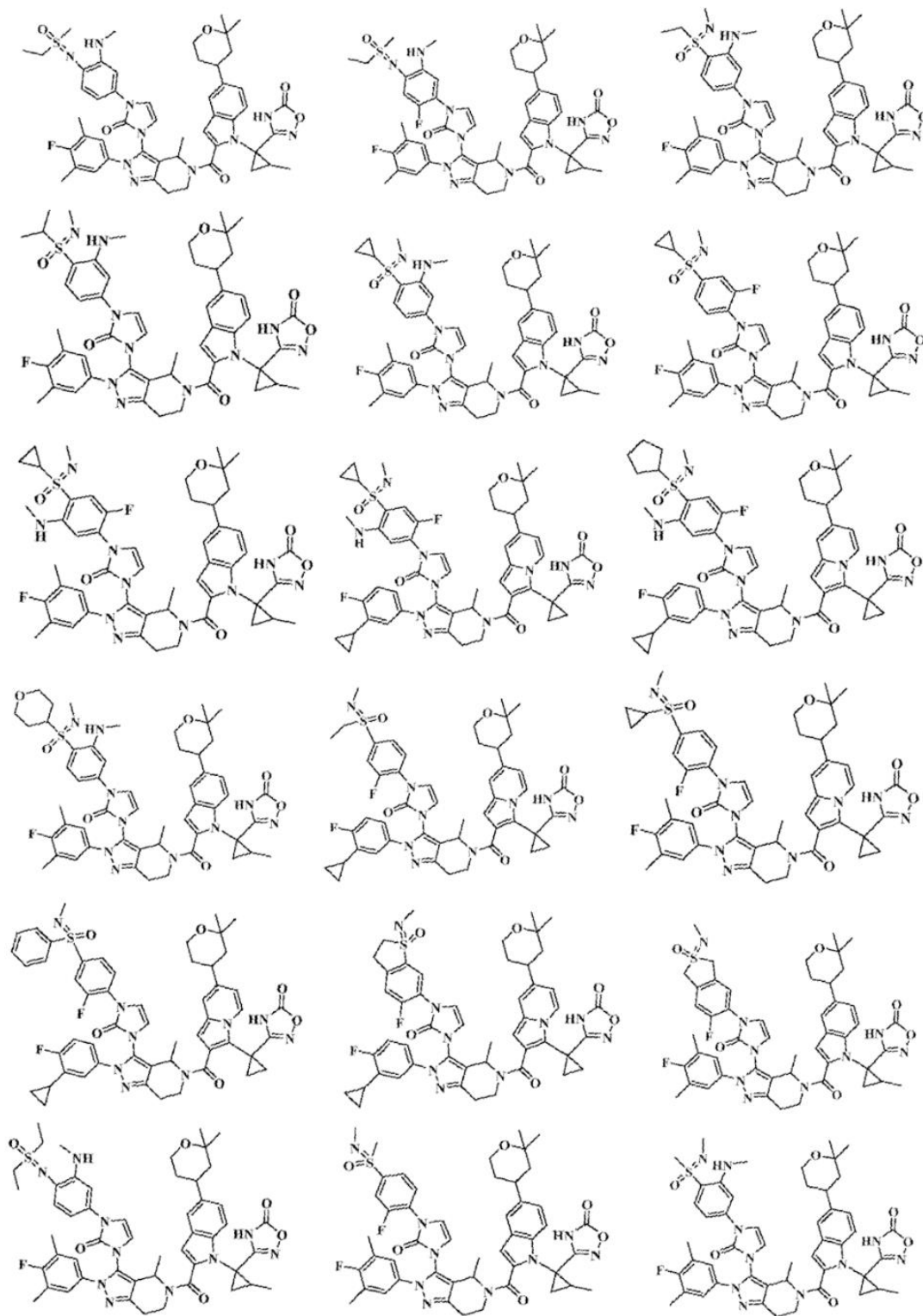


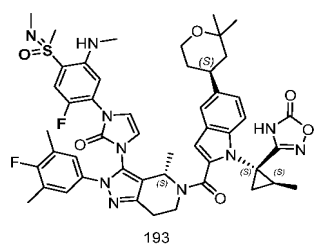
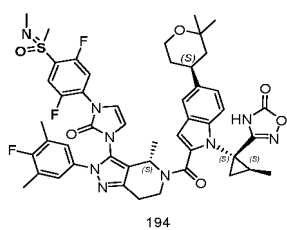
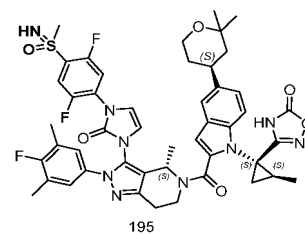
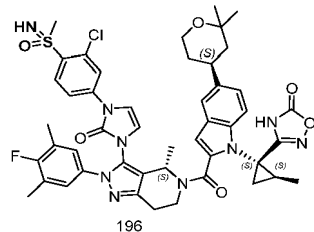
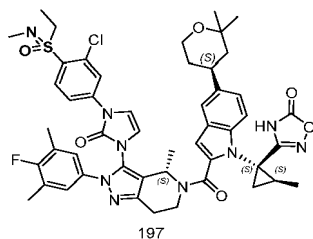
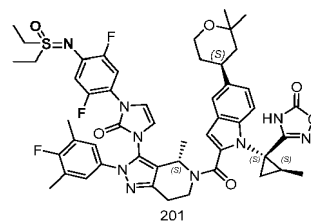
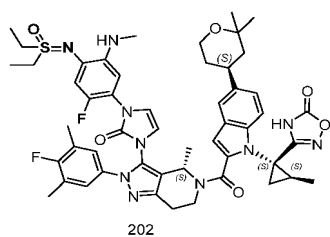
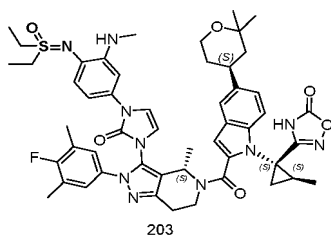
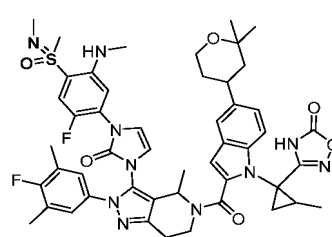
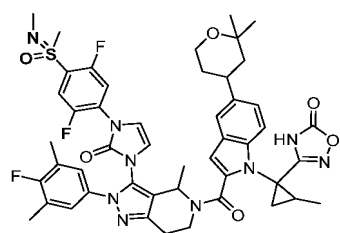
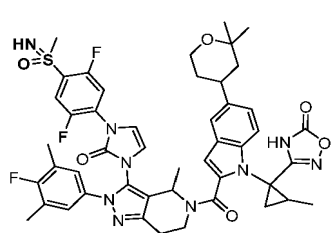
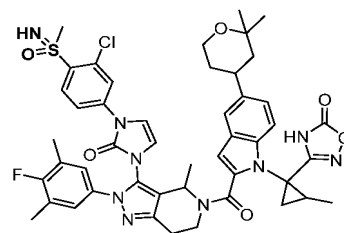
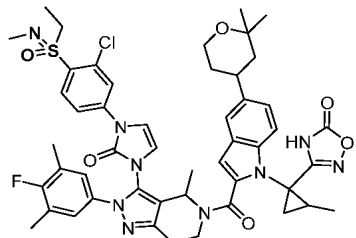
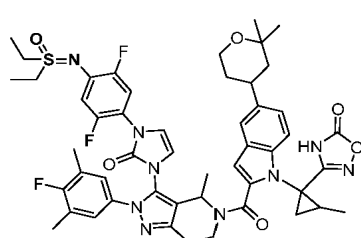
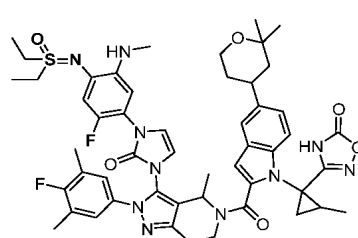




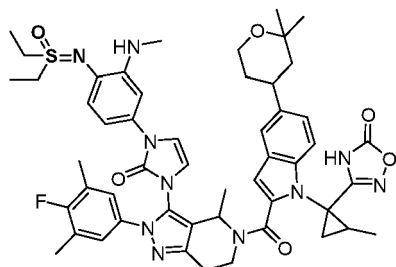




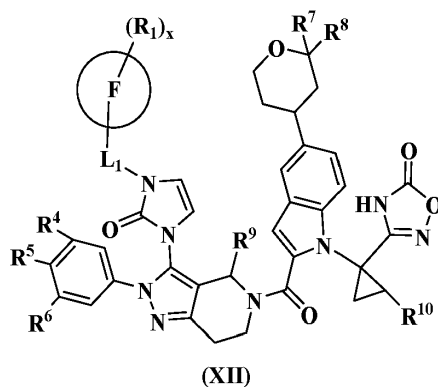




or



26. A compound represented by general formula (XII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

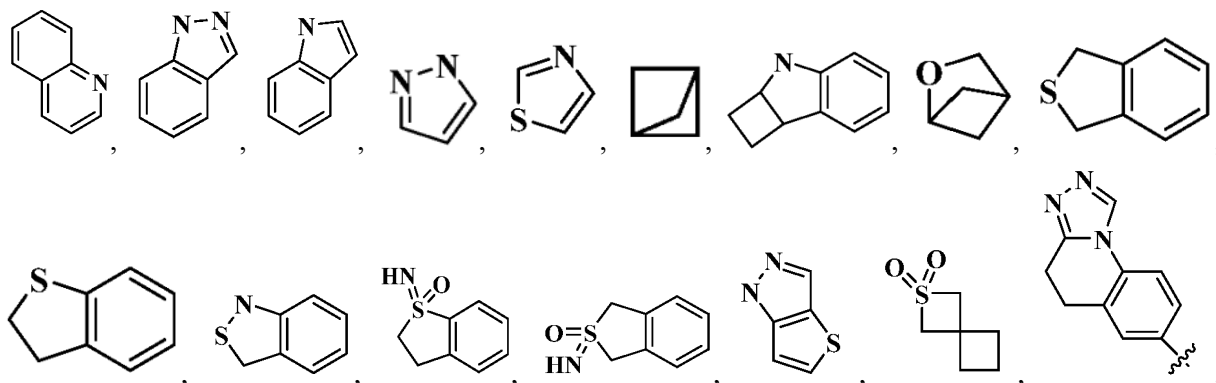
L_1 is selected from a bond, C_{2-4} alkenylene, C_{2-4} alkynylene, $-(CH_2)_{n4}-$ or $-(CH_2)_{n5}NR_{b5}$, wherein the C_{2-4} alkenylene, C_{2-4} alkynylene, $-(CH_2)_{n4}-$ or $-(CH_2)_{n5}NR_{b5}$ is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

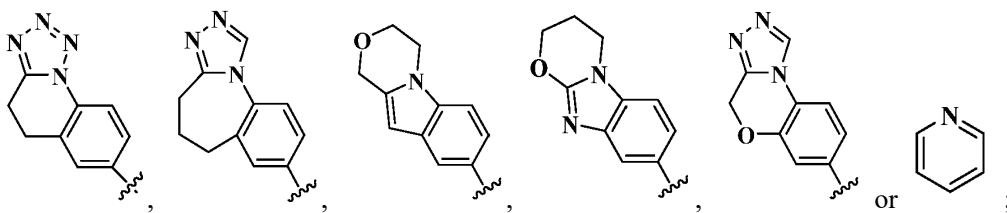
ring F is selected from C_{3-12} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl;

further preferably, ring F is C_{3-10} cycloalkyl, 5- to 14-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, ring F is C_{3-6} bridged cycloalkyl, 8- to 14-membered tricyclic fused heterocyclyl containing 1 to 5 heteroatoms, 3- to 8-membered bridged heterocyclyl containing 1 to 3 heteroatoms, fused heterocyclyl containing 1 to 3 heteroatoms, bridged heterocyclyl containing 1 to 3 heteroatoms, C_{6-10} aryl or 5- to 10-membered fused heteroaryl containing 1 to 3 heteroatoms;

more preferably, ring F is phenyl, pyridyl, pyrimidyl, thiazolyl, pyridazinyl, oxazolyl, morpholinyl,

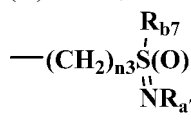




each R^1 is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano,

oxo, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -

5 $NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, -



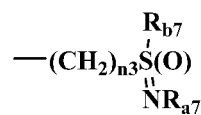
$(CH_2)_{n1}C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$, $-(CH_2)_{n1}NR_{a8}C(O)R_{b8}$ or $-(CH_2)_{n1}S(O)_2R_{b5}$,

wherein the amino, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen,

10 amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-6} alkyl, C_{1-6} deutoalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, each R^1 is independently selected from hydrogen, deuterium, halogen, amino, nitro,

hydroxyl, cyano, oxo, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, -



$(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, $-(CH_2)_{n1}C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$, $-(CH_2)_{n1}NR_{a8}C(O)R_{b8}$

or $-(CH_2)_{n1}S(O)_2R_{b5}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10}

20 aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, $-NS(O)R_{a1}R_{b1}$, C_{1-3} alkyl, C_{1-3} deutoalkyl, C_{1-3} haloalkyl, C_{1-3} hydroxyalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

further preferably, each R^1 is independently selected from amino, oxo, C_{1-3} alkyl, C_{1-3} deuterioalkyl, -
 $NS(O)R_{a1}R_{b1}$, $-(CH_2)_{n1}S(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$, $-NR_{a5}S(O)NR_{a4}R_{b4}$, $-(CH_2)_{n1}O(CH_2)_{n2}R_{a5}$, -
 $-(CH_2)_{n3}\overset{\overset{R_{b7}}{|}}{\underset{\underset{NR_{a7}}{|}}{S}}(O)$
 $(CH_2)_{n1}C(O)NR_{a6}R_{b6}$, $-(CH_2)_{n1}P(O)R_{a3}R_{b3}$, $-(CH_2)_{n1}NR_{a8}C(O)R_{b8}$ or $-(CH_2)_{n1}S(O)_2R_{b5}$,

wherein the amino or C_{1-3} alkyl is optionally further substituted with cyano or C_{1-3} alkyl;

5 alternatively,

R^1 and the C atom connected thereto together with adjacent atom(s) to which they are attached form
 C_{3-10} cycloalkyl, 3- to 10-membered heterocyclyl, C_{6-12} aryl or 5- to 12-membered heteroaryl;

preferably, R^1 and the C atom connected thereto form C_{3-6} cycloalkyl, 3- to 8-membered heterocyclyl,
 C_{6-10} aryl or 5- to 10-membered heteroaryl;

10 further preferably, R^1 and the C atom connected thereto form C_{3-4} cycloalkyl;

each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino, nitro,
hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6}
haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-
membered heteroaryl, wherein the amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6}
15 C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10}
aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected
from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6}
hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered
heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

20 preferably, each R^4 , R^5 or R^6 is independently selected from hydrogen, deuterium, halogen, amino,
 C_{1-3} alkyl, C_{1-3} deuterioalkyl or C_{1-3} haloalkyl;

further preferably, each R^4 , R^5 or R^6 is independently selected from fluorine or methyl;

each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, amino, nitro,
hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6}
25 haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-
membered heteroaryl, which is optionally further substituted with one or more substituents selected from
halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl,

C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from hydrogen, deuterium, halogen, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl or C₁₋₃ haloalkyl;

5 further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deuterioalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

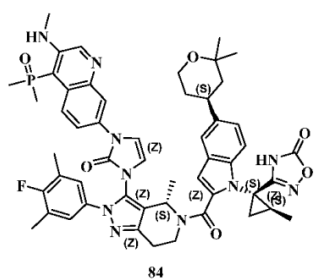
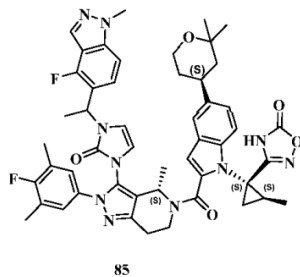
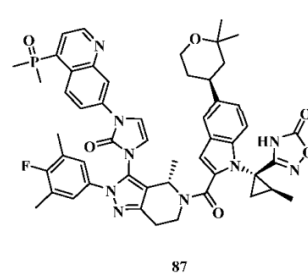
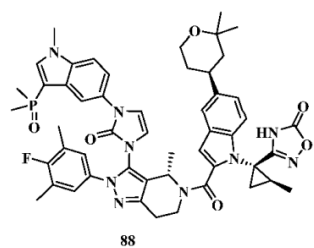
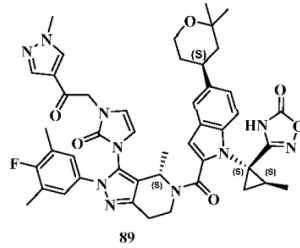
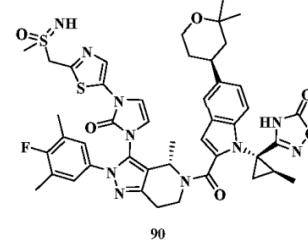
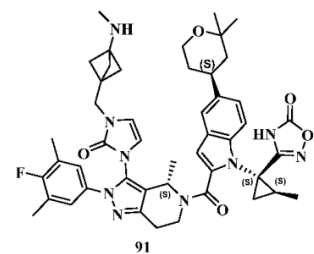
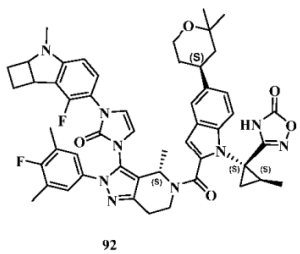
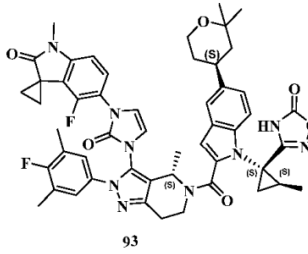
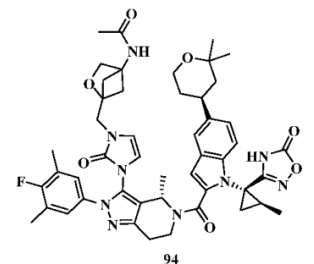
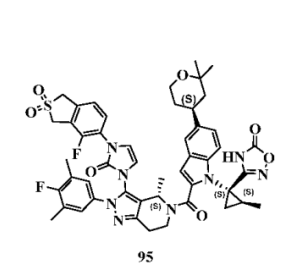
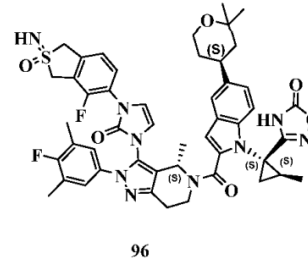
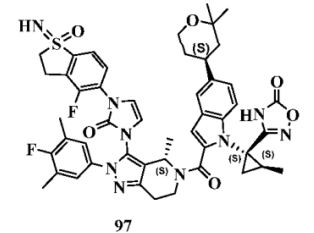
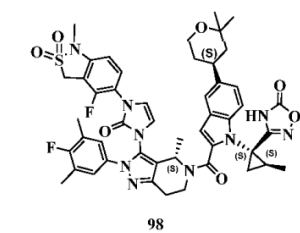
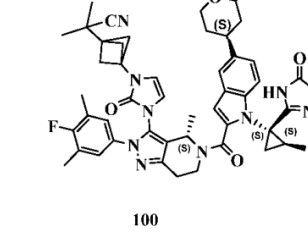
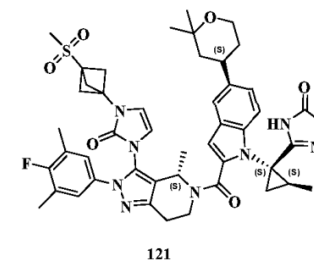
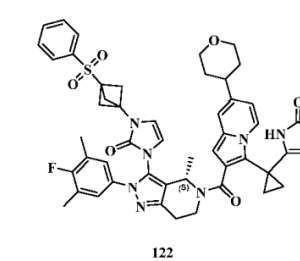
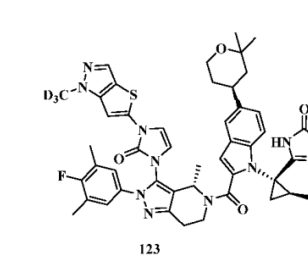
15 preferably, R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently selected from hydrogen, deuterium, halogen, amino, C₁₋₃ alkyl, C₁₋₃ deuterioalkyl, C₁₋₃ haloalkyl, 3- to 8-membered heterocyclyl containing 1 to 3 heteroatoms selected from N, O or S, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl containing 1 to 3 heteroatoms selected from N, O or S;

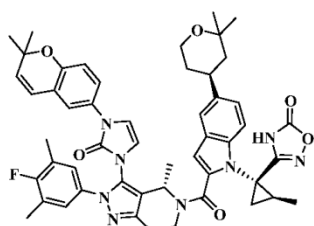
further preferably, R_{a1}, R_{b1}, R_{a2}, R_{b2}, R_{a3}, R_{b3}, R_{a4}, R_{b4}, R_{a5}, R_{b5}, R_{a6}, R_{b6}, R_{a7}, R_{b7}, R_{a8} and R_{b8} are each independently selected from hydrogen, deuterium, halogen, phenyl or methyl;

n₁ to n₅ are integers from 0 to 5.

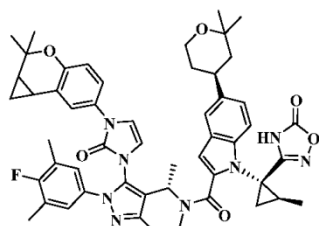
27. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 26, wherein the compound has the following structure:

25

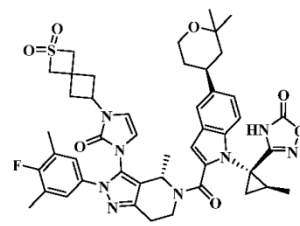




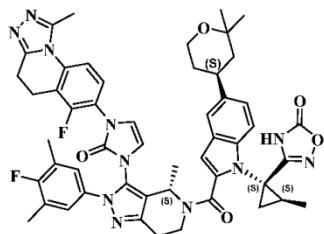
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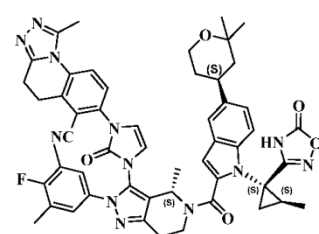
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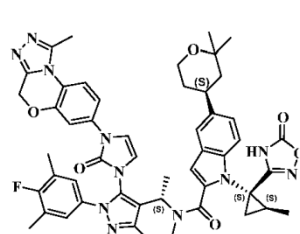
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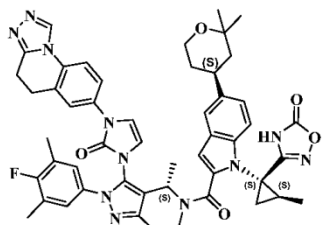
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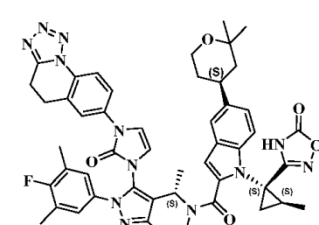
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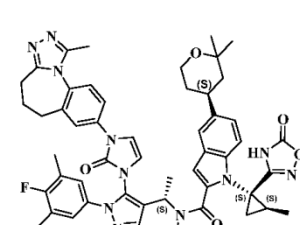
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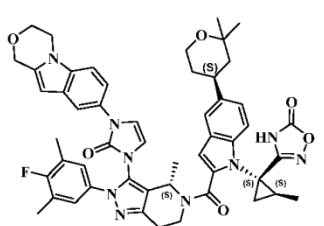
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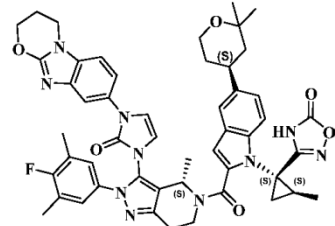
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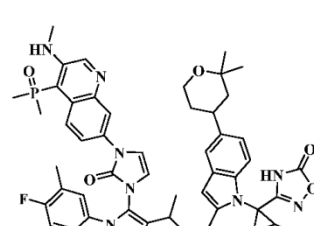
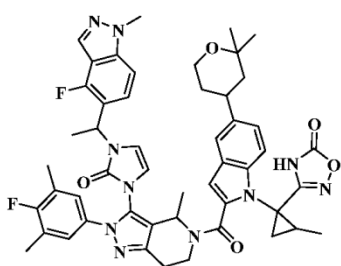
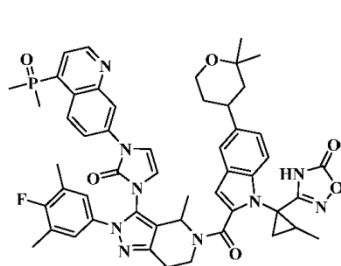
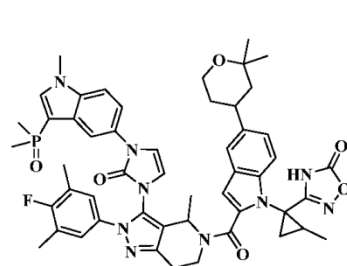
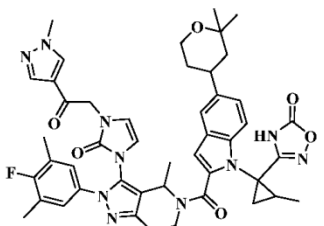
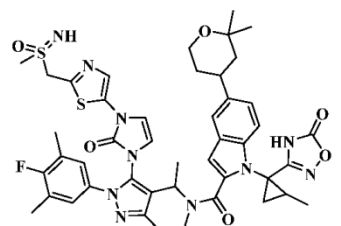
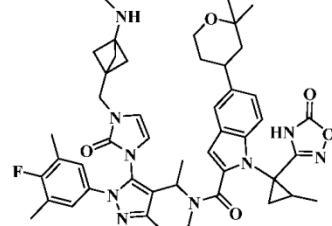
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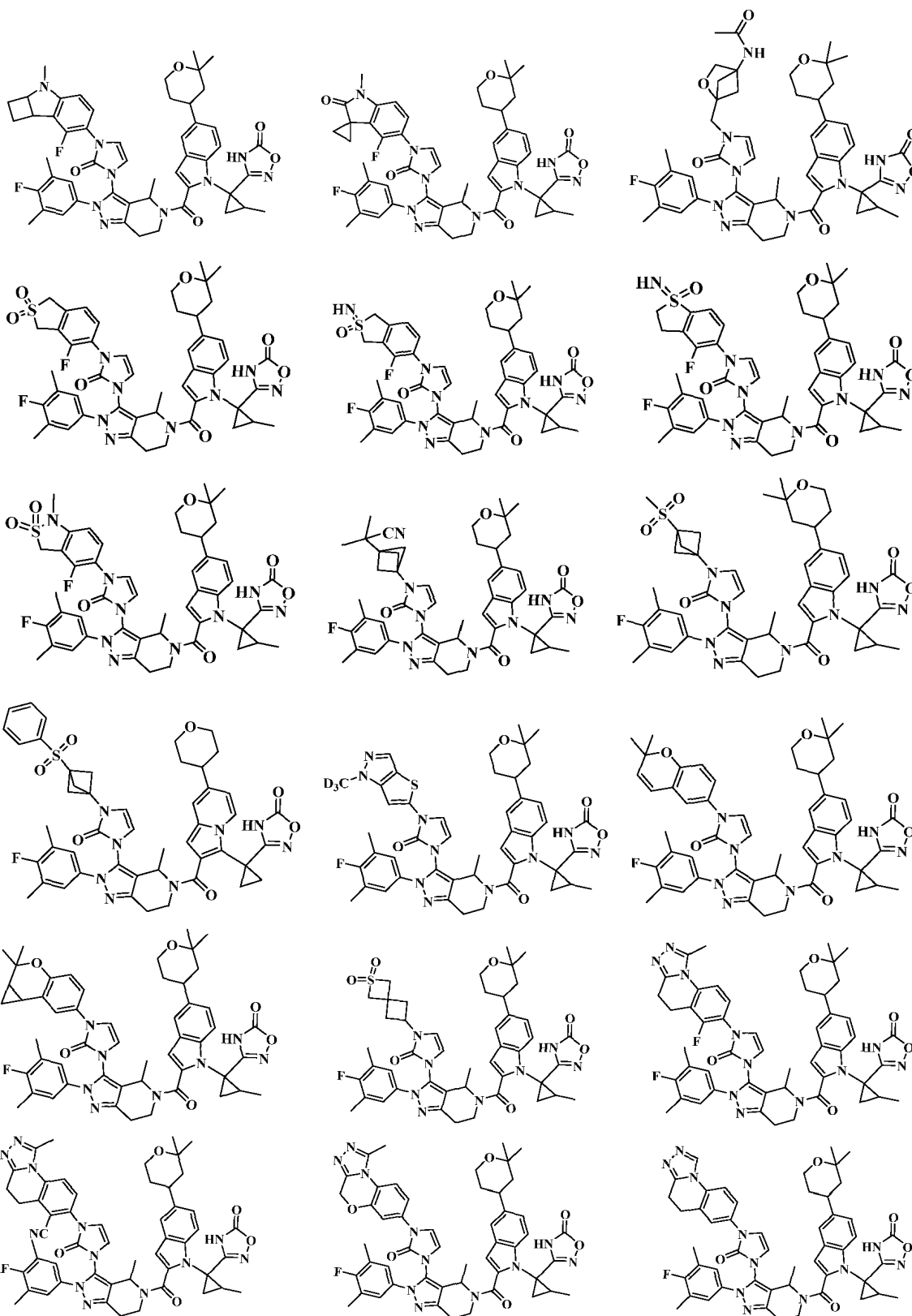


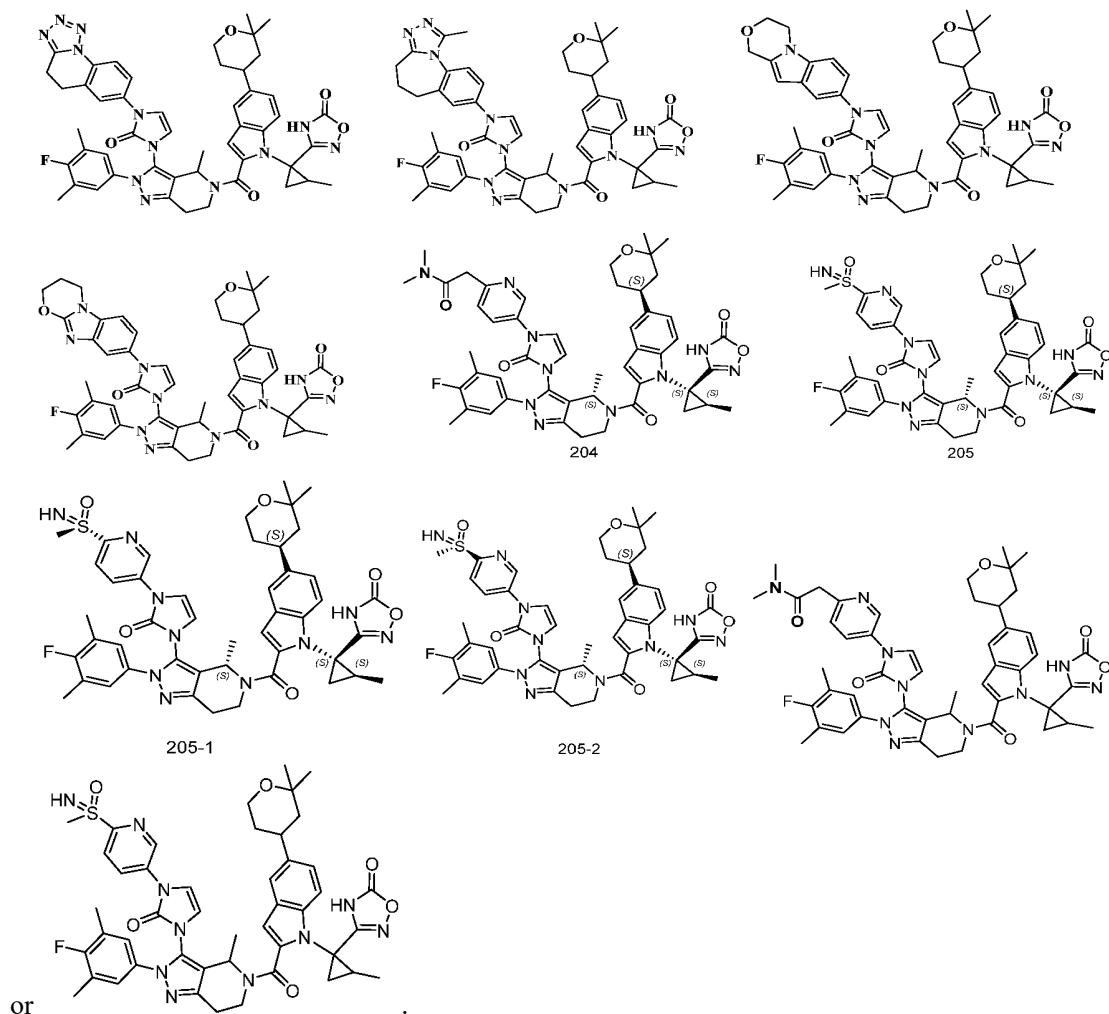
136



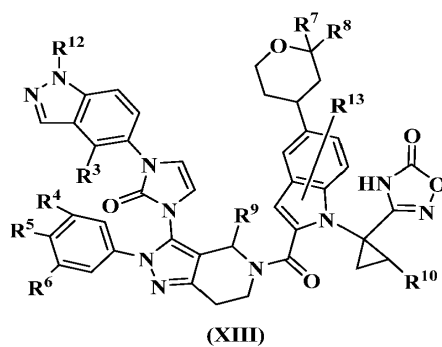
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28. A compound represented by general formula (XIII), or a stereoisomer or a pharmaceutically acceptable salt thereof:



wherein

each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo,

C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ thioalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ thioalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, each R⁴, R⁵ or R⁶ is independently selected from hydrogen, deuterium, halogen, amino,

C₁₋₃ alkyl, C₁₋₃ deutoalkyl or C₁₋₃ haloalkyl;

further preferably, each R⁴, R⁵ or R⁶ is independently further selected from fluorine or methyl;

R³ is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R³ is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 8-membered heteroaryl, -NS(O)R_{a1}R_{b1}, -(CH₂)_{n1}S(O)NR_{a2}R_{b2}, -P(O)R_{a3}R_{b3} or -NR_{a5}S(O)NR_{a4}R_{b4}, wherein the amino, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, -NS(O)R_{a1}R_{b1}, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 8-membered heteroaryl;

more preferably, R^3 is hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, $-NS(O)R_{a1}R_{b1}$, $-(CH_2)_nS(O)NR_{a2}R_{b2}$, $-P(O)R_{a3}R_{b3}$ or $-NR_{a5}S(O)NR_{a4}R_{b4}$, wherein the amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl or C_{1-3} haloalkyl is optionally further substituted with one or more substituents selected from halogen, $-NS(O)R_{a1}R_{b1}$ or C_{1-3} alkyl;

5 each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, amino, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to
10 which they are each attached form C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl
15 or 5- to 10-membered heteroaryl;

preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen, amino, C_{1-3} alkyl, C_{1-3} deuterioalkyl or C_{1-3} haloalkyl;

further preferably, each R_{a1} , R_{b1} , R_{a2} , R_{b2} , R_{a3} , R_{b3} , R_{a4} or R_{b4} is independently selected from hydrogen, deuterium, halogen or methyl;

20 alternatively, R_{a1} and R_{b1} , R_{a2} and R_{b2} , R_{a3} and R_{b3} , and R_{a4} and R_{b4} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl, 3- to 6-membered heterocyclyl, C_{6-10} aryl or 5- to 8-membered heteroaryl;

preferably, R_{a2} and R_{b2} , and R_{a3} and R_{b3} together with adjacent atom(s) to which they are each attached form C_{3-8} cycloalkyl or 3- to 6-membered heterocyclyl containing 1 to 3 heteroatoms;

25 each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C_{1-6} alkyl, C_{1-6} deuterioalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl,
30 C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl or 5- to 10-membered heteroaryl;

preferably, each R^7 , R^8 , R^9 or R^{10} is independently selected from hydrogen, deuterium, halogen, C_{1-3} alkyl, C_{1-3} deuterioalkyl or C_{1-3} haloalkyl;

further preferably, each R⁷, R⁸, R⁹ or R¹⁰ is independently selected from methyl;

R¹² is selected from hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹² is hydrogen, deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R¹² is methyl;

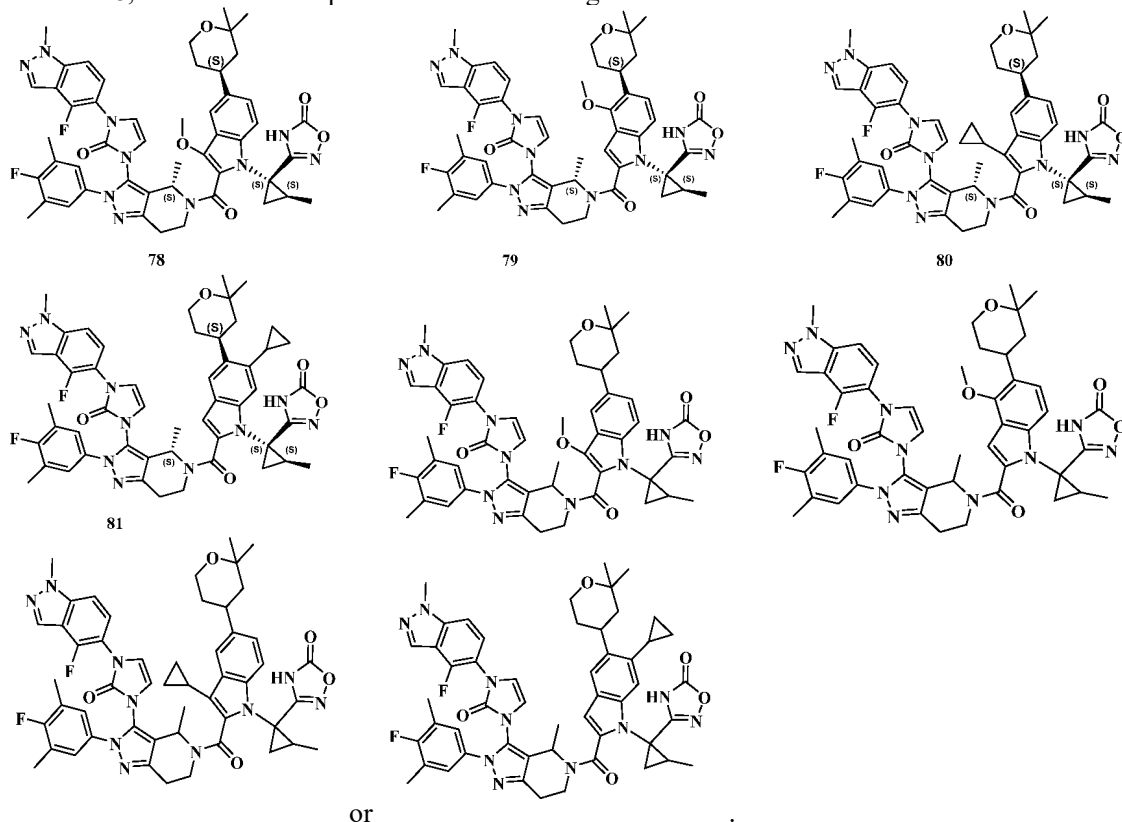
R¹³ is selected from deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₆ alkyl, C₁₋₆ deutoalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 3- to 8-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

preferably, R¹³ is deuterium, halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, which is optionally further substituted with one or more substituents selected from halogen, amino, nitro, hydroxyl, cyano, oxo, C₁₋₃ alkyl, C₁₋₃ deutoalkyl, C₁₋₃ haloalkyl, C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, 3- to 6-membered heterocyclyl, C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

further preferably, R¹³ is methoxy or cyclopropyl;

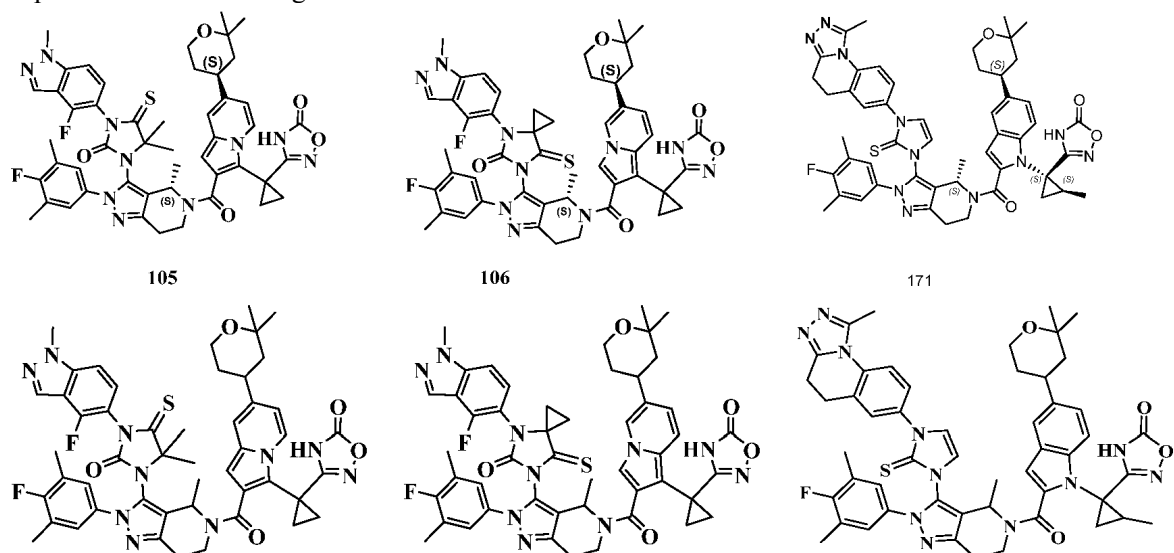
n₁ is an integer from 0 to 5.

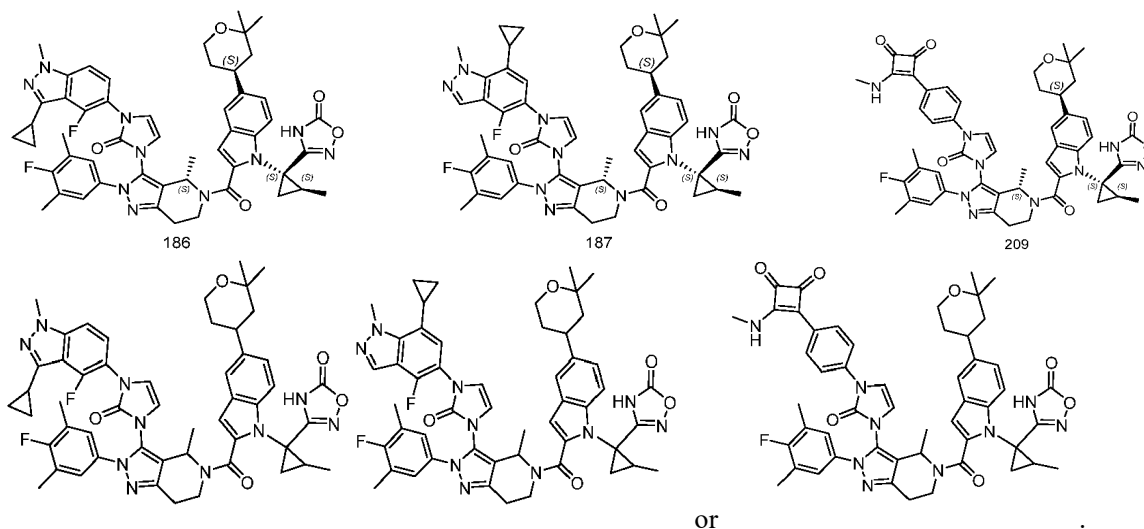
29. The compound, or the stereoisomer or the pharmaceutically acceptable salt thereof according to claim 28, wherein the compound has the following structure:



5

30. A compound, or a stereoisomer or a pharmaceutically acceptable salt thereof, wherein the compound has the following structure:





31. A pharmaceutical composition comprising a therapeutically effective dose of the compound,
 5 or the stereoisomer or the pharmaceutically acceptable salt thereof according to any one of claims 1 to 30,
 and one or more pharmaceutically acceptable carriers or excipients.

32. Use of the compound, or the stereoisomer or the pharmaceutically acceptable salt thereof
 according to any one of claims 1 to 30, or the pharmaceutical composition according to claim 31 in the
 10 preparation of a GLP-1 receptor agonist drug.

33. Use of the compound, or the stereoisomer or the pharmaceutically acceptable salt thereof
 according to any one of claims 1 to 30, or the pharmaceutical composition according to claim 32 in the
 preparation of a drug for treating a metabolic-related disease, wherein the disease is selected from diabetes,
 15 obesity or non-alcoholic steatohepatitis related diseases or other related diseases caused by diabetes, obesity
 or non-alcoholic steatohepatitis.

TRANSLATION CERTIFICATION

Date: April 20, 2025

To whom it may concern:

This is to certify that the attached translation is an accurate representation of the documents CN202311372605.9 filed October 20, 2023, which is a certified copy of priority document of PCT/CN2024/108192, received by this office. The translation was completed from:

- Simplified Chinese

To:

- English

Wenli ZHANG, Senior Reviser in RWS, attests to the following:

“To the best of my knowledge, the aforementioned documents are a true, full and accurate translation of the specified documents.”

Wen Li Zhang

Signature of Wenli ZHANG