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CA 2935494 C 2021/03/30

(11)(21) 2 935 494

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2014/12/29
(87) Date publication PCT/PCT Publication Date: 2015/07/09
(45) Date de délivrance/Issue Date: 2021/03/30
(85) Entrée phase nationale/National Entry: 2016/06/29
(86) N° demande PCT/PCT Application No.: CN 2014/095421
(87) N° publication PCT/PCT Publication No.: 2015/101265
(30) Priorité/Priority: 2013/12/30 (CN201310746752.8)

(51) Cl.Int./Int.Cl. *C07D 409/14* (2006.01), *A61K 31/454* (2006.01), *A61K 31/4545* (2006.01), *A61K 31/46* (2006.01), *A61P 31/18* (2006.01), *C07D 401/14* (2006.01), *C07D 451/04* (2006.01), *C07D 519/00* (2006.01)

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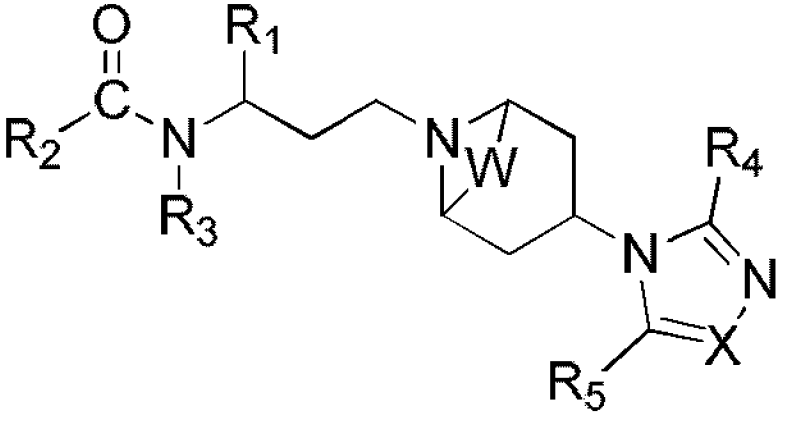
(54) Titre : COMPOSES D'AMINE CYCLIQUE SUBSTITUES EN 1-(3-AMINOPROPYL), PROCEDE DE PREPARATION ET COMPOSITIONS PHARMACEUTIQUES DE CES DERNIERS ET LEURS UTILISATIONS

(54) Title: 1-(3-AMINOPROPYL) SUBSTITUTED CYCLIC AMINE COMPOUNDS, PREPARATION METHOD THEREFOR, AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF



(I)

(57) Abrégé/Abstract:
Provided are 1-(3-aminopropyl) substituted cyclic amine compounds as represented by formula (I), pharmaceutically acceptable salts, enantiomers, diastereoisomers, racemates and mixtures thereof, and a method of synthesizing said 1-(3-aminopropyl) substituted cyclic amine compounds by using aromatic heterocyclic formaldehyde as raw material. Said compounds can be used as CCR 5 antagonist for the treatment of HIV infection.

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(11)(21) 2 935 494
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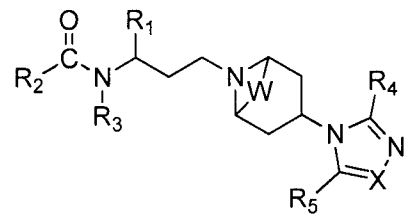
Abstract

Provided are 1-(3-aminopropyl) substituted cyclic amine compounds as represented by formula (I), pharmaceutically acceptable salts, enantiomers, diastereoisomers, racemates and mixtures thereof, and a method of synthesizing said 1-(3-aminopropyl) substituted cyclic amine compounds by using aromatic heterocyclic formaldehyde as raw material. Said compounds can be used as CCR 5 antagonist for the treatment of HIV infection.



(I)

1-(3-AMINOPROPYL) SUBSTITUTED CYCLIC AMINE COMPOUNDS, PREPARATION METHOD THEREFOR, AND PHARMACEUTICAL COMPOSITIONS AND USES THEREOF

Technical Field

The present invention relates to the field of pharmaceutical chemistry and pharmacotherapeutics, particularly to 1-(3-aminopropyl) substituted cyclic amine compounds, preparation method thereof, pharmaceutical compositions containing such compounds and uses thereof.

Background Art

AIDS, Acquired Immune Deficiency Syndrome, is such a Syndrome that humans are infected with human immunodeficiency virus, HIV, followed by immunodeficiency and a series of opportunistic infections and tumors are triggered, severe case of which can lead to death. According to the World Health Organization (WHO), there were 34 million HIV carriers and AIDS patients in the world in 2011, 2.7 million persons were newly infected and 1.8 million patients died. Chinese Center for Disease Control and Prevention estimated that there were 780000 HIV carriers and AIDS patients in China by the end of 2011, 48000 persons were newly infected and 28000 patients died. At present, China is facing high peak of AIDS morbidity and mortality.

At present, medicaments for treating AIDS in clinic are divided into following classes: reverse transcriptase inhibitors, including nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors; protease inhibitors; integrase inhibitors and entry inhibitors. Entry inhibitors can be divided into CCR5 antagonists, CXCR4 antagonists, adhesion inhibitors and fusion inhibitors according to different targets during the entry of HIV into host cells. So far the main therapy for the treatment of AIDS is highly active antiretroviral therapy (HAART) which advocates combination of several drugs acting on different stages of HIV replication to achieve effective anti-HIV effect. In the past decade, highly active antiretroviral therapy has largely reduced the mortality rate of HIV-infected patients. However, the dosage regimen of HAART is complex and drugs combination can

cause long-term severe side effects. Therefore, the development of anti-HIV drugs having new action mechanisms has very important significance.

Chemokines are a class of cytokines guiding directed migration of lymphocytes and have an important role in inflammation, tissue repair, immune surveillance, extravasation of white blood cells, tumorigenesis and embryonic development. Chemokines are proteins belonging to a small molecule cytokine family which currently have about 45 members. Their common features are that they have small molecular weight (about 8-10 kDa) and they contain four position-conserved cysteine (Cys) residues to ensure tertiary structure. According to whether other amino acid is contained between two Cys close to N-terminal, the family is divided into four categories: CC, CXC, CX3C and C chemokine. Wherein, CC chemokine and CXC chemokine are the most important two categories.

The functions of chemokine are mediated by chemokine receptor in vivo. Currently, chemokine receptor is named according to the characteristics of chemokine bound specifically (for example, if its ligand belongd to a CC chemokine subfamily, then it is named CCR). Chemokine receptors belong to the seven transmembrane G-protein coupled receptors (GPCR), are selectively expressed on the surface of target cells, wherein N-terminal thereof is outside the cell and C terminal is in the cell, and they contain seven very conservative transmembrane region consisting of α -helix. So far 19 chemokine receptors have been found. They are CCR1-11, CXCR1-6, XCR1, and CX3CR1. Modulators of chemokine receptor can be used in a variety of diseases, such as inflammatory or allergic diseases and the like.

Studies have shown that CD4 molecule on Th cell is essential for HIV invasion, but only CD4 is not enough to mediate fusion of HIV with cell. Further researches have found that chemokine receptors involve in the HIV invasion process and are known as HIV coreceptors. Coreceptors can be divided into two categories. One is coreceptor CCR5 distributed on the surface of macrophages and involved in entrance of macrophage tropism (M-tropism) HIV into host cells. The other is coreceptor CCR4 distributed on the surface of T cell and involved in entrance of T cell tropism (T-tropism) HIV into host cells. In the initial stages of infection, almost all HIV-1 subtypes use CCR5 as a coreceptor. Therefore, CCR5 plays a very important role in the HIV infection.

It has been found in experimennts in vitro that chemokine RANTES, MIP-1α and

MIP-1 β that can bind to CCR5 can inhibit HIV infection by inhibiting the M-tropism HIV from entering into cells. In the experiment, benign results were obtained bu knockouting gene expressing CCR5 in mice. However, some studies indicate that the immune function of mouse can be changed in some models. In 1996, it was reported that there are natural CCR5 gene-deficient homozygous individuals and such individuals can well protect themselves from HIV infection without any other health problems. Subsequently, it was found that compared with no CCR5 allele-deficient HIV-infected patients, heterozygous individuals with only one CCR5 allele can obviously delay the progression of AIDS. Therefore, CCR5 can be used as a good anti-HIV target.

Macromolecular CCR5 antagonist can bind specifically to the specific extracellular portion of CCR5 to produce inhibiting effects without major toxic effects, but it is unstable, easy to be digested and degraded, expensive, and can not be orally administrated nd even cause the body to produce antibody-induced immune response. Therefore, companies and research institutions have conducted a great deal of effective research on non-peptide small molecule CCR5 antagonist and developed a number of highly active small molecule CCR5 antagonists such as TAK-220, TBR652, Vicriviroc and Maraviroc (trade name Selzentry) approved for marketing by FDA in 2007.

In summary, there is an urgent need to develop compounds as CCR5 antagonist having potential drug use in the art.

Summary of the invention

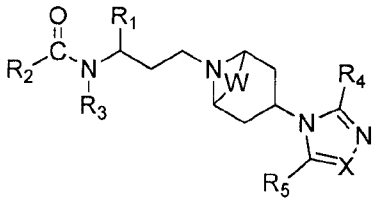
The object of the present invention is to provide 1-(3-aminopropyl) substituted cyclic amine compounds having CCR5 antagonist activity as represented by formula (I), pharmaceutically acceptable salts, enantiomers, diastereoisomers, racemates or mixtures thereof, and a method for synthesizing said 1-(3-aminopropyl) substituted cyclic amine compounds by using aromatic heterocyclic formaldehyde as raw material.

A further object of the present invention is to provide a pharmaceutical composition comprising the above compounds.

A further object of the present invention is to provide a use of above compound in the preparation of medicaments for the treatment of HIV infection.

In one aspect of the present invention, a 1-(3-aminopropyl) substituted cyclic amine

compound of formula (I), a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or a mixture thereof is provided:



I

Wherein,

W is absent or $-CH_2CH_2-$; X is N or CR_6;

R_1 is selected from a 5 to 7-membered heteroaryl unsubstituted or substituted with 1-3 substituents, wherein said heteroaryl contains 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen and each of said substituents is independently selected from a halogen, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkyloxy, a C1-C4 straight or branched haloalkoxy, $-NR_{10}R_{11}$, $-C(=O)R_{12}$, a C1-C4 straight or branched alkanoyloxy, a cyano, a nitro and a hydroxy, or two adjacent substituents together with the attached carbon atom form a 5-7 membered ring;

each of R_{10} and R_{11} is independently selected from a group consisting of H, a C1-C4 straight or branched alkyl and $-C(=O)R_{13}$;

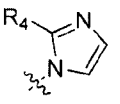
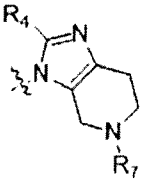
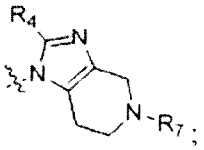
R_{12} is selected from a group consisting of a C1-C4 straight or branched alkyl, a C1-C4 straight or branched alkyloxy, a hydroxyl, an amino (NH_2) and a C1-C4 straight or branched alkylamino;

R_{13} is selected from a group consisting of H and a C1-C4 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a C1-C6 straight or branched alkyl, a C3-C7 cycloalkyl, a 4 to 7-membered heterocyclic group, a C6-C12 aryl or a 5-7 membered heteroaryl; wherein, said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkyloxy, a C1-C4 straight or branched alkyl carbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, a cyano, a nitro, an amino, a carboxy, a phenyl and a phenoxy;

each of R_3, R_4 and R_5 is independently selected from a group consisting of a hydrogen, a C1-C6 straight or branched alkyl and a C3-C7 cycloalkyl;

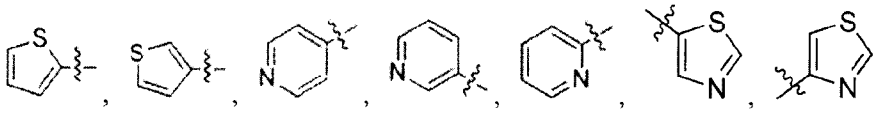
R_6 is selected from a group consisting of H and a C1-C6 straight or branched alkyl;

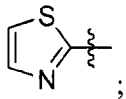
alternatively, R_5 and R_6 may bind together with  to form  or  ;

R_7 is selected from a group consisting of H, C(=O)R_8, C(=O)OR_8, C(=O)NR_8R_9, SO_2R_8 and the following groups substituted by 1-3 substituents: a C1-C6 straight or branched alkyl, a C3-C7 cycloalkyl, a 4 to 7-membered heterocyclic group, a benzyl, a C6-C12 aryl and a 5 to 7-membered heteroaryl; wherein said substituent is selected from a halogen, a hydroxy, a C1-C4 straight or branched alkyloxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino and a carboxyl;

each of R_8 and R_9 is independently selected from a group consisting of a hydrogen and the following groups unsubstituted or substituted with 1-3 substituents: a C1-C6 straight or branched alkyl, a C3-C7 cycloalkyl, a 4 to 7-membered heterocyclic group, a benzyl, a C6-C12 aryl and a 5-7 membered heteroaryl; wherein said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino, and a carboxyl.

In another preferred embodiment, 1-(3-aminopropyl) substituted cyclic amine compound of formula (I) is S configuration or R configuration, preferably, S configuration.

Preferably, R_1 is selected from the following groups unsubstituted or substituted with 1-3 substituents:  and

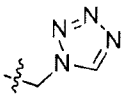
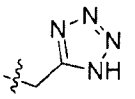
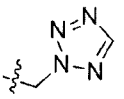
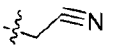

; said substituent is selected from a group consisting of a halogen, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, $-NR_{10}R_{11}$, $-C(=O)R_{12}$, a C1-C4 straight or branched alkylcarbonyloxy, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro and a hydroxyl, or two adjacent substituents together with the attached carbon atom form a 5-7 membered ring; preferably, the substituent is selected from a group consisting of a halogen, a C1-C2 alkyl, a C1-C2 haloalkyl, a C1-C2 alkoxy, $NR_{10}R_{11}$, $-C(=O)R_{12}$, a C1-C2 alkylcarbonyloxy, a C1-C2 haloalkoxy, a cyano, a nitro and a hydroxyl or two adjacent substituents together with the attached carbon atom form a 5-7 membered carbocycle, a 5-7 membered heteroaryl ring or a 5-7 membered heterocycle; and most preferably, the substituent is selected from a group consisting of a halogen, a methyl, a methoxy, an ethyl, an amino, a hydroxyl, a cyano, a nitro, an acetyl, a formamido, an acetamido, a carbamoyl, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, a formyloxy, an acetoxy, a methoxycarbonyl, a trifluoromethyl and a trifluoromethoxy, or two adjacent substituents together with the attached carbon atom form a benzene ring, a cyclopentene ring or dioxole ring.

Preferably, each of R_{10} and R_{11} is independently selected from a group consisting of H, a C1-C2 alkyl and $-C(=O)R_{13}$.

Preferably, R_{12} is selected from a group consisting of a C1-C2 alkyl, a C1-C2 alkoxy, a hydroxy, an amino (NH_2) and a C1-C2 alkylamino.

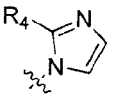
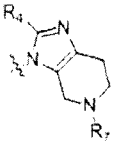
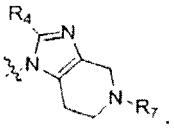
Preferably, R_{13} is selected from a group consisting of H and a C1-C2 straight or branched alkyl.

Preferably, R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group and a phenyl, wherein, said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, a cyano, a nitro, an amino, a carboxyl, a phenyl, a halophenyl, a phenoxy and a halophenoxy; more preferably, R_2 is

selected from a C1-C4 straight or branched alkyl, a cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclohexyl, a tetrahydropyran-4-yl, a 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,  ,  ,  ,  , 4-fluorobenzyl, a phenyl, a difluorocyclohexyl (preferably, 4,4-difluorocyclohexyl) (similarly hereinafter), ethylcyclohexyl and phenoxymethyl.

Preferably, each of R_3, R_4 and R_5 is independently selected from a group consisting of H, a C1-C4 straight or branched alkyl and a C3-C7 cycloalkyl; more preferably, each of R_3, R_4 and R_5 is independently selected from a group consisting of H, a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl, a tertiary butyl, a cyclopropyl, a cyclobutyl, a cyclopentyl and a cyclohexyl; most preferably, each of R_3, R_4 and R_5 is independently selected from a group consisting of H, a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl, a tert-butyl and a cyclopropyl.

Preferably, R_6 is selected from a group consisting of H and a C1-C4 straight or branched alkyl, more preferably, R_6 is selected from a group consisting of H, a methyl and an ethyl.

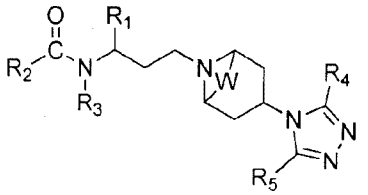
Alternatively, R_5 and R_6 can bind together with  to form  or  .

Preferably, R_7 is selected from a group consisting of H, $C(=O)R_8$, $C(=O)OR_8$, $C(=O)NR_8R_9$, SO_2R_8 and the following groups substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group, a benzyl and a phenyl, wherein, said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino and a carboxyl; more preferably, R_7 is selected from a group consisting of H, $C(=O)R_8$ and SO_2R_8;

each of R_8 and R_9 is independently selected from a group consisting of H and the

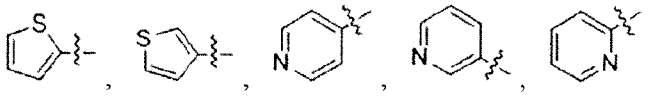
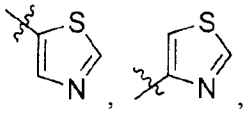
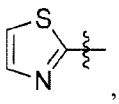
following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group, a benzyl, a phenyl and a 5-7 membered heteroaryl, wherein said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino and a carboxyl, preferably said substituent is selected from a group consisting of a halogen, a hydroxy, a methoxy, an ethoxy, a methyl, an ethyl, a trifluoromethyl, a trifluoromethoxy, a cyano, a nitro, an amino and a carboxyl; preferably, each of R_8 and R_9 is independently selected from a group consisting of H, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C3-C7 cycloalkyl, a benzyl and a phenyl; more preferably, each of R_8 and R_9 is independently selected from a group consisting of a methyl, an ethyl, an n-propyl, a cyclopropyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

In a preferable embodiment, a 1-(3-aminopropyl) substituted cyclic amine compound of formula (II), pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof is provided:



II

wherein the definitions of R_1, R_2, R_3, R_4, R_5 and W are described as those in formula (I).

In formula II, preferably, R_1 is selected from the following groups unsubstituted or substituted with 1-3 substituents:  ,  , and  , said substituent is selected from a group consisting of a halogen, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyloxy, a C1-C4 straight

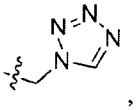
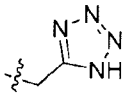
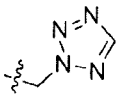
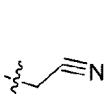
or branched haloalkoxy, $NR_{10}R_{11}$, $-C(=O)R_{12}$, a cyano, a nitro and a hydroxyl, or two adjacent substituents together with the attached carbon atom form a 5-7 membered ring; preferably, said substituent is selected from a group consisting of a halogen, a C1-C2 alkyl, a C1-C2 haloalkyl, a C1-C2 alkylcarbonyloxy, a C1-C2 alkoxy, a C1-C2 haloalkoxy, $NR_{10}R_{11}$, $-C(=O)R_{12}$, a cyano, a nitro and a hydroxyl, or two adjacent substituents together with the attached carbon atom form a 5-7 membered carbocycle, 5-7 membered heteroaryl ring or 5-7 membered heterocycle; most preferably, said substituent is selected from a group consisting of a halogen, a methyl, a trifluoromethyl, a trifluoromethoxy, a methoxy, an ethyl, an amino, a cyano, a nitro, an acetyl, a formamido, an acetamido, a carbamoyl, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, an acetoxy, a formyloxy and a methoxycarbonyl, or two adjacent substituents together with the attached carbon atom form a benzene ring, a cyclopentene ring or dioxole ring;

each of R_{10} and R_{11} is independently selected from a group consisting of H, a C1-C4 straight or branched alkyl and $-C(=O)R_{13}$; preferably, each of R_{10} and R_{11} is independently selected from a group consisting of H, a C1-C2 alkyl and $-C(=O)R_{13}$;

R_{12} is selected from a group consisting of a C1-C4 straight or branched alkyl, a C1-C4 straight or branched alkoxy, a hydroxy, an amino (NH_2) and a C1-C4 straight or branched alkylamino; preferably, R_{12} is selected from a group consisting of a C1-C2 alkyl, a C1-C2 alkoxy, a hydroxy, an amino (NH_2) and a C1-C2 alkylamino;

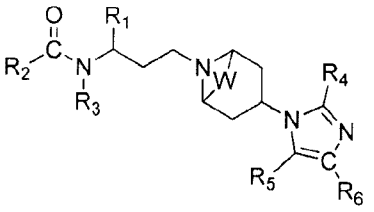
R_{13} is selected from a group consisting of H and a C1-C4 straight or branched alkyl; preferably, R_{13} is selected from a group consisting of H and a C1-C2 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a phenyl, a C1-C4 straight or branched alkyl and a C3-C7 cycloalkyl, wherein said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, an amino, a phenyl, a halophenyl, a phenoxy and a halophenoxy; more preferably, R_2 is selected from a group consisting of a methyl, an ethyl, a

cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclohexyl, tetrahydropyran-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1- methylsulfonylpiperidin-4-yl,  ,  ,  ,  , 4-fluorobenzyl, a phenyl, an ethylcyclohexyl and a difluorocyclohexyl;

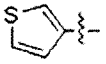
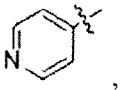
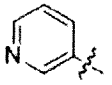
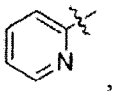
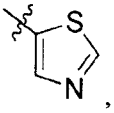
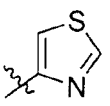
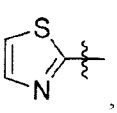
each of R_3, R_4 and R_5 is independently selected from a group consisting of H and a C1-C4 straight or branched alkyl; more preferably, each of R_3, R_4 and R_5 is independently selected from a group consisting of H, a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl; most preferably, each of R_3, R_4 and R_5 is independently selected from a group consisting of H, a methyl, an ethyl, an n-propyl, and an isopropyl.

In another preferable embodiment, a 1-(3-aminopropyl) substituted cyclic amine compound of formula (III), pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof is provided:



III

wherein the definitions of R_1, R_2, R_3, R_4, R_5, R_6 and W are described as thoese in formula I.

In formula III, preferably, R_1 is selected from the following groups unsubstituted or substituted with 1-3 substituents:  ,  ,  ,  ,  ,  ,  and  , said substituent is selected from a group consisting of a halogen, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkylcarbonyloxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight

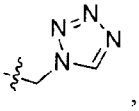
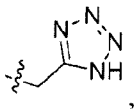
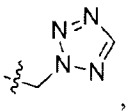
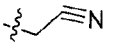
or branched haloalkoxy, $NR_{10}R_{11}$, $-C(=O)R_{12}$, a cyano, a nitro and a hydroxyl, or two adjacent substituents together with the attached carbon atom form a 5-7 membered ring; preferably, said substituent is selected from a group consisting of a halogen, a C1-C2 alkyl, a C1-C2 haloalkyl, a C1-C2 alkoxy, a C1-C2 alkylcarbonyloxy, a C1-C2 haloalkoxy, $NR_{10}R_{11}$, $-C(=O)R_{12}$, a cyano, a nitro and a hydroxyl, or two adjacent substituents together with the attached carbon atom form a 5-7 membered carbocycle, 5-7 membered heteroaryl ring or 5-7 membered heterocycle; most preferably, said substituent is selected from a group consisting of a halogen, a methyl, a trifluoromethyl, a trifluoromethoxy, a methoxy, an ethyl, an amino, a cyano, a nitro, an acetyl, a formamido, an acetamido, a carbamoyl, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, a formyloxy, an acetoxy and a methoxycarbonyl, or two adjacent substituents together with the attached carbon atom form a benzene ring, a cyclopentene ring or dioxole ring;

each of R_{10} and R_{11} is independently selected from a group consisting of H, a C1-C4 straight or branched alkyl and $-C(=O)R_{13}$; preferably, each of R_{10} and R_{11} is independently selected from a group consisting of H, a C1-C2 alkyl and $-C(=O)R_{13}$;

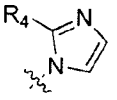
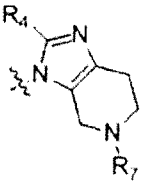
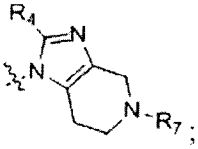
R_{12} is selected from a group consisting of a C1-C4 straight or branched alkyl, a C1-C4 straight or branched alkoxy, a hydroxy, an amino (NH_2) and a C1-C4 straight or branched alkylamino; preferably, R_{12} is selected from a group consisting of a C1-C2 alkyl, a C1-C2 alkoxy, a hydroxy, an amino (NH_2) and a C1-C2 alkylamino;

R_{13} is selected from a group consisting of H and a C1-C4 straight or branched alkyl; preferably, R_{13} is selected from a group consisting of H and a C1-C2 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl and a C3-C7 cycloalkyl, wherein said substituent is selected from a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, a cyano and an amino; more preferably, R_2 is selected from a group consisting of a methyl, an ethyl, a cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclohexyl, a tetrahydropyran-4-yl,

1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,  ,  ,  ,  and a difluorocyclohexyl;

each of R_3 and R_4 is independently selected from a group consisting of H and a C1-C4 straight or branched alkyl; more preferably, each of R_3 and R_4 is independently selected from a group consisting of H, a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl; most preferably, each of R_3 and R_4 is independently selected from a group consisting of H, a methyl and an ethyl;

R_5 and R_6 can bind together with  to form  or  ;

R_7 is selected from a group consisting of H, C(=O)R_8, C(=O)OR_8, C(=O)NR_8R_9 and SO_2R_8; more preferably, R_7 is selected from a group consisting of H, C(=O)R_8 and SO_2R_8;

each of R_8 and R_9 is independently selected from a group consisting of H and the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C3-C7 cycloalkyl and abenzyl, wherein said substituent is selected from a group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy and an amino; preferably said substituent is selected from a group consisting of a halogen, a hydroxy, a methoxy, an ethoxy, a methyl, an ethyl, a trifluoromethyl, a trifluoromethoxy and an amino; preferably, each of R_8 and R_9 is independently selected from a group consisting of H, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl and a C3-C7 cycloalkyl; more preferably, each of R_8 and R_9 is independently selected from a group consisting of a methyl, an ethyl, an n-propyl, a cyclopropyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

In another preferable embodiment, each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, W and X in the compound of formula I of the present invention independently and

preferably is the corresponding group in compounds 1-172 prepared in examples.

The definitions in the present invention are listed as follows: halogen includes F, Cl, Br and I; C3-C7 cycloalkyl refers to a cycloalkyl containing 3-7 carbon atoms on the ring, and includes (but not limited to) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C6-C12 aryl refers to a aromatic ring group containing 6-12 carbon atoms on the ring without heteroatom, and includes (but not limited to) phenyl and naphthyl; 4-7 membered heterocyclic group refers to a nonaromatic cyclic group containing 4-7 atoms and at least one heteroatom which is selected from O, N or S on the ring, and includes (but not limited to) azetidinyl, tetrahydrofuranyl, piperazinyl, morpholinyl and piperidinyl; 5-7membered heteroaryl refers to to an aromatic cyclic group containing 5-7 atoms and at least one heteroatom which is selected from O, N or S on the ring, and includes (but not limited to) thienyl, thiazolyl, pyridyl, furyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, pyrimidinyl and triazinyl. 5-7 membered ring refers to a ring containing 5-7 atoms on the ring with or without a heteroatom which is selected from O, N or S, and includes 5-7 membered carbocycle (saturated or unsaturated ring containing only carbon atoms), 5-7 membered heteroaryl ring (aromatic ring containing 5-7 atoms and at least one heteroatom which is selected from O, N or S on the ring), and 5-7 membered heterocycle (nonaromatic ring containing 5-7 atoms and at least one heteroatom which is selected from O, N or S on the ring), and includes (but not limited to) benzene ring, cyclopentene ring, cyclohexene ring, cycloheptene ring, dioxole ring and the like.

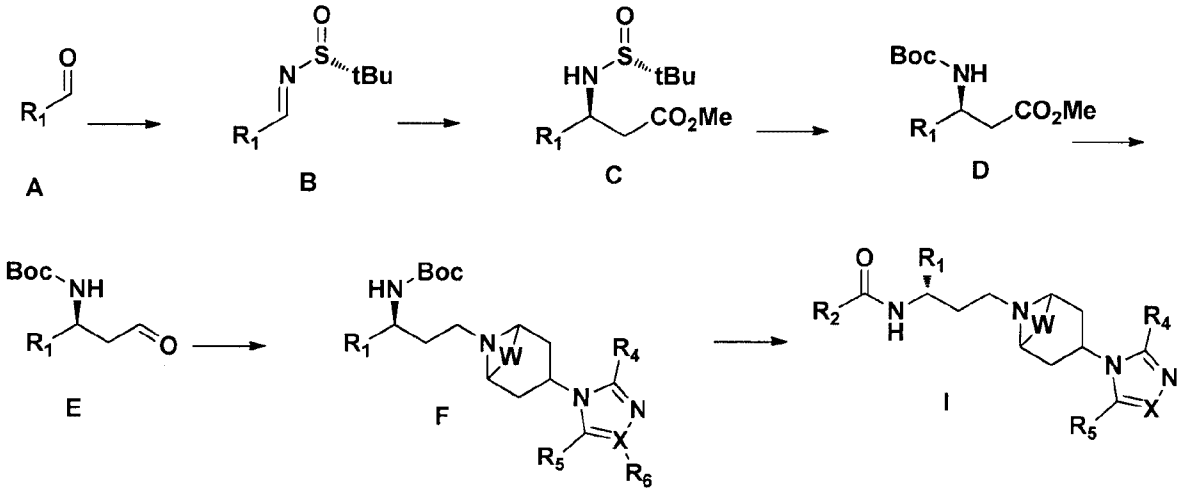
As used herein, the terms "aryl", "phenyl", "phenoxy", "heteroaryl", "heteroaromatic ring" and " heterocycle" include substituted or unsubstituted forms, wherein the substituted form may include, for example, 1 to 5 identical or different non-hydrogen substituents, and the representative substituent includes (but not limited to) C1-C4 alkyl, C3-C4 cycloalkyl, halogen (fluorine, chlorine, bromine or iodine), C1-C4 haloalkyl, or combinations thereof.

As used herein, the term "C1-C4 straight or branched alkylamino" includes mono- or di-substituted amino, and for di-substituted amino, alkyl substituents can be identical or different. Representative example includes (but not limited to) $-NH(CH_3)$, $-N(CH_3)_2$, $-N(CH_3)(C_2H_5)$.

In particular, 1-(3-aminopropyl) substituted cyclic amine compounds according to the

present invention are preferably selected from any one of Compound 1-Compound 172 prepared in the Examples or pharmaceutically acceptable salts thereof.

In another acpect of the present invention, a method for preparing the 1-(3-aminopropyl) substituted cyclic amine compound of formula I is provided . The compound is prepared by using substituted pyridylaldehyde or substituted thiophene carboxaldehyde as raw material through step-wise Mannich reaction, removal of sulfinyl, BOC protection, ester reduction, oxidation, reductive amination, deprotection and condensation reaction. The method is carried out through the following process, wherein R_1, R_2, R_4, R_5, R_6, X and W are defined as described above.



1) Sulfinylimine Compound B is obtained from Compound A through imidization.

As an example, compound A is dissolved in tetrahydrofuran, substituted tetrahydrofuran, methylene chloride or diethyl ether and stirred at room temperature, to which was sequentially added (R)- tert-butyl sulfinamide and tetraethyl titanate. After reacting for 3-6 hours under nitrogen protection, water is added and the filtrate is obtained through filtration. Sulfinylimine compound B is obtained by organic solvent extraction and column chromatography separation.

2) Compound C is obtained from Sulfinylimine compound B through Mannich reaction.

As an example, N,N-diisopropylethylamine or triethylamine is dissolved in tetrahydrofuran, substituted tetrahydrofuran, methylene chloride or diethyl ether at -20-0°C, n-butyl lithium solution in hexane is added dropwise slowly under nitrogen. After reacting for

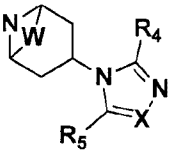
30 to 120 minutes, the mixture is cooled to -78°C and methyl acetate is added. After reacting for 30 to 120 minutes, a solution of chlorotitanium triisopropoxide is added. After reacting for 30 to 60 minutes, compound B is added. After reacting for 3-6 hours, the reaction is quenched with saturated ammonium chloride solution. The filtrate is obtained through filtration. Compound C is obtained by organic solvent extraction and column chromatography separation.

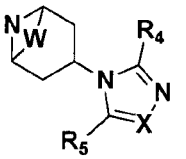
3) Compound D is obtained from Compound C through removal of sulfinyl and BOC protection.

As an example, compound C is dissolved in methanol or ethanol, and an acid solution is added and stirred for 2-5 hours at room temperature. Upon concentration, the mixture is dissolved in dichloromethane or ethyl acetate, a base and di-tert-butyl dicarbonate are added and stirred for 2-5 hours at room temperature. The system is concentrated, extracted with an organic solvent and separated by column chromatography to give compound D.

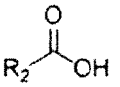
4) Compound E is obtained from Compound D through ester reduction and oxidation.

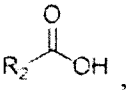
As one example, compound is dissolved in tetrahydrofuran, substituted tetrahydrofuran or diethyl ether at 0-20 °C, and a solution of lithium aluminum hydride is slowly added dropwise and stirred for 2-4 hours at room temperature. The reaction is quenched with water, washed with a basic solution and filtered. The organic phase is washed with saturated brine, dried and concentrated. The concentrate is dissolved in dichloromethane, and Dess-Martin periodinane (DMP) is added and stirred for 0.5-6 hours. A saturated solution of sodium bicarbonate is added, and compound E is obtained by the organic solvent extraction and column chromatographic separation.

5) Compound F is obtained from Compound E and compound  through reductive amination reaction.

As an example, compound E is dissolved in tetrahydrofuran, dichloromethane or 1,2-dichloroethane, and  and triacetoxy sodium borohydride are added and

stirred for 8-16 hours at room temperature. Water is added, and the mixture is extracted with an organic solvent and separated by column chromatography to give compound F.

6) Compound F is subjected to deprotection and condensation reaction with  to give compound I.

As an example, compound F is dissolved in methanol or ethanol, and acid solution is added and stirred for 2-5 hours at room temperature. The reaction mixture is concentrated and dissolved in N,N-dimethylformamide. A base,  , condensing agent such as benzotriazole-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP) or 1-ethyl-(3-dimethylaminopropyl) carbodiimide hydrochloride salt (EDCI) etc. are added successively and stirred at room temperature for 8-16 hours. Water is added, and the mixture is extracted with an organic solvent and separated by column chromatography to give compound I.

In above method, the acid used in each step may be an organic or inorganic acid, the organic acid may be acetic acid, trifluoroacetic acid, formic acid, and the inorganic acid may be hydrogen chloride, sulfuric acid or phosphoric acid; the base may be inorganic or organic bases, the inorganic base is selected from a group consisting of sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium phosphate, monopotassium phosphate, sodium hydroxide, lithium hydroxide and potassium hydroxide, and the organic base is selected from a group consisting of triethylamine, pyridine, diazabicyclo (DBU) and N,N-diisopropylethylamine (of DIPEA); the organic solvent may be selected from a group consisting of tetrahydrofuran (THF), acetonitrile, acetone, 1,4-dioxane, alcohols, diethyl ether, N,N-dimethylformamide, ethylene glycol dimethyl ether, N,N-dimethylformamide (DMF) and dimethylsulfoxide (DMSO); and the condensing agent used in step 6) may be 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), benzotriazole-1-yl oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), 2-(7-azobenzotriazole)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or N,N'-dicyclohexyl carbodiimide (DCC) and the like.

In another aspect of the invention, a pharmaceutical composition is provided comprising

the 1-(3-aminopropyl) substituted cyclic amine compounds according to the present invention, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof and optionally a pharmaceutically acceptable carrier. The pharmaceutical composition may be used in therapy *in vivo* and has biocompatibility. The pharmaceutical composition may be prepared into various forms depending on different route of administration. The pharmaceutical composition of the present invention may be used as CCR5 antagonist for treating HIV infection.

The pharmaceutical composition of the present invention may be provided in various forms, such as tablet, capsule, powder, syrup, solution, suspension, aerosol etc., and may be present in a suitable solid or liquid carrier or diluent and suitable disinfectant container for injection or infusion. The pharmaceutical composition may also comprise odor, flavor, etc., and a desirable ratio is that the compound of formula I as active ingredient accounts for 65% or more based on the total weight, and the rest accounts for 0.5-40%, preferably 1-20%, or preferably is 1 to 10% of a pharmaceutically acceptable carrier, diluent or solution or a salt solution.

The compound according to the present invention as described above may be clinically used to mammals including humans and animals by mouth, nose, skin, lung, or gastrointestinal tract, etc., and more preferably by mouth. Daily dose is preferably 0.01-200 mg/kg body weight, administered at once, or 0.01-100 mg/kg body weight in divided doses. No matter what administration method, optimal dose for an individual should be determined based on the specific treatment. Under normal conditions, a small dose is given at the beginning and the dose is gradually increased until the most suitable dose is found.

In another aspect of the invention, a use of 1-(3-aminopropyl) substituted cyclic amine compound according to the present invention, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof in the preparation of CCR5 antagonist is provided.

In a further aspect of the present invention, a use of 1-(3-aminopropyl) substituted cyclic amine compound according to the present invention, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof in the preparation of a medicament for treating CCR5-mediated disease is provided.

In a further aspect of the present invention, a use of 1-(3-aminopropyl) substituted cyclic amine compound according to the present invention, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof in the preparation of a medicament for treating HIV infection is provided.

In a further aspect of the present invention, a method for treating the disease mediated by CCR5 is provided, which comprises administering 1-(3-aminopropyl) substituted cyclic amine compound of the present invention, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof or a pharmaceutical composition containing one of 1-(3-aminopropyl) substituted cyclic amine compound according to the present invention, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof to a patient in need thereof. In an embodiment, the disease mediated by CCR5 is HIV infection.

Detailed description

The present invention will be further illustrated by the following examples. These examples are intended to illustrate the present invention, but not limit the invention in any way. Unless otherwise stated, all parameters as well as the rest of the description in examples are based on weight.

For the experimental methods in the following examples without particular conditions, they are performed under routine conditions, such as conditions described in Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Laboratory Press, 1989, or as instructed by the manufacturer.

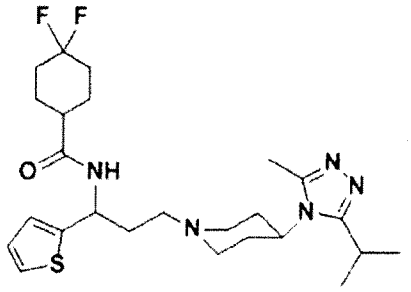
Analysis data of the samples were measured by the following instruments. NMR was measured by GEMINI-300, Bruker AMX-400 and INVOA-600 nuclear magnetic resonance, wherein, TMS (tetramethylsilane) was used as an internal standard, the chemical shift unit was ppm, and coupling constant unit was Hz. Mass spectra was measured by Finnigan MAT-711, MAT-95 and LCQ-DECA mass spectrometer and IonSpec4.7 Tesla mass spectrometer.

Column chromatography was carried out on 200-300 mesh silica gel (Qingdao Marine Chemical Plant). TLC silica gel plate was HSGF-254 thin layer chromatography prefabricated panel produced by Yantai Chemical Plant. The boiling range of petroleum ether was 60-90 ^{o}C.

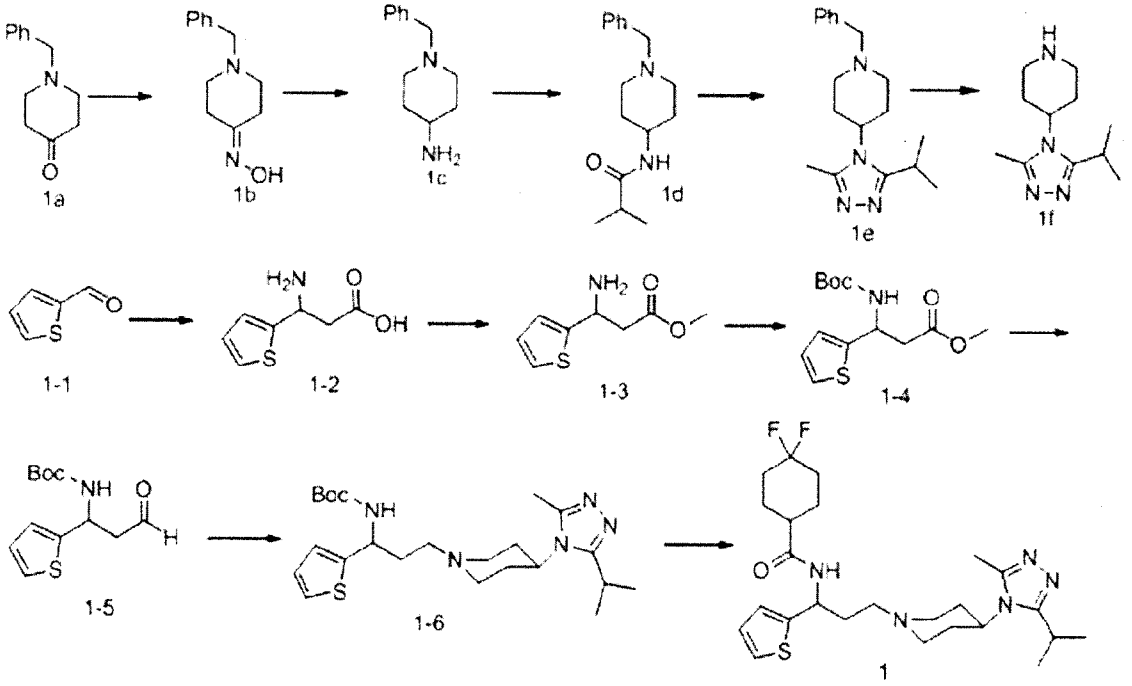
UV light was used and iodine cylinder was used for development. Unless otherwise indicated, the conventional reagents and pharmaceuticals used in the following examples were purchased from Sinopharm. The reagents and solvents used in the experiments are processed according to specific conditions.

Example 1: Synthesis of compound 1

4,4-difluoro-N-[3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophe n-2-yl)propyl]cyclohexane-1-carboxamide



synthesis route:



Synthesis of compound 1b:

compound 1a (1.89 g, 10 mmol) was dissolved in 50mL of absolute ethanol, and potassium carbonate (2.76 g, 20 mmol) and hydroxylamine hydrochloride (1.04 g, 15 mmol) were added successively and stirred at room temperature for 6 hours. After the mixture was concentrated, water was added. Then the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give white solids 1b (2.04 g, yield 100%), MS: 205.0 [M+H]+.

Synthesis of compound 1c:

Compound 1b (2.04 g, 10 mmmol) was dissolved in 50mL of anhydrous n-amyl alcohol and stirred at reflux, to which was added sodium (2.76 g, 120 mmol) in batches. The reaction was maintained for 2.5 hours. Then the reaction mixture was cooled, adjusted with 1M hydrochloric acid to PH 12 and extracted with water. The combined aqueous phase was adjusted with 1M sodium hydroxide to PH 8. Then the mixture was extracted by ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give colourless liquid 1c (1.71g, yield 90%), MS: 191.0[M+H]+.

Synthesis of compound 1d:

Compound 1c (1.90 g, 10 mmmol) was dissolved in 30mL of dichloromethane, and sodium carbonate (1.59g, 15mmol) was added and stirred at room temperature. Isobutyryl chloride (1.6 g, 15 mmol) was slowly added dropwise and the reaction was maintained for 2 hours. Then the reaction mixture was extracted by dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give white solids 1d (2.60 g, yield 100%), MS: 191.0 [M + H] +.

Synthesis of compound 1e:

Compound 1d (1.30g, 5mmmol) was dissolved in 20 mL of dichloromethane and phosphorous pentachloride (1.248g, 5mmmol) was slowly added under ice-bath and stirred for 2 hours at room temperature. Then 5 mL of t-amyl alcohol and acetic hydrazide (0.74g, 10mmol) were added and stirred for 16 hours at room temperature. The mixture was concentrated and redissolved in 10 mL toluene and 10 mL dioxane. Then 32 mg p-toluenesulfonic acid was added. The reaction was refluxed for 5 hour and water was added. The mixture was adjusted to pH 8, extracted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate and separated by column chromatography to give

white solids 1e (0.99g, yield 67%), MS: 299.0[M+H]+.

Synthesis of compound 1f:

Compound 1e (0.507g, 1.7mmol) was dissolved in 10 mL methanol and 20% palladium hydroxide (0.14g, 0.7mmol) and ammonium formate (0.535g, 8.5mmol) were added. The reaction mixture was stirred at reflux for 2.5 hours and then filtered. The reaction solution was concentrated and separated by column chromatography to give white solids 1f (0.336g, yield 95%), MS: 209.0[M+H]+.

Synthesis of compound 1-2:

Compound 1-1 (2.00g, 17.83mmol) was dissolved in 5.5mL of ethanol, to which was successively added ammonium acetate (2.74g, 35.58mmol) and malonic acid (1.85g, 17.78mmol). The reaction was kept with stirring and refluxed for 7 hours. White turbidity appeared in the clear reaction solution. Then the reaction mixture was filtered and washed with hot ethanol (3 x 10 mL) to give white solids 1-2 (2.20g, yield 72%), MS: 172.0 [M + H] +.

Synthesis of compound 1-3:

At room temperature, thionyl chloride (4.0 mL) was slowly added dropwise to a solution of 1-1 (8.55 g, 50.0 mmol) in anhydrous methanol (30.0 mL) with stirring, and the reaction was stirred at reflux for 16 hours. Analysis showed that the reaction was completed. Then the reaction mixture was concentrated and saturated potassium carbonate was added to the residue to adjust PH to 8. Then the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give white solids 1-3 (8.78 g, yield 95%), MS: 185.9[M+H]+.

Synthesis of compound 1-4:

Coumpound 1-3 (6.72g, 36.4mmol) was dissolved in 50 mL methanol, triethylamine (7.6mL, 54.6mmol) and di-tert-butyl dicarbonate (11.9g, 54.6mmol) were added successively and stirred at room temperature for 3 hours. The system was concentrated, extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated to give a colorless oily product 1-4 (10.16 g, yield 98%), MS: 286.1[M+H]+.

Synthesis of compound 1-5:

Under ice-bath, compound 1-4 (285 mg, 1 mmol) was dissolved in 5 mL of anhydrous tetrahydrofuran, and 1.0 M solution of lithium aluminum hydride (1.1 mL, 1.1 mmol) was slowly added dropwise. The mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with water, and the mixture was washed with 15% sodium hydroxide aqueous solution and filtered. Then the organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated to give a colorless oily liquid. The colorless oily liquid was dissolved in dichloromethane (5mL), and Dess-Martin periodinane (466.4 mg, 1.1 mmol) was added and stirred for 2 hours. Then saturated sodium bicarbonate solution was added, and the mixture was extracted with dichloromethane, successively washed with saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give colorless oily liquid 1-5 (156mg, yield 61%), MS: 256.1[M+H]+.

Synthesis of compound 1-6:

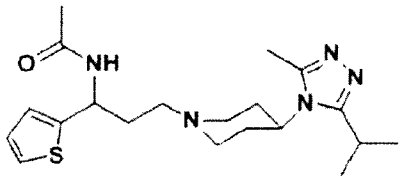
Compound 1-5 (512 mg, 2 mmol) was dissolved in 5mL of dichloromethane, and compound 1f (468 mg, 2 mmol) and triacetoxy sodium borohydride (466 mg, 2.2 mmol) were successively added and stirred for 12 hours at room temperature. Water was added, and then the mixture was extracted by dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, concentrated, and separated by column chromatography to give a pale yellow oily liquid 1-6 (664 mg, yield 70%), MS: 474.3[M+H]+.

Synthesis of compound 1:

Compound 1-6 (47.4 mg, 0.1 mmol) was dissolved in 1mL of methanol, and 1mL solution of HCl in dioxane (4M) was added and stirred for 2 hours at room temperature. The reaction mixture was concentrated, dissolved in 1mL N,N-dimethylformamide, followed by adding triethylamine (28 μL, 0.2 mmol), 4,4-difluoro-cyclohexanecarboxylic acid (18 mg, 0.11 mmol), benzotriazole-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate salt (BOP) (46.4 mg, 0.11 mmol) and stirred for 12 hours at room temperature. Water was added, then the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give white solids 1 (25.6 mg, yield 52%), MS: 494.3[M+H]+. ^{1}H-NMR (400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.11 (d, 1H), 6.97 (d, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s,

3H), 2.43 (m,2H), 2.26-1.99 (m,10H), 1.99-1.61 (m, 9H), 1.34 (d, 6H).

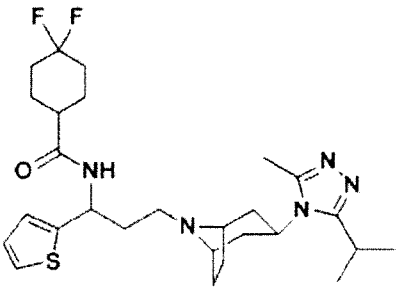
Example 2: Synthesis of compound 2

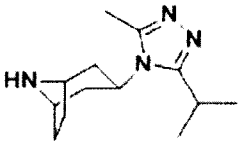


N-[3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-2-yl)propyl]acetamide

According to the synthesis method of Example 1, acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 1 to obtain compound 2. MS: 390.2[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.26 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.10 (m, 1H), 2.51 (s, 3H), 2.43 (m,2H), 2.20-1.69 (m,14H), 1.35 (d, 6H).

Example 3: Synthesis of compound 3





2f

4,4-difluoro-N-[3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl]cyclohexane-1-carboxamide

Synthesis of compound 2f

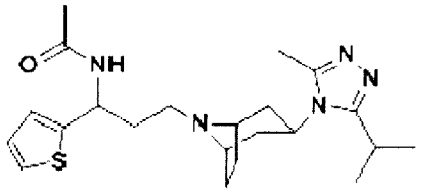
According to the synthesis method of compound 1f in Example 1, N- benzyltropinone was used to replace 1a in Example 1 to obtain compound 2f.

Synthesis of compound 3

According to the synthesis method of Example 1, compound 2f was used to replace 1f in Example 1 to obtain compound 3, MS: 520.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (t, 1H), 7.14 (d, 1H), 6.95 (d, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,2H), 2.27-1.93 (m,12H), 1.93-1.62 (m, 9H), 1.32 (d, 6H).

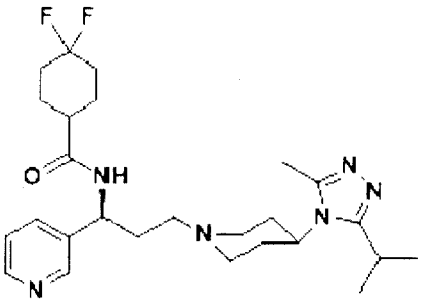
Example 4: Synthesis of compound 4

N-[3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl]acetamide



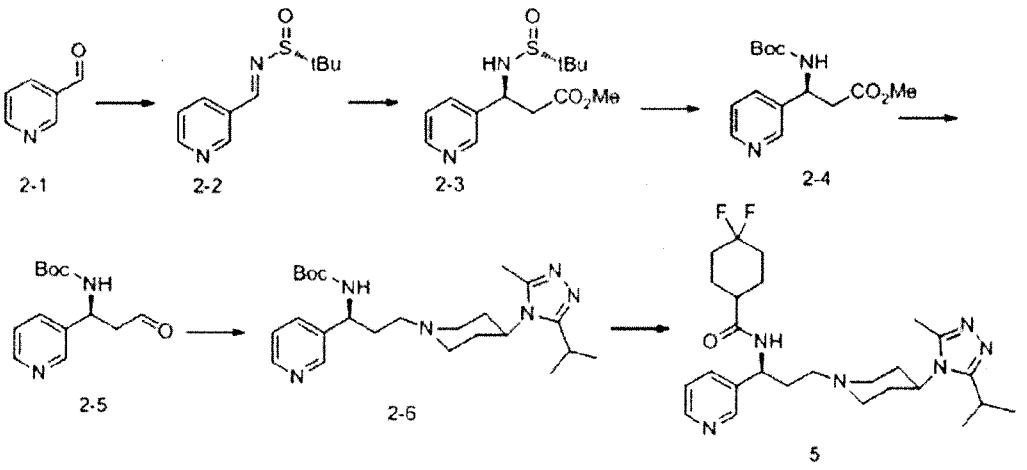
According to the synthesis method of Example 1. Acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 1 and compound 2f was used to replace 1f in Example 1 to obtain compound 4, MS: 416.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.03 (m, 1H), 2.54 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

Example 5: Synthesis of compound 5



4,4-difluoro-N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(pyridin-3-yl)propyl]cyclohexane-1-carboxamide

synthesis route:



Synthesis of compound 2-2:

Compound 2-1 (1.07g, 10mmol) was dissolved in tetrahydrofuran (20mL) and stirred at room temperature, to which was sequentially added (R)-tert-butyl sulfinamide (1.33g, 11mmol) and tetraethyl titanate (4.56 g, 20mmol). Under nitrogen, the reaction was carried out for 3 hours. Then water was added, the mixture was filtered and the filtrate was extracted with ethyl acetate, washed with aturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give a colorless liquid 2-2 (1.94g, yield 92%), MS: 211.2[M+H]+.

Synthesis of compound 2-3:

At 0°C, N,N-diisopropylamine (1.13 mL, 8 mmol) was dissolved in 10 mL of tetrahydrofuran and 2.4 M n-butyl lithium solution (3.3 mL, 8 mmol) was slowly added dropwise under nitrogen. After reacting for 30 minutes, the mixture was cooled to -78 °C. Methyl acetate (0.58 g, 8 mmol) was added and reacted for 45 minutes. 2M solution of titanium triisopropoxide chloride (8 mL, 16 mmol) was added and reacted for 30 minutes. Then compound 2-2 (0.84 g, 4 mmol) was added and reacted for 3 hours. The reaction was quenched with saturated ammonium chloride solution, the mixture was filtered. The filtrate was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated and separated by column chromatography to give colourless liquid 2-3 (0.87 g, yield 74%), MS: 286.2[M+H]+.

Synthesis of compound 2-4:

Compound 2-3 (2.85g, 10mmol) was dissolved in 20 mL of methanol, and 10 mL of 4 M

HCl in dioxane was added and stirred for 2 hours at room temperature. The reaction mixture was concentrated, and then triethylamine (2.8mL, 20mmol) and di-tert-butyl dicarbonate (3.26g, 15mmol) were successively added and stirred at room temperature for 3 hours. The system was concentrated, extracted with ethyl acetate, washed with saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give the product 2-4 (2.43g, yield 87%) as a colorless oil, MS: 281.1[M+H]+.

Synthesis of compound 2-5:

Under ice-bath, compound 2-4 (280 mg, 1 mmol) was dissolved in 5 mL of dry tetrahydrofuran, 1.0 M solution of lithium aluminum hydride (1.1mL, 1.1mmol) was slowly added dropwise and then the mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with water, washed with 15% aqueous solution of sodium hydroxide and filtered. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give a colorless oily liquid. The colorless oily liquid was dissolved in dichloromethane (5 mL), and then Dess-Martin periodinane (466.4 mg, 1.1 mmol) was added and stirred for 2 hours. Then saturated sodium bicarbonate solution was added, and the mixture was extracted with dichloromethane, successively washed with saturated sodium bicarbonate solution and saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give a colorless oily liquid 2-5 (158 mg, yield 63%), MS: 251.1[M+H]+.

Synthesis of compound 2-6:

Compound 2-5 (502 mg, 2 mmol) was dissolved in 5 mL of dichloromethane, and compound 1f (468 mg, 2 mmol) and sodium triacetoxyborohydride (466 mg, 2.2 mmol) were successively added and stirred for 12 hours at room temperature. Water was added, and then the mixture was extracted with dichloromethane, washed with saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give a pale yellow oily liquid 2-6 (686 mg, yield 71%), MS: 469.3[M+H]+.

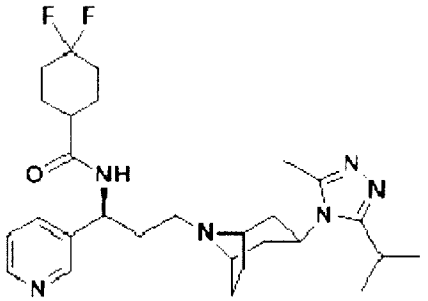
Synthesis of compound 5:

Compound 2-6 (46.8 mg, 0.1 mmol) was dissolved in 1mL of methanol, and then 1 mL of 4 M HCl in dioxane was added and stirred for 2 hours at room temperature. The mixture

was concentrated and then dissolved in 1mL N,N-dimethylformamide, followed by successively adding triethylamine (28 μL, 0.2 mmol), 4,4-difluoro-cyclohexanecarboxylic acid (18 mg, 0.11 mmol), benzotriazol-1-yloxy-tris (dimethylamino) phosphonium hexafluorophosphate salt (BOP) (46.4 mg, 0.11 mmol). The mixture was stirred for 12 hours at room temperature, and then water was added. The mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography (DCM:CH_3OH = 8:1) to give white solids 5 (27.7 mg, yield 57%), MS: 89.3[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.58 (s, 1H), 8.38 (d, 1H), 7.81 (d, 1H), 7.37 (t, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.43 (m,2H), 2.26-1.99 (m,10H), 1.99-1.61 (m, 9H), 1.34 (d, 6H).

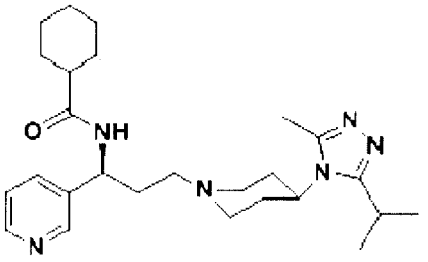
Example 6 Synthesis of compound 6

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(pyridin-3-yl)propyl]cyclohexane-1-carboxamide



According to the synthesis method of Example 5, compound 2f was used to replace 1f in Example 5 to obtain compound 6, MS: 514.9[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.57 (s, 1H), 8.39 (d, 1H), 7.80 (d, 1H), 7.37 (t, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.43 (m,2H), 2.27-1.96 (m,12H), 1.96-1.60 (m, 9H), 1.34 (d, 6H).

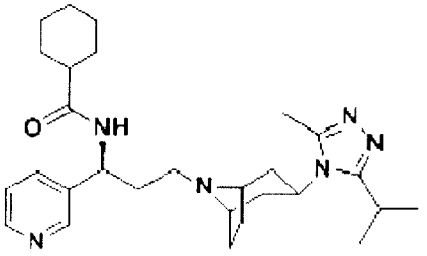
Example 7 Synthesis of compound 7



N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(pyridin-3-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 7, MS: 453.0[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.59 (s, 1H), 8.37 (d, 1H), 7.80 (d, 1H), 7.35 (t, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.43 (m,2H), 2.26-1.99 (m,11H), 1.99-1.61 (m, 10H), 1.34 (d, 6H).

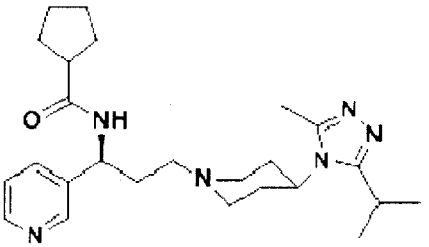
Example 8 Synthesis of compound 8



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(pyridin-3-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Eexample 5, Compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in example 5 to obtain compound 8, MS: 479.0[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.59 (s, 1H), 8.48 (d, 1H), 7.86 (d, 1H), 7.38 (t, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.43 (m,2H), 2.27-1.96 (m,12H), 1.96-1.60 (m, 11H), 1.34 (d, 6H).

Example 9 Synthesis of compound 9

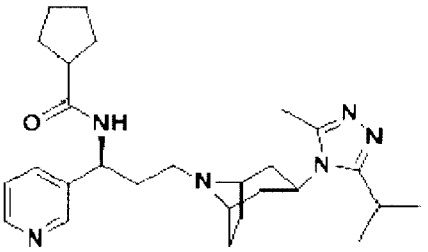


N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(pyridin-3-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, cyclopentanecarboxylic acid was used

to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 9, MS: 439.0[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.59 (s, 1H), 8.37 (d, 1H), 7.80 (d, 1H), 7.35 (t, 1H), 5.18 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.53 (s, 3H), 2.40 (m,2H), 2.25-1.97 (m,10H), 1.97-1.60 (m, 9H), 1.33 (d, 6H).

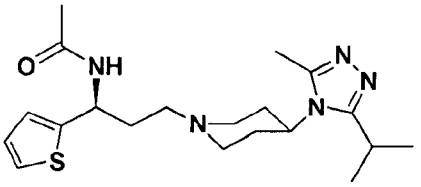
Example 10 Synthesis of compound 10



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(pyridin-3-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 10, MS: 464.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.59 (s, 1H), 8.48 (d, 1H), 7.86 (d, 1H), 7.38 (t, 1H), 5.16 (m,1H), 3.93 (m, 1H), 3.07 (m, 1H), 2.45 (s, 3H), 2.42 (m,2H), 2.27-1.96 (m,12H), 1.96-1.61 (m, 9H), 1.35 (d, 6H).

Example 11 Synthesis of compound 11

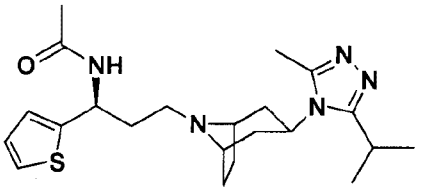


N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-2-yl)propyl]acetamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5 and acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 11, MS: 390.2[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.26 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.10 (m, 1H), 2.51 (s, 3H), 2.43 (m,2H), 2.20-1.69 (m,14H), 1.35 (d,

6H).

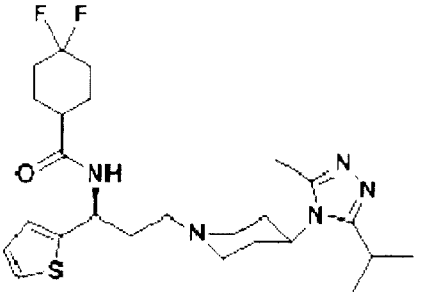
Example 12 Synthesis of compound 12



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl]acetamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 12, MS: 416.2[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.03 (m, 1H), 2.54 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

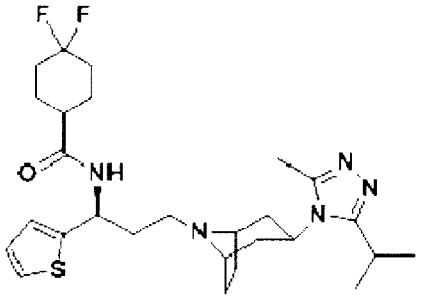
Example 13 Synthesis of compound 13



4,4-difluoro-N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, compound 1-1 was used to replace compound 2-1 in Example 5 to obtain compound 13, MS: 493.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (t, 1H), 7.13 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

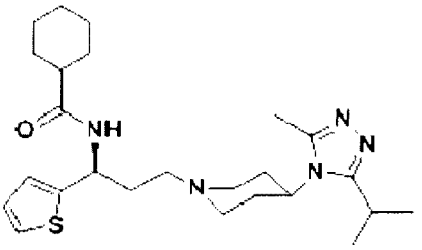
Example 14 Synthesis of compound 14



4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 14, MS: 520.0[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (t, 1H), 7.14 (d, 1H), 6.95 (d, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,2H), 2.27-1.93 (m,12H), 1.93-1.62 (m, 9H), 1.32 (d, 6H).

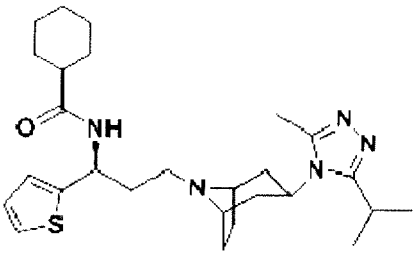
Example 15 Synthesis of compound 15



N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexane carboxylic acid in Example 5 to obtain compound 15, MS: 457.9[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,12H), 1.93-1.61 (m, 9H), 1.36 (d, 6H).

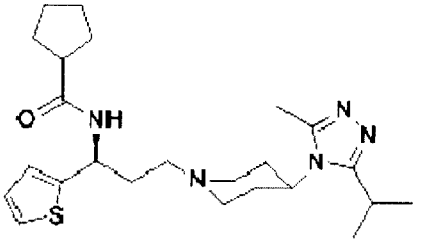
Example 16 Synthesis of compound 16



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-[(thiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 16, MS: 483.9[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

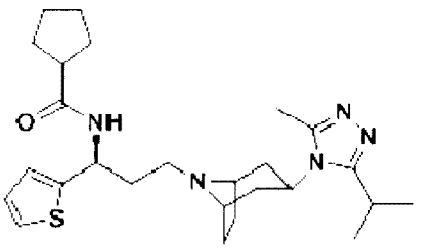
Example 17 Synthesis of compound 17



N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexane carboxylic acid in Example 5 to obtain compound 17, MS: 443.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (t, 1H), 7.13 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.01 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.33 (d, 6H).

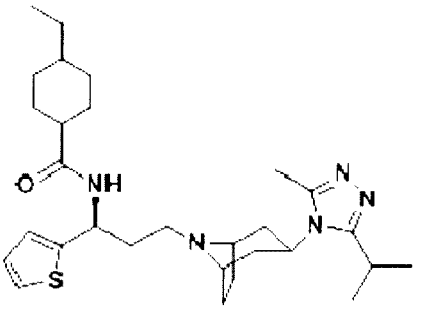
Example 18 Synthesis of compound 18



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5. Compound 1-1 was used to replace compound 2-1 in example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 18, MS: 469.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.25 (t, 1H), 7.13 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

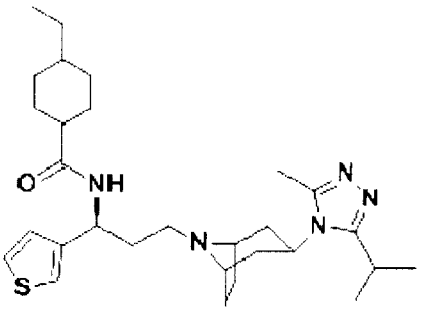
Example 19 Synthesis of compound 19

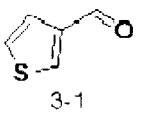


4-ethyl-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and 4-methylcyclohexane carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 19, MS: 511.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.25 (t, 1H), 7.15 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29-1.93 (m,15H), 1.93-1.61 (m, 12H), 1.33 (d, 6H).

Example 20 Synthesis of compound 20



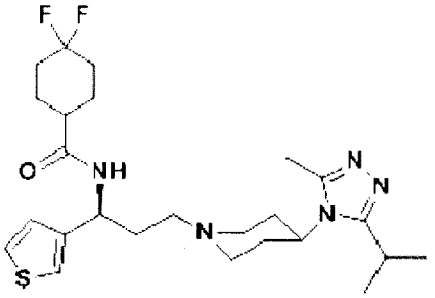


3-1

4-ethyl-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-3-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and 4-methylcyclohexane carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 20, MS: 511.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.25 (t, 1H), 7.15 (s, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29-1.93 (m,15H), 1.93-1.61 (m, 12H), 1.33 (d, 6H).

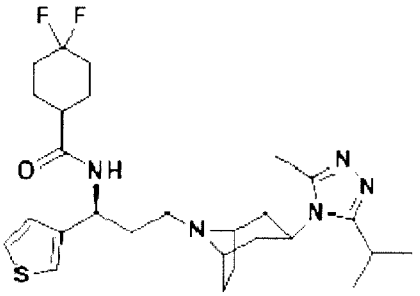
Example 21 Synthesis of compound 21



4,4-difluoro-N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-3-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5 to obtain compound 21, MS: 493.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.26 (t, 1H), 7.15 (s, 1H), 6.97 (d, 1H), 5.17 (m,1H), 3.94 (m, 1H), 3.05 (m, 1H), 2.53(s, 3H), 2.43 (m,2H), 2.25-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

Example 22 Synthesis of compound 22

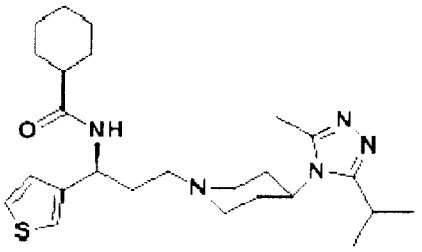


4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-3-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5, and compound 2f was used to replace 1f in Example 5 to obtain compound 22, MS: 520.0[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.26 (d, 1H), 7.14 (s, 1H), 6.95 (d, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,2H), 2.28-1.93 (m,12H), 1.93-1.65 (m, 9H), 1.35 (d, 6H).

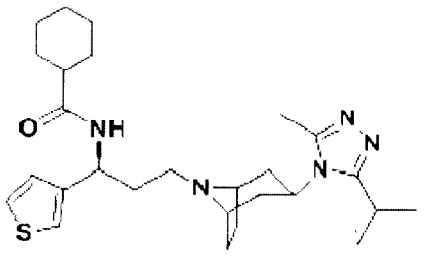
Example 23 Synthesis of compound 23

N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-3-yl)propyl]cyclohexane-1-carboxamide



According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5, and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexane carboxylic acid in Example 5 to obtain compound 23, MS: 457.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (d, 1H), 7.13 (s, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.05 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25-1.93 (m,12H), 1.93-1.61 (m, 9H), 1.35 (d, 6H).

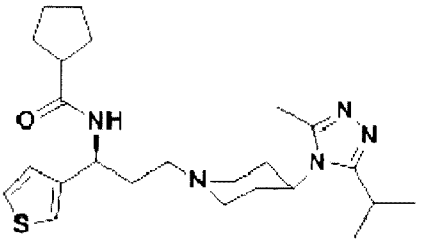
Example 24 Synthesis of compound 24



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-[(thiophen-3-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 24, MS: 483.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (d, 1H), 7.12 (s, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.34 (d, 6H).

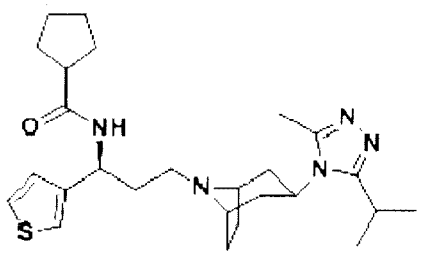
Example 25 Synthesis of compound 25



N-[(1S)-3-[4-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-piperidin-1-yl]-1-(thiophen-3-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5, and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexane carboxylic acid in Example 5 to obtain compound 25, MS: 443.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (d, 1H), 7.13 (s, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.271.95 (m,10H), 1.95-1.61 (m, 9H), 1.33 (d, 6H).

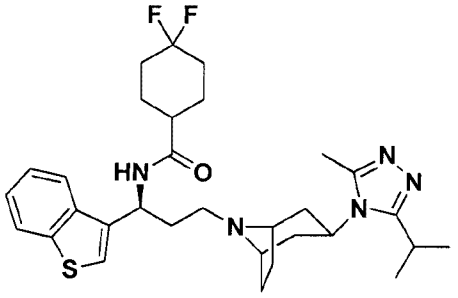
Example 26 Synthesis of compound 26

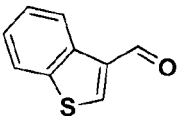


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-3-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 3-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 26, MS: 469.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.25 (d, 1H), 7.13 (s, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 27 Synthesis of compound 27



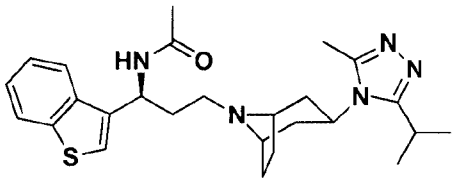


4-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(benzothiophen-3-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 4-1 was used to replace compound 2-1 in Example 5, and compound 2f was used to replace 1f in Example 5 to obtain compound 27, MS: 570.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.36 (d, 1H), δ7.26 (d, 2H), 7.14 (s, 1H), 6.95 (d, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,2H), 2.28-1.93 (m,12H), 1.93-1.65 (m, 9H), 1.35 (d, 6H).

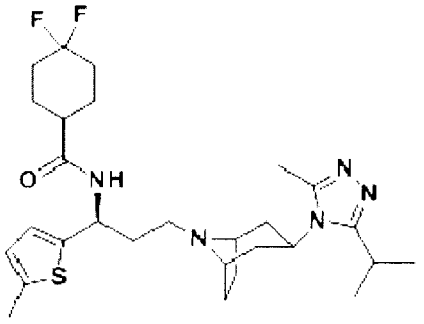
Example 28 Synthesis of compound 28

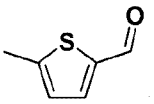


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(benzothiophen-3-yl)propyl]acetamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 28, MS: 520.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.35 (d, 1H), δ7.23 (t, 2H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.03 (m, 1H), 2.54 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

Example 29 Synthesis of compound 29



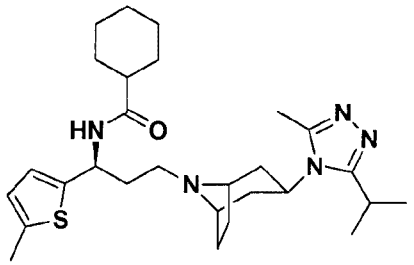


5-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, and compound 2f was used to replace 1f in Example 5 to obtain compound 29, MS: 534.2[M+H]+.δ7.27 (d, 1H), 7.20 (d, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,5H), 2.27-1.93 (m,12H), 1.93-1.62 (m, 9H), 1.32 (d, 6H).

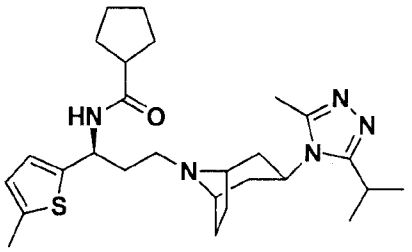
Example 30 Synthesis of compound 30



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 30, MS: 498.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (d, 1H), 7.21 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

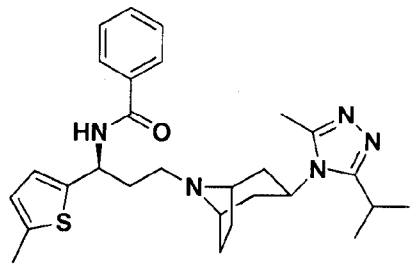
Example 31 Synthesis of compound 31



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 31, MS: 484.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.25 (d, 1H), 7.17 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

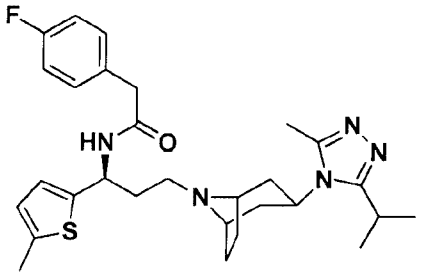
Example 32 Synthesis of compound 32



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl]benzamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and benzoic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 32, MS: 492.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.70 (d, 2H), 7.45 (d, 3H), 7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.03 (m, 1H), 2.54 (s, 3H), 2.40 (m,5H), 2.25-1.67 (m,11H), 1.32 (d, 6H).

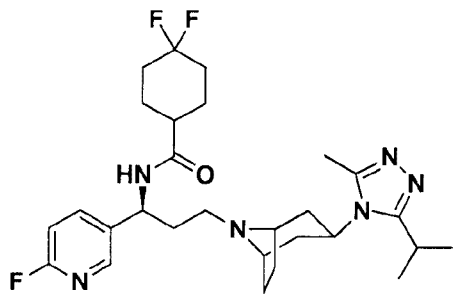
Example 33 Synthesis of compound 33



4-fluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-methylthiophen-2-yl)propyl]phenylacetamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and *p*-fluorophenylacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 33, MS: 524.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.50 (d, 2H), 7.35 (d, 2H), 7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.37 (s, 2H), 3.03 (m, 1H), 2.54 (s, 3H), 2.40 (m,5H), 2.25-1.67 (m,11H), 1.32 (d, 6H).

Example 34 Synthesis of compound 34

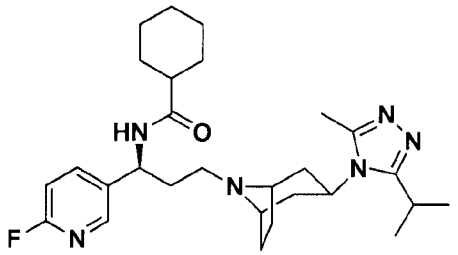


6-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl] -1-(6-fluoropyridin-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 6-1 was used to replace compound 2-1 in Example 5, and compound 2f was used to replace 1f in Example 5 to obtain compound 34, MS: 533.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.19 (d, 1H), 7.80 (d, 1H), 7.37 (t, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.43 (m,2H), 2.27-1.96 (m,12H), 1.96-1.60 (m, 9H), 1.34 (d, 6H).

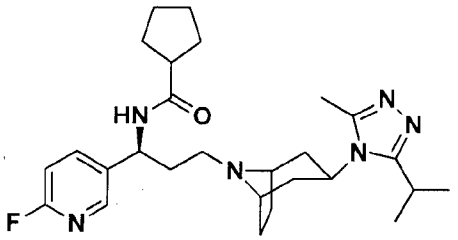
Example 35 Synthesis of compound 35



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(6-fluoropyridin-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 6-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 35, MS: 497.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.08 (d, 1H), 7.66 (d, 1H), 7.31 (t, 1H), 5.17 (m,1H), 3.90 (m, 1H), 3.00 (m, 1H), 2.50 (s, 3H), 2.43 (m,2H), 2.27-1.96 (m,12H), 1.96-1.60 (m, 11H), 1.34 (d, 6H).

Example 36 Synthesis of compound 36

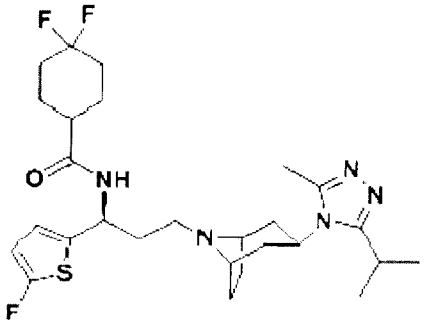


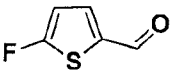
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(6-fluoropyridin-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 6-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 36, MS: 483.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.29 (s, 1H), δ7.86 (d, 1H), 7.48 (t, 1H), 5.16 (m,1H), 3.93 (m, 1H), 3.07 (m, 1H), 2.45 (s, 3H), 2.42 (m,2H), 2.27-1.96 (m,12H), 1.96-1.61 (m, 9H), 1.35 (d, 6H).

Example 37 Synthesis of compound 37

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl] -1-(5-fluorothiophen-2-yl)propyl]cyclohexane-1-carboxamide





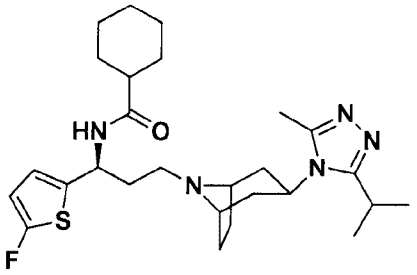
7-1

According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, and compound 2f was used to replace 1f in Example 5 to obtain compound 37, MS: 538.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.07 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

Example 38 Synthesis of compound 38

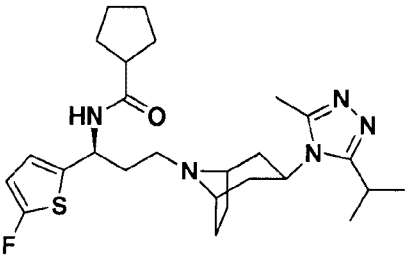
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-y

l]-1-(5-fluorothiophen-2-yl)propyl]cyclohexane-1-carboxamide



According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 38, MS: 502.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

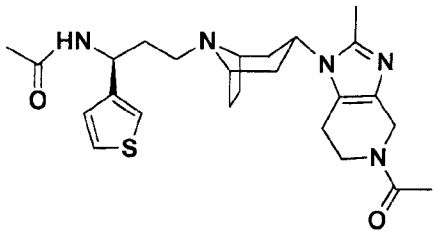
Example 39 Synthesis of compound 39



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-fluorothiophen-2-yl)propyl]cyclopentane-1-carboxamide

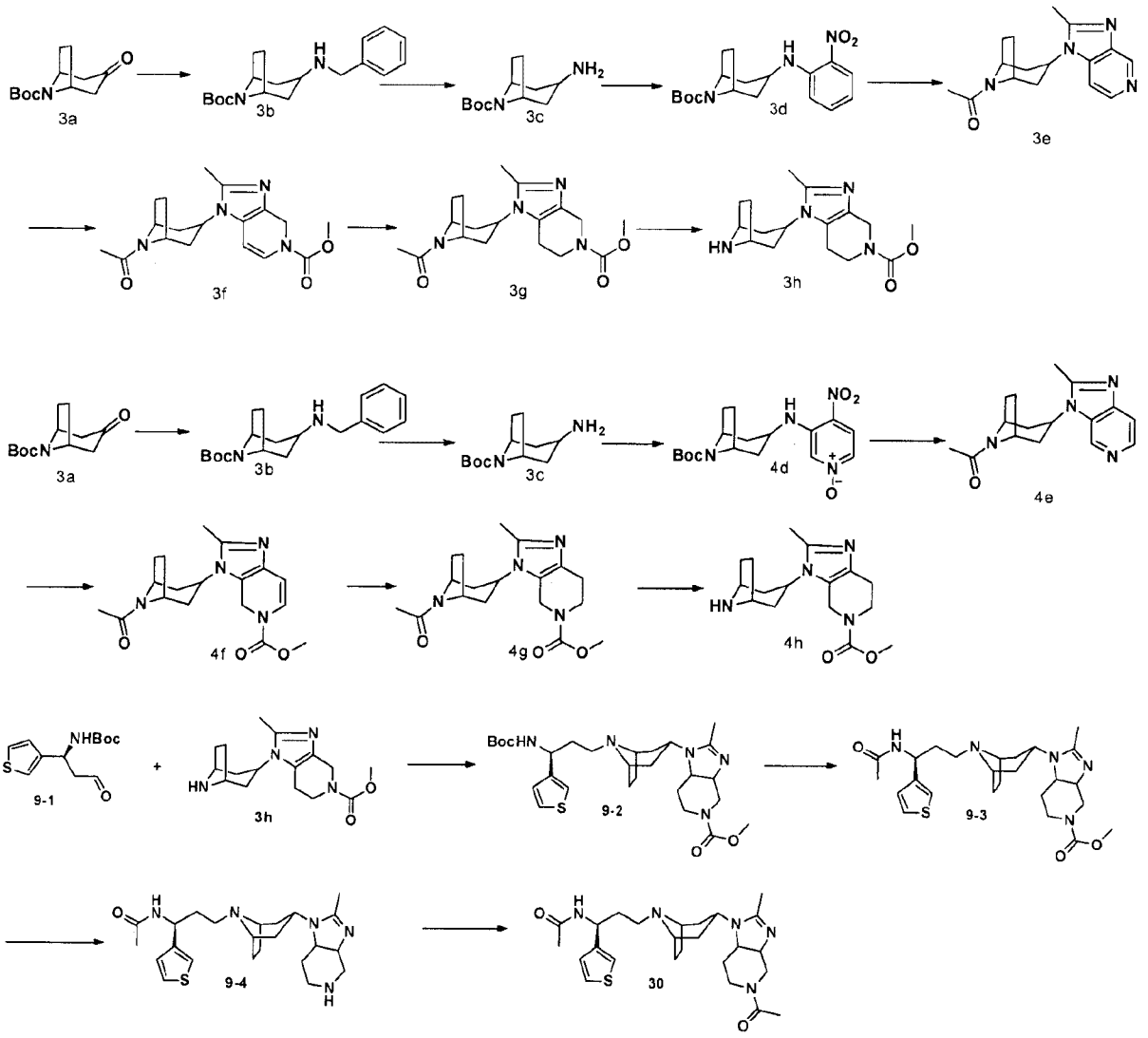
According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 39, MS: 488.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.10 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 40 Synthesis of compound 40



N-{(1S)-1-(thiophen-3-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

synthesis route:



Synthesis of compound 3b:

Compound 3a (10.0g, 44.4mmol), benzylamine (4.85ml, 49.7mmol) and sodium triacetyl borohydride (14.11g, 66.6mmol) were dissolved in a mixed solvent of acetic acid and dichloromethane (1:9 v/v, 290 ml) and stirred for 16 hours at room temperature. After the solvent was removed by rotary evaporation, the residue was dissolved in ethyl acetate, washed with saturated sodium carbonate solution, dried over anhydrous magnesium sulfate, evaporated to dryness *in vacuo* and separated by column chromatography to give compound 3b (7.0g, 50%), MS: 317.2[M+H]+.

Synthesis of compound 3c:

Compound 3b (7.0g, 22.2mmol), ammonium formate (7.0g, 111mmol), and 20% palladium hydroxide / carbon (0.7 g of) was dispersed in ethanol (200ml) and reacted for 2 hours at 50 °C . After cooled, the reaction solution was filtered by suction. Then the filtrate was subjected to rotary evaporation and column chromatography separation to give compound 3c (4.7g, 94%).

Synthesis of compound 3d:

Compound 3c (3.0g, 13.2mmol), 4-ethoxy-3-nitropyridine (2.7g, 13.2mmol) and DIPEA (1.89g, 14.6mmol) were dissolved in N-methylpyrrolidinone (5ml). The reaction mixture was heated to 120 °C for 18 hours. The reaction solution was cooled, extracted with ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated. Then ether was added to precipitate solids, and compound 3d (1.5g, 33%) was obtained by suction filtration. MS: 347.2 [M + H] +.

Synthesis of compound 3e:

Compound 3d (4.4g, 12.6mmol) and iron powder (2.11g, 37.8mmol) were dissolved in acetic acid (50ml) and heated to 60 °C for 2 hours. Then acetic anhydride (8ml) was added and heated to 140 °C for 18 hours. After cooled, the reaction solution was filtered by suction. Then the filtrate was subjected to rotary evaporation and the residue was dispersed in dichloromethane (200ml) and water (200ml). The solution was adjusted with 2N sodium hydroxide to pH 9 and then filtered by suction. Then the filtrate was extracted with dichloromethane, dried over magnesium sulfate and evaporated to dryness *in vacuo* to give compound 3e (3.27g, 91%). MS: 285.1[M+H]+.

Synthesis of compound 3f:

Compound 3e (10g, 35.2mmol) was dissolved in ethanol (95ml) and water (5ml), and under nitrogen methyl chlorofonmate (3.3ml, 42.2mmol) was slowly added dropwise at -70°C. The mixture was stirred for 45 minutes and then sodium borohydride (4.0g, 105.7mmol) was added in batches. The mixture was slowly warmed to room temperature and crushed ice was added and stirred for another 10 minutes. Ethanol was removed by rotary evaporation and the residue was added to 2M aqueous hydrochloric acid (100ml) and washed with ethyl acetate. The aqueous layer was adjusted with solid potassium hydroxide to pH 9, extracted with dichloromethane, dried over magnesium sulfate and separated by column chromatography to give compound 3f(9g, 74%), MS: 345.1[M+H]+.

Synthesis of compound 3g:

Compound 3f(6.75g, 19.6mmol) was dissolved in ethanol (60ml) and 10% Pd/C (500mg) was added. The hydrogenation reaction was carried out at 50°C for 5 h. The reaction mixture was filtered by suction, and the filtrate was evaporated to dryness *in vacuo* and then separated by column chromatography to give compound 3g(6.2g, 91%), MS: 346.2[M+H]+.

Synthesis of compound 3h:

Compound 3g (10.58g, 30mmol) was dissolved in 2M sulfuric acid, and heated to 100°C for 18 hours. The solid potassium hydroxide was added to adjust pH to 11-12. The mixture was extracted with dichloromethane and separated by column chromatography to give compound 3h(7.4g, 80%), MS: 304.1[M+H]+.

Synthesis of compound 4h:

According to the synthesis method of compound 3h, 3-fluoro-4-nitropyridine N-oxide was used to replace 4-ethoxy-3-nitropyridine in the synthesis of compound 3h in Example 30..

Synthesis of compound 9-2:

According to the synthesis method of compound 2-6, Compound 3-1 was used to replace compound 2-1 in Example 5, and compound 3h was used to replace 1f in Example 5 to obtain compound 9-2, MS: 545.3[M+H]+.

Synthesis of compound 9-3:

Compound 9-2 (109mg, 0.2mmol) was dissolved in 1mL of methanol and 1mL 4M solution of HCl in dioxane was added and stirred for 2 hours at room temperature. The mixture was concentrated and dissolved in 1mL N,N-dimethylformamide, followed by adding

triethylamine (30.3mg, 0.3mmol), acetic acid (49mg, 0.3mmol), benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate (BOP) (126.5mg, 0.3 mmol), and stirred for 12 hours at room temperature. Water was added, and then the mixture was extracted with ethyl acetate, washed with saturated brine, dried over anhydrous sodium sulfate, concentrated and separated by column chromatography to give white solids 9-3 (56.7mg, yield 58%), MS: 487.2[M+H]+.

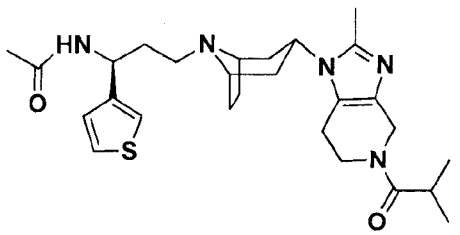
Synthesis of compound 9-4:

Compound 9-3 (85mg, 0.17mmol) was dissolved in isopropanol (2ml) and 2M sodium hydroxide solution (3ml). The reaction mixture was heated at reflux for 48 hours, extracted with ethyl acetate, and separated by column chromatography to give compound 9-4 (55mg, 73%), MS: 429.1[M+H]+.

Synthesis of compound 40:

Compound 9-4 (55mg, 0.13mmol) was dissolved in 4ml of tetrahydrofuran and triethylamine (17mg, 0.17mmol) was added. Then acetyl chloride (18mg, 0.17mmol) was added dropwise and stirred for 2 hours at room temperature.The mixture was extracted with ethyl acetate and separated by column chromatography to give compound 40(50mg, 91%), MS: 500.3[M+H]+. ^{1}H-NMR (400Hz, $CDCl_3$): δ7.25 (m,1H), 7.04 (m, 1H), 6.97 (m,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H).

Example 41 Synthesis of compound 41

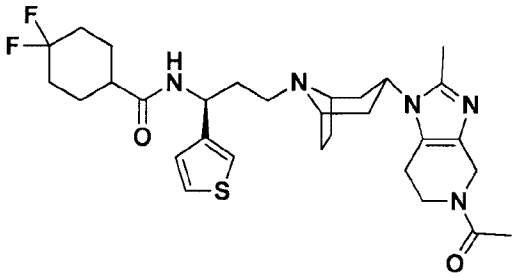


N-{(1S)-1-(thiophen-3-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 41, MS: 498.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.14 (m, 1H), 7.07 (m, 1H), 6.97 (m,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H),

2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H), 1.13- 1.06 (m,6H).

Example 42 Synthesis of compound 42

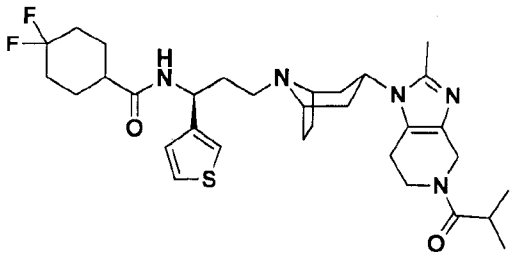


4,4-difluoro-N-{(1S)-1-(thiophen-3-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}cyclohexane-1-carboxamide

According to the synthesis method of compound 40, 4,4-difluoro-cyclohexane carboxylic acid was used to replace acetic acid in Example 40 to obtain compound 42, MS: 574.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.14 (m, 1H), 7.07 (m, 1H), 6.97 (m,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,2H), 2.36-1.84 (m,9H), 1.69-1.53 (m,9H).

Example 43 Synthesis of compound 43

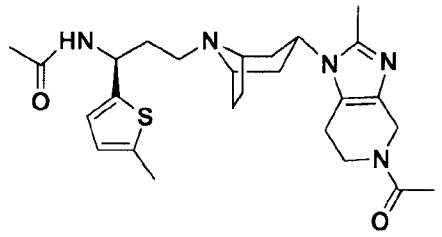
4,4-difluoro-N-{(1S)-1-(thiophen-3-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}cyclohexane-1-carboxamide



According to the synthesis method of compound 40, isobutyryl chloride was used to replace acetyl chloride in Example 40 and 4,4-difluoro-cyclohexanecarboxylic acid was used to replace acetic acid in Example 40 to obtain compound 43, MS: 602.3[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.14 (m, 1H), 7.03 (m, 1H), 6.97 (m,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39

(m,2H), 2.36-1.84 (m,8H), 1.69-1.53 (m, 10H), 1.13- 1.06 (m,6H).

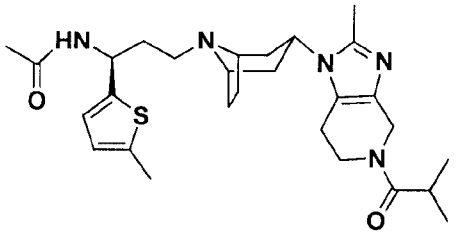
Example 44 Synthesis of compound 44



N-{(1S)-1-(5-methylthiophen-2-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, Compound 5-1 was used to replace 3-1 in Example 40 to obtain compound 44, MS: 470.3[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.10 (d,1H), 7.04 (d, 1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,5H), 2.36-1.84 (m,6H), 1.59-1.30 (m, 4H).

Example 45 Synthesis of compound 45

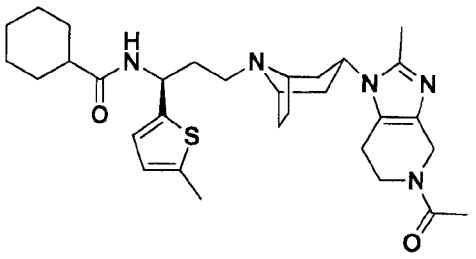


N-{(1S)-1-(5-methylthiophen-2-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, isobutyryl chloride was used to replace acetyl chloride in Example 40 and compound 5-1 was used to replace 3-1 in Example 40 to obtain compound 45, MS: 498.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.14 (d, 1H), 7.07 (d, 1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,5H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H), 1.13- 1.06 (m,6H).

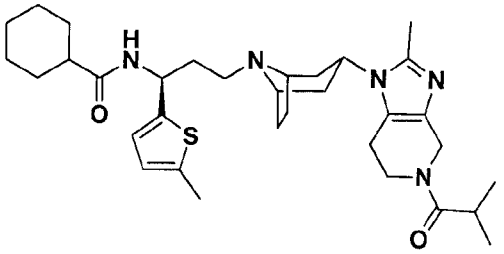
Example 46 Synthesis of compound 46

N-{(1S)-1-(5-methylthiophen-2-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}cyclohexane-1-carboxamide



According to the synthesis method of compound 40, Cyclohexanecarboxylic acid was used to replace acetic acid in Example 40 and compound 5-1 was used to replace 3-1 in Example 40 to obtain compound 46, MS: 538.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.14 (d, 1H), 7.03 (d, 1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,5H), 2.36-1.84 (m,9H), 1.69-1.53 (m, 11H), 1.13- 1.06 (m,6H).

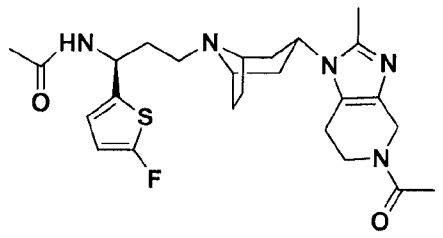
Example 47 Synthesis of compound 47



N-{(1S)-1-(5-methylthiophen-2-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}cyclohexane-1-carboxamide

According to the synthesis method of compound 40, isobutyryl chloride was used to replace acetyl chloride in Example 40, compound 5-1 was used to replace 3-1 in Example 40 and cyclohexanecarboxylic acid was used to replace acetic acid in Example 40 to obtain compound 47, MS: 566.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.14 (d, 1H), 7.03 (d, 1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,8H), 1.69-1.53 (m, 12H), 1.13- 1.06 (m,6H).

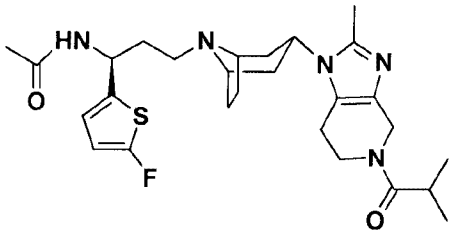
Example 48 Synthesis of compound 48



N-{(1S)-1-(5-fluorothiophen-2-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace 3-1 in Example 40 to obtain compound 48, MS: 488.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.10 (d,1H), 6.97 (d,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.59-1.30 (m, 4H).

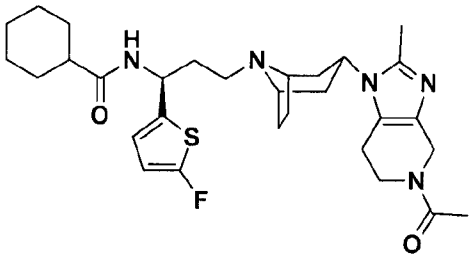
Example 49 Synthesis of compound 49



N-{(1S)-1-(5-fluorothiophen-2-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, isobutyryl chloride was used to replace acetyl chloride in Example 40, and compound 7-1 was used to replace 3-1 in Example 40 to obtain compound 49, MS: 516.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.07 (d, 1H), 6.97 (d,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H), 1.13- 1.06 (m,6H).

Example 50 Synthesis of compound 50

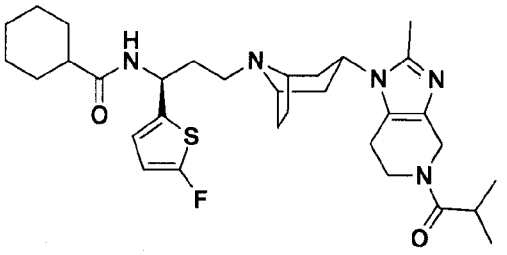


N-{(1S)-1-(5-fluorothiophen-2-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-i

midazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}cyclohexane-1-carboxamid e

According to the synthesis method of compound 40, Cyclohexanecarboxylic acid was used to replace acetic acid in Example 40, and compound 7-1 was used to replace 3-1 in Example 30 to obtain compound 50, MS: 556.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.03 (m, 1H), 6.97 (m,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.19 (m,2H), 3.63(m,2H), 3.27(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,9H), 1.69-1.53 (m, 11H), 1.13- 1.06 (m,6H).

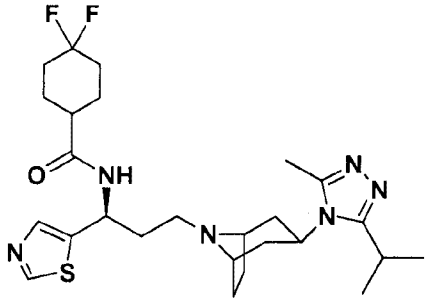
Example 51 Synthesis of compound 51

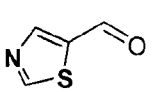


N-{(1S)-1-(5-fluorothiophen-2-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1 H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}cyclohexane-1-carboxa mide

According to the synthesis method of compound 40, Cyclohexanecarboxylic acid was used to replace acetic acid in Example 40, compound 7-1 was used to replace 1-1 in Example 30 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 51, MS: 584.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.05 (m, 1H), 6.97 (m,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.85-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,8H), 1.69-1.53 (m, 12H), 1.13- 1.06 (m,6H).

Example 52 Synthesis of compound 52



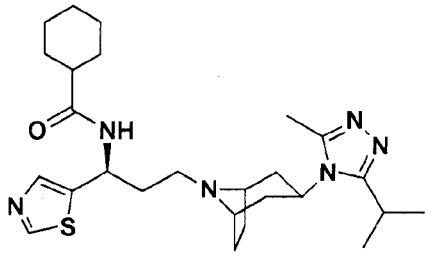


8-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-5-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 8-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace compound 1f in Example 5 to obtain compound 52, MS: 520.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.27 (s, 1H), 7.14 (s, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,2H), 2.27-1.93 (m,12H), 1.93-1.62 (m, 9H), 1.32 (d, 6H).

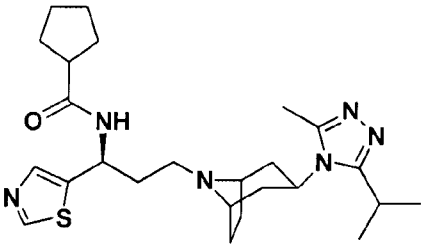
Example 53 Synthesis of compound 53



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-5-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 8-1 was used to replace compound 2-1 in example 5, compound 2f was used to replace compound 1f in example 5 and cyclohexane carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in example 5 to obtain compound 53, MS: 484.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.28 (s, 1H), 7.23 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 54 Synthesis of compound 54

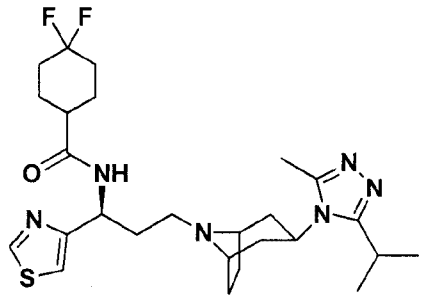


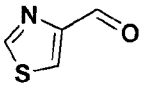
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-5-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 8-1 was used to replace

compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentane carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 54, MS: 470.9 [M+H]+. ^{1}H-NMR (400Hz, $CDCl_3$): δ8.25 (s, 1H), 7.33 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 55 Synthesis of compound 55



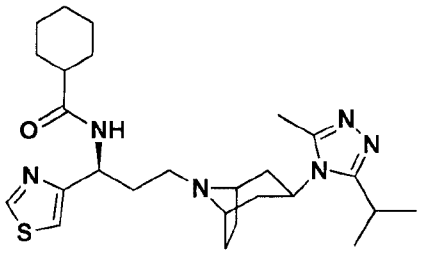


10-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-4-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 10-1 was used to replace compound 2-1 in Example 5, and compound 2f was used to replace compound 1f in Example 5 to obtain compound 55, MS: 520.9[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.20 (s, 1H), 7.19 (s, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (s, 3H), 2.40 (m,2H), 2.27-1.93 (m,12H), 1.93-1.62 (m, 9H), 1.32 (d, 6H).

Example 56 Synthesis of compound 56

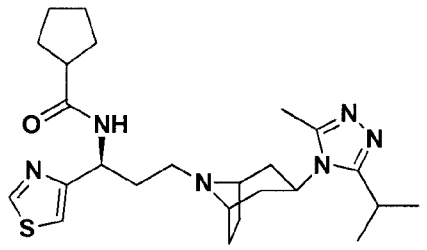


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-5-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 10-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid

in Example 5 to obtain compound 56, MS: 484.9[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.18 (s, 1H), 7.23 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 57 Synthesis of compound 57

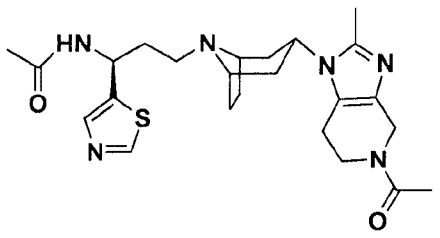


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-5-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 10-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 57, MS: 470.9[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.20 (s, 1H), 7.33 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 58 Synthesis of compound 58

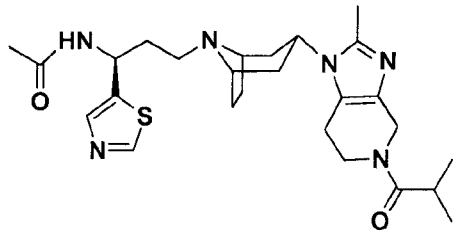
N-{(1S)-1-(thiazol-5-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide



According to the synthesis method of compound 40, Compound 8-1 was used to replace compound 3-1 in Example 40 to obtain compound 58, MS: 471.3[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ8.10 (s,1H), 7.17 (s,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.59-1.30

(m, 4H).

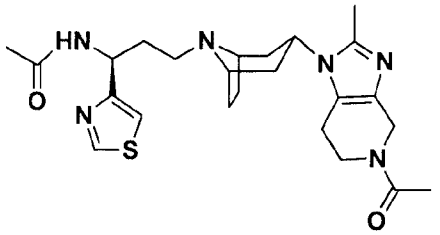
Example 59 Synthesis of compound 59



N-{(1S)-1-(thiazol-5-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, Compound 8-1 was used to replace compound 3-1 in Example 40 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 59, MS: 499.3[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.87 (s, 1H), 7.07 (s,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H), 1.13-1.06 (m,6H).

Example 60 Synthesis of compound 60

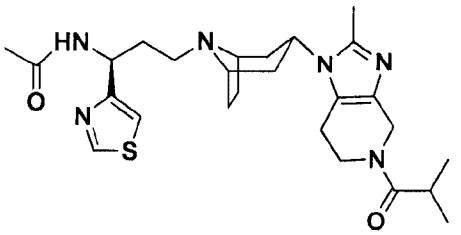


N-{(1S)-1-(thiazol-4-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, Compound 10-1 was used to replace compound 3-1 in Example 40 to obtain compound 60, MS: 471.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.13 (s,1H), 7.13 (s,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.59-1.30 (m, 4H).

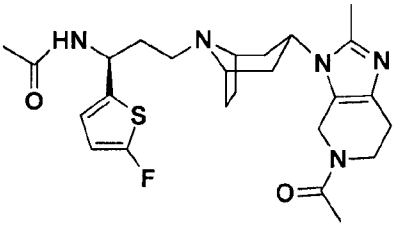
Example 61 Synthesis of compound 61

N-{(1S)-1-(thiazol-4-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide



According to the synthesis method of compound 40, Compound 10-1 was used to replace compound 3-1 in Example 40 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 61, MS: 499.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.07 (s, 1H), 7.37 (s,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H), 1.13-1.06 (m,6H).

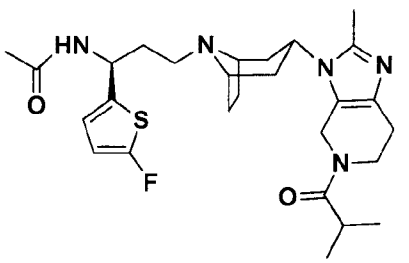
Example 62 Synthesis of compound 62



N-{(1S)-1-(5-fluorothiophen-2-yl)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40, compound 4h was used to replace compound 3h in Example 40 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 62, MS: 488.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.13 (d,1H), 7.03 (d,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,5H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.59-1.30 (m, 4H).

Example 63 Synthesis of compound 63

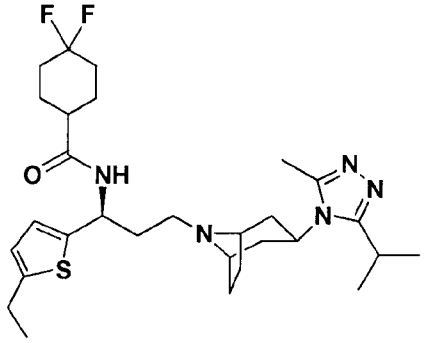


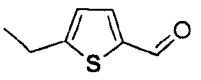
N-{(1S)-1-(5-fluorothiophen-2-yl)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40, and compound 4h was used to replace compound 3h in Example 40 to obtain compound 63, MS: 516.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.37 (d, 1H), 7.01 (d,1H), 5.17 (m, 1H), 4.65 (m,1H), 4.43 (m,2H), 4.09 (m,2H), 3.43(m,2H), 3.07(m,1H), 2.83-2.69 (m,2H), 2.51-2.39 (m,2H), 2.36-1.84 (m,6H), 1.69-1.53 (m, 4H), 1.13-1.06 (m,6H).

Example 64 Synthesis of compound 64

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-ethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

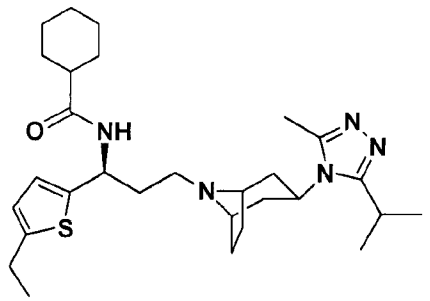




11-1

According to the synthesis method of Example 5, Compound 11-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 64, MS: 548.2[M+H]+.δ7.27 (d, 1H), 7.20 (d, 1H), 5.14 (m,1H), 3.91 (m, 1H), 3.03 (m, 1H), 2.52 (q, 2H), 2.40 (m,5H), 2.27-1.93 (m,12H), 1.93-1.62 (m, 9H), 1.32 (m, 9H).

Example 65 Synthesis of compound 65

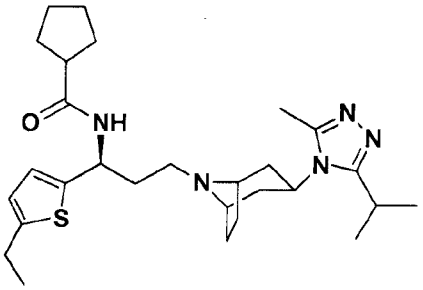


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-ethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 11-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 65, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (d, 1H), 7.21 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(q, 2H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (m, 9H).

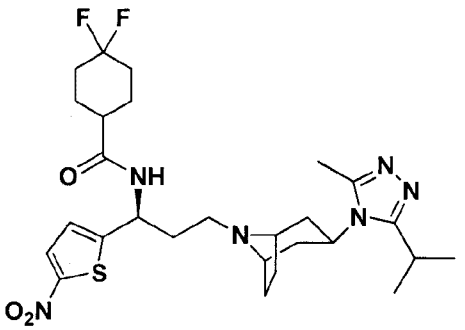
Example 66 Synthesis of compound 66

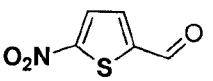
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl]cyclopentane-1-carboxamide



According to the synthesis method of Example 5, Compound 11-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 66, MS: 498.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.25 (d, 1H), 7.17 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(q, 2H), 2.43 (m,5H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (m, 9H).

Example 67 Synthesis of compound 67



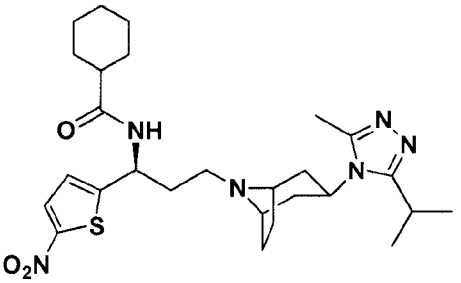


12-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-nitrothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 12-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 67, MS: 565.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.97 (d, 1H), 7.05 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

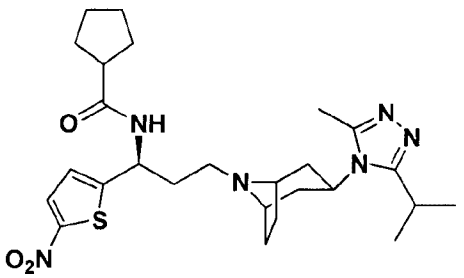
Example 68 Synthesis of compound 68



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-nitrothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 12-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 68, MS: 529.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.93 (d, 1H), 6.94 (d,1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

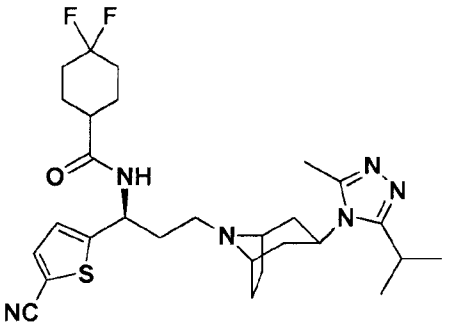
Example 69 Synthesis of compound 69

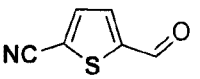


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-nitrothiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 12-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 69, MS: 515.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.90 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 70 Synthesis of compound 70



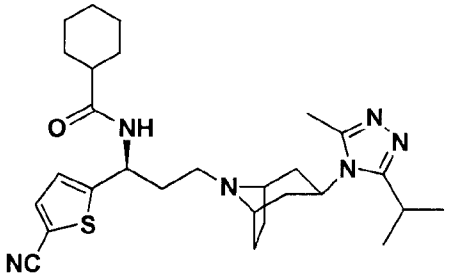


13-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 13-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 70, MS: 545.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

Example 71 Synthesis of compound 71

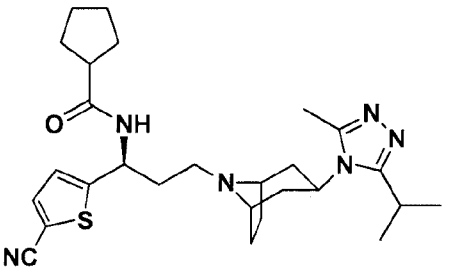


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 13-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 71, MS: 509.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.33 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

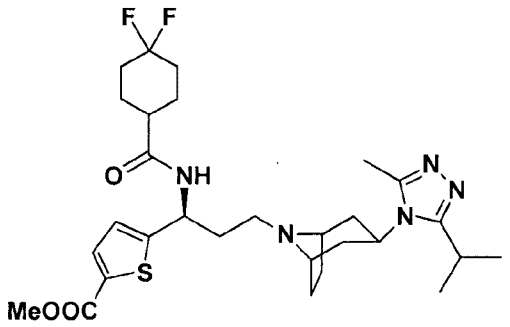
Example 72 Synthesis of compound 72

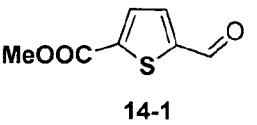
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl]cyclopentane-1-carboxamide



According to the synthesis method of Example 5, Compound 13-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 72, MS: 495.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.30 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 73 Synthesis of compound 73





14-1

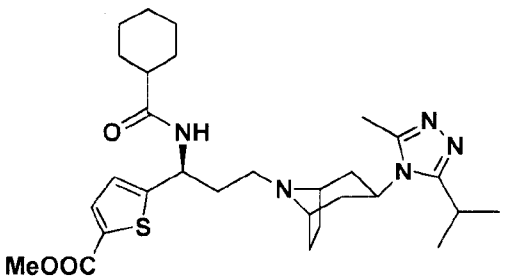
4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxycarbonylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 14-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 73, MS: 578.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.77 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

Example 74 Synthesis of compound 74

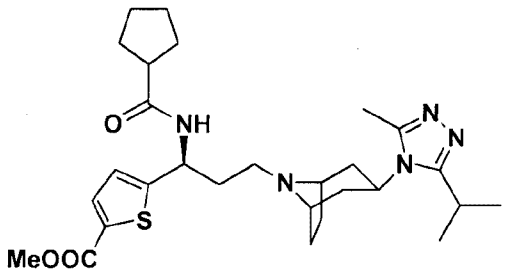
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxycarbonylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 14-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 74.



MS: 542.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.83 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

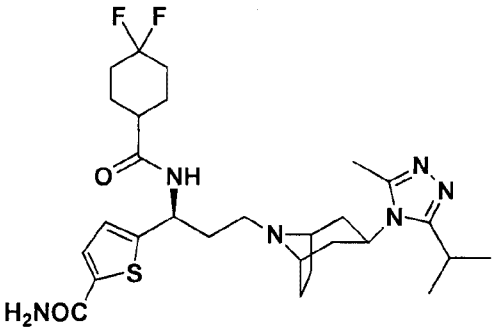
Example 75 Synthesis of compound 75

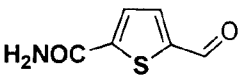


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxycarbonylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 14-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 75, MS: 528.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.80 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 76 Synthesis of compound 76



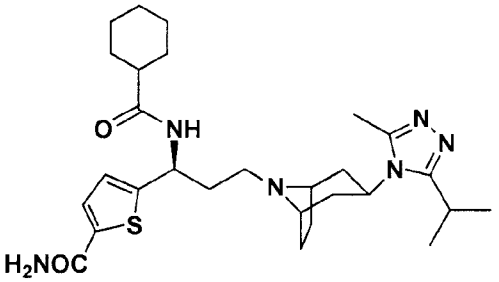


15-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-carbamoylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 15-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 76, MS: 563.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.87 (d, 2H), 7.57 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

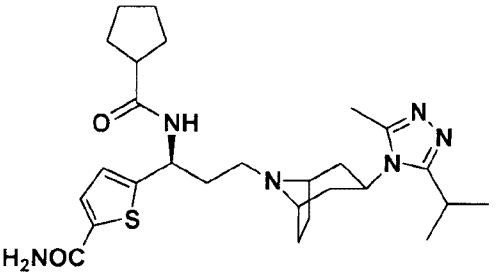
Example 77 Synthesis of compound 77



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-carbamoylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 15-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 77, MS: 528.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.87 (d, 2H), 7.63 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

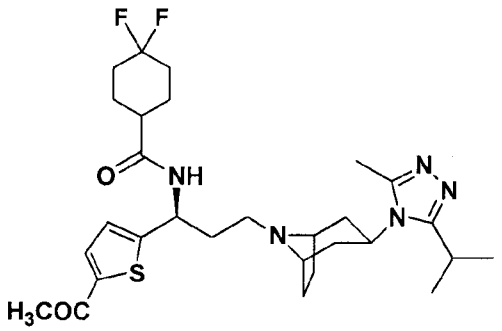
Example 78 Synthesis of compound 78

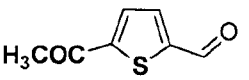


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-carbamoylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 15-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 78, MS: 513.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.87 (d, 2H), 7.60 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 79 Synthesis of compound 79





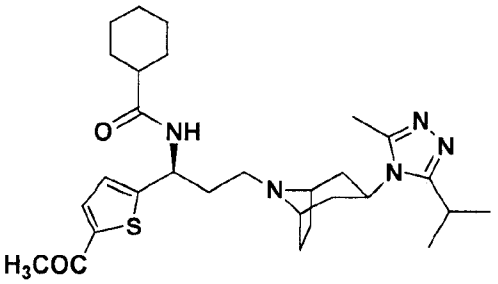
16-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-acetylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 16-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 79, MS: 562.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.27 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

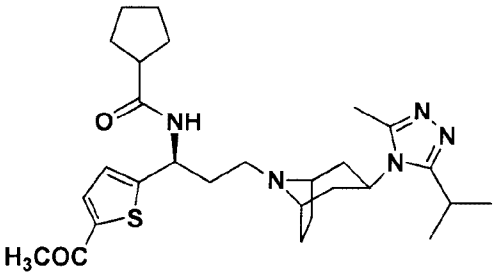
Example 80 Synthesis of compound 80

N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-acetylthiophen-2-yl)propyl]cyclohexane-1-carboxamide



According to the synthesis method of Example 5, Compound 16-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 80, MS: 526.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 81 Synthesis of compound 81



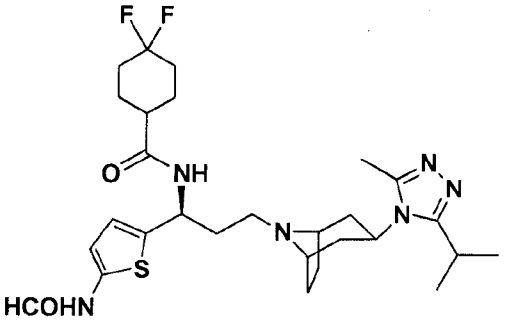
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-acetylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

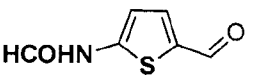
According to the synthesis method of Example 5, Compound 16-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 81, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.20 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 82 Synthesis of compound 82

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-formamidothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 17-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 82.

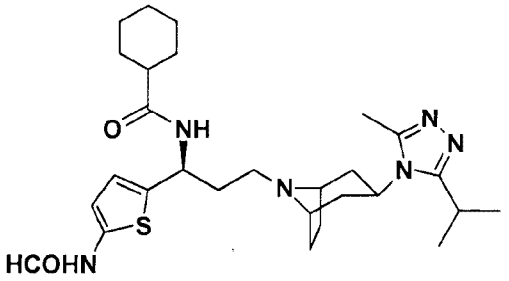




17-1

MS: 562.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.10 (s, 1H), 7.07 (d, 1H), 6.95 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

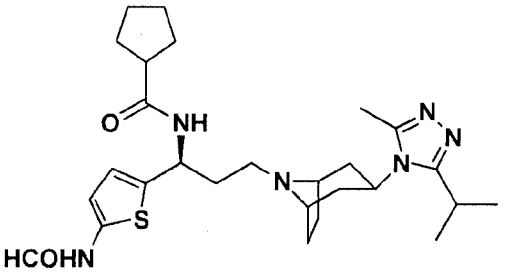
Example 83 Synthesis of compound 83



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-formamidothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 17-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 83, MS: 527.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.10 (s, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

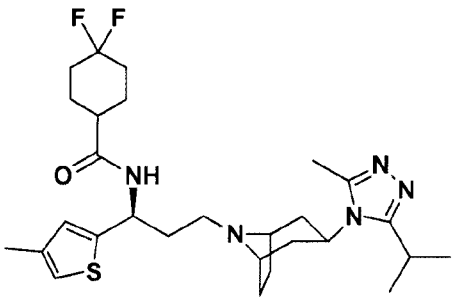
Example 84 Synthesis of compound 84

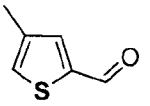


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-formamidothiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 17-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 84, MS: 513.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.10 (s, 1H), 7.10 (d, 1H), 6.97 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 85 Synthesis of compound 85



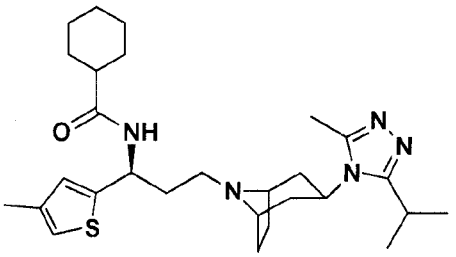


18-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4-methylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 18-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 85, MS: 533.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.07 (s, 1H), 6.95 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

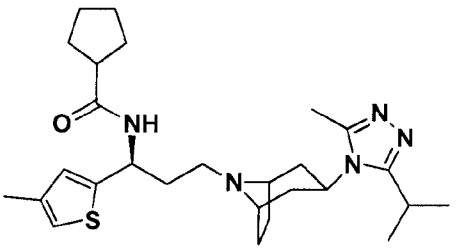
Example 86 Synthesis of compound 86



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4-methylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 18-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 86, MS: 498.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.13 (s, 1H), 6.94 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

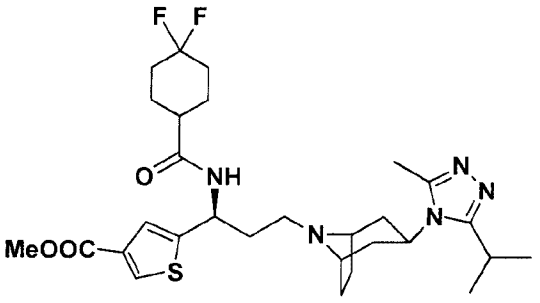
Example 87 Synthesis of compound 87

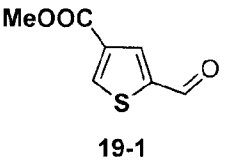


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4-methylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 18-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 87, MS: 484.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.10 (s, 1H), 6.97 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 88 Synthesis of compound 88



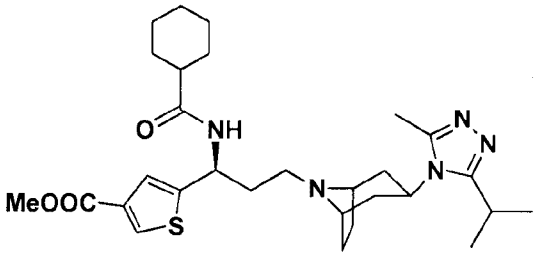


19-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxycarbonylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 19-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 88, MS: 578.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.17 (s, 1H), 7.27 (s, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

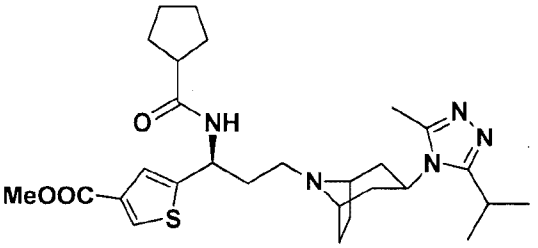
Example 89 Synthesis of compound 89



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxycarbonylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 19-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 89, MS: 542.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.13 (s, 1H), 7.26 (s, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

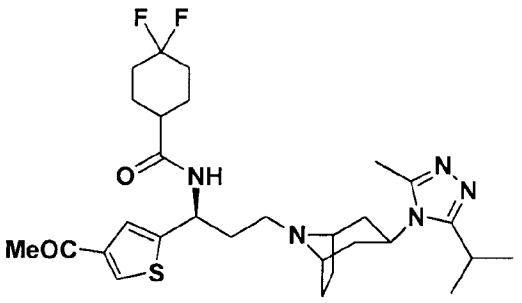
Example 90 Synthesis of compound 90

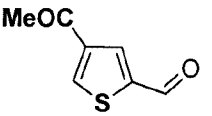


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxycarbonylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 19-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 90, MS: 528.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.10 (s, 1H), 7.27 (s, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 91 Synthesis of compound 91



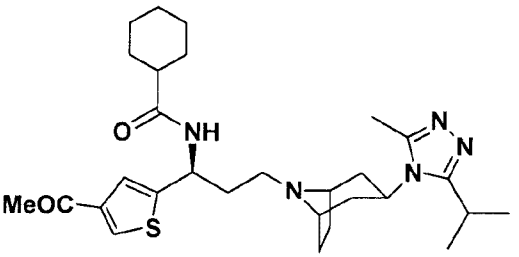


20-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4-acetylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 20-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 91, MS: 562.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.07 (s, 1H), 7.15 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

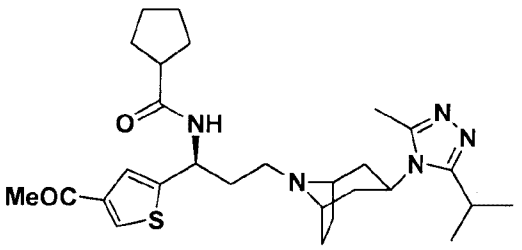
Example 92 Synthesis of compound 92



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4-acetylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 20-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 92, MS: 526.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.13 (s, 1H), 7.14 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 93 Synthesis of compound 93

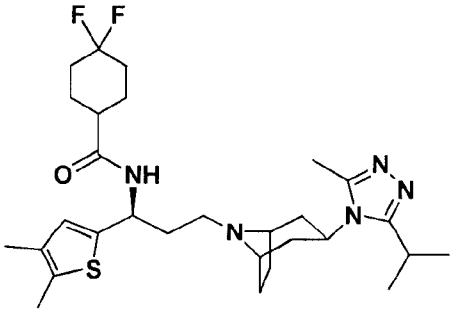


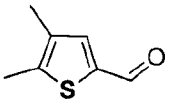
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4-acetylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 20-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 93, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.10 (s, 1H), 6.97 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.27-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 94 Synthesis of compound 94

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4,5-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

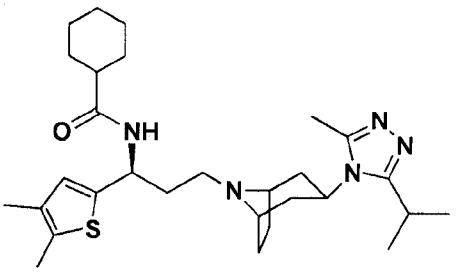




21-1

According to the synthesis method of Example 5, Compound 21-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 94, MS: 548.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.05 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25(s,6H), 2.17-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

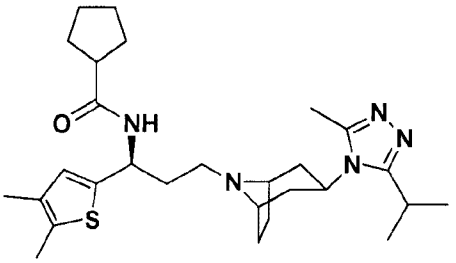
Example 95 Synthesis of compound 95



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4,5-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 21-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 95, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.04 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25(s,6H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

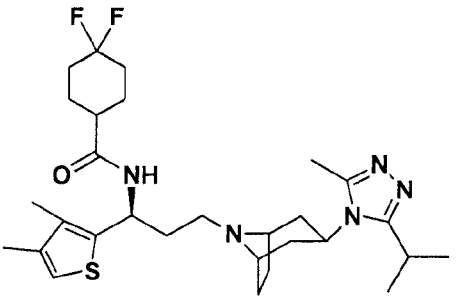
Example 96 Synthesis of compound 96

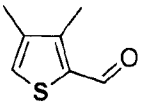


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(4,5-dimethylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 21-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 96, MS: 498.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.07 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25(s,6H), 2.17-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 97 Synthesis of compound 97



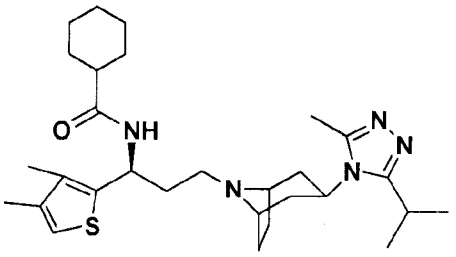


22-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,4-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 22-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 97, MS: 548.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.05 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25(s,6H), 2.17-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

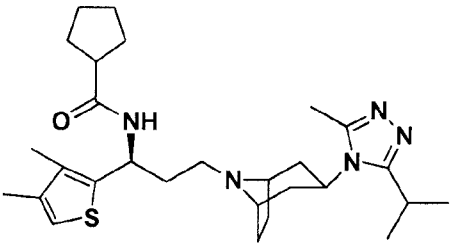
Example 98 Synthesis of compound 98



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,4-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 22-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 98, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.04 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25(s,6H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

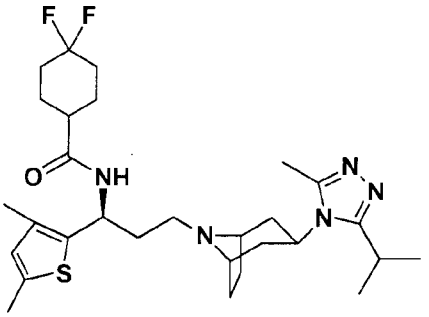
Example 99 Synthesis of compound 99

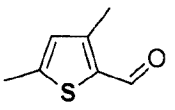


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,4-dimethylthiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 22-1 was used to replace 2-1 in Example 5, compound 2f was used to replace 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 99, MS: 498.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.07 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.25(s,6H), 2.17-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 100 Synthesis of compound 100



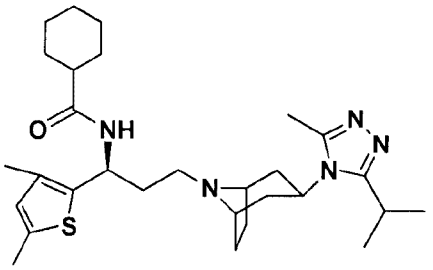


23-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,5-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 23-1 was used to replace 2-1 in Example 5 and compound 2f was used to replace 1f in Example 5 to obtain compound 100, MS: 548.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.15 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29(s,6H), 2.17-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

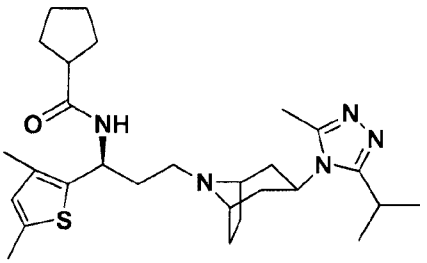
Example 101 Synthesis of compound 101



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,5-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 23-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 101, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.14 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29(s,6H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

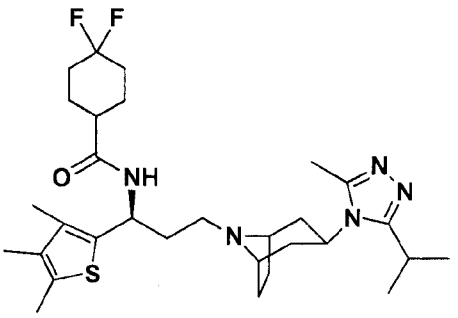
Example 102 Synthesis of compound 102

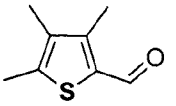


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,5-dimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 23-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 102, MS: 498.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.17 (s, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29(s,6H), 2.17-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 103 Synthesis of compound 103



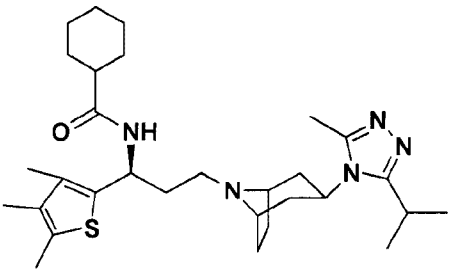


24-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,4,5-trimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 24-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace compound 1f in Example 5 to obtain compound 103, MS: 562.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26(s,9H), 2.17-1.95 (m,10H), 1.95-1.61 (m, 9H), 1.34 (d, 6H).

Example 104 Synthesis of compound 104

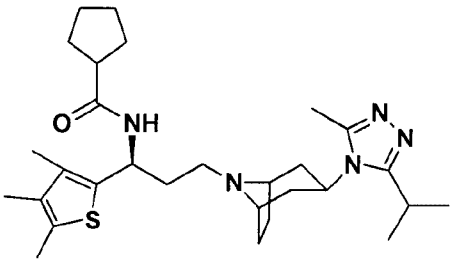


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,4,5-trimethylthiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 24-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 104, MS: 526.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.27(s,9H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

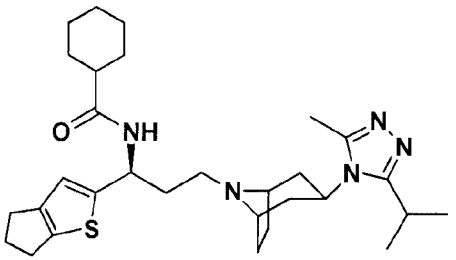
Example 105 Synthesis of compound 105

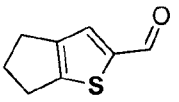
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(3,4,5-trimethylthiophen-2-yl)propyl]cyclopentane-1-carboxamide



According to the synthesis method of Example 5, Compound 24-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 105, MS: 512.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.29(s,9H), 2.17-1.93 (m,11H), 1.93-1.61 (m, 10H), 1.35 (d, 6H).

Example 106 Synthesis of compound 106



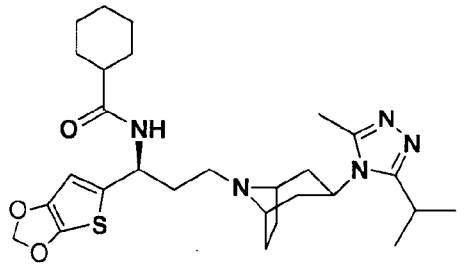


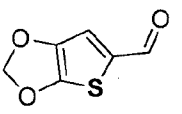
25-1

N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5,6-dihydro-cyclopentathiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 25-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 106, MS: 524.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.83(s,1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 5H), 2.54(s, 3H), 2.43 (m,4H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 107 Synthesis of compound 107





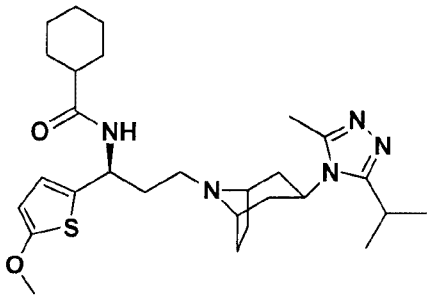
26-1

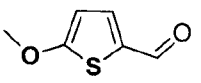
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thieno[2,3-d][1,3]dioxol-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 26-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 107, MS: 528.2[M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ6.03(s,2H), 5.79 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 108 Synthesis of compound 108

N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxythiophen-2-yl)propyl]cyclopentane-1-carboxamide

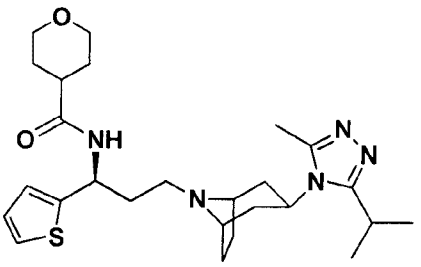




27-1

According to the synthesis method of Example 5, Compound 27-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 108, MS: 514.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.43(m,2H), 5.79 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

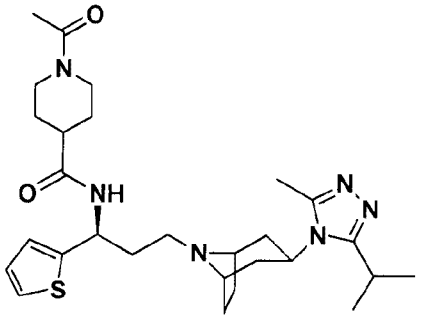
Example 109 Synthesis of compound 109



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] tetrahydropyran-4-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and tetrahydropyran-4-carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 109, MS: 485.9[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.61 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,2H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

Example 110 Synthesis of compound 110

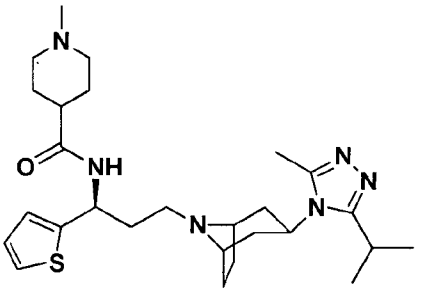


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -1-acetylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-acetyl-4-piperidinecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 110, MS: 527.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.26-1.93

(m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

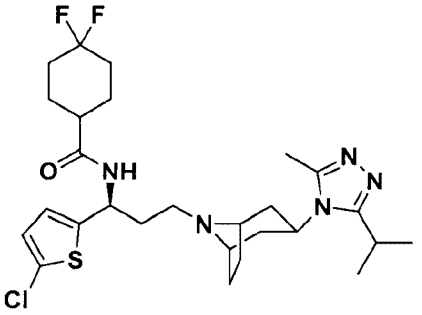
Example 111 Synthesis of compound 111

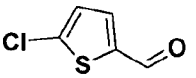


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -1-methylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-methylpiperidine-4-carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 111, MS: 499.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.51(m, 7H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

Example 112 Synthesis of compound 112





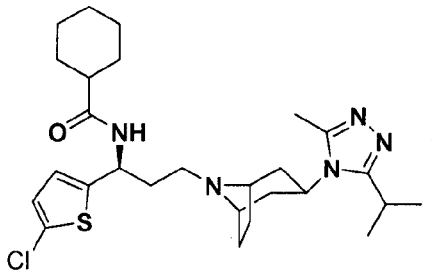
28-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-chlorothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace compound 1f in Example 5 to obtain compound 112, MS: 554.25[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.67 (m, 2H), 4.78 (m,1H), 3.70 (m, 1H), 3.18 (m, 1H), 2.38-2.43(m, 3H), 2.36 (s,3H), 1.40-1.82 (m,20H),

1.26 (d, 6H).

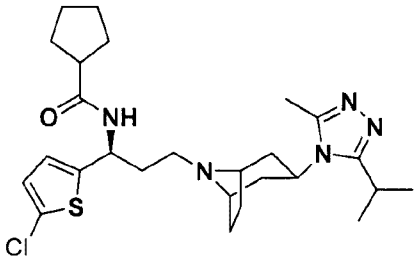
Example 113 Synthesis of compound 113



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-chlorothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 113, MS: 518.26 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.65-6.80 (m, 2H), 4.78 (m,1H), 3.72 (m, 1H), 3.20 (m, 1H), 2.31-2.45(m, 3H), 2.33 (s,3H), 1.44-1.82 (m,22H), 1.36 (d, 6H).

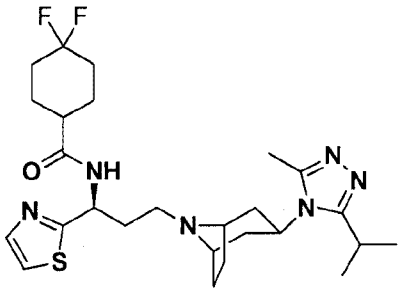
Example 114 Synthesis of compound 114

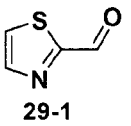


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-chlorothiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 114, MS: 504.25 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.65-6.80 (m, 2H), 4.78 (m,1H), 3.72 (m, 1H), 3.20 (m, 1H), 2.31-2.45(m, 3H), 2.33 (s,3H), 1.44-1.82 (m,20H), 1.36 (d, 6H).

Example 115 Synthesis of compound 115



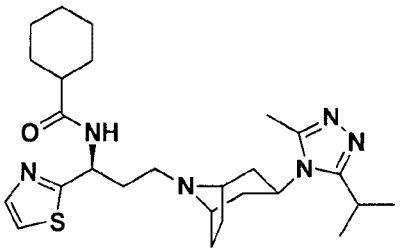


29-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 29-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace compound 1f in Example 5 to obtain compound 115, MS: 521.28 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.67 (d, 1H), 7.20 (d, 1H), 4.78 (m,1H), 3.72 (m, 1H), 3.20 (m, 1H), 2.31-2.45(m, 3H), 2.36 (s,3H), 1.44-1.82 (m,20H), 1.36 (d, 6H).

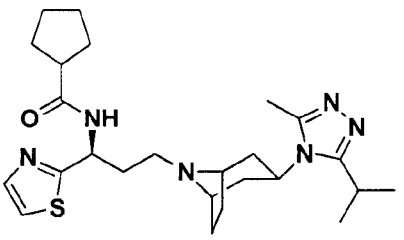
Example 116 Synthesis of compound 116



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 29-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 116, MS: 485.30 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.23 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.31-2.45(m, 3H), 2.33(s,3H), 1.34-1.83 (m,22H), 1.26 (d, 6H).

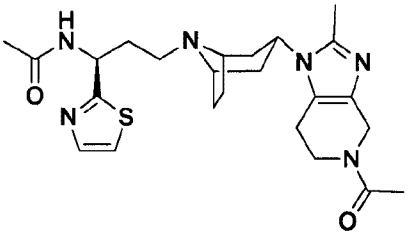
Example 117 Synthesis of compound 117



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiazol-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 29-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 117, MS: 471.28 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.62 (d, 1H), 7.22 (d, 1H), 4.73 (m,1H), 3.74 (m, 1H), 3.22 (m, 1H), 2.31-2.45(m, 3H), 2.33 (s,3H), 1.44-1.82 (m,20H), 1.33 (d, 6H).

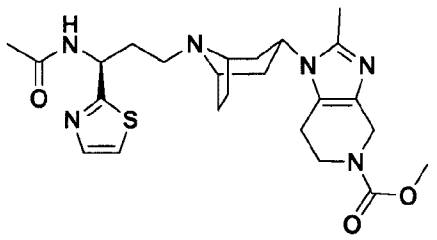
Example 118 Synthesis of compound 118



N-{(1S)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (thiazol-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40 to obtain compound 118, MS: 471.25 [M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

Example 119 Synthesis of compound 119

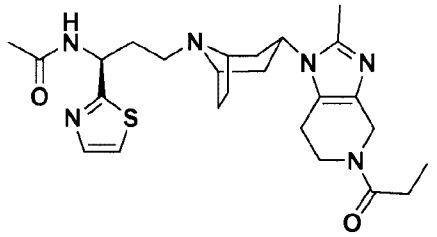


Methyl

1-{(endo)-8-[(S)-3-acetamido-3-(thiazol-2-yl)-propyl]-8-azabicyclo[3.2.1]octan-3-yl}-2-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5- carboxylate

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40 and methyl chloroformate was used to replace acetyl chloride in Example 40 to obtain compound 119, MS: 487.24 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.18 (m,2H), 3.76 (s, 3H),3.65-3.733 (m, 3H), 2.66 (m, 2H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

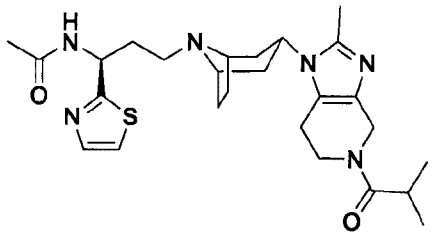
Example 120 Synthesis of compound 120



N-{(1S)-3-[(3-endo)-3-(5-propionyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (thiazol-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40 and propionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 120, MS: 485.26 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.27(q, 2H), 1.44-2.12 (m, 15H), 1.21(t, 3H).

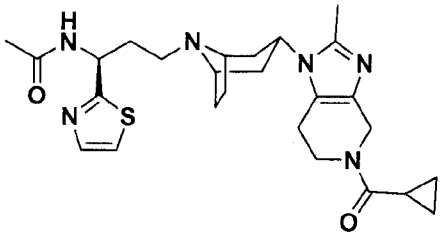
Example 121 Synthesis of compound 121



N-{(1S)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (thiazol-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 121, MS: 499.28 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 3H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 15H), 1.10(d, 6H).

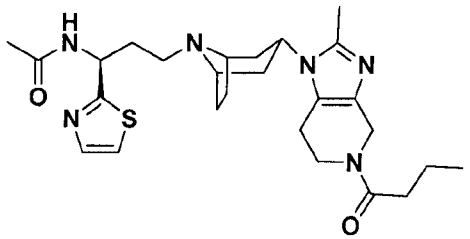
Example 122 Synthesis of compound 122



N-{(1S)-3-[(3-endo)-3-(5-cyclopropionyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (thiazol-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40 and cyclopropionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 122, MS: 497.26 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 16H), 0.53-0.78(m, 4H).

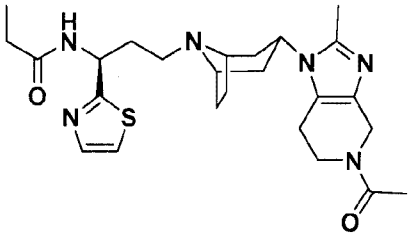
Example 123 Synthesis of compound 123



N-{(1S)-3-[(3-endo)-3-(5-n-butyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (thiazol-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40 and n-butyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 123, MS: 499.28 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.34(m, 2H), 1.44-2.12 (m, 17H), 0.96(t, 3H).

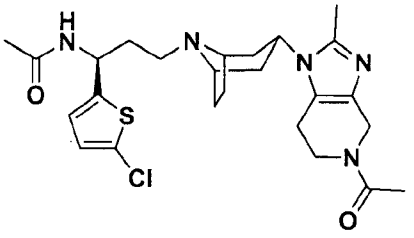
Example 124 Synthesis of compound 124



N-{(1S)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (thiazol-2-yl)-propyl}propanamide

According to the synthesis method of compound 40, Compound 29-1 was used to replace compound 3-1 in Example 40, propionic acid was used to replace acetic acid in Example 40 and n-butyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 124, MS: 485.26 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.65 (d, 1H), 7.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.32(s, 3H), 2.23(q, 2H), 1.44-1.96 (m, 12H), 1.11(t, 3H).

Example 125 Synthesis of compound 125

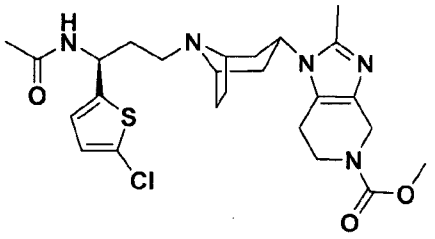


N-{(1S)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-chlorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 28-1 was used to replace compound 3-1 in Example 40 to obtain compound 125, MS: 504.21 [M+H]+.

^{1}H-NMR(400Hz, $CDCl_3$): δ6.65 (d, 1H), 6.26 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

Example 126 Synthesis of compound 126

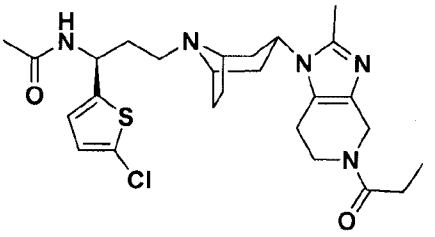


Methyl

1-{(endo)-8-[(S)-3-acetamido-3-(5-chlorothiophen-2-yl)-propyl]-8-azabicyclo[3.2.1]octan-3-yl}-2-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5- carboxylate

According to the synthesis method of compound 40, Compound 28-1 was used to replace compound 3-1 in Example 40 and methyl chloroformate was used to replace acetyl chloride in Example 40 to obtain compound 126, MS: 520.21 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.45 (d, 1H), 6.16 (d, 1H), 4.78 (t,1H), 4.18 (m,2H), 3.76 (s, 3H),3.65-3.733 (m, 3H), 2.66 (m, 2H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

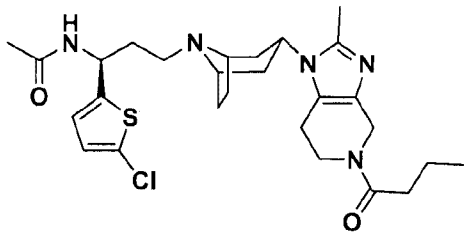
Example 127 Synthesis of compound 127



N-{(1S)-3-[(3-endo)-3-(5-propionyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-chlorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 28-1 was used to replace compound 3-1 in Example 40 and propionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 127, MS: 518.23 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.45 (d, 1H), 6.16 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.27(q, 2H), 1.44-2.12 (m, 15H), 1.21(t, 3H).

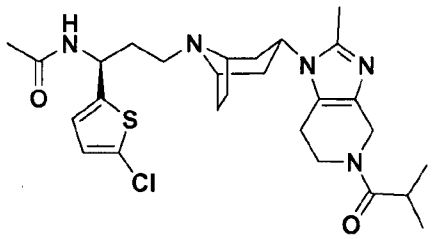
Example 128 Synthesis of compound 128



N-{(1S)-3-[(3-endo)-3-(5-n-butyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-chlorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 28-1 was used to replace compound 3-1 in Example 40 and n-butyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 128, MS: 532.24 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.48 (d, 1H), 6.12 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.34(m, 2H), 1.44-2.12 (m, 17H), 0.96(t, 3H).

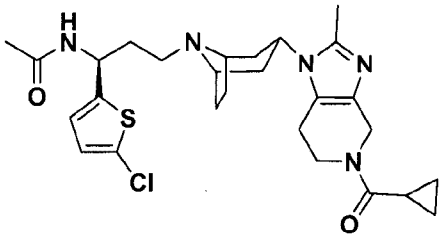
Example 129 Synthesis of compound 129



N-{(1S)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-chlorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 28-1 was used to replace compound 3-1 in Example 40 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 129, MS: 532.24 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.48 (d, 1H), 6.12 (d, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 3H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 15H), 1.10(d, 6H).

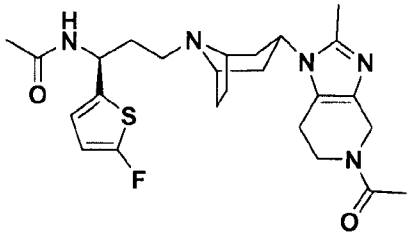
Example 130 Synthesis of compound 130



N-{(1S)-3-[(3-endo)-3-(5-cyclopropionyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-chlorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 28-1 was used to replace compound 3-1 in Example 40 and cyclopropionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 130, MS: 530.23 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.78 (d, 1H), 6.22 (d, 1H), 4.78 (t,1II), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 16H), 0.53-0.78(m, 4H).

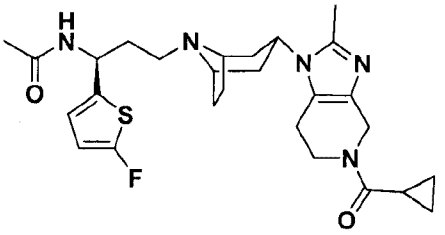
Example 131 Synthesis of compound 131



N-{(1S)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-fluorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40 to obtain compound 131, MS: 488.24 [M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ6.46 (m, 1H), 6.27 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

Example 132 Synthesis of compound 132

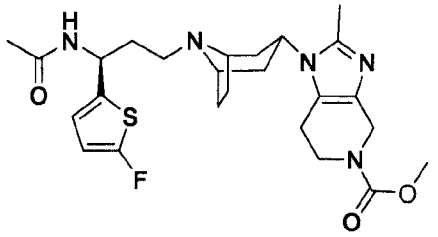


N-{(1S)-3-[(3-endo)-3-(5-cyclopropionyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-fluorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40 and cyclopropionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 132, MS: 514.26 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.36 (m, 1H), 6.15 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H),

2.66-2.69 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 16H), 0.53-0.78(m, 4H).

Example 133 Synthesis of compound 133

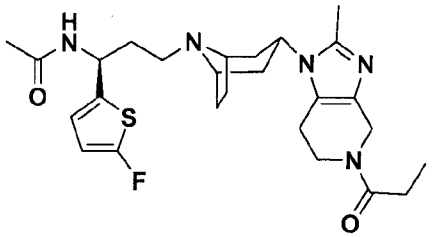


Methyl

1-{(endo)-8-[(S)-3-acetamido-3-(5-fluorothiophen-2-yl)-propyl]-8-azabicyclo[3.2.1]octan-3-yl}-2-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5- carboxylate

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40 and methyl chloroformate was used to replace acetyl chloride in Example 40 to obtain compound 133, MS: 504.24 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.47 (m, 1H), 6.25 (m, 1H), 4.78 (t,1H), 4.18 (m,2H), 3.76 (s, 3H),3.65-3.733 (m, 3H), 2.66 (m, 2H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

Example 134 Synthesis of compound 134

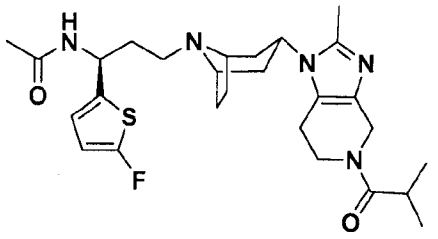


N-{(1S)-3-[(3-endo)-3-(5-propionyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-fluorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40 and propionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 134, MS: 502.26 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.48 (m, 1H), 6.23 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.27(q, 2H), 1.44-2.12 (m, 15H), 1.21(t, 3H).

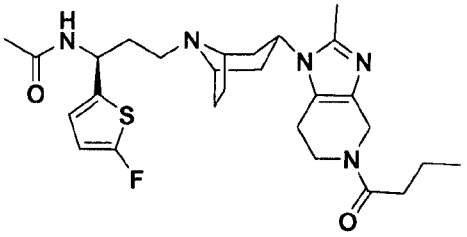
Example 135 Synthesis of compound 135

N-{(1S)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-fluorothiophen-2-yl)-propyl}acetamide



According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40 and isobutyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 135, MS: 516.27 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.42 (m, 1H), 6.13 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 3H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 15H), 1.10(d, 6H).

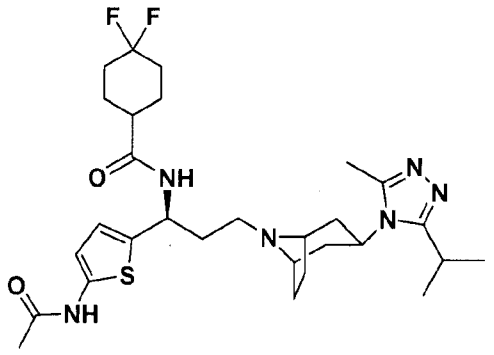
Example 136 Synthesis of compound 136

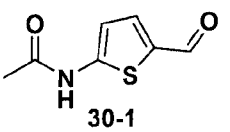


N-{(1S)-3-[(3-endo)-3-(5-n-butyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-fluorothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 7-1 was used to replace compound 3-1 in Example 40 and n-butyryl chloride was used to replace acetyl chloride in Example 40 to obtain compound 136, MS: 516.27 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.41 (m, 1H), 6.12 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.34(m, 2H), 1.44-2.12 (m, 17H), 0.96(t, 3H).

Example 137 Synthesis of compound 137



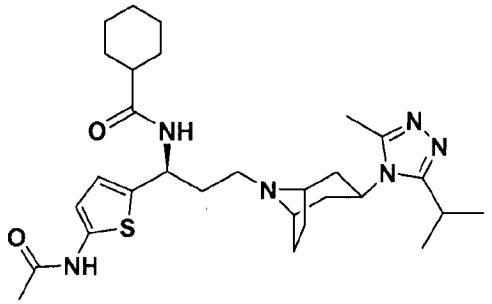


30-1

4,4-difluoro-N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-acetamidothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 30-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace compound 1f in Example 5 to obtain compound 137, MS: 577.31 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.32 (d, 1H), 7.07 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.31-2.45(m, 6H), 2.33(s,3H), 1.34-1.83 (m,20H), 1.26 (d, 6H).

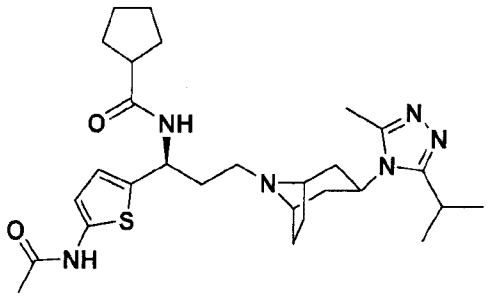
Example 138 Synthesis of compound 138



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-acetamidothiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 30-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 138, MS: 541.32 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.31 (d, 1H), 7.03 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.36-2.43(m, 6H), 2.30(s,3H), 1.34-1.83 (m,22H), 1.26 (d, 6H).

Example 139 Synthesis of compound 139

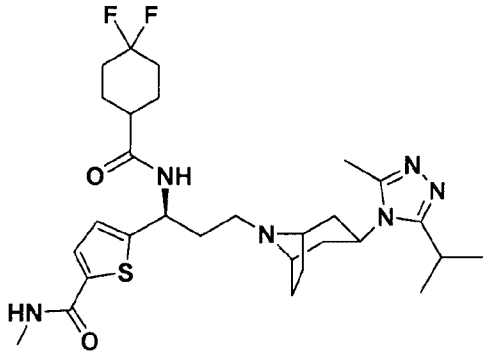


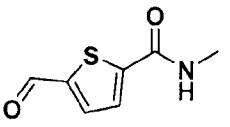
N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-y

l]-1-(5-acetamidothiophen-2-yl)propyl]cyclopentane-1-carboxamide

According to the synthesis method of Example 5, Compound 30-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 139, MS: 527.31 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.31 (d, 1H), 7.03 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.36-2.43(m, 6H), 2.26(s,3H), 1.34-1.83 (m,20H), 1.26 (d, 6H).

Example 140 Synthesis of compound 140



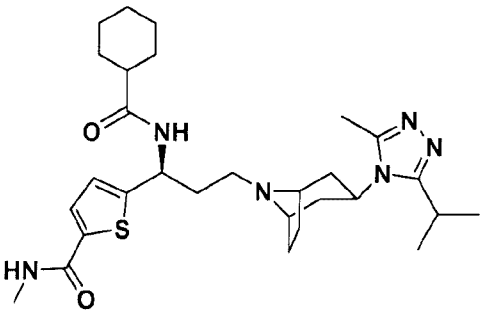


31-1

5-[(1S)-1-(4,4-difluorocyclohexyl-1-formamido)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-propyl]-N-methylthiophene-2carboxamide

According to the synthesis method of Example 5, Compound 31-1 was used to replace compound 2-1 in Example 5 and compound 2f was used to replace compound 1f in Example 5 to obtain compound 140, MS: 577.31 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.26(d, 1H), 7.07 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.86(s,3H), 2.39-2.45(m, 3H), 2.33(s,3H), 1.34-1.83 (m,20H), 1.26 (d, 6H).

Example 141 Synthesis of compound 141

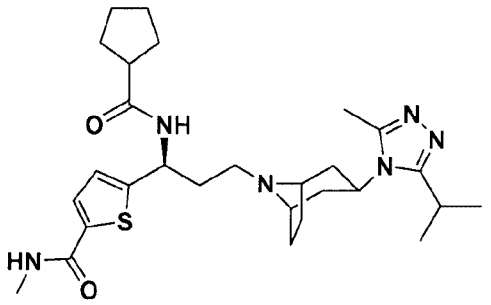


5-[(1S)-1-(cyclohexaneformamido)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-

azabicyclo[3.2.1]octane-8-yl]-propyl]-N-methylthiophene-2carboxamide

According to the synthesis method of Example 5, Compound 31-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 141, MS: 541.32 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.14(d, 1H), 7.13 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.86(s,3H), 2.39-2.45(m, 3H), 2.33(s,3H), 1.34-1.83 (m,22H), 1.26 (d, 6H).

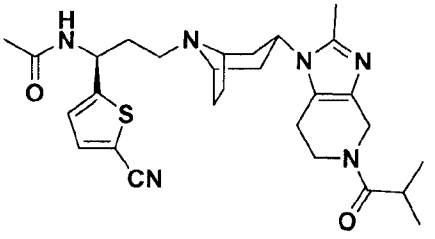
Example 142 Synthesis of compound 142



5-[(1S)-1-(cyclopentaneformamido)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-propyl]-N-methylthiophene-2carboxamide

According to the synthesis method of Example 5, Compound 31-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclopentanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 142, MS: 527.31 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.36(d, 1H), 7.13 (d, 1H), 4.74 (m,1H), 3.71 (m, 1H), 3.21 (m, 1H), 2.86(s,3H), 2.39-2.45(m, 3H), 2.33(s,3H), 1.34-1.83 (m,20H), 1.26 (d, 6H).

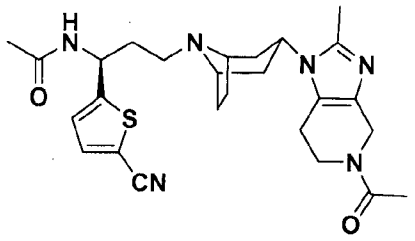
Example 143 Synthesis of compound 143



N-{(1S)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-cyanothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 13-1 was used to replace compound 3-1 in Example 40 and isopropionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 143, MS: 523.28 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.44 (m, 1H), 6.87 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 3H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 15H), 1.10(d, 6H).

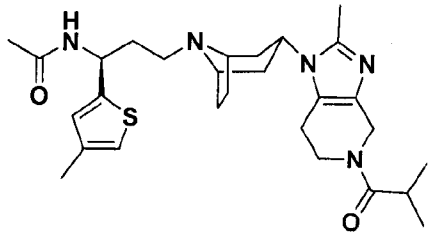
Example 144 Synthesis of compound 144



N-{(1S)-3-[(3-endo)-3-(5-acetyl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (5-cyanothiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 13-1 was used to replace compound 3-1 in Example 40 to obtain compound 144, MS: 495.25 [M+H]+. ^{1}H-NMR(400Hz, $CDCl_3$): δ7.56 (m, 1H), 6.93 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66 (m, 2H), 2.53 (s, 3H), 2.43 (m, 2H), 2.32 (s, 3H), 1.44-2.12 (m, 15H).

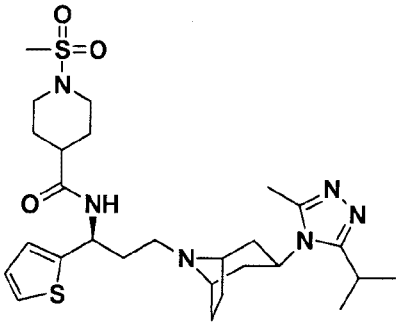
Example 145 Synthesis of compound 145



N-{(1S)-3-[(3-endo)-3-(5-isobutyryl-2-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridin-1-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1- (4-methylthiophen-2-yl)-propyl}acetamide

According to the synthesis method of compound 40, Compound 18-1 was used to replace compound 3-1 in Example 40 and isopropionyl chloride was used to replace acetyl chloride in Example 40 to obtain compound 145, MS: 512.30 [M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.59 (m, 1H), 6.91 (m, 1H), 4.78 (t,1H), 4.38 (m,2H), 3.86 (m,2H), 3.74 (m, 1H), 2.66-2.69 (m, 3H), 2.53 (s, 3H), 2.43 (m, 2H), 1.44-2.12 (m, 15H), 1.10(d, 6H).

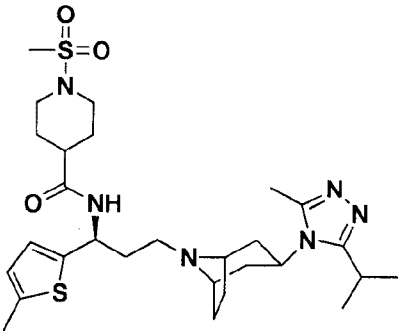
Example 146 Synthesis of compound 146



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -1-methylsulfonylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in example 5, compound 2f was used to replace compound 1f in example 5 and 1-methylsulfonyl-4-piperidine carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 146, MS: 563.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

Example 147 Synthesis of compound 147

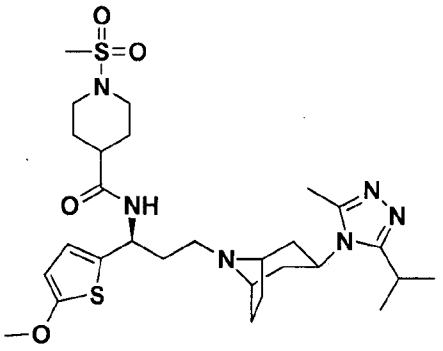


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -1-methylsulfonylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-methylsulfonyl-4-piperidine carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 147, MS:

577.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H), 5.19 (m,1H), 3.91 (m, 1H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.36 (s,3H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

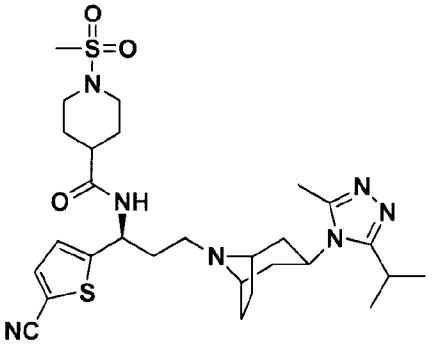
Example 148 Synthesis of compound 148



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxythiophen-2-yl)propyl] -1-methylsulfonylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 27-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-methylsulfonyl-4-piperidine carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 148, MS: 593.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.28 (t, 1H), 7.13 (d, 1H) 5.19 (m,1H), 3.91 (m, 4H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.36 (s,3H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

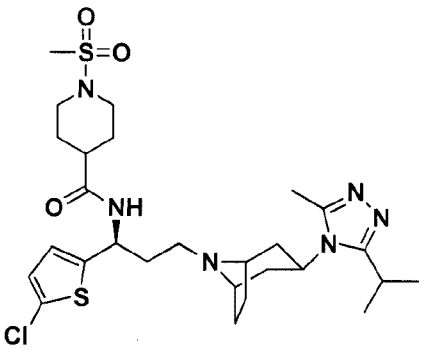
Example 149 Synthesis of compound 149



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl] -1-methylsulfonylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 13-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-methylsulfonyl-4-piperidine carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 149, MS: 588.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.38 (t, 1H), 7.24 (d, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.36 (s,3H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

Example 150 Synthesis of compound 150

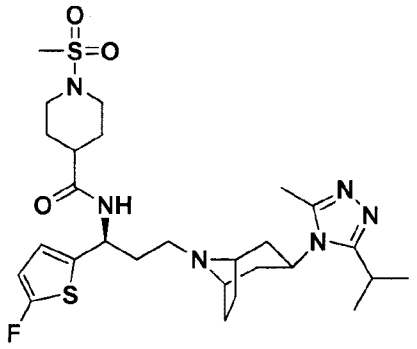


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-chlorothiophen-2-yl)propyl] -1-methylsulfonylpiperidine-4-carboxamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-methylsulfonyl-4-piperidine carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 150, MS: 597.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.38 (t, 1H), 7.23 (d, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.36 (s,3H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

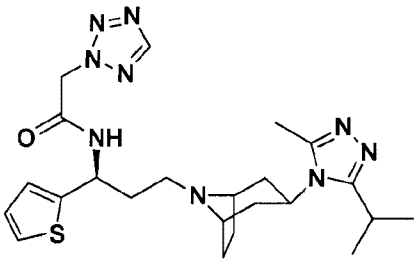
Example 151 Synthesis of compound 151

N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-fluorothiophen-2-yl)propyl] -1-methylsulfonylpiperidine-4-carboxamide



According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 1-methylsulfonyl-4-piperidine carboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 151, MS: 581.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.48 (t, 1H), 7.24 (d, 1H), 5.19 (m,1H), 3.91 (m, 4H), 3.31 (m, 4H), 3.02 (m, 1H), 2.54(s, 3H), 2.43 (m,5H), 2.37 (s,3H), 2.26-1.93 (m,13H), 1.93-1.61 (m, 6H), 1.36 (d, 6H).

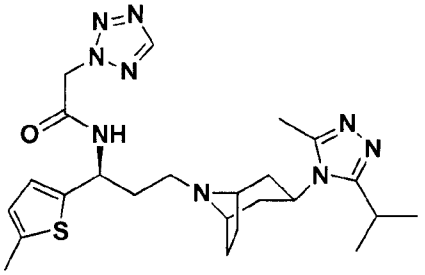
Example 152 Synthesis of compound 152



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -2-(2*H*-tetrazol-2-yl)acetamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(2*H*-tetrazol-2-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 152, MS: 484.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.53 (s, 1H), 7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 4.62 (s, 2H), 3.95 (m, 1H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

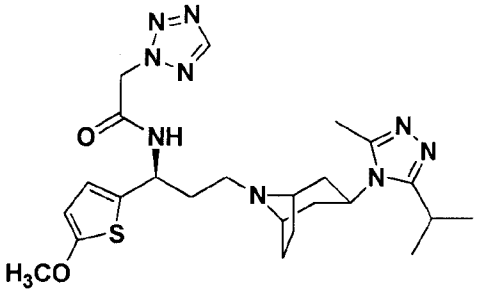
Example 153 Synthesis of compound 153



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl] -2-(2*H*-tetrazol-2-yl)acetamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(2*H*-tetrazol-2-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 153, MS: 498.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.53 (s, 1H), 7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 4.62 (s, 2H), 3.95 (m, 1H), 3.03 (m, 1H), 2.36 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

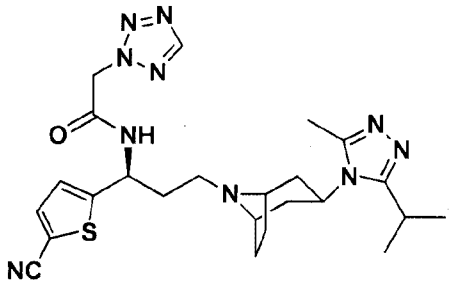
Example 154 Synthesis of compound 154



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl] -2-(2*H*-tetrazol-2-yl)acetamide

According to the synthesis method of Example 5, Compound 27-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(2*H*-tetrazol-2-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 154, MS: 514.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.53 (s, 1H), 7.23 (t, 1H), 5.21 (m,1H), 4.62 (s, 2H), 3.95 (m, 1H), 3.85 (s, 3H), 3.03 (m, 1H), 2.36 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

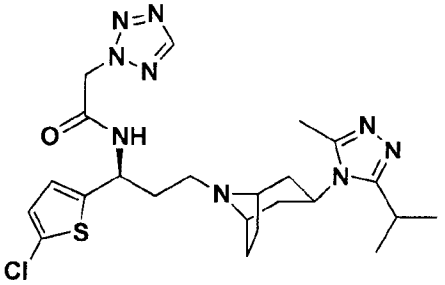
Example 155 Synthesis of compound 155



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl] -2-(2*H*-tetrazol-2-yl)acetamide

According to the synthesis method of Example 5, Compound 13-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(2*H*-tetrazol-2-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 155, MS: 509.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.53 (s, 1H), 7.23 (t, 1H), 5.21 (m,1H), 4.62 (s, 2H), 3.95 (m, 1H), 3.03 (m, 1H), 2.36 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

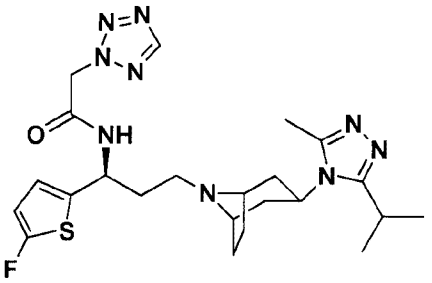
Example 156 Synthesis of compound 156



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-chlorothiophen-2-yl)propyl] -2-(2*H*-tetrazol-2-yl)acetamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(2*H*-tetrazol-2-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 156, MS: 518.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.03 (s, 1H), 7.53 (t, 1H), 5.21 (m,1H), 4.62 (s, 2H), 3.95 (m, 1H), 3.03 (m, 1H), 2.36 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

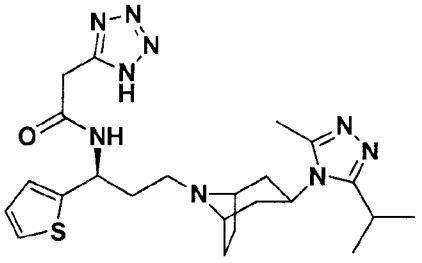
Example 157 Synthesis of compound 157



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-fluorothiophen-2-yl)propyl] -2-(2*H*-tetrazol-2-yl)acetamide

According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(2*H*-tetrazol-2-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 157, MS: 502.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.13 (s, 1H), 7.23 (t, 1H), 5.21 (m,1H), 4.62 (s, 2H), 3.95 (m, 1H), 3.03 (m, 1H), 2.36 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

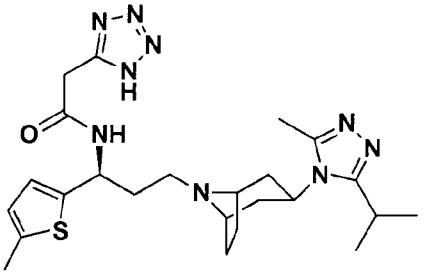
Example 158 Synthesis of compound 158



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -2-(1*H*-tetrazol-5-yl)acetamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-5-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 158, MS: 484.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

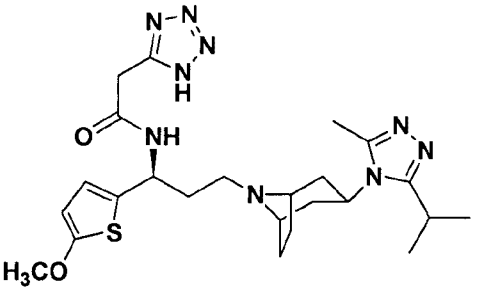
Example 159 Synthesis of compound 159



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl] -2-(1*H*-tetrazol-5-yl)acetamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-5-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 159, MS: 498.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.36 (s,3H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

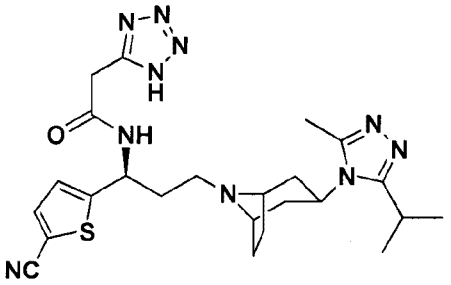
Example 160 Synthesis of compound 160



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxythiophen-2-yl)propyl] -2-(1*H*-tetrazol-5-yl)acetamide

According to the synthesis method of Example 5, Compound 27-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-5-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 160, MS: 514.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

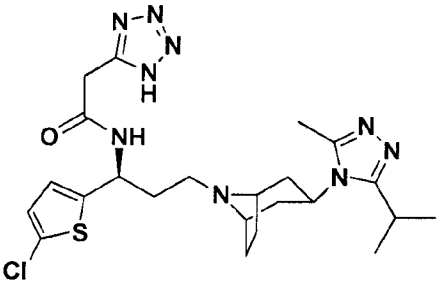
Example 161 Synthesis of compound 161



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl] -2-(1*H*-tetrazol-5-yl)acetamide

According to the synthesis method of Example 5, Compound 13-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-5-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 161, MS: 509.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.43 (t, 1H), 7.35 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

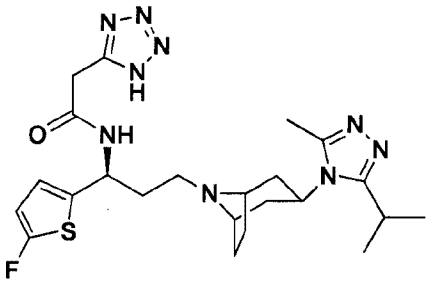
Example 162 Synthesis of compound 162



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-chlorothiophen-2-yl)propyl] -2-(1*H*-tetrazol-5-yl)acetamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-5-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 162, MS: 518.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.53 (t, 1H), 7.45 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

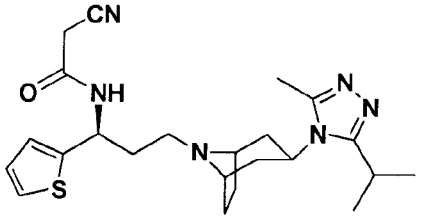
Example 163 Synthesis of compound 163



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-fluorothiophen-2-yl)propyl] -2-(1*H*-tetrazol-5-yl)acetamide

According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-5-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 163, MS: 502.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.63 (t, 1H), 7.55 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

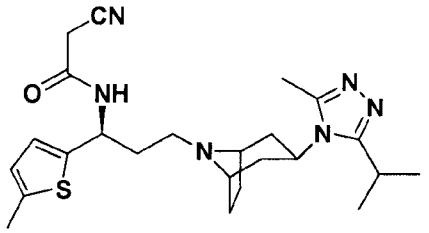
Example 164 Synthesis of compound 164



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -2-cyanoacetamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-cyanoacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 164, MS: 441.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.32 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

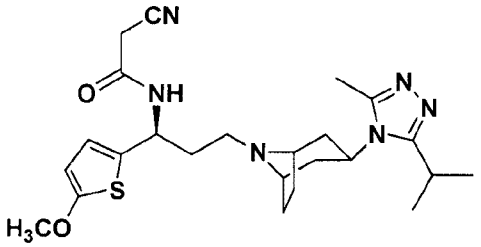
Example 165 Synthesis of compound 165



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methylthiophen-2-yl)propyl] -2-cyanoacetamide

According to the synthesis method of Example 5, Compound 5-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-cyanoacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 165, MS: 454.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.32 (s, 2H), 3.03 (m, 1H), 2.37 (s, 3H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

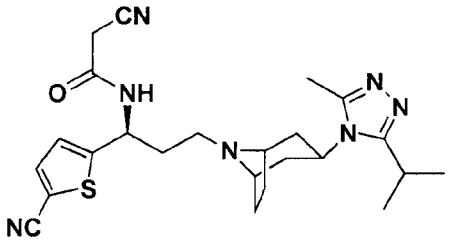
Example 166 Synthesis of compound 166



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-methoxythiophen-2-yl)propyl] -2-cyanoacetamide

According to the synthesis method of Example 5, Compound 27-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-cyanoacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 166, MS: 471.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.87 (s, 3H), 3.32 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

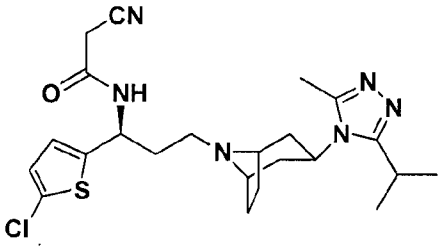
Example 167 Synthesis of compound 167



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-cyanothiophen-2-yl)propyl] -2-cyanoacetamide

According to the synthesis method of Example 5, Compound 13-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-cyanoacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 167, MS: 465.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.23 (t, 1H), 7.15 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.32 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

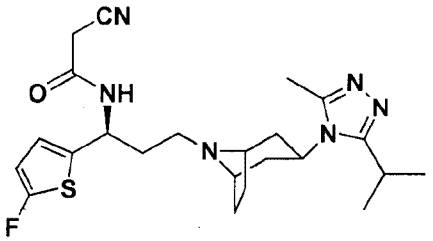
Example 168 Synthesis of compound 168



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -2-cyanoacetamide

According to the synthesis method of Example 5, Compound 28-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-cyanoacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 167, MS: 465.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.43 (t, 1H), 7.35 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.32 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

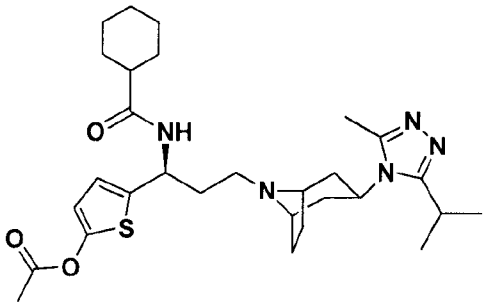
Example 169 Synthesis of compound 169

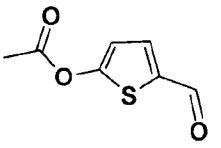


N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -2-cyanoacetamide

According to the synthesis method of Example 5, Compound 7-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-cyanoacetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 169, MS: 458.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ7.48 (t, 1H), 7.37 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.32 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

Example 170 Synthesis of compound 170



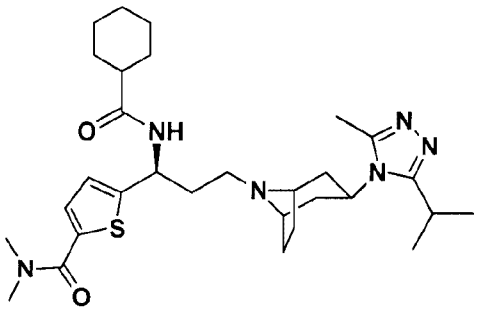


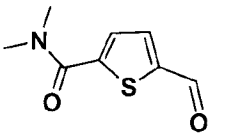
32-1

N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(5-acetoxythiophen-2-yl)propyl]cyclohexane-1-carboxamide

According to the synthesis method of Example 5, Compound 32-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 170, MS: 542.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.43(m,2H), 5.79 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.43 (m,5H), 2.28(s, 3H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 171 Synthesis of compound 171



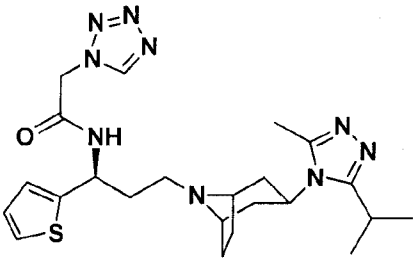


33-1

5-[(1S)-1-(cyclohexaneformamido)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-propyl]-*N,N*-dimethylthiophene-2carboxamide

According to the synthesis method of Example 5, Compound 33-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and cyclohexanecarboxylic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 171, MS: 555.2[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ6.43(m,2H), 5.79 (m,1H), 3.91 (m, 1H), 3.02 (m, 1H), 2.93(s, 6H), 2.85(s, 6H), 2.43 (m,5H), 2.16-1.93 (m,13H), 1.93-1.61 (m, 10H), 1.36 (d, 6H).

Example 172 Synthesis of compound 172



N-[(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane-8-yl]-1-(thiophen-2-yl)propyl] -2-(1*H*-tetrazol-1-yl)acetamide

According to the synthesis method of Example 5, Compound 1-1 was used to replace compound 2-1 in Example 5, compound 2f was used to replace compound 1f in Example 5 and 2-(1*H*-tetrazol-1-yl)acetic acid was used to replace 4,4-difluoro-cyclohexanecarboxylic acid in Example 5 to obtain compound 172, MS: 484.3[M+H]+.^{1}H-NMR(400Hz, $CDCl_3$): δ8.73 (s, 1H), 7.23 (t, 1H), 7.15 (d, 1H), 6.99 (d, 1H), 5.21 (m,1H), 3.95 (m, 1H), 3.42 (s, 2H), 3.03 (m, 1H), 2.40 (m,2H), 2.25-1.67 (m,14H), 1.32 (d, 6H).

Experiment Example

Example 1: Calcium flux inhibition experiment

Experiment apparatus: FlexStation II

Experiment materials: HEK293/CCR5-Gα16 cell line, Fluo-4calcium dye (fluorescent-4 calcium ion dye) and FlexStation instrument.

Experiment theory: Activation of the receptor can cause the activation of Gα16 protein, thereby activating phospholipase C (PLC) to generate IP3 and DAG by establishing CCR5 and Ga16 co-transfected cell line. IP3 can bind to IP3 receptors on the endoplasmic reticulum and mitochondria in a cell, which can cause the release of intracellular calcium. Thus, determination of changes in intracellular calcium can be used as a method to detect CCR5 activation state. Fluo-4/AM is a fluorescent probe indicator for calcium used to measure calcium ion. As a non-polar lipid-soluble compound, after it enters into cells, AM group is dissociated to release Fluo-4 under the effect of cell lipolysis enzyme. Fluo-4 is a polar molecule and not easy to go through the lipid bilayer membrane, therefore it can stay within the cells for a long time. Ultimately, the level of activated Ga protein can be reflected by measuring the excited fluorescence intensity. If the screened compound can activate CCR5, it can greatly increase the calcium flux reaction; on the contrary, if the screened compound can antagonize CCR5, it can greatly reduce calcium flux reaction.

Experiment steps:

1. HEK293 cells which can stably express CCR5 were inoculated in a 96-well plate and incubated overnight.

2. The medium in each well into which cells were innoculated was removed and 40 μl/well of freshly prepared dye was added. The plate was placed in a 37°C incubator and incubated for 40 minutes at constant temperature.

3. The medicament to be determined was diluted with calcium buffer to eight concentration gradients, which is 1×10^{-4}M, 1×10^{-5}M, 1×10^{-6}M, 1×10^{-7}M, 1×10^{-8}M, 1×10^{-9}M, 1×10^{-10}M, and 1×10^{-11}M, respectively, and homogeneously mixed.

4. The dye was removed. Freshly prepared calcium buffer was used to wash for one time, 50 μl of calcium buffer was added.

5. FlexStation II was used for detection. 25 μl of calcium buffer containing the medicament to be determined was added automatically from the 15th second. The

fluorescence value at 525 nm was read ultimately.

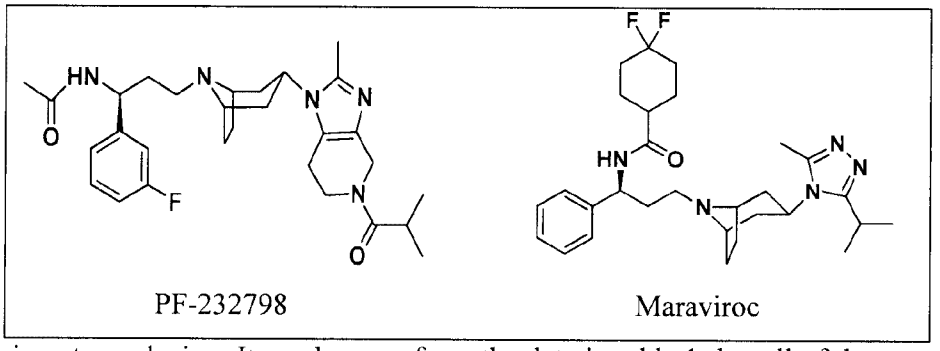
Experiment results:

Table 1 The results from Calcium flux inhibition experiment of compounds

compound	CCR5 IC_{50} (nM)	compound	CCR5 IC_{50} (nM)	compound	CCR5 IC_{50} (nM)
1	36.56	39	1.412	139	12.32
2	32.57	42	15.90	140	13.73
3	1.953	43	8.340	141	8.36
4	15.04	64	4.628	142	9.55
5	29.68	65	1.625	143	13.89
6	6.904	66	2.015	144	8.53
7	35.23	70	9.45	145	13.32
8	21.92	73	8.23	146	1.75
9	79.34	88	9.26	147	2.48
10	36.56	112	10.37	148	3.42
13	3.397	113	8.14	149	7.89
14	2.334	114	9.27	150	2.22
15	9.222	115	10.32	151	3.45
16	2.234	116	15.57	152	7.98
17	2.547	117	16.13	153	13.45
18	3.733	118	16.87	154	23.14
19	21.52	119	4.77	155	8.23
20	5.145	120	27.72	156	9.85
21	11.89	121	32.32	157	1.23
22	1.051	122	24.52	158	14.86
23	27.26	123	12.13	159	8.76
24	44.61	124	11.25	160	1.34
25	37.85	125	12.19	161	8.36
26	5.063	126	21.97	162	1.85

27	11.42	127	22.94	163	13.32
28	68.02	128	17.52	164	7.38
29	7.282	129	14.2	165	8.29
30	24.04	130	18.51	166	6.54
31	9.763	131	6.57	167	7.98
32	8.354	132	22.2	168	1.54
33	25.01	133	1.785	169	6.32
34	143.4	134	22.13	170	1.38
35	270.4	135	8.279	171	1.64
36	31.78	136	22.13	172	9.385
37	9.334	137	8.23	Maraviroc	7.385
38	9.331	138	9.75	PF-232798	8.290

Note: The structures of PF-232798 and Maraviroc used as positive control compounds (similarly hereinafter) are as follows:



PF-232798 Maraviroc

Experiment conclusion: It can be seen from the data in table 1 that all of the compounds have good calcium influx inhibition effects, wherein, compound 3, 6, 13, 14, 16, 17, 18, 20, 22, 26, 29, 39, 64, 65, 66, 119, 123, 124, 131, 133, 146, 147, 148, 150, 151, 157, 160, 162, 164, 166, 168, 169, 170, 171 and 172 are better than the positive control compounds, and compound 15, 21, 27, 31, 32, 37, 38, 135, 137, 138, 141, 142, 149, 152, 155, 156, 159, 161, 165 and 167 are comparable to the positive control compounds.

Example 2: Thermal stability of protein test (CPM-assay)

Experimental theory: many cysteines are present in CCR5 protein sequence. Cysteines located in loop region form disulfide bonds to stabilize the tertiary structure of the protein. Some free cysteines in reduced state are located in the transmembrane region. Under

excitation by incident light of 387 nm, the combination of free sulfhydryl and fluorescent dye CPM can emit excitation light of 436 nm. If the temperature is gradually increased artificially, the tertiary structure of the membrane protein gradually become loose as the temperature rises. The free sulfhydryls originally located in the transmembrane region expose and combine with the fluorescent dye. And then the detector will detect changes in signal enhancement. Therefore, the thermal stability of membrane proteins can be determined according to the temperature (Tm) at the midpoint of changes in signal intensity.

Experimental steps: Upon preliminary purification, the obtained protein solution was transferred into a small concentration tube (100kd, 500ul) for concentration (1000 rcf, 12 min, 4 °C). After centrifugation, the concentration tube was taken out and flicked to prevent protein coagulation due to high local concentration. The final concentrated volume was about 50 μl. 117 μl of purified solution (volume is suitable to make the total volume up to 120 μl), 1 μl fluorescent dye cpm (in-house prepared) and 2 μl of concentrated protein solution (the amount of added protein is 3-5 μg according to the calculated concentration of the protein solution and the concentrated volume) were added to 2 ml Ependorf tube and incubated at room temperature for 20min. And then the mixture was added to the cuvette (Qwan) and put in the testing equipment Cary, wherein the surface of the frosted glass faced out. The temperature was set in the range of 4-90°C with 1°C increase per minute and the program was run. Tm value can be obtained by processing the data and graph with a mapping software and can be used to compare the difference of protein thermal stability under different conditions.

Table 2 The results of effects of compounds on thermal stability of protein

compound	Tm (°C)	compound	Tm (°C)	compound	Tm (°C)
1	60.59	10	63.21	21	64.68
2	65.23	13	65.32	22	68.21
3	67.71	14	68.10	23	63.90
4	65.64	15	64.30	24	62.31
5	57.31	16	71.32	25	62.31
6	58.56	17	66.97	26	71.02
7	57.21	18	71.73	Maraviroc	72.17
8	60.61	19	69.20		

9	61.32	20	70.27		

It can be seen from table 2 that all compounds have good protein stability effect, wherein compound 16, 18, 20 and 26 are comparable with the positive control compound.

Example 3: Preliminary screening test of anti- HIV-1 activity *in vitro*

1. Experiment materials

Phosphate buffered saline (PBS), Streptomycin sulfate, HEPES (N-2 (2-Hydroxyothyl) piperazine-N'-(2-ethanesufonic acid), MTT (3,(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), Penicillin, Glutamine, 2-Mercaptoethanol, RPMI-1640, RPMI-1640 complete medium and fetal bovine serum (FBS).

2. HIV-1 infectivity titration

The virus was titrated according to the modified method of Johnson & Byington. Briefly, the HIV-1 stock solution was subject to four-fold dilution in a 96-well plate (ten gradients) sextuplicate for each gradient, while setting six control-wells. Into each well was added 100 μl (5×10^6/ ml) PHA-stimulated PBMC cells and final volume per well was 200 μl. The cells were cultured at 37°C with 5% CO_2. On the third day, 100 μl of fresh RPMI-1640 complete medium was supplemented. On the seventh day, the infected supernatant was collected and lysed with 0.5% Triton X100. The p24 antigen was detected by ELISA and $TCID_{50}$ of virus was calculated according to Reed & Muench method (50% Tissue culture infection dose).

3. Toxicity test of Compounds on HOS-CD4-CCR5, PM1 and PBMC cells

The compound to be tested was subject to 5-fold dilution in a 96-well microtiter plate with RPMI-1640 or DMEM complete medium (containing 10% FBS) (Six dilution) triplicate for each dilution and 100μl for each well. While wells not containing drugs were set as control. Into each well was added 100 μl of 4×10^5/ml PM1, HOS-CD4-CCR5 cells or 100 μl of 5×10^6/ ml PHA stimulated PBMC. The cells were cultured at 37°C with 5% CO_2 for three days (PBMC cells were cultured for seven days and 100 μl of fresh RPMI-1640 complete medium was supplemented on the third day). Cytotoxicity was tested with MTT assay. OD values were measured by ELx800 microplate reader. The detection wavelength was 570nm, and the reference wavelength was 630nm. CC_{50} values were calculated (50% Cytotoxic concentration).

4. Inhibition assay of compounds on viral replication in HOS-CD4-CCR5 cells infected

with HIV-1_{SF162} or HIV-1_{Ba-L}

On the day before the test, 1×10^5/ml of HOS-CD4-CCR5 cells were inoculated in 96-well plates with 100 μl for each well. The compound to be tested was subject to 5-fold dilution in 96-well microtiter plate with DMEM complete medium (containing 10% FBS). The starting concentration was 1 μM and six dilutions were obtained. Triplicate wells were set for each dilution and each well contained 100μl mixture. While wells not containing drugs were set as control. The supernatant was removed and 100μl of drug was added and incubated for 2h. Then 100μl of HIV-1_{SF162} and HIV-1_{Ba-L} were added to dilute supernatant. The cells were infected for 1h, free virus was washed out and drug with the same final concentration was added. MVC was used as positive control. The cells were cultured at 37°C with 5% CO_2 for three days. The supernatant was collected, lysed and inactivated with 0.5% Triton X-100. The inhibition effect of drug on HIV-1 replication was detected using p24 antigen capture ELISA method.

5. Inhibition assay of compounds on viral replication in PBMC infected with HIV-1_{SF162}, HIV-1_{Ba-L} or HIV-1_{KM018}

The compound to be tested was subject to 5-fold dilution in 48-well plate with RPMI-1640 complete medium (containing 10% FBS). The starting concentration was 1 μM, six dilutions were obtained, and each well contained 200μl mixture. While wells not containing drugs were set as control. Virus (MOI = 0.01) was added to 5×10^6/ml of PBMC cells which have been stimulated by PHA for 72h. After homogeneously mixed, the mixture was immediately added to 48-well plate containing diluted drug and each well was added with 200 μl of mixture. MVC was used as positive control. The cells were cultured at 37°C with 5% CO_2 for seven days (drug with the same concentration was added on the third day). The supernatant was collected, lysed and inactivated with 0.5% Triton X-100. The inhibition effect of drug on HIV-1 replication was detected using p24 antigen capture ELISA method.

6. Experiment results:

Table 3 Inhibition activities of compounds on TZM-bl cells infected with HIV-1_{SF162} virus strain

compound	CC_{50}(μg/mL)	EC_{50}(μg/mL)	therapeutic index (TI)
1	>100	0.29	>340.14

2	>100	0.326	>306.75
3	>100	0.0024	>41666.67
4	42.761	1.46	29.29
6	>100	1.51	66.23
7	>100	2.34	50.31
8	>100	2.69	>37.17
9	>100	1.81	55.42
10	>100	1.42	>70.42
13	>100	0.18296	>1093.14
14	>200	0.00359	>55710.31
15	>200	0.31602	>632.87
16	>200	0.01179	>16963.53
17	>200	0.01295	>15444.02
18	>200	0.00123	>162601.63
19	85.74	0.00959	8940.56
20	69.68	0.00487	14308.01
21	>200	0.14993	>1333.96
22	>200	0.00153	>130718.95
23	>200	0.06001	>3332.78
25	>200	0.16801	>1190.41
26	>200	0.00558	>35842.29
27	96.141	0.511	188.14
28	>200	>40	—
29	>200	0.012	>16666.67
30	>200	0.060	>2150.54
31	>200	0.033	>5714.29
32	>200	>40	—
33	>200	0.147	>328.95
34	>200	>40	—

35	>200	>40	—
36	>200	>40	—
37	>200	0.647	>309.12
38	>200	2.610	>73.64
39	>200	1.020	>196.08
118	>200	0.669	>168.03
119	>200	0.738	>270.84
120	>200	0.831	>240.76
121	>200	0.328	>386.37
122	>200	0.690	>290.06
125	>200	0.286	>699.27
126	>200	0.091	>2207.68
127	>200	0.145	>1379.94
128	>200	0.174	>1150.82
129	>200	0.072	>1526.72
130	>200	0.053	>2562.98
131	>200	0.098	>1302.27
132	>200	0.097	>2063.25
133	>200	0.152	>1313.56
134	>200	0.113	>1772.41
135	>200	0.155	>1222.11
136	>200	0.011	>4834.51
Maraviroc	>200	0.00814	24570

Experimental conclusion: It can be seen from the data shown in the above tablethat for TZM-bl cells infected with HIV-1_{SF162} virus strain, compounds of the present invention exhibit lower cytotoxicity *in vitro* and higher therapeutic index, wherein compounds 3, 14, 18, 22 and 26 are better than positive control compound, and compounds 16, 17, 20 and 29 are comparable with the positive control compound.

Table 4 Inhibition activities of compounds on PBMC cells infected with HIV-1_{SF162} virus strain

compound	EC_{50} (ng/mL)	CC_{50}(μg/mL)	therapeutic index (TI)
3	145.81	273.30	1874
14	1.58	267.79	169487
16	455.15	266.85	586.3
17	41.29	438.58	10621
18	92.74	345.12	3721
22	2.65	634.56	239456
29	5.05	>200	>39604

Experimental conclusion: It can be seen from the data shown in the above table that for PBMC cells infected with HIV-1_{SF162} virus strain, compounds of the present invention exhibit lower cytotoxicity *in vitro* and higher therapeutic index, wherein compounds 14, 22 and 29 have relatively higher therapeutic index, and the therapeutic index of compound 22 even reaches 239456.

Table 5 Inhibition activities of compounds on PBMC cells infected with HIV-1_{KM018} virus strain

compound	EC_{50} (ng/mL)	CC_{50}(μg/mL)	therapeutic index (TI)
3	15.66	273.30	17452.1
14	3.77	267.79	71031.8
16	554.66	266.85	481.1
17	>1000	438.58	<438.6
18	69.93	345.12	4935.2
22	5.33	634.56	119054.4
29	103.24	>200	1937.2

Experimental conclusion: It can be seen from the date shown in the above table that for

PBMC cells infected with HIV-1 $_{KM018}$ virus strain, compounds of the present invention have lower cytotoxicity *in vitro* and higher therapeutic index, wherein compounds 3, 14 and 22 have relatively higher therapeutic index, and the therapeutic index of compound 22 even reaches 119054.4.

Table 6 Inhibition activities of compounds on PBMC cells infected with HIV-1 $_{Ba-L}$ virus strain

compound	EC_{50} (ng/mL)	CC_{50}(μg/mL)	therapeutic index (TI)
3	91.25	273.30	3328.9
14	19.72	267.79	13579.6
16	364.55	266.85	1301.1
17	847.67	438.58	438.6
18	289.12	345.12	2266.5
22	5.13	634.56	123695.9
29	235.84	>200	818.3

Experimental conclusion: It can be seen from the date shown in the above table that for PBMC cells infected with HIV-1 $_{Ba-L}$ virus strain, compounds of the present invention have lower cytotoxicity *in vitro* and higher therapeutic index, wherein compounds 14 and 22 have relatively higher therapeutic index, and the therapeutic index of compound 22 even reach 123695.9.

Table 7 Inhibition activities of compounds on HOS-$CD4^+$-CCR5 cells infected with HIV-1 $_{Ba-L}$ virus strain

compound	EC_{50} (ng/mL)	CC_{50}(μg/mL)	therapeutic index (TI)
3	17.15	334.35	19495
14	0.74	369.63	499500
16	10.46	343.09	32800

17	15.52	439.04	28288
18	3.40	506.78	149052
22	4.83	>800	>165631
29	21.87	>200	>9144

Experimental conclusion: It can be seen from the data shown in the above table that for HOS-CD4$^+$-CCR5 cells infected with HIV-1 $_{Ba-L}$ virus strain, compounds of the present invention have lower cytotoxicity *in vitro* and higher therapeutic index, wherein compounds 14, 16, 17, 18 and 22 have relatively higher therapeutic index, and the therapeutic index of compound 14 even reach 499500.

Table 8 Inhibition activities of compounds on HOS-CD4$^+$-CCR5 cells infected with HIV-1 $_{SF162}$ virus strain

compound	EC_{50} (ng/mL)	CC_{50}(μg/mL)	therapeutic index (TI)
3	24.45	334.35	13674
14	13.06	369.63	28302
16	42.66	343.09	8042
17	50.86	439.04	8632
18	20.31	506.78	24952
22	9.15	>800	>87431
29	18.59	>200	>10758

Experimental conclusion: It can be seen from the data shown in the above table that for PBMC cells infected with HIV-1 $_{Ba-L}$ virus strain, compounds of the present invention have lower cytotoxicity *in vitro* and higher therapeutic index, wherein compounds 3, 14, 18, 22 and 29 have relatively higher therapeutic index, and the therapeutic index of compound 14 even reach 28302.

Example 4: hERG inhibition activity assay

1. Experiment materials:

Fetal calf serum (Gibco, Cat#10099), hygromycin B (Invitrogen, Cat#B13871010), FluxOR™ assay kit (Invitrogen, Cat#F0017), 96-well plate (Corning, Cat#3894), positive control Dofetilide, Cisapride and Maraviroc.

2. Experiment steps:

1. CHO-hERG cells which have been incubated overnight were added with sample buffer and incubated for 90 minutes at room temperature in darkness.

2. The sample buffer was removed and assay buffer was added.

3. The compound is added to the cell plate and incubated for 20 minutes in darkness.

4. Cell plate was placed into FDSS. The fluorescence signal was recorded every second for 10 seconds. Exciting buffer was added to the cells at the 10th second and the fluorescence signal was recorded every second for 180 seconds

5. Data were processed.

3. Experiment results:

Table 9 Results of hERG inhibition activity assay for compounds

compound	IC_{50} (μM)	compound	IC_{50} (μM)	compound	IC_{50} (μM)
8	>40	22	10.58	103	3.47
12	9.45	26	3.51	107	>40
14	3.1	29	8.44	Dofetilide	0.09
16	3.02	43	1.36	Cisapride	0.19
18	1.89	65	0.84	Maraviroc	7.75
20	14.42	101	0.81		

Experiment conclusion: It can be seen from the data shown in the above table that compounds of the present invention have weaker hERG inhibition activity, wherein hERG inhibition activities of compounds 8, 12, 20, 22, 29 and 107 are better that those of positive control compounds.

Example 5: Pharmacokinetic experiment of rats

1. Experiment steps:

Six healthy male rats with weight of 150-200 g were randomly divided into 2 groups with 3 rats for each group. The rats in each group were administrated by gavage or

intravenous injection with compounds 14, 16, 17, 18, 22 and 29, respectively. The administration volume was 10 mL/kg and drug was formulated with DMSO/Tween 80™ /physiological saline (5: 5: 90, v/v/v). The rats were fasted for 12 h and can drink water *ad libitum* before test. 2 h after dosing, the rats ate together.

2. The time point for collecting blood samples and the sample processing:

Intragastric administration: 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h after administration.

Intravenous administration: 5 min, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h after administration.

At above time points, 0.3 ml of venous blood was taken from retrobulbar venous plexus of the rat and loaded into EDTA-2K anticoagulative tube. After centrifuged at 11000 rpm for 5 min, the plasma was separated and frozen at -20°C in a refrigerator.

3. The sample test and data analysis

The concentration of each compound in rat plasma was determined by LC/MS/MS.

The pharmacokinetic parameters after administration were calculated by using non-compartment model of WinNonlin 5.3 software (Pharsight Corporation, USA).

4. Experiment results:

Table 10 Pharmacokinetic experiment results of rats *in vivo*

compound	**Route**	**Dose mg/kg**	**T_{max} h**	**C_{max} ng/mL**	**AUC_{0-t} ng/mL*h**	**$AUC_{0-\infty}$ ng/mL*h**	**MRT h**	**$t_{1/2}$ h**	**CLz L/h/kg**	**F %**
14	gavage	20	4	266.2	1108	1190	3.33	2.12	/	7.85%
	vein	10	0.25	6841	7053	7055	0.71	0.77	1.42	/
16	gavage	20	0.25	631.3	1512.3	1512.3	2.11	1.16	/	14.8%
	vein	10	0.25	4316.7	5114.9	5114.9	0.79	0.31	1.96	/
17	gavage	20	0.5	121.8	347.9	364.5	2.31	1.78	/	46.6%
	vein	10	0.25	245.9	373.5	394.5	1.42	2.22	25.4	/
18	gavage	20	2	690.4	2801.1	3067.8	2.94	2.05	/	90.5%
	vein	10	0.25	771.1	1547.0	1602.5	1.98	1.81	6.24	/
22	gavage	20	2	306.4	1206	1259	2.55	1.55	/	14.5%
	vein	10	0.25	3778	4154	4162	0.84	1.00	2.40	/
29	gavage	20	2	580.2	1870.7	2790.3	4.79	32.84	/	40.1%

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	vein	10	0.25	1692.5	2330.2	2330.2	2.29	1.60	4.29	/

compound 14: After 20 mg/kg of compound 14 was administered to rats through gavage, Tmax (time for the plasma concentration reaching the peak concentration) is 4 h, the peak concentration Cmax is 266.2 ng/ml, the area below the curve of drug vs time AUC0-t is 1108 ng•h/ml, and the terminal elimination half-life t1/2 is 2.12 h. After 10 mg/kg of compound 14 was administered to rats through vein, AUC0-t is 7053 ng•h/ml. After dose-normalized, absolute bioavailability of 20 mg/kg of compound 14 administrated to rats through gavage is 7.85%.

compound 16: After 20 mg/kg of compound 16 was administered to rats through gavage, Tmax (time for the plasma concentration reaching the peak concentration) is 0.25 h, the peak concentration Cmax is 631.3 ng/ml, the area below the curve of drug vs time AUC0-t is 1512.3 ng•h/ml, and the terminal elimination half-life t1/2 is 1.16 h. After 10 mg/kg of compound 16 was administered to rats through vein, AUC0-t is 5114.9 ng•h/ml. After dose-normalized, absolute bioavailability of 20 mg/kg of compound 16 administrated to rats through gavage is 14.8%.

compound 17: After 20 mg/kg of compound 17 was administered to rats through gavage, Tmax (time for the plasma concentration reaching the peak concentration) is 0.5 h, the peak concentration Cmax is 121.8 ng/ml, the area below the curve of drug vs time AUC0-t is 347.9 ng•h/ml, and the terminal elimination half-life t1/2 is 1.78 h. After 10 mg/kg of compound 17 was administered to rats through vein, AUC0-t is 373.5 ng•h/ml. After dose-normalized, absolute bioavailability of 20 mg/kg of compound 17 administrated to rats through gavage is 46.6%.

compound 18: After 20 mg/kg of compound 18 was administered to rats through gavage, Tmax (time for the plasma concentration reaching the peak concentration) is 2 h, the peak concentration Cmax is 690.4 ng/ml, the area below the curve of drug vs time AUC0-t is 2801.1 ng•h/ml, and the terminal elimination half-life t1/2 is 2.05 h. After 10 mg/kg of compound 18 was administered to rats through vein, AUC0-t is 1547.0 ng•h/ml. After dose-normalized, absolute bioavailability of 20 mg/kg of compound 18 administrated to rats through gavage is 90.5%.

compound 22: After 20 mg/kg of compound 22 was administered to rats through gavage,

Tmax (time for the plasma concentration reaching the peak concentration) is 2 h, the peak concentration Cmax is 306.4 ng/ml, the area below the curve of drug vs time AUC0-t is 1206 ng•h/ml, and the terminal elimination half-life t1/2 is 1.55 h. After 10 mg/kg of compound 22 was administered to rats through vein, AUC0-t is 4154 ng•h/ml. After dose-normalized, absolute bioavailability of 20 mg/kg of compound 22 administrated to rats through gavage to the rat is 14.5%.

compound 29: After 20 mg/kg of compound 29 was administered to rats through gavage, Tmax (time for the plasma concentration reaching the peak concentration) is 2 h, the peak concentration Cmax is 580.2 ng/ml, the area below the curve of drug vs time AUC0-t is 1870.7 ng•h/ml, and the terminal elimination half-life t1/2 is 32.84 h. After 10 mg/kg of compound 29 was administered to rats through vein, AUC0-t is 2330.2 ng•h/ml. After dose-normalized, absolute bioavailability of 20 mg/kg of compound 29 administrated to rats through gavage to the rat is 40.1%.

Experimental conclusion: It can be seem from the above test results that in the pharmacokinetic experiment of rats, compound 18 exhibits excellent absolute bioavailability which reach 90.5%; and compounds 17 and 29 exhibit good absolute bioavailability which reach 46.6% and 40.1%, respectively and is much higher than that of Mara Calvino MVC which has been marketed (only 5% bioavailability as reported).

Example 6: Pharmacokinetic experiment on Beagles

1. Experimental steps:

Six healthy male Beagles with the weight of 9-11 kg were randomly divided into 2 groups with 3 in each group. The Beagles in each group were administrated by gavage or intravenous injection with compound 22 of the present invention. The administration volume was 2 mL/kg and 1 mL/kg, respectively. The compound was suspended in 20% PEG400 (4: 96) for gavage and formulated in DMSO/Tween 80/physiological saline (5: 1: 94, v/v/v) for intravenous injection. The Beagles were fasted for 12 h and can drink water *ad libitum* before test. 2 h after dosing, all of Beagles ate together.

2. The time point for collecting blood samples and the sample processing:

Intragastric administration: 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h after administration.

Intravenous administration: 5 min, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h after

administration.

At above time points, 0.6 ml venous blood was taken from limb venous and loaded into EDTA-2K anticoagulative tube. After centrifuged at 11000 rpm for 5 min, the plasma was separated and frozen at -20°C in a refrigerator.

3. The sample test and data analysis

The concentration of compound 22 in plasma of Beagles was determined by LC/MS/MS.

The pharmacokinetic parameters after administration were calculated by using non-compartment model of WinNonlin 5.3 software (Pharsight Corporation, USA).

4. Experiment results:

Table 11 Pharmacokinetic experiment results of compound in Beagles

compound	Route	Dose mg/kg	T_{max} h	C_{max} ng/mL	AUC_{0-t} ng/mL*h	$AUC_{0-\infty}$ ng/mL*h	MRT h	$t_{1/2}$ h	CLz L/h/kg	F %
22	gavage	15	0.833	4613	5426	5520	2.11	3.89	/	9.98%
	vein	3	/	/	10877	10889	1.65	1.73	0.278	/

compound 22: After 15 mg/kg of compound 22 was administered to Beagles through gavage, T_{max} (time for the plasma concentration in Beagles reaching the peak concentration) is 0.8333 h, the peak concentration C_{max} is 4613 ng/ml, the area below the curve of drug vs time AUC_{0-t} is 5426 ng•h/ml, and the terminal elimination half-life t1/2 is 3.89 h. After 3 mg/kg of compound 22 was administered to Beagles through vein, AUC_{0-t} is 10877 ng•h/ml. After dose-normalized, absolute bioavailability of 15 mg/kg of compound 22 administrated through gavage to rats is 9.98%.

Experimental conclusion: It can be seem from the above test results that in the pharmacokinetic experiment of Beagles, compound 22 exhibits good absolute bioavailability.

Example 7: Bacterial reverse mutation assay

1. Experiment design

The mutagenic effects of compounds **18** and **22** of the present invention on *Salmonella typhimurium* strains TA98 and TA100 in non-metabolic activation (-S9) condition were determined. Two strains, TA98 and TA100 were chosen in bacterial reverse mutation assay for compounds **18** and **22**. 9 doses containing 1, 3, 10, 30, 100, 300, 1000, 3000 and 5000 μg/dish, negative and positive controls were set in experiments. 3 dishes were used for each

dose. The experiment was carried out under -S9 condition.

2. Experiment results

Compounds 18 and 22 at each dose did not increase the number of revertant colonies of TA98 and TA100 and no significant bacteria toxicity was observed at each dose. It can be concluded that compounds 18 and 22 have no mutagenic effect on Salmonella typhimurium strains TA98 and TA100.

Table 12 The number of revertant colonies of *Salmonella typhimurium* TA98 and TA100 under compounds 18 and 22 (-S_9)

Group and dose (μg/dish)	number of revertant colonies (Mean± SD)			
	TA98		TA100	
	18	22	18	22
Negative control	24±2.5	24±2.5	105±5.5	105±5.5
1	24±5.0	23±3.2	116±9.0	107±16.7
3	23±2.6	24±3.6	96±10.0	109±9.3
10	20±2.3	23±2.6	95±13.1	112±10.7
30	19±1.5	21±5.2	100±8.3	90±11.0
100	15±4.6	23±6.7	88±0.6	97±4.6
300	20±4.2	23±6.5	91±18.2	102±2.9
1000	18±1.5	19±6.4	106±17.6	90±6.5
3000	21±1.5	22±5.0	108±6.9	86±13.1
5000	20±4.9	25±7.2	95±7.2	109±17.5
Positive control*	999±145.2	999±145.2	1231±146.1	1231±146.1

* TA98: 2-Nitroflucrene (20 μg/dish); TA100: Methyl methanesulfonate (1300 μg /dish)

Experimental conclusion: It can be seen from the above test results that compounds 18 and 22 have no mutagenic effect on *Salmonella typhimurium* strains TA98 and TA100 under the present experiment conditions.

Example 8: Inhibition activity assay of different CYP450 enzyme subfamilies

1. Experiment materials

VividR CYP450 Screening Kits, and Envision 2101 multifunction microplate reader, etc.

2. Experiment theory

VividR CYP450 Screening Kits can be used to evaluate the effects on CYP450 subtypes (CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4-T and CYP3A4-M) and the substrate VividR in the kit can be metabolizd to a product which can emit strong fluorescence in an aqueous solution by specific CYP450 enzymes.

3. Experiment steps

1. The compounds to be tested and positive compound were added to corresponding wells and DMSO was added to control wells.

2. CYP450 enzyme was added to the compounds to be tested, positive compound and DMSO control wells. The enzyme dilution was used to replace enzyme and added to DMSO wells as test background. The mixture was vibrated and mixed for 1 minute, and then incubated at room temperature for 20 minutes.

3. $NADP^+$ regeneration system and the substrate were added to initiate the reaction and incubated at room temperature for 60 minutes.

4. Envision 2101 multifunction microplate reader was used to record the fluorescence signal under the conditions of 480nm excitation and 530nm emission.

4. Experiment results

Table 13 Inhibition activity effects of compounds on CYP450 enzyme of different subfamilies

CYP450 subtype / **compound** (μM)	1A2	2C9	2C19	2D6	3A4-M	3A4-T
16	>25	>25	>25	15.1	12.3	21.7
17	>25	>25	>25	>25	>25	>25
18	>25	>25	>25	16.8	>25	>25
22	>25	>25	>25	>25	>25	>25
29	>25	>25	>25	>25	10.9	23.4
Maraviroc	>25	14.4	>25	>25	3.1	14.9

IC_{50} < 1μM: high inhition; 1 μM < IC_{50} < 10μM: medium inhition; IC_{50} > 10 μM: low inhibition

Experimental conclusion: IC50 values of inhition activities of compounds 16, 17, 18, 22 and 29 on six subtypes of CYP450 are greater than 10 μM. The inhition activities of

compounds are quite weak and better than that of Maraviroc.

Example 9: Four days subacute toxicity test of rats

1. Experiment purpose

After compounds 18 and 22 of the present invention were administrated to SD rats through gavage for 4 consecutive days, the toxic reaction was preliminarily assessed to confirm the possible target organ of toxic reaction.

2. Experiment design

Four dose groups containing 100 and 1000mg / kg of compound 18, 100 and 1000 mg/kg of compound 22 were set. One vehicle control group was set. Each group contained four rats including two male rats and two female rats. During the experiment stage, the animals were daily clinically observated. The body weight was regularly measured. On the 5^{th} day, all animals were subject to pathological examination and gross anatomy.

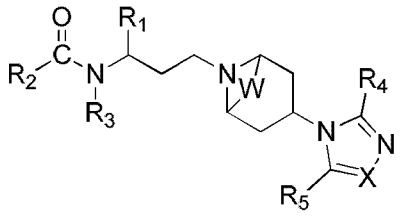
3. Experiment results

Compared with the animals in vehicle control group, the weight gain of some male and female animals in compound 18 (100 and 1000 mg/kg) and compound 22 (100 and 1000 mg/kg) dose group increased slowly or exhibited negative growth. Clinical observations, clinical pathology detection (hematology and serum biochemistry) and macroscopic morphological observation showed no significant drug-related changes.

Experiment conclusion: In summary, under the conditions of this experiment, No Observed Adverse Effect Level (NOAEL) is 1000 mg/ kg for SD rats which have been administrated with compoumd 18 through gavage for 4 days, and NOAEL is 1000 mg/ kg for SD rats which have been administrated with compoumd 22 through gavage for 4 days. Thus, the compounds have good safety.

CLAIMS:

1. A compound of formula I, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof,



(I)

wherein,

W is absent or --CH_2CH_2--;

X is N or CR_6;

R_1 is selected from a 5 to 7-membered heteroaryl unsubstituted or substituted with 1-3 substituents, wherein said heteroaryl contains 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen and each of said substituents is independently selected from a halogen, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkyloxy, a C1-C4 straight or branched chain haloalkoxy, --$NR_{10}R_{11}$, --C(=O) R_{12}, a C1-C4 straight or branched alkanoyloxy, a cyano, a nitro and a hydroxy, or two adjacent R_1 substituents with the atoms to which each is attached are combined to form a fused 5-7 membered ring;

each of R_{10} and R_{11} is independently selected from the group consisting of H, a C1-C4 straight or branched alkyl and --C(=O) R_{13};

R_{12} is selected from the group consisting of a C1-C4 straight or branched alkyl, a C1-C4 straight or branched alkyloxy, a hydroxyl, an amino (NH_2) and a C1-C4 straight or branched alkylamino;

R_{13} is selected from the group consisting of H and a C1-C4 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a C1-C6 straight or branched alkyl, a C3-C7 cycloalkyl, a 4 to 7-membered heterocyclic group, a C6-C12 aryl or a 5-7 membered heteroaryl; wherein, said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched

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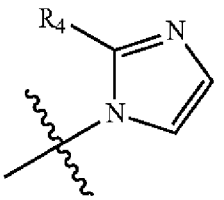
alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkyloxy, a C1-C4 straight or branched alkyl carbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl group, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, a cyano, a nitro, an amino, a carboxy, a phenyl, a halophenyl, a phenoxy, and a halophenoxy;

each of R_3, R_4 and R_5 is independently selected from the group consisting of H, a C1-C6 straight or branched alkyl and a C3-C7 cycloalkyl;

R_6 is selected from the group consisting of H and a C1-C6 straight or branched alkyl; alternatively, R_5 and R_6 may bind together with



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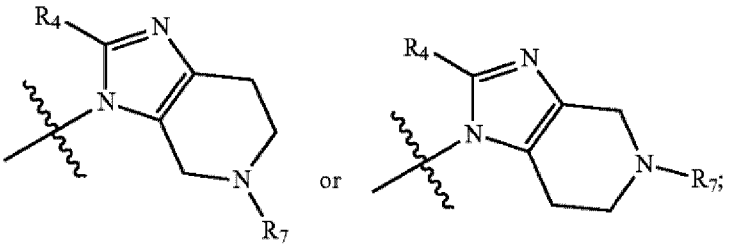

R_7 is selected from the group consisting of H, $C(=O)R_8$, $C(=O)OR_8$, $C(=O)NR_8R_9$, SO_2R_8 and the following groups substituted by 1-3 substituents a C1-C6 straight or branched alkyl, a C3-C7 cycloalkyl, a 4 to 7-membered heterocyclic group, a benzyl, a C6-C12 aryl and a 5-7 membered heteroaryl; wherein said substituent is selected from a halogen, a hydroxy, a C1-C4 straight or branched alkyloxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino and a carboxyl;

each of R_8 and R_9 is independently selected from the group consisting of a hydrogen and the following groups unsubstituted or substituted with 1-3 substituents: a C1-C6 straight

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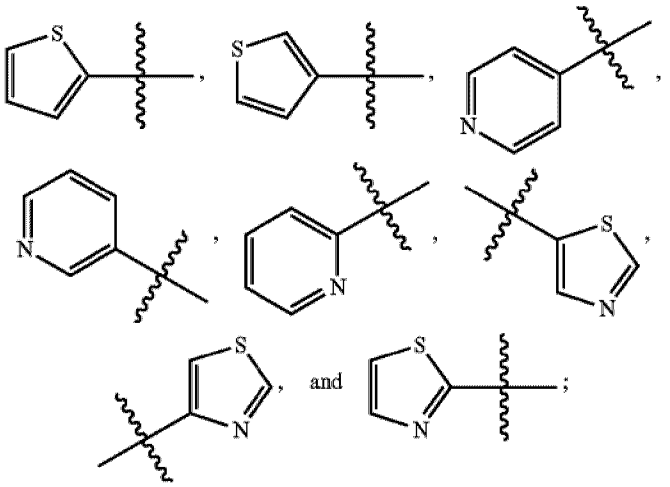
or branched alkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group, a benzyl, a C6-C12 aryl and a 5-7 membered heteroaryl; wherein said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino, and a carboxyl.

2. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein,

R_1 is selected from the following groups unsubstituted or substituted with 1-3 substituents:



said substituent is defined as in claim 1;

each of R_{10} and R_{11} is independently selected from the group consisting of H, a C1-C2 alkyl and --C(=O)R_{13};

R_{12} is selected from the group consisting of a C1-C2 alkyl, a C1-C2 alkoxy, a hydroxy, an amino (NH_2) and a C1-C2 alkylamino;

R_{13} is selected from the group consisting of H and a C1-C2 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group and a phenyl, wherein, said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or

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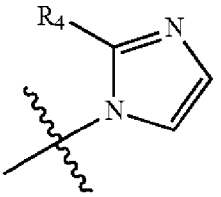
branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, a cyano, a nitro, an amino, a carboxyl, a phenyl, a halophenyl, a phenoxy and a halophenoxy;

each of R_3, R_4 and R5 is independently selected from the group consisting of H, a C1-C4 straight or branched alkyl and a C3-C7 cycloalkyl;

R_6 is selected from the group consisting of H and a C1-C4 straight or branched alkyl, or R_5 and R_6 can bind together with



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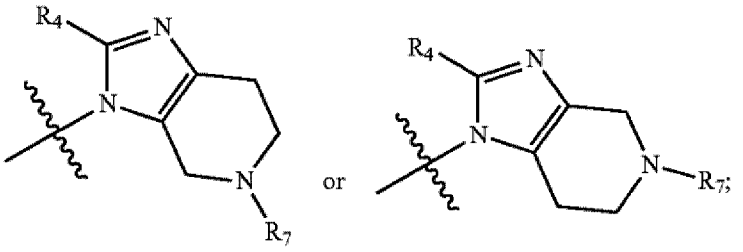

R_7 is selected from the group consisting of H, C(=O)R_8, C(=O)OR_8, C(=O)NR_8R_9, SO_2R_8 and the following groups substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group, a benzyl and a phenyl, wherein, said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, an nitro, an amino and a carboxyl; each of R_8 and R_9 is independently selected from the group consisting of H and the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C3-C7 cycloalkyl, a 4-7 membered heterocyclic group, a benzyl, a phenyl and a 5-7 membered heteroaryl, wherein,

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said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy, a cyano, a nitro, an amino and a carboxyl.

3. The compound according to claim 2, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein said substituent on R_1 is selected from the group consisting of a halogen, a C1-C2 alkyl, a C1-C2 haloalkyl, a C1-C2 alkoxy, $NR_{10}R_{11}$, --C(=O)R_{12}, a C1-C2 alkylcarbonyloxy, a C1-C2 haloalkoxy, a cyano, a nitro and a hydroxyl, or two adjacent R_1 substituents with the atoms to which each is attached are combined to form a fused 5-7 membered carbocycle, 5-7 membered heteroaryl ring or 5-7 membered heterocycle.

4. The compound according to claim 3, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein said substituent on R_1 is selected from the group consisting of a halogen, a methyl, a methoxy, an ethyl, an amino, a hydroxy, a formamido, an acetamido, a carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, a formyloxy, an acetoxy, a methoxycarbonyl, a trifluoromethyl, a cyano, a nitro, an acetyl and a trifluoromethoxy, or two adjacent R_1 substituents together with the atoms to which each is attached form a benzene ring, a cyclopentene ring or dioxole ring.

5. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein R_2 is selected from a C1-C4 straight or branched alkyl, a cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclohexyl, a tetrahydropyran-4-yl, a 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,

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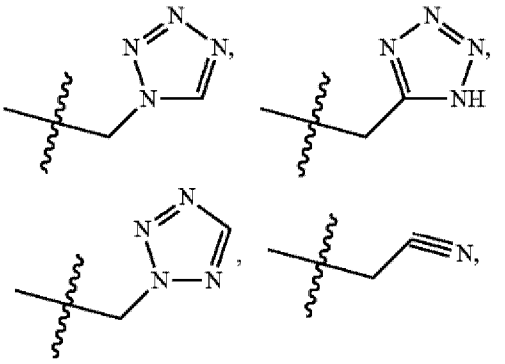

4-fluorobenzyl, a phenyl, a difluorocyclohexyl, an ethylcyclohexyl and a phenoxymethyl.

6. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein R_6 is selected from the group consisting of H, a methyl and an ethyl.

7. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein R_7 is selected from the group consisting of H, $C(=O)R_8$ and SO_2R_8.

8. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein said substituent on each of R_8 and R_9 is selected from the group consisting of halogen, a hydroxy, a methoxy, an ethoxy, a methyl, an ethyl, a trifluoromethyl, a trifluoromethoxy, a cyano, a nitro, an amino and a carboxyl.

9. The compound according to claim 7, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_3, R_4 and R_5 is independently selected from the group consisting of H, a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl, a tertiary butyl, a cyclopropyl, a cyclobutyl, a cyclopentyl and a cyclohexyl.

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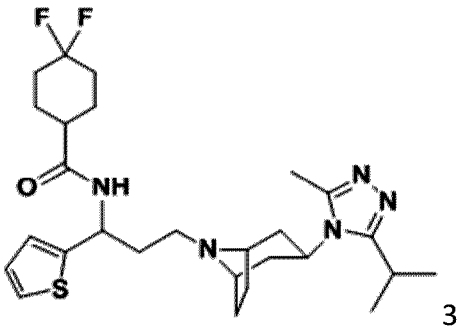
10. The compound according to claim 9, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_3, R_4 and R_5 is independently selected from the group consisting of H, a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl, a tertiary butyl and a cyclopropyl.

11. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_8 and R_9 is independently selected from the group consisting of H, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C3-C7 cycloalkyl, a benzyl and a phenyl.

12. The compound according to claim 11, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_8 and R_9 is independently selected from the group consisting of a methyl, an ethyl, an n-propyl, a cyclopropyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

13. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is selected from the following compounds:



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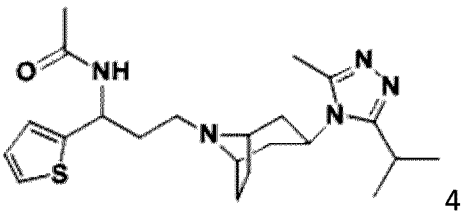

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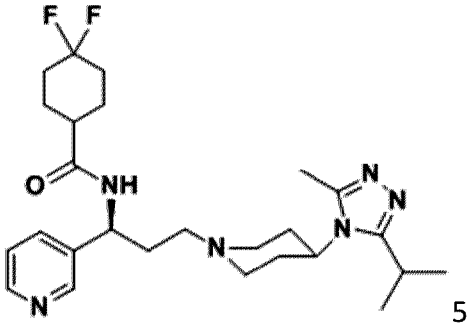
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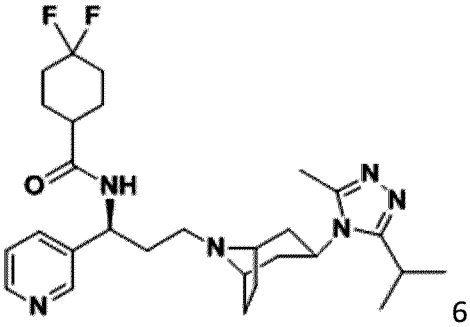
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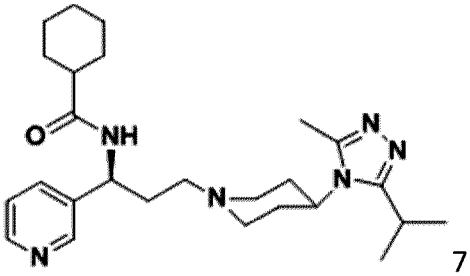
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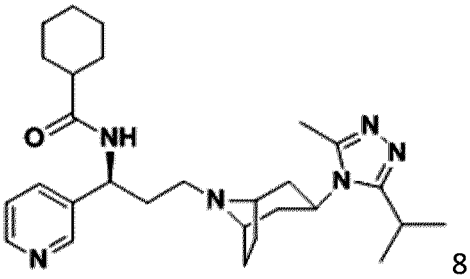
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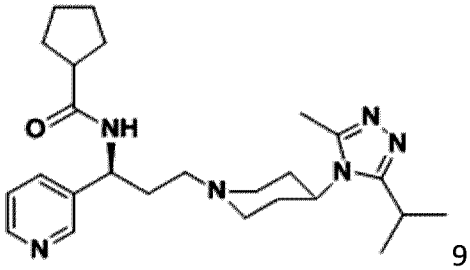
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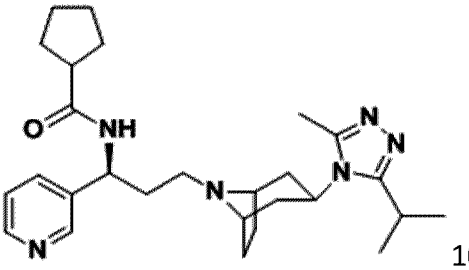
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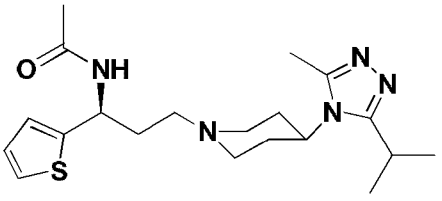
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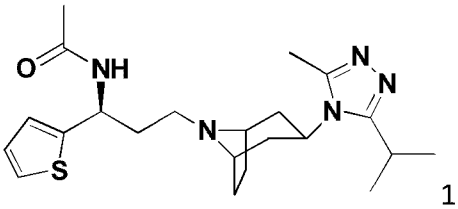
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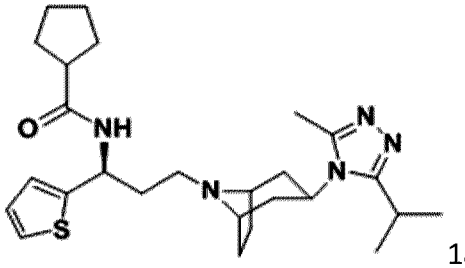

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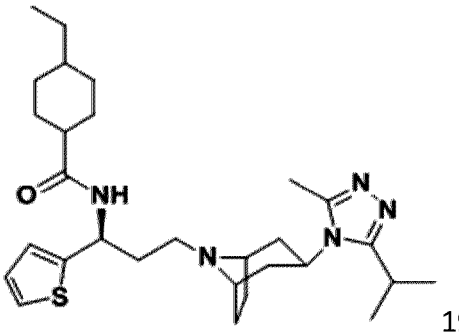

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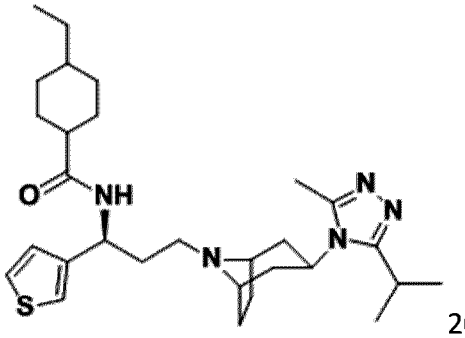

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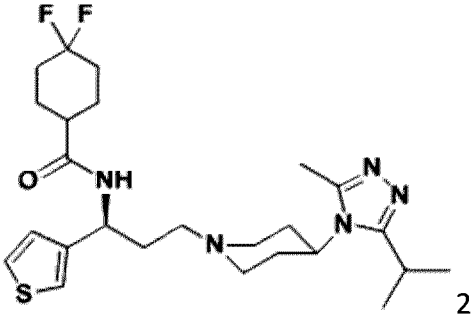

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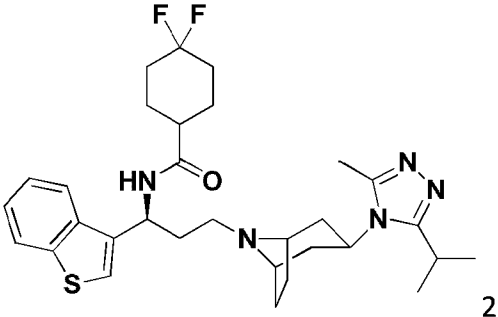

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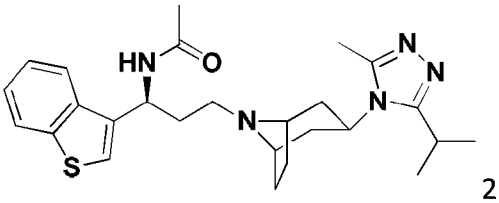

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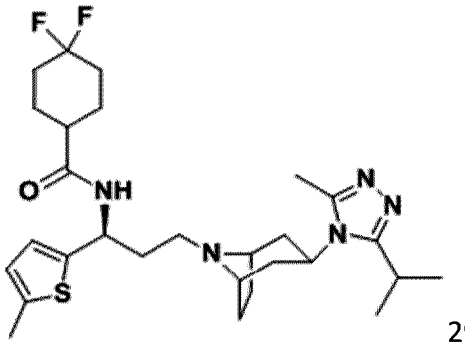
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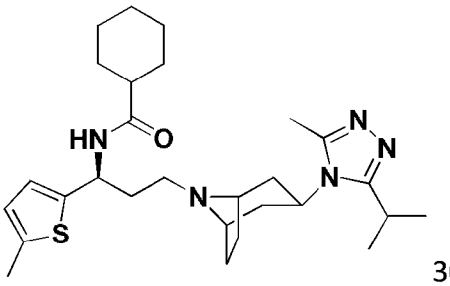
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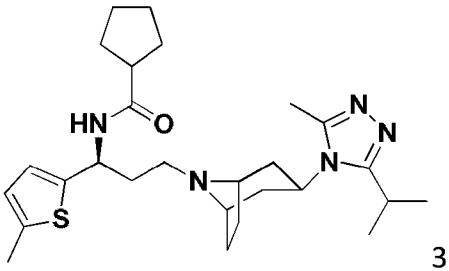
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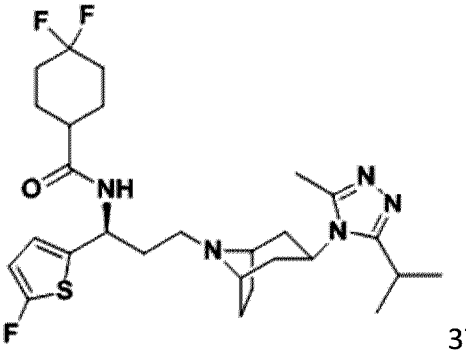
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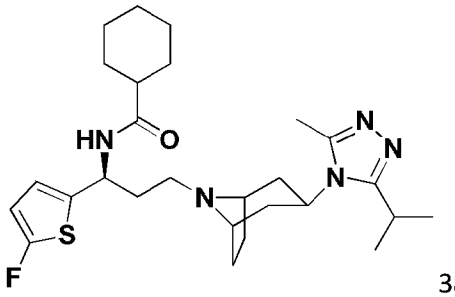
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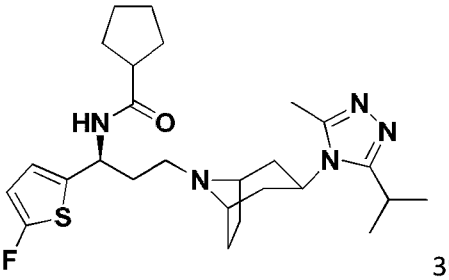
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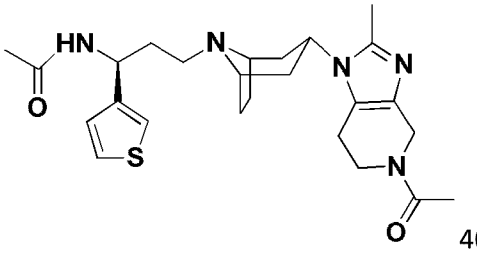
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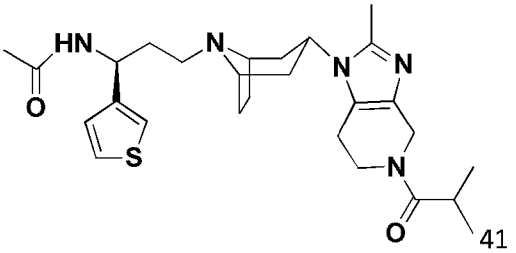
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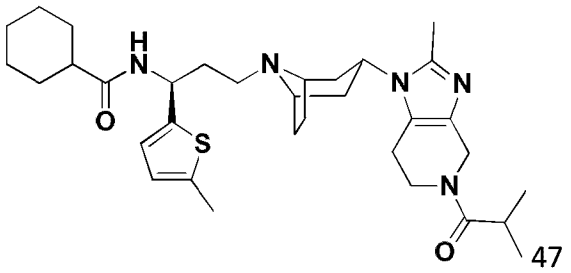
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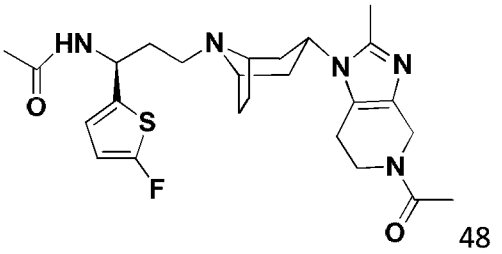
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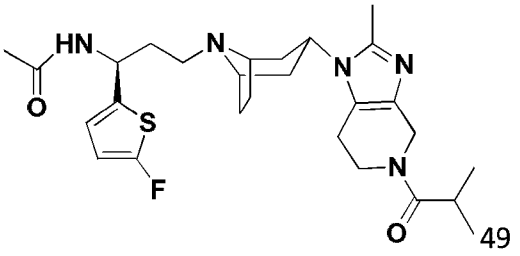
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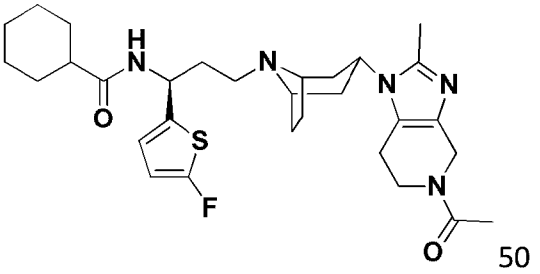
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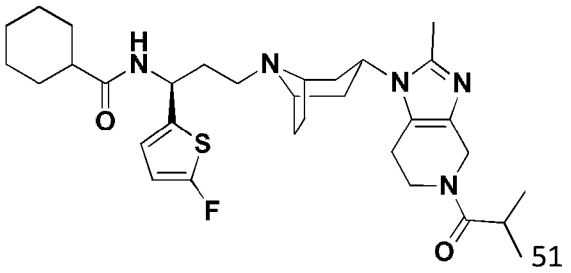
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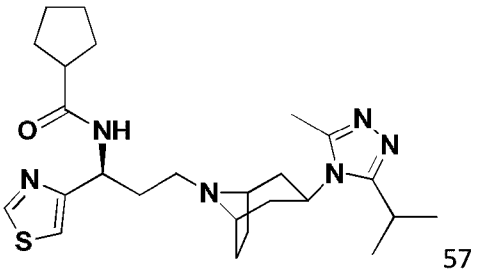
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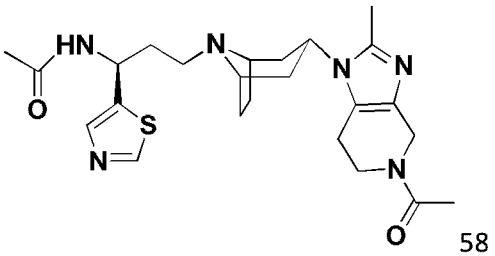
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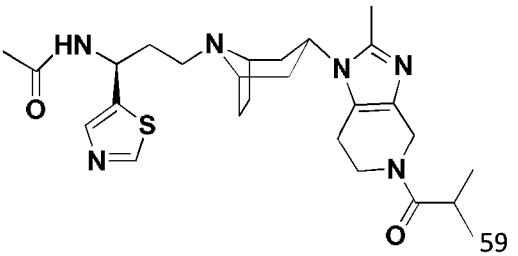
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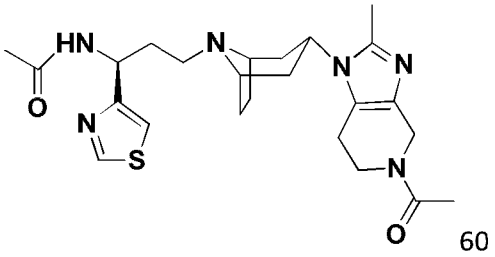
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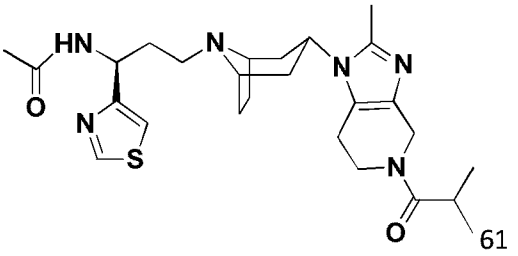
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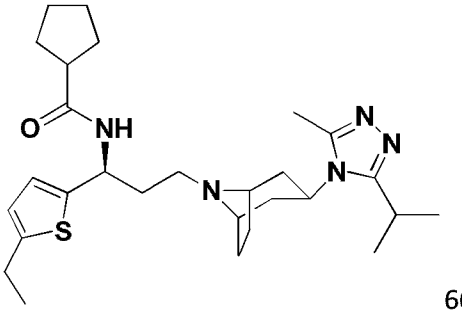

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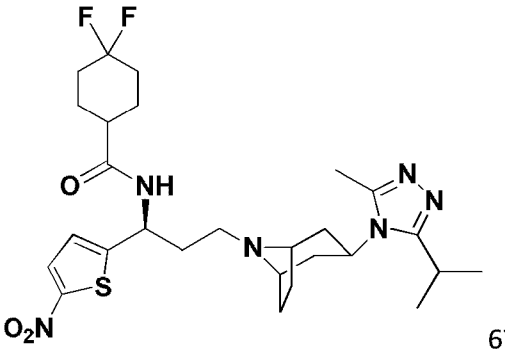

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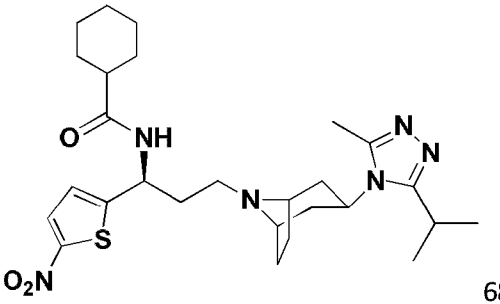

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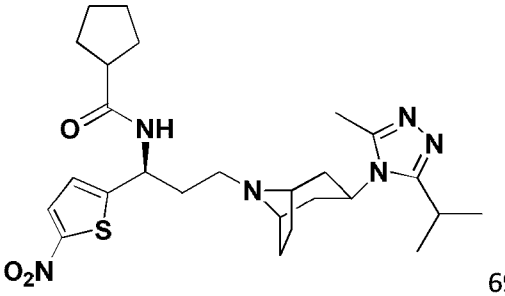

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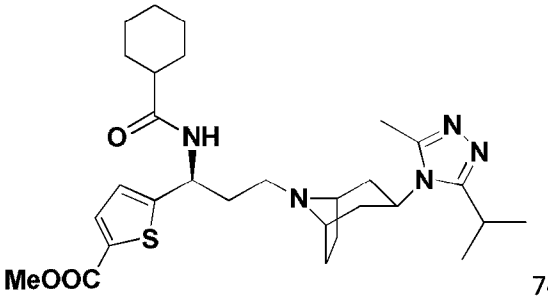

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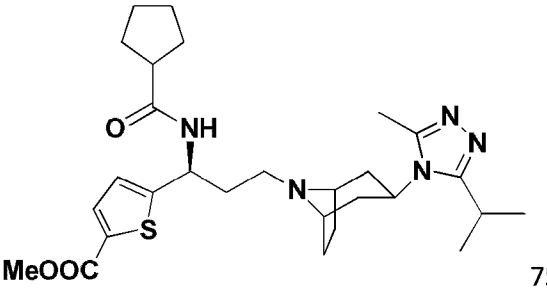

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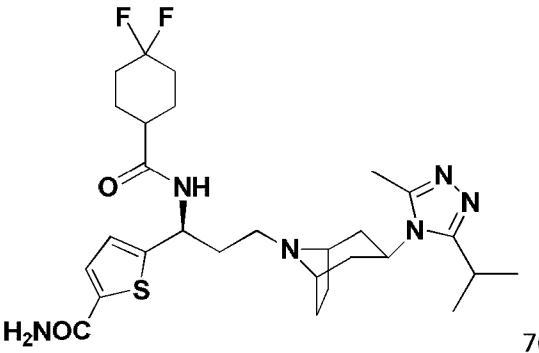

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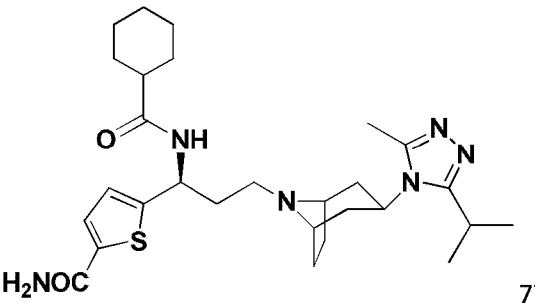

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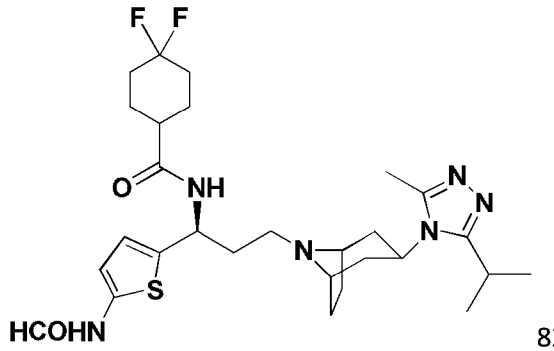

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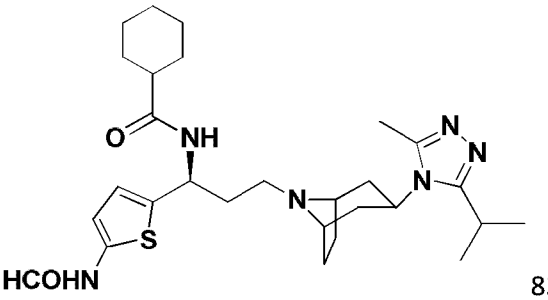

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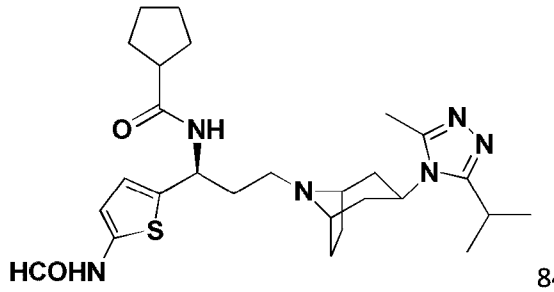

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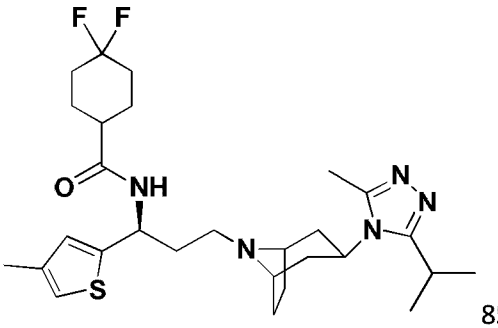

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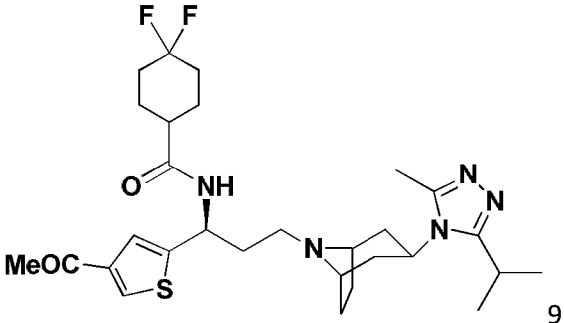

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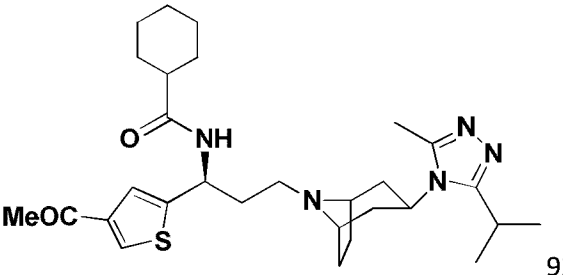

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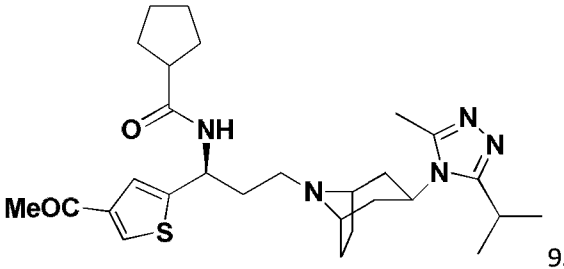

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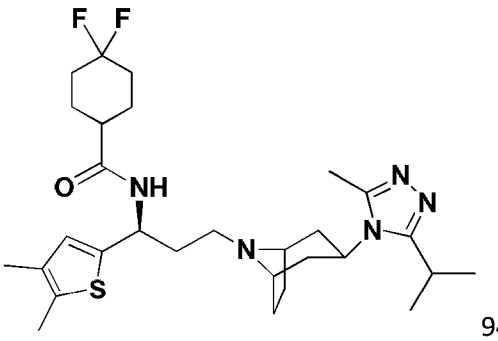

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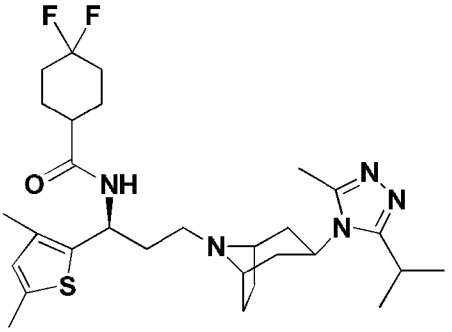

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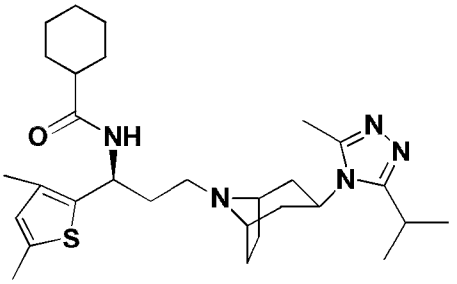

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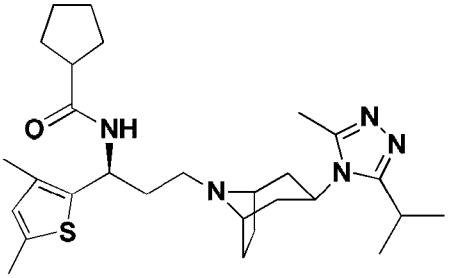

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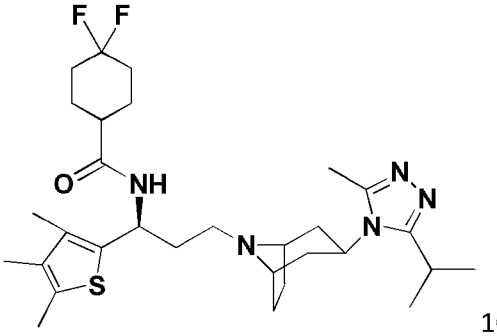

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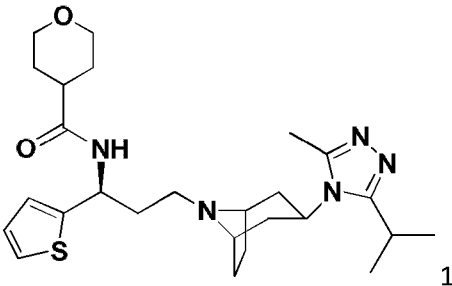

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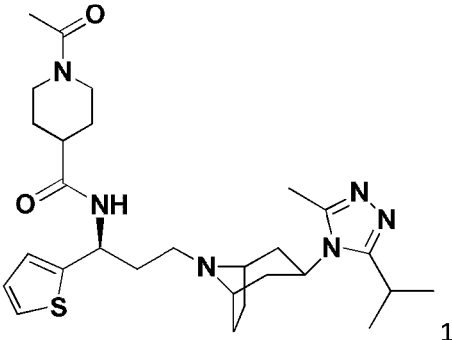

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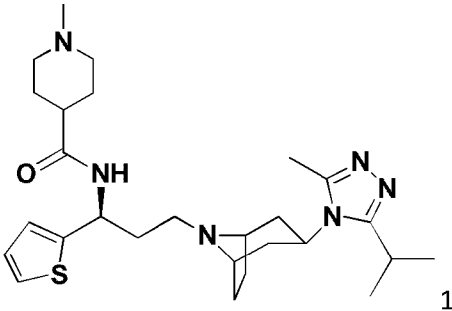

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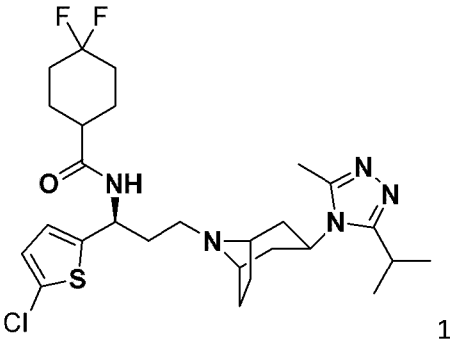

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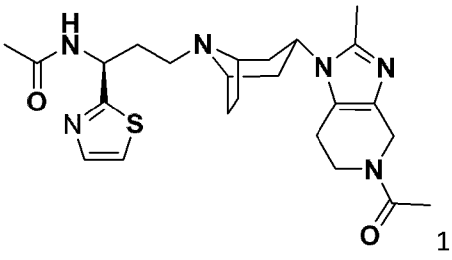

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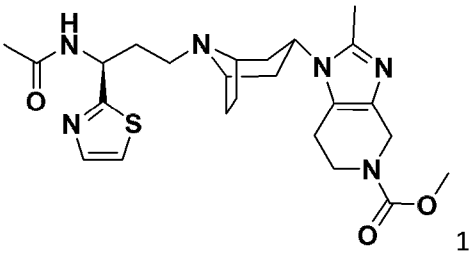

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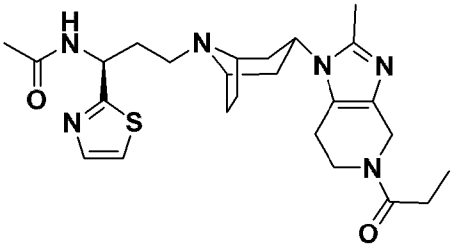

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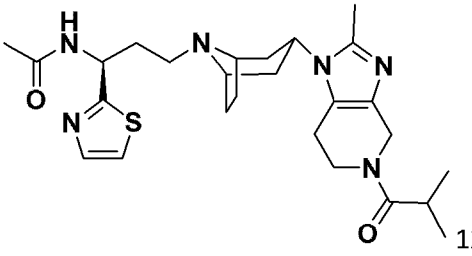

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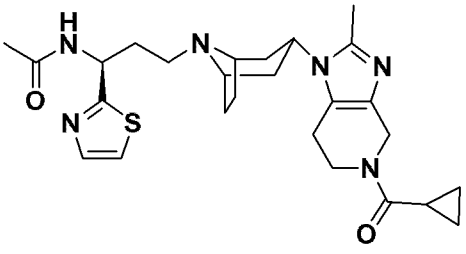

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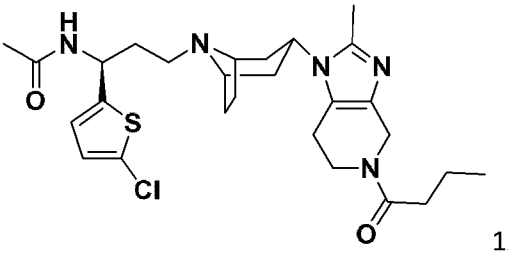

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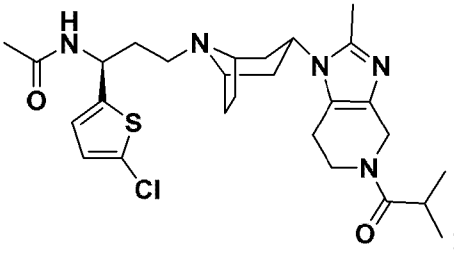

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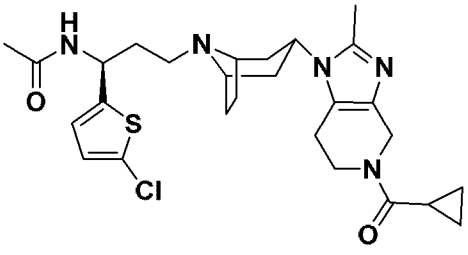

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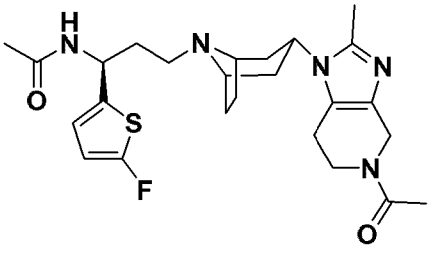

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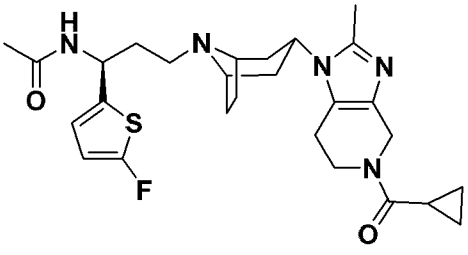

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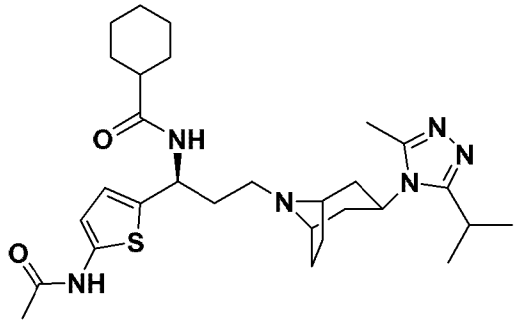

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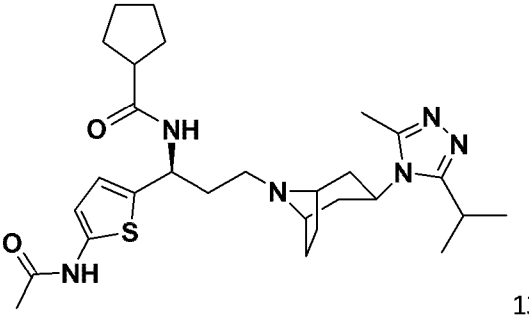

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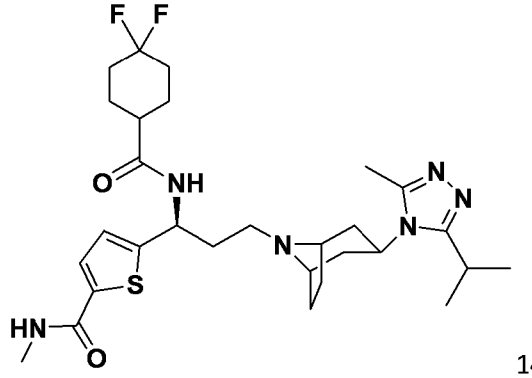

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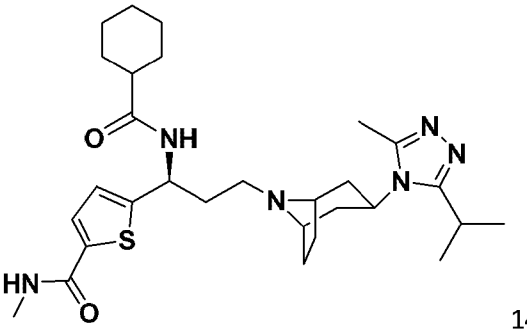

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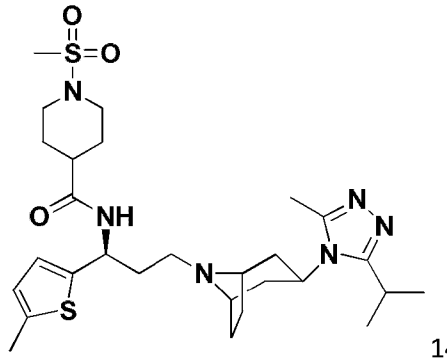

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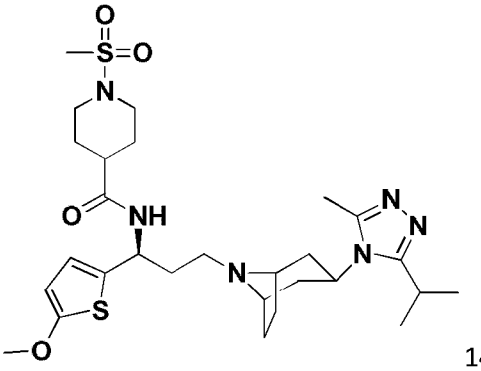

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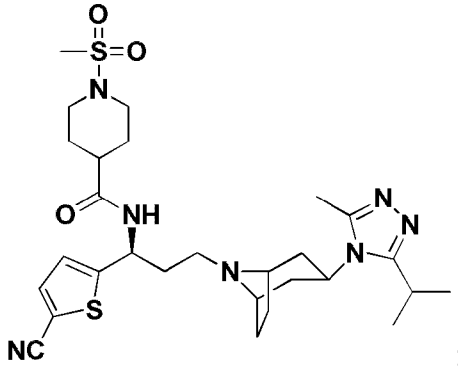

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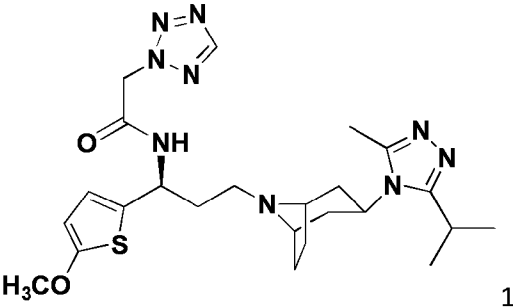

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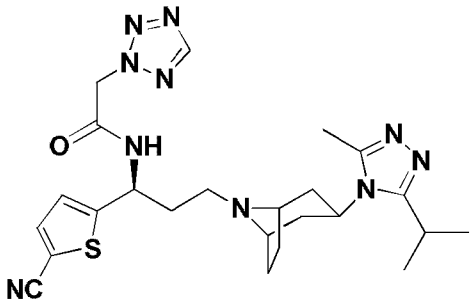
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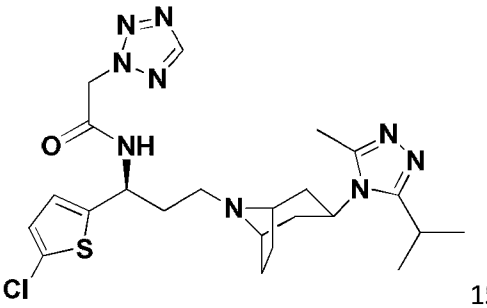
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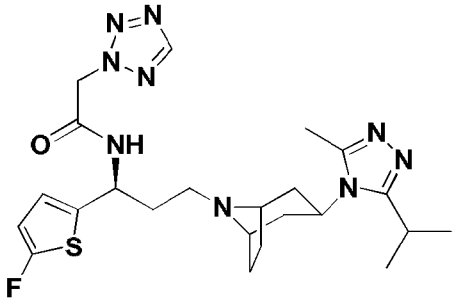
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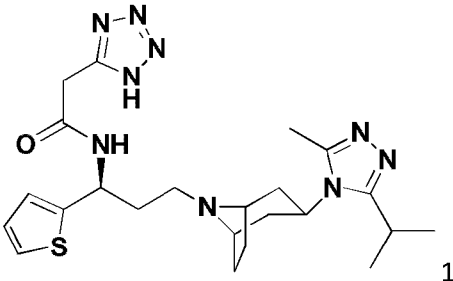
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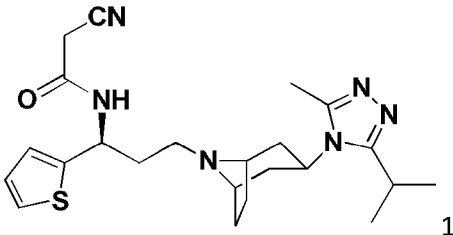
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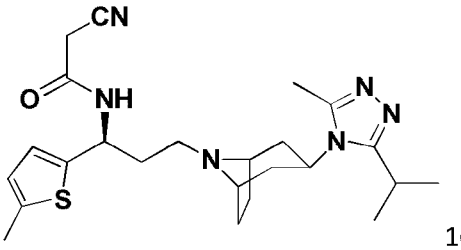
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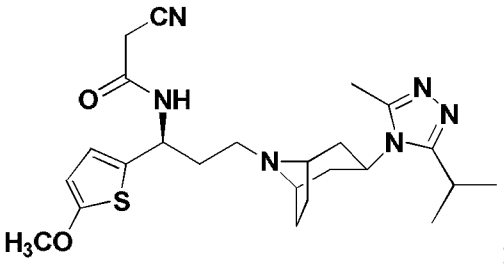
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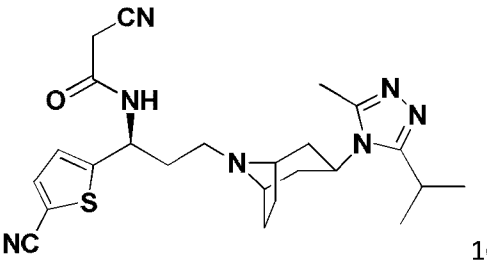
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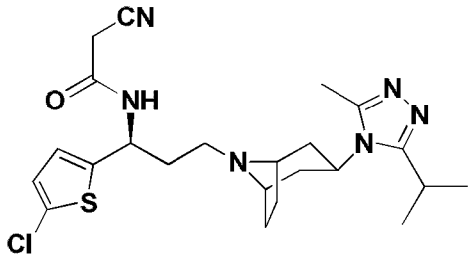

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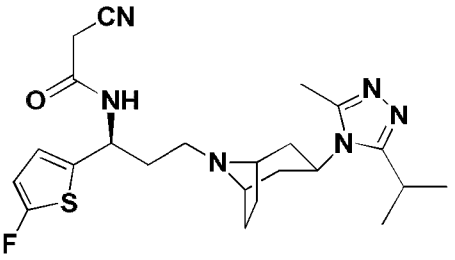

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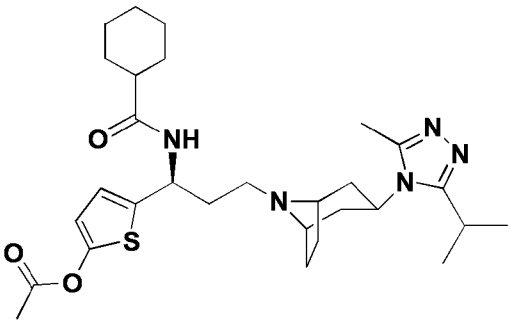

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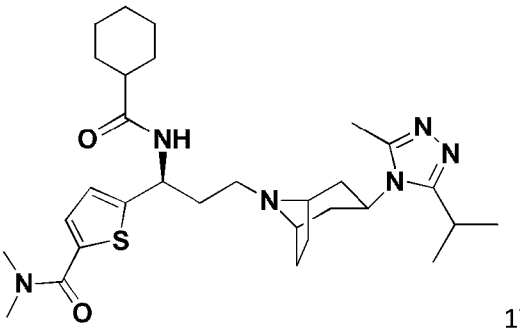

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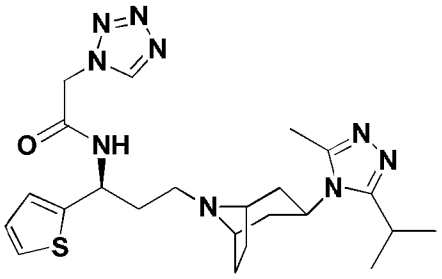
or



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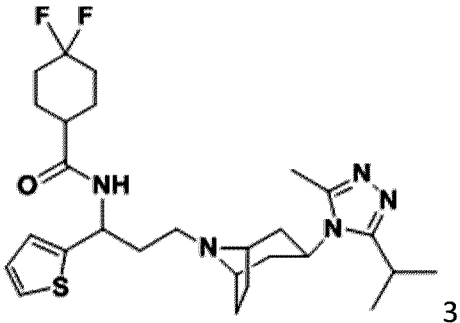
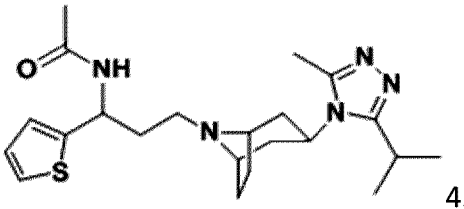
14. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



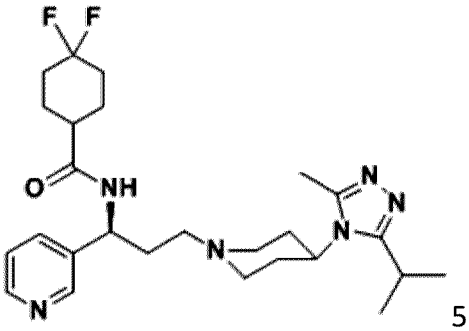
3.

15. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



4.

16. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



5.

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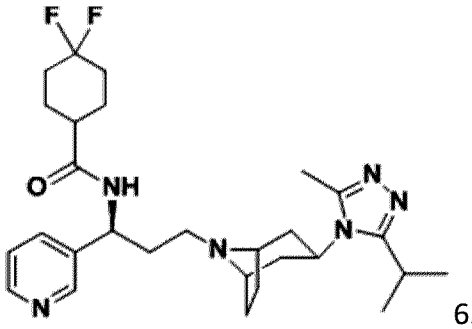
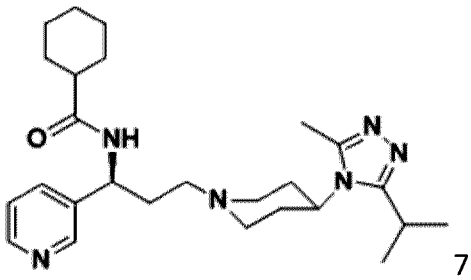
17. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I):



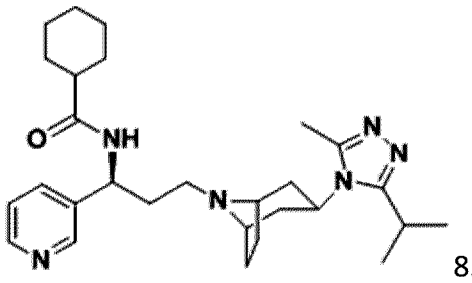
6.

18. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



7.

19. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



8.

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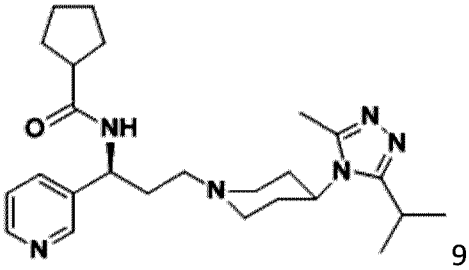
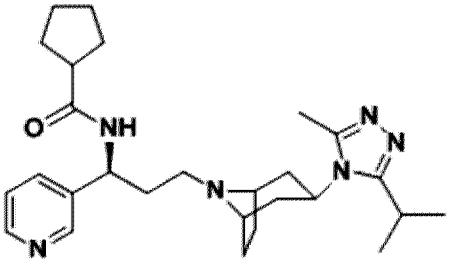
20. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



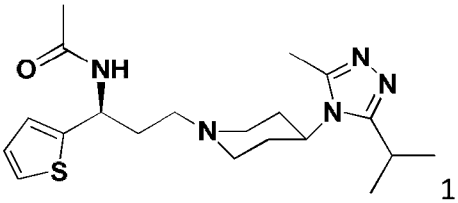
9.

21. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



10.

22. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



11.

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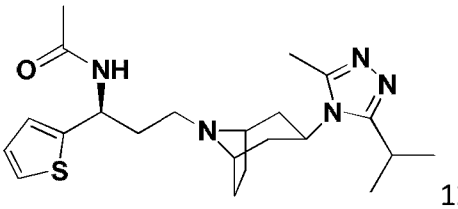
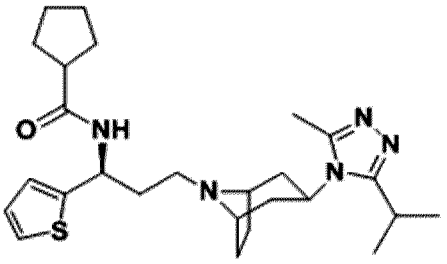
23. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



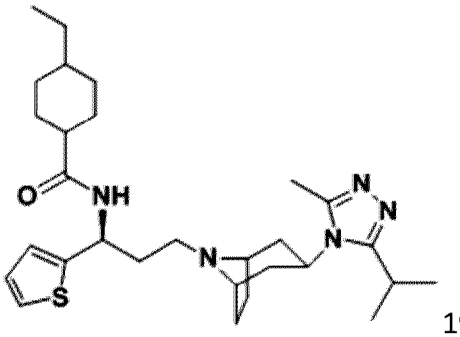
12.

24. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



18.

25. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



19.

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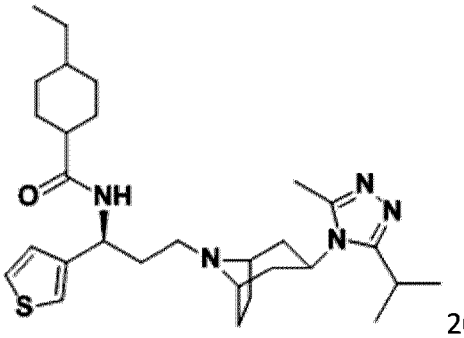
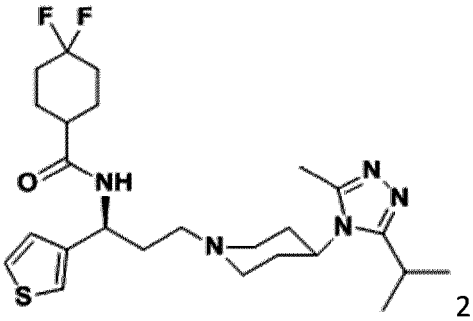
26. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



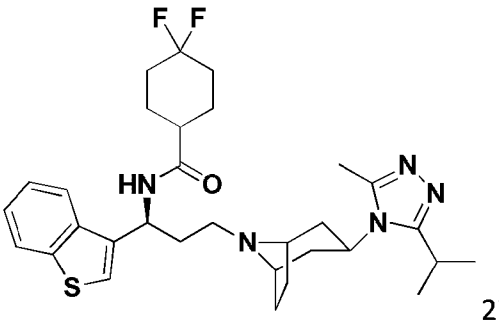
20.

27. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



21.

28. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



27.

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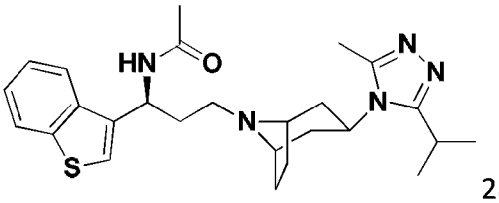
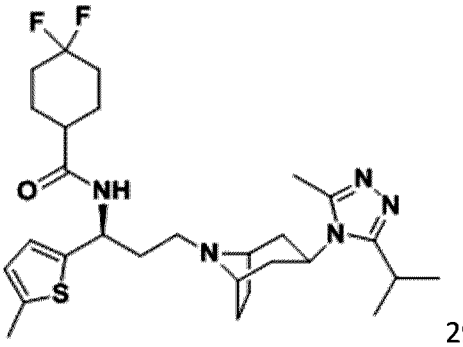
29. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



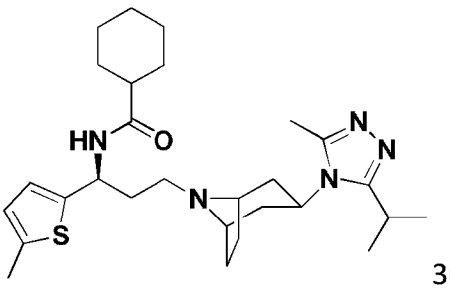
28.

30. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



29.

31. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



30.

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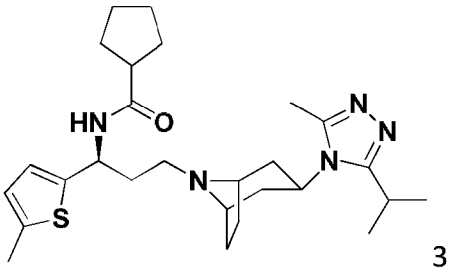
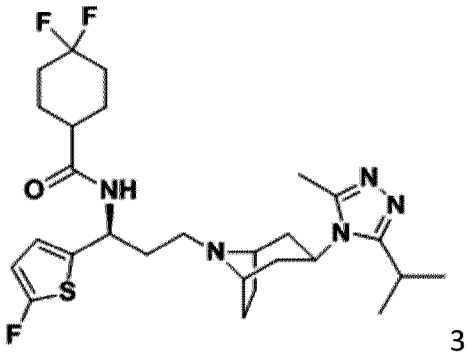
32. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



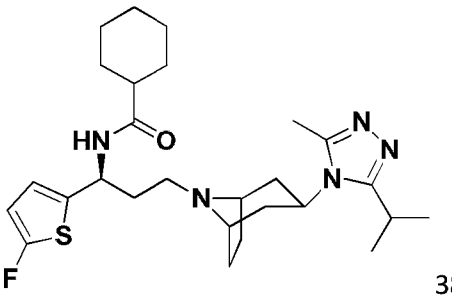
31.

33. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



37.

34. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



38.

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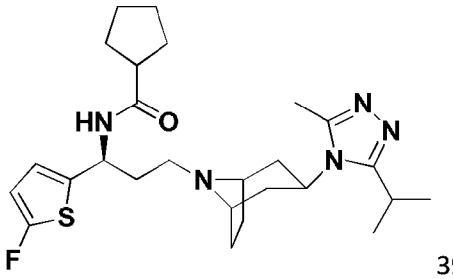
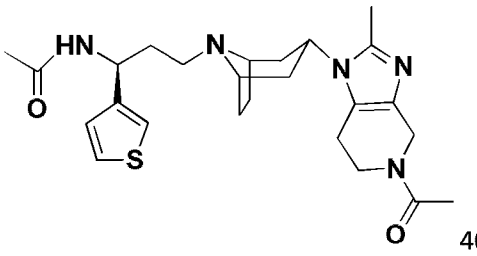
35. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



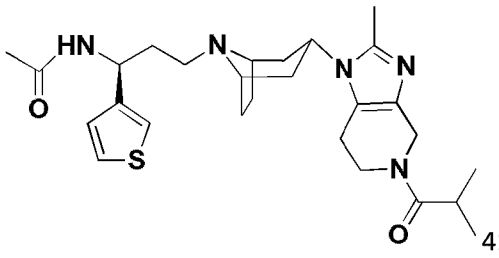
39.

36. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



40.

37. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



41.

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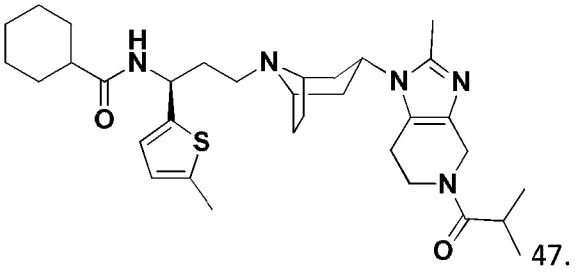
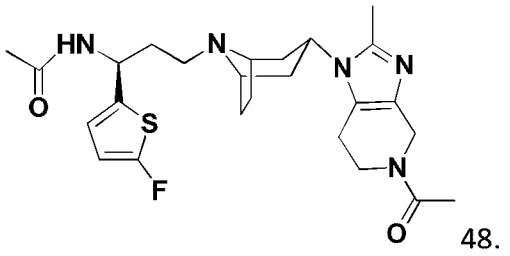
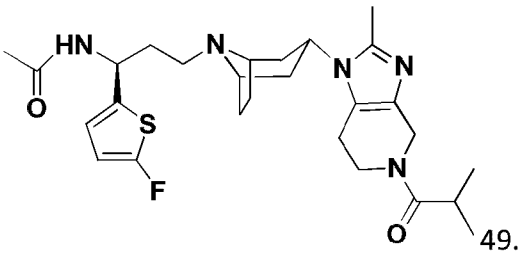
38. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:


47.

39. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:


48.

40. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:


49.

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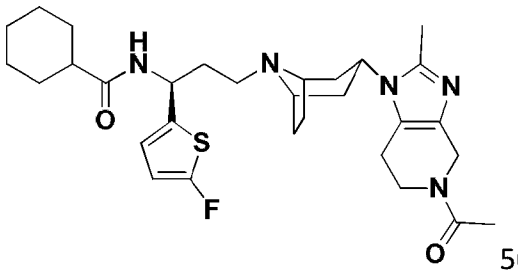
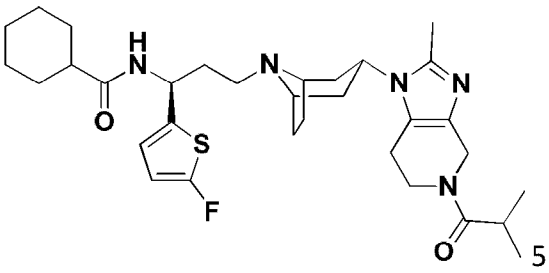
41. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



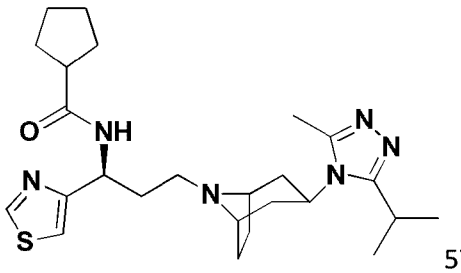
50.

42. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



51.

43. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



57.

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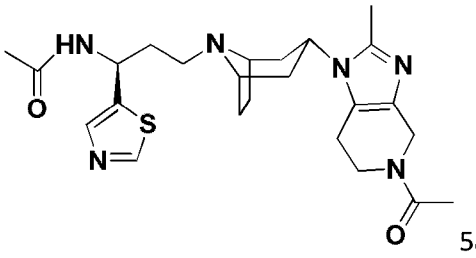
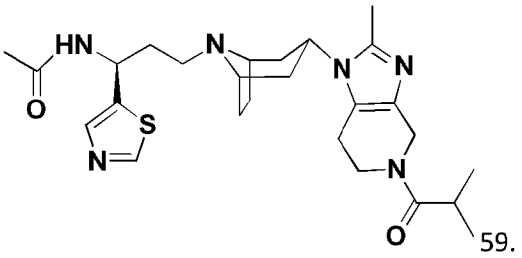
44. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



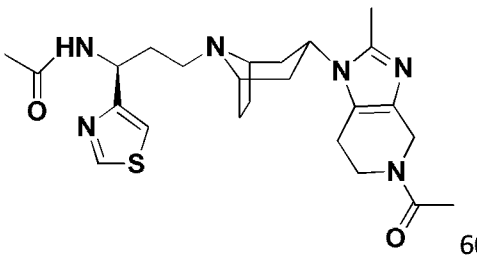
58.

45. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



59.

46. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



60.

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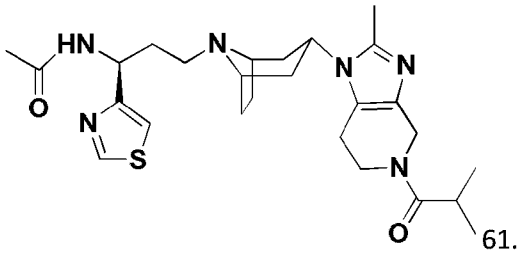
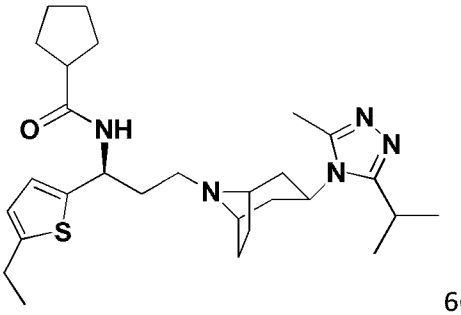
47. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



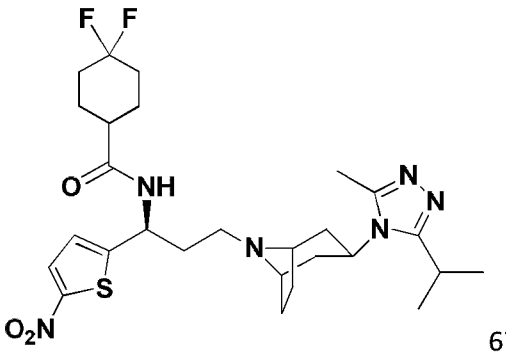
61.

48. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



66.

49. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



67.

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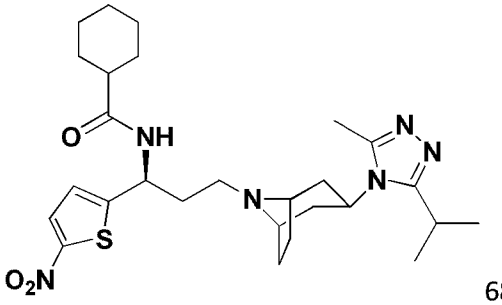
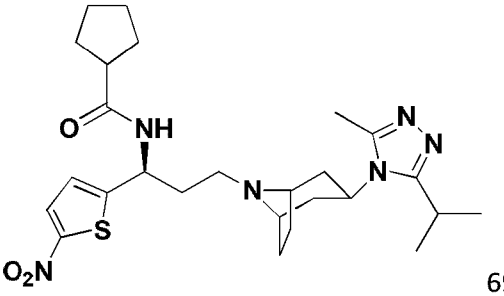
50. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



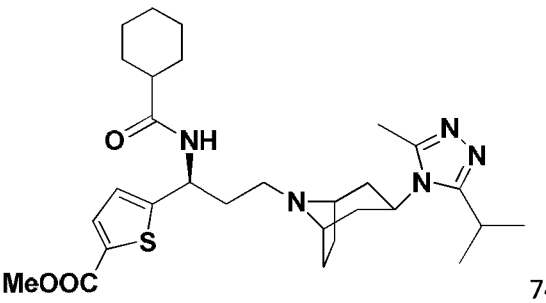
68.

51. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



69.

52. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



74.

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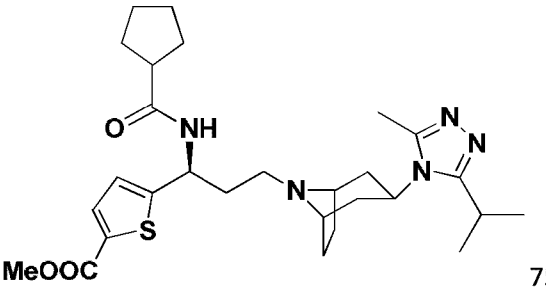
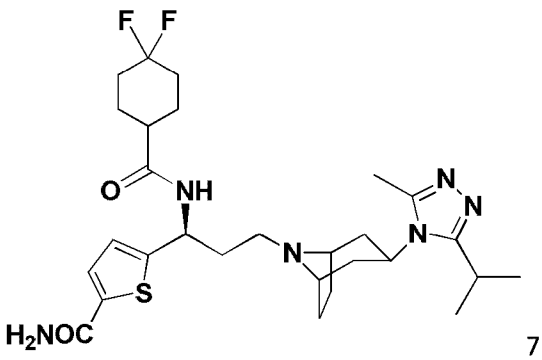
53. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



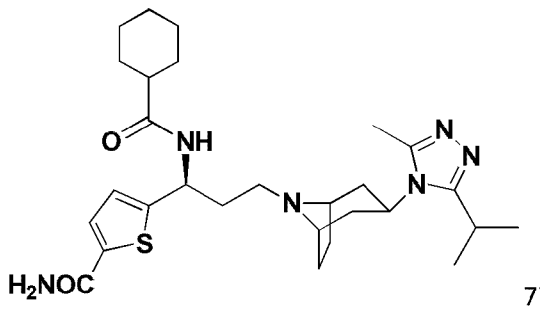
75.

54. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



76.

55. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



77.

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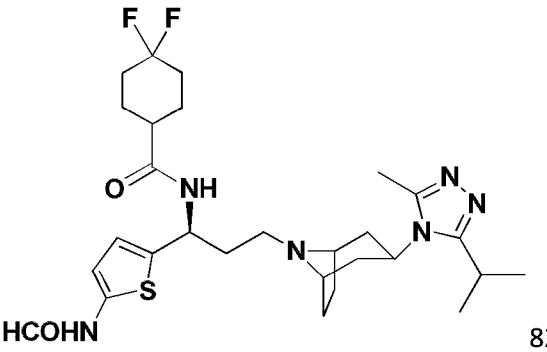
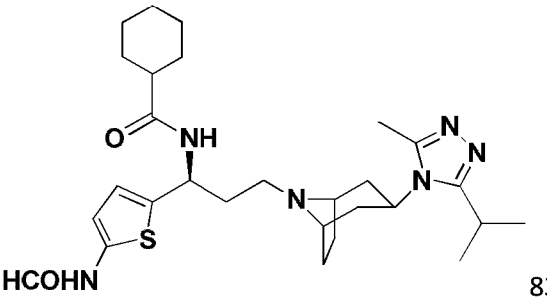
56. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



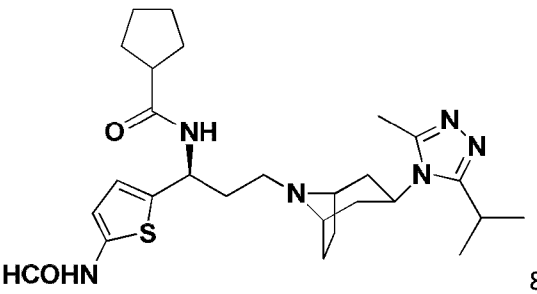
82.

57. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



83.

58. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



84.

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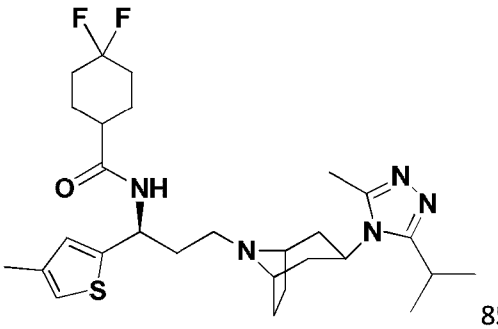
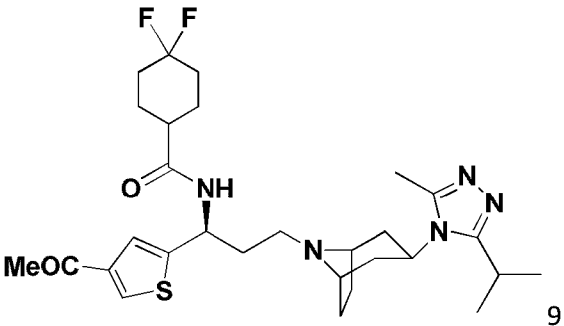
59. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



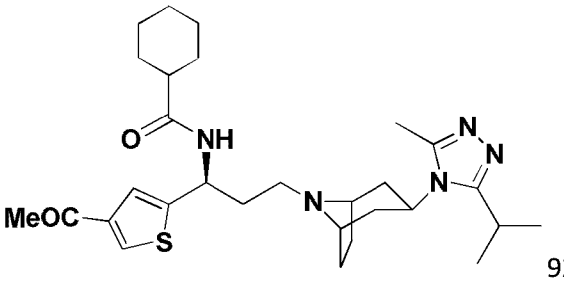
85.

60. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



91.

61. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



92.

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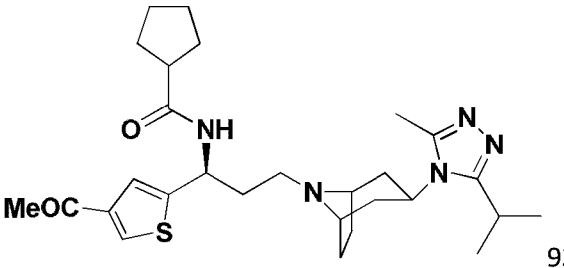
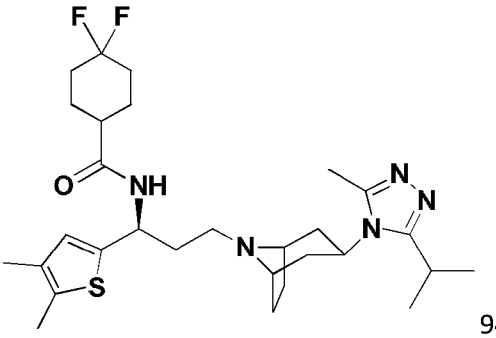
62. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



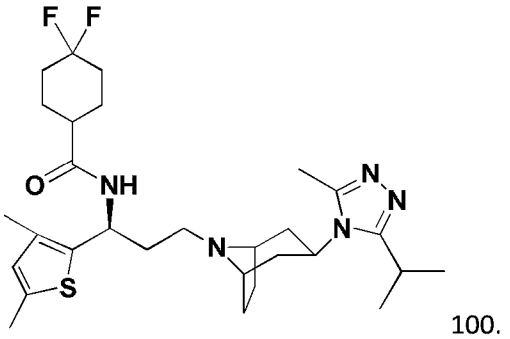
93.

63. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



94.

64. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



100.

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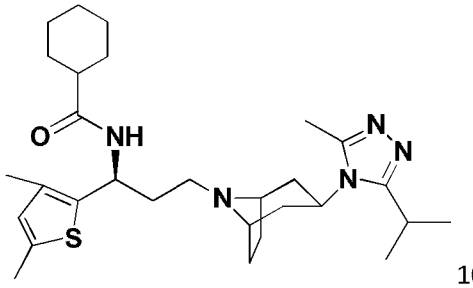
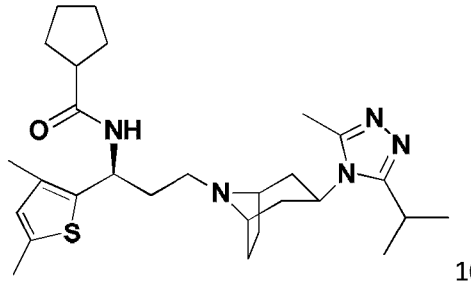
65. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



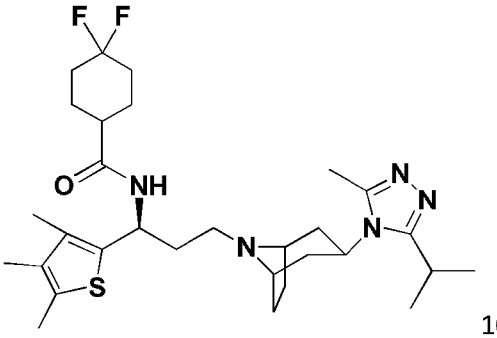
101.

66. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



102.

67. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



103.

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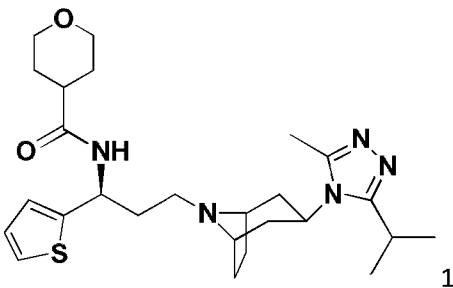
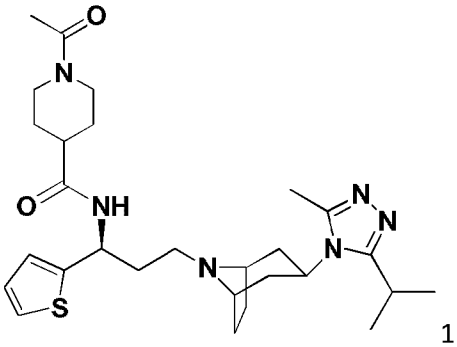
68. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



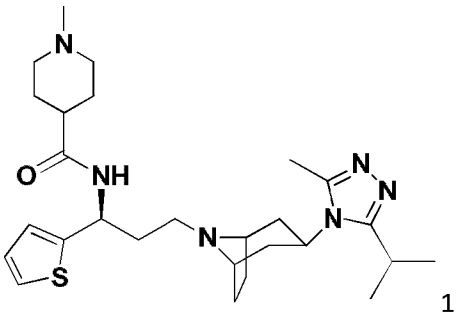
109.

69. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



110.

70. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



111.

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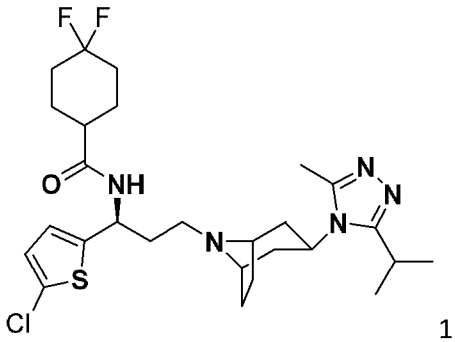
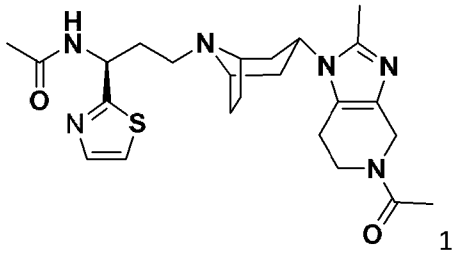
71. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



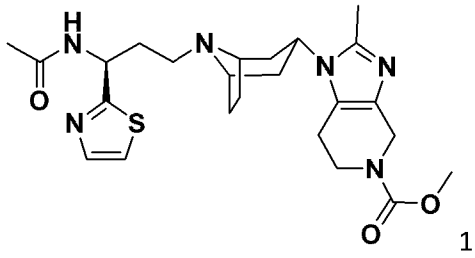
112.

72. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



118.

73. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



119.

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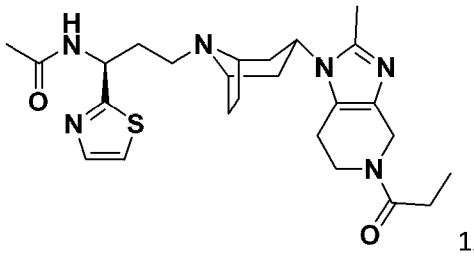
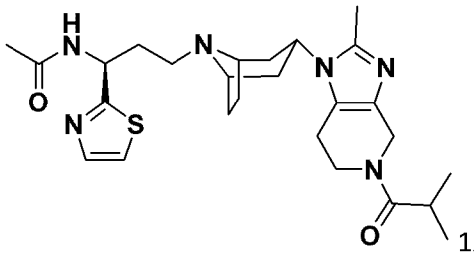
74. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



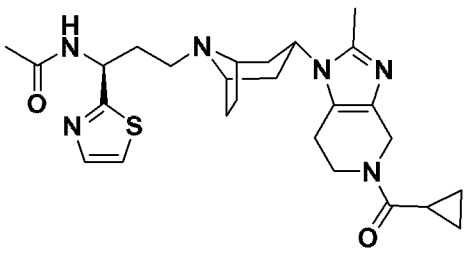
120.

75. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



121.

76. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



122.

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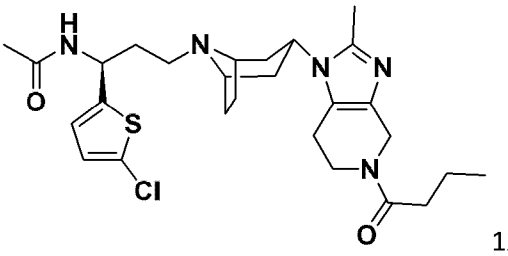
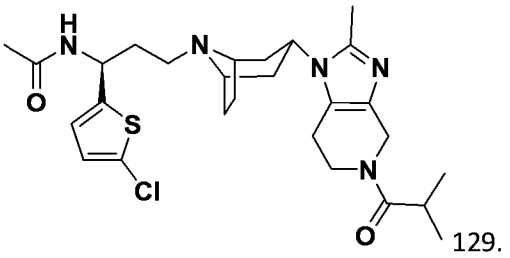
77. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



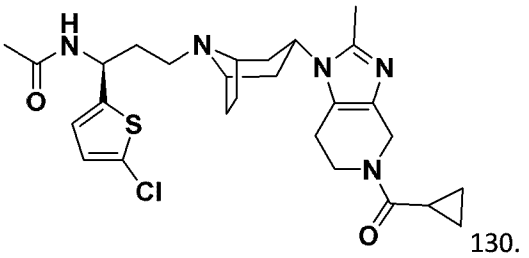
128.

78. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



129.

79. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



130.

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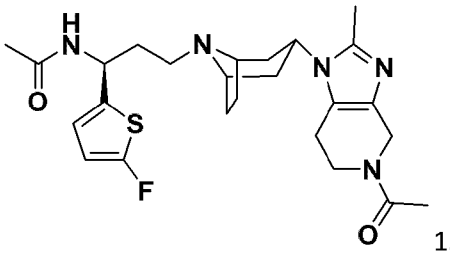
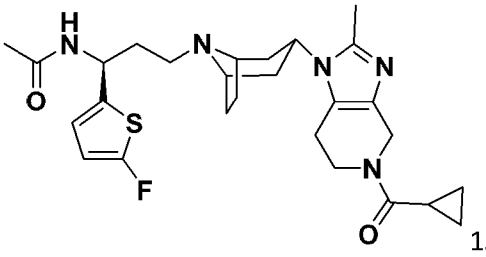
80. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



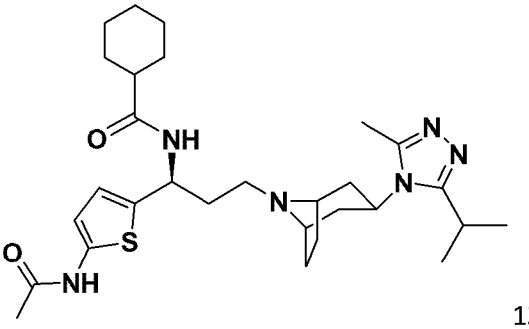
131.

81. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



132.

82. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



138.

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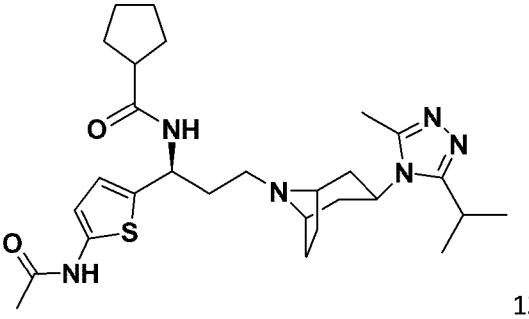
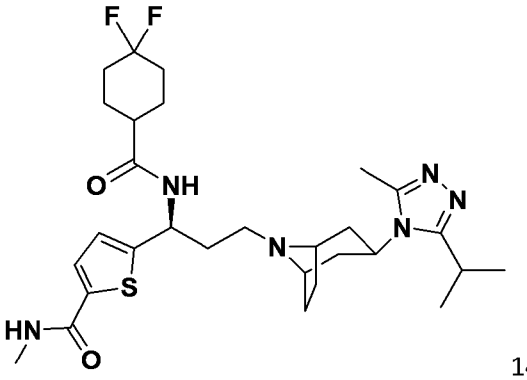
83. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



139.

84. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



140.

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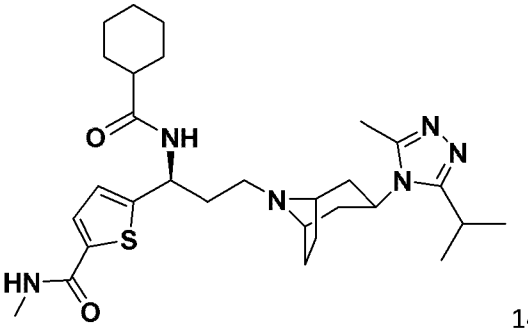
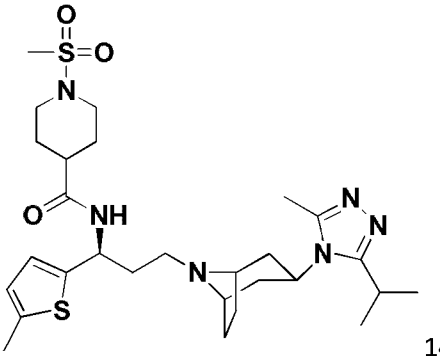
85. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



141.

86. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



147.

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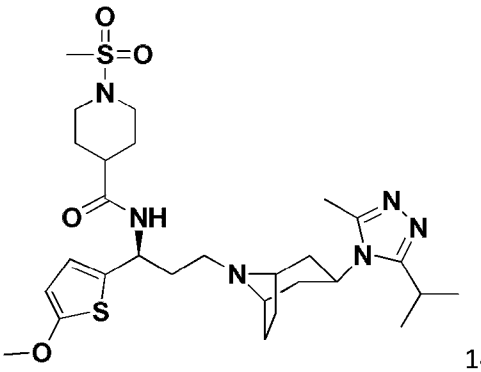
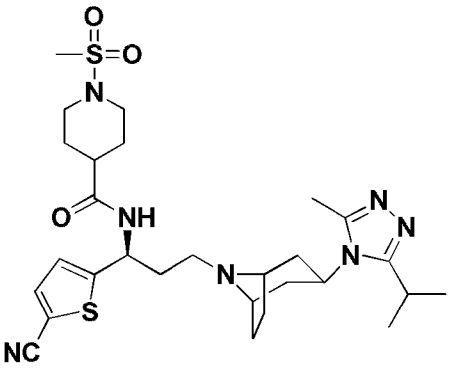
87. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



148.

88. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



149.

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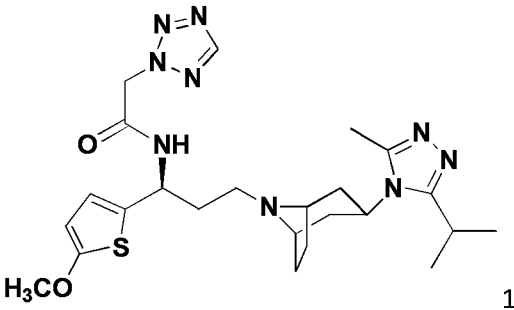
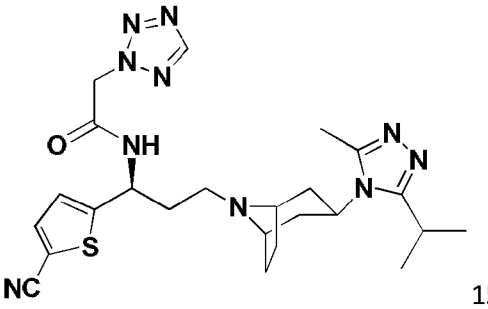
89. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



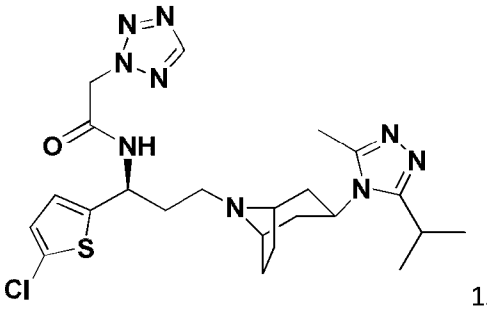
154.

90. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



155.

91. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



156.

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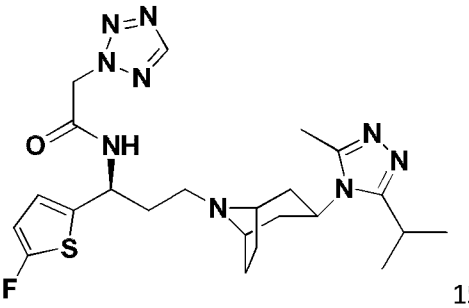
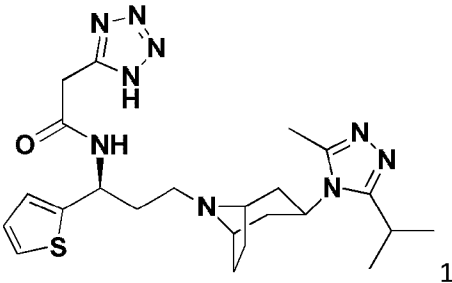
92. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



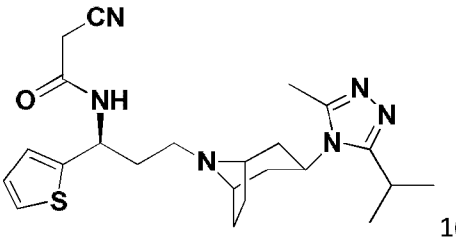
157.

93. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



158.

94. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



164.

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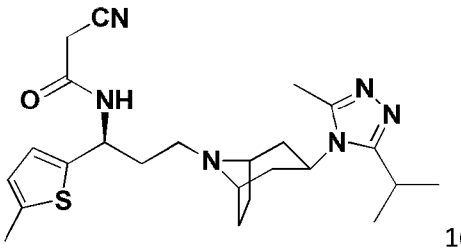
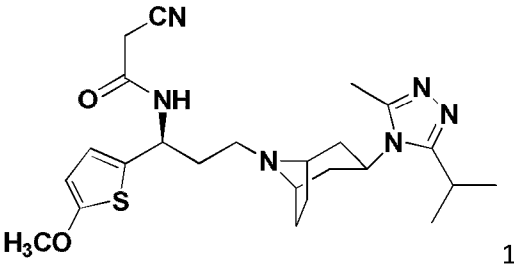
95. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



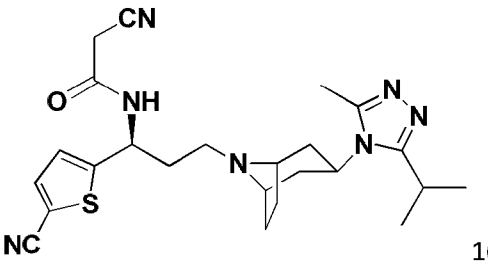
165.

96. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



166.

97. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



167.

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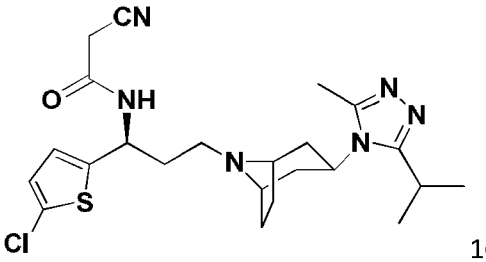
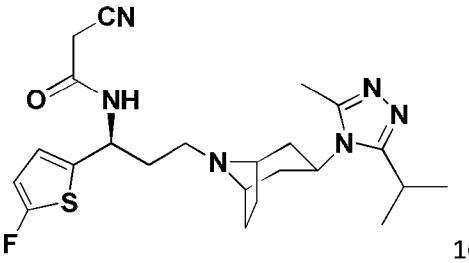
98. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



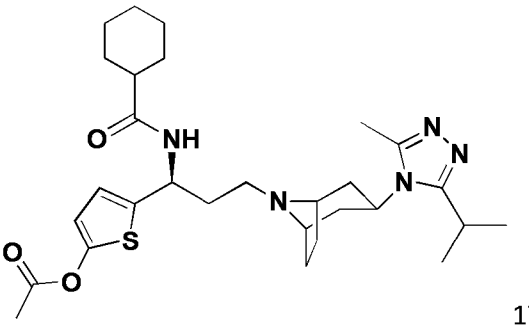
168.

99. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



169.

100. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



170.

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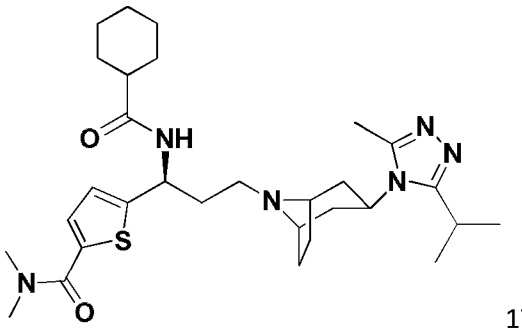
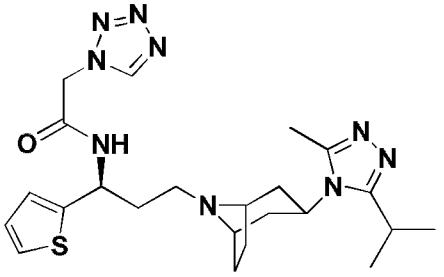
101. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



171.

102. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula (I) is:



172.

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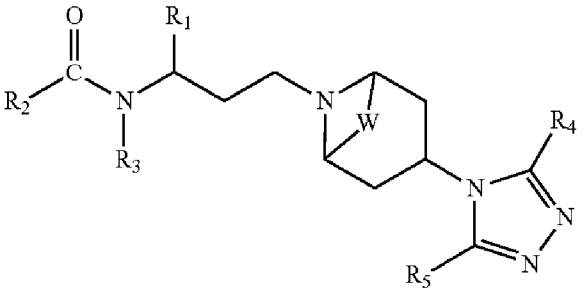
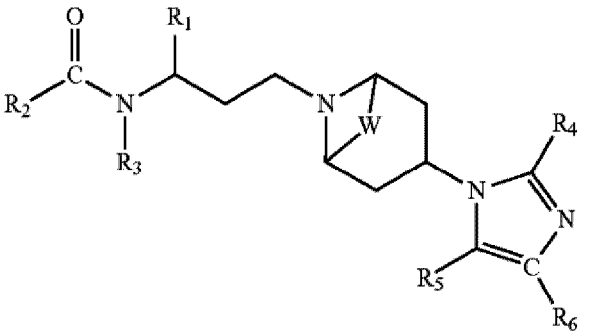
103. The compound according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof, wherein, the compound of formula I is selected from the following compounds:

II



III



wherein, the definitions of R_1, R_2, R_3, R_4, R_5, R_6 and W are described as in claim 1.

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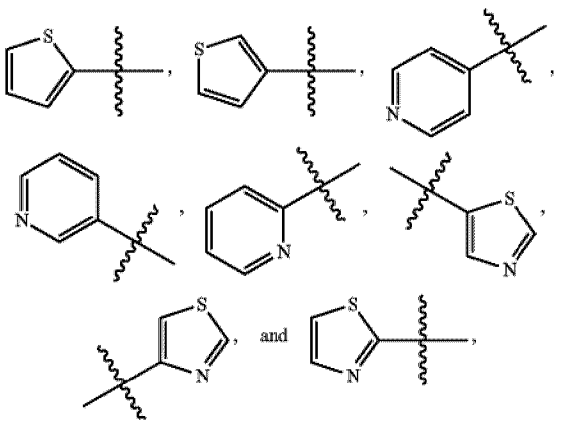
104. The compound according to claim 3, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (II), R_1 is selected from the following groups unsubstituted or substituted with 1-3 substituents:

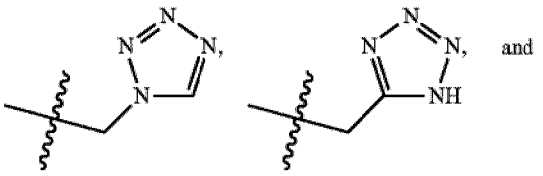


said substituent is defined as in claim 1;

each of R_{10} and R_{11} is independently selected from the group consisting of H, a C1-C4 straight or branched alkyl and --C(=O)R_{13}; R_{12} is selected from the group consisting of a C1-C4 straight or branched alkyl, a C1-C4 straight or branched alkoxy, a hydroxy, an amino (NH_2) and a C1-C4 straight or branched alkylamino;

R_{13} is selected from the group consisting of H and a C1-C4 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a phenyl, a C1-C4 straight or branched alkyl, a C3-C7 cycloalkyl, a tetrahydropyran-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,



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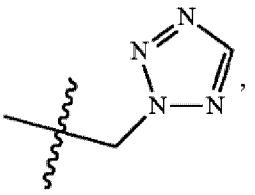
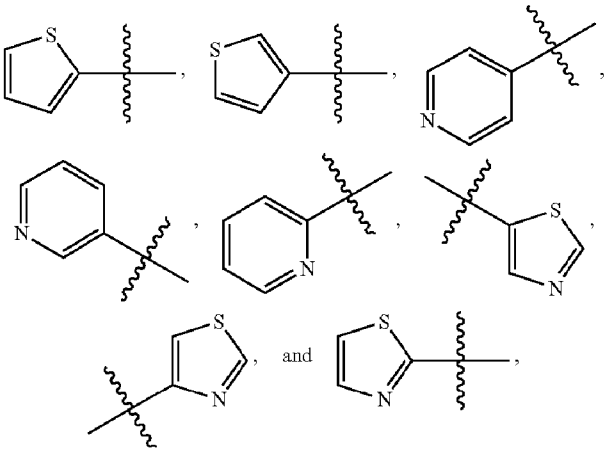


wherein said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, an amino, a phenyl, a halophenyl, a phenoxy and a halophenoxy;

each of R_3, R_4 and R_5 is independently selected from the group consisting of H and a C1-C4 straight or branched alkyl;

in formula (III),

R_1 is selected from the following groups unsubstituted or substituted with 1-3 substituents:



said substituent is defined as in claim 1;

each of R_{10} and R_{11} is independently selected from the group consisting of H, a C1-C4 straight or branched alkyl and --C(=O)R_{13};

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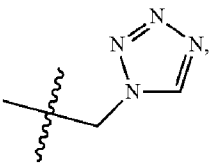
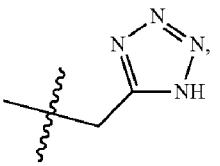
R_{12} is selected from the group consisting of a C1-C4 straight or branched alkyl, a C1-C4 straight or branched alkoxy, a hydroxy, an amino (NH_2) and a C1-C4 straight or branched alkylamino;

R_{13} is selected from the group consisting of H and a C1-C4 straight or branched alkyl;

R_2 is selected from the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C3-C7 cycloalkyl, a tetrahydropyran-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,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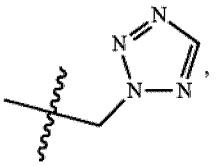
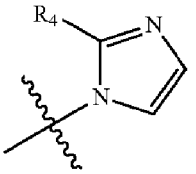


wherein said substituent is selected from a halogen, a hydroxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkylcarbonyl, a C1-C4 straight or branched haloalkoxy, a C1-C4 straight or branched alkylsulfonyl, a C1-C4 straight or branched alkylsulfonylcarbamoyl, a tetrazolyl, a cyano and an amino;

each of R_3 and R_4 is independently selected from the group consisting of H and a C1-C4 straight or branched alkyl; R_5 and R_6 can bind together with



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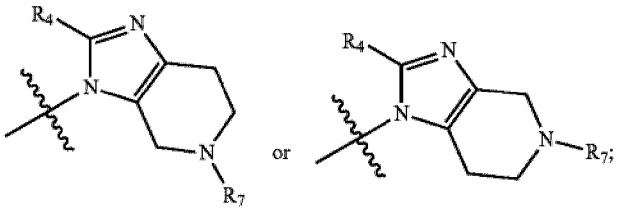

R_7 is selected from the group consisting of H, C(=O)R_8, C(=O)OR_8, C(=O)NR_8R_9 and SO_2R_8;

each of R_8 and R_9 is independently selected from the group consisting of H and the following groups unsubstituted or substituted with 1-3 substituents: a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C3-C7 cycloalkyl and a benzyl, wherein, said substituent is selected from the group consisting of a halogen, a hydroxy, a C1-C4 straight or branched alkoxy, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl, a C1-C4 straight or branched haloalkoxy and an amino.

105. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (II), said substituent on R_1 is selected from the group consisting of a halogen, a C1-C2 alkyl, a C1-C2 haloalkyl, a C1-C2 alkylcarbonyloxy, a C1-C2 alkoxy, a C1-C2 haloalkoxy, NR_{10}, --C(=O)R_{12}, a cyano, a nitro and a hydroxyl, or two adjacent R_1 substituents with the atoms to which each is attached are combined to form a fused 5-7 membered carbocycle, a 5-7 membered heteroaryl ring or a 5-7 membered heterocycle.

106. The compound according to claim 105, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein said substituent on R_1 is selected from the group consisting of a halogen, a methyl, a trifluoromethyl, a trilluoromethoxy, a methoxy, an ethyl, an amino, a cyano, a nitro, an acetyl, a formamido, an acetamido, a carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, an acetoxy, a formyloxy and a methoxycarbonyl, or two adjacent R_1 substituents together with the atoms to which each is attached form a benzene ring, a cyclopentane ring or dioxole ring.

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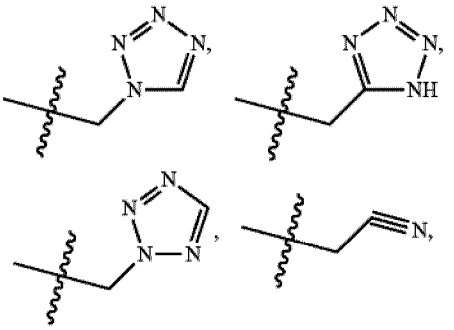
107. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (II), each of R_{10} and R_{11} is independently selected from the group consisting of a C1-C2 alkyl and --C(=O)R_{13}.

108. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (II), R_{12} is selected from the group consisting of a C1-C2 alkyl, a C1-C2 alkoxy, a hydroxy, an amino (NH_2) and a C1-C2 alkylamino.

109. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (II), R_{13} is selected from the group consisting of H and a C1-C2 straight or branched alkyl.

110. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (II), R_2 is selected from the group consisting of a methyl, an ethyl, a cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclohexyl, a tetrahydropyran-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,



a phenyl, 4-fluorobenzyl, an ethylcyclohexyl and a difluorocyclohexyl.

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111. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (11), each of R_3, R_4 and R_5 is independently selected from the group consisting of H and a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

112. The compound according to claim 111, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_3, R_4 and R_5 is independently selected from the group consisting of H, a methyl, an ethyl, an n-propyl and an isopropyl.

113. The compound according to claim 4, a pharmaceutically acceptable salt, enantiomer, diastereoisotner, racemate or mixture thereof; wherein, in formula (III), said substituent on R_1 is selected from the group consisting of a halogen, a C1-C2 alkyl, a C1-C2 haloalkyl, a C1-C2 alkoxy, a C1-C2 alkylcarbonyloxy, a C1-C2 haloalkoxy, $NR_{10}R_{11}$, --C(=O)R_{12}, a cyano, a nitro and a hydroxyl, or two adjacent R_1 substituents with the atoms to which each is attached are combined to form a fused 5-7 membered carbocycle, 5-7 membered heteroaryl ring or 5-7 membered heterocycle.

114. The compound according to claim 113, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein said substituent on R_1 is selected from the group consisting of a halogen, a methyl, a trifluoromethyl, a trifluoromethoxy, a methoxy, an ethyl, an amino, a cyano, a nitro, an acetyl, a formamido, an acetamido, a carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, a formyloxy, an acetoxy and a methoxycarbonyl, or two adjacent R_1 substituents together with the atoms to which each is attached form a benzene ring, a cyclopentene ring or dioxole ring.

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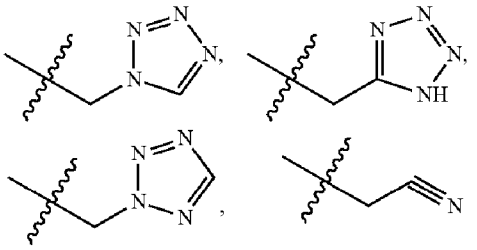
115. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), each of R_{10} and R_{11} is independently selected from the group consisting of H, a C1-C2 alkyl and --C(=O)R_{13}.

116. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), R_{12} is selected from the group consisting of a C1-C2 alkyl, a C1-C2 alkoxy, a hydroxy, an amino (NH_2) and a C1-C2 alkylamino.

117. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), R_{13} is selected from the group consisting of H and a C1-C2 straight or branched alkyl.

118. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), R_2 is selected from the group consisting of a methyl, an ethyl, a cyclopropyl, a cyclobutyl, a cyclopentyl, a cyclohexyl, a tetrahydropyran-4-yl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-methylsulfonylpiperidin-4-yl,



and a difluorocyclohexyl.

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119. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), each of R_3 and R_4 is independently selected from the group consisting of H and a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

120. The compound according to claim 119, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_3 and R_4 is independently selected from the group consisting of H, a methyl and an ethyl.

121. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), R_7 is selected from the group consisting of H, C(=O)R_8 and SO2R_8.

122. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula (III), said substituent on each of Rs and Ry is selected from the group consisting of a halogen, a hydroxy, a methoxy, an ethoxy, a methyl, an ethyl, a trilluoromethyl, a trifluoromethoxy and an amino.

123. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein, in formula each of R_8 and R_9 is independently selected from the group consisting of H, a C1-C4 straight or branched alkyl, a C1-C4 straight or branched haloalkyl and a C3-C7 cycloalkyl.

124. The compound according to claim 122, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_8 and R_9 is independently selected from the group consisting of a methyl, an ethyl, an n-propyl, a cyclopropyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

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125. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_3, R_4 and R_5 is independently selected from the group consisting of H and a methyl, an ethyl, an n-propyl, an isopropyl, an n-butyl, a sec-butyl and a tert-butyl.

126. The compound according to claim 104, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof, wherein each of R_8 and R_9 is independently selected from the group consisting of a halogen, a hydroxy, a methoxy, an ethoxy, a methyl, an ethyl, a trifluoromethyl, a trifluoromethoxy and an amino.

127. A pharmaceutical composition comprising one of the compounds according to claim 1, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof; and a pharmaceutically acceptable carrier.

128. A use, for treatment of HIV infection in a subject in need thereof, of a compound according to any one of claims 1 to 126, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof.

129. A method for preparing a medicament for treating a CCR5-mediated disease comprising combining the compound according to any one of claims 1 to 126, a pharmaceutically acceptable salt, enantiomer, diastereoisomer, racemate or mixture thereof with a pharmaceutically acceptable carrier.

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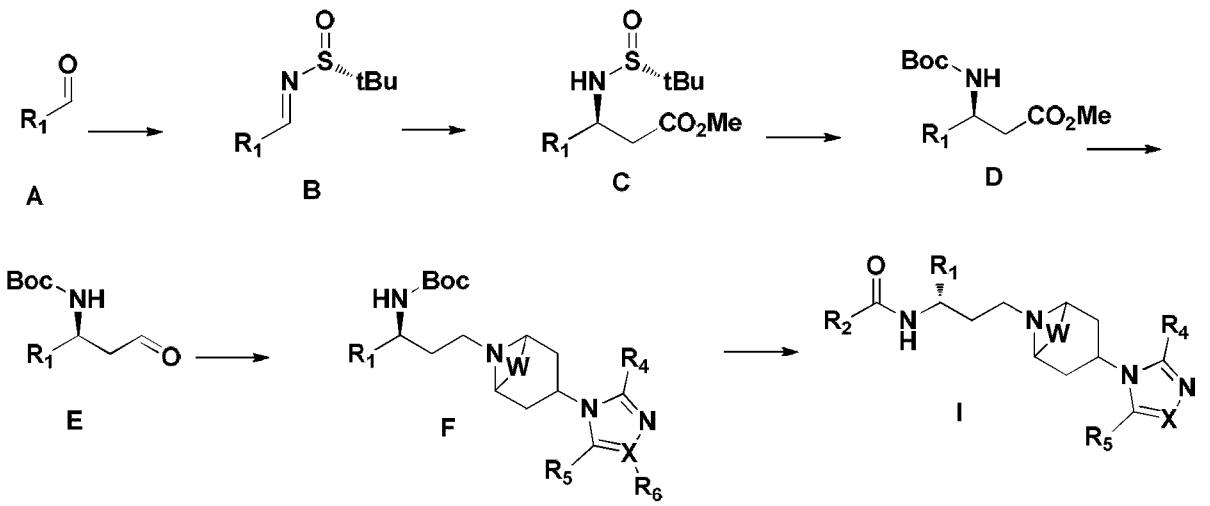
130. A method for preparing a compound of formula I, wherein, the method includes the following steps:



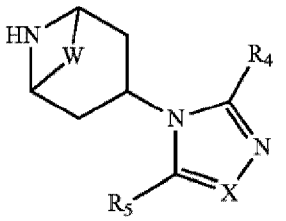
1) Sulfinylimine Compound B is obtained from Compound A through imidization;

2) Compound C is Obtained from Sulfinylimine compound B through Mannich reaction;

3) Compound D is obtained from Compound C through removal of sulfinyl and t-butyloxycarbonyl (BOC) protection;

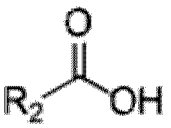
4) Compound E is obtained from Compound D through ester reduction and oxidation;

5) Compound F is obtained from Compound E and



through reductive amination reaction;

6) Compound F is subjected to deprotection and condensation reaction with



to give compound I, in each formula, R_1, R_2, R_4, R_5, R_6, X and W are defined as in claim 1.

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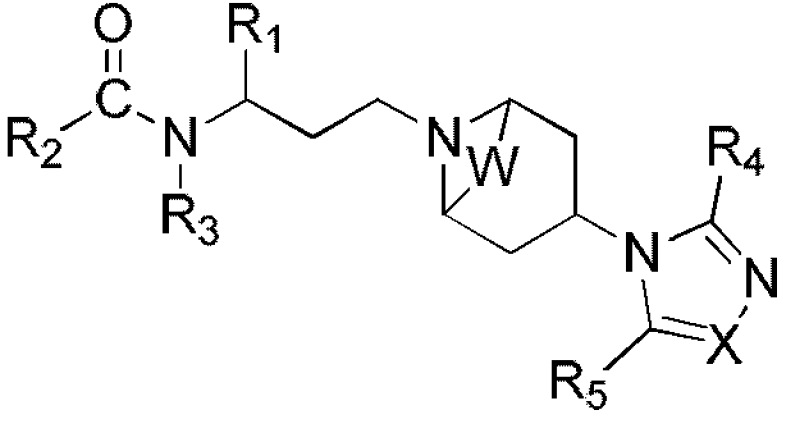

(I)