

PHARMACEUTICAL COMPOSITION HAVING IMPROVED PHARMACOKINETIC PROPERTIES

TECHNICAL FIELD

The present invention belongs to the technical field of medicine, and particularly relates to an alkyl glycoside-containing pharmaceutical composition with improved pharmacokinetic (PK) properties and an application thereof.

BACKGROUND

Migraine, as a common neurovascular disease, is mainly manifested as a recurrent and generally unilateral moderate and severe pulsatile headache, which usually lasts for 4 to 72 hours, accompanied by symptoms such as nausea, vomiting, and sensitivity to sound and light (intolerance of sound and light) [1]. Patients often go through a period of sensory disturbance before the migraine attack, this kind of migraine is called migraine with aura, and 1/7 patients with the migraine in China have aura symptoms [2]. Main aura types comprise visual disorders such as dark spots, bright spots and flashes, and symptoms such as abnormal sense of smell, dizziness, tinnitus and difficulty in language expression. At present, more than 1 billion people in the world are affected by the migraine [3]. A consultation rate of patients with the migraine in China is only 52.9%, a correct diagnosis rate of doctors is only 13.8%, and there are widespread situations such as insufficient preventive treatment and excessive use of analgesic drugs [2]. The migraine attack may last for hours or even days, and may seriously affect normal daily activities, so that there is a significant demand for an acute therapy capable of quickly relieving the migraine. In recent years, with the research progress of the migraine at home and abroad, new therapeutic targets such as a calcitonin gene-related peptide (CGRP) have emerged, thereby enriching therapeutic methods for the migraine.

The calcitonin gene-related peptide (CGRP) is a polypeptide composed of 37 amino acids, in which an N-terminal disulfide bond and an aminated C-terminal play an important role in activating a receptor [4]. The CGRP is mainly located in a c fiber and an A δ fiber in a trigeminal ganglion and a dorsal root ganglion, and in a central nervous system [5]. There are two forms of CGRPs in human body, which are α -CGRP and β -CGRP, with a difference of only 1-3 amino acids in different species, wherein, the α -CGRP is highly expressed in a sensory neuron, while the β -CGRP mainly plays a role in an enteric nervous system [6]. The CGRP exerts its biological function by binding to a membrane receptor. A CGRP receptor is mainly composed of a calcitonin receptor-like receptor (CLR) and a receptor activity modifying protein 1 (RAMP1), and in addition, a receptor component protein (RCP) is also needed to play a role of signal transmission [7]. The CGRP mainly plays a role of vasodilatation in vivo, and studies suggest that the CGRP plays an important role in the occurrence and development of the migraine. Clinical evidences show that a CGRP content in the jugular vein of the patients with the migraine is increased during the attack, and the intravenous injection with the CGRP may cause moderate to severe migraine attacks, and the use of a CGRP antagonist can relieve the pain and related symptoms of the migraine [4].

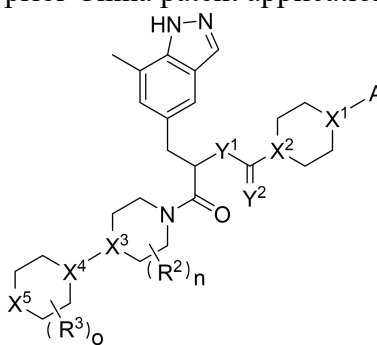
At present, specific methods for acute-stage treatment in guidelines for migraine diagnosis and treatment comprise triptans, ergotamines, ditans and gepants [2]. Triptan drugs are 5-HT_{1B/1D} receptor agonists, which have been widely used in the acute treatment of the migraine in the past twenty years. The triptan drugs have high evidence and recommendation levels in the guidelines, but there is also an obvious cardiovascular risk, and there are also many cases such as a low response rate of the patients. Ditan drugs are 5-HT_{1F} receptor agonists, which cause no adverse

reaction of vasoconstriction in the triptan drugs, but the ditan drugs have an inhibitory effect on the central nervous system [8]. Gepant drugs - antagonists developed for the CGRP receptor are a new treatment method for the migraine, without the cardiovascular risk and the central inhibition effect [7], which provide a new selection for patients who do not respond to the triptan drugs and the ditan drugs. At present, marketed gepant drugs developed for the CGRP receptor comprise ubrogepant and atogepant from AbbVie, and rimegepant from Pfizer. These three drugs are all oral tablets, and the patients with the migraine often have symptoms such as nausea and vomiting, so that the feasibility of oral administration is low at this time. Moreover, the migraine attack lasts for a long time, which severely affects the daily life. A novel drug zavegepant (vazegepant) from Pfizer was marketed in the United States in March 2023 in a marketed dosage form of nasal spray for approved indication of acute treatment of adult migraine with or without aura. However, the drug cannot be used for prevention of the migraine, and causes the most common adverse reactions (an effect of at least 2% ZAVZPRET is greater than that of placebo in treatment of the patients) such as taste disorder, nausea, nasal discomfort and vomiting.

BMS disclosed and protected a compound structure of Zavegepant in CN102834388B applied in 2011. BMS also disclosed a series of heterocyclic CGRP antagonists related to the Zavegepant structure for treatment of the migraine in CN100558728C, CN100558428C, CN1914193A, CN1972929A and other related patents applied in 2003-2005.

Boehringer Ingelheim also disclosed a CGRP antagonist in CN101146799A and WO2005084672A applied in 2005-2006 respectively, and the antagonist was expected to be applied in treatment of pain and other related diseases.

Considering a current treatment status of migraine and neuropathic pain, in order to meet and enrich clinical needs, there is still a demand for a compound with a novel structure for specific treatment of migraine and neuropathic headache. The applicant of the present invention provides a CGRP antagonist compound (referred to as "a compound as represented by formula I") with a novel structure as shown in formula I in the prior China patent application CN202310479996.8 and



the PCT application PCT/CN2024/090110:

(I), and the prior related

patent applications have shown that the compound as represented by formula I can effectively inhibit the generation of cAMP stimulated by CGRP, so that the compound may be used as the CGRP antagonist to prevent, alleviate or treat CGRP-related diseases, especially the migraine or the neuropathic pain. In particular, the compound as represented by formula I has a lower IC₅₀ value, especially some specific structural compounds with common characteristics have a significantly lower IC₅₀ value, which can reach a pM level. Other experimental data show that the compound as represented by formula I also has good liver microsome stability, lower expected potential side effects and better pharmacokinetic properties.

The migraine and the neuropathic headache are acute pains, and patients often expect to get a drug with rapid onset and high safety to control, alleviate and treat the pains quickly. Therefore, measures of improving the pharmacokinetic properties of the drug, such as obtaining shorter T_{max}, to shorten time to peak of the drug, so as to take effect quickly, increasing C_{max} and AUC to improve a bioavailability, and reducing a drug dosage and improving a medication safety are all of great clinical significance for migraine and pain indications.

In practical application, not all active molecules have high bioavailability, fast time to peak and consequent fast onset of action after administration, and these pharmacokinetic properties depend on physical and chemical properties and biological properties of active pharmaceutical molecules. The use of a penetration enhancer is one of the means of drug delivery, but PK improvement effects after penetration enhancement are different based on different active pharmaceutical molecules, which are often unpredictable, and it is rare to see that the application of a single penetration enhancer achieves simultaneous and significant improvement on multiple PK properties.

The alkyl glucoside is one of the optional penetration enhancers. The published Chinese patent applications CN201780081719.4, CN201780044057.3, CN200980157305.0, CN201180053436.1 and CN201980001004.2 respectively disclose a study on improving the PK properties by combining the alkyl glucoside with different pharmaceutical active molecules, and these results demonstrate that different pharmaceutical active molecules lead to different PK improvement results. For example, based on a preliminary comparison before and after combined use with the alkyl glycoside: for C_{max} , some active molecules show no change with or without the combined use with the alkyl glycoside, while C_{max} values of some active molecules can be increased by approximately 3-fold; for AUC, many active molecules show no change with or without the combined use with the alkyl glycoside, or AUC values of the active molecules are slightly increased by approximately 1.5-fold after the combined use with the alkyl glycoside; and for T_{max} , T_{max} values of some active molecules are extended by approximately 2-fold after the combined use with the alkyl glycoside, while T_{max} of some active molecules can be shortened after the combined use with the alkyl glycoside. Therefore, it is unpredictable how the combined use of the active pharmaceutical molecules with the alkyl glycoside will affect the PK properties.

On the above basis, it is still of great practical significance to further optimize and improve the PK properties of the CGRP antagonist, such as compounds as represented by formula I described in the Chinese patent application CN202310479996.8 and the PCT application PCT/CN2024/090110, and compounds with similar activities in the prior arts, such as zavegepant, rimegepant, ubrogepant, atogepant, telcagepant and olcegepant, so as to meet special clinical needs of the migraine and the neuropathic headache.

SUMMARY

The primary objective of the present invention is to improve PK properties of a CGRP antagonist, such as compounds as represented by formula I described in the Chinese patent application CN202310479996.8 and the PCT application PCT/CN2024/090110.

It is unexpectedly found by the inventor of the present application in the follow-up study on the compound as represented by formula I that, when the compound as represented by formula I is used in combination with an alkyl glycoside, many PK properties, such as C_{max} , AUC and T_{max} , can be surprisingly significantly and/or simultaneously improved. The significant improvement of these PK properties, especially the synchronous and significant improvement, has particularly important clinical significance and value for emergency treatment, alleviation and prevention of migraine and neuropathic headache indications of the compound as represented by formula I.

Based on the above primary objective and the corresponding unexpected discovery, the present invention firstly provides a pharmaceutical composition, which comprises a. an active ingredient and b. an alkyl glycoside, and the active ingredient is preferably the compound as represented by formula I in the present invention (comprising an isomer, pharmaceutically acceptable salt or solvate thereof). As confirmed by experimental results provided in examples of the present application, combined use of the compound as represented by formula I with the alkyl glycoside can significantly improve many PK properties of the active ingredient, for example, compared with a pharmaceutical composition without adding b. alkyl glycoside, the pharmaceutical composition

provides 10-fold or more, 30-fold or more, 10-fold to 52.2-fold, or 30-fold to 52.2-fold $C_{\max}$ value of the active ingredient, and/or provides 5.1-fold or more, 8.6-fold or more, 5.1-fold to 17.1-fold, or 8.6-fold to 17.1-fold $AUC_{0-\infty}$ value of the active ingredient, and/or provides a $T_{\max}$ value which is shortened to 0.17 hour or less. Because the $C_{\max}$ value is greatly increased and the $T_{\max}$ value is reduced from 1 hour to below 0.17 hour (about 10 minutes), time to peak is shortened by 83.3%, which means that the pharmaceutical composition may take effect rapidly after administration, thereby treating, alleviating or preventing acute attacks of migraine and neuropathic headache. The substantial increases of the $C_{\max}$ value and the $AUC_{0-\infty}$ value are conducive to further reducing a drug dosage, thereby achieving a low-dose and high-efficiency effect, and reducing a medication safety risk.

In the pharmaceutical composition of the present invention, both of a weight percentage of the active ingredient in the pharmaceutical composition and a content of the active ingredient in the pharmaceutical composition may be selected as required, and generally, the weight percentage of the active ingredient may be in a range of 0.05%-20%, and the content of the active ingredient may be 0.001 mg-1000 mg.

In the pharmaceutical composition of the present invention, the alkyl glycoside is mainly formed by covalently coupling a hydrophobic alkyl carbon chain and a hydrophilic oligosaccharide. In some embodiments, the covalently coupled linking group comprises a glycosidic bond, a thioglycosidic bond or an amide bond. In other embodiments, the hydrophobic alkyl carbon chain is selected from a C_5 - C_{16} alkyl chain, a C_{10} - C_{16} alkyl chain, a C_{11} - C_{14} alkyl chain, a C_{11} alkyl chain, a C_{12} alkyl chain, a C_{13} alkyl chain or a C_{14} alkyl chain. In other embodiments, the hydrophilic oligosaccharide comprises a monosaccharide or a disaccharide, wherein the monosaccharide comprises glucose, and the disaccharide comprises maltose, trehalose or sucrose. In other embodiments, the alkyl glycoside is an undecyl maltoside, a dodecyl maltoside, a tridecyl maltoside or a tetradecyl maltoside.

In some more specific embodiments of the present invention, a weight percentage of the alkyl glycoside in the pharmaceutical composition is optionally 0.05%-20%, 0.05%-10%, 0.05%-5%, 0.1%-5%, 0.1%-0.5%, 0.1%-0.3%, 0.05%, 0.2% or 5%. All types of alkyl glucosides may be selected and used with reference to this weight percentage, especially when the alkyl glucoside is specifically an undecyl maltoside, a dodecyl maltoside, a tridecyl maltoside or a tetradecyl maltoside, and the weight percentage of the alkyl glucoside in the pharmaceutical composition is optionally 0.05%-20%, 0.05%-10%, 0.05%-5%, 0.1%-5%, 0.1%-0.5%, 0.1%-0.3%, 0.05%, 0.2% or 5%.

The pharmaceutical composition provided by the present invention may be prepared into any administration form, comprising, but being not limited to, a nasal administration form, an oral administration form, a transdermal administration form or a mucosal administration form. The pharmaceutical composition is particularly and preferably in the nasal administration form, comprising a nasal drop, a nasal pressurized spray, a nasal spray, a nasal aerosol, a nasal gel, a nasal cream, and the like. Oral administration often fails to meet a requirement of rapid onset because of disintegration, dissolution, absorption and other processes of a drug after the drug enters a gastrointestinal tract, especially for drugs susceptible to food effects. Injection administration enables a drug to take effect rapidly, but patients usually cannot take drugs by themselves, and must go to hospitals or clinics and other places with medical conditions to be administered with the drugs by professionals. However, the migraine and the neuropathic headache are acute pains, and may be treated by the nasal administration form, which can avoid the shortcomings of first-pass effect and slow onset of the oral administration, and can also avoid the problems of poor compliance and certain requirements for medical conditions of the injection administration, thereby being especially suitable for the administration of the compound as represented by formula I, and as verified by the present invention, combined nasal administration with the alkyl glucoside

particularly significantly and surprisingly improves the PK properties, which is of great significance for the acute treatment of the migraine and the neuropathic headache.

In some specific embodiments, the nasal administration form is optionally a single dose form, a double dose form or a multi-dose form. As for the nasal spray, a delivery volume of the nasal spray is optionally 50 ul-200 ul/spray. In some more specific embodiments, the pharmaceutical composition is optionally in a solution form, and further optionally in an aqueous solution form.

In some specific embodiments, the pharmaceutical composition may be in a sterile or non-sterile form.

The present invention further provides other optional technical solutions, in these technical solutions, the pharmaceutical composition provided may or may not be added with other types of pharmaceutical excipients as required, comprising, but being not limited to, one or a combination of two or more of a buffer, an osmotic pressure regulator, a wetting agent, a thickening agent, a pH regulator, a metal chelating agent and a preservative.

In addition to discovering the surprisingly significant improvement effect of the combined use of the alkyl glucoside and the compound as represented by formula I on the PK properties, it is further unexpectedly found by the inventor that many CGRP antagonist drugs of the same class as the compound as represented by formula I in the market or under study, especially gepant-class CGRP antagonist drugs such as zavegepant, also have a certain improvement effect on the PK properties after combined nasal administration with the alkyl glucoside, wherein the C_{max} is increased by 2.7-fold and the AUC is increased by 5.4-fold. This effect is completely unexpected, because according to the description in CN202180077330.9, after combined oral administration of zavegepant with the alkyl glucoside, the C_{max} and the AUC have no obvious changes, but the T_{max} is prolonged to some extent.

On the basis of this discovery, another objective of the present invention is to provide a preparation for nasal administration, which comprises a CGRP antagonist and an alkyl glycoside, wherein the CGRP antagonist is a gepant-class CGRP antagonist drug, such as comprising, but being not limited to, zavegepant, rimegepant, ubrogepant, atogepant, telcagepant, olcegepant, or the compound as represented by formula I according to any one of items of the present invention.

In some specific embodiments, the alkyl glycoside in the preparation for nasal administration provided is mainly formed by covalently coupling a hydrophobic alkyl carbon chain and a hydrophilic oligosaccharide. In some embodiments, the covalently coupled linking group comprises a glycosidic bond, a thioglycosidic bond or an amide bond. In some embodiments, the hydrophobic alkyl carbon chain is selected from a C_5 - C_{16} alkyl chain, a C_{10} - C_{16} alkyl chain, a C_{11} - C_{14} alkyl chain, a C_{11} alkyl chain, a C_{12} alkyl chain, a C_{13} alkyl chain or a C_{14} alkyl chain. In some embodiments, the hydrophilic oligosaccharide comprises a monosaccharide or a disaccharide, wherein the monosaccharide comprises glucose, and the disaccharide comprises maltose, trehalose or sucrose. In some embodiments, the alkyl glycoside is an undecyl maltoside, a dodecyl maltoside, a tridecyl maltoside or a tetradecyl maltoside. In some embodiments, a weight percentage of the alkyl glycoside in the pharmaceutical composition is optionally 0.05%-20%, 0.05%-10%, 0.05%-5%, 0.1%-5%, 0.1%-0.5%, 0.1%-0.3%, 0.05%, 0.2% or 5%.

In some specific embodiments, the present invention further provides a use of the pharmaceutical composition or the preparation for nasal administration of the present invention as a CGRP antagonist.

In some specific embodiments, the present invention provides a use of the pharmaceutical composition or the preparation for nasal administration of the present invention in preparation of a drug for preventing, treating or alleviating a CGRP-mediated disease, wherein the disease comprises a migraine and a neuropathic pain. Correspondingly, the present invention further

Detailed description of the invention

Compound as represented by formula I:

(I)

or, two R² form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R² attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R² attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

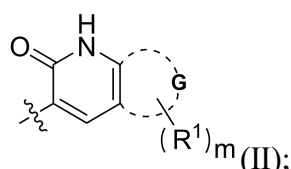
or, $-(R^2)_n$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^2)_n$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

R^3 is independently -H, $-(C_1-C_6)$ alkyl or $-(C_3-C_8)$ cycloalkyl when occurring each time, and o is 0, 1, 2, 3, 4, 5 or 6,

or, two R^3 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^3 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, $-(R^3)_o$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^3)_o$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

A has a structure as represented by the following formula II:



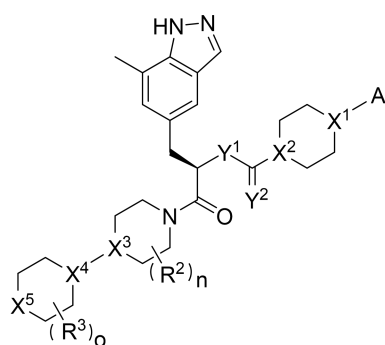
a G-chain group forms a 5-7 membered aliphatic ring or aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, and ring-forming heteroatoms in the aliphatic heterocyclic ring are -O-, -S- or $-\overset{\text{O}}{\parallel}{\text{S}}-$;

R^1 is independently -H, $-(C_1-C_6)$ alkyl or $-(C_3-C_8)$ cycloalkyl when occurring each time, and m is 0, 1, 2, 3, 4, 5 or 6,

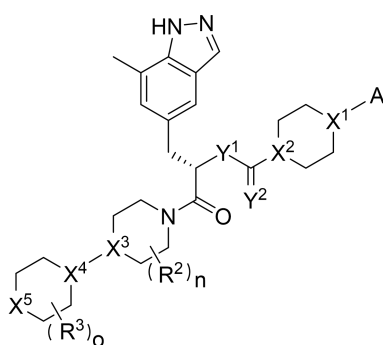
or, two R^1 form a 3-8 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^1 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, $-(R^1)_m$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^1)_m$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^1)_m$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S.

In some embodiments, the compound as represented by the formula I of the present invention has a chiral structure as represented by formula I-2 or formula I-3:



(I-2) and

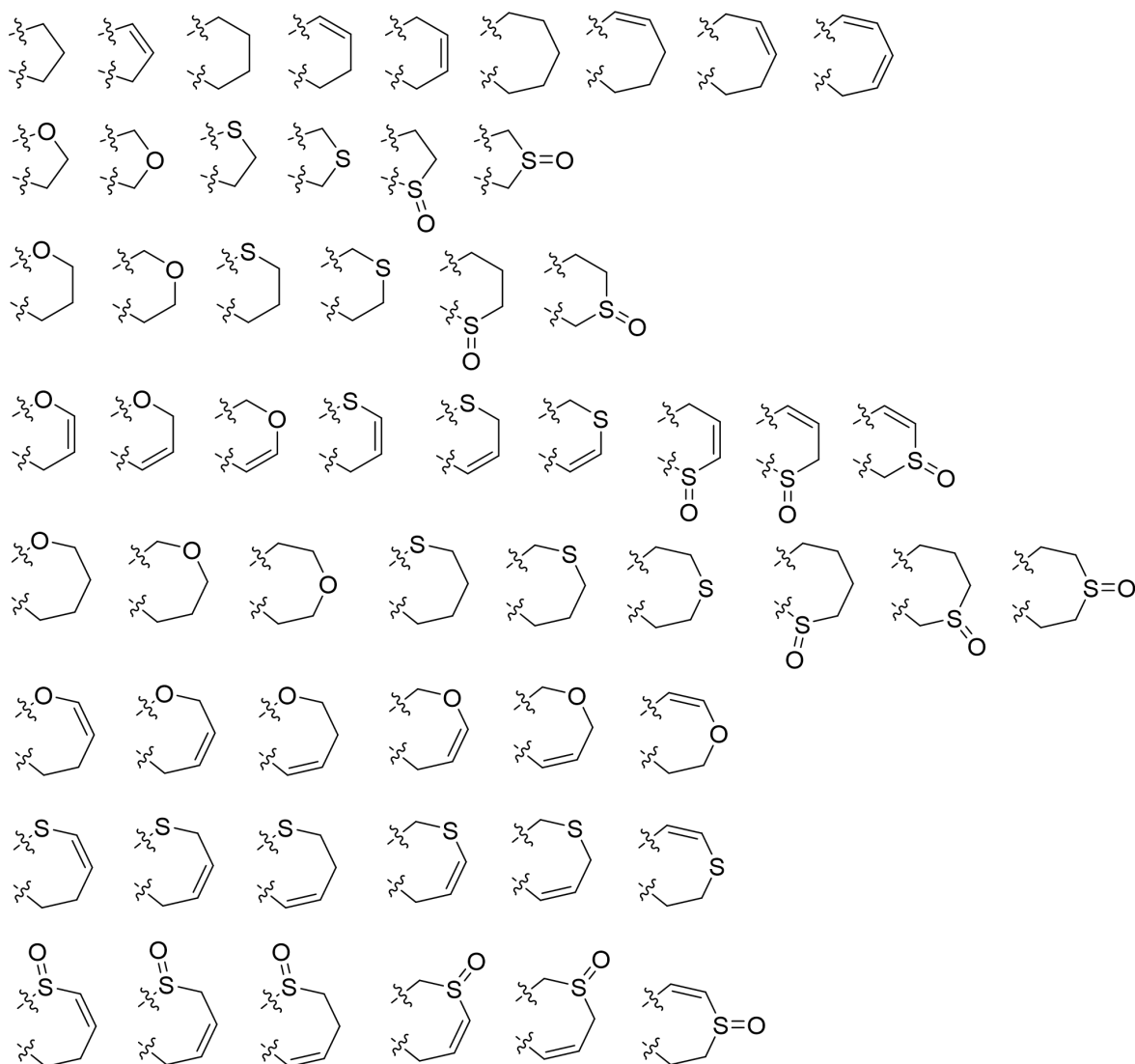


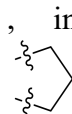
(I-3),

wherein, X^1 , X^2 , X^3 , X^4 , X^5 , Y^1 , Y^2 , A, R^2 , R^3 , n and o are as defined above.

In some embodiments, a further selection is made for an A group in the compound as represented by formula I, I-2 or I-3 as follows:

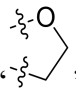
selection of the G-chain group in A: for example, the G-chain group forms a 5 or 6 membered aliphatic ring together with the two carbon atoms to which the G-chain group attaches, and the G-chain group optionally has 0 or 1 double bond, and the remaining bonds are all single bonds; for example, the G-chain group forms a 7 membered aliphatic ring together with the two carbon atoms to which the G-chain group attaches, and the G-chain group optionally has 0, 1 or 2 double bonds, and the remaining bonds are all single bonds; for example, the G-chain group forms a 5 membered aliphatic heterocyclic ring together with the two carbon atoms to which the G-chain group attaches, and bonds on the G-chain group are all single bonds; and for example, the G-chain group forms a 6 or 7 membered aliphatic heterocyclic ring together with the two carbon atoms to which the G-chain group attaches, and the G-chain group optionally has 0 or 1 double bond, and the remaining bonds are all single bonds. In A, the G-chain group may be further specifically selected from:

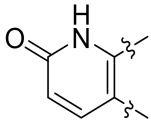


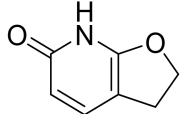
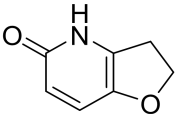
further specific selection of the G-chain group, there are some symmetric groups such as  in

and asymmetric groups such as . Considering an asymmetry of a group attached at two

linking sites of the G-chain group, when the attached asymmetric group is attached, a specific selective structure of the asymmetric group of each G-chain group represents that there are two

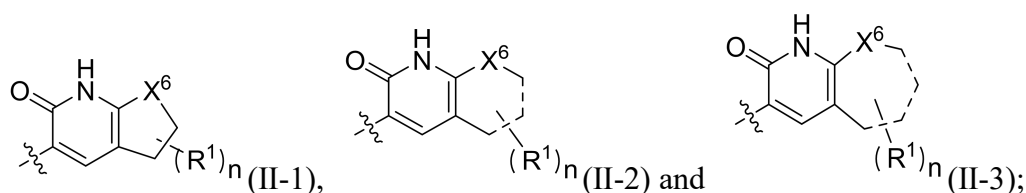
different specific attaching modes, for example, the asymmetric group “” represents two cases “ and ”. As an example, when the attached asymmetric group has an oxo-pyridine

structure , still taking the asymmetric group  of the G-chain group as an example, the two cases represented by the asymmetric group are attached to the oxo-pyridine structure in a

mode of:  or .

Selection of R^1 group in A: R^1 is independently -H, $-(C_1-C_3)$ alkyl or $-(C_3-C_6)$ cycloalkyl when occurring each time, and m is 0, 1, 2 or 3, or, two R^1 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^1 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S, or, $-(R^1)_m$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^1)_m$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^1)_m$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S. Further selection of R^1 group: R^1 is independently -H, methyl, ethyl or cyclopropyl when occurring each time, and m is 0, 1 or 2, or, two R^1 form cyclopropane, cyclobutane or cyclopentane together with atoms to which R^1 attach, and the cyclopropane, the cyclobutane or the cyclopentane forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attach, or, $-(R^1)_m$ forms cyclopropane, cyclobutane or cyclopentane together with atoms to which $-(R^1)_m$ attach, and the cyclopropane, the cyclobutane or the cyclopentane forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^1)_m$ attach.

According to the embodiments of the present invention, the A group preferably has a structure as represented by the following formula II-1, II-2 or II-3:



in the formulas II-1, II-2 and II-3, X^6 is -O-, -S- or $-\overset{\text{O}}{\parallel}{\text{S}}-$;

in the formula II-2, two “---” both refer to single bonds, or any one of the two “---” is a double bond and the other one is a single bond; and

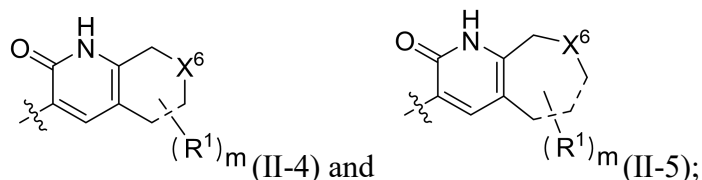
in the formula II-3, three “---” all refer to single bonds, or any one of the three “---” is a double bond and the other two are both single bonds.

When the A group preferably has the structure as represented by the formula II-1, II-2 or II-3, the compound containing the oxo-pyrido-aliphatic ring or aliphatic heterocyclic ring structure provided

by the present invention has a better CGRP antagonistic activity, a lower side reaction and/or a better PK metabolic effect.

As is verified by embodiments of the present invention that, compared with a case that Y^2 is O, when Y^2 is S, a compound in which X^6 is -S- usually has a better CGRP antagonistic activity. Therefore, in one embodiment, Y^2 is S, and X^6 is -S-.

According to the examples of the present invention, the A group may further preferably have a structure as represented by the following formula II-4 or II-5:



in the formula II-4 or II-5, X^6 is -O-, -S- or $\text{---}\overset{\text{O}}{\parallel}\text{S---}$;

in the formula II-4, “---” refers to a single bond or a double bond; and

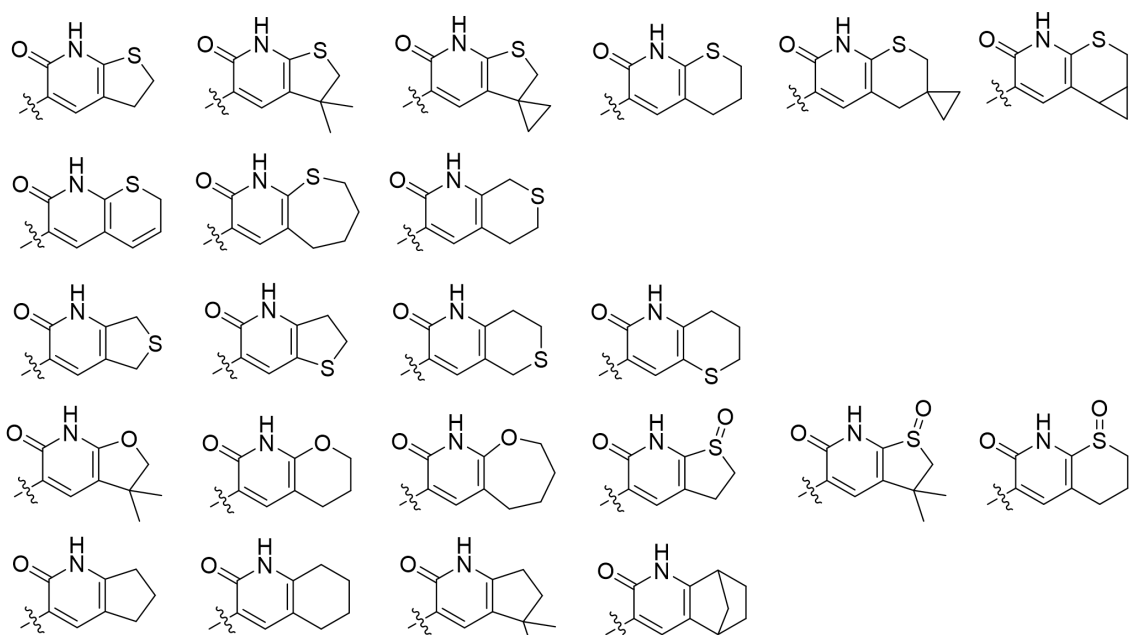
in the formula II-5, two “---” both refer to single bonds, or any one of the two “---” is a double bond and the other one is a single bond.

As is verified by embodiments of the present invention, when the position of the heteroatom X^6 in A is gradually far away from the -NH- group in A, the CGRP antagonistic activity of the compound tends to decrease. However, when the heteroatom X^6 is on a larger ring, such as a 6 membered ring or a 7 membered ring, even if the heteroatom X^6 is in a position as shown in the II-4 or II-5, the CGRP antagonistic activity of the compound is still in an acceptable range at this time.

According to the examples of the present invention, when the G-chain group in A forms the aliphatic ring together with the two carbon atoms to which the G-chain group attaches, the aliphatic ring is preferably unsubstituted.

In one embodiment, the G-chain group in A forms a 5-7 membered aliphatic ring together with two carbon atoms to which the G-chain group attaches, and m is 0.

According to the examples of the present invention, the A group may be specifically selected as follows:



; and the A
from

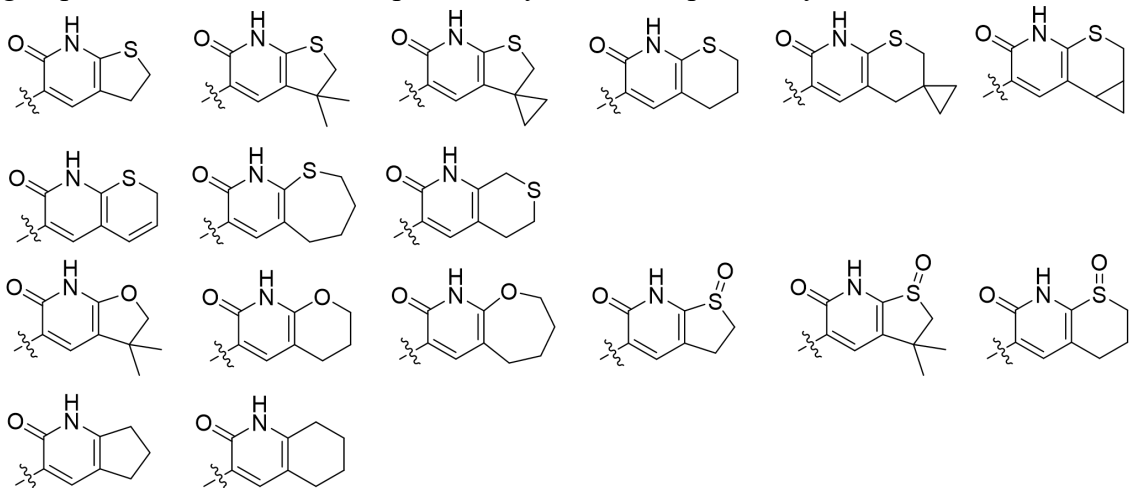
group

is

particularly

preferably

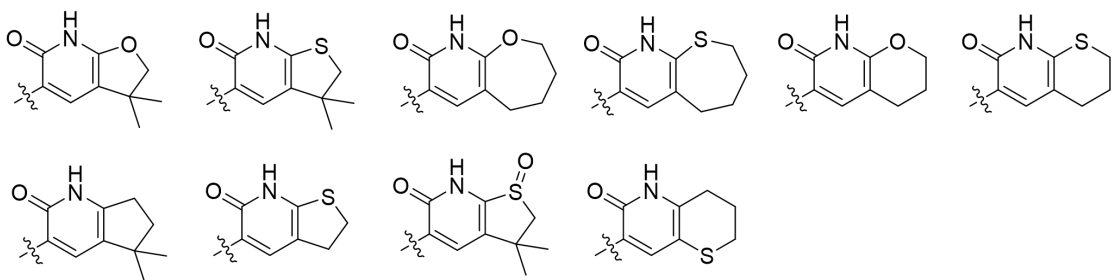
selected



, and based

on the particularly preferred selection of the A group at this time, the compound containing the oxo-pyrido-aliphatic ring or aliphatic heterocyclic ring structure provided by the present invention has a better CGRP antagonistic activity, a lower side reaction and/or a better PK metabolic effect.

According to the examples of the present invention, the A group may be specifically selected as follows:



; and the A
from

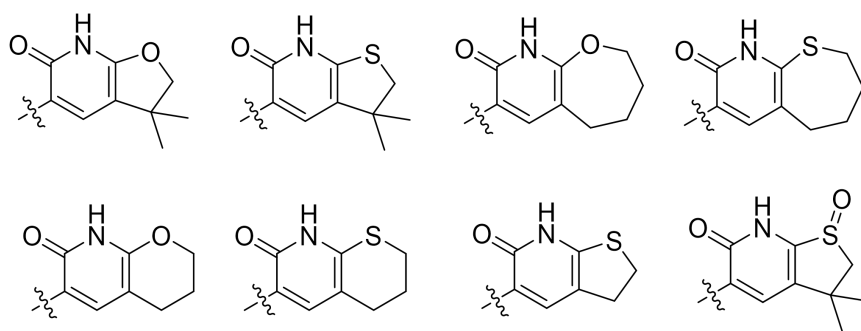
group

is

particularly

preferably

selected



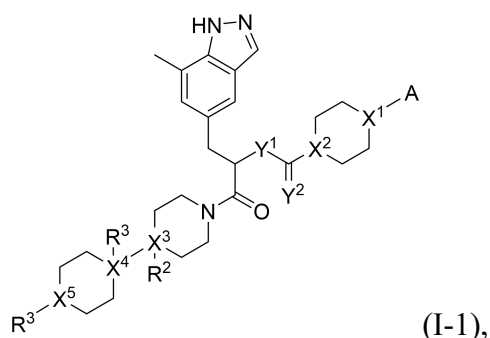
, and based on the particularly preferred selection of the A group at this time, the compound containing the oxo-pyrido-aliphatic ring or aliphatic heterocyclic ring structure provided by the present invention has a better CGRP antagonistic activity, a lower side reaction and/or a better PK metabolic effect.

In other embodiments, further selection of the R^2 group made according to the present invention is as follow: R^2 is independently -H, $-(C_1-C_3)alkyl$ or $-(C_3-C_6)cycloalkyl$ when occurring each time, and n is 0, 1, 2 or 3; or, two R^2 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^2 attach, and ring-carried atoms provided by the two R^2 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^2)_n$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^2)_n$ attach, and ring-carried atoms provided by the $-(R^2)_n$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms. Further selection of R^2 group: R^2 is independently -H, methyl, ethyl, cyclopropyl or cyclobutyl when occurring each time, and n is 0, 1 or 2; or, two R^2 form a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which R^2 attach, and ring-carried atoms provided by the two R^2 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^2)_n$ forms a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which $-(R^2)_n$ attach, and ring-carried atoms provided by the $-(R^2)_n$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms.

In other embodiments, further selection of R^3 group made according to the present invention is as follow: R^3 is independently -H, $-(C_1-C_3)alkyl$ or $-(C_3-C_6)cycloalkyl$ when occurring each time, and n is 0, 1, 2 or 3; or, two R^3 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^3 attach, and ring-carried atoms provided by the two R^3 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^3)_o$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^3)_o$ attach, and ring-carried atoms provided by the $-(R^3)_o$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms. Further selection of R^3 group: R^3 is independently -H, $-(C_1-C_3)alkyl$ or $-(C_3-C_6)cycloalkyl$ when occurring each time, and n is 0, 1, 2 or 3; or, two R^3 form a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which R^3 attach, and ring-carried atoms provided by the two R^3 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^3)_o$ forms a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which $-(R^3)_o$ attach, and

ring-carried atoms provided by the $-(R^3)_o$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms.

In other embodiments, the compound as represented by formula I of the present invention more preferably has a structure as represented by formula I-1:



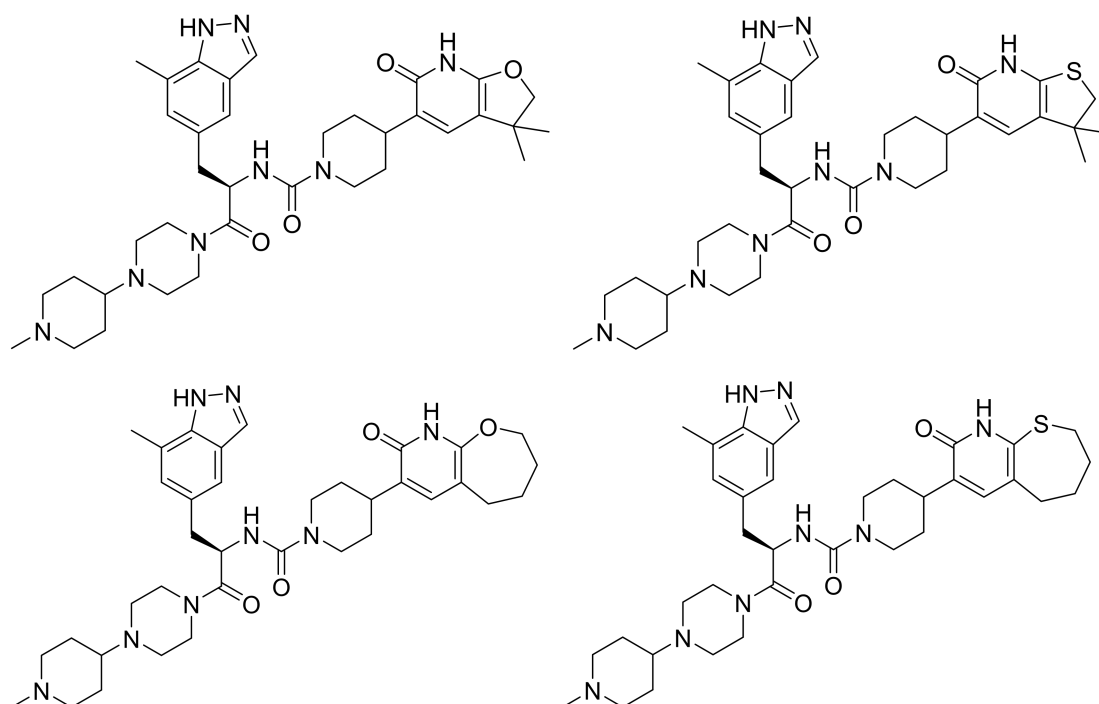
in the formula I-1, X^1 , X^2 , X^3 , X^4 , X^5 , Y^1 , Y^2 and A are optionally as defined in any one of the foregoing items of the present invention when occurring. In the formula I-1, R^2 and R^3 are independently -H, -CH₃ or absent when occurring each time.

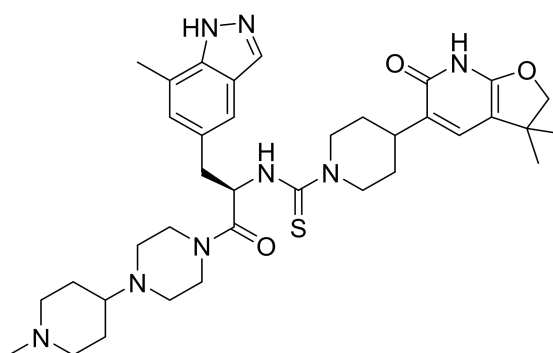
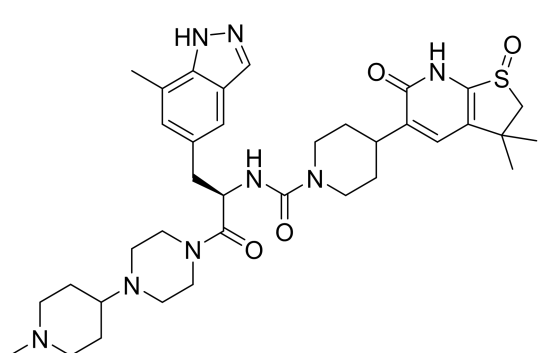
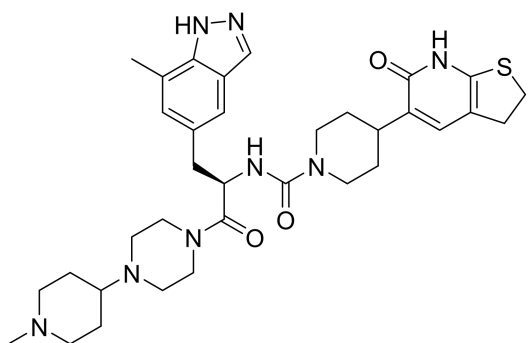
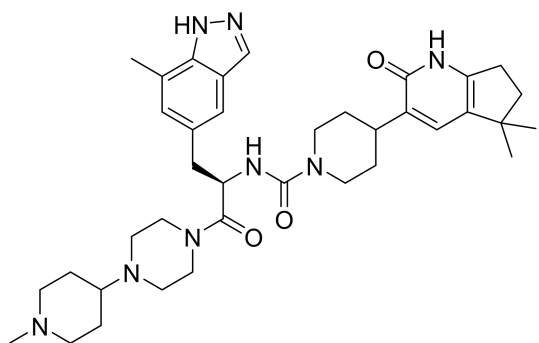
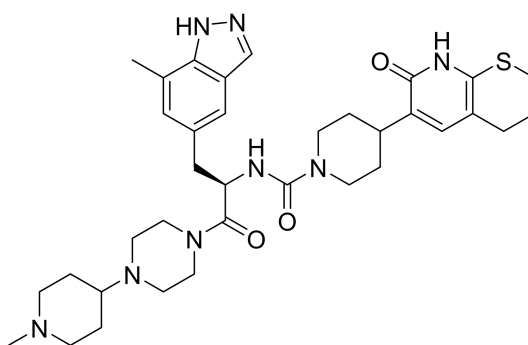
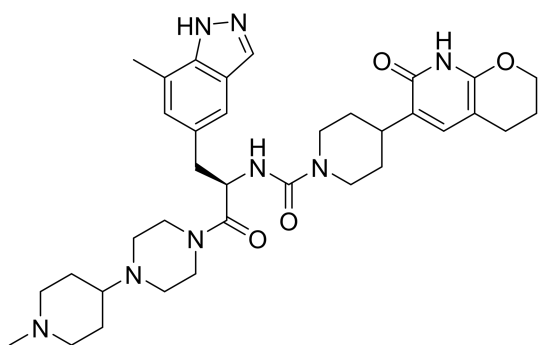
In other embodiments, one or more H in the compound as represented by formula I of the present invention or the more preferred compound as represented by formula I-1 are substituted by D, especially one or more H in the G-chain group or R^1 are substituted by D.

In some embodiments, one or more H in R^3 in the compound as represented by formula I of the present invention, or the more preferred compound as represented by formula I-1, I-2 or I-3 are substituted by D, and in further selection, R^3 attached to X^5 is -CD₃.

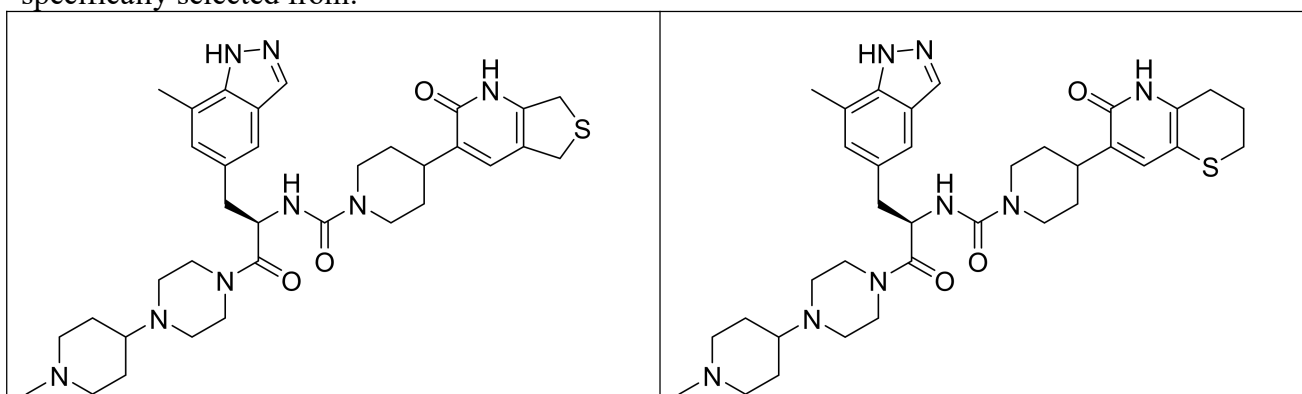
In some embodiments, H on the ring of pyrazole group in indazolyl in the compound as represented by formula I of the present invention, or the more preferred compound as represented by formula I-1, I-2 or I-3 are substituted by D.

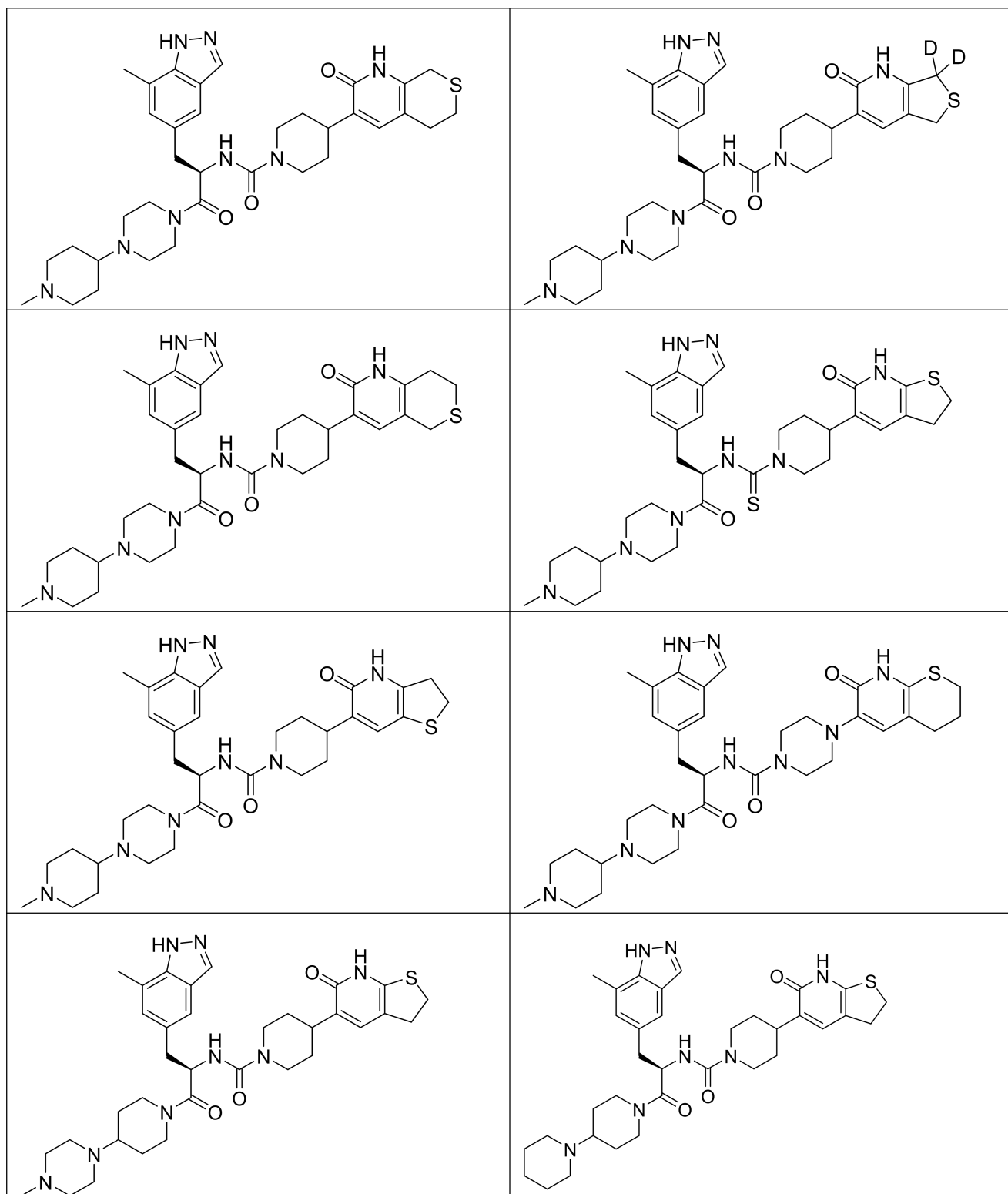
In some embodiments, the compound as represented by formula I of the present invention may be specifically selected from:

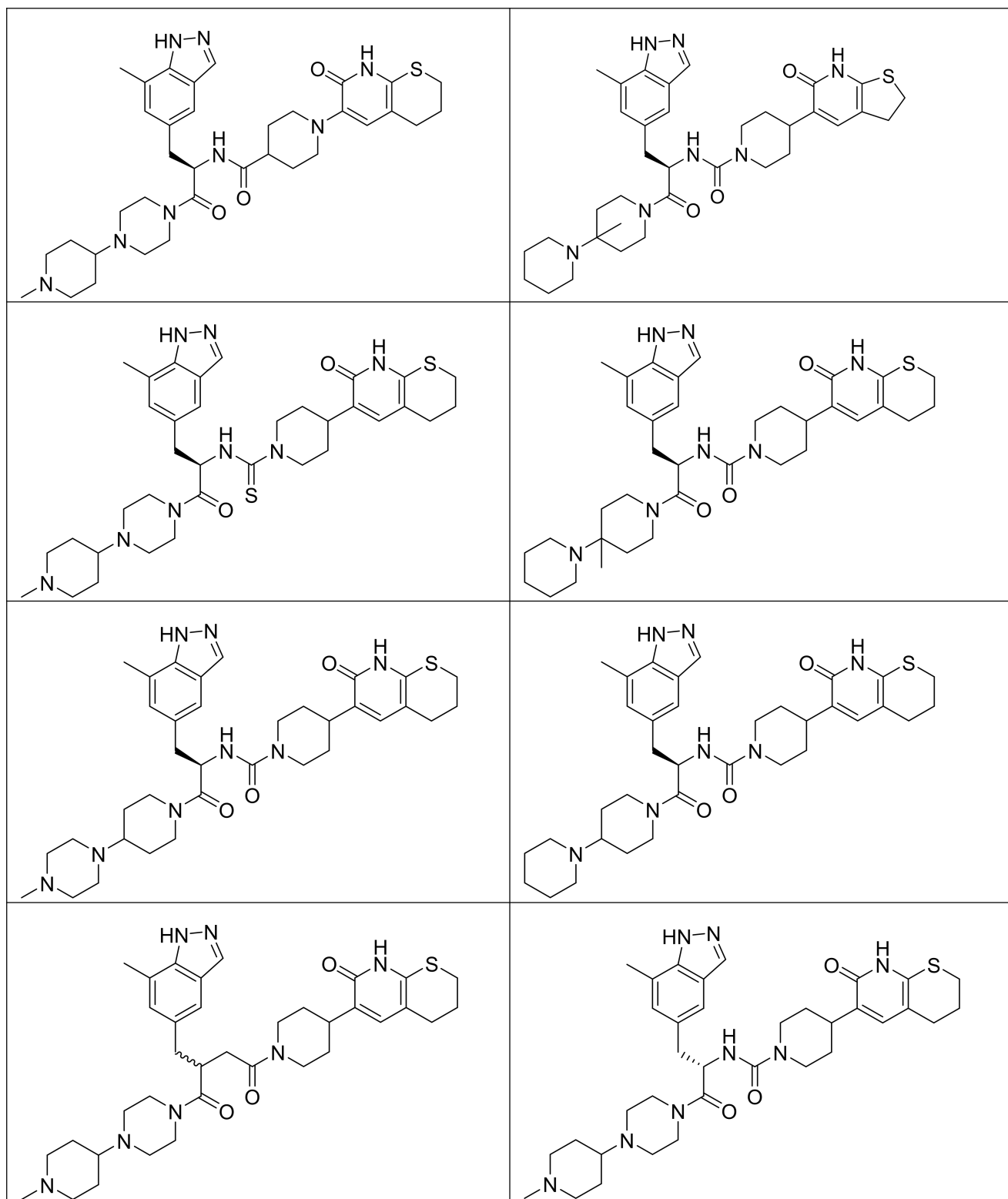


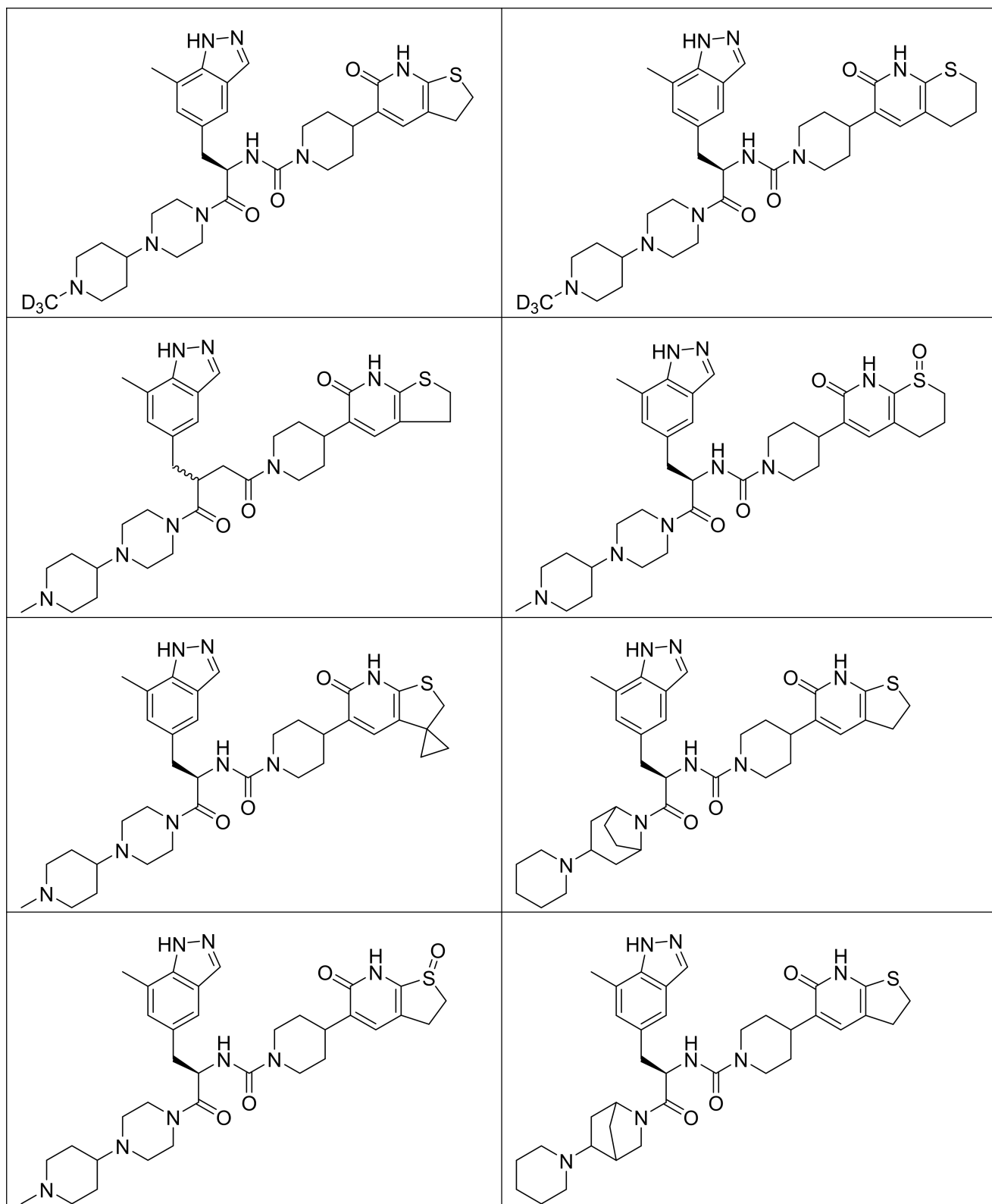


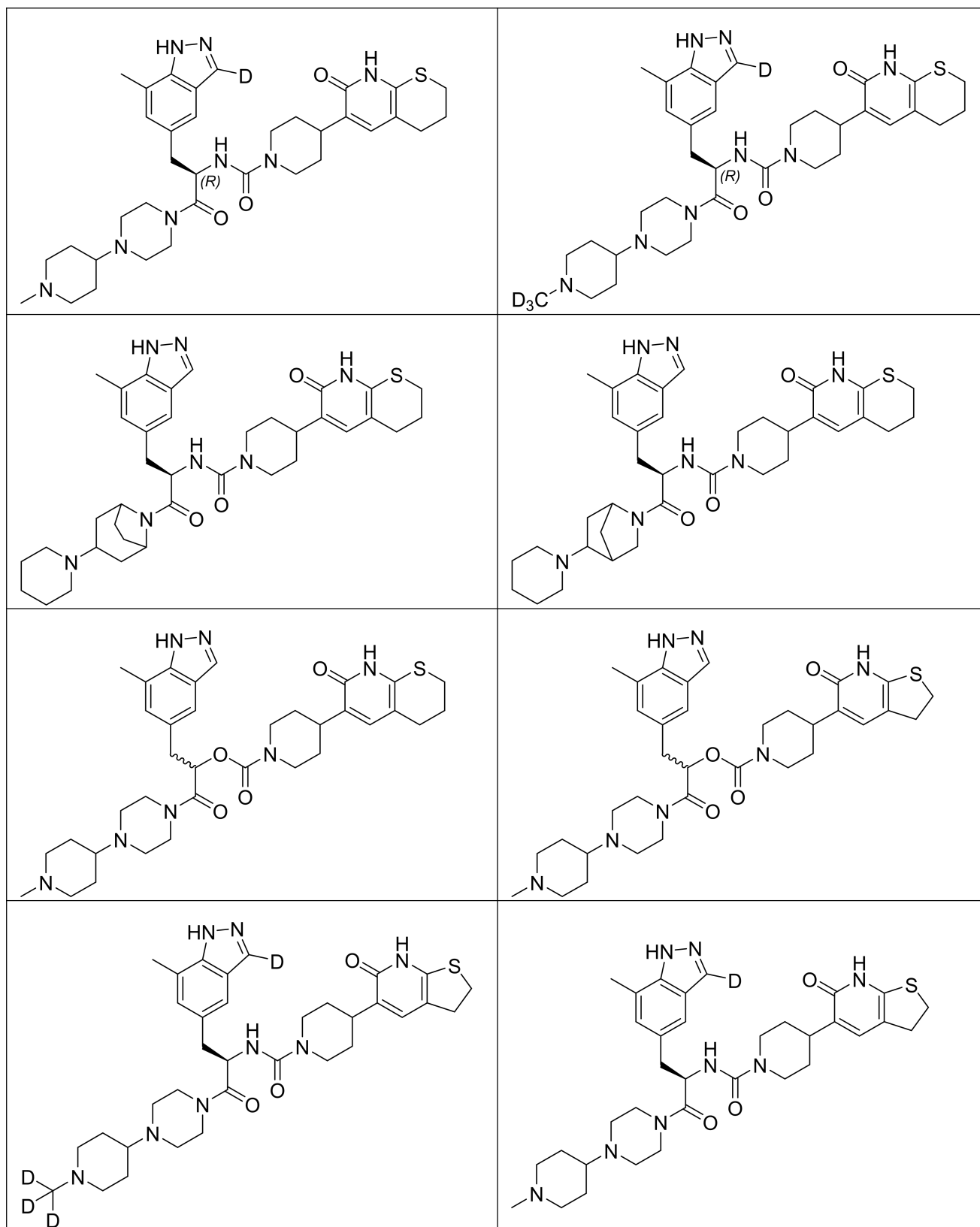
In other embodiments, the compound as represented by formula I of the present invention may be specifically selected from:

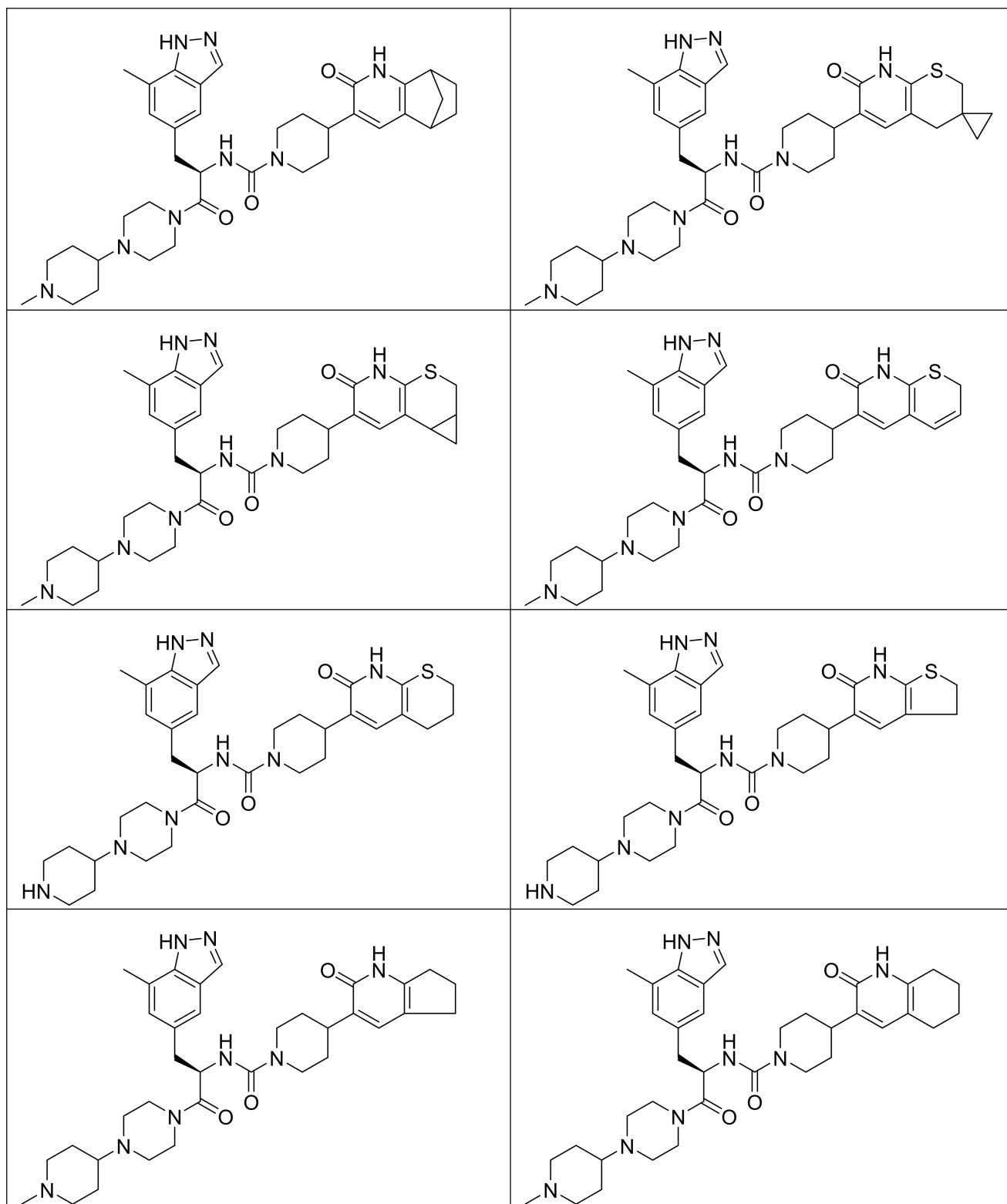












In the present invention, when the latter technical solution further defines the former technical solution, only some technical features may be further defined, and at this time, the undefined technical features may be optionally defined in any occurring part in the former technical solution or the present invention.

EMBODIMENT

Definition

Unless stated to the contrary or defined separately, the following terms used in the specification and the claims have the following meanings.

“Alkyl” refers to an aliphatic hydrocarbon group, and refers to saturated hydrocarbyl. The alkyl may be linear-chain alkyl or branched-chain alkyl, such as $-(C_1-C_6)$ alkyl or $-(C_1-C_3)$ alkyl. The $-(C_1-C_6)$ alkyl refers to alkyl with 1 to 6 carbon atoms, such as alkyl with 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms and 6 carbon atoms. Non-restrictive examples of alkyl comprise methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, and the like.

“Ring” refers to any covalently closed structure, comprising, for example, carbocyclic rings (such as aryl and cycloalkyl), heterocyclic groups (such as heteroaryl and heterocycloalkyl), aromatic groups (such as aryl and heteroaryl) and nonaromatic groups (such as cycloalkyl and heterocycloalkyl). The ring may be a monocyclic ring or a polycyclic ring. Typical polycyclic rings generally comprise a bicyclic ring and a tricyclic ring. The ring of the present invention generally has 3-20 ring atoms, such as 3 ring atoms, 4 ring atoms, 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, 11 ring atoms, 12 ring atoms, 13 ring atoms, 14 ring atoms, 15 ring atoms, 16 ring atoms, 17 ring atoms, 18 ring atoms, 19 ring atoms or 20 ring atoms.

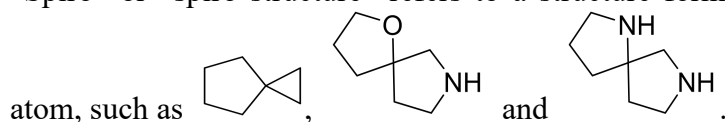
“Aliphatic ring” is saturated or unsaturated cyclic hydrocarbon with no aromatic property, and ring-forming skeleton atoms of the aliphatic ring are all carbon atoms. The aliphatic ring in the present invention may usually have 3-8, 3-6 or 5-7 ring carbon atoms, and may also be called a 3-8 membered aliphatic ring, a 3-6 membered aliphatic ring or a 5-7 membered aliphatic ring, and typical examples of the aliphatic ring are cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclopropene, cyclobutene, cyclopentene, cyclohexene, cycloheptene, and the like.

“Cycloalkyl” refers to a saturated cyclic hydrocarbon substituent, and is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexanyl, cycloheptyl or cyclooctyl. The cycloalkyl may be substituted or unsubstituted.

“Aliphatic heterocyclic ring”, also called “aliphatic heterocycle” in the present invention, is a heterocyclic ring with no aromatic property formed by substituting one or more ring-forming skeleton carbon atom with heteroatoms on the basis of the “aliphatic ring”, and the substituted heteroatoms may usually be O, S, N, and the like.

“Membered” refers to the number of the ring-forming skeleton carbon atoms. Typical 5 membered rings comprise, for example, cyclopentyl, pyrrole, imidazole, thiazole, furan and thiophene; and typical 6 membered rings comprise, for example, cyclohexanyl, pyridine, pyran, pyrazine, thiapyran, pyridazine, pyrimidine and benzene, wherein, a ring formed by skeleton atoms containing heteroatoms is a heterocyclic ring.

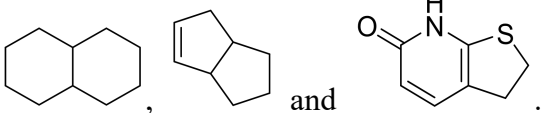
“Spiro” or “spiro structure” refers to a structure formed by two rings sharing one skeleton ring



“Bridged ring” or “bridged ring structure” refers to a structure formed by two rings sharing two skeleton ring atoms, wherein the two shared skeleton ring atoms are not adjacent, such as 



“Fused ring” or “fused ring structure” refers to a structure formed by two rings sharing two

adjacent skeleton ring atoms, such as , and .

“Oxo” means that hydrogens on carbon are substituted by =O.

“Substituted” means that one or more hydrogen atoms, preferably at most 5 (such as 1, 2, 3, 4 and 5) hydrogen atoms, and more preferably 1-3 hydrogen atoms, in a group, are independently substituted by a corresponding number of substituents. It goes without saying that the substituents are only in their possible chemical positions, and those skilled in the art can determine (by experiment or theory) possible or impossible substitutions without excessive efforts. For example, amino or hydroxyl with free hydrogen may be unstable when combined with carbon atoms with unsaturated bonds.

“Antagonist” refers to a drug that has no intrinsic activity, but may block a receptor agonist-mediated action after binding with a receptor.

“Optionally” means that the subsequently described event or environment may, but does not have to, occur, and the description comprises an occasion in which the event or environment occurs or does not occur.

The term "substituted or unsubstituted" herein means that any group is monosubstituted or polysubstituted by a specified substituent to an extent that such monosubstitution or polysubstitution (comprising multi-substitution in the same part) is chemically permitted, and each substituent may be located in any available position on the group and may be linked by any available atom on the substituent. “Any available position” refers to any position on the group that may be chemically obtained by a method known in the art or a method taught herein, and does not produce excessively unstable molecules. When there are two or more substituents on any group, each substituent is defined independently of any other substituent, so that the substituents may be the same or different.

The term “compound of the present invention” used herein is intended to cover a compound as represented by general formula (I) as defined herein or any preferred or specific embodiment thereof (comprising compounds as represented by formula (I-1), and the like, and compounds in the examples), and their stereoisomers, pharmaceutically acceptable salts, tautomers or solvates.

The term “pharmaceutically acceptable” used herein refers to molecular entities and compositions that are approved by or may be approved by corresponding institutions in various countries, or are listed in the generally recognized pharmacopoeia for animals and more specific humans, or will not produce adverse, allergic or other adverse reactions when administered to animals such as humans in appropriate amounts.

The term “pharmaceutically acceptable salt” used herein refers to a salt of the compound of the present invention that is pharmaceutically acceptable and has a pharmacological activity required by a parent compound. Specifically, such salts are nontoxic, and may be inorganic acid addition salts, organic acid addition salts and alkali addition salts.

It should be understood that, when each group in the structure of the compound of the present invention is selected, the groups connected, coordinated or influenced with each other should be selected correspondingly on the premise of conforming to chemical valence-bond rules.

According to the contents of the present invention, on the basis of common technical knowledge and means in the art, other modifications, substitutions or changes may be made in various forms without departing from the above basic technical idea of the present invention.

Preparation of compound as represented by formula I

In order to further explain the present invention, a compound as represented by formula I provided by the present invention, a preparation method therefor and an application thereof, and a pharmaceutical composition thereof, an activity test thereof, and the like, are illustratively described in detail hereinafter with reference to the examples.

The following abbreviations or terms have the following meanings:

K₂CO₃ represents potassium carbonate; H₂O represents water;

DMF represents *N,N*-dimethylformamide; KF represents potassium fluoride;

DIPEA or DIEA represents *N,N*-diisopropylethylamine; *n*-BuLi represents *n*-butyllithium;

THF represents tetrahydrofuran; TFA represents trifluoroacetic acid;

HCl/Dioxane represents a hydrogen chloride dioxane solution; HCl represents a hydrogen chloride solution;

DMSO represents dimethyl sulfoxide; CH₃I or MeI represents methyl iodide;

H₂ represents hydrogen; Pd₂(dba)₃ represents tris(dibenzylideneacetone)dipalladium;

t-BuOK represents potassium *tert*-butoxide; NMP represents *N*-methylpyrrolidone;

MeOH represents methanol; EtOH represents ethanol;

Pd(PPh₃)₂Cl₂ represents bis(triphenylphosphine)palladium dichloride; DIBAL-H represents diisobutyl aluminium hydride;

TEA represents triethylamine; DCM represents dichloromethane;

DCE represents 1,2-dichloroethane; dioxane represents 1,4-dioxane;

NBS represents *N*-bromosuccinimide; NaH represents sodium hydride;

LiHMDS represents lithium bis(trimethylsilyl)amide; NaBH₄ represents sodium borohydride;

Pd(dppf)Cl₂ represents [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride; Zn represents zinc;

Ruphos represents 2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl; I₂ represents iodine;

NaSH represents sodium hydrosulfide; CuI represents cuprous iodide;

Pd/C represents palladium carbon; AcSH represents thioacetic acid;

DIAD represents diisopropyl azodiformate; PPh₃ represents triphenylphosphine;

CH₃CN or MeCN represents acetonitrile; PtO₂ represents platinum dioxide;

NaOMe represents sodium methoxide; KHMDS represents potassium bis(trimethylsilyl)amide;

DEAD represents diethyl azodiformate; MWI represents a microwave-induced reaction;

AcCl represents acetyl chloride; NaOH represents sodium hydroxide;

TBTU represents 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate;

DMAP represents 4-dimethylaminopyridine; Ms₂O represents methanesulfonic anhydride;

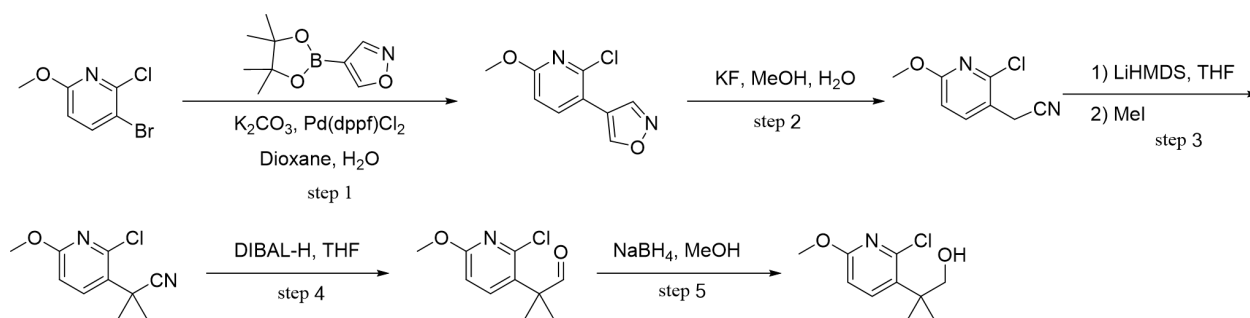
LiOH represents lithium hydroxide; $\text{B}(\text{OCH}_3)_3$ represents trimethyl borate;
 Cs_2CO_3 represents cesium carbonate; TCDI represents *N,N'*-thiocarbonyl diimidazole;
TosCl represents *p*-toluenesulfonyl chloride; DSC represents *N,N'*-disuccinimyl carbonate;
LDA represents lithium diisopropylamide; XantPhos represents 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene;
LAH represents lithium aluminum hydride; DPPA represents diphenylphosphoryl azide;
DMC represents dimethyl carbonate; TMSCN represents trimethylsilyl cyanide;
S-BuLi represents *sec*-butyllithium; PyBOP represents 1*H*-benzotriazol-1-ylxytripyrrolidinophosphonium hexafluorophosphate;
DBU represents 1,8-diazabicyclo[5.4.0]undec-7-ene; DMSu represents dimethyl succinate;
 $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{DCM}$ represents a [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride dichloromethane complex.

In addition, in the following preparation examples and embodiments, when the structural formula of the compound is inconsistent with the chemical name, the structural formula of the compound shall prevail.

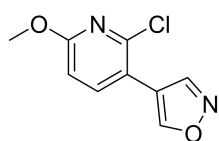
A synthesis method for an intermediate compound of the compound as represented by formula I of the present invention is illustratively provided as follows first. Starting materials and other additive reagent materials used in the synthesis of the intermediate compound provided are all commercially available, or may be acquired through the methods reported in the existing technical literatures combined with the conventional chemical reaction synthesis means. Some intermediate compounds are also commercially available directly, or may be acquired through the methods reported in the existing technical literatures combined with the conventional chemical reaction synthesis means.

EXAMPLES

Preparation Example 1 of intermediate compound: preparation of 2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropane-1-ol (available for Preparation Example 2 of intermediate compound)



Step 1: preparation of 4-(2-chloro-6-methoxypyridine-3-yl)isoxazole

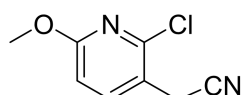


In a nitrogen atmosphere, 3-bromo-2-chloro-6-methoxypyridine (10.0 g) and potassium carbonate (12.4 g) were dissolved in 1,4-dioxane (100 mL) and water (10 mL), and then 4-isoxazole boric

acid (9.7 g) was dissolved in 1,4-dioxane (100 mL), put into a 150 mL constant-pressure dropping funnel, and added with 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (1.63 g). The system was transferred to 90°C and slowly dropwise added with 4-isoxazole boric acid at this temperature for 3 hours, and then to react for 2 hours after the addition. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, added with 500 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 9.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 211.0.

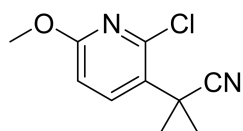
Step 2: preparation of 2-(2-chloro-6-methoxypyridine-3-yl)acetonitrile



4-(2-chloro-6-methoxypyridine-3-yl)isoxazole (9.0 g) was dissolved in methanol (100 mL) and water (10 mL), and added with potassium fluoride (12.4 g). The system was put into a thick-walled reaction bottle to react in a closed mode at 100°C for 6 hours. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, concentrated to remove methanol, added with 500 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 7.1 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 183.0.

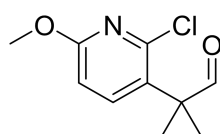
Step 3: preparation of 2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropionitrile



In a nitrogen atmosphere, 2-(2-chloro-6-methoxypyridine-3-yl)acetonitrile (7.1 g) was dissolved in anhydrous tetrahydrofuran (80 mL). The system was cooled to -78°C and slowly added with lithium bis(trimethylsilyl)amide (1 M, 117.0 mL) to react for 10 minutes. The system was added with methyl iodide (12.7 g) to continuously react for 20 minutes. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, added with 200 mL of saturated ammonium chloride aqueous solution, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 8.1 g of crude product.

MS (ESI) m/z (M+H)⁺ = 211.1.

Step 4: preparation of 2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropanal

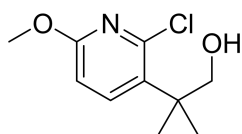


In a nitrogen atmosphere, 2-(2-chloro-6-methoxypyridine-3-yl)-2-methyl propionitrile (8.1 g) was dissolved in anhydrous tetrahydrofuran (80 mL). The system was cooled to -78°C and slowly added with diisobutyl aluminium hydride (1 M, 64.3 mL) to react for 2 hours. After TLC showed

that the reaction was completed, the reaction system was heated to 0°C, diluted with tetrahydrofuran (200 mL), sequentially added with water (3.9 mL), 10% sodium hydroxide aqueous solution (3.9 mL) and water (9.64 mL), transferred to room temperature and stirred for 10 minutes, then added with an appropriate amount of anhydrous sodium sulfate, and continuously stirred for 20 minutes. The mixture was filtered, the filtrate was concentrated, and the obtained crude product was purified by column chromatography to obtain 5.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 214.1.

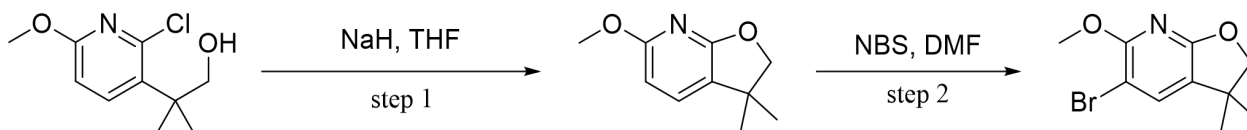
Step 5: preparation of 2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropane-1-ol



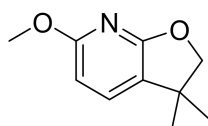
2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropanal (5.0 g) was dissolved in methanol (50 mL) and added with sodium borohydride (446.0 mg) to react at room temperature for 10 minutes. After TLC showed that the reaction was completed, the reaction system was concentrated, and the obtained crude product was purified by column chromatography to obtain 4.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 216.1.

Preparation Example 2 of intermediate compound: preparation of 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine (available for Example 1)



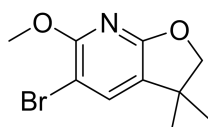
Step 1: preparation of 6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine



2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropane-1-ol (1.0 g) was dissolved in anhydrous tetrahydrofuran (10 mL), slowly added into an anhydrous tetrahydrofuran (10 mL) suspension of sodium hydride (220.8 mg) and heated to 60°C to react for 2 hours. After TLC showed that the reaction was completed, in ice water bath, the reaction system was dropwise added into 50 mL of saturated ammonium chloride aqueous solution, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 516 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 180.1.

Step 2: preparation of 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine

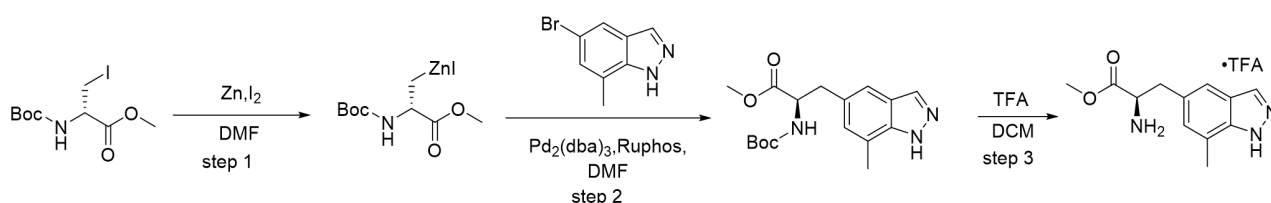


6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine (510.0 mg) was dissolved in anhydrous *N,N*-dimethylformamide (5 mL) and added with *N*-bromosuccinimide (558 mg) to react at room

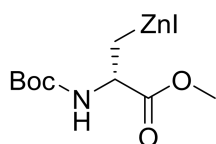
temperature for 20 minutes. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with pure water twice, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 610.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 258.0, 260.0.

Preparation Example 3 of intermediate compound: preparation of methyl (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)propionate trifluoroacetate (available for Example 1)

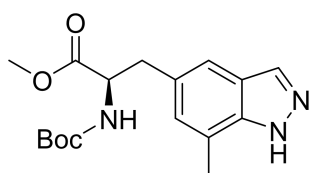


Step 1: preparation of (S)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)zinc iodide (II)



In a nitrogen atmosphere, activated zinc powder (2.37 g) was added into a 100 mL three-necked flask, and iodine (926.37 mg) was dissolved in anhydrous N,N-dimethylformamide, and dropwise added into the three-necked flask. Then, the system was placed at 60°C to react for 15 minutes. (S)-2-((tert-butoxycarbonyl)amino)-3-iodopropionic acid methyl ester (6.00 g) was dissolved in anhydrous N,N-dimethylformamide (35 mL) and slowly dropwise added into the above reaction system to react at 70°C for 2.5 hours. After the reaction was ended, the reaction system was transferred to room temperature, and the obtained reaction solution was directly used in the next step of reaction.

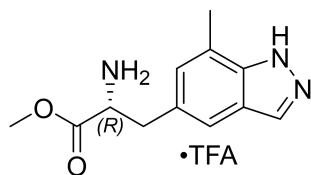
Step 2: preparation of methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(7-methyl-1H-indazole-5-yl)propionate



In a nitrogen atmosphere, 5-bromo-7-methyl-1H-indazole (2.26 g), tris(dibenzylideneacetone)dipalladium (489.52 mg) and 2-dicyclohexylphosphine-2',6'-diisopropoxy-1,1'-biphenyl (499.29 mg) were dissolved in anhydrous N,N-dimethylformamide (5 mL), and then the solution obtained in the step 1 was added into the reaction system and heated at 70°C to react for 3 hours. After the reaction was ended, the reaction system was filtered by diatomite, the filtrate was collected, added with 30 mL of water, and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was separated and purified by silica gel column chromatography to obtain 2.1 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 334.1.

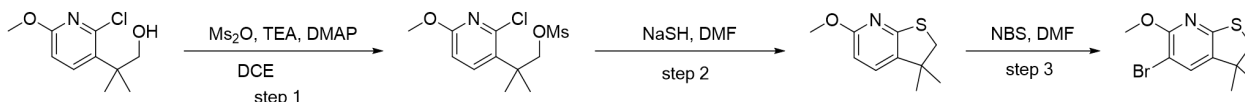
Step 3: preparation of methyl (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)propionate trifluoroacetate



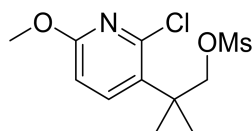
Methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(7-methyl-1H-indazole-5-yl)propionate (1 g) was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (10 mL) to react at room temperature for 1 hour. After the reaction was ended, the reaction system was concentrated to obtain a crude product, which could be directly used in the next step of reaction without purification.

MS (ESI) m/z (M+H)⁺ = 234.1.

Preparation Example 4 of intermediate compound: preparation of 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine (available for Example 2)



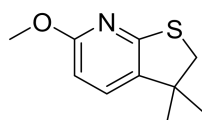
Step 1: preparation of 2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropyl methanesulfonate



2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropan-1-ol (600.0 mg) was dissolved in 1,2-dichloroethane (10 mL), and sequentially added with triethylamine (848.4 mg), 4-dimethylaminopyridine (34.1 mg) and methanesulfonic anhydride (584.6 mg) to react at room temperature for 30 minutes. After TLC showed that the reaction was completed, the reaction system was added into 30 mL of water and extracted with dichloromethane for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 820 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 294.0.

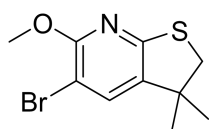
Step 2: preparation of 6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine



The 2-(2-chloro-6-methoxypyridine-3-yl)-2-methylpropyl methanesulfonate crude product (850.0 mg) was dissolved in *N,N*-dimethylformamide (10 mL), added with sodium hydrosulfide (487.4 mg), and heated at 130°C to react for 3 hours. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with pure water twice, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 450.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 196.1.

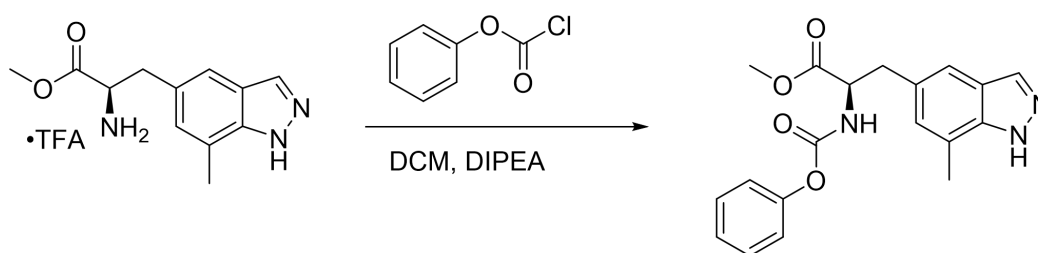
Step 3: preparation of 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine



6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine (450.0 mg) was dissolved in *N,N*-dimethylformamide (5 mL) and added with *N*-bromosuccinimide (452.0 mg) to react at room temperature for 10 minutes. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with pure water twice, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 300.0 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 274.0, 276.0.

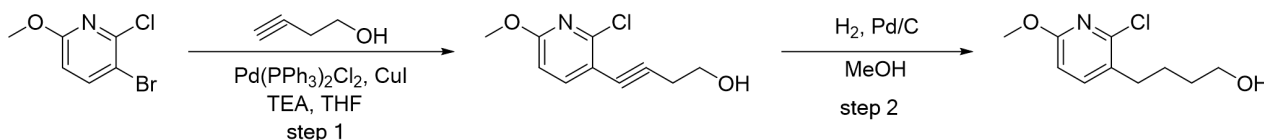
Preparation Example 5 of intermediate compound: preparation of methyl (R)-3-(7-methyl-1H-indazole-5-yl)-2-((phenoxy-carbonyl)amino)propionate (available for Example 2)



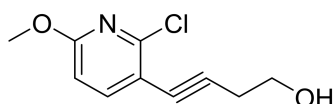
In ice water bath, methyl (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)propionate trifluoroacetate (990 mg) was dissolved in dichloromethane (20 mL) and dropwise added with *N,N*-diisopropylethylamine (1.16 g). Then, phenyl chloroformate (469.71 mg) was dissolved in dichloromethane (10 mL) and dropwise added into the above reaction system to react for 1 hour. After the reaction was ended, the reaction solution was poured into water and extracted with ethyl acetate, and the organic phases were combined, washed with a saturated sodium chloride aqueous solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was separated and purified by silica gel column chromatography to obtain 1 g of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 354.1.

Preparation Example 6 of intermediate compound: preparation of 4-(2-chloro-6-methoxypyridine-3-yl)butan-1-ol (available for Preparation Example 7 of intermediate compound)



Step 1: preparation of 4-(2-chloro-6-methoxypyridine-3-yl)butan-3-yn-1-ol

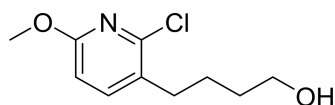


3-bromo-2-chloro-6-methoxypyridine (3.0 g) was dissolved in tetrahydrofuran (20 mL) and

triethylamine (10 mL), and 3-butyne-1-ol (2.9 g) was diluted with tetrahydrofuran (5 mL) and then put into a constant-pressure dropping funnel. After nitrogen replacement, the system was added with bis(triphenylphosphine)palladium dichloride (476.0 mg) and cuprous iodide (64.0 mg). After nitrogen replacement again, the system was heated to 50°C and slowly dropwise added with 3-butyne-1-ol at this temperature for two hours, and then to continuously react at this temperature for 1 hour. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.8 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 212.0.

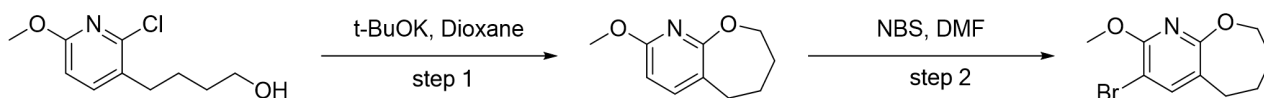
Step 2: preparation of 4-(2-chloro-6-methoxypyridine-3-yl)butan-1-ol



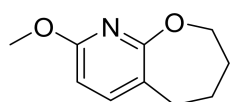
4-(2-chloro-6-methoxypyridine-3-yl)butan-3-yn-1-ol (1.8 g) was dissolved in methanol (100 mL), added with palladium carbon (10%, 180.0 mg), subjected to air replacement, and continuously introduced with hydrogen to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the reaction system was filtered, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 1.5 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 216.0.

Preparation Example 7 of intermediate compound: preparation of 7-bromo-8-methoxy-2,3,4,5-tetrahydro-oxepino[2,3-*b*]pyridine (available for Example 3)



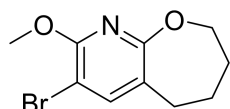
Step 1: preparation of 8-methoxy-2,3,4,5-tetrahydro-oxepino[2,3-*b*]pyridine



4-(2-chloro-6-methoxypyridine-3-yl)butan-1-ol (430.0 mg) was dissolved in 1,4-dioxane (6 mL), added with potassium tert-butoxide (448.0 mg) and heated to 85°C to react for 1 hour. After TLC showed that the reaction was completed, the system was added into dilute hydrochloric acid at 0°C, and a pH value of the system was adjusted to about 7. The reaction system was extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 0.3 g of crude product.

MS (ESI) m/z (M+H)⁺ = 180.1.

Step 2: preparation of 7-bromo-8-methoxy-2,3,4,5-tetrahydro-oxepino[2,3-*b*]pyridine

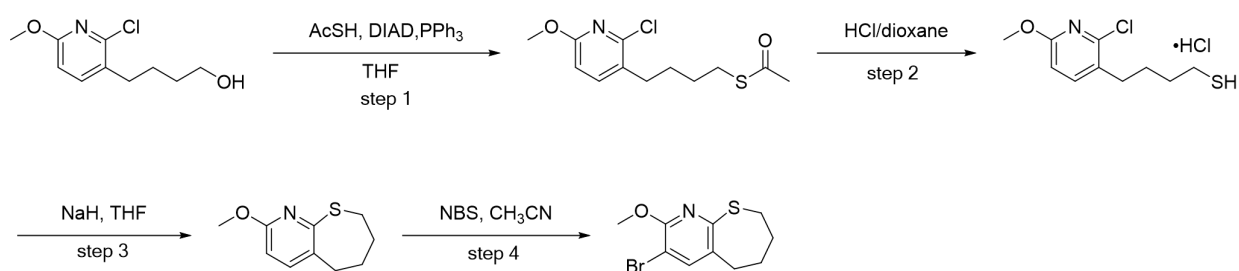


The 8-methoxy-2,3,4,5-tetrahydro-oxepino[2,3-*b*]pyridine crude product (300.0 mg) was dissolved

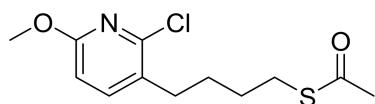
in anhydrous *N,N*-dimethylformamide (4 mL) and added with *N*-bromosuccinimide (298.0 mg) to react at room temperature for 30 minutes. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with pure water twice, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 195.0 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 258.0, 260.0.

Preparation Example 8 of intermediate compound: preparation of 7-bromo-8-methoxy-2,3,4,5-tetrahydro-thiazepino[2,3-*b*]pyridine (available for Example 4)



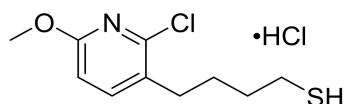
Step 1: preparation of S-4-(2-chloro-6-methoxypyridine-3-yl)butylthioethyl ester



In ice water bath, 4-(2-chloro-6-methoxypyridine-3-yl)butan-1-ol (1.4 g) and triphenylphosphine (2.6 g) were dissolved in dry tetrahydrofuran (20 mL), added with diisopropyl azodiformate (2.0 g) and transferred to room temperature to react for 10 minutes. In ice water bath, the system was added with thioacetic acid (741.7 mg) and transferred to room temperature to react for 30 minutes. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.0 g of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 274.1.

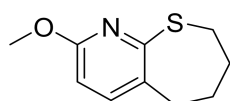
Step 2: preparation of 4-(2-chloro-6-methoxypyridine-3-yl)butane-1-thiol hydrochloride



S-4-(2-chloro-6-methoxypyridine-3-yl)butylthioethyl ester (1.0 g) was dissolved in a 1,4-dioxane-hydrochloric acid solution (4 M, 10 mL) and heated to 40°C to react for 1 hour. After TLC showed that the reaction was completed, the system was directly concentrated to obtain 930.0 mg of crude product.

MS (ESI) m/z ($M+H$)⁺ = 232.0.

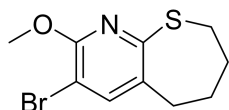
Step 3: preparation of 8-methoxy-2,3,4,5-tetrahydro-thiazepino[2,3-*b*]pyridine



The 4-(2-chloro-6-methoxypyridine-3-yl)butane-1-thiol hydrochloride crude product (930.0 mg) was dissolved in tetrahydrofuran (20 mL), and the above system was slowly dropwise added into a tetrahydrofuran (5 mL) suspension of sodium hydride (288.0 mg) and heated to 80°C to react for 1 hour. After TLC showed that the reaction was completed, in ice water bath, the system was dropwise added into 30 mL of water and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 830.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 196.1.

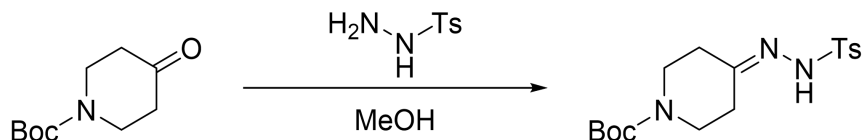
Step 4: preparation of 7-bromo-8-methoxy-2,3,4,5-tetrahydro-thiepino[2,3-*b*]pyridine



The 8-methoxy-2,3,4,5-tetrahydro-thiepino[2,3-*b*]pyridine crude product (800.0 mg) was dissolved in acetonitrile (9 mL) and added with *N*-bromosuccinimide (721.6 mg) to react at room temperature for 10 minutes. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 336.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 274.0, 276.0.

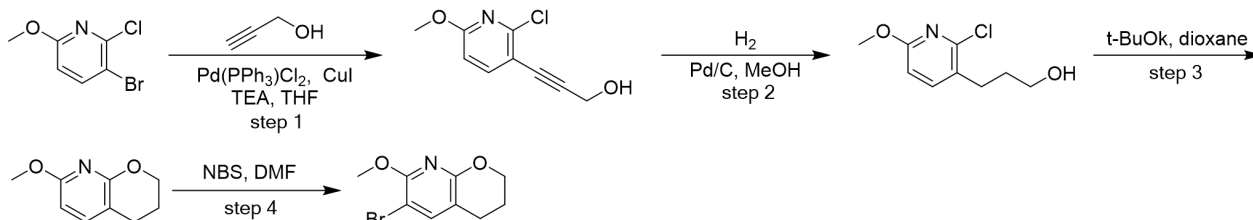
Preparation Example 9 of intermediate compound: preparation of tert-butyl 4-(2-tosylhydrazone)piperidine-1-formate (available for Example 4)



Tert-butyl 4-oxopiperidine-1-formate (4.5 g) was dissolved in methanol (50 mL), added with 4-methylbenzenesulfonyl hydrazine (4.2 g) and heated to 70°C to react for 4 hours. After TLC monitoring showed that the reaction was completed, the reaction solution was concentrated, and the crude product was purified by column chromatography to obtain 7.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 368.1.

Preparation Example 10 of intermediate compound: preparation of 6-bromo-7-methoxy-3,4-dihydro-2H-pyrano[2,3-*b*]pyridine (available for Example 5)

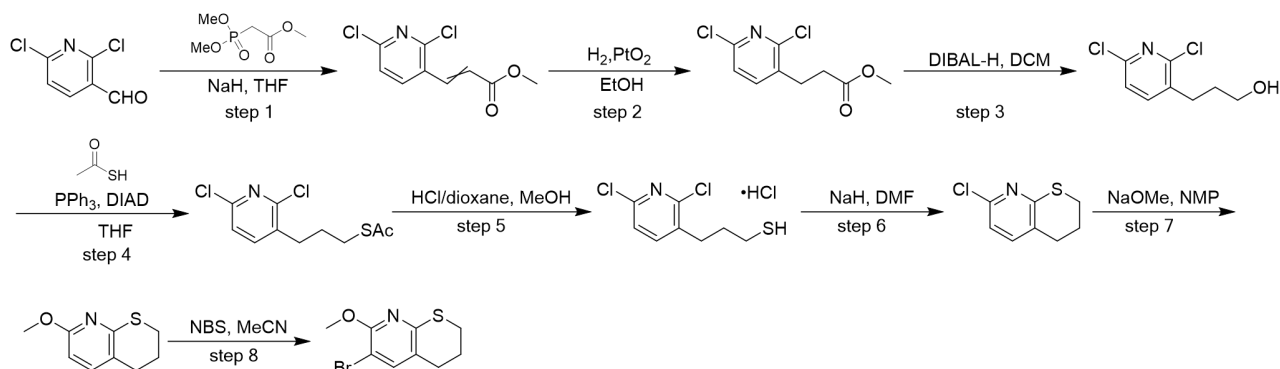


Corresponding common commercially available reagents were used to prepare the title compound by a preparation method similar to those in Preparation Example 6 of intermediate compound and Preparation Example 7 of intermediate compound.

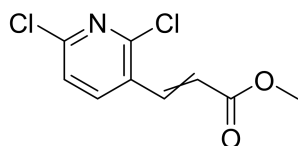
MS (ESI) m/z (M+H)⁺ = 244.0, 246.0.

Preparation Example 11 of intermediate compound: preparation of

6-bromo-7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine (available for Example 6)



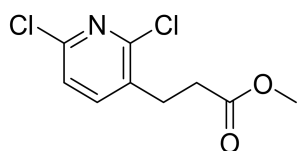
Step 1: preparation of methyl 3-(2,6-dichloropyridine-3-yl)acrylate



In ice water bath, in a nitrogen atmosphere, methyl 2-(dimethoxyphosphonyl)acetate (4.66 g) was slowly added into anhydrous tetrahydrofuran (10 mL) containing sodium hydride (1.02 g) to react for half an hour. An anhydrous tetrahydrofuran (20 mL) solution of 2,6-dichloronicotinaldehyde (3.00 g) was slowly dropwise added into the above system and transferred to room temperature to react for 1 hour. After LCMS showed that the reaction was completed, the system was added with an appropriate amount of water and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 3.7 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 231.9.

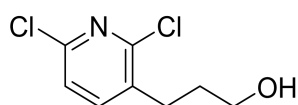
Step 2: preparation of methyl 3-(2,6-dichloropyridine-3-yl)propionate



Methyl 3-(2,6-dichloropyridine-3-yl)acrylate (3.7 g) was dissolved in ethanol (40 mL), added with platinum dioxide (400 mg) and subjected to hydrogen replacement for 3 times to react at room temperature for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was filtered, and the filtrate was collected and concentrated to obtain 3.7 g of crude product.

MS (ESI) m/z (M+H)⁺ = 233.9.

Step 3: preparation of 3-(2,6-dichloropyridine-3-yl)propan-1-ol

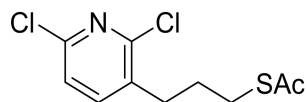


In a nitrogen atmosphere, methyl 3-(2,6-dichloropyridine-3-yl)propionate (3.7 g) was dissolved in dichloromethane (20 mL) at -20°C, slowly added with diisobutyl aluminum hydride (1.5 M, 21.09 mL) and transferred to room temperature to react for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was quenched with a saturated ammonium chloride solution (10 mL) and extracted with dichloromethane for 3 times, the organic phases were

combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 2.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 205.9.

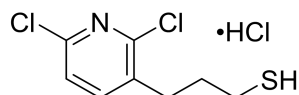
Step 4: preparation of S-(3-(2,6-dichloropyridine-3-yl)propyl)thioacetate



In a nitrogen atmosphere, 3-(2,6-dichloropyridine-3-yl)propan-1-ol (2.2 g) and triphenylphosphine (4.2 g) were dissolved in anhydrous tetrahydrofuran (20 mL), and sequentially added with diisopropyl azodicarbonate (3.24 g) and thioacetic acid (1.22 g) to react at room temperature for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was concentrated. The obtained crude product was purified by column chromatography to obtain 2.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 263.9.

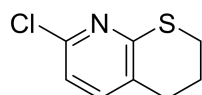
Step 5: preparation of 3-(2,6-dichloropyridine-3-yl)propane-1-thiol hydrochloride



S-(3-(2,6-dichloropyridine-3-yl)propyl)thioacetate (2.0 g) was dissolved in a hydrochloric acid-1,4-dioxane solution (4 M, 20 mL) to react at room temperature overnight. After LCMS showed that the reaction of raw materials was completed, the reaction solution was concentrated to obtain 1.6 g of crude product.

MS (ESI) m/z (M+H)⁺ = 221.9.

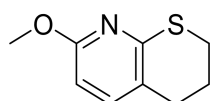
Step 6: preparation of 7-chloro-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine



In ice water bath, in a nitrogen atmosphere, an anhydrous N,N-dimethylformamide (10 mL) solution containing sodium hydride (864.3 mg) was slowly added with an anhydrous N,N-dimethylformamide (10 mL) solution of 3-(2,6-dichloropyridine-3-yl)propane-1-thiol hydrochloride (1.6 g) to react for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was quenched with a saturated ammonium chloride solution and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 186.1.

Step 7: preparation of 7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine

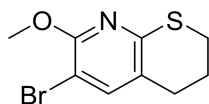


7-chloro-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine (700 mg) and sodium methoxide (814.7 mg) were dissolved in N-methylpyrrolidone (10 mL) and heated at 110°C to react for 15 hours. After LCMS showed that the reaction of raw materials was completed, the reaction solution was added

with an appropriate amount of water and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 580 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 181.9.

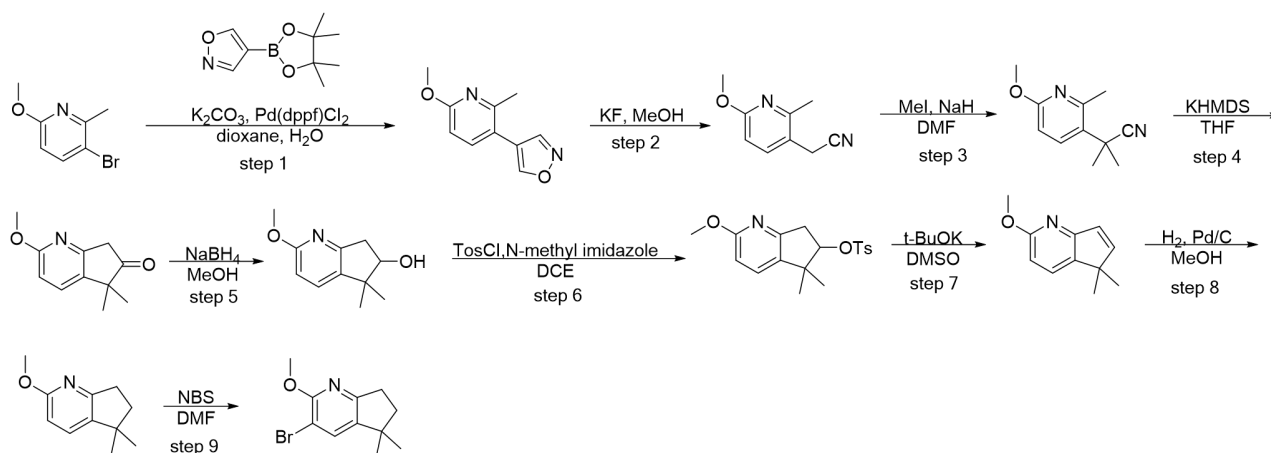
Step 8: preparation of 6-bromo-7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine



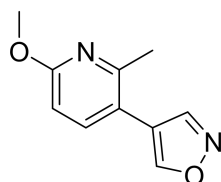
7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine (420 mg) was dissolved in acetonitrile (4 mL), and added with N-bromosuccinimide (412.4 mg) to react at room temperature for 0.5 hour. After LCMS showed that the reaction of raw materials was completed, the reaction system was added with 30 mL of water and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 580 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 260.1, 262.1.

Preparation Example 12 of intermediate compound: preparation of 3-bromo-2-methoxy-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine (available for Example 7)



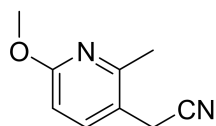
Step 1: preparation of 4-(6-methoxy-2-methylpyridine-3-yl)isoxazole



In a nitrogen atmosphere, 3-bromo-6-methoxy-2-methylpyridine (10.0 g), potassium carbonate (10.25 g) and [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (2.54 g) were dissolved in 1,4-dioxane (70 mL) and water (20 mL). The system was heated to 90°C and dropwise added with a 4-isoxazoleboronic acid pinacol ester (9.65 g, dissolved in 80 mL of 1,4-dioxane) solution at a constant speed within 3 hours to continuously react for 1.5 hours. The system was transferred to room temperature, added with water for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 7.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 191.1.

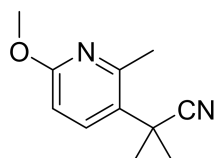
Step 2: preparation of 2-(6-methoxy-2-methylpyridine-3-yl)acetonitrile



4-(6-methoxy-2-methylpyridine-3-yl)isoxazole (7.0 g) was dissolved in methanol (80 mL), added with potassium fluoride (10.7 g) and heated in an autoclave at 120°C in a closed mode to react for 4 hours. The reaction system was cooled to room temperature and concentrated to remove the solvent. The reaction system was added with water for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 5.1 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 163.1.

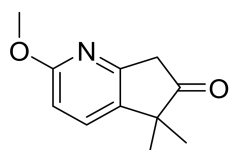
Step 3: preparation of 2-(6-methoxy-2-methylpyridine-3-yl)-2-methylpropionitrile



In a nitrogen atmosphere, 2-(6-methoxy-2-methylpyridine-3-yl)acetonitrile (5.1 g) was dissolved in *N,N*-dimethylformamide (50 mL) and added with sodium hydride (3.78 g) at -20°C to react for 10 minutes. The reaction system was added with methyl iodide (11.18 g) to continuously react for 1.5 hours. The reaction system was added with a saturated ammonium chloride solution for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 5.8 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 191.1.

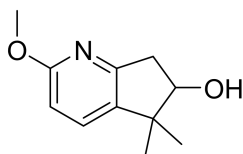
Step 4: preparation of 2-methoxy-5,5-dimethyl-5,7-dihydro-6*H*-cyclopenta[*b*]pyridine-6-one



In a nitrogen atmosphere, 2-(6-methoxy-2-methylpyridine-3-yl)-2-methylpropionitrile (5.8 g) was dissolved in anhydrous tetrahydrofuran (60 mL), dropwise added with potassium bis(trimethylsilyl)amide (1 M, 45 mL) at -40°C and transferred to room temperature to react for 0.5 hour. The reaction system was added with a saturated ammonium chloride solution for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 5.02 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 192.1.

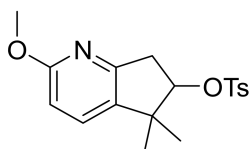
Step 5: preparation of 2-methoxy-5,5-dimethyl-6,7-dihydro-5*H*-cyclopentadieno[*b*]pyridine-6-ol



2-methoxy-5,5-dimethyl-5,7-dihydro-6*H*-cyclopenta[*b*]pyridine-6-one (4.3 g) was dissolved in methanol (40 mL) and added with sodium borohydride (1.08 g) in batches to react at room temperature for 1 hour. After LCMS monitoring showed that the reaction was ended, the reaction system was concentrated to remove the solvent. The reaction system was added with a saturated ammonium chloride solution for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 4.1 g of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 194.1.

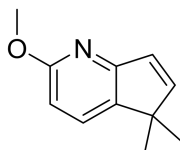
Step 6: preparation of 2-methoxy-5,5-dimethyl-6,7-dihydro-5*H*-cyclopentadieno[*b*]pyridine-6-yl-4-methyl benzenesulfonate



2-methoxy-5,5-dimethyl-6,7-dihydro-5*H*-cyclopentadieno[*b*]pyridine-6-ol (4.1 g) was dissolved in 1,2-dichloroethane (30 mL), sequentially added with *N*-methylimidazole (3.48 g) and *p*-toluenesulfonyl chloride (5.26 g), and heated at 70°C to react for 3 hours. The reaction system was added with water (80 mL) to stop the reaction, and extracted with dichloromethane for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 6.3 g of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 348.1.

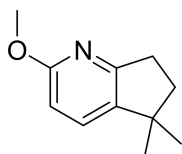
Step 7: preparation of 2-methoxy-5,5-dimethyl-5*H*-cyclopentadieno[*b*]pyridine



2-methoxy-5,5-dimethyl-6,7-dihydro-5*H*-cyclopentadieno[*b*]pyridine-6-yl-4-methyl benzenesulfonate (6.3 g) was dissolved in dimethyl sulfoxide (50 mL), added with potassium tert-butoxide (4.07 g) and heated at 50°C to react for 2 hours. After the reaction was ended, the system was concentrated, added with a saturated ammonium chloride solution for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 2.85 g of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 176.1.

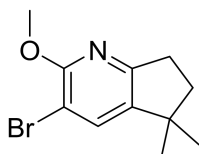
Step 8: preparation of 2-methoxy-5,5-dimethyl-6,7-dihydro-5*H*-cyclopentadieno[*b*]pyridine



2-methoxy-5,5-dimethyl-5H-cyclopentadieno[*b*]pyridine (0.4 g) was dissolved in methanol (10 mL), and added with palladium carbon (10%, 100 mg). The system was subjected to air replacement and heated at 50°C in a hydrogen atmosphere to react for 2 hours. After the reaction was ended, the system was filtered, and the filtrate was collected and concentrated to obtain 400 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 178.1.

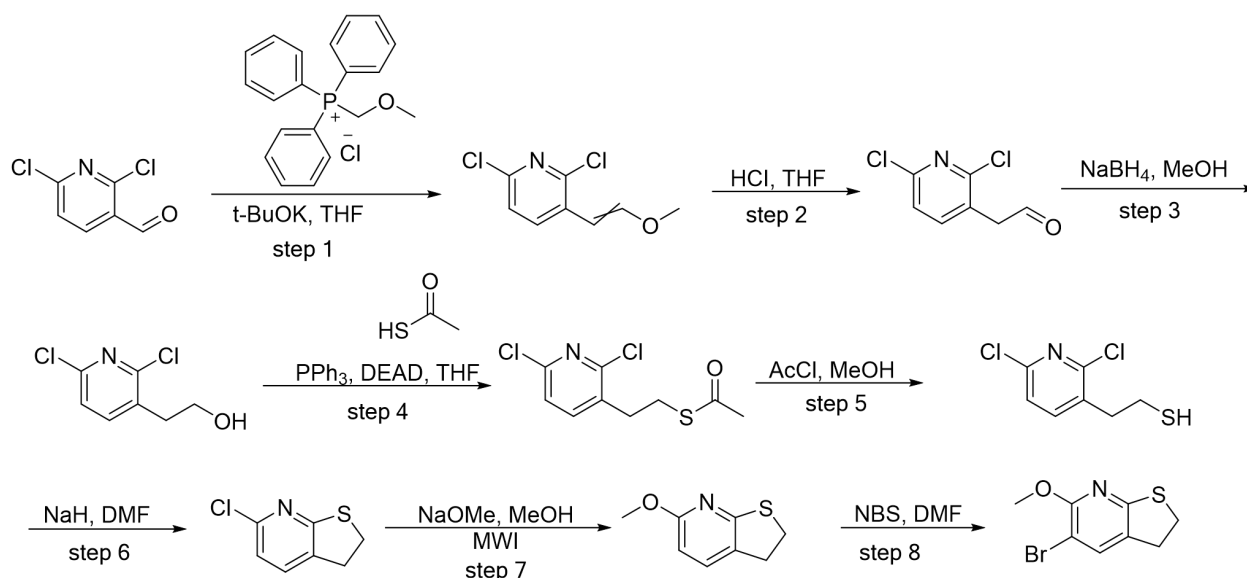
Step 9: preparation of 3-bromo-2-methoxy-5,5-dimethyl-6,7-dihydro-5H-cyclopenta[*b*]pyridine



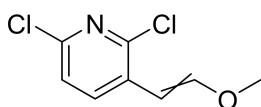
2-methoxy-5,5-dimethyl-6,7-dihydro-5H-cyclopentadieno[*b*]pyridine (0.4 g) was dissolved in *N,N*-dimethylformamide (8 mL), added with *N*-bromosuccinimide (407 mg) and heated 50°C to react for 1 hour. After the reaction was ended, the system was added with an appropriate amount of water and extracted with ethyl acetate for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 520 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 256.1, 258.1.

Preparation Example 13 of intermediate compound: preparation of 5-bromo-6-methoxy-2,3-dihydrothieno[2,3-*b*]pyridine (available for Example 8)



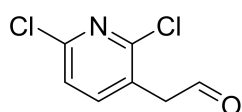
Step 1: preparation of 2,6-dichloro-3-(2-methoxyvinyl)pyridine



In ice water bath, in a nitrogen atmosphere, (methoxymethyl)triphenylphosphonium chloride (20.0 g) was dissolved in tetrahydrofuran (160 mL) and added with a potassium tert-butoxide (6.53 g dissolved in 58.3 mL of tetrahydrofuran) solution to react for 30 minutes. The reaction system was dropwise added with a 2,6-dichloronicotinaldehyde (6.0 g dissolved in 50 mL of tetrahydrofuran) solution to react for 20 minutes. The reaction system was transferred to room temperature to continuously react for 1 hour. The reaction system was added with water for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 6.1 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 204.1.

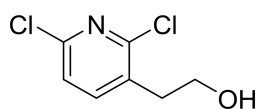
Step 2: preparation of 2-(2,6-dichloropyridine-3-yl)acetaldehyde



2,6-dichloro-3-(2-methoxyvinyl)pyridine (6.1 g) was dissolved in tetrahydrofuran (41 mL) and added with hydrogen chloride aqueous solution (4.0 M, 24 mL). The mixture was heated and refluxed for 3 hours. The reaction system was cooled to room temperature and concentrated to remove the solvent. The residue was dissolved in ethyl acetate, sequentially washed with a saturated sodium bicarbonate solution and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 6.1 g of crude product.

MS (ESI) m/z (M+H)⁺ = 190.1.

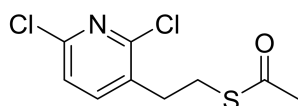
Step 3: preparation of 2-(2,6-dichloropyridine-3-yl)ethanol



In ice water bath, the 2-(2,6-dichloropyridine-3-yl)acetaldehyde crude product (6.1 g) was dissolved in methanol (51 mL) and added with sodium borohydride (1.0 g) to react for 30 minutes. The reaction system was quenched with a saturated ammonium chloride solution and extracted with ethyl acetate for three times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 2.3 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 192.1.

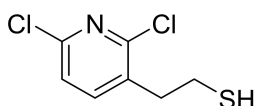
Step 4: preparation of S-(2-(2,6-dichloropyridine-3-yl)ethyl)thioacetate



In ice water bath, 2-(2,6-dichloropyridine-3-yl)ethanol (2.3 g) and triphenylphosphine (6.3 g) were dissolved in anhydrous tetrahydrofuran (60 mL), and added with diethyl azodiformate (3.8 mL). 10 minutes later, the system was added with thioacetic acid (1.72 mL). The reaction system was transferred to room temperature to react for 2 hours. The reaction solution was diluted with n-hexane and filtered to remove precipitates, the filtrate was collected and concentrated, and the crude product was purified by column chromatography to obtain 2.5 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 250.1.

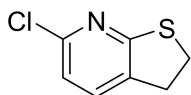
Step 5: preparation of 2-(2,6-dichloropyridine-3-yl)ethane-1-thiol



S-(2-(2,6-dichloropyridine-3-yl)ethyl)thioacetate (1.5 g) was dissolved in methanol (40 mL) and added with acetyl chloride (2.36 g) to react at room temperature for 24 hours. After LCMS monitoring showed that the reaction was ended, the reaction system was concentrated to remove the solvent, so as to obtain 1.6 g of crude product.

MS (ESI) m/z (M+H)⁺ = 208.1.

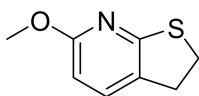
Step 6: preparation of 6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine



In a nitrogen atmosphere, in ice water bath, the 2-(2,6-dichloropyridine-3-yl)ethane-1-thiol crude product (1.6 g) was dissolved in *N,N*-dimethylformamide (30 mL) and added with sodium hydride (720 mg) to react for 1.5 hours. The reaction system was added with water (80 mL) to stop the reaction, and extracted with ethyl acetate for three times, and the organic phases were combined, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 1.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 172.1.

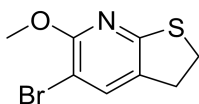
Step 7: preparation of 6-methoxy-2,3-dihydrothieno[2,3-*b*]pyridine



6-chloro-2,3-dihydrothieno[2,3-*b*]pyridine (1.0 g) and sodium methoxide (1.08 g) were dissolved in methanol (15 mL) and heated at 115°C to react under induction of microwave for 8 hours. After the reaction was ended, the system was concentrated, and the crude product was purified by column chromatography to obtain 730 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 168.1.

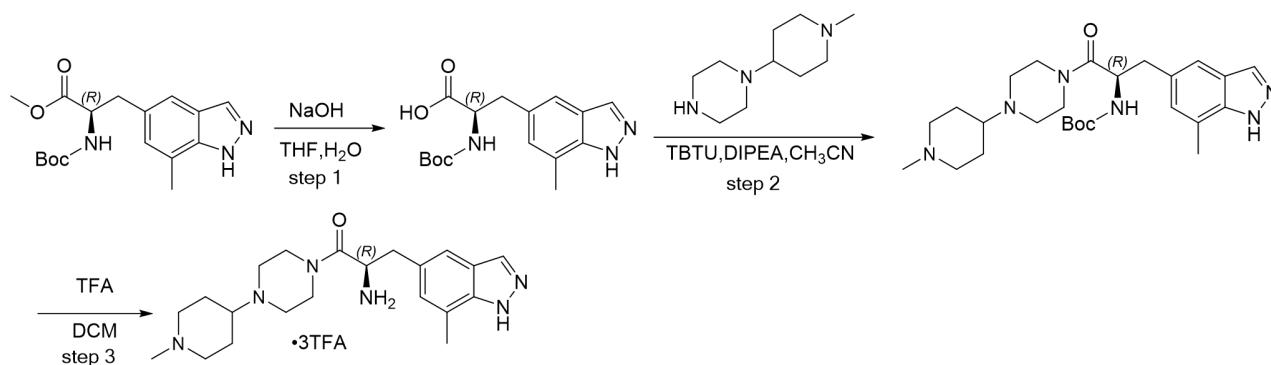
Step 8: preparation of 5-bromo-6-methoxy-2,3-dihydrothieno[2,3-*b*]pyridine



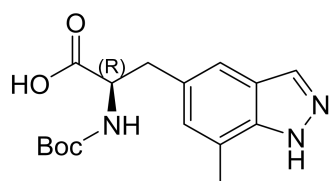
6-methoxy-2,3-dihydrothieno[2,3-*b*]pyridine (0.7 g) was dissolved in *N,N*-dimethylformamide (10 mL) and added with *N*-bromosuccinimide (0.8 g) to react for 1 hour. After the reaction was ended, the system was added into water, extracted with ethyl acetate for three times, sequentially washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 910 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 246.1, 248.1.

Preparation Example 14 of intermediate compound: preparation of (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one trifluoroacetate (available for Example 10)



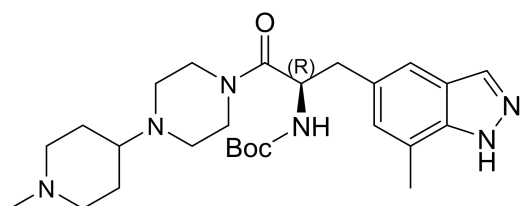
Step 1: preparation of (R)-2-((tert-butoxycarbonyl)amino)-3-(7-methyl-1H-indazole-5-yl)propionic acid



Methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(7-methyl-1H-indazole-5-yl)propionate (100 mg) was dissolved in tetrahydrofuran (3 mL) and water (1 mL), and added with sodium hydroxide (120 mg) to react at room temperature overnight. After the reaction was ended, the system was added with an appropriate amount of hydrochloric acid (0.5 N) to adjust a pH value of the system to be 5-6, and extracted with ethyl acetate for three times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 90.0 mg of crude product.

MS (ESI) m/z ($M+H$)⁺ = 320.1.

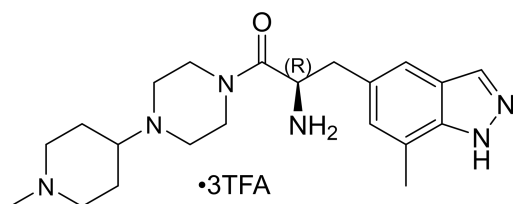
Step 2: preparation of tert-butyl (R)-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-ylcarbamate



(R)-2-((tert-butoxycarbonyl)amino)-3-(7-methyl-1H-indazole-5-yl)propionic acid (50 mg), 1-(1-methylpiperidine-4-yl)piperazine (57.18 mg), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethylurea tetrafluoroborate (60.02 mg) and *N,N*-diisopropylethylamine (40.32 mg) were dissolved in acetonitrile (10 mL) to react at room temperature for 4 hours. After the reaction was ended, the reaction system was concentrated to obtain a crude product, and the crude product was purified by column chromatography to obtain 30 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 485.2.

Step 3: preparation of (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one trifluoroacetate

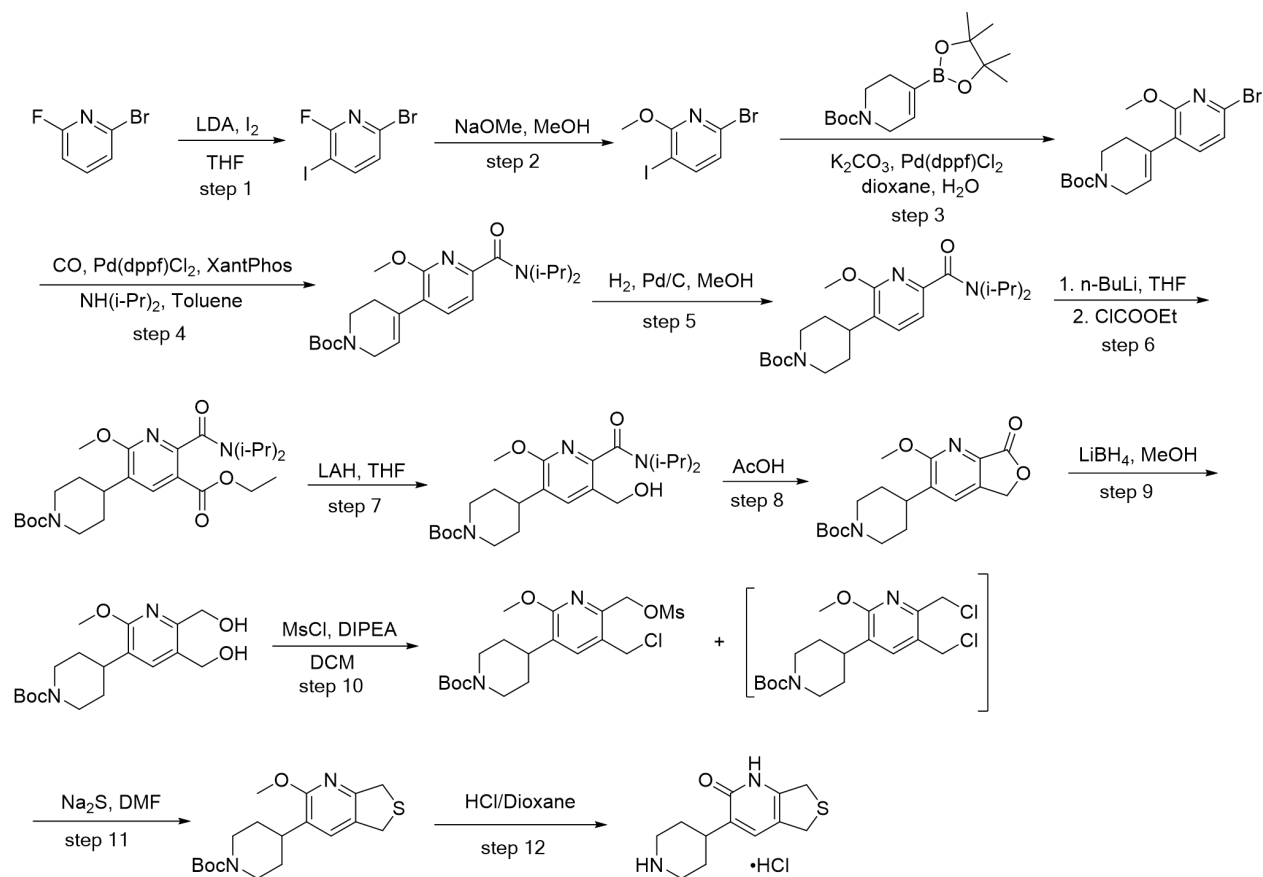


Tert-butyl

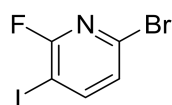
(R)-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)carbamate (30 mg) was dissolved in dichloromethane (1 mL) and trifluoroacetic acid (0.5 mL) to react at room temperature for 1 hour. After the reaction was ended, the reaction system was concentrated to obtain a crude product, which could be used in the next step of reaction without purification.

MS (ESI) m/z ($M+H$)⁺ = 385.2.

Preparation of 3-(piperidine-4-yl)-5,7-dihydrothieno[3,4-*b*]pyridine-2(1H)-one hydrochloride (available for Example 11)



Step 1: preparation of 6-bromo-2-fluoro-3-iodopyridine

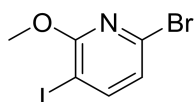


6-bromo-2-fluoropyridine (10.0 g) was dissolved in tetrahydrofuran (70 mL), subjected to nitrogen replacement, then cooled to -78°C, and dropwise added with lithium diisopropylamide (34.3 mL, 68.6 mmol) at this temperature to react at -78°C for 1 hour after the addition. The system was added with a tetrahydrofuran (50 mL) solution of iodine (14.5 g) to react at -78°C for 1.5 hours

after the addition. The system was added with 10 mL of water at -60°C for quenching and transferred to room temperature, the system was added with 100 mL of water and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 8.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 301.8.

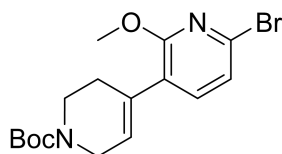
Step 2: preparation of 6-bromo-3-iodo-2-methoxypyridine



6-bromo-2-fluoro-3-iodopyridine (8.2 g) was dissolved in methanol (100 mL), added with sodium methoxide (4.4 g) and heated to 45°C to react for 1 hour. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, added with 500 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 8.4 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 313.9.

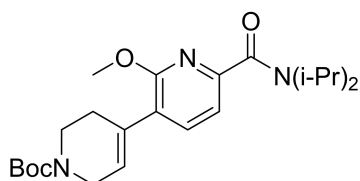
Step 3: preparation of tert-butyl 6-bromo-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'-(2'H)-formate



In a nitrogen atmosphere, 6-bromo-3-iodo-2-methoxypyridine (8.3 g), *N*-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (7.8 g) and potassium carbonate (7.3 g) were dissolved in 1,4-dioxane (100 mL) and water (10 mL), and added with 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (1.9 g) to react at 70°C overnight. After TLC showed that the reaction was completed, the reaction system was added with 100 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 7.3 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 369.1.

Step 4: preparation of tert-butyl 6-(diisopropyl carbamoyl)-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'-(2'H)-formate

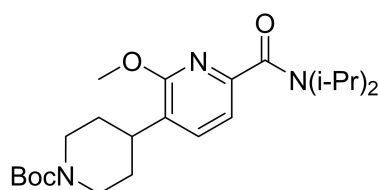


Tert-butyl 6-bromo-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'-(2'H)-formate (1.45 g) was put into a 100 mL autoclave, and added with toluene (15 mL), diisopropylamine (1.2 g), triethylamine (2.0 g), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (445.0 mg) and 1,1-bis(diphenylphosphine)ferrocene palladium dichloride (322.0 mg). The autoclave was sealed

after the addition, carbon monoxide gas was introduced after nitrogen replacement, the pressure was kept at 13 atmospheres, and the reaction system was heated to 90°C to react for 10 hours. After TLC showed that the reaction was completed, the reaction system was added with 50 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.5 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 418.3.

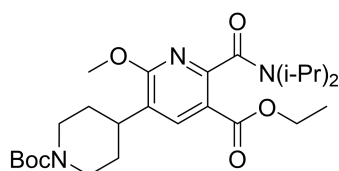
Step 5: preparation of tert-butyl 4-(6-(diisopropyl carbamoyl)-2-methoxypyridine-3-yl)piperidine-1-formate



Tert-butyl 6-(diisopropyl carbamoyl)-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-formate (6.0 g) was dissolved in methanol (100 mL), added with palladium carbon (0.6 g), subjected to nitrogen replacement, and then continuously introduced with hydrogen to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was directly filtered and concentrated to obtain 6.0 g of crude product.

MS (ESI) m/z (M+H)⁺ = 420.3.

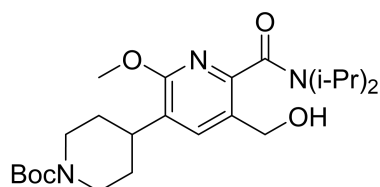
Step 6: preparation of ethyl 5-(1-(tert-butoxycarbonyl)piperidine-4-yl)-2-(diisopropyl carbamoyl)-6-methoxynicotinate.



Tert-butyl 4-(6-(diisopropyl carbamoyl)-2-methoxypyridine-3-yl)piperidine-1-formate (5.8 g) was dissolved in anhydrous tetrahydrofuran (60 mL), subjected to nitrogen replacement, then cooled to -78°C, and dropwise added with a hexane solution of n-butyl lithium (2.5 M, 6.6 mL) to react for 0.5 hour. The above system was slowly dropwise added into a tetrahydrofuran solution (40 mL) of ethyl chloroformate (7.5 g) at -78°C to react for 0.5 hour. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, added into 50 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 3.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 492.3.

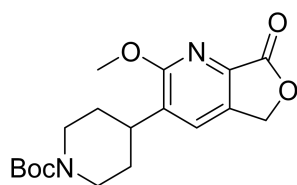
Step 7: preparation of tert-butyl 4-(6-(diisopropyl carbamoyl)-5-(hydroxymethyl)-2-methoxypyridine-3-yl)piperidine-1-formate



In ice water bath, ethyl 5-(1-(tert-butoxycarbonyl)piperidine-4-yl)-2-(diisopropyl carbamoyl)-6-methoxynicotinate (1.0 g) was dissolved in anhydrous tetrahydrofuran (5 mL), and slowly dropwise added into an anhydrous tetrahydrofuran (5 mL) suspension of lithium aluminum tetrahydroxide (77 mg) to react for 20 minutes. After TLC showed that the reaction was completed, the system was sequentially added with 77 μ L of water, 77 μ L of 15% NaOH aqueous solution and 231 μ L of water in ice water bath, transferred to room temperature and stirred for 10 minutes, then added with an appropriate amount of anhydrous sodium sulfate, and stirred at room temperature for 10 minutes. The reaction system was filtered and concentrated to obtain 0.9 g of crude product.

MS (ESI) m/z (M+H)⁺ = 450.3.

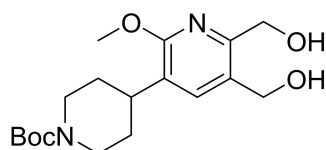
Step 8: preparation of tert-butyl 4-(2-methoxy-7-oxo-5,7-dihydrofuro[3,4-*b*]pyridine-3-yl)piperidine-1-formate



The tert-butyl 4-(6-(diisopropyl carbamoyl)-5-(hydroxymethyl)-2-methoxypyridine-3-yl)piperidine-1-formate crude product (0.9 g) was dissolved in acetic acid (9 mL), and heated to 90 °C to react for 2 hours. After TLC showed that the reaction was completed, the system was concentrated, and the obtained crude product was purified by column chromatography to obtain 502.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 349.2.

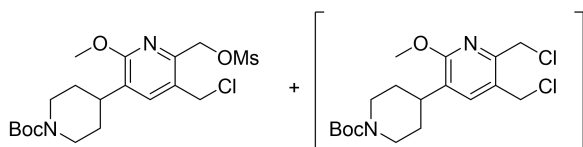
Step 9: preparation of tert-butyl 4-(5,6-bis(hydroxymethyl)-2-methoxypyridine-3-yl)piperidine-1-formate



Tert-butyl 4-(2-methoxy-7-oxo-5,7-dihydrofuro[3,4-*b*]pyridine-3-yl)piperidine-1-formate (300.0 mg) was dissolved in methanol (3 mL), added with lithium borohydride (56.0 mg), and heated to 50°C to react for 2 hours. After TLC showed that the reaction was completed, the reaction solution was added with 1 M dilute hydrochloric acid to adjust pH to be neutral, the system was concentrated, and the obtained crude product was purified by column chromatography to obtain 210.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 353.2.

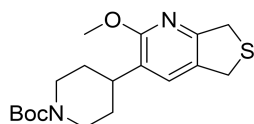
Step 10: preparation of tert-butyl 4-(5-(chloromethyl)-2-methoxy-6-((methylsulfonyl)oxymethyl)pyridine-3-yl)piperidine-1-formate mixture



Methanesulfonyl chloride (195.0 mg) was dissolved in dichloromethane (2 mL), added with a dichloromethane (2 mL) mixed solution of tert-butyl 4-(5,6-bis(hydroxymethyl)-2-methoxypyridine-3-yl)piperidine-1-formate (150.0 mg) and *N,N*-diisopropylethylamine (219.0 mg) in ice water bath, stirred for 20 minutes, and transferred to room temperature to react for 1 hour. After TLC showed that the reaction was completed, the system was concentrated, and the obtained crude product was purified by column chromatography to obtain 180.0 mg of mixture.

MS (ESI) m/z (M+H)⁺ = 449.1 and 389.1.

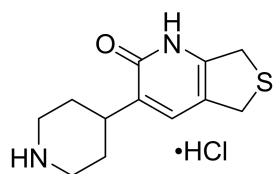
Step 11: preparation of tert-butyl 4-(2-methoxy-5,7-dihydrothieno[3,4-*b*]pyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, the tert-butyl 4-(5-(chloromethyl)-2-methoxy-6-((methylsulfonyl)oxymethyl)pyridine-3-yl)piperidine-1-formate mixture (200.0 mg) was dissolved in *N,N*-dimethylformamide (5 mL), and slowly dropwise added with an *N,N*-dimethylformamide (2 mL) suspension of sodium sulfide (37.0 mg) to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with pure water twice, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 67.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 351.2.

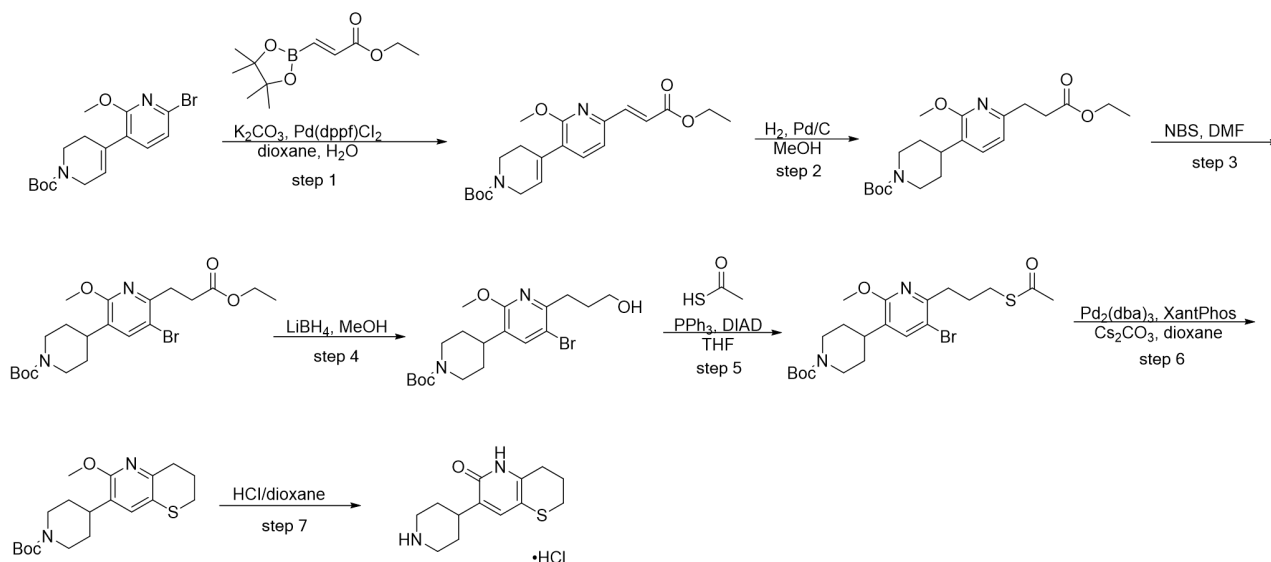
Step 12: preparation of 3-(piperidine-4-yl)-5,7-dihydrothieno[3,4-*b*]pyridine-2(1H)-one hydrochloride



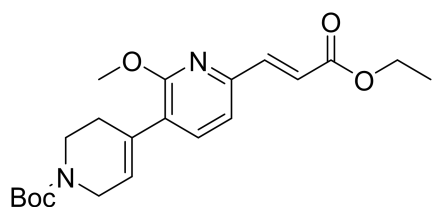
Tert-butyl 4-(2-methoxy-5,7-dihydrothieno[3,4-*b*]pyridine-3-yl)piperidine-1-formate (67.0 mg) was dissolved in a 1,4-dioxane solution (4 M, 5 mL) of hydrochloric acid, and heated to 90°C to react for 3 hours. After TLC showed that the reaction was completed, the system was concentrated to obtain 51.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 237.1.

Preparation Example 16: preparation of 7-(piperidine-4-yl)-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine-6(5H)-one hydrochloride (available for Example 12)



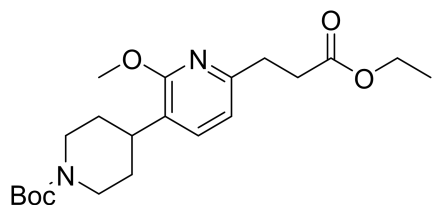
Step 1: preparation of tert-butyl (E)-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-formate



In a nitrogen atmosphere, tert-butyl 6-bromo-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-formate (2.0 g), ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborane-2-yl)acrylate (1.23 g), potassium carbonate (1.11 g) and [1,1'-bis(diphenylphosphine)ferrocene]palladium dichloride (II) (382 mg) were dissolved in 1,4-dioxane (15 mL) and water (1.5 mL) to react at 90°C for 3 hours. After the reaction was ended, the system was added into an appropriate amount of water and extracted with ethyl acetate (200 mL), and the organic phases were combined, washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 2.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 389.1.

Step 2: preparation of tert-butyl 4-(6-(3-ethoxy-3-oxopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate

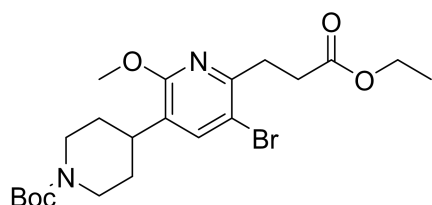


Tert-butyl

(E)-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-formate (2.0 g) was dissolved in methanol (30 mL), added with 10% palladium carbon (0.15 g), and heated at 55°C in a hydrogen atmosphere for 1 hour. After the reaction was ended, the palladium carbon was removed by suction filtration, the solid was washed with methanol (100 mL), and the filtrates were combined and concentrated under a reduced pressure to obtain 2.0 g of crude product.

MS (ESI) m/z (M+H)⁺ = 393.1.

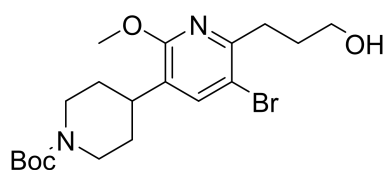
Step 3: preparation of tert-butyl 4-(5-bromo-6-(3-ethoxy-3-oxopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate



Tert-butyl 4-(6-(3-ethoxy-3-oxopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate (850 mg) was dissolved in *N,N*-dimethylformamide (8 mL) and added with *N*-bromosuccinimide (386 mg) to react at room temperature for 2 hours. After the reaction was ended, the system was added into an appropriate amount of water and extracted with ethyl acetate (100 mL), and the organic phases were combined, washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 1.1 g of crude product, which was directly used in the next step of reaction.

MS (ESI) m/z (M+H)⁺ = 471.1.

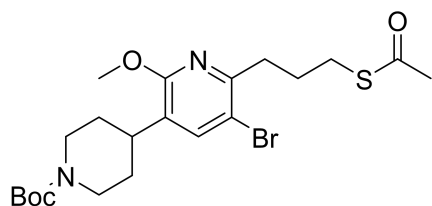
Step 4: preparation of tert-butyl 4-(5-bromo-6-(3-hydroxypropyl)-2-methoxypyridine-3-yl)piperidine-1-formate



The tert-butyl 4-(5-bromo-6-(3-ethoxy-3-oxopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate crude product (1.1 g) was dissolved in methanol (20 mL), and added with lithium borohydride (1.08 g) in batches to react at room temperature for 3 hours. After LCMS monitoring showed that the reaction was ended, the system was concentrated to remove the solvent, added with an appropriate amount of saturated ammonium chloride solution for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtain crude product was purified by column chromatography to obtain 770 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 429.1.

Step 5: preparation of tert-butyl 4-(6-(3-(acetylthio)propyl)-5-bromo-2-methoxypyridine-3-yl)piperidine-1-formate

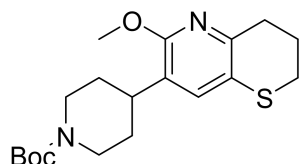


In a nitrogen atmosphere, in ice water bath, tert-butyl 4-(5-bromo-6-(3-hydroxypropyl)-2-methoxypyridine-3-yl)piperidine-1-formate (300 mg) and triphenylphosphine (368 mg) were dissolved in tetrahydrofuran (10 mL), and added with diethyl azodicarboxylate (284 mg). 10 minutes later, the system was added with thioacetic acid (106 mg) and transferred to room temperature to react for 1.5 hours. The reaction system was diluted with an

appropriate amount of hexane, the white precipitate was filtered out, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 330 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 487.1.

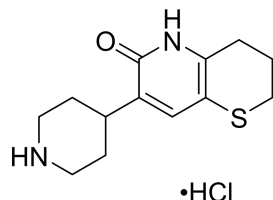
Step 6: preparation of tert-butyl 4-(6-methoxy-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine-7-yl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl 4-(6-(3-(acetylthio)propyl)-5-bromo-2-methoxypyridine-3-yl)piperidine-1-formate (330 mg), cesium carbonate (443 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (23 mg) and tris(dibenzylideneacetone)dipalladium (27 mg) were dissolved in 1,4-dioxane (3 mL), and heated at 100°C for 12 hours. After the reaction was ended, the system was added into an appropriate amount of water and extracted with ethyl acetate (20 mL), and the organic phases were combined, backwashed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 210 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 365.1.

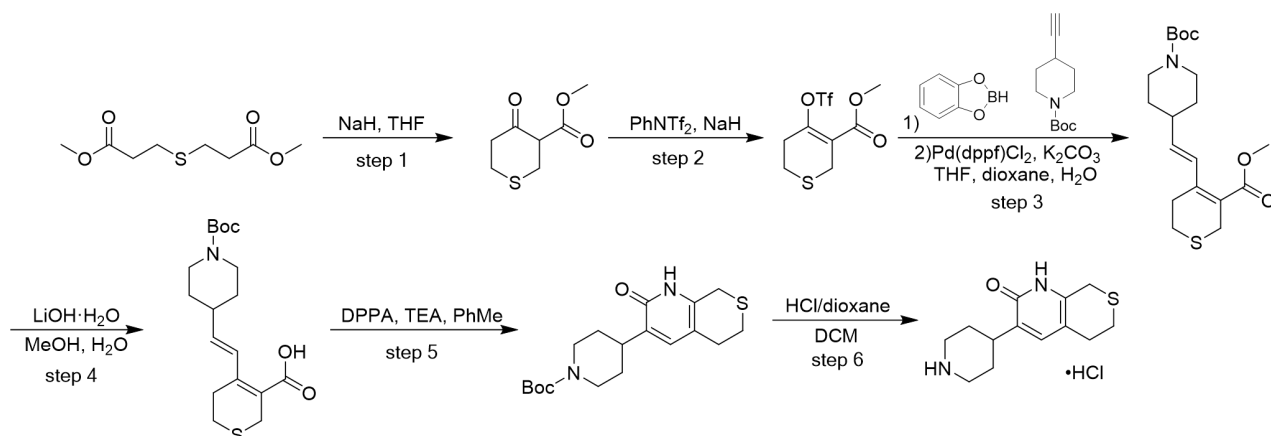
Step 7: preparation of 7-(piperidine-4-yl)-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine-6(5H)-one hydrochloride



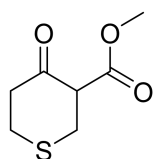
Tert-butyl 4-(6-methoxy-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine-7-yl)piperidine-1-formate (210 mg) was dissolved in hydrogen chloride/1,4-dioxane solution (4.0 M, 5 mL) to react at 90°C for 5 hours. The reaction system was cooled to room temperature, and treated in vacuum to remove the solvent to obtain 230 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 251.1.

Preparation Example 17: preparation of 3-(piperidine-4-yl)-5,8-dihydro-1H-thiopyrano[3,4-*b*]pyridine-2(6H)-one hydrochloride (available for Example 13)



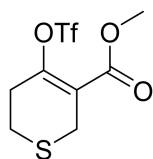
Step 1: preparation of methyl 4-oxotetrahydro-2H-thiopyran-3-formate



In a nitrogen atmosphere, in ice water bath, an anhydrous tetrahydrofuran (15 mL) suspension of sodium hydride (1.45 g) was slowly dropwise added with an anhydrous tetrahydrofuran (30 mL) solution of dimethyl 3,3'-thiodipropionate (5.0 g), and transferred to room temperature to react overnight. After LCMS showed that the reaction of raw materials was completed, the system was added with an appropriate amount of saturated ammonium chloride solution for quenching and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 3.65 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 175.0.

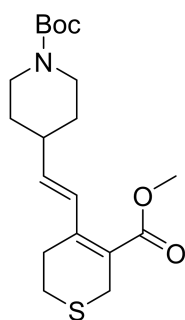
Step 2: preparation of methyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydro-2H-thiopyran-3-formate



In a nitrogen atmosphere, in ice water bath, an anhydrous tetrahydrofuran (10 mL) suspension of sodium hydride (1.09 g) was slowly dropwise added with an anhydrous tetrahydrofuran (30 mL) solution of methyl 4-oxotetrahydro-2H-thiopyran-3-formate (3.65 g), and transferred to room temperature to react for 1 hour. The system was added with an anhydrous tetrahydrofuran (20 mL) solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonylmethanesulfonamide (8.23 g) to react at room temperature overnight. After LCMS showed that the reaction of raw materials was completed, the system was added with an appropriate amount of saturated ammonium chloride solution for quenching and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 5.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 306.9.

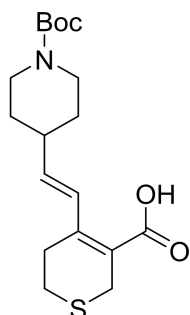
Step 3: preparation of tert-butyl (E)-4-(2-(5-(methoxycarbonyl)-3,6-dihydro-2H-thiopyran-4-yl)vinyl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl 4-ethynyl piperidine-1-formate (1.0 g) was dissolved in anhydrous tetrahydrofuran (4 mL), slowly added with an anhydrous tetrahydrofuran (4 mL) solution of catecholborane (0.69 g) to react at 70°C for 4 hours, and then cooled to room temperature. Methyl 4-((trifluoromethyl)sulfonyl)oxy)-5,6-dihydro-2H-thiopyran-3-formate (1.5 g), 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (II) (183 mg) and potassium carbonate (2.03 g) were dissolved in dioxane (10 mL) and water (1 mL), slowly dropwise added into the above reaction solution, and heated to 70°C to continuously react for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was filtered, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 1.3 g of the title compound.

MS (ESI) m/z (M+H-100)⁺ = 267.9.

Step 4: preparation of (E)-4-(2-(1-(tert-butoxycarbonyl)piperidine-4-yl)vinyl)-5,6-dihydro-2H-thiopyran-3-formic acid

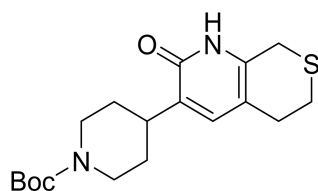


Tert-butyl

(E)-4-(2-(5-(methoxycarbonyl)-3,6-dihydro-2H-thiopyran-4-yl)vinyl)piperidine-1-formate (230 mg) was dissolved in methanol (2 mL) and water (0.5 mL), and added with lithium hydroxide monohydrate (131.4 mg) to react overnight. After LCMS showed that the reaction was completed, the reaction solution was neutralized with 2 M hydrochloric acid and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 200 mg of the title compound.

MS (ESI) m/z (M+H-100)⁺ = 253.9.

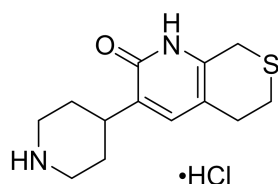
Step 5: preparation of tert-butyl 4-(2-oxo-2,5,6,8-tetrahydro-1H-thiopyrano[3,4-b]pyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, (*E*)-4-(2-(1-(tert-butoxycarbonyl)piperidine-4-yl)vinyl)-5,6-dihydro-2*H*-thiopyran-3-formic acid (200 mg) and diphenylphosphoryl azide (155.7 mg) were dissolved in anhydrous toluene (3 mL), and added with triethylamine (85.9 mg) to react at room temperature for 2 hours. The reaction system was heated to 80°C to continuously react for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was concentrated, and the obtained crude product was purified by column chromatography to obtain 100 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 250.9.

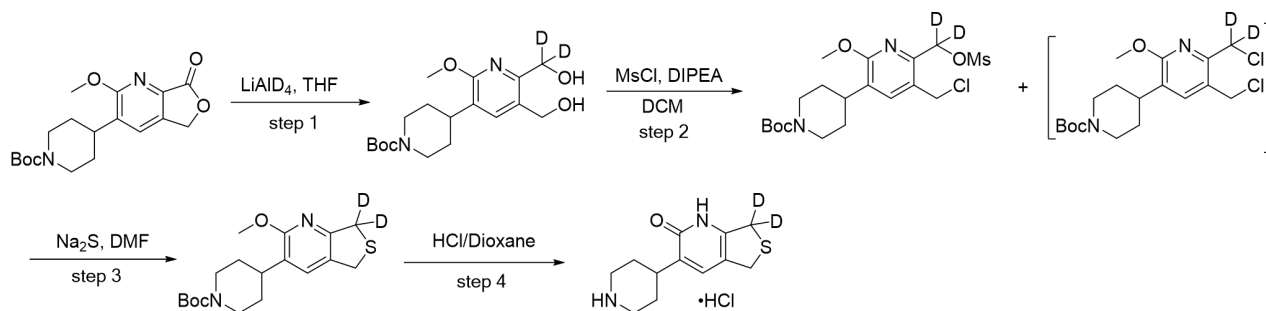
Step 6: preparation of 3-(piperidine-4-yl)-5,8-dihydro-1*H*-thiopyrano[3,4-*b*]pyridine-2(6*H*)-one hydrochloride



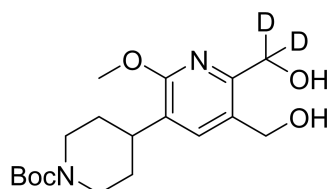
Tert-butyl 4-(2-oxo-2,5,6,8-tetrahydro-1*H*-thiopyrano[3,4-*b*]pyridine-3-yl)piperidine-1-formate (100 mg) was dissolved in dichloromethane (2 mL), and added with hydrochloric acid/1,4-dioxane solution (4 M, 1 mL) to react at room temperature for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was concentrated to obtain 80 mg of crude product, which was directly used in the next step of reaction.

MS (ESI) m/z ($M+H$)⁺ = 250.9.

Preparation of Example 18: 3-(piperidine-4-yl)-5,7-dihydrothieno[3,4-*b*]pyridine-2(1*H*)-one-7,7-*d*2 hydrochloride (available for Example 14)



Step 1: preparation of tert-butyl 4-(5-(hydroxymethyl)-6-(hydroxymethyl-*d*2)-2-methoxypyridine-3-yl)piperidine-1-formate



In ice water bath, tert-butyl 4-(2-methoxy-7-oxo-5,7-dihydrofuro[3,4-*b*]pyridine-3-yl)piperidine-1-formate (200.0 mg) was dissolved in anhydrous tetrahydrofuran (1 mL), and slowly dropwise added into an anhydrous tetrahydrofuran (1 mL) suspension of lithium aluminum deuteride (24.0 mg) to react for 20 minutes. After TLC showed that the reaction was completed, the system was sequentially added with 24 μ L of water, 24 μ L of 15% NaOH aqueous solution and 72 μ L of water, transferred to room

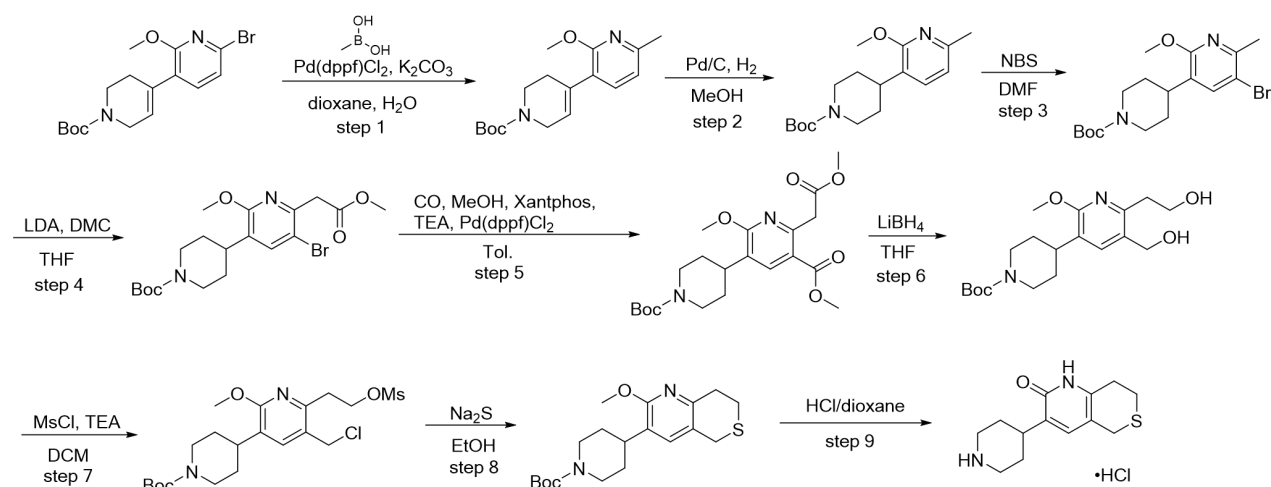
temperature and stirred for 10 minutes, then added with an appropriate amount of anhydrous sodium sulfate, and stirred at room temperature for 10 minutes. The reaction system was filtered, and the filtrate was collected and concentrated to obtain 166.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 355.2.

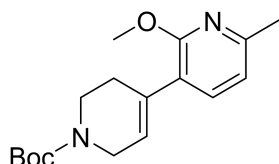
Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to that in Preparation Example 15 of intermediate compound above.

MS (ESI) m/z (M+H)⁺ = 239.1.

Preparation Example 19: preparation of 3-(piperidine-4-yl)-1,5,7,8-tetrahydro-2H-thiopyrano[4,3-b]pyridine-2-one hydrochloride (available for Example 15)



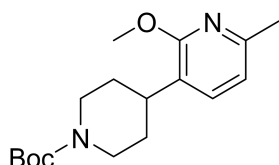
Step 1: preparation of tert-butyl 2-methoxy-6-methyl-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-formate



In a nitrogen atmosphere, tert-butyl 6-bromo-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'H)-formate (3 g) was dissolved in 1,4-dioxane (30 mL) and water (3 mL), and added with methyl boric acid (1.5 g), potassium carbonate (2.3 g) and [1,1'-bis(di-tert-butylphosphine)ferrocene]palladium dichloride (0.53 g) to react at 80°C for 2 hours. After LCMS showed that the reaction was completed, the reaction system was transferred to room temperature, added with a small amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 2.4 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 305.1.

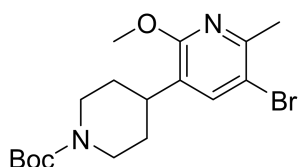
Step 2: preparation of tert-butyl 4-(2-methoxy-6-methylpyridine-3-yl)piperidine-1-formate



Tert-butyl 2-methoxy-6-methyl-3',6'-dihydro-[3,4'-bipyridine]-1'(2'*H*)-formate (2.4 g) was dissolved in methanol (30 mL) and added with palladium carbon (100 mg), and the reaction system was introduced with hydrogen to react at room temperature for 2 hours. After LCMS showed that the reaction was completed, the reaction solution was filtered, and the filtrate was collected and rotationally evaporated to remove excess solvent. The obtained crude product was purified by column chromatography to obtain 2.3 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 307.1.

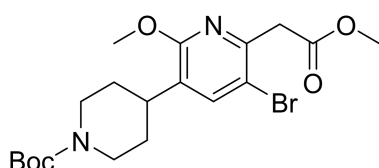
Step 3: preparation of tert-butyl 4-(5-bromo-2-methoxy-6-methylpyridine-3-yl)piperidine-1-formate



Tert-butyl 4-(2-methoxy-6-methylpyridine-3-yl)piperidine-1-formate (2.3 g) was dissolved in *N,N*-dimethylformamide (25 mL) and added with *N*-bromosuccinimide (1.6 g) to react at room temperature for 1 hour. After LCMS showed that the reaction was completed, the reaction system was added with a small amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 2.6 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 385.0.

Step 4: preparation of tert-butyl 4-(5-bromo-2-methoxy-6-(2-methoxy-2-oxoethyl)pyridine-3-yl)piperidine-1-formate

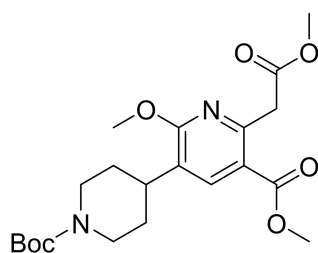


In a nitrogen atmosphere, tert-butyl 4-(5-bromo-2-methoxy-6-methylpyridine-3-yl)piperidine-1-formate (2.6 g) was dissolved in tetrahydrofuran (30 mL) at -78°C, slowly dropwise added with lithium diisopropylamine (1 M, 10.2 mL), and stirred for 20 minutes. Dimethyl carbonate (1.3 g) was dissolved in tetrahydrofuran (10 mL), slowly dropwise added into the above reaction solution, and stirred for 20 minutes. After TLC showed that the reaction was completed, the reaction solution was transferred to room temperature, added with an appropriate amount of saturated ammonium chloride aqueous solution, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 90 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 443.1.

Step 5: preparation of methyl 5-(1-(tert-butoxycarbonyl)piperidine-4-yl)-6-methoxy-2-(2-methoxy

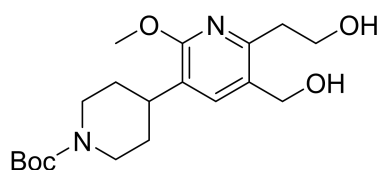
2-oxoethyl)nicotinate



Tert-butyl 4-(5-bromo-2-methoxy-6-(2-methoxy-2-oxoethyl)pyridine-3-yl)piperidine-1-formate (1 g) was dissolved in toluene (10 mL) and methanol (1 mL), and added with triethylamine (0.7 g), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.14 g) and [1,1'-bis(di-tert-butylphosphine)ferrocene]palladium dichloride (0.16 g). The reaction system was fully filled with carbon monoxide to react at 100°C for 10 hours. After LCMS showed that the reaction was completed, the reaction solution was transferred to room temperature, added with a small amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 750 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 423.1.

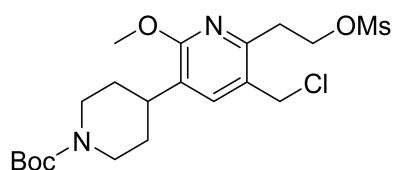
Step 6: preparation of tert-butyl 4-(6-(2-hydroxyethyl)-5-(hydroxymethyl)-2-methoxypyridine-3-yl)piperidine-1-formate



In ice water bath, methyl 5-(1-(tert-butoxycarbonyl)piperidine-4-yl)-6-methoxy-2-(2-methoxy-2-oxoethyl)nicotinate (750 mg) was dissolved in tetrahydrofuran (10 mL), added with lithium borohydride (112 mg), and transferred to room temperature to react for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was added with an appropriate amount of saturated ammonium chloride aqueous solution, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 560 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 367.1.

Step 7: preparation of tert-butyl 4-(5-(chloromethyl)-2-methoxy-6-(2-((methylsulfonyl)oxy)ethyl)pyridine-3-yl)piperidine-1-formate

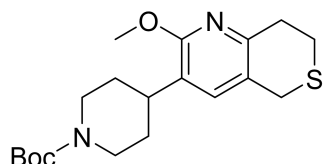


In ice water bath, tert-butyl 4-(6-(2-hydroxyethyl)-5-(hydroxymethyl)-2-methoxypyridine-3-yl)piperidine-1-formate (560 mg) was dissolved in dichloromethane (8 mL), added with triethylamine (455 mg) and methanesulfonyl chloride (431 mg), and transferred to room temperature to react for 1 hour. After LCMS showed

that the reaction was completed, the reaction solution was rotationally evaporated to remove excess solvent. The obtained crude product was purified by column chromatography to obtain 620 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 463.0.

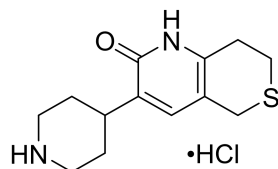
Step 8: preparation of tert-butyl 4-(2-methoxy-7,8-dihydro-5H-thiopyrano[4,3-*b*]pyridine-3-yl)piperidine-1-formate



4-(5-(chloromethyl)-2-methoxy-6-(2-((methylsulfonyl)oxy)ethyl)pyridine-3-yl)piperidine-1-formate (180 mg) was dissolved in ethanol (20 mL) at room temperature, and added with sodium sulfide (70 mg) to react at 80°C for 0.5 hour. After LCMS showed that the reaction was completed, the reaction solution was rotationally evaporated to remove excess solvent, added with water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 110 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 365.1.

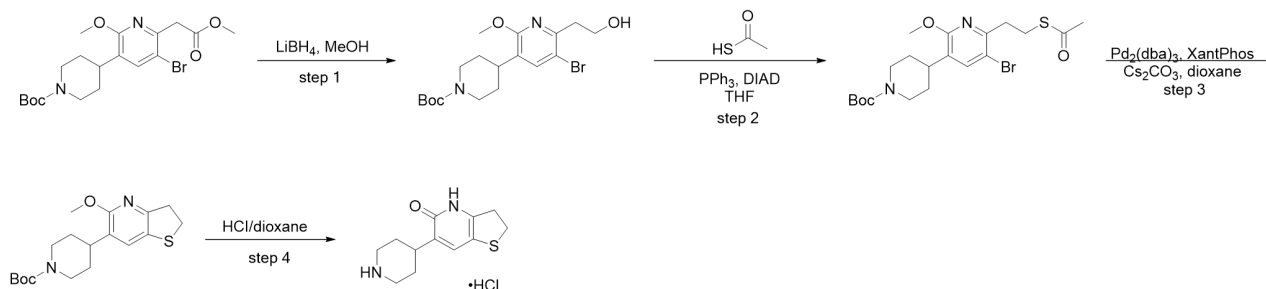
Step 9: preparation of 3-(piperidine-4-yl)-1,5,7,8-tetrahydro-2H-thiopyrano[4,3-*b*]pyridine-2-one hydrochloride



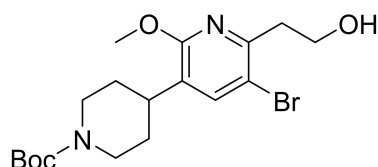
Tert-butyl 4-(2-methoxy-7,8-dihydro-5H-thiopyrano[4,3-*b*]pyridine-3-yl)piperidine-1-formate (100.0 mg, 0.3 mmol) was dissolved in a dioxane solution of 4 N hydrochloric acid (1 ml) at room temperature to react at 90°C for 1 hour. After LCMS monitoring showed that the reaction was completed, the reaction solution was directly spin-dried to obtain a pale yellow solid (110 mg, crude).

MS (ESI) m/z (M+H)⁺ = 251.0.

Preparation Example 20: preparation of 6-(piperidine-4-yl)-2,3-dihydrothieno[3,2-*b*]pyridine-5(4H)-one hydrochloride (available for Example 17)



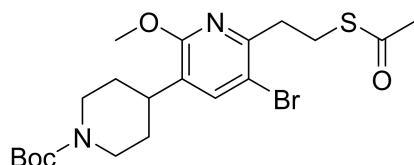
Step 1: preparation of tert-butyl 4-(5-bromo-6-(2-hydroxyethyl)-2-methoxypyridine-3-yl)piperidine-1-formate



Tert-butyl 4-(5-bromo-2-methoxy-6-(2-methoxy-2-oxoethyl)pyridine-3-yl)piperidine-1-formate (120 mg) was dissolved in methanol (5 mL), and added with lithium borohydride (36 mg) in batches to react at room temperature for 3 hours. After LCMS monitoring showed that the reaction was ended, the system was treated in vacuum to remove the solvent, added with an appropriate amount of saturated ammonium chloride solution for quenching, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 100 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 415.1.

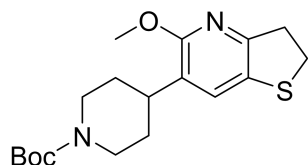
Step 2: preparation of tert-butyl 4-(6-(2-(acetylthio)ethyl)-5-bromo-2-methoxypyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, in ice water bath, tert-butyl 4-(5-bromo-6-(2-hydroxyethyl)-2-methoxypyridine-3-yl)piperidine-1-formate (100 mg) and triphenylphosphine (131 mg) were dissolved in anhydrous tetrahydrofuran (5 mL), and added with diethyl azodiformate (101 mg). 10 minutes later, the system was added with thioacetic acid (38 mg) to react at room temperature for 1.5 hours. The reaction system was diluted with an appropriate amount of hexane, the white precipitate was filtered out, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 80 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 473.1.

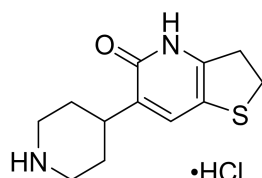
Step 3: preparation of tert-butyl 4-(5-methoxy-2,3-dihydrothieno[3,2-*b*]pyridine-6-yl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl 4-(6-(2-(acetylthio)ethyl)-5-bromo-2-methoxypyridine-3-yl)piperidine-1-formate (80 mg), cesium carbonate (110 mg), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (23 mg) and tris(dibenzylideneacetone)dipalladium (27 mg) were dissolved in 1,4-dioxane (3 mL) to react at 100°C for 12 hours. After the reaction was ended, the system was added into an appropriate amount of water and extracted with ethyl acetate (10 mL), and the organic phases were combined, washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 50 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 351.1.

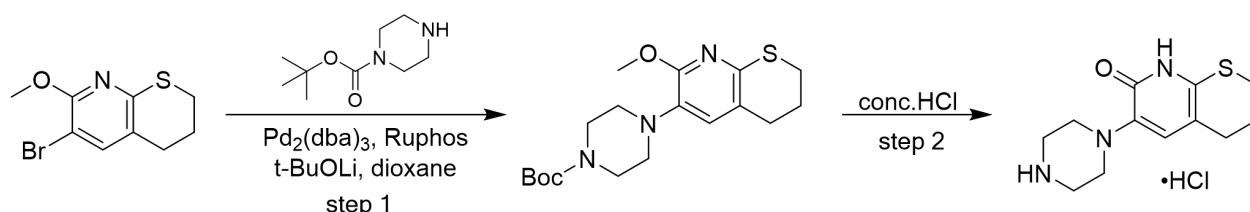
Step 4: preparation of 6-(piperidine-4-yl)-2,3-dihydrothieno[3,2-*b*]pyridine-5(4H)-one hydrochloride



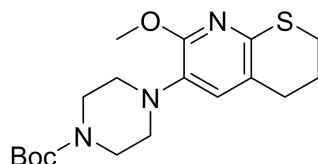
Tert-butyl 4-(5-methoxy-2,3-dihydrothieno[3,2-*b*]pyridine-6-yl)piperidine-1-formate (50 mg) was dissolved in hydrogen chloride/1,4-dioxane solution (4.0 M, 5 mL) to react at 90°C for 5 hours. The reaction system was cooled to room temperature, and treated in vacuum to remove the solvent to obtain 55 mg of crude product, which was directly used in the next step of reaction.

MS (ESI) m/z (M+H)⁺ = 237.1.

Preparation Example 21: preparation of 6-(piperazine-1-yl)-2,3,4,8-tetrahydro-7H-thiopyrano[2,3-*b*]pyridine-7-one hydrochloride (available for Example 18)



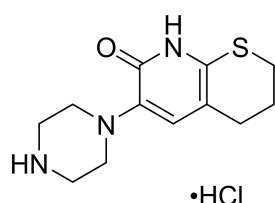
Step 1: preparation of tert-butyl 4-(7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperazine-1-formate



In a nitrogen atmosphere, 6-bromo-7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-*b*]pyridine (50.0 mg), tert-butyl piperazine-1-formate (43.0 mg), tris(dibenzylideneacetone)dipalladium (17.4 mg), 2-dicyclohexylphosphine-2',6'-diisopropylbiphenyl (17.7 mg) and lithium tert-butoxide (30.4 mg) were dissolved in dioxane (1 mL) to react at 100°C for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was filtered, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 60.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 365.9.

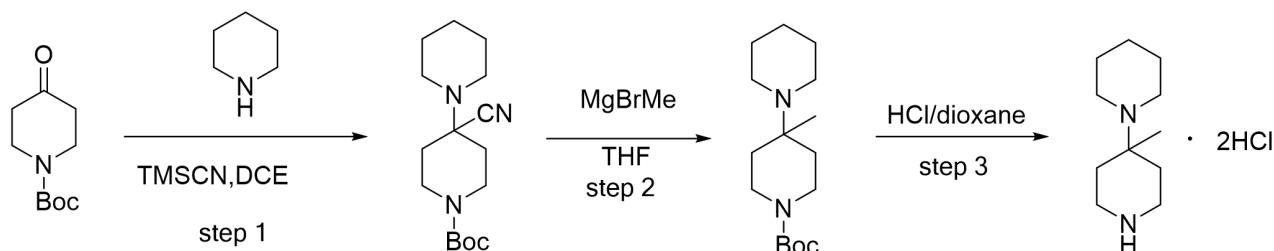
Step 2: preparation of 6-(piperazine-1-yl)-2,3,4,8-tetrahydro-7H-thiopyrano[2,3-*b*]pyridine-7-one hydrochloride



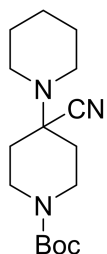
Tert-butyl 4-(7-methoxy-3,4-dihydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperazine-1-formate (60 mg) was dissolved in concentrated hydrochloric acid (2 mL) to react at 95°C for 2 hours. After LCMS showed that the reaction was completed, the reaction solution was concentrated to obtain 40 mg of crude product, which was directly used in the next step of reaction.

MS (ESI) m/z (M+H)⁺ = 251.9.

Preparation Example 22: preparation of 4'-methyl-1,4'-bipiperidine hydrochloride (available for Example 22)



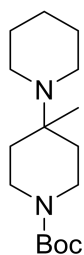
Step 1: preparation of tert-butyl 4'-cyano-[1,4'-bipiperidine]-1'-formate



Tert-butyl 4-oxopiperidine-1-formate (2 g), piperidine (1.7 g) and trimethylsilyl cyanide (1.29 g) were dissolved in 1,2-dichloroethane (20 mL) to react at 70°C overnight. After the reaction was ended, the reaction solution was added with a small amount of water and extracted with ethyl acetate, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was separated and purified by silica gel column chromatography to obtain 1.1 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 294.2.

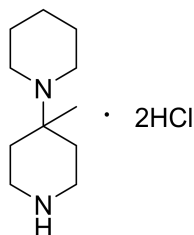
Step 2: preparation of tert-butyl 4'-methyl-[1,4'-bipiperidine]-1'-formate



In a nitrogen atmosphere, in ice water bath, tert-butyl 4'-cyano-[1,4'-bipiperidine]-1'-formate (700 mg) was dissolved in anhydrous tetrahydrofuran (5 mL), and slowly dropwise added with a magnesium methyl bromide solution (3 N, 2.4 mL) to react for 1 hour. The reaction system was recovered to room temperature to continuously react for 1 hour. After the reaction was ended, the reaction system was added with a small amount of water for quenching and extracted with ethyl acetate, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was separated and purified by silica gel column chromatography to obtain 480 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 283.2.

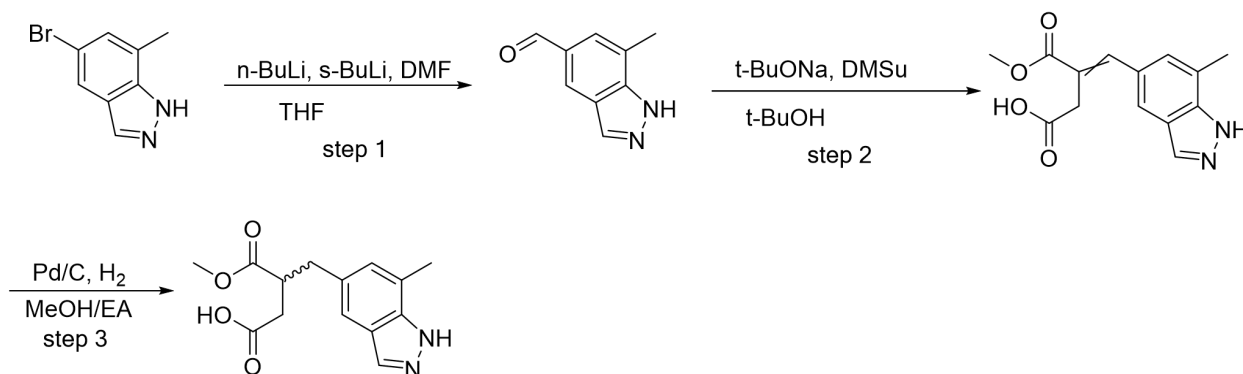
Step 3: preparation of 4'-methyl-1,4'-bipiperidine hydrochloride



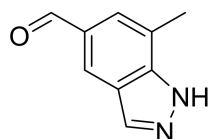
Tert-butyl 4'-methyl-[1,4'-bipiperidine]-1'-formate (100 mg) was dissolved in hydrochloric acid/1,4-dioxane solution (4 N, 4 mL) to react at room temperature for 2 hours. After the reaction was ended, the reaction system was concentrated to obtain 70 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 183.2.

Preparation Example 23: preparation of 4-methoxy-3-((7-methyl-1H-indazole-5-yl)methyl)-4-oxobutyrac acid (available for Example 27)



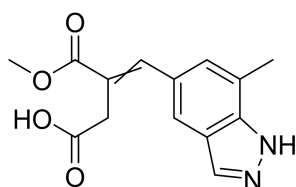
Step 1: preparation of 7-methyl-1H-indazole-5-formaldehyde



In a nitrogen atmosphere, 5-bromo-7-methyl-1H-indazole (500 mg) was dissolved in tetrahydrofuran (5 mL) at -78°C, added with n-butyl lithium (1.5 M, 2.4 mL) and sec-butyl lithium (1 M, 3.6 mL), and stirred for 1 hour. The system was dropwise added with N,N-dimethylformamide (533 mg) to continuously react for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was transferred to room temperature, added with an appropriate amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 350 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 161.1.

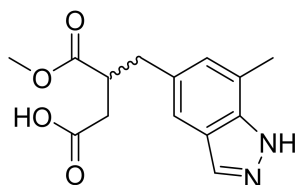
Step 2: preparation of 3-(methoxycarbonyl)-4-(7-methyl-1H-indazole-5-yl)but-3-enoic acid



7-methyl-1H-indazole-5-formaldehyde (350 mg) was dissolved in tert-butyl alcohol (5 mL), and added with sodium tert-butoxide (422.4 mg) and dimethyl succinate (481.8 mg) to react at 50°C for 5 hours. After LCMS monitoring showed that the reaction was completed, the reaction solution was transferred to room temperature, added with an appropriate amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 800 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 275.1

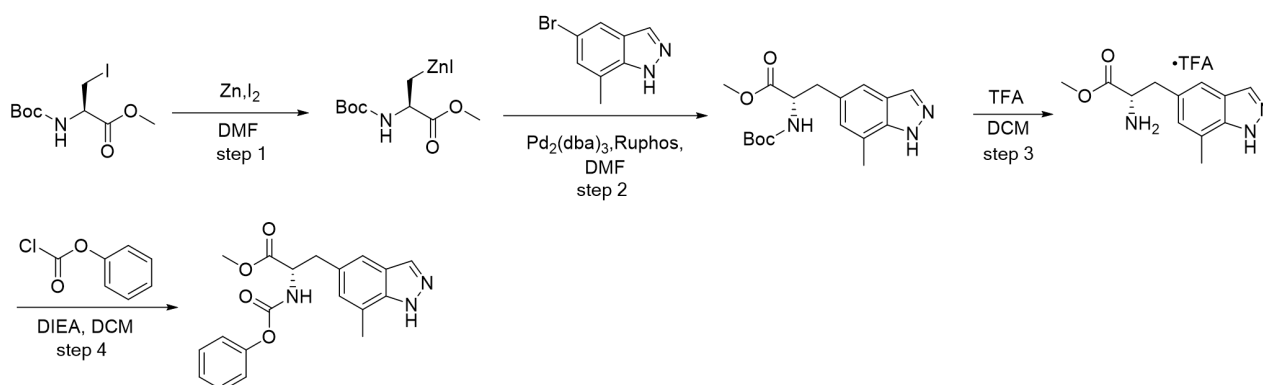
Step 3: preparation of 4-methoxy-3-((7-methyl-1H-indazole-5-yl)methyl)-4-oxobutanoic acid



3-(methoxycarbonyl)-4-(7-methyl-1H-indazole-5-yl)but-3-enoic acid (800 mg) was dissolved in methanol (10 mL) and ethyl acetate (10 mL), and added with palladium carbon (100 mg). The reaction system was introduced with hydrogen to react at room temperature overnight. After LCMS monitoring showed that the reaction was completed, the reaction solution was filtered, and the filtrate was collected and rotationally evaporated to remove excess solvent to obtain 800 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 277.1.

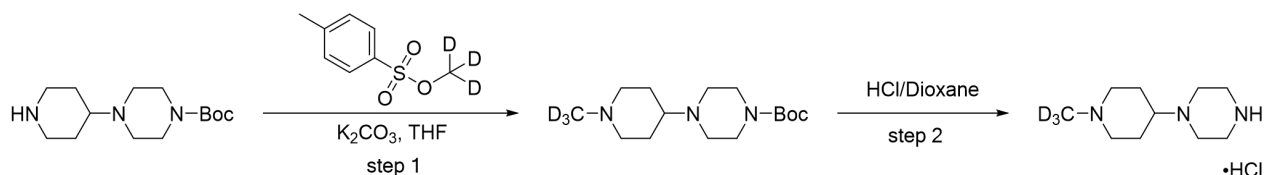
Preparation Example 24: preparation of methyl (S)-3-(7-methyl-1H-indazole-5-yl)-2-((phenoxycarbonyl)amino)propionate (available for Example 28)



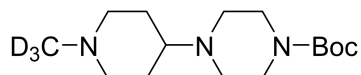
Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to those in Preparation Example 3 of intermediate compound and Preparation Example 5 of intermediate compound above.

MS (ESI) m/z (M+H)⁺ = 354.1.

Preparation Example 25: preparation of 1-(1-(methyl-d3)piperidine-4-yl)piperazine hydrochloride (available for Example 29)



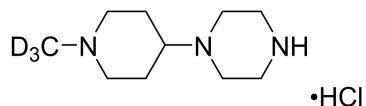
Step 1: preparation of tert-butyl 4-(1-(methyl- d_3)piperidine-4-yl)piperazine-1-formate



1-Boc-4-(piperidine-4-yl)-piperazine (355 mg) and potassium carbonate (365.0 mg) were dissolved in tetrahydrofuran (5 mL), and slowly dropwise added with methyl d_3 -p-toluenesulfonate (250.0 mg) in batches to react at room temperature for 10 hours. After TLC showed that the reaction was completed, the system was filtered, and the mother solution was concentrated. The obtained crude product was purified by column chromatography to obtain 210.0 mg of the title compound.

MS (ESI) m/z ($M+H$) $^+ = 287.2$.

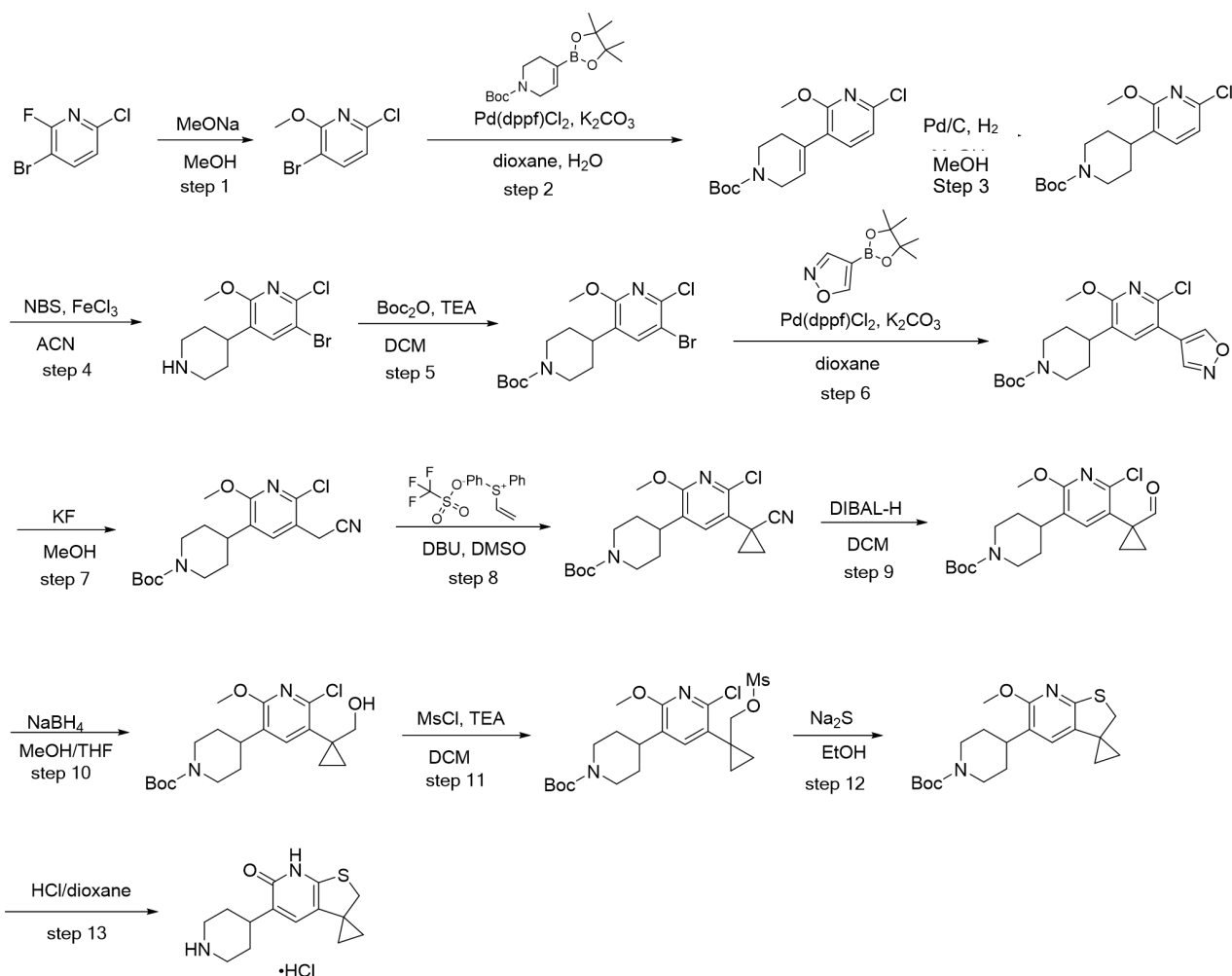
Step 2: preparation of 1-(1-(methyl- d_3)piperidine-4-yl)piperazine hydrochloride



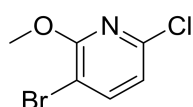
Tert-butyl 4-(1-(methyl- d_3) piperidine-4-yl)piperazine-1-formate (210.0 mg) was dissolved in 1,4-dioxane solution (4 M, 5 mL) of hydrochloric acid to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was concentrated to obtain 180.0 mg of crude product.

MS (ESI) m/z ($M+H$) $^+ = 187.2$.

Preparation Example 26: preparation of
5'-(piperidine-4-yl)-2'H-spiro[cyclopropane-1,3'-thieno[2,3-*b*]pyridine]-6'(7'H)-one
hydrochloride (available for Example 33)

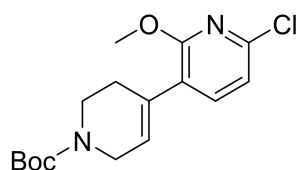


Step 1: preparation of 3-bromo-6-chloro-2-methoxypyridine



3-bromo-6-chloro-2-fluoropyridine (10 g) was dissolved in methanol (100 mL), and added with sodium methoxide (5.2 g) to react at 50°C for 2 hours. After TLC showed that the reaction was completed, the reaction solution was rotationally evaporated to remove excess solvent, added with an appropriate amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 10.1 g of the title compound.

Step 2: preparation of tert-butyl 6-chloro-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1(2'H)-formate

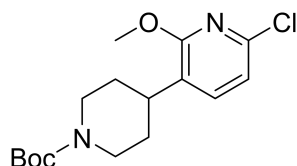


In a nitrogen atmosphere, 3-bromo-6-chloro-2-methoxypyridine (10.1 g) was dissolved in 1,4-dioxane (100 mL) and water (10 mL), and added with potassium carbonate (12.4 g), [1,1'-bis(di-tert-butylphosphine)ferrocene]palladium dichloride (3 g) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborane-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (15.4 g) to react at 80°C for 3 hours. After LCMS showed that the reaction was completed, the reaction

solution was transferred to room temperature, added with an appropriate amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 11.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 325.1.

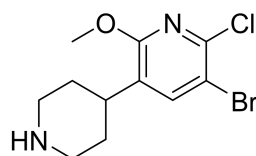
Step 3: preparation of tert-butyl 4-(6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate



Tert-butyl 6-chloro-2-methoxy-3',6'-dihydro-[3,4'-bipyridine]-1'(2'*H*)-formate (9 g) was dissolved in methanol (50 mL) and added with palladium carbon (150 mg), and the reaction system was introduced with hydrogen to react at room temperature overnight. After LCMS showed that the reaction was completed, the reaction solution was filtered, and the filtrate was collected and rotationally evaporated to remove excess solvent. The obtained crude product was purified by column chromatography to obtain 9.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 327.1.

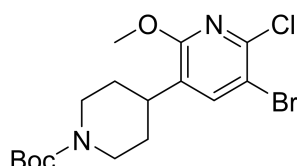
Step 4: preparation of 3-bromo-2-chloro-6-methoxy-5-(piperidine-4-yl)pyridine



In ice water bath, tert-butyl 4-(6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate (9 g) was dissolved in acetonitrile (60 mL), slowly dropwise added with a ferric trichloride (4.5 g dissolved in 10 mL of acetonitrile) solution, added with N-bromosuccinimide (4.8 g), and transferred to room temperature to react for 16 hours. After LCMS showed that the reaction was completed, the reaction solution was added with an appropriate amount of water and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium thiosulfate solution and a sodium chloride solution for three times, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 11 g of crude product.

MS (ESI) m/z (M+H)⁺ = 305.0.

Step 5: preparation of tert-butyl 4-(5-bromo-6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate

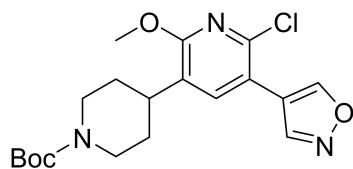


3-bromo-2-chloro-6-methoxy-5-(piperidine-4-yl)pyridine (11 g) was dissolved in dichloromethane (200 mL), and added with triethylamine (9.1 g) and di-tert-butyl dicarbonate (15.7 g) to react at room temperature for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was rotationally evaporated to remove excess solvent and filtered, the solid residue was extracted with ethyl acetate for multiple times, and the filtrate was collected, washed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and

concentrated. The obtained crude product was purified by column chromatography to obtain 4.8 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 405.0.

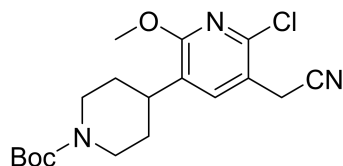
Step 6: preparation of tert-butyl 4-(6-chloro-5-(isoxazole-4-yl)-2-methoxypyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl 4-(5-bromo-6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate (3.9 g) was dissolved in 1,4-dioxane (100 mL) and water (10 mL), and added with potassium carbonate (2.7 g), [1,1'-bis(di-tert-butylphosphine)ferrocene]palladium dichloride (650 mg) and 4-isoxazoleboronic acid pinacol ester (550 mg) to react at 80°C for 3 hours. After LCMS showed that the reaction was completed, the reaction solution was transferred to room temperature, added with a small amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 2.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 394.1.

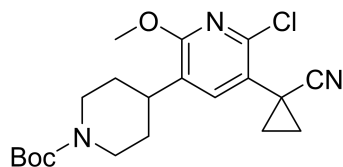
Step 7: preparation of tert-butyl 4-(6-chloro-5-(cyanomethyl)-2-methoxypyridine-3-yl)piperidine-1-formate



Tert-butyl 4-(6-chloro-5-(isoxazole-4-yl)-2-methoxypyridine-3-yl)piperidine-1-formate (2.2 g) was dissolved in methanol (20 mL), and added with potassium fluoride (0.67 g) to react at 90°C for 10 hours. After LCMS showed that the reaction was completed, the reaction solution was transferred to room temperature, rotationally evaporated to remove excess solvent, added with a small amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 2.0 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 366.1.

Step 8: preparation of tert-butyl 4-(6-chloro-5-(1-cyanocyclopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate

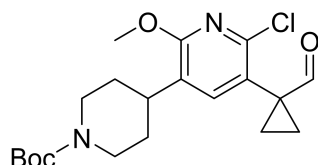


Tert-butyl 4-(6-chloro-5-(cyanomethyl)-2-methoxypyridine-3-yl)piperidine-1-formate (2 g) was dissolved in dimethyl sulfoxide (20 mL), and added with diphenyl(vinyl)sulfonium

trifluoromethanesulfonate (2.4 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.5 g) to react at room temperature for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was added with a small amount of water and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.8 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 392.2.

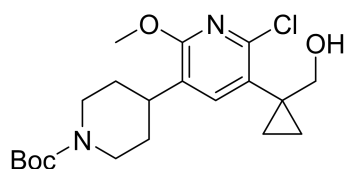
Step 9: preparation of tert-butyl 4-(6-chloro-5-(1-formylcyclopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl 4-(6-chloro-5-(1-cyanocyclopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate (1.8 g) was dissolved in dichloromethane (20 mL) at -78°C, and slowly added with diisobutyl aluminium hydride (1 M, 5 mL) to react for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was transferred to room temperature, added with a small amount of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.4 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 395.2.

Step 10: preparation of tert-butyl 4-(6-chloro-5-(1-(hydroxymethyl)cyclopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate



In ice water bath, tert-butyl 4-(6-chloro-5-(1-formylcyclopropyl)-2-methoxypyridine-3-yl)piperidine-1-formate (1.4 g) was dissolved in tetrahydrofuran (10 mL) and methanol (10 mL), and added with sodium borohydride (356.4 mg) to react at room temperature for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was added with a small amount of water and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 1.3 g of the title compound.

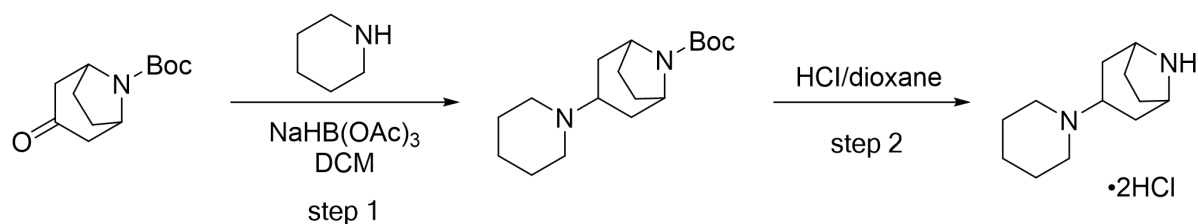
MS (ESI) m/z (M+H)⁺ = 397.2.

Corresponding common commercially available reagents were used to prepare the title compound by a preparation method similar to that in Preparation Example 19 of intermediate compound above.

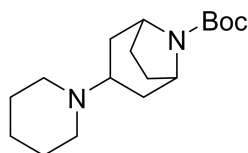
MS (ESI) m/z (M+H)⁺ = 263.1.

Preparation Example 27: preparation of 3-(piperidine-1-yl)-8-azabicyclo[3.2.1]octane

hydrochloride (available for Example 34)



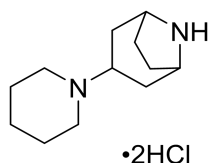
Step 1: preparation of tert-butyl 3-(piperidine-1-yl)-8-azabicyclo[3.2.1]octane-8-formate



N-tert-butoxycarbonyl-nortropine (600 mg) and hexahydropyridine (226 mg) were dissolved in dichloromethane (10 mL), and added with sodium triacetoxyborohydride (848 mg) to react at room temperature for 3 hours. After the reaction was ended, the system was added into an appropriate amount of water and extracted with ethyl acetate (200 mL), and the organic phases were combined, washed with water and a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 430 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 295.1.

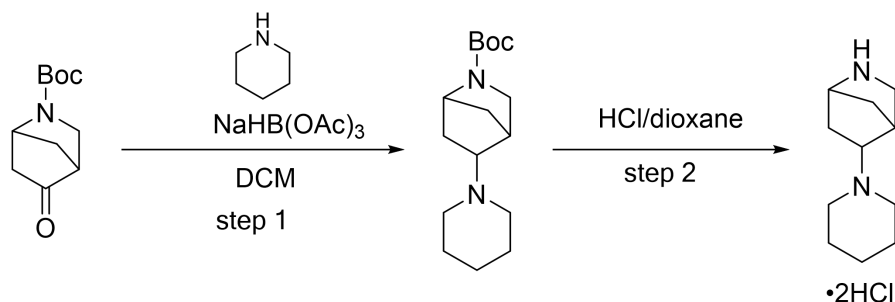
Step 2: preparation of 3-(piperidine-1-yl)-8-azabicyclo[3.2.1]octane hydrochloride



Tert-butyl 3-(piperidine-1-yl)-8-azabicyclo[3.2.1]octane-8-formate (200 mg) was dissolved in hydrogen chloride/1-4 dioxane solution (4.0 M, 5 mL) to react at room temperature for 1 hour. After monitoring showed that the reaction was completed, the reaction system was concentrated to remove the solvent to obtain 130 mg of crude product.

MS (ESI) m/z ($M+H$)⁺ = 195.1.

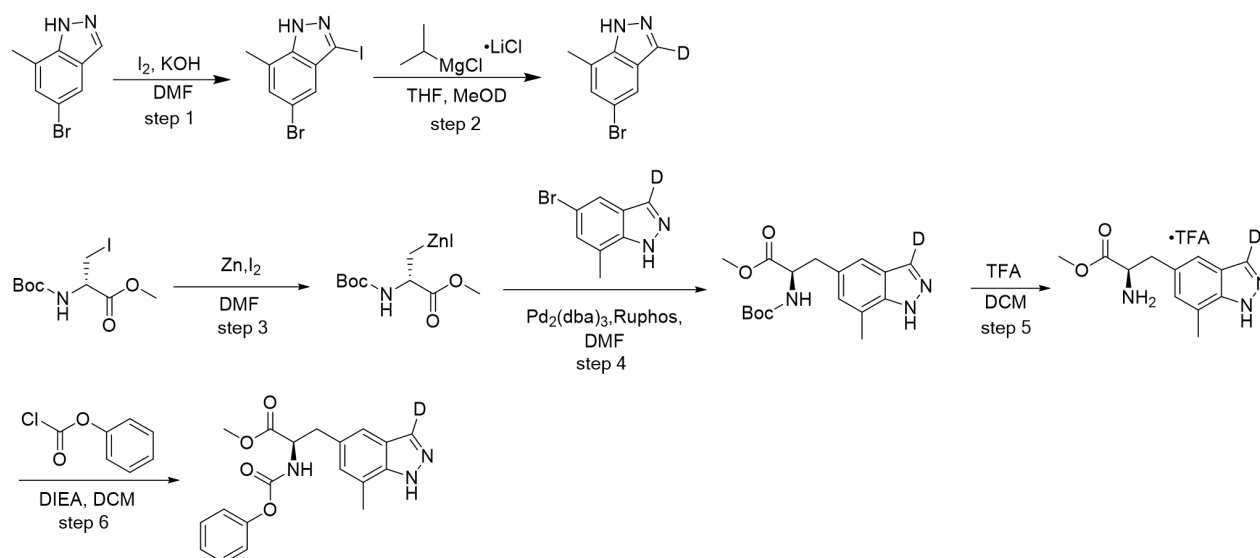
Preparation Example 28: preparation of 5-(piperidine-1-yl)-2-azabicyclo[2.2.1]heptane hydrochloride (available for Example 36)



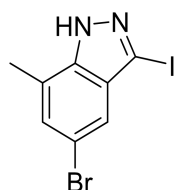
Corresponding common commercially available reagents were used to prepare the title compound by a preparation method similar to that in Preparation Example 27 of intermediate compound above.

MS (ESI) m/z (M+H)⁺ = 181.1.

Preparation Example 29: preparation of methyl (R)-3-(7-methyl-1H-indazole-5-yl-3-d)-2-((phenoxy carbonyl)amino)propionate (available for Example 37)



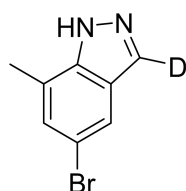
Step 1: preparation of 5-bromo-3-iodo-7-methyl-1H-indazole



In ice water bath, 5-bromo-7-methyl-1H-indazole (250 mg) and potassium hydroxide (146.2 mg) were dissolved in anhydrous *N,N*-dimethylformamide (3 mL), and added with iodine (451 mg) to react for 1 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was quenched with an appropriate amount of saturated sodium sulfite solution and extracted with ethyl acetate for 3 times, and the organic phases were combined, washed with a saturated saline solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 390 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 336.9.

Step 2: preparation of 5-bromo-7-methyl-1H-indazole-3d



In ice water bath, in a nitrogen atmosphere, 5-bromo-3-iodo-7-methyl-1H-indazole (0.39 g) was dissolved in anhydrous tetrahydrofuran (4 mL), and slowly dropwise added with an isopropyl magnesium chloride-lithium chloride complex solution (1.96 mL, 1.3 M in THF) to react for 0.5 hour. The reaction system was added with deuterated methanol (1 mL) and transferred to room temperature to continuously react for 0.5 hour. After LCMS showed that the reaction of raw materials was completed, the reaction solution was concentrated, and the obtained crude product

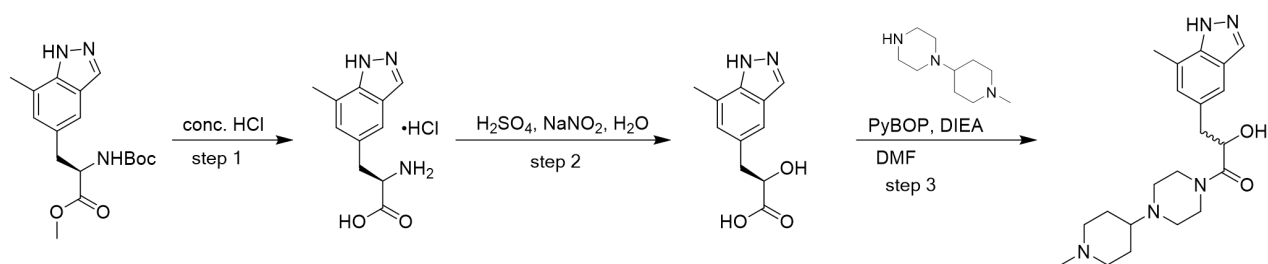
was purified by column chromatography to obtain 0.2 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 211.9.

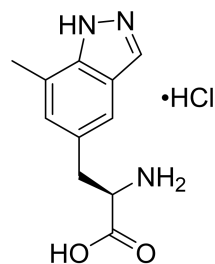
Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to those in Preparation Example 3 of intermediate compound and Preparation Example 5 of intermediate compound above.

MS (ESI) m/z (M+H)⁺ = 354.9.

Preparation Example 30: preparation of 2-hydroxy-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one (available for Example 41)



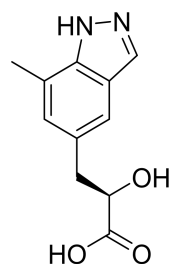
Step 1: preparation of (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)propionic acid hydrochloride



Methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(7-methyl-1H-indazole-5-yl)propionate (500.0 mg) was dissolved in concentrated hydrochloric acid (3 mL) to react at 90°C for 2 hours. After LCMS showed that the reaction of raw materials was completed, the reaction solution was concentrated to obtain 300 mg of crude product, which was directly used in the next step of reaction.

MS (ESI) m/z (M+H)⁺ = 220.1.

Step 2: preparation of (R)-2-hydroxy-3-(7-methyl-1H-indazole-5-yl)propionic acid

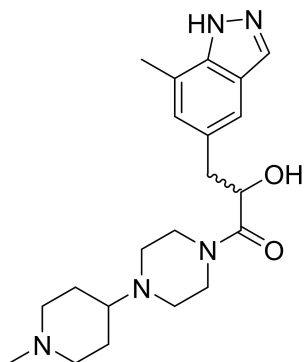


In ice water bath, (R)-2-amino-3-(7-methyl-1H-indazole-5-yl)propionic acid hydrochloride (300 mg) was dissolved in water (3 mL) and slowly dropwise added with concentrated sulfuric acid (0.45 mL). The system was added with sodium nitrite (567 mg) in batches to react at 40°C for 16 hours. After LCMS showed that the reaction was completed, The reaction solution was added with 2 N hydrochloric acid to adjust a pH value to be about 4 and extracted with ethyl acetate for 3 times, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 200 mg of crude product, which was directly used in the next step of

reaction.

MS (ESI) m/z (M+H)⁺ = 220.9.

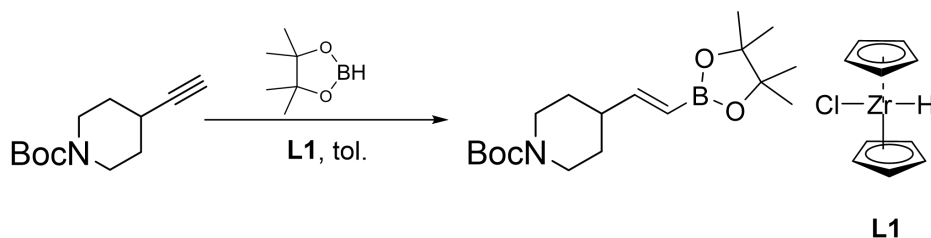
Step 3: preparation of 2-hydroxy-3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one



In ice water bath, (*R*)-2-hydroxy-3-(7-methyl-1*H*-indazole-5-yl)propionic acid (200 mg), 1-(1-methylpiperidine-4-yl)piperazine (332.9 mg) and *N,N*-diisopropylethylamine (234.8 mg) were dissolved in *N,N*-dimethylformamide (2.0 mL), and slowly added with 1*H*-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (519.9 mg) to react for 0.5 hour. After LCMS showed that the reaction was completed, the reaction solution was concentrated, and the crude product was purified by a preparative liquid phase to obtain 100 mg of the title compound.

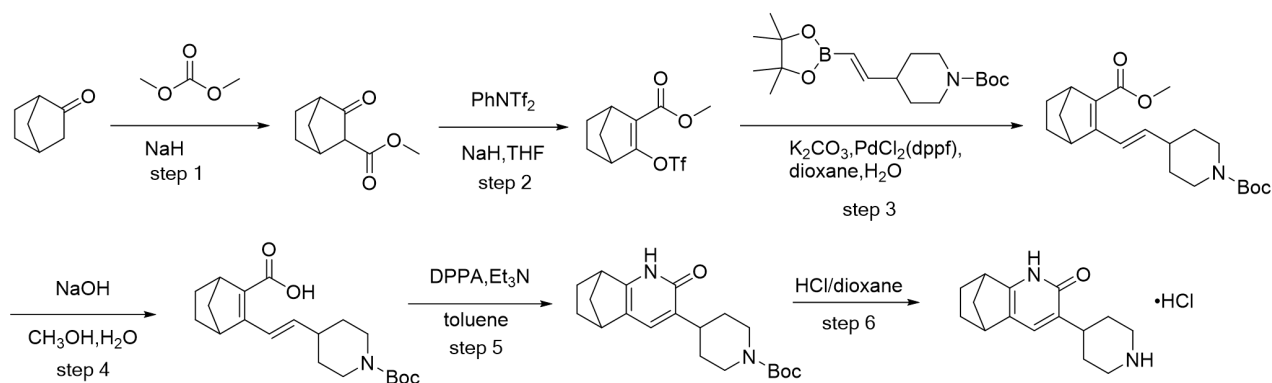
MS (ESI) m/z (M+H)⁺ = 385.9.

Preparation Example 31: preparation of tert-butyl (E)-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborane-2-yl)vinyl)piperidine-1-formate

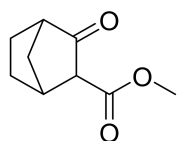


1-Boc-4-ethynyl piperidine (5.0 g) and bis(cyclopentadienyl)zirconium chloride hydride (307.32 mg) were dissolved in toluene (50 mL), dropwise added with 4,4,5,5-tetramethyl-1,3,2-dioxaborane (3.67 g), and heated at 60°C to react overnight. After the reaction was ended, the reaction solution was concentrated, the crude product was purified by column chromatography, and another configuration was removed to obtain 5.3 g of the title compound.

Preparation Example 32: preparation of 3-piperidine-4-yl)-5,6,7,8-tetrahydro-5,8-methanoquinoline-2(1*H*)-one hydrochloride (available for Example 45)



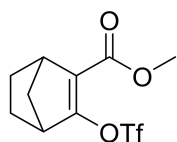
Step 1: preparation of methyl 3-oxobicyclo[2.2.1]heptane-2-formate



In a nitrogen atmosphere, sodium hydride (726 mg) was dissolved in dimethyl carbonate (9 mL), then bicyclo[2.2.1]heptane-2-one (1 g) was dissolved in dimethyl carbonate (6 mL), and the mixture was slowly dropwise added into a sodium hydride system to react at 90°C for 2 hours. After the reaction was ended, the reaction solution was added with water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The obtained crude product was separated and purified by column chromatography to obtain 1.10 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 169.1 .

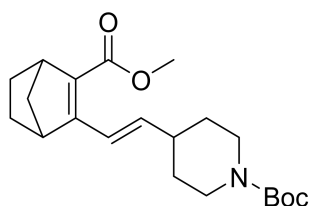
Step 2: preparation of methyl 3-((trifluoromethyl)sulfonyl)oxy)bicyclo[2.2.1]hept-2-ene-2-formate



In ice water bath, sodium hydride (385 mg) was dissolved in anhydrous tetrahydrofuran (10 mL), then methyl 3-oxobicyclo[2.2.1]hept-2-formate (1.08 g) was dissolved in anhydrous tetrahydrofuran (5 mL), and the mixture was slowly dropwise added into a sodium hydride system and stirred for 30 minutes. Then, N-phenyl-bis(trifluoromethanesulfonyl)imide (2.98 g) was dissolved in anhydrous tetrahydrofuran (10 mL) and slowly dropwise added into the above system to react at room temperature overnight. After the reaction was ended, the reaction system was added with water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The obtained crude product was separated and purified by column chromatography to obtain 1.70 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 301.1 .

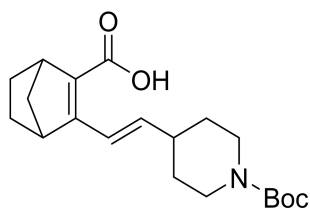
Step 3: preparation of tert-butyl (E)-4-(2-(3-(methoxycarbonyl)bicyclo[2.2.1]hept-2-ene-2-yl)vinyl)piperidine-1-carboxylate



In a nitrogen atmosphere, methyl 3-((trifluoromethyl)sulfonyl)oxy)bicyclo[2.2.1]hept-2-ene-2-formate (600 mg), (E)-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborane-2-yl)vinyl)piperidine 1-formate (742 mg), [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride (163 mg) and potassium carbonate (690 mg) was dissolved in 1,4-dioxane (10 mL) and water (2 mL) to react at 80°C for 2 hours. After the reaction was ended, the reaction system was added with water for quenching, filtered by suction, and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain a crude product. The obtained crude product was separated and purified by column chromatography to obtain 660.00 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 362.2.

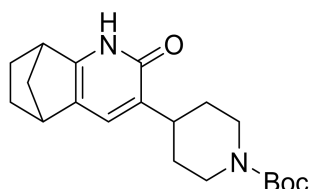
Step 4: preparation of (E)-3-(2-(1-(tert-butoxycarbonyl)piperidine-4-yl)vinyl)bicyclo[2.2.1]hept-2-ene-2-formic acid



Tert-butyl (E)-4-(2-(3-(methoxycarbonyl)bicyclo[2.2.1]hept-2-ene-2-yl)vinyl)piperidine-1-formate (200 mg) was dissolved in methanol (10 mL) and water (1 mL), and added with sodium hydroxide (155 mg) to react at 50°C overnight. After the reaction was ended, the reaction system was added with 1 N hydrochloric acid to adjust to pH 5-6 and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 180 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 348.2 .

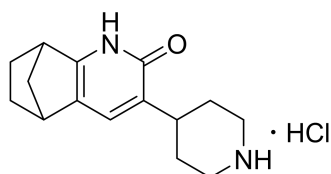
Step 5: preparation of tert-butyl 4-(2-oxo-1,2,5,6,7,8-hexahydro-5,8-methanoquinoline-3-yl)piperidine-1-formate



In a nitrogen atmosphere, (E)-3-(2-(1-(tert-butoxycarbonyl)piperidine-4-yl)vinyl)bicyclo[2.2.1]hept-2-ene-2-formic acid (180 mg) was dissolved in toluene (2 mL), and added with diphenylphosphoryl azide (154 mg) and triethylamine (78 mg) to react at room temperature for 3 hours. After the reaction was completed, the system was pre-purified by preparative thin layer chromatography and dissolved in toluene (2 mL) to continuously react at 90°C for 3 hours. After the reaction was ended, the reaction system was concentrated, and the crude product was separated and purified by preparative thin layer chromatography to obtain 80.00 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 345.2.

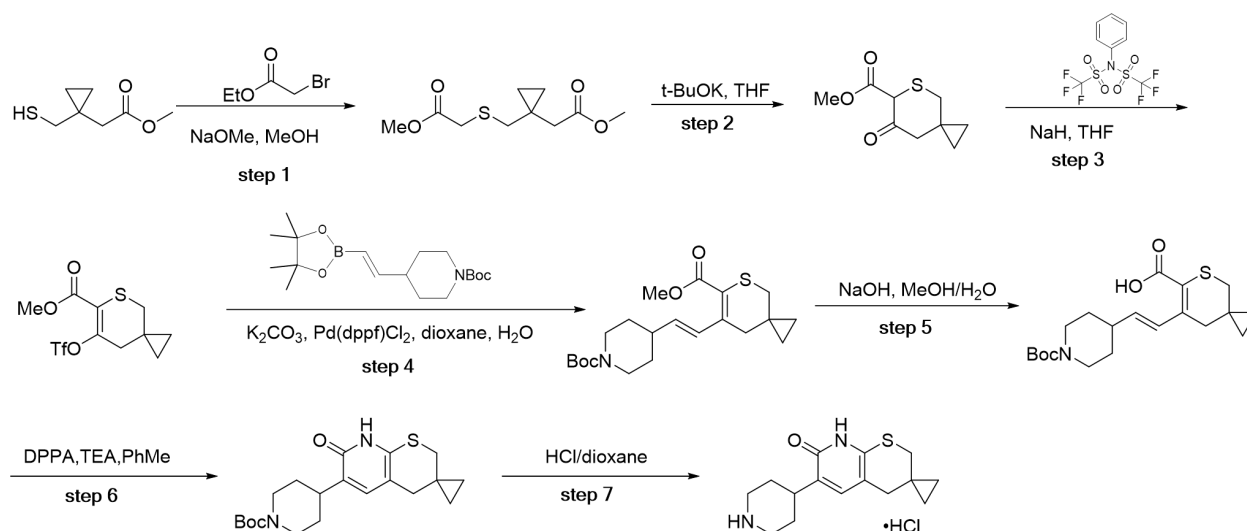
Step 6: preparation of 3-(piperidine-4-yl)-5,6,7,8-tetrahydro-5,8-methanoquinoline-2(1H)-one hydrochloride



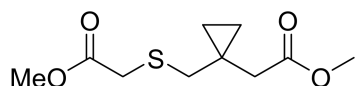
Tert-butyl 4-(2-oxo-1,2,5,6,7,8-hexahydro-5,8-methanoquinoline-3-yl)piperidine-1-formate (80 mg) was dissolved in hydrogen chloride/1,4-dioxane solution (4 M, 1 mL) to react at room temperature for 1 hour. After the reaction was ended, the reaction system was concentrated to obtain 78 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 245.1

Preparation of Example 33: preparation of 6'-(piperidine-4-yl)-4',8'-dihydro-2'H,7'H-spiro[cyclopropane-1,3'-thiopyrano[2,3-*b*]pyridine]-7'-one hydrochloride (available for Example 46)



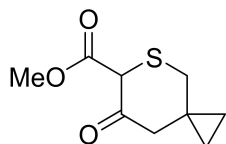
Step 1: preparation of methyl 2-((1-(2-methoxy-2-oxoethyl)cyclopropyl)methyl)thioacetate



In ice water bath, methyl 2-(1-(mercaptomethyl)cyclopropyl)acetate (600 mg) was dissolved in methanol (12 mL), added with sodium methoxide (750 mg), stirred for 10 minutes, and added with ethyl bromoacetate (750 mg) to react for 2 hours. After LCMS showed that the reaction was completed, the reaction system was added with a hydrochloric acid solution (2N) to adjust to pH 7-8 and extracted with ethyl acetate, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 650 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 233.1.

Step 2: preparation of methyl 7-oxo-5-thiaspiro[2.5]octane-6-formate



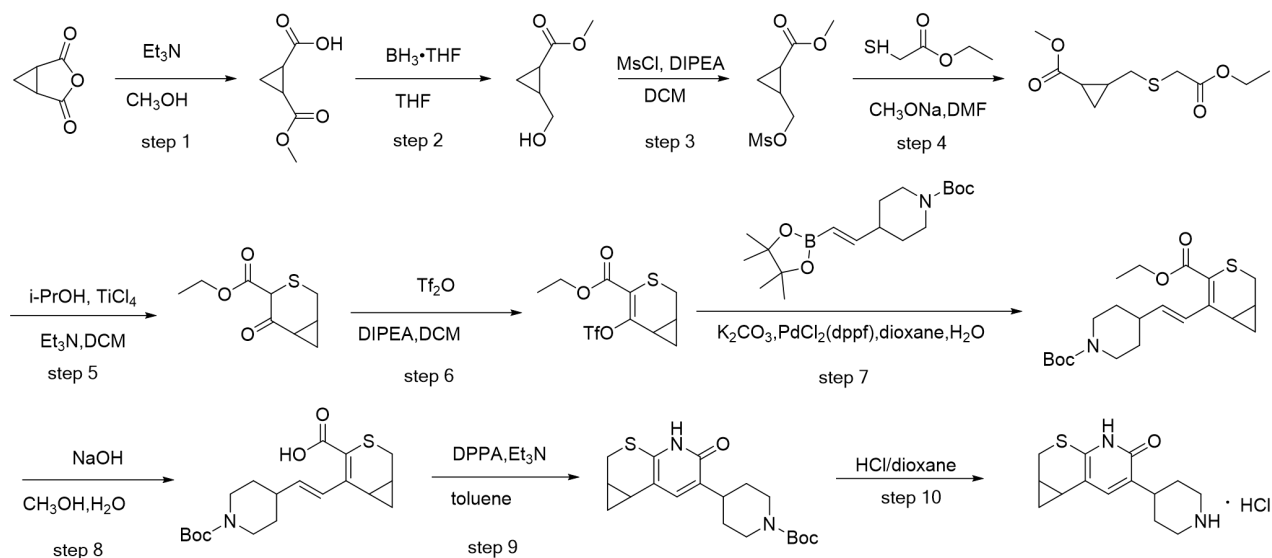
In ice water bath, methyl 2-((1-(2-methoxy-2-oxoethyl)cyclopropyl)methyl)thioacetate (630 mg) was dissolved in tetrahydrofuran (10 mL), and added with potassium tert-butoxide (608 mg) in batches to react for 1 hour. After LCMS showed that the reaction was completed, the reaction system was added with a hydrochloric acid solution (2N) to adjust to pH 5-6 and extracted with ethyl acetate, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography to obtain 380 mg of the target compound.

MS (ESI) m/z (M+H)⁺ = 201.1.

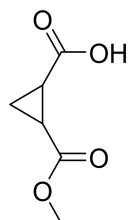
Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to that in Preparation Example 32 of intermediate compound above.

MS (ESI) m/z (M+H)⁺ = 277.1.

Preparation Example 34: preparation of 6-(piperidine-4-yl)-1a,2,4,7b-tetrahydrocyclopropo[4,5]thiopyrano[2,3-b]pyridine-5(1H)-one hydrochloride (available for Example 47)



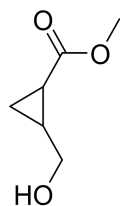
Step 1: preparation of 2-(methoxycarbonyl)cyclopropane-1-formic acid



Triethylamine (901.8 mg) was dissolved in methanol (15 mL), and added with 3-oxabicyclo[3.1.0]hexane-2,4-dione (1 g) in batches to react at room temperature for 1 hour. After the reaction was ended, the reaction system was added with water for quenching to remove excess methanol, added with 1 N hydrochloric acid to adjust to pH 3-4, and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and

concentrated to obtain 1.15 g of crude product.

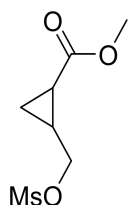
Step 2: preparation of methyl 2-(hydroxymethyl)cyclopropane-1-formate



In ice water bath, 2-(methoxycarbonyl)cyclopropane-1-formic acid (1.15 g) was dissolved in anhydrous tetrahydrofuran (2 mL), dropwise added with a borane tetrahydrofuran solution (1 M, 16 mL), and transferred to room temperature to react for 3 hours. After the reaction was ended, the reaction system was added with an appropriate amount of methanol for quenching and concentrated to obtain a crude product, and the obtained crude product was separated and purified by column chromatography to obtain 750 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 131.1.

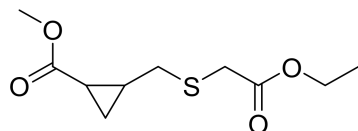
Step 3: preparation of methyl 2-((methylsulfonyl)oxy)methyl)cyclopropane-1-formate



Methyl 2-(hydroxymethyl)cyclopropane-1-formate (750 mg) was dissolved in dichloromethane (10 mL) at -10°C, and added with N,N-diisopropylethylamine (1.49 g). Methanesulfonyl chloride (856 mg) was diluted with dichloromethane (3 mL), dropwise added into the above reaction system, and recovered to room temperature to react for 30 minutes. After the reaction was ended, the reaction system was added with water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by column chromatography to obtain 1.1 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 209.0.

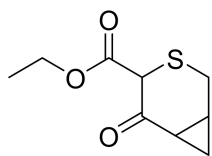
Step 4: preparation of methyl 2-((2-ethoxy-2-oxoethyl)thio)methyl)cyclopropane-1-formate



In ice water bath, in a nitrogen atmosphere, methyl 2-((methylsulfonyl)oxy)methyl)cyclopropane-1-formate (1.1 g) and ethyl 2-mercaptoacetate (936 mg) were dissolved in dry N,N-dimethylformamide (12 mL), added with sodium methoxide (421 mg), and recovered to room temperature to react for 2 hours. After the reaction was ended, the reaction system was added with water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by column chromatography to obtain 1.10 g of the title compound.

MS (ESI) m/z (M+H)⁺ = 233.0.

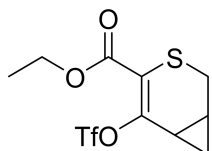
Step 5: preparation of ethyl 5-oxo-3-thiabicyclo[4.1.0]heptane-4-formate



In a nitrogen atmosphere, titanium tetrachloride (1.51 g) was dissolved in dry dichloromethane (20 mL) at -10°C , added with isopropanol (518 mg), and stirred for 30 minutes. Methyl 2-((2-ethoxy-2-oxoethyl)thio)methyl)cyclopropane-1-formate (1.54 g) was dissolved in dry dichloromethane (5 mL), slowly dropwise added into the above reaction system, kept at an internal temperature of -10°C , and continuously stirred for 30 minutes. The reaction system was added with triethylamine (2.35 g) to continuously react for 1.5 hours. After the reaction was ended, the reaction system was added with an appropriate amount of 1 N hydrochloric acid for quenching and extracted with dichloromethane, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by column chromatography to obtain 740 mg of the title compound.

MS (ESI) m/z (M+H) $^{+}$ = 201.0.

Step 6: preparation of ethyl 5-(((trifluoromethyl)sulfonyl)oxy)-3-thiabicyclo[4.1.0]hept-4-ene-4-formate



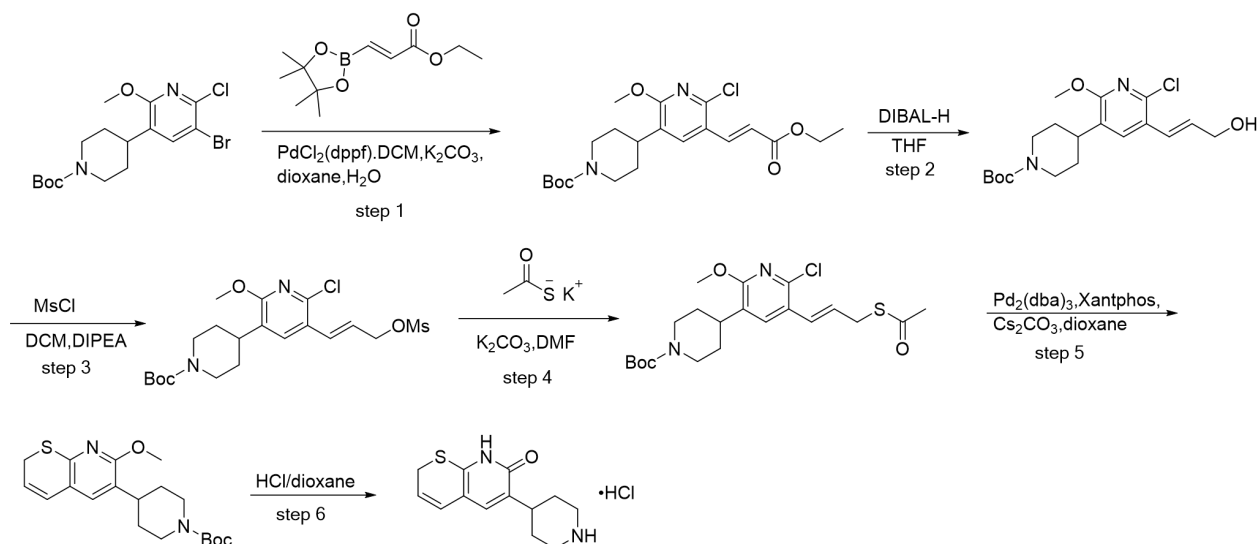
Ethyl 5-oxo-3-thiabicyclo[4.1.0]heptane-4-formate (570 mg) was dissolved in dry dichloromethane (15 mL) at -78°C , and added with N,N-diisopropylethylamine (1.1 g). Trifluoromethanesulfonic anhydride (1.36 g) was diluted with dry dichloromethane (5 mL) and dropwise added into the above system to continuously react for 30 minutes. After the reaction was ended, the reaction system was added with water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by column chromatography to obtain 700 mg of the title compound.

MS (ESI) m/z (M+H) $^{+}$ = 333.0.

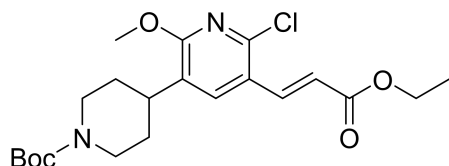
Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to that in Preparation Example 32 of intermediate compound above.

MS (ESI) m/z (M+H) $^{+}$ = 263.1.

Preparation Example 35: preparation of 6-(piperidine-4-yl)-2,8-dihydro-7H-thiopyrano[2,3-b]pyridine-7-one hydrochloride (available for Example 48)



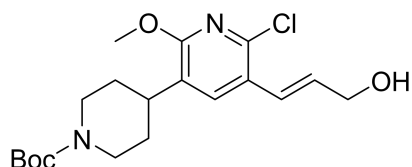
Step 1: preparation of tert-butyl (E)-4-(6-chloro-5-(3-ethoxy-3-oxopropan-1-ene-1-yl)-2-methoxypyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl 4-(5-bromo-6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate (1.4 g), potassium carbonate (1.19 g) and a [1,1'-bis(diphenylphosphino)ferrocene]palladium dichloride dichloromethane complex (281 mg) were dissolved in 1,4-dioxane (30 mL) and water (5 mL). The system was heated at 90 °C, and slowly dropwise added with an ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborane-2-yl)acrylate (1.17 g dissolved in 8 mL of 1,4-dioxane) solution to react for 2 hours. The reaction solution was transferred to room temperature, added with a small amount of water for quenching, and filtered by suction, the filtrate was collected and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by silica gel column chromatography to obtain 1 g of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 425.1.

Step 2: preparation of tert-butyl (E)-4-(6-chloro-5-(3-hydroxypropan-1-alkenyl)-2-methoxypyridine-3-yl)piperidine-1-formate

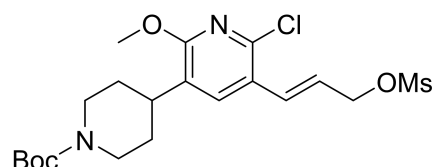


Tert-butyl (E)-4-(6-chloro-5-(3-ethoxy-3-oxopropan-1-ene-1-yl)-2-methoxypyridine-3-yl)piperidine-1-formate (980 mg) was dissolved in dry tetrahydrofuran (20 mL) at -40°C, slowly dropwise added with diisobutyl aluminum hydride (1.5 M, 7.7 mL), and transferred to room temperature to react for 1.5 hours. The reaction solution was added with a small amount of water for quenching, then treated with a sodium hydroxide aqueous solution (2.5 N, 24 mL), and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The

crude product was separated and purified by silica gel column chromatography to obtain 380 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 383.1.

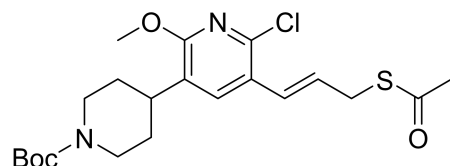
Step 3: preparation of tert-butyl (E)-4-(6-chloro-2-methoxy-5-(3-((methylsulfonyl)oxy)prop-1-ene-1-yl)pyridine-3-yl)piperidine-1-formate



In ice water bath, tert-butyl (E)-4-(6-chloro-5-(3-hydroxyprop-1-en-1-yl)-2-methoxypyridine-3-yl)piperidine-1-formate (370 mg) was dissolved in dichloromethane (10 mL), and added with *N,N*-diisopropylethylamine (499 mg). Methanesulfonyl chloride (172 mg) was dissolved in dichloromethane (2 mL) and slowly dropwise added into the above reaction system to react for 0.5 hour. The reaction solution was added with a small amount of water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated to obtain 442 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 461.1.

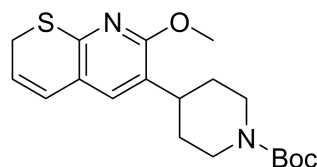
Step 4: preparation of tert-butyl (E)-4-(5-(3-(acetylthio)prop-1-ene-1-yl)-6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate



In a nitrogen atmosphere, tert-butyl (E)-4-(6-chloro-2-methoxy-5-(3-((methylsulfonyl)oxy)prop-1-ene-1-yl)pyridine-3-yl)piperidine-1-formate (445 mg) was dissolved in *N,N*-dimethylformamide (10 mL), and added with potassium carbonate (398 mg) and potassium thioacetate (329 mg) to react at room temperature for 2 hours. After the reaction was ended, the reaction system was added with a small amount of water for quenching and extracted with ethyl acetate, and the organic phases were combined, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was separated and purified by silica gel column chromatography to obtain 390 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 441.1.

Step 5: preparation of tert-butyl 4-(7-methoxy-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formate

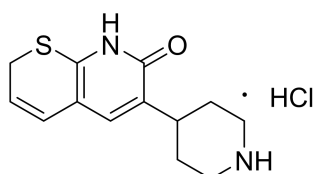


In a nitrogen atmosphere, tert-butyl (E)-4-(5-(3-(acetylthio)prop-1-ene-1-yl)-6-chloro-2-methoxypyridine-3-yl)piperidine-1-formate (150 mg), tris(dibenzylideneacetone)dipalladium (155 mg),

4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (196 mg) and potassium carbonate (276 mg) were dissolved in 1,4-dioxane (10 mL) to react under induction of microwave at 115°C for 5 hours. After the reaction was ended, the reaction solution was filtered by suction through diatomite, and the filtrate was collected and concentrated. The crude product was separated and purified by a preparative high-performance liquid phase to obtain 11 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 363.1.

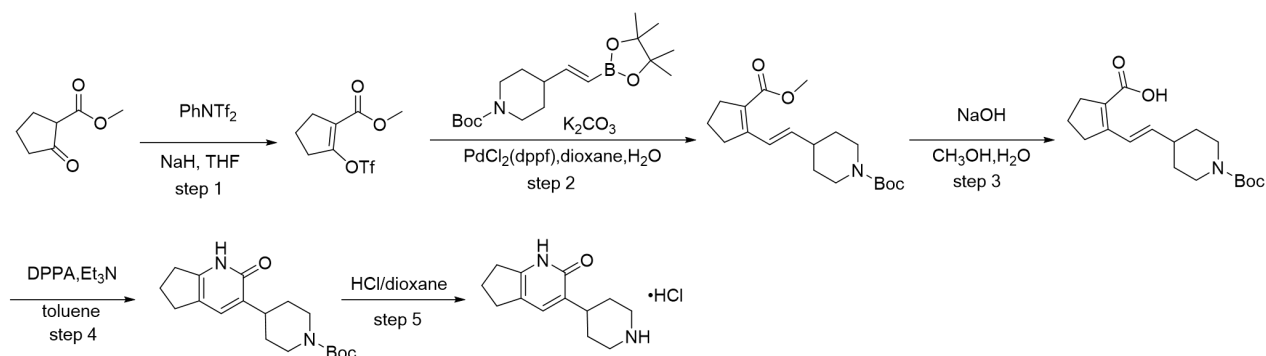
Step 6: preparation of 6-(piperidine-4-yl)-2,8-dihydro-7H-thiopyrano[2,3-*b*]pyridine-7-one hydrochloride



Tert-butyl 4-(7-methoxy-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formate (11 mg) was dissolved in hydrochloric acid/1,4-dioxane solution (4 N, 3 mL) to react at 90°C for 4 hours. After the reaction was ended, the reaction solution was concentrated to obtain 9 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 249.1.

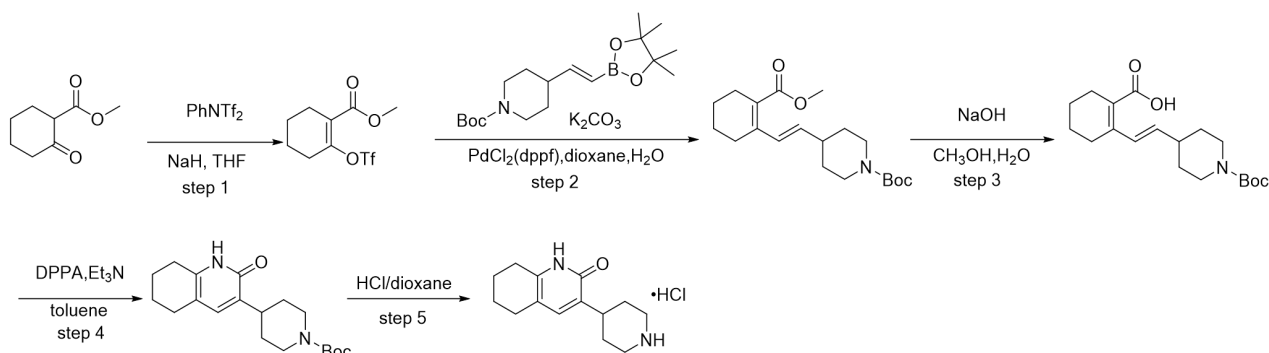
Preparation Example 36: preparation of 3-(piperidine-4-yl)-1,5,6,7-tetrahydro-2H-cyclopentadieno[b]pyridine-2-one hydrochloride (available for Example 51)



Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to that in Preparation Example 32 of intermediate compound above.

MS (ESI) m/z (M+H)⁺ = 219.1.

Preparation Example 37: preparation of 3-(piperidine-4-yl)-5,6,7,8-tetrahydroquinoline-2(1H)-one hydrochloride (available for Example 52)

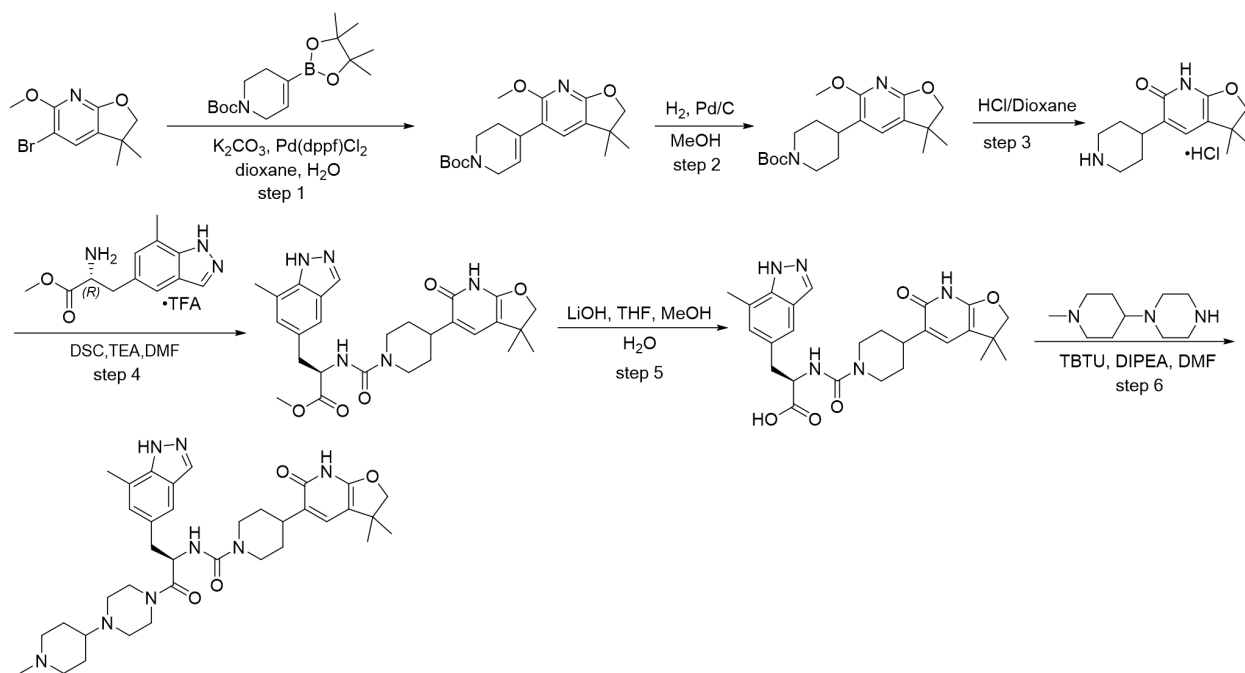


Corresponding common commercially available reagents were used to subsequently prepare the title compound by a preparation method similar to that in Preparation Example 32 of intermediate compound above.

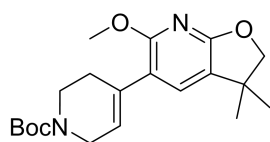
MS (ESI) m/z ($M+H$)⁺ = 233.2.

A synthesis method for the compound as represented by formula I of the present invention is illustratively provided as follows. The raw materials or reagents required for the synthesis of the compound as represented by formula I of the present invention in the following examples may all be commercially available, or may be acquired according to the synthesis method for the intermediate compound provided by the present invention above, or may be acquired through the methods reported in the existing technical literatures combined with the conventional chemical reaction synthesis means.

Example 1: preparation of (R)-4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-b]pyridine-5-yl)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide



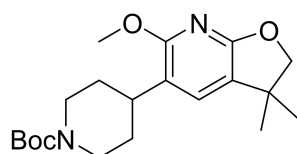
Step 1: preparation of tert-butyl 4-(6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-b]pyridine-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate



In a nitrogen atmosphere, 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine (610.0 mg), *N*-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (880.0 mg) and potassium carbonate (981.0 mg) were dissolved in 1,4-dioxane (7 mL) and water (0.7 mL), and added with 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (173.0 mg) to react at 90°C for 2 hours. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 620.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 361.2.

Step 2: preparation of tert-butyl 4-(6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine-5-yl)piperidine-1-formate

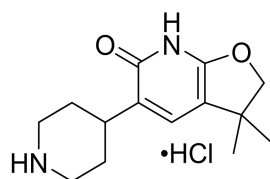


Tert-butyl

4-(6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (610.0 mg) was dissolved in methanol (30 mL), added with palladium carbon (10%, 61.0 mg), subjected to air replacement, and continuously introduced with hydrogen to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was filtered, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 550.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 363.2.

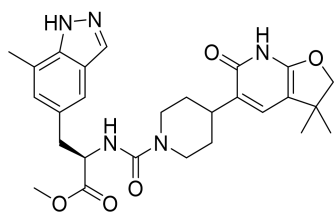
Step 3: preparation of 3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrofuro[2,3-*b*]pyridine-6(2*H*)-one hydrochloride



Tert-butyl 4-(6-methoxy-3,3-dimethyl-2,3-dihydrofuro[2,3-*b*]pyridine-5-yl)piperidine-1-formate (200.0 mg) was dissolved in a hydrochloric acid - 1,4-dioxane solution (4 M, 3 mL) to react at 90°C for 3 hours. After TLC showed that the reaction was completed, the system was concentrated to obtain 230.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 249.2.

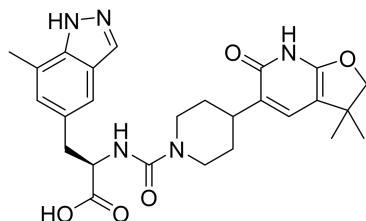
Step 4: preparation of methyl (R)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionate



(*R*)-2-amino-3-(7-methyl-1*H*-indazole-5-yl)methyl propionate trifluoroacetate (187.9 mg) and *N,N'*-disuccinimyl carbonate (206.4 mg) were dissolved in *N,N*-dimethylformamide (3 mL), and added with triethylamine (244.3 mg) to react at room temperature for 30 minutes. The above system was added with 3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrofuro[2,3-*b*]pyridine-6(2*H*)-one hydrochloride (200.0 mg) to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was filtered, and the filtrate was collected. The crude product was subjected to reverse phase preparation to obtain 90.0 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 508.2.

Step 5: preparation of (*R*)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionic acid

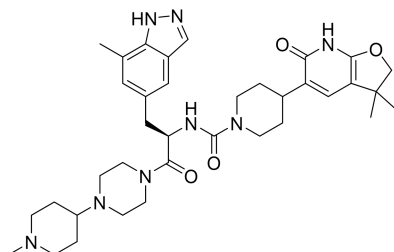


Methyl

(*R*)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionate (90.0 mg) was dissolved in tetrahydrofuran (5 mL) and methanol (1 mL), and added with a lithium hydroxide (8.2 mg) aqueous solution (1 mL) to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was added with 1 M dilute hydrochloric acid to adjust to about pH 7, and the system was concentrated to obtain 100.0 mg of crude product.

MS (ESI) m/z ($M+H$)⁺ = 494.2.

Step 6: preparation of (*R*)-4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-yl)-*N*-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-formamide



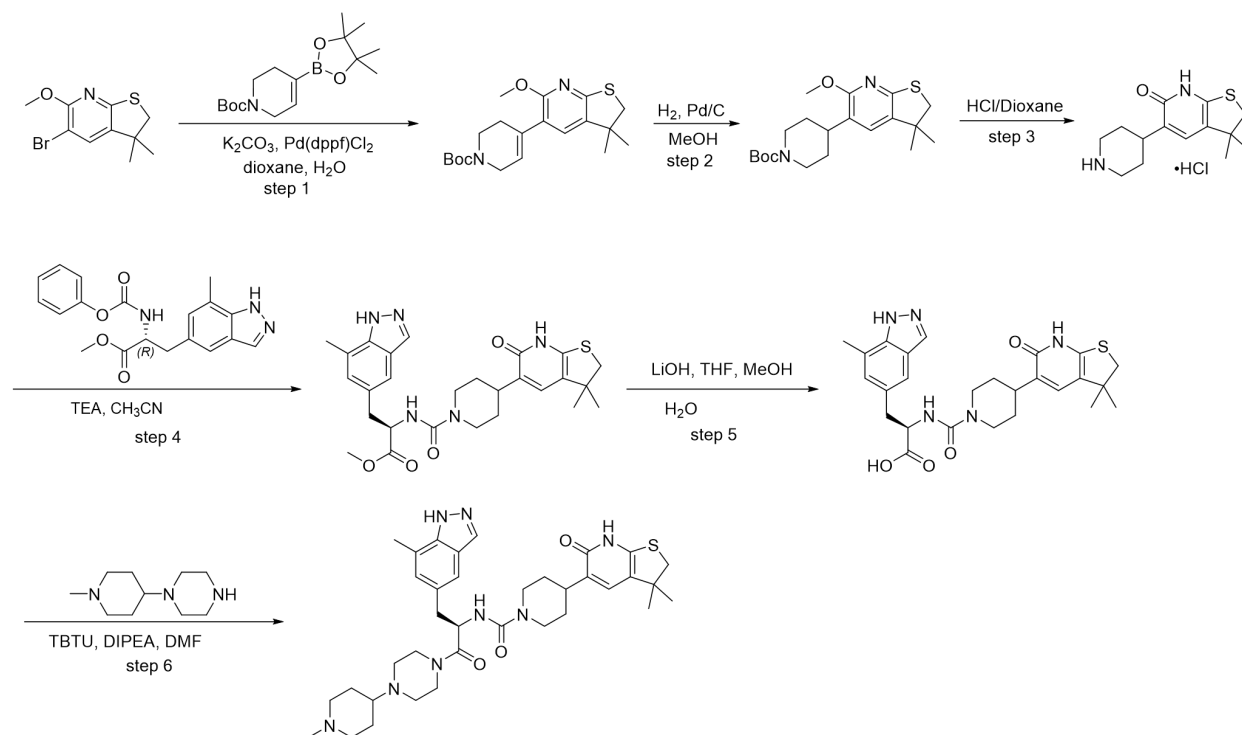
(*R*)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionic acid (100.0 mg) and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (78 mg) was dissolved in *N,N*-dimethylformamide (2 mL), and added with *N,N*-diisopropylethylamine (77.4 mg) to react at room temperature for 10 minutes. The above system was added with 1-(1-methylpiperidine-4-yl)piperazine (43.9 mg) to react at room temperature for 20 minutes. After

TLC showed that the reaction was completed, the system was filtered, and the filtrate was subjected to reverse phase preparation. The crude product was freeze-dried to obtain 36.0 mg of the title compound.

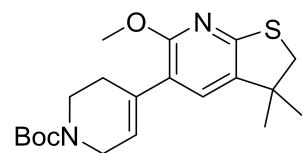
MS (ESI) m/z (M+H)⁺ = 659.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 10.62 (brs, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.78 (q, *J* = 7.7 Hz, 1H), 4.16 (s, 2H), 4.11 (d, *J* = 13.0 Hz, 2H), 3.62 – 3.55 (m, 1H), 3.22 (t, *J* = 9.9 Hz, 2H), 3.12–3.06 (m, 1H), 3.00–2.86 (m, 2H), 2.80–2.63 (m, 5H), 2.47 (s, 3H), 2.35 (d, *J* = 7.7 Hz, 1H), 2.27–2.20 (m, 1H), 2.09 (s, 3H), 1.98–1.85 (m, 2H), 1.75–1.62 (m, 4H), 1.50 (t, *J* = 9.1 Hz, 1H), 1.43–1.34 (m, 4H), 1.25 (d, *J* = 2.2 Hz, 6H), 1.21–1.09 (m, 2H).

Example 2: preparation of (R)-4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)-N-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide



Step 1: preparation of tert-butyl 4-(6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate

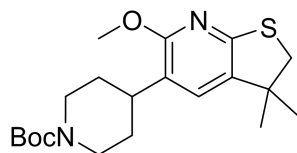


In a nitrogen atmosphere, 5-bromo-6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine (300.0 mg), *N*-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridine-4-boronic acid pinacol ester (441.4 mg) and potassium carbonate (454.9 mg) were dissolved in 1,4-dioxane (4 mL) and water (0.4 mL), added with 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride (80.4 mg), and heated to 90°C to react for 2 hours. After TLC showed that the reaction was completed, the reaction system was added with 30 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with

anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 300.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 377.2.

Step 2: preparation of tert-butyl 4-(6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formate

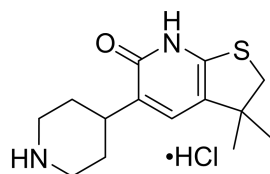


Tert-butyl

4-(6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine-5-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (300.0 mg) was dissolved in methanol (20 mL), added with palladium carbon (10%, 30.0 mg), subjected to air replacement, and continuously introduced with hydrogen to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was filtered, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 550.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 379.2.

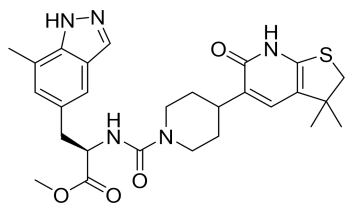
Step 3: preparation of 3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrothieno[2,3-*b*]pyridine-6(2*H*)-one hydrochloride



Tert-butyl 4-(6-methoxy-3,3-dimethyl-2,3-dihydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formate (300.0 mg) was dissolved in a hydrochloric acid - 1,4-dioxane solution (10 mL) to react at 90°C for 3 hours. After TLC showed that the reaction was completed, the system was concentrated to obtain 340.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 265.1.

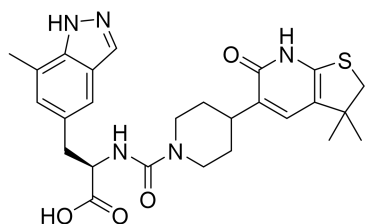
Step 4: preparation of methyl (R)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionate



3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrothieno[2,3-*b*]pyridine-6(2*H*)-one hydrochloride (62.9 mg) and methyl (R)-3-(7-methyl-1*H*-indazole-5-yl)-2-((phenoxy-carbonyl)amino)propionate (67.2 mg) were dissolved in acetonitrile (4 mL), added with triethylamine (121.2 mg), and heated to 60°C to react for 7 hours. After TLC showed that the reaction was completed, the system was concentrated. The obtained crude product was purified by column chromatography to obtain 90.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 524.2.

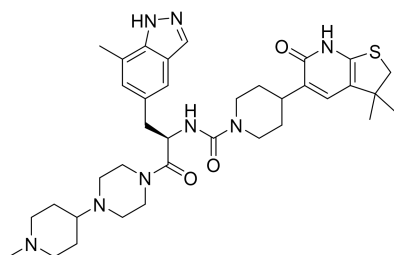
Step 5: preparation of
 (R)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionic acid



Methyl
 (R)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionate (90.0 mg) was dissolved in tetrahydrofuran (3 mL) and methanol (0.6 mL), and added with a lithium hydroxide (22.0 mg) aqueous solution (0.6 mL) to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was added with 1 M dilute hydrochloric acid to adjust to about pH 7, and concentrated to obtain 110.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 510.2.

Step 6: preparation of
 (R)-4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)-*N*-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-formamide

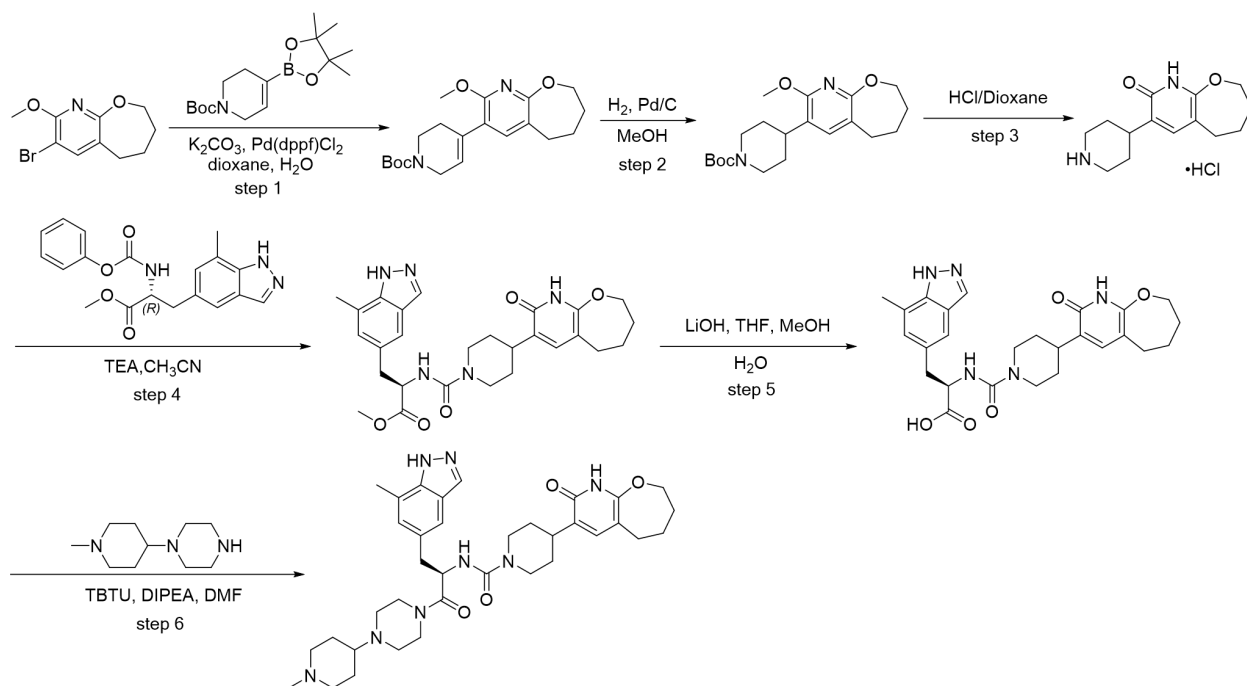


(R)-2-(4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formylamino)-3-(7-methyl-1*H*-indazole-5-yl)propionic acid (80.0 mg) and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (61 mg) was dissolved in *N,N*-dimethylformamide (2 mL), and added with *N,N*-diisopropylethylamine (60.8 mg) to react at room temperature for 10 minutes. The above system was added with 1-(1-methylpiperidine-4-yl)piperazine (34.5 mg) to react at room temperature for 20 minutes. After TLC showed that the reaction was completed, the system was filtered, and the filtrate was subjected to reverse phase preparation. The crude product was freeze-dried to obtain 20.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 675.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.94 (s, 1H), 11.37 (s, 1H), 7.89 (s, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 6.56 (d, *J* = 8.1 Hz, 1H), 4.70 (q, *J* = 7.7 Hz, 1H), 4.04 (d, *J* = 12.9 Hz, 2H), 3.51 (d, *J* = 13.1 Hz, 1H), 3.13 (s, 3H), 3.04 – 2.99 (m, 1H), 2.92 – 2.87 (m, 1H), 2.84 – 2.79 (m, 1H), 2.70 – 2.58 (m, 5H), 2.40 (s, 3H), 2.34 – 2.20 (m, 2H), 2.17 – 2.14 (m, 1H), 2.03 (s, 3H), 1.86 – 1.78 (m, 2H), 1.66 (t, *J* = 11.6 Hz, 2H), 1.57 (d, *J* = 12.3 Hz, 2H), 1.43 (t, *J* = 9.4 Hz, 1H), 1.34 – 1.28 (m, 4H), 1.18 (s, 6H), 1.14 – 1.07 (m, 2H).

Example 3: preparation of
 (R)-*N*-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(8-oxo-2,3,4,5,8,9-hexahydro-oxepino[2,3-*b*]pyridine-7-yl)piperidine-1-formamide

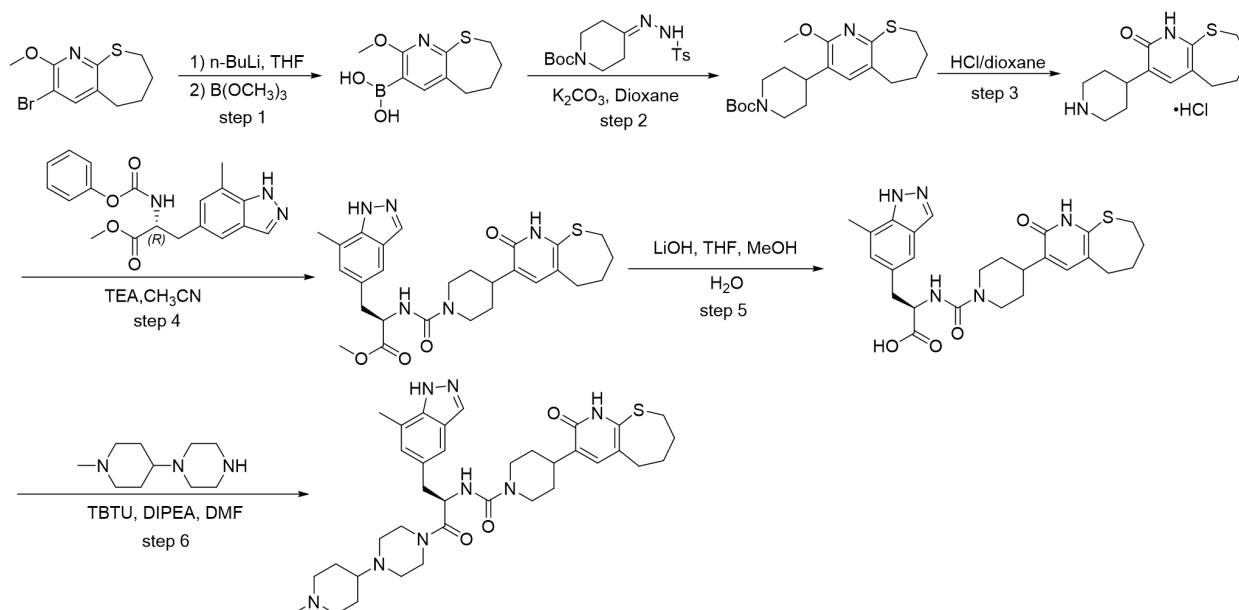


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 2 above.

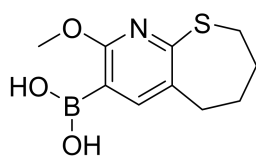
MS (ESI) m/z ($M+H$)⁺ = 659.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.95 (brs, 1H), 11.27 (brs, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.08 (s, 1H), 7.00 (d, J = 1.3 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.78 (q, J = 7.7 Hz, 1H), 4.13 – 4.06 (m, 2H), 4.02 (dd, J = 6.0, 4.0 Hz, 2H), 3.59 – 3.54 (m, 1H), 3.25 – 3.19 (m, 1H), 3.13 – 3.10 (m, 1H), 2.99 – 2.94 (m, 1H), 2.89 – 2.86 (m, 1H), 2.74 – 2.66 (m, 4H), 2.66 – 2.61 (m, 1H), 2.56 – 2.53 (m, 2H), 2.47 (s, 3H), 2.36 – 2.30 (m, 1H), 2.25 – 2.20 (m, 1H), 2.10 (s, 3H), 1.97 – 1.83 (m, 4H), 1.76 – 1.70 (m, 2H), 1.66 – 1.60 (m, 4H), 1.55 – 1.48 (m, 1H), 1.40 – 1.33 (m, 4H), 1.28 – 1.09 (m, 3H).

Example 4: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(8-oxo-2,3,4,5,8,9-hexahydrothiopyrrolo[2,3-*b*]pyridine-7-yl)piperidine-1-formamide



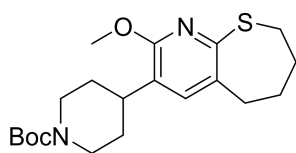
Step 1: preparation of (8-methoxy-2,3,4,5-tetrahydro-thiepine[2,3-*b*]pyridine-7-yl)boric acid



In a nitrogen atmosphere, 7-bromo-8-methoxy-2,3,4,5-tetrahydro-thiepine[2,3-*b*]pyridine (230.0 mg) was dissolved in tetrahydrofuran (3 mL), and dropwise added with *n*-butyl lithium (2.5 M, 0.4 mL) at -78°C to react for 30 minutes. The reaction system was added with trimethyl borate (113.9 mg) to continuously react for 40 minutes. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, added with 10 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 90.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 240.1.

Step 2: preparation of tert-butyl 4-(8-methoxy-2,3,4,5-tetrahydro-thiepine[2,3-*b*]pyridine-7-yl)piperidine-1-formate



(8-methoxy-2,3,4,5-tetrahydro-thiepine[2,3-*b*]pyridine-7-yl)boric acid (90.0 mg), tert-butyl 4-(2-tosylhydrazone)piperidine-1-formate (165.0 mg) and potassium carbonate (156.0 mg) were dissolved in 1,4-dioxane (5 mL), and heated at 120°C to react for 8 hours. After TLC showed that the reaction was completed, the reaction system was transferred to room temperature, added with 10 mL of water, and extracted with ethyl acetate for three times, and the organic phases were combined, backwashed with a saturated sodium chloride solution once, dried with anhydrous sodium sulfate, filtered and concentrated. The obtained crude product was purified by column chromatography to obtain 78.0 mg of the title compound.

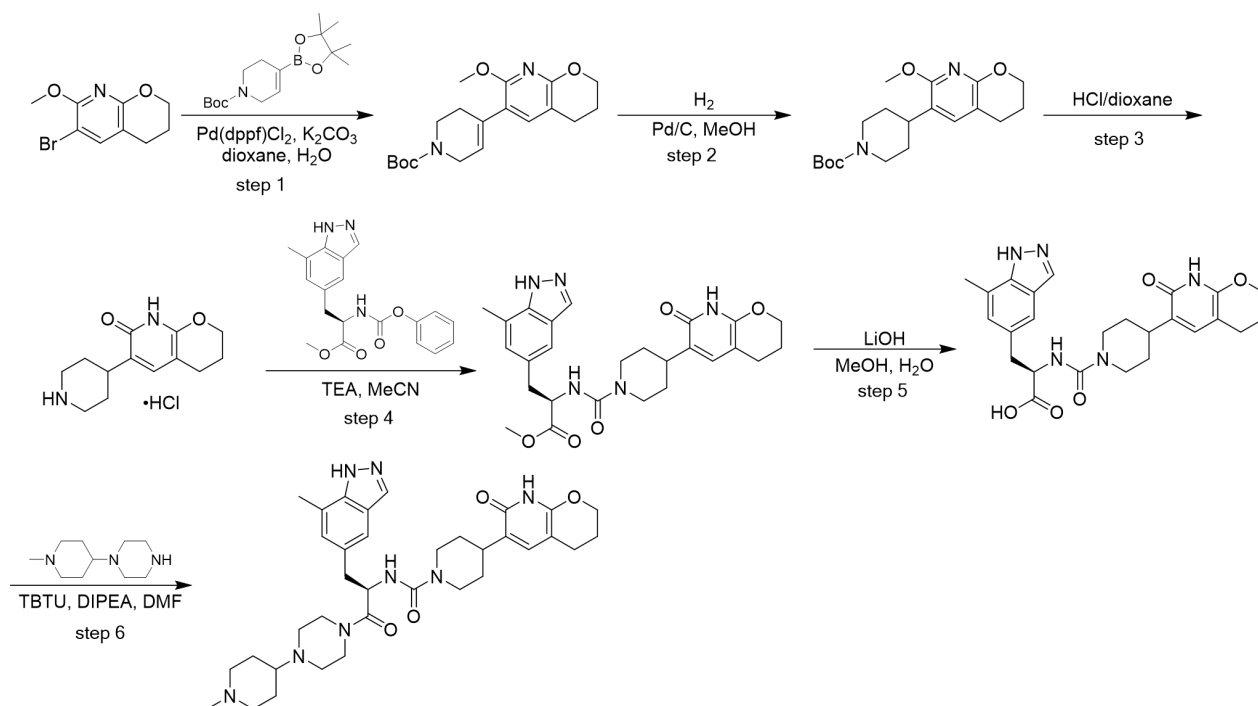
MS (ESI) m/z (M+H)⁺ = 379.2.

Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials in subsequent steps to prepare the title compound by a preparation method similar to that in Example 2 above.

MS (ESI) m/z (M+H)⁺ = 675.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.94 (s, 1H), 11.45 (s, 1H), 7.89 (s, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 4.70 (q, *J* = 7.7 Hz, 1H), 4.03 (d, *J* = 12.4 Hz, 2H), 3.54 – 3.45 (m, 1H), 3.16 (dd, *J* = 11.8, 8.1 Hz, 1H), 3.05 – 3.00 (m, 1H), 2.92 – 2.79 (m, 2H), 2.75 – 2.71 (m, 2H), 2.67 – 2.55 (m, 7H), 2.40 (s, 3H), 2.28 – 2.24 (m, 1H), 2.19 – 2.12 (m, 1H), 2.03 (s, 3H), 1.91 – 1.80 (m, 4H), 1.69 – 1.56 (m, 4H), 1.53 – 1.42 (m, 3H), 1.32 – 1.29 (m, 2H), 1.26 – 1.04 (m, 5H).

Example 5: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-pyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formamide

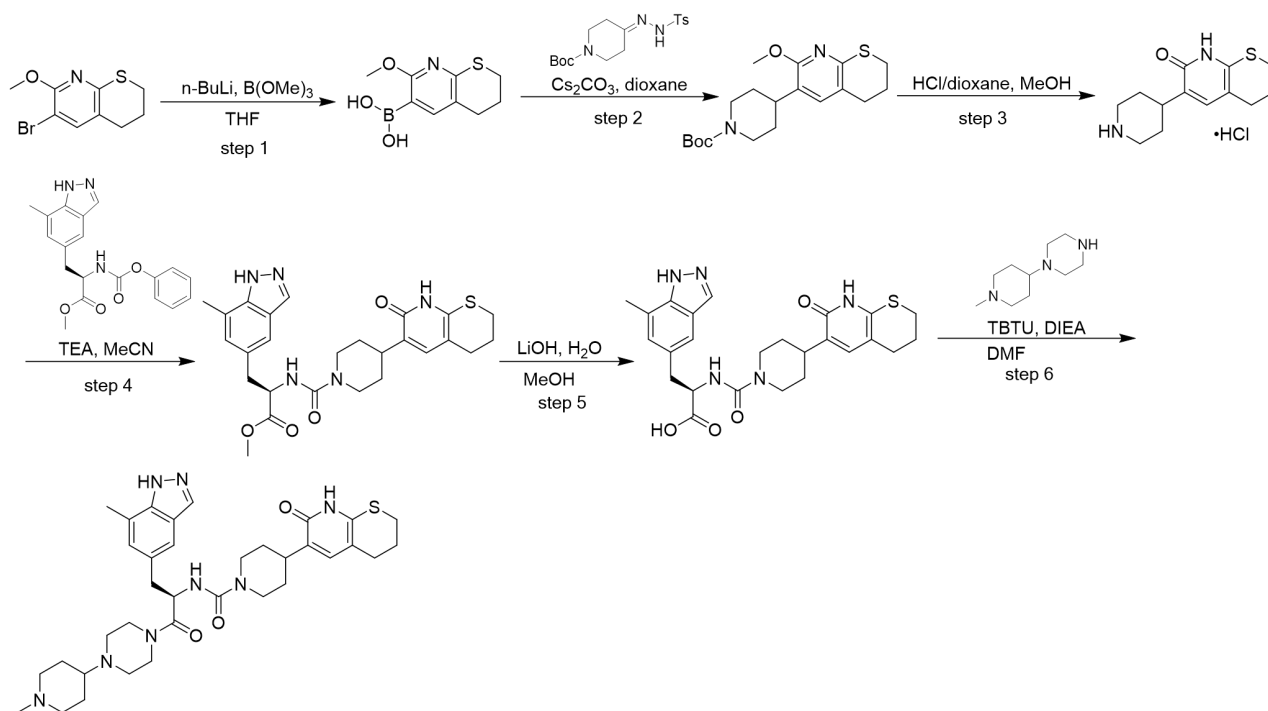


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 2 above.

MS (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 645.4.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 12.99 (s, 1H), 11.15 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.96 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.87-4.69 (m, 1H), 4.24-4.13 (m, 2H), 4.09 (d, J = 12.0, 2H), 3.60-3.52 (m, 1H), 3.30-3.19 (m, 2H), 3.18-3.08 (m, 1H), 3.03-2.93 (m, 1H), 2.92-2.82 (m, 1H), 2.79-2.57 (m, 6H), 2.47 (s, 4H), 2.37-2.30 (m, 1H), 2.26-2.18 (m, 1H), 2.11 (s, 3H), 1.99-1.82 (m, 4H), 1.80-1.70 (m, 2H), 1.68-1.59 (m, 2H), 1.58-1.48 (m, 1H), 1.43-1.34 (m, 2H), 1.31-1.14 (m, 4H).

Example 6: preparation of (*R*)-*N*-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formamide

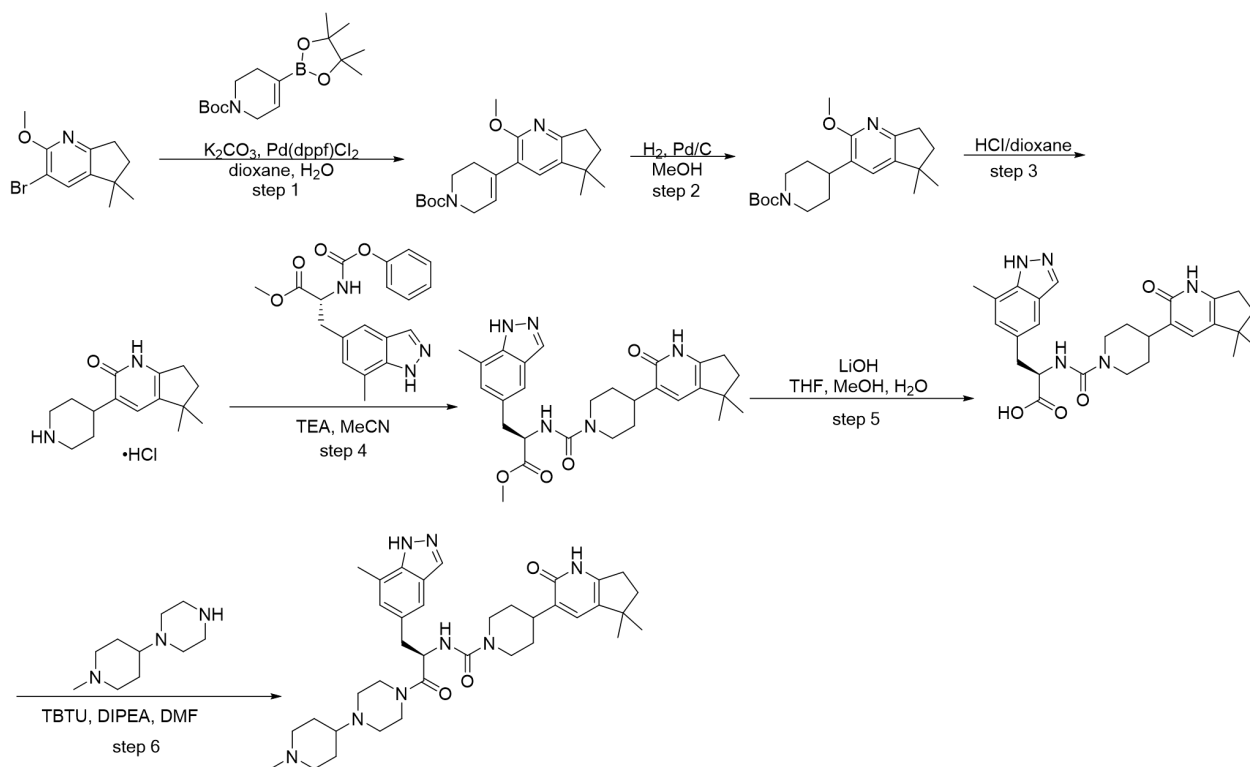


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 4 above.

MS (ESI) m/z ($M+H$)⁺ = 660.8.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.31 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.64 (d, J = 8.0, 1H), 4.80-4.72 (m, 1H), 4.14-4.02 (m, 2H), 3.57-3.53 (m, 1H), 3.27-3.18 (m, 2H), 3.14-3.08 (m, 1H), 3.04-3.00 (m, 2H), 2.98-2.93 (m, 1H), 2.92-2.86 (m, 1H), 2.74-2.60 (m, 6H), 2.56-2.54 (m, 1H), 2.47 (s, 3H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.09 (s, 3H), 2.01-1.89 (m, 4H), 1.74-1.61 (m, 4H), 1.55-1.49 (m, 1H), 1.40-1.34 (m, 2H), 1.30-1.13 (m, 4H).

Example 7: preparation of (R)-4-(5,5-dimethyl-2-oxo-2,5,6,7-tetrahydro-1H-cyclopentadieno[b]pyridine-3-yl)-N-(3,7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-formamide

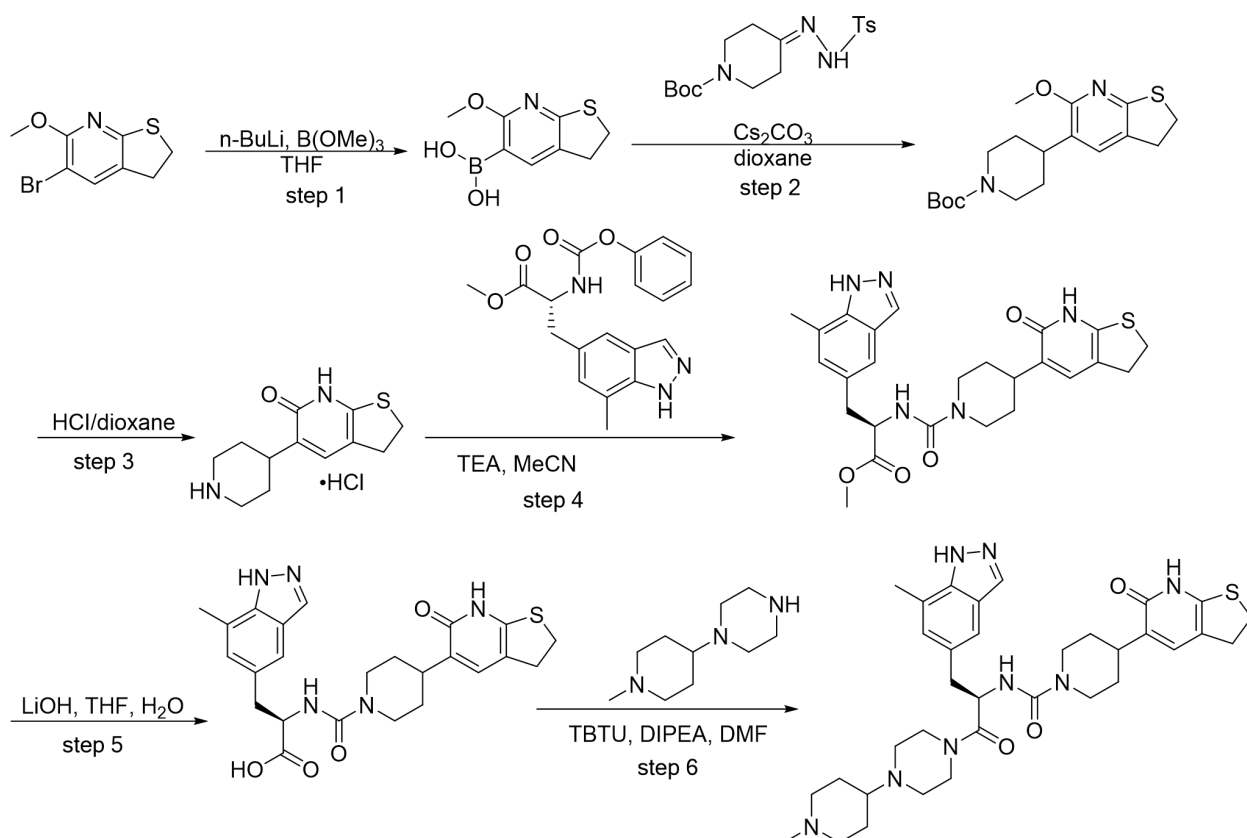


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 2 above.

MS (ESI) m/z ($M+H$)⁺ = 657.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 11.59 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.07 (s, 1H), 7.00 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.10 (d, J = 12.8 Hz, 2H), 3.58 (d, J = 13.0 Hz, 1H), 3.21 (s, 1H), 3.12 – 3.05 (m, 1H), 2.97 – 2.86 (m, 2H), 2.79 – 2.63 (m, 8H), 2.47 (s, 3H), 2.33 (s, 2H), 2.22 (s, 1H), 2.11 (s, 3H), 1.97 – 1.87 (m, 2H), 1.82 (t, J = 7.2 Hz, 2H), 1.76 (s, 1H), 1.66 (d, J = 12.4 Hz, 2H), 1.49 (t, J = 9.1 Hz, 1H), 1.38 (d, J = 12.7 Hz, 2H), 1.32 – 1.20 (m, 4H), 1.14 (d, J = 1.9 Hz, 6H).

Example 8: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formamide

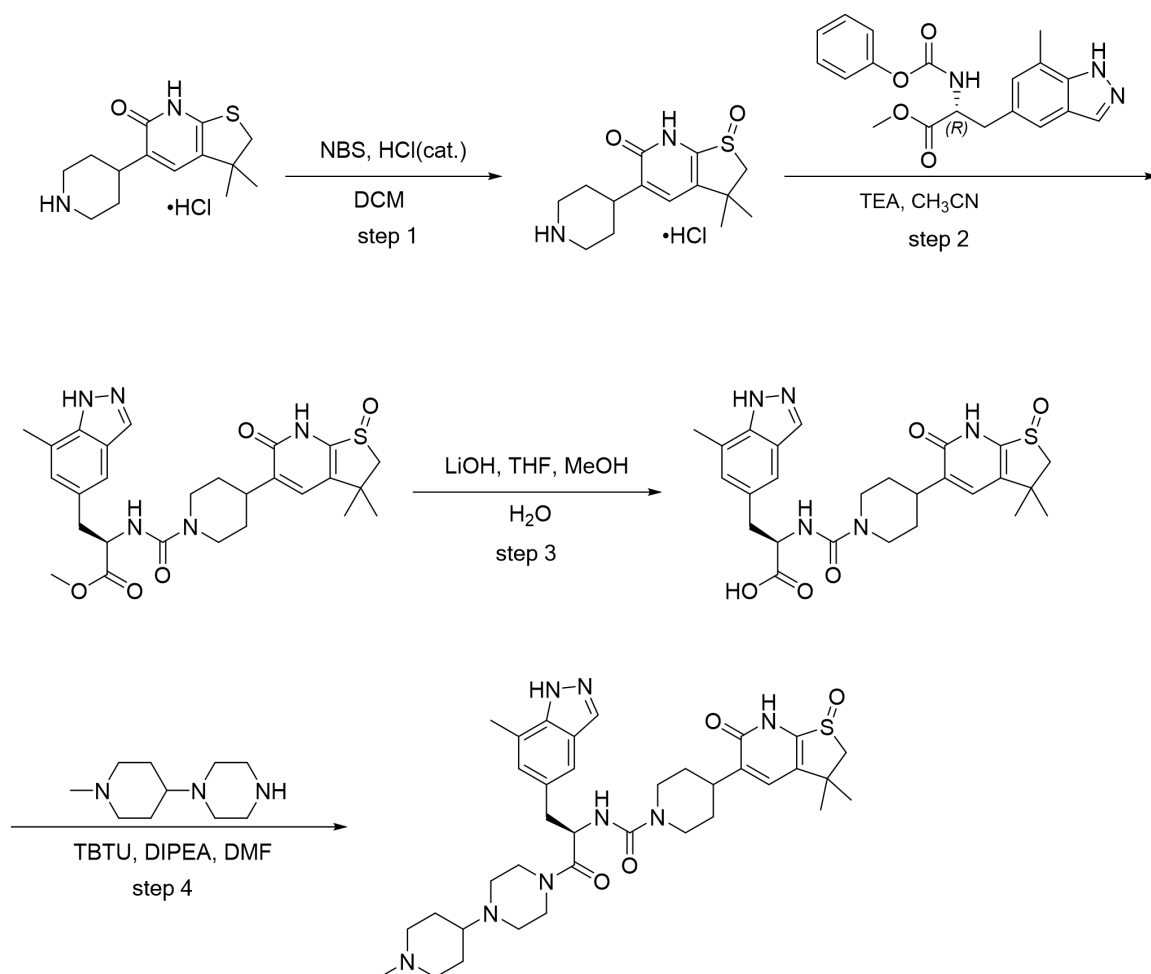


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 4 above.

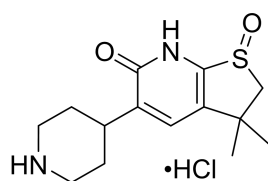
MS (ESI) m/z ($M+H$)⁺ = 647.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.38 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.09 (d, J = 12.5 Hz, 2H), 3.55 (d, J = 13.6 Hz, 1H), 3.40 (s, 2H), 3.24 (s, 1H), 3.11 (s, 1H), 3.06 (t, J = 8.1 Hz, 2H), 2.96 (dd, J = 13.1, 7.8 Hz, 1H), 2.88 (dd, J = 13.1, 7.1 Hz, 1H), 2.74 – 2.67 (m, 4H), 2.63 (d, J = 11.1 Hz, 1H), 2.47 (s, 3H), 2.37 – 2.31 (m, 1H), 2.23 (d, J = 10.1 Hz, 1H), 2.11 (s, 3H), 1.99 – 1.90 (m, 2H), 1.74 (t, J = 11.5 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.57 – 1.51 (m, 1H), 1.38 (d, J = 11.9 Hz, 2H), 1.27 – 1.18 (m, 5H).

Example 9: preparation of 4-(3,3-dimethyl-1-oxidation-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)-*N*-((*R*)-3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-formamide



Step 1: preparation of 3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrothieno[2,3-b]pyridine-6(2H)-1-oxide hydrochloride



3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrothieno[2,3-b]pyridine-6(2H)-one hydrochloride (140.0 mg) was dissolved in dichloromethane (10 mL), and added with dilute hydrochloric acid (2 M, 0.01 mL) and *N*-bromosuccinimide (94.0 mg) to react at room temperature for 30 minutes. After TLC showed that the reaction was completed, the system was concentrated to obtain 210.0 mg of crude product.

MS (ESI) m/z ($M+H$)⁺ = 281.1.

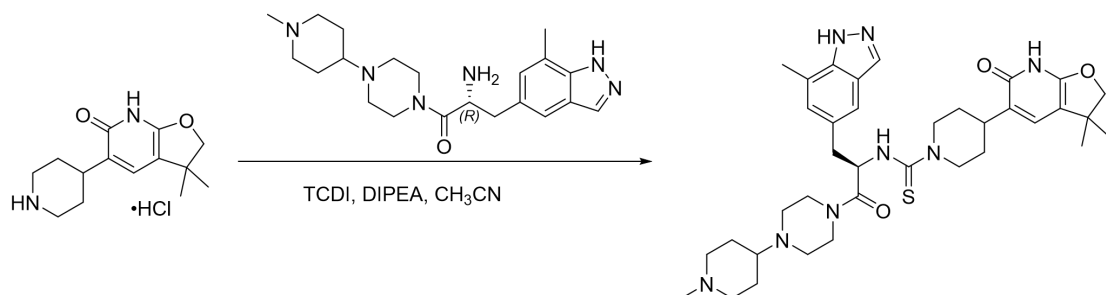
Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials in subsequent steps to prepare the title compound by a preparation method similar to that in Example 2 above.

MS (ESI) m/z ($M+H$)⁺ = 691.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.95 (s, 1H), 7.90 (s, 1H), 7.47 (s, 1H), 7.30 (s, 1H), 6.93 (s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 4.71 (q, J = 7.8 Hz, 1H), 4.09 (d, J = 12.9 Hz, 2H), 3.54 – 3.51 (m, 2H), 3.23 – 3.16 (m, 3H), 3.01 (d, J = 9.3 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.82 – 2.80 (m, 2H), 2.68 –

2.63 (m, 4H), 2.40 (s, 3H), 2.30 – 2.24 (m, 1H), 2.18 – 2.11 (m, 1H), 2.03 (s, 3H), 1.88 – 1.78 (m, 2H), 1.69 – 1.61 (m, 4H), 1.42 – 1.40 (m, 2H), 1.38 (s, 3H), 1.29 (d, $J = 12.2$ Hz, 2H), 1.24 (s, 3H), 1.16 – 1.06 (m, 2H).

Example 10: preparation of (R)-4-(3,3-dimethyl-6-oxo-2,3,6,7-tetrahydrofuro[2,3-*b*]pyridine-5-yl)-*N*-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)piperidine-1-thioformamide

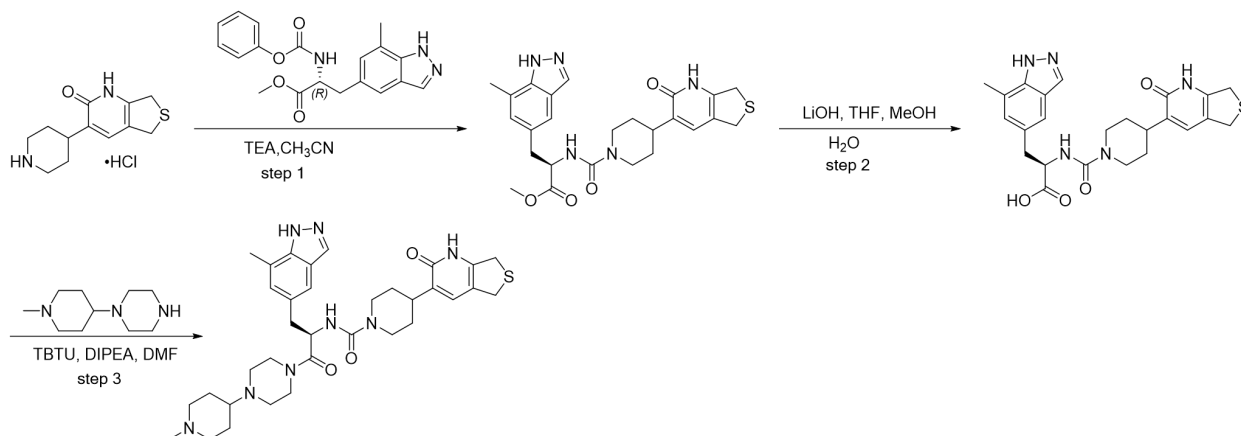


(*R*)-2-amino-3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one (23.0 mg) was dissolved in acetonitrile (1 mL), and added with *N,N*-diisopropylethylamine (54.0 mg) and *N,N'*-thiocarbonyl diimidazole (11.0 mg) to react at room temperature for 1 hour. The system was added with 3,3-dimethyl-5-(piperidine-4-yl)-3,7-dihydrofuro[2,3-*b*]pyridine-6(2*H*)-one hydrochloride (15.0 mg) and heated to 40°C to react for 1 hour. After TLC showed that the reaction was completed, the reaction system was filtered, and the filtrate was collected and purified by reverse phase preparation. The crude product was freeze-dried to obtain 2.0 mg of the title compound.

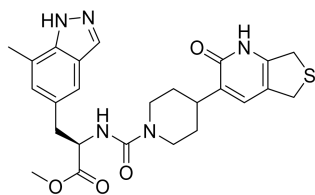
MS (ESI) m/z ($M+H$)⁺ = 675.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.97 (s, 1H), 10.65 (brs, 1H), 7.91 (s, 1H), 7.58 (d, $J = 7.5$ Hz, 1H), 7.32 (s, 1H), 7.23 (s, 1H), 6.95 (s, 1H), 5.47 (q, $J = 7.5$ Hz, 1H), 4.76 (t, $J = 13.3$ Hz, 2H), 4.10 (s, 2H), 3.46–3.41 (m, 1H), 3.22–3.20 (m, 2H), 3.14–3.10 (m, 1H), 3.05 – 2.92 (m, 3H), 2.93 – 2.78 (m, 3H), 2.66–2.63 (m, 2H), 2.41 (s, 3H), 2.28 (d, $J = 6.7$ Hz, 1H), 2.23 – 2.17 (m, 1H), 2.03 (s, 3H), 2.00 – 1.93 (m, 1H), 1.89–1.81 (m, 1H), 1.69–1.63 (m, 4H), 1.44–1.32 (m, 5H), 1.18 (d, $J = 2.9$ Hz, 6H), 1.14–1.09 (m, 1H).

Example 11: preparation of (R)-*N*-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-*b*]pyridine-3-yl)piperidine-1-formamide



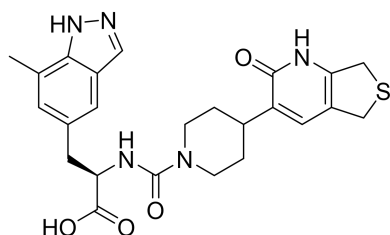
Step 1: preparation of methyl (R)-3-(7-methyl-1H-indazole-5-yl)-2-(4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-b]pyridine-3-yl)piperidine-1-formylamino)propionate



3-(piperidine-4-yl)-5,7-dihydrothieno[3,4-b]pyridine-2(1H)-one hydrochloride (51.0 mg) and methyl (R)-3-(7-methyl-1H-indazole-5-yl)-2-((phenoxy carbonyl)amino)propionate (68.0 mg) were dissolved in acetonitrile (3 mL), added with triethylamine (64.0 mg), and heated to 60°C to react for 8 hours. After TLC showed that the reaction was completed, the system was concentrated, and the obtained crude product was purified by column chromatography to obtain 65.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 496.2.

Step 2: preparation of (R)-3-(7-methyl-1H-indazole-5-yl)-2-(4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-b]pyridine-3-yl)piperidine-1-formylamino)propionic acid

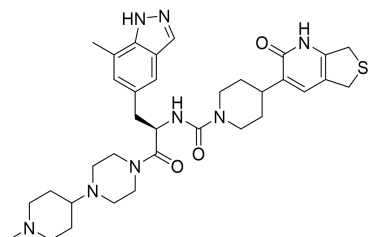


Methyl

(R)-3-(7-methyl-1H-indazole-5-yl)-2-(4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-b]pyridine-3-yl)piperidine-1-formylamino)propionate (30.0 mg) was dissolved in tetrahydrofuran (2 mL) and methanol (0.5 mL), and added with a lithium hydroxide (7.6 mg) aqueous solution (0.5 mL) to react at room temperature for 1 hour. After TLC showed that the reaction was completed, the system was added with 1 M dilute hydrochloric acid to adjust pH to be neutral, and the mother solution was concentrated to obtain 40.0 mg of crude product.

MS (ESI) m/z (M+H)⁺ = 482.2.

Step 3: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-b]pyridine-3-yl)piperidine-1-formamide



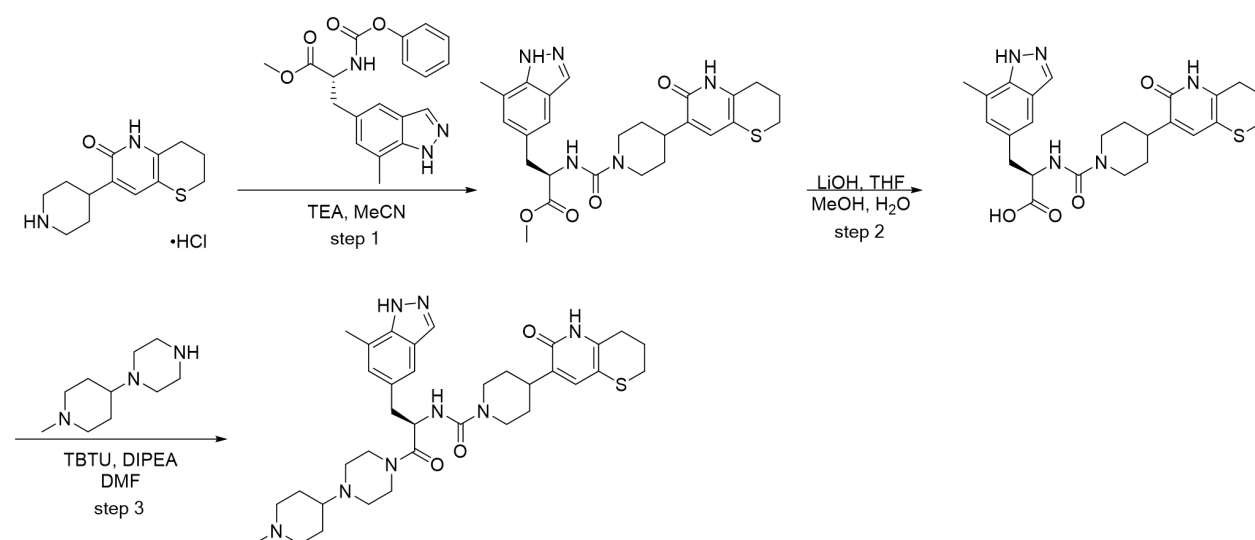
(R)-3-(7-methyl-1H-indazole-5-yl)-2-(4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-b]pyridine-3-yl)piperidine-1-formylamino)propionic acid (30.0 mg) and 2-(1H-benzotriazo-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (22.0 mg) were dissolved in N,N-dimethylformamide (2 mL), and added with N,N-diisopropylethylamine (24.0 mg) to react at

room temperature for 10 minutes. The system was continuously added with 1-(1-methylpiperidine-4-yl)piperazine (17.0 mg) to react at room temperature for 20 minutes. After TLC showed that the reaction was completed, the system was filtered, and the mother solution was purified by reverse phase preparation. The crude product was freeze-dried to obtain 11.3 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 647.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.76 (brs, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 4.77 (q, *J* = 7.7 Hz, 1H), 4.09 (d, *J* = 12.9 Hz, 2H), 4.01 – 3.93 (m, 4H), 3.58 – 3.52 (m, 1H), 3.27 – 3.22 (m, 1H), 3.15 – 3.09 (m, 1H), 2.98 – 2.85 (m, 2H), 2.78 – 2.62 (m, 5H), 2.47 (s, 3H), 2.36 – 2.29 (m, 1H), 2.27 – 2.20 (m, 1H), 2.10 (s, 3H), 1.99 – 1.86 (m, 2H), 1.76 – 1.63 (m, 4H), 1.57 – 1.53 (m, 1H), 1.40 – 1.37 (m, 2H), 1.26 – 1.15 (m, 5H).

Example 12: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-3,4,5,6-tetrahydro-2H-thiopyrano[3,2-*b*]pyridine-7-yl)piperidine-1-formamide

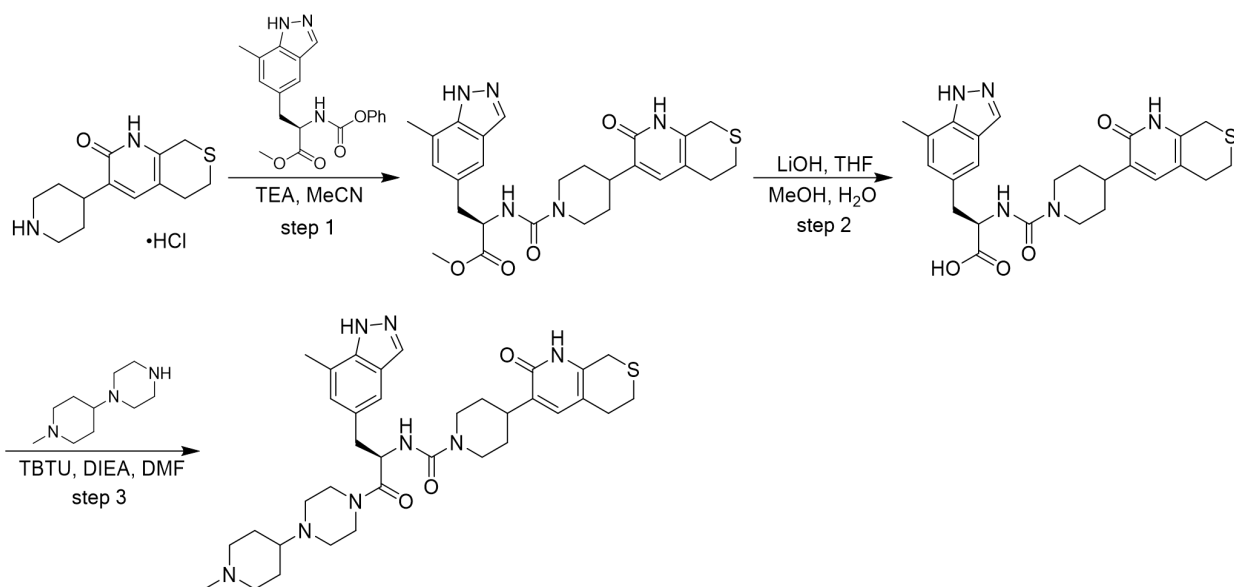


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 661.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.94 (s, 1H), 11.40 (s, 1H), 7.89 (s, 1H), 7.28 (s, 1H), 6.93 (s, 1H), 6.71 (s, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.70 (q, *J* = 7.7 Hz, 1H), 4.02 (s, 2H), 3.49 (d, *J* = 13.5 Hz, 1H), 3.15 (t, *J* = 9.6 Hz, 1H), 3.03 (t, *J* = 9.4 Hz, 1H), 2.92 – 2.79 (m, 4H), 2.69 – 2.55 (m, 5H), 2.48 (t, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.26 (s, 1H), 2.13 (d, *J* = 8.8 Hz, 1H), 2.02 (s, 3H), 1.96 – 1.80 (m, 4H), 1.69 – 1.57 (m, 4H), 1.42 (s, 1H), 1.30 (d, *J* = 12.0 Hz, 2H), 1.21 – 1.07 (m, 5H).

Example 13: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-2,5,6,8-tetrahydro-1H-thiopyrano[3,4-*b*]pyridine-3-yl)piperidine-1-formamide

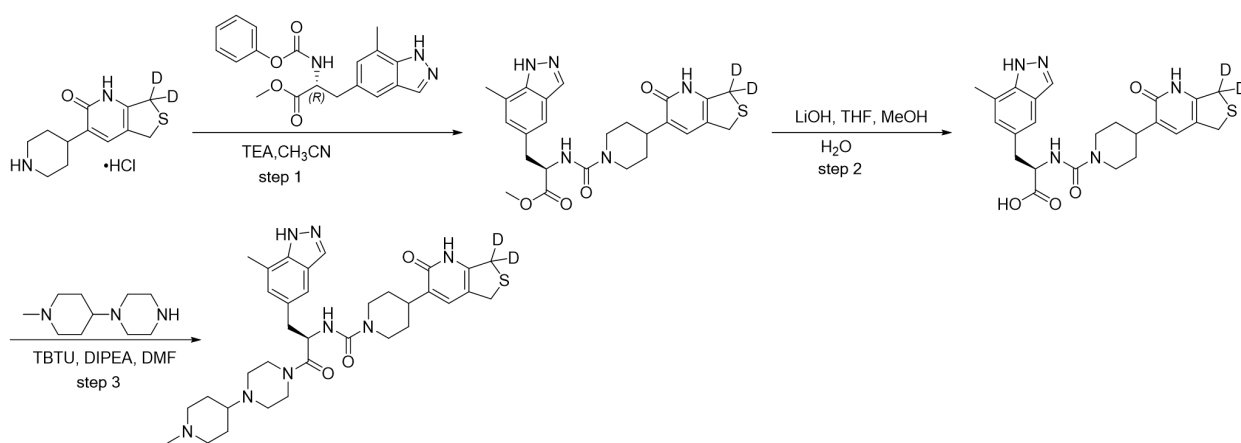


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 660.8.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.36 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.89 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.82-4.72 (m, 1H), 4.10 (d, J = 12.0 Hz, 2H), 3.60-3.54 (m, 1H), 3.50 (s, 2H), 3.25-3.18 (m, 1H), 3.15-3.08 (m, 1H), 2.98-2.92 (m, 1H), 2.90-2.85 (m, 1H), 2.81-2.78 (m, 3H), 2.75-2.62 (m, 6H), 2.47 (s, 3H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.09 (s, 3H), 2.01-1.85 (m, 2H), 1.75-1.64 (m, 4H), 1.58-1.46 (m, 1H), 1.43-1.32 (m, 2H), 1.29-1.11 (m, 5H).

Example 14: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidin-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2,5,7-tetrahydrothieno[3,4-*b*]pyridine-3-yl-7,7-d₂)piperidine-1-formamide



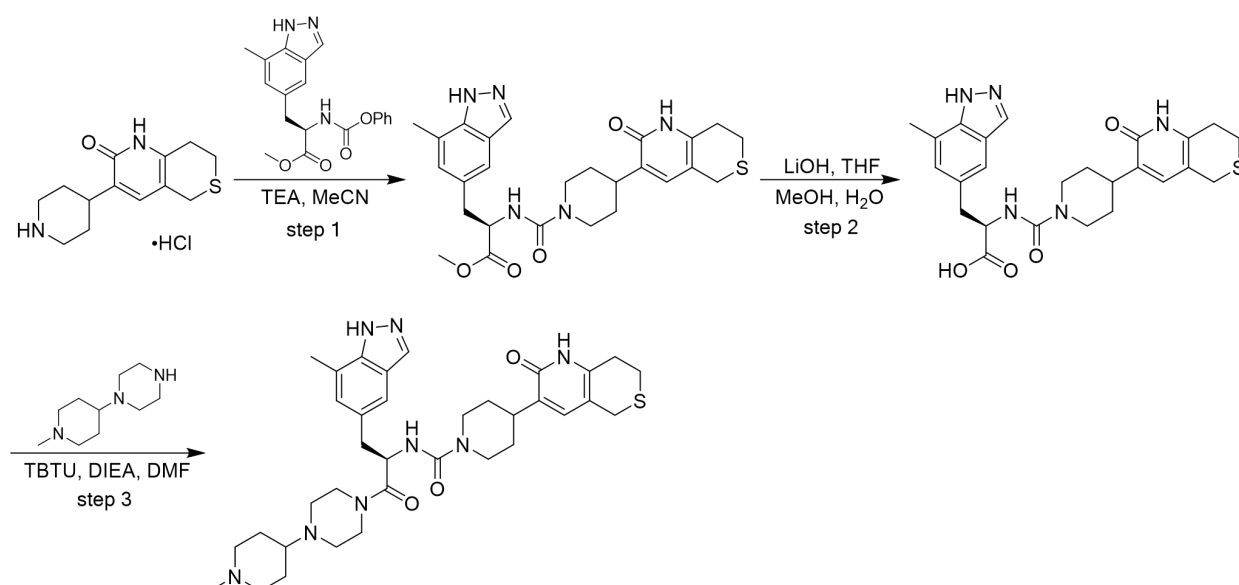
Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 649.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.75 (brs, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.09 (d, J = 12.9 Hz, 2H), 3.95

(d, $J = 2.2$ Hz, 2H), 3.58 – 3.51 (m, 1H), 3.26 – 3.21 (m, 1H), 3.17 – 3.09 (m, 1H), 2.99 – 2.93 (m, 1H), 2.90 – 2.85 (m, 1H), 2.79 – 2.62 (m, 5H), 2.47 (s, 3H), 2.36 – 2.31 (m, 1H), 2.24 – 2.20 (m, 1H), 2.10 (s, 3H), 1.99 – 1.87 (m, 2H), 1.75 – 1.62 (m, 4H), 1.58 – 1.53 (m, 1H), 1.46 – 1.37 (m, 2H), 1.27 – 1.12 (m, 5H).

Example 15: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,5,7,8-tetrahydro-2H-thiopyrano[4,3-*b*]pyridine-3-yl)piperidine-1-formamide

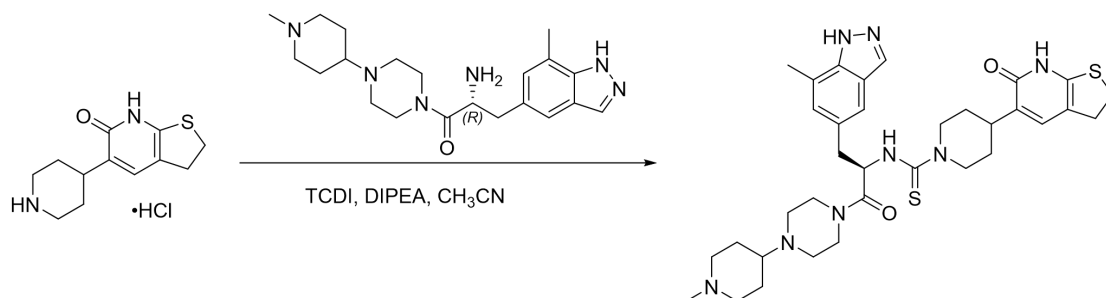


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 661.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.35 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.90 (s, 1H), 6.65 (d, $J = 8.0$ Hz, 1H), 4.77 (q, $J = 7.7$ Hz, 1H), 4.09 (d, $J = 12.8$ Hz, 2H), 3.52 (d, $J = 17.4$ Hz, 3H), 3.23 (s, 1H), 3.15 – 3.06 (m, 1H), 3.01 – 2.83 (m, 2H), 2.82 (t, $J = 5.9$ Hz, 2H), 2.69 (dt, $J = 20.1, 8.4$ Hz, 6H), 2.47 (s, 3H), 2.33 (s, 1H), 2.23 (d, $J = 10.4$ Hz, 1H), 2.10 (s, 3H), 1.95 (dd, $J = 25.7, 15.2, 9.4$ Hz, 3H), 1.75 (d, $J = 11.4$ Hz, 1H), 1.71 – 1.61 (m, 2H), 1.54 (t, $J = 8.9$ Hz, 1H), 1.38 (d, $J = 12.4$ Hz, 2H), 1.30 – 1.10 (m, 6H).

Example 16: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-thioformamide



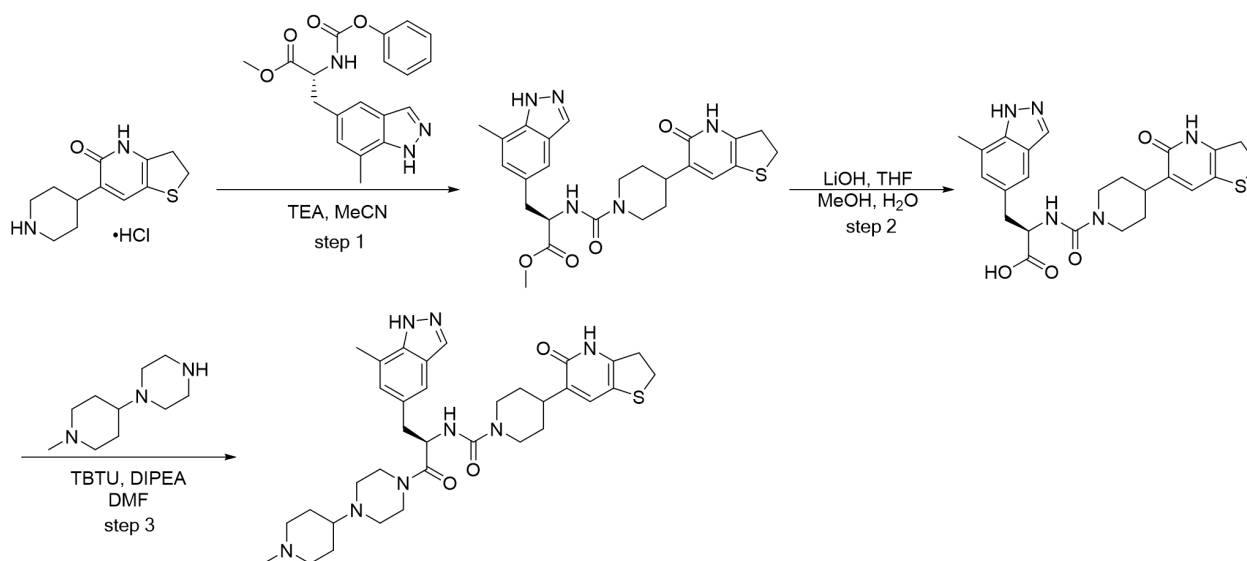
Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare

the title compound by a preparation method similar to that in Example 10 above.

MS (ESI) m/z ($M+H$)⁺ = 663.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.04 (s, 1H), 11.49 (brs, 1H), 7.98 (s, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.40 (s, 1H), 7.10 (s, 1H), 7.02 (s, 1H), 5.54 (q, J = 7.5 Hz, 1H), 4.80 (t, J = 12.5 Hz, 2H), 3.50 – 3.45 (m, 1H), 3.42 – 3.38 (m, 2H), 3.25 – 3.18 (m, 2H), 3.09 – 2.96 (m, 4H), 2.99 – 2.83 (m, 3H), 2.72 (d, J = 10.9 Hz, 2H), 2.48 (s, 3H), 2.35 – 2.23 (m, 2H), 2.10 (s, 3H), 2.08 – 1.99 (m, 1H), 1.97 – 1.89 (m, 1H), 1.77 – 1.67 (m, 4H), 1.65 – 1.59 (m, 1H), 1.44 – 1.31 (m, 4H), 1.29 – 1.10 (m, 3H).

Example 17: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(5-oxo-2,3,4,5-tetrahydrothieno[3,2-*b*]pyridine-6-yl)piperidine-1-formamide

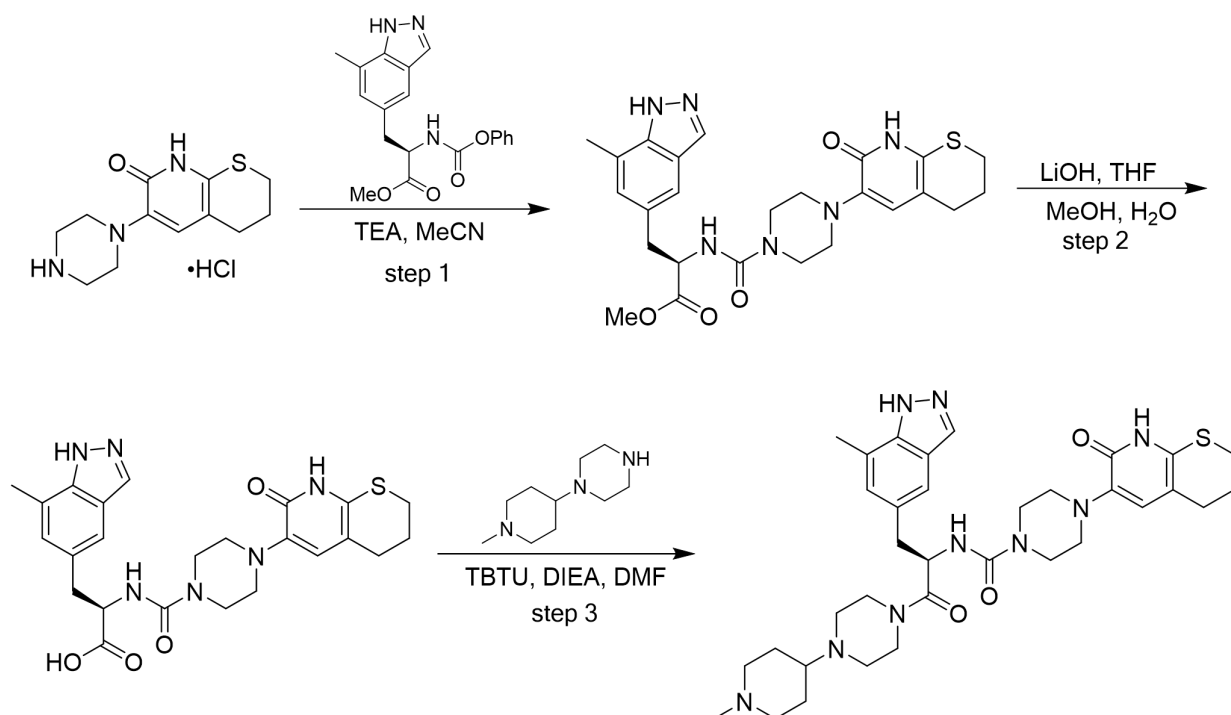


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 647.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.94 (s, 1H), 11.67 (s, 1H), 7.89 (s, 1H), 7.28 (s, 1H), 7.07 (s, 1H), 6.92 (s, 1H), 6.58 (d, J = 8.0 Hz, 1H), 4.70 (q, J = 7.7 Hz, 1H), 4.03 (t, J = 11.1 Hz, 2H), 3.54 – 3.44 (m, 1H), 3.24 (s, 2H), 3.18 – 3.11 (m, 1H), 3.00 (t, J = 8.1 Hz, 3H), 2.90 (dd, J = 13.1, 8.1 Hz, 1H), 2.81 (dd, J = 13.1, 6.8 Hz, 1H), 2.72 – 2.54 (m, 5H), 2.40 (s, 3H), 2.29 – 2.22 (m, 1H), 2.17 – 2.10 (m, 1H), 2.02 (s, 3H), 1.91 – 1.77 (m, 2H), 1.69 – 1.55 (m, 4H), 1.41 (t, J = 9.1 Hz, 1H), 1.32 – 1.05 (m, 7H).

Example 18: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperazine-1-formamide

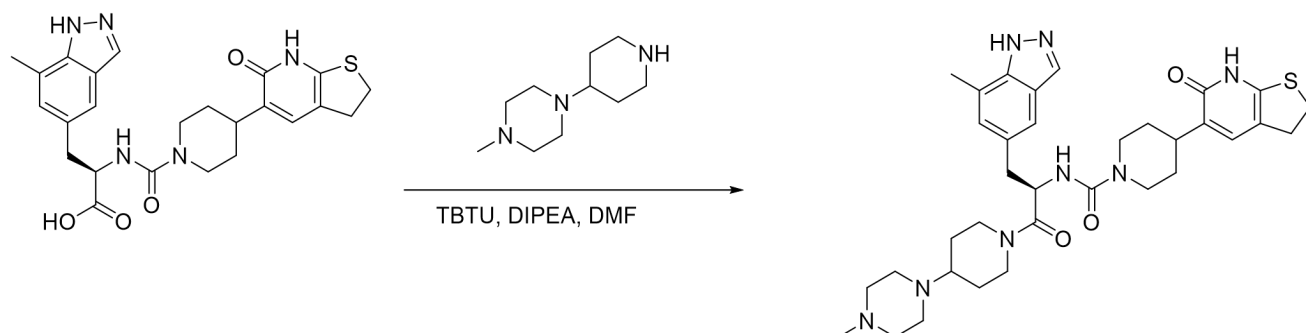


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 661.8.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.41 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 6.99 (s, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.45 (s, 1H), 4.82-4.72 (m, 1H), 3.60-3.53 (m, 1H), 3.40-3.35 (m, 3H), 3.27-3.18 (m, 1H), 3.15-3.05 (m, 1H), 3.05-2.92 (m, 3H), 2.90-2.80 (m, 5H), 2.75-2.62 (m, 2H), 2.55-2.51 (m, 2H), 2.47 (s, 3H), 2.35-2.25 (m, 1H), 2.23-2.18 (m, 1H), 2.09 (s, 3H), 2.01-1.85 (m, 4H), 1.76-1.64 (m, 2H), 1.55-1.46 (m, 1H), 1.42-1.32 (m, 2H), 1.29-1.09 (m, 4H).

Example 19: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(4-methylpiperazine-1-yl)piperidine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formamide



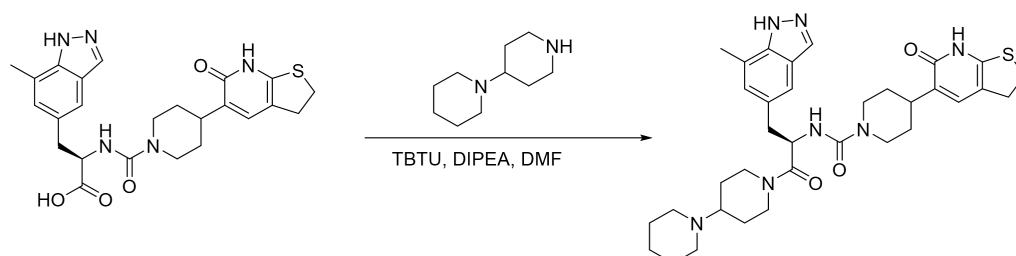
Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 647.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.93 (s, 1H), 11.40 (s, 1H), 7.89 (d, J = 3.2 Hz, 1H), 7.30 (d, J = 14.3 Hz, 1H), 6.94 (d, J = 5.6 Hz, 2H), 6.59 (dd, J = 12.8, 8.1 Hz, 1H), 4.74 (dq, J = 15.2, 7.6 Hz,

1H), 4.26 (d, $J = 12.7$ Hz, 1H), 4.03 (s, 2H), 3.85 (t, $J = 16.0$ Hz, 1H), 3.33 (t, $J = 7.9$ Hz, 2H), 2.99 (t, $J = 8.0$ Hz, 2H), 2.94 – 2.86 (m, 1H), 2.81 (dd, $J = 13.1, 6.4$ Hz, 1H), 2.73 – 2.55 (m, 4H), 2.40 (d, $J = 4.1$ Hz, 3H), 2.34 (s, 1H), 2.30 – 2.07 (m, 5H), 2.04 (d, $J = 5.1$ Hz, 3H), 1.95 – 1.81 (m, 3H), 1.57 (d, $J = 14.5$ Hz, 3H), 1.37 (d, $J = 12.2$ Hz, 1H), 1.27 – 1.10 (m, 4H), 0.82 – 0.42 (m, 1H).

Example 20: preparation of (R)-N-(1-([1,4'-bipiperidine]-1'-yl)-3-(7-methyl-1H-indazole-5-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-b]pyridine-5-yl)piperidine-1-formamide

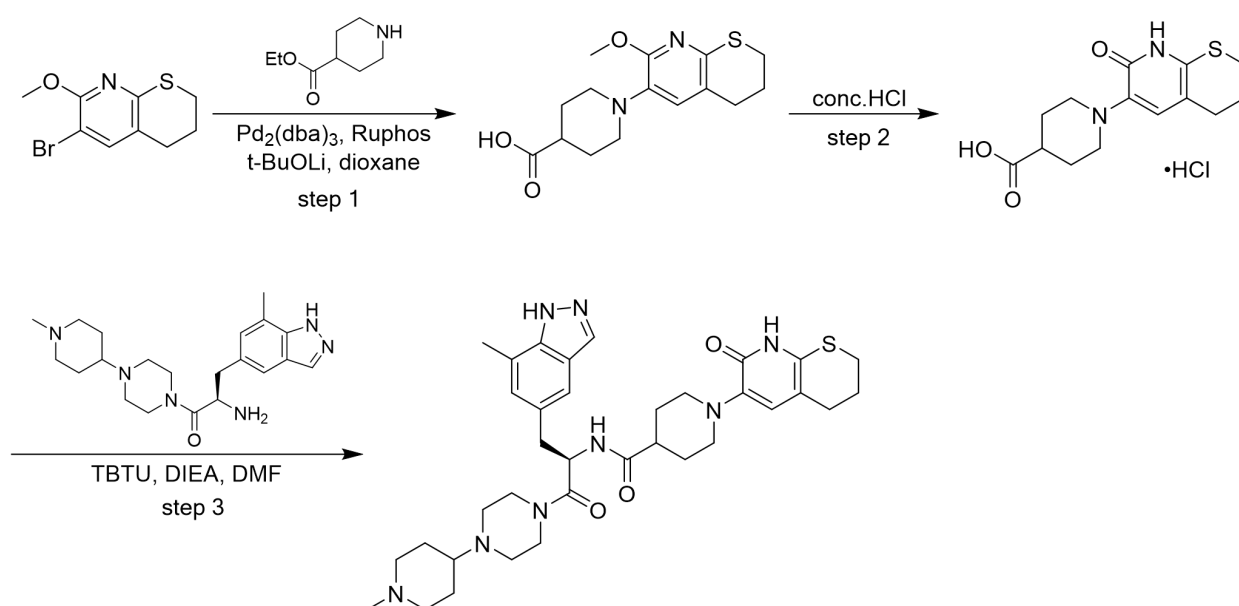


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

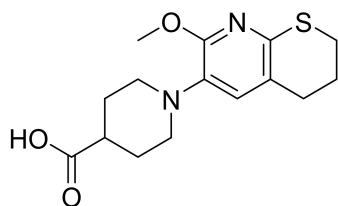
MS (ESI) m/z ($M+H$)⁺ = 632.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 11.45 (s, 1H), 7.96 (d, $J = 3.1$ Hz, 1H), 7.37 (d, $J = 14.4$ Hz, 1H), 7.01 (d, $J = 5.0$ Hz, 2H), 6.65 (dd, $J = 14.3, 8.1$ Hz, 1H), 4.80 (dq, $J = 24.1, 7.9$ Hz, 1H), 4.34 (d, $J = 12.1$ Hz, 1H), 4.10 (s, 2H), 3.94 (t, $J = 16.8$ Hz, 1H), 3.40 (t, $J = 7.9$ Hz, 2H), 3.06 (t, $J = 7.9$ Hz, 2H), 3.00 – 2.92 (m, 1H), 2.88 (dd, $J = 13.3, 6.3$ Hz, 1H), 2.78 – 2.61 (m, 4H), 2.47 (d, $J = 4.7$ Hz, 3H), 2.38 (s, 2H), 2.30 – 2.19 (m, 1H), 2.02 – 1.79 (m, 3H), 1.62 (s, 3H), 1.45 – 1.20 (m, 10H), 0.74 – 0.55 (m, 1H).

Example 21: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-1-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-4-formamide



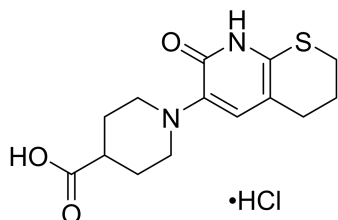
Step 1: preparation of 1-(7-methoxy-3,4-dihydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-4-formic acid



In a nitrogen atmosphere, 6-bromo-7-methoxy-3,4-dihydro-2*H*-thiopyrano[2,3-*b*]pyridine (50.0 mg), ethyl piperidine-4-formate (36.3 mg), tris(dibenzylideneacetone)dipalladium (17.4 mg), 2-dicyclohexylphosphine-2',6'-diisopropylbiphenyl (17.7 mg) and lithium tert-butoxide (30.4 mg) were dissolved in 1,4-dioxane (1 mL) to react at 100°C for 2 hours. After LCMS showed that some raw materials were left, and the reaction was ended, the reaction solution was filtered, and the filtrate was collected and concentrated. The obtained crude product was purified by column chromatography to obtain 40.0 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 308.9.

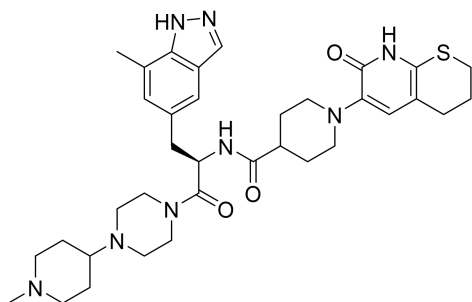
Step 2: preparation of 1-(7-oxo-3,4,7,8-tetrahydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-4-formic acid hydrochloride



1-(7-methoxy-3,4-dihydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-4-formic acid (40 mg) was dissolved in concentrated hydrochloric acid (2 mL) to react at 95°C for 2 hours. After LCMS showed that the reaction was completed, the reaction solution was concentrated to obtain 38 mg of crude product, which was directly used in the next step of reaction.

MS (ESI) m/z (M+H)⁺ = 294.9.

Step 3: preparation of (R)-N-(3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-1-(7-oxo-3,4,7,8-tetrahydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-4-formamide



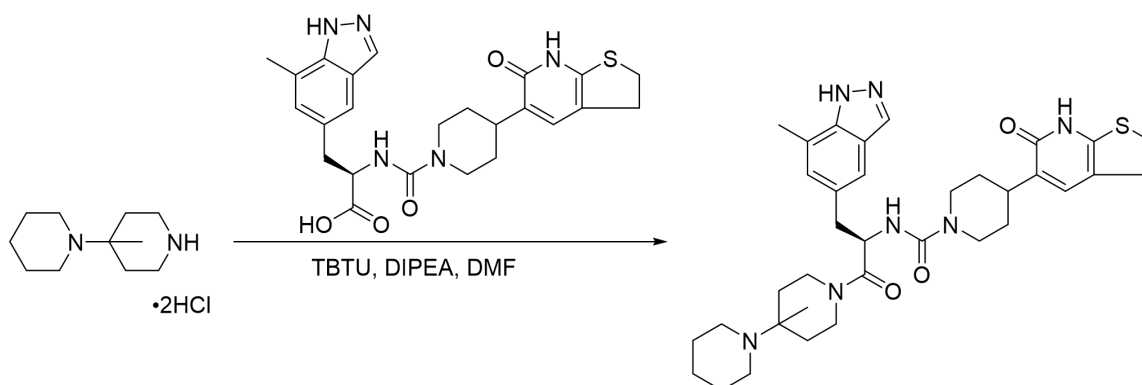
1-(7-oxo-3,4,7,8-tetrahydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-4-formic acid hydrochloride (38 mg), *N,N*-diisopropylethylamine (50.0 mg) and (R)-2-amino-3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one (54.6 mg) were dissolved in *N,N*-dimethylformamide (1.0 mL), and added with 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (62.2 mg) to react for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was concentrated, and the crude product was purified by a preparative liquid phase, and freeze-dried to obtain 17.3 mg of

the title compound.

MS (ESI) m/z (M+H)⁺ = 660.9.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.31 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.34 (s, 1H), 6.99 (s, 1H), 6.45 (s, 1H), 4.94-4.89 (m, 1H), 3.60-3.45 (m, 3H), 3.28-3.23 (m, 2H), 3.20-3.08 (m, 1H), 3.08-2.92 (m, 3H), 2.88-2.80 (m, 1H), 2.75-2.65 (m, 2H), 2.47 (s, 3H), 2.37-2.30 (m, 3H), 2.28-2.19 (m, 2H), 2.09 (s, 3H), 2.05-1.96 (m, 1H), 1.95-1.86 (m, 3H), 1.79-1.68 (m, 2H), 1.65-1.48 (m, 5H), 1.45-1.35 (m, 2H), 1.33-1.08 (m, 4H).

Example 22: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4'-methyl-[1,4'-bipiperidine]-1'-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-6-yl)piperidine-1-formamide

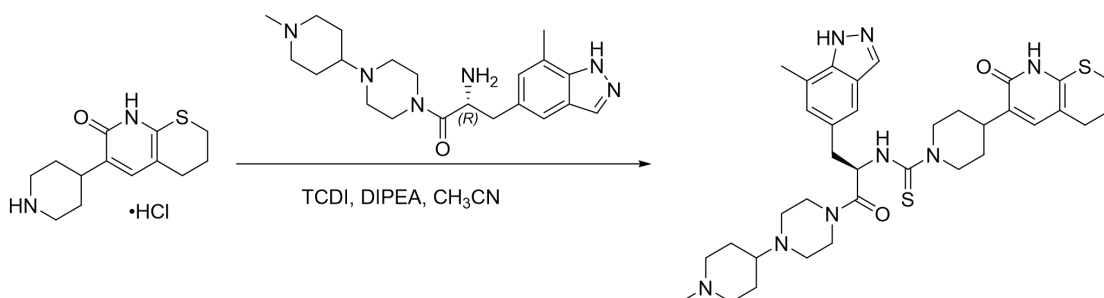


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 646.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 7.96 (d, *J* = 5.7 Hz, 1H), 7.37 (d, *J* = 6.5 Hz, 1H), 7.09 (d, *J* = 13.4 Hz, 1H), 6.99 (d, *J* = 15.0 Hz, 1H), 6.61 (t, *J* = 6.9 Hz, 1H), 4.78 (s, 1H), 4.09 (d, *J* = 13.0 Hz, 2H), 3.40 (s, 1H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.93 (dd, *J* = 19.0, 9.0 Hz, 2H), 2.74 (d, *J* = 14.2 Hz, 1H), 2.66 (d, *J* = 12.7 Hz, 2H), 2.47 (d, *J* = 2.5 Hz, 3H), 2.36 – 2.18 (m, 5H), 2.00 (q, *J* = 7.1 Hz, 1H), 1.62 (s, 3H), 1.52 – 1.39 (m, 4H), 1.38 – 1.30 (m, 4H), 1.30 – 1.17 (m, 5H), 0.85 (t, *J* = 6.5 Hz, 1H), 0.82 – 0.68 (m, 2H), 0.59 – 0.38 (m, 2H).

Example 23: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-thioformamide

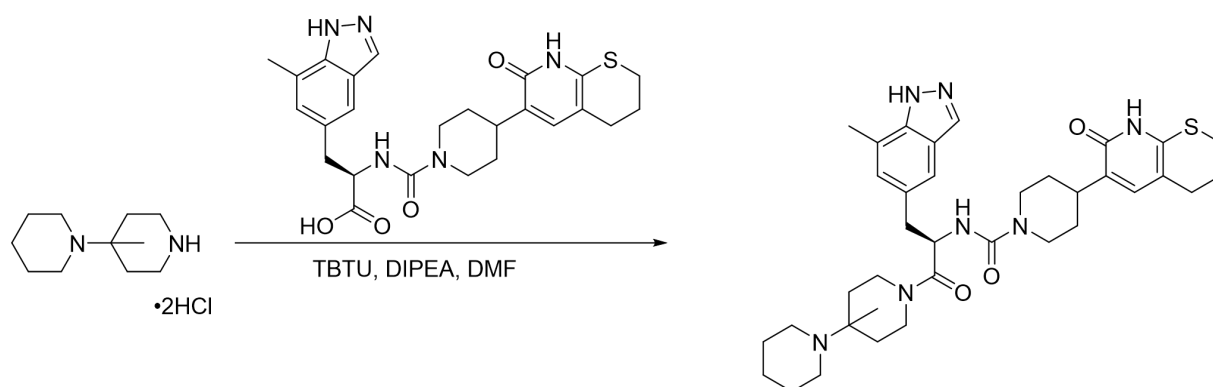


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 10 above.

MS (ESI) m/z (M+H)⁺ = 677.3

¹H NMR (400 MHz, DMSO-d₆) δ 13.03 (s, 1H), 11.36 (s, 1H), 7.97 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 5.54 (q, J = 7.5 Hz, 1H), 4.80 (t, J = 11.3 Hz, 2H), 3.53 – 3.43 (m, 1H), 3.32 – 3.25 (m, 2H), 3.24 – 3.16 (m, 1H), 3.07 – 2.90 (m, 6H), 2.88 – 2.76 (m, 1H), 2.71 (d, J = 11.0 Hz, 2H), 2.53 (t, J = 6.1 Hz, 2H), 2.48 (s, 3H), 2.36 – 2.30 (m, 1H), 2.29 – 2.20 (m, 1H), 2.09 (s, 3H), 2.08 – 2.00 (m, 1H), 1.98 – 1.88 (m, 3H), 1.76 – 1.66 (m, 4H), 1.64 – 1.58 (m, 1H), 1.45 – 1.31 (m, 4H), 1.29 – 1.10 (m, 2H).

Example 24: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4'-methyl-[1,4'-bipiperidine]-1'-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide

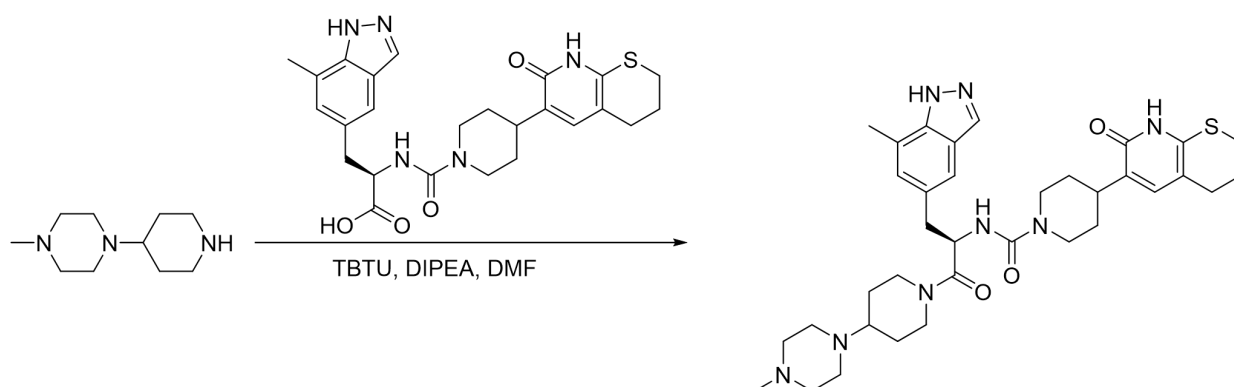


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 660.3 .

¹H NMR (400 MHz, DMSO-d₆) δ 13.01 (s, 1H), 11.33 (s, 1H), 7.96 (s, 0.5H), 7.94 (s, 0.5H), 7.36 (s, 0.5H), 7.35 (s, 0.5H), 7.01 (s, 0.5H), 6.97 (s, 0.5H), 6.87 (s, 0.5H), 6.84 (s, 0.5H), 6.62 – 6.58 (m, 1H), 4.82–4.73 (m, 1H), 4.09 (d, J = 13.0 Hz, 2H), 3.80–3.75 (m, 1H), 3.63 – 3.58 (m, 0.5H), 3.39–3.35 (m, 0.5H), 3.20 (t, J = 11.6 Hz, 0.5H), 3.13 – 3.05 (m, 0.5H), 3.05 – 2.83 (m, 5H), 2.74 – 2.59 (m, 3H), 2.55–2.52 (m, 1.5H), 2.47 (s, 1.5H), 2.46 (s, 1.5H), 2.34–2.18 (m, 4H), 1.98–1.91 (m, 2H), 1.64–1.56 (m, 3H), 1.50 – 1.10 (m, 10.5H), 0.77 (s, 1.5H), 0.76–0.70 (m, 0.5H), 0.47 (s, 1.5H), 0.17–0.11 (m, 0.5H).

Example 25: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(4-methylpiperazine-1-yl)piperidine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide



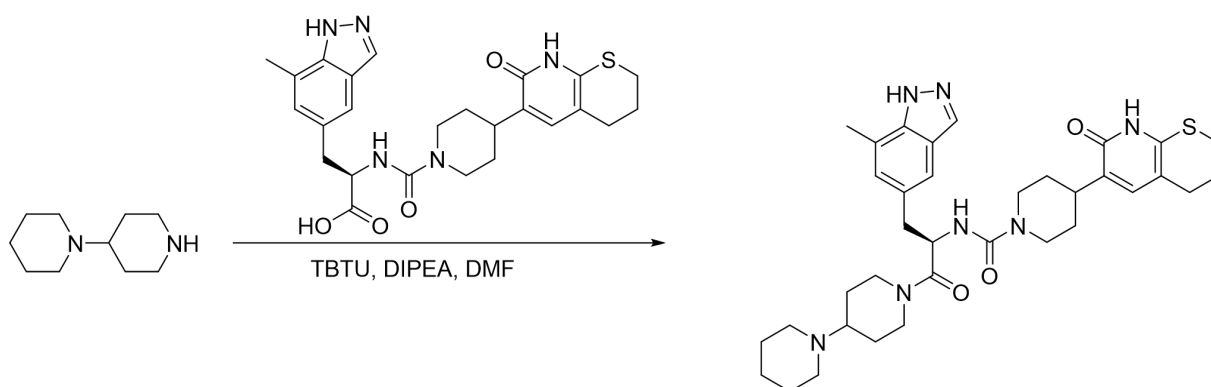
Corresponding common commercially available reagents and the products in the preparation

examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 661.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 11.32 (s, 1H), 7.96 (d, J = 3.1 Hz, 1H), 7.36 (d, J = 13.7 Hz, 1H), 7.00 (d, J = 3.8 Hz, 1H), 6.90 (s, 1H), 6.65 (dd, J = 13.9, 8.1 Hz, 1H), 4.80 (dq, J = 25.6, 7.7 Hz, 1H), 4.34 (d, J = 12.5 Hz, 1H), 4.10 (s, 2H), 3.93 (t, J = 15.5 Hz, 1H), 3.05 – 2.99 (m, 2H), 2.99 – 2.77 (m, 2H), 2.76 – 2.55 (m, 4H), 2.53 (d, J = 6.0 Hz, 4H), 2.47 (d, J = 4.4 Hz, 3H), 2.41 – 2.30 (m, 2H), 2.23 (dd, J = 23.8, 11.9 Hz, 1H), 1.91 (ddt, J = 33.0, 10.8, 5.6 Hz, 4H), 1.65 (d, J = 12.6 Hz, 3H), 1.43 (s, 2H), 1.37 – 0.81 (m, 8H), 0.86 – 0.56 (m, 1H).

Example 26: preparation of (R)-N-(1-([1,4'-bipiperidine]-1'-yl)-3-(7-methyl-1H-indazole-5-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide

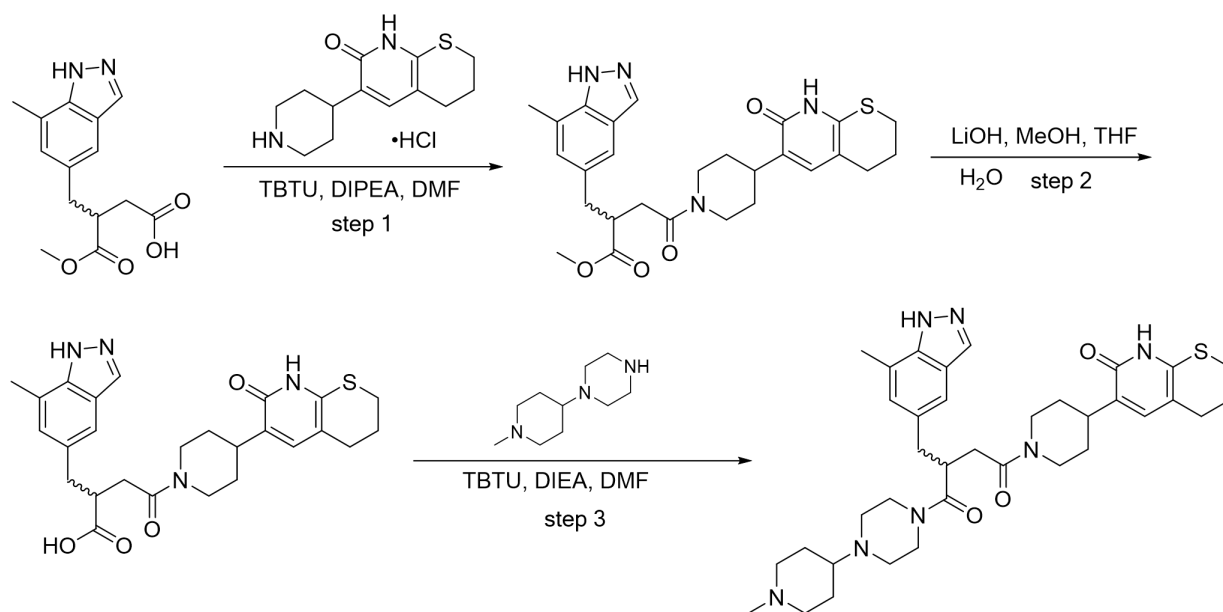


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

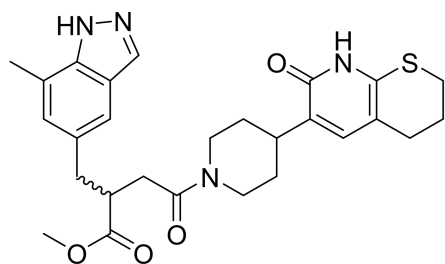
MS (ESI) m/z (M+H)⁺ = 646.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.00 (s, 1H), 11.33 (s, 1H), 7.96 (d, J = 3.3 Hz, 1H), 7.36 (d, J = 13.7 Hz, 1H), 7.01 (d, J = 4.2 Hz, 1H), 6.85 (d, J = 38.7 Hz, 1H), 6.70 – 6.60 (m, 1H), 4.80 (dq, J = 24.2, 7.8 Hz, 1H), 4.32 (d, J = 12.6 Hz, 1H), 4.10 (s, 2H), 3.91 (t, J = 14.3 Hz, 1H), 3.09 – 2.92 (m, 3H), 2.87 (dt, J = 13.1, 6.2 Hz, 1H), 2.69 (td, J = 25.3, 22.8, 11.9 Hz, 4H), 2.54 (t, J = 6.2 Hz, 2H), 2.47 (d, J = 3.7 Hz, 3H), 2.43 – 2.31 (m, 2H), 2.23 (t, J = 28.8 Hz, 4H), 2.10 (d, J = 4.6 Hz, 3H), 1.94 (td, J = 10.8, 5.7 Hz, 5H), 1.65 (d, J = 12.9 Hz, 2H), 1.44 (d, J = 12.3 Hz, 1H), 1.36 – 1.15 (m, 4H), 0.87 – 0.49 (m, 1H).

Example 27: preparation of 2-((7-methyl-1H-indazole-5-yl)methyl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-4-(4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-yl)butane-1,4-dione



Step 1: preparation of methyl 2-((7-methyl-1H-indazole-5-yl)methyl)-4-oxo-4-(4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-yl)butyrate



4-methoxy-3-((7-methyl-1H-indazole-5-yl)methyl)-4-oxobutyric acid (80 mg), 6-(piperidine-4-yl)-2,3,4,8-tetrahydro-7H-thiopyrano[2,3-b]pyridine-7-one hydrochloride (72 mg), O-benzotriazole-N,N,N',N'-tetramethylurea tetrafluoroborate (111 mg) and N,N-diisopropylethylamine (112 mg) were dissolved in N,N-dimethylformamide (2.0 mL) to react at room temperature for 2 hours. After LCMS showed that the reaction was completed, the reaction solution was quenched with a saturated ammonium chloride solution (5mL) and extracted with ethyl acetate, and the organic phases were combined, washed with a saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by a preparative liquid phase to obtain 45 mg of the title compound.

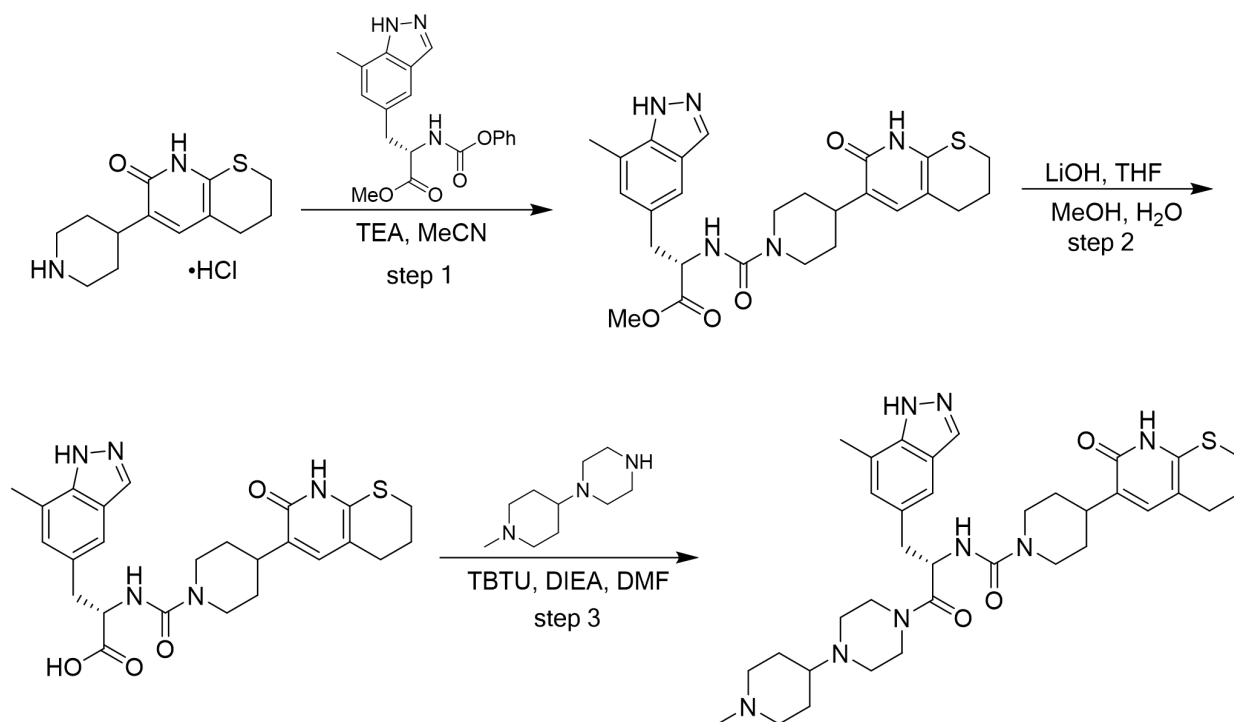
MS (ESI) m/z (M+H)⁺ = 509.2.

Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 660.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.32 (s, 1H), 7.96 (s, 1H), 7.29 (s, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 4.44 (d, *J* = 12.6 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.67 (d, *J* = 12.9 Hz, 1H), 3.43 (s, 1H), 3.32 (s, 1H), 3.11 – 2.97 (m, 4H), 2.93 – 2.77 (m, 3H), 2.71 (dd, *J* = 19.5, 9.4 Hz, 4H), 2.54 (d, *J* = 6.1 Hz, 2H), 2.48 (s, 3H), 2.42 – 2.27 (m, 2H), 2.16 (d, *J* = 11.1 Hz, 1H), 2.08 (s, 3H), 1.94 (p, *J* = 6.1 Hz, 2H), 1.82 – 1.62 (m, 6H), 1.43 – 1.34 (m, 1H), 1.31 – 1.19 (m, 4H), 1.11 (ddt, *J* = 20.4, 11.9, 5.8 Hz, 3H).

Example 28: preparation of (S)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide

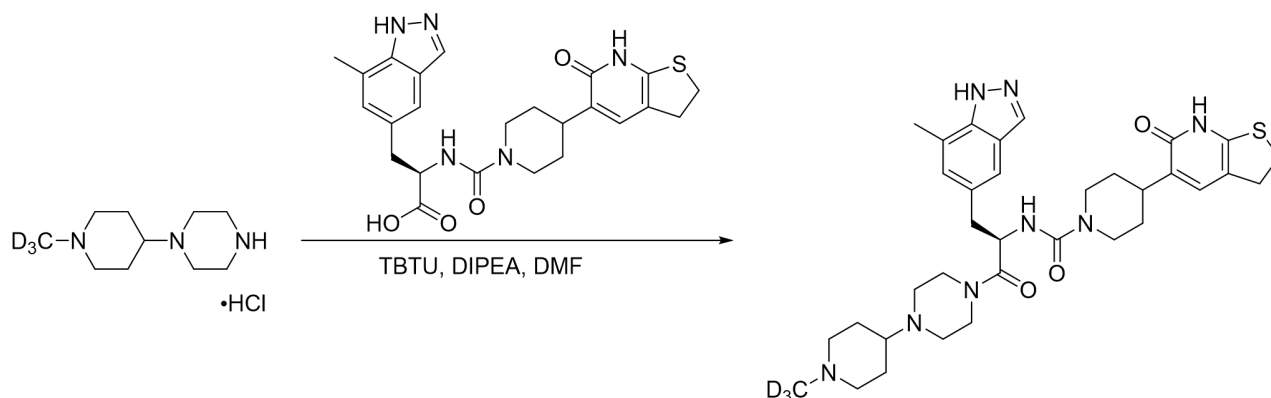


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 661.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.27 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.77 (q, *J* = 7.7 Hz, 1H), 4.09 (d, *J* = 12.9 Hz, 2H), 3.62 – 3.51 (m, 1H), 3.26 – 3.17 (m, 1H), 3.15 – 3.06 (m, 1H), 3.04 – 2.85 (m, 4H), 2.76 – 2.59 (m, 5H), 2.54 (t, *J* = 6.1 Hz, 2H), 2.47 (s, 3H), 2.37 – 2.29 (m, 1H), 2.26 – 2.18 (m, 1H), 2.09 (s, 3H), 2.00 – 1.85 (m, 4H), 1.76 – 1.62 (m, 4H), 1.52 (t, *J* = 9.3 Hz, 1H), 1.37 (d, *J* = 12.2 Hz, 2H), 1.32–1.14 (m, 5H).

Example 29: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-(methyl-d₃)piperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-b]pyridine-5-yl)piperidine-1-formamide

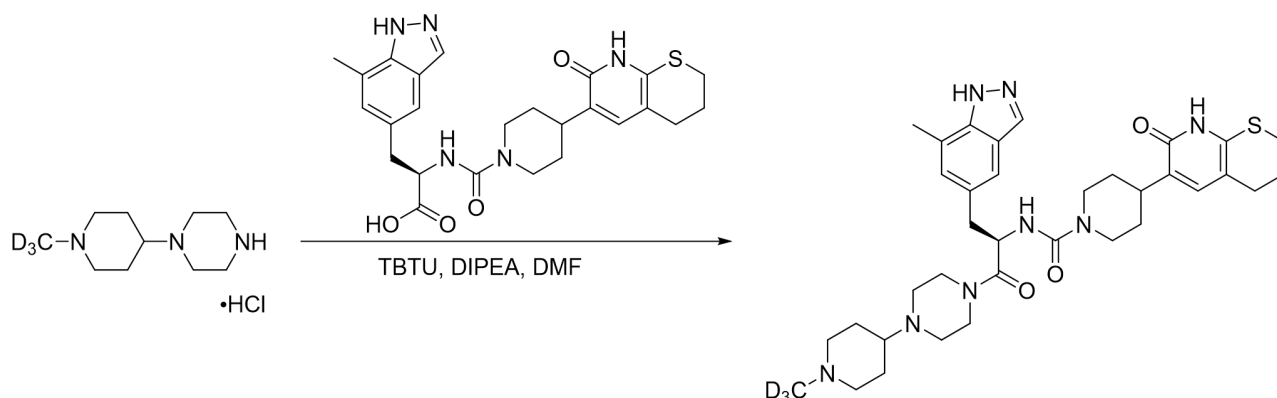


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 650.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.45 (brs, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.77 (q, *J* = 7.7 Hz, 1H), 4.14 – 4.05 (m, 2H), 3.58 – 3.52 (m, 1H), 3.42 – 3.38 (m, 2H), 3.27 – 3.21 (m, 1H), 3.16 – 3.10 (m, 1H), 3.10 – 3.02 (m, 3H), 2.98 – 2.86 (m, 2H), 2.75 – 2.70 (m, 3H), 2.69 – 2.60 (m, 2H), 2.47 (s, 3H), 2.36 – 2.31 (m, 1H), 2.26 – 2.19 (m, 1H), 1.98 – 1.89 (m, 2H), 1.80 – 1.75 (m, 2H), 1.68 – 1.60 (m, 2H), 1.57 – 1.52 (m, 1H), 1.41 – 1.38 (m, 1H), 1.31 – 1.16 (m, 5H).

Example 30: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-(methyl-d₃)piperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formamide

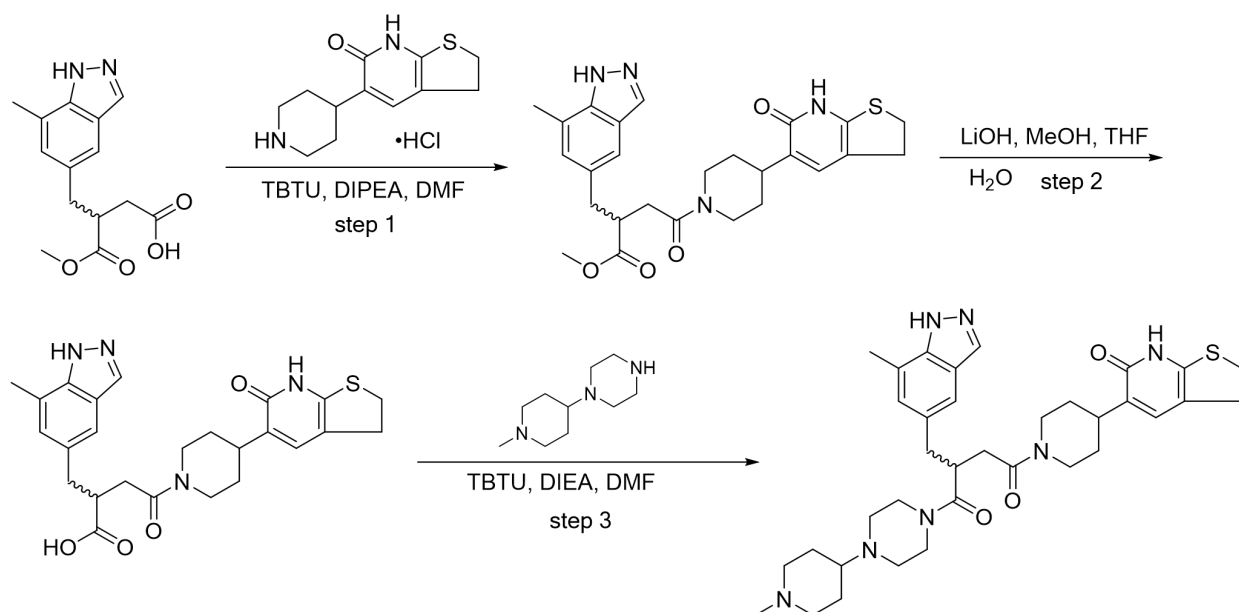


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 664.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.32 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 4.77 (q, *J* = 7.7 Hz, 1H), 4.09 (d, *J* = 12.6 Hz, 2H), 3.57 – 3.54 (m, 1H), 3.25 – 3.20 (m, 1H), 3.13 – 3.07 (m, 1H), 3.04 – 3.01 (m, 2H), 2.98 – 2.86 (m, 2H), 2.72 – 2.67 (m, 4H), 2.64 – 2.61 (m, 1H), 2.58 – 2.54 (m, 2H), 2.47 (s, 3H), 2.35 – 2.32 (m, 1H), 2.25 – 2.19 (m, 1H), 1.98 – 1.93 (m, 3H), 1.92 – 1.84 (m, 1H), 1.75 – 1.70 (m, 2H), 1.68 – 1.63 (m, 2H), 1.55 – 1.51 (m, 1H), 1.39 – 1.36 (m, 2H), 1.29 – 1.14 (m, 5H).

Example 31: preparation of 2-((7-methyl-1H-indazole-5-yl)methyl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-4-(4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-yl)butane-1,4-dione

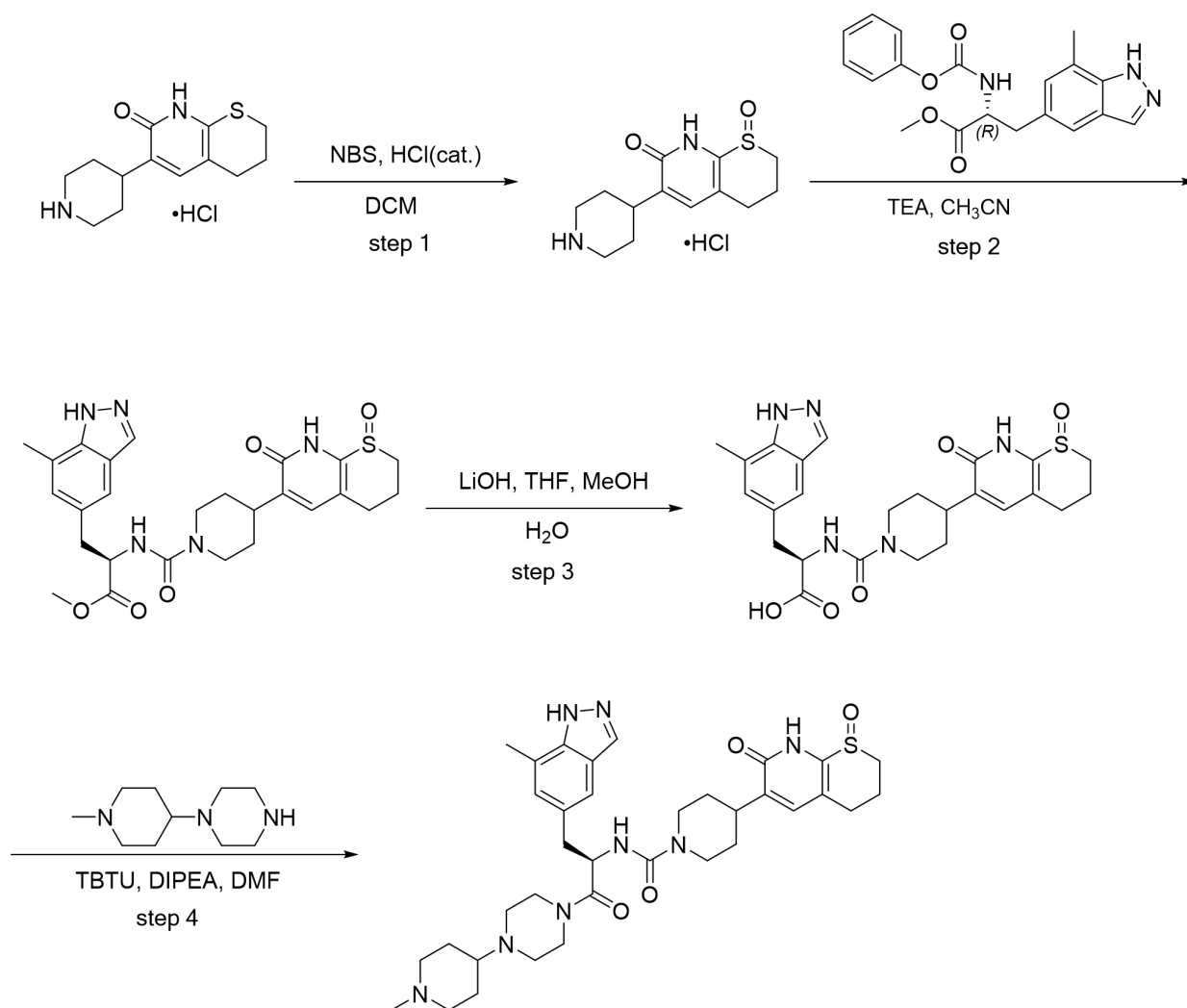


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 27 above.

MS (ESI) m/z (M+H)⁺ = 646.5.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.46 (s, 1H), 7.96 (s, 1H), 7.29 (s, 1H), 7.18 (d, J = 3.3 Hz, 1H), 6.95 (s, 1H), 4.44 (d, J = 12.8 Hz, 1H), 3.95 (d, J = 13.3 Hz, 1H), 3.67 (d, J = 12.4 Hz, 1H), 3.39 (t, J = 7.9 Hz, 3H), 3.29 (s, 1H), 3.04 (q, J = 6.7, 5.7 Hz, 3H), 2.90 – 2.78 (m, 3H), 2.71 (dd, J = 19.5, 9.2 Hz, 4H), 2.48 (s, 3H), 2.40 (dd, J = 15.8, 3.6 Hz, 1H), 2.31 (d, J = 12.4 Hz, 2H), 2.08 (s, 4H), 1.86 – 1.64 (m, 7H), 1.38 (d, J = 12.3 Hz, 1H), 1.32 – 1.21 (m, 5H), 1.20-1.05 (m, 1H).

Example 32: preparation of N-((R)-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(1-oxidation-7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formamide

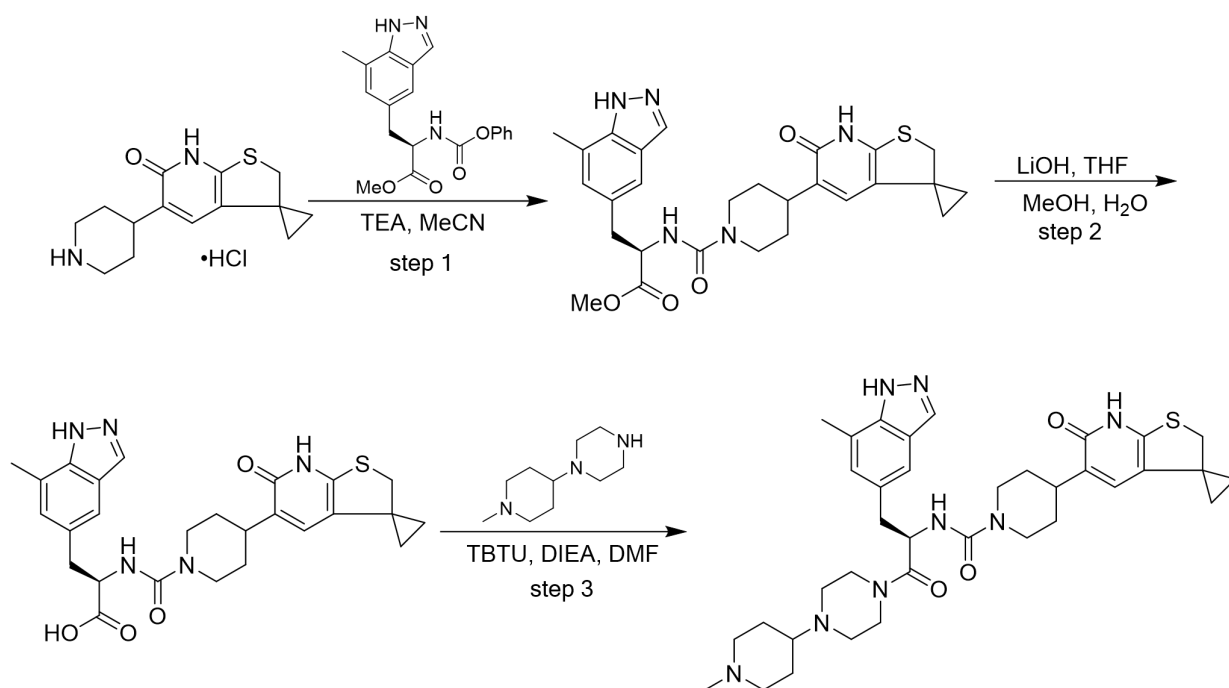


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 9 above.

MS (ESI) m/z ($M+H$) $^+$ = 677.4.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 13.01 (s, 1H), 12.03 (s, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.36 (s, 1H), 7.23 (s, 1H), 7.00 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 4.77 (q, J = 7.6 Hz, 1H), 4.12 (d, J = 13.2 Hz, 2H), 3.56 (d, J = 14.0 Hz, 1H), 3.22 (d, J = 10.4 Hz, 2H), 3.12 (dt, J = 19.2, 9.7 Hz, 2H), 3.04 – 2.93 (m, 2H), 2.91 – 2.81 (m, 2H), 2.77 – 2.63 (m, 5H), 2.47 (s, 3H), 2.33 (dd, J = 11.2, 6.4 Hz, 1H), 2.21 (d, J = 10.4 Hz, 2H), 2.10 (s, 3H), 2.02 – 1.85 (m, 3H), 1.79 – 1.60 (m, 4H), 1.52 (t, J = 9.4 Hz, 1H), 1.43 – 1.28 (m, 4H), 1.19 (ddd, J = 23.6, 12.4, 3.2 Hz, 3H).

Example 33: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6'-oxo-6',7'-dihydro-2'H-spiro[cyclopropane-1,3'-thieno][2,3-*b*]pyridine-5'-yl)piperidine-1-formamide

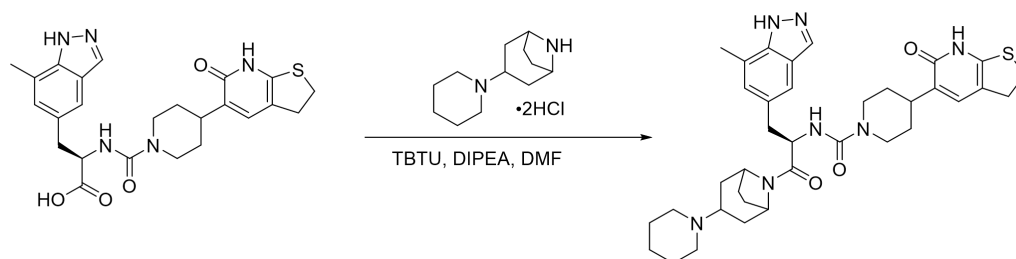


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 673.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.31 (s, 1H), 7.96 (s, 1H), 7.35 (s, 1H), 6.99 (s, 1H), 6.68 (s, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 4.76 (q, *J* = 7.8 Hz, 1H), 4.10 (d, *J* = 12.9 Hz, 2H), 3.57 (d, *J* = 12.8 Hz, 1H), 3.38 (s, 2H), 3.20 (t, *J* = 9.8 Hz, 1H), 3.07 (t, *J* = 10.0 Hz, 1H), 2.96 (dd, *J* = 13.1, 8.1 Hz, 1H), 2.87 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.74 – 2.59 (m, 5H), 2.47 (s, 3H), 2.38 – 2.29 (m, 1H), 2.21 (d, *J* = 11.4 Hz, 1H), 2.09 (s, 3H), 2.03 – 1.83 (m, 2H), 1.72 (tt, *J* = 11.8, 2.9 Hz, 2H), 1.60 (d, *J* = 12.6 Hz, 2H), 1.47 (t, *J* = 9.1 Hz, 1H), 1.34 (tt, *J* = 12.0, 5.3 Hz, 4H), 1.24 (d, *J* = 3.6 Hz, 1H), 1.21 – 1.08 (m, 2H), 0.97 – 0.89 (m, 4H).

Example 34: preparation of N-((2R)-3-(7-methyl-1H-indazole-5-yl)-1-oxo-1-(3-(piperidine-1-yl)-8-azabicyclo[3.2.1]octane-8-yl)propan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-b]pyridine-5-yl)piperidine-1-formamide



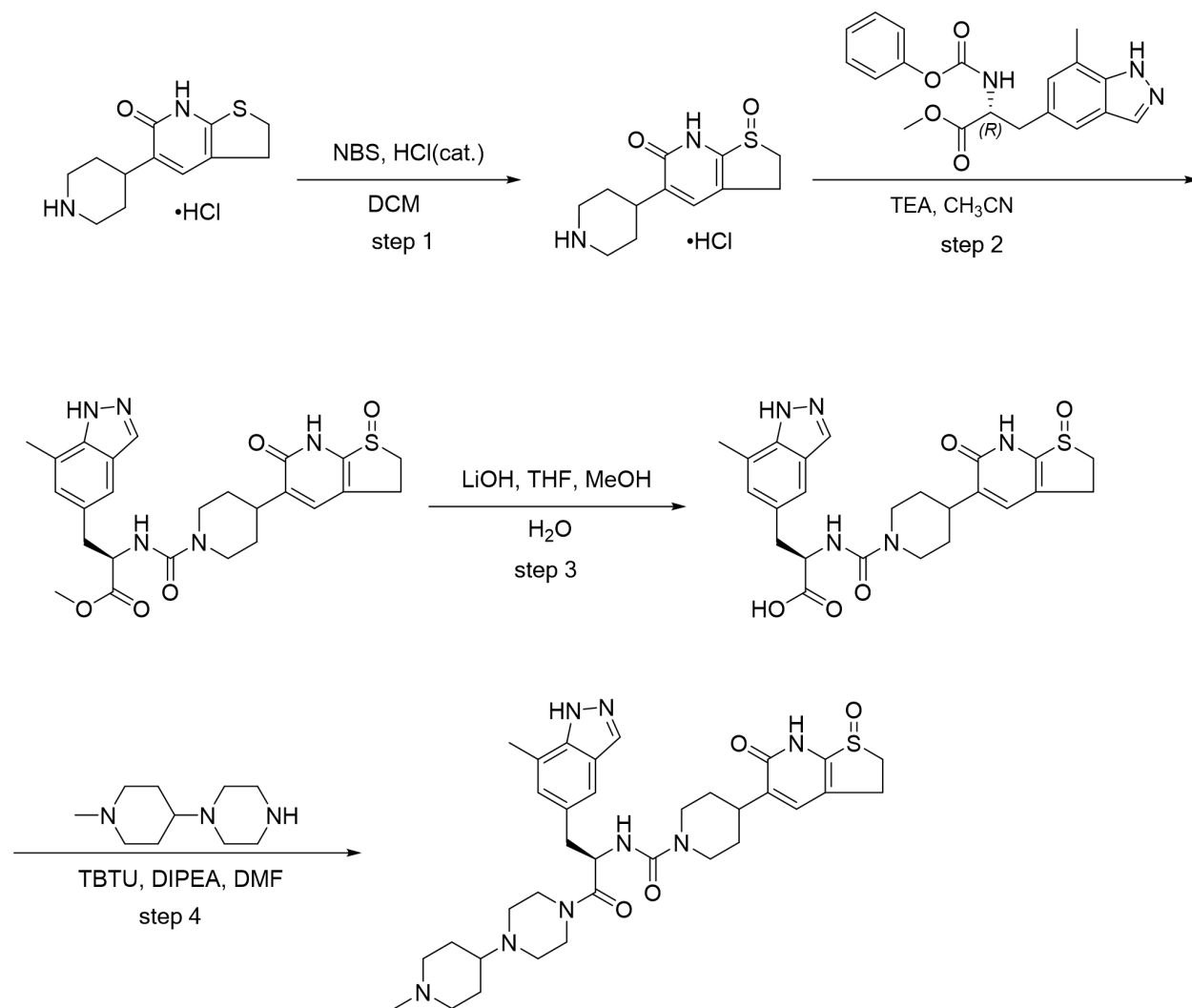
Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 658.1.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 11.38 (s, 1H), 7.95 (t, *J* = 2.3 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.14 – 6.98 (m, 2H), 6.69 (q, *J* = 8.4 Hz, 1H), 4.66 – 4.57 (m, 1H), 4.53 – 4.38 (m,

1H), 4.33 – 3.95 (m, 3H), 3.40 (t, $J = 7.9$ Hz, 2H), 3.05 (t, $J = 7.9$ Hz, 2H), 2.90 (d, $J = 7.1$ Hz, 1H), 2.87 – 2.62 (m, 4H), 2.46 (d, $J = 2.8$ Hz, 3H), 2.34 (d, $J = 20.2$ Hz, 3H), 2.11 – 1.96 (m, 1H), 1.86 – 1.75 (m, 2H), 1.61 (s, 4H), 1.54 – 1.19 (m, 13H).

Example 35: preparation of N-((R)-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(1-oxidation-6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formamide

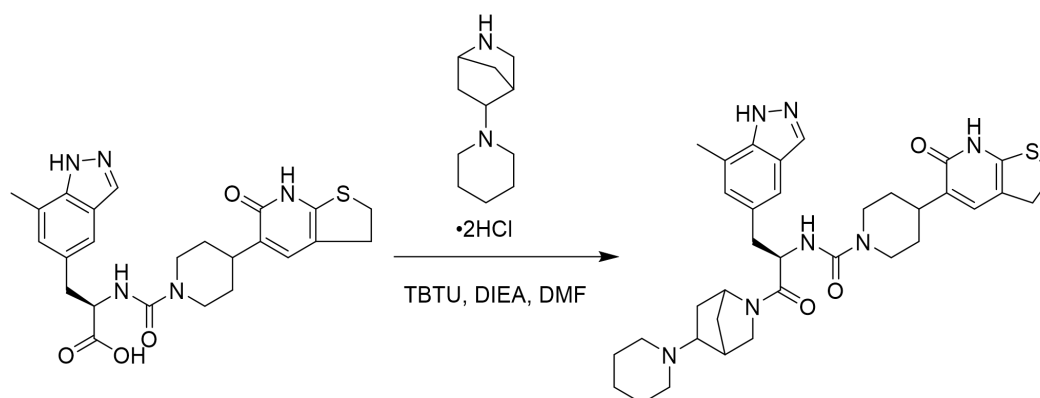


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 9 above.

MS (ESI) m/z ($M+H$)⁺ = 663.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.03 (s, 1H), 12.01 (s, 1H), 7.97 (d, $J = 2.7$ Hz, 1H), 7.45 (d, $J = 2.8$ Hz, 1H), 7.38 (s, 1H), 7.02 (s, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 4.78 (q, $J = 7.8$ Hz, 1H), 4.12 (d, $J = 12.9$ Hz, 2H), 3.64 – 3.37 (m, 5H), 3.26 – 3.02 (m, 6H), 3.01 – 2.81 (m, 3H), 2.78 – 2.53 (m, 5H), 2.48 (s, 3H), 2.44 – 2.09 (m, 3H), 1.99 (q, $J = 13.2, 7.3$ Hz, 2H), 1.79 – 1.53 (m, 3H), 1.46 (s, 1H), 1.40 – 1.14 (m, 5H).

Example 36: preparation of N-((2R)-3-(7-methyl-1H-indazole-5-yl)-1-oxo-1-(3-(piperidine-1-yl)-8-azabicyclo[3.2.1]octane-8-yl)propan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formamide

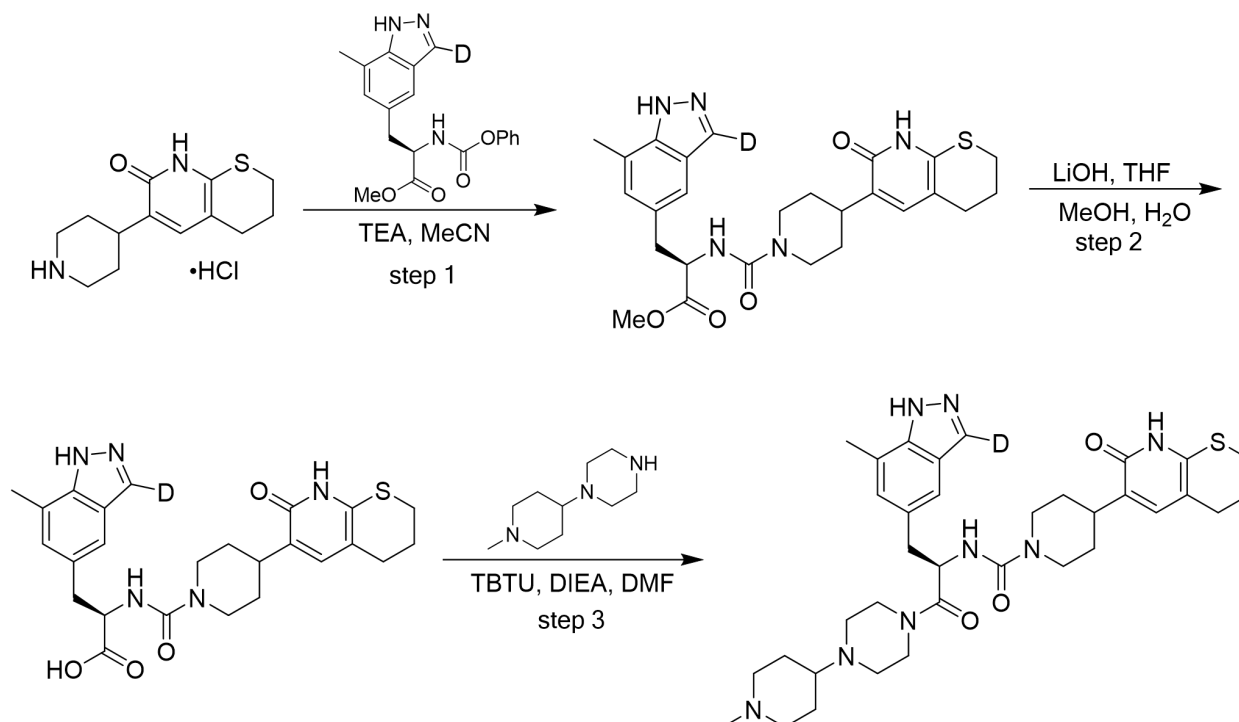


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 644.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 11.46 (s, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.52 – 7.31 (m, 1H), 7.12 – 6.97 (m, 2H), 6.70 – 6.39 (m, 1H), 4.74 – 4.43 (m, 1H), 4.29 (d, J = 23.3 Hz, 1H), 4.08 (t, J = 12.2 Hz, 3H), 3.47 – 3.37 (m, 5H), 3.19 – 2.99 (m, 3H), 2.96 – 2.81 (m, 2H), 2.78 – 2.58 (m, 2H), 2.47 (d, J = 4.4 Hz, 3H), 2.31 (d, J = 64.9 Hz, 3H), 2.04 – 1.88 (m, 1H), 1.74 (t, J = 11.0 Hz, 1H), 1.60 (d, J = 12.5 Hz, 2H), 1.45 (d, J = 10.8 Hz, 2H), 1.40 – 1.28 (m, 6H), 1.24 (d, 3H).

Example 37: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl-3-d)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formamide



Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.31 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.80-4.72 (m, 1H), 4.14-4.02 (m, 2H), 3.57-3.53 (m, 1H), 3.27-3.18 (m, 2H), 3.14-3.08 (m, 1H), 3.04-3.00 (m, 2H), 2.98-2.93 (m, 1H), 2.92-2.86 (m, 1H), 2.74-2.60 (m, 6H), 2.56-2.54 (m, 1H), 2.47 (s, 3H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.09 (s, 3H), 2.01-1.89 (m, 4H), 1.74-1.61 (m, 4H), 1.55-1.49 (m, 1H), 1.40-1.34 (m, 2H), 1.30-1.13 (m, 4H).

Chemical reaction scheme showing the synthesis of compound 10. The reaction involves the coupling of a pyridine-4-ylmethylamine derivative (containing a deuterium label) with a pyridine-2-ylmethylamine derivative (containing a deuterium label) using TBTU, DIEA, and DMF. The product is a bis-pyridine derivative with two deuterium labels.

MS (ESI) m/z (M+H)⁺ = 665.8.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.31 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.80-4.72 (m, 1H), 4.14-4.02 (m, 2H), 3.57-3.53 (m, 1H), 3.27-3.18 (m, 2H), 3.14-3.08 (m, 1H), 3.04-3.00 (m, 2H), 2.98-2.93 (m, 1H), 2.92-2.86 (m, 1H), 2.74-2.60 (m, 6H), 2.56-2.54 (m, 1H), 2.47 (s, 3H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.01-1.89 (m, 4H), 1.74-1.61 (m, 4H), 1.55-1.49 (m, 1H), 1.40-1.34 (m, 2H), 1.30-1.13 (m, 4H).

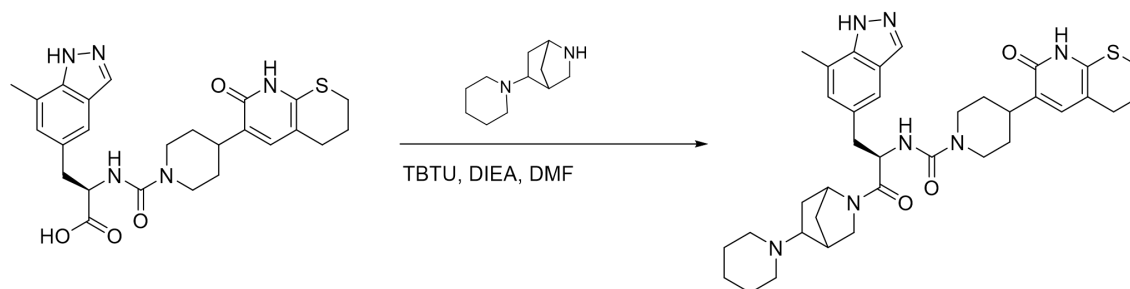
Chemical reaction scheme showing the synthesis of compound 10. The reaction involves the coupling of a 1H-indazole-3-carboxylic acid derivative (with a 4-methylphenyl group) and a 2,3-dihydro-1,4-benzothiazine-5-carboxylic acid derivative (with a 4-methylphenyl group) using TBTU, DIEA, and DMF. The product is a bis-benzothiazine derivative where the two carboxylic acid groups have been coupled via an amide bond.

MS (ESI) m/z (M+H)⁺ = 672.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 10.97 (s, 1H), 8.05 – 7.84 (m, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.07 – 6.97 (m, 1H), 6.91 – 6.80 (m, 1H), 6.68 (dt, *J* = 14.7, 7.6 Hz, 1H), 4.59 (dd, *J* = 17.1, 8.3 Hz, 1H), 4.40 (dd, *J* = 40.4, 32.5 Hz, 2H), 4.05 (d, *J* = 44.4 Hz, 2H), 3.08 – 2.99 (m, 2H),

2.91 (tt, $J = 23.6, 6.7$ Hz, 2H), 2.75 – 2.61 (m, 3H), 2.57 – 2.51 (m, 2H), 2.46 (d, $J = 2.6$ Hz, 3H), 2.43 – 2.21 (m, 3H), 2.07 (s, 1H), 1.99 – 1.93 (m, 2H), 1.87 – 1.73 (m, 2H), 1.63 (t, $J = 10.4$ Hz, 4H), 1.48 – 1.36 (m, 4H), 1.25 (d, $J = 11.2$ Hz, 6H), 0.94 (d, $J = 6.4$ Hz, 3H).

Example 40: preparation of N-((2R)-3-(7-methyl-1H-indazole-5-yl)-1-oxo-1-(5-(piperidine-1-yl)-2-azabicyclo[2.2.1]hept-2-yl)propan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide



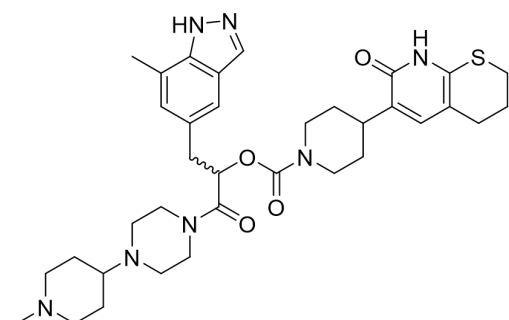
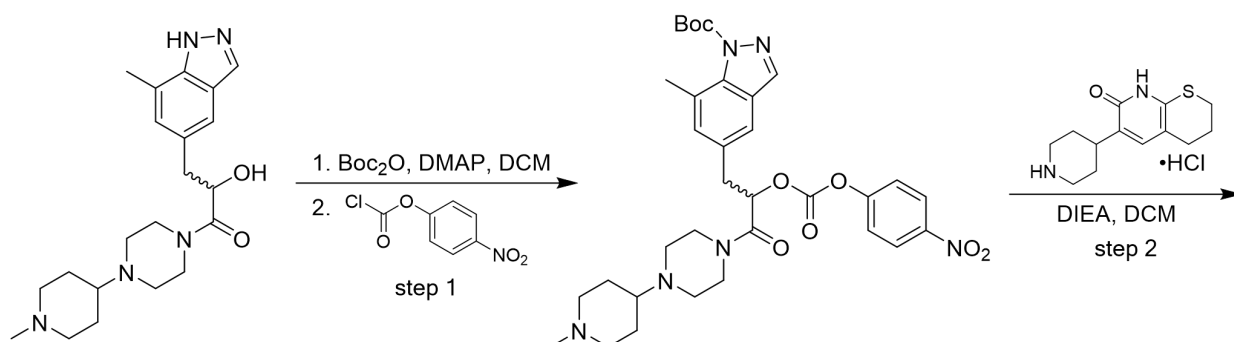
1

Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

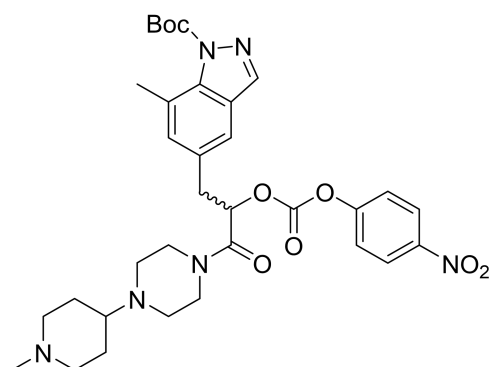
MS (ESI) m/z ($M+H$) $^+$ = 658.3.

^1H NMR (400 MHz, DMSO- d_6) δ 13.01 (d, $J = 15.6$ Hz, 1H), 11.38 (s, 1H), 7.95 (d, $J = 2.4$ Hz, 1H), 7.46 – 7.35 (m, 1H), 7.02 (dd, $J = 13.2, 10.4$ Hz, 1H), 6.83 (d, $J = 14.0$ Hz, 1H), 6.67 – 6.52 (m, 1H), 4.58 (ddt, $J = 30.2, 22.6, 7.6$ Hz, 1H), 4.43 – 4.24 (m, 1H), 4.08 (t, $J = 13.6$ Hz, 2H), 3.67 – 3.37 (m, 1H), 3.04 – 3.00 (m, 2H), 2.94 – 2.84 (m, 2H), 2.67 (t, $J = 13.2$ Hz, 3H), 2.47 (d, $J = 4.4$ Hz, 3H), 2.35 – 2.11 (m, 4H), 1.95 (s, 3H), 1.74 (t, $J = 10.0$ Hz, 1H), 1.62 (d, $J = 12.6$ Hz, 2H), 1.45 (d, $J = 11.3$ Hz, 4H), 1.32 (d, $J = 17.6$ Hz, 4H), 1.23 (s, 5H), 0.90 (dd, $J = 34.6, 6.4$ Hz, 2H).

Example 41: preparation of 3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formate



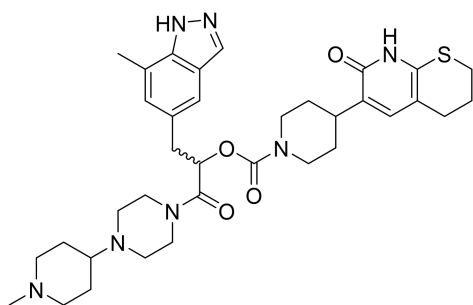
Step 1: preparation of tert-butyl 7-methyl-5-(3-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-2-(((4-nitrophenoxy)carbonyl)oxy)-3-oxopropyl)-1*H*-indazole-1-formate



In ice water bath, 2-hydroxy-3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)propan-1-one (40.0 mg) and 4-dimethylaminopyridine (1.27 mg) were dissolved in anhydrous dichloromethane (2.0 mL), and slowly dropwise added with di-tert-butyl dicarbonate (24.9 mg) to react for 1 hour. The system was added with p-nitrophenyl chloroformate (31.4 mg) in batches and transferred to room temperature to react for 15 hours. After LCMS showed that the reaction was completed, a half of the reaction solution was extracted and directly used in the next step of reaction.

MS (ESI) m/z ($\text{M}+\text{H}$)⁺ = 651.9.

Step 2: preparation of 3-(7-methyl-1*H*-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl-4-(7-oxo-3,4,7,8-tetrahydro-2*H*-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formate

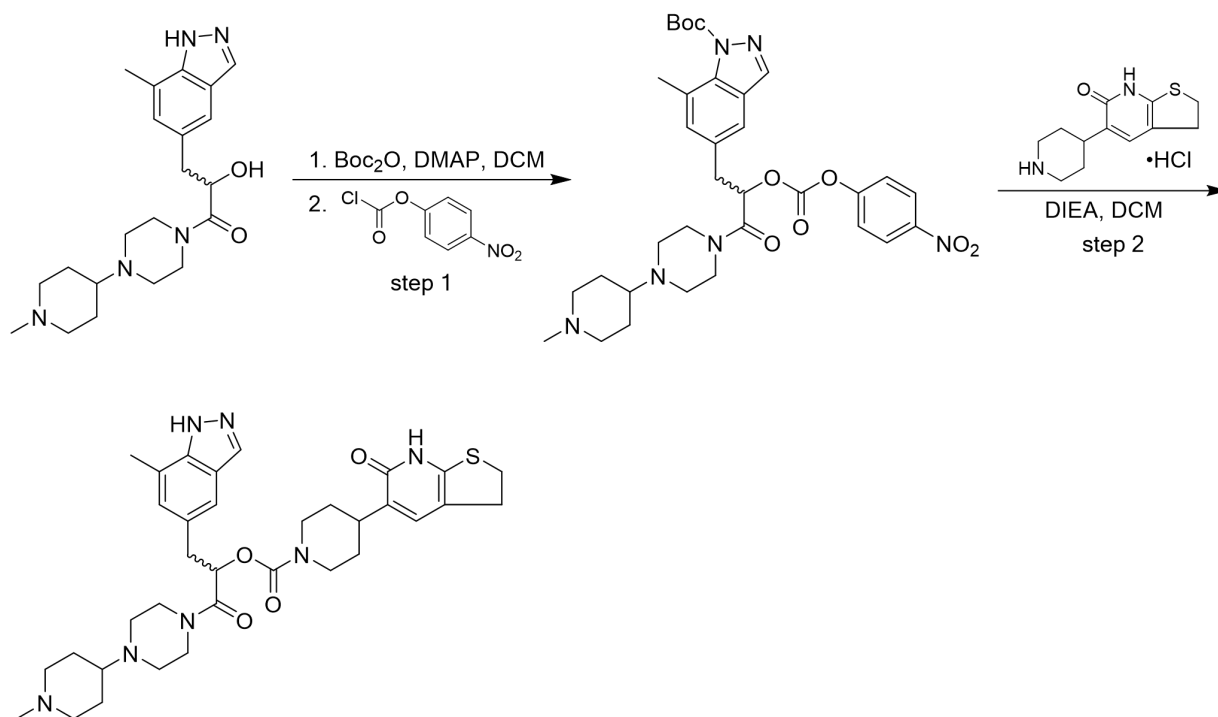


N,N-diisopropylethylamine (7.94 mg) and anhydrous dichloromethane (1.0 mL) were added into the above reaction solution, and added with 6-(piperidine-4-yl)-2,3,4,8-tetrahydro-7*H*-thiopyrano[2,3-*b*]pyridine-7-one hydrochloride (9.23 mg) to react for 1 hour. After LCMS showed that the reaction was completed, the reaction solution was filtered, and the filtrate was collected and concentrated. The crude product was purified by a preparative liquid phase to obtain 4.0 mg of the title compound.

MS (ESI) m/z ($M+H$)⁺ = 661.8.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.99 (s, 1H), 7.98 (s, 1H), 7.41 (s, 1H), 7.04 (s, 1H), 7.05-6.75 (m, 1H), 5.42-5.35 (m, 1H), 4.25-3.89 (m, 3H), 3.65-3.50 (m, 2H), 3.23-2.95 (m, 6H), 2.94-2.66 (m, 5H), 2.48 (s, 3H), 2.43-2.24 (m, 2H), 2.10 (s, 3H), 2.06-1.88 (m, 4H), 1.81-1.60 (m, 5H), 1.50-1.35 (m, 2H), 1.32-1.10 (m, 5H).

Example 42: preparation of 3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formate

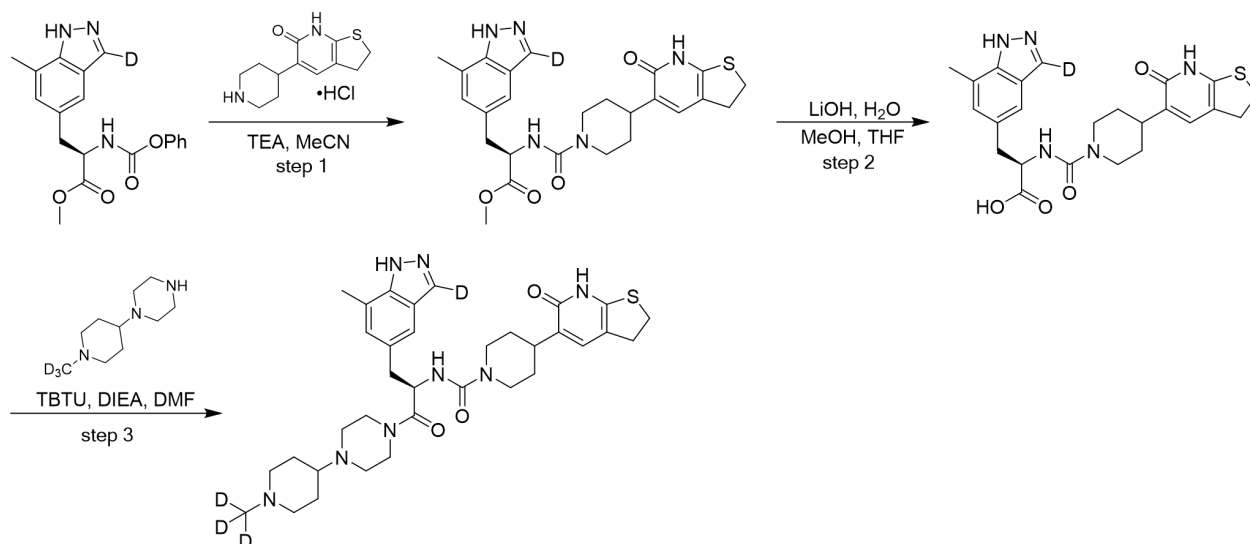


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 41 above.

MS (ESI) m/z ($M+H$)⁺ = 647.8.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 13.06 (s, 1H), 11.44 (s, 1H), 7.98 (s, 1H), 7.42 (s, 1H), 7.04 (s, 1H), 7.05-6.75 (m, 1H), 5.42-5.31 (m, 1H), 4.25-3.89 (m, 2H), 3.75-3.50 (m, 1H), 3.45-23.35 (m, 3H), 3.20-2.95 (m, 5H), 2.92-2.66 (m, 4H), 2.48 (s, 3H), 2.43-2.24 (m, 2H), 2.10 (s, 3H), 2.06-1.88 (m, 2H), 1.81-1.60 (m, 4H), 1.50-1.35 (m, 2H), 1.35-1.10 (m, 7H).

Example 43: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl-3-d)-1-(4-(1-(methyl- d_3)piperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formamide

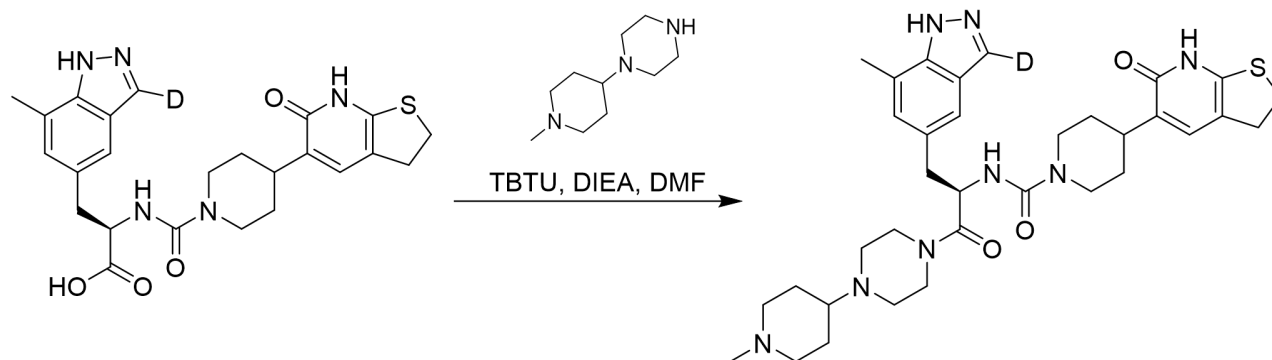


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$) $^+$ = 650.8.

^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 13.00 (s, 1H), 11.43 (s, 1H), 7.36 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.82-4.72 (m, 1H), 4.09 (d, J = 16.0, 2H), 3.65-3.50 (m, 1H), 3.45-3.35 (m, 2H), 3.29-3.21 (m, 1H), 3.17-3.03 (m, 2H), 3.00-2.83 (m, 2H), 2.80-2.60 (m, 4H), 2.47 (s, 3H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.05-1.85 (m, 3H), 1.80-1.69 (m, 2H), 1.67-1.51 (m, 3H), 1.44-1.34 (m, 2H), 1.32-1.13 (m, 6H).

Example 44: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl-3-d)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-*b*]pyridine-5-yl)piperidine-1-formamide



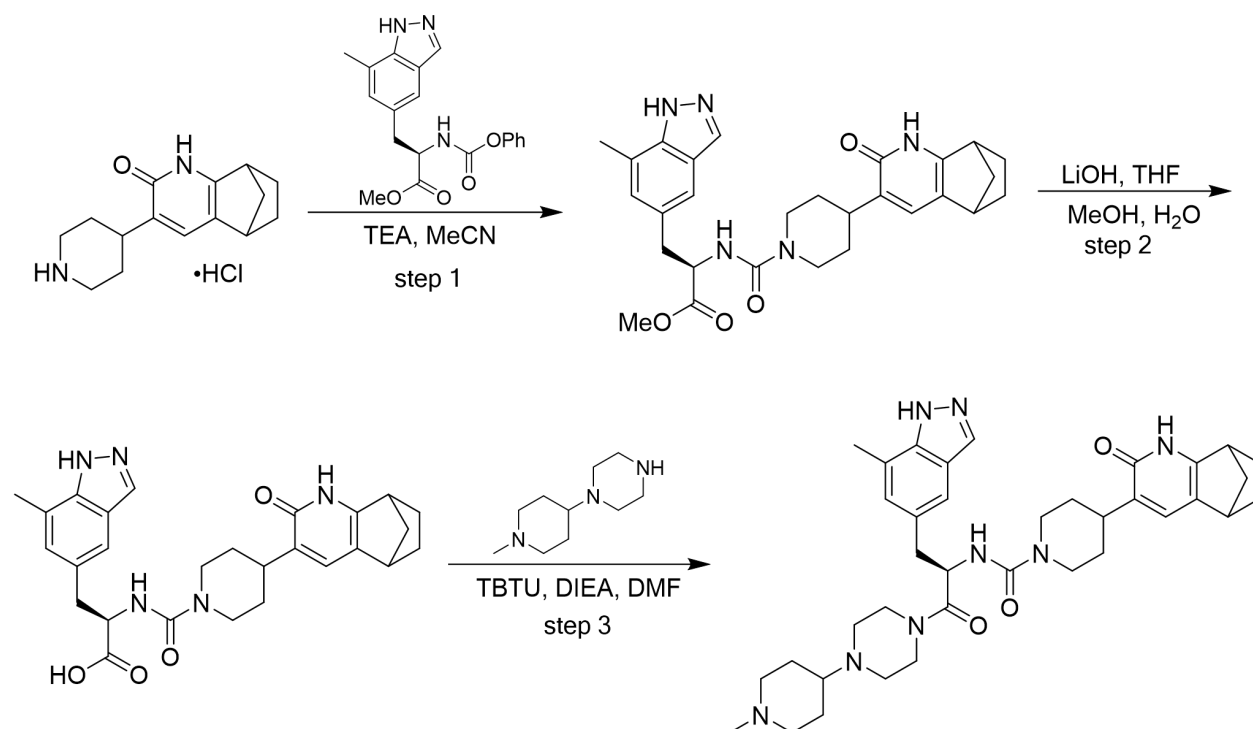
Corresponding common commercially available reagents and the products in the preparation

examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 647.8.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.00 (s, 1H), 11.44 (s, 1H), 7.36 (s, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.82-4.72 (m, 1H), 4.09 (d, *J* = 12.0 Hz, 2H), 3.65-3.50 (m, 1H), 3.45-3.35 (m, 2H), 3.29-3.21 (m, 1H), 3.13-3.02 (m, 2H), 3.00-2.83 (m, 2H), 2.79-2.61 (m, 4H), 2.47 (s, 3H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.10 (s, 3H), 2.05-1.85 (m, 2H), 1.80-1.69 (m, 2H), 1.67-1.51 (m, 3H), 1.44-1.34 (m, 2H), 1.32-1.13 (m, 7H).

Example 45: preparation of N-((R)-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2,5,6,7,8-hexahydro-5,8-methanoquinoline-3-yl)piperidine-1-formamide

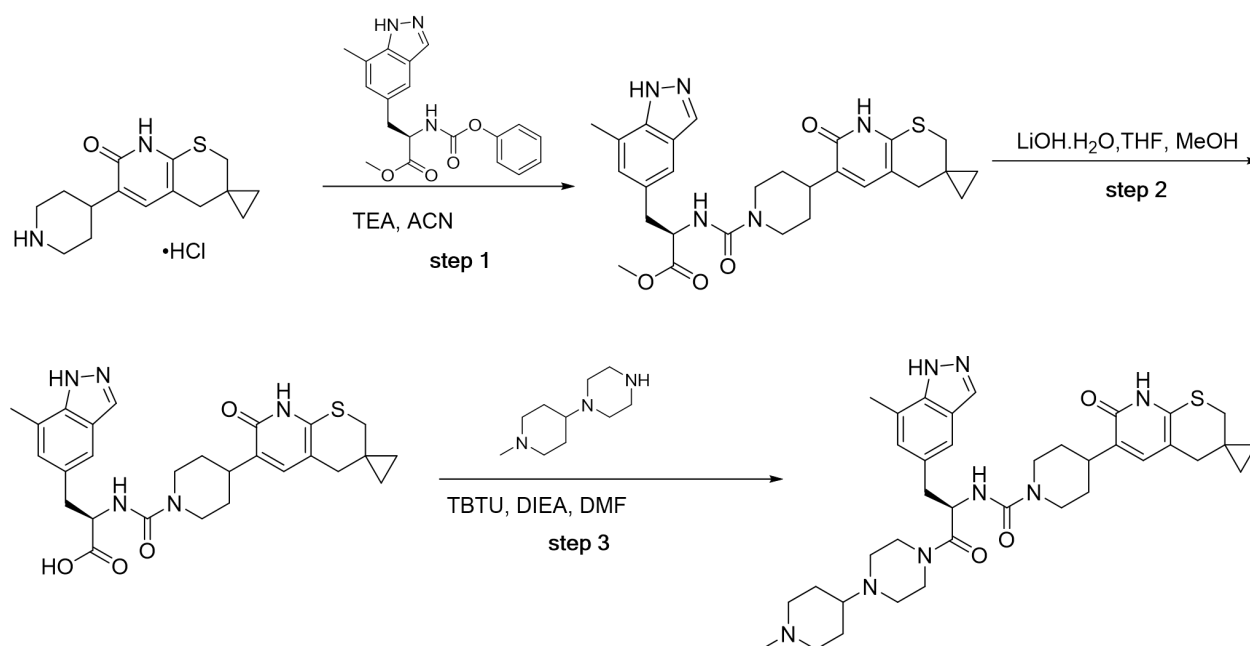


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 655.4

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.72 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.77 (q, *J* = 7.7 Hz, 1H), 4.08 (d, *J* = 12.7 Hz, 2H), 3.55 (d, *J* = 13.6 Hz, 1H), 3.38-3.33 (m, 1H), 3.26 - 3.20 (m, 2H), 3.18 - 3.05 (m, 2H), 3.00 - 2.84 (m, 2H), 2.76-2.60 (m, 5H), 2.47 (s, 3H), 2.37 - 2.29 (m, 1H), 2.27 - 2.18 (m, 1H), 2.09 (s, 3H), 1.99 - 1.52 (m, 10H), 1.43 - 1.33 (m, 3H), 1.29-1.21 (m, 4H), 1.06 - 0.96 (m, 2H).

Example 46: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7'-oxo-7',8'-dihydro-2'H,4'H-spiro[cyclopropane-1,3'-thiopyrano[2,3-b]pyridine]-6'-yl)piperidine-1-formamide

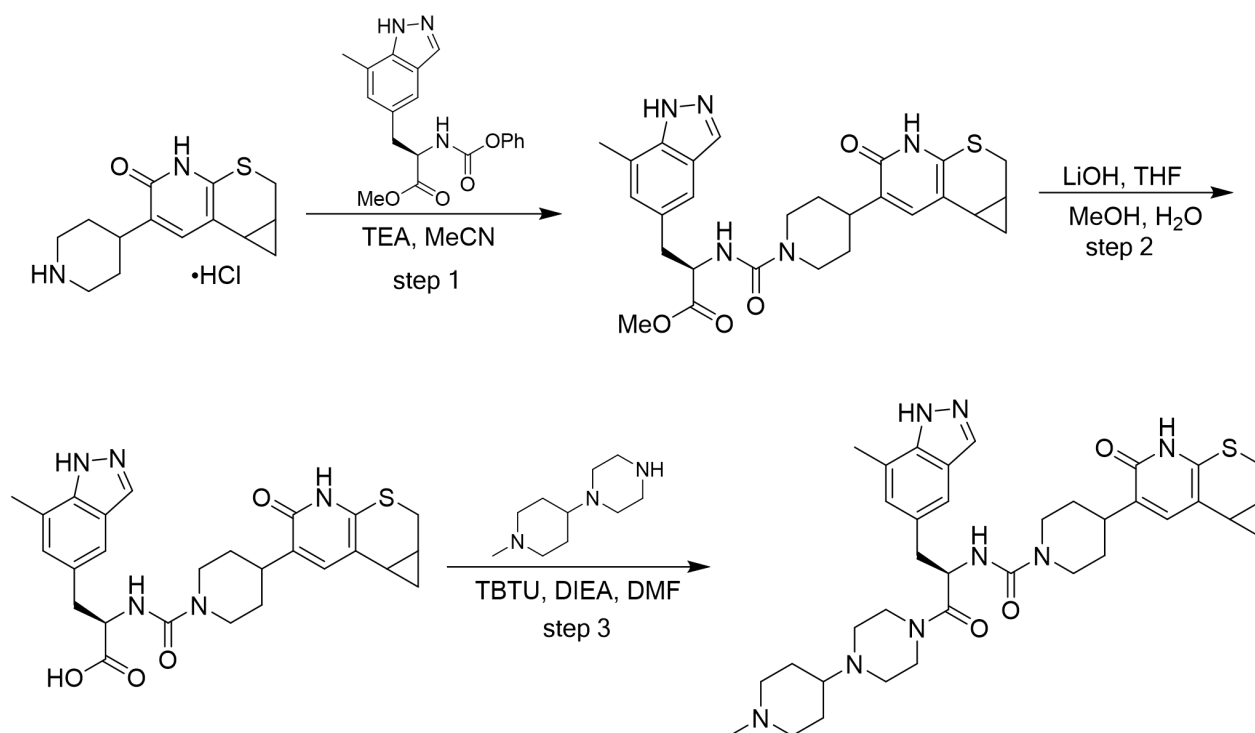


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 687.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.36 (s, 1H), 7.95 (s, 1H), 7.35 (s, 1H), 7.00 (s, 1H), 6.78 (s, 1H), 6.64 (d, J = 8.0 Hz, 1H), 4.76 (q, J = 7.6 Hz, 1H), 4.08 (d, J = 12.8 Hz, 2H), 3.55 (d, J = 13.2 Hz, 1H), 3.23 (s, 1H), 3.10 (t, J = 9.6 Hz, 1H), 2.95 (dd, J = 13.2, 7.6 Hz, 1H), 2.88 (d, J = 16.0 Hz, 3H), 2.67 (dt, J = 25.6, 11.2 Hz, 5H), 2.47 (s, 3H), 2.41 (s, 2H), 2.33 (s, 1H), 2.22 (s, 1H), 2.09 (s, 3H), 1.92 (dt, J = 23.6, 11.2 Hz, 2H), 1.72 (t, J = 11.6 Hz, 2H), 1.64 (d, J = 12.6 Hz, 2H), 1.54 (t, J = 9.2 Hz, 1H), 1.38 (d, J = 12.0 Hz, 2H), 1.32 – 1.09 (m, 5H), 0.68 – 0.50 (m, 4H).

Example 47: preparation of N-((R)-3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(5-oxo-1,1a,2,4,5,7b-hexahydrocyclopropo[4,5]thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide

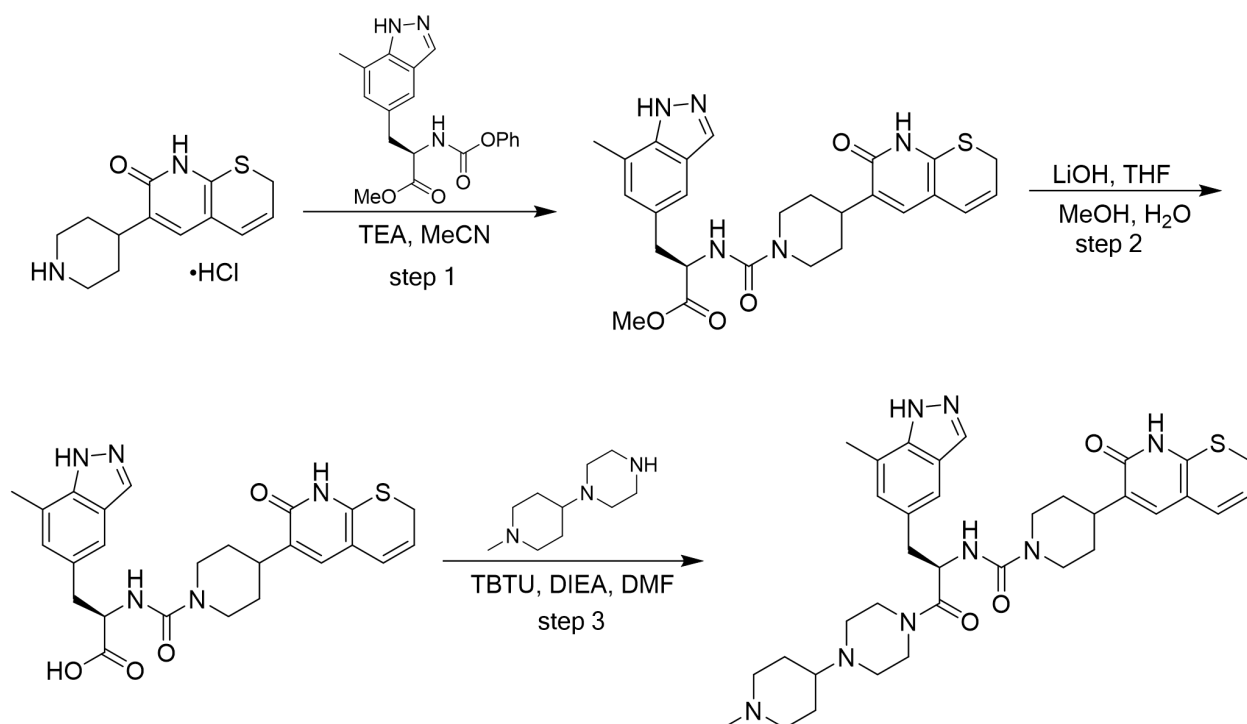


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 673.3

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.31 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.11 (d, J = 12.9 Hz, 2H), 3.56 (d, J = 13.3 Hz, 1H), 3.40-3.36 (m, 1H), 3.24-3.19 (m, 1H), 3.12-3.06 (m, 3H), 2.99-2.93 (m, 1H), 2.90-2.84 (m, 1H), 2.77 – 2.60 (m, 5H), 2.47 (s, 3H), 2.36-2.29 (m, 1H), 2.26 – 2.17 (m, 1H), 2.09 (s, 3H), 1.97 – 1.78 (m, 4H), 1.76 – 1.61 (m, 4H), 1.52 (t, J = 9.8 Hz, 1H), 1.42 – 1.27 (m, 5H), 1.24 – 1.10 (m, 2H), 0.85-0.77 (m, 1H).

Example 48: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(7-oxo-7,8-dihydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide

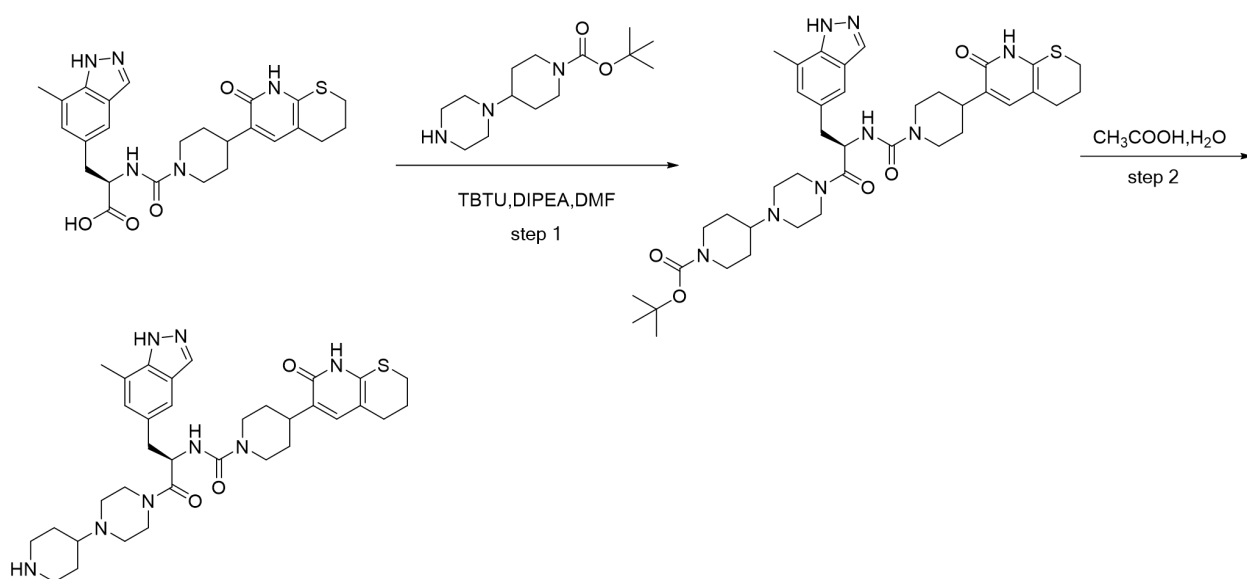


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 659.3.

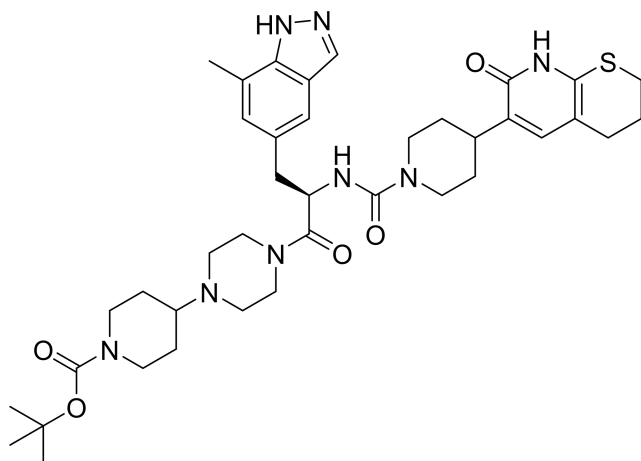
¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.57 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.02 (s, 1H), 6.99 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.33 (d, J = 9.9 Hz, 1H), 5.62-5.57 (m, 1H), 4.79-4.73 (m, 1H), 4.10 (d, J = 12.5 Hz, 2H), 3.63 – 3.50 (m, 3H), 3.30-3.18 (m, 1H), 3.14 – 3.05 (m, 1H), 3.05 – 2.84 (m, 3H), 2.75 – 2.62 (m, 5H), 2.47 (s, 3H), 2.35-2.28 (m, 1H), 2.24-2.16 (m, 1H), 2.10 (s, 3H), 2.00 – 1.86 (m, 2H), 1.77 – 1.61 (m, 4H), 1.51 (t, J = 8.7 Hz, 1H), 1.39 – 1.11 (m, 6H).

Example 49: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-oxo-1-(4-(piperidine-4-yl)piperazine-1-yl)propan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-*b*]pyridine-6-yl)piperidine-1-formamide



Step 1: preparation of tert-butyl

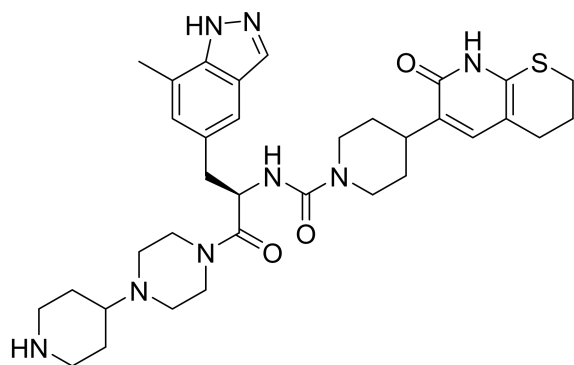
(R)-4-(4-(3-(7-methyl-1H-indazole-5-yl)-2-(4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formylamino)propionyl)piperazine-1-yl)piperidine-1-formate



(R)-3-(7-methyl-1H-indazole-5-yl)-2-(4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formylamino)propionic acid (66 mg), tert-butyl 4-(piperazine-1-yl)piperidine-1-formate (43 mg) and N,N-diisopropylethylamine (43 mg) were dissolved in N,N-dimethylformamide (2 mL), and added with 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethylurea tetrafluoroborate (43 mg) to react at room temperature for 4 hours. After the reaction was ended, the reaction solution was separated and purified by preparative HPLC to obtain 30 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 747.3 .

Step 2: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-oxo-1-(4-(piperidine-4-yl)piperazine-1-yl)propan-2-yl)-4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formamide



Tert-butyl

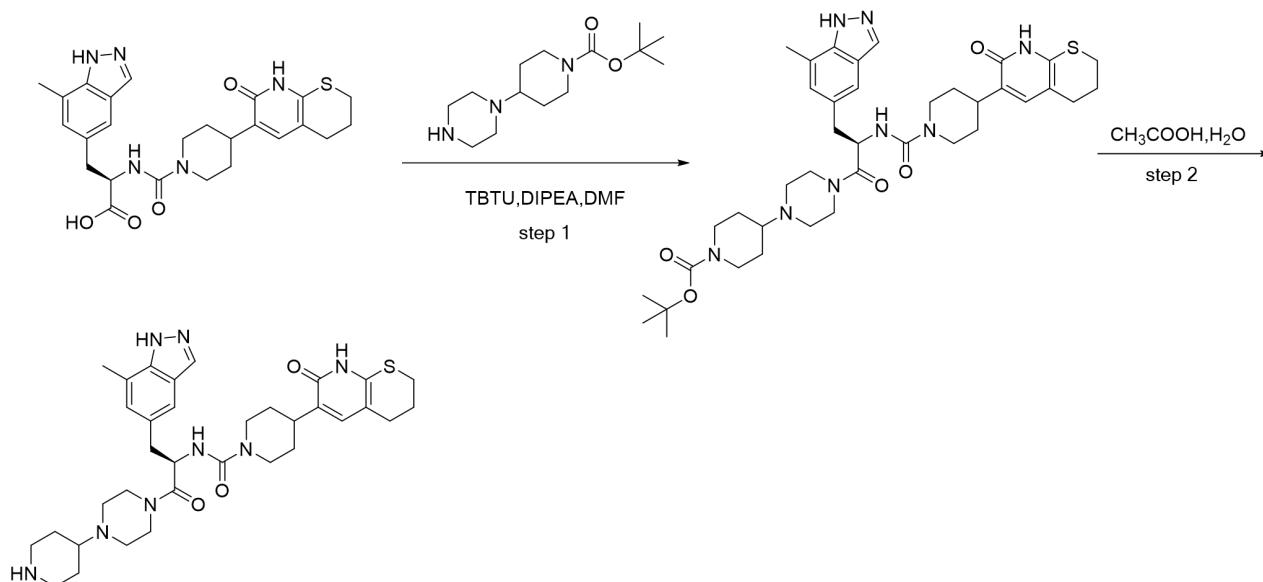
(R)-4-(4-(3-(7-methyl-1H-indazole-5-yl)-2-(4-(7-oxo-3,4,7,8-tetrahydro-2H-thiopyrano[2,3-b]pyridine-6-yl)piperidine-1-formylamino)propionyl)piperazine-1-yl)piperidine-1-formate (30 mg) was dissolved in acetic acid and water (2 mL, v/v = 1/5) to react at 100°C for 2 hours. After the reaction was ended, the reaction system was concentrated, the crude product was dissolved in an appropriate amount of methanol, then added with a saturated potassium carbonate solution to adjust a pH value of the system to be 8-9 and filtered, and the filtrate was separated and purified by preparative HPLC, and freeze-dried to obtain 10.00 mg of the title compound.

MS (ESI) m/z (M+H)⁺ = 647.3.

¹H NMR (400 MHz, DMSO-d₆) δ 13.02 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 6.63 (d, J = 8.0 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.08 (d, J = 12.6 Hz, 2H), 3.60-3.47 (m, 1H),

3.30-3.20 (m, 1H), 3.15-3.06 (m, 2H), 3.05 – 2.84 (m, 7H), 2.75 – 2.59 (m, 3H), 2.56-2.51 (m, 2H), 2.47 (s, 3H), 2.41 – 2.18 (m, 4H), 2.06-1.91 (m, 4H), 1.70 – 1.52 (m, 3H), 1.41 – 1.17 (m, 4H), 1.09 – 0.97 (m, 2H).

Example 50: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-oxo-1-(4-(piperidine-4-yl)piperazine-1-yl)propan-2-yl)-4-(6-oxo-2,3,6,7-tetrahydrothieno[2,3-b]pyridine-5-yl)piperidine-1-formamide

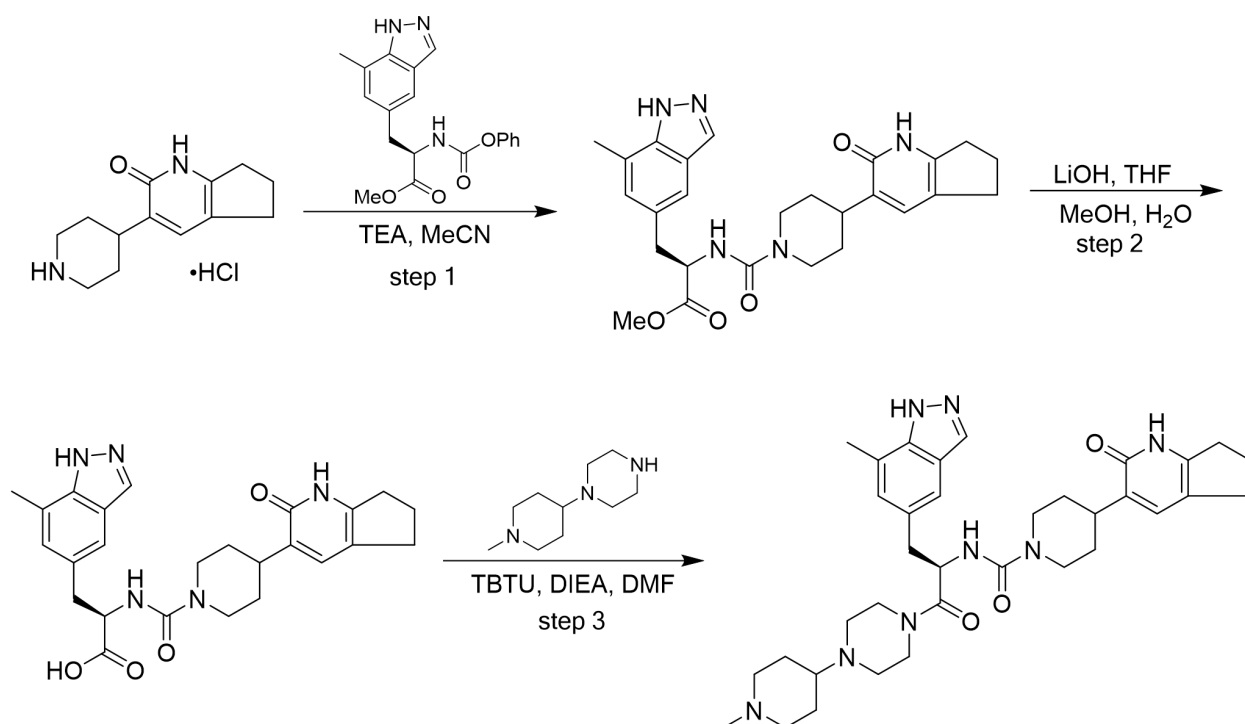


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 49 above.

MS (ESI) m/z ($M+H$)⁺ = 633.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.63-3.48(m, 1H), 3.16 – 3.10 (m, 1H), 3.06 (t, J = 8.1 Hz, 2H), 2.99 - 2.84 (m, 5H), 2.75 – 2.60 (m, 4H), 2.47 (s, 3H), 2.38 – 2.20 (m, 4H), 2.05 – 1.95 (m, 2H), 1.69 – 1.54 (m, 3H), 1.39 – 1.20 (m, 7H), 1.11-0.97 (m, 2H).

Example 51: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-2,5,6,7-tetrahydro-1H-cyclopentadieno[b]pyridine-3-yl)piperidine-1-formamide

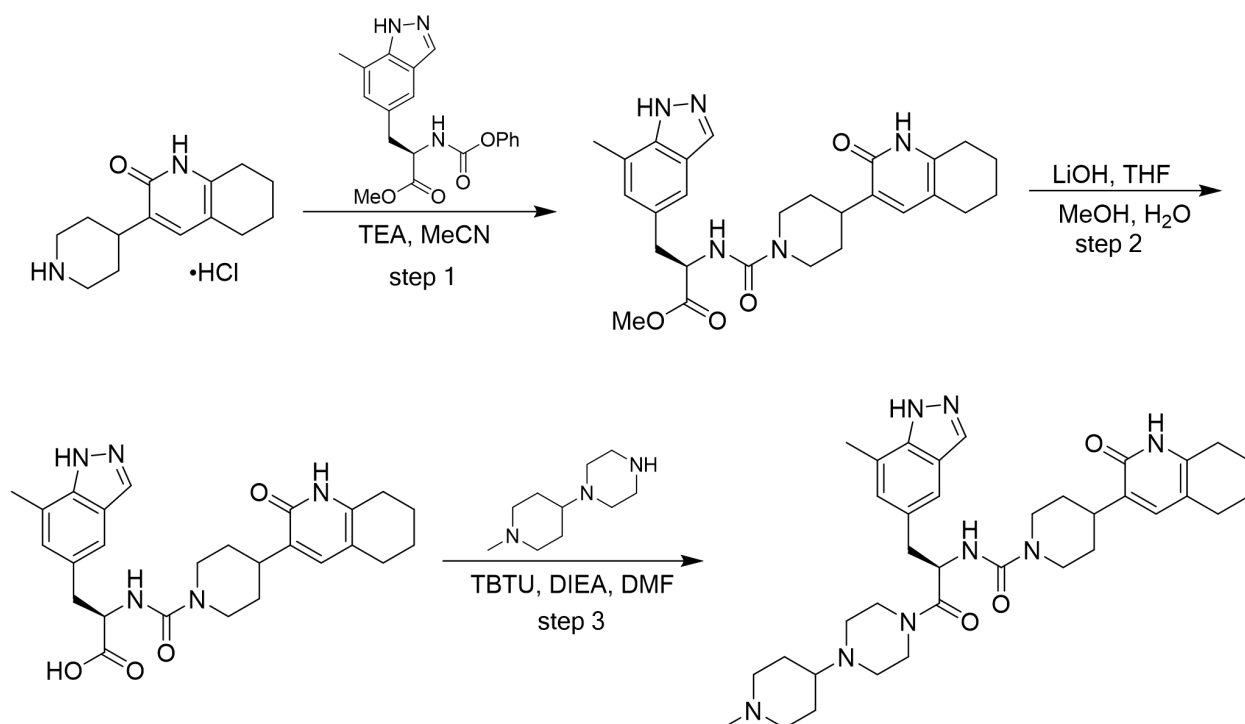


Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z ($M+H$)⁺ = 629.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 11.66 (s, 1H), 7.96 (s, 1H), 7.36 (s, 1H), 7.03 (s, 1H), 7.00 (d, J = 1.2 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.16 – 4.03 (m, 2H), 3.59 – 3.49 (m, 1H), 3.38-3.36 (m, 1H), 3.28 – 3.19 (m, 1H), 3.15-3.07 (m, 1H), 2.99-2.92 (m, 1H), 2.91-2.84 (m, 1H), 2.79 – 2.56 (m, 9H), 2.47 (s, 3H), 2.37 – 2.28 (m, 1H), 2.26 – 2.17 (m, 1H), 2.09 (s, 3H), 2.04 – 1.84 (m, 4H), 1.78 – 1.60 (m, 4H), 1.54 (t, J = 8.8 Hz, 1H), 1.41-1.33 (m, 2H), 1.29 – 1.09 (m, 4H).

Example 52: preparation of (R)-N-(3-(7-methyl-1H-indazole-5-yl)-1-(4-(1-methylpiperidine-4-yl)piperazine-1-yl)-1-oxopropan-2-yl)-4-(2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-yl)piperidine-1-formamide



Corresponding common commercially available reagents and the products in the preparation examples of intermediate compound and the examples above were used as raw materials to prepare the title compound by a preparation method similar to that in Example 11 above.

MS (ESI) m/z (M+H)⁺ = 643.4.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 11.23 (s, 1H), 7.96 (s, 1H), 7.37 (s, 1H), 7.00 (t, J = 1.2 Hz, 1H), 6.85 (s, 1H), 6.64 (d, J = 8.1 Hz, 1H), 4.77 (q, J = 7.7 Hz, 1H), 4.10 (d, J = 12.9 Hz, 2H), 3.56 (d, J = 13.4 Hz, 1H), 3.24 (t, J = 10.2 Hz, 1H), 3.12 (t, J = 9.9 Hz, 1H), 2.97 (dd, J = 13.1, 7.9 Hz, 1H), 2.88 (dd, J = 13.1, 7.0 Hz, 1H), 2.82 – 2.54 (m, 5H), 2.48 (s, 3H), 2.39 (d, J = 19.6 Hz, 5H), 2.23 (d, J = 11.0 Hz, 1H), 2.10 (s, 3H), 2.03 – 1.80 (m, 2H), 1.78 – 1.60 (m, 7H), 1.55 (t, J = 9.2 Hz, 1H), 1.38 (d, J = 12.3 Hz, 2H), 1.32 – 1.08 (m, 6H).

Biological test data

Unless otherwise specified, the experimental materials, reagents, operations and methods used in the following activity test examples were all commercially available, or easily known or prepared based on the prior art.

Test Example 1: determination of cell functional antagonism - cAMP determination

1. Experimental principle

A CGRP receptor complex was coupled with Gs in G protein, the combination of CGRP and CGRP receptor complex led to Gs activation, and cAMP (3',5'-cyclic adenosine monophosphate) was produced.

2. Experimental purpose

The ability of the compound of the present invention to inhibit CGRP-stimulated cAMP formation in SK-N-MC cells was determined.

3. Experimental materials

3.1 Experimental cell line:

SK-N-MC (neuroepithelioma cells) from National Science and Technology Infrastructure - Biomedical Materials and Cell Resources.

3.2 Reagents and consumables

Name	Brand	Article number
LANCE Ultra cAMP Kit	PerkinElmer	TRF0262
α -CGRP (human)	MCE	HY-P1071
IBMX	sigma	I7018-100MG
HBSS (1 $\times$)	Gibco	14025076
HEPES 1M	Gibco	15630080

4. Experimental steps

4.1 Cell preparation:

The SK-N-MC cells were resuscitated and cultured in advance, and a cell confluence degree should be 70%-80% before use.

4.2 A sample dilution, a tested compound and α -CGRP (human) were prepared.

4.3 Cell seeding and drug effect:

The SK-N-MC cells were digested, centrifuged, then resuspended with the sample dilution, and inoculated into a 384-well plate. Each well was added with the α -CGRP (human) and the tested compound respectively, and blown and mixed evenly. The well plate was adhered with a sealing film, and placed on an enzyme-labeled incubator to incubate at 25°C.

4.4 cAMP determination: carried out according to LANCE Ultra cAMP Kit specification Eu-cAMP tracer and ULight-anti-cAMP working solutions were prepared in the dark, respectively added into the well plate, and blown and mixed evenly. The well plate was adhered with a sealing film, and placed on an enzyme-labeled incubator to incubate at 25°C.

4.5 A luminescence value was read by a chemiluminescent module of an automatic enzyme-labeled instrument.

4.6 Data analysis:

A compound concentration LOG value was taken as an abscissa and Inhibition was taken as an ordinate to carry out fitting calculation on an IC₅₀ value by a nonlinear formula, and results were as shown in the table below.

IC₅₀ values of compounds to inhibit CGRP-stimulated cAMP formation in SK-N-MC cells

Serial number of example	IC ₅₀ (nM)	Serial number of example	IC ₅₀ (nM)
1	1.35	2	0.65
3	0.62	4	1.00
5	1.94	6	0.21
7	6.02	8	0.41
9	0.86	10	9.40

11	7.83	12	16.88
13	1.44	14	6.85
15	10.08	16	0.71
17	15.45	18	0.95
19	0.39	20	0.37
21	589.60	22	0.81
23	1.12	24	1.02
25	0.79	26	0.10
27	1.24	28	10.10
29	0.23	30	0.19
31	2.05	32	0.29
33	0.37	34	0.20
35	0.69	36	4.61
37	0.15	38	0.07
39	0.13	40	3.47
41	0.38	42	0.27
43	0.10	44	0.06
45	26.04	46	0.15
47	0.24	48	0.15
49	0.14	50	0.07
51	1.94	52	1.04

5. Conclusion

The novel compounds provided by the present invention could significantly inhibit CGRP-stimulated cAMP formation, and had lower IC₅₀ values. Especially, the compounds represented by Examples 1, 2, 3, 4, 5, 6, 8, and 9 had remarkable inhibitory activities, and the IC₅₀ values of the compounds could reach a pM level.

Test Example 2: stability test in liver microsomes

1. Experimental purpose

The stability of the compound of the present invention in liver microsomes of rat, monkey and human was determined. Tested compounds of the present invention were the compounds in Examples 6 and 8, and a control drug was Zavegepant.

2. Reagents and consumables

Name of reagent	Supplier	Batch number	Concentration (mg protein/mL)
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Liver microsome of rat	RILD	WJYW	20
Liver microsome of monkey	RILD	MZYM	20
Liver microsome of human	BioreclamationIVT	YZB	20

3. Experimental steps

3.1 Test incubation system

Concentration of liver microsome	Tested substance: 0.5 mg/mL; and Verapamil: 0.2 mg/mL
Incubation buffer	Phosphate buffer (100 mM, pH 7.4)
Concentration of tested substance	1.0 μ M
Incubation time	0, 5, 15, 30, 45 and 60 minutes
MgCl ₂	3.0 mM
NADPH	1.0 mM
Parallel test	Two parts

3.2 An appropriate amount of liver microsome solution was transferred into a 1 mL 96-deep-well plate, added with a tested drug liquid (or a probe substrate solution), and pre-incubated in a thermal mixer at 37°C for 5 minutes. Two parts of mixed solutions were taken out from the system and added with 1×PBS to replace NADPH, and the mixed solutions were taken out at 0 and 60 minutes respectively, and added with methanol (containing an internal standard) to terminate the reaction. In the remaining mixed system, each well was added with NADPH to start the reaction. In the tested substance group, mixed solutions were taken out from the system at 0, 5, 15, 30, 45 and 60 minutes, and in the control group, mixed solutions were taken out from the system at 0, 30 and 60 minutes, and the mixed solutions were added methanol (containing an internal standard) to terminate the reaction. All samples of the terminated reaction were mixed evenly and centrifuged in a centrifuge at 3800 rpm for 15 minutes, and the supernatant was taken for LC-MS/MS analysis.

3.3 Data analysis

A peak area was determined by an extracted ion chromatogram. A slope value k was determined by linear regression of a remaining percentage of a parent drug relative to a natural logarithm of an incubation time curve. According to the slope, in-vitro half-life periods ($t_{1/2}$) were respectively calculated, and in-vitro intrinsic clearance rates (CL_{int} , represented by μ L/min/mg protein) were calculated. Calculation formulas were as follows:

$$t_{1/2} = \ln 2/k = 0.693/k; \text{ and } CL_{int} = 0.693/t_{1/2} / \text{liver microsome protein concentration}$$

Experimental results were as shown in the following Table:

Stability data of compounds of the present invention in liver microsomes of rat, monkey and human

Example Species	$t_{1/2}$ (min)			CL_{int} (μ L/min/mg)			% remaining (60 min)		
	Rat	Monkey	Human	Rat	Monkey	Human	Rat	Monkey	Human
6	>120	>120	>120	2.4	0.8	0	91.5	96.9	131
8	>120	88.8	>120	1.6	15.6	3.2	90.7	61.6	85.8
29	>120	>120	>120	0	1.6	0	105	98.9	115

Zavegepant	>120	107	66.6	2.8	13	20.8	95.5	72.1	57.5
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Test Example 3: plasma protein binding rate test

1. Experimental purpose

Protein binding rates of the compound of the present invention in plasma of rat, monkey and human were determined by an equilibrium dialysis method. Tested compounds of the present invention were the compounds in Examples 6 and 8.

2. Test matrix

Matrix/species	Anticoagulant
Plasma of SD rat	EDTA-K ₂
Plasma of cynomolgus monkey	EDTA-K ₂
Plasma of human	EDTA-K ₂

3. Experimental steps

3.1 A dry dialysis membrane was rinsed with ultrapure water for 2-3 times, and then soaked in a phosphate buffer for 1 hour for later use. Polytetrafluoroethylene module was soaked in 20% ethanol for 30 minutes, and then surface moisture was dried with dust-free paper for later use. The pretreated dialysis membrane was assembled into a dialysis plate according to the product specification, and one side (receptor compartment) of an osmotic membrane in each dialysis well was added with 100 μ L of receptor fluid (100 mM phosphate buffer solution plus 0.002% Tween 80).

3.2 The plasma was put into a centrifuge tube, a working solution of a tested substance was added into the plasma, wherein a final concentration was 1 μ M, and the mixture was turned upside down and mixed evenly (this step was carried out in ice bath). 20 μ L of drug-containing plasma each was taken, and was respectively transferred to a 96-well sample plate according to two parts in parallel, and stored in a refrigerator at -20°C as a T₀ sample.

3.3 Another 100 μ L of the above drug-containing plasma was transferred to the other side (sample compartment) of the membrane in the dialysis device according to two parts in parallel, and incubated under vibration at a constant temperature of 37°C for 6 hours. After 6 hours of incubation, 20 μ L of the plasma was respectively taken out from the receptor compartment and the sample compartment after equilibration to obtain samples B and A. The samples B and A were respectively added with corresponding volumes of corresponding blank plasma or phosphate buffer solution (containing 0.002% Tween 80), so that a volume ratio of the plasma to the buffer solution in each sample well was 1: 1.

3.4 All sample wells were added with 250 μ L of methanol solution containing an internal standard, mixed evenly and then centrifuged in a centrifuge at 3800 rpm for 10 minutes. 20 μ L of supernatant was added with 180 μ L of methanol, and mixed evenly in a vortexed mode for LC-MS/MS sample injection analysis.

3.5 Data analysis

A plasma protein binding rate and a recovery rate of the compound in plasma were calculated by the following formulas:

$$\text{dissociation percentage (\%)} = C_B/C_A;$$

plasma protein binding rate (f_b %) = 1- dissociation percentage (%);

$$\text{recovery rate (\%)} = (C_B + C_A) / C_{T0}$$

wherein C_B was a concentration of the compound in the receptor fluid after equilibrium dialysis; C_A was a concentration of the compound in the drug-containing plasma after equilibrium dialysis; and C_{T0} was an initial concentration of the compound in plasma.

Experimental results were as shown in the following Table:

Example / Species	Rat	Monkey	Human
	f_b (%)	f_b (%)	f_b (%)
Example 6	90.0	61.3	76.7
Example 8	69.4	47.7	64.1
Example 29	64.3	56.1	50.2

Test Example 4: in-vivo pharmacokinetic study on SD rats intravenously and intranasally administrated with tested compound

1. Experimental animals

Species: SD rats, male, SPF level. Source: SD rats purchased from Chengdu Dossy Experimental Animals Co., Ltd., with the production license number of experimental animals: SCXK(Chuan)2020-030. Quantity: 2 SD rats were intravenously administered and 4 SD rats were intranasally administered.

2. Preparation of tested sample

2.1 An appropriate amount of drug was accurately weighed and added with 50 mM succinate buffer (diluted with D5W, pH=5-6), and mixed evenly and dissolved fully in an ultrasonic and vortexed mode to obtain a 0.2 mg/mL drug solution for intravenous (IV) administration.

2.2 An appropriate amount of drug was accurately weighed and added with 50 mM succinate buffer (diluted with pure water, pH=5-6), and mixed evenly and dissolved fully in an ultrasonic and vortexed mode to obtain a 10 mg/mL drug solution for intranasal (IN) administration.

3. Experiment design

Group	Number	Dosage (mg/kg)	Concentration (mg/mL)	Administration volume	Administration mode	Sample collection
1	2	1	0.2	5 mL/kg	IV	Plasma
2	4	2	10	50 μ L/animal	IN	Plasma

Tested drugs were the compounds in Examples 6 and 8, and a control drug was Zavegepant.

4. Time point of blood sampling

5 minutes, 10 minutes, 15 minutes, 0.5 hour, 1 hour, 2 hours, 4 hours, 8 hours and 24 hours after administration.

5. Sample collection and disposition

Blood was collected through a jugular vein, about 0.2 mL of each sample was collected, EDTA-K2 was used for anticoagulation, the collected blood sample was placed on ice, and plasma was

centrifugally separated within 2 hours (at 6000 g and 2-8°C for 5 minutes). The collected plasma samples were stored in a refrigerator at -80°C before analysis, and the remaining plasma samples after analysis were continuously stored in the refrigerator at -80°C for temporary storage.

6. Biological analysis and data processing

A concentration of a specified compound in plasma was determined by an LC-MS/MS method, and main pharmacokinetic parameters were calculated by a Winnolin 8.3 non-compartmental model. When the pharmacokinetic parameters were calculated, BLQ before $C_{\max}$ (comprising "No peak") was calculated according to 0; and BLQ (comprising "No peak") after $C_{\max}$ did not participate in the calculation.

Data of in-vivo pharmacokinetic study on SD rats intravenously and intranasally administrated with tested compound

Compound		Example 6	Example 8	Zavegepant
IV@1 mg/kg	Half-life period $t_{1/2}$ (h)	2.52	7.58	2.58
	Area under curve AUC (ng.h/mL)	5992	2852	3622
	Apparent clearance CL (mL/min/kg)	2.77	5.94	4.59
	Volume of distribution steady-state V_{ss} (L/kg)	0.29	0.50	0.35
IN@2 mg/kg	Half-life period $t_{1/2}$ (h)	3.80	3.41	1.08
	Concentration to peak $C_{\max}$ (ng/mL)	540	204	645
	Area under curve AUC (ng.h/mL)	2401	626	385
	Bioavailability F%	20.1	11.0	5.31

Test Example 5: study on influences of different pharmaceutical compositions with or without combination with alkyl glycoside on the PK properties in SD rats

Experimental animals in the Test Example 5 were all SD rats, and the same experimental design, collection and biological analysis data processing methods and processes as those in the Test Example 4 were adopted.

During preparation of a test sample in the Test Example 5, a drug solution group with 0.2% dodecyl- β -D-maltoside (DDM) was also established and prepared in parallel, so as to compare and observe changes of PK properties in rats administered with the drug solution group with 0.2% dodecyl- β -D-maltoside (DDM) and the drug solution group without dodecyl- β -D-maltoside (DDM).

The influences of different pharmaceutical compositions on the PK properties in the rats in the Test Example 5 were as shown in the following table:

Type of CGRP antagonist	Example 6	Example 8	Zavegepant
$T_{\max}$ (DDM 0.2%)/ $T_{\max}$ (DDM 0%)	16.7%	79.9%	83.6%
$C_{\max}$ (DDM 0.2%)/ $C_{\max}$ (DDM 0%)	10.0	27.6	2.73
$AUC_{0-\infty}$ (DDM 0.2%)/ $AUC_{0-\infty}$ (DDM 0%)	5.1	7.5	5.1

Note: when the drug solution group of the compound of Example 6 was added with 0.2% DDM, the $T_{\max}$ was shortened from 1 hour to 0.167 hour; when the drug solution groups of the compound

of Example 8 and the Zavegepant were not added with DDM (0%DDM), the time to peak of the blood drug concentration was already relatively short (the T_{max} values were 0.209 hour and 0.25 hour respectively), so that there was limited room for further shortening the time to peak of the blood drug concentration after adding 0.2% DDM (the T_{max} values were 0.167 hour and 0.209 hour respectively).

It can be learned from the above table:

1. When the compounds as represented by formula I of Examples 6 and 8 were added with the alkyl glycoside for combined use, many key PK parameters were surprisingly synchronously and significantly improved. For example, after the combined use of the compound of Example 6 with the alkyl glucoside: the T_{max} was shortened from 1 hour to 0.167 hour, which was shortened by 83.3%, and the time to peak was extremely short, which laid a good foundation for follow-up rapid onset of drug; the C_{max} was greatly increased by 10-fold, while the AUC was increased by about 5-fold, which could reduce a drug dosage and increase a safety while ensuring a concentration of rapid onset. For another example, after the combined use of the compound of Example 8 with the alkyl glucoside: the C_{max} and the AUC_{0-inf} were increased by 27.6-fold and 7.5-fold respectively, and the T_{max} was obviously shortened by 20.1% and kept at a short level of 0.167 hour.

For the migraine and neuropathic headache indications treated by the compound as represent by formula I, it was of great significance to rapidly alleviate, treat and prevent acute attacks of the diseases, and the surprising improvement on the PK properties, such as shortening the T_{max} and increasing the C_{max} , by the combined use of the compounds of formula I as represented by Examples 6 and 8 with the alkyl glucoside, indicated that such compositions had great clinical application potential.

2. When the gepant-class CGRP antagonist compounds of Examples 6 and 8 and the Zavegepant were added with the alkyl glucoside for nasal administration, many PK parameters could also be improved to some extent, which also indicated that the combination of the gepant-class CGRP antagonist compound with the alkyl glucoside had clinical application potential in producing the preparation for nasal administration.

Test Example 6: study on influences of different pharmaceutical compositions with or without combination with alkyl glycoside on the PK properties in monkeys

1. Experimental animals

Species: cynomolgus monkey, male, 2-5 kg. Source: Ankai Yibo (Zhanjiang) Biotechnology Co., Ltd., Laboratory Animal Production License No.: SCXK (Yue) 2019-0046. Quantity: 3 cynomolgus monkeys were intravenously administered and 3 cynomolgus monkeys were administered by a nasal spray.

2. Preparation of test sample

2.1 An appropriate amount of drug was accurately weighed and added with 50 mM succinate buffer (diluted with D5W, pH=5-6), and mixed evenly and dissolved fully in an ultrasonic and vortexed mode to obtain a 0.5 mg/mL drug solution for intravenous administration.

2.2 An appropriate amount of drug was accurately weighed and added with a solvent 1: 50 mM succinate buffer (diluted with pure water, pH=5-6), and mixed evenly and dissolved fully in an ultrasonic and vortexed mode to obtain a 20 mg/mL drug solution, which was put into a nasal spraying device for administration by the nasal spray, 100 μ L/spray.

2.3 An appropriate amount of drug was accurately weighed and added with a solvent 2: 50 mM succinate buffer (pH=5-6) containing 0.2% dodecyl- β -D-maltoside, and mixed evenly and

dissolved fully in an ultrasonic and vortexed mode to obtain a 20 mg/mL drug solution, which was put into a nasal spraying device for administration by the nasal spray, 100 μ L/spray.

3. Experimental design

Group	Test sample	Quantity	Dosage (mg/kg)	Concentration (mg/mL)	Administration volume	Administration mode	Sample collection
1	Example 6	3	0.5	0.5	1 mL/kg	IV	Plasma
2		3	1	20	200 μ L/animal	IN (solvent 1)	Plasma
3		3	1	20	200 μ L/animal	IN (solvent 2)	Plasma
4	Example 8	3	0.5	0.5	1 mL/kg	IV	Plasma
5		3	1	20	200 μ L/animal	IN (solvent 1)	Plasma
6		3	1	20	200 μ L/animal	IN (solvent 2)	Plasma

4. Time point of blood sampling

5 minutes, 10 minutes, 15 minutes, 0.5 hour, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours and 24 hours after administration.

5. Sample collection and disposition

Blood was collected through a saphenous vein or a cephalic vein, about 0.6 mL of each sample was collected, EDTA-K2 was used for anticoagulation, the collected blood sample was placed on ice, and plasma was centrifugally separated within 2 hours (at 2000 g and 2-8°C for 10 minutes). The collected plasma samples were stored in a refrigerator at -80°C before analysis, and the remaining plasma samples after analysis were continuously stored in the refrigerator at -80°C for temporary storage.

6. Biological analysis and data processing

A concentration of a specified compound in plasma was determined by LC-MS/MS, and main pharmacokinetic parameters were calculated by a Winnolin 8.3 non-compartmental model. When the pharmacokinetic parameters were calculated, BLQ before $C_{\max}$ (comprising "No peak") was calculated as 0; and BLQ (comprising "No peak") after $C_{\max}$ was excluded from the calculation.

Data of in-vivo pharmacokinetic study on cynomolgus monkeys administrated with test compound by intravenous route and nasal spray

Compound		Example 6	Example 8
IV@0.5 mg/kg	Half-life period $t_{1/2}$ (h)	4.98	4.98
	Concentration to peak $C_{\max}$ (ng/mL)	3196	2283
	Area under curve AUC (ng.h/mL)	1141	924
	Apparent clearance CL (mL/min/kg)	7.35	9.27
	Volume of distribution steady-state V_{ss} (L/kg)	0.652	0.738
IN@1 mg/kg (Solvent 1)	Half-life period $t_{1/2}$ (h)	9.00	5.58
	Time to peak $T_{\max}$ (h)	1.00	1.00

	Concentration to peak $C_{\max}$ (ng/mL)	12.7	13.4
	Area under curve AUC (ng.h/mL)	43.2	46.1
	Bioavailability F%	1.99	2.50
IN@1 mg/kg (Solvent 2)	Half-life period $t_{1/2}$ (h)	5.57	4.92
	Time to peak $T_{\max}$ (h)	0.167	0.167
	Concentration to peak $C_{\max}$ (ng/mL)	663	401
	Area under curve AUC (ng.h/mL)	780	412
	Bioavailability F%	29.8	26.4

In-vivo Pharmacokinetics of different pharmaceutical compositions intranasally administered in monkeys

Type of CGRP antagonist	Example 6	Example 8
$T_{\max}$ (DDM 0.2%)/ $T_{\max}$ (DDM 0%)	16.7%	16.7%
$C_{\max}$ (DDM 0.2%)/ $C_{\max}$ (DDM 0%)	52.2	30.0
$AUC_{0-\infty}$ (DDM 0.2%)/ $AUC_{0-\infty}$ (DDM 0%)	17.1	8.6

Result analysis:

Similar to the study test on the influences on the PK properties in the rats in Test Example 5, a study test on influences on the PK properties in the monkeys indicated that, when the compounds as represented by formula I of Examples 6 and 8 were added with the alkyl glycoside for combined use, many key PK parameters were also surprisingly synchronously and significantly improved. It was manifested that: after the combined use of the compounds of Examples 6 and 8 with the alkyl glycoside, the $C_{\max}$ was greatly increased by 52.2-fold and 30-fold, while the $AUC_{0-\infty}$ was increased by 17.1-fold and 8.6-fold, and the $T_{\max}$ was shortened from 1 hour to about 0.17 hours, so that onset time was greatly shortened by 83.3%. That was to say, compared with the rats, in the monkeys, a species closer to humans, when the compound as represented by formula I was used in combination with the alkyl glycoside, excellent improvement effect on the PK properties was further demonstrated, showing good clinical application prospect.

Test Example 7: study on influences of pharmaceutical compositions containing different concentrations of alkyl glycosides on PK properties in SD rats

Experimental animals in the Test Example 7 were all SD rats, and the same experimental design, collection and biological analysis data processing methods and processes as those in the Test Example 4 were adopted.

During preparation of a test sample in the Test Example 7, drug solution groups with 0.05% and 5% dodecyl- β -D-maltosides (DDM) were established and prepared in parallel, so as to compare and observe changes of PK properties in rats administered with the drug solution groups with two different concentrations of dodecyl- β -D-maltosides (DDM).

The influences of different pharmaceutical compositions on the PK properties in the rats in the Test Example 7 were as shown in the following table:

Type of CGRP antagonist	Example 6	Example 8	Zavegepant
$T_{\max}(\text{DDM } 0.05\%)/T_{\max}(\text{DDM } 0\%)$	25.0%	79.9%	1
$C_{\max}(\text{DDM } 0.05\%)/C_{\max}(\text{DDM } 0\%)$	6.51	16.2	1.17
$AUC_{0-\infty}(\text{DDM } 0.05\%)/AUC_{0-\infty}(\text{DDM } 0\%)$	3.8	6.23	2.44
$T_{\max}(\text{DDM } 5\%)/T_{\max}(\text{DDM } 0\%)$	8.3%	39.7%	50%
$C_{\max}(\text{DDM } 5\%)/C_{\max}(\text{DDM } 0\%)$	13.3	73.0	3.03
$AUC_{0-\infty}(\text{DDM } 5\%)/AUC_{0-\infty}(\text{DDM } 0\%)$	3.6	13.5	3.43

It can be learned from the above table:

When the compounds as represented by formula I of Examples 6 and 8 were added with different concentrations of alkyl glycosides for combined use, many key PK parameters were surprisingly synchronously and significantly improved. For example, after combined use of the compound of Example 6 with 0.05% and 5% alkyl glycosides: The $T_{\max}$ values were shortened from 1 hour to 0.25 hour and 0.083 hour respectively, and shortened by 75% and 91.7%, which indicated that the higher the concentration of the alkyl glycoside, the shorter the time to peak; and the $C_{\max}$ values were increased by 6.51-fold and 13.3-fold, and the AUC values were increased by 3.8-fold and 3.6-fold, which could reduce a drug dosage and increase a safety while ensuring a concentration of rapid onset. For another example, after combined use of the compound of Example 8 with 0.05% and 5% alkyl glycosides: the $T_{\max}$ values were shortened from 0.2 hour to 0.167 hour and 0.083 hour respectively, and shortened by 20% and 60%, which indicated that the higher the concentration of the alkyl glycoside, the shorter the time to peak; and the $C_{\max}$ values were increased by 16.2-fold and 73.0-fold, and the AUC values were increased by 6.23-fold and 13.5-fold, which indicated that the higher the concentration of the alkyl glucoside, the stronger the permeation promoting effect.

The present invention is not limited to the above optional embodiments, and anyone can get other products in various forms under the inspiration of the present invention. The above specific embodiments should not be construed as limiting the scope of protection of the present invention, the scope of protection of the present invention should be defined in the claims, and the specification can be used to explain the claims.

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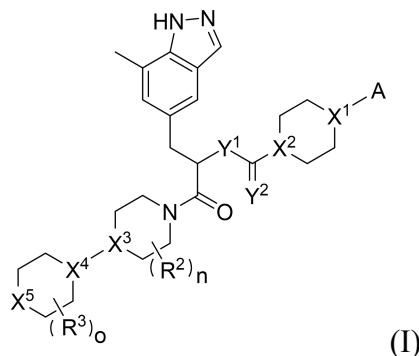
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CLAIMS

1. A pharmaceutical composition, comprising:

- a. an active ingredient, and
- b. an alkyl glycoside;

wherein, the active ingredient is a compound as represented by the following formula I, or an isomer, pharmaceutically acceptable salt or solvate thereof,



wherein,

X¹ and X² are respectively independently CH or N;

X³ and X⁴ are respectively independently C, CH or N;

X⁵ is C, CH, CH₂, NH or N;

Y¹ is CH₂, O or NH;

Y² is O or S;

R² is independently -H, -(C₁-C₆)alkyl or -(C₃-C₈)cycloalkyl when occurring each time, and n is 0, 1, 2, 3, 4, 5 or 6,

or, two R² form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R² attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R² attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

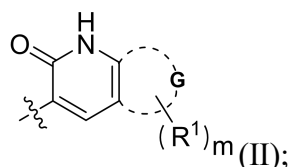
or, -(R²)_n forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -(R²)_n attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -(R²)_n attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

R³ is independently -H, -(C₁-C₆)alkyl or -(C₃-C₈)cycloalkyl when occurring each time, and o is 0, 1, 2, 3, 4, 5 or 6,

or, two R³ form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R³ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R³ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, -(R³)_o forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which -(R³)_o attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which -(R³)_o attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S;

A has a structure as represented by the following formula II:



a G-chain group forms a 5-7 membered aliphatic ring or aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, and ring-forming heteroatoms in the

aliphatic heterocyclic ring are -O-, -S- or $\text{—}\overset{\text{O}}{\parallel}\text{S—}$;

R^1 is independently -H, $-(\text{C}_1\text{-C}_6)\text{alkyl}$ or $-(\text{C}_3\text{-C}_8)\text{cycloalkyl}$ when occurring each time, and m is 0, 1, 2, 3, 4, 5 or 6,

or, two R^1 form a 3-8 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^1 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^1 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S,

or, $-(\text{R}^1)_m$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(\text{R}^1)_m$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(\text{R}^1)_m$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S.

2. The pharmaceutical composition according to claim 1, wherein:

the alkyl glycoside is mainly formed by covalently coupling a hydrophobic alkyl carbon chain and a hydrophilic oligosaccharide,

the covalently coupled linking group comprises a glycosidic bond, a thioglycosidic bond or an amide bond,

the hydrophobic alkyl carbon chain is selected from a $\text{C}_5\text{-C}_{16}$ alkyl chain, a $\text{C}_{10}\text{-C}_{16}$ alkyl chain, a $\text{C}_{11}\text{-C}_{14}$ alkyl chain, a C_{11} alkyl chain, a C_{12} alkyl chain, a C_{13} alkyl chain or a C_{14} alkyl chain, and

the hydrophilic oligosaccharide comprises a monosaccharide or a disaccharide, wherein the monosaccharide comprises glucose, and the disaccharide comprises maltose, trehalose or sucrose.

3. The pharmaceutical composition according to claim 1, wherein:

the alkyl glycoside is an undecyl maltoside, a dodecyl maltoside, a tridecyl maltoside or a tetradecyl maltoside, and

a weight percentage of the alkyl glycoside in the pharmaceutical composition is 0.05%-20%, 0.05%-10%, 0.05%-5%, 0.1%-5%, 0.1%-0.5%, 0.1%-0.3%, 0.05%, 0.2% or 5%.

4. The pharmaceutical composition according to claim 1, wherein:

the pharmaceutical composition is prepared into a nasal administration form, an oral administration form, a transdermal administration form or a mucosal administration form,

the nasal administration form comprises a nasal drop, a nasal spray, a nasal aerosol, a nasal gel or a nasal cream,

the nasal administration form is a single dose form, a double dose form or a multi-dose form,

a delivery volume of the nasal spray is 50 ul-200 ul/spray, and

the pharmaceutical composition is in a solution form, and further in an aqueous solution form.

5. The pharmaceutical composition according to claim 1, wherein:

the pharmaceutical composition further comprises one or a combination of two or more of a buffer, an osmotic pressure regulator, a wetting agent, a thickening agent, a pH regulator, a metal chelating agent and a preservative.

6. The pharmaceutical composition according to claim 1, wherein:

compared with a pharmaceutical composition without adding b. alkyl glycoside, the pharmaceutical composition provides 10-fold or more, 30-fold or more, 10-fold to 52.2-fold, or 30-fold to 52.2-fold C_{max} value of the active ingredient, and/or

compared with the pharmaceutical composition without adding b. alkyl glycoside, the pharmaceutical composition provides 5.1-fold or more, 8.6-fold or more, 5.1-fold to 17.1-fold, or 8.6-fold to 17.1-fold AUC_{0-inf} value of the active ingredient, and/or

compared with the pharmaceutical composition without adding b. alkyl glycoside, the pharmaceutical composition provides a T_{max} value which is shortened to 0.17 hour or less.

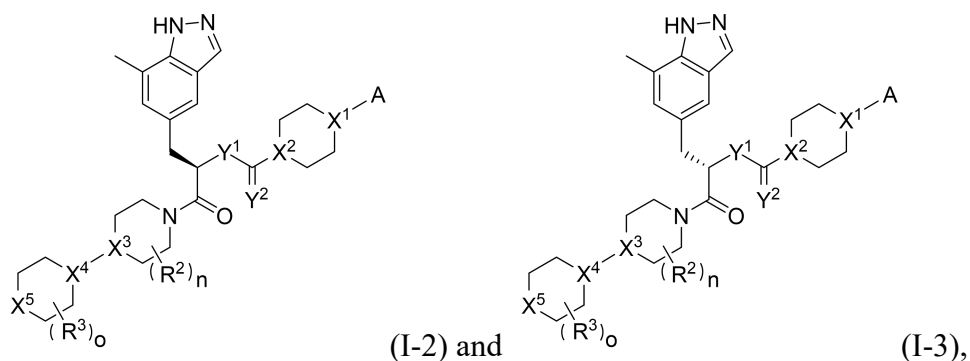
7. The pharmaceutical composition according to claim 1, wherein:

a weight percentage of the active ingredient in the pharmaceutical composition is 0.05%-20%, and/or

a content of the active ingredient in the pharmaceutical composition is 0.001 mg-1000 mg.

8. The pharmaceutical composition according to claim 1, wherein:

the compound as represented by formula I has a chiral structure as represented by formula I-2 or formula I-3:



wherein, X^1 , X^2 , X^3 , X^4 , X^5 , Y^1 , Y^2 , A, R^2 , R^3 , n and o are as defined above.

9. The pharmaceutical composition according to claim 1 or 8, wherein, in A:

in a case that the G-chain group forms a 5 or 6 membered aliphatic ring together with two carbon atoms to which the G-chain group attaches, the G-chain group optionally has 0 or 1 double bond, and the remaining bonds are all single bonds;

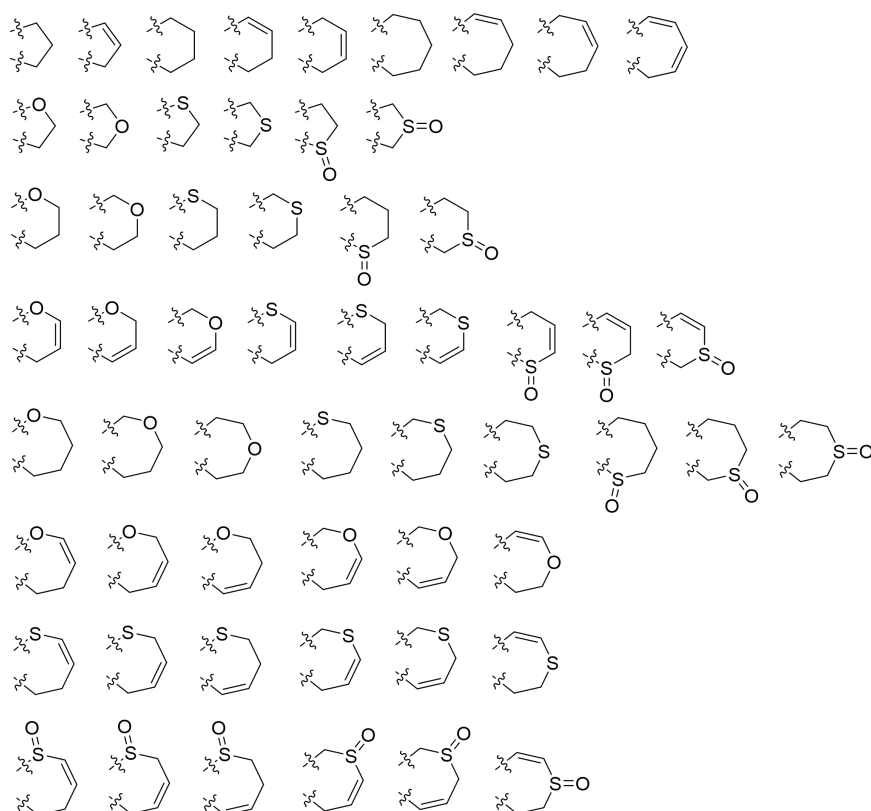
in a case that the G-chain group forms a 7 membered aliphatic ring together with two carbon atoms to which the G-chain group attaches, the G-chain group optionally has 0, 1 or 2 double bonds, and the remaining bonds are all single bonds;

in a case that the G-chain group forms a 5 membered aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, bonds on the G-chain group are all single bonds; and

in a case that the G-chain group forms a 6 or 7 membered aliphatic heterocyclic ring together with two carbon atoms to which the G-chain group attaches, the G-chain group optionally has 0 or 1 double bond, and the remaining bonds are all single bonds.

10. The pharmaceutical composition according to claim 9, wherein:

in A, the G-chain group is selected from:



11. The pharmaceutical composition according to claim 1 or 8, wherein:

in A,

R¹ is independently -H, -(C₁-C₃)alkyl or -(C₃-C₆)cycloalkyl when occurring each time, and m is 0, 1, 2 or 3,

or, two R_1 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R_1 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R_1 attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S, or, $-(R^1)_m$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^1)_m$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^1)_m$ attach, and heteroatoms in the aliphatic heterocyclic ring are O, N or S.

12. The pharmaceutical composition according to claim 11, wherein:

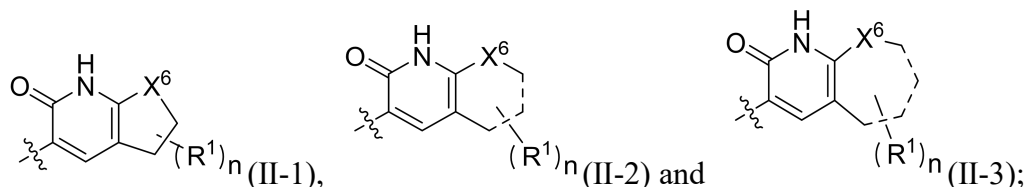
in A,

R^1 is independently -H, methyl, ethyl or cyclopropyl when occurring each time, and m is 0, 1 or 2,

or, two R_1 form cyclopropane, cyclobutane or cyclopentane together with atoms to which R_1 attach, and the cyclopropane, the cyclobutane or the cyclopentane forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R_1 attach, or, $-(R^1)_m$ forms cyclopropane, cyclobutane or cyclopentane together with atoms to which $-(R^1)_m$ attach, and the cyclopropane, the cyclobutane or the cyclopentane forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^1)_m$ attach.

13. The pharmaceutical composition according to claim 1, 8, 11 or 12, wherein:

A has a structure as represented by the following formula II-1, II-2 or II-3:

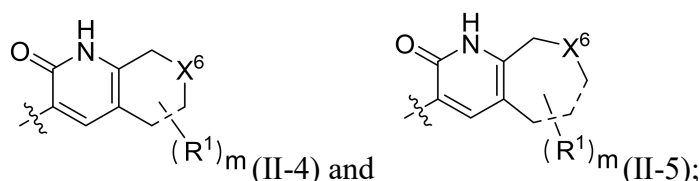


in the formulas II-1, II-2 and II-3, X^6 is -O-, -S- or $-\overset{\text{O}}{\parallel}{\text{S}}-$;

in the formula II-2, two “---” both refer to single bonds, or any one of the two “---” is a double bond and the other one is a single bond; and

in the formula II-3, three “---” all refer to single bonds, or any one of the three “---” is a double bond and the other two are both single bonds; or

A has a structure as represented by the following formula II-4 or II-5:



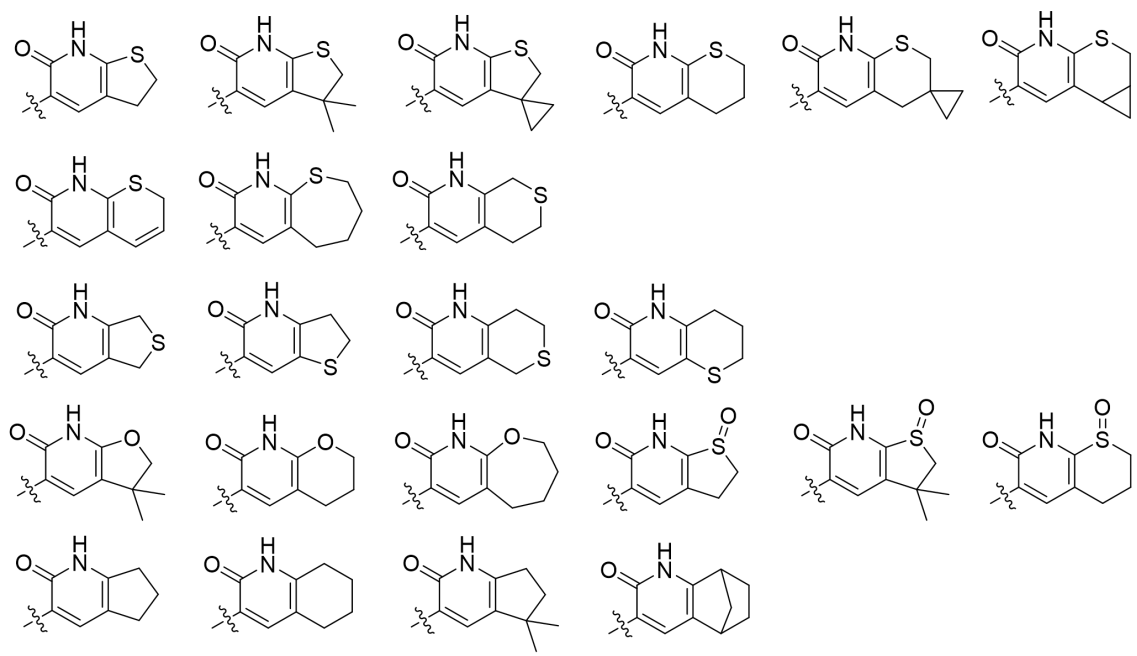
in the formula II-4 or II-5, X^6 is -O-, -S- or $-\overset{\text{O}}{\parallel}{\text{S}}-$;

in the formula II-4, “---” refers to a single bond or a double bond; and

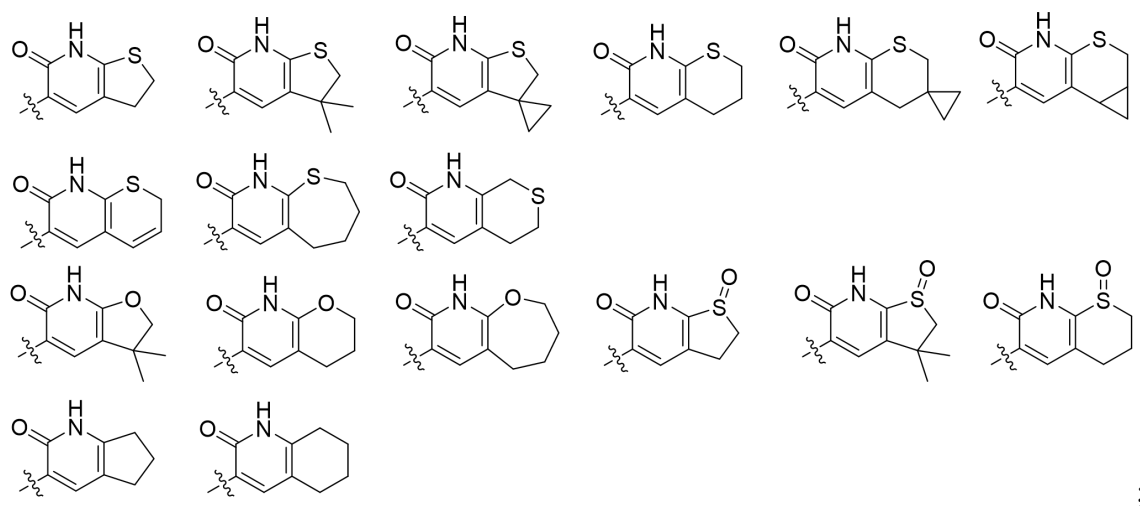
in the formula II-5, two “---” both refer to single bonds, or any one of the two “---” is a double bond and the other one is a single bond.

14. The pharmaceutical composition according to claim 1 or 8, wherein:

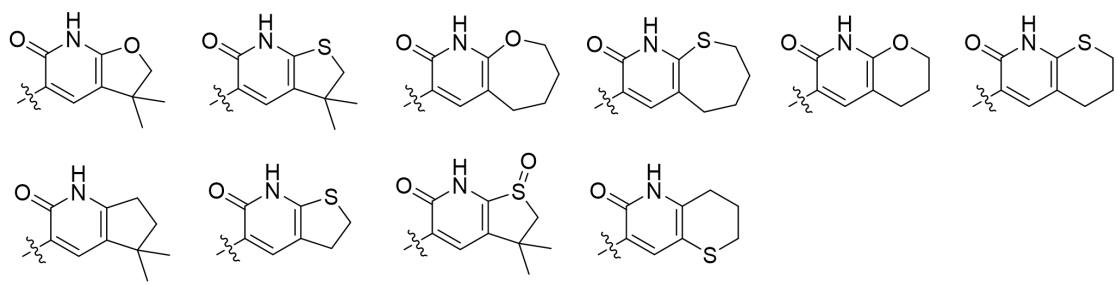
A is selected from



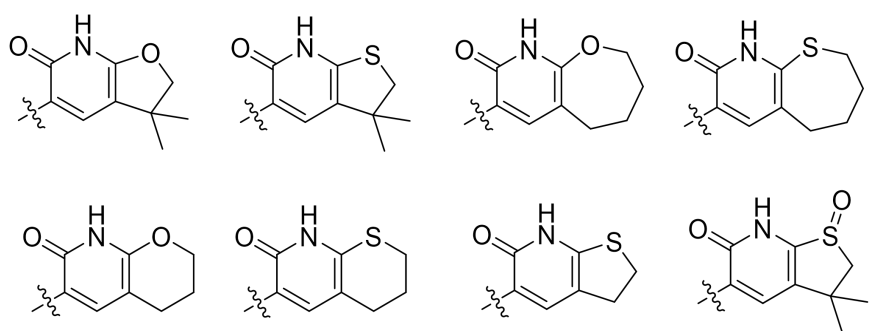
preferably, A is selected from



more preferably, A is selected from:



further preferably, A is selected from:



15. The pharmaceutical composition according to claim 1 or 8, wherein:

R^2 is independently -H, $-(C_1-C_3)alkyl$ or $-(C_3-C_6)cycloalkyl$ when occurring each time, and n is 0, 1, 2 or 3,

or, two R^2 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^2 attach, and ring-carried atoms provided by the two R^2 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^2)_n$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^2)_n$ attach, and ring-carried atoms provided by the $-(R^2)_n$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms;

R^3 is independently -H, $-(C_1-C_3)alkyl$ or $-(C_3-C_6)cycloalkyl$ when occurring each time, and n is 0, 1, 2 or 3,

or, two R^3 form a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which R^3 attach, and ring-carried atoms provided by the two R^3 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^3)_o$ forms a 3-6 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure, a fused ring structure or a bridged ring structure with the ring to which $-(R^3)_o$ attach, and ring-carried atoms provided by the $-(R^3)_o$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms.

16. The pharmaceutical composition according to claim 15, wherein:

R^2 is independently -H, methyl, ethyl, cyclopropyl or cyclobutyl when occurring each time, and n is 0, 1 or 2,

or, two R^2 form a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^2 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which R^2 attach, and ring-carried atoms provided by the two R^2 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^2)_n$ forms a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^2)_n$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which $-(R^2)_n$ attach, and

ring-carried atoms provided by the $-(R^2)_n$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms;

R^3 is independently -H, $-(C_1-C_3)$ alkyl or $-(C_3-C_6)$ cycloalkyl when occurring each time, and n is 0, 1, 2 or 3,

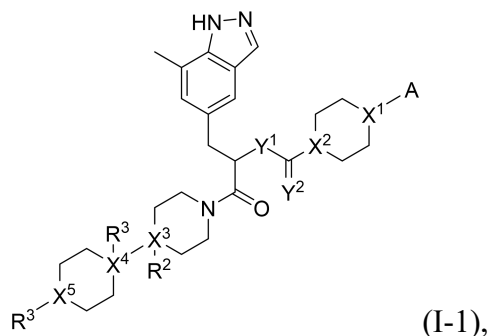
or, two R^3 form a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which R^3 attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which R^3 attach, and ring-carried atoms provided by the two R^3 in the aliphatic ring or aliphatic heterocyclic ring are both C atoms; or, $-(R^3)_o$ forms a 3-5 membered aliphatic ring or aliphatic heterocyclic ring together with atoms to which $-(R^3)_o$ attach, the aliphatic ring or aliphatic heterocyclic ring optionally forms a spiro structure with the ring to which $-(R^3)_o$ attach, and ring-carried atoms provided by the $-(R^3)_o$ in the aliphatic ring or aliphatic heterocyclic ring are all C atoms.

17. The pharmaceutical composition according to claim 1 or 8, wherein:

X^3 and X^4 are not N at the same time.

18. The pharmaceutical composition according to claim 1,

wherein, the active ingredient is a compound as represented by the following formula I-1, or an isomer, pharmaceutically acceptable salt or solvate thereof:



wherein, X^1 , X^2 , X^3 , X^4 , X^5 , Y^1 and Y^2 are as defined in Claim 1, and A is as defined in Claim 13 or 14; and

R^2 and R^3 are independently -H, $-CH_3$ or absent when occurring each time.

19. The pharmaceutical composition according to claim 1, 8 or 18,

wherein, one or more H in the compound are substituted by D.

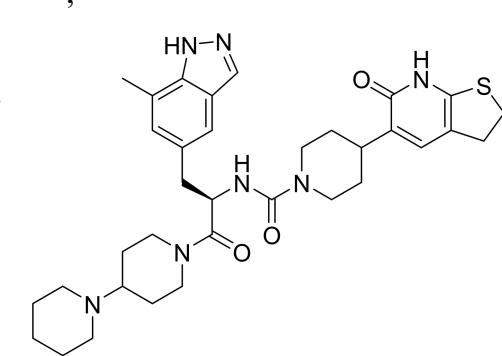
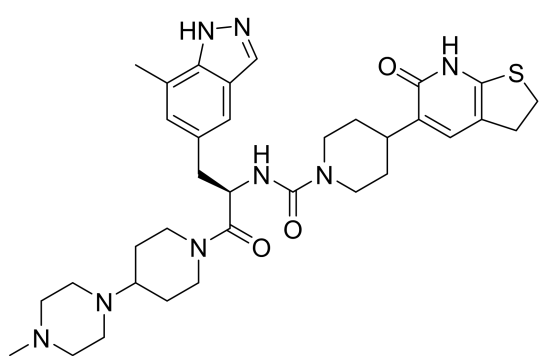
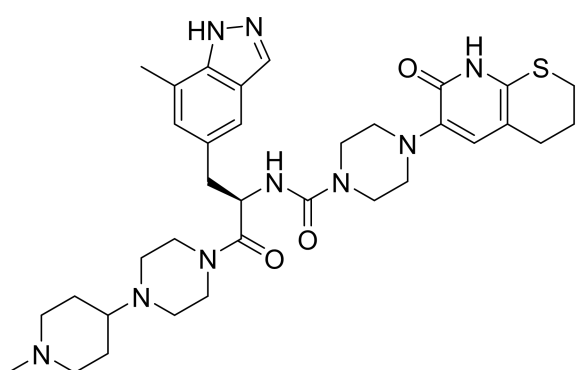
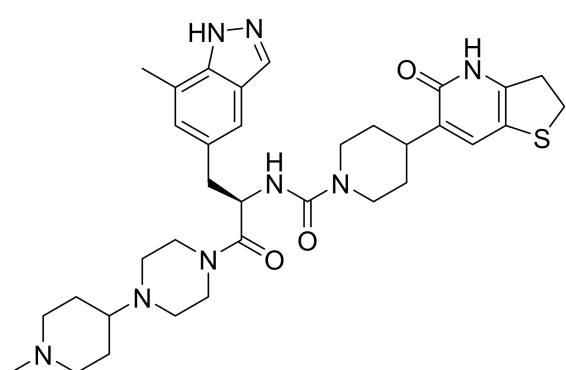
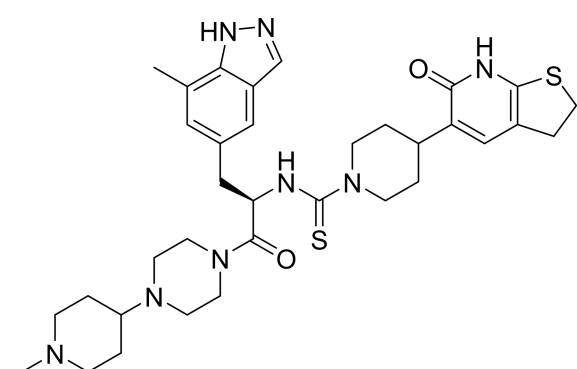
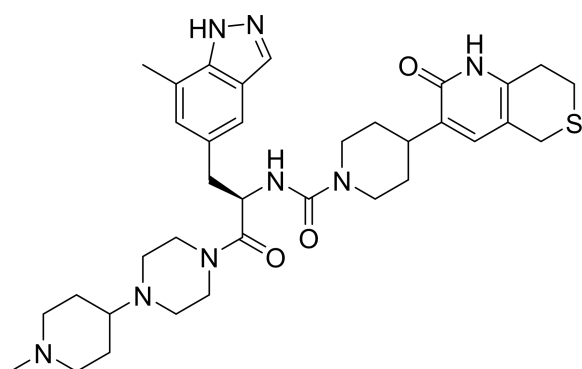
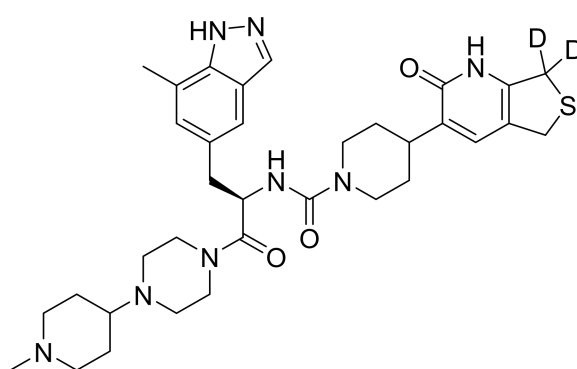
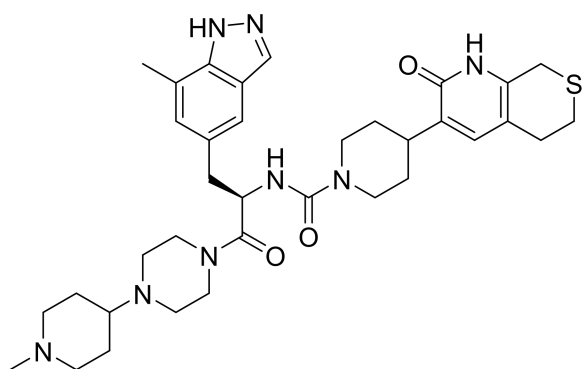
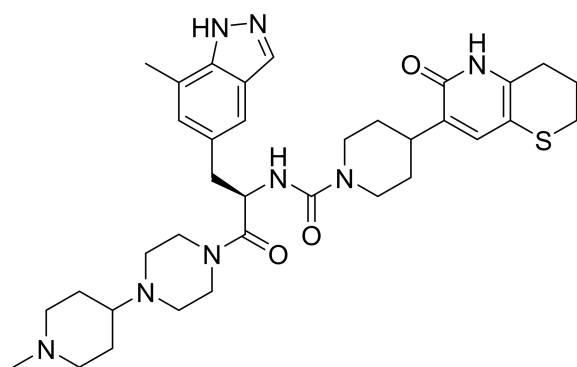
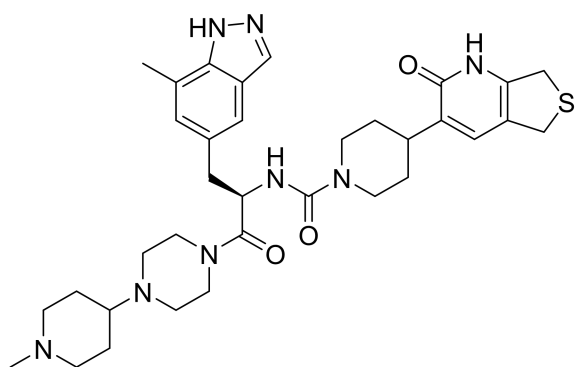
20. The pharmaceutical composition according to claim 19,

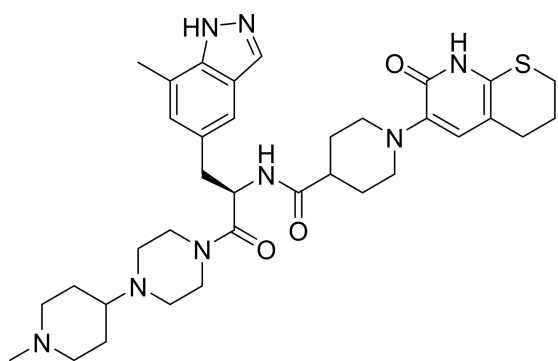
wherein, one or more H in the G-chain group or the R^1 are substituted by D.

21. The pharmaceutical composition according to claim 1,

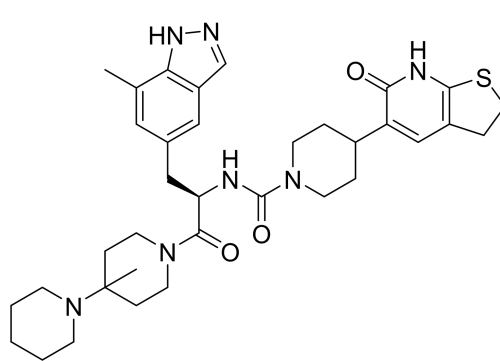
wherein, the compound as represented by formula I is selected from:



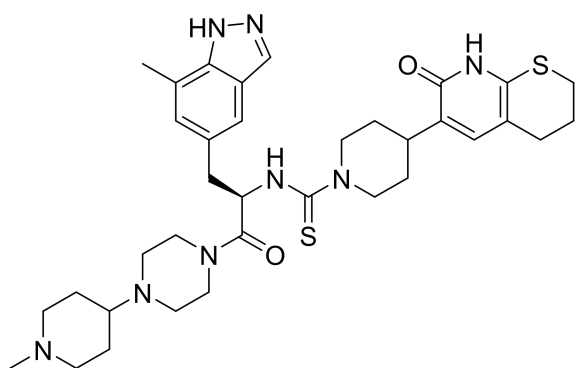




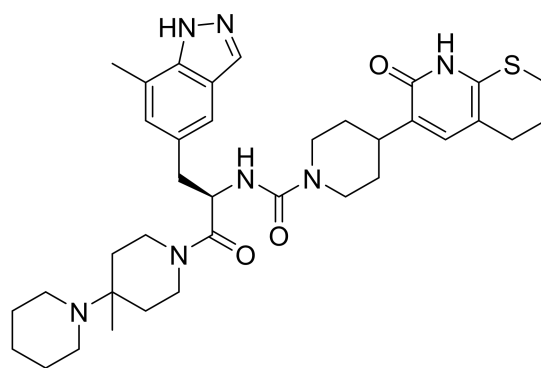
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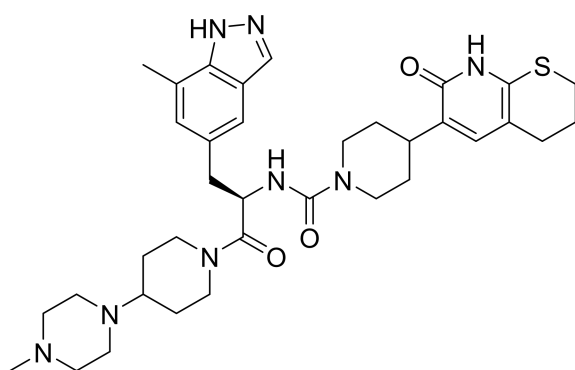
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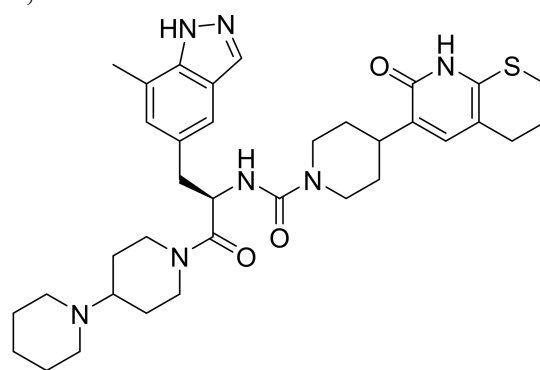
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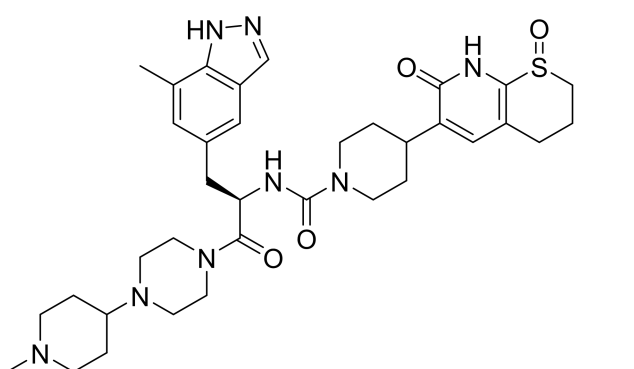
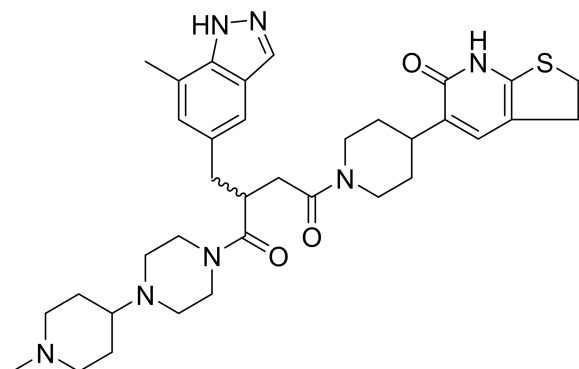
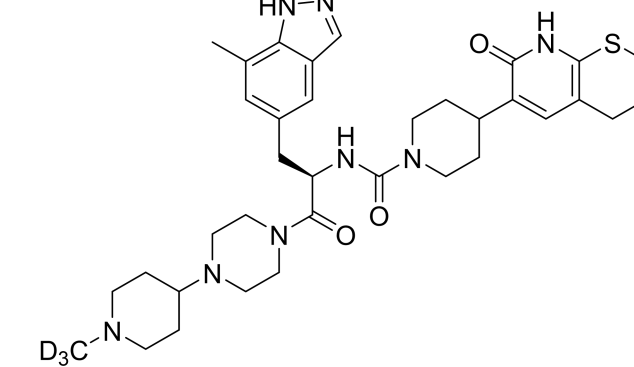
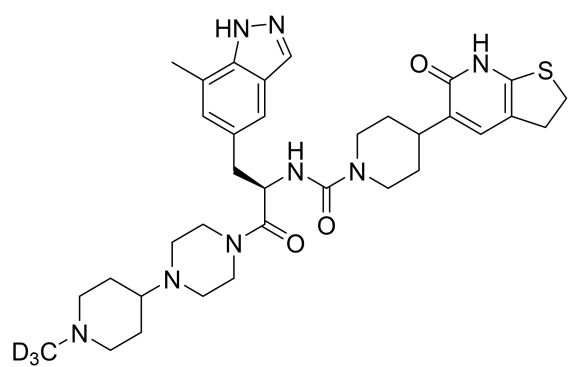
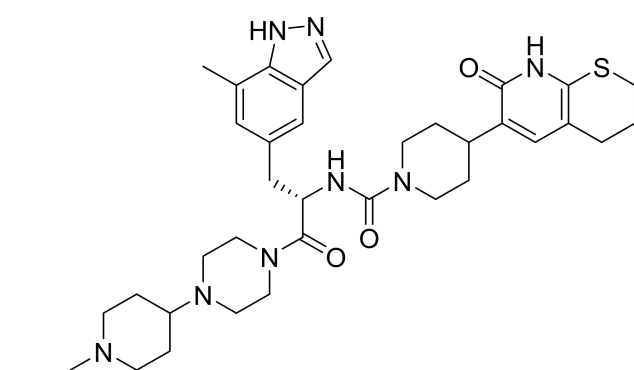
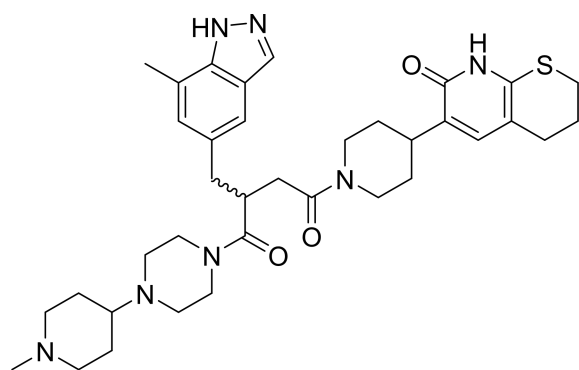
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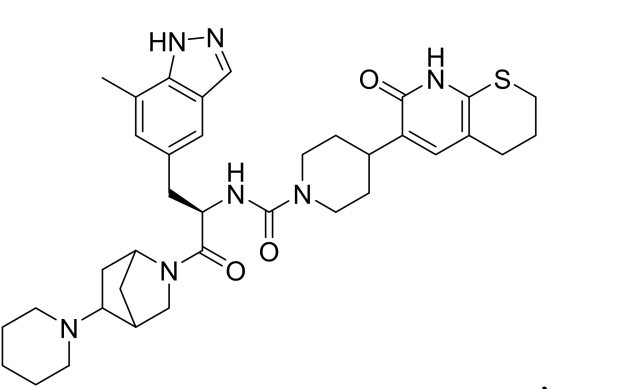
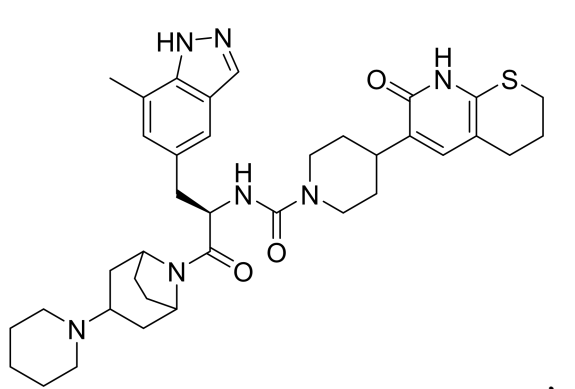
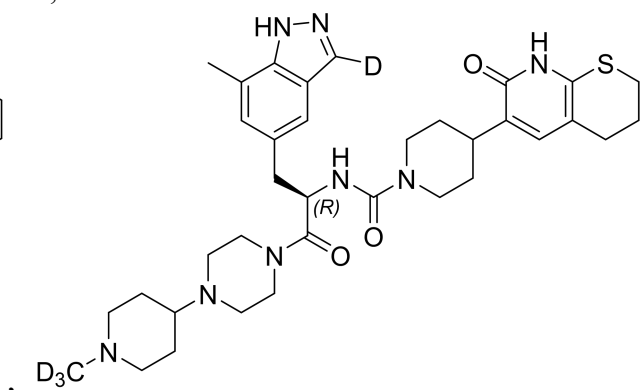
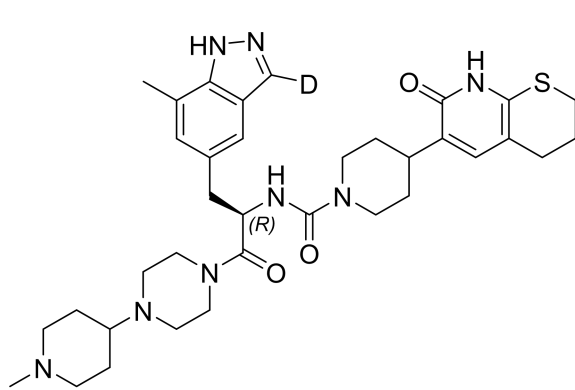
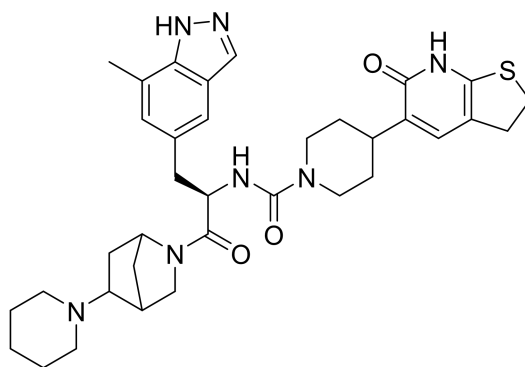
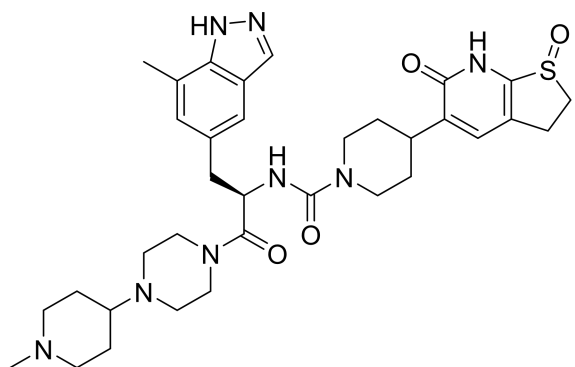
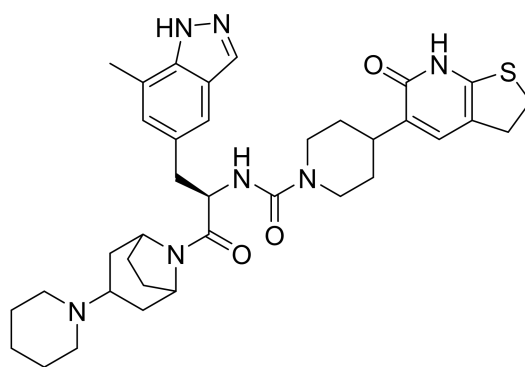
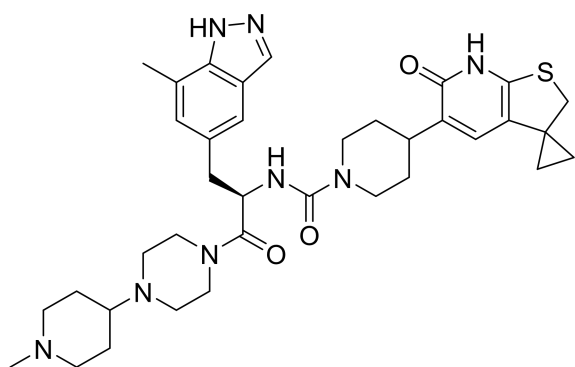


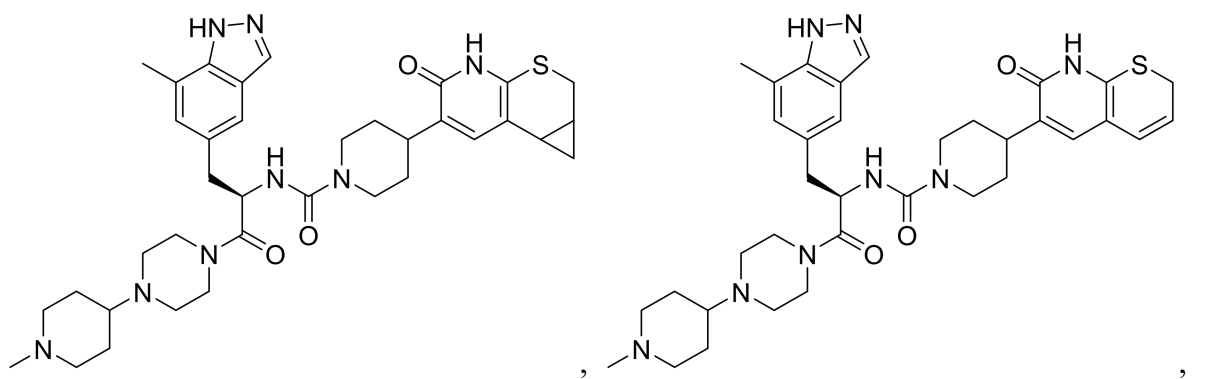
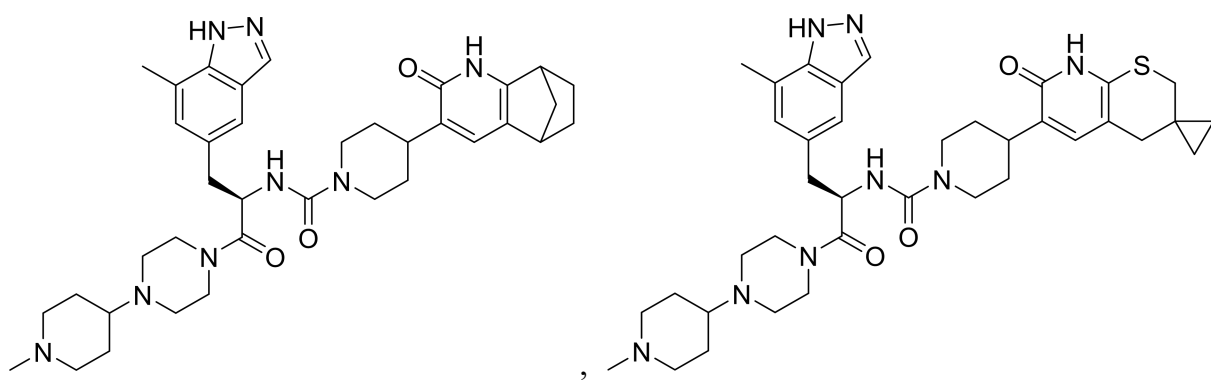
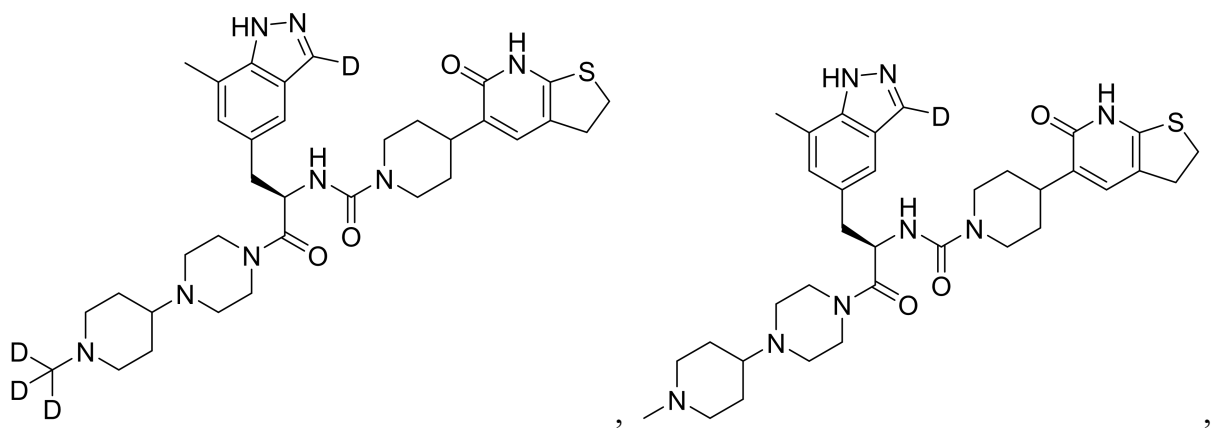
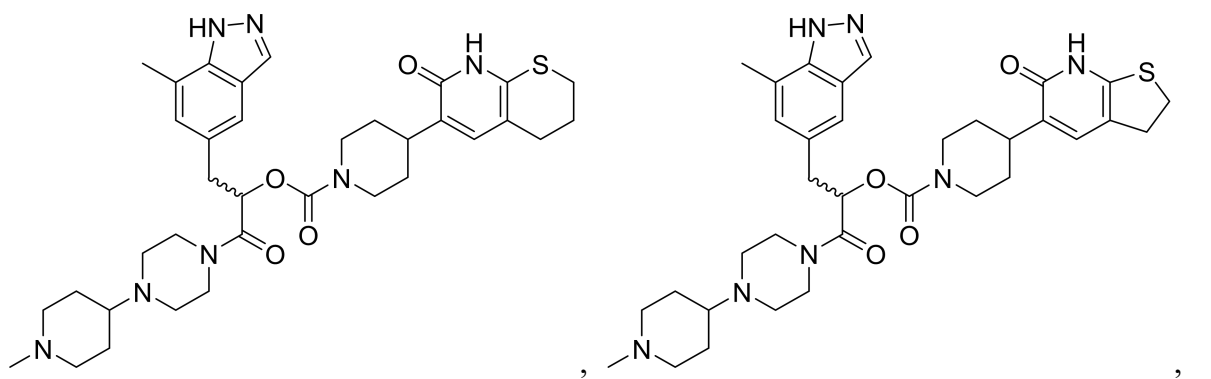
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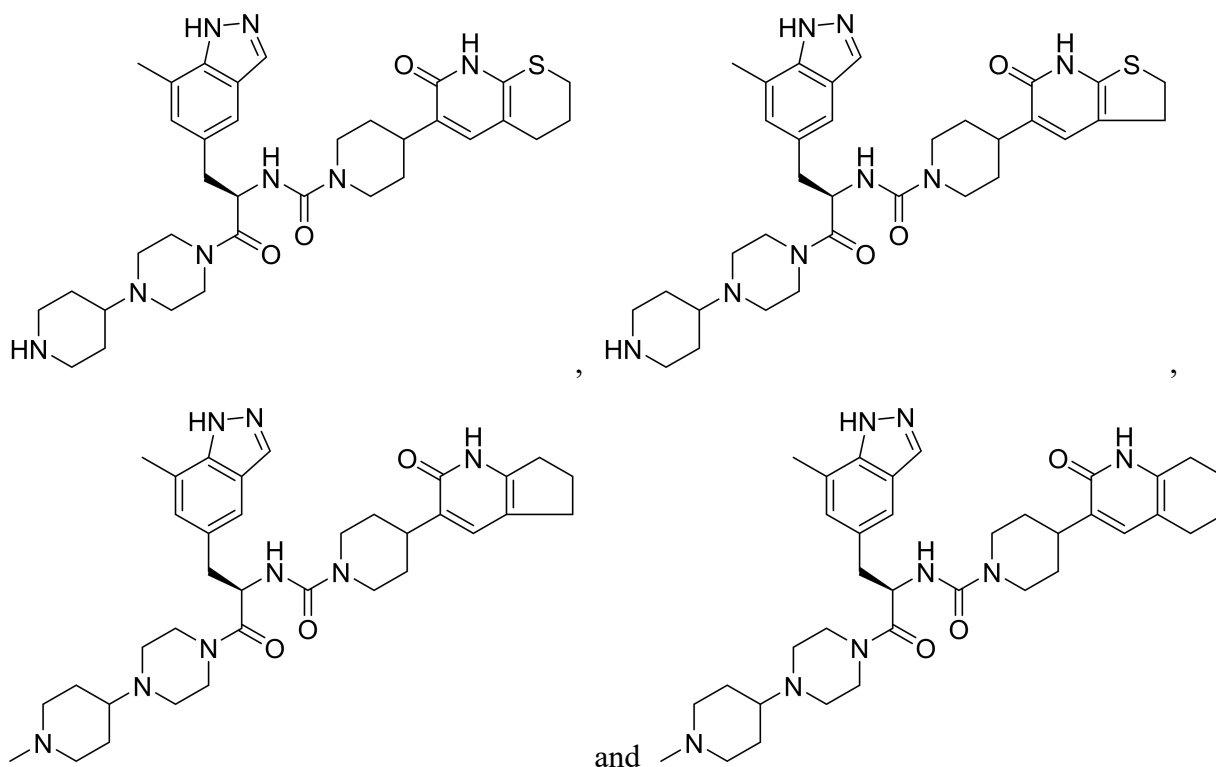


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22. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in a sterile or non-sterile form.

23. A preparation for nasal administration, comprising a CGRP antagonist and an alkyl glycoside, wherein,

the CGRP antagonist is selected from zavegepant, rimegepant, ubrogepant, atogepant, telcagepant, olcegepant, or an active ingredient in the pharmaceutical composition according to any one of claims 1 and 8 to 21.

24. The preparation for nasal administration according to claim 23, wherein:

the alkyl glycoside is mainly formed by covalently coupling a hydrophobic alkyl carbon chain and a hydrophilic oligosaccharide,

the covalently coupled linking group comprises a glycosidic bond, a thioglycosidic bond or an amide bond,

the hydrophobic alkyl carbon chain is selected from a C₅-C₁₆ alkyl chain, a C₁₀-C₁₆ alkyl chain, a C₁₁-C₁₄ alkyl chain, a C₁₁ alkyl chain, a C₁₂ alkyl chain, a C₁₃ alkyl chain or a C₁₄ alkyl chain, and

the hydrophilic oligosaccharide comprises a monosaccharide or a disaccharide, wherein the monosaccharide comprises glucose, and the disaccharide comprises maltose, trehalose or sucrose.

25. The preparation for nasal administration according to claim 23, wherein:

the alkyl glycoside is an undecyl maltoside, a dodecyl maltoside, a tridecyl maltoside or a tetradecyl maltoside, and

a weight percentage of the alkyl glycoside in the pharmaceutical composition is 0.05%-20%, 0.05%-10%, 0.05%-5%, 0.1%-5%, 0.1%-0.5%, 0.1%-0.3%, 0.05%, 0.2% or 5%.

26. A use of the pharmaceutical composition according to any one of claims 1 to 22 or the preparation for nasal administration according to any one of claims 23 to 25 in preparation of a drug for preventing, treating or alleviating a CGRP-mediated/regulated disease.

27. The use according to claim 26, wherein the disease comprises a migraine and a neuropathic pain.