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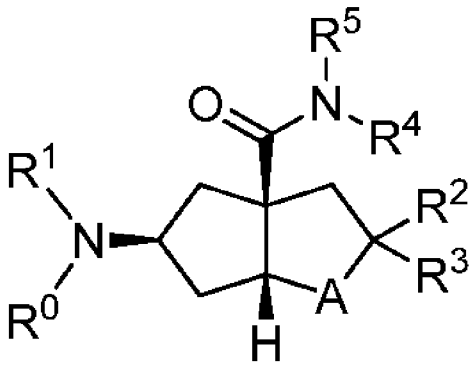
— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) Title: FUSED CYCLOPENTYL ANTAGONISTS OF CCR2



Formula (I)

(57) Abstract: The present invention comprises compounds of Formula (I). Formula (I) wherein: R^0, R^1, R^2, R^3, R^4, R^5, and A are as defined in the specification. The invention also comprises a method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is type II diabetes, obesity and asthma. The invention also comprises a method of inhibiting CCR2 activity in a mammal by administration of a therapeutically effective amount of at least one compound of Formula (I).

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FUSED CYCLOPENTYL ANTAGONISTS OF CCR2

FIELD OF THE INVENTION

The invention is directed to substituted fused cyclopentyl compounds, which are antagonists to the chemoattractant cytokine receptor 2 (CCR2), pharmaceutical compositions, and methods for use thereof. More particularly, the CCR2 antagonists are compounds useful for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease. The present invention is further directed to a crystalline succinate salt of ((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone, pharmaceutical compositions containing said salt and the use of said salt in the treatment of disorders, such as type II diabetes, obesity and asthma. The present invention is further directed to a novel process for the preparation of said crystalline succinate salt.

BACKGROUND OF THE INVENTION

CCR2 is a member of the GPCR family of receptors, as are all known chemokine receptors, and are expressed by monocytes and memory T-lymphocytes. The CCR2 signaling cascade involves activation of phospholipases (PLCβ2), protein kinases (PKC), and lipid kinases (PI-3 kinase).

Chemoattractant cytokines (i.e., chemokines) are relatively small proteins (8-10 kD), which stimulate the migration of cells. The chemokine family is divided into four subfamilies based on the number of amino acid residues between the first and second highly conserved cysteines.

Monocyte chemotactic protein-1 (MCP-1) is a member of the CC chemokine subfamily (wherein CC represents the subfamily having adjacent first and second cysteines) and binds to the cell-surface chemokine receptor 2 (CCR2). MCP-1 is a potent chemotactic factor, which, after binding to CCR2, mediates monocyte and lymphocyte migration (i.e., chemotaxis) toward a site of inflammation. MCP-1 is also expressed by cardiac muscle cells, blood vessel endothelial cells, fibroblasts, chondrocytes, smooth muscle cells, mesangial cells, alveolar cells, T-lymphocytes, marcophages, and the like.

After monocytes enter the inflammatory tissue and differentiate into macrophages, monocyte differentiation provides a secondary source of several proinflammatory modulators, including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-8 (a member of the CXC chemokine subfamily, wherein CXC represents one amino acid residue between the first and second cysteines), IL-12, arachidonic acid metabolites (e.g., PGE_2 and LTB_4), oxygen-derived free radicals, matrix metalloproteinases, and complement components.

Animal model studies of chronic inflammatory diseases have demonstrated that inhibition of binding between MCP-1 and CCR2 by an antagonist suppresses the inflammatory response. The interaction between MCP-1 and CCR2 has been implicated (see Rollins B J, Monocyte chemoattractant protein 1: a potential regulator of monocyte recruitment in inflammatory disease, *Mol. Med. Today,* 1996, 2:198; and Dawson J, et al., Targeting monocyte chemoattractant protein-1 signaling in disease, *Expert Opin. Ther. Targets,* 2003 Feb. 7 (1):35-48) in inflammatory disease pathologies such as psoriasis, uveitis, atherosclerosis, rheumatoid arthritis (RA), multiple sclerosis, Crohn's Disease, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type II diabetes and diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, tuberculosis, sarcoidosis, invasive *staphylococcia*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, Chronic Obstructive Pulmonary Disease (COPD), allergic asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, and stomach.

Monocyte migration is inhibited by MCP-1 antagonists (either antibodies or soluble, inactive fragments of MCP-1), which have been shown to inhibit the development of arthritis, asthma, and uveitis. Both MCP-1 and CCR2 knockout (KO) mice have demonstrated that monocyte infiltration into inflammatory lesions is significantly decreased. In addition, such KO mice are resistant to the development of experimental allergic encephalomyelitis (EAE, a model of human MS), cockroach allergen-induced asthma, atherosclerosis, and uveitis. Rheumatoid arthritis and Crohn's

Disease patients have improved during treatment with TNF-α antagonists (e.g., monoclonal antibodies and soluble receptors) at dose levels correlated with decreases in MCP-1 expression and the number of infiltrating macrophages.

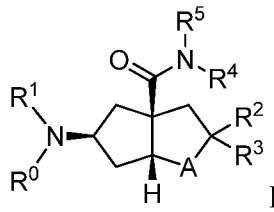
MCP-1 has been implicated in the pathogenesis of seasonal and chronic allergic rhinitis, having been found in the nasal mucosa of most patients with dust mite allergies. MCP-1 has also been found to induce histamine release from basophils in vitro. During allergic conditions, both allergens and histamines have been shown to trigger (i.e. to up-regulate) the expression of MCP-1 and other chemokines in the nasal mucosa of people with allergic rhinitis, suggesting the presence of a positive feedback loop in such patients.

There remains a need for small molecule CCR2 antagonists for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease resulting from MCP-1 induced monocyte and lymphocyte migration to a site of inflammation.

All documents cited herein are incorporated by reference.

SUMMARY OF THE INVENTION

The present invention relates to compounds of Formula (I)



Formula (I)

wherein:

A is O, or S;

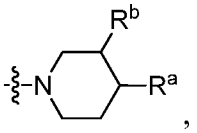
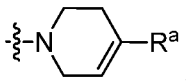
R^0 is H, or $C_{(1-4)}$alkyl;

wherein said $C_{(1-4)}$alkyl is optionally substituted with OH, $C_{(1-4)}$alkyl-$(OCH_2CH_2)_n$-OCH_3, OCH_3, CO_2H, $C(O)NH_2$, SO_2NH_2, or $CO_2C_{(1-4)}$alkyl;

n is 1, 2, or 3;

R^1 is cyclohexyl, or tetrahydropyranyl;

wherein said cyclohexyl or tetrahydropyranyl may be optionally substituted with one substituent selected from the group consisting of OCH_3, OH, CH_2CH_3, -CN, NH_2, $NH(CH_3)$, $N(CH_3)_2$, and OCF_3;

alternatively, R^0 and R^1 are taken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

R^a is phenyl; wherein the phenyl is optionally substituted with $C(O)NH_2$, $C(O)NHC_{(1-4)}alkyl$, SO_2NH_2, $C(O)N(C_{(1-4)}alkyl)_2$, OCH_3, CO_2CH_3, or CO_2H;

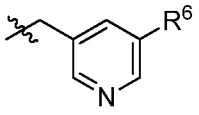
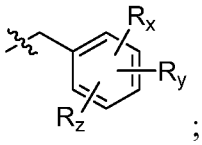
R^b is $C_{(1-4)}alkyl$, or $OC_{(1-4)}alkyl$;

R^2 is selected from the group consisting of H, $C_{(1-4)}alkyl$, cyclopropyl, cyclohexyl, phenyl, pyridyl, pyrimidyl, pyrazyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl, furyl, and thiophenyl;

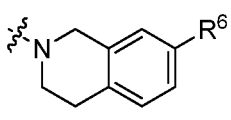
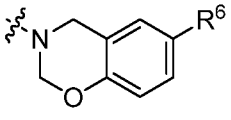
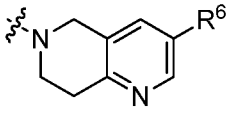
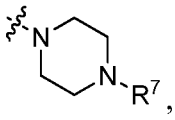
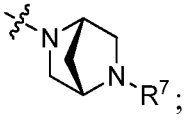
wherein said phenyl, pyridyl, pyrimidyl, pyrazyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, or thiophenyl is optionally substituted with one substituent selected from the group consisting of NH_2, $NHC_{(1-3)}alkyl$, $N(C_{(1-3)}alkyl)_2$, $C_{(1-3)}alkyl$, -CN, $-CH=CH_2$, $-CONH_2$, $-CO_2H$, $-NO_2$, $-CONHC_{(1-4)}alkyl$, $CON(C_{(1-4)}alkyl)_2$, $C_{(1-4)}alkylCONH_2$, $-NHCOC_{(1-4)}alkyl$, $-CO_2C_{(1-4)}alkyl$, CF_3, $SO_2C_{(1-4)}alkyl$, $-SO_2NH_2$, $-SO_2NH(C_{(1-4)}alkyl)$, and $-SO_2N(C_{(1-4)}alkyl)_2$;

R^3 is H, or CH_3;

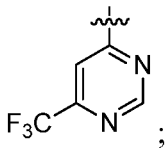
alternatively,R^3 and R^2 are taken together with their attached carbon to form  ;

R^4 is  , or  ;

R^5 is H, or CH_3;

alternatively, R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of  ,  ,  ,  , and  ;

R^6 is CF_3, or OCF_3;

R^7 is a CF_3 substituted heteroaryl, provided that R^7 is not  ;

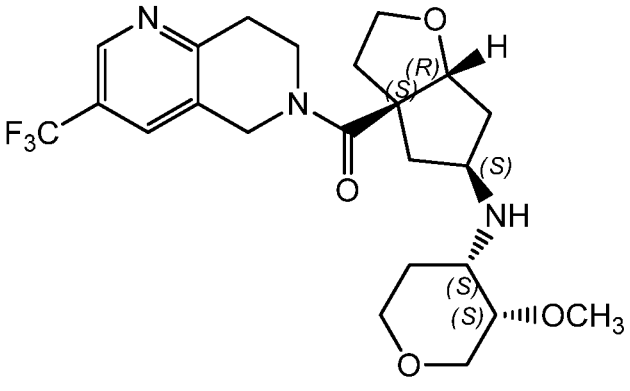
R_x is CF_3, F, Cl, CN, or OCH_3;

R_y is H, F, Cl, or CF_3;

R_z is H, or F;

and pharmaceutically acceptable salts thereof.

The present invention is further directed to a succinate salt of a compound of formula (I-S)



(I-S)

also known as ((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. In an embodiment of the present invention, the succinate salt of the compound of formula (I-S) is crystalline. In another embodiment, the present invention is directed to a succinate salt of the compound of formula (I-S), wherein the salt is crystalline hydrate form; preferably, the hydrate contains about 0.6 moles water per mole of the compound of formula (I-S). In yet another embodiment of the present invention, the succinate salt of the compound of formula (I-S) is crystalline hydrate form containing about 0.6 moles water per mole of the compound of formula (I-S) and is further hygroscopic.

The present invention is further directed to a process for the preparation of a succinate salt of the compound of formula (I-S), preferably a crystalline succinate salt of the compound of formula (I-S), as described in more detail hereinafter.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates a representative pXRD spectrum for the crystalline succinate salt of the compound of formula (I-S).

Figure 2 illustrates a representative DSC scan for the crystalline succinate salt of the compound of formula (I-S)

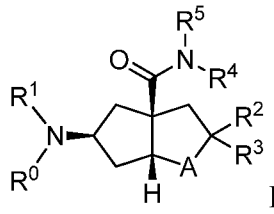
Figure 3 illustrates a representative TGA scan for the crystalline succinate salt of the compound of formula (I-S)

Figure 4 illustrates a representative moisture isotherm for the crystalline succinate salt of the compound of formula (I-S).

Figure 5 illustrates a DSC thermogram showing conversion of a representative sample of the amorphous succinate salt of the compound of formula (I-S) to a crystalline succinate salt of the compound of formula (I-S); and a TGA thermogram for a representative sample of amorphous succinate salt of the compound of formula (I-S).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the compounds of Formula (I)



Formula (I)

wherein:

A, R^0, R^1, R^2, R^3, R^4 and R^5 are as defined above.

In an embodiment, the invention is directed to compounds of formula (I) wherein A is O.

In another embodiment, the invention is directed to compounds of formula (I) wherein

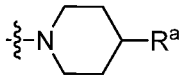
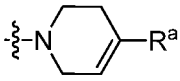
A is O, or S;

R^0 is H, or $C_{(1-4)}$alkyl;

wherein said $C_{(1-4)}$alkyl is optionally substituted with OH, $C_{(1-4)}$alkyl-$(OCH_2CH_2)_n$-OCH_3, or OCH_3;

n is 1, 2, or 3;

R^1 is cyclohexyl, 1-methoxy cyclohex-2-yl, tetrahydropyran-4-yl, or 3-methoxy tetrahydropyran-4-yl;

alternatively,R^0 and R^1 are taken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

R^a is phenyl;

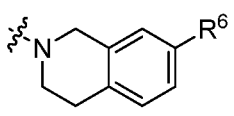
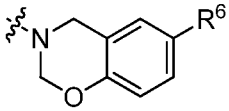
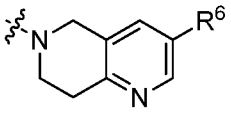
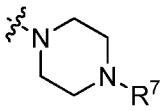
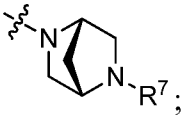
wherein the phenyl is optionally substituted with $C(O)NH_2$, $C(O)NHCH_3$, SO_2NH_2, $C(O)N(CH_3)_2$, OCH_3, CO_2CH_3, or CO_2H;

R^2 is selected from the group consisting of H, $C_{(1-4)}$alkyl, cyclopropyl, cyclohexyl, phenyl, pyridyl, pyrimidyl, pyrazyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl, furyl, and thiophenyl;

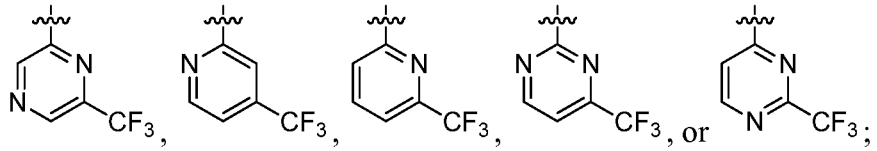
wherein said phenyl, pyridyl, pyrimidyl, pyrazyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, or thiophenyl is optionally substituted with one substituent selected from the group consisting of NH_2, $NHC_{(1-3)}$alkyl, $N(C_{(1-3)}alkyl)_2$, $C_{(1-3)}$alkyl, -CN, $-CH=CH_2$, $-CONH_2$, $-CO_2H$, $-NO_2$, $-CONHC_{(1-4)}$alkyl, $CON(C_{(1-4)}alkyl)_2$, $C_{(1-4)}alkylCONH_2$, $-NHCOC_{(1-4)}$alkyl, $-CO_2C_{(1-4)}$alkyl, CF_3, $SO_2C_{(1-4)}$alkyl, $-SO_2NH_2$, $-SO_2NH(C_{(1-4)}alkyl)$, and $-SO_2N(C_{(1-4)}alkyl)_2$;

R^3 is H, or CH_3;

alternatively,R^3 and R^2 are taken together with their attached carbon to form  ;

R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of  ,  ,  ,  , and  ;

R^6 is CF_3, or OCF_3;

R^7 is  ;

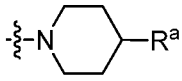
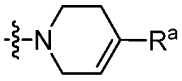
and pharmaceutically acceptable salts thereof.

In another embodiment of the invention

A is O, or S;

R^0 is H, CH_3, $CH_2CH_2CH_2OH$, CH_2CH_2OH, $CH_2CH_2CH_2(OCH_2CH_2)_3OCH_3$, or $CH_2CH_2OCH_3$;

R^1 is tetrahydropyran-4-yl, or 3-methoxy tetrahydropyran-4-yl;

alternatively,R^0 and R^1 are taken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

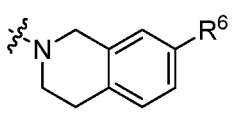
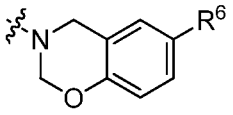
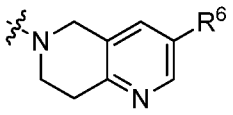
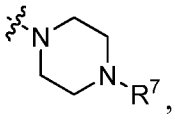
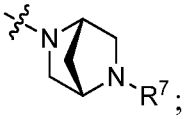
R^a is phenyl;

wherein the phenyl is optionally substituted with $C(O)N(CH_3)_2$, OCH_3, or CO_2H;

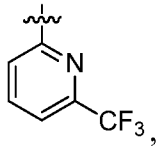
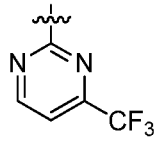
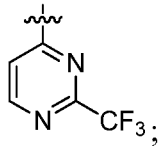
R^2 is H, $C_{(1-4)}$alkyl, cyclopropyl, cyclohexyl, thiazol-2-yl, 1-methyl-imidazol-2-yl, 1-methyl-pyrazol-5-yl, or phenyl;

R^3 is H, or CH_3;

alternatively,R^3 and R^2 are taken together with their attached carbon to form  ;

R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of  ,  ,  ,  ,  ;

R^6 is CF_3, or OCF_3;

R^7 is  ,  , or  ;

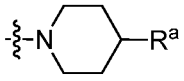
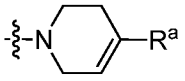
and pharmaceutically acceptable salts thereof.

In another embodiment, the present invention is directed to compounds of formula (I) wherien

A is O;

R^0 is H, CH_3, $CH_2CH_2CH_2OH$, CH_2CH_2OH, $CH_2CH_2CH_2(OCH_2CH_2)_3OCH_3$, or $CH_2CH_2OCH_3$;

R^1 is tetrahydropyran-4-yl, or 3-methoxy tetrahydropyran-4-yl;

alternatively,R^0 and R^1 may be taken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

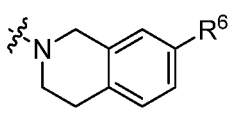
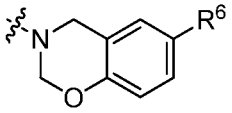
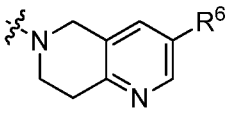
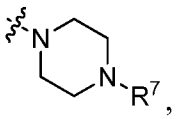
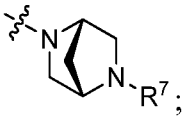
R^a is phenyl;

wherein the phenyl is optionally substituted with $C(O)N(CH_3)_2$, OCH_3, or CO_2H;

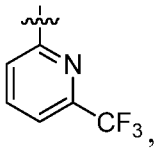
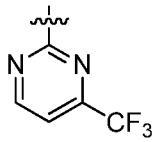
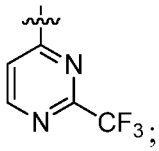
R^2 is H, $C_{(1-4)}$alkyl, cyclopropyl, cyclohexyl, thiazol-2-yl, 1-methyl-imidazol-2-yl, 1-methyl-pyrazol-5-yl, or phenyl;

R^3 is H, or CH_3;

alternatively,R^3 and R^2 are taken together with their attached carbon to form  ;

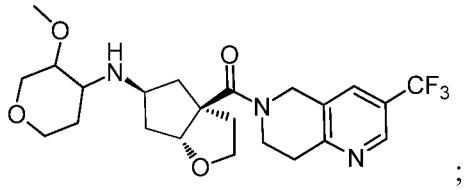
R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of  ,  ,  ,  ,  ;

R^6 is CF_3, or OCF_3;

R^7 is  ,  , or  ;

and pharmaceutically acceptable salts thereof.

In another embodiment, the present invention is directed to any one or more compounds, independently selected from the group consisting of: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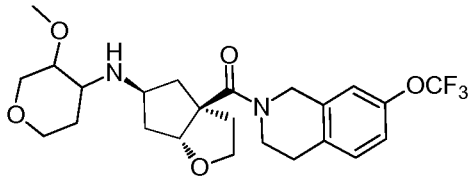
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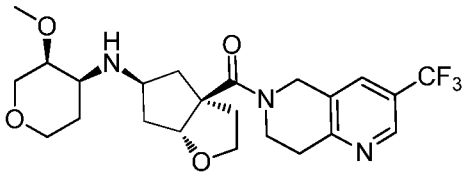
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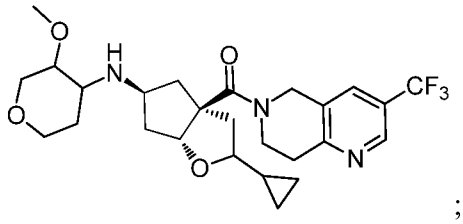
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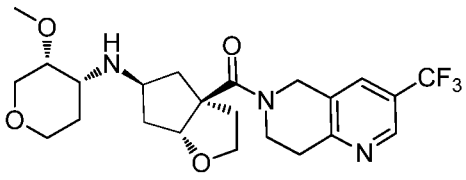
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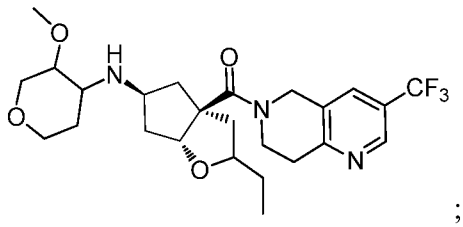
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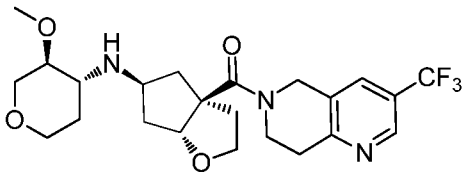
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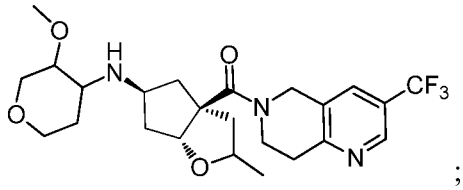
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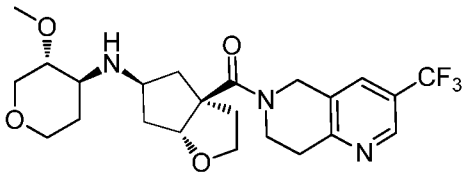
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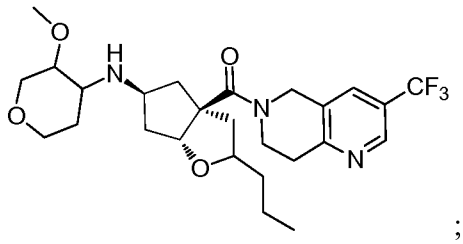
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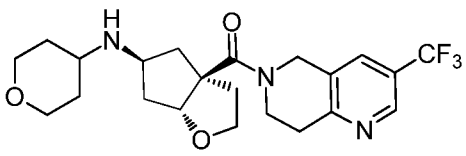
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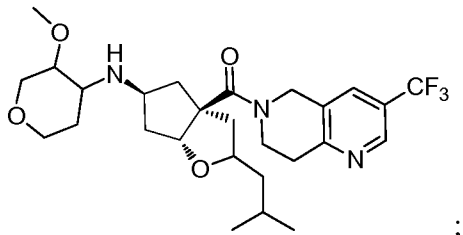
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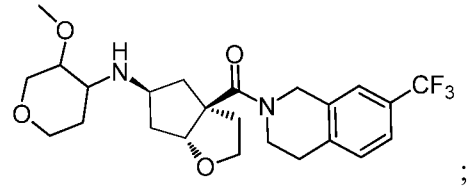
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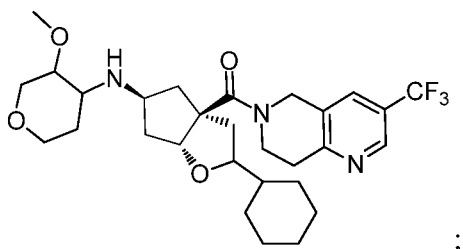
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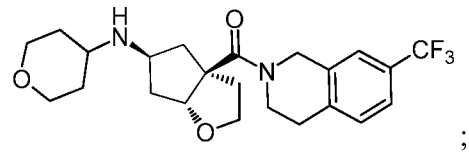
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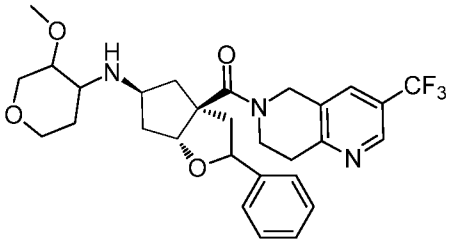
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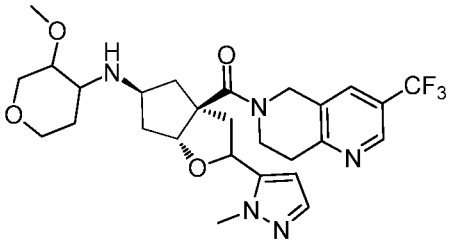
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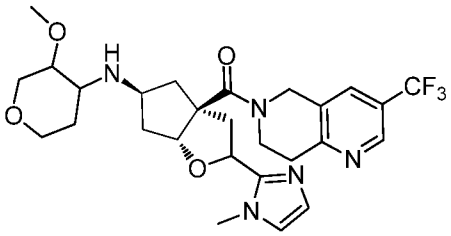
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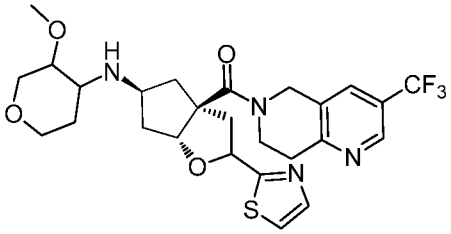
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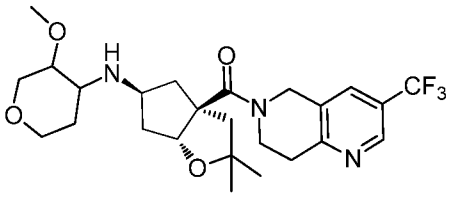
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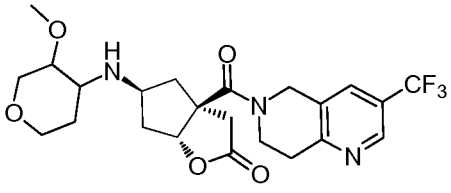
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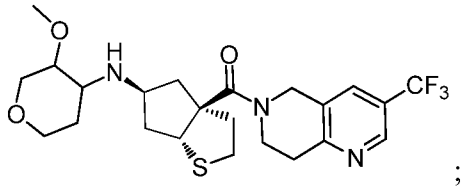
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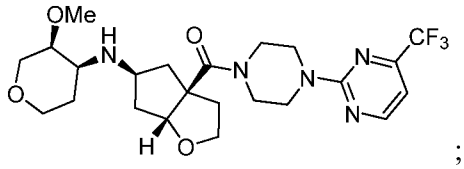
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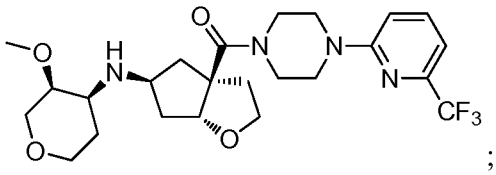
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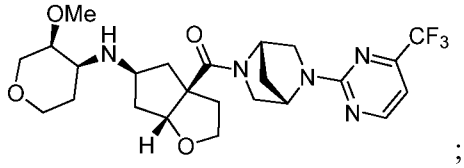
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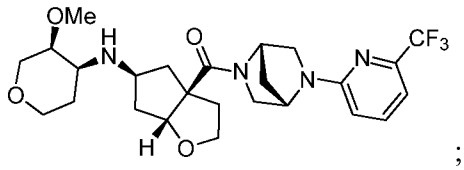
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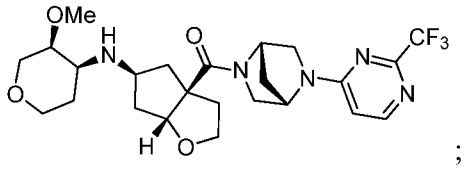
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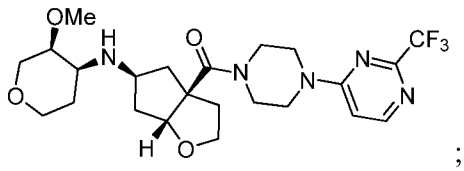
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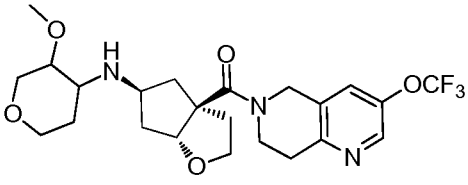
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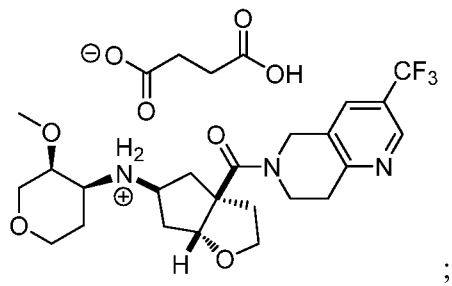
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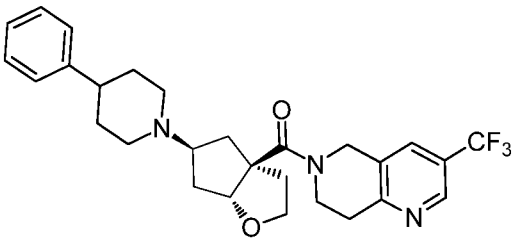
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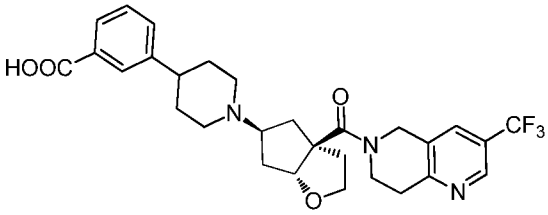
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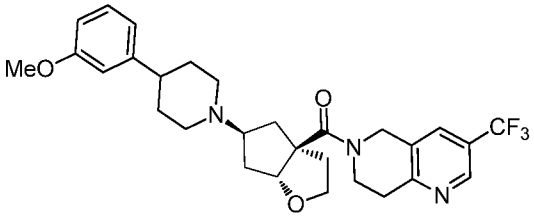
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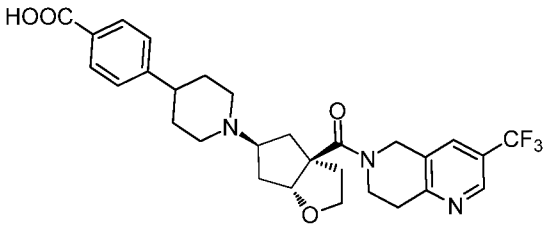
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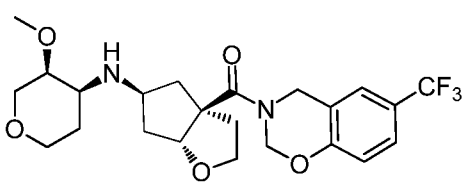
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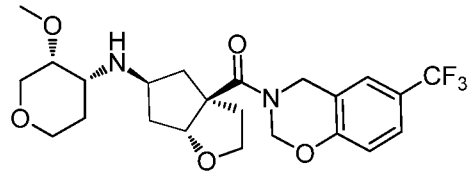
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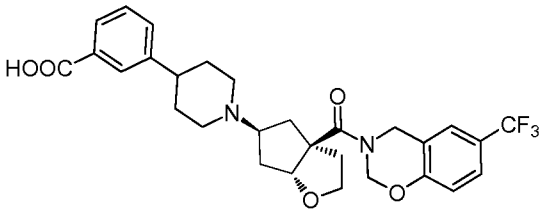
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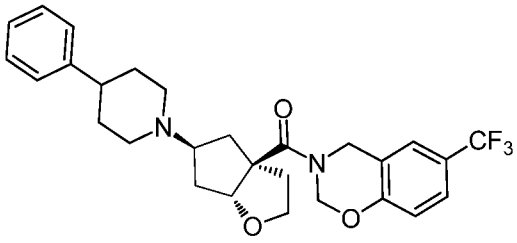
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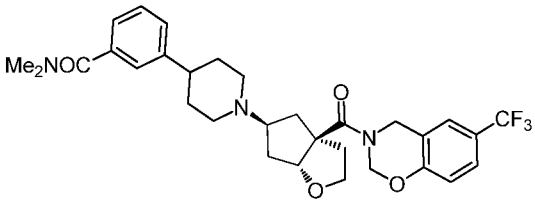
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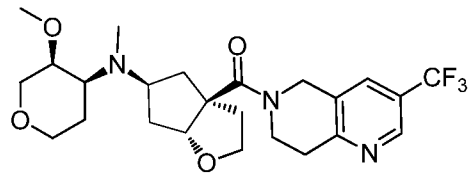
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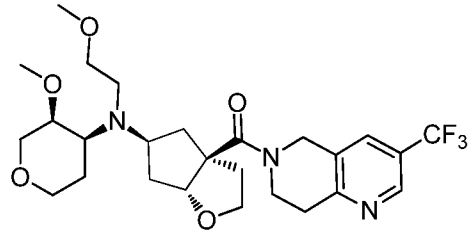
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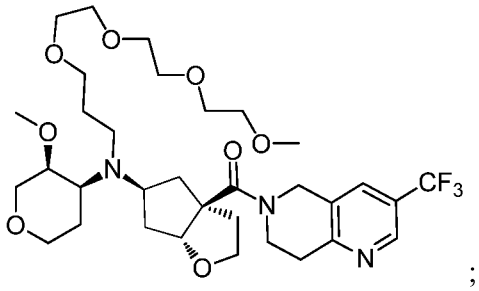
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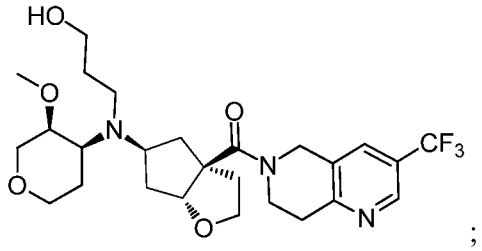
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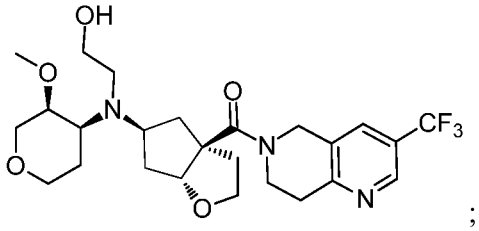
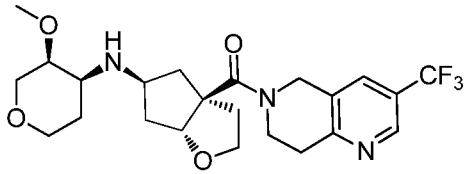

;

and pharmaceutically acceptable salts thereof.

In another embodiment, the present invention is directed to a compound of the formula



or a pharmaceutically acceptable salt thereof.

In another embodiment, the invention relates to a pharmaceutical composition, comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

In another embodiment, the invention relates to a pharmaceutical composition made by mixing a compound of formula (I) and a pharmaceutically acceptable carrier.

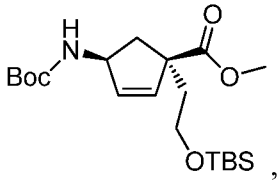
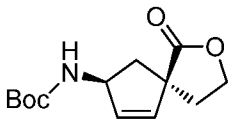
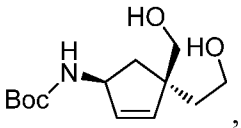
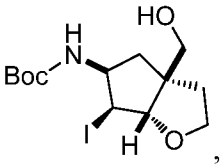
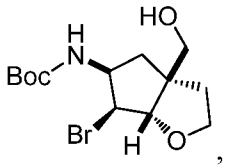
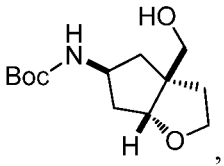
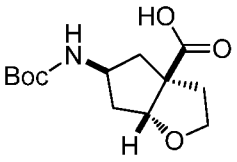
In another embodiment, the invention relates to a process for making a pharmaceutical composition comprising mixing a compound of formula (I) and a pharmaceutically acceptable carrier.

The present invention is further directed to a product prepared according to any of the processes described herein. In another embodiment, the invention relates to the product prepared according to the process as described in Example 31, which follows herein.

In another embodiment, the present invention is directed to a process for the preparation of a compound of formula (I), as described in more detail in the Schemes and

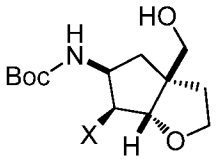
Examples which follow herein. In another embodiment, the present invention is directed to a process for the preparation of a compound of formula (I) as described in more detail in Example 31, which follows herein.

In another embodiment, the present invention relates to a compound selected from the group consisting of

; these compounds are useful as intermediates for the preparation of compounds of formula (I).

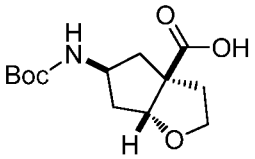
In another embodiment, the invention relates to intermediates useful for the preparation of a compound of formula (I), more particularly, compounds of formula (XIX)



(XIX) ,

wherein X is Br, PhSe, or I.

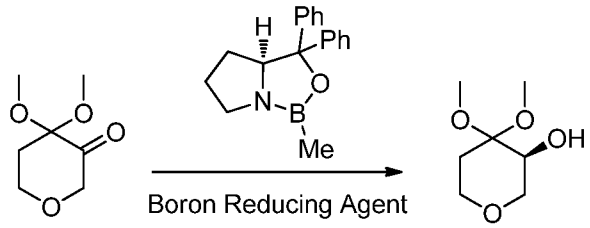
In another embodiment, the present invention relates to a compound of formula (XXI)



(XXI)

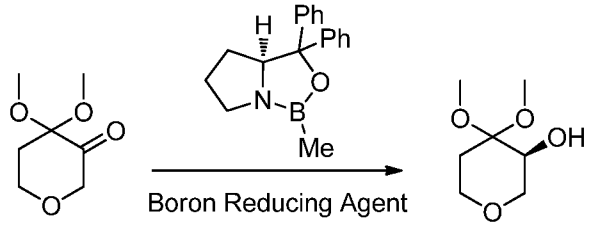
useful as an intermediate for the preparation of compounds of formula (I).

In another embodiment, the present invention relates to the process for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and R-(+)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 60% enantiomeric excess.

In another embodiment, the present invention relates to the process for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and R-(+)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 90% enantiomeric excess.

In another embodiment, the present invention relates to the processes for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, wherein the borane reducing complex is selected from borane- dimethylsulfide complex or borane-N,N-diethylaniline complex.

In another embodiment, the present invention relates to the processes for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, wherein a THF solution of said borane-reducing complex and R-(+)-2-methyl-CBS-oxazaborolidine is added to a solution of the 4-dimethoxydihydro-2H-pyran-3(4H)-one in THF.

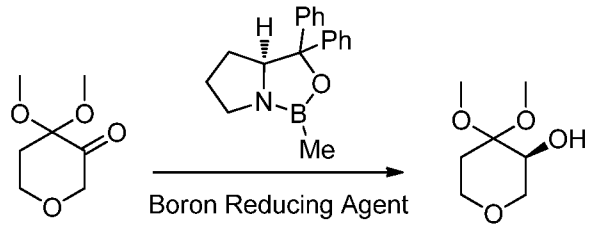
In another embodiment, the present invention relates to any of the processes for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, wherein the reaction is carried out in an inert environment; in another embodiment of the invention, the inert environment is nitrogen gas.

In another embodiment, the present invention relates to any of the processes for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, further

comprising reacting the (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol with dimethyl sulfate to provide (R)-3, 4, 4-trimethoxytetrahydro-2H-pyran.

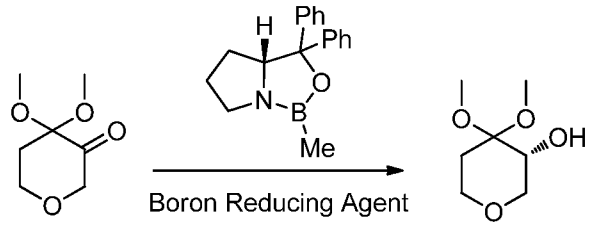
In another embodiment, the present invention relates to any of the processes for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, further comprising reacting the (R)-3, 4, 4-trimethoxytetrahydro-2H-pyran with acid to provide (R)-3-methoxydihydro-2H-pyran-4(3H)-one. In another embodiment, the acid is concentrated hydrochloric acid.

In another embodiment, the present invention relates to the process for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



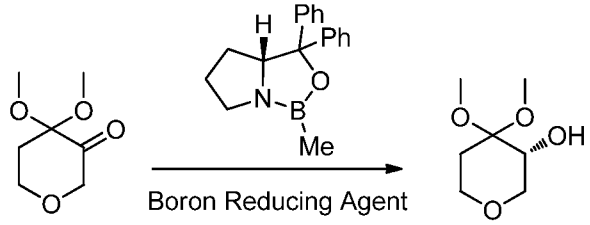
reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and R-(+)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 60% enantiomeric excess, wherein the reaction is run at a temperature range from 20 °C to 60 °C.

In another embodiment, the present invention relates to the process for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and S-(-)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 60% enantiomeric excess.

In another embodiment, the present invention relates to the process for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and S-(-)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, wherein (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol is formed in at least 90% enantiomeric excess.

In another embodiment, the present invention relates to the processes for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, wherein the borane reducing complex is selected from borane- dimethylsulfide complex or borane-N,N-diethylaniline complex.

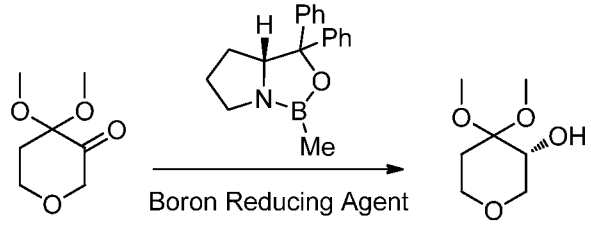
In another embodiment, the present invention relates to the processes for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, wherein the THF solution of said borane-reducing complex and S-(-)-2-methyl-CBS-oxazaborolidine is added to a solution of the 4-dimethoxydihydro-2H-pyran-3(4H)-one in THF.

In another embodiment, the present invention relates to any of the processes for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, wherein the reaction is carried out in an inert environment; in another embodiment of the invention, the inert environment is nitrogen gas.

In another embodiment, the present invention relates to any of the processes for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above,further comprising reacting the (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol with dimethyl sulfate to provide (S)-3, 4, 4-trimethoxytetrahydro-2H-pyran.

In another embodiment, the present invention relates to any of the processes for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above,further comprising reacting the (S)-3, 4, 4-trimethoxytetrahydro-2H-pyran with acid to provide (S)-3-methoxydihydro-2H-pyran-4(3H)-one. In another embodiment, the acid is concentrated hydrochloric acid.

In another embodiment, the present invention relates to any of the processes for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol, as described above, comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and S-(-)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 60% enantiomeric excess, wherein the reaction is run at a temperature range from 20 °C to 60 °C.

In another embodiment, the invention relates to a method for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

In another embodiment, the invention relates to a method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease wherein the syndrome, disorder or disease is associated with elevated MCP-1 expression or MCP-1 overexpression, or is an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

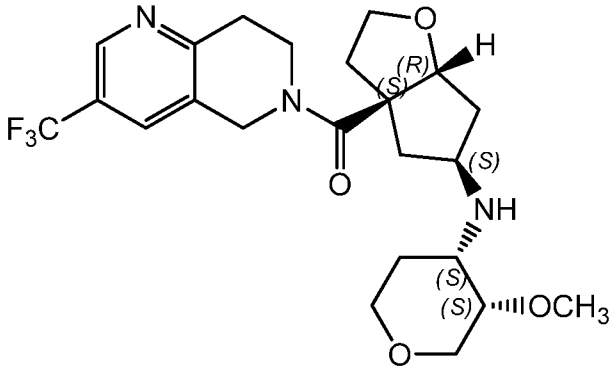
In another embodiment, the invention relates to a method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: Chronic Obstructive Pulmonary Disease (COPD), ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type-I diabetes, type II diabetes, diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, overweight, obesity, obesity-associated insulin resistance, metabolic syndrome, tuberculosis, sarcoidosis, invasive *staphyloccocia*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic

asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, aortic abdominal aneurism, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach and chronic neuroinflammatory disorders including, but not limited to, Alzheimer's disease, ischemic stroke, spinal cord injury, nerve crush injury and traumatic brain injury comprising administering to a subject in need thereof an effective amount of a compound of formula (I).

In another embodiment, the invention relates to a method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: type I diabetes, type II diabetes, diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, obesity, obesity-associated insulin resistance, metabolic syndrome, asthma, and allergic asthma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

In another embodiment, the invention relates to a method of treating a disorder selected from the group consisting of type II diabetes, obesity and asthma comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I).

The present invention is further directed to a succinate salt of a compound of formula (I-S)



(I-S)

wherein the compound of formula (I-S) is also known as ((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. In an embodiment, the succinate salt of the compound of formula (I-S) is crystalline. In another embodiment, the succinate salt of the compound of formula (I-S) is a crystalline hydrate form; wherein the hydrate contains about 0.6 moles water per mole of the compound of formula (I-S). In another embodiment of the present invention, the succinate salt of the compound of formula (I-S) is crystalline hydrate form containing about 0.6 moles water per mole of the compound of formula (I-S); wherein the crystalline hydrate form is further hygroscopic.

The present invention is also directed to a crystalline succinate salt of the compound of formula (I-S), wherein the acidic counter-ion is succinic acid. Additional salt screening was performed on the compound of formula (I-S), using the following additional acidic counter-ions: HCl acid, sulfuric acid, citric acid, malonic acid, maleic acid, L-tartaric acid, p-toluenesulfonic acid, phosphoric acid and acetic acid. X-ray analysis of the resulting solid residues indicated crystalline structures for the sulfate, maleate and phosphate salts; and amorphous structures of the HCl, citrate, malonate, tartrate and tosylate salts.

The crystalline phosphate, sulfate and maleate salts of the compound of formula (I-S) were additional tested in DSC, TGA and moisture sorption / desorption. The sulfate salt showed inter-conversion between salt forms and hygroscopic weight increase of 1.6% up to 60%RH and a total of 26.5% up to 90%RH, with strong hysteresis. The maleate salt showed a form change and hygroscopic weight increase of 18.3% up to 70%RH and a total of 79.9% up to 90%RH. The phosphate salt showed hygroscopic weight increase of 3.3% up to 60%RH and a total of 69.4% up to 90%RH, with strong hysteresis and deliquescence.

DEFINITIONS

The term “alkyl” refers to both linear and branched chain radicals of up to 12 carbon atoms, preferably up to 6 carbon atoms, unless otherwise indicated, and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,

pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl and dodecyl.

The term "$C_{(a-b)}$" (where *a* and *b* are integers referring to a designated number of carbon atoms) refers to an alkyl, alkenyl, alkynyl, alkoxy or cycloalkyl radical or to the alkyl portion of a radical in which alkyl appears as the prefix root containing from *a* to *b* carbon atoms inclusive. For example, $C_{(1-4)}$ denotes a radical containing 1, 2, 3 or 4 carbon atoms.

The term "cycloalkyl" refers to a saturated or partially unsaturated monocyclic or bicyclic hydrocarbon ring radical derived by the removal of one hydrogen atom from a single ring carbon atom. Examples of cycloalkyl radicals include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl and cyclooctyl. Additional examples include $C_{(3-8)}$cycloalkyl, $C_{(5-8)}$cycloalkyl, $C_{(3-12)}$cycloalkyl, $C_{(3-20)}$cycloalkyl, decahydronaphthalenyl, and 2,3,4,5,6,7-hexahydro-1H-indenyl.

The term "boron reducing agent" refers to a boron hydride, often with stabilizers such as ethers, amines, or sulfides. Examples of boron reducing agents include, but are not limited to, borane-tetrahydrofuran complex, catecholborane, borane-dimethyl aniline complex, and borane-dimethyl sulfide complex.

The term "heteroaryl" refers to a radical derived by the removal of one hydrogen atom from a ring carbon atom of a heteroaromatic ring system. A heteroaromatic ring system shall denote any five or six membered monocyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected from the group consisting of O, N and S; or a nine or ten membered bicyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The heteroaryl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure. Examples of heteroaryl radicals include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl,

benzo[*b*]furyl, benzo[*b*]thienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4*H*-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, and pteridinyl.

The term "ee" or "enantiomeric excess" is the the absolute value of the difference in mole fractions of a mixture of enantiomers. The mole fraction of the (+)- and (-)-enantiomers are expressed as F(+) and F(-) (where F(+) + F(-) = 1). The enantiomeric excess is defined as |F(+) - F(-)|. The percent enantiomeric excess is the ee * 100. For example a 50/50 mixture of (+) and (-) enantiomers has 0% ee, a 5/95 mixture of (+) and (-) enantiomers has a 90% ee, and a 70/30 mixture of (+) and (-) enantiomers has a 40% ee.

The term "inert environment" is a local environment for chemical reactions which is substantially depleted of atmospheric oxygen and water vapor. For example, a reaction run under an inert environment includes, but is not limited to, reactions run under argon or nitrogen atmosphere.

The term "isolated form" shall mean that the compound is present in a form which is separate from any solid mixture with another compound(s), solvent system or biological environment. In an embodiment, the present invention is directed to a succinate salt of the compound of formula (I-S), preferably a crystalline succinate salt of the compound of formula (I-S), wherein the salt is present and / or prepared as an isolated form.

The term "substantially free of other salt form(s)" when used to describe the succinate salt of the compound of formula (I-S) shall mean that mole percent of any other salt form(s) in the isolated succinate salt of the compound of formula (I-S) is less than about 5 mole percent, preferably less than about 2 mole percent, more preferably, less than about 0.5 mole percent, most preferably less than about 0.1 mole percent. In an embodiment, the present invention is directed to a succinate salt of the compound of formula (I-S), preferably a crystalline succinate salt of the compound of formula (I-S), wherein the salt is present and / or prepared as form which is substantially free of other salt form(s).

The term "substantially pure form" shall mean that the mole percent of impurities in the isolated compound is less than about 5 mole percent, preferably less than about 2 mole percent, more preferably, less than about 0.5 mole percent, most preferably, less than about 0.1 mole percent. In an embodiment, the present invention is directed to a succinate

salt of the compound of formula (I-S), preferably a crystalline succinate salt of the compound of formula (I-S), wherein the salt is present and / or prepared as a substantially pure form.

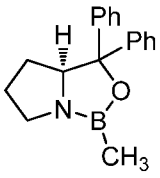
For use in medicines, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." FDA approved pharmaceutically acceptable salt forms (*Ref. International J. Pharm.* 1986, 33, 201-217; *J. Pharm. Sci.*, **1977**, Jan, 66(1), p1) include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Throughout this specification, compounds are described as being separated, usually by silica gel column, although preporatory thin layer chromatography, or high or low pressure liquid choromatography may also be used. It is generally accepted that when eluting compounds through a silica gel-type separation medium, that the least polar compounds elute before the more polar compounds. Therefore, the term "less polar isomer", refers to the isomer that will elute first from a silica gel type separation medium.

ABBREVIATIONS

Herein and throughout this application, the following abbreviations may be used.

AIBN	azobisisobutyronitrile
BOC or Boc	tert-butyloxycarbonyl
DCC	dicyclohexylcarbodiimide
DCM	dicholomethane
EDCI or EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
DIAD	diisopropylazodicarboxylate
DIEA	diisopropylethylamine
DSC	differential scanning calorimetry
Et	ethyl
EtOAc	ethyl acetate
ee	enantiomeric excess
eq	equivalents
HOBt	hydroxybenzotriazole
LiHMDS	lithium bis(trimethylsilyl)amide

M	moles/liter
Me	methyl
MIBK	methyl isobutyl ketone
min.	minutes
n-BuLi	n-butyl lithium
NBS or NIS	N-bromo succinimide or N-iodo succinimide
OAc	acetate
Ph	phenyl
PyBrop hexafluorophosphate	bromo-tris-pyrrolidinophosphonium
RH	relative humidity
rt	room temperature
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TBS or TBDMS	tertbutyldimethylsilyl
TLC	thin layer chromatography
S-(-)-2-methyl-CBS-oxazaborolidine	

Pharmaceutically acceptable acidic/anionic salts include, and are not limited to acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate and triethiodide. Organic or inorganic acids also include, and are not

limited to, hydriodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic or trifluoroacetic acid.

Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tromethane or "TRIS"), ammonia, benzathine, *t*-butylamine, calcium, calcium gluconate, calcium hydroxide, chloroprocaine, choline, choline bicarbonate, choline chloride, cyclohexylamine, diethanolamine, ethylenediamine, lithium, LiOMe, L-lysine, magnesium, meglumine, NH_3, NH_4OH, N-methyl-D-glucamine, piperidine, potassium, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, sodium, sodium carbonate, sodium-2-ethylhexanoate (SEH), sodium hydroxide, triethanolamine or zinc.

METHODS OF USE

The present invention is directed to a method for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) or a form, composition or medicament thereof.

Examples of a CCR2 mediated syndrome, disorder or disease for which the compounds of Formula (I) are useful include chronic obstructive pulmonary disorder (COPD), ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type-I diabetes, type II diabetes, diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, overweight, obesity, obesity-associated insulin resistance, metabolic syndrome, tuberculosis, chronic obstructive pulmonary disease, sarcoidosis, invasive *staphyloccocia*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies, cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, aortic abdominal aneurism, multiple sclerosis, glomerulonephritis, solid tumors and cancers,

chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach, and chronic neuroinflammatory disorders including, but not limited to, Alzheimer's disease, ischemic stroke, spinal cord injury, nerve crush injury and traumatic brain injury.

Some of the quantitative expressions given herein are qualified with the term "about". It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to both the actual given value and the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value. In addition, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that wherein a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

The term "administering" with respect to the methods of the invention, means a method for therapeutically or prophylactically preventing, treating or ameliorating a syndrome, disorder or disease as described herein by using a compound of Formula (I) or a form, composition or medicament thereof. Such methods include administering an effective amount of said compound, compound form, composition or medicament at different times during the course of a therapy or concurrently in a combination form. The methods of the invention are to be understood as embracing all known therapeutic treatment regimens.

The term "subject" refers to a patient, which may be animal, typically a mammal, typically a human, which has been the object of treatment, observation or experiment. In one aspect of the invention, the subject is at risk of (or susceptible to) developing a syndrome, disorder or disease that is associated with elevated MCP-1 expression or MCP-1 overexpression, or a patient with an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression.

The term "therapeutically effective amount" means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a

tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes preventing, treating or ameliorating the symptoms of a syndrome, disorder or disease being treated.

The term "uveitis" generically refers to any inflammatory disease involving the eye. Uveitis can be divided into clinically distinct subtypes based on the part of the eye in which the inflammation is present (percentages correspond to patients known to fit these categories): anterior (51%), intermediate (13%), posterior (20%), or panuveitis (16%) and, according to the course of the disease, as either acute (16%), recurring (26%), or chronic (58%). Those with anterior uveitis (·19%) eventually develop irreparable vision damage despite aggressive treatment such as unilateral blindness (9%), bilateral blindness (2%), or unilateral or bilateral vision impairment (8%). Most cases of uveitis are idiopathic, but known causes include infection (e.g., toxoplasmosis, cytomegalovirus, and the like) or development as a component of a systemic inflammatory and/or autoimmune disorder (e.g., juvenile RA, HLA-B27 associated spondyloarthropathies, sarcoidosis, and the like). (HLA-B27: Human Leukocyte Antigen B*27- is a class I surface antigen encoded by the B locus in the major histocompatibility complex (MHC) on chromosome 6 and presents micobial antigens to T cells. HLA-B27 is strongly associated with a certain set of autoimmune diseases referred to as the seronegative spondyloarthropathies.)

When employed as CCR2 inhibitors, the compounds of the invention may be administered in an effective amount within the dosage range of about 0.5 mg to about 10 g, or any amount or range therein, preferably between about 0.5 mg to about 5 g, or any amount or range therein, in single or divided daily doses. The dosage administered will be affected by factors such as the route of administration, the health, weight and age of the recipient, the frequency of the treatment and the presence of concurrent and unrelated treatments.

It is also apparent to one skilled in the art that the therapeutically effective dose for compounds of the present invention or a pharmaceutical composition thereof will vary according to the desired effect. Therefore, optimal dosages to be administered may be readily determined by one skilled in the art and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being

treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level. The above dosages are thus exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The compounds of Formula (I) may be formulated into pharmaceutical compositions comprising any known pharmaceutically acceptable carriers. Exemplary carriers include, but are not limited to, any suitable solvents, dispersion media, coatings, antibacterial and antifungal agents and isotonic agents. Exemplary excipients that may also be components of the formulation include fillers, binders, disintegrating agents and lubricants.

The pharmaceutically-acceptable salts of the compounds of Formula (I) include the conventional non-toxic salts or the quaternary ammonium salts which are formed from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, citrate, camphorate, dodecylsulfate, hydrochloride, hydrobromide, lactate, maleate, methanesulfonate, nitrate, oxalate, pivalate, propionate, succinate, sulfate and tartrate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamino salts and salts with amino acids such as arginine. Also, the basic nitrogen-containing groups may be quaternized with, for example, alkyl halides.

The pharmaceutical compositions of the invention may be administered by any means that accomplish their intended purpose. Examples include administration by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal or ocular routes. Alternatively or concurrently, administration may be by the oral route. Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, acidic solutions, alkaline solutions, dextrose-water solutions, isotonic carbohydrate solutions and cyclodextrin inclusion complexes.

The present invention also encompasses a method of making a pharmaceutical composition comprising mixing a pharmaceutically acceptable carrier with any of the compounds of the present invention. Additionally, the present invention includes

pharmaceutical compositions made by mixing a pharmaceutically acceptable carrier with any of the compounds of the present invention. As used herein, the term “composition” is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

POLYMORPHS AND SOLVATES

Furthermore, the compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention. In addition, the compounds may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like.

It is intended that the present invention include within its scope polymorphs and solvates of the compounds of the present invention. Thus, in the methods of treatment of the present invention, the term “administering” shall encompass the means for treating, ameliorating or preventing a syndrome, disorder or disease described herein with the compounds of the present invention or a polymorph or solvate thereof, which would obviously be included within the scope of the invention albeit not specifically disclosed.

In another embodiment, the invention relates to a compound as described in the Examples of Formula (I) for use as a medicament.

In another embodiment, the invention relates to the use of a compound as described in the Examples of Formula (I) for the preparation of a medicament for the treatment of a disease associated with an elevated or inappropriate CCR2 activity.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds

which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", Ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

Where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-D-tartaric acid and/or (+)-di-p-toluoyl-L-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Preparation of Crystalline Succinate Salt of the Compound of Formula (I-S)

The crystalline succinate salt of the compound of formula (I-S) of the present invention may be prepared from the corresponding amorphous succinate salt of the compound of formula (I-S) by heating to a temperature in the range of from about 140 °C to about 150 °C, preferably to about 140 °C, and then cooling to about room temperature to effect crystallization, as described in more detail in Example 52, which follows herein.

Alternatively, the crystalline succinate salt of the compound of formula (I-S) of the present invention may be prepared from the corresponding amorphous succinate salt of the compound of formula (I-S) by crystallization from a suitably selected solvent such as methyl isobutyl ketone (MIBK), as described in more detail in Example 53, which follow herein. For the crystallization of the succinate salt of the compound of formula (I-S) the suitably selected solvent is other than water, methanol, ethanol, acetone, acetonitrile. isopropyl acetate, nitromethane, tetrahydrofuran, methyl ethyl ketone, dichloromethane, toluene, methyl isopropyl ketone (MIPK).

The amorphous succinate salt of the compound of formula (I-S) may be prepared, for example, as described in Example 30, which follows herein.

Powder X-Ray Diffraction (pXRD)

The succinate salt of the compound of formula (I-S) was characterized as to its powder X-ray diffraction pattern (pXRD), in example as follows. The sample was examined using an X-ray diffractometer (Philips Model X'PERT PRO PW3040) with X'Celerator detector and graded multilayer parabolic X-ray mirror. The samples were scanned from 3 to 40°2θ, at a step size 0.0165 °2θ and a time per step of 2000.025 seconds. The tube voltage and current were 45 KV and 40 mA, respectively. The sample was packed on a zero background XRD-holder and scanned under ambient temperature and humidity conditions.

A pXRD spectrum was measured for a representative sample of the crystalline succinate salt of the compound of formula (I-S), as shown in Figure 1. In an embodiment, the crystalline succinate salt of the compound of formula (I-S) may be characterized by its powder X-ray diffraction pattern, which comprised the peaks listed in Table 1, below.

Table 1: pXRD Peaks:

Crystalline Succinate Salt of Compound of Formula (I-S)

Position [°2θ]	d-spacing [Å]	Relative Intensity [%]
7.27	12.17	3
10.03	8.82	4
10.51	8.42	4
11.27	7.85	8
12.26	7.22	2
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
24.14	3.69	8
25.78	3.46	17
27.07	3.29	14
27.64	3.23	7
28.40	3.14	6
28.97	3.08	4
30.30	2.95	4
31.91	2.80	3
33.34	2.69	4
35.91	2.50	4

In an embodiment, the crystalline succinate salt of the compound of formula (I-S) is characterized by its pXRD pattern which comprises peaks having a relative intensity greater than or equal to about 3%, as listed in Table 2, below.

Table 2: pXRD Peaks:

Crystalline Succinate Salt of Compound of Formula (I-S)

Position [°2θ]	d-spacing [Å]	Relative Intensity [%]
10.03	8.82	4
10.51	8.42	4
11.27	7.85	8
12.26	7.22	2
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
24.14	3.69	8
25.78	3.46	17
27.07	3.29	14
27.64	3.23	7
28.40	3.14	6
28.97	3.08	4
30.30	2.95	4
33.34	2.69	4
35.91	2.50	4

In an embodiment, the crystalline succinate salt of the compound of formula (I-S) is characterized by its pXRD pattern which comprises peaks having a relative intensity greater than or equal to about 5%, as listed in Table 3, below.

Table 3: pXRD Peaks:

Crystalline Succinate Salt of Compound of Formula (I-S)

Position [°2θ]	d-spacing [Å]	Relative Intensity [%]
11.27	7.85	8
12.26	7.22	2
13.87	6.38	67
14.34	6.18	21

14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
24.14	3.69	8
25.78	3.46	17
27.07	3.29	14
27.64	3.23	7
28.40	3.14	6

In an embodiment, the crystalline succinate salt of the compound of formula (I-S) is characterized by its pXRD pattern which comprises peaks having a relative intensity greater than or equal to about 10%, as listed in Table 4, below.

Table 4: pXRD Peaks:

Crystalline Succinate Salt of Compound of Formula (I-S)

Position [°2θ]	**d-spacing [Å]**	**Relative Intensity [%]**
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
25.78	3.46	17

27.07	3.29	14

In another embodiment, the present invention is directed to a crystalline succinate salt of the compound of formula (I-S) as characterized by the following pXRD peak, listed in °2θ: 10.03, 10.51, 11.27, 13.87, 19.22 and 22.01. In another embodiment, the present invention is directed to a crystalline succinate salt of the compound of formula (I-S) as characterized by the following pXRD peak, listed in °2θ: 11.27, 13.87, 19.22 and 22.01.

Differential Scanning Calorimetry (DSC)

The crystalline succinate salt of the compound of formula (I-S) was further subjected to DSC analysis. A representative sample was tested using a TA Instruments Model Q100O differential scanning calorimeter. The sample was analyzed as received in an open aluminum pan. The DSC was programmed to heat from 25 °C to 300 °C at a heating rate of 10 °C/min with a nitrogen purge.

Thermal analysis (via DSC scanning) was completed for a representative sample of the crystalline succinate salt of the compound of formula (I-S), as shown in Figure 2. The crystalline succinate salt of the compound of formula (I-S) exhibited an onset melting temperature of about 156 °C, a peak temperature of melting of about 158 °C and an enthalpy 68.3 J/g.

Thermogravimetric Analysis (TGA)

The crystalline succinate salt of the compound of formula (I-S) was further subjected to TGA analysis. A representative sample was tested, as received, for total weight loss using a TA Instruments Model Q5000IR TGA thermogravimetric calorimeter. The sample was placed in a tarred aluminum pan, automatically weighed and inserted into the TGA furnace. The sample was scanned from 25 °C to 300 °C at a heating rate of 10 °C/min with a 90 mL/min nitrogen purge and a 10 mL/min helium balance purge.

A TGA trace was measured for a representative sample of the crystalline succinate salt of the compound of formula (I-S), as shown in Figure 3. A 1.8% weight loss was observed between room temperature and 144 °C, due to dehydration / desolvation; followed by decomposition at 151 °C. These results indicate that the crystalline succinate

salt of the compound of formula (I-S) is hydrate; wherein the hydrate contains about 0.6 moles of water per mole of the compound of formula (IS).

Moisture Isothermal Analysis

The crystalline succinate salt of the compound of formula (I-S) was further subjected to moisture sorption analysis. The moisture sorption analysis was performed using Hiden Isochema system Model IGAsorp. The sample (~5 mg) was run in a stainless-steel mesh crucible. The sample was initially dried at 60 °C for 30 minutes, then the moisture profile was evaluated by monitoring vapor adsorption / desorption over the range of 0% RH to 90% RH at 25 °C. The moisture profile consisted of 2 cycles of vapor adsorption / desorption.

Figure 4 illustrates two cycles of vapor sorption / desorption for a representative sample of the crystalline succinate salt of the compound of formula (I-S). The weight of the sample increased 3.8% up to 70% RH, with a total of 70% uptake up to 90% RH. Further, strong hysteresis was observed in the multiple sorption/desorption cycles with about 2.7% moisture (equivalent to 0.9 moles of water) retained at the end of the desorption phase. Thus, the crystalline succinate salt of the compound of formula (I-S) is hygroscopic.

Solubility

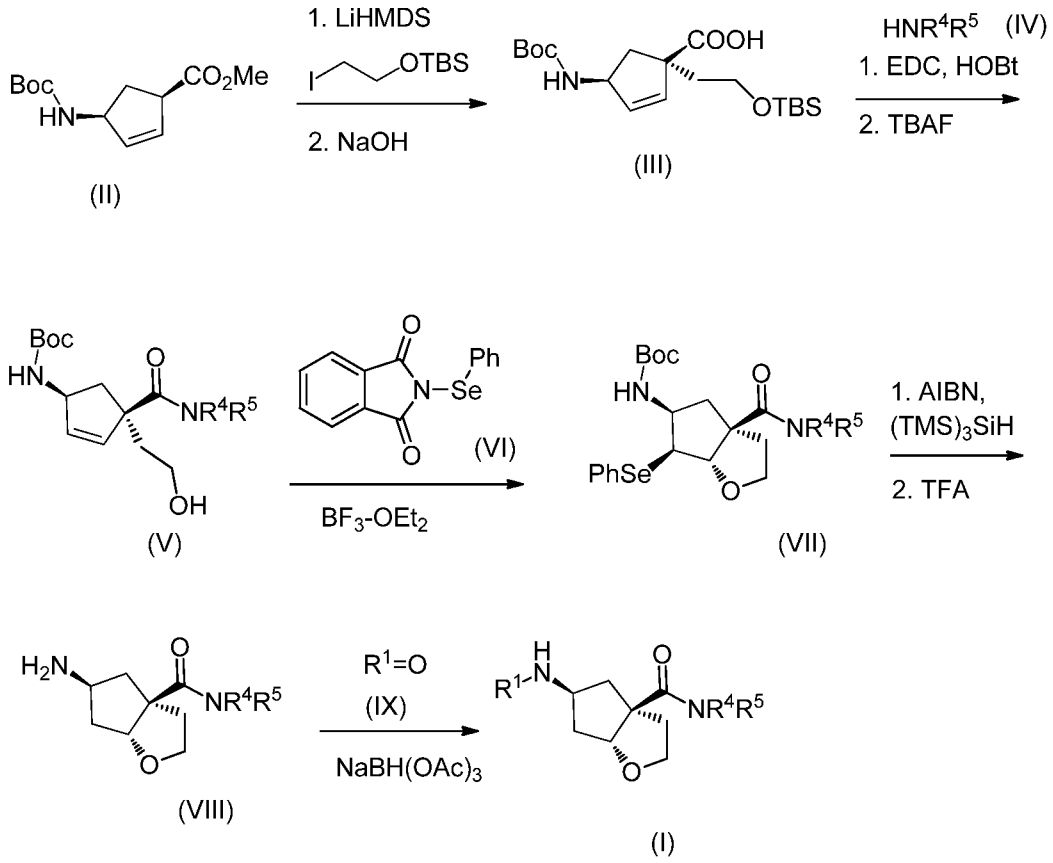
The crystalline succinate salt of the compound of formula (I-S) was tested for solution solubility and measured to be soluble at >50mg/ml in water and at >100 mg/ml in 0.1N NaOH, pH 2, pH4 and pH6 citrate buffers; in pH 8 and pH 10 borate buffers; simulated intestinal fluid, simulated gastric fluid; 0.5% methocel and 20% HpbCD.

GENERAL REACTION SCHEME

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below. Compounds of Formula (I) can be prepared by methods known to those who are skilled in the art. The following reaction schemes are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

Compounds of Formula (I) wherein A is O and wherein R^0, R^2 and R^3 are each hydrogen may be prepared according to the processes outlined in Scheme 1.

Scheme 1



Scheme 1 illustrates a synthetic route leading to compounds of Formula (I) wherein R^0, R^2 and R^3 are each hydrogen. Commercially available esters of formula (II) is alkylated by reacting with a suitable selected base such as LiHMDS, and the like; and then reacted with *t*-butyl(2-iodoethoxy)dimethylsilane, in an organic solvent such as THF or diethyl ether, at a temperature in the range of -78 °C to 20 °C. The resulting alkylated ester is then saponified by reacting with an aqueous base such as NaOH, KOH, or LiOH, in a solvent such as methanol or ethanol, at a temperature in the range of 0 °C to 60 °C, to yield the corresponding acid, a compound of formula (III).

The acid of formula (III) is then reacted with a suitably selected, commercially available amine of formula (IV), in the presence of a coupling reagent such as EDCI/HOBt, PyBrop or DCC, in an organic solvent such as THF, dichloromethane or 1,2-

dichloroethane, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding amide; which is then reacted to de-protect the alcohol functionality, by reacting with a fluoride source such as TBAF, in a solvent such as THF, at a temperature range of about 0 °C to 60 °C, to yield the corresponding, desilylated alcohol of formula (V).

The alcohol of formula (V) is reacted with a reagent such as N-(phenylseleno)phthalimide (VI) or phenylselenyl chloride, and a Lewis Acid such as borontrifluoride etherate, in a solvent such as DCM or 1,2-dichloroethane, at a temperature of 0 °C to 50 °C, to yield the corresponding cyclic ether of formula (VII).

The cyclic ether (VII) is reacted with a suitably selected reducing agent such as tri-*n*-butylstannane or tris(trimethylsilyl)silane, in the presence of a radical initiator such as AIBN, in a solvent such as benzene or toluene, at a temperature of 60 °C to 120 °C; and the resulting intermediate, de-protected at the N-Boc carbamate by reacting with an acid such as TFA or HCl, in a solvent such as DCM, acetonitrile, THF, or dioxane, at a temperature of 0 °C to 80 °C, to yield the corresponding amine of formula (VIII).

The amine of formula (VIII) is reacted with a suitably substituted ketone of formula (IX), in the presence of a suitably selected reducing reagent such as $NaBH_4$, $NaBH_3CN$ or $NaBH(OAc)_3$, in an organic base such as triethylamine, diisopropylethylamine or N-methylmorpholine, with or without molecule sieves, in an organic solvent such as dichloromethane, 1,2-dichloroethane or THF, at a temperature in the range of 0 °C to about 25 °C, to yield the corresponding compound of formula (I) wherein R^0, R^2 and R^3 are each hydrogen.

Those skilled in the art will recognize that compounds of formula (I) where R_0 is not H may be synthesized from compounds of formula (I) where R_0 is H, by standard alkylation procedures. Such alkylation procedures include, but are not limted to, reductive alkylation. For example, a compound of formula (I) where R_0 is H may be dissolved in a solvent, such as THF, and reacted with an aldehyde and a reductant, such as sodium triacetoxyborohydride. Suitable temperatures include a range extending from about 25 °C to 50 °C.

Compounds of Formula (X) may be prepared according to the processes outlined in Scheme 2.

Scheme 2

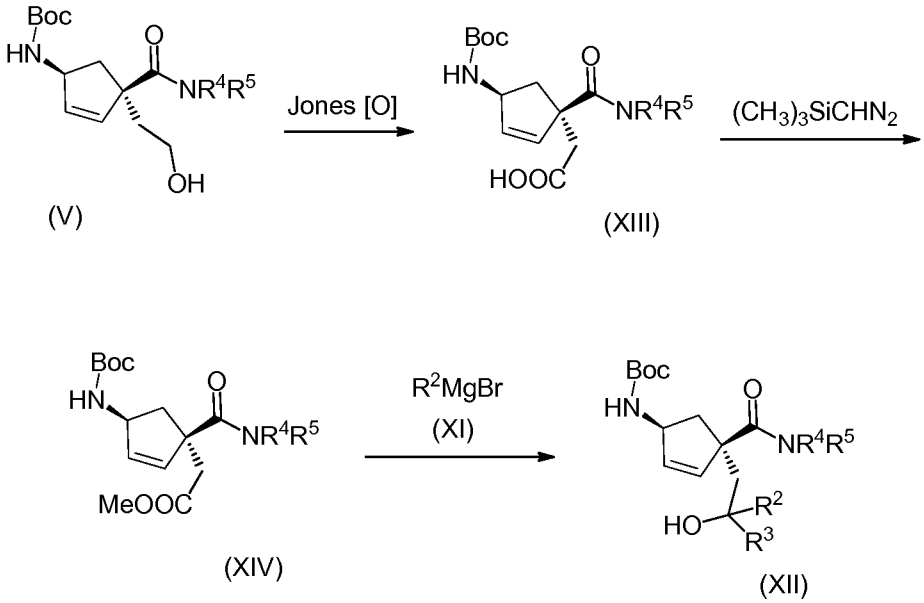
(V) (X)

An alcohol of formula (V), prepared for example, as described in Scheme 1 above, is converted to the corresponding aldehyde by reacting with a suitably selected oxidant such as Dess-Martin periodinane, Swern, or pyridinium chlorochromate, in a solvent such as DCM or 1,2-dichloroethane, at a temperature of 0 °C to 50 °C. The resulting intermediate is then reacted with a suitably selected Grignard reagent or lithium reagent of formula (XI), in a solvent such as diethyl ether, THF, or toluene, at a temperature of -78 °C to 25 °C, to yield the corresponding alcohol of formula (X).

Compounds of Formula (I) wherein A is O and wherein R^2 is other than hydrogen may be prepared from the corresponding compound of Formula (X), by substituting said compound of formula (X) for the compound of formula (V) in Scheme 1, above.

Compounds of Formula (XII) may be prepared according to the processes outlined in Scheme 3.

Scheme 3



An alcohol of formula (V), prepared for example as described in Scheme 1, above, is reacted with a suitably selected oxidant such as CrO_3, $Ru/NaIO_4$, or $KMnO_4$, in a solvent such as acetone or water, at a temperature of 0 °C to 50 °C, to yield the corresponding carboxylic acid of formula (XIII).

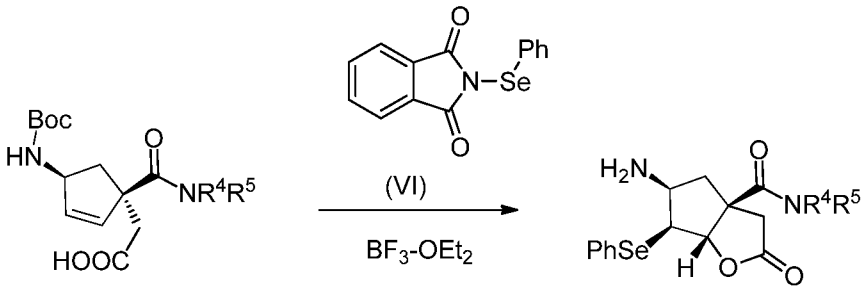
The acid of formula (XIII) is reacted with a suitably selected alkylating agent such as trimethylsilyl(diazomethane) in a solvent such as methanol or ethanol, at a temperature of -20 °C to 25 °C, to yield the corresponding methyl ester of formula (XIV).

The methyl ester of formula (XIV) is reacted with a lithium or Grignard reagent (XI) in a solvent such as diethyl ether, THF, or toluene, at a temperature of -78 °C to 25 °C, to yield the substituted alcohol (XII).

Compounds of Formula (I) wherein A is O and wherein R^2 and R^3 are other than hydrogen may be prepared from the corresponding compound of Formula (XII), by substituting said compound of formula (XII) for the compound of formula (V) in Scheme 1, above.

Compounds of Formula (XV) may be prepared according to the processes outlined in Scheme 4.

Scheme 4



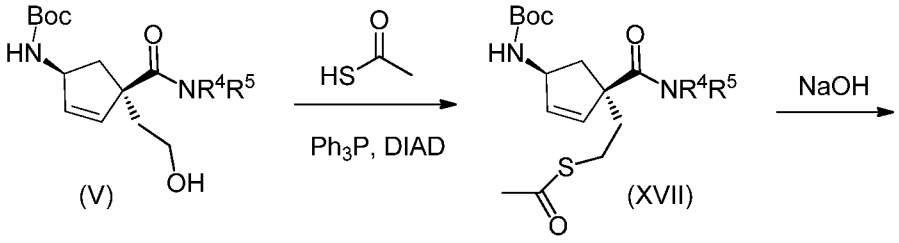
(XIII) (XV)

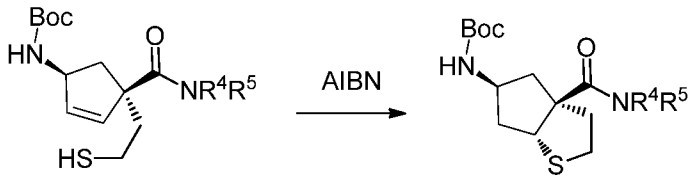
A suitably selected acid of formula (XIII), prepared for example as described in Scheme 3 above, is reacted with a reagent such as N-(phenylseleno)phthalimide (VI) or phenylselenyl chloride, and a Lewis Acid such as borontrifluoride etherate, in a solvent such as DCM or 1,2-dichloroethane, at a temperature of 0 °C to 50 °C, to yield the corresponding bicyclic lactone of formula (XV).

Compounds of Formula (I) wherein A is O and wherein R^2 and R^3 are taken together with the carbon aotm to which they are bound to form C=O may be prepared from the corresponding compound of Formula (XV) by substituting said compound of formula (XV) for the compound of formula (V) in Scheme 1, above.

Compounds of Formula (XVI) may be prepared according to the processes outlined in Scheme 5.

Scheme 5





An alcohol of formula (V), prepared for example as described in Scheme 1, above, is reacted with a thioacid such as thioacetic acid, in the presence of a phosphine such as triphenylphosphine or tributylphosphine and in the presence of an activating agent such as diisopropylazodicarboxylate (DIAD) or diethylazodicarboxylate (DEAD), in a solvent such as THF, diethyl ether, DCM or 1,2-dichloroethane, at a temperature of 0 °C to 60 °C (i.e. under Mitsunobu conditions), to yield the corresponding thioester of formula (XVII).

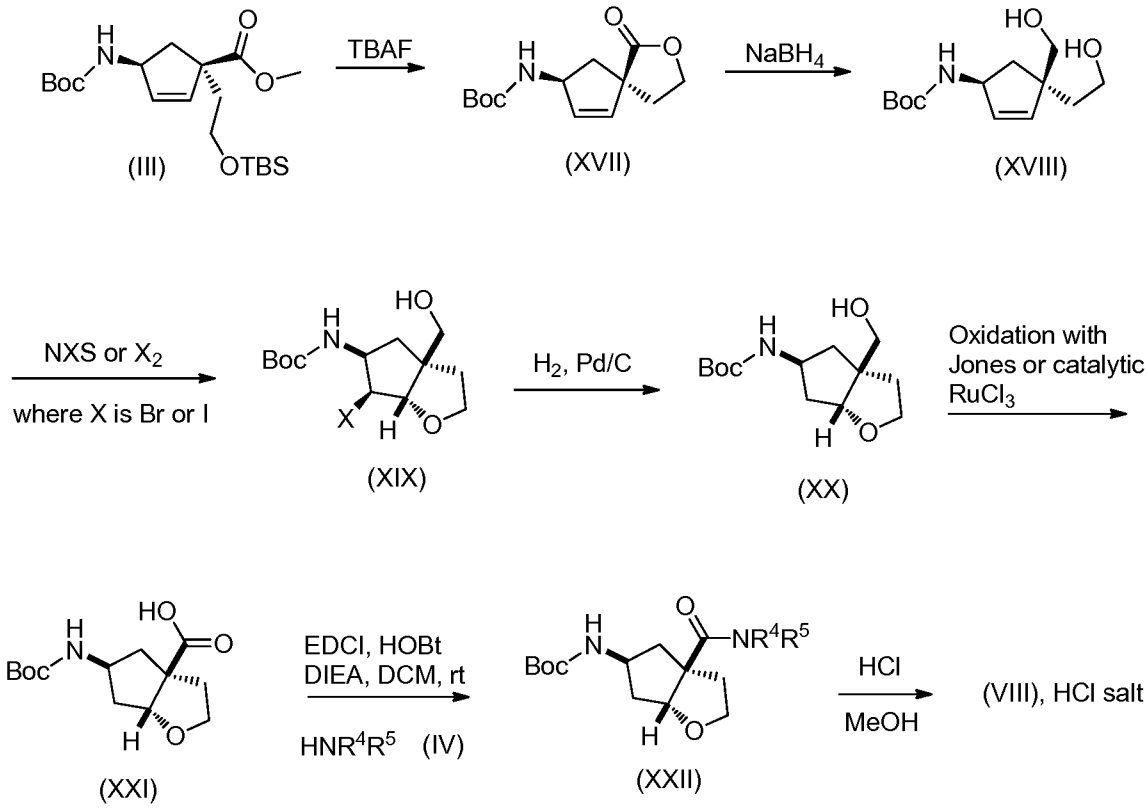
The thioester of formula (XVII) is reacted with an aqueous base such as NaOH, LiOH or KOH, in a solvent such as methanol or ethanol, at a temperature of 0 °C to 60 °C, to yield the corresponding thiol of formula (XVIII).

The thiol of formula (XVIII) is reacted with a radical initiator such as AIBN, in a solvent such as benzene or toluene, at a temperature of 60 °C to 120 °C, to yield the corresponding bicyclic thioether of formula (XVI).

Compounds of formula (I) wherein A is S, R^0 is hydrogen, and wherein R_2 and R_3 are other than hydrogen may be prepared according to the procedures of Scheme 5, by starting with compound (XII) (as prepared in Scheme 3) in place of compound (V). Additionally, reductive alkylation as described in Scheme 1 can be employed by one of ordinary skill in the art as a means for transforming these compounds of formula (I) where A is S and R_0 is H to compounds of formula (I) where A is S and R_0 is other than H.

Compounds of Formula (VIII) may alternatively be prepared according to the procedure of Scheme 6.

Scheme 6



A compound of formula (III), prepared for example as described in Scheme 1 above, is cyclized by reacting with a suitably selected de-silylating agent, such as tetra-butyl ammonium fluoride, and the like, in a solvent such as THF, and the like, at a temperature range from about -20 °C to about 50 °C to yield the corresponding lactone of formula (XVII).

The lactone of formula (XVII) is reacted with a suitably selected reducing agent, such as $NaBH_4$, $LiAlH_4$, and the like, in a suitably selected solvent, such as THF, and the like, at a temperature range of from about -20 °C to about 50 °C, to yield the corresponding diol of formula (XVIII).

The diol of formula (XVIII) is reacted with a suitably selected halogenating reagent such as N-bromo-succinimide, N-iodo-succinimide, Br_2, and the like, in a solvent such as THF, EtOAc, CH_2Cl_2, and the like, at a temperature range of from about 0 °C to about 100 °C, to yield the corresponding intermediate of formula (XIX).

The intermediate of formula (XIX) is hydrogenated by reacted with hydrogen gas, in a solvent or mixture of solvents, such as THF, EtOAc, methanol, and the like, in the

presence of a suitably selected catalyst such as Pd/C, Pt/C, and the like, at about room temperature, to yield the corresponding alcohol of formula (XX).

Alternatively, the intermediate of formula (XIX) may be reacted with a reducing agent such as tri-*n*-butylstannane, tris(trimethylsilyl)silane, and the like, in the presence of a radical initiator such as AIBN, and the like, in a solvent such as benzene, toluene, and the like, at a temperature in the range of from about 60 °C to about 120 °C to yield the corresponding alcohol of formula (XX).

The alcohol of formula (XX) is reacted with a suitably selected oxidant such as CrO_3, $Ru/NaIO_4$, $KMnO_4$ and the like, in a solvent such as acetone, water, and the like, at a temperature in the range of from about 0 °C to about 50 °C, to yield the corresponding carboxylic acid of formula (XXI).

The carboxylic acid of formula (XXI) is reacted with a suitably selected amine of formula (IV), in the presence of a coupling reagent such as EDCI/HOBt, PyBrop, DCC, and the like, in an organic solvent such as THF, dichloromethane, 1,2-dichloroethane, and the like, at a temperature in the range of about 0 °C to about 25 °C, to yield the corresponding amide of formula (XXII).

The amide of formula (XXII) is de-protected by reacting under acidic conditions, such as HCl in MeOH, at temperature ranging from about 25 °C to about 80 °C, to yield the corresponding compound of formula (VIII), which may then be reacted, as described in Scheme 1 above, to yield the corresponding compound of Formula (I) wherein A is O, and wherein R_0, R_2 and R_3 are each hydrogen.

Alternatively, the compound of formula (XVIII) may be reacted with N-(phenylseleno)phthalimide (VI) or phenylselenyl chloride, in the presence of a suitably selected a Lewis Acid such as borontrifluoride etherate, and the like, in a solvent such as DCM, 1,2-dichloroethane, and the like, at a temperature in the range of form about 0 °C to about 50 °C, to yield the corresponding cyclic ether of formula (XIX), where X is Ph-Se.

The cyclic ether of formula (XIX) is then reacted with a suitably selected reducing agent such as tri-*n*-butylstannane, tris(trimethylsilyl)silane, and the like, in the presence of a radical initiator such as AIBN, and the like, in a solvent such as benzene, toluene, and the like, at a temperature in the range of from about 60 °C to about 120 °C to yield the corresponding intermediate of formula (XX).

The intermediate of formula (XX) is then reacted as described above, to yield the corresponding compound of formula (I) wherein A is O, and wherein R_0, R_2 and R_3 are each hydrogen.

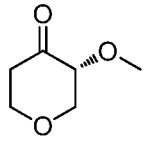
Additionally, reductive alkylation as described in Scheme 1 can be employed by one of ordinary skill in the art as a means for transforming these compounds of formula (I) where A is O and R_0 is H to compounds of formula (I) where A is O and R_0 is other than H.

EXAMPLES

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below. Compounds of Formula (I) can be prepared by methods known to those who are skilled in the art. The following examples are only meant to represent examples of the invention and are in no way meant to be a limit of the invention.

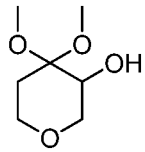
Intermediate 1

(R)-3-methoxydihydro-2H-pyran-4(3H)-one



Step A

4, 4-Dimethoxytetrahydro-2H-pyran-3-ol

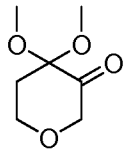


A 12-L 4-neck round bottom flask with an overhead stirrer was charged with MeOH (8.18 L) and potassium hydroxide (400.5 g, 2.4 mol) while stirring at room temperature until base was completely dissolved (an exotherm was observed). The homogeneous mixture was cooled to 0 °C with an ice-acetone bath. To a 500-mL addition funnel was charged with tetrahydro-4H-pyran-4-one (250 g, 2.5 mol) and after the KOH-methanol solution temperature reached 0 °C, the pyranone was added drop wise while maintaining

temperature at <5 °C. After stirring for an additional 1.5 h, iodine (704 g, 1.1 mol) was added portion wise over a 1.5 h period while maintaining the temperature at <5 °C. The reaction mixture was allowed to stir at room temperature for 18 h. The reaction was concentrated and the remaining residue was treated with toluene (1.5 L) and stirred for ½ h. A solid had precipitated, was filtered off and the filtrate was evaporated to afford to afford the title compound (330 g, 81%) as an amber oil.

Step B

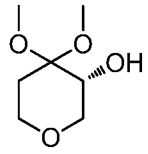
4, 4-Dimethoxydihydro-2H-pyran-3(4H)-one



A 12-L 4-neck Morton flask equipped with an overhead stirrer, thermocouple, and two addition funnels was charged with oxalyl chloride (130 mL, 1.49 mol) and CH_2Cl_2 (2.5 L). The solution was chilled with dry-ice/acetone bath to -72 °C. DMSO (178 mL, 2.50 mol) was added *via* additional funnel in CH_2Cl_2 (530 mL) over ½ h period while maintaining temperature at or below -70 °C. After the addition was complete, the mixture was stirred for an additional 30 min and 4, 4-dimethoxytetrahydro-2H-pyran-3-ol (as prepared in Step A, 200 g, 1.23 mol) in CH_2Cl_2 (630 mL) was added slowly (~1/2 h) from an addition funnel keeping the temperature at or below -70 °C. After stirring an additional 30 min, Et_3N (870 mL, 6.24 mol) was added, the temperature reached -42 °C and dropped back down to approx. -70 °C. The stirred mixture was allowed to stir to room temperature over 18 h. The mixture was filtered and the filtrate was concentrated to provide the crude product plus Et_3N-HCl solid. The mixture was filtered and rinsed with EtOAc (2 x 500 mL). The filtrate was concentrated again to a slurry. The slurry was diluted with EtOAc (approx 1 L), filtered, and concentrated again to give an amber oil containing the product and residual DMSO as the primary components. After purification on silica gel using a mixture of ethyl acetate in heptanes, the title compound (285 g, 90%) was afforded as a brown solid.

Step C1

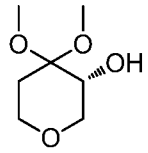
(R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol



A 12-L 4-neck round bottom flask equipped with a overhead air stirrer, addition funnel with nitrogen inlet adapter, condenser, and thermocouple was charged with S-(-)-2-methyl-CBS-oxazaborolidine (40 g, 0.12 mol) and THF (2.2 L). The mixture was warmed under nitrogen to 40 °C then Me_2S-BH_3 (108 mL, 1.15 mol) was added to the THF-catalyst mixture *via* syringe. An addition funnel charged with 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one (as prepared in the previous step, 165 g, 0.59 mol) in THF (2.1 L) was added drop wise over a 7 h period. After the addition was complete, the reaction was allowed to stir for 18 h at 40 °C. The reaction was chilled to 10 °C in an ice-acetone bath and quenched by slow addition of MeOH (1.1 L) over 1 h period. The cooling bath was removed and the mixture allowed to warm to room temperature for 3 h. After the gas evolution ceased, the mixture was concentrated on a rotary evaporator to give 188 g. Purification on silica gel using a mixture of EtOAc and heptanes afforded the title compound (166 g, 99 %, chiral GC 93% ee) as a yellow oil.

Step C (alternative)

(R)-4, 4-Dimethoxytetrahydro-2H-pyran-3-ol

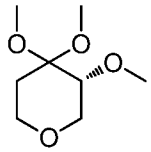


A 12-L 4-neck round bottom flask equipped with a overhead air stirrer, addition funnel with nitrogen inlet adapter, condenser, and thermocouple was charged with S-(-)-2-methyl-CBS-oxazaborolidine (78 g, 0.28 mol) and THF (2.7 L). The mixture was warmed under nitrogen to 40 °C while borane-N,N-diethylaniline complex (280 mL, 1.57 mol) was added to the THF-catalyst mixture *via* addition funnel over 40 min. An 4-L Erlenmeyer flask was charged with a mixture of 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one (as prepared in Step B, 225 g, 1.4 mol) in THF (2.7 L) and was added drop wise over a 8 h period *via* metering pump. After addition, the reaction was allowed to stir for 18 h at 40 °C. The reaction was chilled to 10 °C in an ice-acetone bath and quenched by slow addition of

MeOH (1.35 L) over 1 h period; after MeOH addition was complete, the cooling bath was removed and the mixture allowed to warm to room temperature for 3 h. After the gas evolution ceased, the mixture was concentrated on a rotary evaporator to give 365 g. After purification on silica gel using a mixture of EtOAc in heptanes the title compound (157 g, 69 %, chiral GC 95.5% ee) was afforded as a yellow oil.

Step D

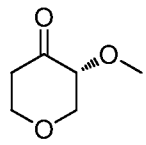
(R)-3, 4, 4-Ttrimethoxytetrahydro-2H-pyran



A 12-L 4-neck round bottom flask equipped with a overhead air stirrer, addition funnel with nitrogen inlet adapter, condenser, and thermocouple was charged with (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol (as prepared in the previous step, 163 g, 1.0 mol) in THF (2.4 L) and stirred in ice/acetone bath until <0 °C. KOtBu (113 g, 1.0 mol) was added in one portion, and after stirring 45 min, dimethyl sulfate (95 mL, 1.0 mol) was added *via* addition funnel over 15 min. The reaction was allowed to stir at room temperature for 2 h. The reaction mixture was poured into a separatory flask containing H_2O (1.2 L) and CH_2Cl_2 (1.2 L) and the layers were separated. The aqueous layer was back-extracted with CH_2Cl_2 (900 mL). The combined organic layers were washed with brine (1.0 L; Note: organic layer was on top), dried over $MgSO_4$, filtered and evaporated to afford the title compound (177.1 g, 99%, chiral GC 94.4% ee) as a light yellow oil.

Step E

(R)-3-methoxydihydro-2H-pyran-4(3H)-one

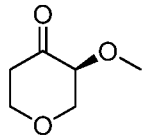


A stirred mixture of (R)-3, 4, 4-trimethoxytetrahydro-2H-pyran (as prepared in the previous step, 141 g, 0.80 mol), in THF (3.6 L) and H_2O (1.1 L) in an ice/acetone bath at <0 °C, was treated with a solution of HCl (conc., 595 mL, 7.21 mol) added *via* addition funnel over 45 min while keeping temperature <3 °C. After the addition was complete, the reaction was allowed to stir for 1.5 h at 0 °C. The reaction was evaporated until ~1.9 L of

concentrate remained. The concentrated was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 1 L). The combined organic fractions were washed with sat. $NaHCO_3$ (1 L), brine (1 L), dried over $MgSO_4$, filtered and evaporated to afford the title compound (71.4 g, 69%, Chiral GC 92% ee) as an oil which solidified upon standing. Optical Rotation: $[\alpha]^{25}(D)$ -6.97° (c = 0.8222, MeOH); Elemental Analysis calc for $C_6H_{10}O_3$: C, 53.59; H, 7.58; Found: C, 53.64; H, 7.65.

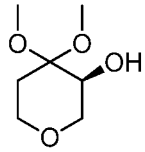
Intermediate 2

(S)-3-methoxydihydro-2H-pyran-4(3H)-one



Step A

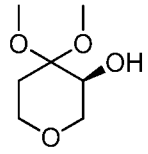
(S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol



A 5-L 4-neck round bottom flask equipped with an overhead air stirrer, addition funnel with nitrogen inlet adapter, condenser, and a thermocouple was charged with (R)-(+)-2-methyl-CBS-oxazaborolidine (34 g, 0.12 mol) and THF (1.2 L). The mixture was warmed under nitrogen to 40 °C then Me_2S-BH_3 (63 mL, 0.67 mol) was added to the THF-catalyst mixture *via* syringe. An addition funnel was charged with 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one (as prepared in Intermediate 1, Step B, 96 g, 0.59 mol) in THF (1.2 L) was added drop wise over an 8 h period. After addition, the reaction was allowed to stir for 18 h at 40 °C. The reaction was chilled to 10 °C in an ice-acetone bath and quenched by slow addition of MeOH (600 mL) over 45 min. The cooling bath was removed and the mixture allowed to warm to room temperature for 3 h. After the gas evolution ceased, the mixture was concentrated on a rotary evaporator to give 132 g. Purification on silica gel using a mixture of EtOAc and heptanes afforded the title compound (80.5 g, 83 %, chiral GC 95% ee) as a yellow oil.

Step A (alternative 1)

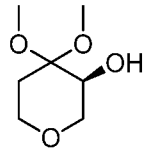
(S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol



The reaction was carried out according to the procedure of Intermediate 2, Step A, using 0.1 equivalents of (R)-(+)-2-methyl-CBS-oxazaborolidine, and substituting BH_3-THF complex for Me_2S-BH_3. The product (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol was obtained in 88% yield and 60% ee.

Step A (alternative 2)

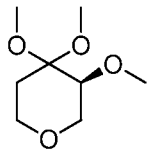
(S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol



The reaction was carried out according to the procedure of Intermediate 2, Step A, using 0.1 equivalents of (R)-(+)-2-methyl-CBS-oxazaborolidine, and substituting catecholborane for Me_2S-BH_3. The product (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol was obtained in <20% yield and 60% ee.

Step B

(S)-3, 4, 4-trimethoxytetrahydro-2H-pyran

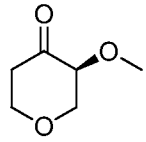


A 3-L 4-neck round bottom flask equipped with a overhead air stirrer, addition funnel with nitrogen inlet adapter, condenser, and thermocouple was charged with (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol (as prepared in the previous step, 80 g, 0.49 mol) in THF (1.1 L) and stirred in ice/acetone bath until <0 °C. KOtBu (56 g, 0.49 mol) was added in one portion, and after stirring 45 min, dimethyl sulfate (47 mL, 0.49 mol) was added *via* addition funnel over 15 min. The reaction was allowed to stir at room temperature for 3 h. The reaction mixture was poured into a separatory flask containing H_2O (1.25 L) and

CH_2Cl_2 (1.25 L) and the layers were separated. The aqueous layer was back- extracted with CH_2Cl_2 (750 mL). The combined organic layers were washed with brine (1 L; Note: organic layer was on top), dried over $MgSO_4$, filtered and evaporated to afford the title compound (83.5 g, 96%, chiral GC 94.6% ee) as a light yellow oil.

Step C

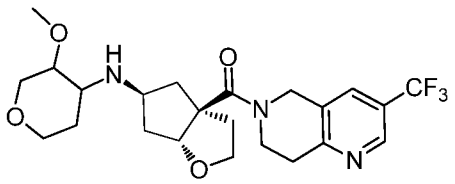
(S)-3-methoxydihydro-2H-pyran-4(3H)-one



A 5-L 4-neck round bottom flask equipped with a overhead air stirrer, nitrogen inlet adapter, thermocouple, and septum was charged with (S)-3, 4, 4-trimethoxytetrahydro-2H-pyran (as prepared in the previous step, 83 g, 0.47 mol), THF (2.1 L), H_2O (670 mL), and stirred in ice/acetone bath until <0 °C, where upon a solution of HCl (conc., 350 mL, 4.24 mol) was added *via* addition funnel over 30 min while keeping temperature <2 °C. After the addition was complete, the reaction was allowed to stir for 1 h at 0 °C. The reaction was evaporated until ~1.2 L of concentrate remained. The concentrate was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 750 mL). The combined organic fractions were washed with sat. $NaHCO_3$ (500 mL), brine (500 mL), dried over $MgSO_4$, filtered and evaporated to afford the title compound (46.9 g, 77%, Chiral GC 91% ee) as an oil which solidified upon sitting. Optical Rotation: $[\alpha]^{25}(D)$ +3.65 ° (c = 1.020, MeOH); Elemental Analysis calc for $C_6H_{10}O_3$: C, 53.39; H, 7.57; Found: 53.59; H, 7.62.

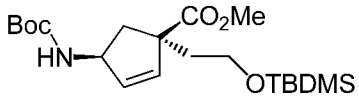
Example 1

((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

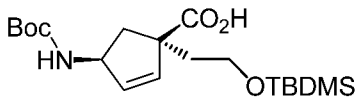
(1S,4S)-methyl 4-((tert-butoxycarbonyl)amino)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)cyclopent-2-enecarboxylate



To a solution of LiHMDS in THF (72.9 mL of a 1 M solution, 72.9 mmol, 2.2 eq) at -78 °C under Ar was added a solution of (1R,4S)-methyl 4-((*t*-butoxycarbonyl)amino)cyclopent-2-enecarboxylate (prepared according to the procedure of US 20050101628 A1 (see page 31, column 1, Procedure B, step B)), 8.00 g, 33.2 mmol, 1 eq) in THF (40 mL) dropwise over 1 hr. After stirring for 30 min, a solution of *t*-butyl(2-iodoethoxy)dimethylsilane (13.29 g, 46.4 mmol, 1.4 eq) in THF (20 mL) was added. The solution was kept at -78 °C for 15 min, then gradually warmed to 0 °C over 2 hrs, and kept at 0 °C for 1 hr. 1 N HCl and water were added, the solution extracted with DCM, the organics combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (400 g column) eluting with 5 to 20% EtOAc/heptane afforded the title compound of Step A. ^{1}H NMR (CHLOROFORM-d) δ: 5.76 - 5.85 (m, 2H), 4.90 (d, J = 9.0 Hz, 1H), 4.72 - 4.82 (m, 1H), 3.69 (s, 3H), 3.57 - 3.64 (m, 2H), 2.24 (dd, J = 13.9, 8.0 Hz, 1H), 2.14 (dd, J = 14.1, 3.5 Hz, 2H), 1.71 - 1.82 (m, 1H), 1.40 - 1.50 (m, 9H), 0.84 - 0.90 (m, 9H), 0.03 (s, 6H). ESI-MS (m/z): Calculated for C20H37NO5Si: 422.2 (M+23); found: 422.2.

Step B

(1S,4S)-4-((tert-butoxycarbonyl)amino)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)cyclopent-2-enecarboxylic acid

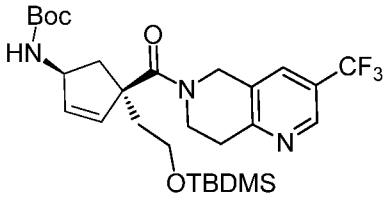


To a solution of the product of Step A (7.89 g, 19.74 mmol, 1 eq) in methanol (100 mL) at rt was added 1 N NaOH (59.2 mL, 59.2 mmol, 3.0 eq). After stirring overnight, the methanol was removed, 1 N HCl was added until the solution was acidic, the solution extracted with DCM, the organics combined, dried over $MgSO_4$, and concentrated to afford the title compound of Step B. ^{1}H NMR (CHLOROFORM-d) δ: 5.85 (br. s., 2H), 4.97 (br. s., 1H), 4.80 (br. s., 1H), 3.71 (br. s., 2H), 1.99 - 2.41 (m, 3H), 1.92 (br. s., 1H),

1.44 (br. s., 9H), 0.88 (s, 9H), 0.06 (br. s., 6H). ESI-MS (m/z): Calculated for C19H35NO5Si: 408.2 (M+23); found: 408.3.

Step C

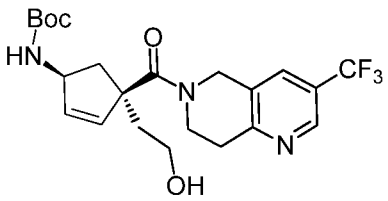
tert-butyl ((1S,4S)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate



To a solution of the product of Step B (3.47 g, 8.99 mmol, 1 eq) in DCM (40 mL) at rt was added HOBt hydrate (2.34 g, 15.3 mmol, 1.7 eq) and EDCI (2.58 g, 13.5 mmol, 1.5 eq). After 15 min, DIEA (7.8 mL, 45.3 mmol, 5 eq) and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2 HCl (3.71 g, 13.5 mmol, 1 eq) were added and the solution stirred overnight at rt. Saturated $NaHCO_3$ was added, the solution extracted with DCM, the organics combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (120 g column) eluting with 25 to 60% EtOAc/heptane afforded the title compound of Step C. ^{1}H NMR (CHLOROFORM-d) δ: 8.71 (s, 1H), 7.69 (s, 1H), 6.19 (d, J = 5.4 Hz, 1H), 5.76 (dd, J = 5.6, 2.0 Hz, 1H), 4.68 - 4.86 (m, 4H), 3.85 - 4.07 (m, 2H), 3.54 - 3.65 (m, 2H), 3.13 (t, J = 5.7 Hz, 2H), 2.58 (dd, J = 13.3, 7.7 Hz, 1H), 1.98 - 2.16 (m, 2H), 1.85 - 1.97 (m, 1H), 1.42 (s, 9H), 0.84 (s, 9H), -0.02 (d, J = 4.4 Hz, 6H). Calculated for C28H42F3N3O4Si: 570.3 (M+1); found: 570.3.

Step D

tert-butyl ((1S,4S)-4-(2-hydroxyethyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate

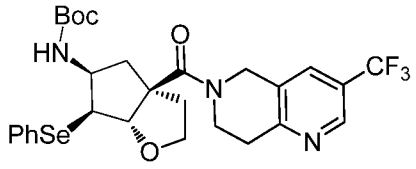


To a solution of the product of Step C (3.52g, 6.18 mmol, 1 eq) in THF (50 mL) at rt was added TBAF in THF (12.36 mL of a 1 M solution, 12.36 mmol, 2 eq). After 1 hr, water was added, the solution extracted with DCM, the organics combined, dried over $MgSO_4$,

and concentrated. Purification by chromatography (80 g column) eluting with 2 to 6% methanol/DCM with ammonia afforded the title compound of Step D. ^{1}H NMR (CHLOROFORM-d) δ: 8.71 (s, 1H), 7.70 (s, 1H), 6.28 (dd, J = 5.9, 2.0 Hz, 1H), 5.78 (dd, J = 5.9, 2.0 Hz, 1H), 4.70 - 4.95 (m, 4H), 3.99 - 4.10 (m, 1H), 3.85 - 3.96 (m, 1H), 3.68 (br. s., 2H), 3.09 - 3.18 (m, 2H), 2.65 (dd, J = 12.9, 7.4 Hz, 1H), 1.99 - 2.21 (m, 3H), 1.82 - 1.93 (m, 1H), 1.38 - 1.49 (m, 9H). Calculated for C22H28F3N3O4: 456.2 (M+1); found: 456.2.

Step E

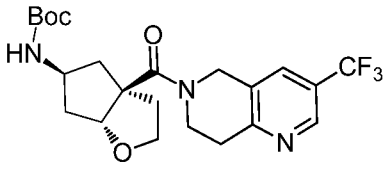
tert-butyl ((3aS,5S,6S,6aS)-6-(phenylselanyl)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)carbamate



To a solution of the product of Step D (1.51 g, 3.32 mmol, 1 eq) in DCM (40 mL) at rt under Ar was added N-(phenylseleno)phthalimide (1.60 g, 4.97 mmol, 1.5 eq) and BF_3-etherate (0.042 mL, 0.33 mmol, 0.1 eq). After 2 hrs, 1 N NaOH was added and stirred 5 min., water was added, the solution extracted with DCM, the organics combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (80 g column) eluting with 50 to 100% EtOAc/heptane afforded the title compound of Step E. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.69 (s, 1H), 7.50 - 7.62 (m, 2H), 7.22 - 7.27 (m, 3H), 5.35 (s, 1H), 5.06 (d, J = 8.1 Hz, 1H), 4.79 - 5.01 (m, 1H), 4.66 - 4.78 (m, 1H), 4.53 (br. s., 1H), 3.78 - 4.06 (m, 4H), 3.68 - 3.78 (m, 1H), 3.05 - 3.19 (m, 2H), 2.32 (dd, J = 11.6, 5.8 Hz, 2H), 2.16 (d, J = 10.9 Hz, 2H), 1.36 (s, 9H). Calculated for C28H32F3N3O4Se: 634.2 (M+23); found: 634.1.

Step F

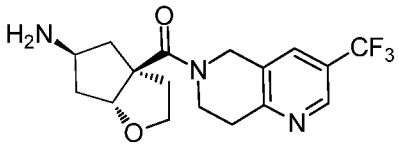
tert-butyl ((3aS,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)carbamate



To a solution of the product of Step E (1.51 g, 2.67 mmol, 1 eq), tris(trimethylsilyl)silane (1.72 mL, 5.34 mmol, 2 eq) and AIBN (438 mg, 2.67 mmol, 1 eq) in benzene (20 mL) was warmed to 80 °C under Ar. After 3 hrs, the solution was concentrated. Purification by chromatography (80 g column) eluting with 50 to 100% EtOAc/heptane afforded the title compound of Step F. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (br. s., 1H), 7.71 (br. s., 1H), 4.97 - 5.09 (m, 1H), 4.70 - 4.91 (m, 2H), 4.56 - 4.69 (m, 1H), 4.28 (br. s., 1H), 3.80 - 4.07 (m, 3H), 3.71 (q, J = 7.3 Hz, 1H), 3.13 (br. s., 2H), 2.07 - 2.53 (m, 4H), 1.81 (br. s., 1H), 1.61 - 1.72 (m, 1H), 1.40 (s, 9H). Calculated for C22H28F3N3O4: 478.2 (M+23); found: 478.2.

Step G

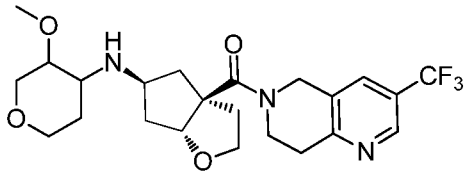
((3aS,5S,6aR)-5-aminohexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



To a solution of the product of Step F (12.54 g, 24.8 mmol, 1 eq) in DCM (100 mL) at rt was added TFA (20 mL, 261 mmol, 10.6 eq). After 1 hr, the solution was concentrated. 3 M NaOH was added and the solution extracted with DCM, the organics combined, dried over $MgSO_4$, and concentrated to afford the title compound of Step G. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.69 (br. s., 1H), 5.07 (d, J = 4.9 Hz, 1H), 4.71 - 4.90 (m, 2H), 3.84 - 4.03 (m, 3H), 3.58 - 3.71 (m, 2H), 3.09 - 3.20 (m, 2H), 2.14 - 2.41 (m, 3H), 1.99 - 2.13 (m, 1H), 1.65 - 1.75 (m, 1H), 1.43 - 1.58 (m, 1H). Calculated for C17H20F3N3O2: 356.2 (M+1); found: 356.3.

Step H

((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

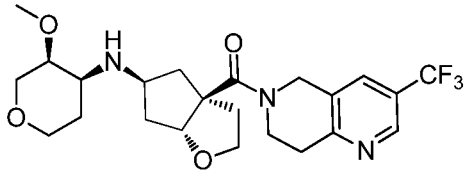


To a solution of the product of Step G (119 mg, 0.33 mmol, 1 eq) in DCM at rt was added acetic acid (0.01 mL, 0.17 mmol, 0.5 eq), 3-methoxytetrahydro-4H-pyran-4-one (131 mg, 1.0 mmol, 3 eq) and sodium triacetoxyborohydride (355 mg, 1.67 mmol, 5 eq). After stirring overnight, saturated $NaHCO_3$ was added, the solution extracted with DCM, the organics combined, dried over $MgSO_4$, and concentrated. Purification by chromatography (12 g) eluting with 4 to 8% methanol/DCM with ammonia afforded the title compound of Example 1. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (br. s., 1H), 7.70 (br. s., 1H), 4.98 - 5.14 (m, 1H), 4.70 - 4.89 (m, 2H), 3.80 - 4.18 (m, 5H), 3.25 - 3.75 (m, 8H), 3.07 - 3.24 (m, 2H), 2.53 - 2.89 (m, 1H), 2.01 - 2.48 (m, 4H), 1.39 - 1.88 (m, 5H). Calculated for C23H30F3N3O4: 470.2 (M+1); found: 470.2.

Separation of Example 1 by chiral HPLC gave 4 products, Example 2, Example 3, Example 4 and Example 5.

Example 2

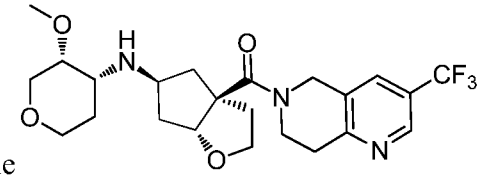
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



^{1}H NMR (CHLOROFORM-d) δ: 8.71 (s, 1H), 7.70 (br. s., 1H), 5.05 (d, J = 4.6 Hz, 1H), 4.68 - 4.88 (m, 2H), 4.08 (dd, J = 12.5, 2.9 Hz, 1H), 3.81 - 4.04 (m, 4H), 3.66 (td, J = 8.8, 6.8 Hz, 1H), 3.50 - 3.62 (m, 1H), 3.34 - 3.46 (m, 4H), 3.24 - 3.34 (m, 2H), 3.14 (br. s., 2H), 2.76 (d, J = 9.5 Hz, 1H), 2.14 - 2.46 (m, 3H), 1.99 - 2.14 (m, 1H), 1.45 - 1.86 (m, 5H). Calculated for C23H30F3N3O4: 470.2 (M+1); found: 470.2.

Example 3

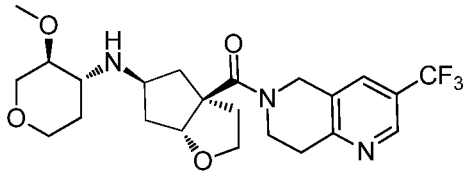
((3aS,5S,6aR)-5-(((3R,4R)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.70 (br. s., 1H), 5.06 (d, J = 4.6 Hz, 1H), 4.78 (br. s., 2H), 4.05 (dd, J = 12.6, 4.0 Hz, 1H), 3.84 - 4.02 (m, 4H), 3.65 (td, J = 8.9, 7.0 Hz, 1H), 3.55 (dt, J = 9.7, 5.0 Hz, 1H), 3.35 - 3.45 (m, 4H), 3.27 - 3.35 (m, 2H), 3.14 (br. s., 2H), 2.75 - 2.85 (m, 1H), 2.35 (br. s., 1H), 2.24 (dd, J = 13.0, 5.4 Hz, 2H), 2.00 - 2.15 (m, 1H), 1.59 - 1.85 (m, 4H), 1.48 (ddd, J = 13.2, 10.8, 4.9 Hz, 1H). Calculated for C23H30F3N3O4: 470.2 (M+1); found: 470.2.

Example 4

((3aS,5S,6aR)-5-(((3S,4R)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (the relative stereochemistry of the methoxypyran ring is trans, the absolute stereochemistry is unknown but opposite that of Example 5)

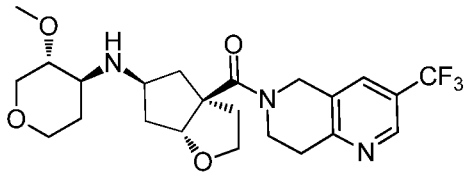


^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.70 (br. s., 1H), 5.01 (d, J = 4.6 Hz, 1H), 4.78 (br. s., 2H), 4.04 - 4.16 (m, 1H), 3.81 - 4.04 (m, 4H), 3.49 - 3.70 (m, 2H), 3.27 - 3.44 (m, 4H), 3.15 (t, J = 5.3 Hz, 2H), 2.96 - 3.09 (m, 2H), 2.59 (br. s., 1H), 2.19 - 2.44 (m, 3H), 2.00 - 2.13 (m, 1H), 1.95 (dt, J = 13.4, 2.1 Hz, 1H), 1.62 - 1.87 (m, 2H), 1.57 (ddd, J = 13.4, 10.9, 5.0 Hz, 1H), 1.38 - 1.51 (m, 1H). Calculated for C23H30F3N3O4: 470.2 (M+1); found: 470.2.

Example 5

((3aS,5S,6aR)-5-(((3R,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

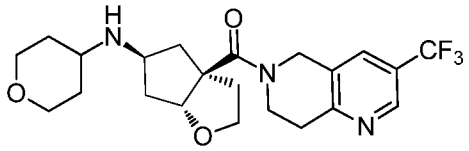
(the relative stereochemistry of the methoxypyran ring is trans, the absolute stereochemistry is unknown but opposite that of Example 4)



^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.69 (br. s., 1H), 5.06 (d, J = 4.6 Hz, 1H), 4.67 - 4.93 (m, 2H), 4.10 (d, J = 7.1 Hz, 1H), 3.79 - 4.04 (m, 4H), 3.48 - 3.69 (m, 2H), 3.29 - 3.42 (m, 4H), 3.14 (br. s., 2H), 2.96 - 3.10 (m, 2H), 2.59 - 2.72 (m, 1H), 2.21 - 2.43 (m, 3H), 2.02 - 2.15 (m, 1H), 1.98 (d, J = 24.5 Hz, 1H), 1.57 - 1.81 (m, 2H), 1.30 - 1.48 (m, 2H). Calculated for C23H30F3N3O4: 470.2 (M+1); found: 470.2.

Example 6

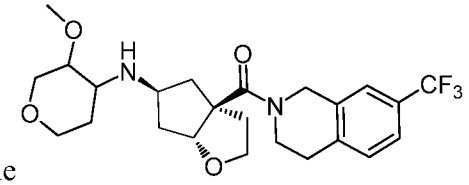
((3aS,5S,6aR)-5-((tetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 1, Step G and tetrahydro-4H-pyran-4-one following the procedure described in Example 1, Step H. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (br. s., 1H), 7.70 (br. s., 1H), 5.04 (d, J = 4.6 Hz, 1H), 4.78 (br. s., 2H), 3.95 (s, 2H), 3.97 (s, 3H), 3.53 - 3.75 (m, 2H), 3.28 - 3.49 (m, 2H), 3.14 (br. s., 2H), 2.62 - 2.81 (m, 1H), 2.29 (dd, J = 12.8, 5.5 Hz, 3H), 1.99 - 2.17 (m, 1H), 1.60 - 1.92 (m, 3H), 1.18 - 1.57 (m, 5H). Calculated for C22H28F3N3O3: 440.2 (M+1); found: 440.2.

Example 7

((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(7-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

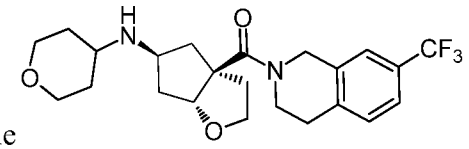


The title compound was prepared from reaction of the product of Step B of Example 1 and 7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline following the procedure described in Example 1, Step C, and then following Example 1 Steps D through H.

^{1}H NMR (CHLOROFORM-d) δ: 7.45 (d, J = 7.6 Hz, 2H), 7.23 - 7.31 (m, 1H), 4.99 - 5.10 (m, 1H), 4.72 (br. s., 2H), 4.02 - 4.16 (m, 1H), 3.70 - 4.02 (m, 4H), 3.47 - 3.59 (m, 1H), 3.22 - 3.46 (m, 6H), 2.86 - 3.09 (m, 3H), 2.77 (br. s., 1H), 2.13 - 2.44 (m, 3H), 1.99 - 2.11 (m, 1H), 1.35 - 1.88 (m, 5H). Calculated for C24H31F3N2O4: 470.2 (M+1); found: 470.2.

Example 8

((3aS,5S,6aR)-5-((tetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(7-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone

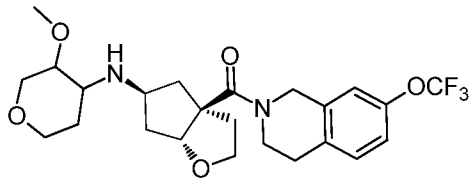


The title compound was prepared from reaction of the product of Step B of Example 1 and 7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline following the procedure described in Example 1, Step C, following Steps D through G, and then using tetrahydro-4H-pyran-4-one following the procedure described in Example 1, Step H.

JNJ46713953, ^{1}H NMR (CHLOROFORM-d) δ: 7.31 - 7.50 (m, 2H), 7.26 - 7.29 (m, 1H), 5.05 (d, J = 4.6 Hz, 1H), 4.72 (br. s., 2H), 3.90 - 4.05 (m, 3H), 3.70 - 3.85 (m, 2H), 3.52 - 3.70 (m, 2H), 3.30 - 3.45 (m, 2H), 2.95 (br. s., 2H), 2.70 (br. s., 1H), 2.18 - 2.44 (m, 3H), 2.00 - 2.12 (m, 1H), 1.60 - 1.89 (m, 2H), 1.23 - 1.53 (m, 5H). Calculated for C23H29F3N2O3: 439.2 (M+1); found: 439.2.

Example 9

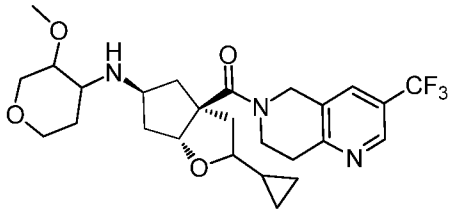
((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(7-(trifluoromethoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



The title compound was prepared from reaction of the product of Step B of Example 1 and 7-(trifluoromethoxy)-1,2,3,4-tetrahydroisoquinoline following the procedure described in Example 1, Step C, and then following Example 1 Steps D through H.
Calculated for C24H31F3N2O5: 485.2 (M+1); found: 485.2.

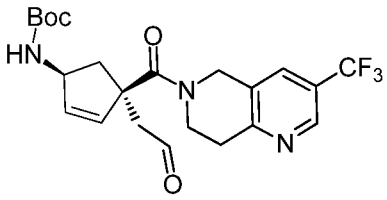
Example 10

((3aS,5S,6aR)-2-cyclopropyl-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

tert-butyl ((1S,4S)-4-(2-oxoethyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate

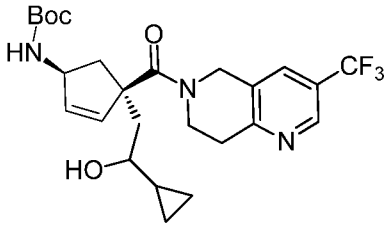


To a solution of the product of Example 1, Step D (417 mg, 0.92 mmol, 1 eq) in DCM (20 mL) at 0 °C was added Dess-Martin periodinane (427 mg, 1.01 mmol, 1.1 eq). After 1 hr, saturated sodium bicarbonate and sodium thiosulfate were added, after 10 minutes, the aqueous was extracted with DCM, the organics combined, dried over $MgSO_4$ and

concentrated. Purification by chromatography (12 g column) eluting with 30 to 60% EtOAc/heptane afforded the title compound of Step A. ^{1}H NMR (CHLOROFORM-d) δ: 9.74 (s, 1H), 8.70 (s, 1H), 7.72 (s, 1H), 6.31 (dd, J = 5.6, 1.7 Hz, 1H), 5.91 (dd, J = 5.6, 1.5 Hz, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.65 - 4.87 (m, 3H), 4.07 - 4.21 (m, 1H), 3.79 - 3.95 (m, 1H), 3.10 (q, J = 5.6 Hz, 2H), 3.03 (d, J = 16.6 Hz, 1H), 2.63 (dd, J = 13.6, 7.2 Hz, 1H), 2.52 (dd, J = 16.6, 1.5 Hz, 1H), 2.11 (dd, J = 13.1, 7.7 Hz, 1H), 1.44 (s, 9H). Calculated for C22H26F3N3O4: 454.2 (M+1); found: 454.2.

Step B

tert-butyl ((1S,4S)-4-(2-cyclopropyl-2-hydroxyethyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate



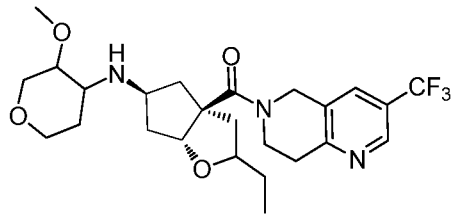
To a solution of cyclopropyl magnesium bromide (6.88 mL of a 0.5 M solution in THF, 3.44 mmol, 8 eq) in THF (5 mL) at 0 °C under Ar was added a solution of the product of Step A (195 mg, 0.43 mmol, 1 eq) in THF (17 mL) dropwise over 30 min. After 45 min, saturated NH_4Cl was added, the solution extracted with ethyl acetate, the organics combined, dried over $MgSO_4$ and concentrated. Purification by chromatography (12 g column) eluting with 30 to 100% EtOAc/heptane afforded the title compound of Step B as a mix of diastereomers. ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (br. s., 1H), 7.70 (br. s., 1H), 6.11 - 6.42 (m, 1H), 5.77 (t, J = 5.1 Hz, 1H), 4.81 (d, J = 12.2 Hz, 4H), 4.03 (dt, J = 12.8, 6.2 Hz, 1H), 3.81 - 3.98 (m, 1H), 3.59 - 3.75 (m, 2H), 3.03 - 3.25 (m, 2H), 2.69 - 3.00 (m, 2H), 2.19 - 2.67 (m, 3H), 1.91 - 2.18 (m, 3H), 1.55 - 1.88 (m, 5H), 1.42 (s, 9H), 0.88 - 0.99 (m, 1H), 0.42 - 0.56 (m, 2H), 0.14 - 0.35 (m, 2H). Calculated for C25H32F3N3O4: 496.2 (M+1); found: 496.2.

The title compound of Example 10 was made by taking the product of Example 10, Step B and following the procedures from Example 1, Steps E through H.

^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.69 (br. s., 1H), 5.01 - 5.29 (m, 1H), 4.65 - 4.90 (m, 2H), 3.74 - 4.15 (m, 5H), 3.70 (dd, J = 11.0, 2.9 Hz, 1H), 3.23 - 3.55 (m, 7H), 3.14 (br. s., 2H), 3.05 (ddd, J = 10.0, 8.2, 6.0 Hz, 1H), 2.69 - 2.87 (m, 1H), 2.36 - 2.52 (m, 1H), 2.06 - 2.36 (m, 3H), 1.66 - 1.97 (m, 2H), 1.33 - 1.52 (m, 1H), 0.83 - 0.98 (m, 1H), 0.43 - 0.66 (m, 2H), 0.36 (dt, J = 8.6, 4.1 Hz, 1H), 0.10 - 0.24 (m, 1H). Calculated for C26H34F3N3O4: 510.3 (M+1); found: 510.3.

Example 11

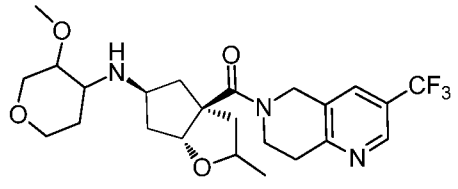
((3aS,5S,6aR)-2-ethyl-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 10, Step A and ethyl magnesium bromide following the procedure described in Example 10, Step B, and then taking that product and following the procedures from Example 1, Steps E through H. ^{1}H NMR (MeOD) δ: 8.72 (s, 1H), 8.05 (br. s., 1H), 4.94 - 5.13 (m, 1H), 4.70 - 4.86 (m, 2H), 4.25 (br. s., 1H), 3.76 - 4.14 (m, 4H), 3.62 - 3.75 (m, 1H), 3.35 - 3.60 (m, 7H), 3.13 (dd, J = 3.3, 1.6 Hz, 2H), 2.33 - 2.75 (m, 3H), 1.69 - 2.10 (m, 5H), 1.39 - 1.69 (m, 2H), 0.87 - 1.01 (m, 3H). Calculated for C25H34F3N3O4: 498.3 (M+1); found: 498.2.

Example 12

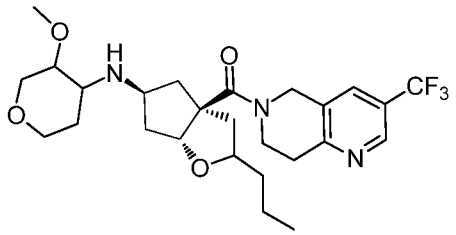
((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2-methylhexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 10, Step A and methyl magnesium bromide following the procedure described in Example 10, Step B, and then taking that product and following the procedures from Example 1, Steps E through H. ^{1}H NMR (MeOD) δ: 8.72 (br. s., 1H), 8.05 (br. s., 1H), 4.96 - 5.21 (m, 1H), 4.70 - 4.87 (m, 2H), 4.21 - 4.36 (m, 1H), 3.77 - 4.18 (m, 5H), 3.32 - 3.62 (m, 7H), 3.00 - 3.23 (m, 2H), 2.32 - 2.76 (m, 3H), 1.68 - 2.06 (m, 5H), 1.16 - 1.29 (m, 3H). Calculated for C24H32F3N3O4: 484.2 (M+1); found: 484.2.

Example 13

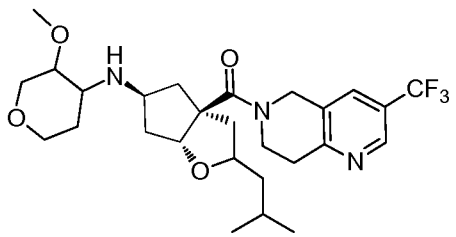
((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2-propylhexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 10, Step A and propyl magnesium bromide following the procedure described in Example 10, Step B, and then taking that product and following the procedures from Example 1, Steps E through H. Calculated for C26H36F3N3O4: 512.3 (M+1); found: 512.2.

Example 14

((3aS,5S,6aR)-2-isobutyl-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

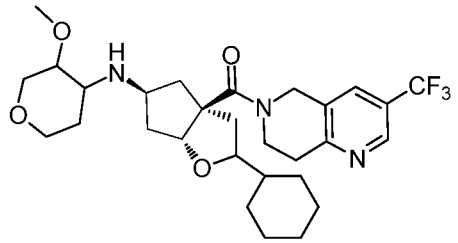


The title compound was prepared from reaction of the product of Example 10, Step A and isobutyl magnesium bromide following the procedure described in Example 10, Step B, and then taking that product and following the procedures from Example 1, Steps E through H.

Calculated for C27H38F3N3O4: 526.3 (M+1); found: 526.3.

Example 15

((3aS,5S,6aR)-2-cyclohexyl-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



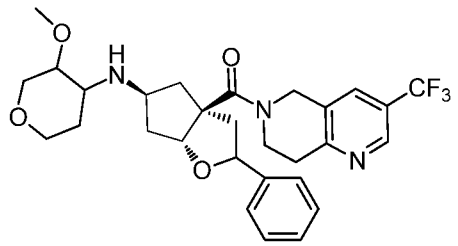
The title compound was prepared from reaction of the product of Example 10, Step A and cyclohexyl magnesium bromide following the procedure described in Example 10, Step B, and then taking that product and following the procedures from Example 1, Steps E through H.

^{1}H NMR (CHLOROFORM-d) δ: 8.71 (br. s., 1H), 7.69 (br. s., 1H), 4.98 - 5.21 (m, 1H), 4.65 - 4.94 (m, 2H), 3.68 - 4.17 (m, 5H), 3.23 - 3.64 (m, 8H), 3.13 (br. s., 2H), 2.69 - 2.86 (m, 1H), 1.86 - 2.35 (m, 6H), 1.32 - 1.79 (m, 8H), 1.10 - 1.30 (m, 3H), 0.86 - 1.06 (m, 2H).

Calculated for C29H40F3N3O4: 552.3 (M+1); found: 553.2.

Example 16

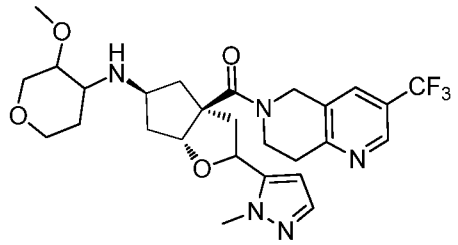
((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2-phenylhexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 10, Step A and phenyl magnesium bromide following the procedure described in Example 10, Step B, and then taking that product and following the procedures from Example 1, Steps E through H. Calculated for C29H34F3N3O4: 546.3 (M+1); found: 546.3.

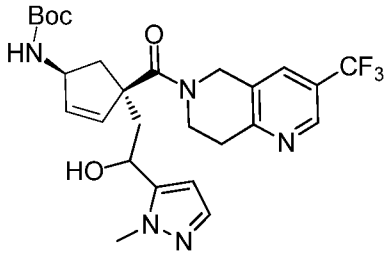
Example 17

((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2-(1-methyl-1H-pyrazol-5-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

tert-butyl ((1S,4S)-4-(2-hydroxy-2-(1-methyl-1H-pyrazol-5-yl)ethyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate



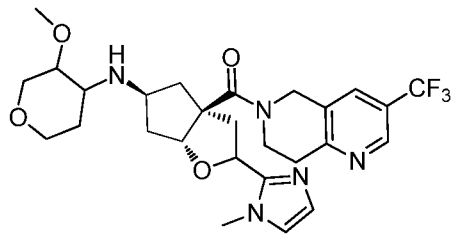
To a solution of 1-methylpyrazole (0.165 mmol, 1.98 mmol, 3 eq) in THF (8 mL) at -78 °C under Ar was added *n*-BuLi (0.77 mL of a 2.5 M solution in hexane, 1.92 mmol, 2.9 eq) and the solution stirred 1 hr. Then a solution of the product of Example 10, Step A (300

mg, 0.66 mmol, 1 eq) in THF (8 mL) was added over 5 min. After 1 hr, saturated NH_4Cl was added, the solution extracted with ethyl acetate, the organics combined, dried over $MgSO_4$ and concentrated. Purification by chromatography (12 g column) eluting with 50 to 100% EtOAc/heptane to 5 to 10% methanol/DCM afforded the title compound of Step A as a mix of diastereomers. ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (s, 1H), 7.62 - 7.80 (m, 1H), 7.33 (d, J = 8.8 Hz, 1H), 6.19 - 6.49 (m, 1H), 6.09 (br. s., 1H), 5.87 (dd, J = 17.9, 5.6 Hz, 1H), 4.54 - 5.03 (m, 5H), 3.74 - 3.96 (m, 4H), 3.48 (s, 1H), 2.90 - 3.23 (m, 2H), 2.46 - 2.87 (m, 2H), 2.06 - 2.39 (m, 2H), 1.73 - 1.98 (m, 1H), 1.43 (br. s., 9H). Calculated for C27H34F3N5O4: 558.2 (M+23); found: 558.2.

The title compound of Example 17 was made by taking the product of Example 17, Step A and following the procedures from Example 1, Steps E through H.
^{1}H NMR (CHLOROFORM-d) δ: 8.73 (br. s., 1H), 7.72 (br. s., 1H), 7.32 - 7.48 (m, 1H), 5.90 - 6.28 (m, 1H), 5.08 - 5.36 (m, 1H), 4.64 - 4.98 (m, 2H), 3.76 - 4.17 (m, 7H), 3.50 - 3.74 (m, 1H), 3.23 - 3.50 (m, 6H), 3.16 (br. s., 2H), 2.66 - 2.86 (m, 1H), 2.15 - 2.64 (m, 4H), 1.96 - 2.05 (m, 1H), 1.42 - 1.91 (m, 3H). Calculated for C27H34F3N5O4: 550.3 (M+1); found: 550.2.

Example 18

((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2-(1-methyl-1H-imidazol-2-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

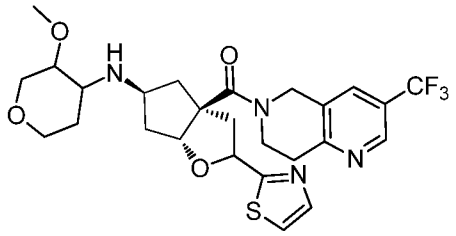


The title compound was prepared from reaction of the product of Example 10, Step A and 1-methylimidazole following the procedure described in Example 17, Step A, and then taking that product and following the procedures described in Example 1, Steps E through H.

Calculated for C27H34F3N5O4: 550.3 (M+1); found: 550.2.

Example 19

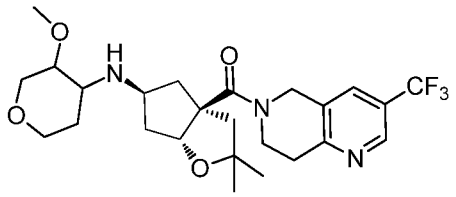
((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2-(thiazol-2-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 10, Step A and thiazole following the procedure described in Example 17, Step A, and then taking that product and following the procedures described in Example 1, Steps E through H. Calculated for C26H31F3N4O4S: 553.3 (M+1); found: 553.3.

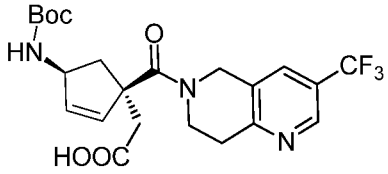
Example 20

((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-2,2-dimethylhexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

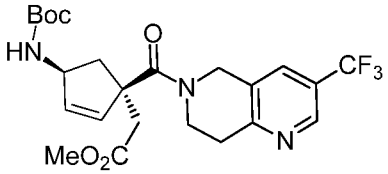
2-((1S,4S)-4-((tert-butoxycarbonyl)amino)-1-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)acetic acid



To a solution of the product of Example 1, Step D (508 mg, 1.12 mmol, 1 eq) in acetone (10 mL) at 0 °C was added Jones oxidation solution (0.46 mL, 1.23 mmol, 1.1 eq). After 2 hr, water was added, the aqueous was extracted with ethyl acetate, the organics combined, dried over $MgSO_4$ and concentrated to afford the product of Step A that was used unpurified in the next step. Calculated for C22H26F3N3O5: 492.2 (M+23); found: 492.1.

Step B

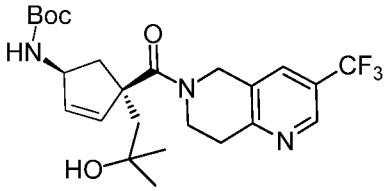
methyl 2-((1S,4S)-4-((tert-butoxycarbonyl)amino)-1-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)acetate



To a solution of the product of Step A (436 mg, 0.84 mmol, 1 eq) in methanol (20 mL) at 0 °C was added trimethylsilyl diazomethane (5 mL of a 2 M solution in hexanes, 10 mmol, 11.9 eq) until the yellow color persisted. The yellow solution was concentrated. Purification by chromatography (24 g column) eluting with 40 to 80% EtOAc/heptane afforded the product of Step B. ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (s, 1H), 7.69 (s, 1H), 6.37 (d, J = 5.4 Hz, 1H), 5.87 (d, J = 5.4 Hz, 1H), 4.98 (d, J = 17.4 Hz, 1H), 4.63 - 4.83 (m, 3H), 4.07 - 4.20 (m, 1H), 3.79 - 3.93 (m, 1H), 3.64 (s, 3H), 3.08 - 3.19 (m, 2H), 3.04 (d, J = 15.9 Hz, 1H), 2.62 (dd, J = 13.4, 7.1 Hz, 1H), 2.46 (d, J = 15.7 Hz, 1H), 2.01 - 2.12 (m, 1H), 1.43 (s, 9H). Calculated for C23H28F3N3O5: 506.2 (M+23); found: 506.2.

Step C

tert-butyl ((1S,4S)-4-(2-hydroxy-2-methylpropyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate



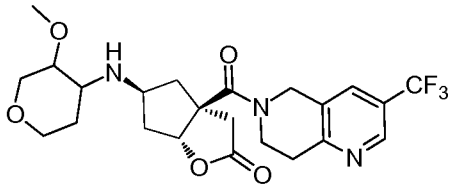
To a solution of methyl magnesium chloride (2.62 mL of a 3 M solution in THF, 7.86 mmol, 20 eq) in THF (6 mL) at 0 °C under Ar was added a solution of the product of Step B (190 mg, 0.39 mmol, 1 eq) in THF (6 mL) dropwise over 30 min. After 30 min,

saturated NH_4Cl was added, the solution extracted with ethyl acetate, the organics combined, dried over $MgSO_4$ and concentrated. Purification by chromatography (12 g column) eluting with 40 to 100% EtOAc/heptane afforded the product of Step C. ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (s, 1H), 7.69 (s, 1H), 6.47 (d, J = 5.4 Hz, 1H), 5.75 (dd, J = 5.6, 1.5 Hz, 1H), 4.60 - 4.96 (m, 4H), 4.05 (d, J = 13.7 Hz, 1H), 3.89 (dt, J = 13.3, 6.4 Hz, 1H), 3.07 - 3.19 (m, 2H), 2.54 (dd, J = 12.6, 6.5 Hz, 1H), 2.10 - 2.27 (m, 2H), 1.80 - 1.96 (m, 2H), 1.35 - 1.49 (m, 9H), 1.26 (s, 3H), 1.22 (s, 3H). Calculated for C24H32F3N3O4: 506.2 (M+23); found: 506.2.

The title compound of Example 20 was made by taking the product of Step C and following the procedures described in Example 1, Steps E through H.
^{1}H NMR (CHLOROFORM-d) δ: 8.72 (br. s., 1H), 7.69 (br. s., 1H), 5.16 - 5.27 (m, 1H), 4.78 (br. s., 2H), 4.01 - 4.13 (m, 1H), 3.75 - 3.99 (m, 4H), 3.53 - 3.67 (m, 1H), 3.22 - 3.48 (m, 6H), 3.12 (br. s., 2H), 2.79 (d, J = 10.0 Hz, 1H), 2.09 - 2.40 (m, 3H), 1.84 - 2.00 (m, 2H), 1.68 - 1.78 (m, 2H), 1.42 - 1.53 (m, 1H), 1.34 (s, 3H), 1.16 (s, 3H). Calculated for C25H34F3N3O4: 498.2 (M+1); found: 498.2.

Example 21

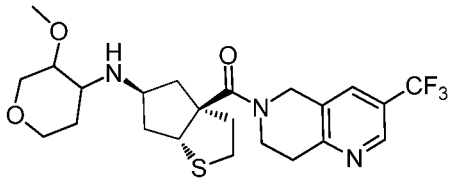
(3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-2-one



The title compound of Example 21 was made by taking the product of Example 20, Step A and following the procedures described in Example 1, Steps E through H.
^{1}H NMR (CHLOROFORM-d) δ: 8.74 (br. s., 1H), 7.71 (br. s., 1H), 5.70 (d, J = 4.2 Hz, 1H), 4.55 - 4.88 (m, 2H), 4.08 (d, J = 11.7 Hz, 1H), 3.93 (d, J = 11.5 Hz, 1H), 3.80 (br. s., 1H), 3.47 - 3.61 (m, 2H), 3.24 - 3.46 (m, 5H), 3.15 (br. s., 2H), 3.03 (d, J = 14.2 Hz, 1H), 2.83 (br. s., 2H), 2.23 - 2.47 (m, 2H), 1.53 - 1.76 (m, 6H). Calculated for C23H28F3N3O5: 484.2 (M+1); found: 484.2.

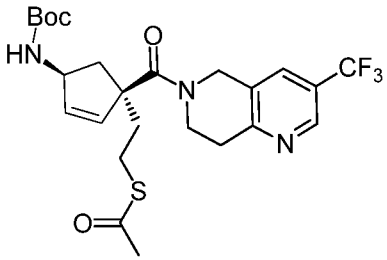
Example 22

((3aR,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]thiophen-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

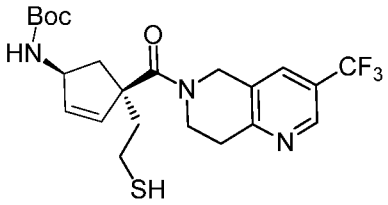
S-(2-((1S,4S)-4-((tert-butoxycarbonyl)amino)-1-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)ethyl) ethanethioate



To a solution of the product of Example 1, Step D (1950 mg, 3.98 mmol, 1 eq) in THF (40 mL) at rt under Ar was added triphenylphosphine (2.09 g, 7.96 mmol, 2 eq), diisopropylazodicarboxylate (1.55 mL, 7.96 mmol, 2 eq) and thioacetic acid (0.59 mL, 7.96 mmol, 2 eq). After 2 hr, water and saturated $NaHCO_3$ were added, the aqueous was extracted with ether, the organics combined, dried over $MgSO_4$ and concentrated. Purification by chromatography (80 g column) eluting with 30 to 60% EtOAc/heptane afforded the product of Step A. ^{1}H NMR (CHLOROFORM-d) δ: 8.71 (s, 1H), 7.71 (s, 1H), 6.21 (dd, J = 5.6, 1.7 Hz, 1H), 5.80 (dd, J = 5.6, 2.0 Hz, 1H), 4.75 - 4.94 (m, 3H), 4.64 - 4.75 (m, 1H), 3.96 - 4.07 (m, 1H), 3.86 - 3.96 (m, 1H), 3.14 (t, J = 5.7 Hz, 2H), 2.69 - 2.79 (m, 2H), 2.65 (dd, J = 13.4, 8.1 Hz, 1H), 2.27 (s, 3H), 1.95 - 2.13 (m, 2H), 1.81 - 1.94 (m, 1H), 1.44 (s, 9H). Calculated for C24H30F3N3O4S: 536.2 (M+23); found: 536.2.

Step B

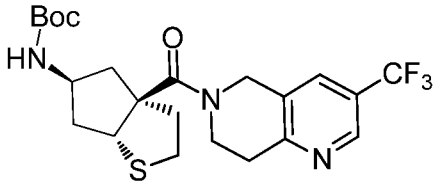
tert-butyl ((1S,4S)-4-(2-mercaptoethyl)-4-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)cyclopent-2-en-1-yl)carbamate



To a solution of the product of Step A (1.74 g, 3.39 mmol, 1 eq) in methanol (100 mL) at rt under Ar (degassed) was added 0.2 N NaOH (85 mL, 85 mmol, 5 eq) that was degassed by bubbling Ar through the solution prior to addition. After 2 hr, the methanol was concentrated, 6 N HCl was added until the solution was acidic, the aqueous was extracted with DCM, the organics combined, dried over $MgSO_4$ and concentrated to afford the product of Step B which was used unpurified in the next step. Calculated for C22H28F3N3O3S: 494.2 (M+23); found: 494.1.

Step C

tert-butyl ((3aR,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]thiophen-5-yl)carbamate



To a solution of the product of Step B (1.25 g, 2.65 mmol, 1 eq) in benzene (300 mL) at rt under Ar (degassed) was added AIBN (435 mg, 2.65 mmol, 1 eq) and the solution heated to 85 °C for 3 days, then concentrated. Purification by chromatography (40 g column) eluting with 25 to 60 to 100% EtOAc/heptane afforded the product of Step C. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.69 (s, 1H), 4.65 - 4.90 (m, 3H), 4.23 - 4.60 (m, 2H), 3.87 - 4.06 (m, 2H), 3.10 - 3.16 (m, 2H), 2.99 - 3.09 (m, 1H), 2.87 - 2.98 (m, 1H), 1.95 - 2.38 (m, 6H), 1.40 (s, 9H). Calculated for C22H28F3N3O3S: 494.2 (M+23); found: 494.1.

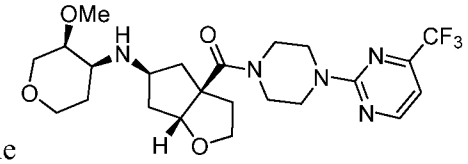
The title compound of Example 22 was made by taking the product of Example 22, Step C and following the procedures described in Example 1, Steps G and H.

^{1}H NMR (CHLOROFORM-d) δ: 8.71 (s, 1H), 7.69 (s, 1H), 4.73 - 4.93 (m, 2H), 4.67 (br. s., 1H), 4.04 - 4.17 (m, 1H), 3.94 (t, J = 5.9 Hz, 3H), 3.61 - 3.77 (m, 1H), 3.36 - 3.47 (m,

4H), 3.26 - 3.36 (m, 2H), 3.06 - 3.19 (m, 2H), 2.80 - 3.05 (m, 3H), 2.31 (br. s., 2H), 2.05 - 2.21 (m, 3H), 1.83 - 1.99 (m, 1H), 1.60 - 1.83 (m, 2H). Calculated for C23H30F3N3O3S: 486.2 (M+1); found: 486.2.

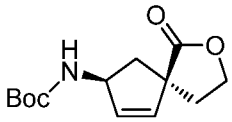
Example 23

((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)methanone



Step A

tert-butyl ((5S,7S)-1-oxo-2-oxaspiro[4.4]non-8-en-7-yl)carbamate

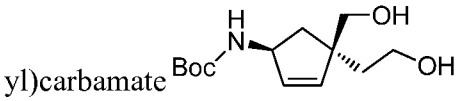


A 12-L three-neck round bottom flask with overhead mechanical stirrer, 2-L addition funnel and nitrogen inlet was charged the product of Example 1, Step A (1149 g, 2.875 mol, 1 eq) and THF (5.75 L). The addition funnel was charged with TBAF (1M solution in THF, 2.875 L, 2.875 mol, 1 eq) and this solution was added dropwise over ~1 h. The temperature increased from 17 to 21 °C and the reaction was clear orange at the end. The reaction was stirred for 1 h at rt, when it was judged complete by TLC and HPLC. The reaction was poured into a 22-L separatory flask charged with EtOAc (4 L) and the organic layer was washed with brine (2 L). The organic layer was washed with additional brine (3 x 2 L) and these aqueous fractions were discarded. Heptane (4 L) was added and the organic layer was washed with water (3 x 2 L), brine (2 x 2 L) and the clear organic layer was checked by NMR for removal of n-Bu_4NX. The organic layer was evaporated at 45 °C to about 750 mL, when the solution became hazy, heptane (800 mL) was added and instant crystallization of a white solid resulted. More heptane (300 mL) was added and the mixture was swirled at 40 °C for 10 min on the rotovap bath. Ice was added to bath and the suspension was stirred at 13 °C for 10 min. The solid was filtered on a Buchner funnel, washed with heptane (3 x 100 mL) and provided the product of Step A. ^{1}H NMR

(CHLOROFORM-d) δ: 6.02 (dd, J = 5.4, 2.4 Hz, 1H), 5.77 (d, J = 5.4 Hz, 1H), 5.21 (d, J = 9.0 Hz, 1H), 4.91 (t, J = 8.7 Hz, 1H), 4.37 (dd, J = 7.5, 6.5 Hz, 2H), 2.21 - 2.39 (m, 3H), 2.07 (dd, J = 13.8, 2.6 Hz, 1H), 1.44 (s, 9H). Calculated for C13H19NO4: 276.1 (M+23); found: 276.1.

Step B

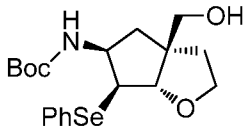
tert-butyl ((1S,4S)-4-(2-hydroxyethyl)-4-(hydroxymethyl)cyclopent-2-en-1-yl)carbamate



To a 5-L three-neck round bottom flask equipped with a mechanical stirrer, Claisen adapter with temperature probe and nitrogen inlet, and N_2 outlet was purged with nitrogen for 2 h before use. The product of Step A (255.9 g, 1.01 mol, 1 eq) and MeOH (2 L) were added and the solution was chilled to 2 °C in an ice bath. $NaBH_4$ (75 g, 1.98 mol, 2 eq) was added in ~5 equal portions; the temperature exothermed to 17 °C before coming back to 6 °C, when the next portion was added. The addition took ~ 2.5 h and the reaction was judged complete by HPLC after the last addition. The reaction was quenched at 7 °C by addition of aqueous NH_4Cl (saturated, 1 L), wherein the temperature rose to about 10 °C. The white hazy mixture was concentrated on a rotary evaporate to about 1 L (45 °C bath) when a white solid with some liquid resulted. The mixture was diluted with water and EtOAc (1 L each), transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 250 mL). The combined organics were washed with brine (125 mL), dried over $MgSO_4$, filtered through Celite and evaporated at a bath temperature of 55 °C and provided the product of Step B as a thick oil. ^1H NMR (CHLOROFORM-d) δ: 5.74 (s, 2H), 4.65 - 4.95 (m, 2H), 3.70 (t, J = 5.7 Hz, 2H), 3.40 - 3.57 (m, 2H), 2.76 (br. s., 1H), 2.28 (br. s., 1H), 2.19 (dd, J = 13.4, 8.8 Hz, 1H), 1.70 (t, J = 5.7 Hz, 2H), 1.55 (dd, J = 13.8, 4.0 Hz, 1H), 1.44 (s, 9H). Calculated for C13H23NO4: 280.2 (M+23); found: 280.2.

Step C

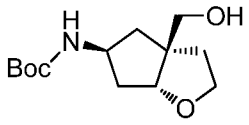
tert-butyl ((3aR,5S,6S,6aS)-3a-(hydroxymethyl)-6-(phenylselanyl)hexahydro-2H-cyclopenta[b]furan-5-yl)carbamate



To a 12-L three-neck round bottom flask equipped with a mechanical stirrer, Claisen adapter with a nitrogen inlet and a temperature probe, and a nitrogen outlet was charged with the product of Step B (382 g, 1.26 mol, 1 eq) and CH_2Cl_2 (6.5 L). N-(phenylseleno)phthalimide (419 g, 1.39 mol, 1.1 eq) was added followed by BF_3 etherate (16 mL, 0.126 mol, 0.1 eq) directly added by graduated cylinder. The reaction steadily climbed from 15 °C to 24 °C and within 10 min, the reaction formed a pink precipitate. Ten min later, the reaction became thick with a white precipitate and the temperature began to decrease. The reaction was checked by HPLC and found to be complete. The reaction was filtered through Celite (removing the phthalimide impurity), the filter cake was washed with CH_2Cl_2 (750 mL) until the filtrate was no longer orange. The filtrate was transferred to a separatory funnel, washed with aqueous NaOH (0.5 M, 2 x 1350 mL), brine (2 x 1 L), and the organic layer was dried over Na_2SO_4. [A second run was conducted with 382 g of the product of Step B, under the same conditions, and was worked up and combined at this point]. With about 3 L organics left, toluene (3 L, ~4 mL/g starting material) was added and the evaporation continued. Shortly after the toluene addition, crystallization occured. The 20-L round bottom flask was transferred to a heating mantel, and the contents heated to 80 °C, until the solid dissolved. The flask was transferred back to the rotary evaporator, reference material was used to seed the crystallization, and the flask swirled (no heat) until the product started to crystallize. Ice was added to the bath and the contents of the flask swirled at 15 °C (external temp) for 30 min. The product was filtered, washed with ice-cold toluene and air-dried for 1 h, and afforded the product of Step C. ^{1}H NMR (CHLOROFORM-d) δ: 7.49 - 7.56 (m, 2H), 7.23 - 7.29 (m, 3H), 5.05 (br. s., 1H), 4.46 (br. s., 1H), 4.29 (s, 1H), 3.86 - 3.97 (m, 2H), 3.57 - 3.69 (m, 3H), 1.98 - 2.08 (m, 1H), 1.86 - 1.97 (m, 2H), 1.73 - 1.86 (m, 2H), 1.41 (s, 9H). Calculated for C19H27NO4Se: 436.1 (M+23); found: 436.1.

Step D

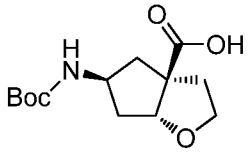
tert-butyl ((3aR,5S,6aR)-3a-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-5-yl)carbamate



A 22-L four-neck round bottom flask equipped with mechanical stirrer, heating mantel, temperature probe, nitrogen inlet, and a reflux condenser with nitrogen outlet was purged with nitrogen for 30 min before use. The product of Step C (603.5 g, 1.46 mol, 1 eq), AIBN (241 g, 1.46 mol, 1 eq), tris(trimethylsilyl)silane (910 mL, 2.93 mol, 2 eq) and toluene (16.3 L) were added and the suspension was degassed with nitrogen purge through the suspension for 20 min. The reaction was heated to 80-83 °C for 1 h after which time the heat was shut off, and the reaction cooled to rt over 12-18 h. TLC showed the reaction was complete. The reaction was poured directly into a BIOTAGE dry 5-kg column that was eluted with 16 L of 50 % EtOAc in heptane, followed by 32 L of EtOAc and provided the product of Step D of a golden thick oil, which slowly crystallized on standing. ^{1}H NMR (CHLOROFORM-d) δ: 4.64 (brd. s, 1H), 4.07 - 4.25 (m, 2H), 3.89 (ddd, J = 8.8, 7.2, 4.5 Hz, 1H), 3.53 - 3.67 (m, 3H), 2.17 (dd, J = 13.3, 6.2 Hz, 1H), 1.98 - 2.06 (m, 1H), 1.86 - 1.97 (m, 1H), 1.68 - 1.81 (m, 2H), 1.46 - 1.56 (m, 2H), 1.44 (s, 9H). Calculated for C13H23NO4: 202.2 (M-55); found: 202.2.

Step E

(3aS,5S,6aR)-5-((tert-butoxycarbonyl)amino)hexahydro-2H-cyclopenta[b]furan-3a-carboxylic acid

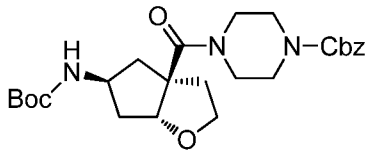


A 22-L four-neck round bottom flask equipped with a mechanical stirrer, nitrogen inlet, 1-L addition funnel with nitrogen outlet, a temperature probe, and an external bath for cooling was purged with nitrogen overnight. A solution of the product of Step D (426 g, 1.57 mol) and acetone (8.1 L) was added, the flask was cooled to 7 °C, and the addition funnel was charged with Jones reagent (710 mL). The oxidant was added dropwise over 1 h 20 min, keeping the temp between 7- 9 °C. After the first 200 mL was added, a green ball formed that made stirring very difficult. After about ½ of the oxidant was added, LCMS was run to follow the reaction. At the end of addition, olive green suspension

resulted with a hint of red (excess Jones). The ice bath was removed, the reaction was stirred at rt for 1 h after which time the reaction was judged complete. Isopropyl alcohol (40 mL) was added, the reaction stirred for 25 min, and water (800 mL) was added, that caused a nice separation of green chunk from the acetone/water layer. The water/acetone was decanted off and evaporated. The green chunk was dissolved in water (1.5 L), transferred to a separatory funnel and extracted with CH_2Cl_2 (1 L). The aqueous layer was checked by TLC and found to contain no product, so it was discarded. The organic extract was saved for combining later. The green water/acetone concentrate was evaporated to about 5-7 L, until the solution looked hazy. The concentrate was transferred to a separatory funnel and extracted with CH_2Cl_2 (1 x 3L, 3 x 1L) and the aqueous layer checked after each extraction for the presence of product. The combined extracts were washed with brine (250 mL) which caused a terrible emulsion. The emulsion was broken by addition of water and EtOAc (~500 mL). The organic layer was dried (Na_2SO_4) but not very effectively as some water came through during the filtration. Near the end of the evaporation, the distillation rate slowed, and a thick yellow oil resulted. MeCN (500 mL) was added to the pot, the rotary evaporator bath warmed to 50 °C, and the contents seeded with reference material. A fine white solid slowly formed within 10 min or so. Seeding was done a second time, and continued swirling for another 10 min at 50 °C. Crystallization was visually detected, the bath was drained and filled with ice, and the flask swirled at 0 °C for 30 min, resulting in a thick white solid. The solid was filtered, washed with ice-cold MeCN (2 x 100 mL) and the solid was air-dried overnight. The product of Step E was isolated as a white, free-flowing solid. ^{1}H NMR (MeOH) δ: 4.43 (d, J = 5.4 Hz, 1H), 4.00 - 4.13 (m, 1H), 3.89 - 3.98 (m, 1H), 3.63 (td, J = 9.1, 5.7 Hz, 1H), 2.54 (ddd, J = 12.6, 5.7, 3.2 Hz, 1H), 1.93 - 2.13 (m, 3H), 1.74 - 1.87 (m, 1H), 1.53 - 1.66 (m, 1H), 1.43 (s, 9H). Calculated for C13H21NO5: 294.1 (M+23); found: 294.1.

Step F

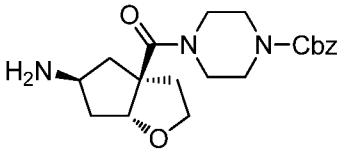
(benzyl 4-((3aS,5S,6aR)-5-((tert-butoxycarbonyl)amino)hexahydro-2H-cyclopenta[b]furan-3a-carbonyl)piperazine-1-carboxylate



The product of Step F was prepared from the reaction of the product of Step E and benzyl piperazine-1-carboxylate following the procedure from Example 1, Step C. Calculated for C25H35N3O6: 496.2 (M+23); found: 496.0.

Step G

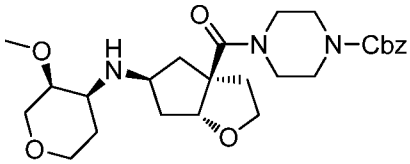
benzyl 4-((3aS,5S,6aR)-5-aminohexahydro-2H-cyclopenta[b]furan-3a-carbonyl)piperazine-1-carboxylate



The product of Step G was prepared from the reaction of the product of Step F following the procedure from Example 1, Step G. Calculated for C20H27N3O4: 374.2 (M+1); found: 374.2.

Step H

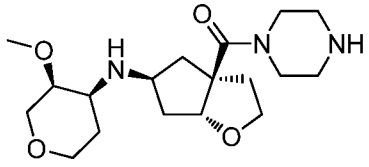
benzyl 4-((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-carbonyl)piperazine-1-carboxylate



The product of Step H was prepared from the reaction of the product of Step G and (R)-3-methoxydihydro-2H-pyran-4(3H)-one (Intermediate 1) following the procedure described in Example 1, Step H. Calculated for C26H37N3O6: 488.3 (M+1); found: 488.1.

Step I

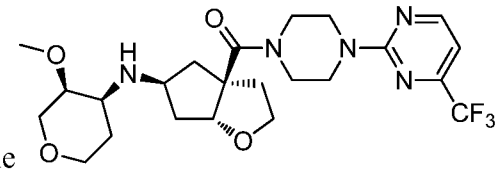
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(piperazin-1-yl)methanone



A solution of the product of Step H (405 mg, 0.83 mmol, 1 eq) and 5% Pd/C (100 mg) in ethanol (10 mL) at rt was placed under a balloon of hydrogen gas overnight. The suspension was filtered through celite, washed with methanol, and the filtrates concentrated to give the product of Step I as a gum. Calculated for C18H31N3O4: 354.2 (M+1); found: 354.2.

Step J

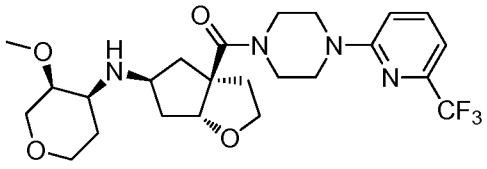
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)methanone



A solution of the product of Step I (40 mg, 0.11 mmol, 1 eq), DIEA (0.06 mL, 0.34 mmol, 3 eq) and 2-chloro-4-(trifluoromethyl)pyrimidine (0.04 mL, 0.34 mmol, 3 eq) in a mixture of 10:1 dioxane/DMSO (1 mL) in a vial under Ar was heated to 100 °C overnight. Water was added, the solution was extracted with DCM, the organics combined, dried over $MgSO_4$ and concentrated. Purification by chromatography (4 g column) eluting with 5 to 10% MeOH/DCM afforded the title compound of Example 23. ^{1}H NMR (CHLOROFORM-d) δ: 8.53 (d, J = 4.6 Hz, 1H), 6.83 (d, J = 4.9 Hz, 1H), 5.05 (d, J = 4.4 Hz, 1H), 4.10 (dd, J = 12.3, 2.8 Hz, 1H), 3.51 - 4.00 (m, 13H), 3.36 - 3.47 (m, 4H), 3.25 - 3.36 (m, 2H), 2.78 (dt, J = 10.2, 3.8 Hz, 1H), 2.34 (ddd, J = 12.3, 6.7, 3.3 Hz, 1H), 2.20 (dt, J = 13.0, 6.6 Hz, 2H), 2.01 (dt, J = 12.3, 8.3 Hz, 1H), 1.45 - 1.90 (m, 4H). Calculated for C23H32F3N5O4: 500.2 (M+1); found: 500.3.

Example 24

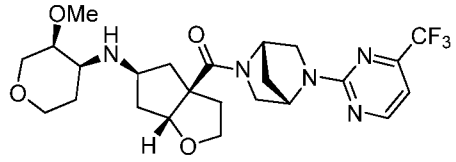
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(4-(6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methanone



The title compound of Example 24 was made by taking the product of Example 23 Step I and reacting with 2-chloro-6-(trifluoromethyl)pyridine following the procedure described in Example 23, Step J. ^{1}H NMR (CHLOROFORM-d) δ: 7.63 (t, J = 8.1 Hz, 1H), 7.01 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 5.05 (d, J = 4.4 Hz, 1H), 4.09 (dd, J = 12.3, 3.1 Hz, 1H), 3.96 (qd, J = 7.8, 3.5 Hz, 2H), 3.47 - 3.88 (m, 10H), 3.37 - 3.47 (m, 4H), 3.26 - 3.37 (m, 2H), 2.78 (dt, J = 10.2, 3.6 Hz, 1H), 2.34 (ddd, J = 12.2, 6.7, 3.4 Hz, 1H), 2.13 - 2.27 (m, 2H), 2.01 (dt, J = 12.3, 8.5 Hz, 1H), 1.60 - 1.88 (m, 4H), 1.54 (ddd, J = 13.1, 10.9, 4.8 Hz, 1H). Calculated for C24H33F3N4O4: 499.3 (M+1); found: 499.4.

Example 25

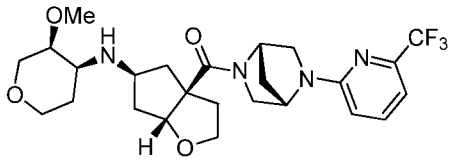
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)((1S,4S)-5-(4-(trifluoromethyl)pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)methanone



The title compound of Example 25 was made by taking the product of Example 23, Step E and reacting with (1S,4S)-N-Cbz-2,5-diaza-bicyclo[2.2.1]heptane following the procedure described in Example 23, Step F, and then following the procedures described in Example 23, Steps G through J. ^{1}H NMR (CHLOROFORM-d) δ: 8.50 (d, J = 4.4 Hz, 1H), 6.83 (d, J = 4.6 Hz, 1H), 4.70 - 5.20 (m, 3H), 4.07 (t, J = 10.1 Hz, 1H), 3.83 - 4.00 (m, 2H), 3.50 - 3.79 (m, 5H), 3.22 - 3.48 (m, 7H), 2.79 (d, J = 9.5 Hz, 1H), 1.82 - 2.30 (m, 7H), 1.40 - 1.82 (m, 4H). Calculated for C24H32F3N5O4: 512.2 (M+1); found: 512.3.

Example 26

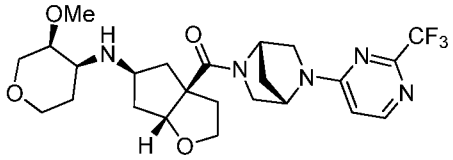
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)((1S,4S)-5-(6-(trifluoromethyl)pyridin-2-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)methanone



The title compound of Example 26 was made by taking the product of Example 23, Step E and reacting with (1S,4S)-N-Cbz-2,5-diaza-bicyclo[2.2.1]heptane following the procedure described in Example 23, Step F, then following the procedures described in Example 23, Steps G through I, and then reacting that product with 2-chloro-6-(trifluoromethyl)pyridine following the procedure described in Example 23, Step J. ^{1}H NMR (CHLOROFORM-d) δ: 7.56 (t, J = 7.9 Hz, 1H), 6.94 (dd, J = 7.0, 3.5 Hz, 1H), 6.40 - 6.57 (m, 1H), 4.65 - 5.18 (m, 3H), 4.05 (d, J = 12.5 Hz, 1H), 3.82 - 3.99 (m, 2H), 3.61 - 3.70 (m, 2H), 3.19 - 3.59 (m, 10H), 2.53 - 2.85 (m, 1H), 1.84 - 2.29 (m, 7H), 1.44 - 1.78 (m, 4H). Calculated for C25H33F3N4O4: 511.3 (M+1); found: 511.2.

Example 27

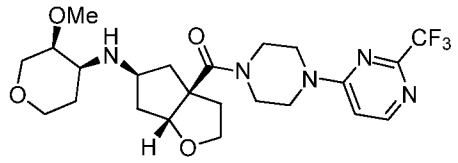
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)((1S,4S)-5-(2-(trifluoromethyl)pyrimidin-4-yl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)methanone



The title compound was made by taking the product of Example 23, Step E and reacting with (1S,4S)-N-Cbz-2,5-diaza-bicyclo[2.2.1]heptane following the procedure described in Example 23, Step F, then following the procedures described in Example 23, Steps G through I, and then reacting that product with 4-chloro-2-(trifluoromethyl)pyrimidine following the procedure described in Example 23, Step J. ^{1}H NMR (CHLOROFORM-d) δ: 8.27 - 8.43 (m, 1H), 6.24 - 6.60 (m, 1H), 5.25 - 5.48 (m, 1H), 4.50 - 5.23 (m, 2H), 4.07 (d, J = 12.2 Hz, 1H), 3.85 - 4.02 (m, 2H), 3.58 - 3.73 (m, 3H), 3.23 - 3.56 (m, 9H), 2.55 - 2.91 (m, 1H), 1.86 - 2.35 (m, 7H), 1.35 - 1.82 (m, 4H). Calculated for C24H32F3N5O4: 512.2 (M+1); found: 512.2.

Example 28

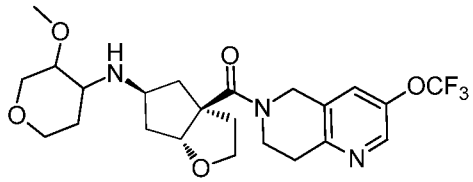
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(4-(2-(trifluoromethyl)pyrimidin-4-yl)piperazin-1-yl)methanone



The title compound was made by taking the product of Example 23, Step I and reacting with 4-chloro-2-(trifluoromethyl)pyrimidine following the procedure described in Example 23, Step J. ^{1}H NMR (CHLOROFORM-d) δ: 8.37 (d, J = 6.4 Hz, 1H), 6.63 (d, J = 6.1 Hz, 1H), 5.04 (d, J = 4.6 Hz, 1H), 4.10 (dd, J = 12.2, 2.7 Hz, 1H), 3.90 - 4.02 (m, 2H), 3.47 - 3.90 (m, 10H), 3.36 - 3.46 (m, 4H), 3.26 - 3.36 (m, 2H), 2.77 (dt, J = 10.1, 3.7 Hz, 1H), 2.32 (ddd, J = 12.1, 6.7, 3.4 Hz, 1H), 2.19 (td, J = 12.8, 6.2 Hz, 2H), 1.95 - 2.08 (m, 1H), 1.59 - 1.86 (m, 4H), 1.54 (ddd, J = 13.1, 11.1, 4.9 Hz, 1H). Calculated for C23H32F3N5O4: 500.2 (M+1); found: 500.2.

Example 29

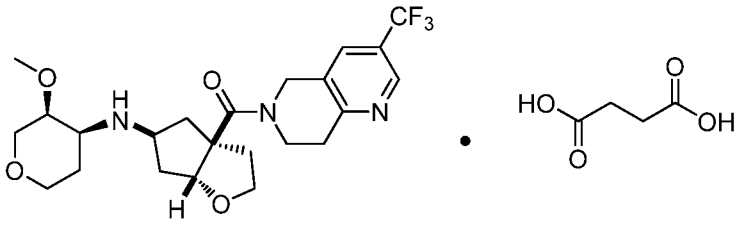
((3aS,5S,6aR)-5-((3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethoxy)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound was prepared from reaction of the product of Example 23, Step E and 3-(trifluoromethoxy)-5,6,7,8-tetrahydro-1,6-naphthyridine following the procedure described in Example 1, Step C, and then following procedures described in Example 1, Steps G and H. ^{1}H NMR (CHLOROFORM-d) δ: 8.40 (br. s., 1H), 7.35 (br. s., 1H), 5.05 (t, J = 4.3 Hz, 1H), 4.74 (br. s., 2H), 3.78 - 4.16 (m, 5H), 3.48 - 3.74 (m, 2H), 3.24 - 3.46 (m, 6H), 3.08 (br. s., 2H), 2.81 (t, J = 9.3 Hz, 1H), 2.17 - 2.40 (m, 3H), 1.91 - 2.12 (m, 3H), 1.53 - 1.88 (m, 3H). Calculated for C23H30F3N3O5: 486.2 (M+1); found: 486.1.

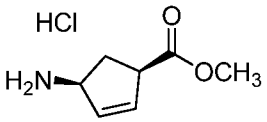
Example 30

((3aS,5S,6aR)-5-((3S,4S)-3-methoxytetrahydro-2H-pyran-4-ylamino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone succinate



Step A

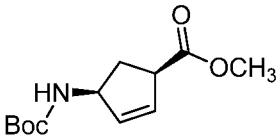
(1R, 4S)-methyl 4-aminocyclopent-2-enecarboxylate hydrochloride



A solution of (1*S*,4*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (725g, 6.64 mol) in MeOH (2.2 L) was stirred in an ice bath to 0 °C. Thionyl chloride (290 mL, 3.99 mol) was added dropwise over a 2.25 h period while keeping the temperature below 13 °C. The reaction was stirred for 2 h at 8 °C. Isopropyl acetate (16.3 L) was added and the slurry stirred for 1 h. The solid was filtered with a Buchner funnel, washed with isopropylacetate (~1 L) and the solid was allowed to air-dry overnight to afforde an off-white solid. ^{1}H NMR (400MHz ,DMSO-d_6) δ = 8.44 (br. s., 3 H), 5.99 - 6.16 (m, 1 H), 5.90 (dt, *J* = 2.4, 5.3 Hz, 1 H), 4.17 (br. s., 1 H), 3.56 - 3.79 (m, 4 H), 2.56 (m, 1 H), 1.84 - 2.04 (m, 1 H).

Step B

(1R, 4S)-methyl 4-(tert-butoxycarbonylamino)cyclopent-2-enecarboxylate

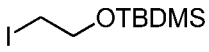


A solution of the product of Step A (551 g, 3.10 mol), CH_2Cl_2 (15.5 L), and di-t-butyldicarbonate (684 g, 3.10 mol) was stirred to 2 °C with an ice bath. Triethylamine (435 mL, 3.12 mol) was added over 1 h 5 min at a rate not to exceed 3 °C. The reaction was stirred for 2 h. The volatiles were evaporated, the crude product was suspended in a mixture of EtOAc and heptane, the solid was filtered through silica gel, and washed with

additional EtOAc in heptane. The organics were evaporated and afforded the product of Step B as a brown solid. ^{1}H NMR (400MHz,) δ = 5.87 (d, *J* = 6.4 Hz, 2 H), 4.85 - 5.02 (m, 1 H), 4.72 - 4.85 (m, 1 H), 3.72 (s, 3 H), 3.47 (m, 1 H), 2.51 (d, *J* = 13.9 Hz, 1 H), 1.88 (s, 1 H), 1.44 (s, 10 H).

Step C

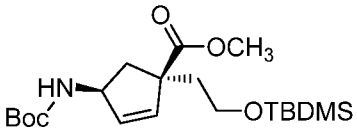
(1,1-dimethylethyl)(2-iodoethoxy)dimethylsilane



Iodoethanol (2.68 kg, 15.4 mol), CH_2Cl_2 (12 L) and imidizaole (1.556 kg, 22.63 mol) were chilled in an ice bath. A solution of t-butyldimethylchlorosilane (2.536 kg, 16.32 mol) in CH_2Cl_2 (2.5 L) was added to the reaction over a 2 h period. The resulting white suspension was allowed to warm to rt over an 18 h. The reaction was worked up by washing with water and brine). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to provide the product of Step C as a light yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ = 3.75 (t, *J* = 7.0 Hz, 2 H), 3.11 (t, *J* = 7.0 Hz, 2 H), 0.77 - 0.89 (m, 10 H), 0.00 (s, 6 H).

Step D

(1S,4S)-methyl 4-(tert-butoxycarbonylamino)-1-(2-(tert-butyldimethylsilyloxy)ethyl)cyclopent-2-enecarboxylate

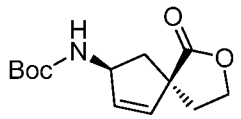


To a -70 °C solution of LiHMDS in THF (1M, 6.97 L, 6.97 mol) was added a solution of the product of Step B (763.5 g, 3.16 mol) in THF (800 mL) over a 2 h period while keeping the temperature at or below -68 °C. The resulting solution was stirred for 45 min at -68 °C. A solution of the product of Step C (1.267 kg, 4.426 mol) in THF (800 mL) was added over 1 h 50 min period while maintaining a temperature of ~ -66 °C. The reaction was stirred at ~-66 °C for 45 min. The reaction was warmed to -15 °C and worked up by addition to mixture of aqueous HCl and ice. The mixture was extracted with toluene, the organic layer was washed with water, brine and dried over $MgSO_4$. The organic layer was concentrated and purified on silica gel using a mixture of EtOAc in heptanes to provide the product of Step D as a clear oil. ^{1}H NMR (400MHz ,CHLOROFORM-d) d = 5.69 - 5.86 (m, 2 H), 4.79 - 4.93 (m, 1 H), 4.68 - 4.80 (m, 1 H), 3.67 (s, 3 H), 3.53 - 3.62 (m, 2

H), 2.16 - 2.30 (m, 1 H), 2.04 - 2.16 (m, 2 H), 1.70 - 1.81 (m, 1 H), 1.41 (s, 9 H), 0.78 - 0.91 (m, 13 H), 0.00 (s, 6 H).

Step E

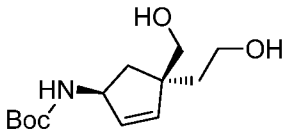
tert-Butyl (5S,7S)-1-oxo-2-oxaspiro[4.4]non-8-en-7-ylcarbamate



To a solution of the product of Step D (1149 g, 2.875 mol) and THF (5.75 L) was added TBAF (1M in THF, 2.875 L) over ~1 h. The reaction was stirred for 1 h at rt, and diluted with EtOAc. The organic layer was washed with brine, diluted with heptanes and the organic layer was further washed with water and brine. The organic layer was evaporated, the crystallized product was filtered, and washed with heptanes to provide the product of Step E as a white solid. ^{1}H NMR (400MHz ,CHLOROFORM-d) d = 5.86 - 5.98 (m, 3 H), 5.67 (d, *J* = 5.4 Hz, 3 H), 5.03 - 5.20 (m, 2 H), 4.76 - 4.87 (m, 3 H), 4.28 (t, *J* = 7.0 Hz, 5 H), 2.08 - 2.31 (m, 8 H), 1.99 (d, *J* = 2.4 Hz, 3 H), 1.34 (s, 25 H).

Step F

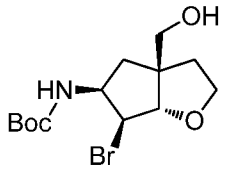
tert-butyl ((1S,4S)-4-(2-hydroxyethyl)-4-(hydroxymethyl)cyclopent-2-en-1-yl)carbamate



To a solution of the product of Step E (255.9 g, 1.01 mol) and MeOH (2 L) chilled to 2 °C was added $NaBH_4$ (75 g) over ~ 2.5 h. The reaction was quenched by addition of aqueous NH_4Cl, concentrated under reduced pressure and the mixture was diluted with water and EtOAc. The layers were separated and the aqueous layer was extracted with additional EtOAc. The combined organics were washed with brine, dried ($MgSO_4$) and evaporated to give the product of Step F as a thick oil. ^{1}H NMR (400MHz ,CHLOROFORM-d) d = 5.74 (d, *J* = 2.0 Hz, 2 H), 4.81 - 4.92 (m, 1 H), 4.67 - 4.79 (m, 1 H), 3.71 (t, *J* = 6.1 Hz, 2 H), 3.50 (d, *J* = 11.7 Hz, 2 H), 2.14 - 2.28 (m, 2 H), 1.70 (td, *J* = 1.6, 6.2 Hz, 4 H), 1.52 - 1.60 (m, 1 H), 1.44 (s, 9 H)

Step G

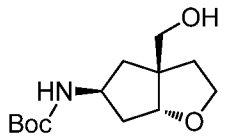
tert-butyl (3aR,5S,6S,6aS)-6-bromo-3a-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-5-ylcarbamate



To a chilled solution of the product of Step F (343.60 g) in EtOAc (4 L) was added N-bromosuccinimide (237.60 g) followed by stirring at rt for 18 h. To the mixture was added water (5 mL) and the reaction heated to 60 °C for 30 min. The reaction was filtered, the filtrate was washed with aqueous sodium thiosulfate until the organic layer was negative for peroxides. The organic layer was washed with aqueous Na_2CO_3 (10%), dried (Na_2SO_4) and the reaction was concentrated under reduced pressure. Near the end of the concentration, heptane (1.2 L) was added, and the product was collected by filtration to provide the product of Step G. ^{1}H NMR (400MHz ,CHLOROFORM-d) δ = 4.78 - 4.91 (m, 1 H), 4.41 (br. s., 1 H), 4.31 (s, 2 H), 3.88 - 3.98 (m, 1 H), 3.61 - 3.77 (m, 3 H), 2.08 - 2.24 (m, 1 H), 1.82 (m, 2 H), 1.60 - 1.70 (t, 1 H), 1.45 (s, 9 H)

Step H

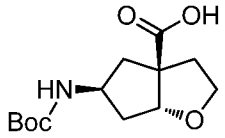
tert-Butyl (3aR,5S,6aR)-3a-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-5-ylcarbamate



A solution of the product of Step G (83 g, 0.245 mol), 10% Pd on C (12.5 g), triethylamine (69 mL, 0.49 mol, 2 eq.) in EtOAc (830 mL) was shaken on a PAAR hydrogenator at 40 psi for 3.5 h until the pressure remained constant. The reaction was filtered with celite, the filter cake was washed with EtOAc, and the collected filtrate was washed with aqueous HCl (1N), brine, dried (Na_2SO_4) and concentrated under reduced pressure to give the product of Step H. ^{1}H NMR (400MHz, CHLOROFORM-d) d = 4.60 - 4.73 (m, 1 H), 4.06 - 4.24 (m, 3 H), 3.84 - 3.93 (m, 1 H), 3.52 - 3.67 (m, 4 H), 2.12 - 2.21 (m, 1 H), 1.98 - 2.04 (m, 1 H), 1.90 (br. s., 3 H), 1.70 - 1.78 (m, 1 H), 1.46 - 1.56 (m, 3 H), 1.44 (s, 11 H).

Step I

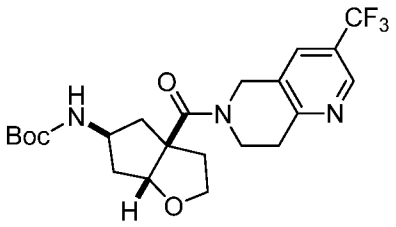
(3aS,5S,6aR)-5-(tert-Butoxycarbonylamino)hexahydro-2H-cyclopenta[b]furan-3a-carboxylic acid



To an ice-cold solution of the product of Step H (426 g, 1.57 mol) and acetone (8.1 L) was added Jones reagent (710 mL) over 1 h 20 min. The resulting suspension was stirred at rt for 1 h, after which isopropyl alcohol (40 mL) was added, and the reaction stirred for 25 min at rt. Water was added, and the water/acetone was decanted off and evaporated. The insoluble material was dissolved separately in water and extracted with CH_2Cl_2. The green water/acetone concentrate was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, diluted with water and EtOAc and the organic layer was dried with Na_2SO_4. The organic layer was filtered, concentrated and the product was crystallized from MeCN, and the product of Step I was isolated by filtration as a white solid. ^{1}H NMR (400MHz ,DMSO-d_6) d = 12.39 - 12.59 (m, 1 H), 6.85 - 7.02 (m, 1 H), 4.28 (d, *J* = 5.4 Hz, 1 H), 3.89 - 3.97 (m, 1 H), 3.79 - 3.85 (m, 1 H), 3.43 - 3.51 (m, 1 H), 3.30 - 3.36 (m, 1 H), 2.35 - 2.42 (m, 1 H), 1.90 (d, *J* = 11.0 Hz, 3 H), 1.59 - 1.70 (m, 1 H), 1.42 - 1.50 (m, 1 H), 1.37 (s, 9 H) . Elemental anal calc for C13H21NO5: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.34; H, 8.18; N, 5.08 mp: 147.4-149.1 °C

Step J

tert-Butyl (3aS,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-ylcarbamate

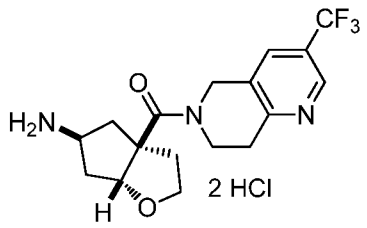


To a solution of the product of Step I (596.8 g, 1.91 mol) in CH_2Cl_2 was added EDC (98.5% pure, 559 g, 2.87 mol) and HOBt (449 g, 3.26 mol) and the suspension was stirred for 15 min at rt. 3-(Trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-2 HCl (790 g, 2.87 mol) was added, followed by DIEA (1.7 L, 9.65 mol) by addition over 45 min. The

reaction was stirred at rt for 20 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was removed, the aqueous layer diluted with water and the aqueous layer extracted with CH_2Cl_2. The combined organics were washed with ½ saturated brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by chromatography using EtOAc in heptane to provide the product of Step J as a thick orange foam. ^{1}H NMR (400MHz ,CHLOROFORM-d) d = 8.72 (s, 1 H), 7.71 (s, 1 H), 5.00 - 5.08 (m, 1 H), 4.77 (br. s., 2 H), 4.61 - 4.68 (m, 1 H), 4.21 - 4.34 (m, 1 H), 3.96 - 4.05 (m, 1 H), 3.85 - 3.93 (m, 2 H), 3.71 (s, 1 H), 3.13 (br. s., 2 H), 2.38 - 2.48 (m, 1 H), 2.28 - 2.33 (m, 1 H), 2.20 - 2.26 (m, 1 H), 2.09 - 2.17 (m, 1 H), 1.75 - 1.85 (m, 1 H), 1.61 - 1.70 (m, 1 H), 1.40 (s, 9 H).

Step K

((3aS,5S,6aR)-5-Aminohexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone dihydrochloride

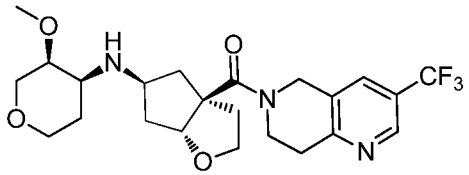


A solution of the product of Step J (773 g, 1.61 mol) and HCl in MeOH (~1.25 M, 14.25 L, 17.81 mol) was heated to 60 °C and after the vigorous bubbling ceased, the reaction was concentrated under reduced pressure. Isopropyl alcohol was added, the contents were evaporated to near-dryness and heptane was added to the flask. The contents were filtered, washed with some isopropyl alcohol/heptane (*ad lib*) and the solid was dried in air, followed by drying in a vacuum oven to afford the product of Step K as an ivory solid. A small sample of the product was converted to the free-based using 1,2-dichloroethane/aqueous 3M NaOH for further analysis by NMR and elemental analysis. Elemental analysis calc for $C_{17}H_{20}F_3N_3O_2$ x 1.6 H_2O: C, 53.14; H, 6.09; F, 14.83; N, 10.93; H_2O = 7.50. Found: C, 52.30; H, 5.78; F, 14.62; N, 10.51; KF = 7.28. ^{1}H NMR (400MHz ,CHLOROFORM-d) δ = 8.72 (s, 1 H), 7.70 (br. s., 1 H), 5.06 (d, *J* = 4.9 Hz, 1 H), 4.78 (s, 2 H), 3.85 - 4.03 (m, 3 H), 3.71 - 3.75 (m, 2 H), 3.59 - 3.70 (m, 2 H), 3.08 -

3.19 (m, 2 H), 2.24 - 2.38 (m, 2 H), 2.19 (dd, *J* = 5.7, 13.3 Hz, 1 H), 2.08 (br. s., 1 H), 1.62 - 1.78 (m, 1 H), 1.46 - 1.57 (m, 1 H), 1.42 (br. s., 3 H)

Step L

((3aS,5S,6aR)-5-((3S,4S)-3-Methoxytetrahydro-2H-pyran-4-ylamino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

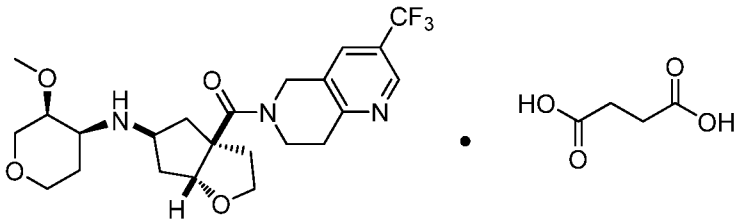


To a mixture of the product of Step K (the free base) (619.7 g, 1.74 mol) in 1,2-dichloroethane/ CH_2Cl_2 (~10 L) was added acetic acid (glacial, 180 mL) and the mixture was cooled to 16 °C. Solid $Na(OAc)_3BH$ (463 g, 2.18 mol) was added and the suspension was stirred for 5-10 min. A solution of (R)-3-methoxydihydro-2H-pyran-4(3H)-one (prepared as described in Intermediate 1, 213 g, 1.63 mol) in 1,2-dichloroethane (1.75 L) was added over 20 min and the resulting mixture was stirred at rt overnight. Additional acetic acid, (R)-3-methoxytetrahydro-4H-pyran-4-one (28 g) and $Na(AcO)_3BH$ were added until TLC showed the reaction was complete. The reaction was quenched with saturated aqueous $NaHCO_3$, the organic layer was separated and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. Purification was affected by chromatography with MeOH (7N NH_3) in CH_2Cl_2. The collected enriched isomer was further purified using chiral chromatography on chiralpak AD column using a mixture of heptanes/EtOH/isopropyl alcohol to provide the product of Step L.

^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.70 (br. s., 1H), 5.05 (d, J = 4.6 Hz, 1H), 4.70 - 4.87 (m, 2H), 4.09 (dd, J = 12.5, 2.7 Hz, 1H), 3.81 - 4.03 (m, 4H), 3.62 - 3.71 (m, 1H), 3.50 - 3.62 (m, 1H), 3.35 - 3.46 (m, 4H), 3.24 - 3.35 (m, 2H), 3.14 (t, J = 4.9 Hz, 2H), 2.71 - 2.82 (m, 1H), 2.14 - 2.43 (m, 3H), 1.99 - 2.13 (m, 1H), 1.46 - 1.86 (m, 5H). Calculated for C24H31F3N2O4: 470.2 (M+1); found: 470.1.

Step M

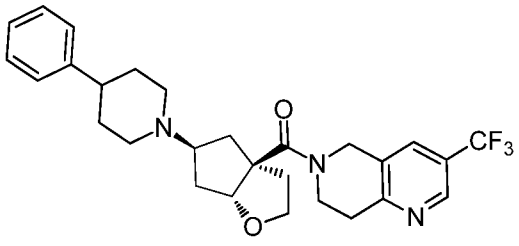
((3aS,5S,6aR)-5-((3S,4S)-3-methoxytetrahydro-2H-pyran-4-ylamino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone succinate



A solution of Example 30, Step L (608 g, 1.18 mol) in MeOH (6 L) was warmed to 40 °C until dissolved. Succinic acid (141.9 g, 1.20 mol) was added and the suspension was warmed to 50 °C which caused everything to dissolve. Darco G-60 charcoal (80 g) was added and the contents swirled for 20 min. The mixture was filtered through Celite, washed with MeOH, and the solvent was evaporated under reduced pressure to provide the title compound (i.e., the succinate salt) as an amorphous foam. The resulting foam was dissolved completely in MIBK (5 L, degassed) at reflux, the heating was stopped and the solution was allowed to cool. The solution was seeded at 104 °C with crystalline material, prepared as described in Example 52, and the solution was cooled to 38 °C over 4 h. The suspension was chilled to 4 °C, filtered, washed with ice-cold 100 mL MIBK and the solid was allowed to dry under a positive nitrogen stream (protected from light) overnight. After some light milling, the product of Step M was collected as a white solid. ^{1}H NMR (400MHz ,MeOD) δ = 8.72 (s, 1 H), 8.04 - 8.12 (m, 1 H), 4.97 (d, *J* = 4.4 Hz, 1 H), 4.94 (s, 3 H), 4.86 (s, 2 H), 4.18 - 4.28 (m, 1 H), 3.98 (d, *J* = 11.7 Hz, 4 H), 3.74 - 3.88 (m, 1 H), 3.62 - 3.73 (m, 1 H), 3.28 - 3.58 (m, 8 H), 3.12 - 3.23 (m, 2 H), 2.58 - 2.68 (m, 1 H), 2.37 - 2.44 (m, 1 H), 2.28 - 2.36 (m, 1 H), 1.88 (m, 4 H). Elemental Analysis calc for C27H36F3N3O8 x 0.2 H_2O: C, 54.85; H, 6.21; F, 9.64; N, 7.11; KF 0.61; Found: C, 55.17; H, 6.07; F, 9.99; N, 7.11; KF, 0.64.

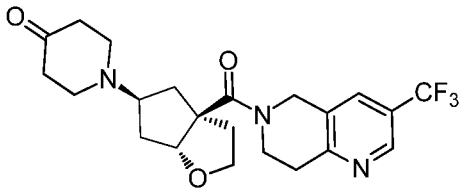
Example 31

((3aS,5S,6aR)-5-(4-phenylpiperidin-1-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

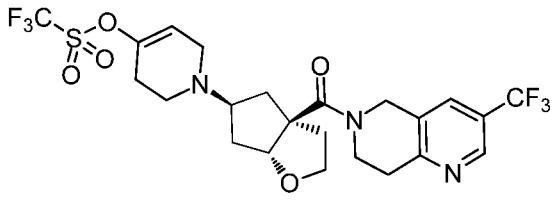
1-((3aS,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)piperidin-4-one



To a suspension of sodium carbonate (2.2 g, 20.7 mmol, 5 eq) in methanol (70 mL) at 60 °C were added solutions of the product of Example 1, Step G (1.77 g, 4.14 mmol, 1 eq) in methanol (35 mL) 1,5-dichloropentan-3-one (0.74 g, 4.55 mmol, 1.1 eq) in methanol (35 mL) simultaneously over 1 hour. After stirring 1 hr at 60 °C, the suspension was cooled to rt, water was added, the methanol was concentrated, and the aqueous extracted with DCM, dried over $MgSO_4$ and concentrated. Purification by chromatography eluting with 2 to 6% MeOH/DCM afforded the title compound of Step A. Calculated for C22H26F3N3O3: 438.2 (M+1); found: 438.2.

Step B

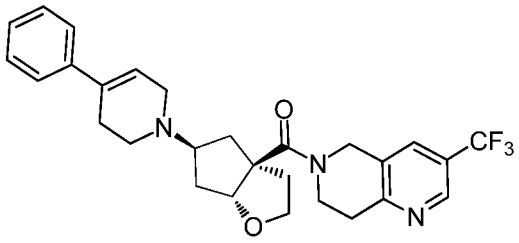
1-((3aS,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate



To the product of Step A (1.06 g, 2.42 mmol, 1 eq) in THF (30 mL) at -78 °C under N_2 was added KHMDS (6.8 mL of a 0.5 M solution in toluene, 3.39 mmol, 1.4 eq), the solution turned purple. After 15 minutes, a solution of N-phenyl-bis(trifluoromethanesulfonimide) (1.21 g, 3.39 mmol, 1.4 eq) in THF (10 mL) was added and the yellow solution stirred 1 hour at -78 °C. Saturated NH_4Cl was added, the aqueous extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. Purification by column chromatography (80g) eluting with 3 to 6% MeOH/ DCM afforded the title compound of Step B. Calculated for C23H25F6N3O5S: 570.1 (M+1); found: 570.0.

Step C

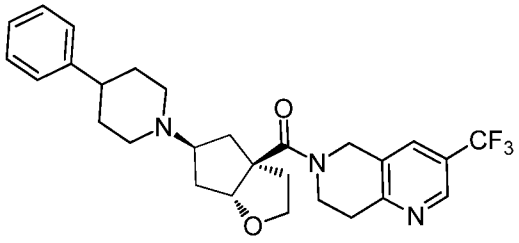
((3aS,5S,6aR)-5-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



A solution of the product of Step B (50 mg, 0.09 mmol, 1 eq), phenylboronic acid (22 mg, 0.18 mmol, 2 eq), $(Ph_3P)_4Pd$ (10 mg, 0.009 mmol, 0.1 eq) and 2 M Na_2CO_3 (0.1 mL) in dimethoxyethane (1 mL) under N_2 was warmed to 80C in a screw-top vial overnight. The solution was cooled to rt, and concentrated. Purification by column chromatography (4 g) eluting with 50 to 100% ethyl acetate/heptane afforded the title compound of Step C. Calculated for C28H30F3N3O2: 498.2 (M+1); found: 498.3.

Step D

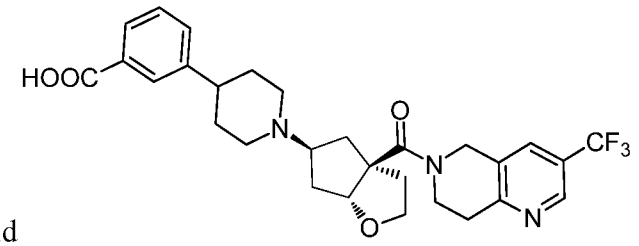
((3aS,5S,6aR)-5-(4-phenylpiperidin-1-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



A suspension of the product of Step D (24 mg, 0.046 mmol, 1 eq) and 5% Pd/C (20 mg) in ethanol (3 mL) was placed under a balloon of hydrogen gas overnight. The solution was filtered through celite and concentrated. Purification by column chromatography (4 g) eluting with 2 to 6% MeOH/DCM afforded the title compound. ^{1}H NMR (CHLOROFORM-d) δ: 8.71 (s, 1H), 7.70 (br. s., 1H), 7.27 - 7.33 (m, 2H), 7.15 - 7.24 (m, 3H), 5.06 (d, J = 4.5 Hz, 1H), 4.78 (br. s., 2H), 4.02 (td, J = 8.1, 3.5 Hz, 1H), 3.81 - 3.96 (m, 2H), 3.61 - 3.73 (m, 1H), 2.90 - 3.21 (m, 5H), 2.45 - 2.57 (m, 1H), 2.22 - 2.32 (m, 2H), 2.08 – 2.15 (m, 3H), 1.99 (br. s., 2H), 1.65 - 1.89 (m, 5H). Calculated for C28H32F3N3O2: 500.2 (M+1); found: 500.3.

Example 32

3-(1-((3aS,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)piperidin-4-yl)benzoic

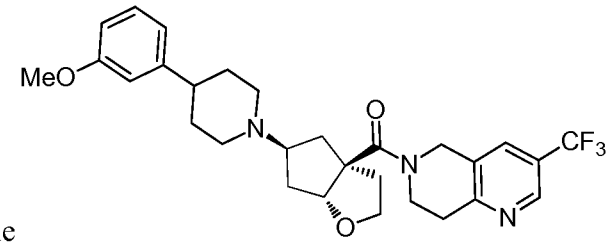


acid

The title compound of Example 32 was made by taking the product of Example 31, Step B and reacting with 3-carboxyphenylboronic acid following the procedure described in Examle 31, Step C, then following the procedures described in Example 31, Step D. Calculated for C29H32F3N3O4: 544.2 (M+1); found: 544.0.

Example 33

((3aS,5S,6aR)-5-(4-(3-methoxyphenyl)piperidin-1-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-

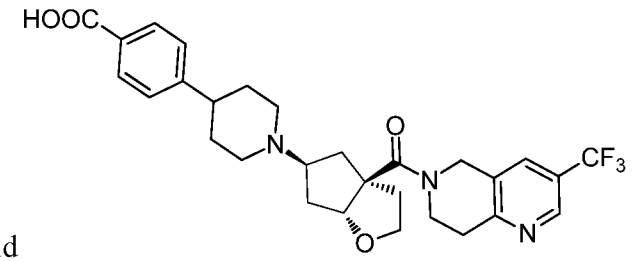


yl)methanone

The title compound of Example 33 was made by taking the product of Example 31, Step B and reacting with 3-methoxyphenylboronic acid following the procedure described in Examle 31, Step C, then following the procedures described in Example 31, Step D. Calculated for C29H34F3N3O3: 530.3 (M+1); found: 530.3.

Example 34

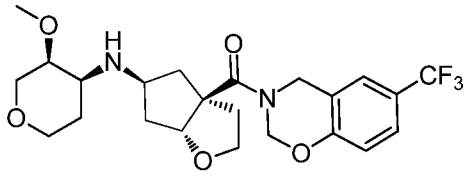
4-(1-((3aS,5S,6aR)-3a-(3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)piperidin-4-yl)benzoic acid



The title compound of Example 34 was made by taking the product of Example 31, Step B and reacting with 4-benzyloxycarbonylphenylboronic acid following the procedure described in Examle 31, Step C, then following the procedures described in Example 31, Step D. ^{1}H NMR (CHLOROFORM-d) δ: 8.68 (s, 1H), 7.79 - 7.88 (m, J = 8.1 Hz, 2H), 7.60 (br. s., 1H), 7.09 - 7.21 (m, J = 8.6 Hz, 2H), 5.01 (d, J = 4.0 Hz, 1H), 4.67 - 4.78 (m, 1H), 4.51 - 4.67 (m, 1H), 4.02 (br. s., 1H), 3.63 - 3.96 (m, 3H), 3.34 - 3.54 (m, 3H), 3.23 (d, J = 11.6 Hz, 1H), 3.09 (br. s., 1H), 2.56 - 2.70 (m, 2H), 2.27 - 2.50 (m, 5H), 1.84 - 2.20 (m, 6H). Calculated for C29H32F3N3O4: 544.2 (M+1); found: 544.2.

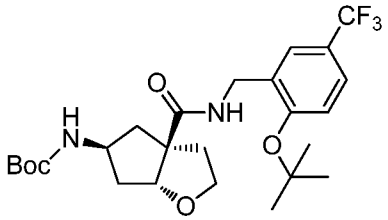
Example 35

((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(6-(trifluoromethyl)-2H-benzo[e][1,3]oxazin-3(4H)-yl)methanone



Step A

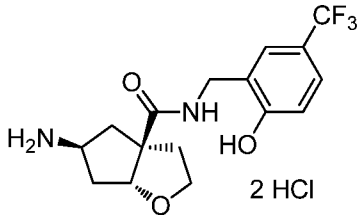
tert-butyl ((3aS,5S,6aR)-3a-((2-(tert-butoxy)-5-(trifluoromethyl)benzyl)carbamoyl)hexahydro-2H-cyclopenta[b]furan-5-yl)carbamate



The product of Step A was prepared from the reaction of the product of Example 23, Step E and (2-(tert-butoxy)-5-(trifluoromethyl)phenyl)methanamine prepared according to procedures in ACS Med. Chem. Letters 2010, 1, 14 following the procedure from Example 1, Step C. Calculated for C25H35F3N2O5: 523.2 (M+23); found: 523.2.

Step B

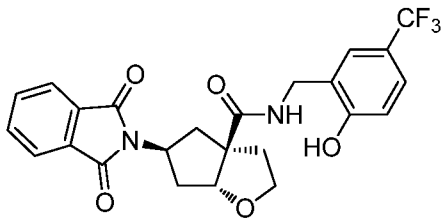
(3aS,5S,6aR)-5-amino-N-(2-hydroxy-5-(trifluoromethyl)benzyl)hexahydro-2H-cyclopenta[b]furan-3a-carboxamide dihydrochloride



A solution of the product of Step A (11.07 g, 20.57 mmol, 1 eq) in methanol (60 mL) and solution of HCl in methanol (82 mL of 1.25 M solution, 103 mmol, 5 eq) was heated to 55 °C for 2.5 days. The solution was concentrated to give the product of step B. Calculated for C16H19F3N2O3: 345.1 (M+1); found: 345.3.

Step C

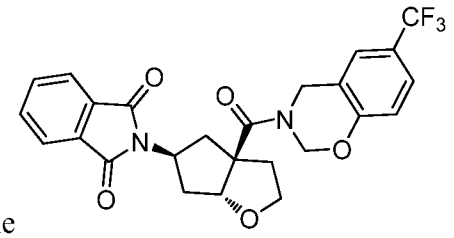
(3aS,5S,6aR)-5-(1,3-dioxoisoindolin-2-yl)-N-(2-hydroxy-5-(trifluoromethyl)benzyl)hexahydro-2H-cyclopenta[b]furan-3a-carboxamide



A solution of the product of Step B (8.58 g, 18.74 mmol, 1 eq), phthalic anhydride (5.55 g, 37.5 mmol, 2 eq) and DIEA (11.3 mL, 55.6 mmol, 3.5 eq) in chloroform (150 mL) was heated to 70 °C for 2 hours. The solution was cooled to rt and carbonyl diimidazole (2.24 g 13.82 mmol, 3 eq) was added and the solution heated to 60 °C for 2 hours. The solution was cooled to rt, 1 N HCl was added, the aqueous extracted with DCM, the organics combined, dried over MgSO4 and concentrated. Purification by chromatography (200 g column) eluting with 30 to 60 to 80% EA/heptane afforded the product of Step C. Calculated for C24H21F3N2O5: 474.1 (M+1); found: 475.1.

Step D

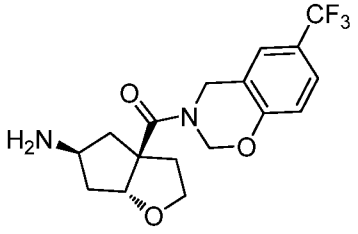
2-((3aS,5S,6aR)-3a-(6-(trifluoromethyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-3-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)isoindoline-1,3-dione



A solution of the product of Step C (7.97 g, 15.5 mmol, 1 eq), paraformaldehyde (9.28 g, 310 mmol, 20 eq) and p-toluenesulfonic acid hydrate (2.94 g, 15.5 mmol, 1 eq) in toluene (300 mL) was heated to 130 °C for 18 hours in a flask equipped with a Dean-Stark trap. The solution was cooled to rt and concentrated. Purification by chromatography (200 g column) eluting with 25 to 60 to 100% ethyl acetate/heptane afforded the product of Step D. Calculated for C25H21F3N2O5: 487.1 (M+1); found: 487.2.

Step E

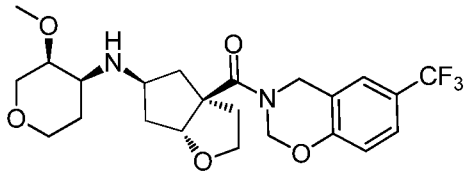
((3aS,5S,6aR)-5-aminohexahydro-2H-cyclopenta[b]furan-3a-yl)(6-(trifluoromethyl)-2H-benzo[e][1,3]oxazin-3(4H)-yl)methanone



A solution of the product of Step D (5.39 g, 11.1 mmol, 1 eq) and hydrazine (7.1 mL, 222 mmol, 20 eq) in ethanol (60 mL) was stirred at rt 18 hours. The white solid was filtered, washed with methanol and DCM, and the filtrates concentrated. Saturated $NaHCO_3$ was added, the aqueous extracted with DCM, the organics combined, dried over $MgSO_4$ and concentrated to afford the product of Step E. Calculated for C17H19F3N2O3: 357.1 (M+1); found: 357.3.

Step F

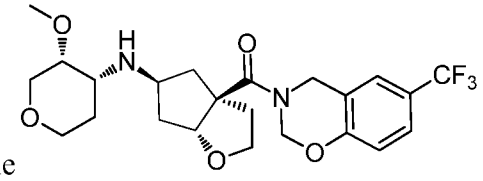
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(6-(trifluoromethyl)-2H-benzo[e][1,3]oxazin-3(4H)-yl)methanone



The title compound was prepared from the reaction of the product of Step E and (R)-3-methoxydihydro-2H-pyran-4(3H)-one (Intermediate 1) following the procedure described in Example 1, Step H. ^{1}H NMR (CHLOROFORM-d) δ: 7.42 (d, J = 8.6 Hz, 1H), 7.36 (br. s., 1H), 6.95 (d, J = 8.1 Hz, 1H), 5.43 (br. s., 2H), 4.96 - 5.11 (m, 1H), 4.82 (br. s., 2H), 3.84 - 4.15 (m, 3H), 3.68 (d, J = 7.1 Hz, 1H), 3.55 (br. s., 1H), 3.32 - 3.45 (m, 4H), 3.20 - 3.32 (m, 2H), 2.69 - 2.84 (m, 1H), 2.39 (br. s., 1H), 2.12 - 2.25 (m, 2H), 1.99 - 2.12 (m, 1H), 1.78 - 1.99 (m, 1H), 1.46 - 1.78 (m, 4H). Calculated for C23H29F3N2O5: 471.2 (M+1); found: 471.2.

Example 36

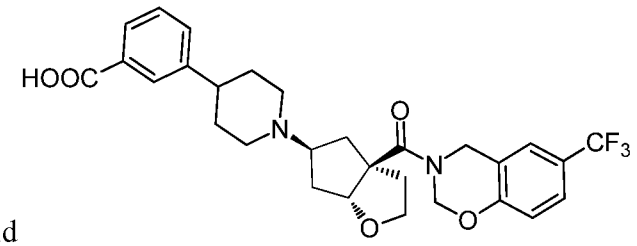
((3aS,5S,6aR)-5-(((3R,4R)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(6-(trifluoromethyl)-2H-benzo[e][1,3]oxazin-3(4H)-yl)methanone



The title compound was prepared from the reaction of the product of Step E and (S)-3-methoxydihydro-2H-pyran-4(3H)-one following the procedure described in Example 1, Step H. ^{1}H NMR (CHLOROFORM-d) δ: 7.42 (d, J = 8.6 Hz, 1H), 7.36 (br. s., 1H), 6.96 (d, J = 8.6 Hz, 1H), 5.35 - 5.49 (m, 2H), 5.05 (d, J = 5.1 Hz, 1H), 4.74 - 4.90 (m, 2H), 4.05 (dd, J = 12.6, 3.5 Hz, 1H), 3.94 - 4.01 (m, 1H), 3.91 (dt, J = 11.4, 3.7 Hz, 1H), 3.61 - 3.71 (m, 1H), 3.48 - 3.60 (m, 1H), 3.24 - 3.41 (m, 6H), 2.78 (dd, J = 6.3, 3.8 Hz, 1H), 2.39 (br. s., 1H), 2.19 (td, J = 12.1, 6.1 Hz, 2H), 2.05 (dt, J = 12.3, 8.3 Hz, 1H), 1.89 (br. s., 1H), 1.43 - 1.75 (m, 4H). Calculated for C23H29F3N2O5: 471.2 (M+1); found: 471.2.

Example 37

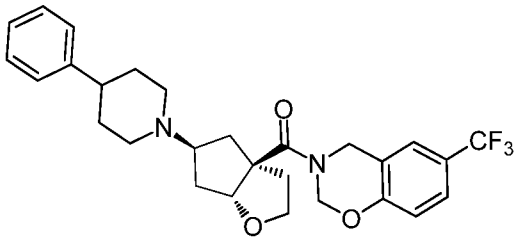
3-(1-((3aS,5S,6aR)-3a-(6-(trifluoromethyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-3-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)piperidin-4-yl)benzoic acid



The title compound of Example 37 was made by taking the product of Example 35, Step E following the procedures described in Example 31, Steps A and B, then reacting that product with 3-benzyloxycarbonylphenylboronic acid following the procedure described in Example 31, Step C, then following the procedure described in Example 31, Step D. ^{1}H NMR (CHLOROFORM-d) δ: 8.04 (s, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.32 - 7.43 (m, 2H), 7.19 - 7.32 (m, 2H), 6.93 (d, J = 8.3 Hz, 1H), 5.16 - 5.66 (m, 2H), 5.06 (d, J = 4.2 Hz, 1H), 4.96 (d, J = 16.9 Hz, 1H), 4.72 (d, J = 16.9 Hz, 1H), 3.96 - 4.11 (m, 1H), 3.55 - 3.75 (m, 2H), 3.47 (s, 1H), 3.29 - 3.45 (m, 2H), 2.59 - 2.80 (m, 2H), 2.35 - 2.59 (m, 5H), 2.30 (dd, J = 12.8, 5.7 Hz, 1H), 2.13 - 2.24 (m, 1H), 1.99 - 2.13 (m, 2H), 1.92 (d, J = 11.7 Hz, 1H), 1.82 (d, J = 13.4 Hz, 1H). Calculated for C29H31F3N2O5: 545.2 (M+1); found: 545.2.

Example 38

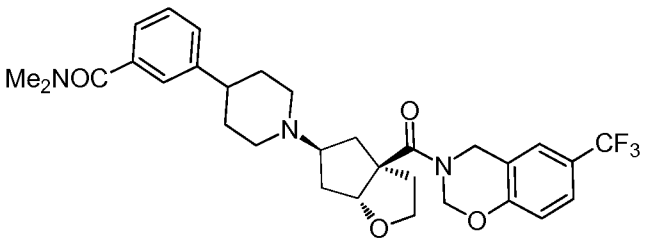
((3aS,5S,6aR)-5-(4-phenylpiperidin-1-yl)hexahydro-2H-cyclopenta[b]furan-3a-yl)(6-(trifluoromethyl)-2H-benzo[e][1,3]oxazin-3(4H)-yl)methanone



The title compound of Example 38 was made by taking the product of Example 35, Step E following the procedures described in Example 31, Steps A through D. ^{1}H NMR (CHLOROFORM-d) δ: 7.42 (d, J = 8.6 Hz, 1H), 7.37 (br. s., 1H), 7.29 (t, J = 7.5 Hz, 2H), 7.15 - 7.24 (m, 3H), 6.96 (d, J = 8.6 Hz, 1H), 5.42 (br. s., 2H), 5.03 (d, J = 4.6 Hz, 1H), 4.69 - 4.95 (m, 2H), 3.95 - 4.07 (m, 1H), 3.60 - 3.73 (m, 1H), 3.04 (br. s., 3H), 2.32 - 2.56 (m, 2H), 2.19 - 2.31 (m, 2H), 1.89 - 2.17 (m, 4H), 1.53 - 1.89 (m, 6H). Calculated for C28H31F3N2O3: 501.2 (M+1); found: 501.2.

Example 39

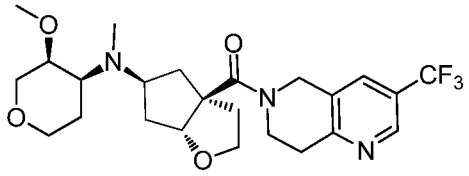
N,N-dimethyl-3-(1-((3aS,5S,6aR)-3a-(6-(trifluoromethyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-3-carbonyl)hexahydro-2H-cyclopenta[b]furan-5-yl)piperidin-4-yl)benzamide



The title compound of Example 39 was made by taking the product of Example 35, Step E following the procedures described in Example 31, Steps A and B, then reacting that product with N,N-dimethylbenzamide-3-boronic acid following the procedure described in Example 31, Step C, then following the procedure described in Example 31, Step D. Calculated for C31H36F3N3O4: 572.3 (M+1); found: 572.3.

Example 40

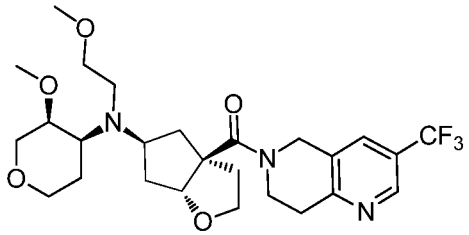
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)(methyl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound of Example 40 was made by taking the product of Example 30 and reacting with formaldehyde following the procedures described in Example 1, Step H. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (br. s., 1H), 7.70 (br. s., 1H), 5.03 (d, J = 4.6 Hz, 1H), 4.67 - 4.92 (m, 2H), 4.15 (d, J = 12.7 Hz, 1H), 3.97 - 4.10 (m, 2H), 3.92 (br. s., 2H), 3.55 - 3.71 (m, 2H), 3.33 - 3.53 (m, 5H), 3.22 (d, J = 12.7 Hz, 1H), 3.14 (br. s., 2H), 2.64 (d, J = 11.7 Hz, 1H), 2.22 - 2.50 (m, 4H), 1.79 - 2.22 (m, 6H), 1.69 (td, J = 12.5, 4.9 Hz, 1H), 1.51 (d, J = 12.0 Hz, 1H). Calculated for C24H32F3N3O4: 484.2 (M+1); found: 484.2.

Example 41

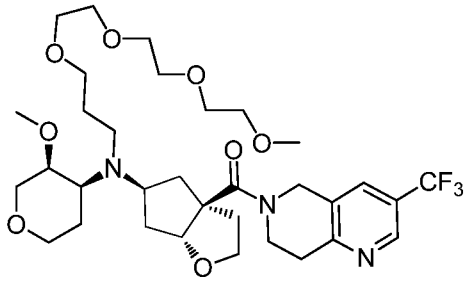
((3aS,5S,6aR)-5-((2-methoxyethyl)((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound of Example 41 was made by taking the product of Example 30 and reacting with methoxyacetaldehyde following the procedures described in Example 1, Step H. Calculated for C26H36F3N3O5: 528.3 (M+1); found: 528.3.

Example 42

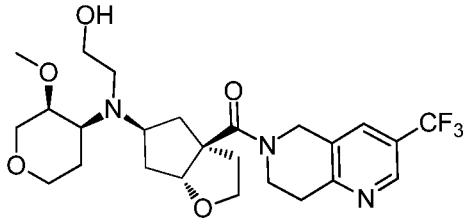
((3aS,5S,6aR)-5-(((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)(2,5,8,11-tetraoxatetradecan-14-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound of Example 42 was made by taking the product of Example 30 and reacting with 4,7,10,13-tetraoxatetradecanal following the procedures described in Example 1, Step H. Calculated for C33H50F3N3O8: 674.4 (M+1); found: 674.4.

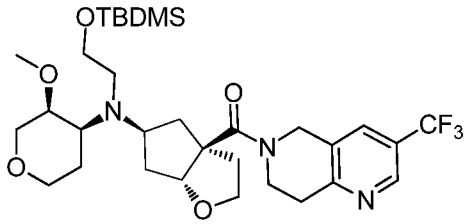
Example 43

((3aS,5S,6aR)-5-((2-hydroxyethyl)((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



Step A

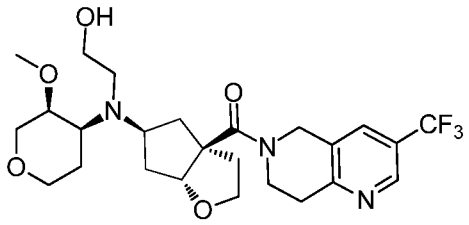
((3aS,5S,6aR)-5-((2-((tert-butyldimethylsilyl)oxy)ethyl)((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound of Step A was made by taking the product of Example 30 and reacting with t-butyldimethylsiloxyacetaldehyde following the procedures described in Example 1, Step H. Calculated for C31H48F3N3O5Si: 628.3 (M+1); found: 628.2.

Step B

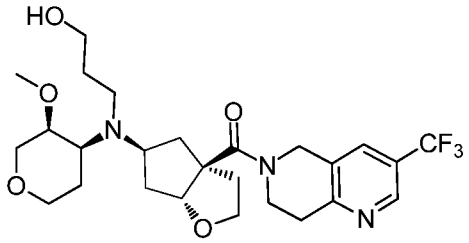
((3aS,5S,6aR)-5-((2-hydroxyethyl)((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



A solution of the product of Step A (210 mg, 0.33 mmol, 1 eq) in 1 N HCl (0.25 mL) and dioxane (5 mL) was heated to 90 °C for 18 hrs, then cooled to rt. Saturated $NaHCO_3$ was added, the aqueous extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. Purification by chromatography (12g) eluting with 3 to 8% MeOH/DCM afforded the title of compound of Example 43 (67 mg, 38%). ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (br. s., 1H), 7.71 (br. s., 1H), 4.96 (d, J = 4.4 Hz, 1H), 4.80 (br. s., 2H), 4.15 (d, J = 12.7 Hz, 1H), 3.77 - 4.10 (m, 5H), 3.56 - 3.70 (m, 1H), 3.30 - 3.52 (m, 7H), 3.23 (d, J = 12.7 Hz, 1H), 3.14 (br. s., 2H), 2.66 - 2.90 (m, 3H), 2.39 (br. s., 1H), 2.13 - 2.27 (m, 1H), 2.05 (dd, J = 12.7, 5.6 Hz, 3H), 1.82 (br. s., 1H), 1.68 (td, J = 12.6, 4.9 Hz, 1H), 1.42 (br. s., 1H). Calculated for C25H34F3N3O5: 514.3 (M+1); found: 514.3.

Example 44

((3aS,5S,6aR)-5-((3-hydroxypropyl)((3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl)amino)hexahydro-2H-cyclopenta[b]furan-3a-yl)(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



The title compound of Example 44 was made by taking the product of Example 30 and reacting with 3-((tert-butyldimethylsilyl)oxy)propanal following the procedures described in Example 43 Steps A and B. ^{1}H NMR (CHLOROFORM-d) δ: 8.72 (s, 1H), 7.72 (s, 1H), 4.97 (d, J = 4.5 Hz, 1H), 4.69 - 4.91 (m, 2H), 4.15 (d, J = 12.6 Hz, 1H), 3.83 - 4.10 (m, 5H), 3.58 - 3.82 (m, 3H), 3.33 - 3.47 (m, 5H), 3.25 (d, J = 12.6 Hz, 1H), 3.14 (br. s., 2H), 2.70 - 2.93 (m, 3H), 2.36 (br. s., 1H), 2.15 - 2.30 (m, 1H), 1.97 - 2.15 (m, 3H), 1.78 - 1.96 (m, 1H), 1.35 - 1.77 (m, 4H). Calculated for C26H36F3N3O5: 528.3 (M+1); found: 528.3.

Example 45

In Vitro Biological Data

Compounds of the invention were subjected to various representative biological tests. The results of these tests are intended to illustrate the invention in a non-limiting fashion.

MCP-1 Receptor Binding Assay in THP-1 Cells

Human monocytic cell line THP-1 cells were obtained from American Type Culture Collection (Manassas, Va., USA). The THP-1 cells were grown in RPMI-1640 (RPMI: Roswell Park Memorial Institute Medium-cell culture growth media) supplemented with 10% fetal bovine serum in a humidified 5% CO_2 atmosphere at 37 °C. The cell density was maintained between 0.5×10^6 cells/mL.

THP-1 (cells were incubated with 0.5 nM ^{125}I labeled MCP-1 (Perkin-Elmer Life Sciences, Inc. Boston, Mass.) in the presence of varying concentrations of either unlabeled MCP-1 (R & D Systems, Minneapolis, Minn.) or test compound for 2 hours at 30 °C. in a 96 well plate. Cells were then harvested onto a filter plate, dried, and 20 µL of Microscint 20 was added to each well. Plates were counted in a TopCount NXT, Microplate Scintillation & Luminescence Counter (Perkin-Elmer Life Sciences, Inc. Boston, Mass.). Blank values (buffer only) were subtracted from all values and drug treated values were compared to vehicle treated values. 1 µM cold MCP-1 was used for nonspecific binding.

Table 1 lists IC_{50} values for inhibition of MCP-1 binding to CCR2 obtained for test compounds of the invention. Where an IC_{50} value was not obtained for a particular compound, the percent inhibition is provided at a test concentration of 25 μM.

Table 1: Inhibition of MCP-1 Binding IC_{50}

Example	CCR2 Binding (nM)
1	16
2	7
3	11
4	93
5	170
6	62
7	2
8	3
9	9
10	16
11	4
12	24
13	20
16	14
21	120

The compounds of Examples 15, 29-31, 33, 35-37, 39, and 40 are believed to have CCR2 binding of less than about 50 nM, those of Examples 14, 20, 22, and 25 are believed to have CCR2 binding of about 50-100 nM, those of Examples 17, 26, 38, and 43-44 are believed to have CCR2 binding of about 100-200 nM, and those of Examples 18, 19, 23, 24, 27, 28, 32, 34, 41 and 42 are believed to have CCR2 binding of greater than about 200 nM.

Example 46

Animals

Mouse CCR2 knock-out / human CCR2 knock-in mice are generated using targeted 129Sv/Evbrd embryonic stem cell clones injected into C57BL/6 mice. Expression of the *hCCR2* transcript is confirmed by quantitative reverse transcription-polymerase chain reaction performed on spleen and blood total RNA from homozygous hCCR2 knock-in mice. Backcrossing into C57BL/6 genetic background continued to the eighth generation.

Transgenic mice are housed in a specific-pathogen-free, temperature-controlled facility that maintained a 12-hour light/12-hour dark cycle. Mice have free access to water and food. Experimental procedures are carried out in accordance with institutional standards for animal care and are approved by the institute's animal care and use committee.

Example 47

Murine In vivo Cell Migration Assay

Animals are orally dosed with vehicle or CCR2 antagonists at 3, 10 and 30 mg/kg bid. Animals undergo anesthesia and laparotomy. A distal loop of small bowel (5 cm in length) is gently eventrated onto moist sterile gauze. Synthetic human MCP-1 (1 mg/100 ml sterile PBS) or PBS alone is administered drop-wise onto the serosa of the eventrated loop. A suture knot is placed into the mesentery to mark the terminus of the treated area. Twenty-four hours later, the animal is sacrificed and the segment of bowel plus the adjacent region is removed. The tissue is opened along the mesenteric border, pinned flat and the mucosa removed. The remaining muscle layer is fixed briefly in 100% EtOH and then stained using Hanker-Yates reagent to detect myeloperoxidase-containing immune cells. At 10 mpk, P.O. bid, a compound is deemed efficacious if the inhibition of cell migration reaches 30% compared with vehicle-treated animals.

Example 48

Thioglycollate-Induced Peritonitis in Mice

Animals were orally dosed with vehicle or the compound of Example 30 at 0, 1, 3, and 10 mg/kg bid). One hour later, the animals were intraperiponeally injected with sterile thioglycollate (25 mL/kg, ip, Sigma) for induction of peritonitis. Animals were orally treated twice daily with vehicle or Example 30. At the 72-hour time point, perinoteal cavities were lavaged with 10 mL of sterile saline. Total cell counts in the peritoneal lavage fluid were performed using a microscope and cell differentiation is performed using cytospin analysis after Giemsa staining (Hema Tek 2000). Percent inhibition of the thioglycollate-induced peritonitis was calculated by comparing the change in number of leukocytes of CCR2 antagonist treated mice to the vehicle-treated mice. When the compound of Example 30 was administered at 1, 3 and 10 mg/kg p.o bid, the thioglycollate

induced cellular infiltrate in hCCR2KI mice at 72 hr was inhibited by 51%, 67% and 95%, respectively. The effect of Example 30 was demonstrated to be dose-dependent with an ED_{50} of 1 mg/kg p.o. bid, and a cmax EC_{50} of 97 nM in plasma (0.5 hour post the last dose).

Example 49

MCP-1-Induced Monocyte Recruitment to Airway of Mice

Animals are orally treated with vehicle or CCR2 antagonists at 3, 10, and 30 mg/kg po bid). One hour later, the animals are intranasally dosed with 4 μg of MCP-1 in sterile saline. The animals are orally treated twice daily with vehicle or CCR2 antagonists. After 48 h, mice are euthanized by intraperitoneal injection of anesthesia solution (Sleepaway-Sodium pentobarbital). Whole bronchoalveolar lavage (BAL) is performed using 1.4 ml of ice-cold PBS containing 3 mM EDTA. Total cell counts in the BAL lavage fluid are performed using a microscope and cell differentiation is performed using cytospin analysis after Giemsa staining (Hema Tek 2000). Percent inhibition is calculated by comparing the change in number of total leukocyte counts (including monocytes/macrophages and lymphocytes) of compound-treated mice to the vehicle-treated mice. Compounds are deemed efficacious if percent inhibition reaches 30%.

Example 50

High-fat Diet Induced Obesity and Insulin Resistance in Mice

Obesity was induced by a high-fat diet that derived approximately 60% calories from fat (D-12492; Research Diets Inc.) in animals for 10-12 weeks at age of 7 weeks. Prior to age 7 weeks, animals were fed a standard pellet diet, in which 5% of calories were provided as fat. Obese animals were randomized by body weight. The obese animals were orally treated with vehicle or the compound of Example 30 at 1, 3, and 10 mg/kg, po bid . Body weight and food intake and fasting blood glucose levels were monitored. Body mass was determined by a NMR analyzer (Bruker MiniSpec). Insulin tolerance test was carried out in animals that fasted for 3 hours. After an intraperitoneal bolus injection of recombinant human insulin (0.5 U/kg), blood glucose concentrations were measured using a

Glucometer before and 15, 30, 45, 60, 90 and 120 minutes after injection. Glucose tolerance tests were performed after an overnight (17-hour) fast. Blood glucose concentrations were measured before and after 15, 30, 60, 90, 120 minutes after an oral dose of glucose dissolved in water (2.5 g/kg). Energy expenditure analysis was monitored by a complete laboratory animal monitor system. After 50 days treatment with vehicle or CCR2 antagonists, the animals were sacrificed by CO_2 asphyxiation. Percent of weight loss was calculated by comparing the body weight changes of the compound-treated mice with the vehicle-treated mice. After 32-days treatment, the compound of Example 30 reduced the high fat-diet induced body weight by 4.94 % ($p > 0.05$), 10.94% ($p < 0.01$) and 15.7 % ($p < 0.01$) when administered at 1, 3 and 10 mg/kg p.o. bid, respectively.

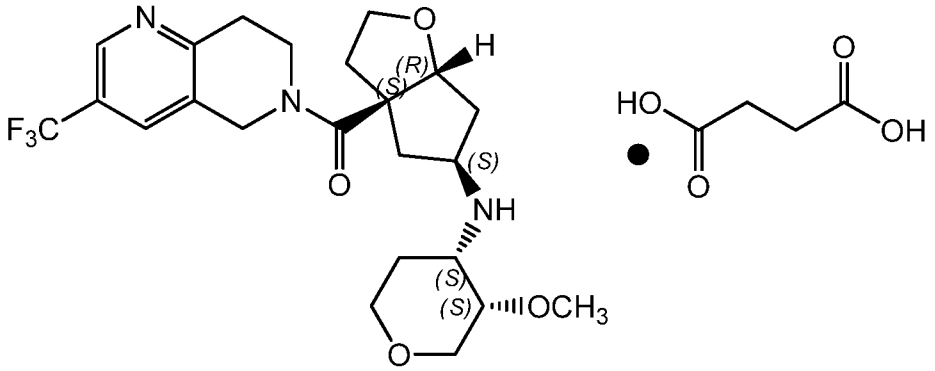
Example 51

Mouse Model of Allergic Asthma

Animals are sensitized by intraperitoneal injection of 10 μg chicken egg albumin (OVA) absorbed to 1 mg Imject® in 100 μL phosphate-buffered saline (PBS) on days 0 and 5. Control animals received PBS ip. OVA-immunized animals are challenged by inhalation of 0.5% OVA aerosol for 10 minutes by an ultrasonic nebulizer on days 12, 16 and 20. Control animals are challenged with PBS in similar fashion. The OVA-sensitized animals receive vehicle (0.5% Methocel) or CCR2 antagonists orally at 3, 10, 30 mg/kg twice daily from days 9-20 and once daily on Day 21, 2 hours before sacrifice. Dexamethason (5 mg/kg) and Montelukast (1 mg/kg) are given orally once a day. On day 21, 2 hours post the last dose of CCR2 compounds, bronchial reactivity to aerosolized methacholine is measured using a Buxco whole body plethysmograpgh. On day 21, the animals are sacrificed. Bronchoalveolar lavage fluid is collected (1 mL) and total cells counted. The numbers of eosinophils, lymphocytes, monocytes and neutrophils are determined using cytospin analysis after Giemsa staining (Hema Tek 2000). Percent inhibition of total BAL leukocyte count (and eosinophil count) is calculated by comparing the compound-treated mice with vehicle-treated mice. Compounds are deemed efficacious if the inhibition reaches 30%.

Example 52

Preparation of Crystalline Succinate Salt of Compound of Formula (I-S)



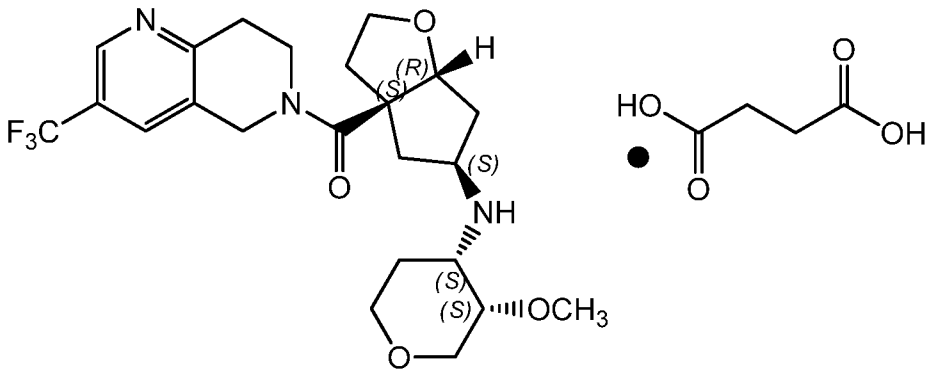
The crystalline succinate salt of the compound of formula (I) was prepared by heating amorphous succinate salt (the amorphous succinate salt is the foam described in Example 30, Step M) of the compound of formula (I) in an open DSC aluminum pan to about 140 °C with a heating rate of 10 °C/min, then cooling to about 30 °C with a cooling rate of 10 °C/min.

Figure 5 illustrates a DSC thermogram measured during the experiment described above. The DSC thermogram shows a first endothermic event at about 50 °C (theorized to be the result of desolvation of the amorphous form); an exothermic event with a maximum at about 138 °C, indicative of crystallization; and a subsequent endothermic event at 155 °C, indicative of the melting of the crystalline solid.

Figure 5 further includes a TGA thermogram for the amorphous succinate salt of the compound of formula (I-S) used in the example described above, which shows about 4.8% weight loss between room temperature and about 80 °C; and decomposition starting at about 172 °C.

Example 53

Preparation of Crystalline Succinate Salt of Compound of Formula (I-S)



The following general procedure was applied in a screening study for identifying solvents suitable for crystallization of the crystalline succinate salt of the compound of formula (I-S). Crystalline succinate salt of the compound of formula (I-S) was prepared from the amorphous succinate salt (the amorphous succinate salt is the foam described in Example 30, Step M) of the compound of formula (I-S), crystallizing from methyl isobutyl ketone. (Note: Water, methanol ethanol, acetone, acetonitrile, isopropyl acetate, nitromethane, tetrahydrofuran, methyl ethyl ketone, dichloromethane, and toluene did not induce crystallization.)

Amorphous succinate salt of the compound of formula (I-S) (5-10 mg) was suspended in 1 – 2 mL of methyl-isobutyl ketone (MIBK). The resulting suspension was heated in an oil bath and at reflux conditions, the suspension formed a clear solution, which upon cooling to room temperature under ambient conditions yielded crystalline solids.

The solids isolated from MIBK were allowed to dry under ambient condition and then analyzed by X-ray. The pXRD pattern of the solid isolated from MIBK was similar to the pXRD pattern of the heat treated sample (prepared as in Example 52 above), indicating the same crystalline form was produced in both cases.

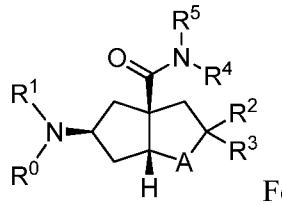
Example 54: Oral Formulation – Prophetic Example

As a specific embodiment of an oral composition, 100 mg of the compound prepared as in Example 53 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

We Claim:

1. A compound of Formula (I):



Formula (I)

wherein:

A is O, or S;

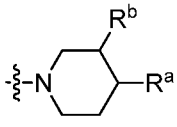
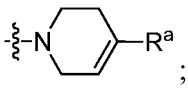
R^0 is H, or $C_{(1-4)}$alkyl;

wherein said $C_{(1-4)}$alkyl is optionally substituted with OH, $C_{(1-4)}$alkyl-$(OCH_2CH_2)_n$-OCH_3, OCH_3, CO_2H, $C(O)NH_2$, SO_2NH_2, or $CO_2C_{(1-4)}$alkyl;

n is 1, 2, or 3;

R^1 is cyclohexyl, or tetrahydropyranyl;

wherein said cyclohexyl or tetrahydropyranyl may be optionally substituted with one substituent selected from the group consisting of: OCH_3, OH, CH_2CH_3, -CN, NH_2, $NH(CH_3)$, $N(CH_3)_2$, or OCF_3;

alternatively, R^0 and R^1 are taken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

R^a is phenyl;

wherein the phenyl is optionally substituted with $C(O)NH_2$, $C(O)NHC_{(1-4)}$alkyl, SO_2NH_2, $C(O)N(C_{(1-4)}alkyl)_2$, OCH_3, CO_2CH_3, or CO_2H;

R^b is $C_{(1-4)}$alkyl, or $OC_{(1-4)}$alkyl;

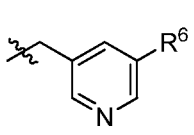
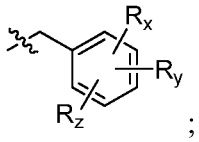
R^2 is selected from the group consisting of H, $C_{(1-4)}$alkyl, cyclopropyl, cyclohexyl, phenyl, pyridyl, pyrimidyl, pyrazyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl, furyl, and thiophenyl;

wherein said phenyl, pyridyl, pyrimidyl, pyrazyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, furyl, or thiophenyl is optionally substituted with one substituent selected from the group consisting of NH_2, $NHC_{(1-3)}$alkyl, $N(C_{(1-3)}alkyl)_2$, $C_{(1-3)}$alkyl, -CN, $-CH=CH_2$, $-CONH_2$, $-CO_2H$, $-NO_2$, $-CONHC_{(1-4)}$alkyl, $CON(C_{(1-4)}alkyl)_2$, $C_{(1-}$

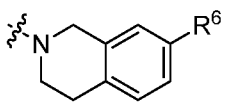
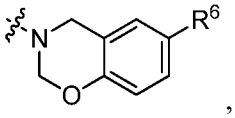
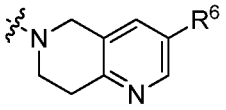
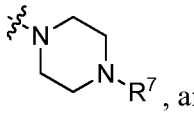
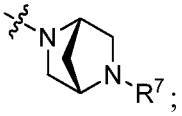
$_{4)}$alkylCONH$_2$, -NHCOC$_{(1-4)}$alkyl, -CO$_2$C$_{(1-4)}$alkyl, CF$_3$, SO$_2$C$_{(1-4)}$alkyl, -SO$_2$NH$_2$, -SO$_2$NH(C$_{(1-4)}$alkyl), and -SO$_2$N(C$_{(1-4)}$alkyl)$_2$;

R^3 is H, or CH$_3$;

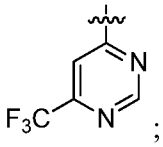
alternativley, R^3 and R^2 are taken together with their attached carbon to form  ;

R^4 is  , or  ;

R^5 is H, or CH$_3$;

alternatively, R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of:  ,  ,  ,  , and  ;

R^6 is CF$_3$, or OCF$_3$;

R^7 is a CF$_3$ substituted heteroaryl, provided that R^7 is not  ;

R$_x$ is CF$_3$, F, Cl, CN, or OCH$_3$;

R$_y$ is H, F, Cl, or CF$_3$;

R$_z$ is H, or F;

or a pharmaceutically acceptable salt thereof.

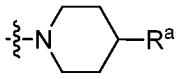
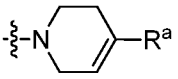
2. A compound of Claim 1, wherein:

A is O, or S;

R^0 is H, or C$_{(1-4)}$alkyl, wherein said C$_{(1-4)}$alkyl is optionally substituted with OH, C$_{(1-4)}$alkyl(OCH$_2$CH$_2$)$_n$OCH$_3$, or OCH$_3$;

n is 1, 2, or 3;

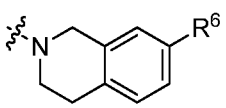
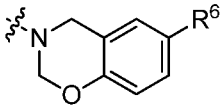
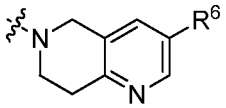
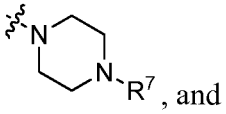
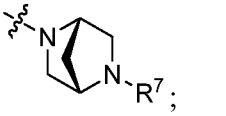
R^1 is cyclohexyl, 1-methoxy cyclohex-2-yl, tetrahydropyran-4-yl, or 3-methoxy tetrahydropyran-4-yl;

alternatively, R^0 and R^1 are taken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

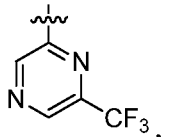
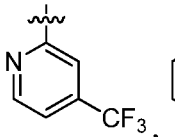
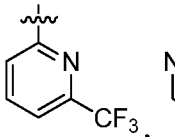
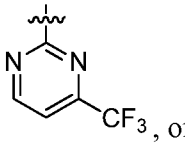
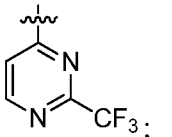
R^a is phenyl;

wherein said phenyl is optionally substituted with $C(O)NH_2$, $C(O)NHCH_3$, SO_2NH_2, $C(O)N(CH_3)_2$, OCH_3, CO_2CH_3, or CO_2H;

R^2 is H, $C_{(1\text{-}4)}$alkyl, cyclopropyl, cyclohexyl, thiazol-2-yl, 1-methyl-imidazol-2-yl, 1-methyl-pyrazol-5-yl, or phenyl;

R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of:  ,  ,  ,  , and  ;

R^6 is CF_3, or OCF_3;

R^7 is  ,  ,  ,  , or  ;

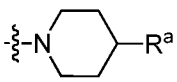
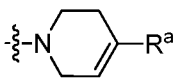
or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 2, wherein:

A is O, or S;

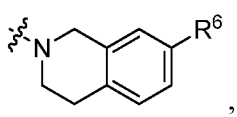
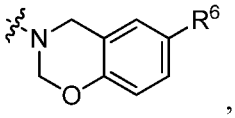
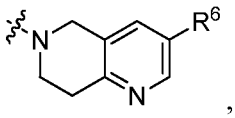
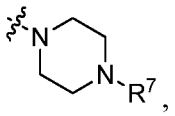
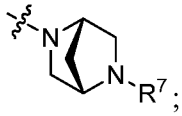
R^0 is H, CH_3, $CH_2CH_2CH_2OH$, CH_2CH_2OH, $CH_2CH_2CH_2$-$(OCH_2CH_2)_3$-OCH_3, or $CH_2CH_2OCH_3$;

R^1 is tetrahydropyran-4-yl, or 3-methoxy tetrahydropyran-4-yl;

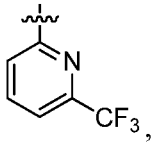
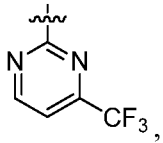
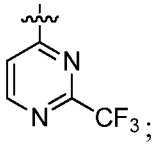
alternatively, R^0 and R^1 aretaken together with their attached nitrogen to form a ring selected from the group consisting of  , and  ;

R^a is phenyl;

wherein said phenyl is optionally substituted with $C(O)N(CH_3)_2$, OCH_3, or CO_2H;

R^4 and R^5 are taken together with their attached nitrogen to form a ring selected from the group consisting of:  ,  ,  ,  ,  ;

R^6 is CF_3, or OCF_3;

R^7 is  ,  , or  ;

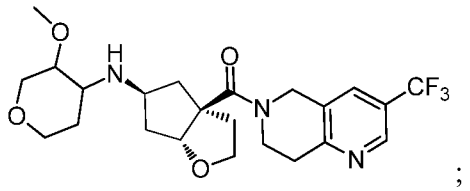
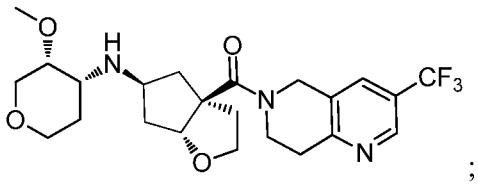
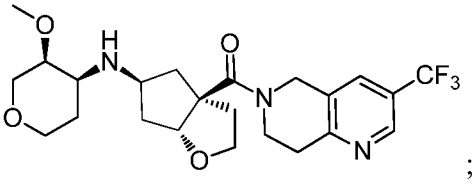
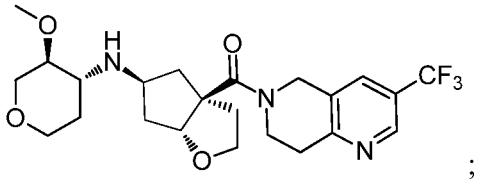
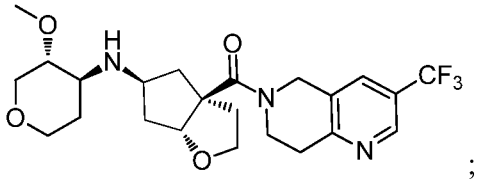
or a pharmaceutically acceptable salt thereof.

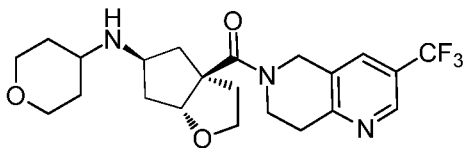
4. A compound of Claim 3, wherein:

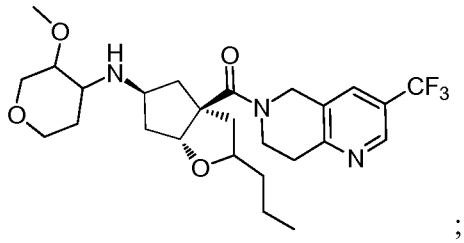
A is O;

or a pharmaceutically acceptable salt thereof.

5. A compound of Claim 1 selected from the group consisting of:

 ;
 ;
 ;
 ;
 ;


;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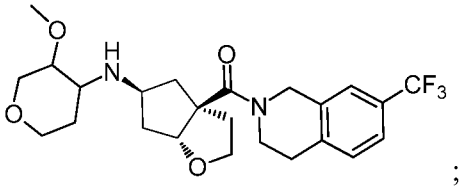
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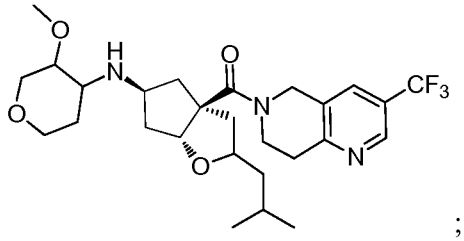
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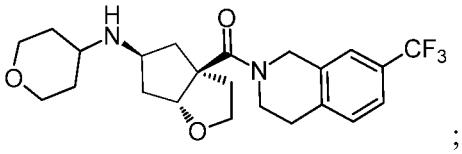
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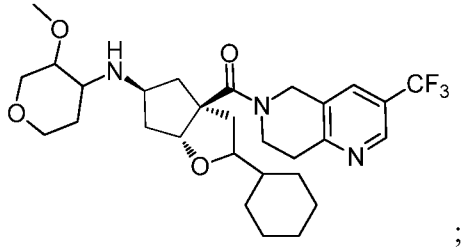
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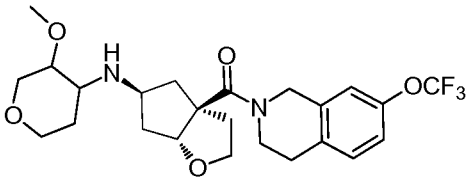
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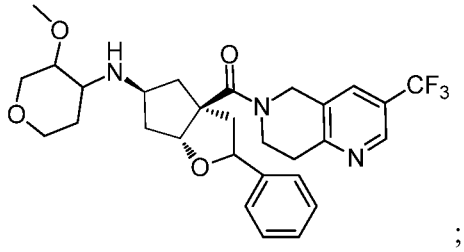
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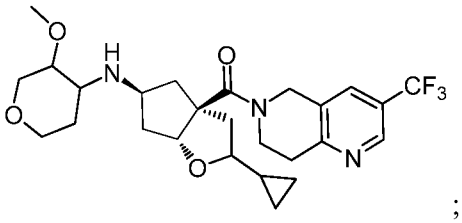
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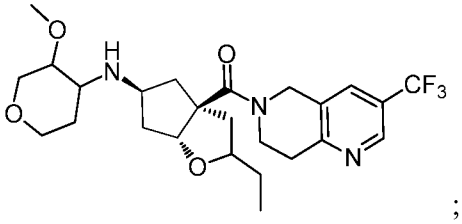
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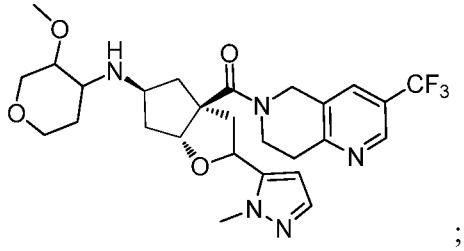
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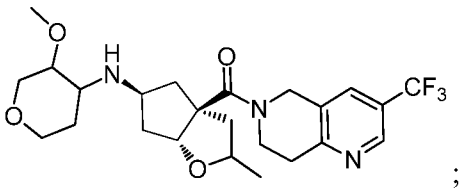
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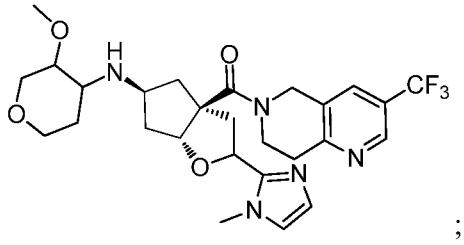
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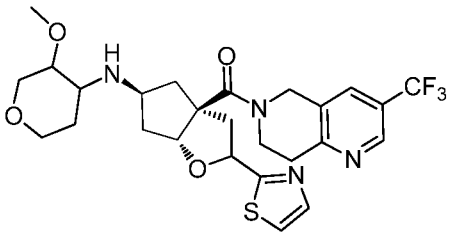
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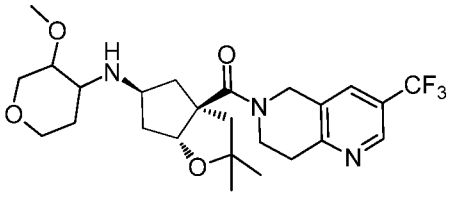
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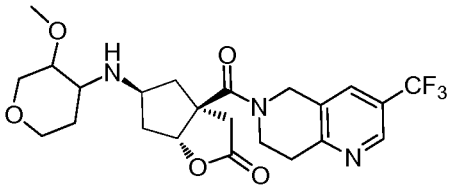
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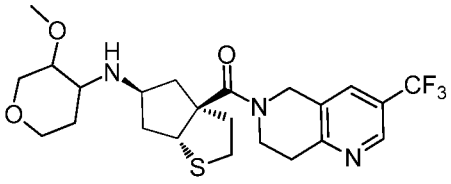
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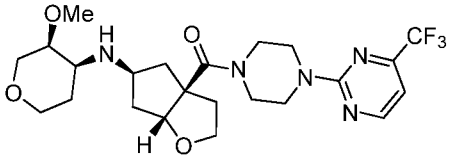
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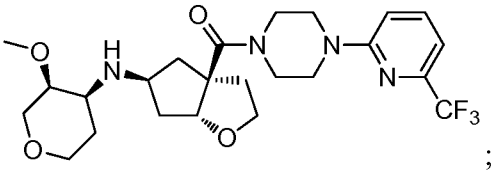
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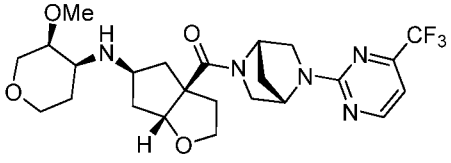
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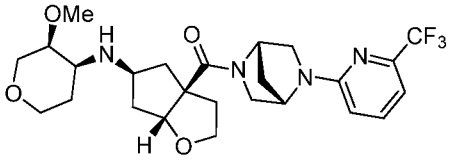
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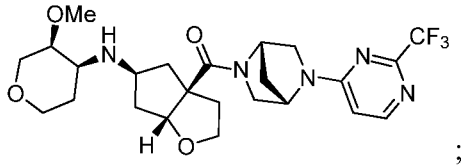
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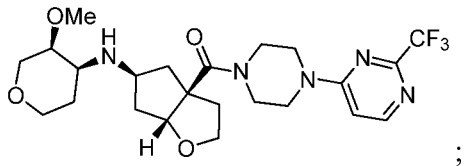
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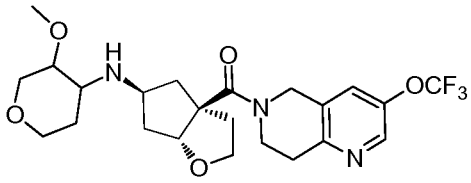
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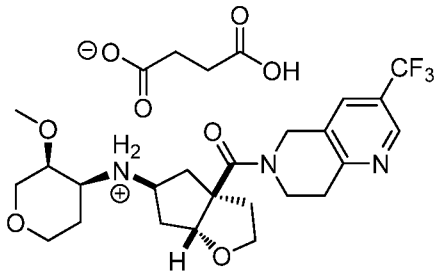
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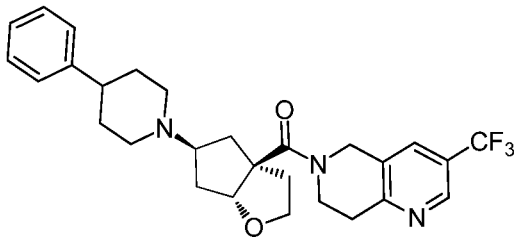
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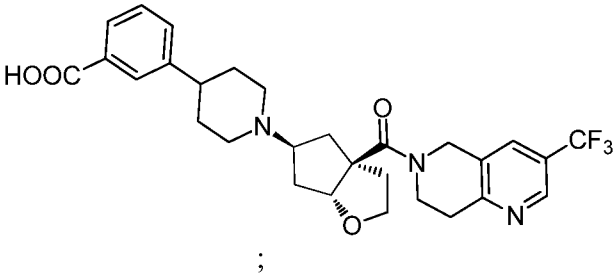
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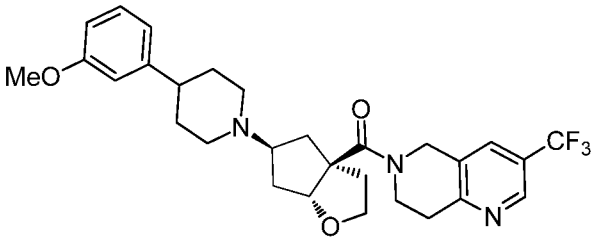
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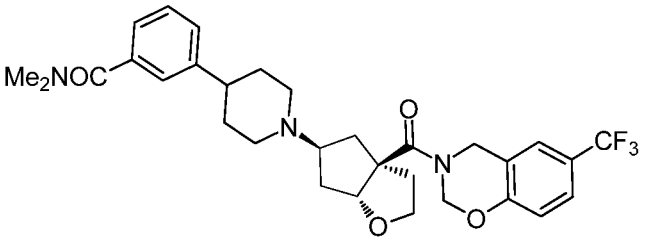
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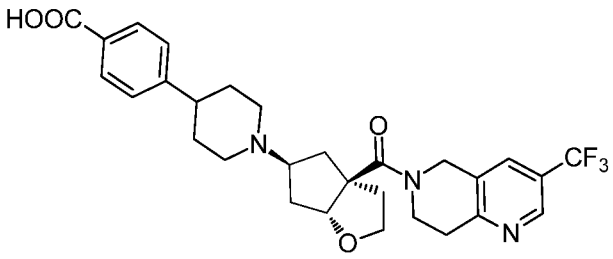
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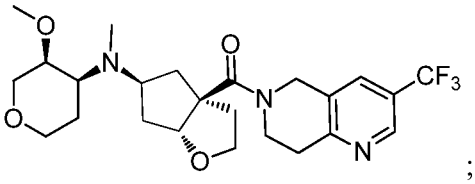
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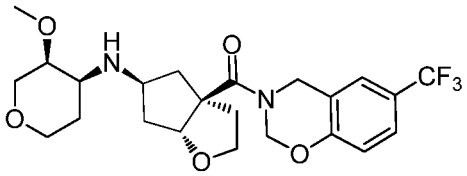
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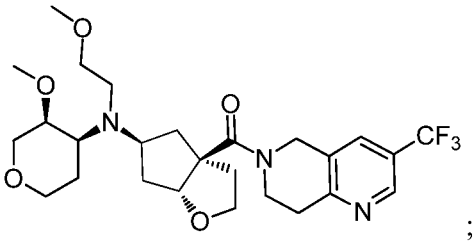
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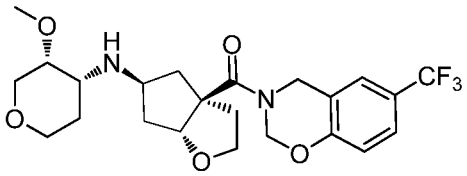
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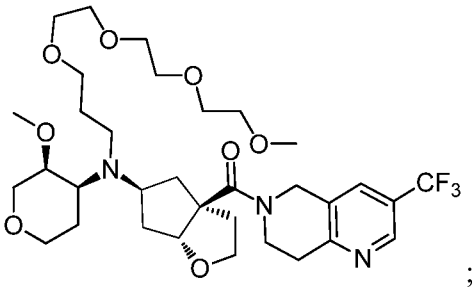
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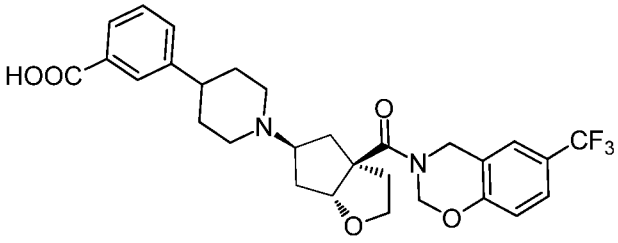
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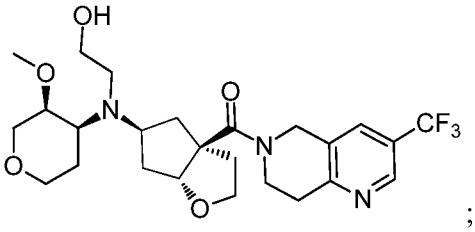
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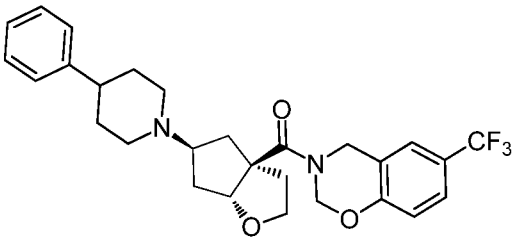
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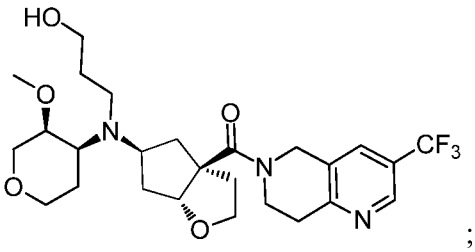
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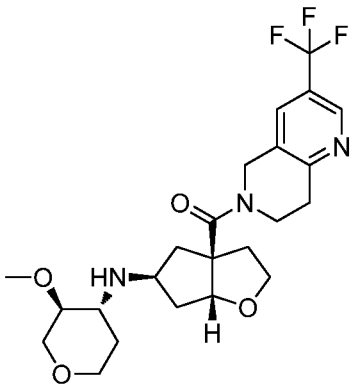
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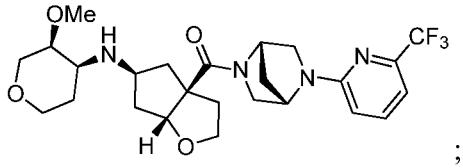
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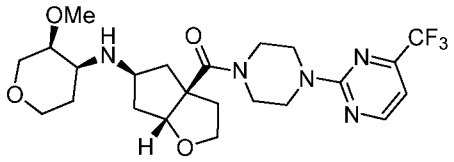
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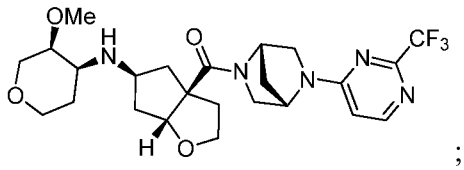
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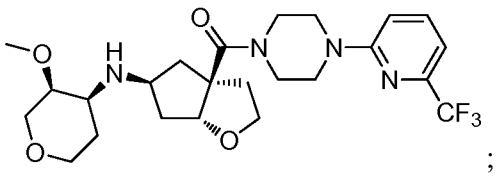
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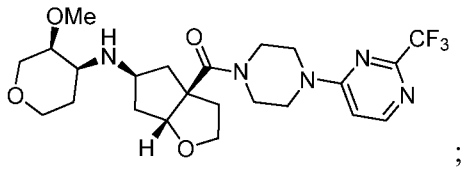
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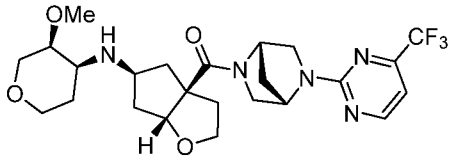
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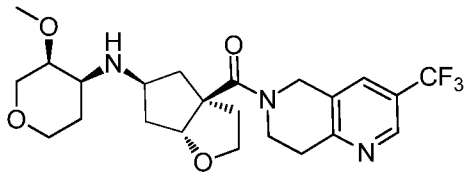
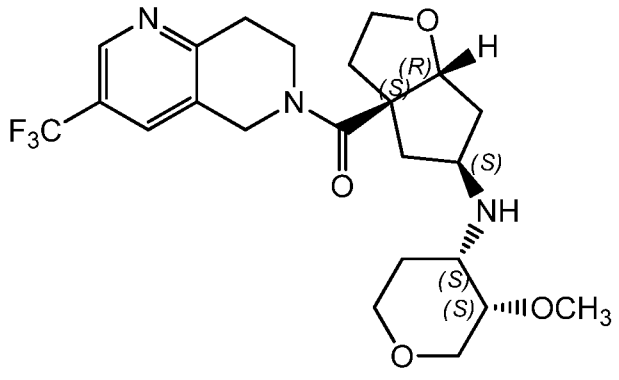
and pharmaceutically acceptable salts thereof.

6. A compound which is



and pharmaceutically acceptable salts thereof.

7. A succinate salt of a compound of formula (I-S)



(I-S).

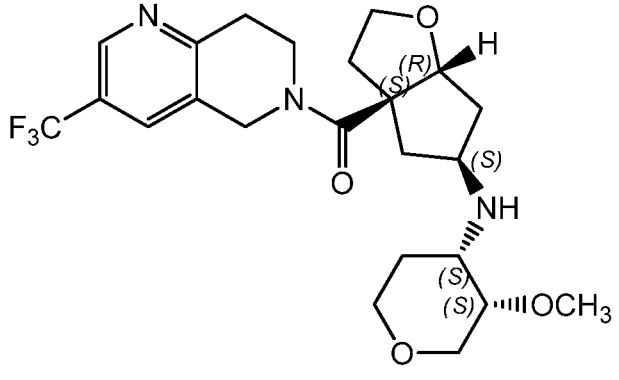
8. A salt as in Claim 7, wherein the salt is crystalline.

9. A salt as in Claim 7, wherein the salt is a crystalline hydrate; and wherein the hydrate contains about 0.6 moles water per mole of the compound of formula (I-S).

10. A salt as in Claim 7, wherein the salt is a crystalline hydrate; and wherein the salt is hygroscopic.

11. A salt as in Claim 7, wherein the salt is crystalline and exhibits a peak temperature of melting, as measured by DSC, of about 158 °C.

12. A crystalline succinate salt of a compound of formula (I-S)



(I-S),

comprising powder X-ray diffraction peaks of 11.27, 13.87, 19.22 and 22.01 °2θ.

13. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition made by mixing a compound of claim 1 and a pharmaceutically acceptable carrier.

15. A process for making a pharmaceutical composition comprising mixing a compound of claim 1 and a pharmaceutically acceptable carrier.

16. A method for preventing, treating or ameliorating a CCR2 mediated syndrome, disorder or disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

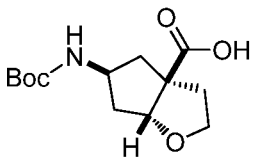
17. A method for preventing, treating or ameliorating a CCR2 mediated inflammatory syndrome, disorder or disease wherein the syndrome, disorder or disease is associated with elevated MCP-1 expression or MCP-1 overexpression, or is an inflammatory condition that accompanies syndromes, disorders or diseases associated with elevated MCP-1 expression or MCP-1 overexpression comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

18. A method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: chronic obstructive pulmonary disorder (COPD), ophthalmic disorders, uveitis, atherosclerosis, rheumatoid arthritis, psoriasis, psoriatic arthritis, atopic dermatitis, multiple sclerosis, Crohn's Disease, ulcerative colitis, nephritis, organ allograft rejection, fibroid lung, renal insufficiency, type-I diabetes, type II diabetes, diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, overweight, obesity, obesity-associated insulin resistance, metabolic syndrome, tuberculosis, sarcoidosis, invasive *staphyloccocia*, inflammation after cataract surgery, allergic rhinitis, allergic conjunctivitis, chronic urticaria, asthma, allergic asthma, periodontal diseases, periodonitis, gingivitis, gum disease, diastolic cardiomyopathies,

cardiac infarction, myocarditis, chronic heart failure, angiostenosis, restenosis, reperfusion disorders, aortic abdominal aneurism, glomerulonephritis, solid tumors and cancers, chronic lymphocytic leukemia, chronic myelocytic leukemia, multiple myeloma, malignant myeloma, Hodgkin's disease, and carcinomas of the bladder, breast, cervix, colon, lung, prostate, or stomach, and chronic neuroinflammatory disorders including, but not limited to, Alzheimer's disease, ischemic stroke, spinal cord injury, nerve crush injury and traumatic brain injury comprising administering to a subject in need thereof an effective amount of a compound of claim 1.

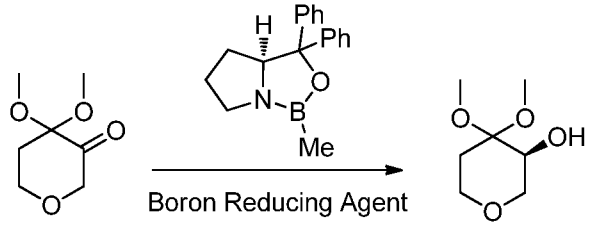
19. A method of preventing, treating or ameliorating a syndrome, disorder or disease, wherein said syndrome, disorder or disease is selected from the group consisting of: type I diabetes, type II diabetes, diabetic complications, diabetic nephropathy, diabetic retinopathy, diabetic retinitis, diabetic microangiopathy, obesity, obesity-associated insulin resistance, metabolic syndrome, asthma, and allergic asthma, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.

20. A method of treating a disorder selected from the group consisting of type II diabetes, obesity and asthma comprising administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1.



21. A compound of formula (XXI) (XXI) .

22. A process for making (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and R-(+)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 60% enantiomeric excess.

23. The process of Claim 22 wherein (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol is formed in at least 90% enantiomeric excess.

24. The process of Claim 22 wherein the borane reducing complex is selected from borane- dimethylsulfide complex or borane-N,N-diethylaniline complex.

25. The process of Claim 24 wherein a THF solution of the borane-reducing complex and R-(+)-2-methyl-CBS-oxazaborolidine is added to a solution of the 4-dimethoxydihydro-2H-pyran-3(4H)-one in THF.

26. The process of Claim 22 wherein the reaction is carried out in an inert environment.

27. The process of Claim 26 wherein the reaction is run under nitrogen gas.

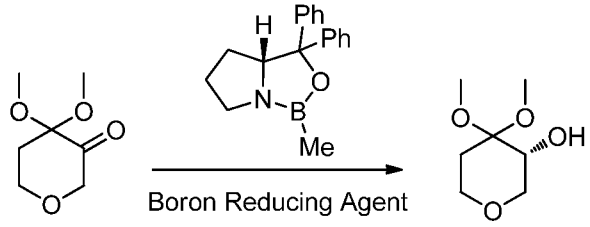
28. The reaction of Claim 22 further comprising reacting the (S)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol with dimethyl sulfate to provide (R)-3, 4, 4-trimethoxytetrahydro-2H-pyran.

29. The reaction of Claim 28, further comprising reacting the (R)-3, 4, 4-trimethoxytetrahydro-2H-pyran with acid to provide (R)-3-methoxydihydro-2H-pyran-4(3H)-one.

30. The reaction of Claim 29 wherein the acid is concentrated hydrochloric acid.

31. The reaction of Claim 22 wherein the reaction is run at a temperature range from 20 °C to 60 °C.

32. A process for making (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol comprising



reacting 4, 4-dimethoxydihydro-2H-pyran-3(4H)-one with a boron reducing agent and S-(-)-2-methyl-CBS-oxazaborolidine, over a period of at least six hours to provide the (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol in at least 60% enantiomeric excess.

33. The process of Claim 32 wherein (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol is formed in at least 90% enantiomeric excess.

34. The process of Claim 32 wherein the borane reducing complex is selected from borane- dimethylsulfide complex or borane-N,N-diethylaniline complex.

35. The process of Claim 34 wherein a THF solution of the borane-reducing complex and S-(-)-2-methyl-CBS-oxazaborolidine is added to a solution of the 4-dimethoxydihydro-2H-pyran-3(4H)-one in THF.

36. The process of Claim 32 wherein the reaction is carried out in an inert environment.

37. The process of Claim 36 wherein the reaction is run under nitrogen gas.

38. The reaction of Claim 32 further comprising reacting the (R)-4, 4-dimethoxytetrahydro-2H-pyran-3-ol with dimethyl sulfate to provide (S)-3, 4, 4-trimethoxytetrahydro-2H-pyran.

39. The reaction of Claim 38, further comprising reacting the (S)-3, 4, 4-trimethoxytetrahydro-2H-pyran with acid to provide (S)-3-methoxydihydro-2H-pyran-4(3H)-one.

40. The reaction of Claim 39 wherein the acid is concentrated hydrochloric acid.

41. The reaction of Claim 32 wherein the reaction is run at a temperature range from 20 °C to 60 °C.

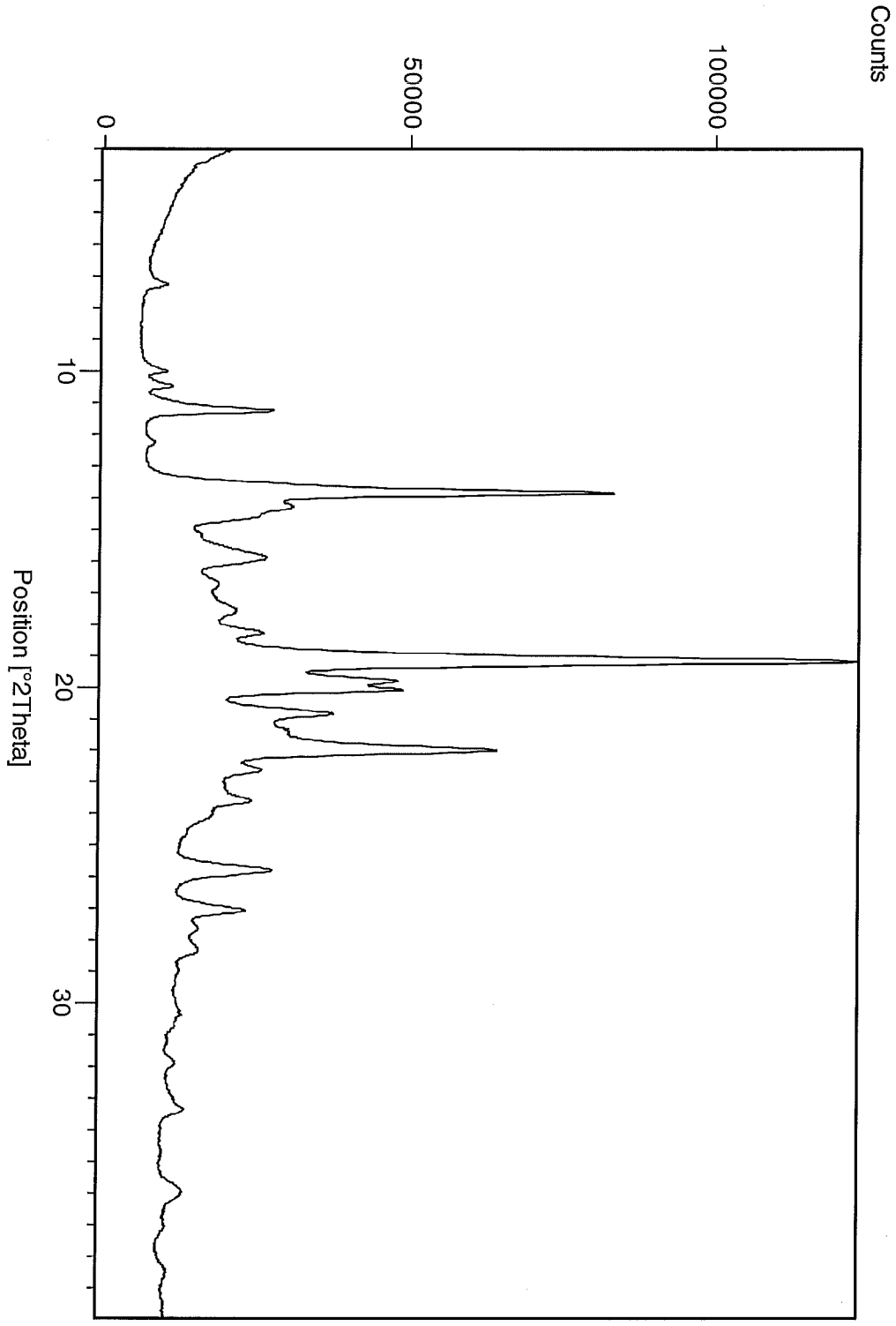


Figure 1: Representative pXRD Spectrum for Crystalline Succinate Salt of Compound of Formula (I-S)

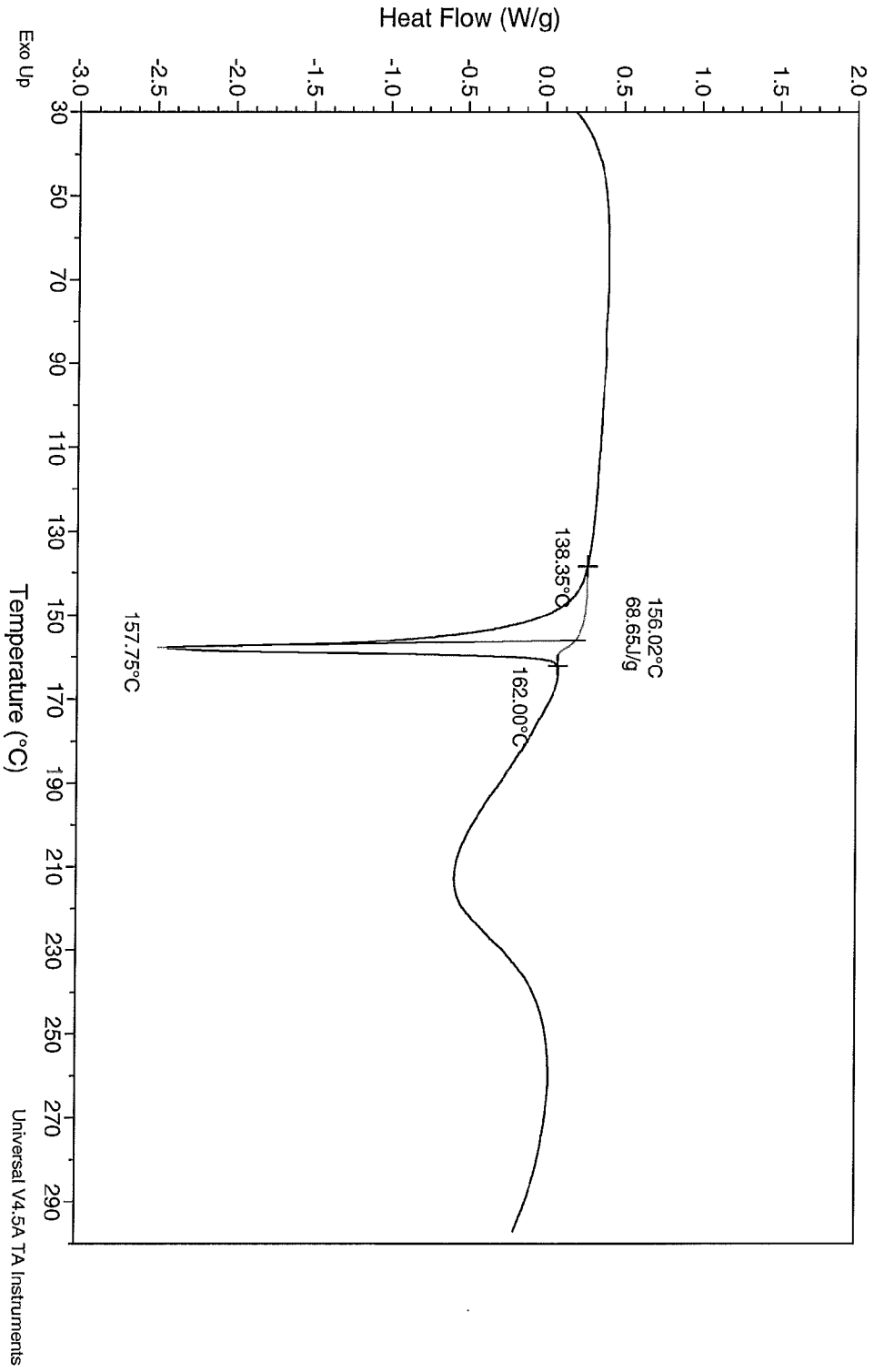


Figure 2: Representative DSC Scan for Succinate Salt of Compound of Formula (I-S)

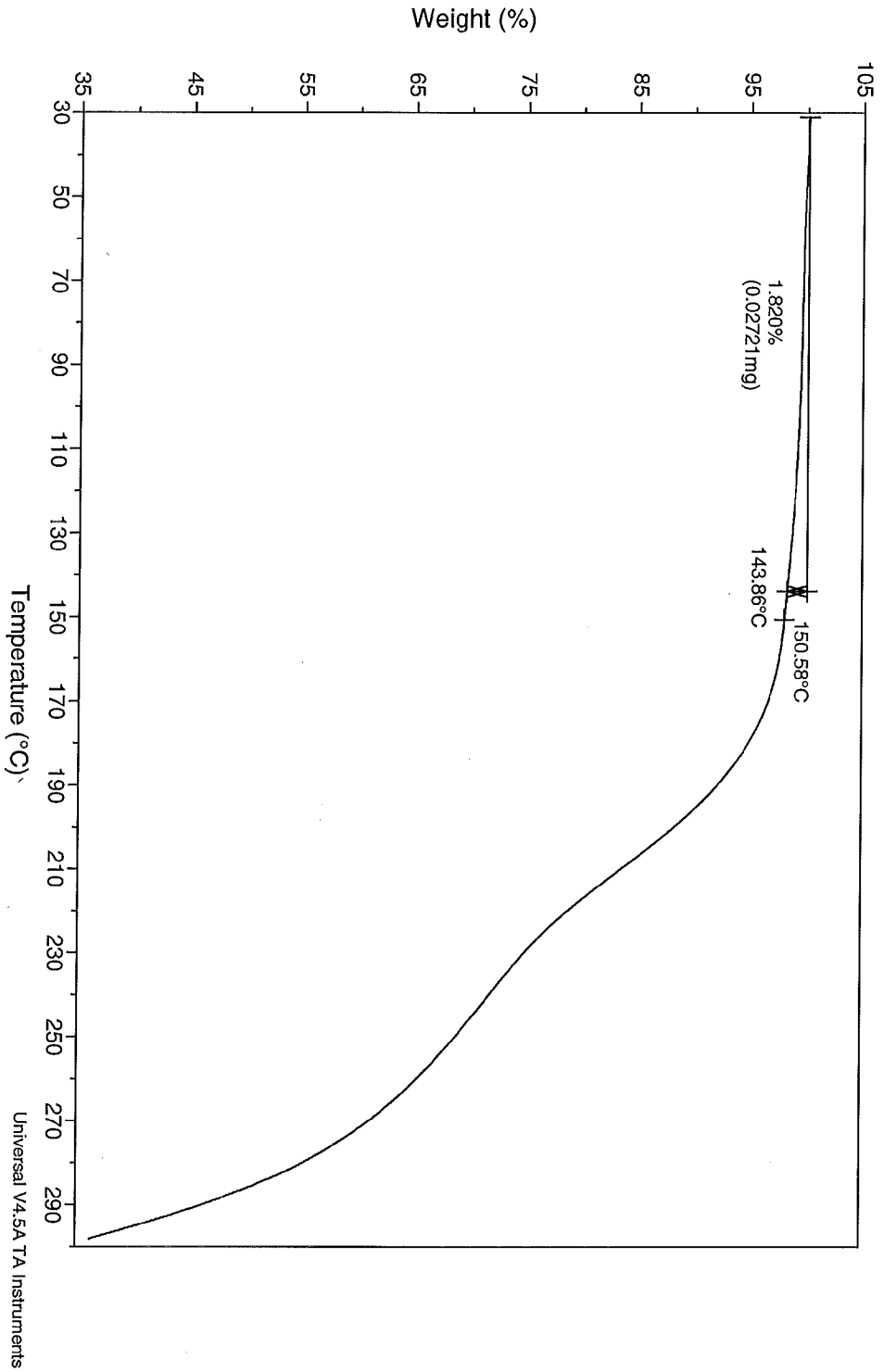


Figure 3: Representative TGA Scan for Succinate Salt of Compound of Formula (I-S)

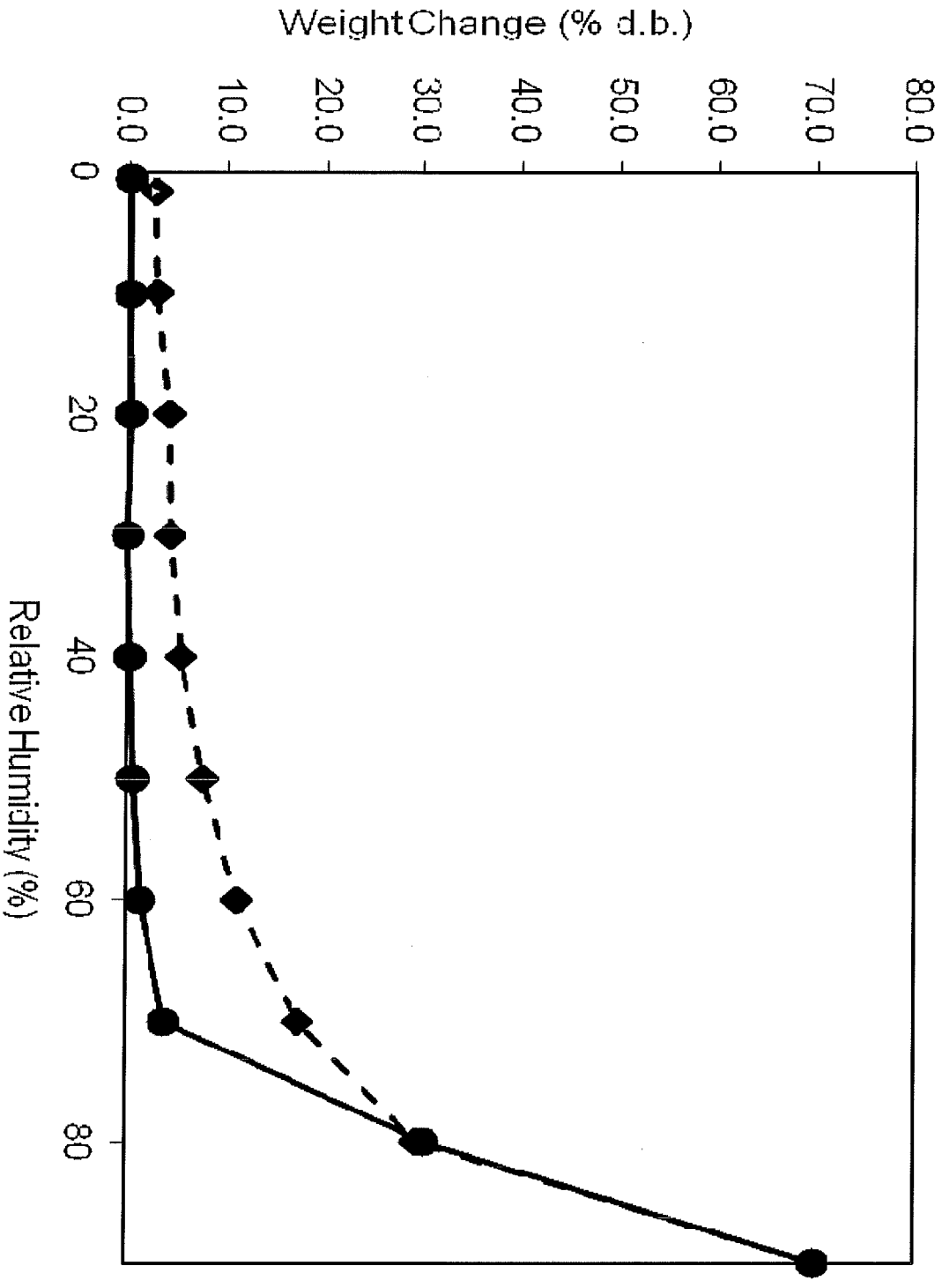


Figure 4: Representative Moisture Isotherm for Succinate Salt of Compound of Formula (I-S)

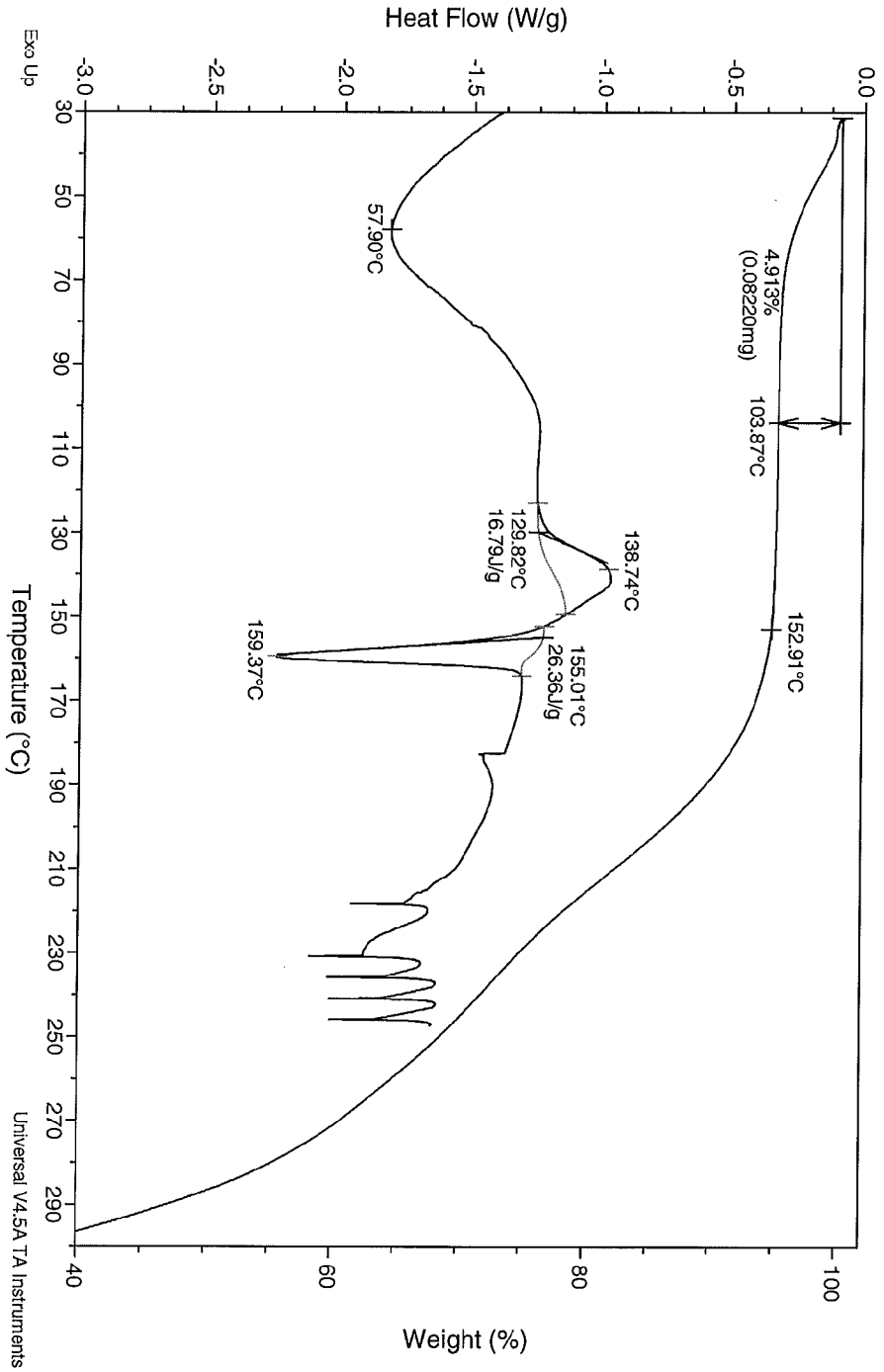


Figure 5: DSC thermogram showing conversion of amorphous to crystalline succinate salt of the compound of formula (I-S); and TGA thermogram for amorphous succinate salt of the compound of formula (I-S).

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/035396

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/14 C07D413/14 C07D413/06 C07D471/04 A61K31/41 A61P29/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/093266 A1 (MERCK & CO INC [US]; MERCK SHARP & DOHME [GB]; JIAO RICHARD [US]; MORR) 13 November 2003 (2003-11-13) claim 1 -----	1-21
A	DAWSON J ET AL: "TARGETING MONOCYTE CHEMOATTRACTANT PROTEIN-1 SIGNALLING IN DISEASE", EXPERT OPINION ON THERAPEUTIC TARGETS, ASHLEY PUBLICATIONS, LONDON, GB, vol. 7, no. 1, 1 January 2003 (2003-01-01) , pages 35-48, XP009014960, ISSN: 1472-8222, DOI: 10.1517/EOTT.7.1.35.21164 p. 43, compound K ----- -/--	1-21

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2013	08/08/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wolf, Claudia

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/035396

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/098959 A1 (MERCK & CO INC [US]; MOORE JEFFREY C [US]; KOSJEK BIRGIT [US]; NTI-GYA) 21 September 2006 (2006-09-21) claim 1	22-41
Y	ELIAS J COREY ET AL: "Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioslsctive Catalysis and a powerful New synthetic Method", ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, WILEY VCH VERLAG, WEINHEIM, vol. 37, no. 15, 17 August 1998 (1998-08-17), pages 1986-2012, XP002427347, ISSN: 1433-7851, DOI: 10.1002/(SICI)1521-3773(19980817)37:15<1986::AID-ANIE1986>3.0.CO;2-Z the whole document	22-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/035396

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-21

Compounds of formula (I), pharmaceutical compositions thereof, process for making those and intermediate of formula (XXI).

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2. claims: 22-41

Process for making a pyran derivative.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/035396

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03093266 A1	13-11-2003	AR 039489 A1	23-02-2005
		AU 2003234251 A1	17-11-2003
		BR 0309650 A	26-04-2005
		CN 1662532 A	31-08-2005
		DO P2003000638 A	30-11-2003
		EC SP045392 A	03-01-2005
		HK 1081967 A1	07-12-2007
		HR P20041023 A2	28-02-2005
		IL 164909 A	15-04-2010
		IS 7512 A	18-10-2004
		JO 2479 B	20-01-2009
		MA 27119 A1	20-12-2004
		MX PA04010702 A	17-02-2005
		MY 129850 A	31-05-2007
		PE 05982004 A1	05-10-2004
		RU 2285004 C2	10-10-2006
		TW I262077 B	21-09-2006
		UA 75828 C2	15-03-2005
		US 2005101628 A1	12-05-2005
		WO 03093266 A1	13-11-2003
WO 2006098959 A1	21-09-2006	AU 2006223459 A1	21-09-2006
		CA 2599897 A1	21-09-2006
		CN 101137637 A	05-03-2008
		EP 1861386 A1	05-12-2007
		JP 2008536484 A	11-09-2008
		US 2008138866 A1	12-06-2008
		WO 2006098959 A1	21-09-2006

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104619702 A
(43)申请公布日 2015.05.13

(21)申请号 201380029978.4
(22)申请日 2013.04.05
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2014.12.05
(86)PCT国际申请的申请数据
PCT/US2013/035396 2013.04.05
(87)PCT国际申请的公布数据
WO2013/152269 EN 2013.10.10
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(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 初明明 彭昶
(51)Int.Cl.
C07D 405/14(2006.01)
C07D 413/14(2006.01)
C07D 413/06(2006.01)
C07D 471/04(2006.01)
A61K 31/41(2006.01)
A61P 29/00(2006.01)

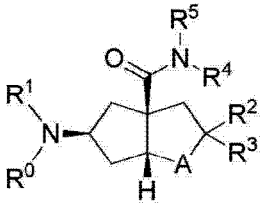
权利要求书10页 说明书77页 附图5页

(54)发明名称

CCR2的稠合环戊基胺抗剂

(57)摘要

本发明包括式(I)的化合物。

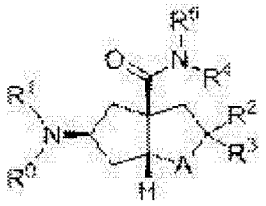


式(I)

其中:R^0、R^1、R^2、R^3、R^4、R^5和A如说明书中定义。本发明还包括预防、治疗或改善综合征、障碍或疾病的方法,其中所述综合征、障碍或疾病是II型糖尿病、肥胖症和哮喘。本发明还包括通过施用治疗有效量的至少一种式(I)的化合物来抑制哺乳动物中的CCR2活性的方法。

CN 104619702 A

1. 一种式（I）的化合物或其药学上可接受的盐：

 　式（I）

其中：

A 为 O 或 S；

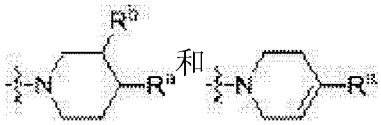
R^0为 H 或 $C_{(1-4)}$烷基；

其中所述$C_{(1-4)}$烷基任选地被 OH、$C_{(1-4)}$烷基-$(OCH_2CH_2)_n$-OCH_3、OCH_3、CO_2H、$C(O)NH_2$、SO_2NH_2或$CO_2C_{(1-4)}$烷基取代；

n 为 1、2 或 3；

R^1为环己基或四氢吡喃基；

其中所述环己基或四氢吡喃基可任选地被一种取代基取代，所述取代基选自：OCH_3、OH、CH_2CH_3、-CN、NH_2、$NH(CH_3)$、$N(CH_3)_2$或OCF_3；

另选地，R^0和 R^1与它们连接的氮一起形成选自下列的环：  和；

R^a为苯基；

其中所述苯基任选地被 $C(O)NH_2$、$C(O)NHC_{(1-4)}$烷基、SO_2NH_2、$C(O)N(C_{(1-4)}$烷基$)_2$、OCH_3、CO_2CH_3或CO_2H取代；

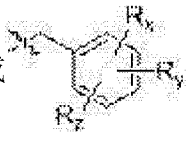
R^b为 $C_{(1-4)}$烷基或 $OC_{(1-4)}$烷基；

R^2选自 H、$C_{(1-4)}$烷基、环丙基、环己基、苯基、吡啶基、嘧啶基、吡嗪基、吡唑基、咪唑基、异噁唑基、噻唑基、呋喃基和噻吩基；

其中所述苯基、吡啶基、嘧啶基、吡嗪基、吡唑基、咪唑基、噁唑基、异噁唑基、噻唑基、呋喃基或噻吩基任选地被一个取代基取代，所述取代基选自：NH_2、$NHC_{(1-3)}$烷基、$N(C_{(1-3)}$烷基$)_2$、$C_{(1-3)}$烷基、-CN、$-CH=CH_2$、$-CONH_2$、$-CO_2H$、$-NO_2$、$-CONHC_{(1-4)}$烷基、$CON(C_{(1-4)}$烷基$)_2$、$C_{(1-4)}$烷基 $CONH_2$、$-NHCOC_{(1-4)}$烷基、$-CO_2C_{(1-4)}$烷基、CF_3、$SO_2C_{(1-4)}$烷基、$-SO_2NH_2$、$-SO_2NH(C_{(1-4)}$烷基）和 $-SO_2N(C_{(1-4)}$烷基$)_2$；

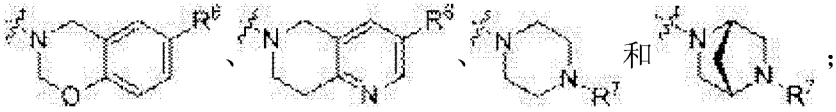
R^3为 H 或 CH_3；

另选地，R^3和 R^2与它们连接的碳一起形成  ；

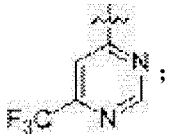
R^4为  或  ；

R^5为 H 或 CH_3；

另选地，R^4和 R^5与它们连接的氮一起形成选自下列的环：  、



R^6为 CF_3或 OCF_3；

R^7为 CF_3取代的杂芳基，前提条件是 R^7不为  ；

R_x为 CF_3、F、Cl、CN 或 OCH_3；

R_y为 H、F、Cl 或 CF_3；

R_z为 H 或 F。

2. 根据权利要求 1 所述的化合物或其药学上可接受的盐，其中：

A 为 O 或 S；

R^0为 H 或 $C_{(1-4)}$烷基，其中所述 $C_{(1-4)}$烷基任选地被 OH、$C_{(1-4)}$烷基 $(OCH_2CH_2)_nOCH_3$或 OCH_3取代；

n 为 1、2 或 3；

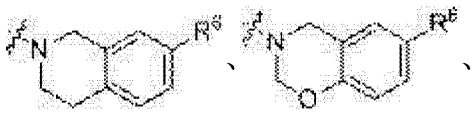
R^1为环己基、1- 甲氧基环己 -2- 基、四氢吡喃 -4- 基或 3- 甲氧基四氢吡喃 -4- 基；

另选地，R^0和 R^1与它们连接的氮一起形成选自下列的环：  ；

R^a为苯基；

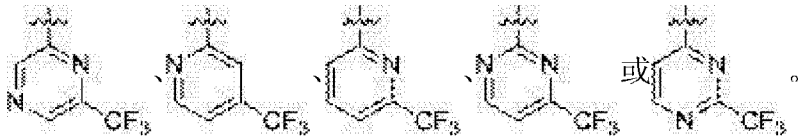
其中所述苯基任选地被 $C(O)NH_2$、$C(O)NHCH_3$、SO_2NH_2、$C(O)N(CH_3)_2$、OCH_3、CO_2CH_3或 CO_2H取代；

R^2为 H、$C_{(1-4)}$烷基、环丙基、环己基、噻唑 -2- 基、1- 甲基 - 咪唑 -2- 基、1- 甲基 - 吡唑 -5- 基或苯基；

R^4和 R^5与它们连接的氮一起形成选自下列的环：  、

 ；

R^6为 CF_3或 OCF_3；

R^7为  。

3. 根据权利要求 2 所述的化合物或其药学上可接受的盐，其中：

A 为 O 或 S；

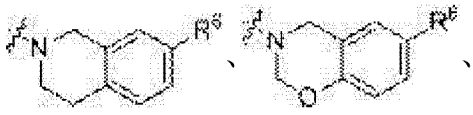
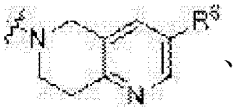
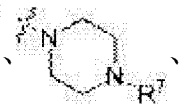
R^0为 H、CH_3、$CH_2CH_2CH_2OH$、CH_2CH_2OH、$CH_2CH_2CH_2-(OCH_2CH_2)_3-OCH_3$或 $CH_2CH_2OCH_3$；

R^1为四氢吡喃 -4- 基或 3- 甲氧基四氢吡喃 -4- 基；

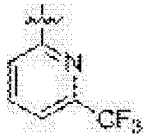
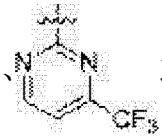
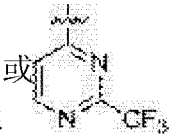
另选地，R^0和 R^1与它们连接的氮一起形成选自下列的环：  ；

R^a为苯基；

其中所述苯基任选地被 $C(O)N(CH_3)_2$、OCH_3或 CO_2H取代；

R^4和 R^5与它们连接的氮一起形成选自下列的环：  、、  、  、  ；

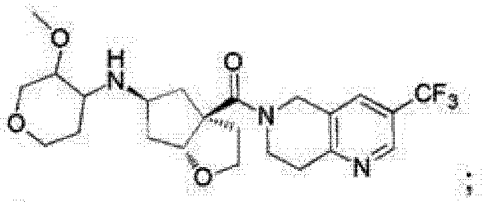
R^6为 CF_3或 OCF_3；

R^7为  、  或  。

4. 根据权利要求 3 所述的化合物或其药学上可接受的盐，其中：

A 为 O。

5. 根据权利要求 1 所述的化合物及其药学上可接受的盐，所述化合物选自：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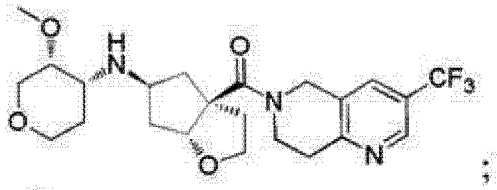
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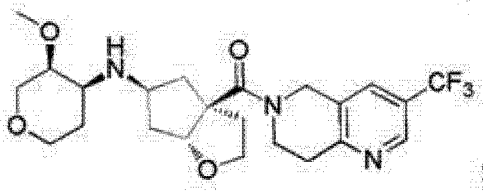
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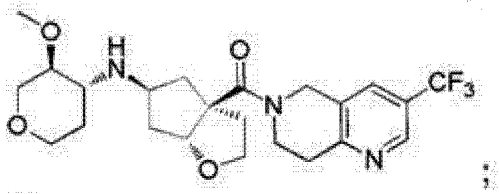
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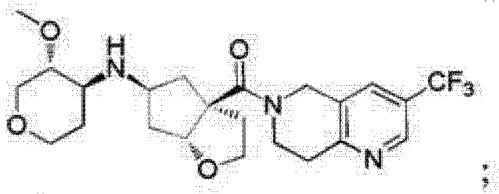
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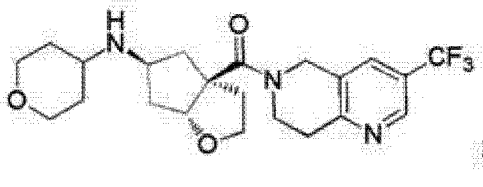
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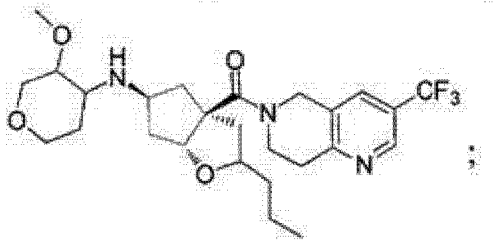
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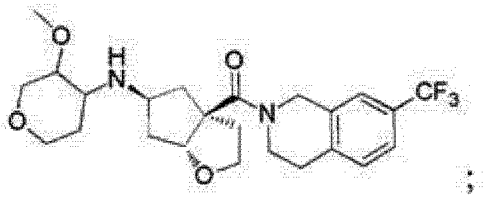
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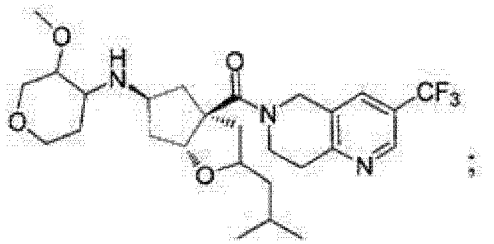
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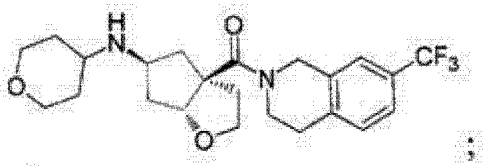
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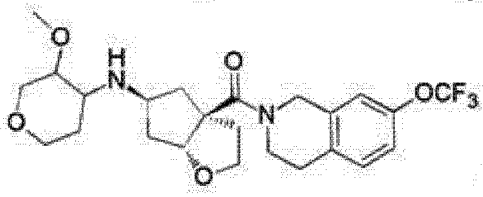
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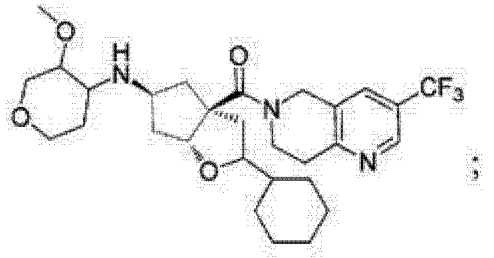
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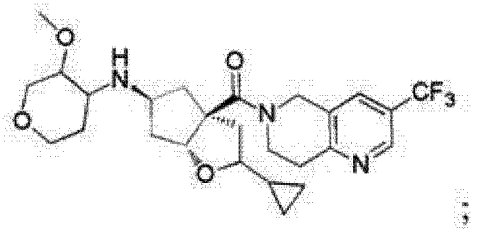
5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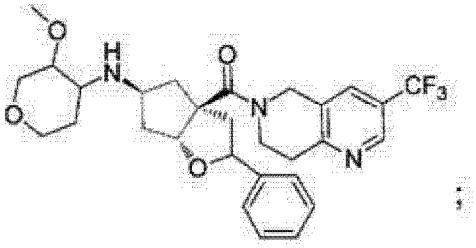
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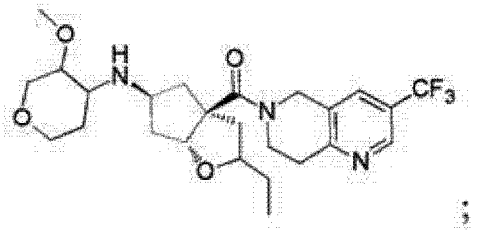
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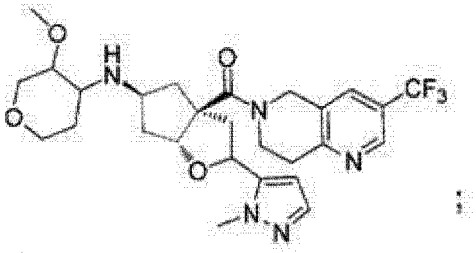
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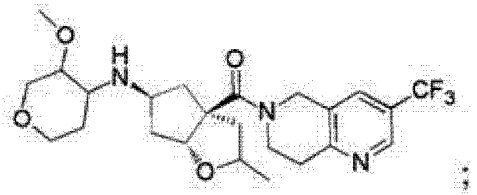
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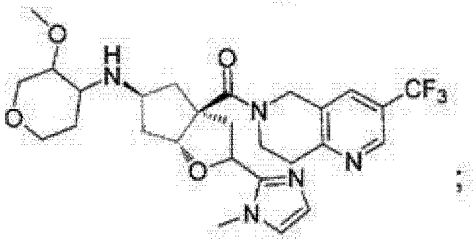
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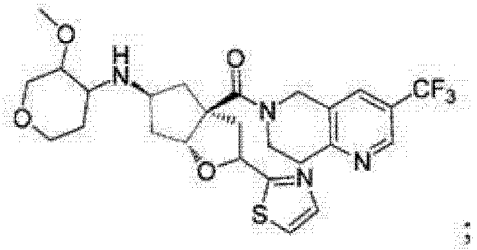
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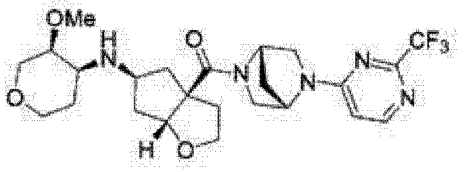
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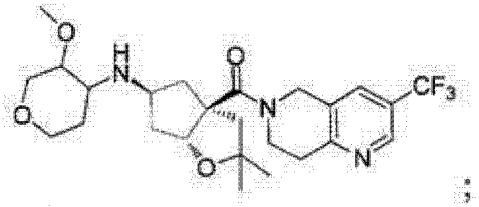
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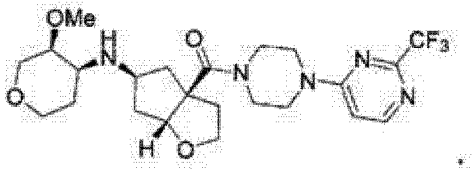
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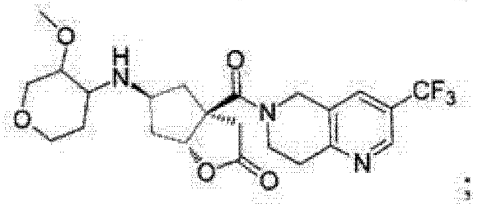
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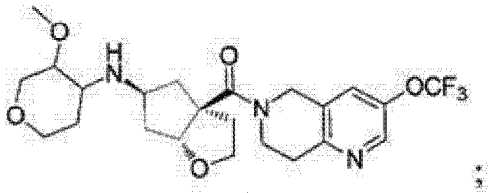
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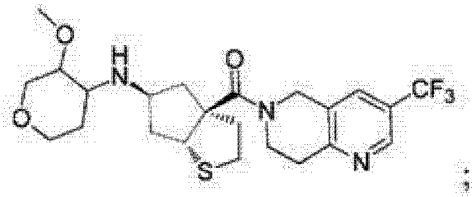
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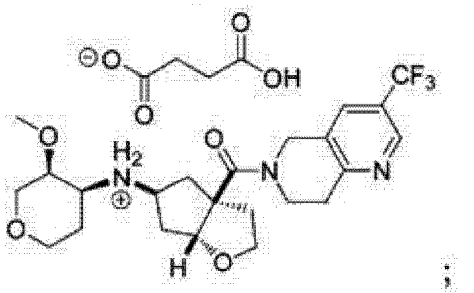
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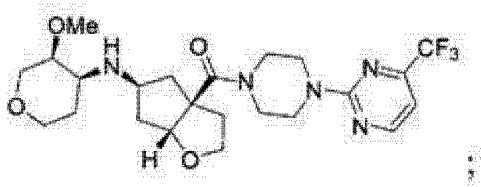
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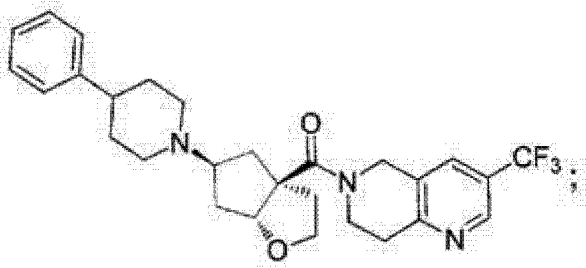
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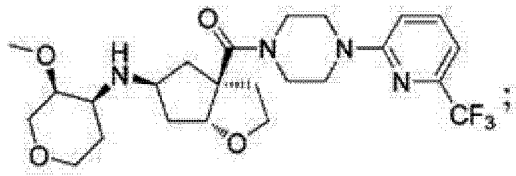
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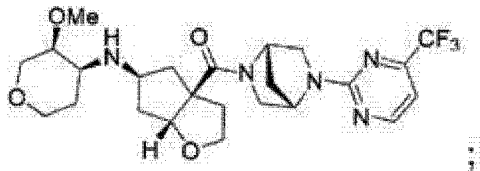
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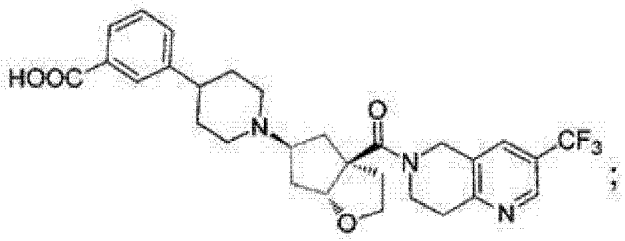
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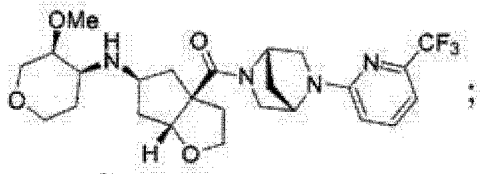
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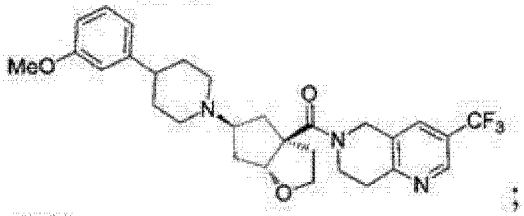
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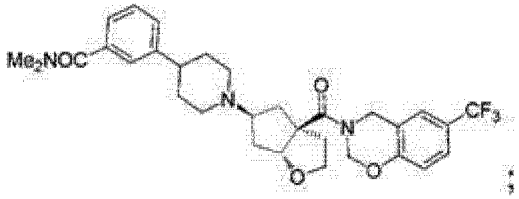
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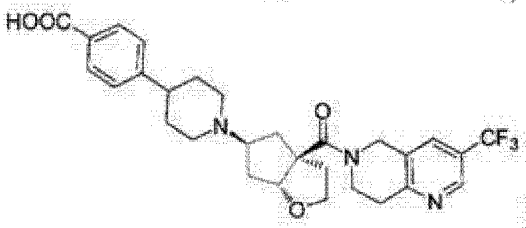
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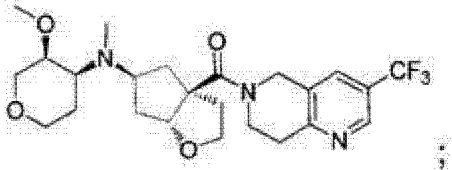
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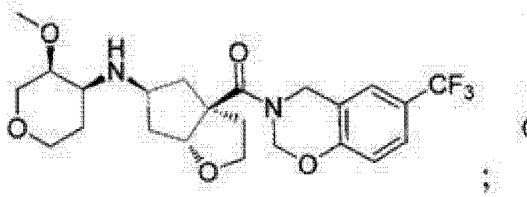
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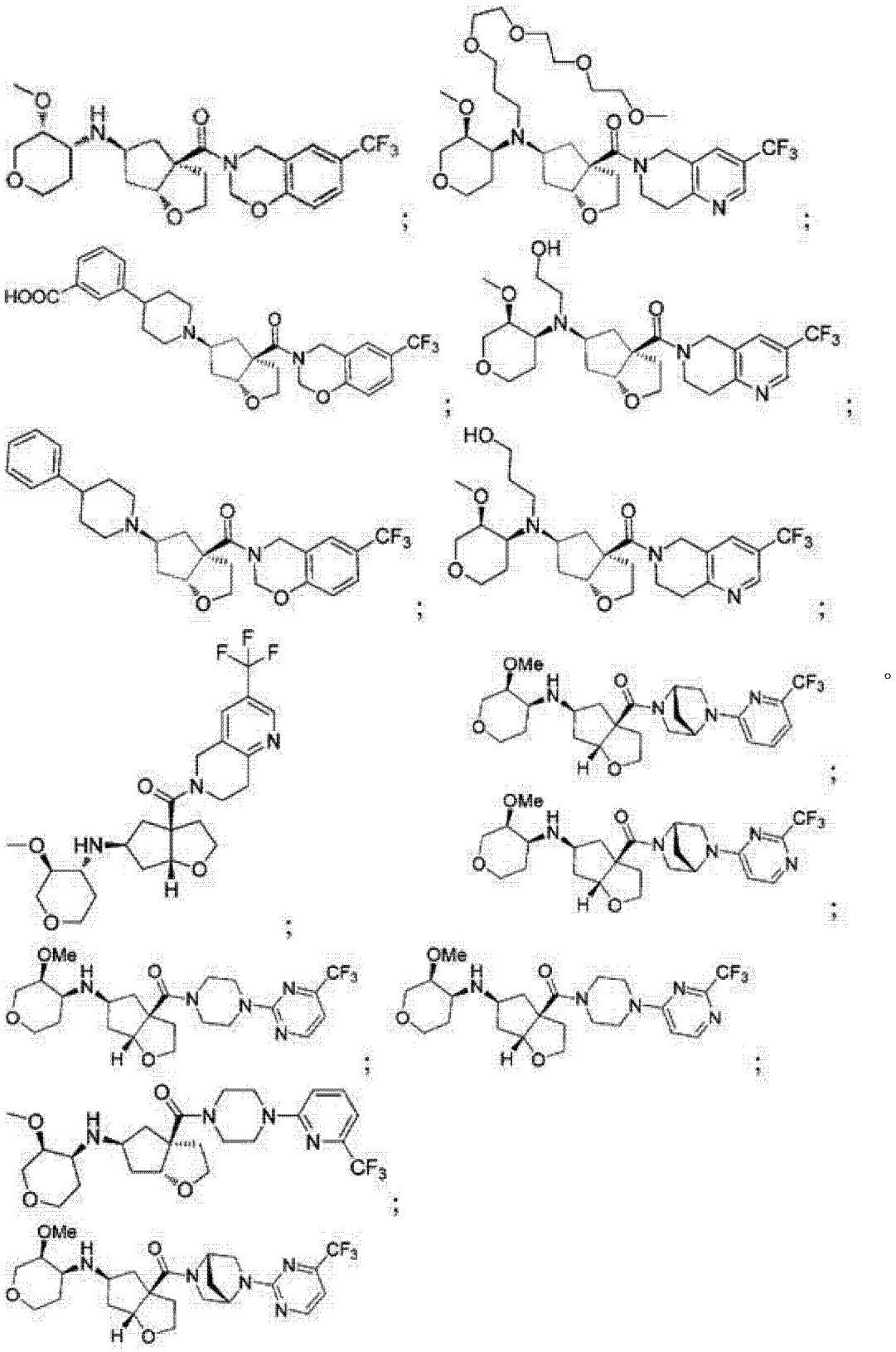
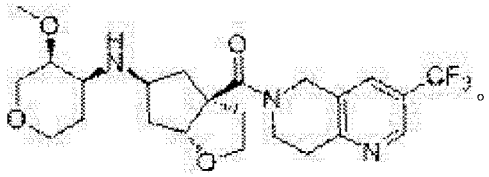
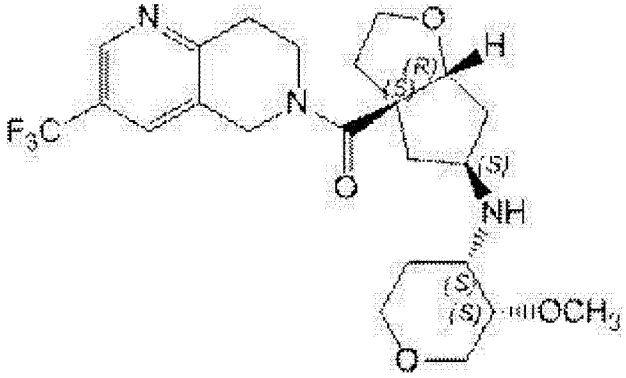


6. 一种化合物及其药学上可接受的盐，所述化合物为



。

7. 一种式 (I-S) 的化合物的琥珀酸盐



(I-S)。

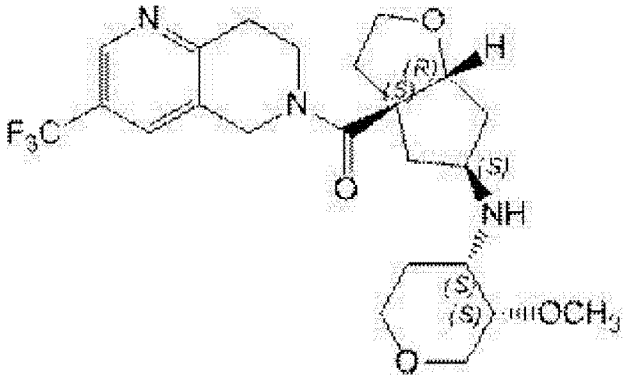
8. 根据权利要求 7 所述的盐，其中所述盐是结晶的。

9. 根据权利要求 7 所述的盐，其中所述盐是结晶水合物；并且其中所述水合物含有约 0.6 摩尔水 / 摩尔式 (I-S) 的化合物。

10. 根据权利要求 7 所述的盐，其中所述盐是结晶水合物；并且其中所述盐是吸湿性的。

11. 根据权利要求 7 所述的盐，其中所述盐是结晶的并表现出如通过 DSC 测量的约 158℃的峰值熔融温度。

12. 一种式 (I-S) 的化合物的结晶琥珀酸盐



(I-S)，

所述式 (I-S) 的化合物的结晶琥珀酸盐包含 11.27、13.87、19.22 和 22.01° 2θ 的 X 射线粉末衍射峰值。

13. 一种药物组合物，所述药物组合物包含权利要求 1 所述的化合物和药学上可接受的载体。

14. 一种药物组合物，所述药物组合物通过将权利要求 1 所述的化合物与药学上可接受的载体混合来制备。

15. 一种用于制备药物组合物的方法，所述方法包括将权利要求 1 所述的化合物与药学上可接受的载体混合。

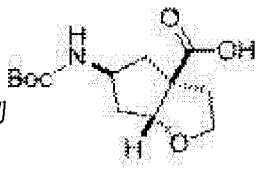
16. 一种用于预防、治疗或改善 CCR2 介导的综合征、障碍或疾病的方法，所述方法包括向对其有需要的受试者施用治疗有效量的权利要求 1 所述的化合物。

17. 一种用于预防、治疗或改善 CCR2 介导的炎性综合征、障碍或疾病的方法，其中所述综合征、障碍或疾病与升高的 MCP-1 表达或 MCP-1 过表达相关，或者是伴随与升高的 MCP-1 表达或 MCP-1 过表达相关的综合征、障碍或疾病的炎性病症，所述方法包括向对其有需要的受试者施用有效量的权利要求 1 所述的化合物。

18. 一种预防、治疗或改善综合征、障碍或疾病的方法，其中所述综合征、障碍或疾病选自：慢性阻塞性肺病 (COPD)、眼部障碍、葡萄膜炎、动脉粥样硬化、类风湿性关节炎、牛皮癣、牛皮癣关节炎、特应性皮炎、多发性硬化、克罗恩氏病、溃疡性结肠炎、肾炎、器官同种异体移植物排斥、纤维化肺、肾功能不全、I 型糖尿病、II 型糖尿病、糖尿病并发症、糖尿病性肾病、糖尿病性视网膜病、糖尿病性视网膜炎、糖尿病性微血管病、超重、肥胖症、肥胖症相关胰岛素抗性、代谢综合征、肺结核、肉样瘤病、侵入性葡萄球菌感染、白内障手术后炎症、过敏性鼻炎、过敏性结膜炎、慢性荨麻疹、哮喘、过敏性哮喘、牙周病、牙周炎、齿龈炎、齿龈疾病、舒张性心肌病、心肌梗死、心肌炎、慢性心力衰竭、血管狭窄、再狭窄、再灌注障碍、腹主动脉瘤、肾小球肾炎、实体瘤和癌症、慢性淋巴细胞性白血病、慢性粒细胞性白血病、多发性骨髓瘤、恶性骨髓瘤、何杰金氏病和膀胱癌、乳腺癌、宫颈癌、结肠癌、肺癌、前列腺癌或胃癌以及慢性神经炎性病症，包括但不限于阿尔茨海默氏病、缺血性中风、脊髓损伤、神经压碾损伤和外伤性脑损伤，所述方法包括向对其有需要的受试者施用有效量的权利要求 1 所述的化合物。

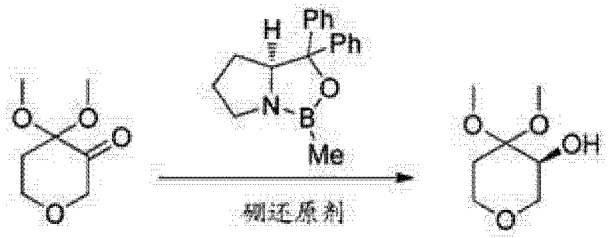
19. 一种预防、治疗或改善综合征、障碍或疾病的方法，其中所述综合征、障碍或疾病选自：I 型糖尿病、II 型糖尿病、糖尿病并发症、糖尿病性肾病、糖尿病性视网膜病、糖尿病性视网膜炎、糖尿病性微血管病、肥胖症、肥胖症相关胰岛素抗性、代谢综合征、哮喘和过敏性哮喘，所述方法包括向对其有需要的受试者施用治疗有效量的权利要求 1 所述的化合物。

20. 一种治疗病症的方法，所述病症选自 II 型糖尿病、肥胖症和哮喘，所述方法包括向对其有需要的受试者施用治疗有效量的权利要求 1 所述的化合物。

21. 一种式 (XXI) 的化合物  。

(XXI)

22. 一种用于制备 (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇的方法，所述方法包括



使 4,4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮与硼还原剂和 R-(+)-2- 甲基 -CBS- 噁唑硼烷经历至少六小时时段的反应，以提供至少 60% 对映体过量的 (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇。

23. 根据权利要求 22 所述的方法，其中 (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇以至

少 90% 对映体过量形成。

24. 根据权利要求 22 所述的方法，其中所述硼烷还原络合物选自硼烷 - 二甲基硫醚络合物或硼烷 -N, N- 二乙基苯胺络合物。

25. 根据权利要求 24 所述的方法，其中将所述硼烷还原络合物和 R-(+)-2- 甲基 -CBS- 噁唑硼烷的 THF 溶液加入在 THF 中的 4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮溶液中。

26. 根据权利要求 22 所述的方法，其中所述反应在惰性环境中执行。

27. 根据权利要求 26 所述的方法，其中所述反应在氮气下进行。

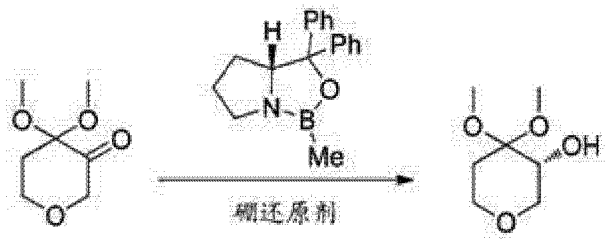
28. 根据权利要求 22 所述的反应，所述反应还包括使所述 (S)-4, 4- 二甲氧基四氢 -2H- 吡喃 -3- 醇与硫酸二甲酯反应，以提供 (R)-3, 4, 4- 三甲氧基四氢 -2H- 吡喃。

29. 根据权利要求 28 所述的反应，所述反应还包括使所述 (R)-3, 4, 4- 三甲氧基四氢 -2H- 吡喃与酸反应，以提供 (R)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮。

30. 根据权利要求 29 所述的反应，其中所述酸是浓盐酸。

31. 根据权利要求 22 所述的反应，其中所述反应在 20℃至 60℃的温度范围内进行。

32. 一种用于制备 (R)-4, 4- 二甲氧基四氢 -2H- 吡喃 -3- 醇的方法，所述方法包括



使 4, 4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮与硼还原剂和 S-(-)-2- 甲基 -CBS- 噁唑硼烷经历至少六小时时段的反应，以提供至少 60% 对映体过量的 (R)-4, 4- 二甲氧基四氢 -2H- 吡喃 -3- 醇。

33. 根据权利要求 32 所述的方法，其中 (R)-4, 4- 二甲氧基四氢 -2H- 吡喃 -3- 醇以至少 90% 对映体过量形成。

34. 根据权利要求 32 所述的方法，其中所述硼烷还原络合物选自硼烷 - 二甲基硫醚络合物或硼烷 -N, N- 二乙基苯胺络合物。

35. 根据权利要求 34 所述的方法，其中将所述硼烷还原络合物和 S-(-)-2- 甲基 -CBS- 噁唑硼烷的 THF 溶液加入在 THF 中的 4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮溶液中。

36. 根据权利要求 32 所述的方法，其中所述反应在惰性环境中执行。

37. 根据权利要求 36 所述的方法，其中所述反应在氮气下进行。

38. 根据权利要求 32 所述的反应，所述反应还包括使所述 (R)-4, 4- 二甲氧基四氢 -2H- 吡喃 -3- 醇与硫酸二甲酯反应，以提供 (S)-3, 4, 4- 三甲氧基四氢 -2H- 吡喃。

39. 根据权利要求 38 所述的反应，所述反应还包括使所述 (S)-3, 4, 4- 三甲氧基四氢 -2H- 吡喃与酸反应，以提供 (S)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮。

40. 根据权利要求 39 所述的反应，其中所述酸是浓盐酸。

41. 根据权利要求 32 所述的反应，其中所述反应在 20℃至 60℃的温度范围内进行。

CCR2 的稠合环戊基拮抗剂

技术领域

[0001] 本发明涉及取代的稠合环戊基化合物、其药物组合物及其使用方法，所述取代的稠合环戊基化合物为趋化性细胞因子受体 2(CCR2) 的拮抗剂。更具体而言，所述 CCR2 拮抗剂是可用于预防、治疗或改善 CCR2 介导的综合征、障碍或疾病的化合物。本发明还涉及((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基）氨基）六氢 -2H- 环戊并[b] 呋喃 -3a- 基）(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基）甲酮的结晶琥珀酸盐，含有所述盐的药物组合物和所述盐在治疗障碍例如 II 型糖尿病、肥胖症和哮喘中的用途。本发明还涉及用于制备所述结晶琥珀酸盐的新方法。

背景技术

[0002] CCR2 是 GPCR 受体家族的成员（统称为趋化因子受体），由单核细胞和记忆性 T- 淋巴细胞表达。CCR2 信号级联放大涉及磷脂酶 (PLC β 2)、蛋白激酶 (PKC) 和脂类激酶 (PI-3 激酶）的激活。

[0003] 趋化性细胞因子（即趋化因子）是相对较小的蛋白质 (8-10kD)，其刺激细胞的迁移。根据第一个高度保守的半胱氨酸和第二个高度保守的半胱氨酸之间的氨基酸残基数将趋化因子家族分成四个亚族。

[0004] 单核细胞趋化蛋白 -1(MCP-1) 是 CC 趋化因子亚族（其中 CC 表示第一个半胱氨酸和第二个半胱氨酸相邻的亚族）的成员，并且与细胞表面趋化因子受体 2(CCR2) 结合。MCP-1 是强效的趋化因子，其在结合至 CCR2 后可介导单核细胞和淋巴细胞向炎症位点迁移（即趋化性）。MCP-1 还由心肌细胞、血管内皮细胞、成纤维细胞、软骨细胞、平滑肌细胞、肾小球膜细胞、肺泡细胞、T- 淋巴细胞、巨噬细胞等表达。

[0005] 在单核细胞进入炎性组织并分化成巨噬细胞后，单核细胞分化提供数种促炎性调节剂的第二来源，所述调节剂包括肿瘤坏死因子 - α (TNF- α)、白介素 -1(IL-1)、IL-8(CXC 趋化因子亚族的成员，其中 CXC 表示在第一个半胱氨酸和第二个半胱氨酸之间的一个氨基酸残基）、IL-12、花生四烯酸代谢物（例如 PGE_2 和 LTB_4）、氧衍生的自由基、基质金属蛋白酶和补体成分。

[0006] 慢性炎性疾病的动物模型研究已证明通过拮抗剂抑制 MCP-1 和 CCR2 之间的结合抑制了炎性应答。MCP-1 和 CCR2 之间的相互作用已牵涉（参见 Rollins B J，Monocyte chemoattractant protein 1 :a potential regulator of monocyte recruitment in inflammatory disease，Mol.Med.Today，1996，2 :198 ； 和 Dawson J 等 人，Targeting monocyte chemoattractant protein-1 signaling in disease，Expert Opin.Ther. Targets，2003Feb.7(1) :35-48) 炎性疾病病理例如牛皮癣、葡萄膜炎、动脉粥样硬化、类风湿性关节炎 (RA)、多发性硬化、克罗恩氏病、肾炎、器官同种异体移植物排斥、纤维化肺、肾功能不全、II 型糖尿病和糖尿病并发症、糖尿病性肾病、糖尿病性视网膜病、糖尿病性视网膜炎、糖尿病性微血管病、肺结核、肉样瘤病、侵入性葡萄球菌 (staphylococcia) 感染、白内障手术后炎症、过敏性鼻炎、过敏性结膜炎、慢性荨麻疹、慢性阻塞性肺病 (COPD)、过敏性

哮喘、牙周病、牙周炎、齿龈炎、齿龈疾病、舒张性心肌病、心肌梗死、心肌炎、慢性心力衰竭、血管狭窄、再狭窄、再灌注障碍、肾小球肾炎、实体瘤和癌症、慢性淋巴细胞性白血病、慢性粒细胞性白血病、多发性骨髓瘤、恶性骨髓瘤、何杰金氏病以及膀胱癌、乳腺癌、宫颈癌、结肠癌、肺癌、前列腺癌和胃癌。

[0007] 单核细胞迁移由MCP-1拮抗剂(MCP-1的抗体或可溶性失活片段)抑制,其已显示出抑制关节炎、哮喘和葡萄膜炎的发展。MCP-1和CCR2敲除(KO)小鼠均已证明显著减少了单核细胞向炎性病变处的浸润。此外,这种KO小鼠可抵抗实验性过敏性脑脊髓炎(EAE,一种人MS模型)、蟑螂过敏原诱导的哮喘、动脉硬化症和葡萄膜炎的发展。类风湿性关节炎和克罗恩氏病患者在用TNF-α拮抗剂(例如单克隆抗体和可溶性受体)以与MCP-1表达及浸润性巨噬细胞数量减少相关的剂量治疗期间得以改善。

[0008] MCP-1已牵涉于季节性过敏性鼻炎和慢性过敏性鼻炎的发病机理中,其被发现于大多数尘螨过敏患者的鼻粘膜中。已发现MCP-1还可体外诱发组胺从嗜碱粒细胞释放。在过敏性病症期间,变应原和组胺均已显示引发(即上调)MCP-1及其他趋化因子在过敏性鼻炎患者的鼻粘膜中的表达,提示这些患者中存在正反馈回路。

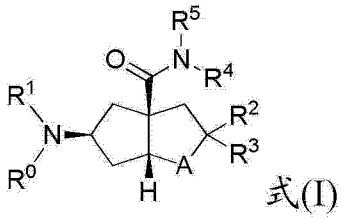
[0009] 仍然需要小分子CCR2拮抗剂来预防、治疗或改善由MCP-1诱导的单核细胞和淋巴细胞向炎性位点的迁移而导致的CCR2介导的炎性综合征、障碍或疾病。

[0010] 将本文引用的所有文献以引用方式并入本文。

发明内容

[0011] 本发明涉及式(I)的化合物及其药学上可接受的盐,

[0012]



式(I)

[0013] 其中:

[0014] A为O或S;

[0015] R^0为H或$C_{(1-4)}$烷基;

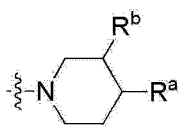
[0016] 其中所述$C_{(1-4)}$烷基任选地被OH、$C_{(1-4)}$烷基-$(OCH_2CH_2)_n$-OCH_3、OCH_3、CO_2H、$C(O)NH_2$、SO_2NH_2或$CO_2C_{(1-4)}$烷基取代;

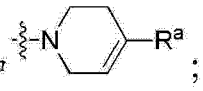
[0017] n为1、2或3;

[0018] R^1为环己基或四氢吡喃基;

[0019] 其中所述环己基或四氢吡喃基可任选地被一种取代基取代,所述取代基选自:OCH_3、OH、CH_2CH_3、-CN、NH_2、$NH(CH_3)$、$N(CH_3)_2$和OCF_3;

[0020] 另选地,R^0和R^1与它们连接的氮一起形成选自下列的环:



和  ；

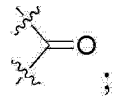
[0021] R^a为苯基；其中所述苯基任选地被 C(O)NH_2、C(O)$NHC_{(1-4)}$烷基、SO_2NH_2、C(O)N($C_{(1-4)}$烷基)$_2$、OCH_3、CO_2CH_3或 CO_2H 取代；

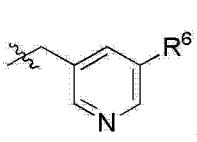
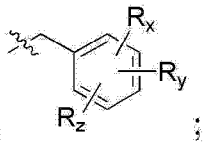
[0022] R^b为 $C_{(1-4)}$烷基或 $OC_{(1-4)}$烷基；

[0023] R^2选自 H、$C_{(1-4)}$烷基、环丙基、环己基、苯基、吡啶基、嘧啶基、吡嗪基、吡唑基、咪唑基、异噁唑基、噻唑基、呋喃基和噻吩基；

[0024] 其中所述苯基、吡啶基、嘧啶基、吡嗪基、吡唑基、咪唑基、噁唑基、异噁唑基、噻唑基、呋喃基或噻吩基任选地被一种取代基取代，所述取代基选自：NH_2、$NHC_{(1-3)}$烷基、N($C_{(1-3)}$烷基)$_2$、$C_{(1-3)}$烷基、-CN、-CH = CH_2、-$CONH_2$、-CO_2H、-NO_2、-$CONHC_{(1-4)}$烷基、CON($C_{(1-4)}$烷基)$_2$、$C_{(1-4)}$烷基 $CONH_2$、-$NHCOC_{(1-4)}$烷基、-$CO_2C_{(1-4)}$烷基、CF_3、$SO_2C_{(1-4)}$烷基、-SO_2NH_2、-SO_2NH($C_{(1-4)}$烷基)和 -SO_2N($C_{(1-4)}$烷基)$_2$；

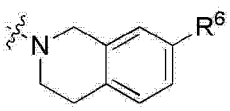
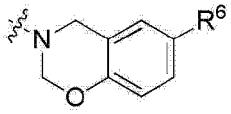
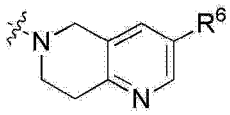
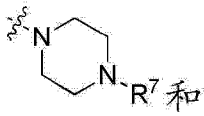
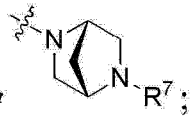
[0025] R^3为 H 或 CH_3；

[0026] 另选地，R^3和 R^2与它们连接的碳一起形成  ；

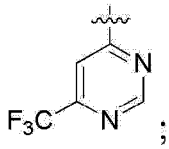
[0027] R^4为  或  ；

[0028] R^5为 H 或 CH_3；

[0029] 另选地，R^4和 R^5与它们连接的氮一起形成选自下列的环：

 、  、  、  和  ；

[0030] R^6为 CF_3或 OCF_3；

[0031] R^7为 CF_3取代的杂芳基，前提条件是 R^7不为  ；

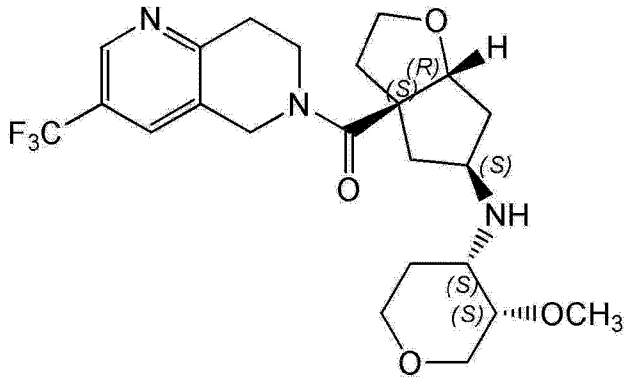
[0032] R_x为 CF_3、F、Cl、CN 或 OCH_3；

[0033] R_y为 H、F、Cl 或 CF_3；

[0034] R_z为 H 或 F。

[0035] 本发明还涉及式 (I-S) 的化合物的琥珀酸盐，

[0036]



(I-S)

[0037] 也称为((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮。在本发明的一个实施例中,式(I-S)的化合物的琥珀酸盐是结晶的。在另一个实施例中,本发明涉及式(I-S)的化合物的琥珀酸盐,其中所述盐是结晶水合物形式;优选地,水合物含有约0.6摩尔水/摩尔式(I-S)的化合物。在本发明的另外一个实施例中,式(I-S)的化合物的琥珀酸盐是含有约0.6摩尔水/摩尔式(I-S)的化合物的结晶水合物形式,并且还是吸湿性的。

[0038] 本发明还涉及如下文更详细地描述的,用于制备式(I-S)的化合物的琥珀酸盐,优选式(I-S)的化合物的结晶琥珀酸盐的方法。

附图说明

[0039] 图1示出了式(I-S)的化合物的结晶琥珀酸盐的代表性pXRD光谱。

[0040] 图2示出了式(I-S)的化合物的结晶琥珀酸盐的代表性DSC扫描。

[0041] 图3示出了式(I-S)的化合物的结晶琥珀酸盐的代表性TGA扫描。

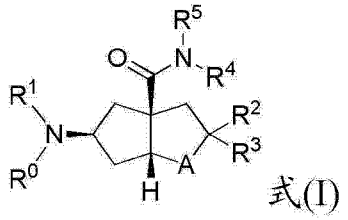
[0042] 图4示出了式(I-S)的化合物的结晶琥珀酸盐的代表性吸湿等温线。

[0043] 图5示出了显示式(I-S)的化合物的无定形琥珀酸盐至式(I-S)的化合物的结晶琥珀酸盐的代表性样品转换的DSC热谱图;和式(I-S)的化合物的无定形琥珀酸盐的代表性样品的TGA热谱图。

具体实施方式

[0044] 本发明涉及式(I)的化合物,

[0045]



式(I)

[0046] 其中:

[0047] A、R^0、R^1、R^2、R^3、R^4和R^5如上定义。

[0048] 在一个实施例中,本发明涉及式(I)的化合物,其中A为O。

[0049] 在另一个实施例中,本发明涉及式(I)的化合物及其药学上可接受的盐,其中

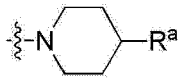
[0050] A 为 O 或 S；

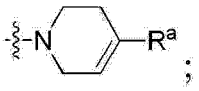
[0051] R^0为 H 或 $C_{(1-4)}$烷基；

[0052] 其中所述 $C_{(1-4)}$烷基任选地被 OH、$C_{(1-4)}$烷基 $-(OCH_2CH_2)_n-OCH_3$或 OCH_3取代；

[0053] n 为 1、2 或 3；

[0054] R^1为环己基、1- 甲氧基环己 -2- 基、四氢吡喃 -4- 基或 3- 甲氧基四氢吡喃 -4- 基；

[0055] 另选地，R^0和 R^1与它们连接的氮一起形成选自下列的环： 

和  ；

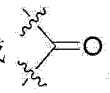
[0056] R^a为苯基；

[0057] 其中所述苯基任选地被 $C(O)NH_2$、$C(O)NHCH_3$、SO_2NH_2、$C(O)N(CH_3)_2$、OCH_3、CO_2CH_3或 CO_2H 取代；

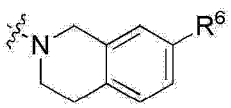
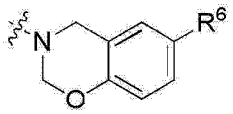
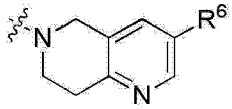
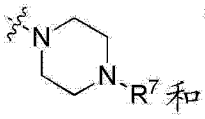
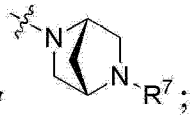
[0058] R^2选自 H、$C_{(1-4)}$烷基、环丙基、环己基、苯基、吡啶基、嘧啶基、吡嗪基、吡唑基、咪唑基、异噁唑基、噻唑基、呋喃基和噻吩基；

[0059] 其中所述苯基、吡啶基、嘧啶基、吡嗪基、吡唑基、咪唑基、噁唑基、异噁唑基、噻唑基、呋喃基或噻吩基任选地被一种取代基取代，所述取代基选自：NH_2、$NHC_{(1-3)}$烷基、$N(C_{(1-3)}$烷基$)_2$、$C_{(1-3)}$烷基、-CN、-CH = CH_2、$-CONH_2$、$-CO_2H$、$-NO_2$、$-CONHC_{(1-4)}$烷基、$CON(C_{(1-4)}$烷基$)_2$、$C_{(1-4)}$烷基 $CONH_2$、$-NHCOC_{(1-4)}$烷基、$-CO_2C_{(1-4)}$烷基、CF_3、$SO_2C_{(1-4)}$烷基、$-SO_2NH_2$、$-SO_2NH(C_{(1-4)}$烷基）和 $-SO_2N(C_{(1-4)}$烷基$)_2$；

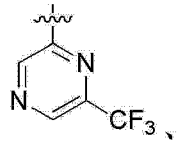
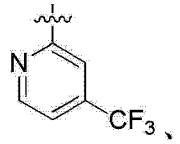
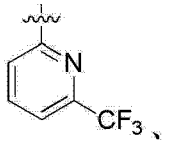
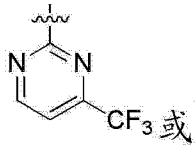
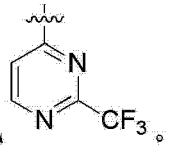
[0060] R^3为 H 或 CH_3；

[0061] 另选地，R^3和 R^2与它们连接的碳一起形成  ；

[0062] 另选地，R^4和 R^5与它们连接的氮一起形成选自下列的环：

 、  、  、  和  ；

[0063] R^6为 CF_3或 OCF_3；

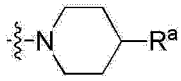
[0064] R^7为  、  、  、  或  。

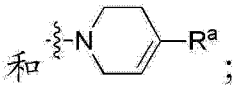
[0065] 在本发明的另一个实施例中，

[0066] A 为 O 或 S；

[0067] R^0为 H、CH_3、$CH_2CH_2CH_2OH$、CH_2CH_2OH、$CH_2CH_2CH_2(OCH_2CH_2)_3OCH_3$或 $CH_2CH_2OCH_3$；

[0068] R^1为四氢吡喃 -4- 基或 3- 甲氧基四氢吡喃 -4- 基；

[0069] 另选地，R^0和 R^1与它们连接的氮一起形成选自下列的环： 

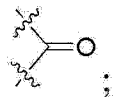


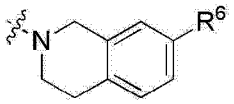
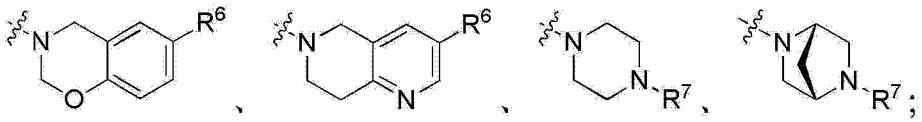
[0070] R^a为苯基；

[0071] 其中所述苯基任选地被$C(O)N(CH_3)_2$、OCH_3或CO_2H取代；

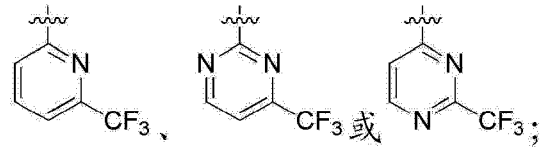
[0072] R^2为H、$C_{(1-4)}$烷基、环丙基、环己基、噻唑-2-基、1-甲基-咪唑-2-基、1-甲基-吡唑-5-基或苯基；

[0073] R^3为H或CH_3；

[0074] 另选地，R^3和R^2与它们连接的碳一起形成  ；

[0075] R^4和R^5与它们连接的氮一起形成选自下列的环：  、  ；

[0076] R^6为CF_3或OCF_3；

[0077] R^7为  ；

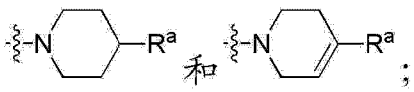
[0078] 及其药学上可接受的盐。

[0079] 在另一个实施例中，本发明涉及式(I)的化合物及其药学上可接受的盐，其中

[0080] A为O；

[0081] R^0为H、CH_3、$CH_2CH_2CH_2OH$、CH_2CH_2OH、$CH_2CH_2CH_2(OCH_2CH_2)_3OCH_3$或$CH_2CH_2OCH_3$；

[0082] R^1为四氢吡喃-4-基或3-甲氧基四氢吡喃-4-基；

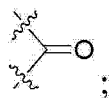
[0083] 另选地，R^0和R^1可与它们连接的氮一起形成选自下列的环：  ；

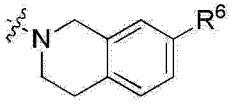
[0084] R^a为苯基；

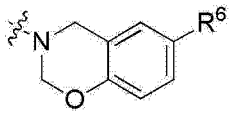
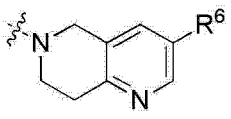
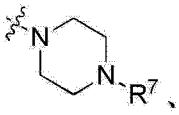
[0085] 其中所述苯基任选地被$C(O)N(CH_3)_2$、OCH_3或CO_2H取代；

[0086] R^2为H、$C_{(1-4)}$烷基、环丙基、环己基、噻唑-2-基、1-甲基-咪唑-2-基、1-甲基-吡唑-5-基或苯基；

[0087] R^3为H或CH_3；

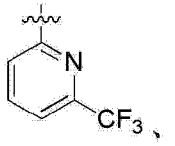
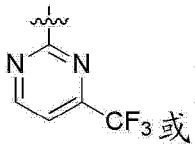
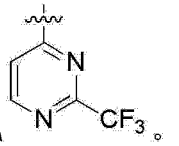
[0088] 另选地，R^3和R^2与它们连接的碳一起形成  ；

[0089] R^4和R^5与它们连接的氮一起形成选自下列的环：  、

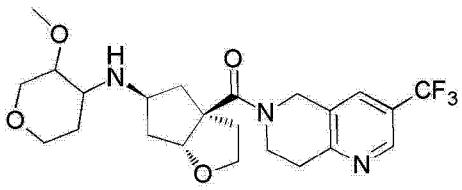
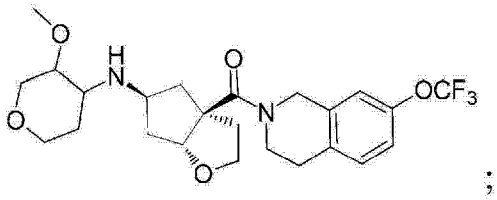
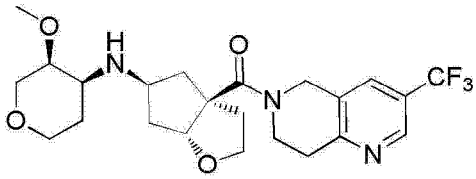

、

、

、

；

[0090] R^6为 CF_3或 OCF_3；

[0091] R^7为

、

或

。

[0092] 在另一个实施例中，本发明涉及独立地选自下列的任何一种或多种化合物及其药学上可接受的盐：

[0093]

；

；

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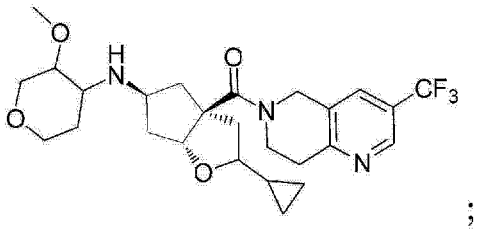
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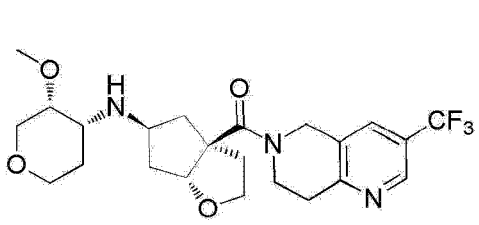
[0094]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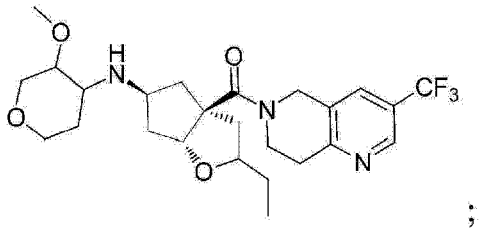
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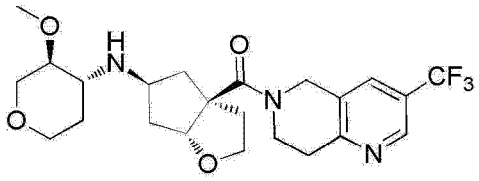
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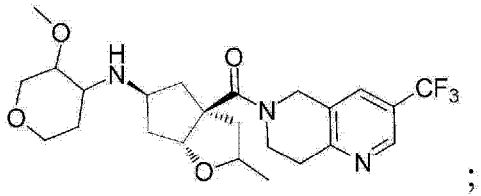
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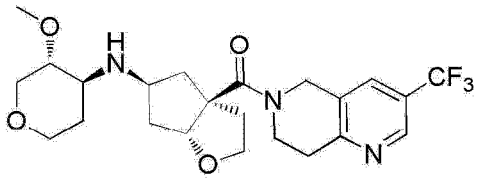
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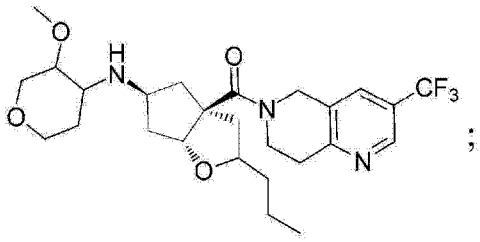
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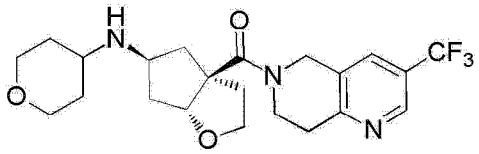
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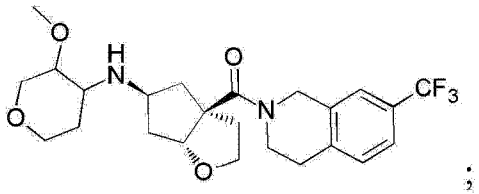
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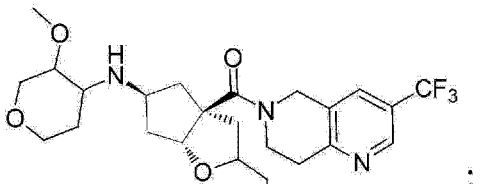
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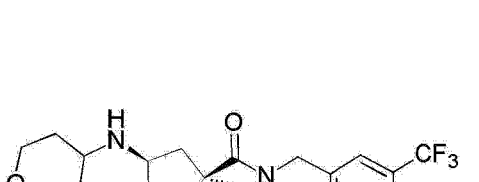
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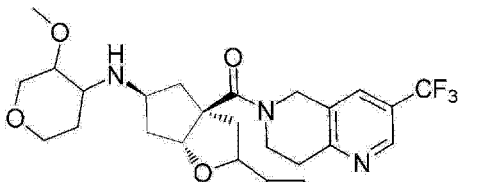
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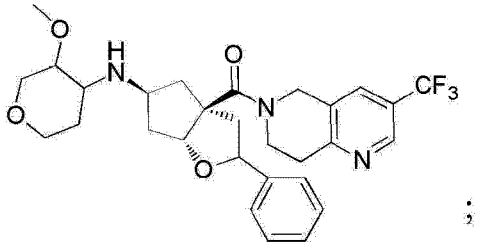
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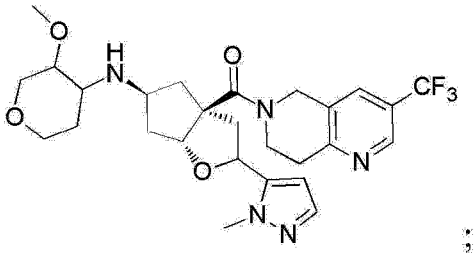
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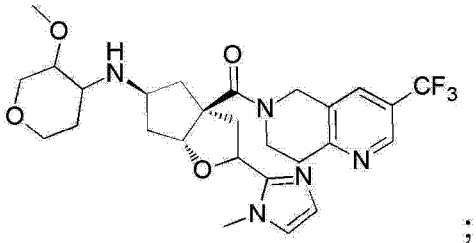
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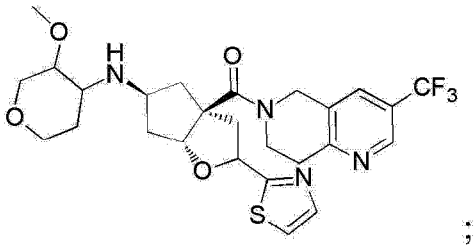
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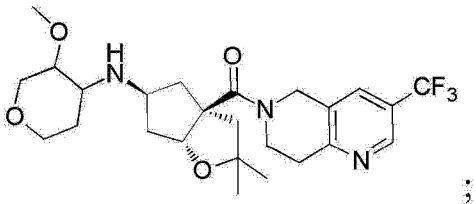
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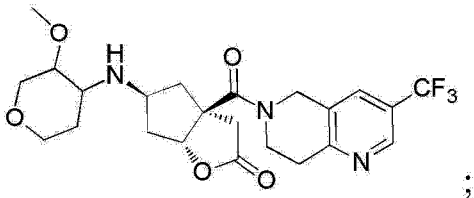
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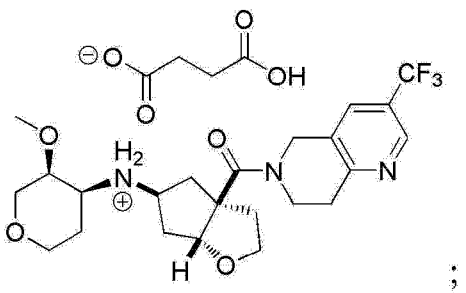
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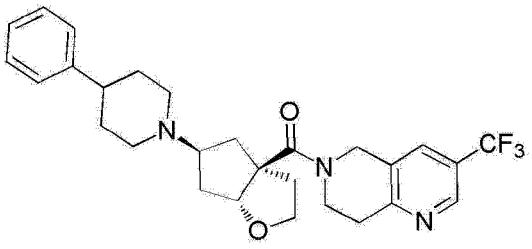
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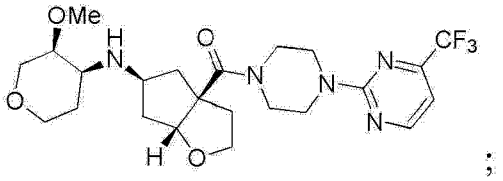
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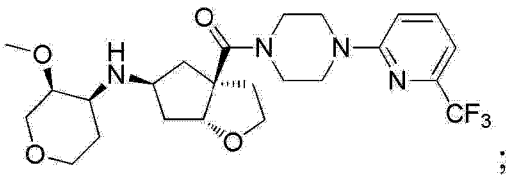
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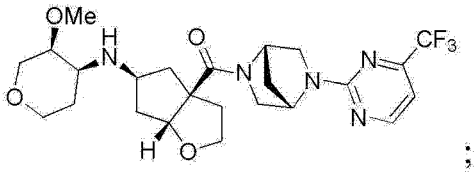
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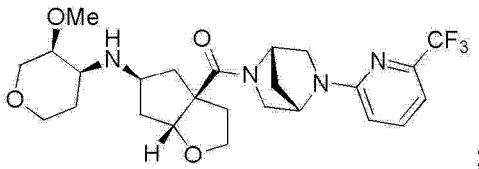
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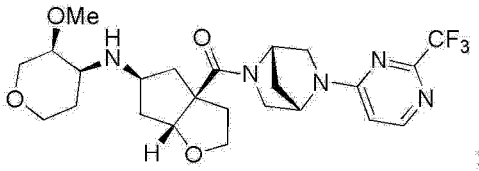
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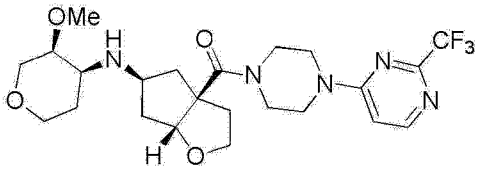
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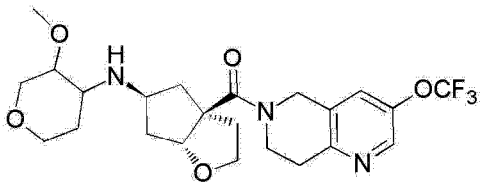
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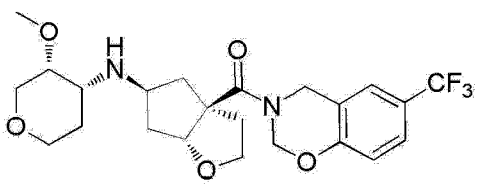
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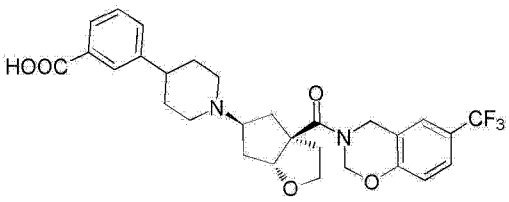
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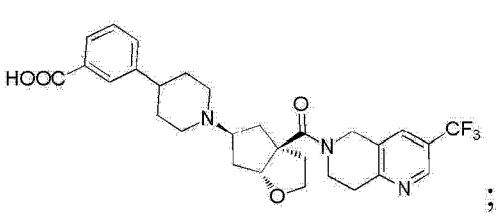
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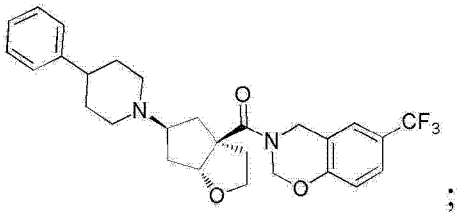
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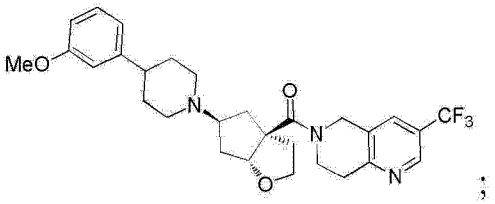
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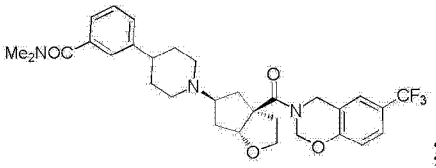
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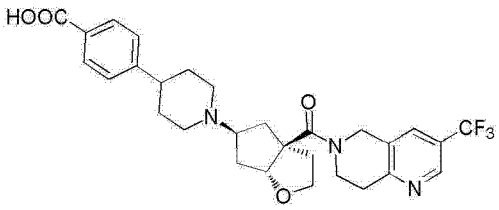
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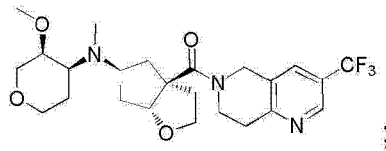
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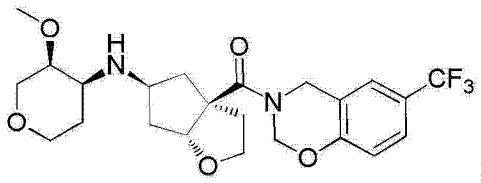
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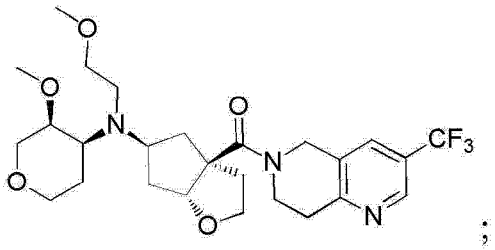
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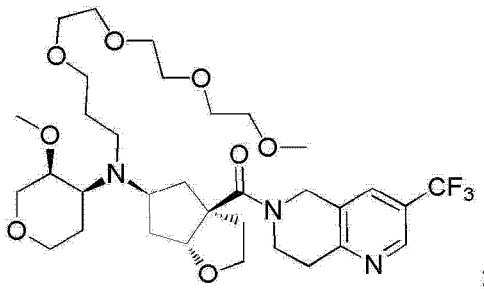
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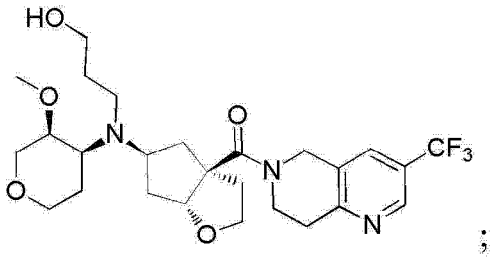
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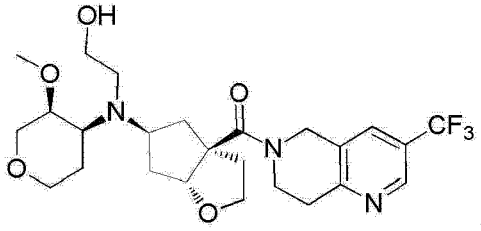
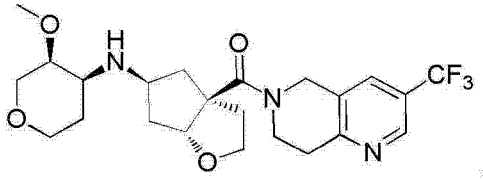

。

[0097] 在另一个实施例中，本发明涉及下式的化合物或其药学上可接受的盐：

[0098]


。

[0099] 在另一个实施例中，本发明涉及包含式（I）的化合物和药学上可接受的载体的药物组合物。

[0100] 在另一个实施例中，本发明涉及通过混合式（I）的化合物和药学上可接受的载体

制备的药物组合物。

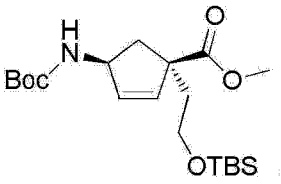
[0101] 在另一个实施例中，本发明涉及用于制备药物组合物的方法，所述方法包括将式(I)的化合物和药学上可接受的载体混合。

[0102] 本发明还涉及根据任何本文所述的方法制备的产物。在另一个实施例中，本发明涉及根据如本文下文的实例31中所述的方法制备的产物。

[0103] 在另一个实施例中，本发明涉及如本文下文的方案和实例中更详细地描述的，用于制备式(I)的化合物的方法。在另一个实施例中，本发明涉及如本文下文的实例31中更详细地描述的，用于制备式(I)的化合物的方法。

[0104] 在另一个实施例中，本发明涉及选自下列的化合物：

[0105]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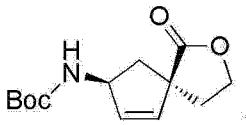
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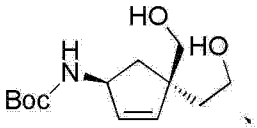
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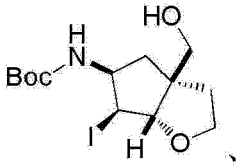
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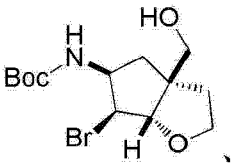
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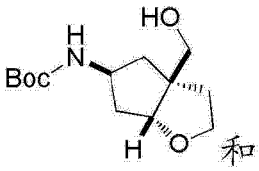
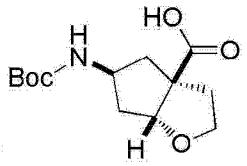
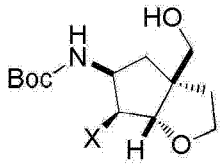

和

；这些化合物可用作式(I)的化合物制备的中间体。

[0106] 在另一个实施例中，本发明涉及可用作式(I)的化合物，更具体而言式(XIX)的化合物制备的中间体，

[0107]

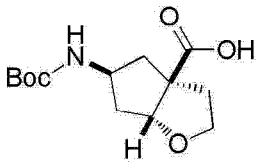


(XIX)，

[0108] 其中X为Br、PhSe或I。

[0109] 在另一个实施例中，本发明涉及可用作式(I)的化合物制备的中间体的式(XXI)的化合物

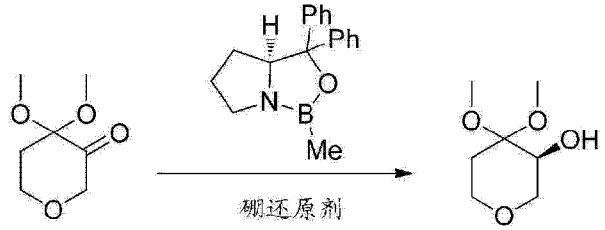
[0110]



(XXI)。

[0111] 在另一个实施例中，本发明涉及用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法，所述方法包括：

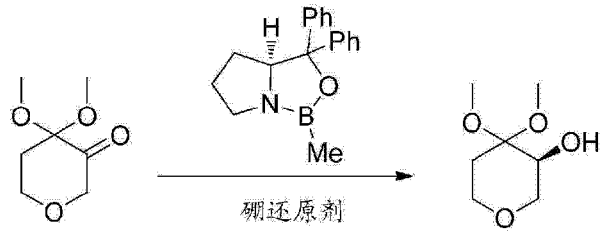
[0112]



[0113] 使4,4-二甲氧基二氢-2H-吡喃-3(4H)-酮与硼还原剂和R-(+)-2-甲基-CBS-噁唑硼烷经历至少六小时时段的反应,以提供至少60%对映体过量的(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇。

[0114] 在另一个实施例中,本发明涉及用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,所述方法包括:

[0115]



[0116] 使4,4-二甲氧基二氢-2H-吡喃-3(4H)-酮与硼还原剂和R-(+)-2-甲基-CBS-噁唑硼烷经历至少六小时时段的反应,以提供至少90%对映体过量的(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇。

[0117] 在另一个实例中,本发明涉及如上所述用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,其中所述硼烷还原络合物选自硼烷-二甲基硫醚络合物或硼烷-N,N-二乙基苯胺络合物。

[0118] 在另一个实施例中,本发明涉及如上所述用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,其中将所述硼烷还原络合物和R-(+)-2-甲基-CBS-噁唑硼烷的THF溶液加入在THF中的4-二甲氧基二氢-2H-吡喃-3(4H)-酮溶液中。

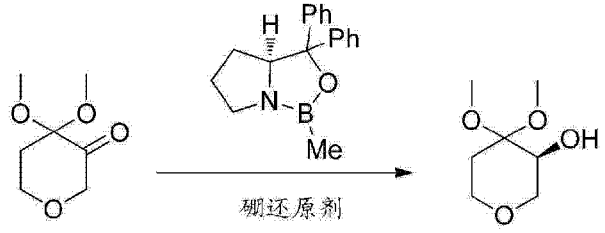
[0119] 在另一个实施例中,本发明涉及如上所述用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法中的任一种,其中所述反应在惰性环境中执行;在本发明的另一个实施例中,惰性环境是氮气。

[0120] 在另一个实施例中,本发明涉及如上所述用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法中的任一种,所述方法还包括使(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇与硫酸二甲酯反应,以提供(R)-3,4,4-三甲氧基四氢-2H-吡喃。

[0121] 在另一个实施例中,本发明涉及如上所述用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法中的任一种,所述方法还包括使(R)-3,4,4-三甲氧基四氢-2H-吡喃与酸反应,以提供(R)-3-甲氧基二氢-2H-吡喃-4(3H)-酮。在另一个实施例中,酸是浓盐酸。

[0122] 在另一个实施例中,本发明涉及用于制备(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,所述方法包括:

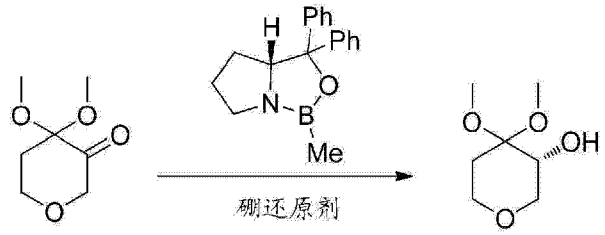
[0123]



[0124] 使4,4-二甲氧基二氢-2H-吡喃-3(4H)-酮与硼还原剂和R-(+)-2-甲基-CBS-噁唑硼烷经历至少六小时时段的反应,以提供至少60%对映体过量的(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇,其中所述反应在20℃至60℃的温度范围内进行。

[0125] 在另一个实施例中,本发明涉及用于制备(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,所述方法包括:

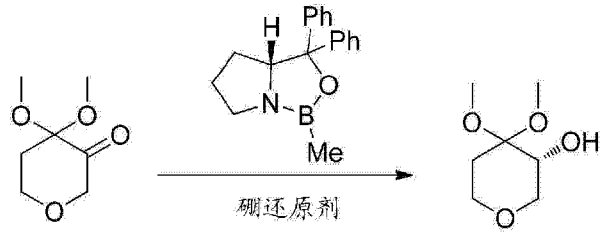
[0126]



[0127] 使4,4-二甲氧基二氢-2H-吡喃-3(4H)-酮与硼还原剂和S-(-)-2-甲基-CBS-噁唑硼烷经历至少六小时时段的反应,以提供至少60%对映体过量的(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇。

[0128] 在另一个实施例中,本发明涉及用于制备(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,所述方法包括:

[0129]



[0130] 使4,4-二甲氧基二氢-2H-吡喃-3(4H)-酮与硼还原剂和S-(-)-2-甲基-CBS-噁唑硼烷经历至少六小时时段的反应,以提供(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇,其中(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇以至少90%对映体过量形成。

[0131] 在另一个实施例中,本发明涉及如上所述用于制备(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,其中所述硼烷还原络合物选自硼烷-二甲基硫醚络合物或硼烷-N,N-二乙基苯胺络合物。

[0132] 在另一个实施例中,本发明涉及如上所述用于制备(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法,其中将所述硼烷还原络合物和S-(-)-2-甲基-CBS-噁唑硼烷的THF溶液加入在THF中的4-二甲氧基二氢-2H-吡喃-3(4H)-酮溶液中。

[0133] 在另一个实施例中,本发明涉及如上所述用于制备(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇的方法中的任一种,其中所述反应在惰性环境中执行;在本发明的另一

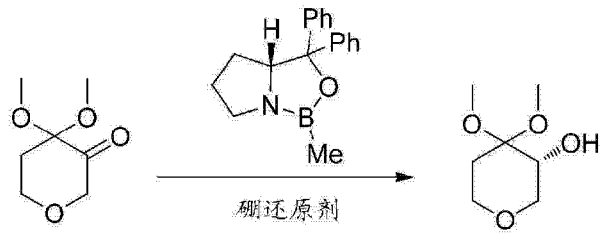
个实施例中，惰性环境是氮气。

[0134] 在另一个实施例中，本发明涉及如上所述用于制备 (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇的方法中的任一种，所述方法还包括使 (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇与硫酸二甲酯反应，以提供 (R)-3,4,4- 三甲氧基四氢 -2H- 吡喃。

[0135] 在另一个实施例中，本发明涉及如上所述用于制备 (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇的方法中的任一种，所述方法还包括使 (S)-3,4,4- 三甲氧基四氢 -2H- 吡喃与酸反应，以提供 (S)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮。在另一个实施例中，酸是浓盐酸。

[0136] 在另一个实施例中，本发明涉及如上所述用于制备 (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇的方法中的任一种，所述方法包括 ：

[0137]



[0138] 使 4,4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮与硼还原剂和 S-(-)-2- 甲基 -CBS- 噁唑硼烷经历至少六小时时段的反应，以提供至少 60％对映体过量的 (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇，其中所述反应在 20℃至 60℃的温度范围内进行。

[0139] 在另一个实施例中，本发明涉及用于预防、治疗或改善 CCR2 介导的综合征、障碍或疾病的方法，所述方法包括向对其有需要的受试者施用治疗有效量的式 (I) 的化合物。

[0140] 在另一个实施例中，本发明涉及用于预防、治疗或改善 CCR2 介导的炎性综合征、障碍或疾病的方法，其中所述综合征、障碍或疾病与升高的 MCP-1 表达或 MCP-1 过表达相关，或者是伴随与升高的 MCP-1 表达或 MCP-1 过表达相关的综合征、障碍或疾病的炎性病症，所述方法包括向对其有需要的受试者施用有效量的权利要求 1 的化合物。

[0141] 在另一个实施例中，本发明涉及预防、治疗或改善综合征、障碍或疾病的方法，其中所述综合征、障碍或疾病选自 ：慢性阻塞性肺病 (COPD)、眼部障碍、葡萄膜炎、动脉粥样硬化、类风湿性关节炎、牛皮癣、牛皮癣关节炎、特应性皮炎、多发性硬化、克罗恩氏病、溃疡性结肠炎、肾炎、器官同种异体移植物排斥、纤维化肺、肾功能不全、I 型糖尿病、II 型糖尿病、糖尿病并发症、糖尿病性肾病、糖尿病性视网膜病、糖尿病性视网膜炎、糖尿病性微血管病、超重、肥胖症、肥胖症相关胰岛素抗性、代谢综合征、肺结核、肉样瘤病、侵入性葡萄球菌感染、白内障手术后炎症、过敏性鼻炎、过敏性结膜炎、慢性荨麻疹、哮喘、过敏性哮喘、牙周病、牙周炎、齿龈炎、齿龈疾病、舒张性心肌病、心肌梗死、心肌炎、慢性心力衰竭、血管狭窄、再狭窄、再灌注障碍、腹主动脉瘤、肾小球肾炎、实体瘤和癌症、慢性淋巴细胞性白血病、慢性粒细胞性白血病、多发性骨髓瘤、恶性骨髓瘤、何杰金氏病和膀胱癌、乳腺癌、宫颈癌、结肠癌、肺癌、前列腺癌或胃癌以及慢性神经炎性病症，包括但不限于阿尔茨海默氏病、缺血性中风、脊髓损伤、神经压碾损伤和外伤性脑损伤，所述方法包括向对其有需要的受试者施用有效量的式 (I) 的化合物。

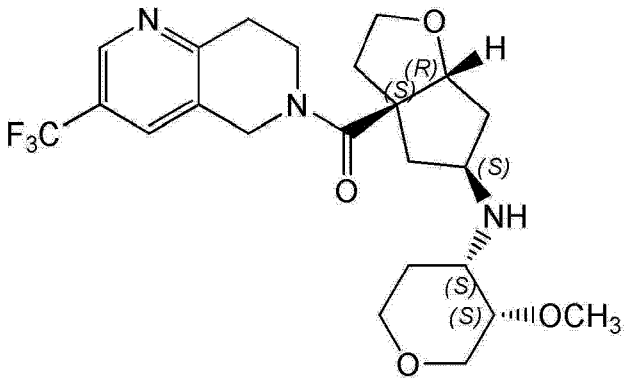
[0142] 在另一个实施例中，本发明涉及预防、治疗或改善综合征、障碍或疾病的方法，其

中所述综合征、障碍或疾病选自：I 型糖尿病、II 型糖尿病、糖尿病并发症、糖尿病性肾病、糖尿病性视网膜病、糖尿病性视网膜炎、糖尿病性微血管病、肥胖症、肥胖症相关胰岛素抗性、代谢综合征、哮喘和过敏性哮喘，所述方法包括向对其有需要的受试者施用治疗有效量的式 (I) 的化合物。

[0143] 在另一个实施例中，本发明涉及治疗病症的方法，所述病症选自 II 型糖尿病、肥胖症和哮喘，所述方法包括向对其有需要的受试者施用治疗有效量的式 (I) 的化合物。

[0144] 本发明还涉及式 (I-S) 的化合物的琥珀酸盐，

[0145]



(I-S)

[0146] 其中式 (I-S) 的化合物也称为 ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基）氨基）六氢 -2H- 环戊并 [b] 呋喃 -3a- 基）(3-（三氟甲基）-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基）甲酮。在一个实施例中，式 (I-S) 的化合物的琥珀酸盐是结晶的。在另一个实施例中，式 (I-S) 的化合物的琥珀酸盐是结晶水合物形式；其中所述水合物含有约 0.6 摩尔水 / 摩尔式 (I-S) 的化合物。在本发明的另一个实施例中，式 (I-S) 的化合物的琥珀酸盐是含有约 0.6 摩尔水 / 摩尔式 (I-S) 的化合物的结晶水合物形式；其中所述结晶水合物形式还是吸湿性的。

[0147] 本发明还涉及式 (I-S) 的化合物的结晶琥珀酸盐，其中所述酸性抗衡离子是琥珀酸。使用下列另外的酸性抗衡离子，对式 (I-S) 的化合物进行另外的盐筛选：HCl 酸、硫酸、柠檬酸、丙二酸、马来酸、L- 酒石酸、对甲苯磺酸、磷酸和乙酸。所得的固体残余的 X 射线分析指示关于硫酸盐、马来酸盐和磷酸盐的晶体结构；以及 HCl 盐、柠檬酸盐、丙二酸盐、酒石酸盐和甲苯磺酸盐的无定形结构。

[0148] 式 (I-S) 的化合物的结晶磷酸盐、硫酸盐和马来酸盐另外在 DSC、TGA 和水分吸附 / 解吸中进行测试。硫酸盐显示在盐形式之间的互换以及 1.6％直至 60％ RH 和总共 26.5％直至 90％ RH 的吸湿性重量增加，伴随强滞后。马来酸盐显示形式变化以及 18.3％直至 70％ RH 和总共 79.9％至 90％ RH 的吸湿性重量增加。磷酸盐显示 3.3％直至 60％ RH 和总共 69.4％直至 90％ RH 的吸湿性重量增加，伴随强滞后和潮解。

[0149] 定义

[0150] 除非另外指明，否则术语“烷基”是指最多 12 个碳原子（优选最多 6 个碳原子）的直链和支链基团，并且其包括但不限于甲基、乙基、丙基、异丙基、丁基、异丁基、仲丁基、叔丁基、戊基、异戊基、己基、异己基、庚基、辛基、2,2,4- 三甲基戊基、壬基、癸基、十一烷基以及十二烷基。

[0151] 术语“$C_{(a-b)}$”（其中 a 和 b 为表示指定数目的碳原子的整数）是指烷基、烯基、炔基、

烷氧基或环烷基，或是指基团中的烷基部分，其中烷基作为前缀词根出现，含有 a 至 b（包括 a 和 b）个碳原子。例如，$C_{(1-4)}$表示含有 1、2、3 或 4 个碳原子的基团。

[0152] 术语“环烷基”是指通过从单个环碳原子中去除一个氢原子而衍生的饱和或部分饱和的单环或二环烃环原子团。环烷基原子团的例子包括但不限于环丙基、环丁基、环戊基、环戊烯基、环己基、环己烯基、环庚基和环辛基。另外的例子包括 $C_{(3-8)}$环烷基、$C_{(5-8)}$环烷基、$C_{(3-12)}$环烷基、$C_{(3-20)}$环烷基、十氢萘基和 2,3,4,5,6,7- 六氢 -1H- 茚基。

[0153] 术语“硼还原剂”是指硼氢化物，通常伴随稳定剂例如醚、胺或硫化物。硼还原剂的例子包括但不限于硼烷 - 四氢呋喃络合物、儿茶酚硼烷、硼烷 - 二甲基苯胺络合物和硼烷 - 二甲基硫醚络合物。

[0154] 术语“杂芳基”是指通过从杂芳环系统的环碳原子中去除一个氢原子而衍生的原子团。杂芳环系统应指示含有选自 O、N 和 S 的至少一个杂原子，任选含有独立地选自 O、N 和 S 的一至三个另外的杂原子的任何五元或六元单环芳环结构；或者含有选自 O、N 和 S 的至少一个杂原子，任选含有独立地选自 O、N 和 S 的一至四个另外的杂原子的九元或十元二环芳环结构。杂芳基可在环的任何杂原子或碳原子处附着，使得结果是稳定结构。杂芳基原子团的例子包括但不限于呋喃基、噻吩基、吡咯基、噁唑基、噻唑基、咪唑基、吡唑基、异噁唑基、异噻唑基、噁二唑基、三唑基、噻二唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、吲嗪基、吲哚基、异吲哚基、苯并 [b] 呋喃基、苯并 [b] 噻吩基、吲唑基、苯并咪唑基、苯并噻唑基、嘌呤基、4H- 喹嗪基、喹啉基、异喹啉基、噌啉基、酞嗪基、喹唑啉基、喹噁啉基、1,8- 萘啶基和蝶啶基。

[0155] 术语“ee”或“对映体过量”是对映体混合物的摩尔分数中的差异的绝对值。(+)- 和 (-)- 对映体的摩尔分数表示为 F(+) 和 F(-)（其中 F(+)+F(-) = 1）。对映体过量定义为 |F(+)-F(-)|。对映体过量百分比为 ee*100。例如，(+) 和 (-) 对映体的 50/50 混合物具有 0% ee，(+) 和 (-) 对映体的 5/95 混合物具有 90% ee，并且 (+) 和 (-) 对映体的 70/30 混合物具有 40% ee。

[0156] 术语“惰性环境”是基本上耗尽大气氧和水蒸气的化学反应的局部环境。例如，在惰性环境下进行的反应包括但不限于在氩或氮大气下进行的反应。

[0157] 术语“分离的形式”应意指化合物以与具有另一种化合物的任何固体混合物、溶剂系统或生物环境分开的形式存在。在一个实施例中，本发明涉及式 (I-S) 的化合物的琥珀酸盐，优选式 (I-S) 的化合物的结晶琥珀酸盐，其中所述盐作为分离的形式存在和 / 或制备。

[0158] 当用于描述式 (I-S) 的化合物的琥珀酸盐时，术语“基本上不含其他盐形式”应意指在式 (I-S) 的化合物中的分离的琥珀酸盐中的任何其他盐形式的摩尔百分比小于约 5 摩尔百分比、优选小于约 2 摩尔百分比、更优选小于约 0.5 摩尔百分比、最优选小于约 0.1 摩尔百分比。在一个实施例中，本发明涉及式 (I-S) 的化合物的琥珀酸盐，优选式 (I-S) 的化合物的结晶琥珀酸盐，其中所述盐作为基本上不含其他盐形式的形式存在和 / 或制备。

[0159] 术语“基本上纯的形式”应意指分离的化合物中杂质的摩尔百分比小于约 5 摩尔百分比、优选小于约 2 摩尔百分比、更优选小于约 0.5 摩尔百分比、最优选小于约 0.1 摩尔百分比。在一个实施例中，本发明涉及式 (I-S) 的化合物的琥珀酸盐，优选式 (I-S) 的化合物的结晶琥珀酸盐，其中所述盐作为基本上纯的形式存在和 / 或制备。

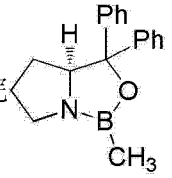
[0160] 对于在医学中的使用，本发明化合物的盐是指无毒的“药学上可接受的盐”。FDA批准的药学上可接受的盐形式（参考 International J. Pharm. 1986, 33, 201-217 ; J. Pharm. Sci., 1977, Jan, 66(1), 第 1 页）包括药学上可接受的酸式 / 阴离子盐或碱式 / 阳离子盐。

[0161] 在本说明书通篇中，化合物被描述为通常通过硅胶柱来分离，但还可使用制备性薄层色谱法或者高压或低压液相色谱法。公认的是，当通过硅胶型分离介质洗脱化合物时，极性最小的化合物在极性较大的化合物之前洗脱。因此，术语“极性较少的异构体”是指首先从硅胶型分离介质中洗脱的异构体。

[0162] 缩写

[0163] 在本专利申请说明书以及整个专利申请中，使用了如下缩写。

[0164]	AIBN	偶氮二异丁腈
[0165]	BOC 或 Boc	叔丁氧羰基
[0166]	DCC	二环己基碳二亚胺
[0167]	DCM	二氯甲烷
[0168]	EDCI 或 EDC	1- 乙基 -3-(3’- 二甲氨基丙基）碳二亚胺
[0169]	DIAD	二异丙基偶氮二羧酸酯
[0170]	DIEA	二异丙基乙胺
[0171]	DSC	差示扫描量热法
[0172]	Et	乙基
[0173]	EtOAc	乙酸乙酯
[0174]	ee	对映体过量
[0175]	eq	当量
[0176]	HOBt	羟基苯并三唑
[0177]	LiHMDS	双（三甲基甲硅烷基）氨基锂
[0178]	M	摩尔 / 升
[0179]	Me	甲基
[0180]	MIBK	甲基异丁基酮
[0181]	min.	分钟
[0182]	n-BuLi	正丁基锂
[0183]	NBS 或 NIS	N- 溴琥珀酰亚胺或 N- 碘琥珀酰亚胺
[0184]	OAc	乙酸根
[0185]	Ph	苯基
[0186]	PyBrop	三吡咯烷基溴化鏻六氟磷酸盐
[0187]	RH	相对湿度
[0188]	rt	室温
[0189]	TBAF	四丁基氟化铵
[0190]	TFA	三氟乙酸
[0191]	THF	四氢呋喃
[0192]	TBS 或 TBDMS	叔丁基二甲基甲硅烷基
[0193]	TLC	薄层色谱法

[0194] S-(-)-2- 甲基 -CBS- 噁唑硼烷 

[0195] 药学上可接受的酸式 / 阴离子盐包括但不限于乙酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、酒石酸氢盐、溴化物、依地酸钙盐、樟脑磺酸盐、碳酸盐、氯化物、柠檬酸盐、二盐酸盐、依地酸盐、乙二磺酸盐、丙酸酯十二烷基硫酸盐、乙磺酸盐、延胡索酸盐、葡庚糖酸盐、葡糖酸盐、谷氨酸盐、乙醇酰对氨基苯肿酸盐、己基间苯二酚盐、海巴明盐、氢溴酸盐、盐酸盐、羟基萘甲酸盐、碘化物、羟乙基磺酸盐、乳酸盐、乳糖酸盐、苹果酸盐、马来酸盐、扁桃酸盐、甲磺酸盐、甲基溴化物、甲基硝酸盐、甲基硫酸盐、粘酸盐、萘磺酸盐、硝酸盐、双羟萘酸盐、泛酸盐、磷酸盐 / 二磷酸盐、聚半乳糖醛酸盐、水杨酸盐、硬脂酸盐、碱式乙酸盐、琥珀酸盐、硫酸盐、鞣酸盐、酒石酸盐、氯茶碱盐、甲苯磺酸盐以及三乙基碘化物。有机酸或无机酸还包括但不限于氢碘酸、过氯酸、硫酸、磷酸、丙酸、乙醇酸、甲磺酸、羟基乙磺酸、草酸、2- 萘磺酸、对甲苯磺酸、环己烷氨基磺酸、糖精酸或三氟乙酸。

[0196] 药学上可接受的碱式 / 阳离子盐包括且不限于铝、2- 氨基 -2- 羟甲基 - 丙烷 -1,3- 二醇 (也称为三 (羟甲基) 氨基甲烷、三羟甲基氨基甲烷 (tromethane) 或“TRIS”)、氨、苄星青霉素、叔丁胺、钙、葡萄糖酸钙、氢氧化钙、氯普鲁卡因、胆碱、胆碱碳酸氢盐、氯化胆碱、环己胺、二乙醇胺、乙二胺、锂、LiOMe、L- 赖氨酸、镁、葡甲胺、NH_3、NH_4OH、N- 甲基 -D- 葡糖胺、哌啶、钾、叔丁醇钾、氢氧化钾 (含水)、普鲁卡因、奎宁、钠、碳酸钠、2- 乙基己酸钠 (SEH)、氢氧化钠、三乙醇胺或锌。

[0197] 使用方法

[0198] 本发明涉及用于预防、治疗或改善 CCR2 介导的综合征、障碍或疾病的方法，所述方法包括向对其有需要的受试者施用有效量的式 (I) 的化合物或其形式、组合物或药物。

[0199] 其中使用式 (I) 的化合物的 CCR2 介导的综合征、障碍或疾病的例子包括慢性阻塞性肺病 (COPD)、眼部障碍、葡萄膜炎、动脉粥样硬化、类风湿性关节炎、牛皮癣、牛皮癣关节炎、特应性皮炎、多发性硬化、克罗恩氏病、溃疡性结肠炎、肾炎、器官同种异体移植物排斥、纤维化肺、肾功能不全、I 型糖尿病、II 型糖尿病、糖尿病并发症、糖尿病性肾病、糖尿病性视网膜病、糖尿病性视网膜炎、糖尿病性微血管病、超重、肥胖症、肥胖症相关胰岛素抗性、代谢综合征、肺结核、慢性阻塞性肺病、肉样瘤病、侵入性葡萄球菌感染、白内障手术后炎症、过敏性鼻炎、过敏性结膜炎、慢性荨麻疹、哮喘、过敏性哮喘、牙周病、牙周炎、齿龈炎、齿龈疾病、舒张性心肌病、心肌梗死、心肌炎、慢性心力衰竭、血管狭窄、再狭窄、再灌注障碍、腹主动脉瘤、多发性硬化、肾小球肾炎、实体瘤和癌症、慢性淋巴细胞性白血病、慢性粒细胞性白血病、多发性骨髓瘤、恶性骨髓瘤、何杰金氏病、膀胱癌、乳腺癌、宫颈癌、结肠癌、肺癌、前列腺癌或胃癌以及慢性神经炎性疾病，包括但不限于阿尔茨海默氏病、缺血性中风、脊髓损伤、神经压碾损伤和外伤性脑损伤。

[0200] 本文给出的一些定量表达由术语“约”进行修饰。应当理解无论术语“约”是否明确使用，本文给出的每一个数量均意指实际给出值以及可根据本领域普通技术合理推断出的此类给出值的近似值，包括由于此类给出值的实验和 / 或测量条件的近似值。另外，本文的一些定量表述叙述为从约量 X 到约量 Y 的范围。应当理解，若叙述了某个范围，则该范围

不限于所叙述的上限和下限，而是包括从约量 X 直至约量 Y 的整个范围，或者其中的任何范围。

[0201] 就本发明方法而言，术语“施用”意指通过使用式 (I) 的化合物或其形式、组合物或药物来治疗性地或预防性地预防、治疗或改善本文所述的综合征、障碍或疾病的方法。这种方法包括在治疗期间以不同的次数施用有效量的所述化合物、配混物形式、组合物或药物，或者以组合形式同时施用。本发明的方法应被理解为涵盖所有已知的治疗性处理方案。

[0202] 术语“受试者”是指患者，其可以是已作为治疗、观察或实验的对象的动物，通常是哺乳动物（通常是人）。在本发明的一个方面，受试者有发展与升高的 MCP-1 表达或 MCP-1 过表达相关联的综合征、障碍或疾病的风险（或易于发生所述发展），或者为具有伴随与升高的 MCP-1 表达或 MCP-1 过表达相关联的综合征、障碍或疾病的炎性病症的患者。

[0203] 术语“治疗有效量”意指在组织系统、动物或人中引起生物学反应或药物反应的活性化合物或药剂的量，而所述生物学反应或药物反应正是研究人员、兽医、医生或其他临床医师所寻求的，包括预防、治疗或改善所治疗的综合征、障碍或疾病的症状。

[0204] 术语“葡萄膜炎”通常是指涉及眼的任何炎性疾病。可基于炎症存在于眼中的部分，将葡萄膜炎分成临床上不同的亚型（百分比对应于已知符合这些种类的患者）：前部 (51％)、中间 (13％)、后部 (20％) 或全葡萄膜炎 (16％)，并且根据疾病的进程，可分为急性 (16％)、复发性 (26％) 或慢性 (58％)。患有前葡萄膜炎的那些患者 (•19％) 尽管进行积极治疗，最终也会发展成不能恢复的视力损伤，例如单侧盲 (9％)、双侧盲 (2％) 或者单侧或双侧视力受损 (8％)。大多数葡萄膜炎案例为特发性的，但已知的原因包括感染（例如弓形体病、细胞巨化病毒等）或作为全身性炎性病症和 / 或自身免疫病症的一部分发展（例如幼年型类风湿性关节炎、HLA-B27 相关脊椎关节病、肉样瘤病等）。(HLA-B27 ：人类白细胞抗原 B*27- 为由在染色体 6 上的主要组织相容性复合体 (MHC) 中的 B 基因座编码的 I 类表面抗原，并将微生物抗原呈递给 T 细胞。HLA-B27 与某一组被称为血清反应阴性脊椎关节病变的自身免疫疾病密切相关联）。

[0205] 当用作 CCR2 抑制剂时，本发明的化合物可以单个或分份日剂量的有效量施用，所述有效量在约 0.5mg 至约 10g 的范围内，或其中的任何量或范围，优选为约 0.5mg 至约 5g，或其中的任何量或范围。施用的剂量将受诸如施用途径，受体的健康状态、体重和年龄，治疗频率以及同期治疗和不相关的治疗的存在等因素影响。

[0206] 对于本领域的技术人员还将显而易见的是，本发明的化合物或其药物组合物的治疗有效剂量将根据所需效果而变化。因此，本领域的技术人员可容易地确定待施用的最佳剂量，并且最佳剂量将随所使用的具体化合物、施用方式、制剂强度和疾病状况的进展而变化。另外，与待治疗的具体受试者相关联的因素（包括受试者年龄、体重、饮食和施用时间）将导致需要将剂量调整至适当的治疗水平。因而上述剂量是一般情况的示例。当然，可能会存在其中较高或较低剂量范围有利的个别情况，并且这类情况也在本发明的范围内。

[0207] 可将式 (I) 的化合物配制成包含任何已知的药学上可接受的载体的药物组合物。示例性载体包括但不限于任何合适的溶剂、分散介质、包衣、抗菌剂和抗真菌剂以及等渗剂。还可作为制剂组分的示例性赋形剂包括填充剂、粘合剂、崩解剂以及润滑剂。

[0208] 式 (I) 的化合物的药学上可接受的盐包括由无机或有机酸或碱形成的常规无毒盐或季铵盐。此类酸加成盐的例子包括乙酸盐、己二酸盐、苯甲酸盐、苯磺酸盐、柠檬酸盐、

樟脑酸盐、十二烷基硫酸盐、盐酸盐、氢溴酸盐、乳酸盐、马来酸盐、甲磺酸盐、硝酸盐、草酸盐、三甲基乙酸盐、丙酸盐、琥珀酸盐、硫酸盐以及酒石酸盐。碱盐包括铵盐、碱金属盐诸如钠盐和钾盐、碱土金属盐例如钙盐和镁盐、有机碱盐例如二环己胺盐以及氨基酸例如精氨酸的盐。还可将碱性含氮基团用例如烷基卤化物进行季铵化。

[0209] 本发明的药物组合物可通过任何能实现其预期目的方式施用。例子包括通过肠胃外、皮下、静脉内、肌内注射、腹膜内注射、透皮、口腔或眼等途径施用。另选地或同时地，可通过口服途径施用。适用于肠胃外施用的制剂包括水溶性形式的活性化合物（例如，水溶性盐）的水溶液、酸性溶液、碱性溶液、右旋糖水溶液、等渗碳水化合物溶液以及环糊精包合复合物。

[0210] 本发明还包括制备药物组合物的方法，所述方法包括将药学上可接受的载体与本发明的任何化合物混合。另外，本发明包括通过将药学上可接受的载体与本发明的任何化合物混合而制备的药物组合物。如本文所用，术语“组合物”旨在涵盖包含规定量的规定成分的产物，以及任何由规定量的规定成分的组合直接或间接得到的产物。

[0211] 多晶型物和溶剂化物

[0212] 此外，本发明的化合物可具有一种或多种多晶型或无定形结晶形式，这些多晶型或无定形结晶形式旨在包括在本发明的范围内。此外，化合物可例如与水（即水合物）形成溶剂化物或与普通有机溶剂形成溶剂化物。如本文所用，术语“溶剂化物”意指本发明的化合物与一个或多个溶剂分子的物理结合。该物理缔合涉及不同程度的离子键合和共价键合，包括氢键合。在某些情况下，溶剂化物将能够在（例如）一个或多个溶剂分子混在结晶固体的晶格中时分离出来。术语“溶剂化物”旨在既涵盖溶液相溶剂化物又涵盖可分离溶剂化物。合适的溶剂化物的非限制性例子包括乙醇化物、甲醇化物等。

[0213] 本发明旨在包括在其范围内的本发明化合物的多晶型物和溶剂化物。因此，在本发明的治疗方法中，术语“施用”应涵盖使用本发明的化合物或其多晶型物或溶剂化物治疗、改善或预防本文所述的综合征、障碍或疾病的方法，其虽然没有被具体公开，但这将明显包括在本发明的范围内。

[0214] 在另一个实施例中，本发明涉及用作药物的如式 (I) 的实例中所述的化合物。

[0215] 在另一个实施例中，本发明涉及如式 (I) 的实例中所述的化合物制备用于治疗与升高的或不适当的 CCR2 活性相关联的疾病的药物的用途。

[0216] 本发明包括在其范围内的本发明化合物的前药。一般来讲，此类前药将为化合物的官能团衍生物，其可在体内容易地转化为所需的化合物。因此，在本发明的治疗方法中，术语“施用”应涵盖用具体公开的化合物或用可能未具体公开的化合物（但该未具体公开的化合物在向患者施用后，在体内转化为具体公开的化合物）来治疗多种病症。选择和制备合适的前药衍生物的常规程序在（例如）“Design of Prodrugs”，H.Bundgaard（编辑），Elsevier，1985 中有所描述。

[0217] 如果根据本发明的化合物具有至少一个手性中心，则它们可因此作为对映体存在。在化合物拥有两个或更多个手性中心的情况下，它们可另外作为非对映体存在。应理解，所有的此类异构体及其混合物涵盖在本发明的范围内。

[0218] 如果制备根据本发明的化合物的方法产生立体异构体的混合物，则这些异构体可以通过常规技术如制备色谱来分离。化合物可以外消旋形式制备，或者单独的对映体可通

过对映体特异性合成或通过拆分制备。例如，可通过标准的技术，如通过与具有旋光活性的酸（如 (-)- 二对甲基苯甲酰基 -D- 酒石酸和 / 或 (+)- 二对甲基苯甲酰基 -L- 酒石酸）成盐来形成非对映体对，然后分级结晶并再生成游离的碱而将化合物拆分成它们的组分对映体。也可通过形成非对映体酯或酰胺，然后进行色谱分离并移除手性助剂而拆分化合物。作为另一种选择，可用手性 HPLC 柱拆分化合物。

[0219] 在任何制备本发明化合物的方法中，可能必需和 / 或期望保护任何有关分子上的敏感或反应性基团。这可借助于常规保护基团来实现，例如在 Protective Groups in Organic Chemistry，编辑 J.F.W.McOmie，Plenum 出版社，1973 年；以及 T.W.Greene 和 P.G.M.Wuts，Protective Groups in Organic Synthesis，John Wiley&Sons，1991 的文献中找到。可使用本领域已知的方法在方便的后续阶段移除保护基团。

[0220] 式 (I-S) 的化合物的结晶琥珀酸盐的制备

[0221] 本发明的式 (I-S) 的化合物的结晶琥珀酸盐可通过下列由相应的式 (I-S) 的化合物的无定形琥珀酸盐进行制备：使式 (I-S) 的化合物的无定形琥珀酸盐加热至在 140℃至约 150℃范围内的温度，优选加热至约 140℃，并且随后冷却至约室温，以实现结晶，如本文下文的实例 52 中更详细地描述的。

[0222] 另选地，本发明的式 (I-S) 的化合物的结晶琥珀酸盐可通过由适当选择的溶剂例如甲基异丁基酮 (MIBK) 结晶，经由相应的式 (I-S) 的化合物的无定形琥珀酸盐进行制备，如本文下文的实例 53 中更详细地描述的。对于式 (I-S) 的化合物的琥珀酸盐的结晶，适当选择的溶剂是除水、甲醇、乙醇、丙酮、乙腈、乙酸异丙酯、硝基甲烷、四氢呋喃、甲基乙基酮、二氯甲烷、甲苯、甲基异丙基酮 (MIPK) 以外。

[0223] 式 (I-S) 的化合物的无定形琥珀酸盐可例如如本文下文的实例 30 中所述进行制备。

[0224] X 射线粉末衍射 (pXRD)

[0225] 式 (I-S) 的化合物的琥珀酸盐如下在实例中关于其 X 射线粉末衍射图 (pXRD) 进行表征。使用配有超能 (X′ Celerator) 探测器和梯度多层抛物面 X 射线反射镜的 X 射线衍射仪 (Philips 型号 X'PERT PRO PW3040 型）检查样品。以 0.0165° 2θ 的步长和 2000.025 秒的每步时间，从 3 至 40° 2θ 对样品进行扫描。管电压和电流分别为 45KV 和 40mA。将样品装填于零背景 XRD 试样架上并在环境温度和湿度条件下进行扫描。

[0226] 如图 1 中所示，对于式 (I-S) 的化合物的琥珀酸盐的代表性样品测量 pXRD 光谱。在一个实施例中，式 (I-S) 的化合物的结晶琥珀酸盐可通过其 X 射线粉末衍射图进行表征，所述 X 射线粉末衍射图包含下表 1 中列出的峰值。

[0227] 表 1 ：pXRD 峰值：

[0228] 式 (I-S) 的化合物的结晶琥珀酸盐

[0229]

位置[°2θ]	d-间距[Å]	相对强度[%]
7.27	12.17	3
10.03	8.82	4
10.51	8.42	4
11.27	7.85	8
12.26	7.22	2
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
24.14	3.69	8
25.78	3.46	17
27.07	3.29	14
27.64	3.23	7
28.40	3.14	6

[0230]

28.97	3.08	4
30.30	2.95	4
31.91	2.80	3
33.34	2.69	4
35.91	2.50	4

[0231] 在一个实施例中，式 (I-S) 的化合物的结晶琥珀酸盐通过其 pXRD 图进行表征，所述 pXRD 图包含具有大于或等于约 3％的相对强度的峰值，如下表 2 所列出的。

[0232] 表 2 :pXRD 峰值：

[0233] 式 (I-S) 的化合物的结晶琥珀酸盐

[0234]

位置[°2θ]	d-间距[Å]	相对强度[%]
10.03	8.82	4
10.51	8.42	4
11.27	7.85	8
12.26	7.22	2
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
24.14	3.69	8
25.78	3.46	17
27.07	3.29	14
27.64	3.23	7
28.40	3.14	6
28.97	3.08	4
30.30	2.95	4
33.34	2.69	4
35.91	2.50	4

[0235] 在一个实施例中，式（I-S）的化合物的结晶琥珀酸盐通过其 pXRD 图进行表征，所述 pXRD 图包含具有大于或等于约 5％的相对强度的峰值，如下表 3 所列出的。

[0236] 表 3 ：pXRD 峰值：

[0237] 式（I-S）的化合物的结晶琥珀酸盐

[0238]

位置[°2θ]	d-间距[Å]	相对强度[%]
11.27	7.85	8
12.26	7.22	2
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16
15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
24.14	3.69	8
25.78	3.46	17
27.07	3.29	14
27.64	3.23	7
28.40	3.14	6

[0239] 在一个实施例中，式（I-S）的化合物的结晶琥珀酸盐通过其 pXRD 图进行表征，所述 pXRD 图包含具有大于或等于约 10％的相对强度的峰值，如下表 4 所列出的。

[0240] 表 4 ：pXRD 峰值：

[0241] 式（I-S）的化合物的结晶琥珀酸盐

[0242]

位置[°2θ]	d-间距[Å]	相对强度[%]
13.87	6.38	67
14.34	6.18	21
14.63	6.05	16

[0243]

15.96	5.55	17
16.73	5.30	11
17.66	5.02	13
18.33	4.84	16
19.22	4.62	100
19.78	4.49	36
20.11	4.42	36
20.86	4.26	26
21.34	4.16	20
22.01	4.04	50
22.67	3.92	16
23.62	3.77	15
25.78	3.46	17
27.07	3.29	14

[0244] 在另一个实施例中，本发明涉及如通过以° 2θ 列出的下列 pXRD 峰值表征的式 (I-S) 的化合物的结晶琥珀酸盐：10.03、10.51、11.27、13.87、19.22 和 22.01。在另一个实施例中，本发明涉及如通过以° 2θ 列出的下列 pXRD 峰值表征的式 (I-S) 的化合物的结晶琥珀酸盐：11.27、13.87、19.22 和 22.01。

[0245] 差示扫描量热法 (DSC)

[0246] 对式 (I-S) 的化合物的结晶琥珀酸盐进一步实施 DSC 分析。使用 TA 仪器型号 Q1000 差示扫描量热仪测试代表性样品。在敞口铝盘中按原样分析样品。DSC 被编程为在氮吹扫下以 10℃ / 分钟的加热速率从 25℃加热到 300℃。

[0247] 对式 (I-S) 的化合物的结晶琥珀酸盐的代表性样品完成热分析 (经由 DSC 扫描)，如图 2 所示。式 (I-S) 的化合物的结晶琥珀酸盐表现出约 156℃的开始熔融温度，约 158℃的峰值熔融温度和焓 68.3J/g。

[0248] 热重分析 (TGA)

[0249] 对式 (I-S) 的化合物的结晶琥珀酸盐进一步实施 TGA 分析。使用 TA 仪器型号 Q5000IR TGA 热重分析热量计，就总重量减轻测试如接受的代表性样品。将样品置于去皮重 (tarred) 的铝盘中，自动称重并插入 TGA 炉中。样品以 10℃ / 分钟的加热速率从 25℃到 300℃进行扫描，伴随 90mL/ 分钟氮吹扫和 10mL/ 分钟氦平衡吹扫。

[0250] 如图 3 中所示，对于式 (I-S) 的化合物的琥珀酸盐的代表性样品测量 TGA 迹线。由于脱水 / 去溶剂化，在室温和 144℃之间观察到 1.8％重量减轻；随后为在 151℃下的分解。这些结果指示式 (I-S) 的化合物的结晶琥珀酸盐是水合物；其中所述水合物含有约 0.6 摩尔水 / 摩尔式 (IS) 的化合物。

[0251] 水分等温分析

[0252] 对式 (I-S) 的化合物的结晶琥珀酸盐进一步实施水分吸附分析。使用 Hiden Isochema 系统型号 IGAsorp 进行水分吸附分析。样品 (～ 5mg) 在不锈钢丝网坩埚中进行处理。样品最初在 60℃下干燥 30 分钟，随后通过在 25℃下监测经过 0％ RH 至 90％ RH 范围的蒸气吸附 / 解吸进行评估。水分特征图由 2 个蒸气吸附 / 解吸循环组成。

[0253] 图 4 示出了关于式 (I-S) 的化合物的结晶琥珀酸盐的代表性样品的两个蒸气吸附 / 解吸循环。样品的重量增加 3.8％直至 70％ RH，具有总共 70％摄取直至 90％ RH。此外，

在多个吸附 / 解吸循环中观察到强滞后，其中约 2.7％水分（等于 0.9 摩尔水）在解吸期结束时保留。因此，式 (I-S) 的化合物的结晶琥珀酸盐是吸湿性的。

[0254] 溶解度

[0255] 式 (I-S) 的化合物的结晶琥珀酸盐就溶液溶解度进行测试，并且测量为在水中以 ＞ 50mg/ml 可溶，并且在 0.1N NaOH、pH2、pH4 和 pH6 柠檬酸缓冲液 ；pH8 和 pH10 硼酸盐缓冲液 ；模拟肠液、模拟胃液 ；0.5％甲醇和 20％ HpbCD 中以＞ 100mg/ml 可溶。

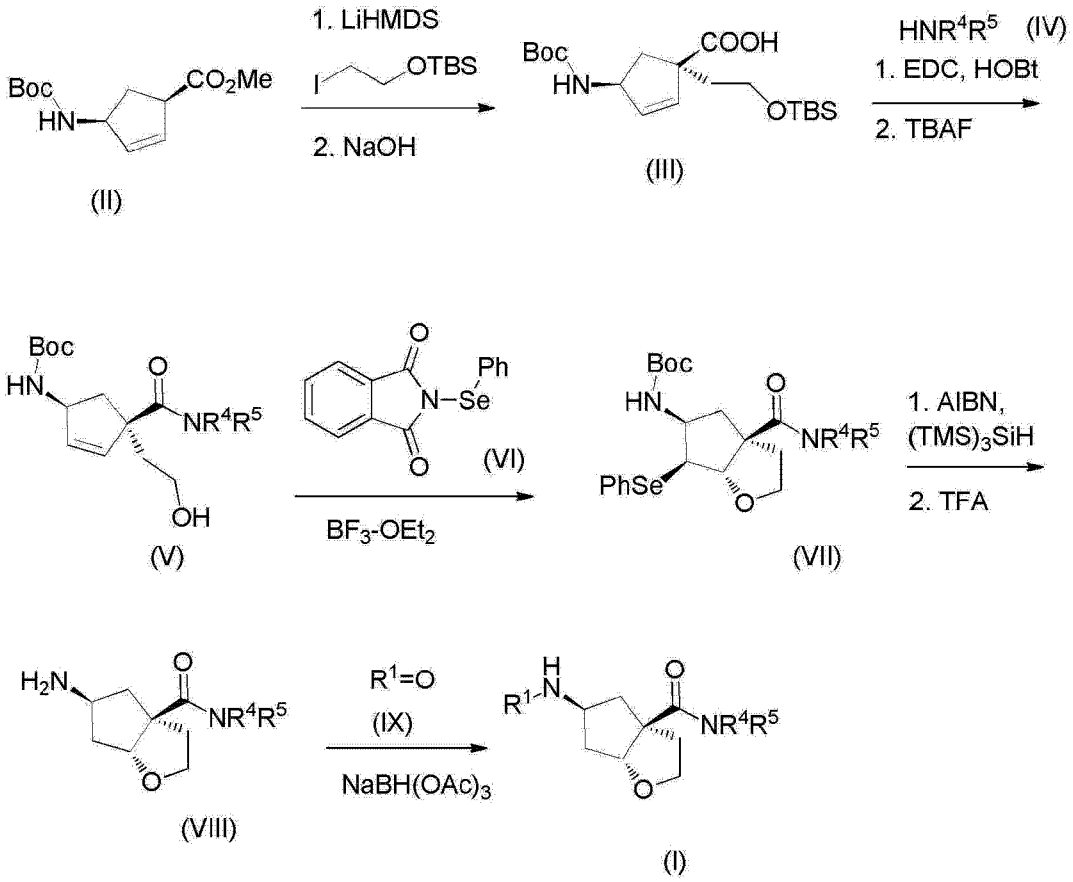
[0256] 一般反应方案

[0257] 本发明的代表性化合物可根据下文所述的一般合成方法合成。式 (I) 的化合物可通过本领域的技术人员已知的方法制备。以下反应方案仅意在表示本发明的实例且绝不意在限制本发明。

[0258] 其中 A 为 O，并且其中 R^0、R^2和 R^3各自为氢的式 (I) 的化合物可根据方案 1 中概述的方法进行制备。

[0259] 方案 1

[0260]



[0261] 方案 1 示出了导致其中 R^0、R^2和 R^3各自为氢的式 (I) 的化合物的合成路线。商购可得的式 (II) 的酯通过与适当选择的碱例如 LiHMDS 等等反应进行烷基化 ；并且随后在有机溶剂例如 THF 或二乙醚中在 -78℃至 20℃范围内的温度下与叔丁基 (2- 碘乙氧基）二甲基硅烷反应。所得的烷基化酯随后通过在 0℃至 60℃范围内的温度下与含水碱例如 NaOH、KOH 或 LiOH 反应进行皂化，以获得相应的酸，式 (111) 的化合物。

[0262] 随后在偶联剂例如 EDCI/HOBt、PyBrop 或 DCC 的存在下，在有机溶剂例如 THF、二氯

甲烷或 1,2- 二氯乙烷中，在约 0℃至约 25℃范围内的温度下，使式 (III) 的酸与适当选择的、商购可得的式 (IV) 的胺反应，以获得相应的酰胺；随后通过在溶剂例如 THF 中在约 0℃至 60℃的温度范围内与氟化物源例如 TBAF 反应，所述酰胺进行反应以使醇官能团脱保护，以获得相应的式 (V) 的脱甲硅烷基醇。

[0263] 在溶剂例如 DCM 或 1,2- 二氯乙烷中，在 0℃至 50℃的温度下，使式 (V) 的醇与试剂例如 N-(苯基硒) 邻苯二甲酰亚胺 (VI) 或苯基氯化硒和路易斯酸例如三氟化硼醚化物反应，以获得相应的式 (VII) 的环状醚。

[0264] 在自由基引发剂例如 AIBN 的存在下，在溶剂例如苯或甲苯中，在 60℃至 120℃的温度下，使环状醚 (VII) 与适当选择的还原剂例如三 - 正丁基锡烷或三 (三甲基甲硅烷基) 硅烷反应；并且通过在溶剂例如 DCM、乙腈、THF 或二噁烷中，在 0℃至 80℃的温度下与酸例如 TFA 或 HCl 反应，所得的中间体在 N-Boc 氨基甲酸酯处脱保护，以获得相应的式 (VIII) 的胺。

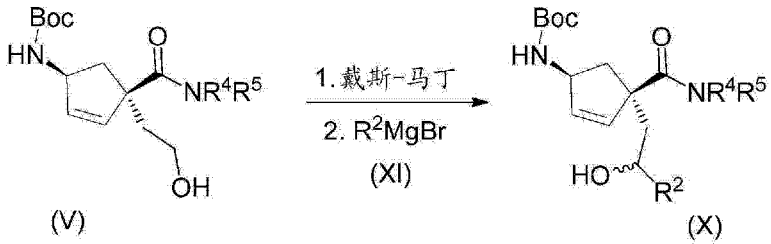
[0265] 在适当选择的还原剂例如 $NaBH_4$、$NaBH_3CN$ 或 $NaBH(OAc)_3$ 的存在下，在有机碱例如三乙胺、二异丙基乙胺或 N- 甲基吗啉中，连同或不连同分子筛，在有机溶剂例如二氯甲烷、1,2- 二氯乙烷或 THF 中，在 0℃至约 25℃范围内的温度下，使式 (VIII) 与式 (IX) 的适当取代的酮反应，以获得相应的其中 R^0、R^2 和 R^3 各自是氢的式 (I) 的化合物。

[0266] 本领域技术人员应认识到其中 R_0 不是 H 的式 (I) 的化合物可通过标准烷基化操作由其中 R_0 为 H 的式 (I) 的化合物合成。此类烷基化操作包括但不限于还原烷基化。例如，其中 R_0 为 H 的式 (I) 的化合物可溶解于溶剂例如 THF 中，并且与醛和还原剂例如三乙酰氧基硼氢化钠反应。合适的温度包括从约 25℃延伸到 50℃的范围。

[0267] 式 (X) 的化合物可根据方案 2 中概述的方法进行制备。

[0268] 方案 2

[0269]



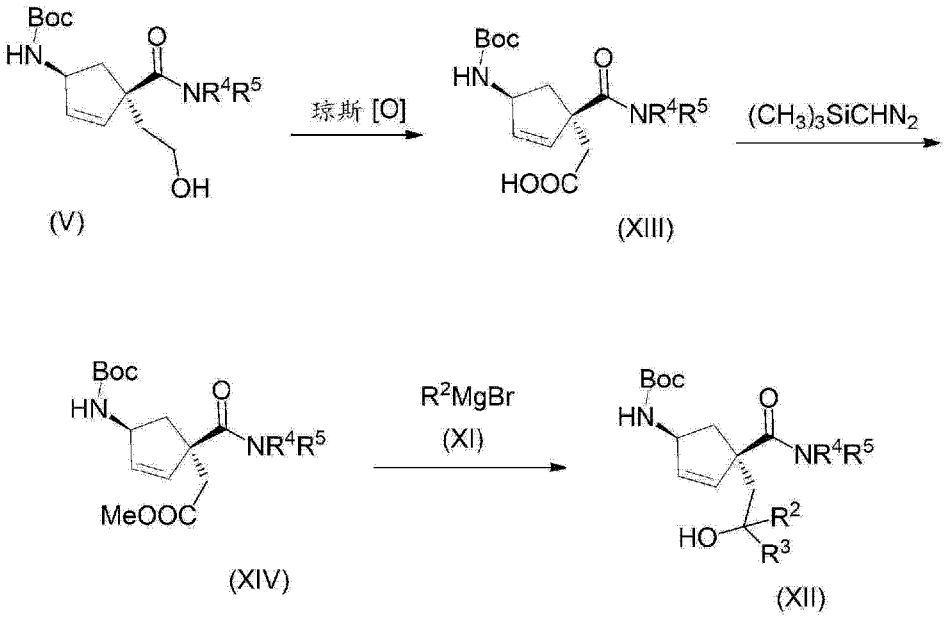
[0270] 通过在溶剂例如 DCM 或 1,2- 二氯乙烷，在 0℃至 50℃的温度下，与适当选择的氧化剂例如戴斯 - 马丁氧化剂、斯文或氯铬酸吡啶盐反应，例如如上文方案 1 中所述制备的式 (V) 的醇转换为相应的醛。随后在溶剂例如二乙醚、THF 或甲苯的存在下，在 -78℃至 25℃的温度下，所得的中间体与适当选择的式 (XI) 的格氏试剂或锂试剂反应，以获得相应的式 (X) 的醇。

[0271] 可通过用所述式 (X) 的化合物取代上文方案 1 中的式 (V) 的化合物，由相应的 (X) 的化合物制备其中 A 为 O 并且其中 R^2 除氢以外的式 (I) 的化合物。

[0272] 式 (XII) 的化合物可根据方案 3 中概述的方法进行制备。

[0273] 方案 3

[0274]



[0275] 在溶剂例如丙酮或水中，在 0℃至 50℃的温度下，例如如上文方案 1 中所述制备的式 (V) 的醇与适当选择的氧化剂例如 CrO_3、$Ru/NaIO_4$ 或 $KMnO_4$ 反应，以获得相应的式 (XIII) 的羧酸。

[0276] 在溶剂例如甲醇或乙醇中，在 -20℃至 25℃的温度下，使式 (XIII) 的酸与适当选择的烷化剂例如三甲基甲硅烷基（重氮甲烷）反应，以获得相应的式 (XIV) 的甲酯。

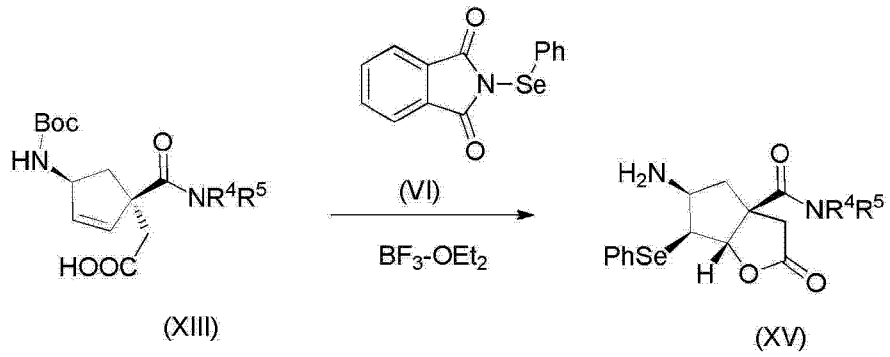
[0277] 在二乙醚、THF 或甲苯的存在下，在 -78℃至 25℃的温度下，使式 (XIV) 的甲酯与锂或格氏试剂 (XI) 反应，以获得取代的醇 (XII)。

[0278] 可通过用所述式 (XII) 的化合物取代上文方案 1 中的式 (V) 的化合物，由相应的 (XII) 的化合物制备其中 A 为 O 并且其中 R^2 和 R^3 除氢以外的式 (I) 的化合物。

[0279] 式 (XV) 的化合物可根据方案 4 中概述的方法进行制备。

[0280] 方案 4

[0281]



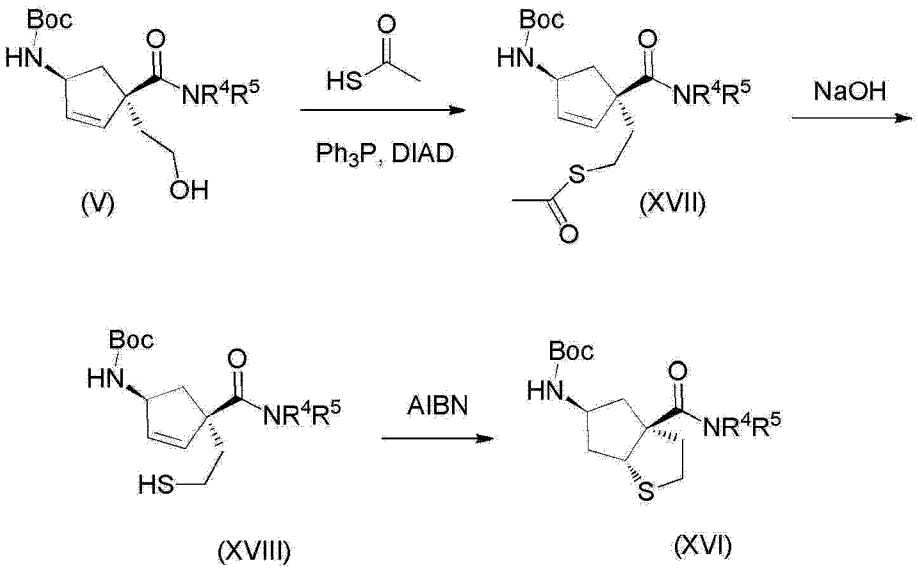
[0282] 在溶剂例如 DCM 或 1,2- 二氯乙烷中，在 0℃至 50℃的温度下，使如上文方案 3 中所述制备的适当选择的式 (XIII) 的酸与试剂例如 N-（苯基硒）邻苯二甲酰亚胺 (VI) 或苯基氯化硒和路易斯酸例如三氟化硼醚化物反应，以获得相应的式 (XV) 的二环内酯。

[0283] 可通过用所述式 (XV) 的化合物取代上文方案 1 中的式 (V) 的化合物，由相应的 (XV) 的化合物制备其中 A 为 O 并且其中 R^2 和 R^3 与它们结合的碳原子一起形成 C ＝ O 的式 (I) 的化合物。

[0284] 式 (XVI) 的化合物可根据方案 5 中概述的方法进行制备。

[0285] 方案 5

[0286]



[0287] 在膦例如三苯基膦或三丁基膦的存在下并且在活化剂例如偶氮二甲酸二异丙酯 (DIAD) 或偶氮二甲酸二乙酯 (DEAD) 的存在下，在溶剂例如 THF、二乙醚、DCM 或 1,2- 二氯乙烷中，在 0℃至 60℃的温度下 (即在 Mitsunobu 条件下)，例如如上文方案 1 中所述制备的式 (V) 的醇与硫代酸例如硫代乙酸反应，以获得相应的式 (XVII) 的硫酯。

[0288] 在溶剂例如甲醇或乙醇中，在 0℃至 60℃的温度下，使式 (XVII) 的硫酯与含水碱例如 NaOH、LiOH 或 KOH 反应，以获得相应的式 (XVIII) 的硫醇。

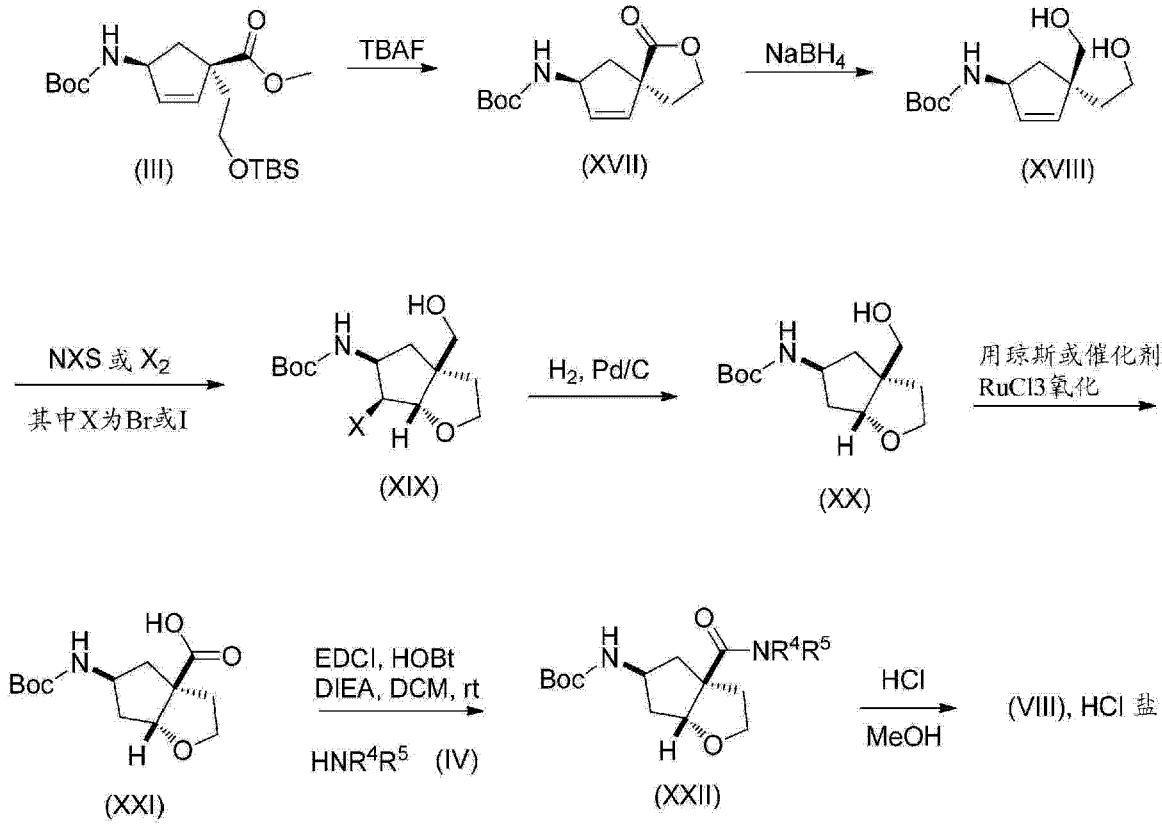
[0289] 在溶剂例如苯或甲苯中，在 60℃至 120℃的温度下，式 (XVIII) 的硫醇与自由基引发剂例如 AIBN 反应，以获得相应的式 (XVI) 的二环硫醚。

[0290] 可根据方案 5 的操作，通过用化合物 (XII)(如方案 3 中制备) 代替化合物 (V) 起始，制备其中 A 为 S，R^0为氢并且其中 R_2和 R_3除氢以外的式 (I) 的化合物。另外，如方案 1 中所述的还原性烷化可由本领域普通技术人员用作将其中 A 为 S 并且 R_0为 H 的式 (I) 的这些化合物转化为其中 A 为 S 并且 R_0除 H 以外的式 (I) 的化合物的方法。

[0291] 式 (VIII) 的化合物可替代地可根据方案 6 的操作进行制备。

[0292] 方案 6

[0293]



[0294] 通过在溶剂例如 THF 等等中，在约 -20℃至约 50℃的温度范围内，与适当选择的脱甲硅烷基试剂例如四丁基氟化铵等等反应，使例如如上文方案 1 中所述制备的式 (III) 的化合物环化，以获得相应的式 (XVII) 的内酯。

[0295] 在适当选择的溶剂例如 THF 等等中，在约 -20℃至约 50℃的温度范围内，使式 (XVII) 的内酯与适当选择的还原剂例如 $NaBH_4$、$LiAlH_4$等等反应，以获得相应的式 (XVIII) 的二醇。

[0296] 在溶剂例如 THF、EtOAc、CH_2Cl_2等等中，在约 0℃至约 100℃的温度范围内，使式 (XVIII) 的二醇与适当选择的卤化试剂例如 N- 溴 - 琥珀酰亚胺、N- 碘 - 琥珀酰亚胺、Br_2等等反应，以获得相应的式 (XIX) 的中间体。

[0297] 通过在溶剂或溶剂混合物例如 THF、EtOAc、甲醇等等中，在适当选择的催化剂例如 Pd/C、Pt/C 等等的存在下，在约室温下与氢气反应，使式 (XIX) 的中间体氢化，以获得相应的式 (XX) 的醇。

[0298] 另选地，在自由基引发剂例如 AIBN 等等的存在下，在溶剂例如苯、甲苯等等中，在约 60℃至约 120℃范围内的温度下，式 (XIX) 的中间体可与还原剂例如三正丁基锡烷、三 (三甲基甲硅烷基) 硅烷等等反应，以获得相应的式 (XX) 的醇。

[0299] 在溶剂例如丙酮、水等等中，在约 0℃至约 50℃范围内的温度下，使式 (XX) 的醇与适当选择的氧化剂例如 CrO_3、Ru/$NaIO_4$、$KMnO_4$等等反应，以获得相应的式 (XXI) 的羧酸。

[0300] 随后在偶联剂例如 EDCI/HOBt、PyBrop、DCC 等等的存在下，在有机溶剂例如 THF、二氯甲烷、1,2- 二氯乙烷等等中，在约 0℃至约 25℃范围内的温度下，使式 (XXI) 的酸与适当选择的式 (IV) 的胺反应，以获得相应的式 (XXII) 的酰胺。

[0301] 式 (XXII) 的酰胺通过在酸性条件例如在 MeOH 中的 HCl 下，在范围为约 25℃至约

80℃的温度下反应进行脱保护，以获得相应的式 (VIII) 的化合物，所述式 (VIII) 的化合物随后可如上文方案 1 中所述进行反应，以获得相应的其中 A 为 O 并且其中 R_0、R_2和 R_3各自为氢的式 (I) 的化合物。

[0302] 另选地，在适当选择的路易斯酸例如三氟化硼醚化物等等的存在下，在溶剂例如 DCM、1,2- 二氯乙烷等等中，在约 0℃至约 50℃范围内的温度下，式 (XVIII) 的化合物可与 N-(苯基硒) 邻苯二甲酰亚胺 (VI) 或苯基氯化硒反应，以获得相应的其中 X 为 Ph-Se 的式 (XIX) 的环状醚。

[0303] 在自由基引发剂例如 AIBN 等等的存在下，在溶剂例如苯、甲苯等等中，在约 60℃至约 120℃范围内的温度下，式 (XIX) 的环状醚随后与适当选择的还原剂例如三正丁基锡烷、三 (三甲基甲硅烷基) 硅烷等等反应，以获得相应的式 (XX) 的中间体。

[0304] 式 (XX) 的中间体随后如上所述反应，以获得相应的其中 A 为 O 并且其中 R_0、R_2和 R_3各自为氢的式 (I) 的化合物。

[0305] 另外，如方案 1 中所述的还原性烷化可由本领域普通技术人员用作将其中 A 为 O 并且 R_0为 H 的式 (I) 的这些化合物转化为其中 A 为 O 并且 R_0除 H 以外的式 (I) 的化合物的方法。

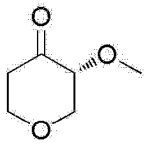
[0306] 实例

[0307] 本发明的代表性化合物可根据下文所述的一般合成方法合成。式 (I) 的化合物可通过本领域的技术人员已知的方法制备。以下实例仅意在表示本发明的实例且绝不意在限制本发明。

[0308] 中间体 1

[0309] (R)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮

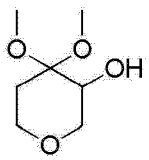
[0310]



[0311] 步骤 A

[0312] 4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇

[0313]



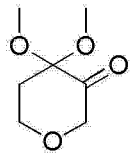
[0314] 向具有顶置式搅拌器的 12-L 4 颈圆底烧瓶中装入 MeOH(8.18L) 和氢氧化钾 (400.5g,2.4 摩尔)，同时在室温下搅拌直至碱完全溶解 (观察到放热)。将均质混合物用冰 - 丙酮浴冷却至 0℃。向 500-mL 添加漏斗中装入四氢 -4H- 吡喃 -4- 酮 (250g,2.5 摩尔)，并且在 KOH- 甲醇溶液温度达到 0℃后，逐滴加入吡喃酮，同时使温度维持在＜ 5℃。在搅拌另外 1.5 小时后，经历 1.5 小时时段分批加入碘 (704g,1.1 摩尔)，同时使温度维持在＜ 5℃。允许反应混合物在室温下搅拌 18 小时。使反应浓缩，并且用甲苯 (1.5L) 处理剩余残余并搅拌 1/2 小时。固体已沉淀，被过滤掉，并且使滤液蒸发，以提供作为琥珀油的标题

化合物 (330g,81%)。

[0315] 步骤 B

[0316] 4,4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮

[0317]

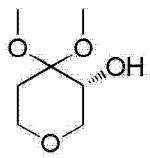


[0318] 向配备顶置式搅拌器、热电偶和两个添加漏斗的 12-L 4 颈莫顿烧瓶中装入草酰氯 (130mL,1.49 摩尔) 和 CH_2Cl_2(2.5L)。该溶液用干冰 / 丙酮浴冷却至 -72℃。经历 1/2 小时时段经由添加漏斗加入在 CH_2Cl_2(530mL) 中的 DMSO(178mL,2.50 摩尔),同时使温度维持在或低于 -70℃。在添加完成后,将混合物搅拌另外 30 分钟,并且从添加漏斗缓慢加入 (～ 1/2 小时) 在 CH_2Cl_2(630mL) 中的 4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇 (如步骤 A 中制备,200g,1.23 摩尔),使温度维持在或低于 -70℃。在搅拌另外 30 分钟,加入 Et_3N(870mL,6.24 摩尔),使温度达到 -42℃,并且回降至大约 -70℃。允许搅拌的混合物经过 18 小时搅拌至室温。将混合物过滤,并且使滤液浓缩,以提供粗产物加上 Et_3N-HCl 固体。将混合物过滤,并且用 EtOAc(2x500mL) 清洗。将滤液再次浓缩为浆。浆用 EtOAc(大约 1L) 稀释,过滤并再次浓缩,以获得含有产物和残留 DMSO 作为主要组分的琥珀油。使用在庚烷中的乙酸乙酯混合物在硅胶上纯化后,标题化合物 (285g,90%) 作为褐色固体提供。

[0319] 步骤 C1

[0320] (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇

[0321]

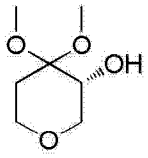


[0322] 向配备顶置式空气搅拌器、具有氮入口适配器的添加漏斗、冷凝器和热电偶的 12-L 4 颈圆底烧瓶中装入 S-(-)-2- 甲基 -CBS- 噁唑硼烷 (40g,0.12 摩尔) 和 THF(2.2L)。使混合物在氮下加温至 40℃,随后经由注射器将 Me_2S-BH_3(108mL,1.15 摩尔) 加入 THF 催化剂混合物内。经历 7 小时时段逐滴加入装入在 THF(2.1L) 中的 4,4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮 (如先前步骤中制备,165g,0.59 摩尔) 的添加漏斗。在添加完成后,允许反应在 40℃下搅拌 18 小时。使反应在冰 - 丙酮浴中冷却至 10℃,并且通过经历 1 小时时段缓慢加入 MeOH(1.1L) 得到淬灭。去除冷却浴,并且允许混合物加温至室温 3 小时。在气体逸出停止后,使混合物在旋转蒸发器上浓缩,以获得 188g。使用 EtOAc 和庚烷的混合物在硅胶上的纯化提供作为黄色油的标题化合物 (166g,99%,手性 GC 93% ee)。

[0323] 步骤 C(替代方案)

[0324] (R)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇

[0325]

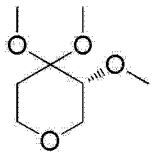


[0326] 向配备顶置式空气搅拌器、具有氮入口适配器的添加漏斗、冷凝器和热电偶的12-L 4颈圆底烧瓶中装入S-(-)-2-甲基-CBS-噁唑硼烷(78g,0.28摩尔)和THF(2.7L)。使混合物在氮下加温至40℃,同时经过40分钟经由添加漏斗将硼烷-N,N-二乙基苯胺络合物(280mL,1.57摩尔)加入THF-催化剂混合物中。向4-L锥形瓶中装入在THF(2.7L)中的4,4-二甲氧基二氢-2H-吡喃-3(4H)-酮(如步骤B中制备,225g,1.4摩尔),并且经由计量泵经历8小时时段逐滴加入。在添加后,允许反应在40℃下搅拌18小时。使反应在冰-丙酮浴中冷却至10℃,并且通过经历1小时时段缓慢加入MeOH(1.35L)得到淬灭;在MeOH添加完成后,去除冷却浴,并且允许混合物加温至室温3小时。在气体逸出停止后,使混合物在旋转蒸发器上浓缩,以获得365g。使用在庚烷中的ETOAC混合物在硅胶上的纯化提供作为黄色油的标题化合物(157g,69%,手性GC 95.5% ee)。

[0327] 步骤D

[0328] (R)-3,4,4-T三甲氧基四氢-2H-吡喃

[0329]

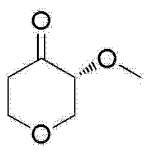


[0330] 向配备顶置式空气搅拌器、具有氮入口适配器的添加漏斗、冷凝器和热电偶的12-L 4颈圆底烧瓶中装入在THF(2.4L)中的(R)-4,4-二甲氧基四氢-2H-吡喃-3-醇(如先前步骤中制备,163g,1.0摩尔),并且在冰/丙酮浴中搅拌直至<0℃。一次性加入KOtBu(113g,1.0摩尔),并且在搅拌45分钟后,经过15分钟经由添加漏斗加入硫酸二甲酯(95mL,1.0摩尔)。允许反应在室温下搅拌2小时。将反应混合物倾入含有H_2O(1.2L)和CH_2Cl_2(1.2L)的分离烧瓶内,并且使层分离。用CH_2Cl_2(900mL)反萃取水层。将合并的有机层用卤水(1.0L;注:有机层在顶部)洗涤,在$MgSO_4$上干燥,过滤并蒸发,以提供作为淡黄色油的标题化合物(177.1g,99%,手性GC 94.4% ee)。

[0331] 步骤E

[0332] (R)-3-甲氧基二氢-2H-吡喃-4(3H)-酮

[0333]



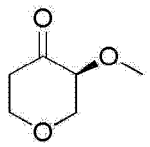
[0334] 用经过45分钟经由添加漏斗加入的HCl溶液(浓缩的,595mL,7.21摩尔)处理在<0℃下在冰/丙酮浴中的THF(3.6L)和H_2O(1.1L)中的(R)-3,4,4-三甲氧基四氢-2H-吡喃(如先前步骤中制备,141g,0.80摩尔)的搅拌混合物,同时使温度保持在<3℃下。在添加完成后,允许反应在0℃下搅拌1.5小时。使反应蒸发直至~1.9L浓缩物剩余。将浓

缩物转移至分液漏斗，并且用 CH_2Cl_2(3×1L) 萃取。将合并的有机级分用饱和 $NaHCO_3$(1L)、卤水 (1L) 洗涤，在 $MgSO_4$上干燥，过滤并蒸发，以提供作为油的标题化合物 (71.4g，69％，手性 GC 92％ ee)，所述油在静止后固化。旋光度：$[\alpha]^{25}$(D)-6.97° (c = 0.8222，MeOH)；对于 $C_6H_{10}O_3$的元素分析计算值为：C，53.59；H，7.58；实测值为：C，53.64；H，7.65。

[0335] 中间体 2

[0336] (S)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮

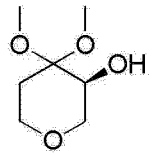
[0337]



[0338] 步骤 A

[0339] (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇

[0340]

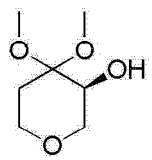


[0341] 向配备顶置式空气搅拌器、具有氮入口适配器的添加漏斗、冷凝器和热电偶的 5-L 4 颈圆底烧瓶中装入 (R)-(+)-2- 甲基 -CBS- 噁唑硼烷 (34g，0.12 摩尔) 和 THF(1.2L)。使混合物在氮下加温至 40℃，随后经由注射器将 Me_2S-BH_3(63mL，0.67 摩尔) 加入 THF 催化剂混合物内。经历 8 小时时段逐滴加入装入在 THF(1.2L) 中的 4,4- 二甲氧基二氢 -2H- 吡喃 -3(4H)- 酮 (如中间体 1，步骤中制备，96g，0.59 摩尔) 的添加漏斗。在添加后，允许反应在 40℃下搅拌 18 小时。使反应在冰 - 丙酮浴中冷却至 10℃，并且通过经过 45 分钟缓慢加入 MeOH(600mL) 得到淬灭。去除冷却浴，并且允许混合物加温至室温 3 小时。在气体逸出停止后，使混合物在旋转蒸发器上浓缩，以获得 132g。使用 EtOAc 和庚烷的混合物在硅胶上的纯化提供作为黄色油的标题化合物 (80.5g，83％，手性 GC 95％ ee)。

[0342] 步骤 A(替代方案 1)

[0343] (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇

[0344]

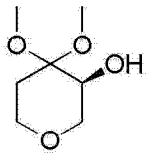


[0345] 反应根据中间体 2，步骤 A 的操作执行，使用 0.1 当量的 (R)-(+)-2- 甲基 -CBS- 噁唑硼烷，并且用 BH_3-THF 复合物替代 Me_2S-BH_3。产物 (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇以 88％得率和 60％ ee 获得。

[0346] 步骤 A(替代方案 2)

[0347] (S)-4,4- 二甲氧基四氢 -2H- 吡喃 -3- 醇

[0348]

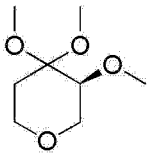


[0349] 反应根据中间体2，步骤A的操作执行，使用0.1当量的(R)-(+)-2-甲基-CBS-噁唑硼烷，并且用儿茶酚硼烷替代Me_2S-BH_3。产物(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇以20％得率和60％ ee获得。

[0350] 步骤B

[0351] (S)-3,4,4-三甲氧基四氢-2H-吡喃

[0352]

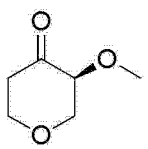


[0353] 向配备顶置式空气搅拌器、具有氮入口适配器的添加漏斗、冷凝器和热电偶的3-L 4颈圆底烧瓶中装入在THF(1.1L)中的(S)-4,4-二甲氧基四氢-2H-吡喃-3-醇（如先前步骤中制备，80g，0.49摩尔），并且在冰/丙酮浴中搅拌直至＜0℃。一次性加入KOtBu(56g，0.49摩尔)，并且在搅拌45分钟后，经过15分钟经由添加漏斗加入硫酸二甲酯(47mL，0.49摩尔)。允许反应在室温下搅拌3小时。将反应混合物倾入含有H_2O(1.25L)和CH_2Cl_2(1.25L)的分离烧瓶内，并且使层分离。用CH_2Cl_2(750mL)反萃取水层。将合并的有机层用卤水(1L；注：有机层在顶部）洗涤，在$MgSO_4$上干燥，过滤并蒸发，以提供作为淡黄色油的标题化合物(83.5g，96％，手性GC 94.6％ ee)。

[0354] 步骤C

[0355] (S)-3-甲氧基二氢-2H-吡喃-4(3H)-酮

[0356]



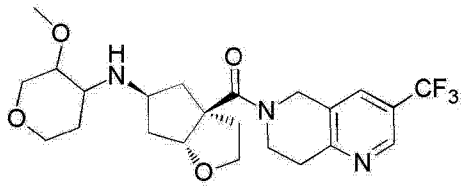
[0357] 向配备顶置式空气搅拌器、氮入口适配器、热电偶和隔膜的5-L 4颈圆底烧瓶中装入(S)-3,4,4-三甲氧基四氢-2H-吡喃（如先前步骤中制备，83g，0.47摩尔）、THF(2.1L)、H_2O(670mL)，并且在冰/丙酮浴中搅拌直至＜0℃，其后经过30分钟经由添加漏斗加入HCl溶液（浓缩的，350mL，4.24摩尔），同时使温度保持在＜2℃。在添加完成后，允许反应在0℃下搅拌1小时。使反应蒸发直至～1.2L浓缩物剩余。将浓缩物转移至分液漏斗，并且用CH_2Cl_2(3×750mL)萃取。将合并的有机级分用饱和$NaHCO_3$(500mL)、卤水(500mL)洗涤，在$MgSO_4$上干燥，过滤并蒸发，以提供作为油的标题化合物(46.9g，77％，手性GC 91％ ee)，所述油在静止后固化。旋光度：$[\alpha]^{25}$(D)+3.65° (c＝1.020，MeOH)；对于$C_6H_{10}O_3$的元素分析计算值为：C，53.39；H，7.57；实测值为：53.59；H，7.62。

[0358] 实例1

[0359] ((3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基）氨基）六氢-2H-环戊并

[b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

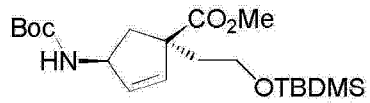
[0360]



[0361] 步骤 A

[0362] (1S,4S)-4-((叔丁氧羰基) 氨基)-1-(2-((叔丁基二甲基甲硅烷基) 氧基) 乙基) 环戊 -2- 烯基甲酸甲酯

[0363]

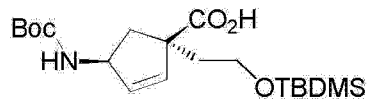


[0364] 在 -78℃下在 Ar 下经过 1 小时向在 THF 中的 LiHMDS 溶液 (72.9mL 1M 溶液, 72.9mmol,2.2 当量) 中,逐滴加入在 THF(40mL) 中的 (1R,4S)-4-((- 叔丁氧羰基) 氨基) 环戊 -2- 烯基甲酸甲酯溶液 (根据 US 20050101628 A1 的操作 (参见第 31 页,第 1 列,操作 B,步骤 B) 制备),8.00g,33.2mmol,1 当量)。在搅拌 30 分钟后,加入在 THF(20mL) 中的叔丁基 (2- 碘乙氧基) 二甲基硅烷溶液 (13.29g,46.4mmol,1.4 当量)。使溶液在 -78℃下保持 15 分钟,随后经过 2 小时逐步加温至 0℃,并且在 0℃下保持 1 小时。加入 1N HCl 和水,用 DCM 萃取溶液,合并有机物,在 $MgSO_4$ 上干燥并浓缩。通过用 5 至 20 % EtOAc/ 庚烷洗脱的色谱法 (400g 柱) 的纯化提供步骤 A 的标题化合物。^1H NMR(氯仿 -d) δ : 5.76-5.85(m,2H),4.90(d, J = 9.0Hz,1H),4.72-4.82(m,1H),3.69(s,3H),3.57-3.64(m, 2H),2.24(dd, J = 13.9,8.0Hz,1H),2.14(dd, J = 14.1,3.5Hz,2H),1.71-1.82(m,1H), 1.40-1.50(m,9H),0.84-0.90(m,9H),0.03(s,6H)。ESI-MS(m/z) :对于 C20H37NO5Si 的计算值为 :422.2(M+23) ;实测值为 :422.2。

[0365] 步骤 B

[0366] (1S,4S)-4-((叔丁氧羰基) 氨基)-1-(2-((叔丁基二甲基甲硅烷基) 氧基) 乙基) 环戊 -2- 烯羧酸

[0367]



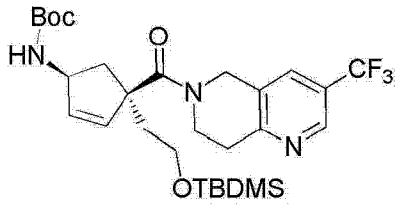
[0368] 在室温下向在甲醇 (100mL) 中的步骤 A 产物 (7.89g,19.74mmol,1 当量) 溶液中加入 1N NaOH(59.2mL,59.2mmol,3.0 当量)。在搅拌过夜后,去除甲醇,加入 1N HCl 直至溶液为酸性,用 DCM 萃取溶液,合并有机物,在 $MgSO_4$ 上干燥并浓缩,以提供步骤 B 的标题化合物。^1H NMR(氯仿 -d) δ :5.85(br. s. ,2H),4.97(br. s. ,1H),4.80(br. s. ,1H),3.71(br. s. , 2H),1.99-2.41(m,3H),1.92(br. s. ,1H),1.44(br. s. ,9H),0.88(s,9H),0.06(br. s. ,6H)。 ESI-MS(m/z) :对于 C19H35NO5Si 的计算值为 :408.2(M+23) ;实测值为 :408.3。

[0369] 步骤 C

[0370] 叔丁基 ((1S,4S)-4-(2-((叔丁基二甲基甲硅烷基) 氧基) 乙基)-4-(3-(三氟甲

基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)氨基甲酸酯

[0371]

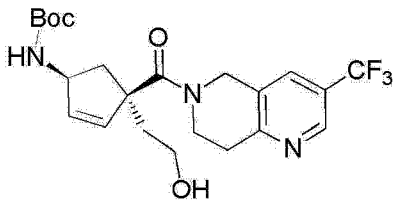


[0372] 在室温下向在DCM(40mL)中的步骤B产物(3.47g,8.99mmol,1当量)溶液中加入HOBt水合物(2.34g,15.3mmol,1.7当量)和EDCI(2.58g,13.5mmol,1.5当量)。在15分钟后,加入DIEA(7.8mL,45.3mmol,5当量)和3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-2HCl(3.71g,13.5mmol,1当量),并且将溶液在室温下搅拌过夜。加入饱和$NaHCO_3$,用DCM萃取溶液,合并有机物,在$MgSO_4$上干燥并浓缩。通过用25至60%EtOAc/庚烷洗脱的色谱法(120g柱)的纯化提供步骤C的标题化合物。^1H NMR(氯仿-d)δ:8.71(s,1H),7.69(s,1H),6.19(d,J = 5.4Hz,1H),5.76(dd,J = 5.6,2.0Hz,1H),4.68-4.86(m,4H),3.85-4.07(m,2H),3.54-3.65(m,2H),3.13(t,J = 5.7Hz,2H),2.58(dd,J = 13.3,7.7Hz,1H),1.98-2.16(m,2H),1.85-1.97(m,1H),1.42(s,9H),0.84(s,9H),-0.02(d,J = 4.4Hz,6H)。对于C28H42F3N3O4Si的计算值为:570.3(M+1);实测值为:570.3。

[0373] 步骤D

[0374] 叔丁基((1S,4S)-4-(2-羟乙基)-4-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)氨基甲酸酯

[0375]

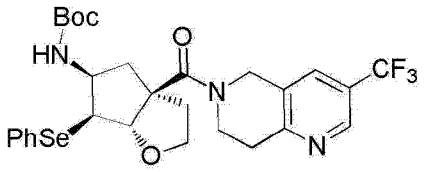


[0376] 在室温下向在THF(50mL)中的步骤C产物(3.52g,6.18mmol,1当量)溶液中加入在THF中的TBAF(12.36mL 1M溶液,12.36mmol,2当量)。在1小时后,加入水,用DCM萃取溶液,合并有机物,在$MgSO_4$上干燥并浓缩。通过用2至6%甲醇/DCM洗脱的色谱法(80g柱)的纯化提供步骤D的标题化合物。^1H NMR(氯仿-d)δ:8.71(s,1H),7.70(s,1H),6.28(dd,J = 5.9,2.0Hz,1H),5.78(dd,J = 5.9,2.0Hz,1H),4.70-4.95(m,4H),3.99-4.10(m,1H),3.85-3.96(m,1H),3.68(br.s.,2H),3.09-3.18(m,2H),2.65(dd,J = 12.9,7.4Hz,1H),1.99-2.21(m,3H),1.82-1.93(m,1H),1.38-1.49(m,9H)。对于C22H28F3N3O4的计算值为:456.2(M+1);实测值为:456.2。

[0377] 步骤E

[0378] 叔丁基((3aS,5S,6S,6aS)-6-(苯基硒烷基)-3a-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)六氢-2H-环戊并[b]呋喃-5-基)氨基甲酸酯

[0379]

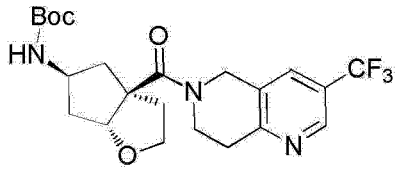


[0380] 在室温下在 Ar 下向在 DCM(40mL) 中的步骤 D 产物 (1.51g,3.32mmol,1 当量) 溶液中加入 N-(苯基硒) 邻苯二甲酰亚胺 (1.60g,4.97mmol,1.5 当量) 和 BF_3- 醚化物 (0.042mL,0.33mmol,0.1 当量)。在 2 小时后,加入 1N NaOH 并搅拌 5 分钟,加入水,用 DCM 萃取溶液,合并有机物,在 $MgSO_4$上干燥并浓缩。通过用 50 至 100% EtOAc/ 庚烷洗脱的色谱法 (80g 柱) 的纯化提供步骤 E 的标题化合物。^{1}H NMR(氯仿 -d) δ :8.72(s,1H),7.69(s,1H),7.50-7.62(m,2H),7.22-7.27(m,3H),5.35(s,1H),5.06(d, J = 8.1Hz,1H),4.79-5.01(m,1H),4.66-4.78(m,1H),4.53(br. s.,1H),3.78-4.06(m,4H),3.68-3.78(m,1H),3.05-3.19(m,2H),2.32(dd, J = 11.6,5.8Hz,2H),2.16(d, J = 10.9Hz,2H),1.36(s,9H)。对于 C28H32F3N3O4Se 的计算值为 :634.2(M+23) ;实测值为 :634.1。

[0381] 步骤 F

[0382] 叔丁基 ((3aS,5S,6aR)-3a-(3-(三氟甲基)-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基) 氨基甲酸酯

[0383]

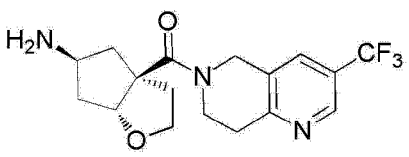


[0384] 在 Ar 下使在苯 (20mL) 中的步骤 E 产物 (1.51g,2.67mmol,1 当量)、三 (三甲基甲硅烷基) 硅烷 (1.72mL,5.34mmol,2 当量) 和 AIBN(438mg,2.67mmol,1 当量) 溶液加温至 80℃。在 3 小时后,使溶液浓缩。通过用 50 至 100% EtOAc/ 庚烷洗脱的色谱法 (80g 柱) 的纯化提供步骤 F 的标题化合物。^{1}H NMR(氯仿 -d) δ :8.72(br. s.,1H),7.71(br. s.,1H),4.97-5.09(m,1H),4.70-4.91(m,2H),4.56-4.69(m,1H),4.28(br. s.,1H),3.80-4.07(m,3H),3.71(q, J = 7.3Hz,1H),3.13(br. s.,2H),2.07-2.53(m,4H),1.81(br. s.,1H),1.61-1.72(m,1H),1.40(s,9H)。对于 C22H28F3N3O4 的计算值为 :478.2(M+23) ;实测值为 :478.2。

[0385] 步骤 G

[0386] ((3aS,5S,6aR)-5- 氨基六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0387]



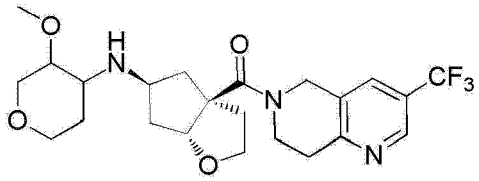
[0388] 在室温下向在 DCM(100mL) 中的步骤 F 产物 (12.54g,24.8mmol,1 当量) 溶液中加入 TFA(20mL,261mmol,10.6 当量)。在 14、时后,使溶液浓缩。加入 3M NaOH,用 DCM 萃取溶液,合并有机物,在 $MgSO_4$上干燥并浓缩,以提供步骤 G 的标题化合物。^{1}H NMR(氯

仿 -d) δ :8.72(s,1H),7.69(br.s.,1H),5.07(d,J = 4.9Hz,1H),4.71-4.90(m,2H),3.84-4.03(m,3H),3.58-3.71(m,2H),3.09-3.20(m,2H),2.14-2.41(m,3H),1.99-2.13(m,1H),1.65-1.75(m,1H),1.43-1.58(m,1H)。对于C17H20F3N3O2的计算值为:356.2(M+1);实测值为:356.3。

[0389] 步骤H

[0390] ((3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0391]



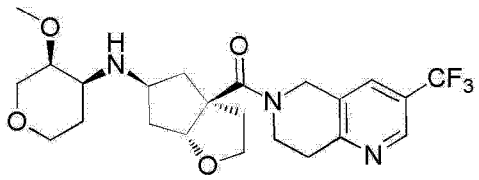
[0392] 在室温下向在DCM中的步骤G产物(119mg,0.33mmol,1当量)溶液中加入乙酸(0.01mL,0.17mmol,0.5当量)、3-甲氧基四氢-4H-吡喃-4-酮(131mg,1.0mmol,3当量)和三乙酰氧基硼氢化钠(355mg,1.67mmol,5当量)。在搅拌过夜后,加入饱和$NaHCO_3$,用DCM萃取溶液,合并有机物,在$MgSO_4$上干燥并浓缩。通过用4至8%甲醇/含氨DCM洗脱的色谱法(12g柱)的纯化提供实例1的标题化合物。^1H NMR(氯仿-d) δ :8.72(br.s.,1H),7.70(br.s.,1H),4.98-5.14(m,1H),4.70-4.89(m,2H),3.80-4.18(m,5H),3.25-3.75(m,8H),3.07-3.24(m,2H),2.53-2.89(m,1H),2.01-2.48(m,4H),1.39-1.88(m,5H)。 对于C23H30F3N3O4的计算值为:470.2(M+1);实测值为:470.2。

[0393] 通过手性HPLC分离实例1获得4种产物,实例2、实例3、实例4和实例5。

[0394] 实例2

[0395] ((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0396]

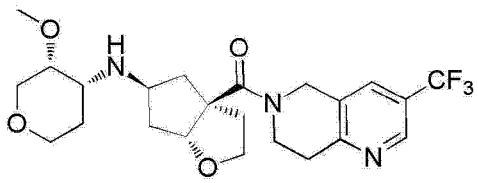


[0397] ^1H NMR(氯仿-d) δ :8.71(s,1H),7.70(br.s.,1H),5.05(d,J = 4.6Hz,1H),4.68-4.88(m,2H),4.08(dd,J = 12.5,2.9Hz,1H),3.81-4.04(m,4H),3.66(td,J = 8.8,6.8Hz,1H),3.50-3.62(m,1H),3.34-3.46(m,4H),3.24-3.34(m,2H),3.14(br.s.,2H),2.76(d,J = 9.5Hz,1H),2.14-2.46(m,3H),1.99-2.14(m,1H),1.45-1.86(m,5H)。 对于C23H30F3N3O4的计算值为:470.2(M+1);实测值为:470.2。

[0398] 实例3

[0399] ((3aS,5S,6aR)-5-(((3R,4R)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0400]

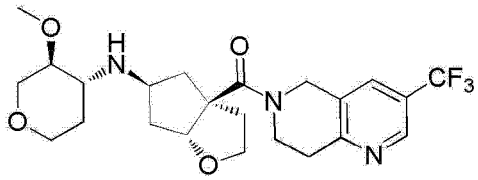


[0401] ^{1}H NMR(氯仿-d)δ:8.72(s,1H),7.70(br.s.,1H),5.06(d,J = 4.6Hz,1H),4.78(br.s.,2H),4.05(dd,J = 12.6,4.0Hz,1H),3.84-4.02(m,4H),3.65(td,J = 8.9,7.0Hz,1H),3.55(dt,J = 9.7,5.0Hz,1H),3.35-3.45(m,4H),3.27-3.35(m,2H),3.14(br.s.,2H),2.75-2.85(m,1H),2.35(br.s.,1H),2.24(dd,J = 13.0,5.4Hz,2H),2.00-2.15(m,1H),1.59-1.85(m,4H),1.48(ddd,J = 13.2,10.8,4.9Hz,1H)。对于C23H30F3N3O4的计算值为:470.2(M+1);实测值为:470.2。

[0402] 实例4

[0403] ((3aS,5S,6aR)-5-(((3S,4R)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮(甲氧基吡喃环的相对立体化学是反式的,绝对立体化学是未知的,但与实例5的相反)

[0404]

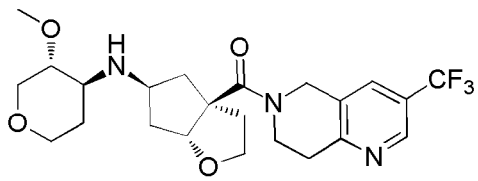


[0405] ^{1}H NMR(氯仿-d)δ:8.72(s,1H),7.70(br.s.,1H),5.01(d,J = 4.6Hz,1H),4.78(br.s.,2H),4.04-4.16(m,1H),3.81-4.04(m,4H),3.49-3.70(m,2H),3.27-3.44(m,4H),3.15(t,J = 5.3Hz,2H),2.96-3.09(m,2H),2.59(br.s.,1H),2.19-2.44(m,3H),2.00-2.13(m,1H),1.95(dt,J = 13.4,2.1Hz,1H),1.62-1.87(m,2H),1.57(ddd,J = 13.4,10.9,5.0Hz,1H),1.38-1.51(m,1H)。对于C23H30F3N3O4的计算值为:470.2(M+1);实测值为:470.2。

[0406] 实例5

[0407] ((3aS,5S,6aR)-5-(((3R,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮(甲氧基吡喃环的相对立体化学是反式的,绝对立体化学是未知的,但与实例4的相反)

[0408]



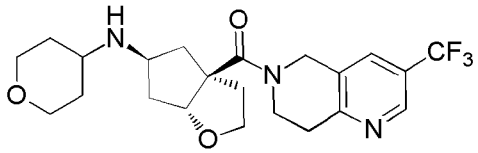
[0409] ^{1}H NMR(氯仿-d)δ:8.72(s,1H),7.69(br.s.,1H),5.06(d,J = 4.6Hz,1H),4.67-4.93(m,2H),4.10(d,J = 7.1Hz,1H),3.79-4.04(m,4H),3.48-3.69(m,2H),3.29-3.42(m,4H),3.14(br.s.,2H),2.96-3.10(m,2H),2.59-2.72(m,1H),2.21-2.43(m,3H),2.02-2.15(m,1H),1.98(d,J = 24.5Hz,1H),1.57-1.81(m,2H),1.30-1.48(m,2H)。对

于 C23H30F3N3O4 的计算值为 :470.2(M+1) ;实测值为 :470.2。

[0410] 实例 6

[0411] ((3aS,5S,6aR)-5-((四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0412]



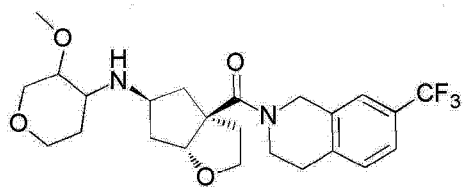
[0413] 遵循实例 1,步骤 H 中所述的操作,由实例 1,步骤 G 的产物和四氢 -4H- 吡喃 -4- 酮的反应制备标题化合物。

[0414] ^{1}H NMR(氯 仿 -d) δ :8.72(br.s.,1H),7.70(br.s.,1H),5.04(d, J = 4.6Hz, 1H),4.78(br.s.,2H),3.95(s,2H),3.97(s,3H),3.53-3.75(m,2H),3.28-3.49(m,2H), 3.14(br.s.,2H),2.62-2.81(m,1H),2.29(dd, J = 12.8,5.5Hz,3H),1.99-2.17(m,1H), 1.60-1.92(m,3H),1.18-1.57(m,5H)。对于 C22H28F3N3O3 的计算值为 :440.2(M+1) ;实测值为 :440.2。

[0415] 实例 7

[0416] ((3aS,5S,6aR)-5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(7-(三氟甲基)-3,4- 二氢异喹啉 -2(1H)- 基) 甲酮

[0417]



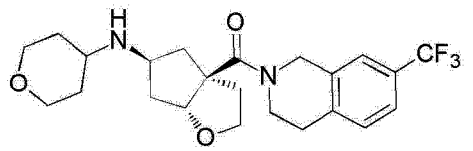
[0418] 遵循实例 1,步骤 C 中所述的操作,并且随后遵循实例 1 步骤 D 直到 H,由实例 1,步骤 B 的产物和 7-(三氟甲基)-1,2,3,4- 四氢异喹啉的反应制备标题化合物。

[0419] ^{1}H NMR(氯 仿 -d) δ :7.45(d, J = 7.6Hz,2H),7.23-7.31(m,1H),4.99-5.10(m, 1H),4.72(br.s.,2H),4.02-4.16(m,1H),3.70-4.02(m,4H),3.47-3.59(m,1H), 3.22-3.46(m,6H),2.86-3.09(m,3H),2.77(br.s.,1H),2.13-2.44(m,3H),1.99-2.11(m, 1H),1.35-1.88(m,5H)。对于 C24H31F3N2O4 的计算值为 :470.2(M+1) ;实测值为 :470.2。

[0420] 实例 8

[0421] ((3aS,5S,6aR)-5-((四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(7-(三氟甲基)-3,4- 二氢异喹啉 -2(1H)- 基) 甲酮

[0422]



[0423] 遵循实例 1,步骤 C 中所述的操作,遵循步骤 D 直到 G,并且随后使用四氢 -4H- 吡喃 -4- 酮遵循实例 1,步骤 H 中所述的操作,由实例 1 步骤 B 的产物和 7-(三氟甲基)-1,2,

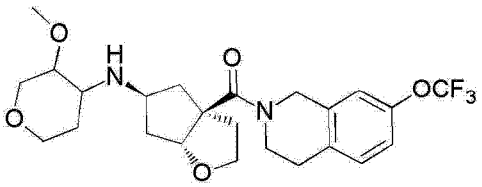
3,4- 四氢异喹啉的反应制备标题化合物。

[0424] JNJ46713953,^{1}H NMR(氯仿 -d) δ :7.31-7.50(m,2H),7.26-7.29(m,1H),5.05(d, J = 4.6Hz,1H),4.72(br. s.,2H),3.90-4.05(m,3H),3.70-3.85(m,2H),3.52-3.70(m,2H), 3.30-3.45(m,2H),2.95(br. s.,2H),2.70(br. s.,1H),2.18-2.44(m,3H),2.00-2.12(m, 1H),1.60-1.89(m,2H),1.23-1.53(m,5H)。对于C23H29F3N2O3 的计算值为 :439.2(M+1) ;实测值为 :439.2。

[0425] 实例 9

[0426] ((3aS,5S,6aR)-5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(7-(三氟甲氧基)-3,4- 二氢异喹啉 -2(1H)- 基) 甲酮

[0427]



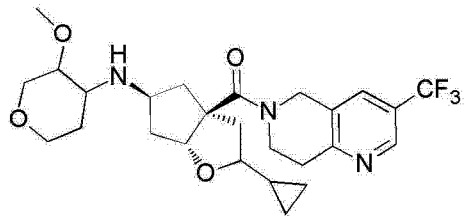
[0428] 遵循实例 1,步骤 C 中所述的操作,并且随后遵循实例 1 步骤 D 直到 H,由实例 1 步骤 B 的产物和 7-(三氟甲氧基)-1,2,3,4- 四氢异喹啉的反应制备标题化合物。

[0429] 对于 C24H31F3N2O5 的计算值为 :485.2(M+1) ;实测值为 :485.2。

[0430] 实例 10

[0431] ((3aS,5S,6aR)-2- 环丙基 -5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

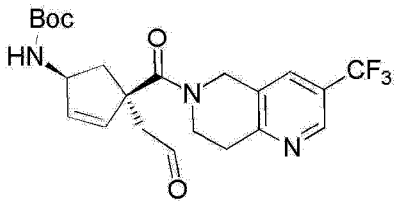
[0432]



[0433] 步骤 A

[0434] 叔丁基 ((1S,4S)-4-(2- 氧代乙基)-4-(3-(三氟甲基)-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基) 环戊 -2- 烯 -1- 基) 氨基甲酸酯

[0435]



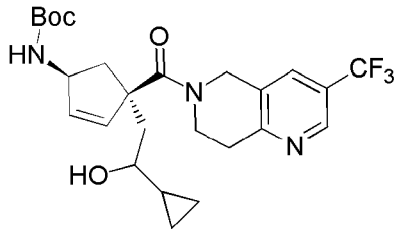
[0436] 在 0℃下向在 DCM(20mL) 中的实例 1,步骤 D 产物 (417mg,0.92mmol,1 当量) 溶液中加入戴斯 - 马丁氧化剂 (427mg,1.01mmol,1.1 当量)。在 1 小时后,加入饱和碳酸氢钠和硫代硫酸钠,在 10 分钟后,用 DCM 萃取水溶液,合并有机物,在 $MgSO_4$ 上干燥并浓缩。通过用 30 至 60% EtOAc/ 庚烷洗脱的色谱法 (12g 柱) 的纯化提供步骤 A 的标题化合物。

^{1}H NMR(氯仿-d) δ :9.74(s,1H),8.70(s,1H),7.72(s,1H),6.31(dd,J = 5.6,1.7Hz,1H),5.91(dd,J = 5.6,1.5Hz,1H),5.01(d,J = 17.1Hz,1H),4.65-4.87(m,3H),4.07-4.21(m,1H),3.79-3.95(m,1H),3.10(q,J = 5.6Hz,2H),3.03(d,J = 16.6Hz,1H),2.63(dd,J = 13.6,7.2Hz,1H),2.52(dd,J = 16.6,1.5Hz,1H),2.11(dd,J = 13.1,7.7Hz,1H),1.44(s,9H)。对于C22H26F3N3O4的计算值为:454.2(M+1);实测值为:454.2。

[0437] 步骤B

[0438] 叔丁基((1S,4S)-4-(2-环丙基-2-羟乙基)-4-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)氨基甲酸酯

[0439]



[0440] 在0℃下在Ar下经过30分钟,向在THF(5mL)中的环丙基溴化镁溶液(6.88mL在THF中的0.5M溶液,3.44mmol,8当量)中,逐滴加入在THF(17mL)中的步骤A产物(195mg,0.43mmol,1当量)溶液。在45分钟后,加入饱和NH_4Cl,用乙酸乙酯萃取溶液,合并有机物,在$MgSO_4$上干燥并浓缩。通过用30至100%EtOAc/庚烷洗脱的色谱法(12g柱)的纯化提供作为非对映体混合物的步骤B的标题化合物。^{1}H NMR(氯仿-d) δ :8.70(br.s.,1H),7.70(br.s.,1H),6.11-6.42(m,1H),5.77(t,J = 5.1Hz,1H),4.81(d,J = 12.2Hz,4H),4.03(dt,J = 12.8,6.2Hz,1H),3.81-3.98(m,1H),3.59-3.75(m,2H),3.03-3.25(m,2H),2.69-3.00(m,2H),2.19-2.67(m,3H),1.91-2.18(m,3H),1.55-1.88(m,5H),1.42(s,9H),0.88-0.99(m,1H),0.42-0.56(m,2H),0.14-0.35(m,2H)。对于C25H32F3N3O4的计算值为:496.2(M+1);实测值为:496.2。

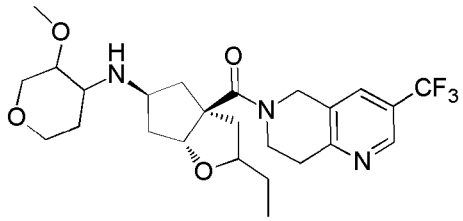
[0441] 通过获得实例10,步骤B的产物并遵循从实例1,步骤E直到H的操作,来制备实例10的标题化合物。

[0442] ^{1}H NMR(氯仿-d) δ :8.72(s,1H),7.69(br.s.,1H),5.01-5.29(m,1H),4.65-4.90(m,2H),3.74-4.15(m,5H),3.70(dd,J = 11.0,2.9Hz,1H),3.23-3.55(m,7H),3.14(br.s.,2H),3.05(ddd,J = 10.0,8.2,6.0Hz,1H),2.69-2.87(m,1H),2.36-2.52(m,1H),2.06-2.36(m,3H),1.66-1.97(m,2H),1.33-1.52(m,1H),0.83-0.98(m,1H),0.43-0.66(m,2H),0.36(dt,J = 8.6,4.1Hz,1H),0.10-0.24(m,1H)。对于C26H34F3N3O4的计算值为:510.3(M+1);实测值为:510.3。

[0443] 实例11

[0444] ((3aS,5S,6aR)-2-乙基-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0445]



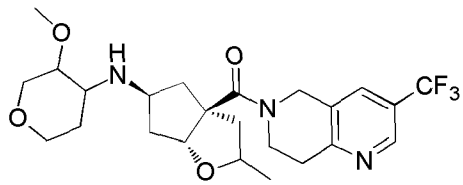
[0446] 遵循实例 10，步骤 B 中所述的操作，并且随后获得该产物并遵循从实例 1，步骤 E 直到 II 的操作，由实例 10，步骤 A 的产物和乙基溴化镁的反应制备标题化合物。

[0447] ^{1}H NMR(MeOD) δ :8.72(s,1H),8.05(br. s.,1H),4.94-5.13(m,1H),4.70-4.86(m,2H),4.25(br. s.,1H),3.76-4.14(m,4H),3.62-3.75(m,1H),3.35-3.60(m,7H),3.13(dd, J = 3.3,1.6Hz,2H),2.33-2.75(m,3H),1.69-2.10(m,5H),1.39-1.69(m,2H),0.87-1.01(m,3H)。对于 C25H34F3N3O4 的计算值为 :498.3(M+1) ;实测值为 :498.2。

[0448] 实例 12

[0449] ((3aS,5S,6aR)-5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基)-2- 甲基六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0450]



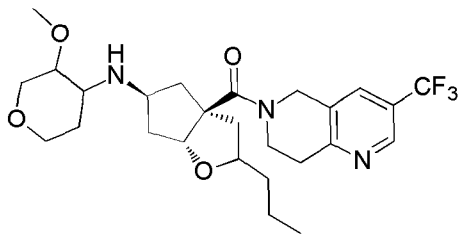
[0451] 遵循实例 10，步骤 B 中所述的操作，并且随后获得该产物并遵循从实例 1，步骤 E 直到 H 的操作，由实例 10，步骤 A 的产物和甲基溴化镁的反应制备标题化合物。

[0452] ^{1}H NMR(MeOD) δ :8.72(br. s.,1H),8.05(br. s.,1H),4.96-5.21(m,1H),4.70-4.87(m,2H),4.21-4.36(m,1H),3.77-4.18(m,5H),3.32-3.62(m,7H),3.00-3.23(m,2H),2.32-2.76(m,3H),1.68-2.06(m,5H),1.16-1.29(m,3H)。对于 C24H32F3N3O4 的计算值为 :484.2(M+1) ;实测值为 :484.2。

[0453] 实例 13

[0454] ((3aS,5S,6aR)-5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基)-2- 丙基六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0455]



[0456] 遵循实例 10，步骤 B 中所述的操作，并且随后获得该产物并遵循从实例 1，步骤 E 直到 H 的操作，由实例 10，步骤 A 的产物和丙基溴化镁的反应制备标题化合物。

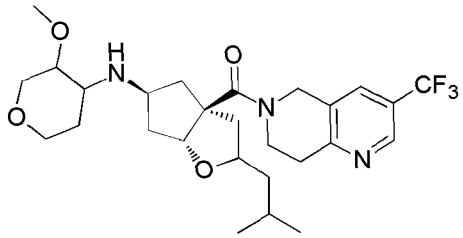
[0457] 对于 C26H36F3N3O4 的计算值为 :512.3(M+1) ;实测值为 :512.2。

[0458] 实例 14

[0459] ((3aS,5S,6aR)-2- 异丁基 -5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六

氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0460]



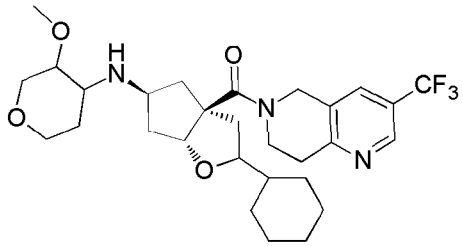
[0461] 遵循实例 10,步骤 B 中所述的操作,并且随后获得该产物并遵循从实例 1,步骤 E 直到 H 的操作,由实例 10,步骤 A 的产物和异丁基溴化镁的反应制备标题化合物。

[0462] 对于 C27H38F3N3O4 的计算值为 :526.3(M+1) ;实测值为 :526.3。

[0463] 实例 15

[0464] ((3aS,5S,6aR)-2- 环己基 -5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0465]



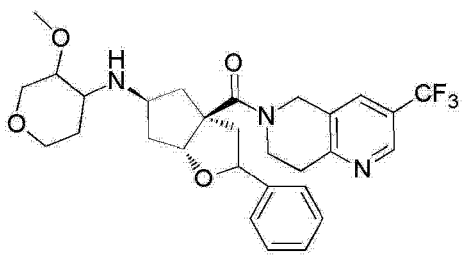
[0466] 遵循实例 10,步骤 B 中所述的操作,并且随后获得该产物并遵循从实例 1,步骤 E 直到 H 的操作,由实例 10,步骤 A 的产物和环己基溴化镁的反应制备标题化合物。

[0467] ^{1}H NMR(氯 仿 -d) δ :8.71(br. s.,1H),7.69(br. s.,1H),4.98-5.21(m,1H),4.65-4.94(m,2H),3.68-4.17(m,5H),3.23-3.64(m,8H),3.13(br. s.,2H),2.69-2.86(m,1H),1.86-2.35(m,6H),1.32-1.79(m,8H),1.10-1.30(m,3H),0.86-1.06(m,2H)。 对 于 C29H40F3N3O4 的计算值为 :552.3(M+1) ;实测值为 :553.2。

[0468] 实例 16

[0469] ((3aS,5S,6aR)-5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基)-2- 苯基六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0470]



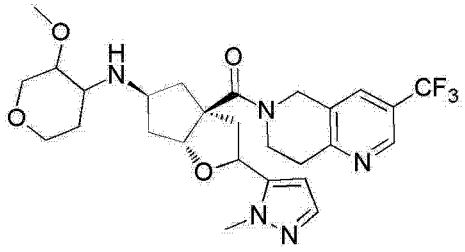
[0471] 遵循实例 10,步骤 B 中所述的操作,并且随后获得该产物并遵循从实例 1,步骤 E 直到 H 的操作,由实例 10,步骤 A 的产物和苯基溴化镁的反应制备标题化合物。

[0472] 对于 C29H34F3N3O4 的计算值为 :546.3(M+1) ;实测值为 :546.3。

[0473] 实例 17

[0474] ((3aS,5S,6aR)-5-((3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基)-2-(1- 甲基 -1H- 吡唑 -5- 基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

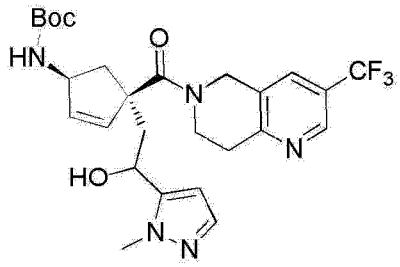
[0475]



[0476] 步骤 A

[0477] 叔丁基 ((1S,4S)-4-(2- 羟基 -2-(1- 甲基 -1H- 吡唑 -5- 基) 乙基)-4-(3-(三氟甲基)-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基) 环戊 -2- 烯 -1- 基) 氨基甲酸酯

[0478]



[0479] 在 -78℃下在 Ar 下向在 THF(8mL) 中的 1- 甲基吡唑 (0.165mmol,1.98mmol,3 当量) 溶液中加入 n-BuLi(0.77mL 在己烷中的 2.5M 溶液,1.92mmol,2.9 当量),并且将溶液搅拌 1 小时。随后经过 5 分钟加入在 THF(8mL) 中的实例 10,步骤 A(300mg,0.66mmol,1 当量) 溶液。在 1 小时后,加入饱和 NH_4Cl,用乙酸乙酯萃取溶液,合并有机物,在 $MgSO_4$ 上干燥并浓缩。通过用 50 至 100% EtOAc/ 庚烷到 5 至 10% 甲醇 /DCM 洗脱的色谱法 (12g 柱) 的纯化提供作为非对映体混合物的步骤 A 的标题化合物。^1H NMR(氯仿 -d) δ :8.70(s,1H),7.62-7.80(m,1H),7.33(d, J = 8.8Hz,1H),6.19-6.49(m,1H),6.09(br.s.,1H),5.87(dd, J = 17.9,5.6Hz,1H),4.54-5.03(m,5H),3.74-3.96(m,4H),3.48(s,1H),2.90-3.23(m,2H),2.46-2.87(m,2H),2.06-2.39(m,2H),1.73-1.98(m,1H),1.43(br.s.,9H)。 对于 C27H34F3N5O4 的计算值为 :558.2(M+23) ;实测值为 :558.2。

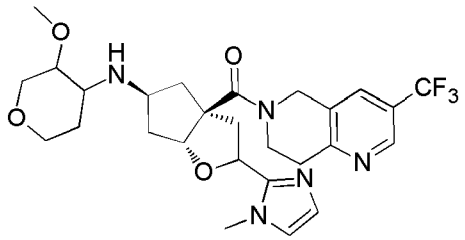
[0480] 通过获得实例 17,步骤 A 的产物并遵循从实例 1,步骤 E 直到 H 的操作,来制备实例 17 的标题化合物。

[0481] ^1H NMR(氯仿 -d) δ :8.73(br.s.,1H),7.72(br.s.,1H),7.32-7.48(m,1H),5.90-6.28(m,1H),5.08-5.36(m,1H),4.64-4.98(m,2H),3.76-4.17(m,7H),3.50-3.74(m,1H),3.23-3.50(m,6H),3.16(br.s.,2H),2.66-2.86(m,1H),2.15-2.64(m,4H),1.96-2.05(m,1H),1.42-1.91(m,3H)。对于 C27H34F3N5O4 的计算值为 :550.3(M+1) ;实测值为 :550.2。

[0482] 实例 18

[0483] ((3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)-2-(1-甲基-1H-咪唑-2-基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0484]



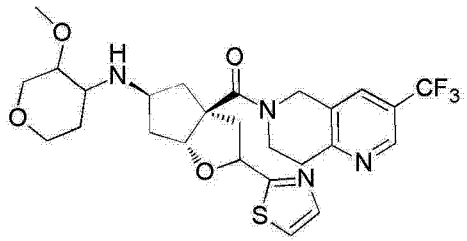
[0485] 遵循实例17,步骤A中所述的操作,并且随后获得该产物并遵循从实例1,步骤E直到H中所述的操作,由实例10,步骤A的产物和1-甲基咪唑的反应制备标题化合物。

[0486] 对于C27H34F3N5O4的计算值为:550.3(M+1);实测值为:550.2。

[0487] 实例19

[0488] ((3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)-2-(噻唑-2-基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0489]



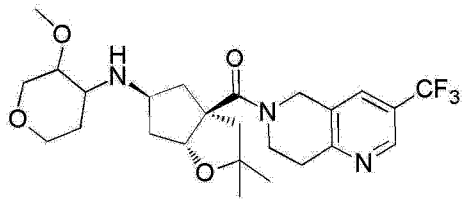
[0490] 遵循实例17,步骤A中所述的操作,并且随后获得该产物并遵循从实例1,步骤E直到H中所述的操作,由实例10,步骤A的产物和噻唑的反应制备标题化合物。

[0491] 对于C26H31F3N4O4S的计算值为:553.3(M+1);实测值为:553.3。

[0492] 实例20

[0493] ((3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)-2,2-二甲基六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

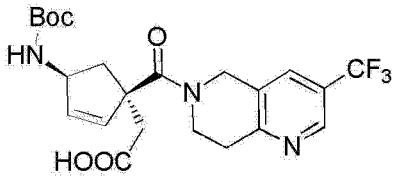
[0494]



[0495] 步骤A

[0496] 2-((1S,4S)-4-((叔丁氧羰基)氨基)-1-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)乙酸

[0497]

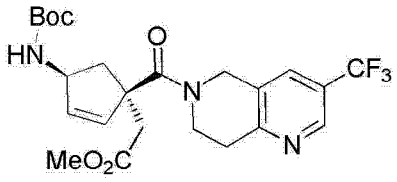


[0498] 在0℃下向在丙酮(10mL)中的实例1,步骤D产物(508mg,1.12mmol,1当量)溶液中加入琼斯氧化溶液(0.46mL,1.23mmol,1.1当量)。在2小时后,加入水,用乙酸乙酯萃取水溶液,合并有机物,在$MgSO_4$上干燥并浓缩,以提供未纯化在下一步中使用的步骤A的产物。对于C22H26F3N3O5的计算值为:492.2(M+23);实测值为:492.1。

[0499] 步骤B

[0500] 甲基2-((1S,4S)-4-((叔丁氧羰基)氨基)-1-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)乙酸酯

[0501]

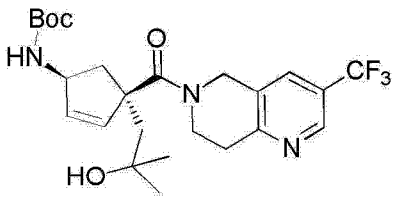


[0502] 在0℃下向在甲醇(20mL)中的步骤A产物(436mg,0.84mmol,1当量)溶液中加入三甲基甲硅烷基重氮甲烷(5mL在己烷中的2M溶液,10mmol,11.9当量),直至黄色持续。使黄色溶液浓缩。通过用40至80%EtOAc/庚烷洗脱的色谱法(24g柱)的纯化提供步骤B的产物。^1H NMR(氯仿-d)δ:8.70(s,1H),7.69(s,1H),6.37(d,J=5.4Hz,1H),5.87(d,J=5.4Hz,1H),4.98(d,J=17.4Hz,1H),4.63-4.83(m,3H),4.07-4.20(m,1H),3.79-3.93(m,1H),3.64(s,3H),3.08-3.19(m,2H),3.04(d,J=15.9Hz,1H),2.62(dd,J=13.4,7.1Hz,1H),2.46(d,J=15.7Hz,1H),2.01-2.12(m,1H),1.43(s,9H)。对于C23H28F3N3O5的计算值为:506.2(M+23);实测值为:506.2。

[0503] 步骤C

[0504] 叔丁基((1S,4S)-4-(2-羟基-2-甲基丙基)-4-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)氨基甲酸酯

[0505]



[0506] 在0℃下在Ar下经过30分钟,向在THF(6mL)中的甲基氯化镁溶液(2.62mL在THF中的3M溶液,7.86mmol,20当量)中,逐滴加入在THF(6mL)中的步骤B产物(190mg,0.39mmol,1当量)溶液。在30分钟后,加入饱和NH_4Cl,用乙酸乙酯萃取溶液,合并有机物,在$MgSO_4$上干燥并浓缩。通过用40至100%EtOAc/庚烷洗脱的色谱法(12g柱)的纯化提供步骤C的产物。^1H NMR(氯仿-d)δ:8.70(s,1H),7.69(s,1H),6.47(d,J=5.4Hz,1H),5.75(dd,J=5.6,1.5Hz,1H),4.60-4.96(m,4H),4.05(d,J=13.7Hz,1H),3.89(dt,J=13.3,6.4Hz,1H),3.07-3.19(m,2H),2.54(dd,J=12.6,6.5Hz,1H),2.10-2.27(m,2H),

1.80-1.96(m,2H),1.35-1.49(m,9H),1.26(s,3H),1.22(s,3H)。对于C24H32F3N3O4的计算值为:506.2(M+23);实测值为:506.2。

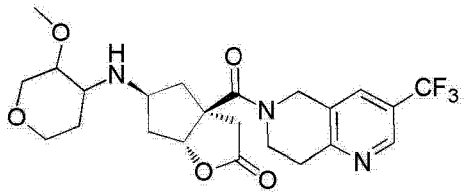
[0507] 通过获得步骤C的产物并遵循从实例1,步骤E直到H中所述的操作,来制备实例20的标题化合物。

[0508] ^{1}H NMR(氯仿-d)δ:8.72(br.s.,1H),7.69(br.s.,1H),5.16-5.27(m,1H),4.78(br.s.,2H),4.01-4.13(m,1H),3.75-3.99(m,4H),3.53-3.67(m,1H),3.22-3.48(m,6H),3.12(br.s.,2H),2.79(d,J = 10.0Hz,1H),2.09-2.40(m,3H),1.84-2.00(m,2H),1.68-1.78(m,2H),1.42-1.53(m,1H),1.34(s,3H),1.16(s,3H)。对于C25H34F3N3O4的计算值为:498.2(M+1);实测值为:498.2。

[0509] 实例21

[0510] (3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)-3a-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)六氢-2H-环戊并[b]呋喃-2-酮

[0511]



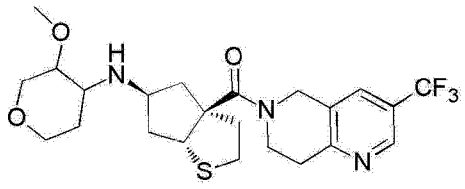
[0512] 通过获得实例20,步骤A的产物并遵循从实例1,步骤E直到H中所述的操作,来制备实例21的标题化合物。

[0513] ^{1}H NMR(氯仿-d)δ:8.74(br.s.,1H),7.71(br.s.,1H),5.70(d,J = 4.2Hz,1H),4.55-4.88(m,2H),4.08(d,J = 11.7Hz,1H),3.93(d,J = 11.5Hz,1H),3.80(br.s.,1H),3.47-3.61(m,2H),3.24-3.46(m,5H),3.15(br.s.,2H),3.03(d,J = 14.2Hz,1H),2.83(br.s.,2H),2.23-2.47(m,2H),1.53-1.76(m,6H)。对于C23H28F3N3O5的计算值为:484.2(M+1);实测值为:484.2。

[0514] 实例22

[0515] ((3aR,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]噻吩-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

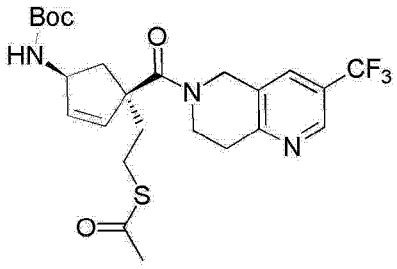
[0516]



[0517] 步骤A

[0518] S-(2-((1S,4S)-4-((叔丁氧羰基)氨基)-1-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)环戊-2-烯-1-基)乙基)硫代乙酸酯

[0519]

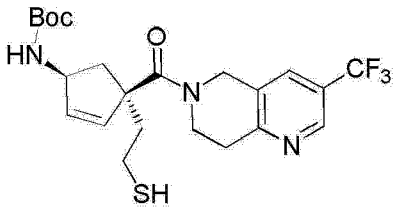


[0520] 在室温下在 Ar 下向在 THF(10mL) 中的实例 1，步骤 D 产物 (1950mg，3.98mmol，1 当量）溶液中加入三苯基膦 (2.09g，7.96mmol，2 当量）、偶氮二甲酸二异丙酯 (1.55mL，7.96mmol，2 当量）和硫代乙酸 (0.59mL，7.96mmol，2 当量）。在 2 小时后，加入水和饱和 $NaHCO_3$，用醚萃取水溶液，合并有机物，在 $MgSO_4$ 上干燥并浓缩。通过用 30 至 60％ EtOAc/ 庚烷洗脱的色谱法 (80g 柱）的纯化提供步骤 A 的产物。^1H NMR（氯仿 -d) δ：8.71(s,1H)，7.71(s,1H)，6.21(dd，J = 5.6,1.7Hz,1H)，5.80(dd，J = 5.6,2.0Hz,1H)，4.75-4.94(m,3H)，4.64-4.75(m,1H)，3.96-4.07(m,1H)，3.86-3.96(m,1H)，3.14(t，J = 5.7Hz,2H)，2.69-2.79(m,2H)，2.65(dd，J = 13.4,8.1Hz,1H)，2.27(s,3H)，1.95-2.13(m,2H)，1.81-1.94(m,1H)，1.44(s,9H)。对于 C24H30F3N3O4S 的计算值为：536.2(M+23)；实测值为：536.2。

[0521] 步骤 B

[0522] 叔丁基 ((1S,4S)-4-(2- 巯乙基）-4-(3-（三氟甲基）-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基）环戊 -2- 烯 -1- 基）氨基甲酸酯

[0523]

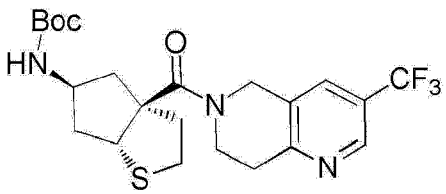


[0524] 在室温下在 Ar 下向在甲醇 (100mL) 中的步骤 A 产物 (1.74g，3.39mmol，1 当量）溶液（除气的）中加入 0.2N NaOH(85mL，85mmol，5 当量），所述 NaOH 通过在添加前使 Ar 鼓泡经过该溶液进行除气。在 2 小时后，使甲醇浓缩，加入 6N HCl 直至溶液为酸性，用 DCM 萃取水溶液，合并有机层，在 $MgSO_4$ 上干燥并浓缩，以提供未纯化在下一步中使用的步骤 B 的产物。对于 C22H28F3N3O3S 的计算值为：494.2(M+23)；实测值为：494.1。

[0525] 步骤 C

[0526] 叔丁基 ((3aR,5S,6aR)-3a-(3-（三氟甲基）-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基）六氢 -2H- 环戊并 [b] 噻吩 -5- 基）氨基甲酸酯

[0527]



[0528] 在室温下在 Ar 下向在苯 (300mL) 中的步骤 B 产物 (1.25g，2.65mmol，1 当量）溶

液（除气的）中加入AIBN(435mg,2.65mmol,1当量），并且使溶液加热至85℃共3天，随后浓缩。通过用25至60至100％ EtOAc/庚烷洗脱的色谱法（40g柱）的纯化提供步骤C的产物。^{1}H NMR(氯仿-d) δ :8.72(s,1H),7.69(s,1H),4.65-4.90(m,3H),4.23-4.60(m,2H),3.87-4.06(m,2H),3.10-3.16(m,2H),2.99-3.09(m,1H),2.87-2.98(m,1H),1.95-2.38(m,6H),1.40(s,9H)。对于C22H28F3N3O3S的计算值为:494.2(M+23);实测值为:494.1。

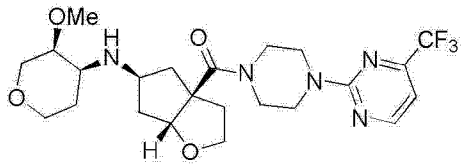
[0529] 通过获得实例22,步骤C的产物并遵循实例1,步骤G和H中所述的操作,来制备实例22的标题化合物。

[0530] ^{1}H NMR(氯仿-d) δ :8.71(s,1H),7.69(s,1H),4.73-4.93(m,2H),4.67(br.s.,1H),4.04-4.17(m,1H),3.94(t,J = 5.9Hz,3H),3.61-3.77(m,1H),3.36-3.47(m,4H),3.26-3.36(m,2H),3.06-3.19(m,2H),2.80-3.05(m,3H),2.31(br.s.,2H),2.05-2.21(m,3H),1.83-1.99(m,1H),1.60-1.83(m,2H)。对于C23H30F3N3O3S的计算值为:486.2(M+1);实测值为:486.2。

[0531] 实例23

[0532] ((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基）氨基）六氢-2H-环戊并[b]呋喃-3a-基)(4-(4-(三氟甲基）嘧啶-2-基）哌嗪-1-基）甲酮

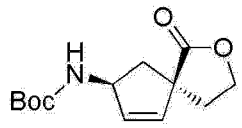
[0533]



[0534] 步骤A

[0535] 叔丁基((5S,7S)-1-氧代-2-氧杂螺[4.4]壬-8-烯-7-基）氨基甲酸酯

[0536]



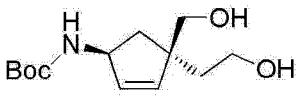
[0537] 向具有顶置式空气搅拌器、2-L添加漏斗和氮入口的12-L三颈圆底烧瓶中装入实例1,步骤A的产物(1149g,2.875摩尔,1当量）和THF(5.75L)。向添加漏斗中装入TBAF(1M在THF中的溶液,2.875L,2.875摩尔,1当量），并且经过～1小时逐滴加入该溶液。使温度从17增加到21℃,并且反应在结束时为透明橙色。将反应在室温下搅拌1小时,通过TLC和HPLC判断反应何时完全。将反应倾入装入EtOAc(4L)的22-L分离烧瓶,并且用卤水(2L)洗涤有机层。将有机层用另外的卤水(3×2L)洗涤,并且弃去这些水性级分。加入庚烷(4L),并且用水(3×2L)、卤水(2×2L)洗涤有机层,并且通过NMR就n-Bu_4NX的去除检查澄清的有机层。使有机层在45℃下蒸发至约750mL,当溶液变得混浊时,加入庚烷(800mL),并且导致白色固体的瞬间结晶。加入更多庚烷(300mL),并且使混合物在40℃下在旋转蒸发仪(rotovap)浴上涡旋10分钟。将冰加入浴中,并且使悬浮液在13℃下搅拌10分钟。固体在布氏漏斗上进行过滤,用庚烷(3×100mL)洗涤并提供步骤A的产物。^{1}H NMR(氯仿-d) δ :6.02(dd,J = 5.4,2.4Hz,1H),5.77(d,J = 5.4Hz,1H),5.21(d,J = 9.0Hz,1H),4.91(t,J = 8.7Hz,1H),4.37(dd,J = 7.5,6.5Hz,2H),2.21-2.39(m,3H),2.07(dd,J = 13.8,2.6Hz,

1H),1.44(s,9H)。对于 C13H19NO4 的计算值为 :276.1(M+23) ;实测值为 :276.1。

[0538] 步骤 B

[0539] 叔丁基 ((1S,4S)-4-(2- 羟乙基)-4-(羟基甲基) 环戊 -2- 烯 -1- 基) 氨基甲酸酯

[0540]

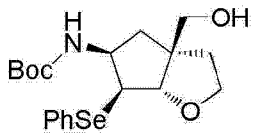


[0541] 在使用前用氮吹扫配备机械搅拌器、具有温度探头和氮入口的克莱森 (Claisen) 适配器和 N_2 出口的 5-L 三颈圆底烧瓶 2 小时。加入步骤 A 的产物 (255.9g,1.01 摩尔,1 当量) 和 MeOH(2L),并且使溶液在冰浴中冷却至 2℃。$NaBH_4$(75g,1.98 摩尔,2 当量) 以～ 5 相等份加入 ;在回到 6℃之前,使温度放热至 17℃,这时加入下一份。添加花费～ 2.5 小时,在末次添加后通过 HPLC 判断反应完全。通过添加含水 NH_4Cl(饱和的,1L),在 7℃下淬灭反应,其中温度升高至约 10℃。使白色混浊混合物在旋转蒸发下浓缩至约 1L(45℃浴),这时导致具有一些液体的白色固体。将混合物用水和 EtOAc(各 1L) 稀释,转移至分液漏斗并且使层分离。用 EtOAc(3×250mL) 萃取水层。将合并的有机物用卤水 (125mL) 洗涤,在 $MgSO_4$ 上干燥,通过硅藻土过滤,并且在 55℃的浴温下蒸发,并且提供作为稠油的步骤 B 产物。^1H NMR(氯仿 -d) δ :5.74(s,2H),4.65-4.95(m,2H),3.70(t, J = 5.7Hz, 2H),3.40-3.57(m,2H),2.76(br. s. ,1H),2.28(br. s. ,1H),2.19(dd, J = 13.4,8.8Hz,1H), 1.70(t,J = 5.7Hz,2H),1.55(dd,J = 13.8,4.0Hz,1H),1.44(s,9H)。对于 C13H23NO4 的计算值为 :280.2(M+23) ;实测值为 :280.2。

[0542] 步骤 C

[0543] 叔丁基 ((3aR,5S,6S,6aS)-3a-(羟基甲基)-6-(苯基硒烷基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基) 氨基甲酸酯

[0544]



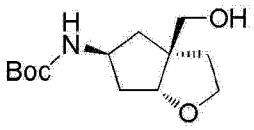
[0545] 向配备机械搅拌器、具有氮入口和温度探头的克莱森适配器以及氮出口的 12-L 三颈圆底烧瓶中装入步骤 B 产物 (382g,1.26 摩尔,1 当量) 和 CH_2Cl_2(6.5L)。加入 N-(苯基硒) 邻苯二甲酰亚胺 (419g,1.39 摩尔,1.1 当量),随后通过刻度量筒直接加入 BF_3 醚化物 (16mL,0.126 摩尔,0.1 当量)。使反应从 15℃稳定上升到 24℃,并且在 10 分钟内,反应形成粉红色沉淀物。十分钟后,反应变稠,具有白色沉淀物,并且温度开始降低。反应通过 HPLC 进行检查,并且发现是完全的。反应通过硅藻土进行过滤 (去除邻苯二甲酰亚胺杂质),将滤饼用 CH_2Cl_2(750mL) 洗涤直至滤液不再是橙色。将滤液转移至分液漏斗,用含水 NaOH(0.5M,2×1350mL)、卤水 (2×1L) 洗涤,并且在 Na_2SO_4 上干燥有机层。[第二次处理用 382g 步骤 B 产物在相同条件下进行,并且逐步建立并在该点时合并]。剩下约 3L 有机物时,加入甲苯 (3L,～ 4mL/g 原材料),并且继续蒸发。在甲苯添加后不久,发生结晶。将 20-L 圆底烧瓶转移至加热罩,并且使内容物加热至 80℃,直至固体溶解。将烧瓶转移回旋转蒸发器,参考材料用于接种结晶,并且使烧瓶涡旋 (不含热) 直至产物开始结晶。将

冰加入浴中，并且使烧瓶的内容物在 15℃（外部温度）下涡旋 30 分钟。将产物过滤，用冰冷的甲苯洗涤并风干 1 小时，并且提供步骤 C 的产物。^{1}H NMR（氯仿 -d）δ ：7.49-7.56(m,2H)，7.23-7.29(m,3H)，5.05(br. s.，1H)，4.46(br. s.，1H)，4.29(s,1H)，3.86-3.97(m,2H)，3.57-3.69(m,3H)，1.98-2.08(m,1H)，1.86-1.97(m,2H)，1.73-1.86(m,2H)，1.41(s,9H)。对于 C19H27NO4Se 的计算值为 ：436.1(M+23) ；实测值为 ：436.1。

[0546] 步骤 D

[0547] 叔丁基 ((3aR,5S,6aR)-3a-（羟基甲基）六氢 -2H- 环戊并 [b] 呋喃 -5- 基）氨基甲酸酯

[0548]

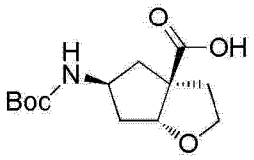


[0549] 在使用前用氮吹扫配备机械搅拌器、加热罩、温度探头、氮入口和具有氮出口的回流冷凝器的 22-L 四颈圆底烧瓶 30 分钟。加入步骤 C 的产物 (603.5g,1.46 摩尔，1 当量）、AIBN(241g,1.46 摩尔，1 当量）、三（三甲基甲硅烷基）硅烷 (910mL,2.93 摩尔，2 当量）和甲苯 (16.3L)，并且用氮吹扫通过悬浮液 20 分钟使悬浮液除气。使反应加热至 80-83℃共 1 小时，这个时间后将热关闭，并且使反应经过 12-18 小时冷却至室温。TLC 显示反应完全。将反应直接倾入 BIOTAGE 干燥 5-kg 柱内，所述柱用 16L 在庚烷中的 50％ EtOAc 洗脱，随后为 32L EtOAc，并且提供金色稠油的步骤 D 产物，所述金色稠油在静置时缓慢结晶。^{1}H NMR（氯仿 -d）δ ：4.64(brd. s,1H)，4.07-4.25(m,2H)，3.89(ddd, J ＝ 8.8,7.2,4.5Hz,1H)，3.53-3.67(m,3H)，2.17(dd, J ＝ 13.3,6.2Hz,1H)，1.98-2.06(m,1H)，1.86-1.97(m,1H)，1.68-1.81(m,2H)，1.46-1.56(m,2H)，1.44(s,9H)。对于 C13H23NO4 的计算值为 ：202.2(M-55) ；实测值为 ：202.2。

[0550] 步骤 E

[0551] (3aS,5S,6aR)-5-((叔丁氧羰基）氨基）六氢 -2H- 环戊并 [b] 呋喃 -3a- 羧酸

[0552]



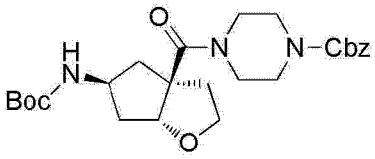
[0553] 用氮吹扫配备机械搅拌器、氮入口、具有氮出口的 1-L 添加漏斗、温度探头和用于冷却的外部浴的 22-L 四颈圆底烧瓶过夜。加入步骤 D 产物 (426g,1.57 摩尔）和丙酮 (8.1L) 的溶液，并且使烧瓶冷却至 7℃，并且向添加漏斗中装入琼斯试剂 (710mL)。经过 1 小时 20 分钟逐滴加入氧化剂，使温度保持在 7-9℃之间。在加入前 200mL 后，形成使得搅拌非常困难的绿色球。在加入约 1/2 氧化剂后，运行 LCMS 以跟踪反应。在添加结束时，导致具有一点红色（过量琼斯）的橄榄绿色悬浮液。去除冰浴，使反应在室温下搅拌 1 小时，在这个时间后判断反应完全。加入异丙醇 (40mL)，将反应搅拌 25 分钟，并且加入水 (800mL)，所述水引起绿色块与丙酮 / 水层的良好分离。使水 / 丙酮滗出并蒸发。使绿色块溶解于水 (1.5L) 中，转移至分液漏斗并用 CH_2Cl_2(1L) 萃取。通过 TLC 检查水层，并且发现不含产物，因此将水层弃去。保存有机萃取物用于以后合并。使绿色水 / 丙酮浓缩物蒸发至约 5-7L，直至溶

液看起来混浊。将浓缩物转移至分液漏斗，并且用 CH_2Cl_2(1×3L,3×1L) 萃取，并且在每次萃取后就产物的存在检查水层。将合并的萃取物用卤水 (250mL) 洗涤，所述洗涤引起可怕的乳状液。通过添加水和 EtOAc(～ 500mL) 破坏乳状液。使有机层干燥 (Na_2SO_4)，但不是非常有效，因为一些水在过滤期间漏了进来。接近蒸发结束，蒸馏速率减慢，并且导致黄色稠油。将 MeCN(500mL) 加入罐中，使旋转蒸发器浴加温至 50℃，并且用参考材料接种内容物。白色细小固体在 10 分钟左右内缓慢形成。接种第二次完成，并且在 50℃下继续涡旋另外 10 分钟。在视觉上检测到结晶，使浴排出并用冰填充，并且使烧瓶在 0℃下涡旋 30 分钟，导致浓稠的白色固体。将固体过滤，用冰冷的 MeCN(2×100mL) 洗涤并使固体风干过夜。步骤 E 的产物作为白色、自由流动的固体分离。^{1}H NMR(MeOH) δ :4.43(d, J = 5.4Hz,1H), 4.00-4.13(m,1H),3.89-3.98(m,1H),3.63(td, J = 9.1,5.7Hz,1H),2.54(ddd, J = 12.6, 5.7,3.2Hz,1H),1.93-2.13(m,3H),1.74-1.87(m,1H),1.53-1.66(m,1H),1.43(s,9H)。对于 C13H21NO5 的计算值为 :294.1(M+23) ;实测值为 :294.1。

[0554] 步骤 F

[0555] (苄基 4-((3aS,5S,6aR)-5-((叔丁氧羰基)氨基)六氢 -2H- 环戊并 [b] 呋喃 -3a- 羰基) 哌嗪 -1- 羧酸酯

[0556]

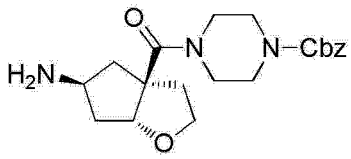


[0557] 遵循来自实例 1，步骤 C 的操作，由步骤 E 的产物和苄基哌嗪 -1- 羧酸酯的反应制备步骤 F 的产物。对于 C25H35N3O6 的计算值为 :496.2(M+23) ;实测值为 :496.0。

[0558] 步骤 G

[0559] 苄基 4-((3aS,5S,6aR)-5- 氨基六氢 -2H- 环戊并 [b] 呋喃 -3a- 羰基) 哌嗪 -1- 羧酸酯

[0560]

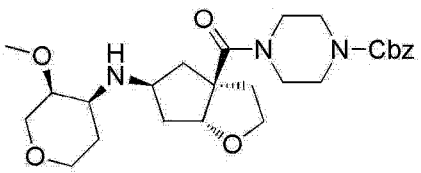


[0561] 遵循来自实例 1，步骤 G 的操作，由步骤 F 的产物的反应制备步骤 G 的产物。对于 C20H27N3O4 的计算值为 :374.2(M+1) ;实测值为 :374.2。

[0562] 步骤 H

[0563] 苄基 4-((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 羰基) 哌嗪 -1- 羧酸酯

[0564]

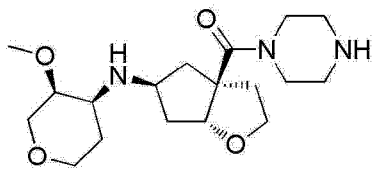


[0565] 遵循实例 1 中所述的操作，由步骤 G 的产物和 (R)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮（中间体 1）的反应制备步骤 H 的产物。对于 C26H37N3O6 的计算值为：488.3(M+1)；实测值为：488.1。

[0566] 步骤 I

[0567] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基）氨基）六氢 -2H- 环戊并 [b] 呋喃 -3a- 基）（哌嗪 -1- 基）甲酮

[0568]

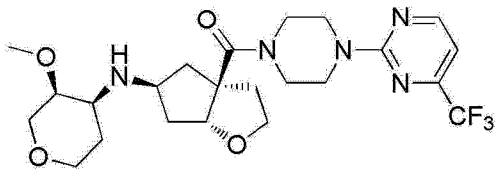


[0569] 使在乙醇 (10mL) 中的步骤 H 产物 (405mg,0.83mmol,1 当量）和 5% Pd/C(100mg) 溶液在室温下在氢气球下放置过夜。将悬浮液通过硅藻土过滤，用甲醇洗涤，并且将滤液浓缩，以获得作为胶质的步骤 I 产物。对于 C18H31N3O4 的计算值为：354.2(M+1)；实测值为：354.2。

[0570] 步骤 J

[0571] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基）氨基）六氢 -2H- 环戊并 [b] 呋喃 -3a- 基）(4-(4-（三氟甲基）嘧啶 -2- 基）哌嗪 -1- 基）甲酮

[0572]

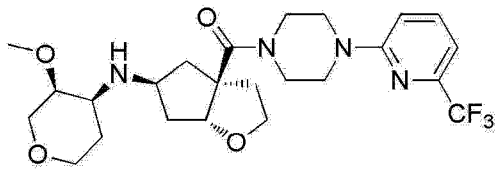


[0573] 在 Ar 下使在小瓶中的 10 ：1 二噁烷 /DMSO(1mL) 的混合物中的步骤 I 产物 (40mg,0.11mmol,1 当量）、DIEA(0.06mL,0.34mmol,3 当量）和 2- 氯 -4-（三氟甲基）嘧啶 (0.04mL,0.34mmol,3 当量）溶液加热至 100℃过夜。加入水，用 DCM 萃取溶液，合并有机物，在 $MgSO_4$ 上干燥并浓缩。通过用 5 至 10% MeOH/DCM 洗脱的色谱法 (4g 柱）的纯化提供实例 23 的标题化合物。^1H NMR（氯仿 -d) δ ：8.53(d, J = 4.6Hz,1H),6.83(d, J = 4.9Hz,1H),5.05(d, J = 4.4Hz,1H),4.10(dd, J = 12.3,2.8Hz,1H),3.51-4.00(m,13H),3.36-3.47(m,4H),3.25-3.36(m,2H),2.78(dt, J = 10.2,3.8Hz,1H),2.34(ddd, J = 12.3,6.7,3.3Hz,1H),2.20(dt, J = 13.0,6.6Hz,2H),2.01(dt, J = 12.3,8.3Hz,1H),1.45-1.90(m,4H)。对于 C23H32F3N5O4 的计算值为：500.2(M+1)；实测值为：500.3。

[0574] 实例 24

[0575] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基）氨基）六氢 -2H- 环戊并 [b] 呋喃 -3a- 基）(4-(6-（三氟甲基）吡啶 -2- 基）哌嗪 -1- 基）甲酮

[0576]

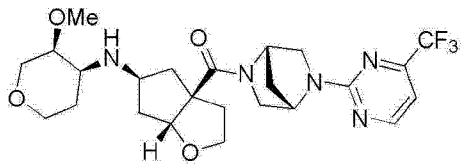


[0577] 通过遵循实例 23，步骤 J 中所述的操作，获得实例 23 步骤 I 的产物并与 2- 氯 -6-(三氟甲基) 吡啶反应，来制备实例 24 的标题化合物。^{1}H NMR(氯仿 -d) δ ：7.63(t, J = 8.1Hz,1H),7.01(d, J = 7.3Hz,1H),6.81(d, J = 8.6Hz,1H),5.05(d, J = 4.4Hz,1H),4.09(dd, J = 12.3,3.1Hz,1H),3.96(qd, J = 7.8,3.5Hz,2H),3.47-3.88(m, 10H),3.37-3.47(m,4H),3.26-3.37(m,2H),2.78(dt, J = 10.2,3.6Hz,1H),2.34(ddd, J = 12.2,6.7,3.4Hz,1H),2.13-2.27(m,2H),2.01(dt, J = 12.3,8.5Hz,1H),1.60-1.88(m, 4H),1.54(ddd, J = 13.1,10.9,4.8Hz,1H)。对于 C24H33F3N4O4 的计算值为 :499.3(M+1) ；实测值为 :499.4。

[0578] 实施例 25

[0579] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)((1S,4S)-5-(4-(三氟甲基) 嘧啶 -2- 基)-2,5- 二氮杂双环 [2.2.1] 庚 -2- 基) 甲酮

[0580]

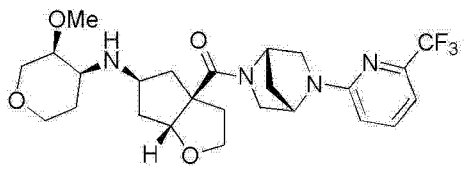


[0581] 通过遵循实例 23，步骤 F 中所述的操作，并且随后遵循实例 23，步骤 G 直到 J 中所述的操作，获得实例 23，步骤 E 的产物并与 (1S,4S)-N-Cbz-2,5- 二氮杂 - 双环 [2.2.1] 庚烷反应，来制备实例 25 的标题化合物。^{1}H NMR(氯仿 -d) δ :8.50(d, J = 4.4Hz,1H), 6.83(d, J = 4.6Hz,1H),4.70-5.20(m,3H),4.07(t, J = 10.1Hz,1H),3.83-4.00(m, 2H),3.50-3.79(m,5H),3.22-3.48(m,7H),2.79(d, J = 9.5Hz,1H),1.82-2.30(m,7H), 1.40-1.82(m,4H)。对于 C24H32F3N5O4 的计算值为 :512.2(M+1) ；实测值为 :512.3。

[0582] 实例 26

[0583] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)((1S,4S)-5-(6-(三氟甲基) 吡啶 -2- 基)-2,5- 二氮杂双环 [2.2.1] 庚 -2- 基) 甲酮

[0584]



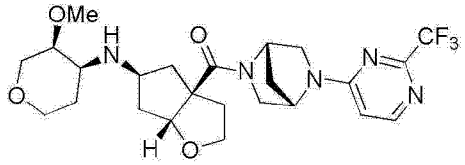
[0585] 通过遵循实例 23，步骤 F 中所述的操作，随后遵循实例 23，步骤 G 直到 I 中所述的操作，获得实例 23，步骤 E 的产物并与 (1S,4S)-N-Cbz-2,5- 二氮杂 - 双环 [2.2.1] 庚烷反应，并且随后遵循实例 23，步骤 J 中所述的操作，使该产物与 2- 氯 -6-(三氟甲基) 吡啶反应，来制备实例 26 的标题化合物。^{1}H NMR(氯仿 -d) δ :7.56(t, J = 7.9Hz,1H),6.94(dd,

J = 7.0,3.5Hz,1H),6.40-6.57(m,1H),4.65-5.18(m,3H),4.05(d,J = 12.5Hz,1H),3.82-3.99(m,2H),3.61-3.70(m,2H),3.19-3.59(m,10H),2.53-2.85(m,1H),1.84-2.29(m,7H),1.44-1.78(m,4H)。对于C25H33F3N4O4的计算值为:511.3(M+1);实测值为:511.2。

[0586] 实例27

[0587] ((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)((1S,4S)-5-(2-(三氟甲基)嘧啶-4-基)-2,5-二氮杂双环[2.2.1]庚-2-基)甲酮

[0588]

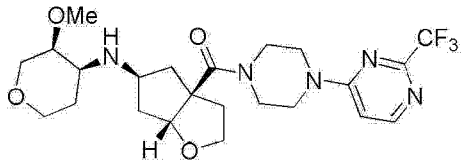


[0589] 通过遵循实例23,步骤F中所述的操作,随后遵循实例23,步骤G直到I中所述的操作,获得实例23,步骤E的产物并与(1S,4S)-N-Cbz-2,5-二氮杂-双环[2.2.1]庚烷反应,并且随后遵循实例23,步骤J中所述的操作,使该产物与4-氯-2-(三氟甲基)嘧啶反应,来制备标题化合物。^{1}H NMR(氯仿-d)δ:8.27-8.43(m,1H),6.24-6.60(m,1H),5.25-5.48(m,1H),4.50-5.23(m,2H),4.07(d,J = 12.2Hz,1H),3.85-4.02(m,2H),3.58-3.73(m,3H),3.23-3.56(m,9H),2.55-2.91(m,1H),1.86-2.35(m,7H),1.35-1.82(m,4H)。对于C24H32F3N5O4的计算值为:512.2(M+1);实测值为:512.2。

[0590] 实例28

[0591] ((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(4-(2-(三氟甲基)嘧啶-4-基)哌嗪-1-基)甲酮

[0592]

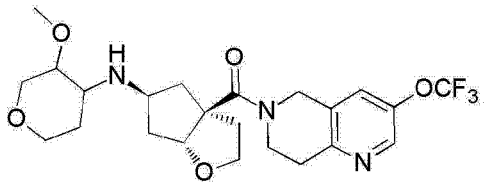


[0593] 通过遵循实例23,步骤J中所述的操作,获得实例23,步骤I的产物并与4-氯-2-(三氟甲基)嘧啶反应,来制备标题化合物。^{1}H NMR(氯仿-d)δ:8.37(d,J = 6.4Hz,1H),6.63(d,J = 6.1Hz,1H),5.04(d,J = 4.6Hz,1H),4.10(dd,J = 12.2,2.7Hz,1H),3.90-4.02(m,2H),3.47-3.90(m,10H),3.36-3.46(m,4H),3.26-3.36(m,2H),2.77(dt,J = 10.1,3.7Hz,1H),2.32(ddd,J = 12.1,6.7,3.4Hz,1H),2.19(td,J = 12.8,6.2Hz,2H),1.95-2.08(m,1H),1.59-1.86(m,4H),1.54(ddd,J = 13.1,11.1,4.9Hz,1H)。对于C23H32F3N5O4的计算值为:500.2(M+1);实测值为:500.2。

[0594] 实例29

[0595] ((3aS,5S,6aR)-5-((3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲氧基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0596]

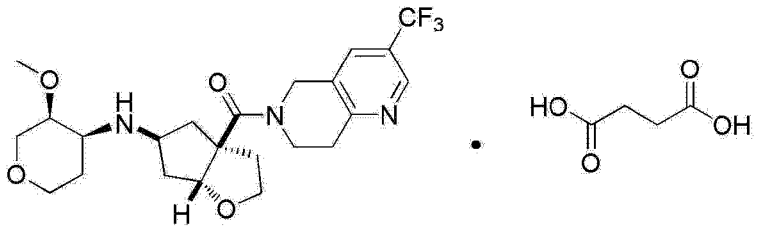


[0597] 遵循实例 1，步骤 C 中所述的操作，并且随后遵循实例 1，步骤 G 和 H 中所述的操作，由实例 23，步骤 E 的产物和 3-（三氟甲氧基）-5,6,7,8- 四氢 -1,6- 萘啶的反应制备化合物。^{1}H NMR（氯仿 -d）δ ：8.40(br. s.，1H)，7.35(br. s.，1H)，5.05(t，J ＝ 4.3Hz，1H)，4.74(br. s.，2H)，3.78-4.16(m,5H)，3.48-3.74(m,2H)，3.24-3.46(m,6H)，3.08(br. s.，2H)，2.81(t，J ＝ 9.3Hz，1H)，2.17-2.40(m,3H)，1.91-2.12(m,3H)，1.53-1.88(m,3H)。对于 C23H30F3N3O5 的计算值为 ：486.2(M+1) ；实测值为 ：486.1。

[0598] 实例 30

[0599] ((3aS,5S,6aR)-5-((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基氨基）六氢 -2H- 环戊并 [b] 呋喃 -3a- 基）(3-（三氟甲基）-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基）甲酮琥珀酸酯

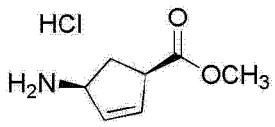
[0600]



[0601] 步骤 A

[0602] (1R,4S)-4- 氨基环戊 -2- 烯基甲酸甲酯盐酸盐

[0603]

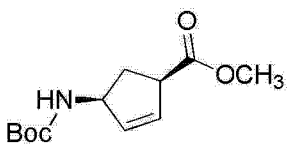


[0604] 使在 MeOH(2.2L) 中的 (1S,4R)-2- 氮杂双环 [2.2.1] 庚 -5- 烯 -3- 酮 (725g,6.64 摩尔）溶液在冰浴中搅拌至 0℃。经历 2.25 小时时段逐滴加入亚硫酰氯 (290mL,3.99 摩尔)，同时使温度保持低于 13℃。将反应在 8℃下搅拌 2 小时。加入乙酸异丙酯 (16.3L)，并使浆搅拌 1 小时。将固体用布氏漏斗过滤，用乙酸异丙酯（～ 1L) 洗涤，并且允许固体风干过夜，以提供灰白色固体。^{1}H NMR(400MHz，DMSO-d_6) δ ＝ 8.44(br. s.，3H)，5.99-6.16(m，1H)，5.90(dt，J ＝ 2.4,5.3Hz，1H)，4.17(br. s.，1H)，3.56-3.79(m,4H)，2.56(m,1H)，1.84-2.04(m,1H)。

[0605] 步骤 B

[0606] (1R,4S)-4-（叔丁氧羰基氨基）环戊 -2- 烯基甲酸甲酯

[0607]



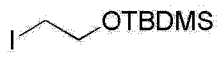
[0608] 使步骤 A 产物 (551g,3.10 摩尔）、CH_2Cl_2(15.5L) 和二碳酸二叔丁酯 (684g,3.10 摩

尔）溶液伴随冰浴搅拌至2℃。经过1小时5分钟以不超过3℃的速率加入三乙胺(435mL，3.12摩尔)。将反应搅拌2小时。将挥发物蒸发，将粗产物悬浮于EtOAc和庚烷的混合物中，将固体通过硅胶过滤，并且用在庚烷中的另外EtOAc洗涤。将有机物蒸发并提供作为褐色固体的步骤B产物。^{1}H NMR(400MHz，)δ ＝5.87(d，J＝6.4Hz，2H)，4.85-5.02(m，1H)，4.72-4.85(m，1H)，3.72(s，3H)，3.47(m，1H)，2.51(d，J ＝ 13.9Hz，1H)，1.88(s，1H)，1.44(s，10H)。

[0609] 步骤C

[0610] (1，1-二甲基乙基)(2-碘乙氧基)二甲基硅烷

[0611]

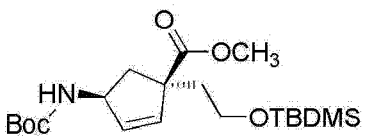


[0612] 使碘乙醇(2.68kg，15.4摩尔)、CH_2Cl_2(12L)和咪唑(1.556kg，22.63摩尔)在冰浴中冷却。经历2小时时段将在CH_2Cl_2(2.5L)中的叔丁基二甲基氯硅烷(2.536kg，16.32摩尔)溶液加入反应中。允许所得的白色悬浮液经过18小时加温至室温。反应通过用水和卤水洗涤逐步建立)。使有机层干燥($MgSO_4$)，并且在减压下蒸发，以提供作为淡黄色油的步骤C产物。^{1}H NMR(400MHz，$CDCl_3$)δ ＝3.75(t，J＝7.0Hz，2H)，3.11(t，J＝7.0Hz，2H)，0.77-0.89(m，10H)，0.00(s，6H)。

[0613] 步骤D

[0614] (1S，4S)-4-(叔丁氧羰基氨基)-1-(2-(叔丁基二甲基甲硅烷基氧基)乙基)环戊-2-烯基甲酸甲酯

[0615]

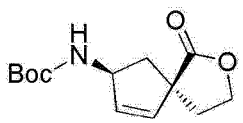


[0616] 经历2小时时段向在THF(1M，6.97L，6.97摩尔)中的-70℃ LiHMDS溶液中加入在THF(800mL)中的步骤B产物(763.5g，3.16摩尔)溶液，同时使温度维持在或低于-68℃。将所得的溶液在-68℃下搅拌45分钟。经历1小时50分钟时段加入在THF(800mL)中的步骤C产物(1.267kg，4.426摩尔)溶液，同时维持在～-66℃的温度下。将反应在～-66℃下搅拌45分钟。使反应加温至-15℃，并且通过加入含水HCl和冰的混合物逐步建立。将混合物用甲苯萃取，将有机层用水、盐水洗涤并在$MgSO_4$上干燥。使有机层浓缩并使用在庚烷中的EtOAc混合物在硅胶上纯化，以提供作为澄清油的步骤D产物。^{1}H NMR(400MHz，氯仿-d)d＝5.69-5.86(m，2H)，4.79-4.93(m，1H)，4.68-4.80(m，1H)，3.67(s，3H)，3.53-3.62(m，2H)，2.16-2.30(m，1H)，2.04-2.16(m，2H)，1.70-1.81(m，1H)，1.41(s，9H)，0.78-0.91(m，13H)，0.00(s，6H)。

[0617] 步骤E

[0618] 叔丁基(5S，7S)-1-氧代-2-氧杂螺[4.4]壬-8-烯-7-基氨基甲酸酯

[0619]

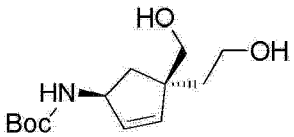


[0620] 经过～ 1 小时向步骤 D 产物 (1149g,2.875 摩尔) 和 THF(5.75L) 的溶液中加入 TBAF(在 THF 中的 1M,2.875L)。将反应在室温下搅拌 1 小时,并用 EtOAc 稀释。将有机层用卤水洗涤,用庚烷稀释并将有机层进一步用水和卤水洗涤。将有机层蒸发,将结晶产物过滤,并用庚烷洗涤,以提供作为白色固体的步骤 E 产物。^{1}H NMR(400MHz,氯仿 -d)d = 5.86-5.98(m,3H),5.67(d,J = 5.4Hz,3H),5.03-5.20(m,2H),4.76-4.87(m,3H),4.28(t,J = 7.0Hz,5H),2.08-2.31(m,8H),1.99(d,J = 2.4Hz,3H),1.34(s,25H)。

[0621] 步骤 F

[0622] 叔丁基 ((1S,4S)-4-(2- 羟乙基)-4-(羟基甲基) 环戊 -2- 烯 -1- 基) 氨基甲酸酯

[0623]

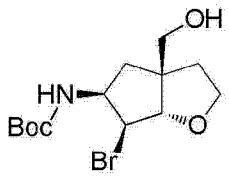


[0624] 经过～ 2.5 小时向冷却至 2℃的步骤 E 产物 (255.9g,1.01 摩尔) 和 MeOH(2L) 溶液中加入 $NaBH_4$(75g)。通过添加含水 NH_4Cl 将反应淬灭,在减压下浓缩并用水和 EtOAc 稀释混合物。将层分离并用另外的 EtOAc 萃取水层。将合并的有机物用卤水洗涤,干燥 ($MgSO_4$) 并蒸发,以获得作为稠油的步骤 F 产物。^{1}H NMR(400MHz,氯仿 -d)d = 5.74(d, J = 2.0Hz, 2H),4.81-4.92(m,1H),4.67-4.79(m,1H),3.71(t, J = 6.1Hz,2H),3.50(d, J = 11.7Hz, 2H),2.14-2.28(m,2H),1.70(td,J = 1.6,6.2Hz,4H),1.52-1.60(m,1H),1.44(s,9H)

[0625] 步骤 G

[0626] 叔丁基 (3aR,5S,6S,6aS)-6- 溴 -3a-(羟基甲基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基氨基甲酸酯

[0627]

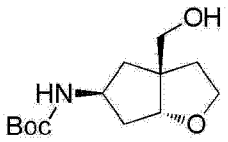


[0628] 向在 EtOAc(4L) 中的步骤 F 产物 (343.60g) 的冷却溶液中加入 N- 溴琥珀酰亚胺 (237.60g),随后在室温下搅拌 18 小时。向混合物中加入水 (5mL),并且使反应加热至 60℃共 30 分钟。将反应过滤,并且将滤液用含水硫代硫酸钠洗涤直至有机层对于过氧化物为阴性。将有机层用含水 Na_2CO_3(10％) 洗涤,干燥 (Na_2SO_4),并使反应在减压下浓缩。接近浓缩结束,加入庚烷 (1.2L),并且通过过滤收集产物,以提供步骤 G 的产物。^{1}H NMR(400MHz,氯仿 -d) δ = 4.78-4.91(m,1H),4.41(br.s.,1H),4.31(s,2H),3.88-3.98(m, 1H),3.61-3.77(m,3H),2.08-2.24(m,1H),1.82(m,2H),1.60-1.70(t,1H),1.45(s,9H)

[0629] 步骤 H

[0630] 叔丁基 (3aR,5S,6aR)-3a-(羟基甲基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基氨基甲酸酯

[0631]

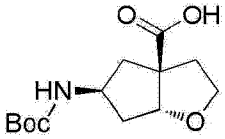


[0632] 使在EtOAc(830mL)中的步骤G产物(83g,0.245摩尔)、10%碳载钯(12.5g)、三乙胺(69mL,0.49摩尔,2当量)溶液在PAAR氢化器上以40psi振荡3.5小时,直至压力保持恒定。将反应用硅藻土过滤,将滤饼用EtOAc洗涤,并且将收集的滤液用含水HCl(1N)、卤水洗涤,干燥(Na_2SO_4)并在减压下浓缩,以获得步骤H的产物。^{1}H NMR(400MHz,氯仿-d)d = 4.60-4.73(m,1H),4.06-4.24(m,3H),3.84-3.93(m,1H),3.52-3.67(m,4H),2.12-2.21(m,1H),1.98-2.04(m,1H),1.90(br. s.,3H),1.70-1.78(m,1H),1.46-1.56(m,3H),1.44(s,11H)。

[0633] 步骤I

[0634] (3aS,5S,6aR)-5-(叔丁氧羰基氨基)六氢-2H-环戊并[b]呋喃-3a-羧酸

[0635]

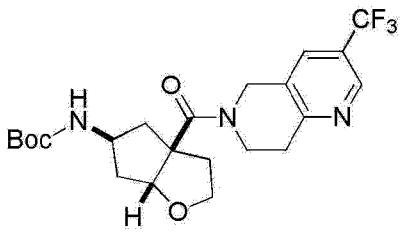


[0636] 经过1小时20分钟向步骤H产物(426g,1.57摩尔)和丙酮(8.1L)的冰冷溶液中加入琼斯试剂(710mL)。将所得的悬浮液在室温下搅拌1小时,这之后加入异丙醇(40mL),并且将反应在室温下搅拌25分钟。加入水,并且将水/丙酮滗出并蒸发。将不溶性材料在水中分开溶解并用CH_2Cl_2萃取。将绿色水/丙酮浓缩物用CH_2Cl_2萃取,并将合并的有机萃取物用卤水洗涤,用水和EtOAc稀释,并且用Na_2SO_4干燥有机层。将有机层过滤,浓缩并由MeCN结晶产物,并且通过过滤分离作为白色固体的步骤I产物。^{1}H NMR(400MHz,DMSO-d_6) d = 12.39-12.59(m,1H),6.85-7.02(m,1H),4.28(d,J = 5.4Hz,1H),3.89-3.97(m,1H),3.79-3.85(m,1H),3.43-3.51(m,1H),3.30-3.36(m,1H),2.35-2.42(m,1H),1.90(d,J = 11.0Hz,3H),1.59-1.70(m,1H),1.42-1.50(m,1H),1.37(s,9H)。对于C13H21NO5的元素分析计算值为:C,57.55;H,7.80;N,5.16。实测值为:C,57.34;H,8.18;N,5.08mp:147.4-149.1℃

[0637] 步骤J

[0638] 叔丁基(3aS,5S,6aR)-3a-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)六氢-2H-环戊并[b]呋喃-5-基氨基甲酸酯

[0639]



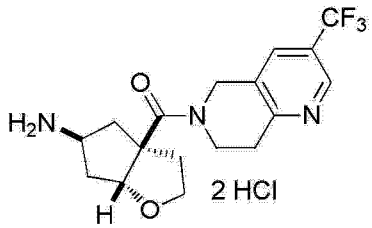
[0640] 向在CH_2Cl_2中的步骤I产物(596.8g,1.91摩尔)溶液中加入EDC(98.5%纯,559g,2.87摩尔)和HOBt(449g,3.26摩尔),并且使悬浮液在室温下搅拌15分钟。通过经过45

分钟的添加而加入 3-(三氟甲基)-5,6,7,8- 四氢 -1,6- 萘啶 -2HCl(790g,2.87 摩尔),随后为 DIEA(1.7L,9.65 摩尔)。将反应在室温下搅拌 20 小时。反应在饱和含水 $NaHCO_3$ 和 CH_2Cl_2 之间分开。去除有机层,用水稀释水层,并且用 CH_2Cl_2 萃取水层。将合并的有机物用 1/2 饱和卤水洗涤,在 Na_2SO_4 上干燥,并在减压下浓缩。通过使用在庚烷中的 EtOAc 的色谱法纯化所得的粗产物,以提供作为浓稠橙色泡沫的步骤 J 产物。^1H NMR(400MHz,氯仿 -d) d = 8.72(s,1H),7.71(s,1H),5.00-5.08(m,1H),4.77(br. s.,2H),4.61-4.68(m,1H),4.21-4.34(m,1H),3.96-4.05(m,1H),3.85-3.93(m,2H),3.71(s,1H),3.13(br. s.,2H),2.38-2.48(m,1H),2.28-2.33(m,1H),2.20-2.26(m,1H),2.09-2.17(m,1H),1.75-1.85(m,1H),1.61-1.70(m,1H),1.40(s,9H)。

[0641] 步骤 K

[0642] ((3aS,5S,6aR)-5- 氨基六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮二盐酸盐

[0643]

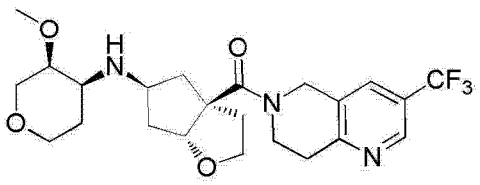


[0644] 使在 MeOH(~ 1.25M,14.25L,17.81 摩尔)中的步骤 J 产物 (773g,1.61 摩尔)和 HCl 溶液加热至 60℃,并且在剧烈鼓泡停止后,使反应在减压下浓缩。加入异丙醇,将内容物蒸发至接近干燥,并且将庚烷加入烧瓶中。将内容物过滤,用一些异丙醇 / 庚烷(随意)洗涤,并且使固体在空气中干燥,随后在真空炉中干燥,以提供作为乳白色固体的步骤 K 产物。使用 1,2- 二氯乙烷 / 含水 3M NaOH 将产物的小样品转换为游离碱的,用于通过 NMR 和元素分析的进一步分析。对于 $C_{17}H_{20}F_3N_3O_2 \times 1.6\ H_2O$ 的元素分析计算值为 :C,53.14 ;H,6.09 ;F,14.83 ;N,10.93 ;H_2O = 7.50。实测值为 :C,52.30 ;H,5.78 ;F,14.62 ;N,10.51 ;KF = 7.28。^1H NMR(400MHz,氯仿 -d) δ = 8.72(s,1H),7.70(br. s.,1H),5.06(d,J = 4.9Hz,1H),4.78(s,2H),3.85-4.03(m,3H),3.71-3.75(m,2H),3.59-3.70(m,2H),3.08-3.19(m,2H),2.24-2.38(m,2H),2.19(dd, J = 5.7,13.3Hz,1H),2.08(br. s.,1H),1.62-1.78(m,1H),1.46-1.57(m,1H),1.42(br. s.,3H)

[0645] 步骤 L

[0646] ((3aS,5S,6aR)-5-((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基氨基)六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0647]



[0648] 向在 1,2- 二氯乙烷 /CH_2Cl_2(~ 10L)中的步骤 K 产物(游离碱)(619.7g,1.74 摩尔)混合物中加入乙酸(冰的,180mL),并且将混合物冷却至 16℃。加入固体

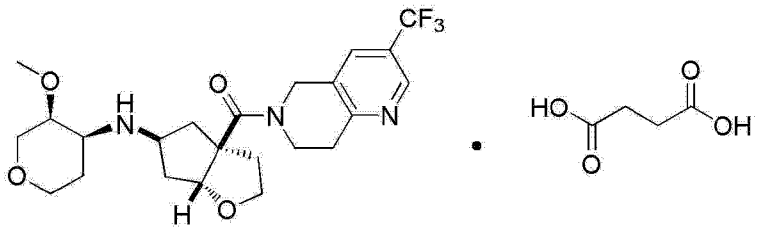
$Na(OAc)_3BH$(463g,2.18 摩尔),并且将悬浮液搅拌 5-10 分钟。经过 20 分钟加入在 1,2- 二氯乙烷 (1.75L) 中的 (R)-3- 甲氧基二氢 -2H- 吡喃 -4(3H)- 酮 (如中间体 1 中所述制备,213g,1.63 摩尔) 溶液,并且将所得的混合物在室温下搅拌过夜。加入另外的乙酸、(R)-3- 甲氧基四氢 -4H- 吡喃 -4- 酮 (28g) 和 $Na(AcO)_3BH$,直至 TLC 显示反应完全。用饱和含水 $NaHCO_3$ 淬灭反应,使有机层分离,并且用 CH_2Cl_2 反萃取水层。将合并的有机层用卤水洗涤,干燥 (Na_2SO_4) 并在减压下蒸发。通过用在 CH_2Cl_2 中的 MeOH(7N NH_3) 的色谱法实现纯化。使用庚烷 /EtOH/ 异丙醇的混合物,使用在 chiralpak AD 柱上的手性色谱法进一步纯化收集的富集异构体,以提供步骤 L 的产物。

[0649] ^1H NMR(氯 仿 -d) δ :8.72(s,1H),7.70(br.s.,1H),5.05(d, J = 4.6Hz,1H),4.70-4.87(m,2H),4.09(dd, J = 12.5,2.7Hz,1H),3.81-4.03(m,4H),3.62-3.71(m,1H),3.50-3.62(m,1H),3.35-3.46(m,4H),3.24-3.35(m,2H),3.14(t, J = 4.9Hz,2H),2.71-2.82(m,1H),2.14-2.43(m,3H),1.99-2.13(m,1H),1.46-1.86(m,5H)。 对 于 C24H31F3N2O4 的计算值为 :470.2(M+1) ;实测值为 :470.1。

[0650] 步骤 M

[0651] ((3aS,5S,6aR)-5-((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮琥珀酸酯

[0652]

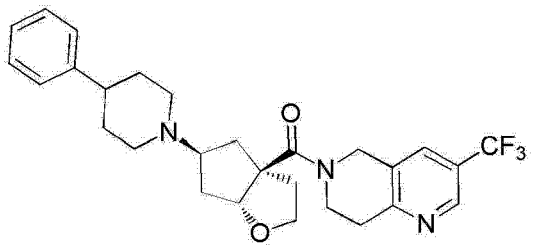


[0653] 使在 MeOH(6L) 中的实例 30,步骤 L(608g,1.18 摩尔) 溶液加温至 40℃直至溶解时。加入琥珀酸 (141.9g,1.20 摩尔),并且使悬浮液加温至 50℃,这促使所有一切溶解。加入 Darco G-60 活性炭 (80g) 并使内容物涡旋 20 分钟。将混合物通过硅藻土过滤,用 MeOH 洗涤,并且使溶剂在减压下蒸发,以提供作为无定形泡沫的标题化合物 (即琥珀酸盐)。将所得的泡沫在 MIBK(5L, 除气的) 在回流下完全溶解,停止加热并允许溶液冷却。将溶液在 104℃下用结晶材料接种,如实例 52 中所述制备,并使溶液经过 4 小时冷却至 38℃。使悬浮液冷却至 4℃,过滤,用冰冷的 100mL MIBK 洗涤,并允许固体在正氮流 (避光) 下干燥过夜。在一些光铣后,收集作为白色固体的步骤 M 产物。^1H NMR(400MHz,MeOD) δ = 8.72(s,1H),8.04-8.12(m,1H),4.97(d, J = 4.4Hz,1H),4.94(s,3H),4.86(s,2H),4.18-4.28(m,1H),3.98(d, J = 11.7Hz,4H),3.74-3.88(m,1H),3.62-3.73(m,1H),3.28-3.58(m,8H),3.12-3.23(m,2H),2.58-2.68(m,1H),2.37-2.44(m,1H),2.28-2.36(m,1H),1.88(m,4H)。对于 $C27H36F3N3O8x0.2H_2O$ 的元素分析计算值为 :C,54.85 ;H,6.21 ;F,9.64 ;N,7.11 ;KF 0.61 ;实测值为 :C,55.17 ;H,6.07 ;F,9.99 ;N,7.11 ;KF,0.64。

[0654] 实例 31

[0655] ((3aS,5S,6aR)-5-(4- 苯基哌啶 -1- 基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

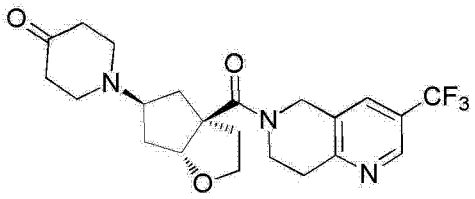
[0656]



[0657] 步骤 A

[0658] 1-((3aS,5S,6aR)-3a-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)六氢-2H-环戊并[b]呋喃-5-基)哌啶-4-酮

[0659]

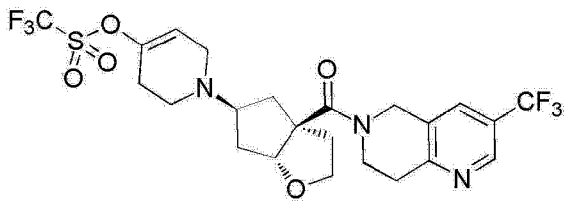


[0660] 经过 1 小时在 60℃下向在甲醇 (70mL) 中的碳酸钠 (2.2g,20.7mmol,5 当量) 悬浮液中同时加入在甲醇 (35mL) 中的实例 1,步骤 G 产物 (1.77g,4.14mmol,1 当量) 和在甲醇 (35mL) 中的 1,5-二氯戊-3-酮 (0.74g,4.55mmol,1.1 当量) 溶液。在 60℃下搅拌 1 小时后,使悬浮液冷却至室温,加入水,将甲醇浓缩,并且用 DCM 萃取水溶液,在 $MgSO_4$ 上干燥并浓缩。通过用 2 至 6% MeOH/DCM 洗脱的色谱法的纯化提供步骤 A 的标题化合物。对于 C22H26F3N3O3 的计算值为 :438.2(M+1) ;实测值为 :438.2。

[0661] 步骤 B

[0662] 1-((3aS,5S,6aR)-3a-(3-(三氟甲基)-5,6,7,8-四氢-1,6-萘啶-6-羰基)六氢-2H-环戊并[b]呋喃-5-基)-1,2,3,6-四氢吡啶-4-基三氟甲磺酸酯

[0663]

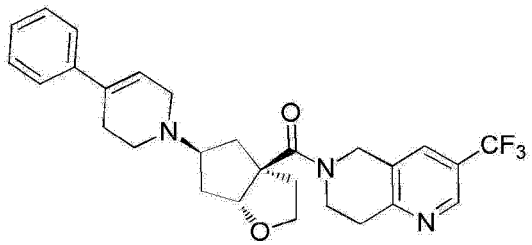


[0664] 在 -78℃下在 N_2 下向在 THF(30mL) 中的步骤 A 产物 (1.06g,2.42mmol,1 当量) 中加入 KHMDS(6.8mL 在甲苯中的 0.5M 溶液,3.39mmol,1.4 当量),溶液变成紫色。在 15 分钟后,加入在 THF(10mL) 中的 N-苯基-双(三氟甲烷磺酰亚胺)(1.21g,3.39mmol,1.4 当量) 溶液,并且将黄色溶液在 -78℃下搅拌 1 小时。加入饱和 NH_4Cl,用乙酸乙酯萃取水溶液,在 $MgSO_4$ 上干燥并浓缩。通过用 3 至 6% MeOH/DCM 洗脱的柱色谱法 (80g) 的纯化提供步骤 B 的标题化合物。对于 C23H25F6N3O5S 的计算值为 :570.1(M+1) ;实测值为 :570.0。

[0665] 步骤 C

[0666] ((3aS,5S,6aR)-5-(4-苯基-5,6-二氢吡啶-1(2H)-基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0667]

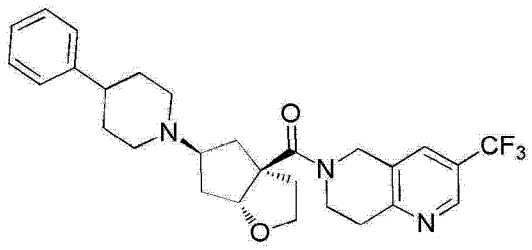


[0668] 使在二甲氧基乙烷 (1mL) 中的步骤 B 产物 (50mg,0.09mmol,1 当量)、苯硼酸 (22mg,0.18mmol,2 当量)、$(Ph_3P)_4Pd$(10mg,0.009mmol,0.1 当量) 和 2M Na_2CO_3(0.1mL) 溶液在 N2 下在螺旋盖小瓶中加温至 80C 过夜。使溶液冷却至室温并浓缩。通过用 50 至 100% 乙酸乙酯 / 庚烷洗脱的柱色谱法 (4g) 的纯化提供步骤 C 的标题化合物。对于 C28H30F3N3O2 的计算值为 :498.2(M+1) ;实测值为 :498.3。

[0669] 步骤 D

[0670] ((3aS,5S,6aR)-5-(4- 苯基哌啶 -1- 基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0671]

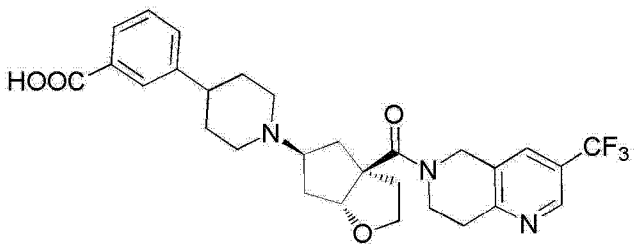


[0672] 使在乙醇 (3mL) 中的步骤 D 产物 (24mg,0.046mmol,1 当量) 和 5% Pd/C(20mg) 悬浮液在氢气球下放置过夜。将溶液通过硅藻土过滤并浓缩。通过用 2 至 6% MeOH/DCM 洗脱的柱色谱法 (4g) 的纯化提供标题化合物。^1H NMR(氯仿 -d) δ :8.71(s,1H),7.70(br.s.,1H),7.27-7.33(m,2H),7.15-7.24(m,3H),5.06(d, J = 4.5Hz,1H),4.78(br.s.,2H),4.02(td, J = 8.1,3.5Hz,1H),3.81-3.96(m,2H),3.61-3.73(m,1H),2.90-3.21(m,5H),2.45-2.57(m,1H),2.22-2.32(m,2H),2.08-2.15(m,3H),1.99(br.s.,2H),1.65-1.89(m,5H)。对于 C28H32F3N3O2 的计算值为 :500.2(M+1) ;实测值为 :500.3。

[0673] 实例 32

[0674] 3-(1-((3aS,5S,6aR)-3a-(3-(三氟甲基)-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基) 哌啶 -4- 基) 苯甲酸

[0675]

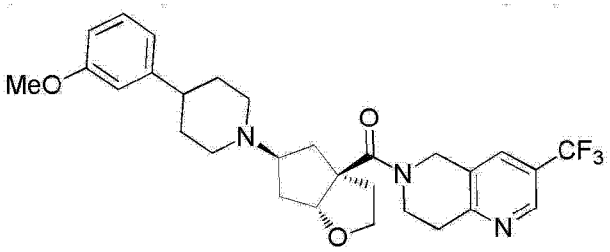


[0676] 通过遵循实例 31,步骤 C 中所述的操作,随后遵循实例 31,步骤 D 中所述的操作,获得实例 31,步骤 B 的产物并与 3- 羧基苯硼酸反应,来制备实例 32 的标题化合物。对于 C29H32F3N3O4 的计算值为 :544.2(M+1) ;实测值为 :544.0。

[0677] 实例 33

[0678] ((3aS,5S,6aR)-5-(4-(3- 甲氧基苯基) 哌啶 -1- 基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0679]

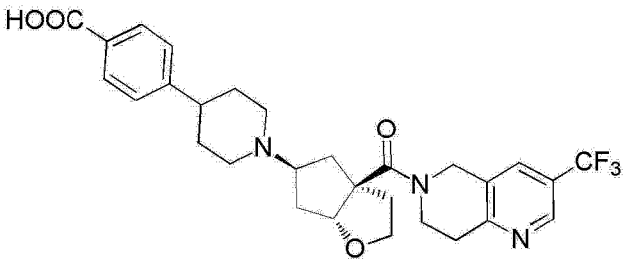


[0680] 通过遵循实例 31,步骤 C 中所述的操作,随后遵循实例 31,步骤 D 中所述的操作,获得实例 31,步骤 B 的产物并与 3- 甲氧基苯硼酸反应,来制备实例 33 的标题化合物。对于 C29H34F3N3O3 的计算值为 :530.3(M+1) ;实测值为 :530.3。

[0681] 实例 34

[0682] 4-(1-((3aS,5S,6aR)-3a-(3-(三氟甲基)-5,6,7,8- 四氢 -1,6- 萘啶 -6- 羰基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基) 哌啶 -4- 基) 苯甲酸

[0683]

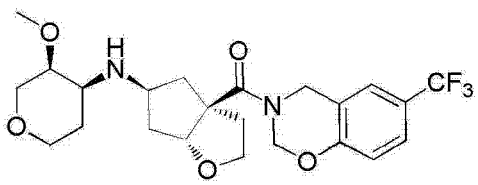


[0684] 通过遵循实例 31,步骤 C 中所述的操作,随后遵循实例 31,步骤 D 中所述的操作,获得实例 31,步骤 B 的产物并与 4- 苄氧基羰基苯硼酸反应,来制备实例 34 的标题化合物。^{1}H NMR(氯仿 -d) δ :8.68(s,1H),7.79-7.88(m, J = 8.1Hz,2H),7.60(br.s.,1H),7.09-7.21(m, J = 8.6Hz,2H),5.01(d, J = 4.0Hz,1H),4.67-4.78(m,1H),4.51-4.67(m,1H),4.02(br.s.,1H),3.63-3.96(m,3H),3.34-3.54(m,3H),3.23(d, J = 11.6Hz,1H),3.09(br.s.,1H),2.56-2.70(m,2H),2.27-2.50(m,5H),1.84-2.20(m,6H)。 对于 C29H32F3N3O4 的计算值为 :544.2(M+1) ;实测值为 :544.2。

[0685] 实例 35

[0686] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(6-(三氟甲基)-2H- 苯并 [e][1,3] 噁嗪 -3(4H)- 基) 甲酮

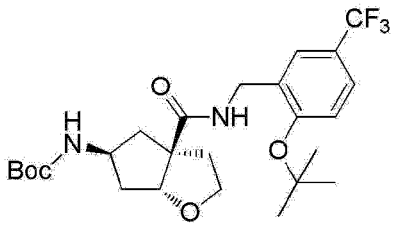
[0687]



[0688] 步骤 A

[0689] 叔丁基((3aS,5S,6aR)-3a-((2-(叔丁氧基)-5-(三氟甲基)苄基)氨基甲酰基)六氢-2H-环戊并[b]呋喃-5-基)氨基甲酸酯

[0690]

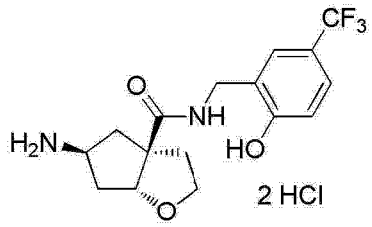


[0691] 遵循来自实例1,步骤C的操作,由实例23,步骤E的产物和根据ACS Med.Chem. Letters 2010,1,14中的操作制备的(2-(叔丁氧基)-5-(三氟甲基)苯基)甲酰胺的反应制备步骤A的产物。对于C25H35F3N2O5的计算值为:523.2(M+23);实测值为:523.2。

[0692] 步骤B

[0693] (3aS,5S,6aR)-5-氨基-N-(2-羟基-5-(三氟甲基)苄基)六氢-2H-环戊并[b]呋喃-3a-甲酰胺二盐酸盐

[0694]

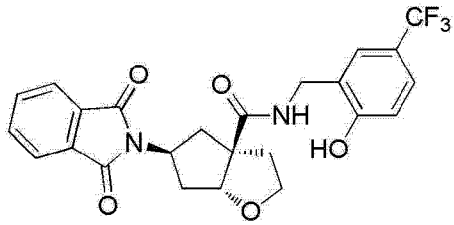


[0695] 使在甲醇(60mL)中的步骤A产物(11.07g,20.57mmol,1当量)溶液和在甲醇中的HCl溶液(82mL 1.25M溶液,103mmol,5当量)加热至55℃共2.5天。使溶液浓缩以获得步骤B的产物。对于C16H19F3N2O3的计算值为:345.1(M+1);实测值为:345.3。

[0696] 步骤C

[0697] (3aS,5S,6aR)-5-(1,3-二氧代异吲哚啉-2-基)-N-(2-羟基-5-(三氟甲基)苄基)六氢-2H-环戊并[b]呋喃-3a-甲酰胺

[0698]

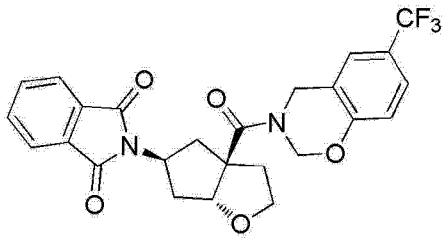


[0699] 使在氯仿(150mL)中的步骤B产物(8.58g,18.74mmol,1当量)、邻苯二甲酸酐(5.55g,37.5mmol,2当量)和DIEA(11.3mL,55.6mmol,3.5当量)溶液加热至70℃共2小时。使溶液冷却至室温,并加入羰基二咪唑(2.24g 13.82mmol,3当量),并且将溶液加热至60℃共2小时。将溶液冷却至室温,加入1N HCl,用DCM萃取水溶液,合并有机物,在MgSO4上干燥并浓缩。通过用30至60至80%EA/庚烷洗脱的色谱法(200g柱)的纯化提供步骤C的产物。对于C24H21F3N2O5的计算值为:474.1(M+1);实测值为:475.1。

[0700] 步骤D

[0701] 2-((3aS,5S,6aR)-3a-(6-(三氟甲基)-3,4-二氢-2H-苯并[e][1,3]噁嗪-3-羰基)六氢-2H-环戊并[b]呋喃-5-基)异吲哚啉-1,3-二酮

[0702]

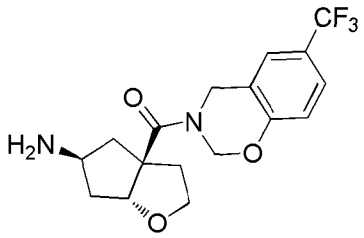


[0703] 使在甲苯(300mL)中的步骤C产物(7.97g,15.5mmol,1当量)、多聚甲醛(9.28g,310mmol,20当量)和对甲苯磺酸水合物(2.94g,15.5mmol,1当量)溶液在配备迪安-斯脱克分水器的烧瓶中加热至130℃共18小时。使溶液冷却至室温并浓缩。通过用25至60至100%乙酸乙酯/庚烷洗脱的色谱法(200g柱)的纯化提供步骤D的产物。对于C25H21F3N2O5的计算值为:487.1(M+1);实测值为:487.2。

[0704] 步骤E

[0705] ((3aS,5S,6aR)-5-氨基六氢-2H-环戊并[b]呋喃-3a-基)(6-(三氟甲基)-2H-苯并[e][1,3]噁嗪-3(4H)-基)甲酮

[0706]

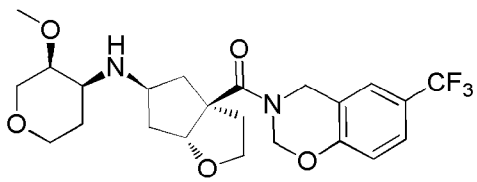


[0707] 使在乙醇(60mL)中的步骤D产物(5.39g,11.1mmol,1当量)和肼(7.1mL,222mmol,20当量)溶液在室温下搅拌18小时。将白色固体过滤,用甲醇和DCM洗涤,并将滤液浓缩。加入饱和$NaHCO_3$,用DCM萃取水溶液,合并有机物,在$MgSO_4$上干燥并浓缩,以提供步骤E的产物。对于C17H19F3N2O3的计算值为:357.1(M+1);实测值为:357.3。

[0708] 步骤F

[0709] ((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(6-(三氟甲基)-2H-苯并[e][1,3]噁嗪-3(4H)-基)甲酮

[0710]



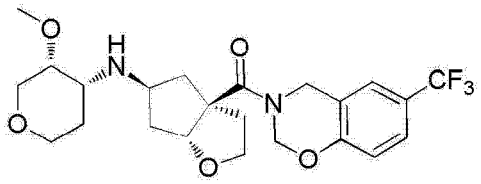
[0711] 遵循实例1,步骤H中所述的操作,由步骤E的产物和(R)-3-甲氧基二氢-2H-吡喃-4(3H)-酮(中间体1)的反应制备标题化合物。^1H NMR(氯仿-d)δ:7.42(d,J=8.6Hz,1H),7.36(br.s.,1H),6.95(d,J=8.1Hz,1H),5.43(br.s.,2H),4.96-5.11(m,

1H),4.82(br.s.,2H),3.84-4.15(m,3H),3.68(d,J = 7.1Hz,1H),3.55(br.s.,1H),3.32-3.45(m,4H),3.20-3.32(m,2H),2.69-2.84(m,1H),2.39(br.s.,1H),2.12-2.25(m,2H),1.99-2.12(m,1H),1.78-1.99(m,1H),1.46-1.78(m,4H)。对于C23H29F3N2O5的计算值为:471.2(M+1);实测值为:471.2。

[0712] 实例36

[0713] ((3aS,5S,6aR)-5-(((3R,4R)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(6-(三氟甲基)-2H-苯并[e][1,3]噁嗪-3(4H)-基)甲酮

[0714]

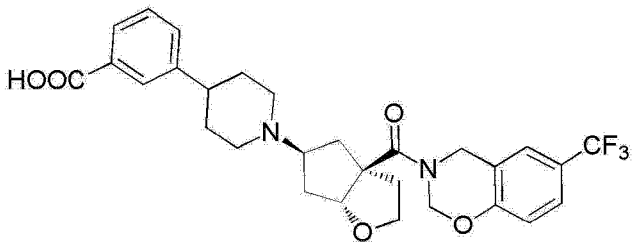


[0715] 遵循实例1,步骤H中所述的操作,由步骤E的产物和(S)-3-甲氧基二氢-2H-吡喃-4(3H)-酮的反应制备标题化合物。^{1}H NMR(氯仿-d)δ:7.42(d,J = 8.6Hz,1H),7.36(br.s.,1H),6.96(d,J = 8.6Hz,1H),5.35-5.49(m,2H),5.05(d,J = 5.1Hz,1H),4.74-4.90(m,2H),4.05(dd,J = 12.6,3.5Hz,1H),3.94-4.01(m,1H),3.91(dt,J = 11.4,3.7Hz,1H),3.61-3.71(m,1H),3.48-3.60(m,1H),3.24-3.41(m,6H),2.78(dd,J = 6.3,3.8Hz,1H),2.39(br.s.,1H),2.19(td,J = 12.1,6.1Hz,2H),2.05(dt,J = 12.3,8.3Hz,1H),1.89(br.s.,1H),1.43-1.75(m,4H)。对于C23H29F3N2O5的计算值为:471.2(M+1);实测值为:471.2。

[0716] 实例37

[0717] 3-(1-((3aS,5S,6aR)-3a-(6-(三氟甲基)-3,4-二氢-2H-苯并[e][1,3]噁嗪-3-羰基)六氢-2H-环戊并[b]呋喃-5-基)哌啶-4-基)苯甲酸

[0718]

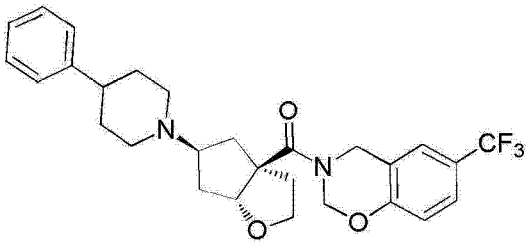


[0719] 通过遵循实例31,步骤A和B中所述的操作,获得实例35,步骤E的产物,随后遵循实例31,步骤C中所述的操作,使该产物与3-苄氧基羰基苯硼酸反应,随后遵循实例31,步骤D中所述的操作,来制备实例37的标题化合物。^{1}H NMR(氯仿-d)δ:8.04(s,1H),7.78(d,J = 6.8Hz,1H),7.32-7.43(m,2H),7.19-7.32(m,2H),6.93(d,J = 8.3Hz,1H),5.16-5.66(m,2H),5.06(d,J = 4.2Hz,1H),4.96(d,J = 16.9Hz,1H),4.72(d,J = 16.9Hz,1H),3.96-4.11(m,1H),3.55-3.75(m,2H),3.47(s,1H),3.29-3.45(m,2H),2.59-2.80(m,2H),2.35-2.59(m,5H),2.30(dd,J = 12.8,5.7Hz,1H),2.13-2.24(m,1H),1.99-2.13(m,2H),1.92(d,J = 11.7Hz,1H),1.82(d,J = 13.4Hz,1H)。对于C29H31F3N2O5的计算值为:

545.2(M+1)；实测值为：545.2。

[0720] 实例 38

[0721] ((3aS,5S,6aR)-5-(4- 苯 基 哌 啶 -1- 基) 六 氢 -2H- 环 戊 并 [b] 呋喃 -3a- 基)(6-(三 氟 甲 基)-2H- 苯 并 [e][1,3] 噁 嗪 -3(4H)- 基) 甲 酮

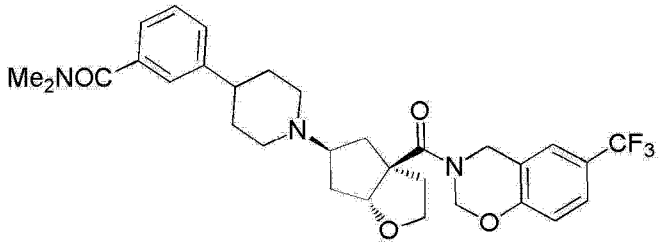


[0722] 通过遵循实例 31，步骤 A 直到 D 中所述的操作获得实例 35，步骤 E 的产物，来制备实例 38 的标题化合物。^{1}H NMR(氯仿 -d) δ：7.42(d, J = 8.6Hz,1H),7.37(br.s.,1H),7.29(t, J = 7.5Hz,2H),7.15-7.24(m,3H),6.96(d, J = 8.6Hz,1H),5.42(br.s.,2H),5.03(d, J = 4.6Hz,1H),4.69-4.95(m,2H),3.95-4.07(m,1H),3.60-3.73(m,1H),3.04(br.s.,3H),2.32-2.56(m,2H),2.19-2.31(m,2H),1.89-2.17(m,4H),1.53-1.89(m,6H)。 对 于 C28H31F3N2O3 的计算值为：501.2(M+1)；实测值为：501.2。

[0723] 实例 39

[0724] N,N- 二甲基 -3-(1-((3aS,5S,6aR)-3a-(6-(三氟甲基)-3,4- 二氢 -2H- 苯并 [e][1,3] 噁嗪 -3- 羰基) 六氢 -2H- 环戊并 [b] 呋喃 -5- 基) 哌啶 -4- 基) 苯甲酰胺

[0725]

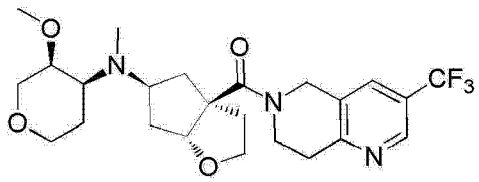


[0726] 通过遵循实例 31，步骤 A 和 B 中所述的操作，获得实例 35，步骤 E 的产物，随后遵循实例 31，步骤 C 中所述的操作，使该产物与 N, N- 二甲基苯甲酰胺 -3- 硼酸反应，随后遵循实例 31，步骤 D 中所述的操作，来制备实例 39 的标题化合物。对于 C31H36F3N3O4 的计算值为：572.3(M+1)；实测值为：572.3。

[0727] 实例 40

[0728] ((3aS,5S,6aR)-5-(((3S,4S)-3- 甲氧基四氢 -2H- 吡喃 -4- 基)(甲基) 氨基) 六氢 -2H- 环戊并 [b] 呋喃 -3a- 基)(3-(三氟甲基)-7,8- 二氢 -1,6- 萘啶 -6(5H)- 基) 甲酮

[0729]



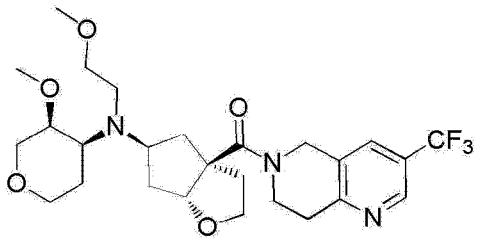
[0730] 通过遵循实例 1，步骤 H 中所述的操作获得实例 30 的产物并与甲醛反应，来制备

实例 40 的标题化合物。^{1}H NMR(氯仿-d) δ :8.72(br.s.,1H),7.70(br.s.,1H),5.03(d,J = 4.6Hz,1H),4.67-4.92(m,2H),4.15(d,J = 12.7Hz,1H),3.97-4.10(m,2H),3.92(br.s.,2H),3.55-3.71(m,2H),3.33-3.53(m,5H),3.22(d,J = 12.7Hz,1H),3.14(br.s.,2H),2.64(d,J = 11.7Hz,1H),2.22-2.50(m,4H),1.79-2.22(m,6H),1.69(td,J = 12.5,4.9Hz,1H),1.51(d,J = 12.0Hz,1H)。对于 C24H32F3N3O4 的计算值为 :484.2(M+1) ;实测值为 :484.2。

[0731] 实例 41

[0732] ((3aS,5S,6aR)-5-((2-甲氧基乙基)((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0733]

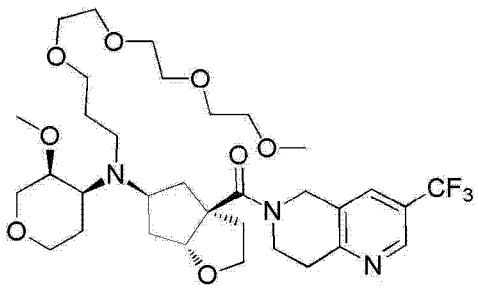


[0734] 通过遵循实例 1,步骤 H 中所述的操作,获得实例 30 的产物并与甲氧基乙醛反应,来制备实例 41 的标题化合物。对于 C26H36F3N3O5 的计算值为 :528.3(M+1) ;实测值为 :528.3。

[0735] 实例 42

[0736] ((3aS,5S,6aR)-5-(((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)(2,5,8,11-四氧十四烷-14-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0737]

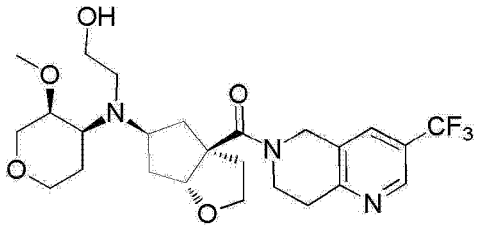


[0738] 通过遵循实例 1,步骤 H 中所述的操作,获得实例 30 的产物并与 4,7,10,13-四氧十四醛反应,来制备实例 42 的标题化合物。对于 C33H50F3N3O8 的计算值为 :674.4(M+1) ;实测值为 :674.4。

[0739] 实例 43

[0740] ((3aS,5S,6aR)-5-((2-羟乙基)((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

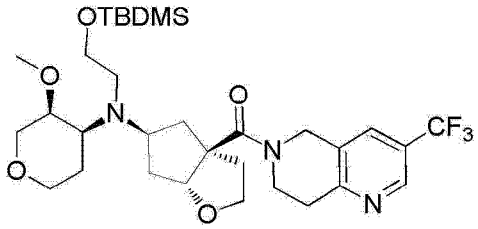
[0741]



[0742] 步骤 A

[0743] ((3aS,5S,6aR)-5-((2-((叔丁基二甲基甲硅烷基)氧基)乙基)((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0744]

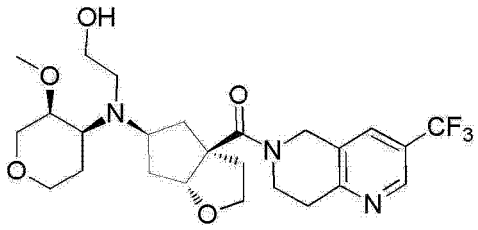


[0745] 通过遵循实例 1,步骤 H 中所述的操作,获得实例 30 的产物并与叔丁基二甲基硅氧烷基乙醛反应,来制备步骤 A 的标题化合物。对于 C31H48F3N3O5Si 的计算值为:628.3(M+1);实测值为:628.2。

[0746] 步骤 B

[0747] ((3aS,5S,6aR)-5-((2-羟乙基)((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨基)六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0748]



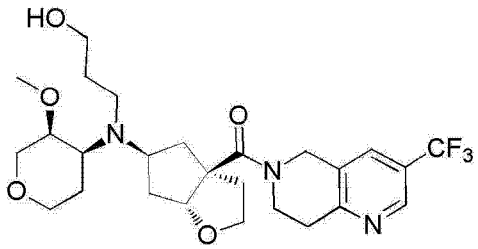
[0749] 使在 1N HCl(0.25mL)和二噁烷(5mL)中的步骤 A 产物(210mg,0.33mmol,1 当量)溶液加热至 90℃共 18 小时,随后冷却至室温。加入饱和 $NaHCO_3$,用 CH_2Cl_2 萃取水溶液,在 $MgSO_4$ 上干燥并浓缩。通过用 3 至 8% MeOH/DCM 洗脱的色谱法(12g)的纯化提供实例 43 的标题化合物(67mg,38%)。^1H NMR(氯仿-d)δ:8.72(br.s.,1H),7.71(br.s.,1H),4.96(d,J = 4.4Hz,1H),4.80(br.s.,2H),4.15(d,J = 12.7Hz,1H),3.77-4.10(m,5H),3.56-3.70(m,1H),3.30-3.52(m,7H),3.23(d,J = 12.7Hz,1H),3.14(br.s.,2H),2.66-2.90(m,3H),2.39(br.s.,1H),2.13-2.27(m,1H),2.05(dd,J = 12.7,5.6Hz,3H),1.82(br.s.,1H),1.68(td,J = 12.6,4.9Hz,1H),1.42(br.s.,1H)。对于 C25H34F3N3O5 的计算值为:514.3(M+1);实测值为:514.3。

[0750] 实例 44

[0751] ((3aS,5S,6aR)-5-((3-羟基丙基)((3S,4S)-3-甲氧基四氢-2H-吡喃-4-基)氨

基）六氢-2H-环戊并[b]呋喃-3a-基)(3-(三氟甲基)-7,8-二氢-1,6-萘啶-6(5H)-基)甲酮

[0752]



[0753] 通过遵循实例43步骤A和B中所述的操作,获得实例30的产物并与3-((叔丁基二甲基硅氧烷基）氧基）丙醛反应,来制备实例44的标题化合物。^{1}H NMR(氯仿-d) δ：8.72(s,1H),7.72(s,1H),4.97(d,J = 4.5Hz,1H),4.69-4.91(m,2H),4.15(d,J = 12.6Hz,1H),3.83-4.10(m,5H),3.58-3.82(m,3H),3.33-3.47(m,5H),3.25(d,J = 12.6Hz,1H),3.14(br.s.,2H),2.70-2.93(m,3H),2.36(br.s.,1H),2.15-2.30(m,1H),1.97-2.15(m,3H),1.78-1.96(m,1H),1.35-1.77(m,4H)。对于C26H36F3N3O5的计算值为:528.3(M+1);实测值为:528.3。

[0754] 实例45

[0755] 体外生物学数据

[0756] 使本发明化合物经受多种代表性的生物学测试。

[0757] 这些测试的结果旨在以非限制性的方式说明本发明。

[0758] 在THP-1细胞中的MCP-1受体结合测定法

[0759] 人单核细胞细胞系THP-1细胞得自美国典型培养物中心(Manassas,Va.,USA)。THP-1细胞在补充有10％胎牛血清的RPMI-1640(RPMI:洛斯维帕克纪念研究所培养基(Roswell Park Memorial Institute Medium)-细胞培养生长培养基）中在潮湿5％ CO_2大气中在37℃下生长。将细胞密度维持在0.5×10^6个细胞/mL之间。

[0760] 在各种浓度的未标记的MCP-1(R&D Systems,Minneapolis,Minn.))或测试化合物的存在下,使THP-1细胞与0.5nM ^{125}I标记的MCP-1(Perkin-Elmer Life Sciences,Inc.Boston,Mass.)一起在30℃下在96孔板中温育2小时。然后将细胞收获至滤板上,干燥,并将20μL的Microscint 20加入至每孔中。板在TopCount NXT,微板闪烁和发光计数器(Microplate Scintillation&Luminescence Counter)(Perkin-Elmer Life Sciences,Inc.Boston,Mass.)中进行计数。从所有值减去空白值（仅有缓冲液）并将药物处理值与媒介物处理值进行比较。将1μM冷MCP-1用于非特异性结合。

[0761] 表1列出了针对本发明的测试化合物获得的抑制MCP-1与CCR2结合的IC_{50}值。当对于特定化合物未获得IC_{50}值时,抑制百分比以25μM的测试浓度提供。

[0762] 表1:MCP-1结合IC_{50}的抑制

[0763]

实例	CCR2结合(nM)
1	16

2	7
3	11
4	93
5	170
6	62
7	2
8	3
9	9
10	16
11	4
12	24
13	20
16	14
21	120

[0764] 实例 15、29-31、33、35-37、39 和 40 的化合物被认为具有小于约 50nM 的 CCR2 结合，实例 14、20、22 和 25 的化合物被认为具有约 50-100nM 的 CCR2 结合，实例 17、26、38 和 43-44 的化合物被认为具有约 100-200nM 的 CCR2 结合，并且实例 18、19、23、24、27、28、32、34、41 和 42 的化合物被认为具有大于约 200nM 的 CCR2 结合。

[0765] 实例 46

[0766] 动物

[0767] 使用注射到 C57BL/6 小鼠内的靶向 129Sv/Evbrd 胚胎干细胞克隆生成小鼠 CCR2 敲除 / 人 CCR2 敲入小鼠。hCCR2 转录物的表达通过在来自纯合 hCCR2 敲入小鼠的脾脏和血液全 RNA 上进行的定量逆转录聚合酶链反应进行确认。向 C57BL/6 遗传背景的回交继续进行到第八代。转基因小鼠在无特异性病原体、温控的设施中饲养，所述设施维持 12 小时光照 /12 小时黑暗的周期。小鼠自由接近水和食物。实验程序依据动物管理的机构标准来执行，并由机构动物管理和使用委员会批准。

[0768] 实例 47

[0769] 鼠体内细胞迁移测定法

[0770] 动物以 3、10 和 30mg/kg bid 口服给予媒介物或 CCR2 拮抗剂。动物经历麻醉和剖腹手术。将远侧小肠襻 (loop)(5cm 长) 轻轻从腹腔取出至湿润消毒纱布上。将合成的人

MCP-1(1mg/100mL 无菌 PBS) 或单独的 PBS 逐滴施用至取出的肠襻的绒毛膜上。将缝线结置于肠系膜中以标记处理的区域的末端。二十四小时后，处死动物，并移出该肠节段及相邻区域。沿肠系膜边界打开组织，钉平并去除粘膜。剩余的肌肉层在 100％ EtOH 中稍作固定，然后使用 Hanker-Yates 试剂染色，以检测含有髓过氧化物酶的免疫细胞。在以 10mg/kg，一日两次经口施用时，如果与媒介物处理动物相比细胞迁移的抑制达到 30％，则认为化合物是有效的。

[0771] 实例 48

[0772] 在小鼠中硫代乙醇酸酯诱导的腹膜炎

[0773] 动物用媒介物或实例 30 的化合物以 0、1、3 和 10mg/kg bid) 经口给予。一小时后，给动物腹腔内注射无菌硫代乙醇酸酯 (25mL/kg，ip，Sigma) 用于诱导腹膜炎。每天用媒介物或实例 30 经口处理动物两次。在 72 小时时间点，用 10mL 的无菌盐水灌洗腹腔。使用显微镜进行腹腔灌洗液中的总细胞计数，并在吉姆萨染色 (Hema Tek 2000) 后使用细胞离心涂片器 (cytospin) 分析进行细胞区别。通过比较 CCR2 拮抗剂处理小鼠与媒介物处理的小鼠的白细胞数的变化，来计算硫代乙醇酸酯诱导的腹膜炎的抑制百分比。当实例 30 的化合物以 1、3 和 10mg/kg p.o bid 进行施用时，在 72 小时在 hCCR2KI 小鼠中硫代乙醇酸酯诱导的细胞浸润分别被抑制 51％、67％和 95％。实例 30 的效应证实为剂量依赖性的，具有在血浆中的 ED_{50}1mg/kg p.o.bid 和 cmax EC_{50}97nM(最后一次剂量后 0.5 小时)。

[0774] 实例 49

[0775] MCP-1- 诱导的单核细胞至小鼠气道的募集

[0776] 用以 3、10 和 30mg/kg 一日两次经口服的媒介物或 CCR2 拮抗剂经口处理动物。一小时后，将动物鼻内给予在无菌盐水中的 4μg MCP-1。每天用媒介物或 CCR2 拮抗剂经口处理动物两次。在 48 小时后，通过腹膜内注射麻醉溶液 (Sleepaway- 戊巴比妥钠) 对小鼠实施安乐死。使用 1.4ml 含有 3mM EDTA 的冰冷 PBS 执行整个支气管肺泡灌洗 (BAL)。使用显微镜执行 BAL 灌洗液中的总细胞计数并在 Giemsa 染色 (Hema Tek 2000) 后利用细胞离心涂片器分析执行细胞分化。通过比较化合物处理小鼠和媒介物处理小鼠的总白细胞计数 (包括单核细胞 / 巨噬细胞和淋巴细胞) 的变化来计算抑制百分比。如果抑制百分比达到 30％，则认为化合物是有效的。

[0777] 实例 50

[0778] 小鼠中高脂肪饮食诱导的肥胖症和胰岛素抗性

[0779] 在处于 7 周龄的动物中通过大约 60％卡里路源自脂肪的高脂饲料 (D-12492；Research Diets Inc.) 诱导肥胖症，共 10-12 周。在 7 周龄之前，给动物喂养标准颗粒饮食，其中 5％的卡路里作为脂肪提供。肥胖动物通过体重进行随机化。肥胖动物用媒介物或实例 30 的化合物以 1、3 和 10mg/kg，po bid 进行经口处理。监测体重和食物摄入以及空腹血糖水平。通过 NMR 分析器 (Bruker MiniSpec) 来测定体重指数。在禁食 3 小时的动物中执行胰岛素耐受性测试。在腹膜内弹丸式注射重组人胰岛素 (0.5U/kg) 后，在注射前以及在注射后 15、30、45、60、90 和 120 分钟，使用血糖仪测量血糖浓度。在过夜 (17 小时) 禁食后进行葡萄糖耐受性测试。在溶于水中的葡萄糖 (2.5g/kg) 的口服剂量前以及在口服 15、30、60、90、120 分钟后测量血糖浓度。通过完备的实验室动物监测系统监测能量消耗分析。在用媒介物或 CCR2 拮抗剂处理 50 天后，通过 CO_2 窒息处死动物。通过比较化合物处理的小

鼠与媒介物处理的小鼠的体重变化，来计算体重减轻百分比。在 32 天处理后，当分别以 1、3 和 10mg/kg p.o.bid 施用时，实例 30 的化合物使高脂饮食诱导的体重减少 4.94% ($p > 0.05$)、10.94% ($p < 0.01$) 和 15.7% ($p < 0.01$)。

[0780] 实例 51

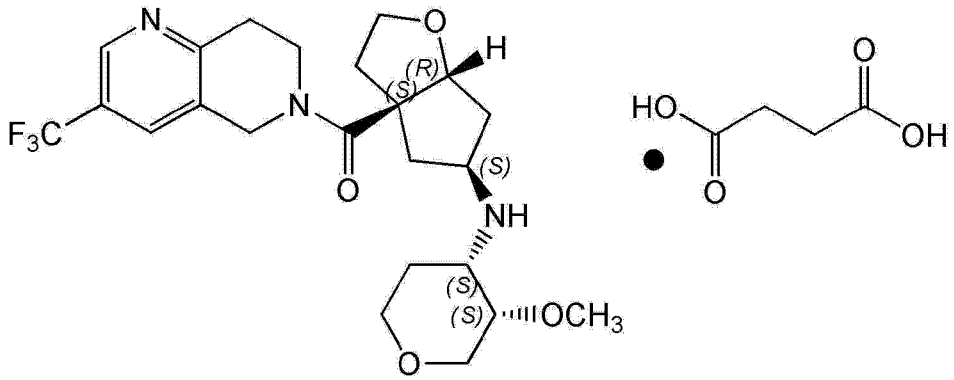
[0781] 过敏性哮喘的小鼠模型

[0782] 通过在第 0 天和第 5 天腹膜内注射在 100μL 磷酸盐缓冲盐水 (PBS) 中吸收至 1mg Imject® 的 10μg 鸡蛋清白蛋白 (OVA) 而使动物敏化。对照动物接受 PBS ip。在第 12、16 和 20 天，利用超声雾化器通过吸入 0.5% OVA 气雾剂 10 分钟来攻击 OVA 免疫动物。对照动物以类似方式用 PBS 来攻击。OVA 敏化动物从第 9-20 天每天两次且在第 21 天每天一次（处死前 2 小时），以 3、10、30mg/kg 经口接受媒介物 (0.5% 甲基纤维素 (Methocel)) 或 CCR2 拮抗剂。每天一次经口服地塞米松 (5mg/kg) 和孟鲁斯特 (1mg/kg)。在第 21 天，在最后一次按剂量给服 CCR2 化合物后 2 小时，利用 Buxco 全身体积描记术测量对气雾化乙酰甲胆碱的支气管反应性。在第 21 天，处死动物。收集支气管肺泡罐洗液 (1mL)，并对总细胞进行计数。在 Giemsa 染色 (Hema Tek 2000) 后用细胞离心涂片器分析来确定嗜酸性粒细胞、淋巴细胞、单核细胞和中性粒细胞的数量。通过将化合物处理小鼠与媒介物处理小鼠相比来计算对总 BAL 白细胞计数（和嗜酸性粒细胞计数）的抑制百分比。如果抑制百分比达到 30%，则认为化合物是有效的。

[0783] 实例 52

[0784] 式 (I-S) 的化合物的结晶琥珀酸盐的制备

[0785]



[0786] 通过使式 (I) 的化合物的无定形琥珀酸盐（无定形琥珀酸盐是实例 30，步骤 M 中所述的泡沫）在敞口 DSC 铝盘中以 10℃ / 分钟的加热速率加热至约 140℃，随后以 10℃ / 分钟的冷却速率冷却至 30℃，来制备式 (I) 的化合物的结晶琥珀酸盐。

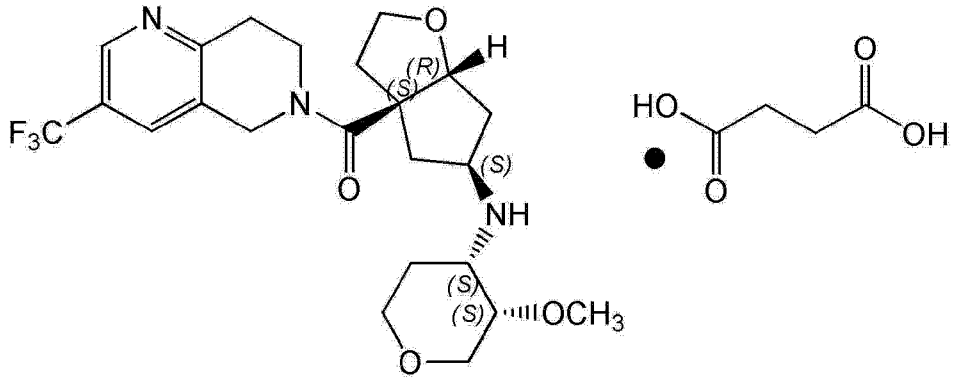
[0787] 图 5 示出了在上述实验期间测量的 DSC 热谱图。DSC 热谱图显示在约 50℃下的第一吸热事件（理论上为无定形形式的去溶剂化结果）；在约 138℃下具有最大值的放热事件，指示结晶；和在 155℃下的后续吸热事件，指示结晶固体的熔解。

[0788] 图 5 还包括关于在上文描述的实例中使用的式 (I-S) 的化合物的无定形琥珀酸盐的 TGA 热谱图，所述无定形琥珀酸盐显示在室温和约 80℃之间的约 4.8% 重量减轻；和在约 172℃下开始的分解。

[0789] 实例 53

[0790] 式 (I-S) 的化合物的结晶琥珀酸盐的制备

[0791]



[0792] 下述一般操作应用于筛选研究中，用于鉴定适合于式 (I-S) 的化合物的结晶琥珀酸盐结晶的溶剂。由式 (I-S) 的化合物的无定形琥珀酸盐（无定形琥珀酸盐是实例 30，步骤 M 中所述的泡沫）制备式 (I-S) 的化合物的结晶琥珀酸盐，由甲基异丁基酮结晶。（注：水、甲醇、乙醇、丙酮、乙腈、乙酸异丙酯、硝基甲烷、四氢呋喃、甲基乙基酮、二氯甲烷和甲苯不诱导结晶）。

[0793] 将式 (I-S) 的化合物的无定形琥珀酸盐 (5-10mg) 悬浮于 1-2mL 甲基异丁基酮 (MIBK) 中。将所得的悬浮液在油浴中在回流条件下加热，悬浮液形成澄清溶液，所述澄清溶液在冷却至室温后在环境条件下获得结晶固体。

[0794] 允许从 MIBK 中分离的固体在环境条件下干燥，并且随后通过 X 射线进行分析。从 MIBK 中分离的固体的 pXRD 图类似于热处理样品（如上文实例 52 中制备）的 pXRD 图，指示在两种情况下产生相同结晶形式。

[0795] 实例 54：口服制剂 - 假想例实例

[0796] 作为口服组合物的具体实施例，将 100mg 如实例 53 制备的化合物与足量细分的乳糖一起配制，提供 580 至 590mg 总量以填充 0 号硬胶囊。

[0797] 尽管上述说明书教导了本发明的原理，以示例为目的提供了实例，但应该理解本发明的实施涵盖落入所附的权利要求及它们的等同形式的范围内的所有通常的变型形式、改变形式和 / 或修改形式。

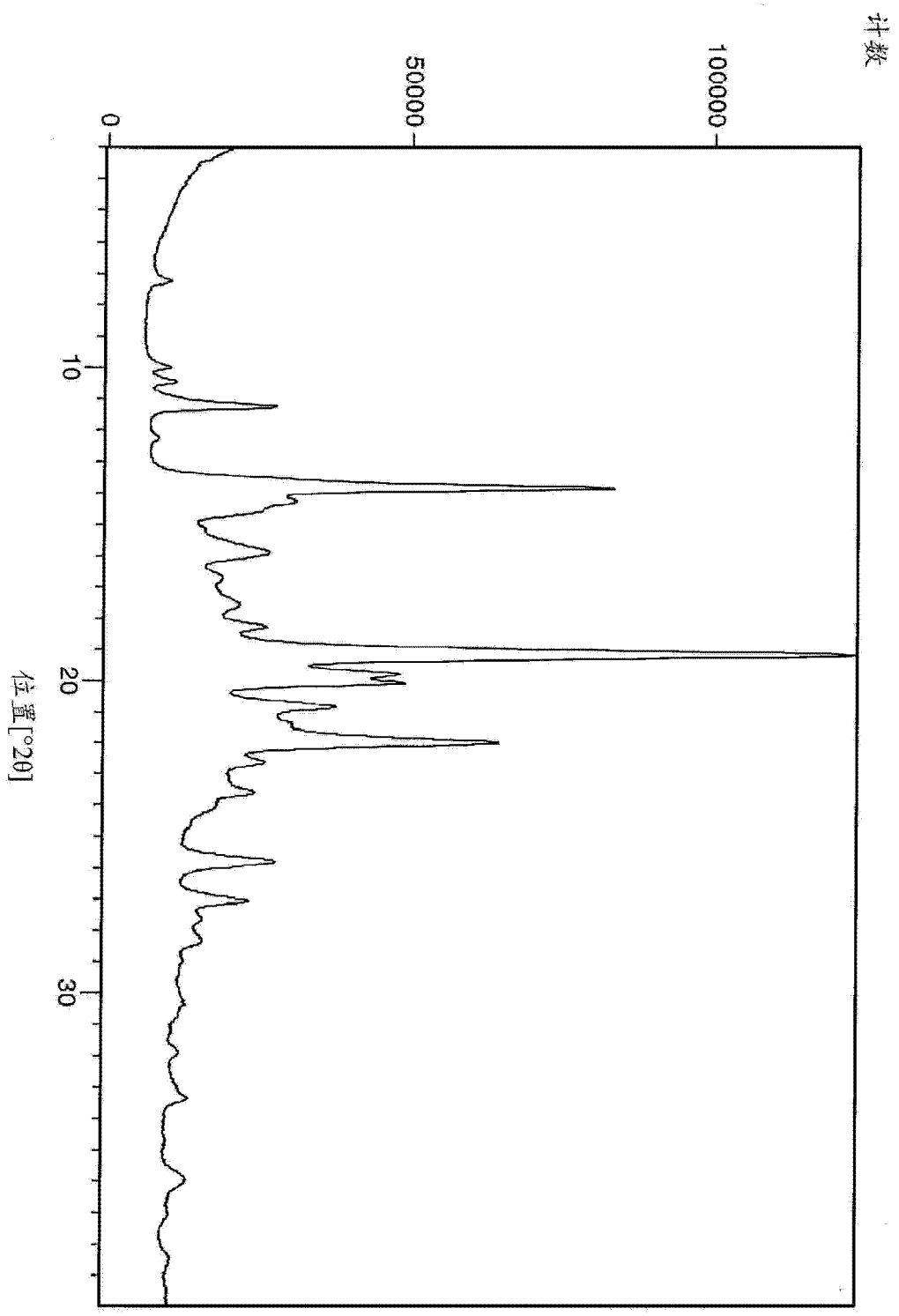


图 1 :式 (I-S) 的化合物的结晶琥珀酸盐的代表性 pXRD 光谱

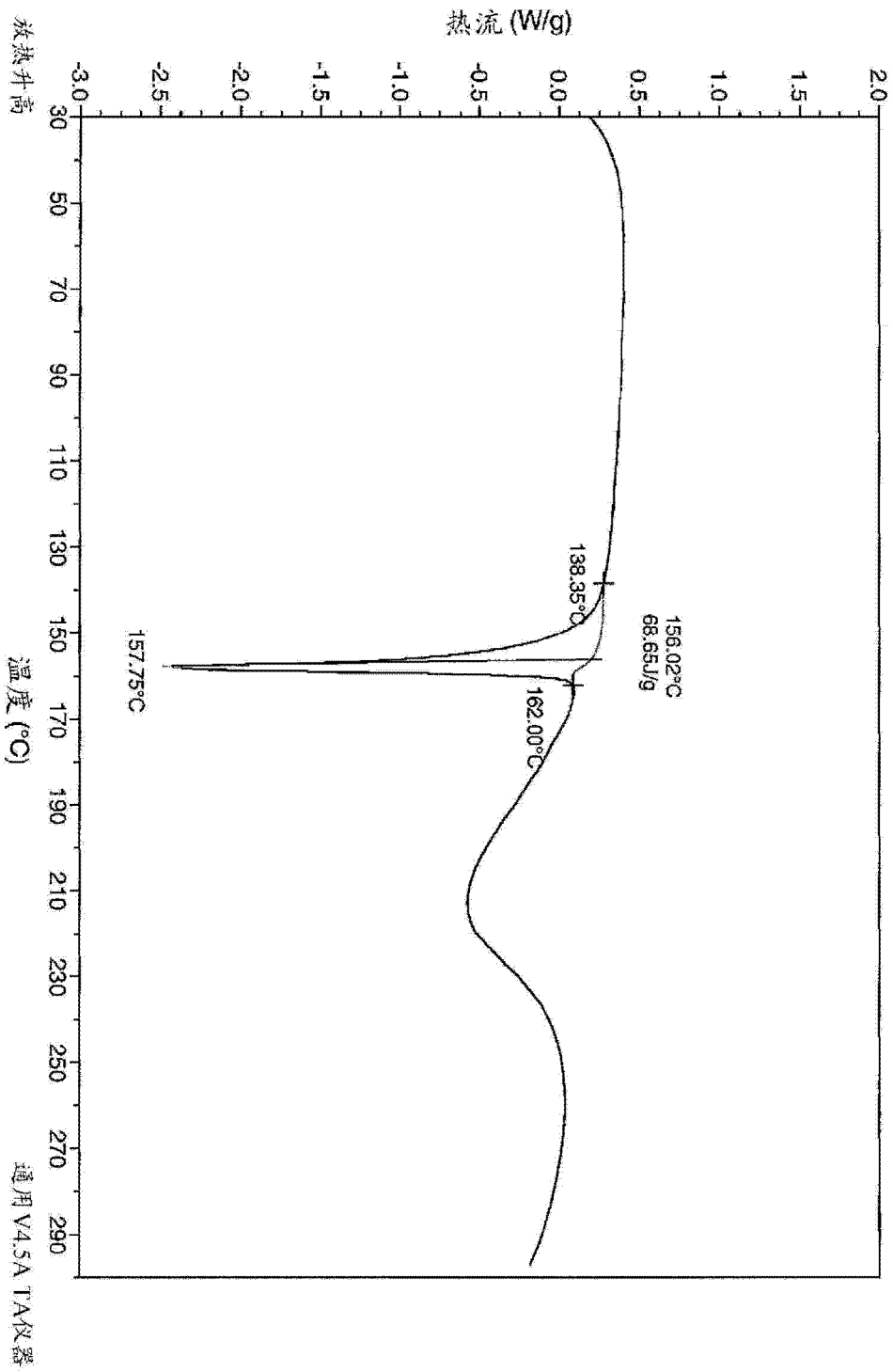


图 2 :式 (I-S) 的化合物的琥珀酸盐的代表性 DSC 扫描

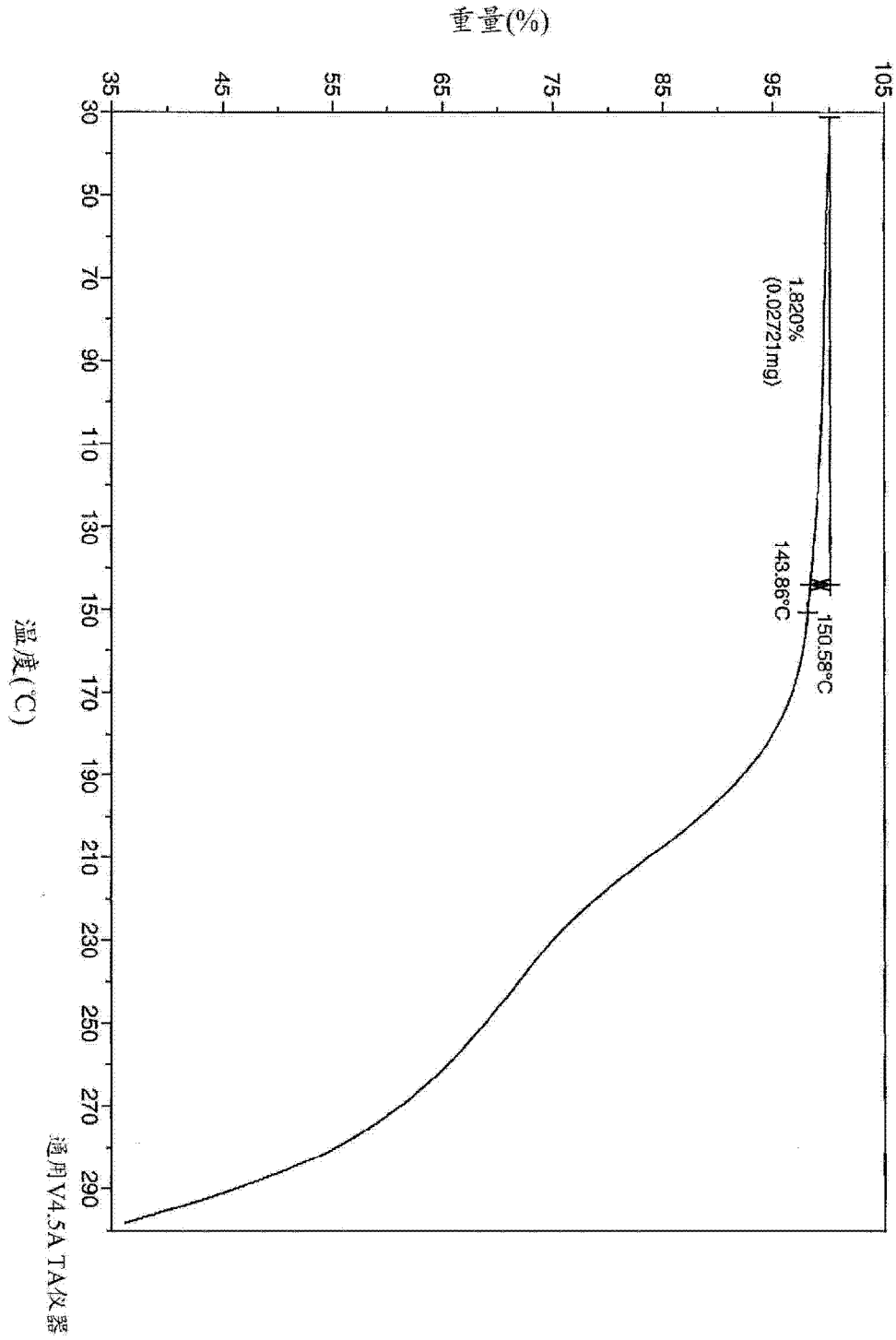


图 3 :式 (I-S) 的化合物的琥珀酸盐的代表性 TGA 扫描

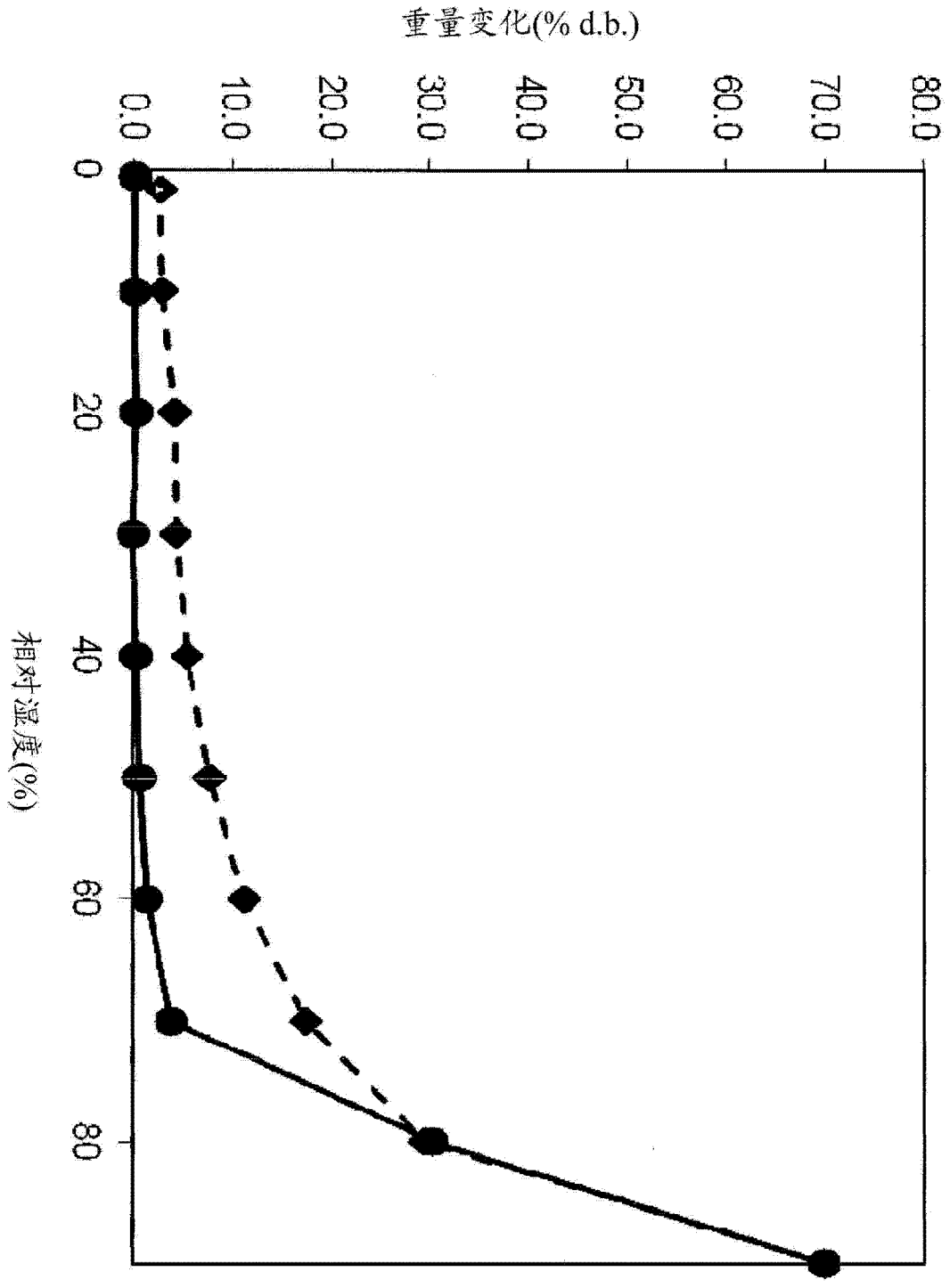


图 4 :式 (1-S) 的化合物的琥珀酸盐的代表性吸湿等温线

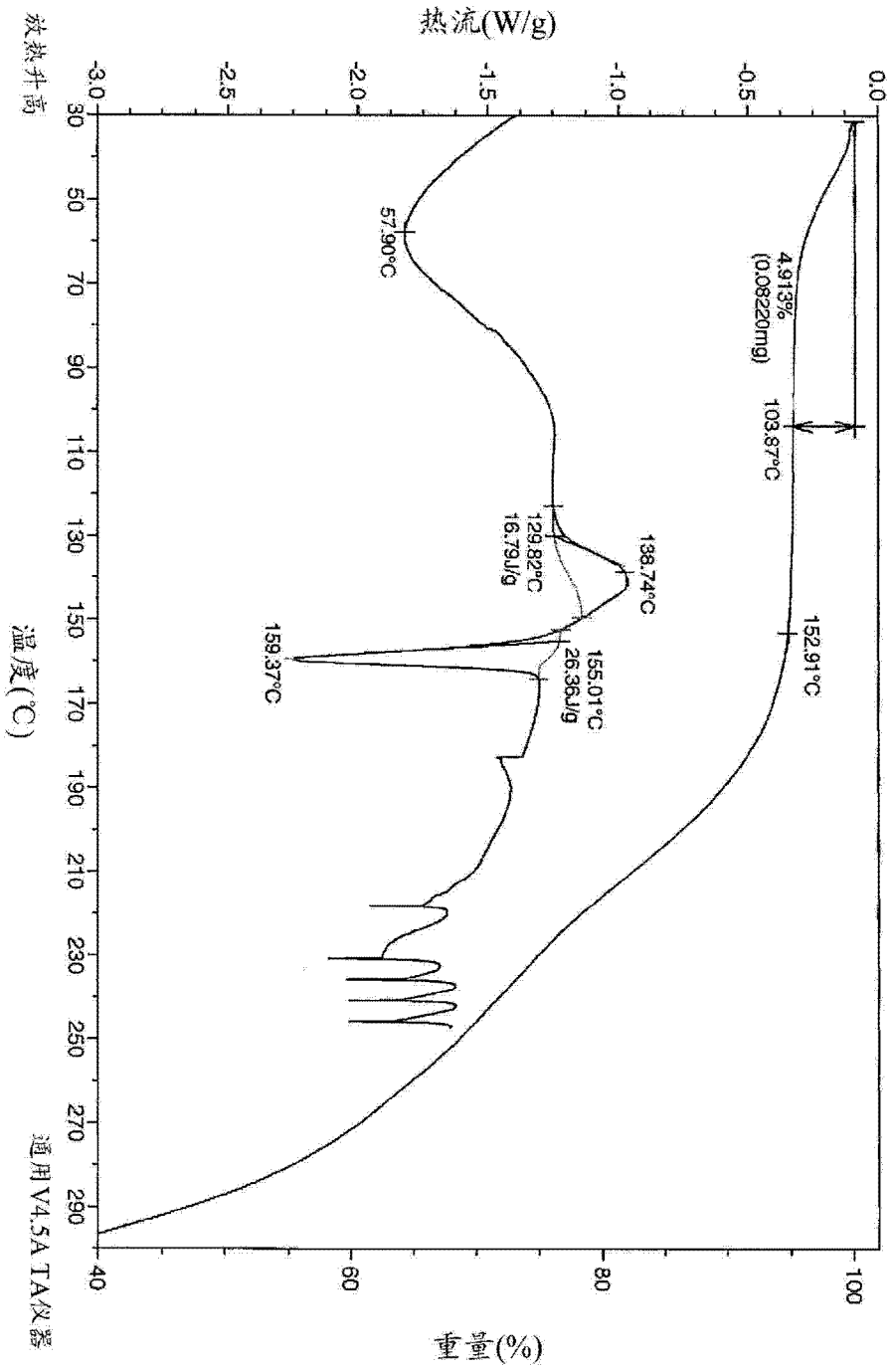


图 5：显示式 (I-S) 的化合物的无定形至结晶琥珀酸盐转换的 DSC 热谱图；和式 (I-S) 的化合物的无定形琥珀酸盐的 TGA 热谱图