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(54) Title: SUBSTITUTED HETEROCYCLIC COMPOUNDS FOR DISEASE TREATMENT

(57) Abstract: The present invention relates generally to compositions and methods for treating neurodegenerative diseases and disorders, particularly ophthalmic diseases and disorders. Provided herein are substituted heterocyclic amine derivative compound and pharmaceutical compositions comprising these compounds. The subject compositions are useful for treating and preventing ophthalmic diseases and disorders, including age-related macular degeneration (AMD) and Stargardt's Disease.

# SUBSTITUTED HETEROCYCLIC COMPOUNDS FOR DISEASE TREATMENT

## CROSS REFERENCE

**[0001]** This application claims the benefit of U.S. Provisional Application No. 61/589,108, filed January 20, 2012, which is incorporated herein by reference in its entirety.

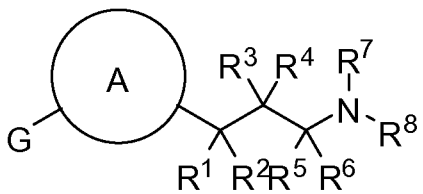
## BACKGROUND

**[0002]** Neurodegenerative diseases, such as glaucoma, macular degeneration, and Alzheimer's disease, affect millions of patients throughout the world. Because the loss of quality of life associated with these diseases is considerable, drug research and development in this area is of great importance. Age-related macular degeneration (AMD) affects between ten and fifteen million patients in the United States, and it is the leading cause of blindness in aging populations worldwide. AMD affects central vision and causes the loss of photoreceptor cells in the central part of retina called the macula. Due to the great unmet medical need of patients suffering from AMD, new treatments are in great demand.

## BRIEF SUMMARY OF THE INVENTION

**[0003]** A need exists in the art for an effective treatment of ophthalmic diseases or disorders resulting in ophthalmic dysfunction including those described above. In particular, there exists a pressing need for compositions and methods for treating Stargardt's disease and age-related macular degeneration (AMD) without causing further unwanted side effects such as progressive retinal degeneration, LCA-like conditions, night blindness, or systemic vitamin A deficiency. A need also exists in the art for effective treatments for other ophthalmic diseases and disorders that adversely affect the retina.

**[0004]** One embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-$C(R^9)_2$-,–O-C(=O)-, –S-$C(R^9)_2$-, –S(O)-$C(R^9)_2$-, –$S(O)_2$-$C(R^9)_2$-, –$SO_2(NR^9)$-, –$NR^9$-$C(R^9)_2$-, –$NR^9$-C(=O)-, –$NR^9$-$S(O)_2$-, –$C(R^9)_2$-$C(R^9)_2$-, –C(=O)-$C(R^9)_2$-, – $C(R^9)_2$-C(=O)-, –$C(R^9)$=$C(R^9)$-, -C ≡ C-, –C(=O)-$N(R^9)$-, –C(=O)-O-, –$C(R^9)_2$-O-, and –$C(R^9)_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

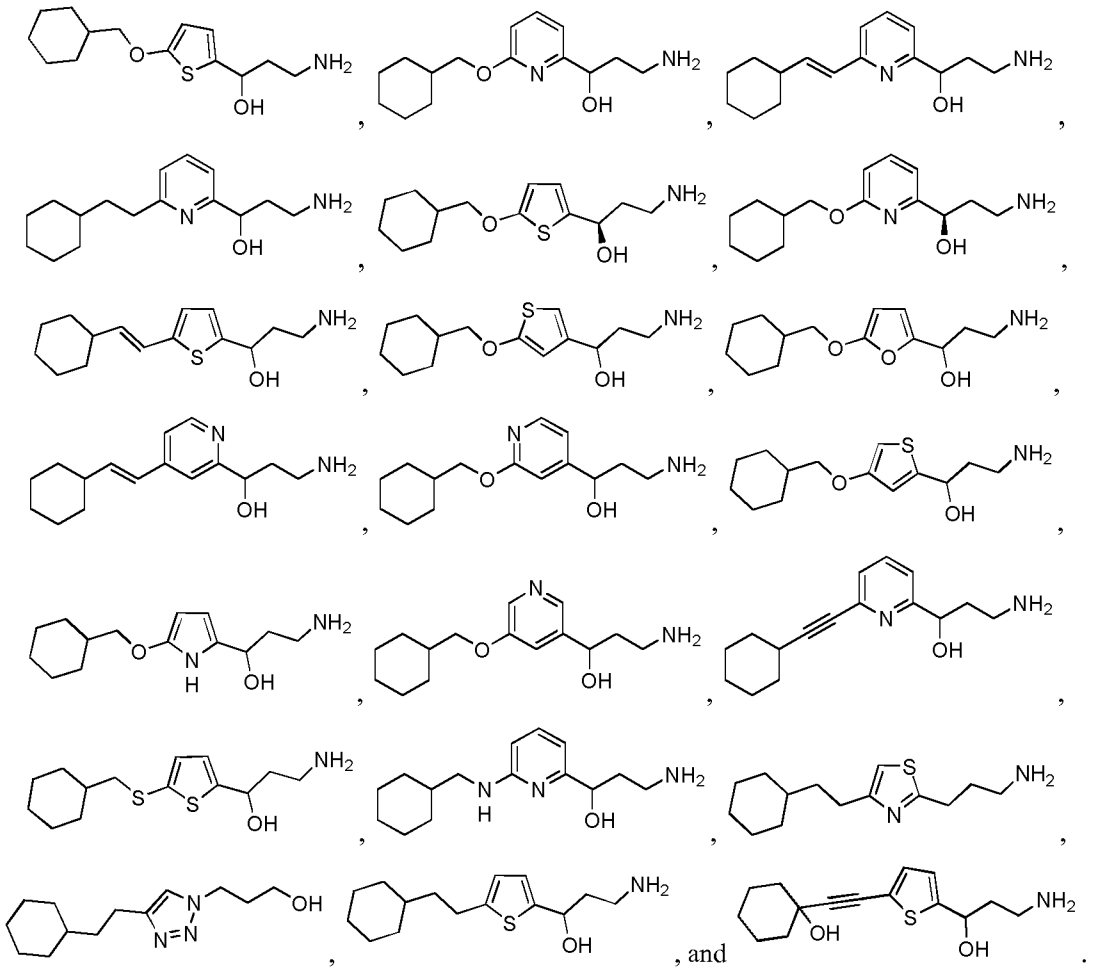
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

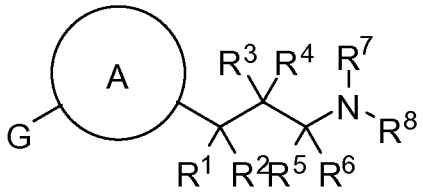
each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0005]** One embodiment provides a compound, or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof, selected from the group consisting of:



**[0006]** One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:



Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

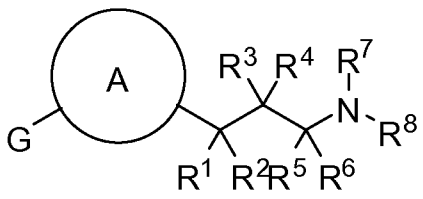
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0007]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

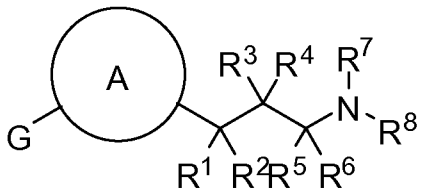
each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0008]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, wherein the ophthalmic disease or disorder is age-related macular degeneration or Stargardt's macular dystrophy.

**[0009]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, wherein the ophthalmic disease or disorder is selected from retinal detachment, hemorrhagic retinopathy, retinitis pigmentosa, cone-rod dystrophy, Sorsby's fundus dystrophy, optic neuropathy, inflammatory retinal disease, diabetic retinopathy,

diabetic maculopathy, retinal blood vessel occlusion, retinopathy of prematurity, or ischemia reperfusion related retinal injury, proliferative vitreoretinopathy, retinal dystrophy, hereditary optic neuropathy, uveitis, a retinal injury, a retinal disorder associated with Alzheimer's disease, a retinal disorder associated with multiple sclerosis, a retinal disorder associated with Parkinson's disease, a retinal disorder associated with viral infection, a retinal disorder related to light overexposure, myopia, and a retinal disorder associated with AIDS.

**[0010]** One embodiment provides a method of modulating chromophore flux in a retinoid cycle comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –SO$_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$

together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

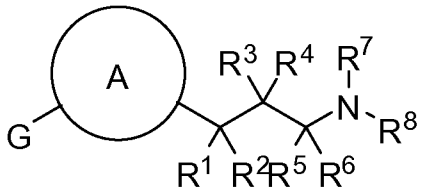
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0011]** One embodiment provides a method of inhibiting dark adaptation of a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -O$R^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

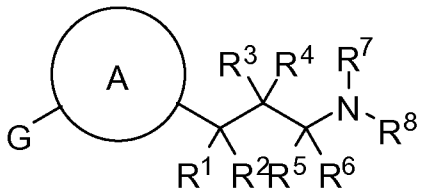
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0012]** One embodiment provides a method of inhibiting regeneration of rhodopsin in a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-$C(R^9)_2$-,–O-C(=O)-, –S-$C(R^9)_2$-, –S(O)-$C(R^9)_2$-, –$S(O)_2$-$C(R^9)_2$-, –$SO_2(NR^9)$-, –$NR^9$-$C(R^9)_2$-, –$NR^9$-C(=O)-, –$NR^9$-$S(O)_2$-, –$C(R^9)_2$-$C(R^9)_2$-, –C(=O)-$C(R^9)_2$-, – $C(R^9)_2$-C(=O)-, –$C(R^9)$=$C(R^9)$-, -C ≡ C-, –C(=O)-$N(R^9)$-, –C(=O)-O-, –$C(R^9)_2$-O-, and –$C(R^9)_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

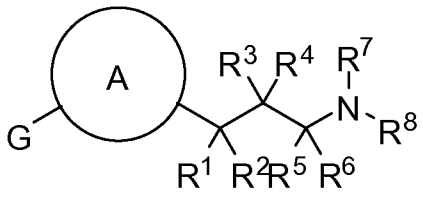
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0013]** One embodiment provides a method of reducing ischemia in an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –

$C(=O)-C(R^9)_2-$, $-C(R^9)_2-C(=O)-$, $-C(R^9)=C(R^9)-$, $-C\equiv C-$, $-C(=O)-N(R^9)-$, $-C(=O)-O-$, $-C(R^9)_2-O-$, and $-C(R^9)_2-NR^9-$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, $-OR^9$, $-NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, $-OR^9$ or $-NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

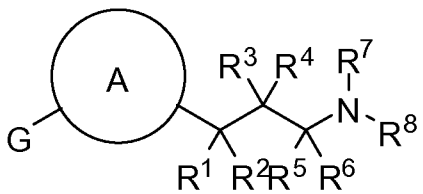
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, $-C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, $-C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0014]** One embodiment provides a method of inhibiting neovascularization in the retina of an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

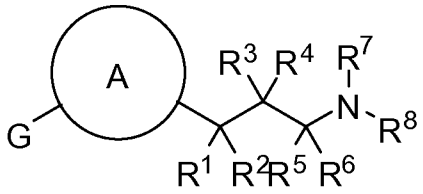
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0015]** One embodiment provides a method of inhibiting degeneration of a retinal cell in a retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:



Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

## INCORPORATION BY REFERENCE

**[0016]** All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

## DETAILED DESCRIPTION OF THE INVENTION

**[0017]** As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

**Definitions**

**[0018]** As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

**[0019]** As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of such compounds, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an

approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may "consist of" or "consist essentially of" the described features.

**[0020]** "Amino" refers to the $-NH_2$ radical.

**[0021]** "Cyano" refers to the -CN radical.

**[0022]** "Nitro" refers to the $-NO_2$ radical.

**[0023]** "Oxa" refers to the -O- radical.

**[0024]** "Oxo" refers to the =O radical.

**[0025]** "Thioxo" refers to the =S radical.

**[0026]** "Imino" refers to the =N-H radical.

**[0027]** "Hydrazino" refers to the $=N-NH_2$ radical.

**[0028]** "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (*e.g.*, $C_1$-$C_{15}$ alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, $C_1$-$C_{13}$ alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, $C_1$-$C_8$ alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, $C_1$-$C_5$ alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, $C_1$-$C_4$ alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, $C_1$-$C_3$ alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, $C_1$-$C_2$ alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, $C_1$ alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, $C_5$-$C_{15}$ alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, $C_5$-$C_8$ alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, $C_2$-$C_5$ alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, $C_3$-$C_5$ alkyl). In other embodiments, the alkyl group is selected from methyl (Me), ethyl (Et), 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*s*-butyl), 2-methylpropyl (*i*-butyl), 1,1-dimethylethyl (*t*-butyl), or *n*-pentyl. The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro,

oxo, thioxo, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2) and -$S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

**[0029]** "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2) and -$S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

**[0030]** "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -$OR^a$, -$SR^a$, -$OC(O)$-$R^a$, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2) and -$S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

**[0031]** "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of

carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments the point of attachment of the alkylene chain to the rest of the molecule and to the radical group is through one carbon in the alkylene chain. In other embodiments the point of attachment of the alkylene chain to the rest of the molecule and to the radical group is through any two carbons within the alkylene chain. Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl.

**[0032]** "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, for example, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a double bond or a single bond and to the radical group through a double bond or a single bond. In some embodiments, the point of attachment of the alkenylene chain to the rest of the molecule and to the radical group is through one carbon. In other embodiments, the point of attachment of the alkenylene chain to the rest of the molecule and to the radical group is through any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, and where each of the above substituents is unsubstituted unless otherwise indicated.

**[0033]** "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from six to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Aryl groups include, but are not limited to, groups such as phenyl, fluorenyl, and naphthyl. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

**[0034]** "Aralkyl" refers to a radical of the formula $-R^c$-aryl where $R^c$ is an alkylene chain as defined above, for example, benzyl, diphenylmethyl and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

**[0035]** "Aralkenyl" refers to a radical of the formula $–R^d$-aryl where $R^d$ is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

**[0036]** "Aralkynyl" refers to a radical of the formula $-R^e$-aryl, where $R^e$ is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally

substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

**[0037]** "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. Carbocyclyl are saturated, (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds). A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-SR^a$, $-R^b-OC(O)-R^a$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

**[0038]** "Carbocyclylalkyl" refers to a radical of the formula $-R^c$-carbocyclyl where $R^c$ is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

**[0039]** "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

**[0040]** "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

**[0041]** "Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, including fused or bridged ring systems. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. The heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-SR^a$, $-R^b-OC(O)-R^a$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or

branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

**[0042]** "*N*-heterocyclyl" or "N-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. An *N*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *N*-heterocyclyl radicals include, but are not limited to, 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl, pyrazolidinyl, imidazolinyl, and imidazolidinyl.

**[0043]** "*C*-heterocyclyl" or "C-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one heteroatom and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a carbon atom in the heterocyclyl radical. A *C*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *C*-heterocyclyl radicals include, but are not limited to, 2-morpholinyl, 2- or 3- or 4-piperidinyl, 2-piperazinyl, 2- or 3-pyrrolidinyl, and the like.

**[0044]** "Heterocyclylalkyl" refers to a radical of the formula $-R^c$-heterocyclyl where $R^c$ is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

**[0045]** "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl,

benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl,isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-SR^a$, $-R^b-OC(O)-R^a$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2)

and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each $R^a$ is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl, each $R^b$ is independently a direct bond or a straight or branched alkylene or alkenylene chain, and $R^c$ is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

**[0046]** "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

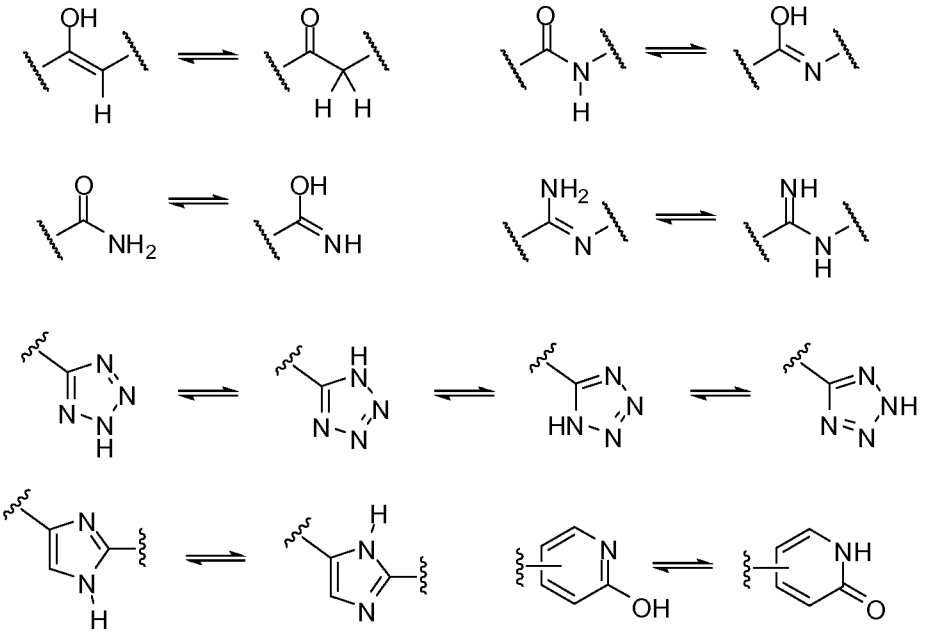
**[0047]** "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

**[0048]** "Heteroarylalkyl" refers to a radical of the formula $-R^c$-heteroaryl, where $R^c$ is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

**[0049]** The compounds, or their pharmaceutically acceptable salts, in some embodiments, contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers (*e.g., cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included.

**[0050]** A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. It is therefore contemplated that various stereoisomers and mixtures thereof and includes "enantiomers," which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

**[0051]** The compounds presented herein, in some embodiments, exist as tautomers. A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule, accompanied by an isomerization of an adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Some examples of tautomeric interconversions include:



**[0052]** "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

**[0053]** "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the substituted heterocyclic amine derivative compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

**[0054]** "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric

acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and. aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997), which is hereby incorporated by reference in its entirety). Acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

**[0055]** "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine,

methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

**[0056]** "Non-retinoid compound" refers to any compound that is not a retinoid. A retinoid is a compound that has a diterpene skeleton possessing a trimethylcyclohexenyl ring and a polyene chain that terminates in a polar end group. Examples of retinoids include retinaldehyde and derived imine/hydrazide/oxime, retinol and any derived ester, retinyl amine and any derived amide, retinoic acid and any derived ester or amide. In some embodiments, a non-retinoid compound optionally comprises an internal cyclic group (e.g., aromatic group).

**[0057]** As used herein, "treatment" or "treating," or "palliating" or "ameliorating" are used interchangeably herein. These terms refers to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

**[0058]** "Prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

**[0059]** A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

**[0060]** The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a

mammalian subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

**[0061]** Age-related macular degeneration (AMD) affects between ten and fifteen million patients in the United States, and it is the leading cause of blindness in aging populations worldwide. AMD affects central vision and causes the loss of photoreceptor cells in the central part of retina called the macula. Macular degeneration can be classified into two types: dry-form and wet-form. The dry-form is more common than the wet; about 90% of age-related macular degeneration patients are diagnosed with the dry-form. The wet-form of the disease and geographic atrophy, which is the end-stage phenotype of dry-form AMD, causes the most serious vision loss. All patients who develop wet-form AMD are believed to previously have developed dry-form AMD for a prolonged period of time. The exact causes of AMD are still unknown. The dry-form of AMD may result from the senescence and thinning of macular tissues associated with the deposition of pigment in the macular retinal pigment epithelium. In wet-form AMD, new blood vessels grow beneath the retina, form scar tissue, bleed, and leak fluid. The overlying retina can be severely damaged, creating "blind" areas in the central vision.

**[0062]** For the vast majority of patients who have the dry-form of AMD, no effective treatment is yet available. Because the dry-form of AMD precedes development of the wet-form of AMD, therapeutic intervention to prevent or delay disease progression in the dry-form AMD would benefit patients with dry-form of AMD and might reduce the incidence of the wet-form of AMD.

**[0063]** Decline of vision noticed by the patient or characteristic features detected by an ophthalmologist during a routine eye exam may be the first indicator of AMD. The formation of "drusen," or membranous debris beneath the retinal pigment epithelium of the macula is often the first physical sign that AMD is developing. Late symptoms include the perceived distortion of straight lines and, in advanced cases, a dark, blurry

area or area with absent vision appears in the center of vision; and/or there may be color perception changes.

**[0064]** Different forms of genetically-linked macular degenerations may also occur in younger patients. In other maculopathies, factors in the disease are heredity, nutritional, traumatic, infection, or other ecologic factors.

**[0065]** Glaucoma is a broad term used to describe a group of diseases that causes a slowly progressive visual field loss, usually asymptomatically. The lack of symptoms may lead to a delayed diagnosis of glaucoma until the terminal stages of the disease. The prevalence of glaucoma is estimated to be 2.2 million in the United States, with about 120,000 cases of blindness attributable to the condition. The disease is particularly prevalent in Japan, which has four million reported cases. In many parts of the world, treatment is less accessible than in the United States and Japan, thus glaucoma ranks as a leading cause of blindness worldwide. Even if subjects afflicted with glaucoma do not become blind, their vision is often severely impaired.

**[0066]** The progressive loss of peripheral visual field in glaucoma is caused by the death of ganglion cells in the retina. Ganglion cells are a specific type of projection neuron that connects the eye to the brain. Glaucoma is usually accompanied by an increase in intraocular pressure. Current treatment includes use of drugs that lower the intraocular pressure; however, contemporary methods to lower the intraocular pressure are often insufficient to completely stop disease progression. Ganglion cells are believed to be susceptible to pressure and may suffer permanent degeneration prior to the lowering of intraocular pressure. An increasing number of cases of normal-tension glaucoma are observed in which ganglion cells degenerate without an observed increase in the intraocular pressure. Current glaucoma drugs only treat intraocular pressure and are ineffective in preventing or reversing the degeneration of ganglion cells.

**[0067]** Recent reports suggest that glaucoma is a neurodegenerative disease, similar to Alzheimer's disease and Parkinson's disease in the brain, except that it specifically affects retinal neurons. The retinal neurons of the eye originate from diencephalon neurons of the brain. Though retinal neurons are often mistakenly thought not to be part of the brain, retinal cells are key components of the central nervous system, interpreting the signals from the light-sensing cells.

**[0068]** Alzheimer's disease (AD) is the most common form of dementia among the elderly. Dementia is a brain disorder that seriously affects a person's ability to carry out daily activities. Alzheimer's is a disease that affects four million people in the United

States alone. It is characterized by a loss of nerve cells in areas of the brain that are vital to memory and other mental functions. Currently available drugs can ameliorate AD symptoms for a relatively finite period of time, but no drugs are available that treat the disease or completely stop the progressive decline in mental function. Recent research suggests that glial cells that support the neurons or nerve cells may have defects in AD sufferers, but the cause of AD remains unknown. Individuals with AD seem to have a higher incidence of glaucoma and age-related macular degeneration, indicating that similar pathogenesis may underlie these neurodegenerative diseases of the eye and brain. (*See* Giasson et al., *Free Radic. Biol. Med.* 32:1264-75 (2002); Johnson et al., *Proc. Natl. Acad. Sci. USA* 99:11830-35 (2002); Dentchev et al., *Mol. Vis.* 9:184-90 (2003)).

**[0069]** Neuronal cell death underlies the pathology of these diseases. Unfortunately, very few compositions and methods that enhance retinal neuronal cell survival, particularly photoreceptor cell survival, have been discovered. A need therefore exists to identify and develop compositions that can be used for treatment and prophylaxis of a number of retinal diseases and disorders that have neuronal cell death as a primary, or associated, element in their pathogenesis.

**[0070]** In vertebrate photoreceptor cells, the irradiance of a photon causes isomerization of 11-*cis*-retinylidene chromophore to all-*trans*-retinylidene and uncoupling from the visual opsin receptors. This photoisomerization triggers conformational changes of opsins, which, in turn, initiate the biochemical chain of reactions termed phototransduction (Filipek et al., *Annu. Rev. Physiol.* 65:851-79 (2003)). Regeneration of the visual pigments requires that the chromophore be converted back to the 11-*cis*-configuration in the processes collectively called the retinoid (visual) cycle (*see, e.g.,* McBee et al., *Prog. Retin. Eye Res.* 20:469-52 (2001)). First, the chromophore is released from the opsin and reduced in the photoreceptor by retinol dehydrogenases. The product, all-*trans*-retinol, is trapped in the adjacent retinal pigment epithelium (RPE) in the form of insoluble fatty acid esters in subcellular structures known as retinosomes (Imanishi et al., *J. Cell Biol.* 164:373-87 (2004)).

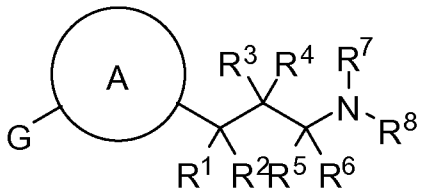
**[0071]** In Stargardt's disease (Allikmets et al., *Nat. Genet.* 15:236-46 (1997)), a disease associated with mutations in the ABCR transporter that acts as a flippase, the accumulation of all-*trans*-retinal may be responsible for the formation of a lipofuscin pigment, A2E, which is toxic towards retinal pigment epithelial cells and causes progressive retinal degeneration and, consequently, loss of vision (Mata et al., *Proc. Natl. Acad. Sci. USA* 97:7154-59 (2000); Weng et al., *Cell* 98:13-23 (1999)). Treating

patients with an inhibitor of retinol dehydrogenases, 13-*cis*-RA (Isotretinoin, Accutane®, Roche), has been considered as a therapy that might prevent or slow the formation of A2E and might have protective properties to maintain normal vision (Radu et al., *Proc. Natl. Acad. Sci. USA* 100:4742-47 (2003)). 13-*cis*-RA has been used to slow the synthesis of 11-*cis*-retinal by inhibiting 11-*cis*-RDH (Law et al., *Biochem. Biophys. Res. Commun.* 161:825-9 (1989)), but its use can also be associated with significant night blindness. Others have proposed that 13-*cis*-RA works to prevent chromophore regeneration by binding RPE65, a protein essential for the isomerization process in the eye (Gollapalli et al., *Proc. Natl. Acad. Sci. USA* 101:10030-35 (2004)). Gollapalli et al. reported that 13-*cis*-RA blocked the formation of A2E and suggested that this treatment may inhibit lipofuscin accumulation and, thus, delay either the onset of visual loss in Stargardt's disease or age-related macular degeneration, which are both associated with retinal pigment-associated lipofuscin accumulation. However, blocking the retinoid cycle and forming unliganded opsin may result in more severe consequences and worsening of the patient's prognosis (*see, e.g.,* Van Hooser et al., *J. Biol. Chem.* 277:19173-82 (2002); Woodruff et al., *Nat. Genet.* 35:158-164 (2003)). Failure of the chromophore to form may lead to progressive retinal degeneration and may produce a phenotype similar to Leber Congenital Amaurosis (LCA), which is a very rare genetic condition affecting children shortly after birth.

**Substituted Heterocyclic Amine Derivative Compounds**

**[0072]** Substituted heterocyclic amine derivative compounds are described herein that inhibit an isomerization step of the retinoid cycle. These compounds, and compositions comprising these compounds, are useful for inhibiting degeneration of retinal cells or for enhancing retinal cell survival. The compounds described herein are, therefore, useful for treating ophthalmic diseases and disorders, including retinal diseases or disorders, such as age related macular degeneration and Stargardt's disease.

**[0073]** One embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$-;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

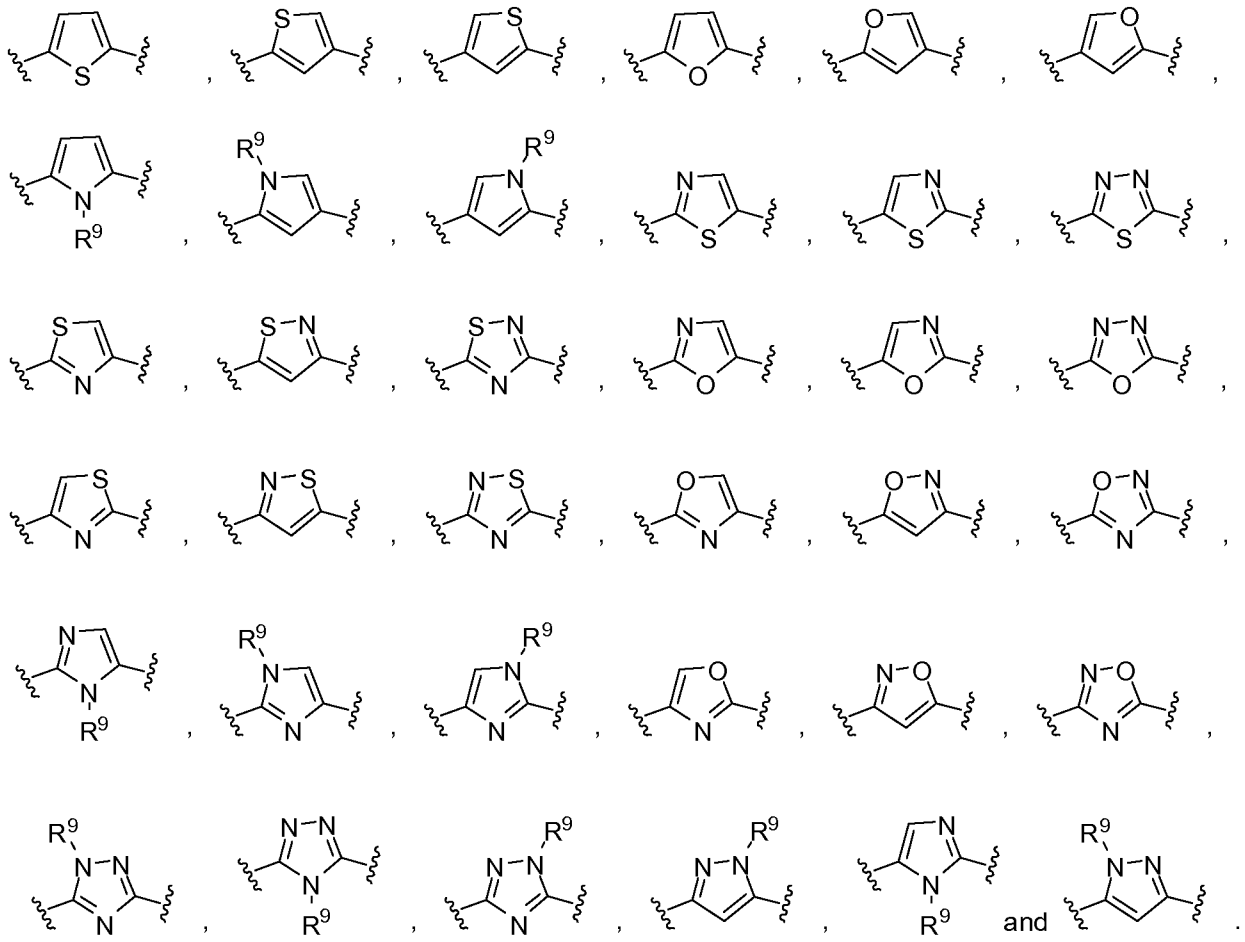
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

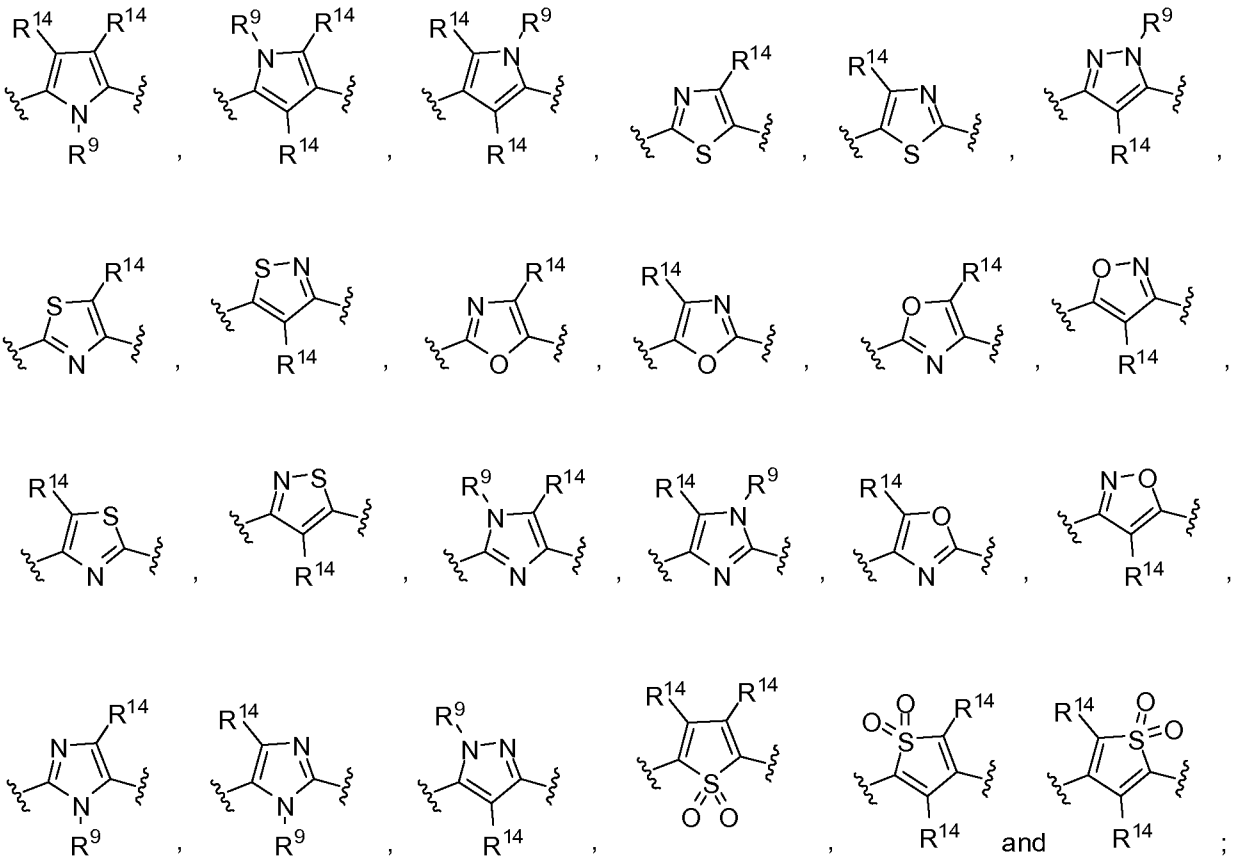
each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[0074]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

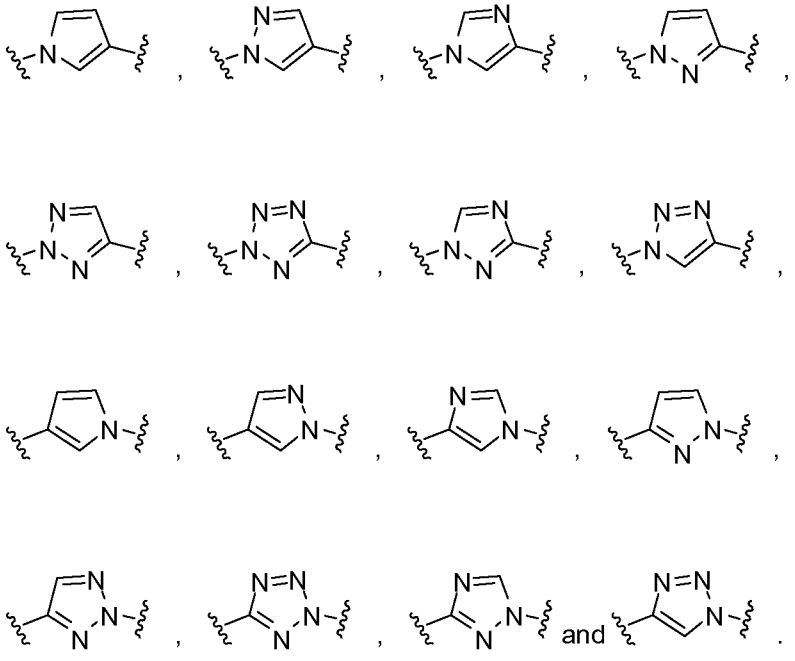


**[0075]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

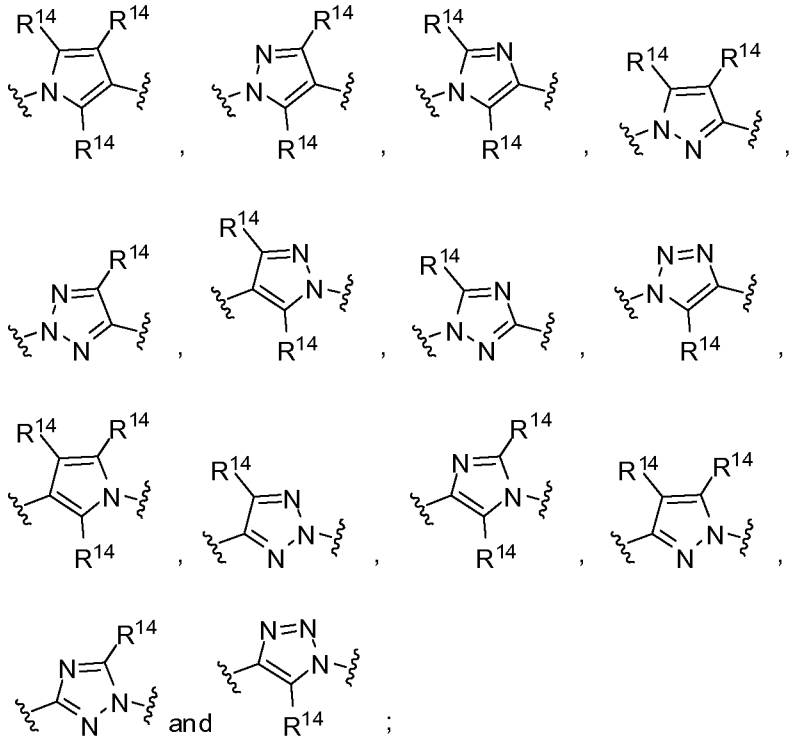


and each $R^{14}$ is independently selected from hydrogen, halogen, $OR^9$, alkyl, or fluoroalkyl.

**[0076]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

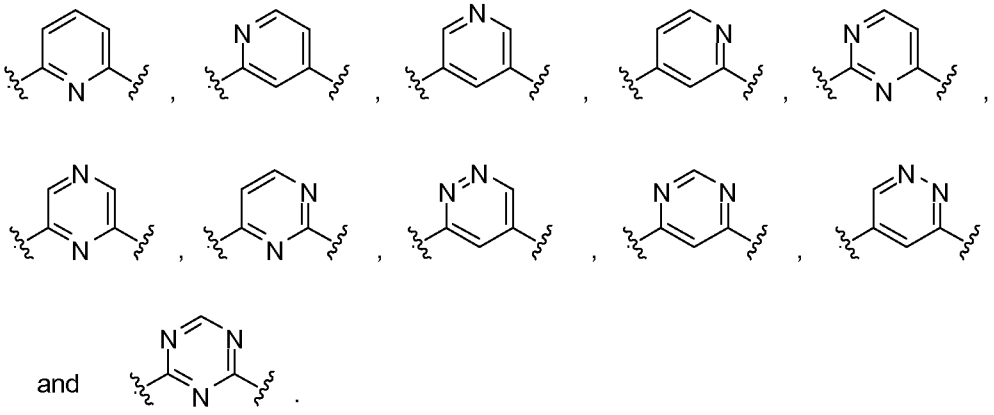


**[0077]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

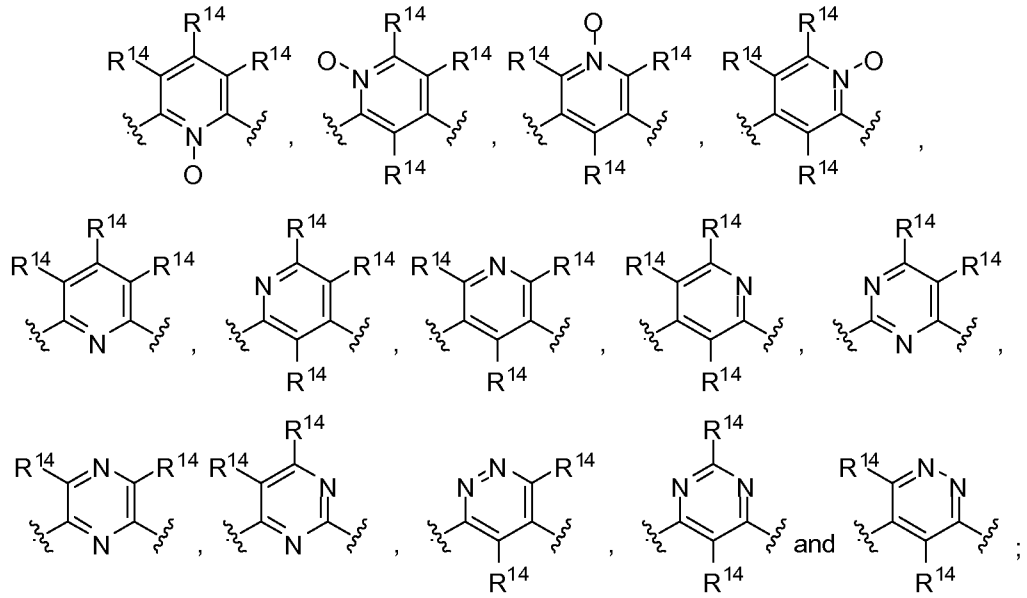


and each $R^{14}$ is independently selected from hydrogen, halogen, $OR^9$, alkyl, or fluoroalkyl.

**[0078]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

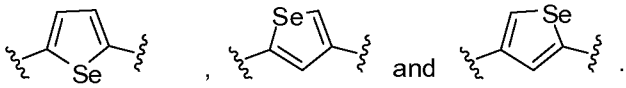


**[0079]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

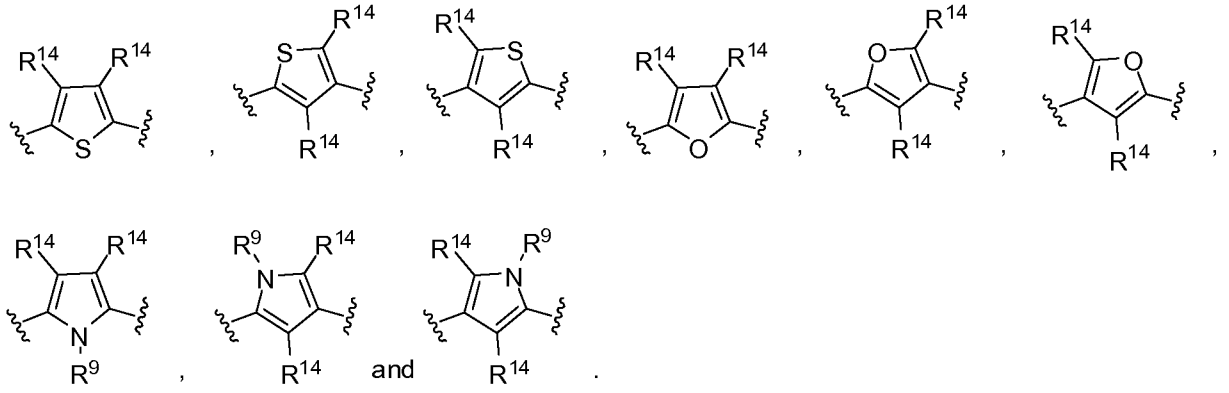


and each $R^{14}$ is independently selected from hydrogen, halogen, $OR^9$, alkyl, or fluoroalkyl.

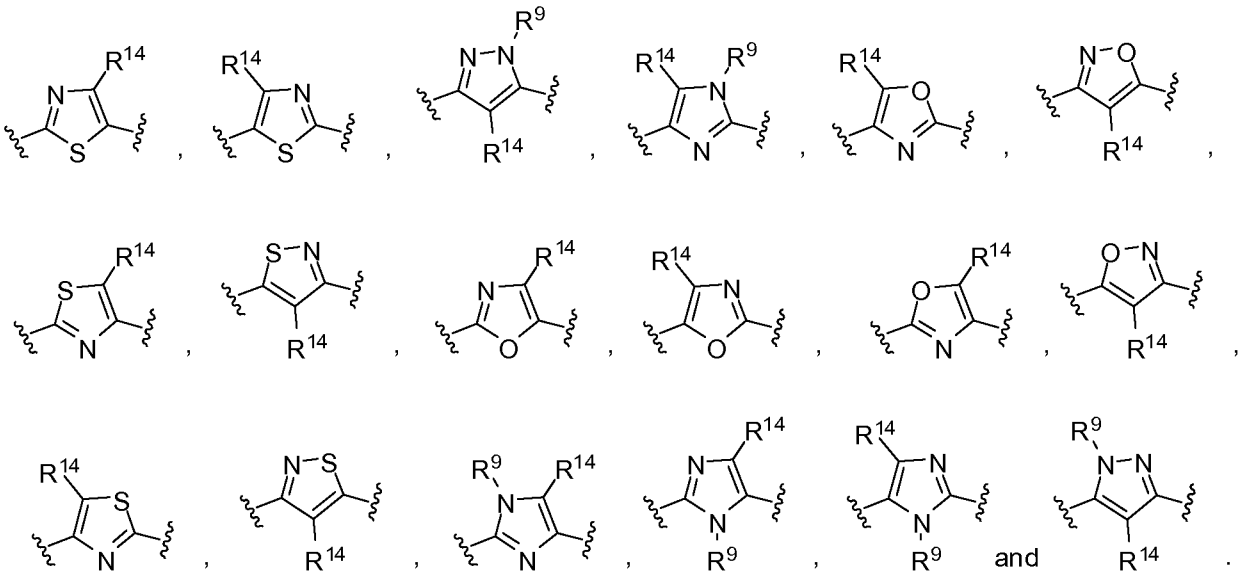
**[0080]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



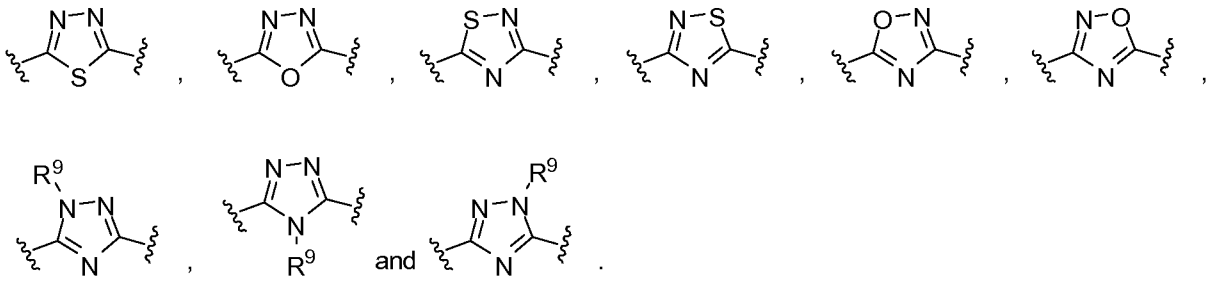
**[0081]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



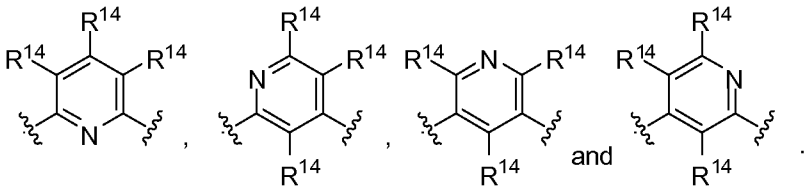
**[0082]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



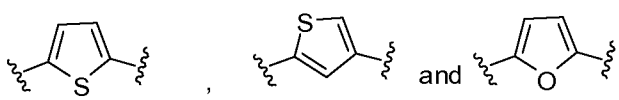
**[0083]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



**[0084]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof,wherein Ring A is selected from:

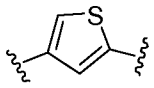


**[0085]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

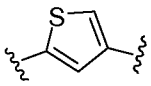


**[0086]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a

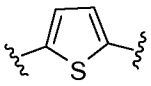
compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



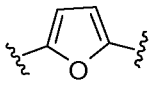
**[0087]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



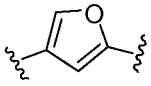
**[0088]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



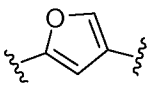
**[0089]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



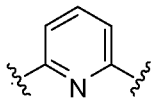
**[0090]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



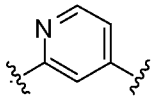
**[0091]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



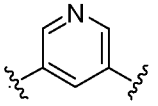
**[0092]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



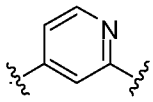
**[0093]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



**[0094]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



**[0095]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



**[0096]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is alkyl, carbocyclyl or heterocyclyl.

**[0097]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is alkyl, carbocyclyl or heterocyclyl.

**[0098]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl; and

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl.

**[0099]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^{16}$ and $R^{17}$, together with the carbon to which they are attached, form a carbocyclyl or heterocyclyl.

**[00100]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^{16}$ and $R^{17}$, together with the carbon to which they are attached, form a cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and $R^{18}$ is hydrogen or hydroxy.

**[00101]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^{16}$ and $R^{17}$, together with the carbon to which they are attached, form a cyclopentyl, cyclohexyl, or cycloheptyl, and $R^{18}$ is hydrogen or hydroxy.

**[00102]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^{16}$ and $R^{17}$ is independently selected from $C_1$-$C_{13}$ alkyl; and $R^{18}$ is hydrogen, hydroxy or alkoxy.

**[00103]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from $-O-C(R^9)_2-$, $-S(O)_2-C(R^9)_2-$, $-SO_2(NR^9)-$, $-NR^9-C(R^9)_2-$, $-NR^9-C(=O)-$, and $-NR^9-S(O)_2-$.

**[00104]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from $-C(R^9)_2-C(R^9)_2-$, $-C(R^9)=C(R^9)-$, $-C\equiv C-$, $-C(=O)-N(R^9)-$, $-C(R^9)_2-O-$, and $-C(R^9)_2-NR^9-$.

**[00105]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$.

**[00106]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is $-C(R^9)_2-C(R^9)_2-$.

**[00107]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is $-O-C(R^9)_2-$.

**[00108]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^3$ and $R^4$ are both hydrogen.

**[00109]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^5$ and $R^6$ are both hydrogen.

**[00110]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen.

**[00111]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ are both hydrogen.

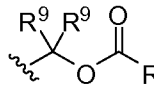
**[00112]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ is hydrogen and $R^2$ is -OH.

**[00113]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ together form an oxo.

**[00114]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^7$ and $R^8$ are both hydrogen.

**[00115]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^7$ is hydrogen and $R^8$ is $-C(=O)R^{13}$ or $CO_2R^{13}$.

**[00116]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^{13}$ is an alkyl.

**[00117]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^8$ is $CO_2R^{13}$ and $R^{13}$ is  .

**[00118]** Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

**[00119]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein

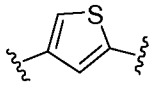
Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O\text{-}C(R^9)_2$-,or $-C(R^9)_2\text{-}C(R^9)_2-$; and

ring A is:



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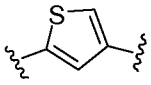
**[00120]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O\text{-}C(R^9)_2$-,or $-C(R^9)_2\text{-}C(R^9)_2-$; and

ring A is:



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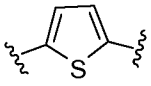
**[00121]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O\text{-}C(R^9)_2$-,or $-C(R^9)_2\text{-}C(R^9)_2-$; and

ring A is:

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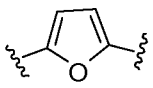
**[00122]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O\text{-}C(R^9)_2$-,or $-C(R^9)_2\text{-}C(R^9)_2-$; and

ring A is:

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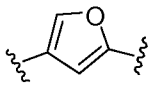
**[00123]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O\text{-}C(R^9)_2$-,or $-C(R^9)_2\text{-}C(R^9)_2-$; and

ring A is:



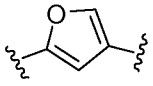
**[00124]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



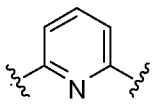
**[00125]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



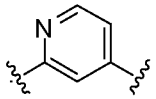
**[00126]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



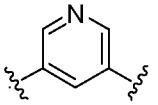
**[00127]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



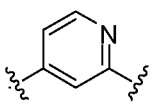
**[00128]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



**[00129]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

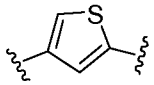
Y is $–C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $–O\text{-}C(R^9)_2$-,or $–C(R^9)_2\text{-}C(R^9)_2–$; and

ring A is:



**[00130]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

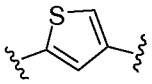
Y is $–C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $–O\text{-}C(R^9)_2$-,or $–C(R^9)_2\text{-}C(R^9)_2–$; and

ring A is:



**[00131]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

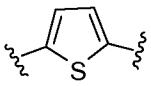
Y is $–C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



**[00132]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

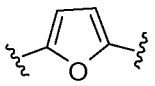
Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



**[00133]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

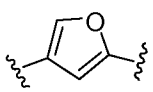
Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $-O-C(R^9)_2-$,or $-C(R^9)_2-C(R^9)_2-$; and

ring A is:



**[00134]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

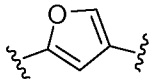
Y is $–C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $–O\text{-}C(R^9)_2$-,or $–C(R^9)_2\text{-}C(R^9)_2–$; and

ring A is:



**[00135]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

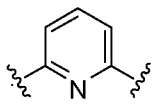
Y is $–C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from $–O\text{-}C(R^9)_2$-,or $–C(R^9)_2\text{-}C(R^9)_2–$; and

ring A is:



**[00136]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

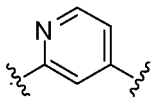
Y is $–C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from –O-C($R^9$)$_2$-,or –C($R^9$)$_2$-C($R^9$)$_2$–; and

ring A is:



**[00137]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

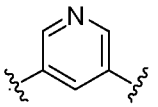
Y is –C($R^{16}$)($R^{17}$)($R^{18}$);

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from –O-C($R^9$)$_2$-,or –C($R^9$)$_2$-C($R^9$)$_2$–; and

ring A is:



**[00138]** Another embodiment provides a compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein,

$R^1$ is hydrogen, $R^2$ is –OH, $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen;

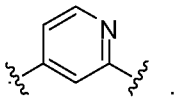
Y is –C($R^{16}$)($R^{17}$)($R^{18}$);

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl;

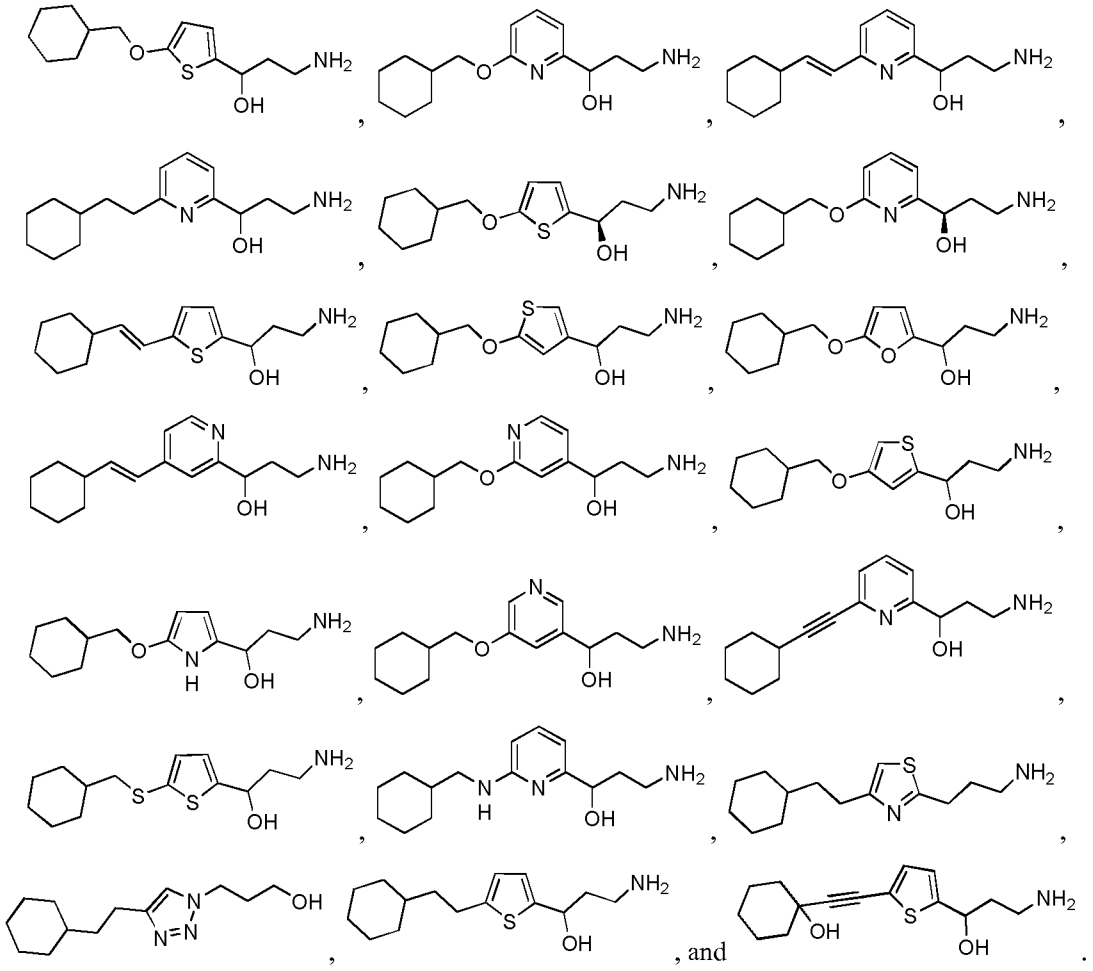
$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl;

X is selected from –O-C($R^9$)$_2$-,or –C($R^9$)$_2$-C($R^9$)$_2$–; and

ring A is:



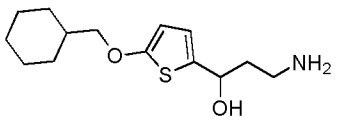
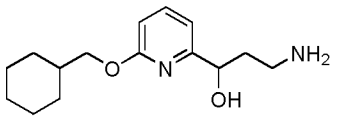
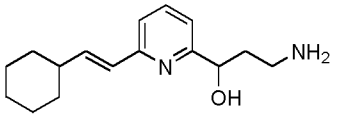
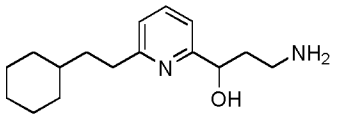
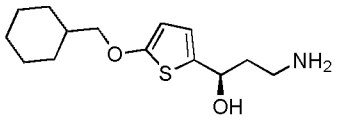
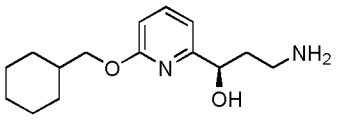
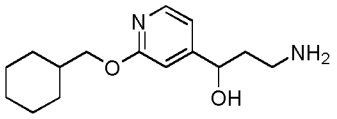
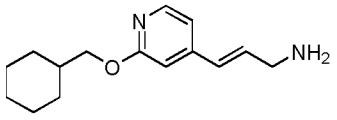
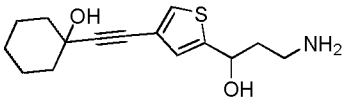
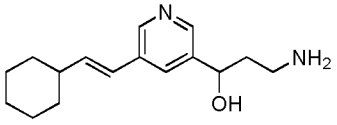
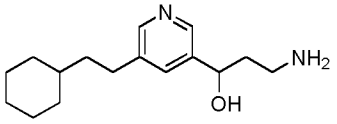
**[00139]** One embodiment provides a compound, or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof, selected from the group consisting of:

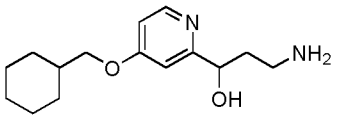
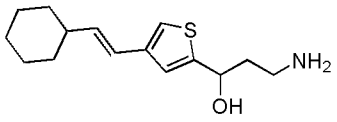
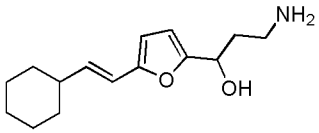
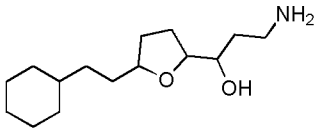
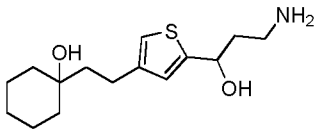
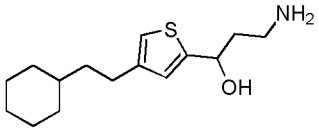
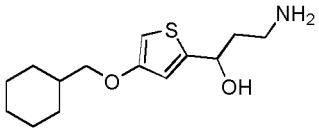
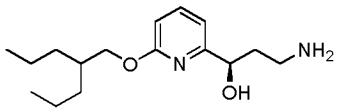
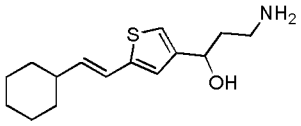
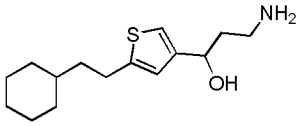
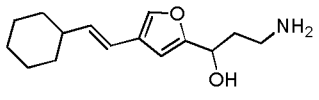


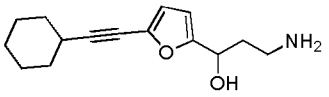
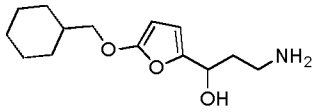
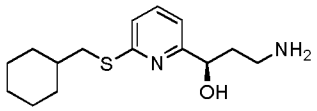
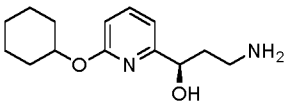
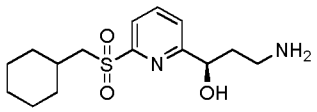
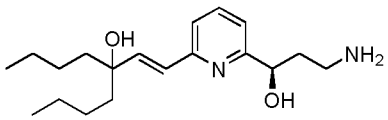
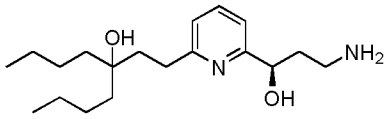
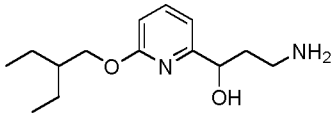
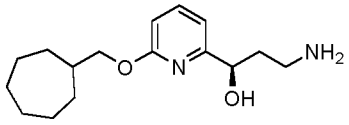
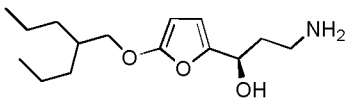
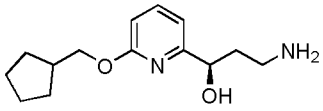
**[00140]** In some embodiments the compounds of Formula (A) disclosed herein have the structure provided in Table 1A.

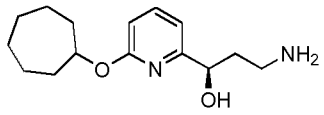
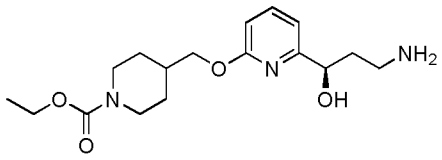
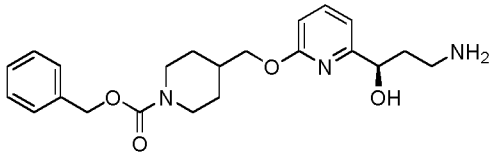
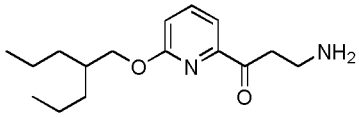
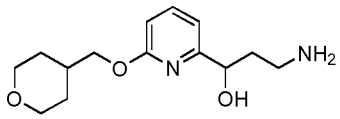
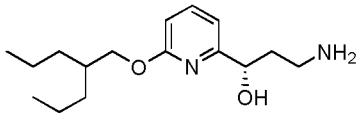
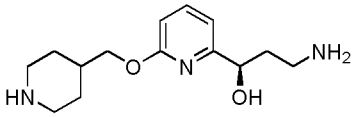
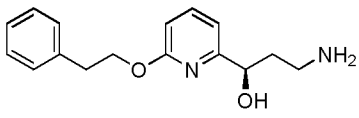
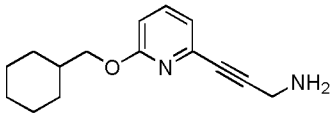
**TABLE 1A**

| Synthesis Example | Structure | Name |
|---|---|---|

| | | |
|---|---|---|
| 1 |  | 3-Amino-1-(5-(cyclohexylmethoxy)-thiophen-2-yl)propan-1-ol |
| 2 |  | 3-Amino-1-(6-(cyclohexylmethoxy)-pyridin-2-yl)propan-1-ol |
| 3 |  | (*E*)-3-Amino-1-(6-(2-cyclohexylvinyl)pyridin-2-yl)propan-1-ol |
| 4 |  | 3-Amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol |
| 5 |  | (*R*)-3-Amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol |
| 6 |  | (*R*)-3-Amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol |
| 7 |  | 3-Amino-1-(2-(cyclohexylmethoxy)pyridin-4-yl)propan-1-ol |
| 8 |  | (*E*)-3-(2-(Cyclohexylmethoxy)pyridin-4-yl)prop-2-en-1-amine |
| 9 |  | 1-((5-(3-Amino-1-hydroxypropyl)thiophen-3-yl)ethynyl)cyclohexanol |
| 10 |  | (*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)pyridin-3-yl)propan-1-ol |
| 11 |  | 3-Amino-1-(5-(2-cyclohexylethyl)pyridin-3-yl)propan-1-ol |

| | | |
|---|---|---|
| 12 |  | 3-Amino-1-(4-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol |
| 13 |  | (*E*)-3-Amino-1-(4-(2-cyclohexylvinyl)thiophen-2-yl)propan-1-ol |
| 14 |  | (E)-3-Amino-1-(5-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol |
| 15 |  | 3-Amino-1-(5-(2-cyclohexylethyl)tetrahydrofuran-2-yl)propan-1-ol |
| 16 |  | 1-(2-(5-(3-Amino-1-hydroxypropyl)thiophen-3-yl)ethyl)cyclohexanol |
| 17 |  | 3-Amino-1-(4-(2-cyclohexylethyl)thiophen-2-yl)propan-1-ol |
| 18 |  | 3-Amino-1-(4-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol |
| 19 |  | (*R*)-3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol |
| 20 |  | (*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)thiophen-3-yl)propan-1-ol |
| 21 |  | 3-Amino-1-(5-(2-cyclohexylethyl)thiophen-3-yl)propan-1-ol |
| 22 |  | (*E*)-3-Amino-1-(4-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol |

| | | |
|---|---|---|
| 23 |  | 3-Amino-1-(5-(cyclohexylethynyl)furan-2-yl)propan-1-ol |
| 24 |  | 3-Amino-1-(5-(cyclohexylmethoxy)furan-2-yl)propan-1-ol |
| 25 |  | (*R*)-3-Amino-1-(6-((cyclohexylmethyl)thio)pyridin-2-yl)propan-1-ol |
| 26 |  | (*R*)-3-Amino-1-(6-(cyclohexyloxy)pyridin-2-yl)propan-1-ol |
| 27 |  | (*R*)-3-Amino-1-(6-((cyclohexylmethyl)sulfonyl)pyridin-2-yl)propan-1-ol |
| 28 |  | (*R*,*E*)-5-(2-(6-(3-Amino-1-hydroxypropyl)pyridin-2-yl)vinyl)nonan-5-ol |
| 29 |  | (*R*)-5-(2-(6-(3-Amino-1-hydroxypropyl)pyridin-2-yl)ethyl)nonan-5-ol |
| 30 |  | 3-Amino-1-(6-(2-ethylbutoxy)pyridin-2-yl)propan-1-ol |
| 31 |  | (*R*)-3-Amino-1-(6-(cycloheptylmethoxy)pyridin-2-yl)propan-1-ol |
| 32 |  | (*R*)-3-Amino-1-(5-((2-propylpentyl)oxy)furan-2-yl)propan-1-ol |
| 33 |  | (*R*)-3-Amino-1-(6-(cyclopentylmethoxy)pyridin-2-yl)propan-1-ol |

| | | |
|---|---|---|
| 34 |  | (*R*)-3-Amino-1-(6-(cycloheptyloxy)pyridin-2-yl)propan-1-ol |
| 35 |  | (*R*)-Ethyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate |
| 36 |  | (*R*)-Benzyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate |
| 37 |  | 3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-one |
| 38 |  | 3-Amino-1-(6-((tetrahydro-2*H*-pyran-4-yl)methoxy)pyridin-2-yl)propan-1-ol |
| 39 |  | (*S*)-3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol |
| 40 |  | (*R*)-3-Amino-1-(6-(piperidin-4-ylmethoxy)pyridin-2-yl)propan-1-ol |
| 41 |  | (*R*)-3-Amino-1-(6-phenethoxypyridin-2-yl)propan-1-ol |
| 42 |  | 3-(6-(Cyclohexylmethoxy)pyridin-2-yl)prop-2-yn-1-amine |

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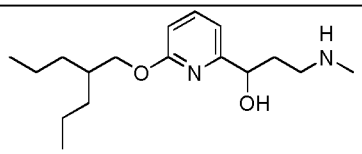
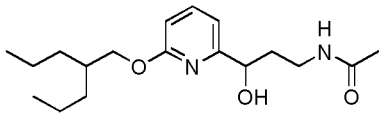
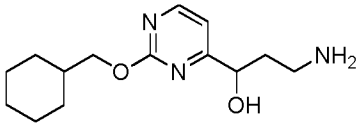
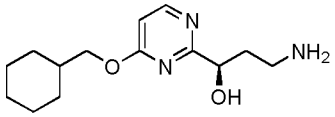
|---|---|---|
| 43 |  | 3-(Methylamino)-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol |
| 44 |  | *N*-(3-Hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)acetamide |
| 45 |  | 3-Amino-1-(2-(cyclohexylmethoxy)pyrimidin-4-yl)propan-1-ol |
| 46 |  | (R)-3-amino-1-(4-(cyclohexylmethoxy)pyrimidin-2-yl)propan-1-ol |

**[00141]** In another embodiment is a compound selected from the group consisting of:

3-Amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol;

3-Amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol;

(*E*)-3-Amino-1-(6-(2-cyclohexylvinyl)pyridin-2-yl)propan-1-ol;

3-Amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol;

(*R*)-3-Amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol;

(*R*)-3-Amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol;

3-Amino-1-(2-(cyclohexylmethoxy)pyridin-4-yl)propan-1-ol;

(*E*)-3-(2-(Cyclohexylmethoxy)pyridin-4-yl)prop-2-en-1-amine;

1-((5-(3-Amino-1-hydroxypropyl)thiophen-3-yl)ethynyl)cyclohexanol;

(*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)pyridin-3-yl)propan-1-ol;

3-Amino-1-(5-(2-cyclohexylethyl)pyridin-3-yl)propan-1-ol;

3-Amino-1-(4-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol;

(*E*)-3-Amino-1-(4-(2-cyclohexylvinyl)thiophen-2-yl)propan-1-ol;

(E)-3-Amino-1-(5-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol;

3-Amino-1-(5-(2-cyclohexylethyl)tetrahydrofuran-2-yl)propan-1-ol;

1-(2-(5-(3-Amino-1-hydroxypropyl)thiophen-3-yl)ethyl)cyclohexanol;

3-Amino-1-(4-(2-cyclohexylethyl)thiophen-2-yl)propan-1-ol;

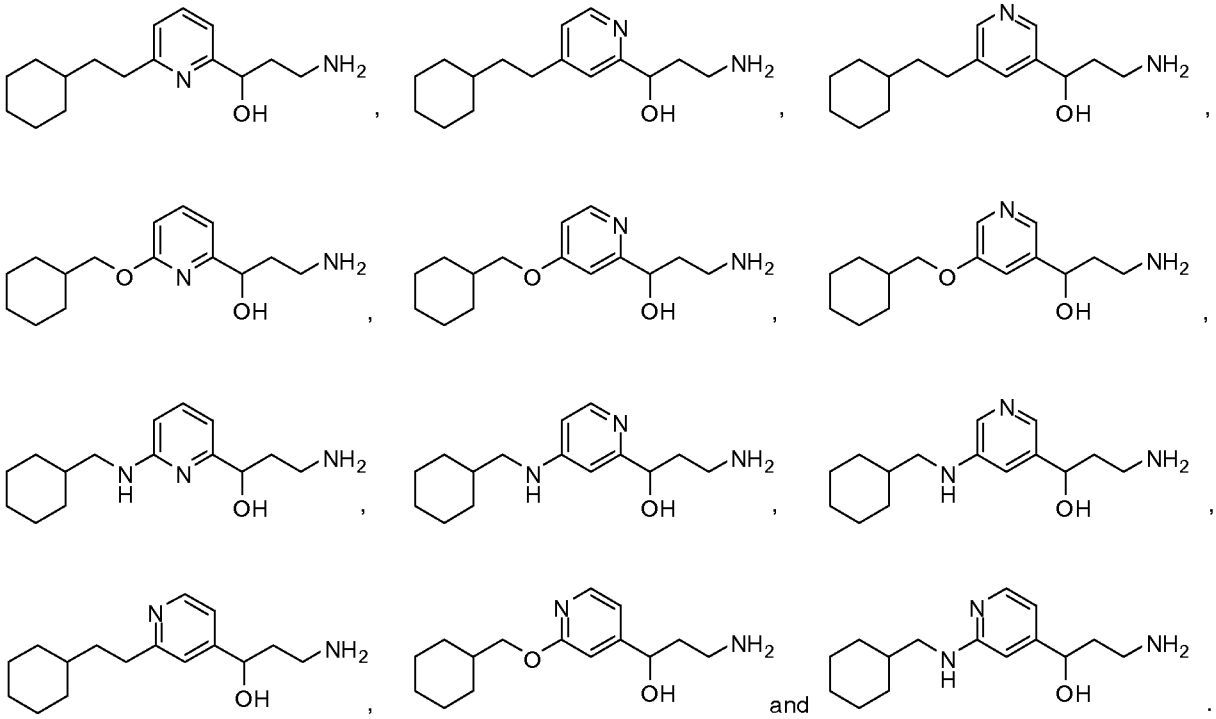
3-Amino-1-(4-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol;

(*R*)-3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol;

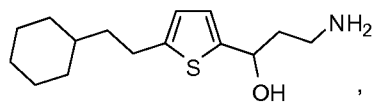
(*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)thiophen-3-yl)propan-1-ol;

3-Amino-1-(5-(2-cyclohexylethyl)thiophen-3-yl)propan-1-ol;
(*E*)-3-Amino-1-(4-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol;
3-Amino-1-(5-(cyclohexylethynyl)furan-2-yl)propan-1-ol;
3-Amino-1-(5-(cyclohexylmethoxy)furan-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-((cyclohexylmethyl)thio)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-(cyclohexyloxy)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-((cyclohexylmethyl)sulfonyl)pyridin-2-yl)propan-1-ol;
(*R*,*E*)-5-(2-(6-(3-Amino-1-hydroxypropyl)pyridin-2-yl)vinyl)nonan-5-ol;
(*R*)-5-(2-(6-(3-Amino-1-hydroxypropyl)pyridin-2-yl)ethyl)nonan-5-ol;
3-Amino-1-(6-(2-ethylbutoxy)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-(cycloheptylmethoxy)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(5-((2-propylpentyl)oxy)furan-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-(cyclopentylmethoxy)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-(cycloheptyloxy)pyridin-2-yl)propan-1-ol;
(*R*)-Ethyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate;
(*R*)-Benzyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate;
3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-one;
3-Amino-1-(6-((tetrahydro-2*H*-pyran-4-yl)methoxy)pyridin-2-yl)propan-1-ol;
(*S*)-3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-(piperidin-4-ylmethoxy)pyridin-2-yl)propan-1-ol;
(*R*)-3-Amino-1-(6-phenethoxypyridin-2-yl)propan-1-ol;
3-(6-(Cyclohexylmethoxy)pyridin-2-yl)prop-2-yn-1-amine;
3-(Methylamino)-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol;
*N*-(3-Hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)acetamide;
3-Amino-1-(2-(cyclohexylmethoxy)pyrimidin-4-yl)propan-1-ol; and
(R)-3-amino-1-(4-(cyclohexylmethoxy)pyrimidin-2-yl)propan-1-ol.

**[00142]** In additional embodiments, the compound of Formula (A) is selected from the group consisting of:



**[00143]** In additional embodiments, the compound of Formula (A) is selected from the group consisting of: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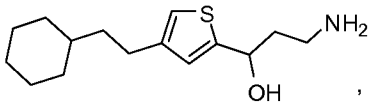
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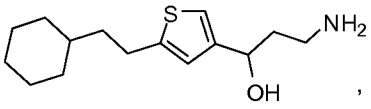
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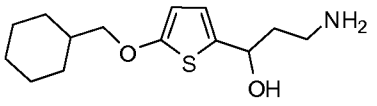
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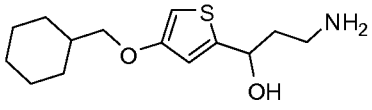
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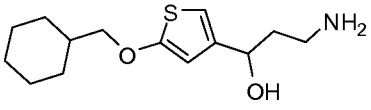
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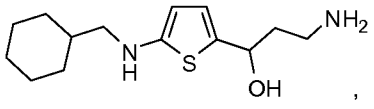
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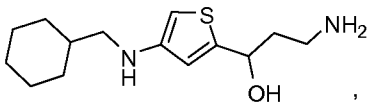
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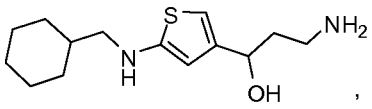
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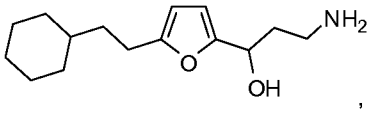
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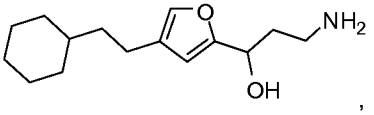
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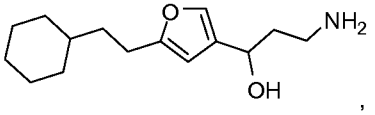
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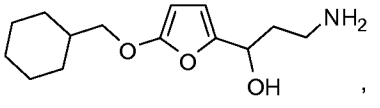
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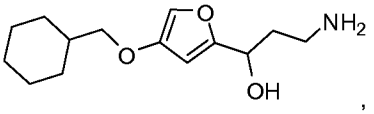
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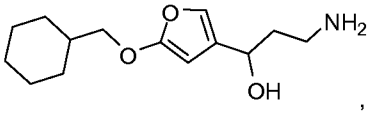
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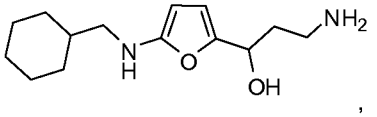
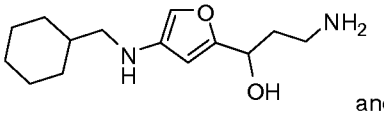
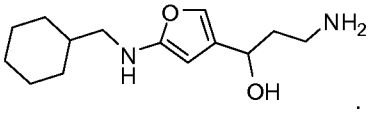
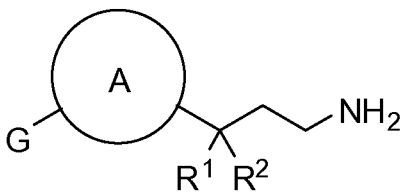

,

and

.

**[00144]** One embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:



Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

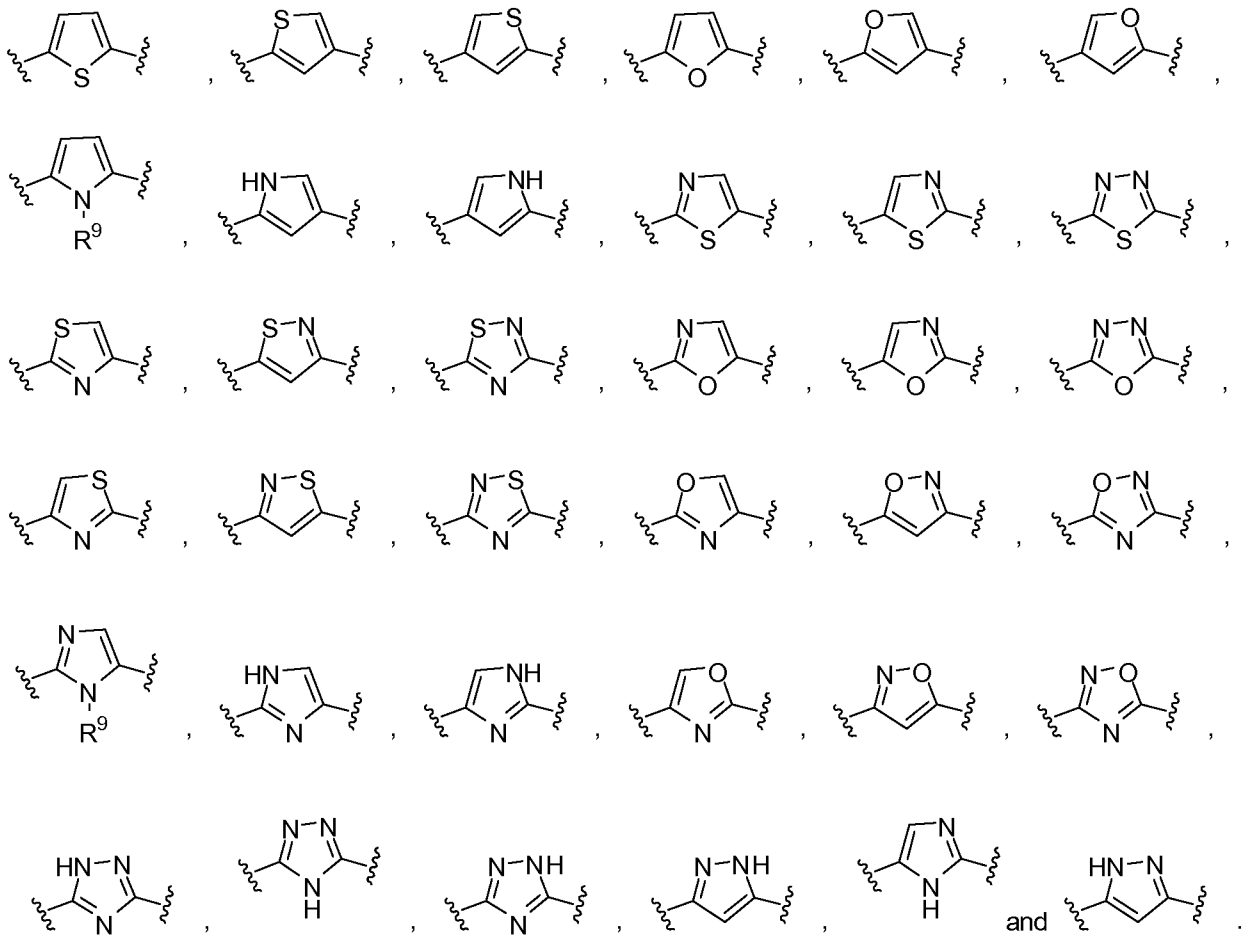
G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

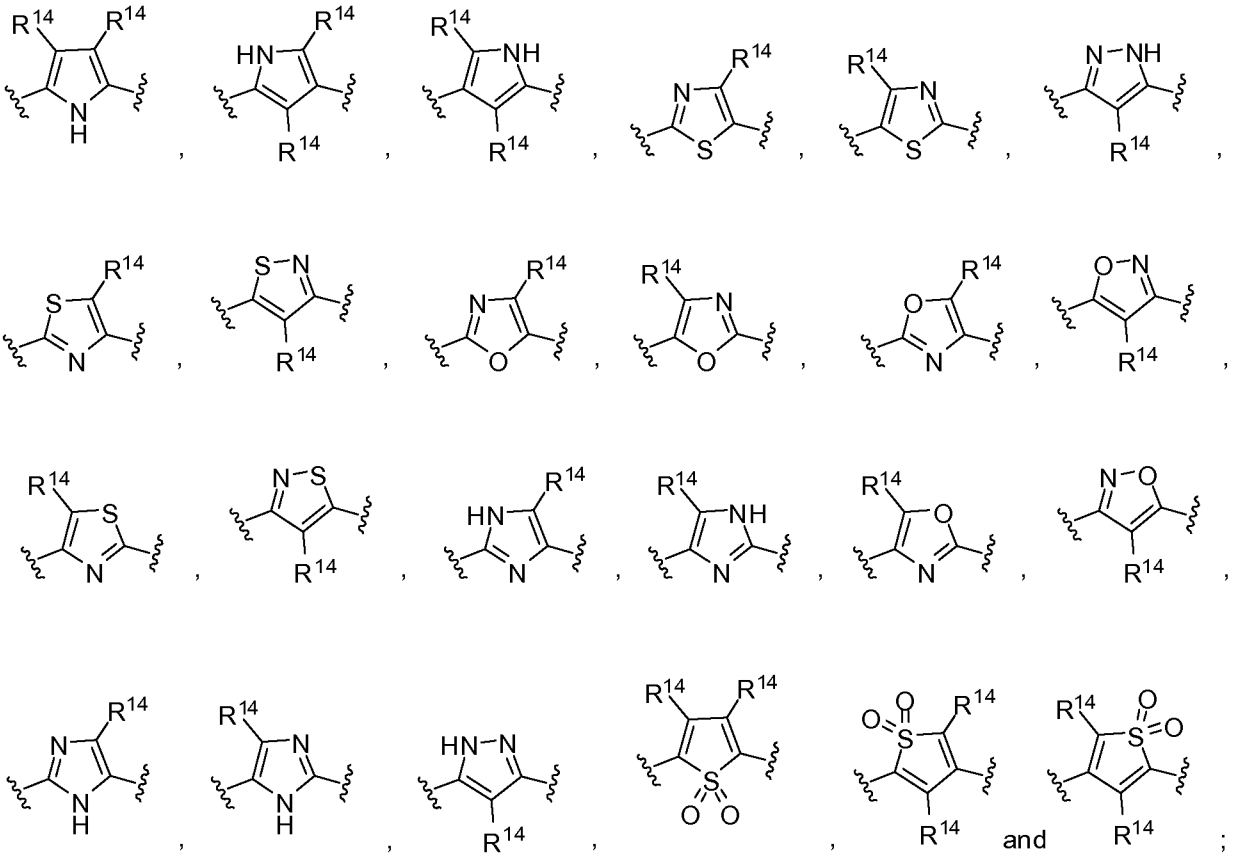
Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00145]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

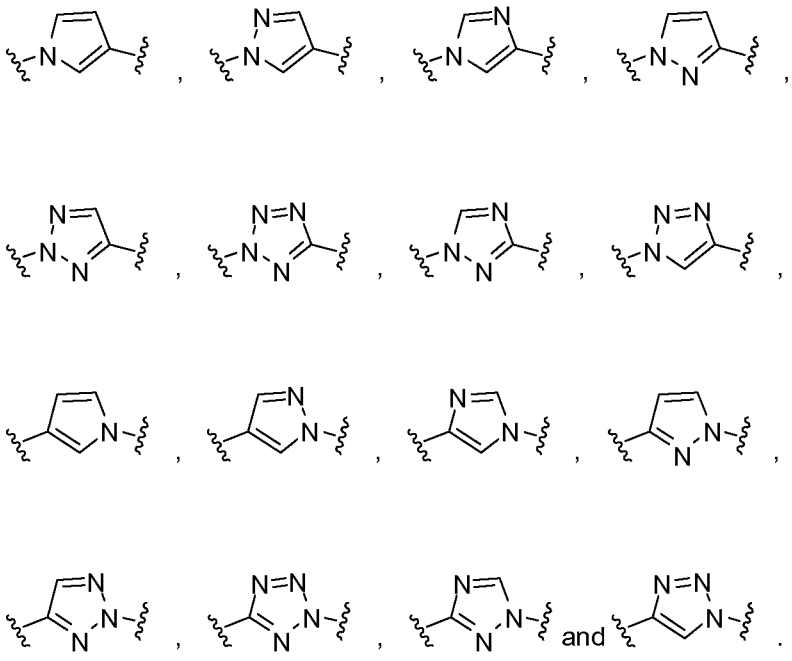


**[00146]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

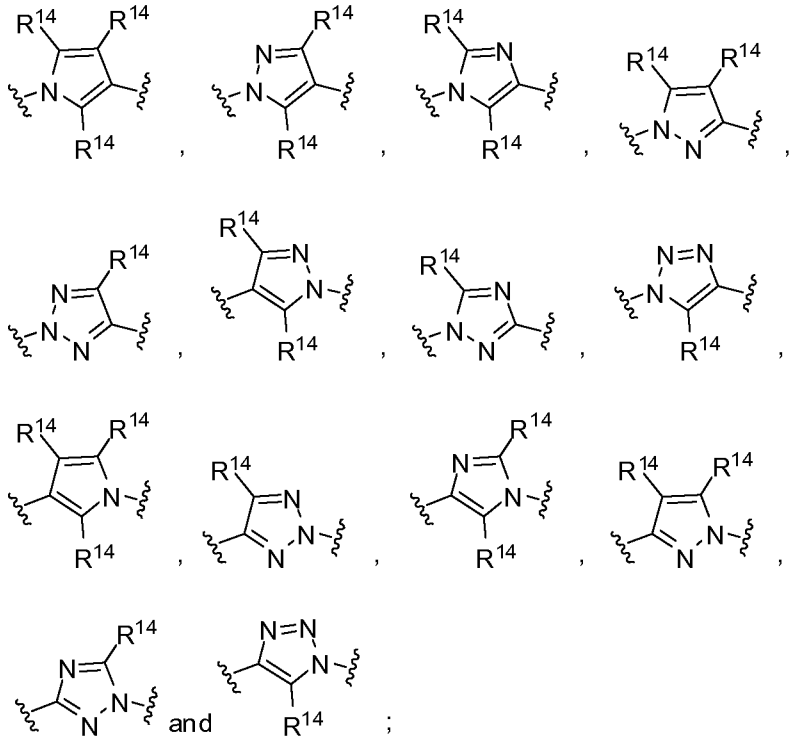


and each $R^{14}$ is independently selected from hydrogen, halogen, alkyl, or fluoroalkyl.

**[00147]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

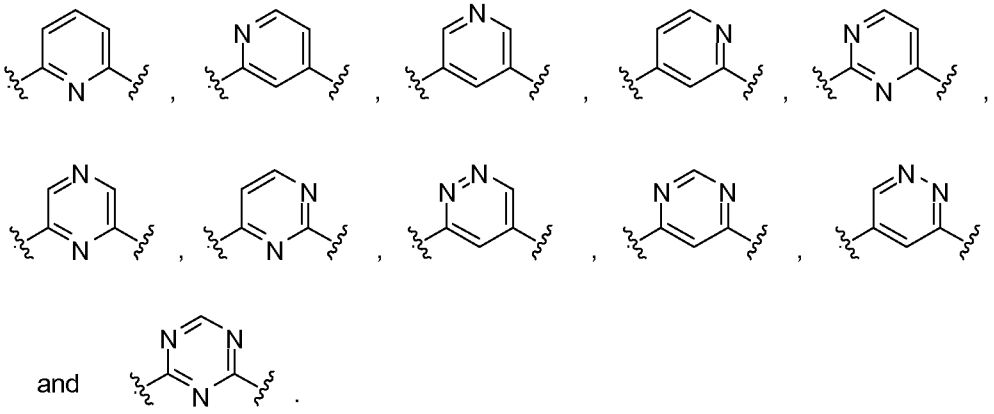


**[00148]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

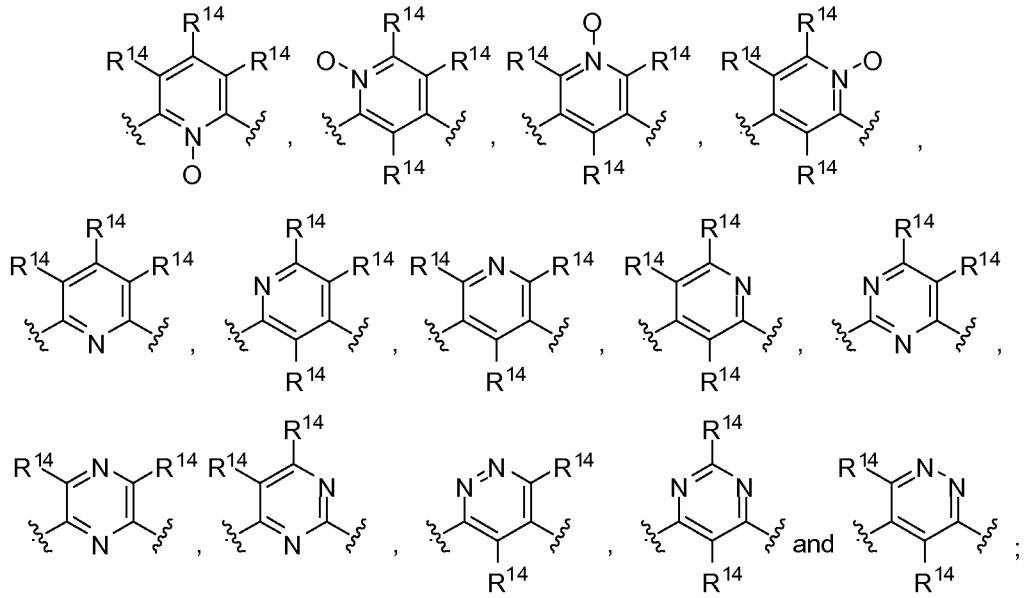


and each $R^{14}$ is independently selected from hydrogen, halogen, alkyl, or fluoroalkyl.

**[00149]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

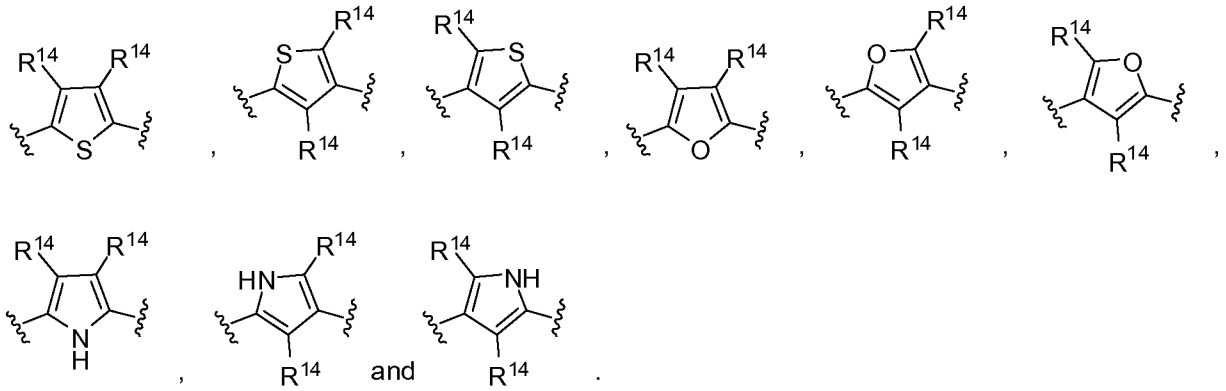


**[00150]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:

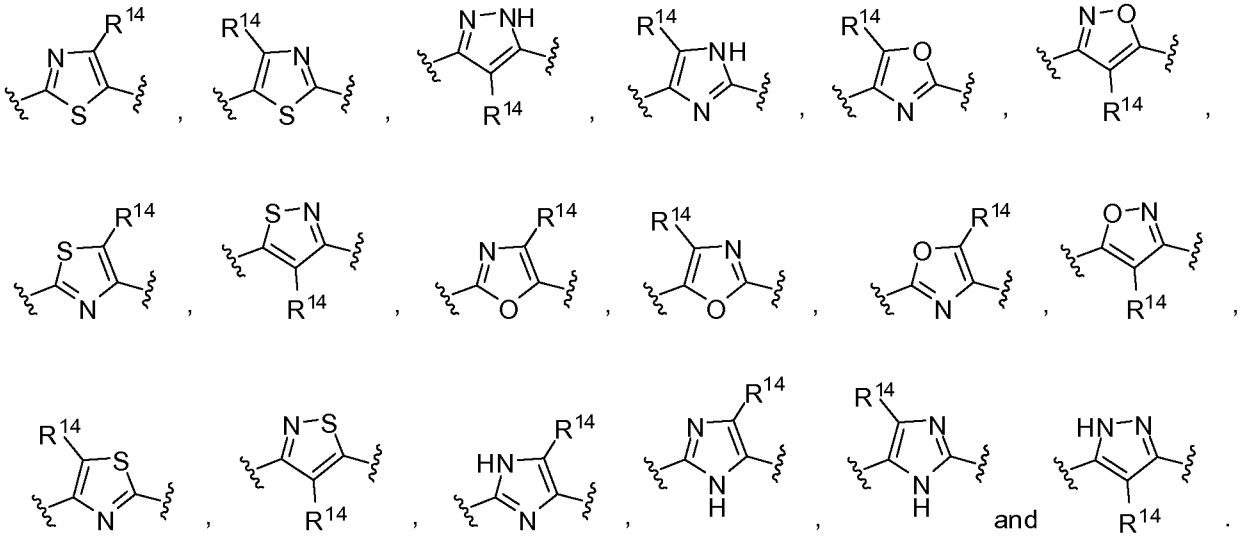


and each $R^{14}$ is independently selected from hydrogen, halogen, alkyl, or fluoroalkyl.

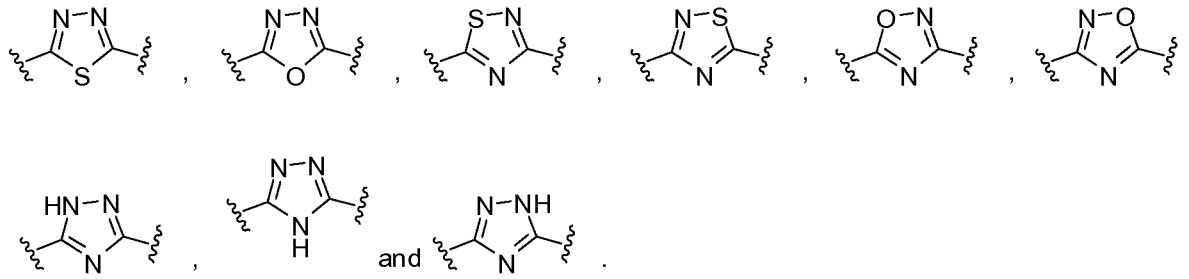
**[00151]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



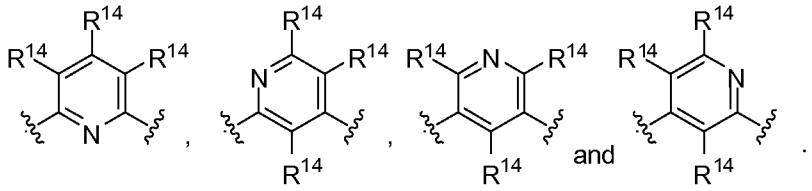
**[00152]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



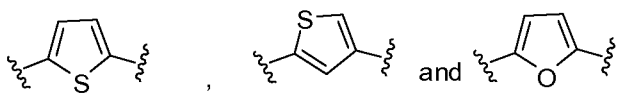
**[00153]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



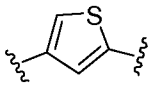
**[00154]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof,wherein Ring A is selected from:



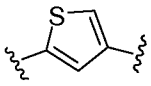
**[00155]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is selected from:



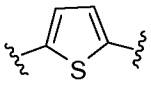
**[00156]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



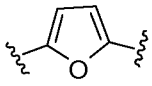
**[00157]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



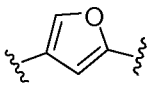
**[00158]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



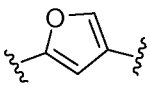
**[00159]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



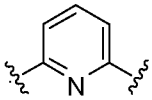
**[00160]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



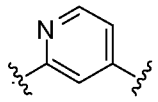
**[00161]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



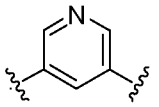
**[00162]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



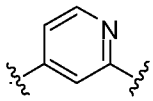
**[00163]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



**[00164]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



**[00165]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Ring A is:



**[00166]** For any and all of the embodiments, substituents are selected from among from a subset of the listed alternatives. For example, in some embodiments is provided a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is a 4-, 5-, 6-, or 7-membered carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

**[00167]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-.

**[00168]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –S-.

**[00169]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –NH-.

**[00170]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is $-CH_2-$.

**[00171]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, and Y is carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, and Y is a 4-, 5-, 6-, or 7-membered carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, and Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

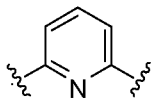
**[00172]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ are both hydrogen. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ are both hydrogen, X is selected from –O-, and Y is carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ are both hydrogen, X is selected from –O-, and Y is a 4-, 5-, 6-, or 7-membered carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ are both hydrogen, X is selected from –O-, and Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

**[00173]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ is hydrogen and $R^2$ is -OH. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ is hydrogen and $R^2$ is –OH, X is selected from –O-, and Y is carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof,

wherein $R^1$ is hydrogen and $R^2$ is –OH, X is selected from –O-, and Y is a 4-, 5-, 6-, or 7-membered carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ is hydrogen and $R^2$ is –OH, X is selected from –O-, and Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

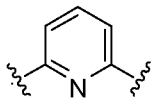
**[00174]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ together form an oxo. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ together form an oxo, X is selected from –O-, and Y is carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ together form an oxo, X is selected from –O-, and Y is a 4-, 5-, 6-, or 7-membered carbocyclyl. Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ and $R^2$ together form an oxo, X is selected from –O-, and Y is a 4-, 5-, 6-, or 7-membered carbocyclyl.

**[00175]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, and ring A is:



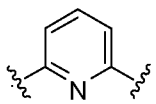

.

**[00176]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is carbocyclyl, and ring A is:



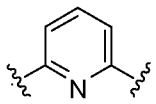

.

**[00177]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is a 4-, 5-, 6-, or 7-membered carbocyclyl, and ring A is:

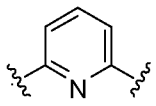



.

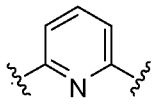
**[00178]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and ring A is:



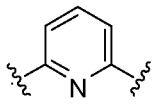
**[00179]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, Y is carbocyclyl, and ring A is:



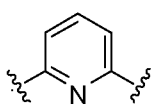
**[00180]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, Y is a 4-, 5-, 6-, or 7-membered carbocyclyl, and ring A is:



**[00181]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein X is selected from –O-, Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and ring A is:

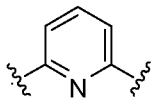


**[00182]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ is hydrogen, $R^2$ is –OH, X is selected from –O-, Y is carbocyclyl, and ring A is:

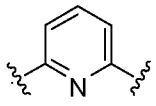


**[00183]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or

*N*-oxide thereof, wherein $R^1$ is hydrogen, $R^2$ is –OH, X is selected from –O-, Y is a 4-, 5-, 6-, or 7-membered carbocyclyl, and ring A is:



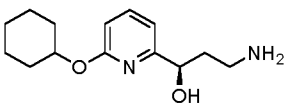
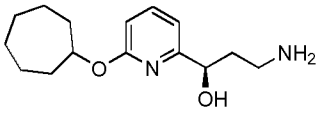
**[00184]** Another embodiment provides a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein $R^1$ is hydrogen, $R^2$ is –OH, X is selected from –O-, Y is cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, and ring A is:



**[00185]** Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

**[00186]** In some embodiments the compounds of Formula (B) disclosed herein have the structure provided in Table 1B.

**TABLE 1B**

| Synthesis Example | Structure | Name |
|---|---|---|
| 26 |  | (*R*)-3-Amino-1-(6-(cyclohexyloxy)pyridin-2-yl)propan-1-ol |
| 34 |  | (*R*)-3-Amino-1-(6-(cycloheptyloxy)pyridin-2-yl)propan-1-ol |

**Preparation of the Substituted Heterocyclic Amine Derivative Compounds**

**[00187]** The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh PA), Aldrich Chemical (Milwaukee WI,

including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park UK), Avocado Research (Lancashire U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.),Chemservice Inc. (West Chester PA), Crescent Chemical Co. (Hauppauge NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester NY), Fisher Scientific Co. (Pittsburgh PA), Fisons Chemicals (Leicestershire UK), Frontier Scientific (Logan UT), ICN Biomedicals, Inc. (Costa Mesa CA), Key Organics (Cornwall U.K.), Lancaster Synthesis (Windham NH), Maybridge Chemical Co. Ltd. (Cornwall U.K.), Parish Chemical Co. (Orem UT), Pfaltz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland OR), Trans World Chemicals, Inc. (Rockville MD), and Wako Chemicals USA, Inc. (Richmond VA).

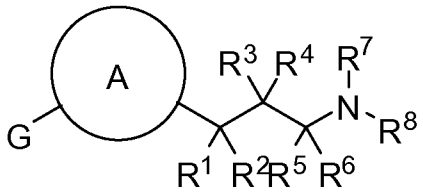
**[00188]** Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Quin, L.D. et al. "A Guide to Organophosphorus Chemistry" (2000) Wiley-Interscience, ISBN: 0-471-31824-8; Solomons, T. W. G. "Organic

Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

**[00189]** Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the substituted heterocyclic amine derivative compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

**Treatment of Ophthalmic Diseases and Disorders**

**[00190]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00191]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, wherein the ophthalmic disease or disorder is age-related macular degeneration or Stargardt's macular dystrophy.

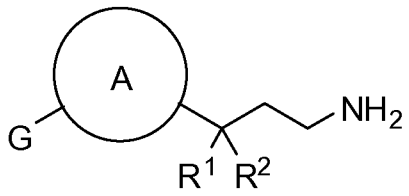
**[00192]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, wherein the ophthalmic disease or disorder is selected from retinal detachment, hemorrhagic retinopathy, retinitis pigmentosa, cone-rod dystrophy, Sorsby's fundus dystrophy, optic neuropathy, inflammatory retinal disease, diabetic retinopathy, diabetic maculopathy, retinal blood vessel occlusion, retinopathy of prematurity, or ischemia reperfusion related retinal injury, proliferative vitreoretinopathy, retinal dystrophy, hereditary optic neuropathy, uveitis, a retinal injury, a retinal disorder associated with Alzheimer's disease, a retinal disorder associated with multiple sclerosis, a retinal disorder associated with Parkinson's disease, a retinal disorder associated with

viral infection, a retinal disorder related to light overexposure, myopia, and a retinal disorder associated with AIDS.

**[00193]** Another embodiment provides a method for treating an ophthalmic disease or disorder in a subject resulting in a reduction of lipofuscin pigment accumulated in an eye of the subject.

**[00194]** Another embodiment provides a method for treating an ophthalmic disease or disorder in a subject resulting in a reduction of lipofuscin pigment accumulated in an eye of the subject wherein the lipofuscin pigment is *N*-retinylidene-*N*-retinyl-ethanolamine (A2E).

**[00195]** One embodiment provides a method for treating an ophthalmic disease or disorder in a subject, comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

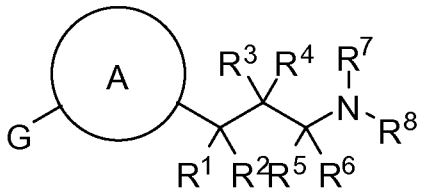
G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo. Another embodiment provides a method for treating an ophthalmic disease or disorder in a subject, comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof, wherein the ophthalmic disease or disorder is age-related macular degeneration or Stargardt's macular dystrophy.

**[00196]** One embodiment provides a method of modulating chromophore flux in a retinoid cycle comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

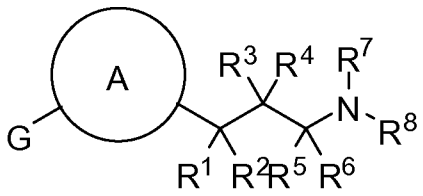
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00197]** One embodiment provides a method of inhibiting dark adaptation of a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

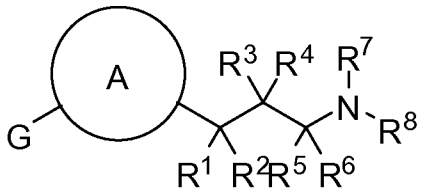
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00198]** One embodiment provides a method of inhibiting regeneration of rhodopsin in a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

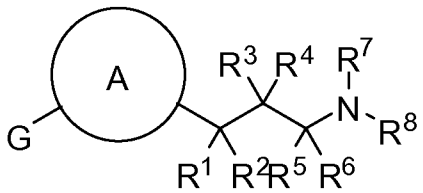
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00199]** One embodiment provides a method of reducing ischemia in an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

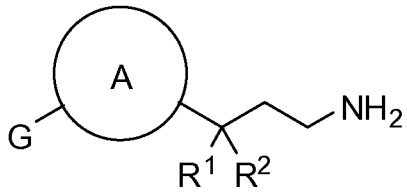
each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00200]** Another embodiment provides a method of reducing ischemia in an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof, wherein the pharmaceutical composition is administered under conditions and at a time sufficient to inhibit dark adaptation of a rod photoreceptor cell, thereby reducing ischemia in the eye.

**[00201]** One embodiment provides a method of modulating chromophore flux in a retinoid cycle comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

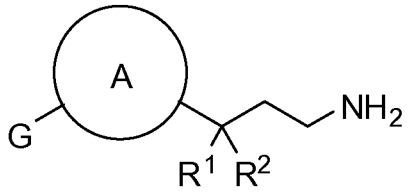
G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00202]** One embodiment provides a method of inhibiting dark adaptation of a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

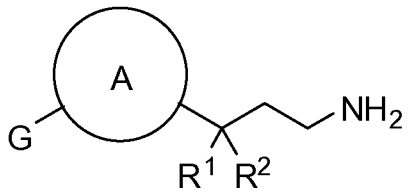
G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00203]** One embodiment provides a method of inhibiting regeneration of rhodopsin in a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

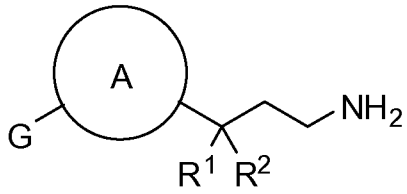
X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00204]** One embodiment provides a method of reducing ischemia in an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a

compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

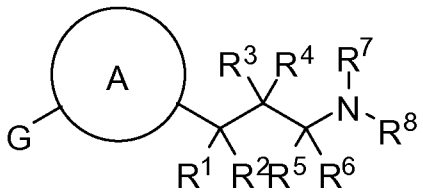
G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00205]** One embodiment provides a method of inhibiting neovascularization in the retina of an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-$C(R^9)_2$-,–O-C(=O)-, –S-$C(R^9)_2$-, –S(O)-$C(R^9)_2$-, –$S(O)_2$-$C(R^9)_2$-, –$SO_2(NR^9)$-, –$NR^9$-$C(R^9)_2$-, –$NR^9$-C(=O)-, –$NR^9$-$S(O)_2$-, –$C(R^9)_2$-$C(R^9)_2$-, –C(=O)-$C(R^9)_2$-, – $C(R^9)_2$-C(=O)-, –$C(R^9)$=$C(R^9)$-, -C ≡ C-, –C(=O)-$N(R^9)$-, –C(=O)-O-, –$C(R^9)_2$-O-, and –$C(R^9)_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

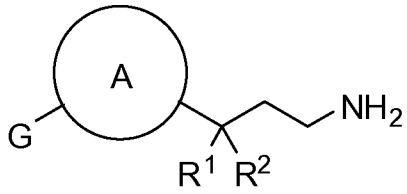
each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00206]** One embodiment provides a method of inhibiting neovascularization in the retina of an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof wherein the pharmaceutical composition is administered under conditions and at a time sufficient to inhibit dark adaptation of a rod photoreceptor cell, thereby inhibiting neovascularization in the retina.

**[00207]** One embodiment provides a method of inhibiting neovascularization in the retina of an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

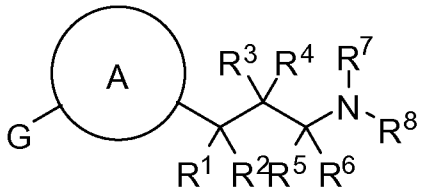
G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00208]** One embodiment provides a method of inhibiting degeneration of a retinal cell in a retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-$C(R^9)_2$-,–O-C(=O)-, –S-$C(R^9)_2$-, –S(O)-$C(R^9)_2$-, –$S(O)_2$-$C(R^9)_2$-, –$SO_2(NR^9)$-, –$NR^9$-$C(R^9)_2$-, –$NR^9$-C(=O)-, –$NR^9$-$S(O)_2$-, –$C(R^9)_2$-$C(R^9)_2$-, –C(=O)-$C(R^9)_2$-, – $C(R^9)_2$-C(=O)-, –$C(R^9)$=$C(R^9)$-, -C ≡ C-, –C(=O)-$N(R^9)$-, –C(=O)-O-, –$C(R^9)_2$-O-, and –$C(R^9)_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and

$R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

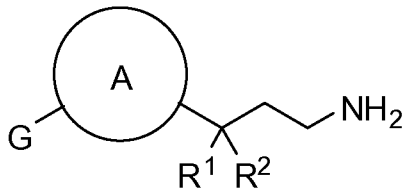
each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -$C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00209]** One embodiment provides a method of inhibiting degeneration of a retinal cell in a retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof wherein the retinal cell is a retinal neuronal cell. One embodiment provides a method of inhibiting degeneration of a retinal cell in a retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof wherein the retinal neuronal cell is a photoreceptor cell.

**[00210]** One embodiment provides a method of inhibiting degeneration of a retinal cell in a retina comprising contacting the retina with a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00211]** Substituted heterocyclic amine derivative compounds as described in detail herein, including a compound having the structure as set forth in Formula (A) or Formula (B) and substructures thereof, and the specific substituted heterocyclic amine compounds described herein that are useful for treating an ophthalmic disease or disorder, inhibit one or more steps in the visual cycle, for example, by inhibiting or blocking a functional activity of a visual cycle *trans-cis* isomerase (also including a visual cycle *trans-cis* isomerohydrolase). The compounds described herein, inhibit, block, or in some manner interfere with the isomerization step in the visual cycle. In a particular embodiment, the compound inhibits isomerization of an all-*trans*-retinyl ester; in certain embodiments, the all-*trans*-retinyl ester is a fatty acid ester of all-*trans*-retinol, and the compound inhibits isomerization of all-*trans*-retinol to 11-*cis*-retinol. The compound binds to, or in some manner interact with, and inhibit the isomerase activity of at least one visual cycle isomerase, which is also referred to herein and in the art as a retinal isomerase or an isomerohydrolase. The compound blocks or inhibits binding of an all-*trans*-retinyl ester substrate to an isomerase. Alternatively, or in addition, the compound binds to the catalytic site or region of the isomerase, thereby inhibiting the capability of the enzyme to catalyze isomerization of an all-*trans*-retinyl ester substrate. On the basis of scientific data to date, at least one isomerase that catalyzes the isomerization of all-*trans*-retinyl esters is believed to be located in the cytoplasm of RPE cells. As discussed herein, each step, enzyme, substrate, intermediate, and product of the visual cycle is not yet elucidated *(see, e.g.,* Moiseyev et al., *Proc. Natl. Acad. Sci. USA* 102:12413-18 (2004); Chen et al., *Invest. Ophthalmol. Vis. Sci.* 47:1177-84 (2006); Lamb et al. *supra*).

**[00212]** A method for determining the effect of a compound on isomerase activity is performed *in vitro* as described herein and in the art (Stecher et al., *J Biol Chem* 274:8577-85 (1999); *see also* Golczak et al., *Proc. Natl. Acad. Sci. USA* 102:8162-67 (2005)). Retinal pigment epithelium (RPE) microsome membranes isolated from an animal (such as bovine, porcine, human, for example) may serve as the source of the isomerase. The capability of the substituted heterocyclic amine derivative compounds to

inhibit isomerase is also determined by an *in vivo* murine isomerase assay. Brief exposure of the eye to intense light ("photobleaching" of the visual pigment or simply "bleaching") is known to photo-isomerize almost all 11-*cis*-retinal in the retina. The recovery of 11-*cis*-retinal after bleaching can be used to estimate the activity of isomerase *in vivo* (*see, e.g.,* Maeda et al., *J. Neurochem* 85:944-956 (2003); Van Hooser et al., *J Biol Chem* 277:19173-82, 2002). Electroretinographic (ERG) recording may be performed as previously described (Haeseleer et al., *Nat. Neurosci.* 7:1079-87 (2004); Sugitomo et al., *J. Toxicol. Sci.* 22 Suppl 2:315-25 (1997); Keating et al., *Documenta Ophthalmologica* 100:77-92 (2000)). See also Deigner et al., *Science*, 244: 968-971 (1989); Gollapalli et al., *Biochim Biophys Acta.* 1651: 93-101 (2003); Parish, et al., *Proc. Natl. Acad. Sci. USA* 95:14609-13 (1998); Radu, et al., *Proc Natl Acad Sci USA* 101: 5928-33 (2004)). In certain embodiments, compounds that are useful for treating a subject who has or who is at risk of developing any one of the ophthalmic and retinal diseases or disorders described herein have $IC_{50}$ levels (compound concentration at which 50% of isomerase activity is inhibited) as measured in the isomerase assays described herein or known in the art that is less than about 1 μM; in other embodiments, the determined $IC_{50}$ level is less than about 10 nM; in other embodiments, the determined $IC_{50}$ level is less than about 50 nM; in certain other embodiments, the determined $IC_{50}$ level is less than about 100 nM; in other certain embodiments, the determined $IC_{50}$ level is less than about 10 μM; in other embodiments, the determined $IC_{50}$ level is less than about 50 μM; in other certain embodiments, the determined $IC_{50}$ level is less than about 100 μM or about 500 μM ; in other embodiments, the determined $IC_{50}$ level is between about 1 μM and 10 μM ; in other embodiments, the determined $IC_{50}$ level is between about 1 nM and 10 nM. When adminstered into a subject, one or more compounds of the present invention exhibits an $ED_{50}$ value of about 5 mg/kg, 5 mg/kg or less as ascertained by inhibition of an isomerase reaction that results in production of 11-*cis* retinol. In some embodiments, the compounds of the present invention have $ED_{50}$ values of about 1 mg/kg when administered into a subject. In other embodiments, the compounds of the present invention have $ED_{50}$ values of about 0.1 mg/kg when administered into a subject. The $ED_{50}$ values can be measured after about 2 hours, 4 hours, 6 hours, 8 hours or longer upon administering a subject compound or a pharmaceutical composition thereof.

**[00213]** The compounds described herein are useful for treating a subject who has an ophthalmic disease or disorder, particularly a retinal disease or disorder such as age-related macular degeneration or Stargardt's macular dystrophy. In one embodiment, the

compounds described herein inhibit (*i.e.,* prevent, reduce, slow, abrogate, or minimize) accumulation of lipofuscin pigments and lipofuscin-related and/or associated molecules in the eye. In another embodiment, the compounds inhibit (*i.e.,* prevent, reduce, slow, abrogate, or minimize) *N*-retinylidene-*N*-retinylethanolamine (A2E) accumulation in the eye. The ophthalmic disease results, at least in part, from lipofuscin pigments accumulation and/or from accumulation of A2E in the eye. Accordingly, in certain embodiments, methods are provided for inhibiting or preventing accumulation of lipofuscin pigments and/or A2E in the eye of a subject. These methods comprise administering to the subject a composition comprising a pharmaceutically acceptable or suitable excipient (*i.e.,* pharmaceutically acceptable or suitable carrier) and a substituted heterocyclic amine derivative compound as described in detail herein, including a compound having the structure as set forth in Formula (A) or Formula (B), and substructures thereof, and the specific substituted heterocyclic amine derivative compounds described herein.

**[00214]** Accumulation of lipofuscin pigments in retinal pigment epithelium (RPE) cells has been linked to progression of retinal diseases that result in blindness, including age-related macular degeneration (De Laey et al., *Retina* 15:399-406 (1995)). Lipofuscin granules are autofluorescent lysosomal residual bodies (also called age pigments). The major fluorescent species of lipofuscin is A2E (an orange-emitting fluorophore), which is a positively charged Schiff-base condensation-product formed by *all-trans* retinaldehyde with phosphatidylethanolamine (2:1 ratio) (*see, e.g.,* Eldred et al., *Nature* 361:724-6 (1993); *see also*, Sparrow, *Proc. Natl. Acad. Sci. USA* 100:4353-54 (2003)). Much of the indigestible lipofuscin pigment is believed to originate in photoreceptor cells; deposition in the RPE occurs because the RPE internalize membranous debris that is discarded daily by the photoreceptor cells. Formation of this compound is not believed to occur by catalysis by any enzyme, but rather A2E forms by a spontaneous cyclization reaction. In addition, A2E has a pyridinium bisretinoid structure that once formed is resistant to enzymatic degradation. Lipofuscin, and thus A2E, accumulate with aging of the human eye and also accumulate in a juvenile form of macular degeneration called Stargardt's disease, and in several other congenital retinal dystrophies.

**[00215]** A2E may induce damage to the retina via several different mechanisms. At low concentrations, A2E inhibits normal proteolysis in lysosomes (Holz et al., *Invest. Ophthalmol. Vis. Sci.* 40:737-43 (1999)). At higher, sufficient concentrations, A2E may

act as a positively charged lysosomotropic detergent, dissolving cellular membranes, and may alter lysosomal function, release proapoptotic proteins from mitochondria, and ultimately kill the RPE cell (*see, e.g.,* Eldred et al., *supra*; Sparrow et al., *Invest. Ophthalmol. Vis. Sci.* 40:2988-95 (1999); Holz et al., *supra*; Finneman et al., *Proc. Natl. Acad. Sci. USA* 99:3842-347 (2002); Suter et al., *J. Biol. Chem.* 275:39625-30 (2000)). A2E is phototoxic and initiates blue light-induced apoptosis in RPE cells (*see, e.g.,* Sparrow et al., *Invest. Ophthalmol. Vis. Sci.* 43:1222-27 (2002)). Upon exposure to blue light, photooxidative products of A2E are formed (*e.g.,* epoxides) that damage cellular macromolecules, including DNA (Sparrow et al., *J. Biol. Chem.* 278(20):18207-13 (2003)). A2E self-generates singlet oxygen that reacts with A2E to generate epoxides at carbon-carbon double bonds (Sparrow et al., *supra*). Generation of oxygen reactive species upon photoexcitation of A2E causes oxidative damage to the cell, often resulting in cell death. An indirect method of blocking formation of A2E by inhibiting biosynthesis of the direct precursor of A2E, *all-trans*-retinal, has been described (*see* U.S. Patent Application Publication No. 2003/0032078). However, the usefulness of the method described therein is limited because generation of *all-trans* retinal is an important component of the visual cycle. Other therapies described include neutralizing damage caused by oxidative radical species by using superoxide-dismutase mimetics (*see, e.g.,* U.S. Patent Application Publication No. 2004/0116403) and inhibiting A2E-induced cytochrome C oxidase in retinal cells with negatively charged phospholipids (*see, e.g.,* U.S. Patent Application Publication No. 2003/0050283).

**[00216]** The substituted heterocyclic amine derivative compounds described herein is useful for preventing, reducing, inhibiting, or decreasing accumulation (*i.e.,* deposition) of A2E and A2E-related and/or derived molecules in the RPE. Without wishing to be bound by theory, because the RPE is critical for the maintenance of the integrity of photoreceptor cells, preventing, reducing, or inhibiting damage to the RPE may inhibit degeneration (*i.e.,* enhance the survival or increase or prolong cell viability) of retinal neuronal cells, particularly, photoreceptor cells. Compounds that bind specifically to or interact with A2E, A2E-related and/or derived molecules, or that affect A2E formation or accumulation may also reduce, inhibit, prevent, or decrease one or more toxic effects of A2E or of A2E-related and/or derived molecules that result in retinal neuronal cell (including a photoreceptor cell) damage, loss, or neurodegeneration, or in some manner decrease retinal neuronal cell viability. Such toxic effects include induction of apoptosis, self-generation of singlet oxygen and generation of oxygen reactive species; self-

generation of singlet oxygen to form A2E-epoxides that induce DNA lesions, thus damaging cellular DNA and inducing cellular damage; dissolving cellular membranes; altering lysosomal function; and effecting release of proapoptotic proteins from mitochondria.

**[00217]** In other embodiments, the compounds described herein are useful for treating other ophthalmic diseases or disorders, for example, glaucoma, cone-rod dystrophy, retinal detachment, hemorrhagic or hypertensive retinopathy, retinitis pigmentosa, optic neuropathy, inflammatory retinal disease, proliferative vitreoretinopathy, genetic retinal dystrophies, traumatic injury to the optic nerve (such as by physical injury, excessive light exposure, or laser light), hereditary optic neuropathy, neuropathy due to a toxic agent or caused by adverse drug reactions or vitamin deficiency, Sorsby's fundus dystrophy, uveitis, a retinal disorder associated with Alzheimer's disease, a retinal disorder associated with multiple sclerosis; a retinal disorder associated with viral infection (cytomegalovirus or herpes simplex virus), a retinal disorder associated with Parkinson's disease, a retinal disorder associated with AIDS, or other forms of progressive retinal atrophy or degeneration. In another specific embodiment, the disease or disorder results from mechanical injury, chemical or drug-induced injury, thermal injury, radiation injury, light injury, laser injury. The subject compounds are useful for treating both hereditary and non-hereditary retinal dystrophy. These methods are also useful for preventing ophthalmic injury from environmental factors such as light-induced oxidative retinal damage, laser-induced retinal damage, "flash bomb injury," or "light dazzle", refractive errors including but not limited to myopia (see, e.g., Quinn GE et al. Nature 1999;399:113-114; Zadnik K et al. Nature 2000;404:143-144; Gwiazda J et al. Nature 2000;404: 144), etc.

**[00218]** In other embodiments, methods are provided herein for inhibiting neovascularization (including but not limited to neovascular glycoma) in the retina using any one or more of the substituted heterocyclic amine derivative compound as described in detail herein, including a compound having the structure as set forth in Formula (A) or Formula (B), and substructures thereof, and the specific substituted heterocyclic amine derivative compounds described herein. In certain other embodiments, methods are provided for reducing hypoxia in the retina using the compounds described herein. These methods comprise administering to a subject, in need thereof, a composition comprising a pharmaceutically acceptable or suitable excipient (*i.e.,* pharmaceutically acceptable or suitable carrier) and a substituted heterocyclic amine derivative compound

as described in detail herein, including a compound having the structure as set forth in Formulae (A), and substructures thereof, and the specific substituted heterocyclic amine derivative compounds described herein.

**[00219]** Merely by way of explanation and without being bound by any theory, and as discussed in further detail herein, dark-adapted rod photoreceptors engender a very high metabolic demand (*i.e.,* expenditure of energy (ATP consumption) and consumption of oxygen). The resultant hypoxia may cause and/or exacerbate retinal degeneration, which is likely exaggerated under conditions in which the retinal vasculature is already compromised, including, but not limited to, such conditions as diabetic retinopathy, macular edema, diabetic maculopathy, retinal blood vessel occlusion (which includes retinal venous occlusion and retinal arterial occlusion), retinopathy of prematurity, ischemia reperfusion related retinal injury, as well as in the wet form of age-related macular degeneration (AMD). Furthermore, retinal degeneration and hypoxia may lead to neovascularization, which in turn may worsen the extent of retinal degeneration. In some embodiments, the substituted heterocyclic amine derivative compounds described herein that modulate the visual cycle are administered to prevent, inhibit, and/or delay dark adaptation of rod photoreceptor cells, and therefore reduce metabolic demand, thereby reducing hypoxia and inhibiting neovascularization.

**[00220]** By way of background, oxygen is a critical metabolite for preservation of retinal function in mammals, and retinal hypoxia may be a factor in many retinal diseases and disorders that have ischemia as a component. In most mammals (including humans) with dual vascular supply to the retina, oxygenation of the inner retina is achieved through the intraretinal microvasculature, which is sparse compared to the choriocapillaris that supplies oxygen to the RPE and photoreceptors. The different vascular supply networks create an uneven oxygen tension across the thickness of the retina (Cringle et al., *Invest. Ophthalmol. Vis. Sci.* 43:1922-27 (2002)). Oxygen fluctuation across the retinal layers is related to both the differing capillary densities and disparity in oxygen consumption by various retinal neurons and glia.

**[00221]** Local oxygen tension can significantly affect the retina and its microvasculature by regulation of an array of vasoactive agents, including, for example, vascular endothelial growth factor (VEGF). (*See, e.g.,* Werdich et al., *Exp. Eye Res.* 79:623 (2004); Arden et al., *Br. J. Ophthalmol.* 89:764 (2005)). Rod photoreceptors are believed to have the highest metabolic rate of any cell in the body (*see, e.g.,* Arden et al., *supra*). During dark adaptation, the rod photoreceptors recover their high cytoplasmic

calcium levels via cGMP-gated calcium channels with concomitant extrusion of sodium ions and water. The efflux of sodium from the cell is an ATP-dependent process, such that the retinal neurons consume up to an estimated five times more oxygen under scotopic (*i.e.,* dark adapted), compared with photopic (*i.e.,* light adapted) conditions. Thus, during characteristic dark adaptation of photoreceptors, the high metabolic demand leads to significant local reduction of oxygen levels in the dark-adapted retina (Ahmed et al, *Invest. Ophthalmol. Vis. Sci.* 34:516 (1993)).

**[00222]** Without being bound by any one theory, retinal hypoxia may be further increased in the retina of subjects who have diseases or conditions such as, for example, central retinal vein occlusion in which the retinal vasculature is already compromised. Increasing hypoxia may increase susceptibility to sight-threatening, retinal neovascularization. Neovascularization is the formation of new, functional microvascular networks with red blood cell perfusion, and is a characteristic of retinal degenerative disorders, including, but not limited to, diabetic retinopathy, retinopathy of prematurity, wet AMD and central retinal vein occlusions. Preventing or inhibiting dark adaptation of rod photoreceptor cells, thereby decreasing expenditure of energy and consumption of oxygen (*i.e.,* reducing metabolic demand), may inhibit or slow retinal degeneration, and/or may promote regeneration of retinal cells, including rod photoreceptor cells and retinal pigment epithelial (RPE) cells, and may reduce hypoxia and may inhibit neovascularization.

**[00223]** Methods are described herein for inhibiting (*i.e.,* reducing, preventing, slowing or retarding, in a biologically or statistically significant manner) degeneration of retinal cells (including retinal neuronal cells as described herein and RPE cells) and/or for reducing (*i.e.,* preventing or slowing, inhibiting, abrogating in a biologically or statistically significant manner) retinal ischemia. Methods are also provided for inhibiting (*i.e.,* reducing, preventing, slowing or retarding, in a biologically or statistically significant manner) neovascularization in the eye, particularly in the retina. Such methods comprise contacting the retina, and thus, contacting retinal cells (including retinal neuronal cells such as rod photoreceptor cells, and RPE cells) with at least one of the substituted heterocyclic amine derivative compounds described herein that inhibits at least one visual cycle *trans-cis* isomerase (which may include inhibition of isomerization of an all-*trans*-retinyl ester), under conditions and at a time that may prevent, inhibit, or delay dark adaptation of a rod photoreceptor cell in the retina. As described in further detail herein, in particular embodiments, the compound that contacts the retina interacts

with an isomerase enzyme or enzymatic complex in a RPE cell in the retina and inhibits, blocks, or in some manner interferes with the catalytic activity of the isomerase. Thus, isomerization of an all-*trans*-retinyl ester is inhibited or reduced. The at least one substituted heterocyclic amine derivative compound (or composition comprising at least one compound) is administered to a subject who has developed and manifested an ophthalmic disease or disorder or who is at risk of developing an ophthalmic disease or disorder, or to a subject who presents or who is at risk of presenting a condition such as retinal neovascularization or retinal ischemia.

**[00224]** By way of background, the visual cycle (also called retinoid cycle) refers to the series of enzyme and light-mediated conversions between the 11-*cis* and all-*trans* forms of retinol/retinal that occur in the photoreceptor and retinal pigment epithelial (RPE) cells of the eye. In vertebrate photoreceptor cells, a photon causes isomerization of the 11-*cis*-retinylidene chromophore to all-*trans*-retinylidene coupled to the visual opsin receptors. This photoisomerization triggers conformational changes of opsins, which, in turn, initiate the biochemical chain of reactions termed phototransduction (Filipek et al., *Annu. Rev. Physiol.* 65 851-79 (2003)). After absorption of light and photoisomerization of 11-*cis*-retinal to all-*trans* retinal, regeneration of the visual chromophore is a critical step in restoring photoreceptors to their dark-adapted state. Regeneration of the visual pigment requires that the chromophore be converted back to the 11-*cis*-configuration (reviewed in McBee et al., *Prog. Retin. Eye Res.* 20:469-52 (2001)). The chromophore is released from the opsin and reduced in the photoreceptor by retinol dehydrogenases. The product, all-*trans*-retinol, is trapped in the adjacent retinal pigment epithelium (RPE) in the form of insoluble fatty acid esters in subcellular structures known as retinosomes (Imanishi et al., *J. Cell Biol.* 164:373-78 (2004)).

**[00225]** During the visual cycle in rod receptor cells, the 11-*cis* retinal chromophore within the visual pigment molecule, which is called rhodopsin, absorbs a photon of light and is isomerized to the all-*trans* configuration, thereby activating the phototransduction cascade. Rhodopsin is a G-protein coupled receptor (GPCR) that consists of seven membrane-spanning helices that are interconnected by extracellular and cytoplasmic loops. When the all-*trans* form of the retinoid is still covalently bound to the pigment molecule, the pigment is referred to as metarhodopsin, which exists in different forms (*e.g.,* metarhodopsin I and metarhodopsin II). The all-trans retinoid is then hydrolyzed and the visual pigment is in the form of the apoprotein, opsin, which is also called apo-rhodopsin in the art and herein. This all-*trans* retinoid is transported or chaperoned out

of the photoreceptor cell and across the extracellular space to the RPE cells, where the retinoid is converted to the 11-*cis* isomer. The movement of the retinoids between the RPE and photoreceptors cells is believed to be accomplished by different chaperone polypeptides in each of the cell types. See Lamb et al., *Progress in Retinal and Eye Research* 23:307-80 (2004).

**[00226]** Under light conditions, rhodopsin continually transitions through the three forms, rhodopsin, metarhodopsin, and apo-rhodopsin. When most of the visual pigment is in the rhodopsin form (*i.e.,* bound with 11-*cis* retinal), the rod photoreceptor cell is in a "dark-adapted" state. When the visual pigment is predominantly in the metarhodopsin form (*i.e.,* bound with all-*trans*-retinal), the state of the photoreceptor cell is referred to as a "light-adapted," and when the visual pigment is apo-rhodopsin (or opsin) and no longer has bound chromophore, the state of the photoreceptor cell is referred to as "rhodopsin-depleted." Each of the three states of the photoreceptor cell has different energy requirements, and differing levels of ATP and oxygen are consumed. In the dark-adapted state, rhodopsin has no regulatory effect on cation channels, which are open, resulting in an influx of cations ($Na^+$ / $K^+$ and $Ca^{2+}$). To maintain the proper level of these cations in the cell during the dark state, the photoreceptor cells actively transport the cations out of the cell via ATP-dependent pumps. Thus maintenance of this "dark current" requires a large amount of energy, resulting in high metabolic demand. In the light-adapted state, metarhodopsin triggers an enzymatic cascade process that results in hydrolysis of GMP, which in turn, closes cation-specific channels in the photoreceptor cell membrane. In the rhodopsin-depleted state, the chromophore is hydrolyzed from metarhodopsin to form the apoprotein, opsin (apo-rhodopsin), which partially regulates the cation channels such that the rod photoreceptor cells exhibit an attenuated current compared with the photoreceptor in the dark-adapted state, resulting in a moderate metabolic demand.

**[00227]** Under normal light conditions, the incidence of rod photoreceptors in the dark adapted state is small, in general, 2% or less, and the cells are primarily in the light-adapted or rhodopsin-depleted states, which overall results in a relatively low metabolic demand compared with cells in the dark-adapted state. At night, however, the relative incidence of the dark-adapted photoreceptor state increases profoundly, due to the absence of light adaptation and to the continued operation of the "dark" visual cycle in RPE cells, which replenishes the rod photoreceptor cells with 11-*cis*-retinal. This shift to dark adaptation of the rod photoreceptor causes an increase in metabolic demand (that is,

increased ATP and oxygen consumption), leading ultimately to retinal hypoxia and subsequent initiation of angiogenesis. Most ischaemic insults to the retina therefore occur in the dark, for example, at night during sleep.

**[00228]** Without being bound by any theory, therapeutic intervention during the "dark" visual cycle may prevent retinal hypoxia and neovascularization that are caused by high metabolic activity in the dark-adapted rod photoreceptor cell. Merely by way of one example, altering the "dark" visual cycle by administering any one of the compounds described herein, which is an isomerase inhibitor, rhodopsin (*i.e.,* 11-*cis* retinal bound) may be reduced or depleted, preventing or inhibiting dark adaptation of rod photoreceptors. This in turn may reduce retinal metabolic demand, attenuating the nighttime risk of retinal ischemia and neovascularization, and thereby inhibiting or slowing retinal degeneration.

**[00229]** In one embodiment, at least one of the compounds described herein (*i.e.,* a substituted heterocyclic amine derivative compound as described in detail herein, including a compound having the structure as set forth in Formula (A) or Formula (B) and substructures thereof, and the specific substituted heterocyclic amine derivative compounds described herein) that, for example, blocks, reduces, inhibits, or in some manner attenuates the catalytic activity of a visual cycle isomerase in a statistically or biologically significant manner, prevents, inhibits, or delays dark adaptation of a rod photoreceptor cell, thereby inhibiting (*i.e.,* reducing, abrogating, preventing, slowing the progression of, or decreasing in a statistically or biologically significant manner) degeneration of retinal cells (or enhancing survival of retinal cells) of the retina of an eye. In another embodiment, the substituted heterocyclic amine derivative compounds prevents or inhibits dark adaptation of a rod photoreceptor cell, thereby reducing ischemia (*i.e.,* decreasing, preventing, inhibiting, slowing the progression of ischemia in a statistically or biologically significant manner). In yet another embodiment, the substituted heterocyclic amine derivative compounds described herein prevent dark adaptation of a rod photoreceptor cell, thereby inhibiting neovascularization in the retina of an eye. Accordingly, methods are provided herein for inhibiting retinal cell degeneration, for inhibiting neovascularization in the retina of an eye of a subject, and for reducing ischemia in an eye of a subject wherein the methods comprise administering at least one substituted heterocyclic amine derivative compound described herein, under conditions and at a time sufficient to prevent, inhibit, or delay dark adaptation of a rod photoreceptor cell. These methods and compositions are therefore useful for treating an

ophthalmic disease or disorder including, but not limited to, diabetic retinopathy, diabetic maculopathy, retinal blood vessel occlusion, retinopathy of prematurity, or ischemia reperfusion related retinal injury.

**[00230]** The substituted heterocyclic amine derivative compounds described herein (*i.e.,* a substituted heterocyclic amine derivative compound as described in detail herein, including a compound having the structure as set forth in Formula (A) or Formula (B), and substructures thereof, and the specific substituted heterocyclic amine derivative compounds described herein) prevent (*i.e.,* delay, slow, inhibit, or decrease) recovery of the visual pigment chromophore, which prevents or inhibits or retards the formation of retinals and increases the level of retinyl esters, which perturbs the visual cycle, inhibiting regeneration of rhodopsin, and which prevents, slows, delays or inhibits dark adaptation of a rod photoreceptor cell. In certain embodiments, when dark adaptation of rod photoreceptor cells is prevented in the presence of the compound, dark adaptation is substantially prevented, and the number or percent of rod photoreceptor cells that are rhodopsin-depleted or light adapted is increased compared with the number or percent of cells that are rhodopsin-depleted or light-adapted in the absence of the agent. Thus, in certain embodiments when dark adaptation of rod photoreceptor cells is prevented (*i.e.,* substantially prevented), only at least 2% of rod photoreceptor cells are dark-adapted, similar to the percent or number of cells that are in a dark-adapted state during normal, light conditions. In other certain embodiments, at least 5-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, or 60-70% of rod photoreceptor cells are dark-adapted after administration of an agent. In other embodiments, the compound acts to delay dark adaptation, and in the presence of the compound dark adaptation of rod photoreceptor cells is delayed 30 minutes, one hour, two hours, three hours, or four hours compared to dark adaptation of rod photoreceptors in the absence of the compound. By contrast, when a substituted heterocyclic amine derivative compound is administered such that the compound effectively inhibits isomerization of substrate during light-adapted conditions, the compound is administered in such a manner to minimize the percent of rod photoreceptor cells that are dark-adapted, for example, only 2%, 5%, 10%, 20%, or 25% of rod photoreceptors are dark-adapted (*see e.g.,* U.S. Patent Application Publication No. 2006/0069078; Patent Application No. PCT/US2007/002330).

**[00231]** In the retina in the presence of at least one substituted heterocyclic amine derivative compound, regeneration of rhodopsin in a rod photoreceptor cell is inhibited or the rate of regeneration is reduced (*i.e.,* inhibited, reduced, or decreased in a

statistically or biologically significant manner), at least in part, by preventing the formation of retinals, reducing the level of retinals, and/or increasing the level of retinyl esters. To determine the level of regeneration of rhodopsin in a rod photoreceptor cell, the level of regeneration of rhodopsin (which may be called a first level) is determined prior to permitting contact between the compound and the retina (*i.e.,* prior to administration of the agent). After a time sufficient for the compound and the retina and cells of the retina to interact, (*i.e.,* after administration of the compound), the level of regeneration of rhodopsin (which may be called a second level) is determined. A decrease in the second level compared with the first level indicates that the compound inhibits regeneration of rhodopsin. The level of rhodopsin generation may be determined after each dose, or after any number of doses, and ongoing throughout the therapeutic regimen to characterize the effect of the agent on regeneration of rhodopsin.

**[00232]** In certain embodiments, the subject in need of the treatments described herein, has a disease or disorder that results in or causes impairment of the capability of rod photoreceptors to regenerate rhodopsin in the retina. By way of example, inhibition of rhodopsin regeneration (or reduction of the rate of rhodopsin regeneration) may be symptomatic in patients with diabetes. In addition to determining the level of regeneration of rhodopsin in the subject who has diabetes before and after administration of a substituted heterocyclic amine derivative compound described herein, the effect of the compound is also characterized by comparing inhibition of rhodopsin regeneration in a first subject (or a first group or plurality of subjects) to whom the compound is administered, to a second subject (or second group or plurality of subjects) who has diabetes but who does not receive the agent.

**[00233]** In another embodiment, a method is provided for preventing or inhibiting dark adaptation of a rod photoreceptor cell (or a plurality of rod photoreceptor cells) in a retina comprising contacting the retina and at least one of the substituted heterocyclic amine derivative compounds described herein (*i.e.,* a compound as described in detail herein, including a compound having the structure as set forth in Formula (A) or Formula (B), and substructures thereof, and the specific substituted heterocyclic amine derivative compounds described herein), under conditions and at a time sufficient to permit interaction between the agent and an isomerase present in a retinal cell (such as an RPE cell). A first level of 11-*cis*-retinal in a rod photoreceptor cell in the presence of the compound is determined and compared to a second level of 11-*cis*-retinal in a rod photoreceptor cell in the absence of the compound. Prevention or inhibition of dark

adaptation of the rod photoreceptor cell is indicated when the first level of 11-*cis*-retinal is less than the second level of 11-*cis*-retinal.

**[00234]** Inhibiting regeneration of rhodopsin also includes increasing the level of 11-*cis*-retinyl esters present in the RPE cell in the presence of the compound compared with the level of 11-*cis*-retinyl esters present in the RPE cell in the absence of the compound (*i.e.,* prior to administration of the agent). A two-photon imaging technique is used to view and analyze retinosome structures in the RPE, which structures are believed to store retinyl esters (*see, e.g.,* Imanishi et al., *J. Cell Biol.* 164:373-83 (2004), Epub 2004 January 26.). A first level of retinyl esters may be determined prior to administration of the compound, and a second level of retinyl esters may be determined after administration of a first dose or any subsequent dose, wherein an increase in the second level compared to the first level indicates that the compound inhibits regeneration of rhodopsin.

**[00235]** Retinyl esters are analyzed by gradient HPLC according to methods practiced in the art (see, for example, Mata et al., *Neuron* 36:69-80 (2002); Trevino et al. *J. Exp. Biol.* 208:4151-57 (2005)). To measure 11-*cis* and all-*trans* retinals, retinoids are extracted by a formaldehyde method (*see, e.g.,* Suzuki et al., *Vis. Res.* 28:1061-70 (1988); Okajima and Pepperberg, *Exp. Eye Res.* 65:331-40 (1997)) or by a hydroxylamine method (*see, e.g.,* Groenendijk et al., *Biochim. Biophys. Acta.* 617:430-38 (1980)) before being analyzed on isocratic HPLC (*see, e.g.,* Trevino et al., *supra*). The retinoids are monitored spectrophotometrically (s*ee, e.g.,* Maeda et al., *J. Neurochem.* 85**:**944-956 (2003); Van Hooser et al., *J. Biol. Chem.* 277**:**19173-82 (2002)).

**[00236]** In another embodiment of the methods described herein for treating an ophthalmic disease or disorder, for inhibiting retinal cell degeneration (or enhancing retinal cell survival), for inhibiting neovascularization, and for reducing ischemia in the retina, preventing or inhibiting dark adaptation of a rod photoreceptor cell in the retina comprises increasing the level of apo-rhodopsin (also called opsin) in the photoreceptor cell. The total level of the visual pigment approximates the sum of rhodopsin and apo-rhodopsin and the total level remains constant. Therefore, preventing, delaying, or inhibiting dark adaptation of the rod photoreceptor cell may alter the ratio of apo-rhodopsin to rhodopsin. In particular embodiments, preventing, delaying, or inhibiting dark adaptation by administering a substituted heterocyclic amine derivative compound described herein may increase the ratio of the level of apo-rhodopsin to the level of rhodopsin compared to the ratio in the absence of the agent (for example, prior to

administration of the agent). An increase in the ratio (*i.e.,* a statistically or biologically significant increase) of apo-rhodopsin to rhodopsin indicates that the percent or number of rod photoreceptor cells that are rhodopsin-depleted is increased and that the percent or number of rod photoreceptor cells that are dark-adapted is decreased. The ratio of apo-rhodopsin to rhodopsin may be determined throughout the course of therapy to monitor the effect of the agent.

**[00237]** Determining or characterizing the capability of compound to prevent, delay, or inhibit dark adaptation of a rod photoreceptor cell may be determined in animal model studies. The level of rhodopsin and the ratio of apo-rhodopsin to rhodopsin may be determined prior to administration (which may be called a first level or first ratio, respectively) of the agent and then after administration of a first or any subsequent dose of the agent (which may be called a second level or second ratio, respectively) to determine and to demonstrate that the level of apo-rhodopsin is greater than the level of apo-rhodopsin in the retina of animals that did not receive the agent. The level of rhodopsin in rod photoreceptor cells may be performed according to methods practiced in the art and provided herein (*see, e.g.,* Yan et al. *J. Biol. Chem.* 279:48189–96 (2004)).

**[00238]** A subject in need of such treatment is a human or is a non-human primate or other animal (*i.e.,* veterinary use) who has developed symptoms of an ophthalmic disease or disorder or who is at risk for developing an ophthalmic disease or disorder. Examples of non-human primates and other animals include but are not limited to farm animals, pets, and zoo animals (*e.g.,* horses, cows, buffalo, llamas, goats, rabbits, cats, dogs, chimpanzees, orangutans, gorillas, monkeys, elephants, bears, large cats, etc.).

**[00239]** Also provided herein are methods for inhibiting (reducing, slowing, preventing) degeneration and enhancing retinal neuronal cell survival (or prolonging cell viability) comprising administering to a subject a composition comprising a pharmaceutically acceptable carrier and a substituted heterocyclic amine derivative compound described in detail herein, including a compound having any one of the structures set forth in Formula (A) or Formula (B), substructures thereof, and specific substituted heterocyclic amine derivative compounds recited herein. Retinal neuronal cells include photoreceptor cells, bipolar cells, horizontal cells, ganglion cells, and amacrine cells. In another embodiment, methods are provided for enhancing survival or inhibiting degeneration of a mature retinal cell such as a RPE cell or a Müller glial cell. In other embodiments, a method for preventing or inhibiting photoreceptor degeneration in an eye of a subject are provided. A method that prevents or inhibits photoreceptor degeneration may include a

method for restoring photoreceptor function in an eye of a subject. Such methods comprise administering to the subject a composition comprising a substituted heterocyclic amine derivative compound as described herein and a pharmaceutically or acceptable carrier (*i.e.,* excipient or vehicle). More specifically, these methods comprise administering to a subject a pharmaceutically acceptable excipient and a substituted heterocyclic amine derivative compound described herein, including a compound having the structures set forth in Formula (A) or Formula (B) or substructures thereof described herein. Without wishing to be bound by theory, the compounds described herein may inhibit an isomerization step of the retinoid cycle (*i.e.,* visual cycle) and/or may slow chromophore flux in a retinoid cycle in the eye.

**[00240]** The ophthalmic disease may result, at least in part, from lipofuscin pigment(s) accumulation and/or from accumulation of *N*-retinylidene-*N*-retinylethanolamine (A2E) in the eye. Accordingly, in certain embodiments, methods are provided for inhibiting or preventing accumulation of lipofuscin pigment(s) and/or A2E in the eye of a subject. These methods comprise administering to the subject a composition comprising a pharmaceutically acceptable carrier and a substituted heterocyclic amine derivative compound as described in detail herein, including a compound having the structure as set forth in Formulae (A) or substructures thereof.

**[00241]** In some embodiments, a substituted heterocyclic amine derivative compound is administered to a subject who has an excess of a retinoid in an eye (*e.g.*, an excess of 11-*cis*-retinol or 11-*cis*-retinal), an excess of retinoid waste products or intermediates in the recycling of all-*trans*-retinal, or the like. Methods described herein and practiced in the art may be used to determine whether the level of one or more endogenous retinoids in a subject are altered (increased or decreased in a statistically significant or biologically significant manner) during or after administration of any one of the compounds described herein. Rhodopsin, which is composed of the protein opsin and retinal (a vitamin A form), is located in the membrane of the photoreceptor cell in the retina of the eye and catalyzes the only light-sensitive step in vision. The 11-*cis*-retinal chromophore lies in a pocket of the protein and is isomerized to all-trans retinal when light is absorbed. The isomerization of retinal leads to a change of the shape of rhodopsin, which triggers a cascade of reactions that lead to a nerve impulse that is transmitted to the brain by the optic nerve.

**[00242]** Methods of determining endogenous retinoid levels in a vertebrate eye, and an excess or deficiency of such retinoids, are disclosed in, for example, U.S. Patent

Application Publication No: 2005/0159662 (the disclosure of which is incorporated by reference herein in its entirety). Other methods of determining endogenous retinoid levels in a subject, which is useful for determining whether levels of such retinoids are above the normal range, and include for example, analysis by high pressure liquid chromatography (HPLC) of retinoids in a biological sample from a subject. For example, retinoid levels can be determined in a biological sample that is a blood sample (which includes serum or plasma) from a subject. A biological sample may also include vitreous fluid, aqueous humor, intraocular fluid, subretinal fluid, or tears.

**[00243]** For example, a blood sample can be obtained from a subject, and different retinoid compounds and levels of one or more of the retinoid compounds in the sample can be separated and analyzed by normal phase high pressure liquid chromatography (HPLC) (*e.g.*, with a HP1100 HPLC and a Beckman, Ultrasphere-Si, 4.6 mm x 250 mm column using 10% ethyl acetate/90% hexane at a flow rate of 1.4 ml/minute). The retinoids can be detected by, for example, detection at 325 nm using a diode-array detector and HP Chemstation A.03.03 software. An excess in retinoids can be determined, for example, by comparison of the profile of retinoids (*i.e.,* qualitative, *e.g.,* identity of specific compounds, and quantitative, *e.g.,* the level of each specific compound) in the sample with a sample from a normal subject. Persons skilled in the art who are familiar with such assays and techniques and will readily understand that appropriate controls are included.

**[00244]** As used herein, increased or excessive levels of endogenous retinoid, such as 11-*cis*-retinol or 11-*cis*-retinal, refer to levels of endogenous retinoid higher than those found in a healthy eye of a young vertebrate of the same species. Administration of a substituted heterocyclic amine derivative compound can reduce or eliminate the requirement for endogenous retinoid. In certain embodiments, the level of endogenous retinoid may be compared before and after any one or more doses of a substituted heterocyclic amine derivative compound is administered to a subject to determine the effect of the compound on the level of endogenous retinoids in the subject.

**[00245]** In another embodiment, the methods described herein for treating an ophthalmic disease or disorder, for inhibiting neovascularization, and for reducing ischemia in the retina comprise administering at least one of the substituted heterocyclic amine derivative compounds described herein, thereby effecting a decrease in metabolic demand, which includes effecting a reduction in ATP consumption and in oxygen consumption in rod photoreceptor cells. As described herein, consumption of ATP and

oxygen in a dark-adapted rod photoreceptor cell is greater than in rod photoreceptor cells that are light-adapted or rhodopsin-depleted; thus, use of the compounds in the methods described herein reduces the consumption of ATP in the rod photoreceptor cells that are prevented, inhibited, or delayed from dark adaptation compared with rod photoreceptor cells that are dark-adapted (such as the cells prior to administration or contact with the compound or cells that are never exposed to the compound).

**[00246]** The methods described herein prevent or inhibit dark adaptation of a rod photoreceptor cell therefore reduce hypoxia (*i.e.,* reduce in a statistically or biologically significant manner) in the retina. For example, the level of hypoxia (a first level) may be determined prior to initiation of the treatment regimen, that is, prior to the first dosing of the compound (or a composition, as described herein, comprising the compound). The level of hypoxia (for example, a second level) may be determined after the first dosing, and/or after any second or subsequent dosing to monitor and characterize hypoxia throughout the treatment regimen. A decrease (reduction) in the second (or any subsequent) level of hypoxia compared to the level of hypoxia prior to initial administration indicates that the compound and the treatment regiment prevent dark adaptation of the rod photoreceptor cells and may be used for treating ophthalmic diseases and disorders. Consumption of oxygen, oxygenation of the retina, and/or hypoxia in the retina may be determined using methods practiced in the art. For example, oxygenation of the retina may be determined by measuring the fluorescence of flavoproteins in the retina (*see, e.g.,* U.S. Patent No. 4,569,354). Another exemplary method is retinal oximetry that measures blood oxygen saturation in the large vessels of the retina near the optic disc. Such methods may be used to identify and determine the extent of retinal hypoxia before changes in retinal vessel architecture can be detected.

**[00247]** A biological sample is a blood sample (from which serum or plasma may be prepared), biopsy specimen, body fluids (*e.g.,* vitreous fluid, aqueous humor, intraocular fluid, subretinal fluid, or tears), tissue explant, organ culture, or any other tissue or cell preparation from a subject or a biological source. A sample may further refer to a tissue or cell preparation in which the morphological integrity or physical state has been disrupted, for example, by dissection, dissociation, solubilization, fractionation, homogenization, biochemical or chemical extraction, pulverization, lyophilization, sonication, or any other means for processing a sample derived from a subject or biological source. The subject or biological source may be a human or non-human animal, a primary cell culture (*e.g.*, a retinal cell culture), or culture adapted cell line,

including but not limited to, genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, immortalized or immortalizable cell lines, somatic cell hybrid cell lines, differentiated or differentiatable cell lines, transformed cell lines, and the like. Mature retinal cells, including retinal neuronal cells, RPE cells, and Müller glial cells, may be present in or isolated from a biological sample as described herein. For example, the mature retinal cell may be obtained from a primary or long-term cell culture or may be present in or isolated from a biological sample obtained from a subject (human or non-human animal).

Retinal Cells

**[00248]** The retina is a thin layer of nervous tissue located between the vitreous body and choroid in the eye. Major landmarks in the retina are the fovea, the macula, and the optic disc. The retina is thickest near the posterior sections and becomes thinner near the periphery. The macula is located in the posterior retina and contains the fovea and foveola. The foveola contains the area of maximal cone density and, thus, imparts the highest visual acuity in the retina. The foveola is contained within the fovea, which is contained within the macula.

**[00249]** The peripheral portion of the retina increases the field of vision. The peripheral retina extends anterior to the ciliary body and is divided into four regions: the near periphery (most posterior), the mid-periphery, the far periphery, and the ora serrata (most anterior). The ora serrata denotes the termination of the retina.

**[00250]** The term neuron (or nerve cell) as understood in the art and used herein denotes a cell that arises from neuroepithelial cell precursors. Mature neurons (*i.e.,* fully differentiated cells) display several specific antigenic markers. Neurons may be classified functionally into four groups: (1) afferent neurons (or sensory neurons) that transmit information into the brain for conscious perception and motor coordination; (2) motor neurons that transmit commands to muscles and glands; (3) interneurons that are responsible for local circuitry; and (4) projection interneurons that relay information from one region of the brain to anther region and therefore have long axons. Interneurons process information within specific subregions of the brain and have relatively shorter axons. A neuron typically has four defined regions: the cell body (or soma); an axon; dendrites; and presynaptic terminals. The dendrites serve as the primary input of information from other neural cells. The axon carries the electrical signals that are initiated in the cell body to other neurons or to effector organs. At the presynaptic

terminals, the neuron transmits information to another cell (the postsynaptic cell), which may be another neuron, a muscle cell, or a secretory cell.

**[00251]** The retina is composed of several types of neuronal cells. As described herein, the types of retinal neuronal cells that may be cultured *in vitro* by this method include photoreceptor cells, ganglion cells, and interneurons such as bipolar cells, horizontal cells, and amacrine cells. Photoreceptors are specialized light-reactive neural cells and comprise two major classes, rods and cones. Rods are involved in scotopic or dim light vision, whereas photopic or bright light vision originates in the cones. Many neurodegenerative diseases, such as AMD, that result in blindness affect photoreceptors.

**[00252]** Extending from their cell bodies, the photoreceptors have two morphologically distinct regions, the inner and outer segments. The outer segment lies furthermost from the photoreceptor cell body and contains disks that convert incoming light energy into electrical impulses (phototransduction). The outer segment is attached to the inner segment with a very small and fragile cilium. The size and shape of the outer segments vary between rods and cones and are dependent upon position within the retina. *See* Hogan, "Retina" *in Histology of the Human Eye: an Atlas and Text Book* (Hogan et al. (eds). WB Saunders; Philadelphia, PA (1971)); *Eye and Orbit*, 8$^{th}$ Ed., Bron et al., (Chapman and Hall, 1997).

**[00253]** Ganglion cells are output neurons that convey information from the retinal interneurons (including horizontal cells, bipolar cells, amacrine cells) to the brain. Bipolar cells are named according to their morphology, and receive input from the photoreceptors, connect with amacrine cells, and send output radially to the ganglion cells. Amacrine cells have processes parallel to the plane of the retina and have typically inhibitory output to ganglion cells. Amacrine cells are often subclassified by neurotransmitter or neuromodulator or peptide (such as calretinin or calbindin) and interact with each other, with bipolar cells, and with photoreceptors. Bipolar cells are retinal interneurons that are named according to their morphology; bipolar cells receive input from the photoreceptors and sent the input to the ganglion cells. Horizontal cells modulate and transform visual information from large numbers of photoreceptors and have horizontal integration (whereas bipolar cells relay information radially through the retina).

**[00254]** Other retinal cells that may be present in the retinal cell cultures described herein include glial cells, such as Müller glial cells, and retinal pigment epithelial cells (RPE). Glial cells surround nerve cell bodies and axons. The glial cells do not carry

electrical impulses but contribute to maintenance of normal brain function. Müller glia, the predominant type of glial cell within the retina, provide structural support of the retina and are involved in the metabolism of the retina (*e.g.,* contribute to regulation of ionic concentrations, degradation of neurotransmitters, and remove certain metabolites (*see, e.g.,* Kljavin et al., *J. Neurosci.* 11:2985 (1991))). Müller's fibers (also known as sustentacular fibers of retina) are sustentacular neuroglial cells of the retina that run through the thickness of the retina from the internal limiting membrane to the bases of the rods and cones where they form a row of junctional complexes.

**[00255]** Retinal pigment epithelial (RPE) cells form the outermost layer of the retina, separated from the blood vessel-enriched choroids by Bruch's membrane. RPE cells are a type of phagocytic epithelial cell, with some functions that are macrophage-like, which lies immediately below the retinal photoreceptors. The dorsal surface of the RPE cell is closely apposed to the ends of the rods, and as discs are shed from the rod outer segment they are internalized and digested by RPE cells. Similar process occurs with the disc of the cones. RPE cells also produce, store, and transport a variety of factors that contribute to the normal function and survival of photoreceptors. Another function of RPE cells is to recycle vitamine A as it moves between photoreceptors and the RPE during light and dark adaptation in the process known as the visual cycle.

**[00256]** Described herein is an exemplary long-term *in vitro* cell culture system that permits and promotes the survival in culture of mature retinal cells, including retinal neurons, for at least 2-4 weeks, over 2 months, or for as long as 6 months. The cell culture system may be used for identifying and characterizing the substituted heterocyclic amine derivative compounds that are useful in the methods described herein for treating and/or preventing an ophthalmic disease or disorder or for preventing or inhibiting accumulation in the eye of lipofuscin(s) and/or A2E. Retinal cells are isolated from non-embryonic, non-tumorigenic tissue and have not been immortalized by any method such as, for example, transformation or infection with an oncogenic virus. The cell culture system comprises all the major retinal neuronal cell types (photoreceptors, bipolar cells, horizontal cells, amacrine cells, and ganglion cells), and also may include other mature retinal cells such as retinal pigment epithelial cells and Müller glial cells.

**[00257]** For example, a blood sample can be obtained from a subject, and different retinoid compounds and levels of one or more of the retinoid compounds in the sample can be separated and analyzed by normal phase high pressure liquid chromatography (HPLC) (*e.g.*, with a HP1100 HPLC and a Beckman, Ultrasphere-Si, 4.6 mm x 250 mm

column using 10% ethyl acetate/90% hexane at a flow rate of 1.4 ml/minute). The retinoids can be detected by, for example, detection at 325 nm using a diode-array detector and HP Chemstation A.03.03 software. An excess in retinoids can be determined, for example, by comparison of the profile of retinoids (*i.e.,* qualitative, *e.g.,* identity of specific compounds, and quantitative, *e.g.,* the level of each specific compound) in the sample with a sample from a normal subject. Persons skilled in the art who are familiar with such assays and techniques and will readily understand that appropriate controls are included.

**[00258]** As used herein, increased or excessive levels of endogenous retinoid, such as 11-*cis*-retinol or 11-*cis*-retinal, refer to levels of endogenous retinoid higher than those found in a healthy eye of a young vertebrate of the same species. In some embodiments, administration of a substituted heterocyclic amine derivative compound will reduce or eliminate the requirement for endogenous retinoid.

*In Vivo* and *In Vitro* Methods for Determining Therapeutic Effectiveness of Compounds

**[00259]** In one embodiment, methods are provided for using the compounds described herein for enhancing or prolonging retinal cell survival, including retinal neuronal cell survival and RPE cell survival. Also provided herein are methods for inhibiting or preventing degeneration of a retinal cell, including a retinal neuronal cell (*e.g.,* a photoreceptor cell, an amacrine cell, a horizontal cell, a bipolar cell, and a ganglion cell) and other mature retinal cells such as retinal pigment epithelial cells and Müller glial cells using the compounds described herein. Such methods comprise, in certain embodiments, administration of a substituted heterocyclic amine derivative compound as described herein. Such a compound is useful for enhancing retinal cell survival, including photoreceptor cell survival and retinal pigment epithelia survival, inhibiting or slowing degeneration of a retinal cell, and thus increasing retinal cell viability, which can result in slowing or halting the progression of an ophthalmic disease or disorder or retinal injury, which are described herein.

**[00260]** The effect of a substituted heterocyclic amine derivative compound on retinal cell survival (and/or retinal cell degeneration) may be determined by using cell culture models, animal models, and other methods that are described herein and practiced by persons skilled in the art. By way of example, and not limitation, such methods and assays include those described in Oglivie et al., *Exp. Neurol.* 161:675-856 (2000); U.S. Patent No. 6,406,840; WO 01/81551; WO 98/12303; U.S. Patent Application No. 2002/0009713; WO 00/40699; U.S. Patent No. 6,117,675; U.S. Patent No. 5,736,516;

WO 99/29279; WO 01/83714; WO 01/42784; U.S. Patent No. 6,183,735; U.S. Patent No. 6,090,624; WO 01/09327; U.S. Patent No. 5,641,750; U.S. Patent Application Publication No. 2004/0147019; and U.S. Patent Application Publication No. 2005/0059148.

**[00261]** Compounds described herein that are useful for treating an ophthalmic disease or disorder (including a retinal disease or disorder) inhibit, block, impair, or in some manner interfere with one or more steps in the visual cycle (also called the retinoid cycle herein and in the art). Without wishing to be bound by a particular theory, a substituted heterocyclic amine derivative compound inhibis or blocks an isomerization step in the visual cycle, for example, by inhibiting or blocking a functional activity of a visual cycle *trans-cis* isomerase. The compounds described herein inhibit, directly or indirectly, isomerization of all-*trans*-retinol to 11-*cis*-retinol. The compounds bind to, or in some manner interact with, and inhibit the isomerase activity of at least one isomerase in a retinal cell. The compounds described herein also directly or indirectly inhibit or reduce the activity of an isomerase that is involved in the visual cycle. The compound blocks or inhibits the capability of the isomerase to bind to one or more substrates, including but not limited to, an all-*trans*-retinyl ester substrate or all-*trans*-retinol. Alternatively, or in addition, the compound may bind to the catalytic site or region of the isomerase, thereby inhibiting the capability of the enzyme to catalyze isomerization of at least one substrate. On the basis of scientific data to date, and at least one isomerase that catalyzes the isomerization of a substrate during the visual cycle is believed to be located in the cytoplasm of RPE cells. As discussed herein, each step, enzyme, substrate, intermediate, and product of the visual cycle is not yet elucidated. While a polypeptide called RPE65, which has been found in the cytoplasm and membrane bound in RPE cells, is hypothesized to have isomerase activity (and has also been referred to in the art as having isomerohydrolase activity) (*see, e.g.,* Moiseyev et al., *Proc. Natl. Acad. Sci. USA* 102:12413-18 (2004); Chen et al., *Invest. Ophthalmol. Vis. Sci.* 47:1177-84 (2006)), other persons skilled in the art believe that the RPE65 acts primarily as a chaperone for all-*trans*-retinyl esters (*see, e.g.,* Lamb et al. *supra*).

**[00262]** Exemplary methods are described herein and practiced by persons skilled in the art for determining the level of enzymatic activity of a visual cycle isomerase in the presence of any one of the compounds described herein. A compound that decreases isomerase activity is useful for treating an ophthalmic disease or disorder. Thus, methods are provided herein for detecting inhibition of isomerase activity comprising

contacting (*i.e.,* mixing, combining, or in some manner permitting the compound and isomerase to interact) a biological sample comprising the isomerase and a substituted heterocyclic amine derivative compound described herein and then determining the level of enzymatic activity of the isomerase. A person having skill in the art will appreciate that as a control, the level of activity of the isomerase in the absence of a compound or in the presence of a compound known not to alter the enzymatic activity of the isomerase can be determined and compared to the level of activity in the presence of the compound. A decrease in the level of isomerase activity in the presence of the compound compared to the level of isomerase activity in the absence of the compound indicates that the compound is useful for treating an ophthalmic disease or disorder, such as age-related macular degeneration or Stargardt's disease. A decrease in the level of isomerase activity in the presence of the compound compared to the level of isomerase activity in the absence of the compound indicates that the compound is also useful in the methods described herein for inhibiting or preventing dark adaptation, inhibiting neovascularization and reducing hypoxia and thus useful for treating an ophthalmic disease or disorder, for example, diabetic retinopathy, diabetic maculopathy, retinal blood vessel occlusion, retinopathy of prematurity, or ischemia reperfusion related retinal injury.

**[00263]** The capability of a substituted heterocyclic amine derivative compound described herein to inhibit or to prevent dark adaptation of a rod photoreceptor cell by inhibiting regeneration of rhodopsin is determined by *in vitro* assays and/or *in vivo* animal models. By way of example, inhibition of regeneration is determined in a mouse model in which a diabetes-like condition is induced chemically or in a diabetic mouse model (*see, e.g.,* Phipps et al*., Invest. Ophthalmol. Vis. Sci.* 47:3187-94 (2006); Ramsey et al., *Invest. Ophthalmol. Vis. Sci.* 47:5116-24 (2006)). The level of rhodopsin (a first level) may be determined (for example, spectrophotometrically) in the retina of animals prior to administration of the agent and compared with the level (a second level) of rhodopsin measured in the retina of animals after administration of the agent. A decrease in the second level of rhodopsin compared with the first level of rhodopsin indicates that the agent inhibits regeneration of rhodopsin. The appropriate controls and study design to determine whether regeneration of rhodopsin is inhibited in a statistically significant or biologically significant manner can be readily determined and implemented by persons skilled in the art.

**[00264]** Methods and techniques for determining or characterizing the effect of any one of the compounds described herein on dark adaptation and rhodopsin regeneration in rod photoreceptor cells in a mammal, including a human, may be performed according to procedures described herein and practiced in the art. For example, detection of a visual stimulus after exposure to light (*i.e.,* photobleaching) versus time in darkness may be determined before administration of the first dose of the compound and at a time after the first dose and/or any subsequent dose. A second method for determining prevention or inhibition of dark adaptation by the rod photoreceptor cells includes measurement of the amplitude of at least one, at least two, at least three, or more electroretinogram components, which include, for example, the a-wave and the b-wave. See, for example, Lamb et al., *supra*; Asi et al., *Documenta Ophthalmologica* 79:125-39 (1992).

**[00265]** Inhibiting regeneration of rhodopsin by a substituted heterocyclic amine derivative compound described herein comprises reducing the level of the chromophore, 11-*cis*-retinal, that is produced and present in the RPE cell, and consequently reducing the level of 11-*cis*-retinal that is present in the photoreceptor cell. Thus, the compound, when permitted to contact the retina under suitable conditions and at a time sufficient to prevent dark adaptation of a rod photoreceptor cell and to inhibit regeneration of rhodopsin in the rod photoreceptor cell, effects a reduction in the level of 11-*cis*-retinal in a rod photoreceptor cell (*i.e.,* a statistically significant or biologically significant reduction). That is, the level of 11-*cis* retinal in a rod photoreceptor cell is greater prior to administration of the compound when compared with the level of 11-*cis*-retinal in the photoreceptor cell after the first and/or any subsequent administration of the compound. A first level of 11-*cis*-retinal may be determined prior to administration of the compound, and a second level of 11-*cis*-retinal may be determined after administration of a first dose or any subsequent dose to monitor the effect of the compound. A decrease in the second level compared to the first level indicates that the compound inhibits regeneration of rhodopsin and thus inhibits or prevents dark adaptation of the rod photoreceptor cells.

**[00266]** An exemplary method for determining or characterizing the capability of a substituted heterocyclic amine derivative compound to reduce retinal hypoxia includes measuring the level of retinal oxygenation, for example, by Magnetic Resonance Imaging (MRI) to measure changes in oxygen pressure (*see, e.g.,* Luan et al., *Invest. Ophthalmol. Vis. Sci.* 47:320-28 (2006)). Methods are also available and routinely practiced in the art to determine or characterize the capability of compounds described

herein to inhibit degeneration of a retinal cell (see, e.g., Wenzel et al., *Prog. Retin. Eye Res.* 24:275-306 (2005)).

**[00267]** Animal models may be used to characterize and identify compounds that may be used to treat retinal diseases and disorders. A recently developed animal model may be useful for evaluating treatments for macular degeneration has been described by Ambati et al. (*Nat. Med.* 9:1390-97 (2003); Epub 2003 Oct 19). This animal model is one of only a few exemplary animal models presently available for evaluating a compound or any molecule for use in treating (including preventing) progression or development of a retinal disease or disorder. Animal models in which the *ABCR* gene, which encodes an ATP-binding cassette transporter located in the rims of photoreceptor outer segment discs, may be used to evaluate the effect of a compound. Mutations in the ABCR gene are associated with Stargardt's disease, and heterozygous mutations in ABCR have been associated with AMD. Accordingly, animals have been generated with partial or total loss of ABCR function and may used to characterize the substituted heterocyclic amine derivative compound described herein. (*See, e.g.,* Mata et al., *Invest. Ophthalmol. Sci.* 42:1685-90 (2001); Weng et al., *Cell* 98:13-23 (1999); Mata et al., *Proc. Natl. Acad. Sci. USA* 97:7154-49 (2000); US 2003/0032078; U.S. Patent No. 6,713,300). Other animal models include the use of mutant ELOVL4 transgenic mice to determine lipofuscin accumulation, electrophysiology, and photoreceptor degeneration, or prevention or inhibition thereof (*see, e.g.,* Karan et al., *Proc. Natl. Acad. Sci. USA* 102:4164-69 (2005)).

**[00268]** The effect of any one of the compounds described herein may be determined in a diabetic retinopathy animal model, such as described in Luan et al. or may be determined in a normal animal model, in which the animals have been light or dark adapted in the presence and absence of any one of the compounds described herein. Another exemplary method for determining the capability of the agent to reduce retinal hypoxia measures retinal hypoxia by deposition of a hydroxyprobe (*see, e.g.,* de Gooyer et al. (*Invest. Ophthalmol. Vis. Sci.* 47:5553-60 (2006)). Such a technique may be performed in an animal model using $Rho^{-}/Rho^{-}$ knockout mice (*see* de Gooyer et al., *supra*) in which at least one compound described herein is administered to group(s) of animals in the presence and absence of the at least one compound, or may be performed in normal, wildtype animals in which at least one compound described herein is administered to group(s) of animals in the presence and absence of the at least one compound. Other animal models include models for determining photoreceptor

function, such as rat models that measure elctroretinographic (ERG) oscillatory potentials (*see, e.g.,* Liu et al., *Invest. Ophthalmol. Vis. Sci.* 47:5447-52 (2006); Akula et al., *Invest. Ophthalmol. Vis. Sci.* 48:4351-59 (2007); Liu et al., *Invest. Ophthalmol. Vis. Sci.* 47:2639-47 (2006); Dembinska et al., *Invest. Ophthalmol. Vis. Sci.* 43:2481-90 (2002); Penn et al., *Invest. Ophthalmol. Vis. Sci.* 35:3429-35 (1994); Hancock et al., *Invest. Ophthalmol. Vis. Sci.* 45:1002-1008 (2004)).

**[00269]** A method for determining the effect of a compound on isomerase activity is performed *in vitro* as described herein and in the art (Stecher et al., *J. Biol. Chem.* 274**:**8577-85 (1999); *see also* Golczak et al., *Proc. Natl. Acad. Sci. USA* 102:8162-67 (2005)). Retinal pigment epithelium (RPE) microsome membranes isolated from an animal (such as bovine, porcine, human, for example) serves as the source of the isomerase. The capability of the substituted heterocyclic amine derivative compounds to inhibit isomerase is also determined by an *in vivo* murine isomerase assay. Brief exposure of the eye to intense light ("photobleaching" of the visual pigment or simply "bleaching") is known to photo-isomerize almost all 11-*cis*-retinal in the retina. The recovery of 11-*cis*-retinal after bleaching can be used to estimate the activity of isomerase *in vivo* (*see, e.g.,* Maeda et al., *J. Neurochem.* 85**:**944-956 (2003); Van Hooser et al., *J. Biol. Chem.* 277**:**19173-82, 2002). Electroretinographic (ERG) recording is performed as previously described (Haeseleer et al., *Nat. Neurosci.* 7:1079-87 (2004); Sugitomo et al., *J. Toxicol. Sci.* 22 Suppl 2:315-25 (1997); Keating et al., *Documenta Ophthalmologica* 100:77-92 (2000)). See also Deigner et al., *Science*, 244**:** 968-971 (1989); Gollapalli et al., *Biochim. Biophys. Acta* 1651**:** 93-101 (2003); Parish, et al., *Proc. Natl. Acad. Sci. USA* 95:14609-13 (1998); Radu et al., *Proc Natl Acad Sci USA* 101**:** 5928-33 (2004).

**[00270]** Cell culture methods, such as the method described herein, are also useful for determining the effect of a compound described herein on retinal neuronal cell survival. Exemplary cell culture models are described herein and described in detail in U.S. Patent Application Publication No. US 2005-0059148 and U.S. Patent Application Publication No. US2004-0147019 (which are incorporated by reference in their entirety), which are useful for determining the capability of a substituted heterocyclic amine derivative compound as described herein to enhance or prolong survival of neuronal cells, particularly retinal neuronal cells, and of retinal pigment epithelial cells, and inhibit, prevent, slow, or retard degeneration of an eye, or the retina or retinal cells thereof, or

the RPE, and which compounds are useful for treating ophthalmic diseases and disorders.

**[00271]** The cell culture model comprises a long-term or extended culture of mature retinal cells, including retinal neuronal cells (*e.g.,* photoreceptor cells, amacrine cells, ganglion cells, horizontal cells, and bipolar cells). The cell culture system and methods for producing the cell culture system provide extended culture of photoreceptor cells. The cell culture system may also comprise retinal pigment epithelial (RPE) cells and Müller glial cells.

**[00272]** The retinal cell culture system may also comprise a cell stressor. The application or the presence of the stressor affects the mature retinal cells, including the retinal neuronal cells, *in vitro*, in a manner that is useful for studying disease pathology that is observed in a retinal disease or disorder. The cell culture model provides an *in vitro* neuronal cell culture system that will be useful in the identification and biological testing of a substituted heterocyclic amine derivative compound that is suitable for treatment of neurological diseases or disorders in general, and for treatment of degenerative diseases of the eye and brain in particular. The ability to maintain primary, *in vitro*-cultured cells from mature retinal tissue, including retinal neurons over an extended period of time in the presence of a stressor enables examination of cell-to-cell interactions, selection and analysis of neuroactive compounds and materials, use of a controlled cell culture system for *in vitro* CNS and ophthalmic tests, and analysis of the effects on single cells from a consistent retinal cell population.

**[00273]** The cell culture system and the retinal cell stress model comprise cultured mature retinal cells, retinal neurons, and a retinal cell stressor, which may be used for screening and characterizing a substituted heterocyclic amine derivative compound that are capable of inducing or stimulating the regeneration of CNS tissue that has been damaged by disease. The cell culture system provides a mature retinal cell culture that is a mixture of mature retinal neuronal cells and non-neuronal retinal cells. The cell culture system comprises all the major retinal neuronal cell types (photoreceptors, bipolar cells, horizontal cells, amacrine cells, and ganglion cells), and may also include other mature retinal cells such as RPE and Müller glial cells. By incorporating these different types of cells into the *in vitro* culture system, the system essentially resembles an "artificial organ" that is more akin to the natural *in vivo* state of the retina.

**[00274]** Viability of one or more of the mature retinal cell types that are isolated (harvested) from retinal tissue and plated for tissue culture may be maintained for an

extended period of time, for example, from two weeks up to six months. Viability of the retinal cells may be determined according to methods described herein and known in the art. Retinal neuronal cells, similar to neuronal cells in general, are not actively dividing cells *in vivo* and thus cell division of retinal neuronal cells would not necessarily be indicative of viability. An advantage of the cell culture system is the ability to culture amacrine cells, photoreceptors, and associated ganglion projection neurons and other mature retinal cells for extended periods of time, thereby providing an opportunity to determine the effectiveness of a substituted heterocyclic amine derivative compound described herein for treatment of retinal disease.

**[00275]** The biological source of the retinal cells or retinal tissue may be mammalian (*e.g.,* human, non-human primate, ungulate, rodent, canine, porcine, bovine, or other mammalian source), avian, or from other genera. Retinal cells including retinal neurons from post-natal non-human primates, post-natal pigs, or post-natal chickens may be used, but any adult or post-natal retinal tissue may be suitable for use in this retinal cell culture system.

**[00276]** In certain instances, the cell culture system may provide for robust long-term survival of retinal cells without inclusion of cells derived from or isolated or purified from non-retinal tissue. Such a cell culture system comprises cells isolated solely from the retina of the eye and thus is substantially free of types of cells from other parts or regions of the eye that are separate from the retina, such as the ciliary body, iris, choroid, and vitreous. Other cell culture methods include the addition of non-retinal cells, such as ciliary body cell and/or stem cells (which may or may not be retinal stem cells) and/or additional purified glial cells.

**[00277]** The *in vitro* retinal cell culture systems described herein may serve as physiological retinal models that can be used to characterize aspects of the physiology of the retina. This physiological retinal model may also be used as a broader general neurobiology model. A cell stressor may be included in the model cell culture system. A cell stressor, which as described herein is a retinal cell stressor, adversely affects the viability or reduces the viability of one or more of the different retinal cell types, including types of retinal neuronal cells, in the cell culture system. A person skilled in the art would readily appreciate and understand that as described herein a retinal cell that exhibits reduced viability means that the length of time that a retinal cell survives in the cell culture system is reduced or decreased (decreased lifespan) and/or that the retinal cell exhibits a decrease, inhibition, or adverse effect of a biological or biochemical

function (*e.g.,* decreased or abnormal metabolism; initiation of apoptosis; etc.) compared with a retinal cell cultured in an appropriate control cell system (*e.g.,* the cell culture system described herein in the absence of the cell stressor). Reduced viability of a retinal cell may be indicated by cell death; an alteration or change in cell structure or morphology; induction and/or progression of apoptosis; initiation, enhancement, and/or acceleration of retinal neuronal cell neurodegeneration (or neuronal cell injury).

**[00278]** Methods and techniques for determining cell viability are described in detail herein and are those with which skilled artisans are familiar. These methods and techniques for determining cell viability may be used for monitoring the health and status of retinal cells in the cell culture system and for determining the capability of the substituted heterocyclic amine derivative compounds described herein to alter (preferably increase, prolong, enhance, improve) retinal cell or retinal pigment epithelial cell viability or retinal cell survival.

**[00279]** The addition of a cell stressor to the cell culture system is useful for determining the capability of a substituted heterocyclic amine derivative compound to abrogate, inhibit, eliminate, or lessen the effect of the stressor. The retinal cell culture system may include a cell stressor that is chemical (*e.g.,* A2E, cigarette smoke concentrate); biological (for example, toxin exposure; beta-amyloid; lipopolysaccharides); or non-chemical, such as a physical stressor, environmental stressor, or a mechanical force (*e.g.,* increased pressure or light exposure) (*see, e.g.,* US 2005-0059148).

**[00280]** The retinal cell stressor model system may also include a cell stressor such as, but not limited to, a stressor that may be a risk factor in a disease or disorder or that may contribute to the development or progression of a disease or disorder, including but not limited to, light of varying wavelengths and intensities; A2E; cigarette smoke condensate exposure; oxidative stress (*e.g.,* stress related to the presence of or exposure to hydrogen peroxide, nitroprusside, Zn++, or Fe++); increased pressure (*e.g.,* atmospheric pressure or hydrostatic pressure), glutamate or glutamate agonist (*e.g., N*-methyl-D-aspartate (NMDA); alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionate (AMPA); kainic acid; quisqualic acid; ibotenic acid; quinolinic acid; aspartate; *trans*-1-aminocyclopentyl-1,3-dicarboxylate (ACPD)); amino acids (*e.g.,* aspartate, L-cysteine; beta-N-methylamine-L-alanine); heavy metals (such as lead); various toxins (for example, mitochondrial toxins (*e.g.,* malonate, 3-nitroproprionic acid; rotenone, cyanide); MPTP (1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine), which metabolizes to its active, toxic

metabolite MPP+ (1-methyl-4-phenylpryidine)); 6-hydroxydopamine; alpha-synuclein; protein kinase C activators (*e.g.,* phorbol myristate acetate); biogenic amino stimulants (for example, methamphetamine, MDMA (3-4 methylenedioxymethamphetamine)); or a combination of one or more stressors. Useful retinal cell stressors include those that mimic a neurodegenerative disease that affects any one or more of the mature retinal cells described herein. A chronic disease model is of particular importance because most neurodegenerative diseases are chronic. Through use of this *in vitro* cell culture system, the earliest events in long-term disease development processes may be identified because an extended period of time is available for cellular analysis.

**[00281]** A retinal cell stressor may alter (*i.e.,* increase or decrease in a statistically significant manner) viability of retinal cells such as by altering survival of retinal cells, including retinal neuronal cells and RPE cells, or by altering neurodegeneration of retinal neuronal cells and/or RPE cells. Preferably, a retinal cell stressor adversely affects a retinal neuronal cell or RPE cell such that survival of a retinal neuronal cell or RPE cell is decreased or adversely affected (*i.e.,* the length of time during which the cells are viable is decreased in the presence of the stressor) or neurodegeneration (or neuron cell injury) of the cell is increased or enhanced. The stressor may affect only a single retinal cell type in the retinal cell culture or the stressor may affect two, three, four, or more of the different cell types. For example, a stressor may alter viability and survival of photoreceptor cells but not affect all the other major cell types (*e.g.,* ganglion cells, amacrine cells, horizontal cells, bipolar cells, RPE, and Müller glia). Stressors may shorten the survival time of a retinal cell (*in vivo* or *in vitro*), increase the rapidity or extent of neurodegeneration of a retinal cell, or in some other manner adversely affect the viability, morphology, maturity, or lifespan of the retinal cell.

**[00282]** The effect of a cell stressor (in the presence and absence of a substituted heterocyclic amine derivative compound) on the viability of retinal cells in the cell culture system may be determined for one or more of the different retinal cell types. Determination of cell viability may include evaluating structure and/or a function of a retinal cell continually at intervals over a length of time or at a particular time point after the retinal cell culture is prepared. Viability or long term survival of one or more different retinal cell types or one or more different retinal neuronal cell types may be examined according to one or more biochemical or biological parameters that are indicative of reduced viability, such as apoptosis or a decrease in a metabolic function, prior to observation of a morphological or structural alteration.

**[00283]** A chemical, biological, or physical cell stressor may reduce viability of one or more of the retinal cell types present in the cell culture system when the stressor is added to the cell culture under conditions described herein for maintaining the long-term cell culture. Alternatively, one or more culture conditions may be adjusted so that the effect of the stressor on the retinal cells can be more readily observed. For example, the concentration or percent of fetal bovine serum may be reduced or eliminated from the cell culture when cells are exposed to a particular cell stressor (*see, e.g.,* US 2005-0059148). Alternatively, retinal cells cultured in media containing serum at a particular concentration for maintenance of the cells may be abruptly exposed to media that does not contain any level of serum.

**[00284]** The retinal cell culture may be exposed to a cell stressor for a period of time that is determined to reduce the viability of one or more retinal cell types in the retinal cell culture system. The cells may be exposed to a cell stressor immediately upon plating of the retinal cells after isolation from retinal tissue. Alternatively, the retinal cell culture may be exposed to a stressor after the culture is established, or any time thereafter. When two or more cell stressors are included in the retinal cell culture system, each stressor may be added to the cell culture system concurrently and for the same length of time or may be added separately at different time points for the same length of time or for differing lengths of time during the culturing of the retinal cell system. A substituted heterocyclic amine derivative compound may be added before the retinal cell culture is exposed to a cell stressor, may be added concurrently with the cell stressor, or may be added after exposure of the retinal cell culture to the stressor.

**[00285]** Photoreceptors may be identified using antibodies that specifically bind to photoreceptor-specific proteins such as opsins, peripherins, and the like. Photoreceptors in cell culture may also be identified as a morphologic subset of immunocytochemically labeled cells by using a pan-neuronal marker or may be identified morphologically in enhanced contrast images of live cultures. Outer segments can be detected morphologically as attachments to photoreceptors.

**[00286]** Retinal cells including photoreceptors can also be detected by functional analysis. For example, electrophysiology methods and techniques may be used for measuring the response of photoreceptors to light. Photoreceptors exhibit specific kinetics in a graded response to light. Calcium-sensitive dyes may also be used to detect graded responses to light within cultures containing active photoreceptors. For analyzing stress-inducing compounds or potential neurotherapeutics, retinal cell cultures can be

processed for immunocytochemistry, and photoreceptors and/or other retinal cells can be counted manually or by computer software using photomicroscopy and imaging techniques. Other immunoassays known in the art (*e.g.,* ELISA, immunoblotting, flow cytometry) may also be useful for identifying and characterizing the retinal cells and retinal neuronal cells of the cell culture model system described herein.

**[00287]** The retinal cell culture stress models may also be useful for identification of both direct and indirect pharmacologic agent effects by the bioactive agent of interest, such as a substituted heterocyclic amine derivative compound as described herein. For example, a bioactive agent added to the cell culture system in the presence of one or more retinal cell stressors may stimulate one cell type in a manner that enhances or decreases the survival of other cell types. Cell/cell interactions and cell/extracellular component interactions may be important in understanding mechanisms of disease and drug function. For example, one neuronal cell type may secrete trophic factors that affect growth or survival of another neuronal cell type (*see, e.g.,* WO 99/29279).

**[00288]** In another embodiment, a substituted heterocyclic amine derivative compound is incorporated into screening assays comprising the retinal cell culture stress model system described herein to determine whether and/or to what level or degree the compound increases or prolongs viability (*i.e.,* increases in a statistically significant or biologically significant manner) of a plurality of retinal cells. A person skilled in the art would readily appreciate and understand that as described herein a retinal cell that exhibits increased viability means that the length of time that a retinal cell survives in the cell culture system is increased (increased lifespan) and/or that the retinal cell maintains a biological or biochemical function (normal metabolism and organelle function; lack of apoptosis; etc.) compared with a retinal cell cultured in an appropriate control cell system (*e.g.,* the cell culture system described herein in the absence of the compound). Increased viability of a retinal cell may be indicated by delayed cell death or a reduced number of dead or dying cells; maintenance of structure and/or morphology; lack of or delayed initiation of apoptosis; delay, inhibition, slowed progression, and/or abrogation of retinal neuronal cell neurodegeneration or delaying or abrogating or preventing the effects of neuronal cell injury. Methods and techniques for determining viability of a retinal cell and thus whether a retinal cell exhibits increased viability are described in greater detail herein and are known to persons skilled in the art.

**[00289]** In certain embodiments, a method is provided for determining whether a substituted heterocyclic amine derivative compound, enhances survival of photoreceptor

cells. One method comprises contacting a retinal cell culture system as described herein with an substituted heterocyclic amine derivative compound under conditions and for a time sufficient to permit interaction between the retinal neuronal cells and the compound. Enhanced survival (prolonged survival) may be measured according to methods described herein and known in the art, including detecting expression of rhodopsin.

**[00290]** The capability of a substituted heterocyclic amine derivative compound to increase retinal cell viability and/or to enhance, promote, or prolong cell survival (that is, to extend the time period in which retinal cells, including retinal neuronal cells, are viable), and/or impair, inhibit, or impede degeneration as a direct or indirect result of the herein described stress may be determined by any one of several methods known to those skilled in the art. For example, changes in cell morphology in the absence and presence of the compound may be determined by visual inspection such as by light microscopy, confocal microscopy, or other microscopy methods known in the art. Survival of cells can also be determined by counting viable and/or nonviable cells, for instance. Immunochemical or immunohistological techniques (such as fixed cell staining or flow cytometry) may be used to identify and evaluate cytoskeletal structure (*e.g.,* by using antibodies specific for cytoskeletal proteins such as glial fibrillary acidic protein, fibronectin, actin, vimentin, tubulin, or the like) or to evaluate expression of cell markers as described herein. The effect of a substituted heterocyclic amine derivative compound on cell integrity, morphology, and/or survival may also be determined by measuring the phosphorylation state of neuronal cell polypeptides, for example, cytoskeletal polypeptides (*see, e.g.*, Sharma et al., *J. Biol. Chem.* 274:9600-06 (1999); Li et al., *J. Neurosci.* 20:6055-62 (2000)). Cell survival or, alternatively cell death, may also be determined according to methods described herein and known in the art for measuring apoptosis (for example, annexin V binding, DNA fragmentation assays, caspase activation, marker analysis, *e.g.*, poly(ADP-ribose) polymerase (PARP), etc.).

**[00291]** In the vertebrate eye, for example, a mammalian eye, the formation of A2E is a light-dependent process and its accumulation leads to a number of negative effects in the eye. These include destabilization of retinal pigment epithelium (RPE) membranes, sensitization of cells to blue-light damage, and impaired degradation of phospholipids. Products of the oxidation of A2E (and A2E related molecules) by molecular oxygen (oxiranes) were shown to induce DNA damage in cultured RPE cells. All these factors lead to a gradual decrease in visual acuity and eventually to vision loss. If reducing the formation of retinals during vision processes were possible, this reduction would lead to

decreased amounts of A2E in the eye. Without wishing to be bound by theory, decreased accumulation of A2E may reduce or delay degenerative processes in the RPE and retina and thus may slow down or prevent vision loss in dry AMD and Stargardt's Disease.

**[00292]** In another embodiment, methods are provided for treating and/or preventing degenerative diseases and disorders, including neurodegenerative retinal diseases and ophthalmic diseases, and retinal diseases and disorders as described herein. A subject in need of such treatment is a human or non-human primate or other animal who has developed symptoms of a degenerative retinal disease or who is at risk for developing a degenerative retinal disease. As described herein a method is provided for treating (which includes preventing or prophylaxis) an ophthalmic disease or disorder by administrating to a subject a composition comprising a pharmaceutically acceptable carrier and a substituted heterocyclic amine derivative compound (*e.g.,* a compound having the structure of Formula (A) or Formula (B), and substructures thereof.) As described herein, a method is provided for enhancing survival of neuronal cells such as retinal neuronal cells, including photoreceptor cells, and/or inhibiting degeneration of retinal neuronal cells by administering the pharmaceutical compositions described herein comprising a substituted heterocyclic amine derivative compound.

**[00293]** Enhanced survival (or prolonged or extended survival) of one or more retinal cell types in the presence of a substituted heterocyclic amine derivative compound indicates that the compound is an effective agent for treatment of a degenerative disease, particularly a retinal disease or disorder, and including a neurodegenerative retinal disease or disorder. Cell survival and enhanced cell survival may be determined according to methods described herein and known to a skilled artisan including viability assays and assays for detecting expression of retinal cell marker proteins. For determining enhanced survival of photoreceptor cells, opsins may be detected, for instance, including the protein rhodopsin that is expressed by rods.

**[00294]** In another embodiment, the subject is being treated for Stargardt's disease or Stargardt's macular degeneration. In Stargardt's disease, which is associated with mutations in the ABCA4 (also called ABCR) transporter, the accumulation of all-*trans*-retinal has been proposed to be responsible for the formation of a lipofuscin pigment, A2E, which is toxic towards retinal cells and causes retinal degeneration and consequently loss of vision.

**[00295]** In yet another embodiment, the subject is being treated for age-related macular degeneration (AMD). In various embodiments, AMD can be wet- or dry-form. In

AMD, vision loss primarily occurs when complications late in the disease either cause new blood vessels to grow under the macula or the macula atrophies. Without intending to be bound by any particular theory, the accumulation of all-*trans*-retinal has been proposed to be responsible for the formation of a lipofuscin pigment, *N*-retinylidene-*N*-retinylethanolamine (A2E) and A2E related molecules, which are toxic towards RPE and retinal cells and cause retinal degeneration and consequently loss of vision.

**[00296]** A neurodegenerative retinal disease or disorder for which the compounds and methods described herein may be used for treating, curing, preventing, ameliorating the symptoms of, or slowing, inhibiting, or stopping the progression of, is a disease or disorder that leads to or is characterized by retinal neuronal cell loss, which is the cause of visual impairment. Such a disease or disorder includes but is not limited to age-related macular degeneration (including dry-form and wet-form of macular degeneration) and Stargardt's macular dystrophy.

**[00297]** Age-related macular degeneration as described herein is a disorder that affects the macula (central region of the retina) and results in the decline and loss of central vision. Age-related macular degeneration occurs typically in individuals over the age of 55 years. The etiology of age-related macular degeneration may include both environmental influences and genetic components (*see, e.g.*, Lyengar et al., *Am. J. Hum. Genet.* 74:20-39 (2004) (Epub 2003 December 19); Kenealy et al., *Mol. Vis.* 10:57-61 (2004); Gorin et al., *Mol. Vis.* 5:29 (1999)). More rarely, macular degeneration occurs in younger individuals, including children and infants, and generally, these disorders results from a genetic mutation. Types of juvenile macular degeneration include Stargardt's disease (*see, e.g.,* Glazer et al., *Ophthalmol. Clin. North Am.* 15:93-100, viii (2002); Weng et al., *Cell* 98:13-23 (1999)); Doyne's honeycomb retinal dystrophy (*see, e.g.,* Kermani et al., *Hum. Genet.* 104:77-82 (1999)); Sorsby's fundus dystrophy, Malattia Levintinese, fundus flavimaculatus, and autosomal dominant hemorrhagic macular dystrophy (*see also* Seddon et al., *Ophthalmology* 108:2060-67 (2001); Yates et al., *J. Med. Genet.* 37:83-7 (2000); Jaakson et al., *Hum. Mutat.* 22:395-403 (2003)). Geographic atrophy of the RPE is an advanced form of non-neovascular dry-type age-related macular degeneration, and is associated with atrophy of the choriocapillaris, RPE, and retina.

**[00298]** Stargardt's macular degeneration, a recessive inherited disease, is an inherited blinding disease of children. The primary pathologic defect in Stargardt's disease is also an accumulation of toxic lipofuscin pigments such as A2E in cells of the retinal pigment

epithelium (RPE). This accumulation appears to be responsible for the photoreceptor death and severe visual loss found in Stargardt's patients. The compounds described herein slow the synthesis of 11-*cis*-retinaldehyde (11cRAL or retinal) and regeneration of rhodopsin by inhibiting isomerase in the visual cycle. Light activation of rhodopsin results in its release of all-*trans*-retinal, which constitutes the first reactant in A2E biosynthesis. Treatment with substituted heterocyclic amine derivative compounds inhibits lipofuscin accumulation and thus delays the onset of visual loss in Stargardt's and AMD patients without toxic effects that would preclude treatment with a substituted heterocyclic amine derivative compound. The compounds described herein are used for effective treatment of other forms of retinal or macular degeneration associated with lipofuscin accumulation.

**[00299]** Administration of a substituted heterocyclic amine derivative compound to a subject can prevent formation of the lipofuscin pigment, A2E (and A2E related molecules), that is toxic towards retinal cells and causes retinal degeneration. In certain embodiments, administration of a substituted heterocyclic amine derivative compound reduces the production of waste products, *e.g.*, lipofuscin pigment, A2E (and A2E related molecules), ameliorate the development of AMD (*e.g.,* dry-form) and Stargardt's disease, and reduce or slow vision loss (*e.g.*, choroidal neovascularization and/or chorioretinal atrophy). In previous studies, with 13-*cis*-retinoic acid (Accutane® or Isotretinoin), a drug commonly used for the treatment of acne and an inhibitor of 11-*cis*-retinol dehydrogenase, has been administered to patients to prevent A2E accumulation in the RPE. However, a major drawback in this proposed treatment is that 13-*cis*-retinoic acid can easily isomerize to all-*trans*-retinoic acid. All-*trans*-retinoic acid is a very potent teratogenic compound that adversely affects cell proliferation and development. Retinoic acid also accumulates in the liver and may be a contributing factor in liver diseases.

**[00300]** In yet other embodiments, a substituted heterocyclic amine derivative compound is administered to a subject such as a human with a mutation in the ABCA4 transporter in the eye. In some embodiments, the substituted heterocyclic amine derivative compound is administered to an aging subject. As used herein, an aging human subject is typically at least 45, or at least 50, or at least 60, or at least 65 years old. In Stargardt's disease, which is associated with mutations in the ABCA4 transporter, the accumulation of all-*trans*-retinal has been proposed to be responsible for the formation of a lipofuscin pigment, A2E (and A2E related molecules), that is toxic

towards retinal cells and causes retinal degeneration and consequently loss of vision. Without wishing to be bound by theory, a substituted heterocyclic amine derivative compound described herein is a strong inhibitor of an isomerase involved in the visual cycle. Treating patients with a substituted heterocyclic amine derivative compound as described herein prevents or slows the formation of A2E (and A2E related molecules) and can has protective properties for normal vision.

**[00301]** In other certain embodiments, one or more of the compounds described herein are used for treating other ophthalmic diseases or disorders, for example, glaucoma, retinal detachment, hemorrhagic retinopathy, retinitis pigmentosa, an inflammatory retinal disease, proliferative vitreoretinopathy, retinal dystrophy, hereditary optic neuropathy, Sorsby's fundus dystrophy, uveitis, a retinal injury, optical neuropathy, and retinal disorders associated with other neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease or other neurodegenerative diseases that affect brain cells, a retinal disorder associated with viral infection, or other conditions such as AIDS. A retinal disorder also includes light damage to the retina that is related to increased light exposure (*i.e.,* overexposure to light), for example, accidental strong or intense light exposure during surgery; strong, intense, or prolonged sunlight exposure, such as at a desert or snow covered terrain; during combat, for example, when observing a flare or explosion or from a laser device, and the like. Retinal diseases can be of degenerative or non-degenerative nature. Non-limiting examples of degenerative retinal diseases include age-related macular degeneration, and Stargardt's macular dystrophy. Examples of non-degenerative retinal diseases include but are not limited hemorrhagic retinopathy, retinitis pigmentosa, optic neuropathy, inflammatory retinal disease, diabetic retinopathy, diabetic maculopathy, retinal blood vessel occlusion, retinopathy of prematurity, or ischemia reperfusion related retinal injury, proliferative vitreoretinopathy, retinal dystrophy, hereditary optic neuropathy, Sorsby's fundus dystrophy, uveitis, a retinal injury, a retinal disorder associated with Alzheimer's disease, a retinal disorder associated with multiple sclerosis, a retinal disorder associated with Parkinson's disease, a retinal disorder associated with viral infection, a retinal disorder related to light overexposure, and a retinal disorder associated with AIDS.

**[00302]** In other certain embodiments, at least one of the compounds described herein is used for treating, curing, preventing, ameliorating the symptoms of, or slowing, inhibiting, or stopping the progression of, certain ophthalmic diseases and disorders including but not limited to diabetic retinopathy, diabetic maculopathy, diabetic macular

edema, retinal ischemia, ischemia-reperfusion related retinal injury, and retinal blood vessel occlusion (including venous occlusion and arterial occlusion).

**[00303]** Diabetic retinopathy is a leading cause of blindness in humans and is a complication of diabetes. Diabetic retinopathy occurs when diabetes damages blood vessels inside the retina. Non-proliferative retinopathy is a common, usually mild form that generally does not interfere with vision. Abnormalities are limited to the retina, and vision is impaired only if the macula is involved. If left untreated retinopathy can progress to proliferative retinopathy, the more serious form of diabetic retinopathy. Proliferative retinopathy occurs when new blood vessels proliferate in and around the retina. Consequently, bleeding into the vitreous, swelling of the retina, and/or retinal detachment may occur, leading to blindness.

**[00304]** Other ophthalmic diseases and disorders that may be treated using the methods and compositions described herein include diseases, disorders, and conditions that are associated with, exacerbated by, or caused by ischemia in the retina. Retinal ischemia includes ischemia of the inner retina and the outer retina. Retinal ischemia can occur from either choroidal or retinal vascular diseases, such as central or branch retinal vision occlusion, collagen vascular diseases and thrombocytopenic purpura. Retinal vasculitis and occlusion is seen with Eales disease and systemic lupus erythematosus.

**[00305]** Retinal ischemia may be associated with retinal blood vessel occlusion. In the United States, both branch and central retinal vein occlusions are the second most common retinal vascular diseases after diabetic retinopathy. About 7% - 10% of patients who have retinal venous occlusive disease in one eye eventually have bilateral disease. Visual field loss commonly occurs from macular edema, ischemia, or vitreous hemorrhage secondary to disc or retinal neovascularization induced by the release of vascular endothelial growth factor.

**[00306]** Arteriolosclerosis at sites of retinal arteriovenous crossings (areas in which arteries and veins share a common adventitial sheath) causes constriction of the wall of a retinal vein by a crossing artery. The constriction results in thrombus formation and subsequent occlusion of the vein. The blocked vein may lead to macular edema and hemorrhage secondary to breakdown in the blood-retina barrier in the area drained by the vein, disruption of circulation with turbulence in venous flow, endothelial damage, and ischemia. Clinically, areas of ischemic retina appear as feathery white patches called cotton-wool spots.

**[00307]** Branch retinal vein occlusions with abundant ischemia cause acute central and paracentral visual field loss corresponding to the location of the involved retinal quadrants. Retinal neovascularization due to ischemia may lead to vitreous hemorrhage and subacute or acute vision loss.

**[00308]** Two types of central retinal vein occlusion, ischemic and nonischemic, may occur depending on whether widespread retinal ischemia is present. Even in the nonischemic type, the macula may still be ischemic. Approximately 25% central retinal vein occlusion is ischemic. Diagnosis of central retinal vein occlusion can usually be made on the basis of characteristic ophthalmoscopic findings, including retinal hemorrhage in all quadrants, dilated and tortuous veins, and cotton-wool spots. Macular edema and foveal ischemia can lead to vision loss. Extracellular fluid increases interstitial pressure, which may result in areas of retinal capillary closure (*i.e.*, patchy ischemic retinal whitening) or occlusion of a cilioretinal artery.

**[00309]** Patients with ischemic central retinal vein occlusion are more likely to present with a sudden onset of vision loss and have visual acuity of less than 20/200, a relative afferent pupillary defect, abundant intraretinal hemorrhages, and extensive nonperfusion on fluorescein angiography. The natural history of ischemic central retinal vein occlusion is associated with poor outcomes: eventually, approximately two-thirds of patients who have ischemic central retinal vein occlusion will have ocular neovascularization and one-third will have neovascular glaucoma. The latter condition is a severe type of glaucoma that may lead to rapid visual field and vision loss, epithelial edema of the cornea with secondary epithelial erosion and predisposition to bacterial keratitis, severe pain, nausea and vomiting, and, eventually, phthisis bulbi (atrophy of the globe with no light perception).

**[00310]** As used herein, a patient (or subject) is any mammal, including a human, that is afflicted with a neurodegenerative disease or condition, including an ophthalmic disease or disorder, or that may be free of detectable disease. Accordingly, the treatment may be administered to a subject who has an existing disease, or the treatment may be prophylactic, administered to a subject who is at risk for developing the disease or condition. Treating or treatment refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology, or condition more tolerable to the patient; slowing in the rate of degeneration

or decline; making the final point of degeneration less debilitating; or improving a subject's physical or mental well-being.

**[00311]** The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination. Accordingly, the term "treating" includes the administration of the compounds or agents described herein to treat pain, hyperalgesia, allodynia, or nociceptive events and to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with pain, hyperalgesia, allodynia, nociceptive events, or other disorders. The term "therapeutic effect" refers to the reduction, elimination, or prevention of the disease, symptoms of the disease, or sequelae of the disease in the subject. Treatment also includes restoring or improving retinal neuronal cell functions (including photoreceptor function) in a vertebrate visual system, for example, such as visual acuity and visual field testing etc., as measured over time (*e.g.,* as measured in weeks or months). Treatment also includes stabilizing disease progression (*i.e.,* slowing, minimizing, or halting the progression of an ophthalmic disease and associated symptoms) and minimizing additional degeneration of a vertebrate visual system. Treatment also includes prophylaxis and refers to the administration of a substituted heterocyclic amine derivative compound to a subject to prevent degeneration or further degeneration or deterioration or further deterioration of the vertebrate visual system of the subject and to prevent or inhibit development of the disease and/or related symptoms and sequelae.

**[00312]** Various methods and techniques practiced by a person skilled in the medical and ophthalmological arts to determine and evaluate a disease state and/or to monitor and assess a therapeutic regimen include, for example, fluorescein angiogram, fundus photography, indocyanine green dye tracking of the choroidal circulatory system, opthalmoscopy, optical coherence tomography (OCT), and visual acuity testing.

**[00313]** A fluorescein angiogram involves injecting a fluorescein dye intravenously and then observing any leakage of the dye as it circulates through the eye. Intravenous injection of indocyanine green dye may also be used to determine if vessels in the eye are compromised, particularly in the choroidal circulatory system that is just behind the retina. Fundus photography may be used for examining the optic nerve, macula, blood vessels, retina, and the vitreous. Microaneurysms are visible lesions in diabetic retinopathy that may be detected in digital fundus images early in the disease (*see, e.g.,* U.S. Patent Application Publication No. 2007/0002275). An ophthalmoscope may be used to examine the retina and vitreous. Opthalmoscopy is usually performed with

dilated pupils, to allow the best view inside the eye. Two types of ophthalmoscopes may be used: direct and indirect. The direct ophthalmoscope is generally used to view the optic nerve and the central retina. The periphery, or entire retina, may be viewed by using an indirect ophthalmoscope. Optical coherence tomography (OCT) produces high resolution, high speed, non-invasive, cross-sectional images of body tissue. OCT is noninvasive and provides detection of microscopic early signs of disruption in tissues.

**[00314]** A subject or patient refers to any vertebrate or mammalian patient or subject to whom the compositions described herein is administered. The term "vertebrate" or "mammal" includes humans and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals, such as domestic pets (such as cats, dogs, horses), farm animals, and zoo animals. Subjects in need of treatment using the methods described herein may be identified according to accepted screening methods in the medical art that are employed to determine risk factors or symptoms associated with an ophthalmic disease or condition described herein or to determine the status of an existing ophthalmic disease or condition in a subject. These and other routine methods allow the clinician to select patients in need of therapy using the methods and formulations described herein.

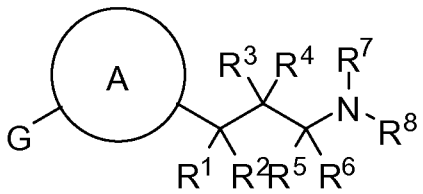
**Pharmaceutical Compositions**

**[00315]** In certain embodiments, a substituted heterocyclic amine derivative compound is administered as a pure chemical. In other embodiments, the substituted heterocyclic amine derivative compound is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21$^{st}$ Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference, in its entirety.

**[00316]** Accordingly, provided herein is a pharmaceutical composition comprising one or more a substituted heterocyclic amine derivative compounds, or a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N-oxide or isomorphic crystalline form thereof, of a compound described herein, together with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to

the recipient (*i.e.,* the subject) of the composition. A pharmaceutically acceptable or suitable composition includes an ophthalmologically suitable or acceptable composition.

**[00317]** One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

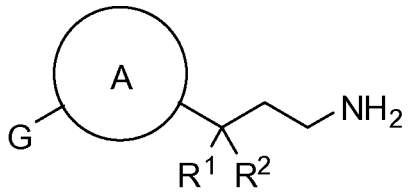
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

**[00318]** One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (B) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (B)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-, -S-, -NH-, or -$CH_2$-;

Y is selected from carbocyclyl, or heterocyclyl; and

$R^1$ and $R^2$ are each independently selected from hydrogen, or -OH; or $R^1$ and $R^2$ form an oxo.

**[00319]** A pharmaceutical composition (*e.g.,* for oral administration or delivery by injection, or combined devices, or for application as an eye drop) may be in the form of a liquid or solid. A liquid pharmaceutical composition may include, for example, one or more of the following: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils that may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents; antioxidants; chelating agents; buffers and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is commonly used as an excipient, and an injectable pharmaceutical composition or a composition that is delivered ocularly is preferably sterile.

**[00320]** In certain embodiments, the compound is substantially pure, in that it contains less than about 5% or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method. In other embodiments, a combination of one or more substituted heterocyclic amine derivative compounds is administered.

**[00321]** In some embodiments, a substituted heterocyclic amine derivative compound is delivered to a subject by any suitable means, including, for example, orally, parenterally, intraocularly, intravenously, intraperitoneally, intranasally (or other delivery methods to the mucous membranes, for example, of the nose, throat, and bronchial tubes), or by local administration to the eye, or by an intraocular or periocular device. Modes of local administration include, for example, eye drops, intraocular injection or periocular injection. Periocular injection typically involves injection of the synthetic isomerization inhibitor, *i.e.*, substituted heterocyclic amine derivative compound under the conjunctiva or into the Tennon's space (beneath the fibrous tissue overlying the eye). Intraocular injection typically involves injection of the substituted heterocyclic amine derivative compound into the vitreous. In certain embodiments, the administration is non-invasive, such as by eye drops or oral dosage form, or as a combined device.

**[00322]** In some embodiments, a substituted heterocyclic amine derivative compound is formulated for administration using pharmaceutically acceptable (suitable) carriers or vehicles as well as techniques routinely used in the art. A pharmaceutically acceptable or suitable carrier includes an ophthalmologically suitable or acceptable carrier. A carrier is selected according to the solubility of the substituted heterocyclic amine derivative compound. Suitable ophthalmological compositions include those that are administrable locally to the eye, such as by eye drops, injection or the like. In the case of eye drops, the formulation also optionally includes, for example, ophthalmologically compatible agents such as isotonizing agents such as sodium chloride, concentrated glycerin, and the like; buffering agents such as sodium phosphate, sodium acetate, and the like; surfactants such as polyoxyethylene sorbitan mono-oleate (also referred to as Polysorbate 80), polyoxyl stearate 40, polyoxyethylene hydrogenated castor oil, and the like; stabilization agents such as sodium citrate, sodium edentate, and the like; preservatives such as benzalkonium chloride, parabens, and the like; and other ingredients. Preservatives can be employed, for example, at a level of from about 0.001

to about 1.0% weight/volume. The pH of the formulation is usually within the range acceptable to ophthalmologic formulations, such as within the range of about pH 4 to 8.

**[00323]** For injection, the substituted heterocyclic amine derivative compound is provided in an injection grade saline solution, in the form of an injectable liposome solution, slow-release polymer system or the like. Intraocular and periocular injections are known to those skilled in the art and are described in numerous publications including, for example, Spaeth, Ed., *Ophthalmic Surgery: Principles of Practice*, W. B. Sanders Co., Philadelphia, Pa., 85-87, 1990.

**[00324]** For delivery of a composition comprising at least one of the compounds described herein via a mucosal route, which includes delivery to the nasal passages, throat, and airways, the composition may be delivered in the form of an aerosol. The compound may be in a liquid or powder form for intramucosal delivery. For example, the composition may be delivered via a pressurized aerosol container with a suitable propellant, such as a hydrocarbon propellant (*e.g.,* propane, butane, isobutene). The composition may be delivered via a non-pressurized delivery system such as a nebulizer or atomizer.

**[00325]** Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. Suitable nontoxic solid carriers can be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See*, *e.g.*, *Remington: The Science and Practice of Pharmacy* (Gennaro, 21$^{st}$ Ed. Mack Pub. Co., Easton, PA (2005)).

**[00326]** The substituted heterocyclic amine derivative compounds described herein, in some embodiments, are formulated for sustained or slow-release. Such compositions may generally be prepared using well known technology and administered by, for example, oral, periocular, intraocular, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain an agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained-release formulation depends upon the site of implantation,

the rate and expected duration of release, and the nature of the condition to be treated or prevented.

**[00327]** Systemic drug absorption of a drug or composition administered via an ocular route is known to those skilled in the art (*see, e.g.,* Lee et al., *Int. J. Pharm.* 233:1-18 (2002)). In one embodiment, a substituted heterocyclic amine derivative compound is delivered by a topical ocular delivery method (*see, e.g., Curr. Drug Metab.* 4:213-22 (2003)). The composition, in some embodiments, is in the form of an eye drop, salve, or ointment or the like, such as, aqueous eye drops, aqueous ophthalmic suspensions, non-aqueous eye drops, and non-aqueous ophthalmic suspensions, gels, ophthalmic ointments, etc. For preparing a gel, for example, carboxyvinyl polymer, methyl cellulose, sodium alginate, hydroxypropyl cellulose, ethylene maleic anhydride polymer and the like can be used.

**[00328]** The dose of the composition comprising at least one of the substituted heterocyclic amine derivative compounds described herein differs, depending upon the patient's (*e.g.,* human) condition, that is, stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose. When the composition is used as eye drops, for example, one to several drops per unit dose, preferably 1 or 2 drops (about 50 μl per 1 drop), may be applied about 1 to about 6 times daily.

**[00329]** Pharmaceutical compositions may be administered in a manner appropriate to the disease to be treated (or prevented) as determined by persons skilled in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.,* an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). For prophylactic use, a dose should be sufficient to prevent, delay the onset of, or diminish the severity of a disease associated with neurodegeneration of retinal neuronal cells and/or degeneration of other mature retinal cells such as RPE cells. Optimal doses may generally be determined using experimental models and/or clinical trials. The optimal dose may depend upon the body mass, weight, or blood volume of the patient.

**[00330]** The doses of the substituted heterocyclic amine derivative compound is suitably selected depending on the clinical status, condition and age of the subject, dosage form and the like. In the case of eye drops, a substituted heterocyclic amine derivative compound is administered, for example, from about 0.01 mg, about 0.1 mg, or about 1 mg, to about 25 mg, to about 50 mg, to about 90 mg per single dose. Eye drops are administered one or more times per day, as needed. In the case of injections, suitable doses are, for example, about 0.0001 mg, about 0.001 mg, about 0.01 mg, or about 0.1 mg to about 10 mg, to about 25 mg, to about 50 mg, or to about 90 mg of the substituted heterocyclic amine derivative compound, one to seven times per week. In other embodiments, about 1.0 to about 30 mg of the substituted heterocyclic amine derivative compound is administered one to seven times per week.

**[00331]** Oral doses typically range from 1.0 to 1000 mg, one to four times, or more, per day. An exemplary dosing range for oral administration is from 10 to 250 mg one to three times per day. If the composition is a liquid formulation, the composition comprises at least 0.1% active compound at particular mass or weight (*e.g.,* from 1.0 to 1000 mg) per unit volume of carrier, for example, from about 2% - about 60%.

**[00332]** In certain embodiments, at least one substituted heterocyclic amine derivative compound described herein is administered under conditions and at a time that inhibits or prevents dark adaptation of rod photoreceptor cells. In certain embodiments, the compound is administered to a subject at least 30 minutes (half hour), 60 minutes (one hour), 90 minutes (1.5 hour), or 120 minutes (2 hours) prior to sleeping. In certain embodiments, the compound is administered at night before the subject sleeps. In other embodiments, a light stimulus may be blocked or removed during the day or under normal light conditions by placing the subject in an environment in which light is removed, such as placing the subject in a darkened room or by applying an eye mask over the eyes of the subject. When the light stimulus is removed in such a manner or by other means contemplated in the art, the agent may be administered prior to sleeping.

**[00333]** The doses of the compounds that are administered to prevent or inhibit dark adaptation of a rod photoreceptor cell can be suitably selected depending on the clinical status, condition and age of the subject, dosage form and the like. In the case of eye drops, the compound (or the composition comprising the compound) can be administered, for example, from about 0.01 mg, about 0.1 mg, or about 1 mg, to about 25 mg, to about 50 mg, to about 90 mg per single dose. In the case of injections, suitable doses are, for example, about 0.0001 mg, about 0.001 mg, about 0.01 mg, or about 0.1

mg to about 10 mg, to about 25 mg, to about 50 mg, or to about 90 mg of the compound, administered any number of days between one to seven days per week prior to sleeping or prior to removing the subject from all light sources. In certain other embodiments, for administration of the compound by eye drops or injection, the dose is between 1-10 mg (compound)/kg (body weight of subject) (*i.e.,* for example, 80-800 mg total per dose for a subject weighing 80 kg). In other embodiments, about 1.0 to about 30 mg of compound is administered one to seven times per week. Oral doses typically range from about 1.0 to about 1000 mg, administered any number of days between one to seven days per week. An exemplary dosing range for oral administration is from about 10 to about 800 mg once per day prior to sleeping. In other embodiments, the composition is delivered by intravitreal administration.

**[00334]** Also provided are methods of manufacturing the compounds and pharmaceutical compositions described herein. A composition comprising a pharmaceutically acceptable excipient or carrier and at least one of the substituted heterocyclic amine derivative compounds described herein is prepared by synthesizing the compound according to any one of the methods described herein or practiced in the art and then formulating the compound with a pharmaceutically acceptable carrier. Formulation of the composition will be appropriate and dependent on several factors, including but not limited to, the delivery route, dose, and stability of the compound.

**[00335]** Other embodiments and uses will be apparent to one skilled in the art in light of the present disclosures. The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

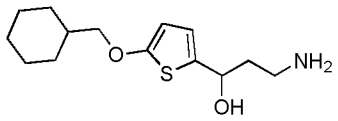
## EXAMPLES

### I. Chemical Synthesis

**[00336]** Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times are approximate and were not optimized. Flash column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted. Proton and carbon nuclear magnetic resonance spectra were obtained with a Varian VnmrJ 400 at 400 MHz for proton. Spectra are given in ppm ($\delta$) and coupling constants *J* are reported in Hertz. For proton spectra the solvent peak was used as the reference peak. HPLC/LC-MS was performed using the following method: Agilent HP 1100 system with diode array detection at 220 nm on Phenomenex Gemini

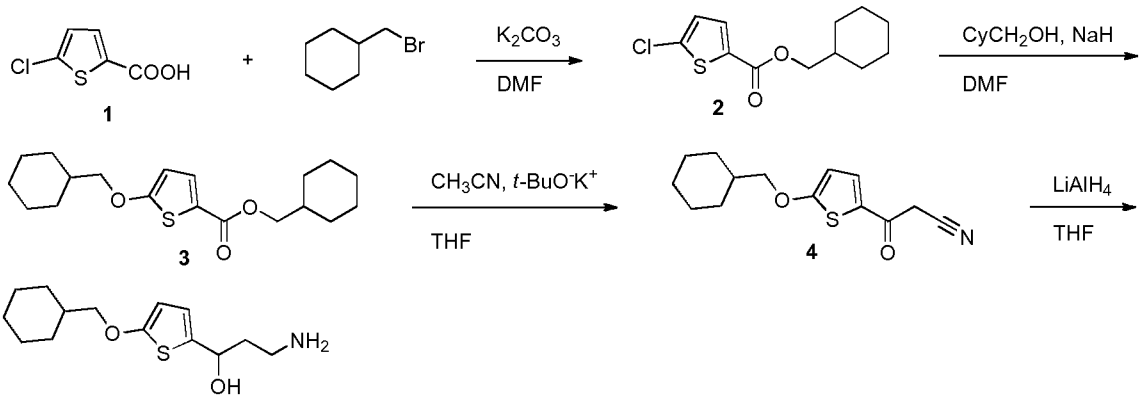
4.6x150 mm 5µ column, mobile phase $CH_3CN$ - $H_2O$ with 0.05% TFA (10% - 70% for 15 mins, 70% - 95% for 2 mins, 95% for 3 min, then 10% for 4 min) with mass-spectral detection using electrospray ionization (ESI+) mode.

EXAMPLE 1 - Preparation of 3-amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol



**[00337]** 3-Amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol was prepared following the method shown in Scheme 1.

Scheme 1



**[00338]** Step 1: A mixture of 5-chlorothiophene-2-carboxylic acid (3.01 g, 19.0 mmol), cyclohexylmethyl bromide (3.51 g, 19.8 mmol) and potassium carbonate (2.81 g, 20.33 mmol) was stirred under Ar at +85 °C for 3 days and colled to room temperature. Reaction mixture was diluted with water and extracted with hexanes three times. Combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (2% - 15 % EtOAc – hexanes gradient) gave cyclohexylmethyl 5-chlorothiophene-2-carboxylate as a colorless oil. Yield (4.76 g, 97%); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.56-7.60 (m, 1H), 6.90-6.94 (m, 1H), 4.08 (d, $J$ = 6.10 Hz, 2H), 1.64-1.82 (m, 6H), 1.10-1.34 (m, 3H), 0.97-1.10 (m, 2H).

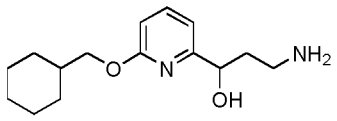
**[00339]** Step 2: Cyclohexylmethanol (1.0 mL, 8.13 mmol) was added under Ar at room temperature to a stirred suspension of NaH (0.19 g, 7.92 mmol) in anhydrous DMF (3 mL). The mixture was stirred for 5 hrs and then chloride (**2**) (1.20 g, 4.64 mmol) was added. The reaction mixture was stirred at +65 °C for 1h, quenched with aqueous 25% NH4Cl and extracted with MBTE twice. Combined organic layers were washed with brine and concentrated under reduced pressure. Purification by flash chromatography

(1% - 5% EtOAc – hexanes gradient) gave ether (**3**) as a light yellow solid. Yield (0.90 g, 58%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.49-7.53 (m, 1H), 6.38-6.43 (m, 1H), 3.98 (d, $J$ = 6.07 Hz, 2H), 3.94 (d, $J$ = 5.87 Hz, 2H), 1.56-1.80 (m, 12H), 1.17-1.28 (m, 6H), 0.90-1.16 (m, 4H).

**[00340]** Step 3: Anhydrous $CH_3CN$ (0.07 mL, 1.34 mmol) was added under Ar to a cold (-50 °C) solution of $t$-$BuO^-K^+$ (1M/THF, 1.5 mL, 1.5 mmol), the mixture was stirred for 10 min after which a solution of ester (**3**) (0.303 g, 0.90 mmol) in anhydrous THF (2 mL) was added. The reaction mixture was stirred under Ar while gradually warming to 0 °C over 3 hrs and then stirred on ice bath for 1h. 5% Aqueous $NaHSO_4$ was added to the reaction mixture and the resulting mixture was extracted twice with EtOAc. Combined organic layers were washed with brine. Purification by flash chromatography (5% - 30% EtOAc – hexanes gradient) gave ketonitrile (**4**) as a white solid. Yield (0.12 g, 51%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.75-7.79 (m, 1H), 6.51-6.55 (m, 1H), 4.52 (s, 2H), 4.00 (d, $J$ = 6.10 Hz, 2H), 1.58-1.80 (m, 6 H), 1.10-1.27 (m, 3H), 0.96-1.08 (m, 2H).

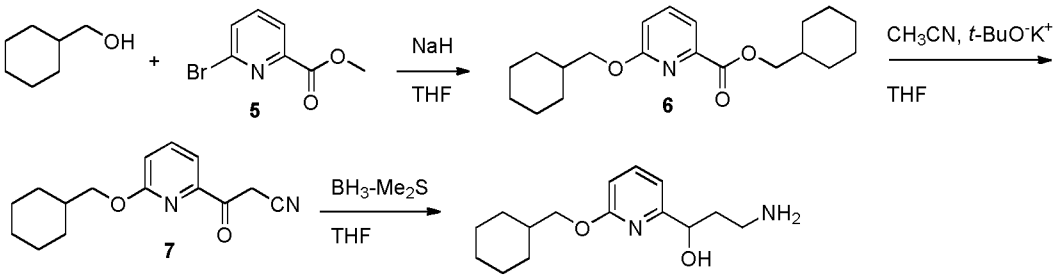
**[00341]** Step 4: A solution of $LiAlH_4$ (1M/THF, 0.7 mL, 0.7 mmol) was added under Ar to a solution of ketonitrile (**4**) (0.12 g, 0.456 mmol) in anhydrous THF (8 mL) at 0 °C under Ar. The reaction mixture was stirred for 30 min at 0 °C and quenched by slow addition of saturated aqueous $Na_2SO_4$. Filtration throught Celite, followed by concentration under reduced pressure and flash chromatography purification (2% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) gave Example 1 as a light yellow solid. Yield (0.015 g, 12%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.54-6.59 (m, 1H), 6.00-6.40 (m, 1H), 4.77 (t, $J$ = 7.24 Hz, 1H), 3.80 (d, $J$ = 5.87 Hz, 2H), 2.86-2.77 (m, 2H), 1.65-1.96 (m, 8 H), 1.18-1.36 (m, 3H), 1.00-1.12 (m, 2H); RP-HPLC $t_R$ = 10.12 min; ESI-MS m/z 252.2 [M-$H_2O$+H]$^+$.

EXAMPLE 2 - Preparation of 3-amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol




**[00342]** 3-Amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol was prepared following the method shown in Scheme 2.

SCHEME 2



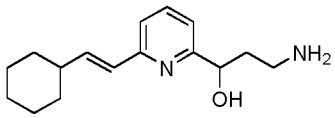

**[00343]** Step 1: NaH (0.15 g, 6.90 mmol) was added to a solution of cyclohexylmethanol (0.79 g, 6.90 mmol) in anhydrous THF (20 mL) at room temperature. The reaction mixture was stirred at 60 °C for 1 hour and then methyl 6-bromopicolinate (**5**) (1.0 g, 4.60 mmol) was added. The reaction mixture was stirred at 60 °C for 18 hours, cooled to room temperature, filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography (30% - 50% EtOAc – hexanes gradient) gave ether (**6**) as a colorless oil. Yield (0.60 g, 41%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.83 (t, $J$ = 8.0 Hz, 1H), 7.63 (d, $J$ = 8.0 Hz, 1H), 7.03 (d, $J$ = 8.4Hz, 1H), 4.08 (d, $J$ = 6.0 Hz, 2H), 3.79 (d, $J$ = 6.0 Hz, 2H), 1.84-1.58 (m, 12H), 0.88-1.26 (m, 10H).

**[00344]** Step 2: $CH_3CN$ (0.22 g, 5.46 mmol) was added to a solution of potassium *tert*-butoxide (1 M/THF, 6.4 mL, 6.40 mmol) in THF (20 mL) at -35 °C. The reaction mixture was stirred at this temperature for 15 min and then ester (**6**) (0.6 g, 1.84 mmol) in THF (15 ml) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour, quenched by acetic acid (0.42 ml, 6.4 mmol), diluted with with sat. $NH_4Cl$ (30 ml). The mixture was extracted with ethyl acetate (50 ml), dried over amhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% - 50% EtOAc – hexanes gradient) gave ketonitrile (**7**) as a yellow oil. Yield (0.20 g, 42%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.12 (t, $J$ = 8.0 Hz, 1H), 7.67 (d, $J$ = 7.2 Hz, 1H), 6.99 (d, $J$ = 8.0 Hz, 1H), 4.26 (s, 2H), 1.88-1.64 (m, 6H), 1.08-1.02 (m, 5H).

**[00345]** Step 3: $BH_3$·$Me_2S$ (0.22 g, 2.96 mmol) was added to a stirred solution of ketonitrile (**7**) (0.2 g, 0.74 mmol) in anhydrous THF (20 mL). The reaction mixture was stirred at 60 °C for 2 hours and at room temperature for 60 hours, quenched 3N HCl (pH = 0). The resulting mixture was stirred at room temperature for 12 hours, diluted with water (20 ml) and MTBE (40 ml) and pH was adjusted to 14 with concentrated NaOH. Organic layer was separated, dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (5% - 20% 7N $NH_3$-MeOH – $CH_2Cl_2$ gradient) gave Example 2 as a yellow oil. Yield (0.05 g, 4%): $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.64 (t, $J$ = 8.0 Hz, 1H), 7.03 (d, $J$ = 7.6 Hz, 1H), 6.63 (d, $J$ = 8.0 Hz, 1H),

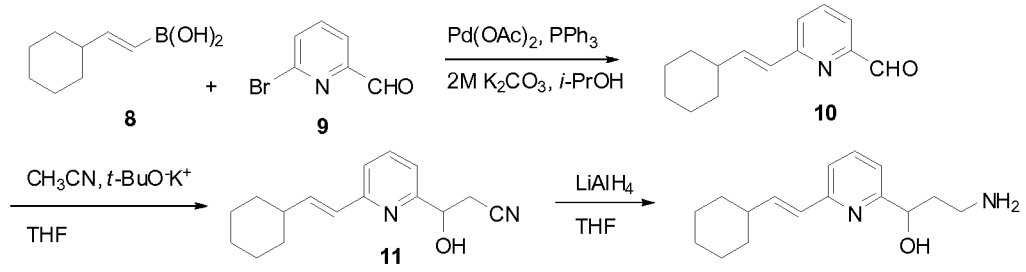
4.72-4.66 (m, 1H), 4.06 (d, *J*=6.4 Hz, 2H), 2.86 (t, *J*=6.1 Hz, 2H), 1.92-1.68 (m, 8H), 1.38-1.02 (m, 5H); RP-HPLC $t_R$ = 9.02 min; ESI-MS m/z 265.2 $[M+H]^+$.

EXAMPLE 3 - Preparation of (*E*)-3-amino-1-(6-(2-cyclohexylvinyl)pyridin-2-yl)propan-1-ol




**[00346]** (*E*)-3-Amino-1-(6-(2-cyclohexylvinyl)pyridin-2-yl)propan-1-ol was prepared following the method shown in Scheme 3.

SCHEME 3



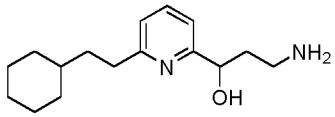

**[00347]** Step 1: To an argon saturated mixture of (*E*)-(2-cyclohexylvinyl)boronic acid (**8**) (2.74 g, 16.0 mmol), 6-bromopicolinaldehyde (**9**) (3.0 g, 16 mmol), $Pd(OAc)_2$ (0.04 g, 0.18 mmol), $K_2CO_3$ (2M in *i*-PrOH, 30 mmol) was added $PPh_3$ (0.20 g, 0.76 mmol). The reaction mixture was stirred at 70 °C for 20 hours under $N_2$, concentrated under reduced pressure and partitioned between $H_2O$ (80 ml) and ethyl acetate (80 ml). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% - 50% EtOAc – hexanes gradient) gave alkene (**10**) as a pale yellow oil. Yield (3.1 g, 90%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.34 (s, 1H), 7.93 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 6.8, 16.0 Hz, 1H), 6.54 (d, *J* = 16 Hz, 1H), 2.26-2.16 (m, 1H), 1.84-1.58 (m, 5H), 1.36-1.10 (m, 5H).

**[00348]** Step 2: $CH_3CN$ (0.56 g, 15.8 mmol) was added to a solution of potassium *tert*-butoxide (1 M in THF, 15 mL, 15.0 mmol) in THF (20 mL) at -35 °C. The reaction mixture was stirred at this temperature for 15 min and then aldehyde (**10**) (1.0 g, 4.6 mmol) in anhydrous THF (15 ml) was added dropwise. The reaction mixture was stirred at -35 °C for 30 min and quenched by aqueous $NH_4Cl$ (30 ml), extracted with ethyl acetate (50 ml), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% - 50% EtOAc – hexanes gradient) gave hydroxynitrile (**11**) as a yellow oil. Yield (0.55 g, 46%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$

7.37 (t, $J$ = 7.6 Hz, 1H), 7.34 (d, $J$ = 7.6 Hz, 1H), 7.28 (d, $J$ = 7.6 Hz, 1H), 6.73 (dd, $J$ = 6.8, 16.0 Hz, 1H), 6.40 (d, $J$ = 16 Hz, 1H), 6.16-6.06 (m, 1H), 4.90-4.80 (m, 1H), 3.04-2.87 (m, 2H), 2.21-2.08 (m, 1H), 1.82-1.58 (m, 5H), 1.36-1.10 (m, 5H).

**[00349]** Step 3: $LiAlH_4$ (1M in THF, 2.6 mL, 2.6 mmol) was added to a solution of hydroxynitrile (**11**) (0.55 g, 2.15 mmol) in diethyl ether (20 mL) at 0 °C under argon flow. The reaction mixture was stirred at 0 °C for 20 min, quenched by slow addition of saturated $Na_2SO_4$ and stirred at room temperature for 2 hours. Organic layer was separated, dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (5% - 20% 7N $NH_3$-MeOH – $CH_2Cl_2$ gradient) gave Example 3 as a pale yellow oil. Yield (0.3 g, 54%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.71 (t, $J$ = 7.6Hz, 1H), 7.34-7.30 (m, 2H), 6.66 (dd, $J$ = 16 and 6.8Hz, 1H), 6.45 (d, $J$ = 16Hz, 1H), 6.16-6.06 (m, 1H), 4.78-4.76 (m, 1H), 2.24-2.16 (m, 2H), 2.21-2.08 (m, 1H), 2.04-1.66 (m, 5H), 1.44-1.16 (m, 5H); RP-HPLC $t_R$ = 6.54 min; ESI-MS $m/z$ 261.2 $[M+H]^+$.

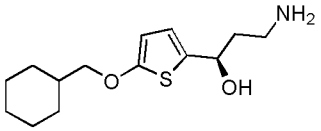
EXAMPLE 4 - Preparation of 3-amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol




**[00350]** 3-Amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol was prepared following the method described below.

**[00351]** Step 1: Pd/C (10% wt, 0.015 g) was added to a solution of Example 3 (0.28 g, 1.22 mmol) in MeOH (20 mL) saturated with argon. The resulting mixture was stirred under $H_2$ (1 atm) for 20 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (5% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) gave Example 4 as a pale yellow oil. Yield (0.20 g, 71%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.71 (t, $J$ = 7.6 Hz, 1H), 7.35 (d, $J$ = 7.6 Hz, 1H), 7.13 (d, $J$ = 8.0 Hz, 1H), 4.78-4.76 (m, 1H), 2.83-2.76 (m, 4H), 1.84-1.56 (m, 9H), 1.36-0.95 (m, 6H); RP-HPLC $t_R$ = 6.46 min; ESI-MS $m/z$ 263.2 $[M+H]^+$.

EXAMPLE 5 - Preparation of (*R*)-3-amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol

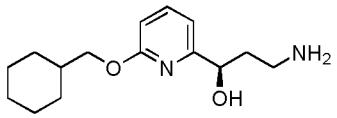


**[00352]** (*R*)-3-Amino-1-(5-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol was prepared following the method described in Example 1 and below.

**[00353]** Step 1: (*1R*,2*R*)-RuCl(TsDPEN)(*p*-cymene) (6.3 mg, 0.01 mmol) was added to a degassed solution of 3-(5-(cyclohexylmethoxy)thiophen-2-yl)-3-oxopropanenitrile (**4**) (0.27 g, 1.03 mmol) in HCOOH:$Et_3N$ (1:1, 4.0 M in EtOH) and the reaction mixture was stirred at room temperature for 24 hrs. Aqueous $NH_4Cl$ (25%) was added and the mixture was extracted twice with MTBE. Combined organic layers were washed with brine and concentrated under reduced pressure. Purification by flash chromatography gave (*R*)-3-(5-(cyclohexylmethoxy)thiophen-2-yl)-3-hydroxypropanenitrile as an off-white solid which was used directly in the next step. Yield (0.21 g, 77%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.64-6.78 (m, 1H), 6.02-6.10 (m, 1H), 4.99-5.09 (m, 1H), 3.79-3.88 (m, 2H), 2.79-2.91 (m, 2H), 1.62-1.90 (m, 6H), 1.12-1.39 (m, 3H), 0.98-1.12 (m, 2H).

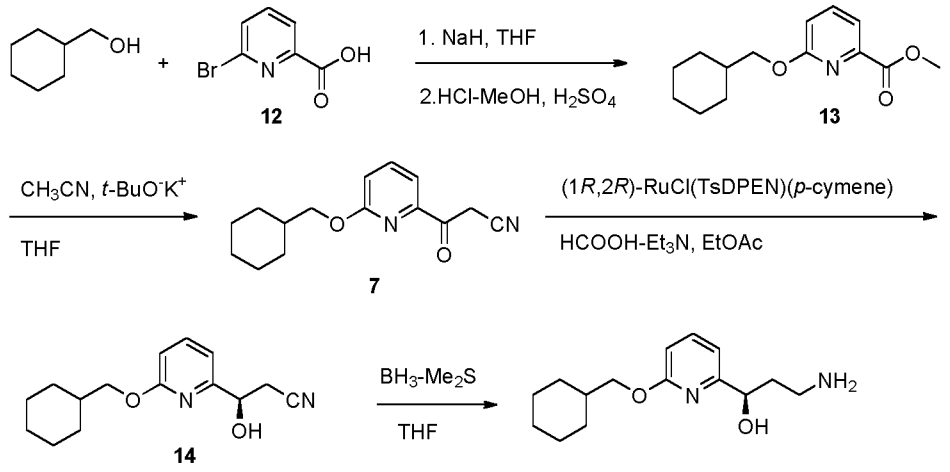
**[00354]** Step 2: Reduction of (*R*)-3-(5-(cyclohexylmethoxy)thiophen-2-yl)-3-hydroxypropanenitrile following the method used in Example 1, with the exception that $Et_2O$ was used as the solvent, gave after purification by flash chromatography ( 4% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 5 as a colorless oil. Yield (0.0185 g, 9%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.54-6.59 (m, 1H), 6.00-6.40 (m, 1H), 4.77 (t, $J$ = 7.2 Hz, 1H), 3.80 (d, $J$ = 5.9 Hz, 2H), 2.86-2.77 (m, 2H), 1.65-1.96 (m, 8 H), 1.18-1.36 (m, 3H), 1.00-1.12 (m, 2H); RP-HPLC $t_R$ = 10.01 min; ESI-MS m/z 252.2 $[M-H_2O+H]^+$.

EXAMPLE 6 - Preparation of (*R*)-3-amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol




**[00355]** (*R*)-3-Amino-1-(6-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol was prepared following the method shown in Scheme 4.

SCHEME 4.




**[00356]** Step 1: NaH (0.355 g, 15 mmol) was added to a suspension of 6-bromopicolinic acid (**12**) (1.0 g, 4.9 mmol) and cyclohexylmethanol (0.79 g, 6.90 mmol) in THF (20 mL) at room temperature. The reaction mixture was stirred at 60 °C for 18 hours then concentrated under reduced pressure. Methanol (20 ml) was added to the residue followed by 1.25 M HCl/MeOH (10 ml) and conc. $H_2SO_4$ (1 ml). The resulting mixture was stirred at 60 °C for 18 hours, concentrated under reduced pressure, partitioned between saturated $NaHCO_3$ (50 ml) and ethyl acetate (100 ml). Organic layer was separated, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Crude methyl 6-(cyclohexylmethoxy)picolinate (**13**) was used in next reaction without purification. Yield (1.22 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.84 (t, $J$ = 8.0 Hz, 1H), 7.63 (d, $J$ = 8.0 Hz, 1H), 7.03 (d, $J$ = 8.4 Hz, 1H), 4.08 (d, $J$=6.0 Hz, 2H), 3.84 (s, 3H), 1.84-1.58 (m, 6H), 0.88-1.26 (m, 5H).

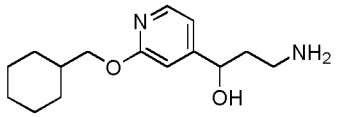
**[00357]** Step 2: $CH_3CN$ (0.41 g, 10 mmol) was added to a solution of potassium *tert*-butoxide (1M in THF, 11 mL, 11 mmol) in THF (20 mL) at -35 °C. The reaction mixture was stirred at this temperature for 15 min. Methyl 6-(cyclohexylmethoxy)picolinate (4.9 mmol) in THF (15 ml) was added dropwise to the reaction mixture. The reaction mixture was stirred at 0 °C for 1 hour and quenched by addition of aqueous HCl (1M, 11 ml, 11 mmol), washed with saturated aqueous $NH_4Cl$ (30 ml), extracted with ethyl acetate (50 ml). Combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Crude ketonitrile **7** was used in the next step without purification. Yield (1.26 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.90 (t, $J$ = 7.6 Hz, 1H), 7.60 (d, $J$ = 7.6 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 1H), 4.66 (s, 2H), 4.15 (d, $J$=6.4 Hz, 2H), 1.84-1.58 (m, 6H), 0.88-1.26 (m, 5H).

**[00358]** Step 3: Solution of HCOOH-$Et_3N$ (4 M) in EtOH (5 mL) was added to a solution of ketonitrile **7** (4.9 mmol) in EtOAc (5 ml), followed by triethylamine (1 ml)

and (*1R*,2*R*)-RuCl(TsDPEN)(*p*-cymene) (30 mg, 0.047 mmol). The mixture was saturated with argon, stirred at room temperature for 18 hr, quenched by addition of aqueous HCl (1N, 11 ml, 11 mmol), washed with saturated $NH_4Cl$ (30 ml), extracted with ethyl acetate (50 ml), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% - 50% EtOAc – hexane gradient) gave (*R*)-hydroxynitrile **14** as a pale yellow oil. Yield (1.1 g, 87%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.66 (t, $J$ = 7.6 Hz, 1H), 7.11 (d, $J$ = 7.6 Hz, 1H), 6.67 (d, $J$ = 8.0 Hz, 1H), 4.88 (t, $J$ = 5.2 Hz, 1H), 4.09 (d, $J$ = 6.8 Hz, 2H), 3.04-2.86 (m, 2H), 1.88-1.66 (m, 6H), 1.38-1.02 (m, 5H).

**[00359]** Step 4: Reduction of (*R*)-hydroxynitrile **14** with $BH_3$-$Me_2S$ following the method used in Example 2 gave Example 6 as a colorless oil. Yield (1.0 g, 89%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.63 (t, $J$ = 7.6 Hz, 1H), 7.02 (d, $J$ = 7.2 Hz, 1H), 6.61 (d, $J$ = 8.0 Hz, 1H), 4.69-4.66 (m, 1H), 4.07 (d, $J$=6.4 Hz, 2H), 2.79 (t, $J$=6.4 Hz, 2H), 1.92-1.64 (m, 8H), 1.38-1.02 (m, 5H); RP-HPLC $t_R$ = 8.99 min; ESI-MS m/z 265.2 $[M+H]^+$.

EXAMPLE 7 - Preparation of 3-amino-1-(2-(cyclohexylmethoxy)pyridin-4-yl)propan-1-ol



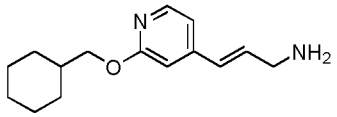

**[00360]** 3-Amino-1-(2-(cyclohexylmethoxy)pyridin-4-yl)propan-1-ol was prepared following the method described in Examples 2 and 6.

**[00361]** Step 1: Reaction between 2-bromoisonicotinic acid and cyclohexylmethanol following the method used in Example 6 gave methyl 2-(cyclohexylmethoxy)isonicotinate which was used in the next step without additional purification. Yield (1.27 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.31 (d, $J$ = 4.2 Hz, 1H), 7.38-7.40 (m, 1H), 7.17 (s, 1H), 4.08 (d, $J$=6.4 Hz, 2H), 3.86 (s, 3H), 1.80-1.54 (m, 6H), 1.30-0.96 (m, 5H).

**[00362]** Step 2: Addition of $CH_3CN$ to methyl 2-(cyclohexylmethoxy)isonicotinate following the method used in Example 2 gave after flash chromatography purification (50% - 60% EtOAc – hexanes gradient) 3-(2-(cyclohexylmethoxy)pyridin-4-yl)-3-oxopropanenitrile as a yellow oil. Yield (0.65 g, 51%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.29 (d, $J$ = 5.2 Hz, 1H), 7.34 (d, $J$ = 5.6 Hz, 1H), 7.23 (s, 1H), 4.13 (d, $J$ = 6.0 Hz, 2H), 3.34-3.30 (m, 2H), 1.88-1.64 (m, 6H), 1.08-1.02 (m, 5H).

**[00363]** Step 3: Reduction of 3-(2-(cyclohexylmethoxy)pyridin-4-yl)-3-oxopropanenitrile following the method described in Example 2 gave after flash chromatography purification (5% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 7 and Example 8 (see below) as yellow oils. Yield (0.16 g, 24%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.02-8.00 (m, 1H), 6.92 (d, $J$ = 5.2 Hz, 1H), 6.79 (s, 1H), 4.76-4.71 (m, 1H), 4.04-4.01 (m, 2H), 2.78 (t, $J$ = 6.8 Hz, 2H), 1.90-1.66 (m, 8H), 1.40-1.02 (m, 5H); RP-HPLC $t_R$ = 6.79 min; ESI-MS m/z 265.2 $[M+H]^+$.

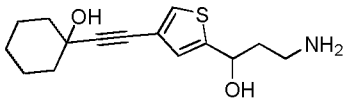
EXAMPLE 8 - Preparation of (*E*)-3-(2-(cyclohexylmethoxy)pyridin-4-yl)prop-2-en-1-amine




**[00364]** (*E*)-3-(2-(Cyclohexylmethoxy)pyridin-4-yl)prop-2-en-1-amine was prepared following the method described in Example 7.

**[00365]** Step 1: Example 8 was prepared following the method used in Example 7 and isolated during step 3 chromatography (see above). Yield (0.04 g, 6%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.98 (d, $J$ = 5.2 Hz, 1H), 6.97 (d, $J$ = 5.6 Hz, 1H), 6.73 (s, 1H), 6.63-6.53 (m, 1H), 6.47 (d, $J$ = 16 Hz, 1H), 4.01 (d, $J$ = 5.6 Hz, 2H), 3.41 (d, $J$ = 6.0 Hz, 2H), 1.88-1.66 (m, 6H), 1.38-1.02 (m, 5H); RP-HPLC $t_R$ = 7.79 min; ESI-MS m/z 247.2 $[M+H]^+$.

EXAMPLE 9 - Preparation of 1-((5-(3-amino-1-hydroxypropyl)thiophen-3-yl)ethynyl)cyclohexanol




**[00366]** 1-((5-(3-Amino-1-hydroxypropyl)thiophen-3-yl)ethynyl)cyclohexanol was prepared following the method described below.

**[00367]** Step 1: Addition of $CH_3CN$ to 4-bromothiophene-2-carbaldehyde following the method used in Example 2 gave 3-(4-bromothiophen-2-yl)-3-hydroxypropanenitrile as a light brown oil which was used in the next step without additional purification.Yield (1.95 g, 80%).

**[00368]** Step 2: $LiAlH_4$ reduction of 3-(4-bromothiophen-2-yl)-3-hydroxypropanenitrile following the method used in Example 1 gave after flash chromatography purification (2% - 10% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) 3-amino-1-(4-bromothiophen-2-

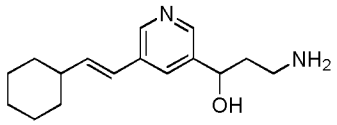
yl)propan-1-ol with was used directly in the next step. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.26 (d, $J$ = 1.5 Hz, 1H), 6.85-6.92 (m, 1H), 4.94 (t, $J$ = 5.0 Hz, 1H), 2.70-2.80 (m, 2H), 1.86-1.94 (m, 2H).

**[00369]** Step 3: 3-Amino-1-(4-bromothiophen-2-yl)propan-1-ol and ethyl trifluoroacetate (2.0 mL) were stirred in $CH_2Cl_2$ (10 mL) at room temperature overnight. Concentration under reduced pressure gave *N*-(3-(4-bromothiophen-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide which was used in the next step without additional purification. Yield (0.77g, 28% in three steps); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.36 (br.s, 1H), 7.51 (d, J = 1.5 Hz, 1H), 6.90-7.00 (m, 1H), 5.86 (d, J = 5.0 Hz, 1H), 4.75-4.83 (m, 1H), 3.20-3.30 (m, 2H), 1.80-1.94 (m, 2H).

**[00370]** Step 4: Solution of *N*-(3-(4-bromothiophen-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide (0.77 g, 2.32 mmol) and 1-ethynylcyclohexanol (0.48 g, 3.87 mmol) in $Et_3N$ (10 mL) was degassed by bubbling Ar for 5 min. CuI (0.0482 g, 0.253 mmol) and $PdCl_2(PPh_3)_2$ (0.0874 g, 0.125 mmol) were added to the reaction mixture and degassed by alternating vacuum/Ar once. The reaction mixture was stirred at +80 °C overnight, partitioned between EtOAc and aqueous $NH_4Cl$ (25%). Aqueous layer was additionally extracted with EtOAc and combined organic layers were washed with brine. Concentration under reduced pressure followed by flash chromatography purification (10% - 75% EtOAc – hexanes gradient) gave 2,2,2-trifluoro-*N*-(3-hydroxy-3-(4-((1-hydroxycyclohexyl)ethynyl)thiophen-2-yl)propyl)acetamide as a light yellow oil. Yield (0.52 g, 60%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.37 (br.s, 1H), 7.52 (d, $J$ = 1.3 Hz, 1H), 6.92 (d, $J$ = 1.3 Hz, 1H), 5.78 (d, $J$ = 4.7 Hz, 1H), 5.34 (s, 1H), 4.74-4.81 (m, 1H), 3.20-3.30 (m, 2H), 1.84-1.91 (m, 2H), 1.74-1.84 (m, 2H), 1.56-1.65 (m, 2H), 1.38-1.56 (m, 6H).

**[00371]** Step 5: A mixture of 2,2,2-trifluoro-*N*-(3-hydroxy-3-(4-((1-hydroxycyclohexyl)ethynyl)thiophen-2-yl)propyl)acetamide (0.52 g, 1.39 mmol) and $K_2CO_3$ (0.43 g, 3.11 mmol) in MeOH:$H_2O$ (3:1, 16 mL) was stirred at room temperature overnight and concentrated under reduced pressure. Purification by flash chromatography (7% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) gave Example 9 as a light yellow oil. Yield (0.105 g, 27%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.37 (d, $J$ = 1.5 Hz, 1H), 6.94 (s, 1H), 4.93 (dd, $J$ = 5.8, 7.3 Hz, 1H), 2.70-2.80 (m, 2H), 1.86-2.00 (m, 4H), 1.67-1.76 (m, 2H), 1.52-1.67 (m, 5H), 1.22-1.36 (m, 1H); RP-HPLC $t_R$ = 6.98 min; ESI-MS m/z 280.2 $[M-H_2O+H]^+$.

EXAMPLE 10 - Preparation of (*E*)-3-amino-1-(5-(2-cyclohexylvinyl)pyridin-3-yl)propan-1-ol



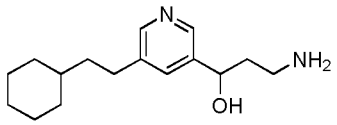

**[00372]** (*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)pyridin-3-yl)propan-1-ol was prepared following the method described in Example 3 and below.

**[00373]** Step 1: Coupling of (*E*)-(2-cyclohexylvinyl)boronic acid with 5-bromonicotinaldehyde following the method used in Example 3 gave (*E*)-5-(2-cyclohexylvinyl)nicotinaldehyde as a yellow oil. Yield (0.8 g, 69%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.08 (s, 1H), 8.32 (s, 1H), 8.75 (s, 1H), 8.28 (s, 1H), 6.51-6.38 (m, 2H), 2.26-2.13 (m, 1H), 1.88-1.58 (m, 5H), 1.42-1.18 (m, 5H).

**[00374]** Step 2: Addition of $CH_3CN$ to (*E*)-5-(2-cyclohexylvinyl)nicotinaldehyde following the method used in Example 3 gave (*E*)-3-(5-(2-cyclohexylvinyl)pyridin-3-yl)-3-hydroxypropanenitrile as a yellow oil. Yield (0.9 g, 95%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.43 (s, 1H), 8.41 (s, 1H), 7.93 (s, 1H), 6.42 (s, 2H), 5.05 (t, $J$ = 5.6 Hz, 1H), 2.98-2.82 (m, 2H), 2.24-2.12 (m, 1H), 1.88-1.66 (m, 5H), 1.42-1.18 (m, 5H).

**[00375]** Step 3: $LiAlH_4$ reduction of (*E*)-3-(5-(2-cyclohexylvinyl)pyridin-3-yl)-3-hydroxypropanenitrile following the method used in Example 3 gave after flash chromatography purification (10% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 10 as a light yellow oil. Yield (0.5 g, 59%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.37 (d, $J$ = 2.0 Hz, 1H), 8.33 (d, $J$ = 1.5 Hz, 1H), 7.85 (t, $J$ = 2.0 Hz, 1H), 6.40-6.38 (m, 2H), 4.84-4.76 (m, 1H), 2.86-2.78 (m, 2H), 2.24-2.08 (m, 1H), 1.98-1.66 (m, 7H), 1.44-1.28 (m, 5H); RP-HPLC $t_R$ = 6.23 min; ESI-MS m/z 261.2 $[M+H]^+$.

EXAMPLE 11 - Preparation of 3-amino-1-(5-(2-cyclohexylethyl)pyridin-3-yl)propan-1-ol

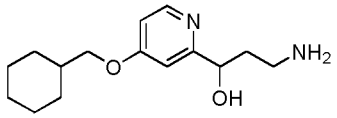



**[00376]** 3-Amino-1-(5-(2-cyclohexylethyl)pyridin-3-yl)propan-1-ol was prepared following the method described in Example 10 and below.

**[00377]** Step 1: A solution of (*E*)-3-amino-1-(5-(2-cyclohexylvinyl)pyridin-3-yl)propan-1-ol (0.40 g, 1.54 mmol), Pd/C (10% wt, 30 mg) in methanol (20 ml) was stirred under hydrogen atmosphere at room temperature and for 18 hrs. The reaction mixture was

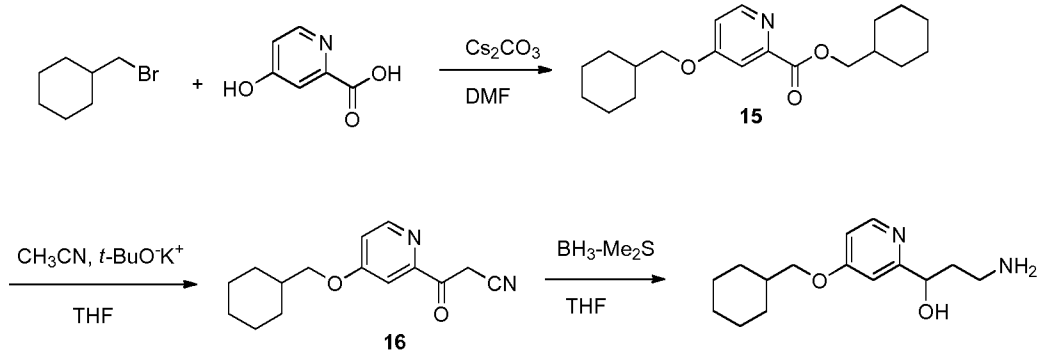
filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ (gradient) to give Example 11 as a pale yellow oil. Yield (0.14 g, 34%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.30 (s, 1H), 8.24 (s, 1H), 7.50 (s, 1H), 4.70-4.67 (m, 1H), 2.64-2.60 (m, 4H), 1.78-1.56 (m, 8H), 1.50-1.38 (m, 2H), 1.24-0.95 (m, 5H), 0.98-0.82 (m, 2H); RP-HPLC $t_R$ = 6.28 min; ESI-MS: *m/z* 263.2 $[M+H]^+$.

EXAMPLE 12 - Preparation of 3-amino-1-(4-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol




**[00378]** 3-Amino-1-(4-(cyclohexylmethoxy)pyridin-2-yl)propan-1-ol was prepared following the method shown in Scheme 5.

SCHEME 5.

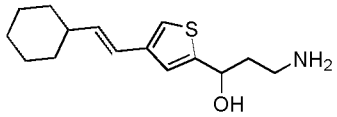



**[00379]** Step 1: $Cs_2CO_3$ (11.8 g, 36.7 mmol) was added to a mixture of 4-hydroxypicolinic acid (1.0 g, 7.2 mmol) and (bromomethyl)cyclohexane (3.25 g, 18.4 mmol) in DMF (30 ml). The resulting mixture was stirred at 80 °C for 18 hrs and concentrated under reduced pressure. EtOAc (50 ml) was added to the residue, sonicated, filtered, concentrated under reduced pressure. Purification by flash chromatography (50% - 75% EtOAc – hexane gradient) gave ester **15** as a colorless oil. Yield (0.66 g, 28%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.46 (d, $J$ = 4.9 Hz, 1H), 7.46 (d, $J$ = 2.3 Hz, 1H), 7.18 (dd, $J$ = 5.5, 2.3 Hz, 1H), 4.08 (d, $J$ = 6.2 Hz, 2H), 3.92 (d, $J$ = 6.2 Hz, 2H), 1.82-1.58 (m, 12H), 1.28-1.00 (m, 10H).

**[00380]** Step 2: Addition of $CH_3CN$ to ester **15** following the method used in Example 2 gave ketonitrile **16** as a yellow oil. Yield (0.30 g, 59%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.47 (d, $J$ = 4.9 Hz, 1H), 7.46 (d, $J$ = 2.3 Hz, 1H), 7.18 (dd, $J$ = 5.5, 2.3 Hz, 1H), 4.48 (s, 2H), 3.94 (d, $J$ = 5.8 Hz, 2H), 1.82-1.58 (m, 6H), 1.28-1.02 (m, 5H).

**[00381]** Step 3: Reduction of 3-(4-(cyclohexylmethoxy)pyridin-2-yl)-3-oxopropanenitrile with borane-dimethylsulfide following the method used in Example 2 gave after flash chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 12 as a yellow oil. Yield (0.13 g, 43%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.22 (d, $J$ = 4.5 Hz, 1H), 6.98 (d, $J$ = 2.3 Hz, 1H), 6.76 (dd, $J$ = 5.9, 2.8 Hz, 1H), 4.62-4.58 (m, 1H), 3.94 (d, $J$ = 5.8 Hz, 2H), 2.72-2.58 (m, 2H), 1.88-1.58 (m, 8H), 1.40-1.02 (m, 5H); RP-HPLC $t_R$ = 5.91 min; ESI-MS m/z 265.2 $[M+H]^+$.

EXAMPLE 13 - Preparation of (*E*)-3-amino-1-(4-(2-cyclohexylvinyl)thiophen-2-yl)propan-1-ol




**[00382]** (*E*)-3-Amino-1-(4-(2-cyclohexylvinyl)thiophen-2-yl)propan-1-ol was prepared following the method described in Example 3.

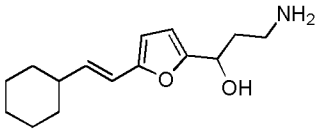
**[00383]** Step 1: Coupling of (*E*)-(2-cyclohexylvinyl)boronic acid with 4-bromothiophene-2-carbaldehyde following the method used in Example 3 gave after flash chromatography purification (30% - 40% EtOAc – hexanes gradient) (*E*)-4-(2-cyclohexylvinyl)thiophene-2-carbaldehyde as a yellow oil. Yield (1.2 g, 91%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.88 (d, $J$ = 1.6 Hz, 1H), 8.15 (d, $J$ = 1.6 Hz, 1H), 7.89 (s, 1H), 6.37 (d, $J$ = 16.8 Hz, 1H), 6.22 (dd, $J$ = 16.8, 6.8 Hz, 1H), 2.08-2.02 (m, 1H), 1.80-1.58 (m, 5H), 1.32-1.18 (m, 5H).

**[00384]** Step 2: Addition of $CH_3CN$ to (*E*)-4-(2-cyclohexylvinyl)thiophene-2-carbaldehyde following the method used in Example 3 gave after flash chromatography purification (10% - 50% EtOAc – hexanes gradient) (*E*)-3-(4-(2-cyclohexylvinyl)thiophen-2-yl)-3-hydroxypropanenitrile as a yellow oil. Yield (1.2 g, 84%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.19 (s, 1H), 7.17 (s, 1H), 6.27 (d, $J$ = 16.8 Hz, 1H), 6.29-6.26 (m, 1H), 6.00 (dd, $J$ = 16.0, 6.4 Hz, 1H), 5.05 (q, $J$ = 5.6 Hz, 1H), 3.0-2.86 (m, 2H), 2.24-2.12 (m, 1H), 1.78-1.56 (m, 5H), 1.38-1.08 (m, 5H).

**[00385]** Step 3: $LiAlH_4$ reduction of (*E*)-2-(4-(2-cyclohexylvinyl)thiophen-2-yl)-2-hydroxyacetonitrile following the method used in Example 3 gave after flash chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 13 as a light yellow oil. Yield (0.44 g, 36%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.19 (s, 1H), 7.13 (s, 1H), 6.25 (d, $J$ = 16.8 Hz, 1H), 5.98 (dd, $J$ = 16.0, 6.4 Hz, 1H), 4.84 (t, $J$ =

6.0 Hz, 1H), 2.72-2.58 (m, 2H), 2.24-2.08 (m, 1H), 1.78-1.58 (m, 7H), 1.38-1.02 (m, 5H); RP-HPLC $t_R$ = 10.49 min; ESI-MS m/z 219.1.2 $[M+H]^+$.

EXAMPLE 14 - Preparation of (*E*)-3-amino-1-(5-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol




**[00386]** (*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol was prepared following the method described in Example 3 and below.

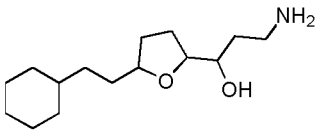
**[00387]** Step 1: A mixture of 5-bromofuran-2-carbaldehyde (1.03 g, 5.89 mmol), vinylcyclohexane (0.86 g, 7.80 mmol), P(*o*-Tol)$_3$ (0.089 g, 0.29 mmol), Pd(OAc)$_2$ (0.070 g, 0.31 mmol) and $Et_3N$ (2.0 mL) in anhydrous DMF (3.0 mL) was degassed by bubbling Ar then alternating vacuum/Ar three times. The reaction mixture was heated under inert atmosphere at +90 °C for 20 hrs and cooled to room temperature. Aqueous $NH_4Cl$ was added to the reaction mixture and the mixture was extracted twice with hexanes and EtOAc. Combined organic layers were washed with brine, concentrated under reduced pressure. Purification by flash chromatography (3% - 8% EtOAc – hexanes gradient) gave (*E*)-5-(2-cyclohexylvinyl)furan-2-carbaldehyde as a yellow oil. Yield (0.40 g, 33%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.53 (s, 1H), 7.19 (d, $J$ = 3.8 Hz, 1H), 6.55 (dd, $J$ = 7.0, 16.1 Hz, 1H), 6.34 (d, $J$ = 3.5 Hz, 1H), 6.19-6.26 (m, 1H), 2.10-2.19 (m, 1H), 1.52-1.92 (m, 6H), 1.10-1.42 (m, 4H).

**[00388]** Step 2: Acetonitrile addition to (*E*)-5-(2-cyclohexylvinyl)furan-2-carbaldehyde following the method used in Example 3 gave after flash chromatography purification (10% - 50% EtOAc – hexanes gradient) (*E*)-3-(5-(2-cyclohexylvinyl)furan-2-yl)-3-hydroxypropanenitrile as a yellow oil. Yield (0.45 g, 94%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.32 (d, $J$ = 2.9 Hz, 1H), 6.23 (d, $J$ = 3.5 Hz, 1H), 6.15 (m, 1H), 6.05 (dd, $J$ = 3.9, 17.6 Hz, 1H), 4.76-4.87 (m, 1H), 2.84-3.00 (m, 2H), 2.02-2.14 (m, 1H), 1.40-1.80 (m, 4H), 1.02-1.36 (m, 6H).

**[00389]** Step 3: Reduction of (*E*)-3-(5-(2-cyclohexylvinyl)furan-2-yl)-3-hydroxypropanenitrile following the method used in Example 1, with the exception that $Et_2O$ was used as the solvent, gave after flash chromatography purification (2% - 16% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) crude (*E*)-3-amino-1-(5-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol which was additionally purified as described below. Yield (0.25 g, 55%).

**[00390]** Step 4: (*E*)-3-amino-1-(5-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol (0.25 g, 1.0 mmol) was dissolved in $CH_2Cl_2$ ( 5 mL) and ethyl trifluoroacetate (0.5 mL) was added. The reaction mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. Purification by flash chromatography (10% - 50% EtOAc – hexanes gradient) gave (*E*)-*N*-(3-(5-(2-cyclohexylvinyl)furan-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide as a colorless oil. Yield (0.26 g, 75%). (*E*)-*N*-(3-(5-(2-Cyclohexylvinyl)furan-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide (0.15 g, 0.434 mmol) was dissolved in MeOH:$H_2O$ (3:1, 8 mL) and $K_2CO_3$ (0.13 g, 0.94 mmol) was added. The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. Flash chromatography purification (2% - 16% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) gave Example 14 as a light yellow oil. Yield (0.025 g, 23%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.00-6.40 (m, 4H), 4.64-4.74 (m, 1H), 2.70-2.80 (m, 2H), 2.01-2.14 (m, 1H), 1.90-2.00 (m, 2H), 1.50-1.80 (m, 5H), 1.10-1.40 (m, 5H); RP-HPLC $t_R$ = 10.06 min; ESI-MS m/z 232.2 $[M-H_2O+H]^+$.

EXAMPLE 15 - Preparation of 3-amino-1-(5-(2-cyclohexylethyl)tetrahydrofuran-2-yl)propan-1-ol



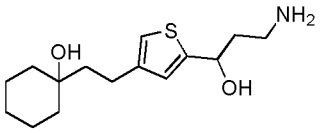

**[00391]** 3-Amino-1-(5-(2-cyclohexylethyl)tetrahydrofuran-2-yl)propan-1-ol was prepared following the method described in Example 14 and below.

**[00392]** Step 1: A mixture of (*E*)-*N*-(3-(5-(2-cyclohexylvinyl)furan-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide (0.11 g, 0.319 mmol) and Pd/C (10% wt, 0.037 g) in EtOAc (10 mL) was degassed by alternating vacuum/$H_2$ three times and then stirred under $H_2$ atmosphere at room temperature for 40 hrs, filtered through Celite and concentrated under reduced pressure to give *N*-(3-(5-(2-cyclohexylethyl)tetrahydrofuran-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide which was used directly in the next step without additional purification.

**[00393]** Step 2: Deprotection of *N*-(3-(5-(2-cyclohexylethyl)tetrahydrofuran-2-yl)-3-hydroxypropyl)-2,2,2-trifluoroacetamide following the method used in Example 14 gave after flash chromatography purification (4% - 16% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 15 as a colorless oil. Yield (0.033 g, 40%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 3.62-3.84 (m, 2H), 3.45-3.57 (m, 2H), 2.71-2.88 (m, 2H), 1.80-2.05 (m, 2H), 1.39-1.80

(m, 10H), 1.09-1.37 (m, 6H), 0.87-0.99 (m, 2H); RP-HPLC $t_R$ = 9.75 min; ESI-MS m/z 256.3 $[M+H]^+$.

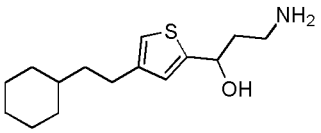
EXAMPLE 16 - Preparation of 1-(2-(5-(3-amino-1-hydroxypropyl)thiophen-3-yl)ethyl)cyclohexanol




**[00394]** 1-(2-(5-(3-Amino-1-hydroxypropyl)thiophen-3-yl)ethyl)cyclohexanol was prepared following the method described in Example 11.

**[00395]** Step 1: Hydrogenation of Example 9 following the method used in Example 15, except that EtOH was used as the solvent, gave after filtration throught Celite and concentration under reduced pressure Example 16 as a colorless oil. Yield (0.055 g, 77%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.88 (s, 1H), 6.85 (s, 1H), 4.91 (dd, J = 5.8, 7.8 Hz, 1H), 2.68-2.80 (m, 2H), 2.58-2.68 (m, 2H), 1.86-2.05 (m, 2H), 1.40-1.78 (m, 12H), 1.2-1.4 (m, 1H); RP-HPLC $t_R$ = 7.25 min; ESI-MS m/z 284.2 $[M+H]^+$.

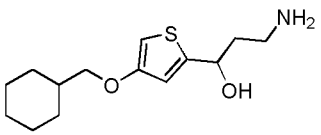
EXAMPLE 17 - Preparation of 3-amino-1-(4-(2-cyclohexylethyl)thiophen-2-yl)propan-1-ol




**[00396]** 3-Amino-1-(4-(2-cyclohexylethyl)thiophen-2-yl)propan-1-ol was prepared following the method described in Examples 11 and 13.

**[00397]** Hydrogenation of (*E*)-3-amino-1-(4-(2-cyclohexylvinyl)thiophen-2-yl)propan-1-ol (Example 13) following the method used in Example 11 gave Example 17 as a pale yellow oil. Yield (0.3 g, 75%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.89 (s, 1H), 6.73 (s, 1H), 4.82 (t, $J$ = 6.0 Hz, 1H), 2.72-2.58 (m, 4H), 1.78-1.56 (m, 9H), 1.46-1.36 (m, 2H ), 1.24-1.06 (m, 5H), 0.98-0.80 (m, 2H ); RP-HPLC $t_R$ = 10.85 min; ESI-MS m/z 221.2 $[M+H]^+$.

EXAMPLE 18 - Preparation of 3-amino-1-(4-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol



**[00398]** 3-Amino-1-(4-(cyclohexylmethoxy)thiophen-2-yl)propan-1-ol was prepared following the method described in Examples 1,2 and below.

**[00399]** Step 1: A solution of oxalyl chloride (1.4 mL, 16.1 mmol) in anhydrous $CH_2Cl_2$ (10 mL) was added dropwise to a solution of 4-bromothiophene-2-carboxylic acid (3.08 g, 14.9 mmol) and DMF (0.2 mL) in anhydrous $CH_2Cl_2$ (40 mL) over 30 mins. The reaction mixture was stirred at room temperature for 35 min then concentrated under reduced pressure. $CH_2Cl_2$ (30 mL) was added to the residue followed by cyclohexylmethanol (1.9 mL, 15.44 mmol) and $Et_3N$ (2.5 mL, 17.94 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between EtOAc and aqueous 25% $NH_4Cl$. Organic layer was washed with brine, concentrated under reduced pressure and purified by flash chromatography (2% - 20% EtOAc – hexanes gradient) to give cyclohexylmethyl 4-bromothiophene-2-carboxylate as a colorless oil which was directly used in the next step. Yield (3.61 g, 80 %).

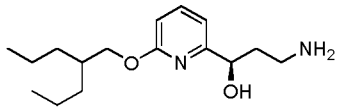
**[00400]** Step 2: Cyclohexylmethanol (0.50 mL, 4.06 mmol) was added to a suspension of NaH (0.080 g, 3.33 mmol) in anhydrous THF (5 mL). Then cyclohexylmethyl 4-bromothiophene-2-carboxylate (0.56 g, 1.847 mmol) was added to the reaction mixture followed by CuI (0.34 g, 1.79 mmol). The reaction mixture was stirred at room temperature for 12 days then aqueous $NH_4Cl$ (25%) was added. Aqueous layer was extracted with EtOAc and combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography purification (2% - 10% EtOAc – hexanes gradient) gave cyclohexylmethyl 4-(cyclohexylmethoxy)thiophene-2-carboxylate as a colorless oil. Yield (0.17 g, 27%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.35 (d, $J$ = 1.7 Hz, 1H), 6.75 (d, $J$ = 1.7 Hz, 1H), 4.07 (d, $J$ = 6.3 Hz, 2H), 3.78 (d, $J$ = 6.3 Hz, 2H), 1.65-1.90 (m, 12H), 1.15-1.38 (m, 6H), 1.00-1.15 (m, 4H).

**[00401]** Step 3: Acetonitrile addition to cyclohexylmethyl 4-(cyclohexylmethoxy)thiophene-2-carboxylate following the method used in Example 1 gave after flash chromatography purification (5% - 20% EtOAc – hexanes gradient) 3-(4-(cyclohexylmethoxy)thiophen-2-yl)-3-oxopropanenitrile as a white solid. Yield (0.084 g, 63%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (d, $J$ = 2Hz, 1H), 6.72 (d, $J$ = 1.5 Hz, 1H), 3.93 (s, 2H), 3.76 (d, $J$ = 5.9 Hz, 2H), 1.67-1.86 (m, 6H), 1.13-1.38 (m, 3H), 0.95-1.13 (m, 2H).

**[00402]** Step 4: Borane-dimethylsulfide reduction of 3-(4-(cyclohexylmethoxy)thiophen-2-yl)-3-oxopropanenitrile following the method used in

Example 2 gave after flash chromatography purification (2% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 18 as a colorless oil. Yield (0.037 g, 43%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.62 (dm $J$ = 1 Hz, 1H), 6.22 (d, $J$ = 1.4 Hz, 1H), 4.85 (m, 1H), 3.71 (d, $J$ = 6.3 Hz, 2H), 2.71-2.78 (m, 2H), 1.64-1.97 (m, 8H), 1.15-1.37 (m, 3H), 1.05-1.15 (m, 2H); RP-HPLC $t_R$ = 9.63 min; ESI-MS m/z 223.1 $[C_{13}H_{18}OS_2\bullet+H]^+$ or $[M-H_2O-CH_2NH_2+H]^+$.

EXAMPLE 19 - Preparation of (*R*)-3-amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol




**[00403]** (*R*)-3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

**[00404]** Step 1: Reaction of 6-bromopicolinic acid with 2-propylpentan-1-ol following the method used in Example 6 gave methyl 6-((2-propylpentyl)oxy)picolinate as an off-white solid which was directly used in next reaction without further purification. Yield (1.29 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.84 (t, $J$ = 8.3 Hz, 1H), 7.63 (d, $J$ = 7.2 Hz, 1H), 7.04 (d, $J$ = 8.4 Hz, 1H), 4.18 (d, $J$ = 6.0 Hz, 2H), 3.84 (s, 3H), 1.84-1.58 (m, 1H), 1.40-1.20 (m, 8H), 0.91-0.80 (m, 6H).

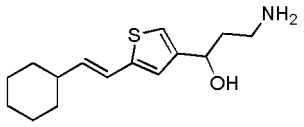
**[00405]** Step 2: $CH_3CN$ addition to methyl 6-((2-propylpentyl)oxy)picolinate following the method used in Example 6 gave 3-oxo-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile in quantitative yield as a solid which was directly used in next reaction without further purification.

**[00406]** Step 3: Chiral reduction of 3-oxo-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile following the method used in Example 6 gave (*R*)-3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile as an off-white solid which was directly used in next reaction without further purification. Yield (1.34 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.69 (t, $J$ = 8.0 Hz, 1H), 7.09 (d, $J$ = 6.8 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 6.09 (d, $J$ = 5.2 Hz, 1H), 4.80-4.75 (m, 1H), 4.20-4.08 (m, 2H), 3.01-2.81 (m, 2H), 1.80-1.68 (m, 1H), 1.40-1.21 (m, 8H), 0.92-0.80 (m, 6H).

**[00407]** Step 4: Reduction of (*R*)-3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile following the method used in Example 6 gave Example 19 as a colorless oil. Yield (0.5 g, 39%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.62 (t, $J$ = 8.0 Hz, 1H), 7.02 (d, $J$ = 7.6 Hz, 1H), 6.58 (d, $J$ = 8.0 Hz, 1H), 4.56-4.52 (m, 1H), 4.08-4.11 (m,

2H), 3.18-3.44 (br.m, 2H), 2.65-2.74 (m, 2H), 1.78-1.84 (m, 2H), 1.64-1.56 (m, 1H), 1.38-1.20 (m, 10H), 0.92-0.78 (m, 6H); RP-HPLC $t_R$ = 10.56 min; ESI-MS *m/z* 281.3 $[M+H]^+$.

EXAMPLE 20 - Preparation of (*E*)-3-amino-1-(5-(2-cyclohexylvinyl)thiophen-3-yl)propan-1-ol



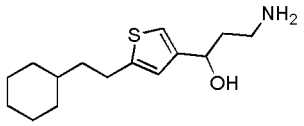

**[00408]** (*E*)-3-Amino-1-(5-(2-cyclohexylvinyl)thiophen-3-yl)propan-1-ol was prepared following the method described in Example 3.

**[00409]** Step 1: Coupling of (*E*)-(2-cyclohexylvinyl)boronic acid with 5-chlorothiophene-3-carbaldehyde in the presence of tetrabutylamonium bromide (1.2 g, 3.72 mmol) following the method used in Example 3 gave after flash chromatography purification (10% - 50% EtOAc – hexanes gradient) (*E*)-5-(2-cyclohexylvinyl)thiophene-3-carbaldehyde as a yellow oil. Yield (0.4 g, 53%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.77 (s, 1H), 8.38 (s, 1H), 7.29 (s, 1H), 6.55 (d, $J$ = 8.0 Hz, 1H), 6.13 (dd, $J$ = 16.4, 6.8 Hz, 1H), 2.08-2.02 (m, 1H), 1.80-1.58 (m, 5H), 1.38-1.08 (m, 5H).

**[00410]** Step 2: Addition of $CH_3CN$ to (*E*)-5-(2-cyclohexylvinyl)thiophene-3-carbaldehyde following the method used in Example 3 gave (*E*)-3-(5-(2-cyclohexylvinyl)thiophen-3-yl)-3-hydroxypropanenitrile as a yellow oil which was used in the next step without further purification.Yield (0.47 g, quant.).

**[00411]** Step 3: $LiAlH_4$ reduction of (*E*)-3-(5-(2-cyclohexylvinyl)thiophen-3-yl)-3-hydroxypropanenitrile following the method used in Example 3 gave Example 20 as a light yellow oil. Yield (0.2 g, 49%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.99 (s, 1H), 6.88 (s, 1H), 6.45 (d, $J$ = 16.8 Hz, 1H), 5.91 (dd, $J$ = 16.0, 6.8 Hz, 1H), 4.60 (t, $J$ = 6.4 Hz, 1H), 2.66-2.56 (m, 2H), 2.18-2.08 (m, 1H), 1.78-1.58 (m, 7H), 1.38-1.02 (m, 5H); RP-HPLC $t_R$ = 10.62 min; ESI-MS *m/z* 219.1 $[M+H]^+$.

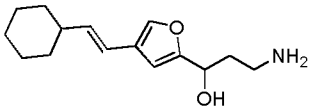
EXAMPLE 21 - Preparation of 3-amino-1-(5-(2-cyclohexylethyl)thiophen-3-yl)propan-1-ol



**[00412]** 3-Amino-1-(5-(2-cyclohexylethyl)thiophen-3-yl)propan-1-ol was prepared following the method described in 20 and 11.

**[00413]** Step 1: Hydrogenation of (E)-3-amino-1-(5-(2-cyclohexylvinyl)thiophen-3-yl)propan-1-ol following the method used in Example 11 gave Example 21 as a pale yellow oil. Yield (0.08 g, 90%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.99 (s, 1H), 6.78 (s, 1H), 4.72 (t, $J$ = 6.0 Hz, 1H), 2.82-2.68 (m, 4H), 1.98-1.82 (m, 2H), 1.81-1.61 (m, 6H), 1.58-1.46 (m, 2H), 1.38-1.06 (m, 3H), 0.98-0.80 (m, 2H); RP-HPLC $t_R$ = 10.78 min; ESI-MS $m/z$ 221.1 $[M+H]^+$.

EXAMPLE 22 - Preparation of (*E*)-3-amino-1-(4-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol



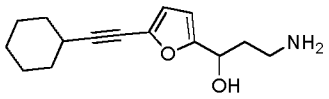

**[00414]** (*E*)-3-Amino-1-(4-(2-cyclohexylvinyl)furan-2-yl)propan-1-ol was prepared following the method described in Examples 1 and 3.

**[00415]** Step 1: Suzuki coupling between (*E*)-(2-cyclohexylvinyl)boronic acid and 4-bromofuran-2-carbaldehyde following the method used in Example 3 gave after flash chromatography purification (1% - 15% EtOAc – hexanes gradient) (*E*)-4-(2-cyclohexylvinyl)furan-2-carbaldehyde as a yellow oil. Yield (0.18 g, 21%).

**[00416]** Step 2: Acetonitrile addition to (*E*)-4-(2-cyclohexylvinyl)furan-2-carbaldehyde following the method used in Example 3 gave after flash chromatography purification (10% - 50% EtOAc – hexanes gradient) (*E*)-3-(4-(2-cyclohexylvinyl)furan-2-yl)-3-hydroxypropanenitrile as a light yellow oil. Yield (0.13 g, 60%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.38 (s, 1H), 6.53 (s, 1H), 6.17 (d, $J$ = 16.1 Hz, 1H), 5.90 (dd, $J$ = 6.9, 16.2 Hz, 1H), 4.90 (t, $J$ = 6.3 Hz, 1H), 2.84-2.97 (m, 2H), 1.99-2.12 (m, 1H), 1.63-1.81 (m, 5H), 1.10-1.40 (m, 5H).

**[00417]** Step3: $LiAlH_4$ reduction of (*E*)-3-(4-(2-cyclohexylvinyl)furan-2-yl)-3-hydroxypropanenitrile following the method used in Example 1 gave after flash chromatography purification (2% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 22 as a colorless oil. Yield (0.07 g, 53%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.34 (s, 1H), 6.41 (s, 1H), 6.17 (d, $J$ = 17.2 Hz, 1H), 5.88 (dd, $J$ = 7.3, 16.1 Hz, 1H), 4.67 (t, $J$ = 6.9 Hz, 1H), 2.67-2.80 (m, 2H), 2.00-2.10 9m, 1H), 1.90-2.00 (m, 2H), 1.63-1.81 (m, 5H), 1.10-1.40 (m, 5H); RP-HPLC $t_R$ = 10.42 min; ESI-MS m/z 232.2 $[M-H_2O+H]^+$.

EXAMPLE 23 - Preparation of 3-amino-1-(5-(cyclohexylethynyl)furan-2-yl)propan-1-ol




**[00418]** 3-Amino-1-(5-(cyclohexylethynyl)furan-2-yl)propan-1-ol was prepared following the method described in Example 1 and below.

**[00419]** Step 1: A mixture of 5-bromofuran-2-carboxylic acid (2.64 g, 13.8 mmol), (cyclohexylmethyl)bromide (2.62 g, 14.8 mmol), $K_2CO_3$ (2.30 g, 16.64 mmol) in anhydrous NMP was stirred under Ar at +70 °C for 8 hrs after which additional (cyclohexylmethyl)bromide (1.55 g, 8.75 mmol) was added. Stirring continued overnight then the reaction mixture was concentrated under reduced pressure. The residue was partitioned between aqueous $NaHCO_3$ (10%) and hexanes, and then aqueous layer was extracted with hexanes. Combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give cyclohexylmethyl 5-bromofuran-2-carboxylate as a light yellow oil. Yield (2.22 g, 56%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.10 (d, $J$ = 3.9 Hz, 1H), 6.44 (d, $J$ = 3.4 Hz, 1H), 4.10 (d, $J$ = 6.4 Hz, 2H), 1.64-1.84 (m, 6H), 1.12-1.34 (m, 3H), 0.95-1.09 (m, 2H).

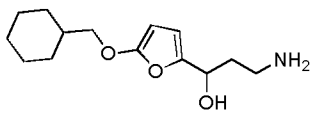
**[00420]** Step 2: A mixture of cyclohexylmethyl 5-bromofuran-2-carboxylate (0.63 g, 2.19 mmol) and ethynylcyclohexane (0.32 g, 2.96 mmol) in $Et_3N$ (10 mL) was degassed by bubbling Ar. CuI (0.023 g, 0.119 mmol) and $PdCl_2(Ph_3P)_2$ (0.0412 g, 0.0587 mmol) were added and the reaction mixture was degassed by alternating vac/Ar three 3 times. The reaction mixture was stirred at +70 °C under Ar overnight and concentrated under reduced pressure. The residue was partitioned between hexanes and aqueous $NH_4Cl$ (25%) and aqueous layer was extracted twice with hexanes. Combined organic layers were washed with brine, treated with activated charcoal and dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave cyclohexylmethyl 5-(cyclohexylethynyl)furan-2-carboxylate as an orange solid which was used directly in the next step without additional purification. Yield (0.75 g, quant.); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.10 (d, $J$ = 3.9 Hz, 1H), 6.50 (d, $J$ = 3.9 Hz, 1H), 4.10 (d, $J$ = 6.4 Hz, 2H), 1.56-2.66 (m, 1H), 1.63-1.84 (m, 9H), 1.42-1.60 (m, 4H), 1.10-1.40 (m, 6H), 0.96-1.10 (m, 2H).

**[00421]** Step 3: Acetonitrile addition to cyclohexylmethyl 5-(cyclohexylethynyl)furan-2-carboxylate following the method used in Example 1 gave after flash chromatography purification (10% - 75% EtOAc – hexanes gradient) 3-(5-(cyclohexylethynyl)furan-2-

yl)-3-oxopropanenitrile an an orange solid which was directly used in the next step without additional purification.Yield (0.64 g, quant.).

**[00422]** Step 4: $LiAlH_4$ reduction of 3-(5-(cyclohexylethynyl)furan-2-yl)-3-oxopropanenitrile following the method used in Example 1 gave after flash chromatography purification (2% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) followed by treatment with activated charcoal Example 23 as a light yellow oil. Yield (0.14 g, 26%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.39 (d, $J$ = 3.4 Hz, 1H), 6.24 (d, $J$ = 3.9 Hz, 1H), 4.68 (t, $J$ = 6.8 Hz, 1H), 2.69-2.79 (m, 2H), 2.56-2.64 (m, 1H), 1.90-1.98 (m, 2H), 1.81-1.90 (m, 2H), 1.68-1.80 (m, 2H), 1.28-1.68 (m, 6H); RP-HPLC $t_R$ = 9.95 min; ESI-MS m/z 230.2 $[M-H_2O+H]^+$.

EXAMPLE 24 - Preparation of 3-amino-1-(5-(cyclohexylmethoxy)furan-2-yl)propan-1-ol




**[00423]** 3-Amino-1-(5-(cyclohexylmethoxy)furan-2-yl)propan-1-ol was prepared following the method described in Examples 1, 23 and below.

**[00424]** Step 1: Cyclohexylmethanol (1.60 g, 14.0 mmol) was slowly added to a cooled (0 °C) suspension of sodium hydride (0.30 g, 12.5 mmol) in anhydrous NMP (5 mL) under Ar. A solution of cyclohexylmethyl 5-bromofuran-2-carboxylate (1.79 g, 6.23 mmol) in anhydrous NMP (6 mL) was added to the reaction mixture and stirred overnight at room temperature. The reaction mixture was partitioned between aqueous $NH_4Cl$ (25%) and hexanes. Aqueous layer was extracted with hexanes and combined organic layers were washed with brine and concentrated under reduced pressure. Purification by flash chromatography (2% - 10% EtOAc – hexanes gradient) gave cyclohexylmethyl 5-(cyclohexylmethoxy)furan-2-carboxylate as a colorless oil. Yield (1.05 g, 53%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.10 (d, $J$ = 3.4 Hz, 1H), 5.27 (d, $J$ = 3.9 Hz, 1H), 4.05 (d, $J$ = 6.4 Hz, 2H), 3.91 (d, $J$ = 5.9 Hz, 2H), 1.62-1.85 (m, 12H), 1.10-1.33 (m, 6H), 0.94-1.10 (m, 4H).

**[00425]** Step 2: $LiAlH_4$ reduction of cyclohexylmethyl 5-(cyclohexylmethoxy)furan-2-carboxylate following the method used in Example 1 gave after flash chromatography purification (10% - 50% EtOAc – hexanes gradient) (5-(cyclohexylmethoxy)furan-2-yl)methanol as a mixture with cyclohexylmethanol which was used in the next step without further purification. Yield (0.75 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$

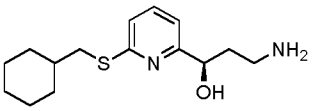
6.09 (d, $J$ = 3.4 Hz, 1H), 5.17 (d, $J$ = 2.9 Hz, 1H), 4.98 (t, $J$ = 5.4 Hz, 1H), 4.19 (d, $J$ = 5.9 Hz, 2H), 3.77 (d, $J$ = 5.9 Hz, 2H), 1.55-1.77 (m, 6H), 1.05-1.25 (m, 3H), 0.94-1.05 (m, 2H).

**[00426]** Step 3: A mixture of (5-(cyclohexylmethoxy)furan-2-yl)methanol and cyclohexylmethanol (0.75 g) and $MnO_2$ (3.16 g, 36.3 mmol) in anhydrous $CH_2Cl_2$ (16 mL) was stirred at room temperature for 3 days. The reaction mixture was filtered through Celite and concentrated under reduced pressure. Flash chromatography purification (10% - 50% EtOAc – hexanes gradient) gave 5-(cyclohexylmethoxy)furan-2-carbaldehyde with cyclohexylmethanol as an impurity as a light yellow. Yield (0.68 g, 99%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.20 (s, 1H), 7.52 (d, $J$ = 3.8 Hz, 1H), 5.79 (d, $J$ = 3.8 Hz, 1H), 4.03 (d, $J$ = 5.8 Hz, 2H), 1.55-1.80 (m, 6H), 0.96-1.25 (m, 5H).

**[00427]** Step 4: Acetonitrile addition to 5-(cyclohexylmethoxy)furan-2-carbaldehyde following the method used in Example 3 gave after flash chromatography purification (10% - 50% EtOAc – hexanes gradient) followed by treatment with activated charcoal 3-(5-(cyclohexylmethoxy)furan-2-yl)-3-hydroxypropanenitrile as a colorless oil which was directly used in the next step. Yield (0.56 g, 69%).

**[00428]** Step 5: $LiAlH_4$ reduction of 3-(5-(cyclohexylmethoxy)furan-2-yl)-3-hydroxypropanenitrile following the method used in Example 1 gave after flash chromatography purification (2% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 24 as a light yellow oil which solidified upon standing. Yield (0.26 g, 46%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 6.11 (d, $J$ = 3.4 Hz, 1H), 5.10 (d, $J$ = 3.4 Hz, 1H), 4.56 (t, $J$ = 6.8 Hz, 1H), 3.79 (d, $J$ = 6.3 Hz, 2H), 2.65-2.77 (m, 2H), 1.82-1.96 (m, 2H), 1.66-1.82 (m, 6H), 1.15-1.37 (m, 3H), 1.00-1.13 (m, 2H); ESI-MS $m/z$ 254.2 $[M+H]^+$.

EXAMPLE 25 - Preparation of (*R*)-3-amino-1-(6-((cyclohexylmethyl)thio)pyridin-2-yl)propan-1-ol




**[00429]** (*R*)-3-Amino-1-(6-((cyclohexylmethyl)thio)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6 and below.

**[00430]** Step 1: A suspension of (bromomethyl)cyclohexane (0.95 g, 5.4 mmol) and AcSK (0.65, 5.4 mmol) in DMF was degassed by bubbling Ar and stirred at 60 °C for 4 hrs. $Cs_2CO_3$ (3.1 g, 10.8 mmol), followed by MeOH (1 ml) and 6-bromopicolinic acid (1.0 g, 4.9 mmol) were then added to the reaction mixture. Stirring was continued at 70

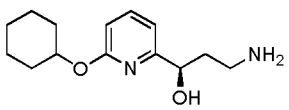
°C for 18 hr. The reaction mixture was filtered through celite and concentrated under reduced pressure. Methanol (20 ml) followed by 1.25 M HCl-MeOH (10 ml) and conc. $H_2SO_4$ (1 ml) was added to the residue. The resulting mixture was stirred at 60 °C for 18 hours, concentrated, partitioned between saturated $NaHCO_3$ (50 ml) and ethyl acetate (100 ml). Organic layer was separated, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (30% - 50% EtOAc – hexane gradient) gave methyl 6-((cyclohexylmethyl)thio)picolinate. Yield (0.6 g, 46%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 8.0 Hz, 1H), 7.58 (t, $J$ = 8.0 Hz, 1H), 7.31 (d, $J$ = 8.0 Hz, 1H), 3.96 (s, 3H), 3.14 (d, $J$=6.4 Hz, 2H), 1.96-1.84 (m, 2H), 1.78-1.58 (m, 4H), 1.26-1.00 (m, 5H).

**[00431]** Step 2: Addition of $CH_3CN$ to methyl 6-((cyclohexylmethyl)thio)picolinate following the method used in Example 6 gave 3-(6-((cyclohexylmethyl)thio)pyridin-2-yl)-3-oxopropanenitrile as a yellow oil which was used in the next step without further purification. Yield (0.63 g, quant.).

**[00432]** Step 3: Chiral reduction of 3-(6-((cyclohexylmethyl)thio)pyridin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gave (*R*)-3-(6-((cyclohexylmethyl)thio)pyridin-2-yl)-3-hydroxypropanenitrile as a yellow oil which was used in the next step without further purification. Yield (0.63 g, quant.).

**[00433]** Step 4: Reduction of (*R*)-3-(6-((cyclohexylmethyl)thio)pyridin-2-yl)-3-hydroxypropanenitrile following the method described in Example 6 gave after flash chromatography purification (15% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 25 as a colorless oil. Yield (0.3 g, 43%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.56 (t, $J$ = 7.6 Hz, 1H), 7.17 (d, $J$ = 7.6 Hz, 1H), 7.09 (d, $J$ = 8.0 Hz, 1H), 4.75-4.72 (m, 1H), 3.04 (d, $J$=7.2 Hz, 2H), 2.80 (t, $J$=7.6 Hz, 2H), 2.03-1.98 (m, 1H), 1.94-1.54 (m, 7H), 1.30-0.99 (m, 5H); RP-HPLC $t_R$ = 9.63 min; ESI-MS $m/z$ 281.2 $[M+H]^+$.

EXAMPLE 26 - Preparation of (*R*)-3-amino-1-(6-(cyclohexyloxy)pyridin-2-yl)propan-1-ol




**[00434]** (*R*)-3-Amino-1-(6-(cyclohexyloxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

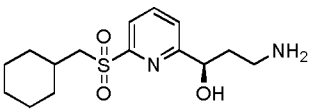
**[00435]** Step 1: Reaction of 6-bromopicolinic acid with cyclohexanol following the method used in Example 6 gave methyl 6-(cyclohexyloxy)picolinate as a yellow oil which was used in the next step without additional purification. Yield (1.15 g, quant.).

**[00436]** Step 2: $CH_3CN$ addition to methyl 6-(cyclohexyloxy)picolinate following the method described in Example 6 gave 3-(6-(cyclohexyloxy)pyridin-2-yl)-3-oxopropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.2 g, quant.).

**[00437]** Step 3: Chrial reduction of 3-(6-(cyclohexyloxy)pyridin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gave (*R*)-3-(6-(cyclohexyloxy)pyridin-2-yl)-3-hydroxypropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.2 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.77 (t, $J$ = 7.6 Hz, 1H), 7.06 (d, $J$ = 7.6 Hz, 1H), 6.63 (d, $J$ = 8.4 Hz, 1H), 6.07 (d, $J$ = 5.2 Hz, 1H), 5.02-4.92 (m, 1H), 4.76 (q, $J$ = 5.6 Hz, 1H), 3.0-2.86 (m, 2H), 2.0-1.06 (m, 10H).

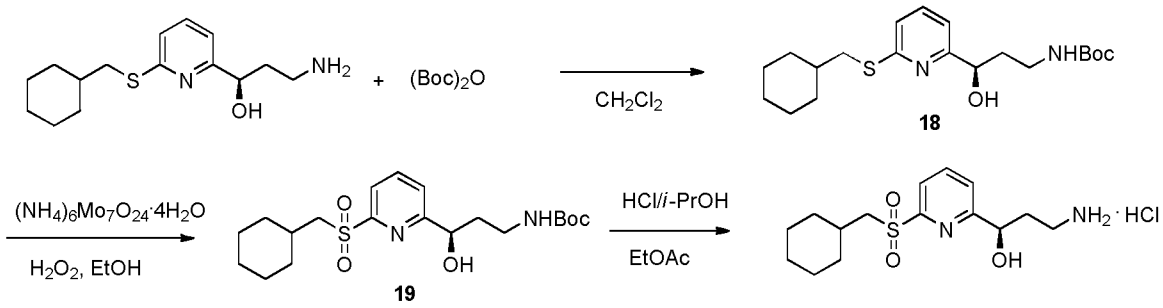
**[00438]** Step 4: Reduction of (*R*)-3-(6-(cyclohexyloxy)pyridin-2-yl)-3-hydroxypropanenitrile following the method described in Example 6 gave after flash chromatography purification (15% - 25% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 26 as a colorless oil. Yield (0.4 g, 33%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.61 (t, $J$ = 7.8 Hz, 1H), 7.00 (d, $J$ = 7.6 Hz, 1H), 6.58 (d, $J$ = 8.4 Hz, 1H), 5.05-4.96 (m, 1H), 4.40-4.28 (m, 1H), 2.84 (t, $J$ = 6.8 Hz, 2H), 2.08-1.74 (m, 6H), 1.62-1.32 (m, 6H); RP-HPLC $t_R$ = 7.04 min; ESI-MS *m/z* 251.2 $[M+H]^+$.

EXAMPLE 27 - Preparation of (*R*)-3-amino-1-(6-((cyclohexylmethyl)sulfonyl)pyridin-2-yl)propan-1-ol




**[00439]** (*R*)-3-Amino-1-(6-((cyclohexylmethyl)sulfonyl)pyridin-2-yl)propan-1-ol was prepared following the method shown in Scheme 6

SCHEME 6.

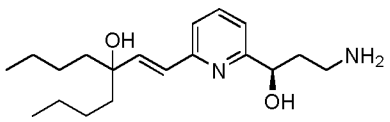



**[00440]** Step 1: A mixture of Example 25 (0.2 g, 0.71 mmol) and di-*tert*-butyl carbonate (0.17 g, 0.78 mmol) in DCM (10 ml) was stirred at room temperature for 18 hrs. Concentration under reduced pressure gave carbamate **18** as a pale yellow oil which was used in the next step without further purification. Yield (0.27 g, quant.).

**[00441]** Step 2: Hydrogen peroxide (1 ml, 30%) was added to a mixture of thioether **18** (0.27 g, 0.71 mmol) and ammonium molybdate tetrahydrate (0.28 g, 0.22 mmol) in ethanol (10 ml). The reaction mixture was stirred at room temperature for 18 hrs, diluted with water (15 ml), concentrated under reduced pressure. Aqueous layer was extracted with EtOAc (3x20 ml) and combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (60% - 75% EtOAc – hexanes gradient) gave sulfone **19** as a colorless oil. Yield (0.16 g, 55%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.10 (t, $J$ = 7.6 Hz, 1H), 7.95 (d, $J$ = 7.6 Hz, 1H), 7.83 (d, $J$ = 7.6 Hz, 1H), 4.84-4.81 (m, 1H), 3.47-3.42 (m, 2H), 3.30-3.12 (m, 2H), 2.10-1.98 (m, 1H), 1.94-1.54 (m, 7H), 1.43 (s, 9H), 1.30-0.99 (m, 5H).

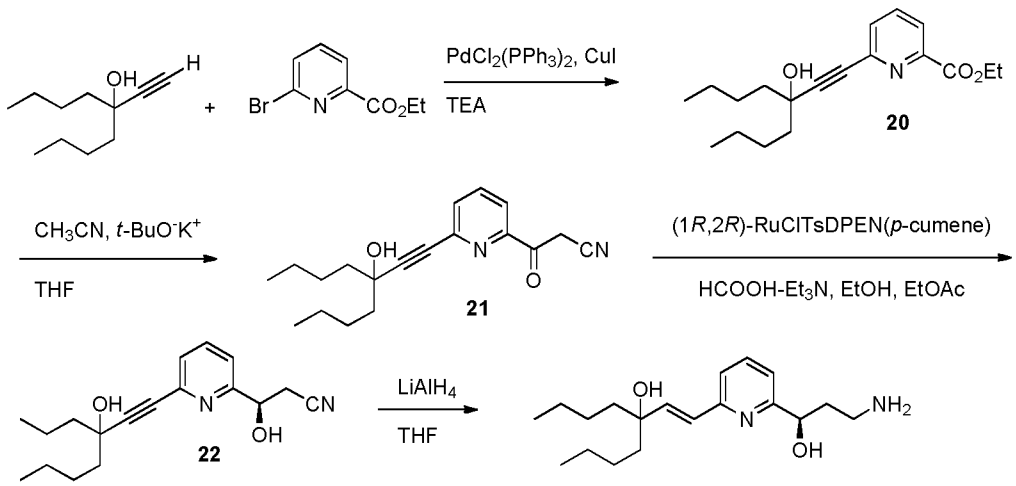
**[00442]** Step 3: A mixture of carbamate **19** (0.16 g, 0.39 mmol) and HCl/*i*-PrOH (2.0 ml, 11 mmol) in EtOAc (5 ml) was stirred at room temperature for 18 hrs and concentrated under reduced pressure to give Example 27 hydrochloride as a colorless oil. Yield (0.12 g, 88%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.10 (t, $J$ = 6.8 Hz, 1H), 7.95 (d, $J$ = 7.2 Hz, 1H), 7.83 (d, $J$ = 8.0 Hz, 1H), 4.94-4.86 (m, 1H), 3.14-3.04 (m, 2H), 2.24-2.14 (m, 1H), 2.06-1.96 (m, 1H), 1.94-1.54 (m, 7H), 1.30-0.99 (m, 6H); RP-HPLC $t_R$ = 7.82 min; ESI-MS: *m/z* 313.2 $[M+H]^+$.

EXAMPLE 28 - Preparation of (*R*,*E*)-5-(2-(6-(3-amino-1-hydroxypropyl)pyridin-2-yl)vinyl)nonan-5-ol




**[00443]** (*R*,*E*)-5-(2-(6-(3-Amino-1-hydroxypropyl)pyridin-2-yl)vinyl)nonan-5-ol was prepared following the method shown in Scheme 7.

SCHEME 7.



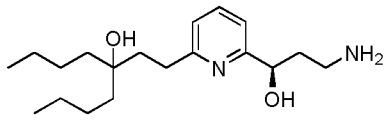

**[00444]** Step 1: CuI (0.07 g, 0.37 mmol) was added to a mixture of 5-ethynylnonan-5-ol (0.76 g, 5.0 mmol), ethyl 6-bromopicolinate (1.0 g, 5.0 mmol) and $PdCl_2(PPh_3)_2$ (0.1 g, 0.14 mmol) in TEA (20 ml). The reaction mixture was bubbled with argon and then stirred at +70 °C for 18 hrs, cooled to room temperature, diluted with EtOAc (40 ml) and filtered through Celite. Concentration under reduced pressure gave alkyne **20** with was used in the next step without further purification. Yield (1.59 g, quant.).

**[00445]** Step 2: $CH_3CN$ addition to ester **20** following the method described in Example 6 gave ketonitrile **21** as a yellow oil which was used in the next step without further purification. Yield (1.63 g, quant.).

**[00446]** Step 3: Chrial reduction of ketonitrile **21** following the method used in Example 6 gave after purification by flash chromatography (35% - 50% EtOAc – hexanes gradient) (*R*)-hydroxynitrile **22** as a white solid. Yield (1.20 g, 70%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.85 (t, $J$ = 8.0 Hz, 1H), 7.49 (d, $J$ = 7.6 Hz, 1H), 7.33 (d, $J$ = 8.0 Hz, 1H), 4.88-4.82 (m, 1H), 3.02-2.82 (m, 2H), 1.66-1.52 (m, 4H), 1.50-1.34 (m, 4H), 1.32-1.22 (m, 4H), 0.92-0.80 (m, 6H).

**[00447]** Step 4: $LiAlH_4$ reduction of (*R*)-hydroxynitrile **22** following the method used in Example 3 gave after flash chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 28 as a light yellow oil. Yield (0.23 g, 21%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.65 (t, $J$ = 7.80 Hz, 1H), 7.26-7.20 (m, 2H), 6.63 (d, $J$ = 16 Hz, 1H), 6.50 (d, $J$ = 16 Hz, 1H), 4.65-4.56 (m, 1H), 2.72-2.58 (m, 2H), 1.82-1.72 (m, 2H), 1.50-1.38 (m, 4H), 1.32-1.10 (m, 8H), 0.86-0.76 (m, 6H); RP-HPLC $t_R$ = 7.62 min; ESI-MS *m/z* 321.1 $[M+H]^+$.

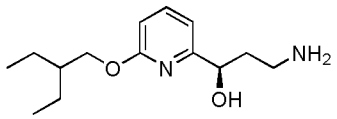
EXAMPLE 29 - Preparation of (*R*)-5-(2-(6-(3-amino-1-hydroxypropyl)pyridin-2-yl)ethyl)nonan-5-ol




**[00448]** (*R*)-5-(2-(6-(3-Amino-1-hydroxypropyl)pyridin-2-yl)ethyl)nonan-5-ol was prepared following the method described in Example 11 and below.

**[00449]** Step 1: Hydrogenation of Example 28 following the method used in Example 11 gave Example 29 as pale yellow oil. Yield (0.09 g, 90%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.60 (t, $J$ = 7.80 Hz, 1H), 7.24 (d, $J$ = 8.0 Hz, 1H), 7.04 (d, $J$ = 8.0 Hz, 1H), 4.65-4.56 (m, 1H), 2.72-2.58 (m, 4H), 1.84-1.68 (m, 2H), 1.66-1.54 (m, 2H), 1.36-1.26 (m, 4H), 1.25-1.14 (m, 8H), 0.88-0.78 (m, 6H); RP-HPLC $t_R$ = 7.50 min; ESI-MS *m/z* 323.3 [M+H].

EXAMPLE 30 - Preparation of (*R*)-3-amino-1-(6-(2-ethylbutoxy)pyridin-2-yl)propan-1-ol




**[00450]** (*R*)-3-amino-1-(6-(2-ethylbutoxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

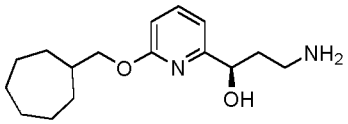
**[00451]** Step 1: Reaction of 6-bromopicolinic acid with 2-ethylbutan-1-ol following the method used in Example 6 gave methyl 6-(2-ethylbutoxy)picolinate as a yellow oil which was used in the next step without further purification. Yield (1.19 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.83 (t, $J$ = 8.0 Hz, 1H), 7.62 (d, $J$ = 7.6 Hz, 1H), 7.02 (d, $J$ = 8.0 Hz, 1H), 4.18 (d, $J$ = 6.0 Hz, 2H), 3.82 (s, 3H), 1.66-1.56 (m, 1H), 1.42-1.32 (m, 4H), 0.86 (t, $J$ = 7.6 Hz, 6H).

**[00452]** Step 2: $CH_3CN$ addition to methyl 6-(2-ethylbutoxy)picolinate following the method described in Example 6 gave 3-(6-(2-ethylbutoxy)pyridin-2-yl)-3-oxopropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.2 g, quant.).

**[00453]** Step 3: Borane reduction of 3-(6-(2-ethylbutoxy)pyridin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gave after flash chromatography purification (25% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 30 as a colorless oil. Yield (0.11 g, 25%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.61 (t, $J$ = 7.6 Hz, 1H), 7.0 (d, $J$ = 7.6 Hz, 1H), 6.57 (d, $J$ = 8.4 Hz, 1H), 4.57-4.50 (m, 1H), 4.15-

4.06 (m, 2H), 2.70-2.58 (m, 2H), 1.84-1.76 (m, 1H), 1.64-1.52 (m, 2H), 1.42-1.28 (m, 4H), 0.85 (t, $J$ = 7.2 Hz, 6H); RP-HPLC $t_R$ = 8.51 min; ESI-MS *m/z* 253.2 $[M+H]^+$.

EXAMPLE 31 - Preparation of (*R*)-3-amino-1-(6-(cycloheptylmethoxy)pyridin-2-yl)propan-1-ol




**[00454]** (*R*)-3-Amino-1-(6-(cycloheptylmethoxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

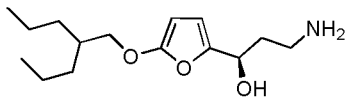
**[00455]** Step 1: Reaction of 6-bromopicolinic acid with cycloheptylmethanol following the method used in Example 6 gave methyl 6-(cycloheptylmethoxy)picolinate as a yellow oil which was used in the next step without further purification. Yield (2.0 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.82 (t, $J$ = 8.0 Hz, 1H), 7.61 (d, $J$ = 7.2 Hz, 1H), 7.03 (d, $J$ = 8.0 Hz, 1H), 4.05 (d, $J$ = 6.4 Hz, 2H), 3.82 (s, 3H), 1.99-1.01 (m, 13H).

**[00456]** Step 2: $CH_3CN$ addition to methyl 6-(cycloheptylmethoxy)picolinate following the method used in Example 6 gave 3-(6-(cycloheptylmethoxy)pyridin-2-yl)-3-oxopropanenitrile as a yellow oil which was used in the next step without further purification. Yield (2.12 g, quant.).

**[00457]** Step 3: Chrial reduction of 3-(6-(cycloheptylmethoxy)pyridin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gave (*R*)-3-(6-(cycloheptylmethoxy)pyridin-2-yl)-3-hydroxypropanenitrile as a yellow oil after purification by flash chromatography (30% - 50% EtOAc – hexanes gradient). Yield (0.77 g, 36%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.67 (t, $J$ = 8.0 Hz, 1H), 7.06 (d, $J$ = 7.4 Hz, 1H), 6.66 (d, $J$ = 8.2 Hz, 1H), 6.05 (d, $J$ = 5.0 Hz, 1H), 4.78-4.70 (m, 1H), 4.18-3.96 (m, 2H), 3.01-2.82 (m, 2H), 1.99-1.01 (m, 13H).

**[00458]** Step 4: $LiAlH_4$ reduction of (*R*)-3-(6-(cycloheptylmethoxy)pyridin-2-yl)-3-hydroxypropanenitrile following the method described in Example 1 gave after flash chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient)Example 31 as a colorless oil. Yield (0.11 g, 25%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.60 (t, $J$ = 8.0 Hz, 1H), 7.00 (d, $J$ = 6.8 Hz, 1H), 6.67 (d, $J$ = 7.6 Hz, 1H), 4.56-4.50 (m, 1H), 4.02-3.98 (m, 2H), 2.72-2.60 (m, 2H), 1.92-1.6 (m, 15H); RP-HPLC $t_R$ = 9.59 min; ESI-MS *m/z* 279.2 $[M+H]^+$.

EXAMPLE 32 - Preparation of (*R*)-3-amino-1-(5-((2-propylpentyl)oxy)furan-2-yl)propan-1-ol




**[00459]** (*R*)-3-Amino-1-(5-((2-propylpentyl)oxy)furan-2-yl)propan-1-ol was prepared following the method described in Examples 5, 18 and below.

**[00460]** Step 1: Esterification of 5-bromofuran-2-carboxylic acid with 2-propylpentan-1-ol following the method used in Example 18 gave after flash chromatography purification (5% - 20% EtOAc – hexanes gradient) 2-propylpentyl 5-bromofuran-2-carboxylate as a colorless oil. Yield (4.85 g, 98%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.07 (d, $J$ = 3.9 Hz, 1H), 6.43 (d, $J$ = 3.4 Hz, 1H), 4.18 (d, $J$ = 5.9 Hz, 2H), 1.70-1.80 (m, 1H), 1.25-1.40 (m, 8H), 0.83-0.95 (m, 6H).

**[00461]** Step 2: Reaction between 2-propylpentan-1-ol and 2-propylpentyl 5-bromofuran-2-carboxylate following the method used in Example 18, except that NMP was used as the solvent, no CuI was used and the reaction mixture was heated at +50 °C under Ar for 1.5 hrs, gave after flash chromatography purification (2% - 5% EtOAc – hexanes gradient) 2-propylpentyl 5-((2-propylpentyl)oxy)furan-2-carboxylate as a colorless oil. Yield (0.62 g, 48%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.15 (d, $J$ = 3.9 Hz, 1H), 5.47 (d, $J$ = 3.9 Hz, 1H), 4.14 (d, $J$ = 5.9 Hz, 2H), 4.06 (d, $J$ = 5.9 Hz, 2H), 1.70-1.84 (m, 2H), 1.28-1.44 (m, 16H), 0.86-0.97 (m, 12H).

**[00462]** Step 3: 2-Propylpentyl 5-((2-propylpentyl)oxy)furan-2-carboxylate (0.62 g, 1.76 mmol), NaOMe (30% in MeOH, 2 mL) in anhydrous MeOH (75 mL) were stirred at room temperature overnight then concentrated under reduced pressure. The residue was partitioned between aqueous $NH_4Cl$ (25%) and hexanes. Organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. Flash chromatography purification (5% - 20% EtOAc – hexanes gradient) gave methyl 5-((2-propylpentyl)oxy)furan-2-carboxylate as a colorless oil. Yield (0.38 g, 85%); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.12 (d, $J$ = 4.0 Hz, 1H), 5.27 (d, $J$ = 3.5 Hz, 1H), 3.99 (d, $J$ = 5.9 Hz, 2H), 3.03 (s, 3H), 1.74-1.83 (m, 1H), 1.20-1.40 (8H), 0.86-0.94 (m, 6H).

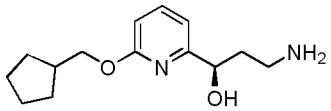
**[00463]** Step 4: Anhydrous $CH_3CN$ (0.15 mL, 2.87 mmol) was added to a solution of LiHMDS (1M/THF, 3.0 mL, 3.0 mmol) at -75 °C under inert atmosphere and the reaction mixture was stirred for 5 min. A solution of methyl 5-((2-propylpentyl)oxy)furan-2-carboxylate (1.337 mmol) in anhydrous THF (7 mL) was added to the reaction mixture and the reaction mixture was stirred under inert atmosphere

while slowly warming to 0 °C for over 75 min. The reaction mixture was partitioned between aqueous $NaHSO_4$ (10%) and EtOAc. Organic layer was washed with brine, concentrated under reduced pressure. Flash chromatography purification (10% - 50% EtOAc – hexanes gradient) gave 3-oxo-3-(5-((2-propylpentyl)oxy)furan-2-yl)propanenitrile as an off-white solid. Yield (0.23 g, 66%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.57 (d, $J$ = 3.8 Hz, 1H), 5.78 (d, $J$ = 3.8 Hz, 1H), 4.30 (s, 2H), 4.08 (d, $J$ = 5.6 Hz, 2H), 1.69-1.79 (m, 1H), 1.23-1.35 (m, 8H), 0.80-0.88 (m, 6H).

**[00464]** Step 5: Chiral reduction of 3-oxo-3-(5-((2-propylpentyl)oxy)furan-2-yl)propanenitrile following the method used in Example 5 gave after flash chromatography purification (20% - 100% EtOAc – hexanes gradient) (*R*)-3-hydroxy-3-(5-((2-propylpentyl)oxy)furan-2-yl)propanenitrile as a yellow oil. Yield (0.14 g, 61%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.19 (d, $J$ = 2.4 Hz, 1H), 5.86 (d, $J$ = 5.4 Hz, 1H), 5.22 (d, J = 3.4 Hz, 1H), 4.67 (q, J = 5.8 Hz, 1H), 3.84 (d, J = 5.4 Hz, 2H), 2.77-2.91 (m, 2H), 1.64-1.75 (m, 1H), 1.20-1.35 (m, 8H), 0.78-0.90 (m, 6H).

**[00465]** Step 6: $LiAlH_4$ reduction of (*R*)-3-hydroxy-3-(5-((2-propylpentyl)oxy)furan-2-yl)propanenitrile following the method used in Example 1 gave after flash chromatography purification (2% - 20% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 32 as a colorless oil. Yield (0.080 g, 61%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ .6.11 (d, $J$ = 2.9 Hz, 1H), 5.11 (d, $J$ = 2.9 Hz, 1H), 4.56 (t, J = 6.9 Hz, 1H), 3.88 (d, J = 5.9 Hz, 2H), 2.65-2.78 (m, 2H), 1.88-1.96 (m, 2H), 1.70-1.80 (m, 1H), 1.30-1.44 (m, 8H), .085-0.97 (m, 6H); ESI-MS 270.2 m/z $[M+H]^+$.

EXAMPLE 33 - Preparation of (*R*)-3-amino-1-(6-(cyclopentylmethoxy)pyridin-2-yl)propan-1-ol




**[00466]** (*R*)-3-Amino-1-(6-(cyclopentylmethoxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

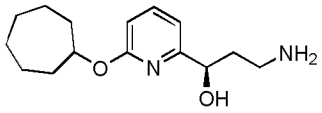
**[00467]** Step 1: Reaction of 6-bromopicolinic acid with cyclopentylmethanol following the method used in Example 6 gave methyl 6-(cyclopentylmethoxy)picolinate as a yellow oil which was used in the next step without further purification. Yield (1.1 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.83 (t, $J$ = 8.0 Hz, 1H), 7.62 (d, $J$ = 7.2 Hz, 1H), 7.03 (d, $J$ = 8.0 Hz, 1H), 4.14 (d, $J$ = 6.4 Hz, 2H), 3.82 (s, 3H), 2.32-2.22 (m, 1H), 1.80-1.62 (m, 2H), 1.60-1.44 (m, 4H), 1.38-1.21 (m, 2H).

**[00468]** Step 2: $CH_3CN$ addition to methyl 6-(cyclopentylmethoxy)picolinate following the method described in Example 6 gave 3-(6-(cyclopentylmethoxy)pyridin-2-yl)-3-oxopropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.22 g, quant.).

**[00469]** Step 3: Chrial reduction of 3-(6-(cyclopentylmethoxy)pyridin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gave (*R*)-3-(6-(cyclopentylmethoxy)pyridin-2-yl)-3-hydroxypropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.22 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.68 (t, $J$ = 7.6 Hz, 1H), 7.07 (d, $J$ = 7.6 Hz, 1H), 6.66 (d, $J$ = 8.0 Hz, 1H), 6.06 (d, $J$ = 5.6 Hz, 1H), 4.78-4.72 (m, 1H), 4.18-4.04 (m, 2H), 3.01-2.82 (m, 2H), 2.32-2.02 (m, 1H), 1.78-1.62 (m, 2H), 1.60-1.42 (m, 4H), 1.36-1.21 (m, 2H).

**[00470]** Step 4: $LiAlH_4$ reduction of (*R*)-3-(6-(cyclopentylmethoxy)pyridin-2-yl)-3-hydroxypropanenitrile following the method described in Example 1 gave after flash chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 33 as a colorless oil. Yield (0.33 g, 24%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.60 (t, $J$ = 7.6 Hz, 1H), 7.00 (d, $J$ = 6.8 Hz, 1H), 6.56 (d, $J$ = 8.0 Hz, 1H), 4.57-4.51 (m, 1H), 4.10-4.04 (m, 2H), 2.71-2.58 (m, 2H), 2.30-2.02 (m, 1H), 1.82-1.21 (m, 10H); RP-HPLC $t_R$ = 7.71 min; ESI-MS *m/z* 251.3 $[M+H]^+$.

EXAMPLE 34 - Preparation of (*R*)-3-amino-1-(6-(cycloheptyloxy)pyridin-2-yl)propan-1-ol




**[00471]** (*R*)-3-Amino-1-(6-(cycloheptyloxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

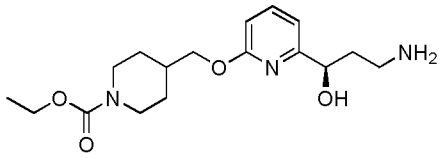
**[00472]** Step 1: Reaction of 6-bromopicolinic acid with cycloheptanol following the method used in Example 6 gave methyl 6-(cycloheptyloxy)picolinate as a yellow oil which was used in the next step without further purification. Yield (1.24 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.80 (t, $J$ = 8.0 Hz, 1H), 7.58 (d, $J$ = 7.2 Hz, 1H), 6.57 (d, $J$ = 8.8 Hz, 1H), 5.25-5.15 (m, 1H), 3.80 (s, 3H), 2.0-1.82 (m, 2H), 1.76-1.40 (m, 10H).

**[00473]** Step 2: $CH_3CN$ addition to methyl 6-(cycloheptyloxy)picolinate following the method described in Example 6 gave 3-(6-(cycloheptyloxy)pyridin-2-yl)-3-oxopropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.29 g, quant.).

**[00474]** Step 3: Chrial reduction of 3-(6-(cycloheptyloxy)pyridin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gave (*R*)-3-(6-(cycloheptyloxy)pyridin-2-yl)-3-hydroxypropanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.29 g, quant.).

**[00475]** Step 4: $LiAlH_4$ reduction of (*R*)-3-(6-(cycloheptyloxy)pyridin-2-yl)-3-hydroxypropanenitrile following the method described in Example 1 gave after flash chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 34 as a colorless oil. Yield (0.19 g, 14%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.58 (t, $J$ = 8.0 Hz, 1H), 6.97 (d, $J$ = 7.2 Hz, 1H), 6.51 (d, $J$ = 8.0 Hz, 1H), 5.16-5.08 (m, 1H), 4.56-4.48 (m, 1H), 2.72-2.56 (m, 2H), 1.98-1.36 (m, 14H); RP-HPLC $t_R$ = 7.98 min; ESI-MS *m/z* 265.2 $[M+H]^+$.

EXAMPLE 35 - Preparation of (*R*)-ethyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate




**[00476]** (*R*)-Ethyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate was prepared following the method described in Example 6 and below.

**[00477]** Step 1: Reaction of 6-bromopicolinic acid with piperidin-4-ylmethanol following the method used in Example 6 gave methyl 6-(piperidin-4-ylmethoxy)picolinate as a yellow oil. Yield (0.3 g, 24%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.82 (t, $J$ = 8.0 Hz, 1H), 7.62 (d, $J$ = 7.4 Hz, 1H), 7.02 (d, $J$ = 8.0 Hz, 1H), 4.08 (d, $J$ = 6.4 Hz, 2H), 3.82 (s, 3H), 2.98-2.86 (m, 2H), 2.51-2.28 (m, 2H), 1.84-1.71 (m, 1H), 1.66-1.58 (m, 2H), 1.20-1.06 (m, 24H).

**[00478]** Step 2: To a mixture of methyl 6-(piperidin-4-ylmethoxy)picolinate (0.3 g, 1.2 mmol), $Et_3N$ (0.2 g, 1.8 mmol) in DCM (10 ml) was added ethyl chlorofomate (0.2 g, 1.8 mmol) at 0 °C. The reaction was warmed to room temperature, washed with 1N HCl (20 ml), dried over $Na_2SO_4$ and concentrated under reduced pressure to give methyl 6-((1-(ethoxycarbonyl)piperidin-4-yl)methoxy)picolinate which used in the next step without further purification. Yield (0.38 g, quant.).

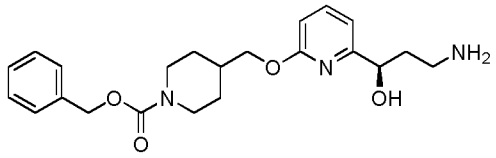
**[00479]** Step 3: $CH_3CN$ addition to methyl 6-((1-(ethoxycarbonyl)piperidin-4-yl)methoxy)picolinate following the method described in Example 6 gave ethyl 4-(((6-

(2-cyanoacetyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate in ethyl acetate solution which was used in the next step without further purification.

**[00480]** Step 4: Chiral reduction of ethyl 4-(((6-(2-cyanoacetyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate following the method described in Example 6 gave after flash chromatography purification (20% - 75% EtOAc – hexanes gradient) (*R*)-ethyl 4-(((6-(2-cyano-1-hydroxyethyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate as a yellow oil. Yield (0.27 g, 81%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.67 (t, $J$ = 8.0 Hz, 1H), 7.12 (d, $J$ = 7.2 Hz, 1H), 6.68 (d, $J$ = 8.4 Hz, 1H), 4.92-4.83 (m, 1H), 4.21-4.04 (m, 6H), 3.02-2.68 (m, 4H), 2.04-1.98 (m, 1H), 1.88-1.78 (m, 2H), 1.38-1.21 (m, 5H).

**[00481]** Step 5: A mixture of of (*R*)-ethyl 4-(((6-(2-cyano-1-hydroxyethyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate (0.27g, 0.81 mmol), Sponge Nickel catalyst A-4000 (0.1 g, Johnson Mathey) in 7N $NH_3$/MeOH (20 ml) was shaked under $H_2$ at 50 psi pressure at 50 °C in a Parr hydrogenator for 18 hrs, cooled to room temperature, filtered, concentrated under reduced pressure. Purification by flash chromatography (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) gave Example 35 as a light yellow oil. Yield (0.26 g, 95%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.64 (t, $J$ = 8.4 Hz, 1H), 7.04 (d, $J$ = 8.4 Hz, 1H), 6.63 (d, $J$ = 8.0 Hz, 1H), 4.70-4.62 (m, 1H), 4.18-4.08 (m, 6H), 2.82-2.78 (m, 4H), 2.08-1.81 (m, 5H), 1.25-1.21 (m, 5H); RP-HPLC $t_R$ = 6.99 min; ESI-MS *m/z* 338.3 $[M+H]^+$.

EXAMPLE 36 - Preparation of (*R*)-benzyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate




**[00482]** (*R*)-Benzyl 4-(((6-(3-amino-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate was prepared following the method described in Example 6 and 35.

**[00483]** Step 1: Reaction of methyl 6-(piperidin-4-ylmethoxy)picolinate with benzyoxy chlorofomate following the method described in Example 35 gave after flash chromatography purification (30% - 50% EtOAc – hexanes gradient) methyl 6-((1-((benzyloxy)carbonyl)piperidin-4-yl)methoxy)picolinate. Yield (1.5 g, 61%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.84 (t, $J$ = 8.4 Hz, 1H), 7.63 (d, $J$ = 8.0 Hz, 1H), 7.36-7.24 (m,

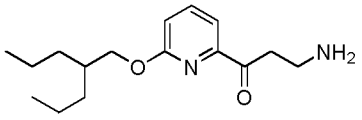
5H), 7.04 (d, $J$ = 8.0 Hz, 1H), 5.04 (s, 2H), 4.12 (d, $J$ = 6.8 Hz, 2H), 4.07-3.96 (m, 4H), 3.02 (s, 3H), 2.01-1.81 (m, 1H), 1.78-1.66 (m, 2H), 1.21-1.12 (m, 2H).

**[00484]** Step 2: $CH_3CN$ addition to 6-((1-((benzyloxy)carbonyl)piperidin-4-yl)methoxy)picolinate following the method described in Example 6 gave benzyl 4-(((6-(2-cyanoacetyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate in which was used in the next step without further purification. Yield (1.53 g, quant).

**[00485]** Step 3: Chiral reduction of benzyl 4-(((6-(2-cyanoacetyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate following the method described in Example 6 gave after flash chromatography purification (50% - 75% EtOAc – hexanes gradient) (*R*)-benzyl 4-(((6-(2-cyano-1-hydroxyethyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate as a yellow oil. Yield (1.0 g, 65%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.66 (t, $J$ = 8.0 Hz, 1H), 7.36-7.25 (m, 5H), 7.12 (d, $J$ = 7.2 Hz, 1H), 6.67 (d, $J$ = 8.4 Hz, 1H), 5.10 (s, 2H), 4.87 (t, $J$ = 6.0 Hz, 1H), 4.21-4.10 (m, 4H), 3.02-2.76 (m, 4H), 2.06-1.98 (m, 1H), 1.90-1.78 (m, 2H), 1.36-1.20 (m, 2H).

**[00486]** Step 4: Borane-dimethylsulfide reduction of (*R*)-benzyl 4-(((6-(2-cyano-1-hydroxyethyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate following the method described in Example 2 gave after flash chromatography purification (30% - 40% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 36 as a colorless oil. Yield (0.27 g, 27%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.63 (t, $J$ = 8.4 Hz, 1H), 7.38-7.25 (m, 5H), 7.03 (d, $J$ = 7.2 Hz, 1H), 6.62 (d, $J$ = 8.0 Hz, 1H), 5.10 (s, 2H), 4.70-4.62 (m, 1H), 4.21-4.10 (m, 4H), 2.88-2.78 (m, 4H), 2.02-1.70 (m, 5H), 1.34-1.20 (m, 2H); RP-HPLC $t_R$ = 9.40 min; ESI-MS $m/z$ 400.3 $[M+H]^+$.

EXAMPLE 37 - Preparation of 3-amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-one



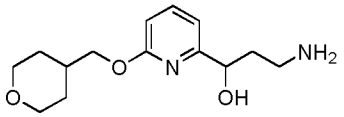

**[00487]** 3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-one was prepared following the method used in Example 27 and below.

**[00488]** Step 1: Reaction of Example 19 with di-*tert*-butyl carbonate following the method described in Example 27 gave (*R*)-*tert*-butyl (3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)carbamate in solution which was treated in situ with PCC (0.16 g, 0.76 mmol) at room temperature for 18 hrs. The reaction mixture was filtered via Celite, concentrated under reduced pressure, purified by flash

chromatography (50% - 75% EtOAc – hexanes gradient) to give *tert*-butyl (3-oxo-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)carbamate as a pale yellow oil without further purification. Yield (0.03 g, 21%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.80 (t, $J$ = 8.4 Hz, 1H), 7.58 (d, $J$ = 7.2 Hz, 1H), 6.97 (d, $J$ = 8.0 Hz, 1H), 4.31 (d, $J$ = 5.6 Hz, 2H), 3.48-3.40 (m, 2H), 3.38-3.32 (m, 2H), 1.91-1.84 (m, 1H), 1.48-1.35 (m, 17H), 0.92-0.82 (m, 6H).

**[00489]** Step 2: Deprotection of *tert*-butyl (3-oxo-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)carbamate following the method described in Example 27 gave Example 37 hydrochloride as a colorless oil. Yield (0.01 g, 38%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.84 (t, $J$ = 8.4 Hz, 1H), 7.66 (d, $J$ = 8.0 Hz, 1H), 7.04 (d, $J$ = 8.4 Hz, 1H), 4.30 (d, $J$ = 5.6 Hz, 2H), 3.60 (t, $J$ = 6.4 Hz, 2H), 3.38-3.32 (m, 2H), 1.92-1.82 (m, 1H), 1.54-1.35 (m, 8H), 0.92-0.82 (m, 6H); RP-HPLC $t_R$ = 11.33 min; ESI-MS *m/z* 279.3 $[M+H]^+$.

EXAMPLE 38 - Preparation of 3-amino-1-(6-((tetrahydro-2*H*-pyran-4-yl)methoxy)pyridin-2-yl)propan-1-ol



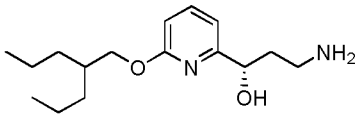

**[00490]** 3-Amino-1-(6-((tetrahydro-2*H*-pyran-4-yl)methoxy)pyridin-2-yl)propan-1-ol is prepared following the method used in Examples 2 and 6.

**[00491]** Step 1: Reaction between (tetrahydro-2*H*-pyran-4-yl)methanol and NaH followed by addition of 6-bromopicolinic acid **12** following the method used in Example 6 gives, after esterification with HCl/MeOH, methyl 6-((tetrahydro-2*H*-pyran-4-yl)methoxy)picolinate.

**[00492]** Step 2: Reaction between methyl 6-((tetrahydro-2*H*-pyran-4-yl)methoxy)picolinate and $CH_3CN$ following the method used in Example 6 gives 3-oxo-3-(6-((tetrahydro-2*H*-pyran-4-yl)methoxy)pyridin-2-yl)propanenitrile.

**[00493]** Step 3: Reduction of 3-oxo-3-(6-((tetrahydro-2*H*-pyran-4-yl)methoxy)pyridin-2-yl)propanenitrile by $LiAlH_4$ following the method used in Example 2 gives Example 38.

EXAMPLE 39 - Preparation of (*S*)-3-amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol

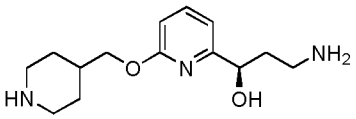


**[00494]** (*S*)-3-Amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol was prepared following the method used in Example 6.

**[00495]** Step 1: Chiral reduction of 3-oxo-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile following the method used in Example 6 using (*1S*,2*S*)-RuCl(TsDPEN)(*p*-cymene) as the catalyst gave (*S*)-3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile as an off-white solid which was used directly in next step without purification. Yield (0.83 g, quant.).

**[00496]** Step 2: Reduction of (*S*)-3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile following the method used in Example 6 followed by treating with HCl-MeOH gave Example 39 as a colorless oil. Yield (0.25 g, 39%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.63 (t, $J$ = 8.4 Hz, 1H), 7.03 (d, $J$ = 8.0 Hz, 1H), 6.62 (d, $J$ = 7.6 Hz, 1H), 4.70-4.66 (m, 1H), 4.20-4.14 (m, 2H), 2.82-2.78 (m, 2H), 2.02-1.78 (m, 3H), 1.44-1.38 (m, 8H), 0.98-0.84 (m, 6H); RP-HPLC $t_R$ = 10.38 min; ESI-MS *m/z* 281.2 $[M+H]^+$.

EXAMPLE 40 - Preparation of (*R*)-3-amino-1-(6-(piperidin-4-ylmethoxy)pyridin-2-yl)propan-1-ol




**[00497]** (*R*)-3-amino-1-(6-(piperidin-4-ylmethoxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6 and below.

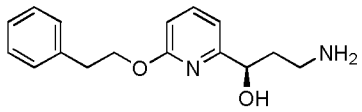
**[00498]** Step 1: Reaction of Example 36 with di-*tert*-butyl carbonate following the method used in Example 27 gave after flash chromatography purification (50% - 75% EtOAc – hexanes gradient) (*R*)-benzyl 4-(((6-(3-((*tert*-butoxycarbonyl)amino)-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate as a colorless oil. Yield (0.3 g, 61%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.62 (t, $J$ = 8.4 Hz, 1H), 7.36-7.28 (m, 5H), 7.01 (d, $J$ = 7.6 Hz, 1H), 6.61 (d, $J$ = 7.6 Hz, 1H), 5.10 (s, 2H), 4.64-4.57 (m, 1H), 4.21-4.04 (m, 4H), 3.22-3.08 (m, 2H), 2.98-2.78 (m, 2H), 2.08-1.98 (m, 1H), 1.88-1.66 (m, 2H), 1.42 (s, 9H), 1.36-1.08 (m, 2H).

**[00499]** Step 2: Deprotection of (*R*)-benzyl 4-(((6-(3-((*tert*-butoxycarbonyl)amino)-1-hydroxypropyl)pyridin-2-yl)oxy)methyl)piperidine-1-carboxylate by hydrogenation following the method used in Example 11 gave (*R*)-*tert*-butyl (3-hydroxy-3-(6-(piperidin-4-ylmethoxy)pyridin-2-yl)propyl)carbamate as a colorless oil. Yield (0.25 g, quant); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.62 (t, $J$ = 8.4 Hz, 1H), 7.02 (d, $J$ = 6.8 Hz, 1H), 6.61 (d, $J$ = 7.6 Hz, 1H), 4.64-4.58 (m, 1H), 4.18-4.12 (m, 2H), 3.10-3.06 (m, 2H), 2.72-

2.61 (m, 2H), 2.06-1.84 (m, 3H), 1.86-1.78 (m, 4H), 1.45-1.20 (m, 11H); ESI-MS *m/z* 366.3 $[M+H]^+$.

**[00500]** Step 3: Deprotection of (*R*)-*tert*-butyl (3-hydroxy-3-(6-(piperidin-4-ylmethoxy)pyridin-2-yl)propyl)carbamate following the method described in Example 27 except 2M HCl-$Et_2O$ and $CH_2Cl_2$ as the solvent were used, gave Example 40 hydrochloride as a colorless oil. Yield (0.16 g, 86%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 8.30 (t, $J$ = 8.0 Hz, 1H), 7.47 (d, $J$ = 7.6 Hz, 1H), 7.34 (d, $J$ = 8.8 Hz, 1H), 5.06-5.03 (m, 1H), 4.38 (d, $J$ = 6.4 Hz, 2H), 3.52-3.44 (m, 2H), 3.18-3.14 (m, 2H), 3.10-3.04 (m, 2H), 2.36-2.02 (m, 5H), 1.78-1.64 (m, 2H); RP-HPLC $t_R$ = 1.69 min; ESI-MS *m/z* 266.2 $[M+H]^+$.

EXAMPLE 41 - Preparation of (*R*)-3-amino-1-(6-phenethoxypyridin-2-yl)propan-1-ol




**[00501]** (*R*)-3-Amino-1-(6-phenethoxypyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

**[00502]** Step 1: Reaction of 6-bromopicolinic acid with 2-phenylethanol following the method used in Example 6 gave methyl 6-phenethoxypicolinate as a yellow oil which was used in the next step without further purification. Yield (1.28 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.85 (t, $J$ = 8.4 Hz, 1H), 7.65 (d, $J$ = 8.4 Hz, 1H), 7.15-7.35 (m, 5H), 7.04 (d, $J$ = 8.0 Hz, 1H), 4.48 (t, $J$ = 7.2 Hz, 2H), 3.84 (s, 3H), 3.04 (t, $J$ = 6.8 Hz, 2H).

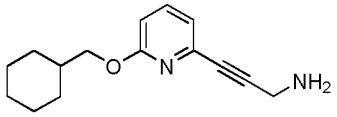
**[00503]** Step 2: $CH_3CN$ addition to methyl 6-phenethoxypicolinate following the method described in Example 6 gave 3-oxo-3-(6-phenethoxypyridin-2-yl)propanenitrile as a yellow oil which was used in the next step without further purification. Yield (1.33 g, quant.).

**[00504]** Step 3: Chiral reduction of 3-oxo-3-(6-phenethoxypyridin-2-yl)propanenitrile following the method described in Example 6 gave after flash chromatography purification (40% - 50% EtOAc – hexanes gradient) (*R*)-3-hydroxy-3-(6-phenethoxypyridin-2-yl)propanenitrile as a colorless oil. Yield (0.6 g, 45%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.66 (t, $J$ = 8.0 Hz, 1H), 7.30-7.15 (m, 5H), 7.11 (d, $J$ = 8.0 Hz, 1H), 6.65 (d, $J$ = 8.0 Hz, 1H), 4.90-4.86 (m, 1H), 4.55-4.51 (m, 2H), 3.08-2.84 (m, 4H).

**[00505]** Step 4: $LiAlH_4$ reduction of (*R*)-3-hydroxy-3-(6-phenethoxypyridin-2-yl)propanenitrile following the method described in Example 1 gave after flash

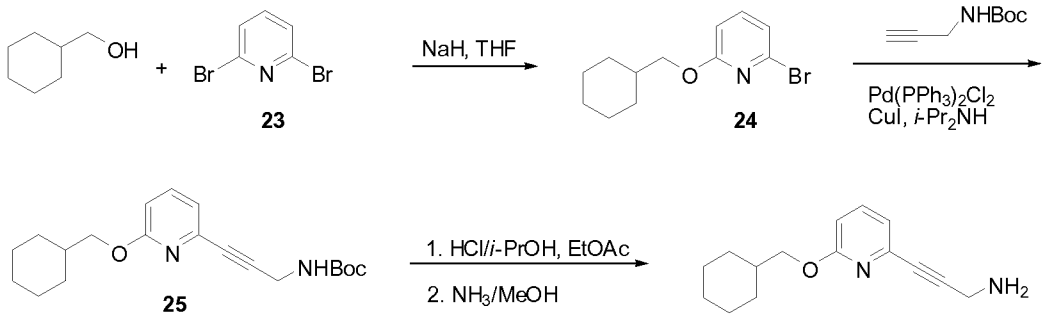
chromatography purification (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 41 as a colorless oil. Yield (0.13 g, 21%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.62 (t, $J$ = 8.0 Hz, 1H), 7.28-7.16 (m, 5H), 7.02 (d, $J$ = 8.0 Hz, 1H), 6.60 (d, $J$ = 8.0 Hz, 1H), 4.70-4.68 (m, 1H), 4.78 (t, $J$ = 7.2 Hz, 2H), 3.05 (t, $J$ = 7.2 Hz, 2H), 2.78 (t, $J$ = 6.8 Hz, 2H), 2.04-1.82 (m, 2H); RP-HPLC $t_R$ = 7.83 min; ESI-MS $m/z$ 273.2 $[M+H]^+$.

EXAMPLE 42 - Preparation of 3-(6-(cyclohexylmethoxy)pyridin-2-yl)prop-2-yn-1-amine




**[00506]** 3-(6-(cyclohexylmethoxy)pyridin-2-yl)prop-2-yn-1-amine was prepared following the method shown in Scheme 8.

SCHEME 8.

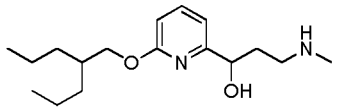



**[00507]** Step 1: Reaction of 2,6-dibromopyridine (**23**) with cyclohexylmethanol following the method used in Example 6 gave alkoxypyridine **24** as a yellow oil which was used in the next step without additional purification. Yield (1.34 g, quant.); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.61 (t, $J$ = 8.0 Hz, 1H), 7.17 (d, $J$ = 8.0 Hz, 1H), 6.82 (d, $J$ = 8.4 Hz, 1H), 4.00 (d, $J$ = 6.0 Hz, 2H), 1.80-1.61 (m, 6H), 1.24-0.98 (m, 5H).

**[00508]** Step 2: A solution of 2-bromopyridine **24** (0.68 g, 2.53 mmol), $Pd(PPh_3)_2Cl_2$ (0.09 g, 0.12 mmol), CuI (0.03g, 0.15 mmol) in $i$-$Pr_2NH$ (15 ml) was saturated with nitrogen and *tert*-butyl prop-2-yn-1-ylcarbamate (0.35 g, 2.25 mmol) was added to the reaction mixture. The resulting mixture was stirred at 50 °C for 18 hr, concentrated under reduced pressure, partitioned between 1N HCl (10 ml), $NH_4Cl$ (30 ml) and EtOAc (80 ml). Organic layer was dried over $Na_2SO_4$, concentrated under reduced pressure and purified by flash chromatography (50% - 75% EtOAc – hexanes gradient) to give propargylpyridine **25** as a light yellow oil. Yield (0.38 g, 44%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.59 (t, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 7.2 Hz, 1H), 6.72 (d, $J$ = 8.4 Hz, 1H), 4.08-4.02 (m, 4H), 1.88-1.66 (m, 6H), 1.46 (s, 9H), 1.38-1.02 (m, 5H).

**[00509]** Step 3: Hydrogen chloride deprotection of carbamate **25** following the method used in Example 27 gave after flash chromatography purification (15% - 25% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 42 as a yellow oil. Yield (0.03 g, 27%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.62 (t, $J$ = 8.0 Hz, 1H), 7.36 (d, $J$ = 7.6 Hz, 1H), 6.64 (d, $J$ = 8.8 Hz, 1H), 4.09 (d, $J$ = 6.4 Hz, 2H), 3.54 (s, 2H), 1.86-1.64 (m, 6H), 1.28-1.02 (m, 5H); RP-HPLC $t_R$ = 10.42 min; ESI-MS *m/z* 281.1 $[M+H]^+$.

EXAMPLE 43 - Preparation of 3-(methylamino)-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol



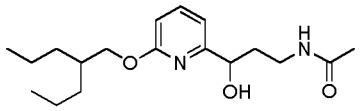

**[00510]** 3-(Methylamino)-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol was prepared following the method described in Example 6.

**[00511]** Step 1: Reduction of 3-oxo-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propanenitrile following the method used in Example 6 gave after flash chromatography (20% - 30% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) 3-amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol as a colorless oil. Yield (0.16 g, 28%); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.63 (t, $J$ = 8.4 Hz, 1H), 7.03 (d, $J$ = 8.0 Hz, 1H), 6.62 (d, $J$ = 8.0 Hz, 1H), 4.70-4.67 (m, 1H), 4.21-4.14 (m, 2H), 2.82-2.78 (m, 2H), 2.06-1.78 (m, 3H), 1.48-1.28 (m, 8H), 0.98-0.86 (m, 6H); ESI-MS *m/z* 281.2 $[M+H]^+$.

**[00512]** Step 2: Reaction of 3-amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol with di-*tert*-butyl carbonate following the method described in Example 27 gave after flash chromatography purification (50% - 75% EtOAc – hexanes gradient) *tert*-butyl (3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)carbamate as a colorless oil which was used in the next step without purification. Yield (0.09 g, 41%).

**[00513]** Step 3: $LiAlH_4$ reduction of *tert*-butyl (3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)carbamate following the method described in Example 1 gave after flash chromatography purification (30% - 40% 7N $NH_3$/MeOH – $CH_2Cl_2$ gradient) Example 43 as a colorless oil; Yield (0.04 g, 62%); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.63 (t, $J$ = 8.4 Hz, 1H), 7.03 (d, $J$ = 8.0 Hz, 1H), 6.62 (d, $J$ = 8.0 Hz, 1H), 4.69-4.66 (m, 1H), 4.18-4.16 (m, 2H), 2.76-2.72 (m, 2H), 2.40 (s, 3H), 2.10-1.68 (m, 3H), 1.46-1.26 (m, 8H), 0.96-0.88 (m, 6H); RP-HPLC $t_R$ = 10.66 min; ESI-MS *m/z* 295.3 $[M+H]^+$.

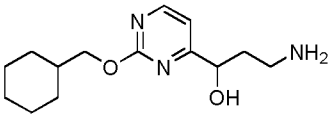
EXAMPLE 44 - Preparation of *N*-(3-hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)acetamide



**[00514]** *N*-(3-Hydroxy-3-(6-((2-propylpentyl)oxy)pyridin-2-yl)propyl)acetamide is prepared following the method used in Example 43 and below.

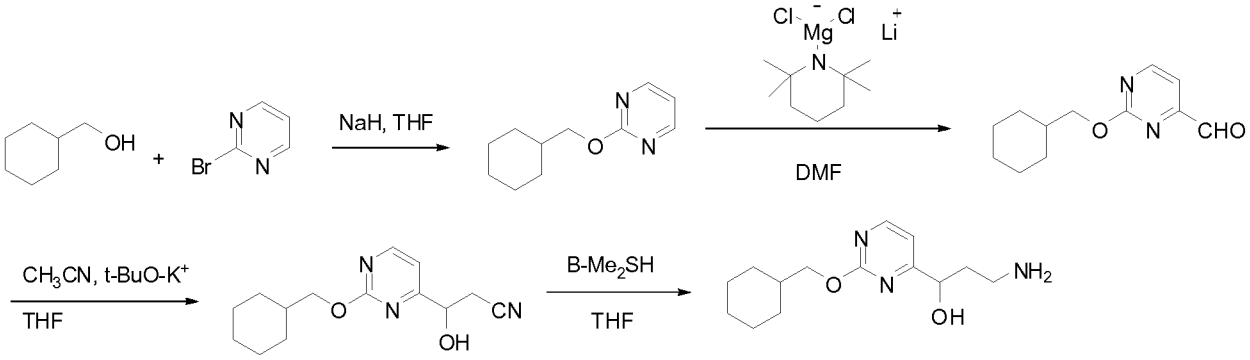
**[00515]** Step 1: Acetylation of 3-amino-1-(6-((2-propylpentyl)oxy)pyridin-2-yl)propan-1-ol with $Ac_2O$ or AcCl in the presence of tertiary base, such as $Et_3N$, in an appropriate solvent gives Example 44.

EXAMPLE 45 - Preparation of 3-amino-1-(2-(cyclohexylmethoxy)pyrimidin-4-yl)propan-1-ol



**[00516]** 3-Amino-1-(2-(cyclohexylmethoxy)pyrimidin-4-yl)propan-1-ol is prepared following the method described in Example 6 and shown in Scheme 9.

Scheme 9.



**[00517]** Step 1: NaH (1.1 equivalent) is added to an equimolar mixture of 2-bromopyrimidine and cyclohexylmethanol in THF. The reaction mixture is stirred at +60 °C for 18 hours, cooled to room temperature, partitioned between $H_2O$ and ethyl acetate. Organic portion is separated, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give 2-(cyclohexylmethoxy)pyrimidine.

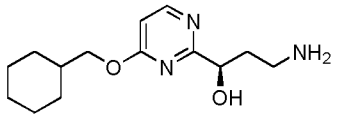
**[00518]** Step 2: Knochel-Hauser reagent (2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex) is added to a mixture of 2-(cyclohexylmethoxy)pyrimidine in THF at -78 °C, stirred for 15 min, then DMF is added. The reaction mixture is stirred at -30 °C, quenched by aqueous $NH_4Cl$, extracted

with ethyl acetate. Combined organic layers are dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give 2-(cyclohexylmethoxy)-pyrimidine-4-carbaldehyde.

**[00519]** Step 3: $CH_3CN$ addition to 2-(cyclohexylmethoxy)pyrimidine-4-carbaldehyde following the method described in Example 6 gives 3-(2-(cyclohexylmethoxy)pyrimidin-4-yl)-3-hydroxypropanenitrile.

**[00520]** Step 4: Reduction of 3-(2-(cyclohexylmethoxy)pyrimidin-4-yl)-3-hydroxypropanenitrile with $BH_3$-$Me_2S$ following the method described in Example 2 gives Example 45.

EXAMPLE 46 - Preparation of (*R*)-3-amino-1-(4-(cyclohexylmethoxy)pyrimidin-2-yl)propan-1-ol




**[00521]** (R)-3-Amino-1-(4-(cyclohexylmethoxy)pyrimidin-2-yl)propan-1-ol is prepared following the method described in Example 6.

**[00522]** Step 1: Reaction of cyclohexylmethanol and 4-bromopyrimidine-2-carboxylic acid following the method described in Example 6 gives methyl 4-(cyclohexylmethoxy)pyrimidine-2-carboxylate.

**[00523]** Step 2: $CH_3CN$ addition to methyl 4-(cyclohexylmethoxy)pyrimidine-2-carboxylate following the method described in Example 6 gives 3-(4-(cyclohexylmethoxy)pyrimidin-2-yl)-3-oxopropanenitrile.

**[00524]** Step 3: Chiral reduction of 3-(4-(cyclohexylmethoxy)pyrimidin-2-yl)-3-oxopropanenitrile following the method described in Example 6 gives (R)-3-(4-(cyclohexylmethoxy)pyrimidin-2-yl)-3-hydroxypropanenitrile

**[00525]** Step 4: Reduction of (R)-3-(4-(cyclohexylmethoxy)pyrimidin-2-yl)-3-hydroxypropanenitrile with $BH_3$-$Me_2S$ following the method described in Example 2 gives Example 46.

## II. Biological Evaluation

**Example 1** – In Vitro Isomerase Inhibition

**[00526]** The capability of compounds disclosed herein to inhibit the activity of a visual cycle isomerase was determined. In particular, the human *in vitro* isomerase assay was

performed essentially as in Golczak et al. Proc. Natl. Acad. Sci. (2005) 102, 8162-8167, and in Imanishi, et al. J. Cell Biol. (2004), 164, 373-383.

Isolation of Human Apo Cellular Retinaldehyde-Binding Protein (CRALBP)

**[00527]** Recombinant human apo cellular retinaldehyde-binding protein (CRALBP) was cloned and expressed according to standard molecular biology methods (*see* Crabb et al., *Protein Science* 7:746-57 (1998); Crabb et al., *J. Biol. Chem.* 263:18688-92 (1988)). Briefly, total RNA was prepared from confluent ARPE19 cells (American Type Culture Collection, Manassas, VA), cDNA was synthesized using an oligo$(dT)_{12-18}$ primer, and then DNA encoding CRALBP was amplified by two sequential polymerase chain reactions (*see* Crabb et al., *J. Biol. Chem.* 263:18688-92 (1988); Intres, et al., *J. Biol. Chem.* 269:25411-18 (1994); GenBank Accession No. L34219.1). The PCR product was sub-cloned into pTrcHis2-TOPO TA vector according to the manufacturer's protocol (Invitrogen Inc., Carlsbad, CA; catalog no. K4400-01), and then the sequence was confirmed according to standard nucleotide sequencing techniques. Recombinant 6xHis-tagged human CRALBP was expressed in One Shot TOP 10 chemically competent E. *coli* cells (Invitrogen), and the recombinant polypeptide was isolated from E. *coli* cell lysates by nickel affinity chromatography using nickel (Ni) Sepharose XK16-20 columns for HPLC (Amersham Bioscience, Pittsburgh, PA; catalog no.17-5268-02). The purified 6xHis-tagged human CRALBP was dialyzed against 10 mM bis-tris-Propane (BTP) and analyzed by SDS-PAGE. The molecular weight of the recombinant human CRALBP was approximately 39 kDal.

Isomerase Assay

**[00528]** Compounds disclosed herein and control compounds were reconstituted in ethanol to 0.1 M. Ten-fold serial dilutions ($10^{-2}$, $10^{-3}$, $10^{-4}$, $10^{-5}$, $10^{-6}$ M) in ethanol of each compound were prepared for analysis in the isomerase assay.

**[00529]** A homogenate of HEK293 cell clone expressing recombinant human RPE65 and LRAT were the source of the visual enzymes, and exogenous all-*trans*-retinol (about 20μM) was used as the substrate. Recombinant human CRALBP (about 80ug/mL) was added to enhance the formation of 11-*cis*-retinal. The 200 μL Bis-Tris Phosphate buffer (10mM, pH 7.2) based reaction mixture also contains 0.5% BSA, and 1mM NaPPi. In this assay, the reaction was carried out at 37°C in duplicates for one hour and was terminated by addition of 300 μL methanol. The amount of reaction product, 11-*cis*-retinol, was measured by HPLC analysis following Heptane extraction of the reaction mixture. The Peak Area Units (PAUs) corresponding to 11-*cis*-retinol in the HPLC

chromatograms were recorded and concentration dependent curves analyzed by GraphPad Prism for $IC_{50}$ values. The ability of the compounds disclosed herein to inhibit isomerization reaction was quantified and the respective $IC_{50}$ value was determined. Tables 2 below summarize the $IC_{50}$ values of various compounds disclosed herein determined as described above.

**TABLE 2 Human *in vitro* Inhibition data**

| $IC_{50}$ (μM) | Example Number |
|---|---|
| ≤ 0.1 μM | 1, 2, 3, 4, 5, 6, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 39, 41, 43 |
| >0.1 μM - ≤ 1 μM | 7, 8, 9, 15, 27, 29 |
| >1 μM - ≤ 10 μM | 40 |
| >10 μM | |
| No detectable activity | |

**Example 2** – In Vivo Murine Isomerase Assay

**[00530]** The capability of compounds described herein to inhibit isomerase was determined by an *in vivo* murine isomerase assay. Brief exposure of the eye to intense light ("photobleaching" of the visual pigment or simply "bleaching") is known to photo-isomerize almost all 11-*cis*-retinal in the retina. The recovery of 11-*cis*-retinal after bleaching was used to estimate the activity of isomerase *in vivo*. Delayed recovery, as represented by lower 11-*cis*-retinal oxime levels, indicates inhibition of isomerization reaction. Procedures were performed essentially as described by Golczak et al., *Proc. Natl. Acad. Sci. USA* 102:8162-67 (2005). See also Deigner et al., *Science*, 244**:** 968-71 (1989); Gollapalli et al., *Biochim Biophys Acta.* 1651**:** 93-101 (2003); Parish, et al., *Proc. Natl. Acad. Sci. USA*, 14609-13 (1998); Radu, et al., *Proc Natl Acad Sci USA* 101**:** 5928-33 (2004).

**[00531]** Six-week old dark-adapted CD-1 (albino) male mice were orally gavaged with compound (0.03 – 3 mg/kg) dissolved in 100 μl corn oil containing 10% ethanol (five animals per group). After 2-24 hours in the dark, the mice were exposed to photobleaching of 5,000 lux of white light for 10 minutes. The mice were allowed to recover 2 hours in the dark. The animals were then sacrificed by carbon dioxide

inhalation. Retinoids were extracted from the eye and the regeneration of 11-*cis*-retinal was assessed at various time intervals.

Eye Retinoid Extraction

**[00532]** All steps were performed in darkness with minimal redlight illumination (low light darkroom lights and red-filtered flashlights for spot illumination as needed) (*see, e.g.,* Maeda *et al.*, J. *Neurochem* 85:944-956, 2003; Van Hooser *et al.*, *J Biol Chem* 277:19173-82, 2002). After the mice were sacrificed, the eyes were immediately removed and placed in liquid nitrogen for storage.

**[00533]** The eyes were placed in 500 μL of bis-tris propane buffer (10 mM, pH ~7.3) and 20 μL of 0.8M hydroxile amine (pH~7.3). The eyes were cut up into small pieces with small iris scissors and then thoroughly homogenized at 30000 rpm with a mechanical homogenizer (Polytron PT 1300 D) in the tube until no visible tissue remained. 500 μL of methanol and 500 μL of heptane were added to each tube. The tubes were attached to a vortexer so that the contents were mixed thoroughly for 15 minutes in room temperature. The organic phase was separated from the aqueous phase by centrifugation for 10 min at 13K rpm, 4 °C. 240 μL of the solution from the top layer (organic phase) was removed and transferred to clean 300 μl glass inserts in HPLC vials using glass pipette and the vials were crimped shut tightly.

**[00534]** The samples were analyzed on an Agilent 1100 HPLC system with normal phase column: SILICA (Beckman Coutlier, dp 5 μm, 4.6 mM x 250 mM). The running method had a flow rate of 1.5ml/min; solvent components are 15% solvent 1 (1% isopropanol in ethyl acetate), and 85% solvent 2 (100% hexanes). Loading volume for each sample was 100 μl; detection wavelength is 360nm. The area under the curve for 11-*cis* retinal oxime was calculated by Agilent Chemstation software and was recorded manually. Data processing was performed using Prizm software.

**[00535]** Positive control mice (no compound administered) were sacrificed fully dark-adapted and the eye retinoids analyzed. Light (bleached) control mice (no compound administered) were sacrificed and retinoids isolated and analyzed immediately after light treatment.

**[00536]** A time course study was performed to determine the isomerase inhibitory activity of the test compound. Male Balb/c mice (4/group) receive test compound orally by gavage. The animals were then "photo-bleached" (5000 Lux white light for 10 minutes) at 2, 4, 8, 16 and 24 hours after dosing, and returned to darkness to allow

recovery of the 11-*cis*-retinal content of the eyes. Mice were sacrificed 2 hours after bleaching, eyes were enucleated, and retinoid content was analyzed by HPLC.

**[00537]** Recovery control mice (vehicle-only treated) were light-treated and left to recover for 2 hours in the dark before sacrifice and analysis. Light control mice (vehicle only treated) were sacrificed for analysis immediately after photo-bleaching.

**[00538]** Table 3 provides *in vivo* murine isomerase assay results of various compounds disclosed herein at the dose and time point indicated.

**TABLE 3 In Vivo Murine Isomerase Assay data**

| Synthesis Example | Inhibition, % | Dose (mg/kg) | Time (hour) |
|---|---|---|---|
| 1 | 0 | 1 | 2 |
| 1 | 0 | 1 | 4 |
| 3 | 0 | 1 | 2 |
| 4 | 29.3±4.3 | 1 | 2 |
| 5 | 0 | 1 | 2 |
| 6 | 68.9±6.5 | 1 | 2 |
| 6 | 37.7±14.9 | 1 | 4 |
| 6 | 93.2±0.9 | 3 | 2 |
| 6 | 85.5±2.9 | 3 | 4 |
| 6 | 62.3±3.8 | 3 | 6 |
| 6 | 30.8±9.9 | 3 | 8 |
| 6 | 0 | 3 | 16 |
| 6 | 0 | 3 | 24 |
| 9 | 8.6±4.2 | 1 | 2 |
| 12 | 0 | 1 | 2 |
| 19 | 98.2±2.3 | 1 | 4 |
| 19 | 90.7±3.3 | 1 | 8 |

**Example 3** – In Vivo Light Damage Mouse Model

**[00539]** This Example describes the effect of a compound disclosed herein in an *in vivo* light damage mouse model.

**[00540]** Exposure of the eye to intense white light can cause photo-damage to the retina. The extent of damage after light treatment is evaluated by measuring cytoplasmic histone-associated-DNA-fragment (mono- and oligonucleosomes) content in the eye (*see, e.g.,* Wenzel et al., *Prog. Retin. Eye Res.* 24:275-306 (2005)).

**[00541]** Dark adapted male Balb/c (albino, 10/group) mice are gavaged with text compound at various doses (0.03, 0.1, 0.3, 1, and 3 mg/kg) or vehicle only was administered. Six hours after dosing, the animals are subjected to light treatment (8,000 lux of white light for 1 hour). Mice are sacrificed after 40 hours of recovery in dark, and retinas are dissected. A cell death detection ELISA assay is performed according to the manufacturer's instructions (ROCHE APPLIED SCIENCE, Cell Death Detection ELISA plus Kit). Contents of fragmented DNA in the retinas are measured to estimate the retinal-protective activity of the test compound.

**Example 4** – Electroretinographic (ERG) Study

**[00542]** ERG experiments are performed using 11-16 week old BALB/c mice of both genders (n = 5). All studies involve the pharmacodynamic assessment of dark-adapted (scotopic, rod-dominated) and light-adapted (photopic, cone-dominated) ERG responses. Experiments are performed using test compound. All recording procedures are performed according to the same protocol and with the same equipment. Data are aggregated across individual studies to generate summary graphs.

**[00543]** Results from four independent studies are combined to build the dose-response function between administration of test compound and changes in the amplitude of the scotopic b-wave (0.01 cd.s/$m^2$), 4 hours after single oral administration of the test compound (dissolved in corn oil).

**[00544]** The effect on the cone system is estimated based on recording and measurement of the ERG b-wave intensity-response function under photopic conditions. In such studies, two parameters are typically evaluated: maximal response ($V_{max}$), measured in microvolts, and semi-saturation constant (k), measured in cd.s/$m^2$.

**[00545]** Results from three independent studies are combined to estimate the effect of single dosing of test compound on the photopic ERG (11-16 week old BALB/c mice of both genders, n = 5).

**III. Preparation of Dosage Forms**

**Example 1: Parenteral Composition**

**[00546]** To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula (A) is dissolved

in sterile water and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

**Example 2: Oral Composition**

**[00547]** To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula (A) is mixed with 750 mg of starch. The mixture is incorporated into an oral dosage unit, such as a hard gelatin capsule, which is suitable for oral administration.

**Example 3: Sublingual (Hard Lozenge) Composition**

**[00548]** To prepare a pharmaceutical composition for buccal delivery, such as a hard lozenge, combine 100 mg of a compound of Formula (A) with 420 mg of powdered sugar, 1.6 mL of light corn syrup, 2.4 mL distilled water, and 0.42 mL mint extract. The mixture is gently blended and poured into a mold to form a lozenge suitable for buccal administration.

**Example 4: Fast-Disintegrating Sublingual Tablet**

**[00549]** A fast-disintegrating sublingual tablet is prepared by mixing 48.5% by weigh of a compound of Formula (A), 44.5% by weight of microcrystalline cellulose (KG-802), 5% by weight of low-substituted hydroxypropyl cellulose (50 μm), and 2% by weight of magnesium stearate. Tablets are prepared by direct compression (AAPS PharmSciTech. 2006;7(2):E41). The total weight of the compressed tablets is maintained at 150 mg. The formulation is prepared by mixing the amount of compound of Formula (A) with the total quantity of microcrystalline cellulose (MCC) and two-thirds of the quantity of low-substituted hydroxypropyl cellulose (L-HPC) by using a three dimensional manual mixer (Inversina ®, Bioengineering AG, Switzerland) for 4.5 minutes. All of the magnesium stearate (MS) and the remaining one-third of the quantity of L-HPC are added 30 seconds before the end of mixing.

**Example 5: Inhalation Composition**

**[00550]** To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound of Formula (A) is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

**Example 6: Rectal Gel Composition**

**[00551]** To prepare a pharmaceutical composition for rectal delivery, 100 mg of a compound of Formula (A) is mixed with 2.5 g of methylcelluose (1500 mPa), 100 mg of methylparaben, 5 g of glycerin and 100 mL of purified water. The resulting gel mixture

is then incorporated into rectal delivery units, such as syringes, which are suitable for rectal administration.

**Example 7: Topical Gel Composition**

**[00552]** To prepare a pharmaceutical topical gel composition, 100 mg of a compound of Formula (A) is mixed with 1.75 g of hydroxypropyl celluose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical administration.

**Example 8: Ophthalmic Solution Composition**

**[00553]** To prepare a pharmaceutical opthalmic solution composition, 100 mg of a compound of Formula (A) is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

**Example 9: Nasal spray solution**

**[00554]** To prepare a pharmaceutical nasal spray solution, 10 g of a compound of Formula (A) is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100 μl of spray for each application.

**VI. Clinical Trial**

**Example 1 – Phase 1A study of safety and pharmacodynamics effect**

**[00555]** A single-center, randomized, double masked, placebo controlled, dose-escalating Phase 1A study to determine the safety and pharmacodynamic effect of single oral dose of a compound of Formuala (A) such as 3-amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol (example 4), measured by dark-adapted electroretinogram (ERG), is performed. Study participants are healthy volunteers of both genders, aged 55-80, weighing between 50 and 110 kg. Major exclusion criteria include other ocular conditions (e.g. cataracts, glaucoma, uveitis, diabetic retinopathy, active conjunctivitis), change in prescription chronic medications within the preceeding 28 days, treatment with a retinoid compound within the last year, treatment with sildenafil citrate, tadalafil, or vardenafil citrate within the last week, or concomitant treatment with hypnotics, anti-depressants, psychoactive substances, digitalis glycosides, L-DOPA, chloroquine, hydroxychloroquine, systemic corticosteroids, topical anti-glaucoma

medications, or medications for the treatment of wet AMD. Eight cohorts are randomized 5:1/drug:placebo and assigned to dosage cohorts of 2 mg, 7 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 75 mg. Plasma concentration versus time is determined. Peak plasma concentrations ($C_{max}$), time of peak plasma concentration ($T_{max}$) and mean terminal elimination half-life ($t_{1/2}$) will be determined across all doses.

**[00556]** ERG studies are performed prior to dosing, 4-6 hours post-dose (Day 1 ERG), 24 hours post-dose (Day 2 ERG), Day 4, and on Day 7. For patients given placebo, the ERG readout will be monitored for a rapid rise in amplitude such that the response is 90% recovered by about 20 minutes. For patients given a test compound of Formula (A) such as such as 3-amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol (example 4), the ERG readout will be monitored for a clear dose-related slowing of the rate of recovery; i.e. the slope of the recovery function became slower with increasing dose.

**Example 2 – Treatment of dry-form age related macular degeneration**

**[00557]** An individual diagnosed with dry-form age related macular degeneration is treated with an oral dose of 5 mg of the test compound of Formula (A) such as 3-amino-1-(6-(2-cyclohexylethyl)pyridin-2-yl)propan-1-ol (example 4). On days 2, 4, 6, 8, 12, 18, 24 and 30 the individual is subjected to an electroretinogram determination to evaluate treatment response and the individual is monitored for instances of delayed dark adaptation and achromatopsia, as well as systemic adverse effects.

**[00558]** When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included.

**[00559]** The various embodiments described herein can be combined to provide further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications, and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference in their entireties.

**[00560]** From the foregoing it will be appreciated that, although specific embodiments have been described herein for purposes of illustration, various modifications may be made. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims. In general, in the following claims, the terms used should not be construed to limit the claims to the

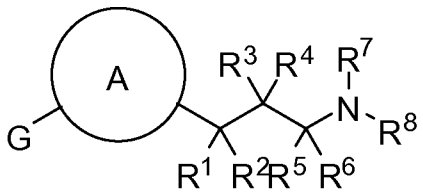
specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

**[00561]** While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

## CLAIMS

We claim:

1. A compound of Formula (A) or tautomer, stereoisomer, geometric isomer or a pharmaceutically acceptable solvate, hydrate, salt, or *N*-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

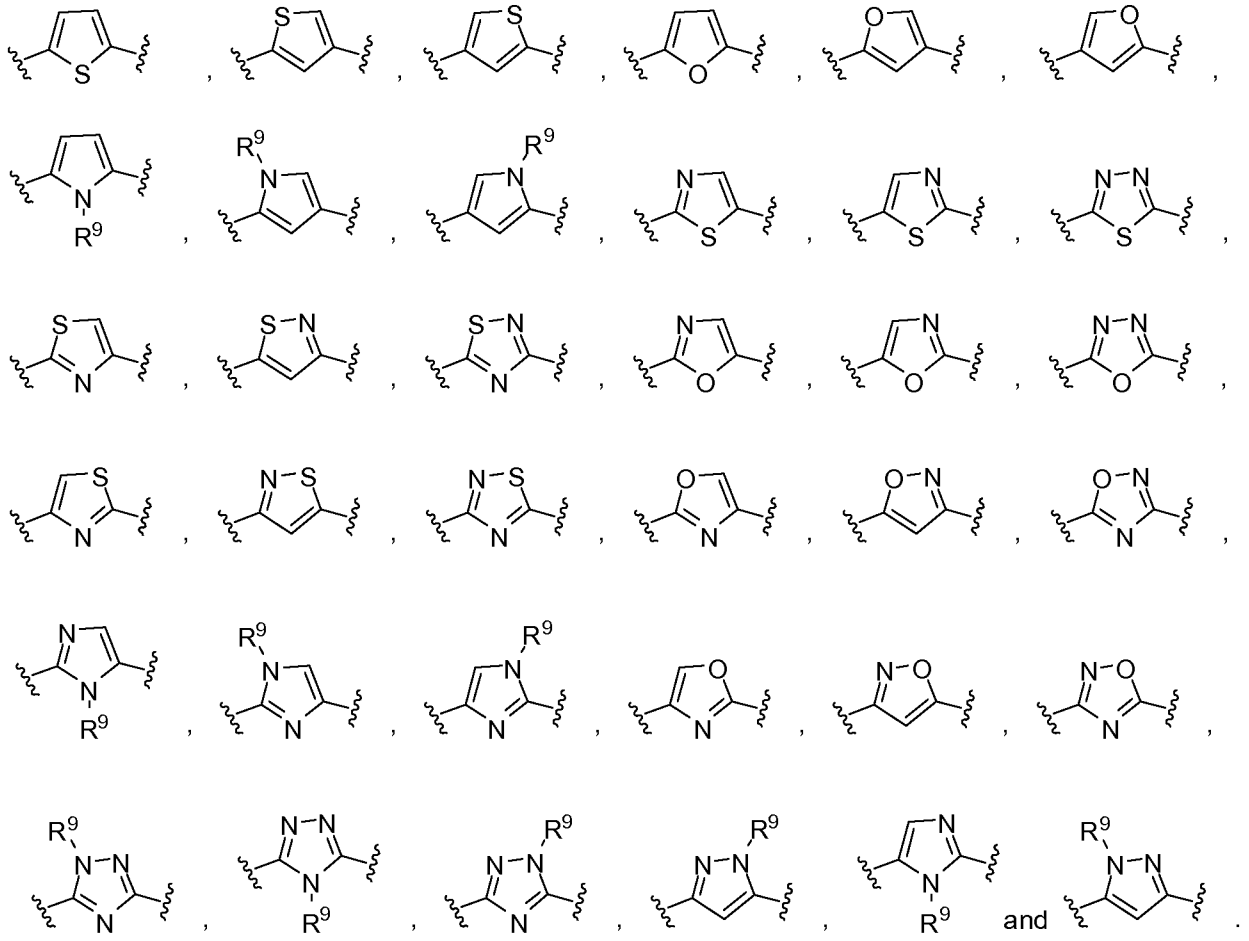
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

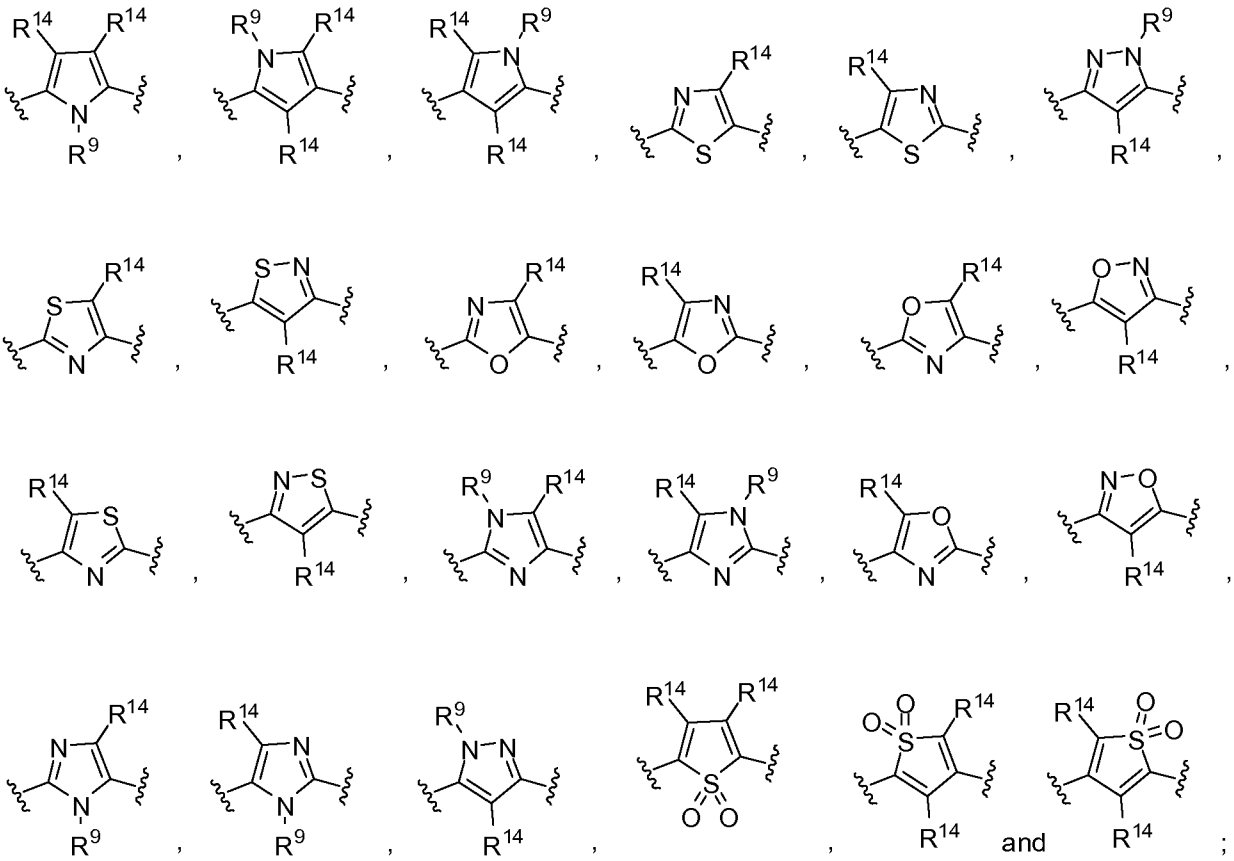
each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

2. The compound of claim 1 wherein Ring A is selected from:

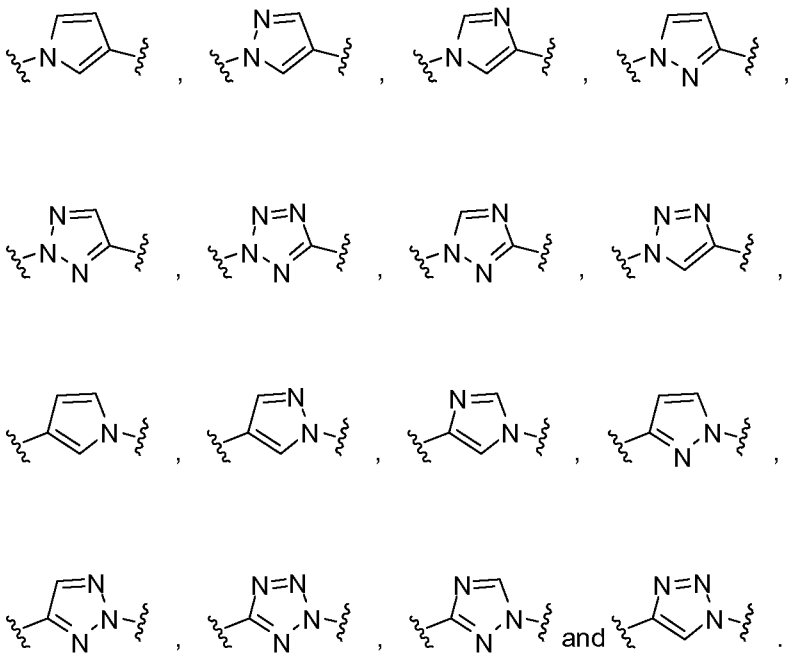


3. The compound of claim 1 wherein Ring A is selected from:

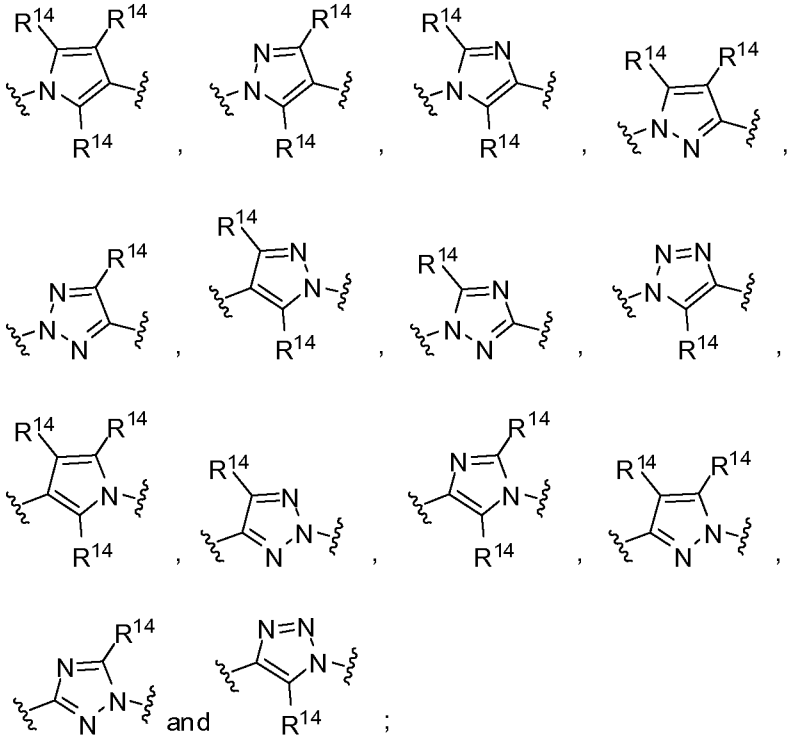


and each $R^{14}$ is independently selected from hydrogen, halogen, $OR^9$, alkyl, or fluoroalkyl.

4. The compound of claim 1 wherein Ring A is selected from:

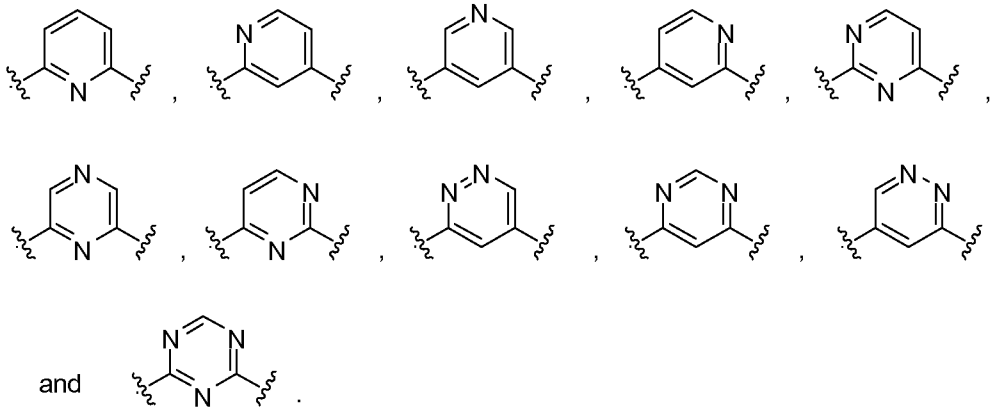


5. The compound of claim 1 wherein Ring A is selected from:

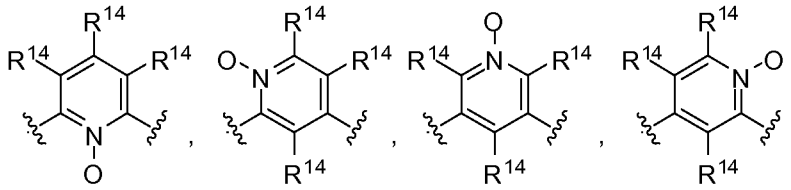


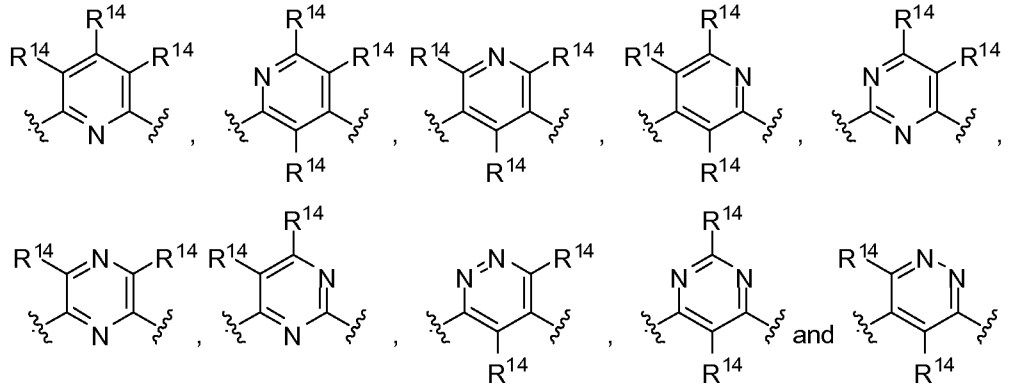
and each $R^{14}$ is independently selected from hydrogen, halogen, $OR^9$, alkyl, or fluoroalkyl.

6. The compound of claim 1 wherein Ring A is selected from:



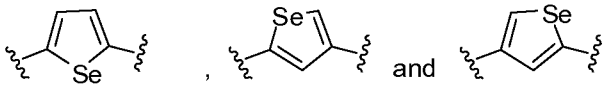
7. The compound of claim 1 wherein Ring A is selected from:



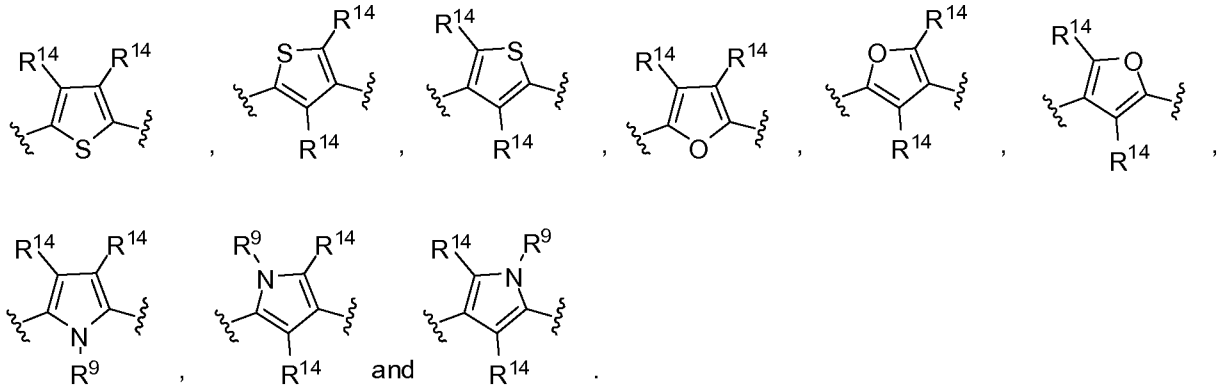


and each $R^{14}$ is independently selected from hydrogen, halogen, $OR^9$, alkyl, or fluoroalkyl.

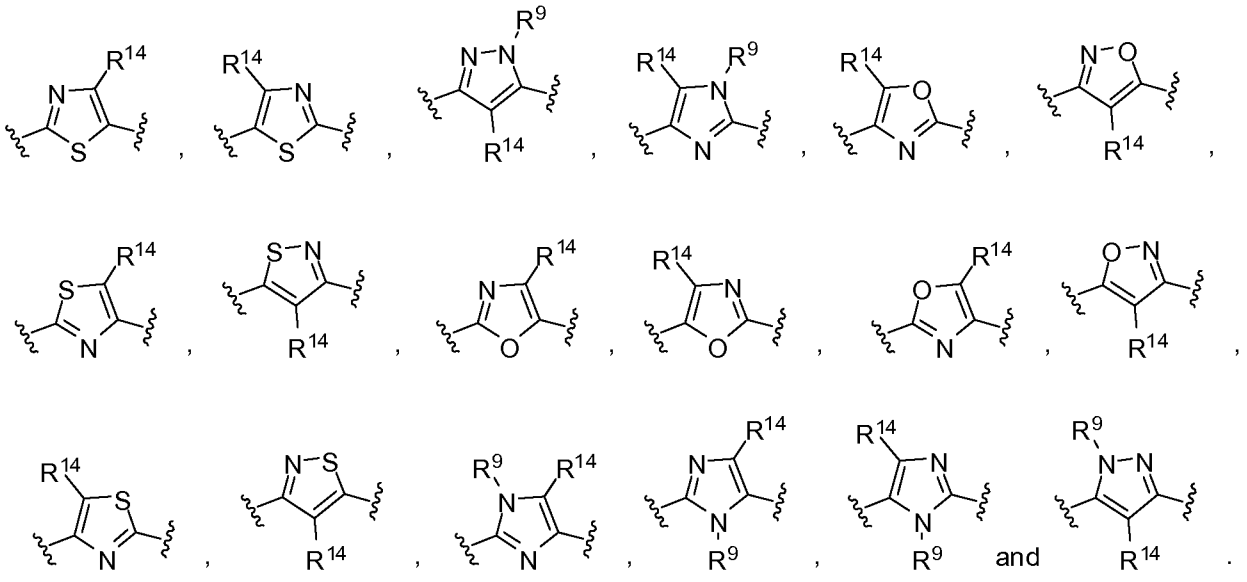
8. The compound of claim 1 wherein Ring A is selected from:



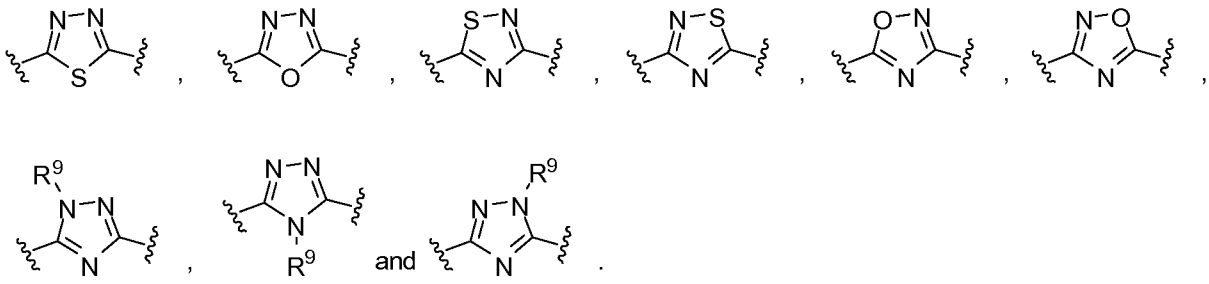
9. The compound of claim 1 wherein Ring A is selected from:



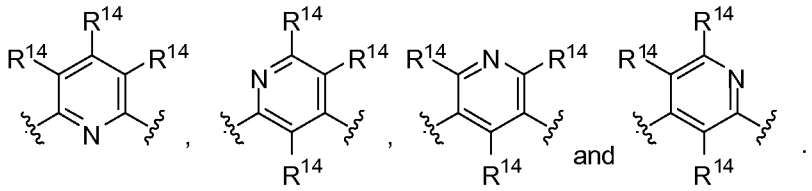
10. The compound of claim 3 wherein Ring A is selected from:



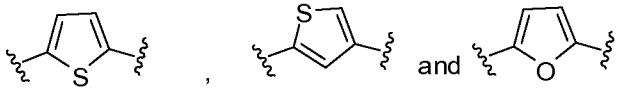
11. The compound of claim 2 wherein Ring A is selected from:



12. The compound of claim 7 wherein Ring A is selected from:



13. The compound of claim 2 wherein Ring A is selected from:



14. The compound of claim 1 wherein Y is alkyl, carbocyclyl or heterocyclyl.

15. The compound of claim 14 wherein Y is $-C(R^{16})(R^{17})(R^{18})$;

$R^{16}$ and $R^{17}$ are each independently selected from hydrogen, $C_1$-$C_{13}$ alkyl, halo or fluoroalkyl; or $R^{16}$ and $R^{17}$, together with the carbon to which they are attached form a carbocyclyl or heterocyclyl; and

$R^{18}$ is selected from a hydrogen, alkyl, alkoxy, hydroxy, halo or fluoroalkyl.

16. The compound of claim 15 wherein $R^{16}$ and $R^{17}$, together with the carbon to which they are attached, form a carbocyclyl or heterocyclyl.

17. The compound of claim 16 wherein $R^{16}$ and $R^{17}$, together with the carbon to which they are attached, form a cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and $R^{18}$ is hydrogen or hydroxy.

18. The compound of claim 17 wherein $R^{16}$ and $R^{17}$, together with the carbon to which they are attached, form a cyclopentyl, cyclohexyl, or cycloheptyl, and $R^{18}$ is hydrogen or hydroxy.

19. The compound of claim 15 wherein $R^{16}$ and $R^{17}$ is independently selected from $C_1$-$C_{13}$ alkyl; and $R^{18}$ is hydrogen, hydroxy or alkoxy.

20. The compound of claim 1 wherein X is selected from $-O-C(R^9)_2$, $-S(O)_2-C(R^9)_2$-, $-SO_2(NR^9)$-, $-NR^9-C(R^9)_2$-, $-NR^9-C(=O)$-, and $-NR^9-S(O)_2$-.

21. The compound of claim 1 wherein X is selected from $-C(R^9)_2-C(R^9)_2-$, $-C(R^9)=C(R^9)$-, -C ≡ C-, $-C(=O)-N(R^9)$-, $-C(R^9)_2-O$-, and $-C(R^9)_2-NR^9$.

22. The compound of claim 1 wherein X is selected from $-O-C(R^9)_2$,or $-C(R^9)_2-C(R^9)_2-$.

23. The compound of claim 1 wherein $R^3$ and $R^4$ are both hydrogen.

24. The compound of claim 1 wherein $R^5$ and $R^6$ are both hydrogen.

25. The compound of claim 1 wherein $R^3$, $R^4$, $R^5$ and $R^6$ are hydrogen.

26. The compound of claim 1 wherein $R^1$ and $R^2$ are both hydrogen.

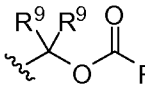
27. The compound of claim 1 wherein $R^1$ is hydrogen and $R^2$ is -OH.

28. The compound of claim 1 wherein $R^1$ and $R^2$ together form an oxo.

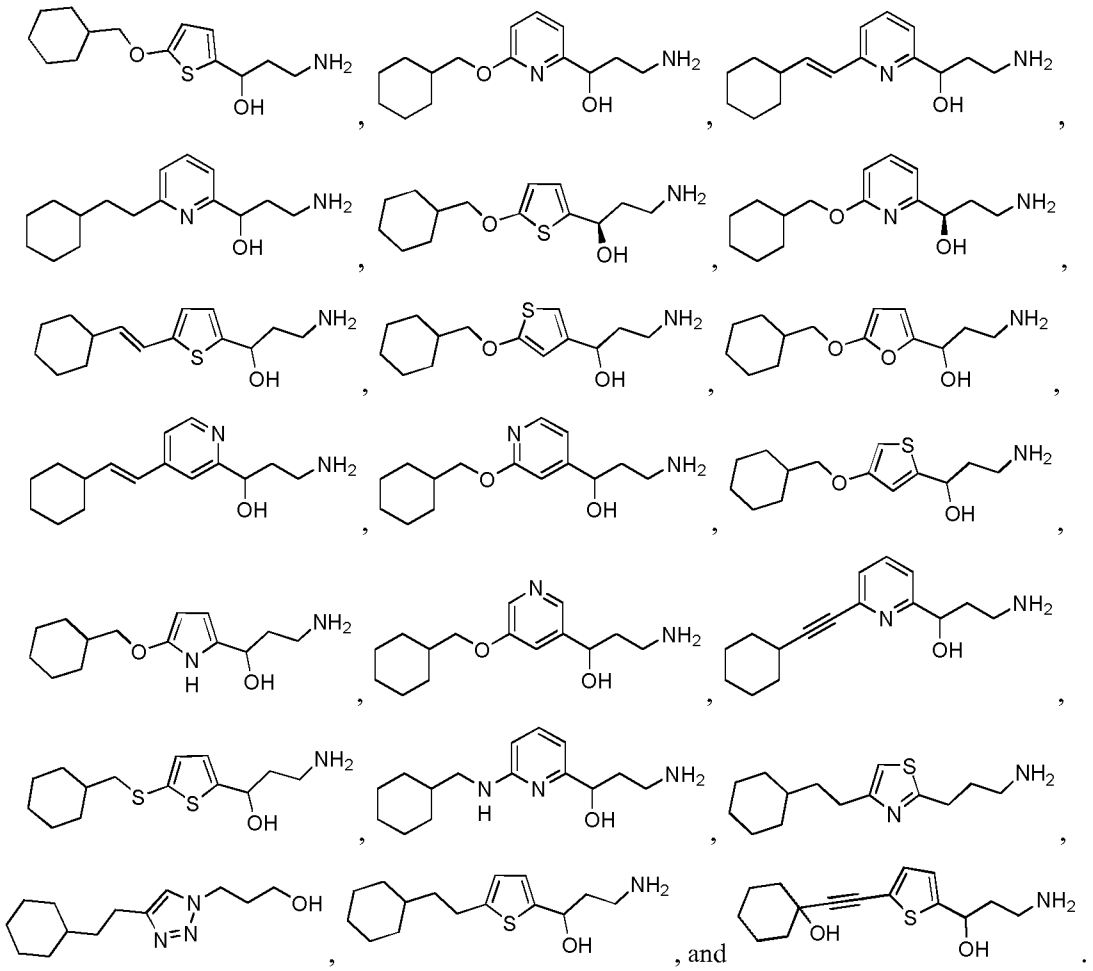
29. The compound of claim 1 wherein $R^7$ and $R^8$ are both hydrogen.

30. The compound of claim 1 wherein $R^7$ is hydrogen and $R^8$ is $-C(=O)R^{13}$ or $CO_2R^{13}$.

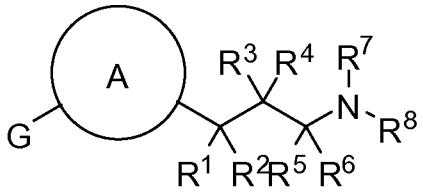
31. The compound of claim 30 wherein $R^{13}$ is an alkyl.

32. The compound of claim 30 wherein $R^8$ is $CO_2R^{13}$ and $R^{13}$ is  .

33. A compound, or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof, selected from the group consisting of:



34. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:



Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

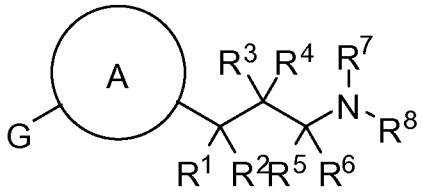
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

35. A method for treating an ophthalmic disease or disorder in a subject, comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, $-C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

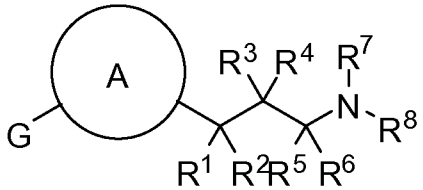
36. The method of claim 35 wherein the ophthalmic disease or disorder is age-related macular degeneration or Stargardt's macular dystrophy.

37. The method of claim 35 wherein the ophthalmic disease or disorder is selected from retinal detachment, hemorrhagic retinopathy, retinitis pigmentosa, cone-rod dystrophy, Sorsby's fundus dystrophy, optic neuropathy, inflammatory retinal disease, diabetic retinopathy, diabetic maculopathy, retinal blood vessel occlusion, retinopathy of prematurity, or ischemia reperfusion related retinal injury, proliferative vitreoretinopathy, retinal dystrophy, hereditary optic neuropathy, Sorsby's fundus dystrophy, uveitis, a retinal injury, a retinal disorder associated with Alzheimer's disease, a retinal disorder associated with multiple sclerosis, a retinal disorder associated with Parkinson's disease, a retinal disorder associated with viral infection, a retinal disorder related to light overexposure, myopia, and a retinal disorder associated with AIDS.

38. The method according to claim 36 or 37 resulting in a reduction of lipofuscin pigment accumulated in an eye of the subject.

39. The method according to claim 38 wherein the lipofuscin pigment is *N*-retinylidene-*N*-retinyl-ethanolamine (A2E).

40. A method of modulating chromophore flux in a retinoid cycle comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from $-O-C(R^9)_2-$, $-O-C(=O)-$, $-S-C(R^9)_2-$, $-S(O)-C(R^9)_2-$, $-S(O)_2-C(R^9)_2-$, $-SO_2(NR^9)-$, $-NR^9-C(R^9)_2-$, $-NR^9-C(=O)-$, $-NR^9-S(O)_2-$, $-C(R^9)_2-C(R^9)_2-$, –

$C(=O)-C(R^9)_2-$, $-C(R^9)_2-C(=O)-$, $-C(R^9)=C(R^9)-$, $-C \equiv C-$, $-C(=O)-N(R^9)-$, $-C(=O)-O-$, $-C(R^9)_2-O-$, and $-C(R^9)_2-NR^9-$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, $-OR^9$, $-NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, $-OR^9$ or $-NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

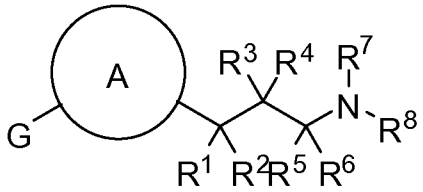
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, $-C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, $-C(=O)R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

41. A method of inhibiting dark adaptation of a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

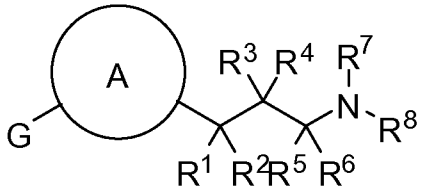
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

42. A method of inhibiting regeneration of rhodopsin in a rod photoreceptor cell of the retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

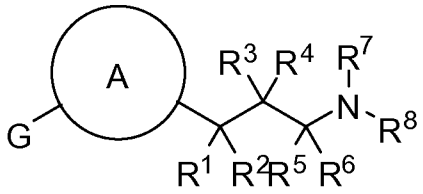
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

43. A method of reducing ischemia in an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:



Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

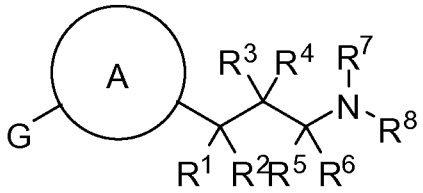
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

44. A method of inhibiting neovascularization in the retina of an eye of a subject comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclyalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

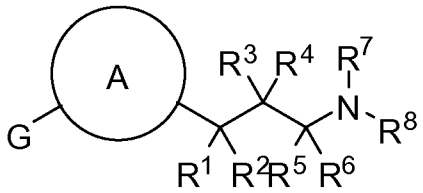
$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

45. A method of inhibiting degeneration of a retinal cell in a retina comprising contacting the retina with a compound of Formula (A) or tautomer, stereoisomer, geometric isomer, or pharmaceutically acceptable solvate, hydrate, salt, or N-oxide thereof:




Formula (A)

wherein,

Ring A is selected from a 1,3-disubstituted heterocycle;

G is –X-Y;

X is selected from –O-C($R^9$)$_2$-,–O-C(=O)-, –S-C($R^9$)$_2$-, –S(O)-C($R^9$)$_2$-, –S(O)$_2$-C($R^9$)$_2$-, –$SO_2$($NR^9$)-, –$NR^9$-C($R^9$)$_2$-, –$NR^9$-C(=O)-, –$NR^9$-S(O)$_2$-, –C($R^9$)$_2$-C($R^9$)$_2$-, –C(=O)-C($R^9$)$_2$-, – C($R^9$)$_2$-C(=O)-, –C($R^9$)=C($R^9$)-, -C ≡ C-, –C(=O)-N($R^9$)-, –C(=O)-O-, –C($R^9$)$_2$-O-, and –C($R^9$)$_2$-$NR^9$;

Y is selected from $C_3$-$C_{15}$ alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, aryl or aralkyl;

$R^1$ and $R^2$ are each independently selected from hydrogen, halogen, alkyl, fluoroalkyl, -$OR^9$, -$NR^{10}R^{11}$ or carbocyclyl; or $R^1$ and $R^2$ form an oxo; or optionally, $R^1$ and $R^3$ together form a direct bond to provide a double bond; or optionally, $R^1$ and $R^3$ together form a direct bond, and $R^2$ and $R^4$ together form a direct bond to provide a triple bond;

$R^3$ and $R^4$ are each independently selected from hydrogen, halogen, $C_1$-$C_5$ alkyl, fluoroalkyl, -$OR^9$ or –$NR^{10}R^{11}$; or $R^3$ and $R^4$ together form an oxo;

$R^5$ and $R^6$ are each independently selected from hydrogen, alkyl, alkenyl, fluoroalkyl, aryl, heteroaryl, carbocyclyl or *C*-attached heterocyclyl; or $R^5$ and $R^6$ together with the carbon atom to which they are attached, form a carbocyclyl or heterocyclyl; or $R^5$ and $R^6$ together form an imino;

$R^7$ and $R^8$ are each independently selected from hydrogen, alkyl, carbocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^7$ and $R^8$, together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl;

each $R^9$ independently hydrogen or alkyl;

each $R^{10}$ and $R^{11}$ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, -C(=O)$R^{13}$, $SO_2R^{13}$, $CO_2R^{13}$ or $SO_2NR^{10}R^{11}$; or $R^{10}$ and $R^{11}$ together with the nitrogen atom to which they are attached, form an *N*-heterocyclyl; and

each $R^{13}$ is independently selected from alkyl, heteroalkyl, alkenyl, aryl, aralkyl, carbocyclyl, heteroaryl or heterocyclyl.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/022304

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/44 (2013.01)
USPC - 514/351
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)
IPC(8) - A61K 31/341, 381, 40, 4192, 426, 44 (2013.01)
USPC - 514/252.01, 255.05, 256, 345, 351, 357, 362, 364, 365, 372, 374, 378, 381, 383, 399, 438, 471

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/341, 381, 40, 4192, 426, 44 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit.com, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 2008/0167307 A1 (TOZAWA et al) 10 July 2008 (10.07.2008) entire document | 1-45 |
| A | US 2011/0003895 A1 (KUBOTA et al) 06 January 2011 (06.01.2011) entire document | 1-45 |
| A | US 2011/0082181 A1 (SEIDERS et al) 07 April 2011 (07.04.2011) entire document | 1-45 |
| A | US 2010/0081702 A1 (SHIMOZATO et al) 01 April 2010 (01.04.2010) entire document | 1-45 |
| A | US 2009/0088435 A1 (MATA et al) 02 April 2009 (02.04.2009) entire document | 1-45 |
| A | US 2005/0043386 A1 (NISHI et al) 24 February 2005 (24.02.2005) entire document | 1-45 |

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 28 February 2013 | 25 MAR 2013 |
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(54)发明名称

用于疾病治疗的取代的杂环化合物

(57)摘要

本发明总体上涉及用于治疗的神经变性疾病和病症，特别是眼科疾病和病症的组合物和方法。本文提供了取代的杂环胺衍生物化合物和包含这些化合物的药物组合物。本发明的组合物可用于治疗和预防眼科疾病和病症，包括年龄相关性黄斑变性(AMD)和斯塔加特病。

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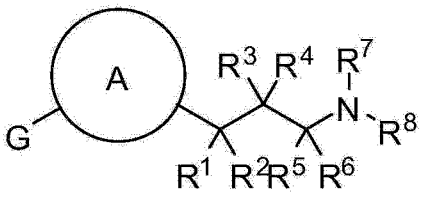
1. 一种式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :




式(A)

其中,

环 A 选自 1,3- 二取代的杂环 ;

G 为 -X-Y ;

X 选自 -O-C($R^9$)$_2$-、-O-C( = O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C( = O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C( = O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C( = O)-、-C($R^9$) = C($R^9$)-、-C ≡ C-、-C( = O)-N($R^9$)-、-C( = O)-O-、-C($R^9$)$_2$-O- 和 -C($R^9$)$_2$-$NR^9$- ;

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基 ;

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基 ;或者 $R^1$和 $R^2$形成氧代基团 ;或者任选地,$R^1$和 $R^3$一起形成直接键以提供双键 ;或者任选地,$R^1$和 $R^3$一起形成直接键,且 $R^2$和 $R^4$一起形成直接键以提供三键 ;

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或 -$NR^{10}R^{11}$;或者 $R^3$和 $R^4$一起形成氧代基团 ;

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基 ;或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基 ;或者 $R^5$和 $R^6$一起形成亚氨基 ;

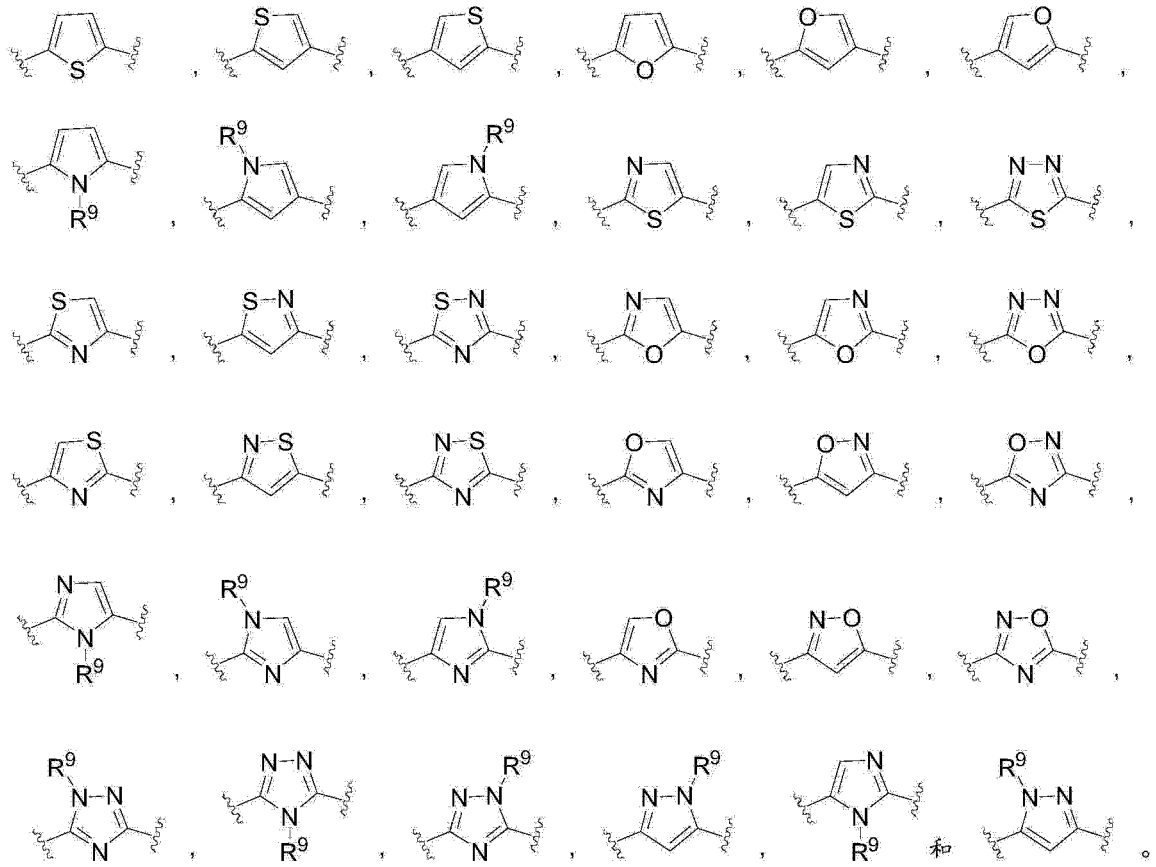
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、-C( = O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基 ;

各 $R^9$独立地为氢或烷基 ;

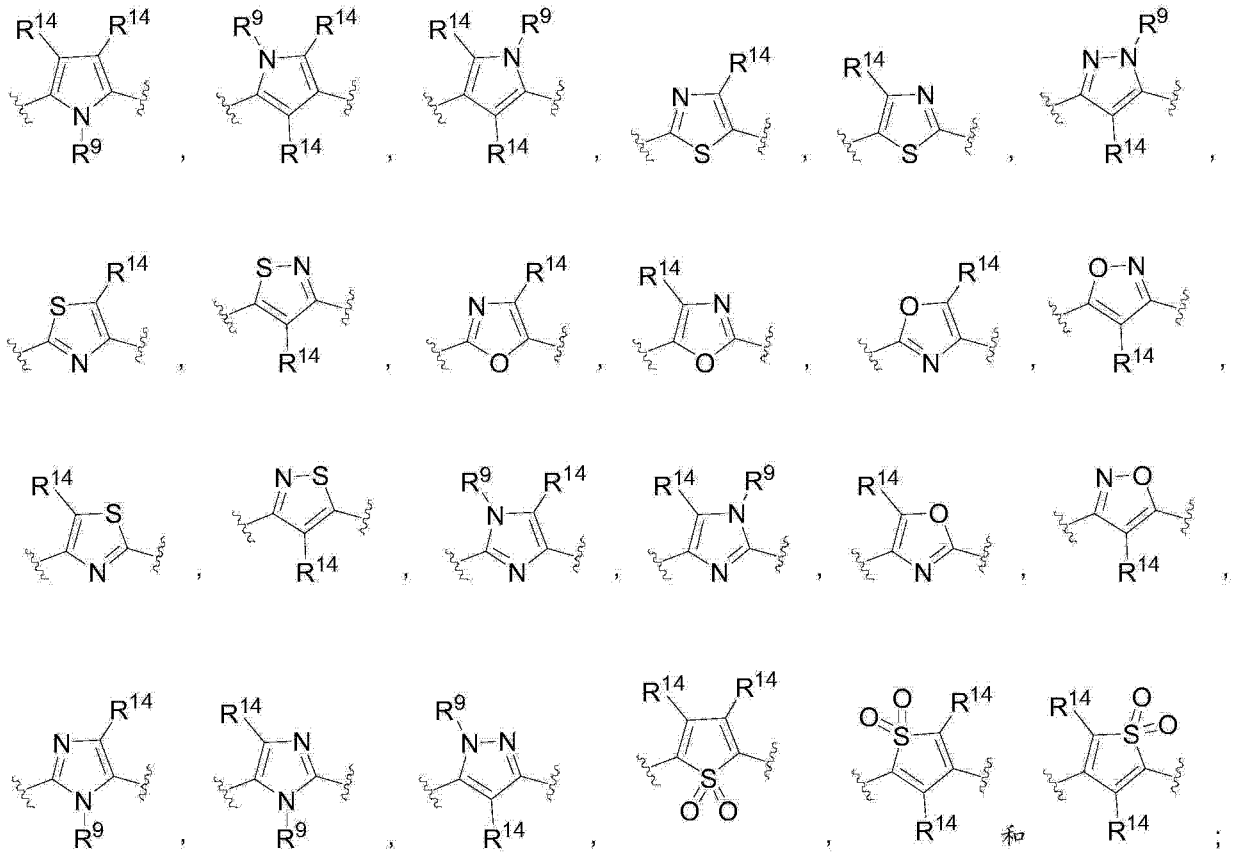
各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C( = O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基 ;且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

2. 如权利要求 1 所述的化合物,其中环 A 选自 :

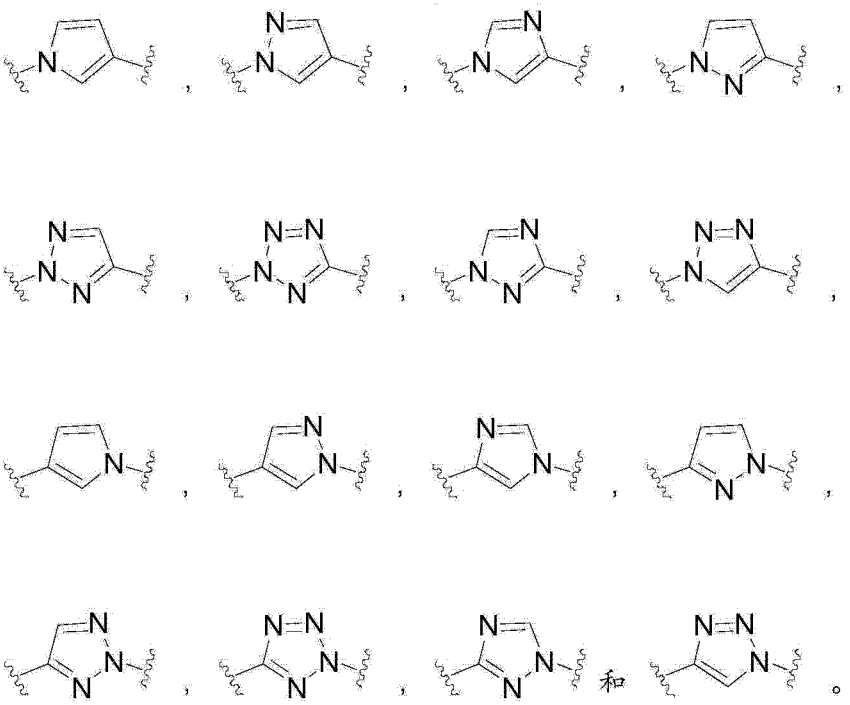


3. 如权利要求 1 所述的化合物，其中环 A 选自：

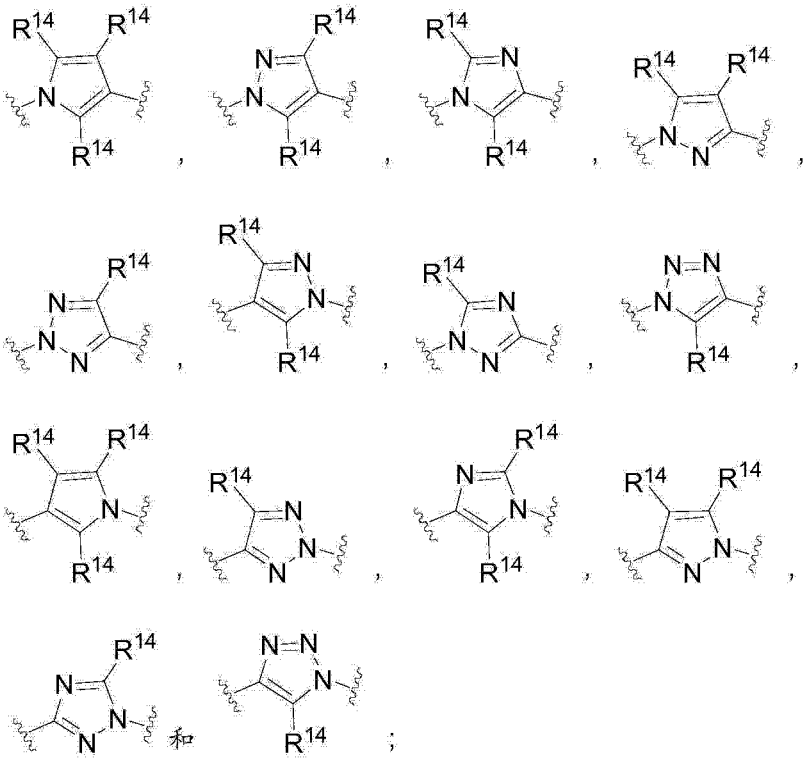


且各 $R^{14}$ 独立地选自氢、卤素、$OR^9$、烷基或氟代烷基。

4. 如权利要求 1 所述的化合物，其中环 A 选自：

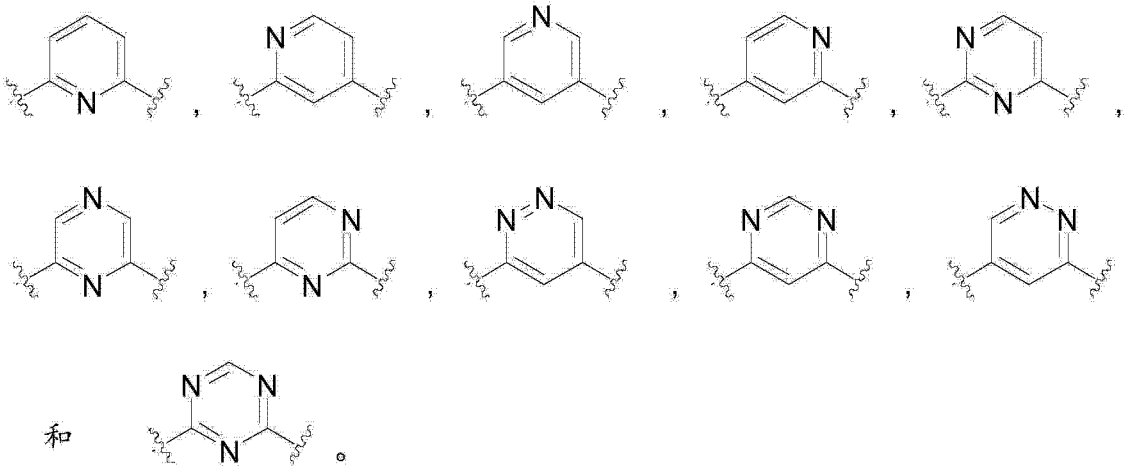


5. 如权利要求 1 所述的化合物，其中环 A 选自：



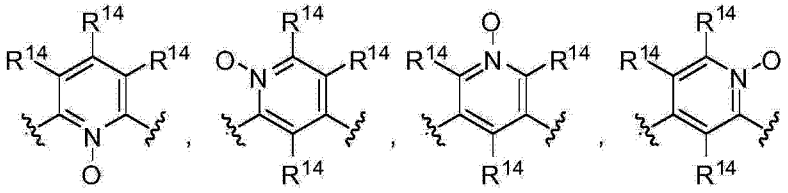
且各 $R^{14}$ 独立地选自氢、卤素、$OR^{9}$、烷基或氟代烷基。

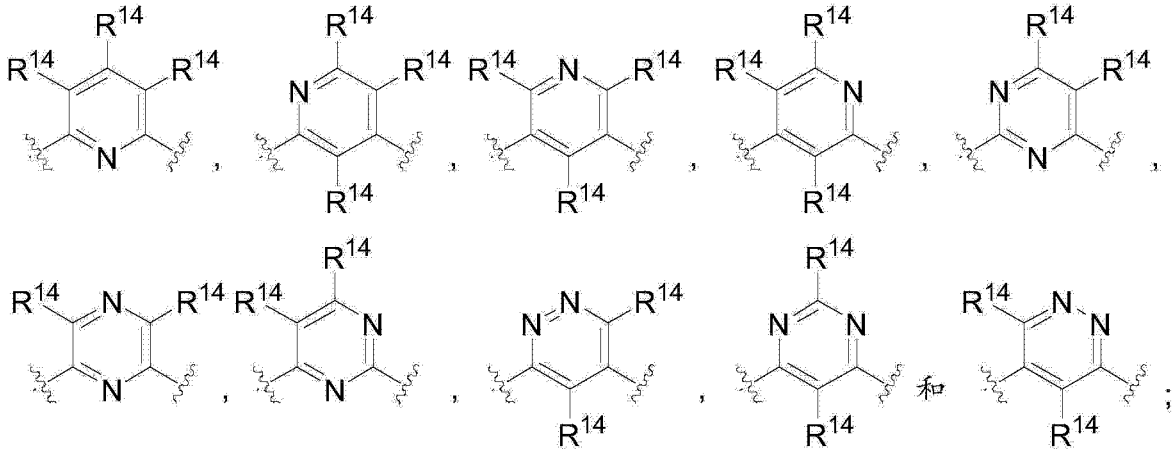
6. 如权利要求 1 所述的化合物，其中环 A 选自：



和 。

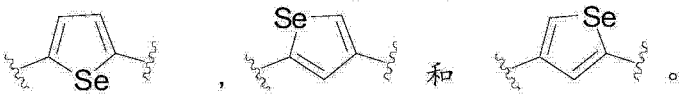
7. 如权利要求 1 所述的化合物，其中环 A 选自：



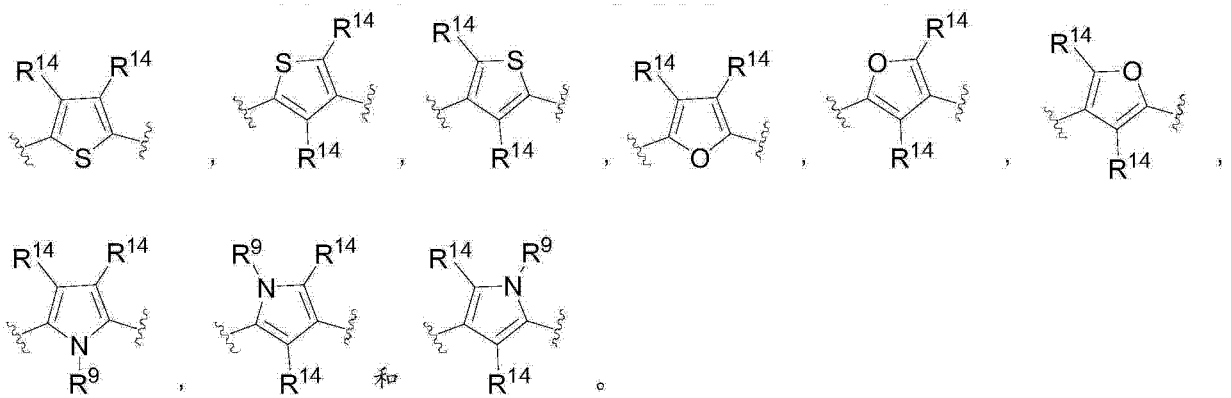


且各 $R^{14}$ 独立地选自氢、卤素、$OR^9$、烷基或氟代烷基。

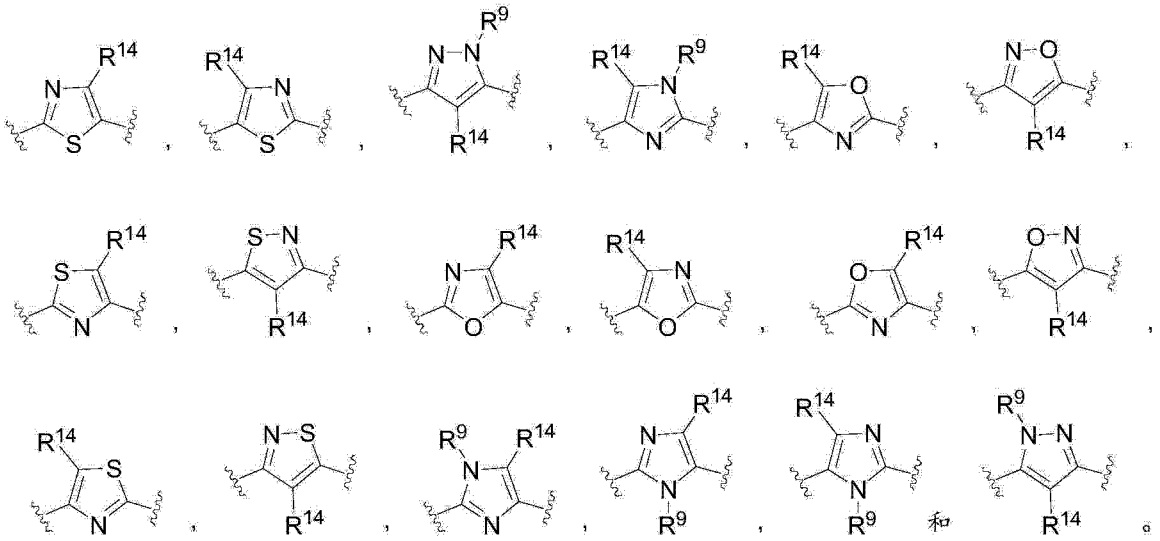
8. 如权利要求 1 所述的化合物，其中环 A 选自：



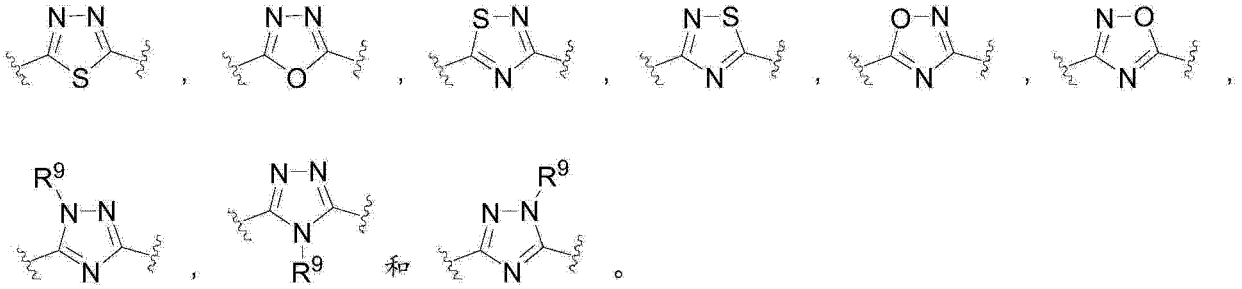
9. 如权利要求 1 所述的化合物，其中环 A 选自：



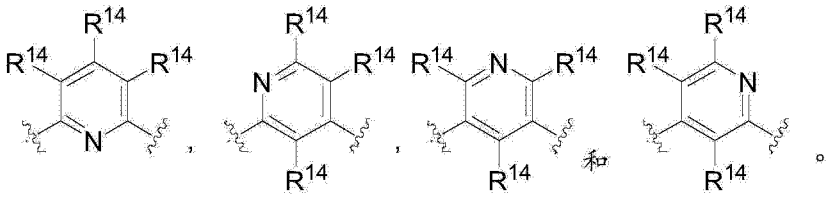
10. 如权利要求 3 所述的化合物，其中环 A 选自：



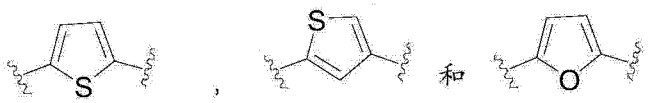
11. 如权利要求 2 所述的化合物，其中环 A 选自：



12. 如权利要求 7 所述的化合物，其中环 A 选自：



13. 如权利要求 2 所述的化合物，其中环 A 选自：



14. 如权利要求 1 所述的化合物，其中 Y 为烷基、碳环基或杂环基。

15. 如权利要求 14 所述的化合物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者

$R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；且

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基。

16. 如权利要求 15 所述的化合物，其中 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基。

17. 如权利要求 16 所述的化合物，其中 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成环丁基、环戊基、环己基、环庚基或环辛基，且 $R^{18}$为氢和羟基。

18. 如权利要求 17 所述的化合物，其中 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成环戊基、

环己基、环庚基，且 $R^{18}$ 为氢和羟基。

19. 如权利要求 15 所述的化合物，其中 $R^{16}$ 和 $R^{17}$ 各自独立地选自 $C_1$-$C_{13}$ 烷基；且 $R^{18}$ 为氢、羟基或烷氧基。

20. 如权利要求 1 所述的化合物，其中 X 选自 $-O-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$ 和 $-NR^9-S(O)_2-$。

21. 如权利要求 1 所述的化合物，其中 X 选自 $-C(R^9)_2-C(R^9)_2-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9$。

22. 如权利要求 1 所述的化合物，其中 X 选自 $-O-C(R^9)_2$ 或 $-C(R^9)_2-C(R^9)_2-$。

23. 如权利要求 1 所述的化合物，其中 $R^3$ 和 $R^4$ 均为氢。

24. 如权利要求 1 所述的化合物，其中 $R^5$ 和 $R^6$ 均为氢。

25. 如权利要求 1 所述的化合物，其中 $R^3$、$R^4$、$R^5$ 和 $R^6$ 均为氢。

26. 如权利要求 1 所述的化合物，其中 $R^1$ 和 $R^2$ 均为氢。

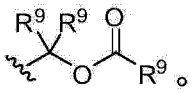
27. 如权利要求 1 所述的化合物，其中 $R^1$ 为氢且 $R^2$ 为 -OH。

28. 如权利要求 1 所述的化合物，其中 $R^1$ 和 $R^2$ 一起形成氧代基团。

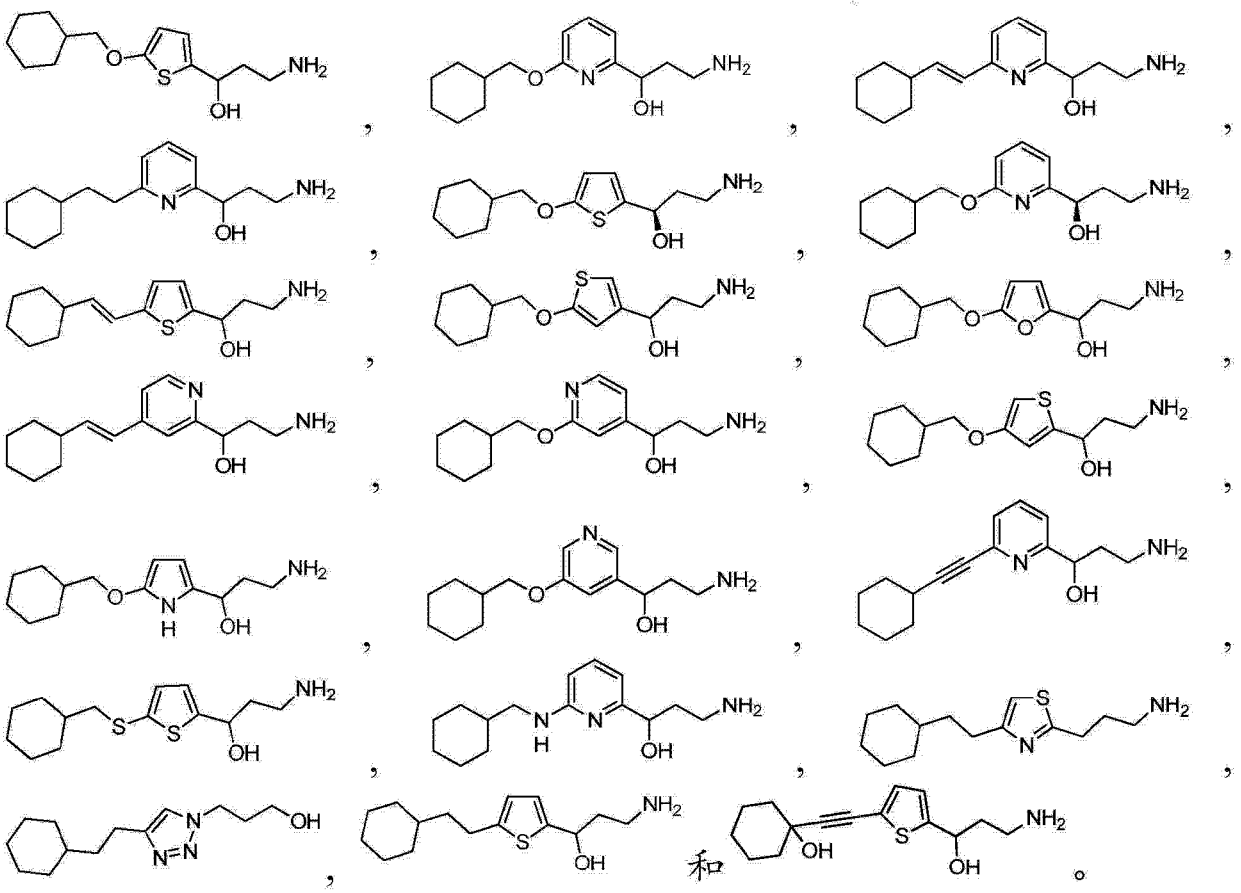
29. 如权利要求 1 所述的化合物，其中 $R^7$ 和 $R^8$ 均为氢。

30. 如权利要求 1 所述的化合物，其中 $R^7$ 为氢且 $R^8$ 为 $-C(=O)R^{13}$ 或 $CO_2R^{13}$。

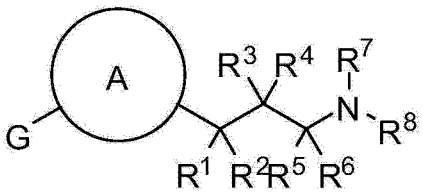
31. 如权利要求 30 所述的化合物，其中 $R^{13}$ 为烷基。

32. 如权利要求 30 所述的化合物，其中 $R^8$ 为 $CO_2R^{13}$ 且 $R^{13}$ 为  。

33. 一种化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其选自：



34. 一种药物组合物，其包含药学上可接受的载体和式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：



式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$

一起形成氧代基团；

$R^5$和$R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或C-连接的杂环基；或者$R^5$和$R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者$R^5$和$R^6$一起形成亚氨基；

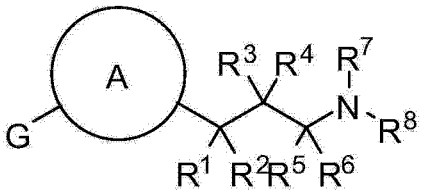
$R^7$和$R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^7$和$R^8$和与它们连接的氮原子一起形成N-杂环基；

各$R^9$独立地为氢或烷基；

各$R^{10}$和$R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^{10}$和$R^{11}$和与它们连接的氮原子一起形成N-杂环基；且

各$R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

35.一种治疗受试者的眼科疾病或病症的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式(A)的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或N-氧化物：




式(A)

其中，

环A选自1,3-二取代的杂环；

G为 -X-Y；

X选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$和 $-C(R^9)_2-NR^9-$；

Y选自$C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和$R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基；或者$R^1$和$R^2$形成氧代基团；或者任选地，$R^1$和$R^3$一起形成直接键以提供双键；或者任选地，$R^1$和$R^3$一起形成直接键，且$R^2$和$R^4$一起形成直接键以提供三键；

$R^3$和$R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、$-OR^9$或$-NR^{10}R^{11}$；或者$R^3$和$R^4$一起形成氧代基团；

$R^5$和$R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或C-连接的杂环基；或者$R^5$和$R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者$R^5$和$R^6$一起形成亚氨基；

$R^7$和$R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^7$和$R^8$和与它们连接的氮原子一起形成N-杂环基；

各$R^9$独立地为氢或烷基；

各$R^{10}$和$R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或

$SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

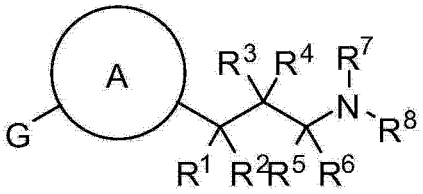
36. 如权利要求 35 所述的方法，其中所述眼科疾病或病症为年龄相关性黄斑变性或斯塔加特氏黄斑营养不良。

37. 如权利要求 35 所述的方法，其中所述眼科疾病或病症选自视网膜脱落、出血性视网膜病、色素性视网膜炎、视锥 - 视杆营养不良、Sorsby 眼底营养不良、视神经病变、炎性视网膜病、糖尿病视网膜病变、糖尿病性斑丘疹病、视网膜血管闭塞、早产儿视网膜病、或缺血再灌注相关性视网膜损伤、增生性玻璃体视网膜病、视网膜营养性萎缩、遗传性视神经病、Sorsby 眼底营养不良、葡萄膜炎、视网膜损伤、与阿尔茨海默病相关的视网膜病症、与多发性硬化症相关的视网膜病症、与帕金森病相关的视网膜病症、与病毒感染相关的视网膜病症、与光暴露过度相关的视网膜病症、近视以及与 AIDS 相关的视网膜病症。

38. 根据权利要求 36 或 37 所述的方法，其导致受试者眼睛中积聚的脂褐质色素的减少。

39. 根据权利要求 38 所述的方法，其中，所述脂褐质色素为 N- 亚视黄基 -N- 视黄基 - 乙醇胺 (A2E)。

40. 一种调节类视黄醇循环中的生色团通量的方法，该方法包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1-C_5$烷基、氟代烷基、$-OR^9$或 $-NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形

成亚氨基；

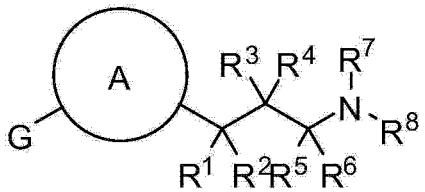
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

41. 一种抑制视网膜的视杆细胞的暗适应的方法，该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、$-OR^9$或 $-NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

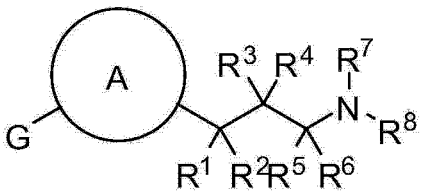
各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

42. 一种抑制视网膜的视杆细胞中的视紫质再生的方法，该方法包括使视网膜接触式

(A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :



式(A)

其中,

环 A 选自 1,3- 二取代的杂环 ;

G 为 -X-Y ;

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$ ;

Y 选自 $C_3-C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基 ;

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基 ;或者 $R^1$和 $R^2$形成氧代基团 ;或者任选地,$R^1$和 $R^3$一起形成直接键以提供双键 ;或者任选地,$R^1$和 $R^3$一起形成直接键,且 $R^2$和 $R^4$一起形成直接键以提供三键 ;

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1-C_5$烷基、氟代烷基、$-OR^9$或 $-NR^{10}R^{11}$;或者 $R^3$和 $R^4$一起形成氧代基团 ;

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基 ;或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基 ;或者 $R^5$和 $R^6$一起形成亚氨基 ;

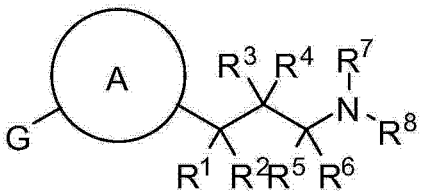
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基 ;

各 $R^9$独立地为氢或烷基 ;

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基 ;且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

43. 一种减轻受试者眼睛中的局部缺血的方法,其包括向受试者施用一种药物组合物,该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :



式(A)

其中,

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

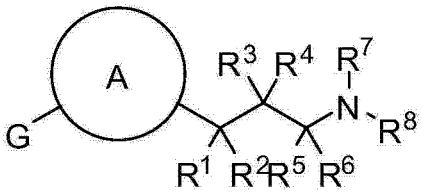
$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

44. 一种抑制受试者眼睛的视网膜中的新生血管形成的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$

形成氧代基团；或者任选地，$R^1$和$R^3$一起形成直接键以提供双键；或者任选地，$R^1$和$R^3$一起形成直接键，且$R^2$和$R^4$一起形成直接键以提供三键；

$R^3$和$R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或-$NR^{10}R^{11}$；或者$R^3$和$R^4$一起形成氧代基团；

$R^5$和$R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或C-连接的杂环基；或者$R^5$和$R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者$R^5$和$R^6$一起形成亚氨基；

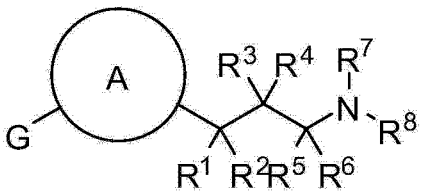
$R^7$和$R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^7$和$R^8$和与它们连接的氮原子一起形成N-杂环基；

各$R^9$独立地为氢或烷基；

各$R^{10}$和$R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^{10}$和$R^{11}$和与它们连接的氮原子一起形成N-杂环基；且

各$R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

45. 一种抑制视网膜中的视网膜细胞变性的方法，该方法包括使视网膜接触式(A)的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或N-氧化物：




式(A)

其中，

环A选自1,3-二取代的杂环；

G为 -X-Y；

X选自 -O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O-和 -C($R^9$)$_2$-$NR^9$-；

Y选自$C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和$R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基；或者$R^1$和$R^2$形成氧代基团；或者任选地，$R^1$和$R^3$一起形成直接键以提供双键；或者任选地，$R^1$和$R^3$一起形成直接键，且$R^2$和$R^4$一起形成直接键以提供三键；

$R^3$和$R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或-$NR^{10}R^{11}$；或者$R^3$和$R^4$一起形成氧代基团；

$R^5$和$R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或C-连接的杂环基；或者$R^5$和$R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者$R^5$和$R^6$一起形成亚氨基；

$R^7$和$R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者

$R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

# 用于疾病治疗的取代的杂环化合物

交叉引用

[0001] 本申请要求 2012 年 1 月 20 日提交的美国临时申请第 61/589,108 号的权益，该临时申请通过引用整体并入本文。

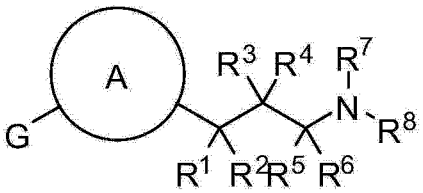
## 背景技术

[0002] 神经变性疾病，如青光眼、黄斑变性和阿尔茨海默病，影响到全世界数百万患者。由于与这些疾病相关的生活质量的下降是相当可观的，因此该领域中的药物研究和开发是非常重要的。年龄相关性黄斑变性 (AMD) 在美国影响到 1000 万至 1500 万患者，并且它是全世界老年人口中失明的首要原因。AMD 影响中央视觉，并且导致视网膜中央部分中的感光细胞（称作黄斑）的丧失。由于罹患 AMD 的患者的巨大医学需求尚未得到满足，因此非常需要新的治疗。

## 发明内容

[0003] 在本领域中存在着对导致眼机能障碍的眼科疾病或病症（包括上述疾病或病症）的有效治疗的需求。特别是，迫切需要用于治疗斯塔加特病和年龄相关性黄斑变性 (AMD) 而不引起其它不必要的副作用（例如进行性视网膜变性、LCA 样病状、夜盲症或全身性维生素 A 缺乏）的组合物及方法。在本领域中也需要对其它不利地影响视网膜的眼科疾病和病症的有效治疗。

[0004] 一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起

形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1$-$C_5$ 烷基、氟代烷基、-$OR^9$ 或 -$NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

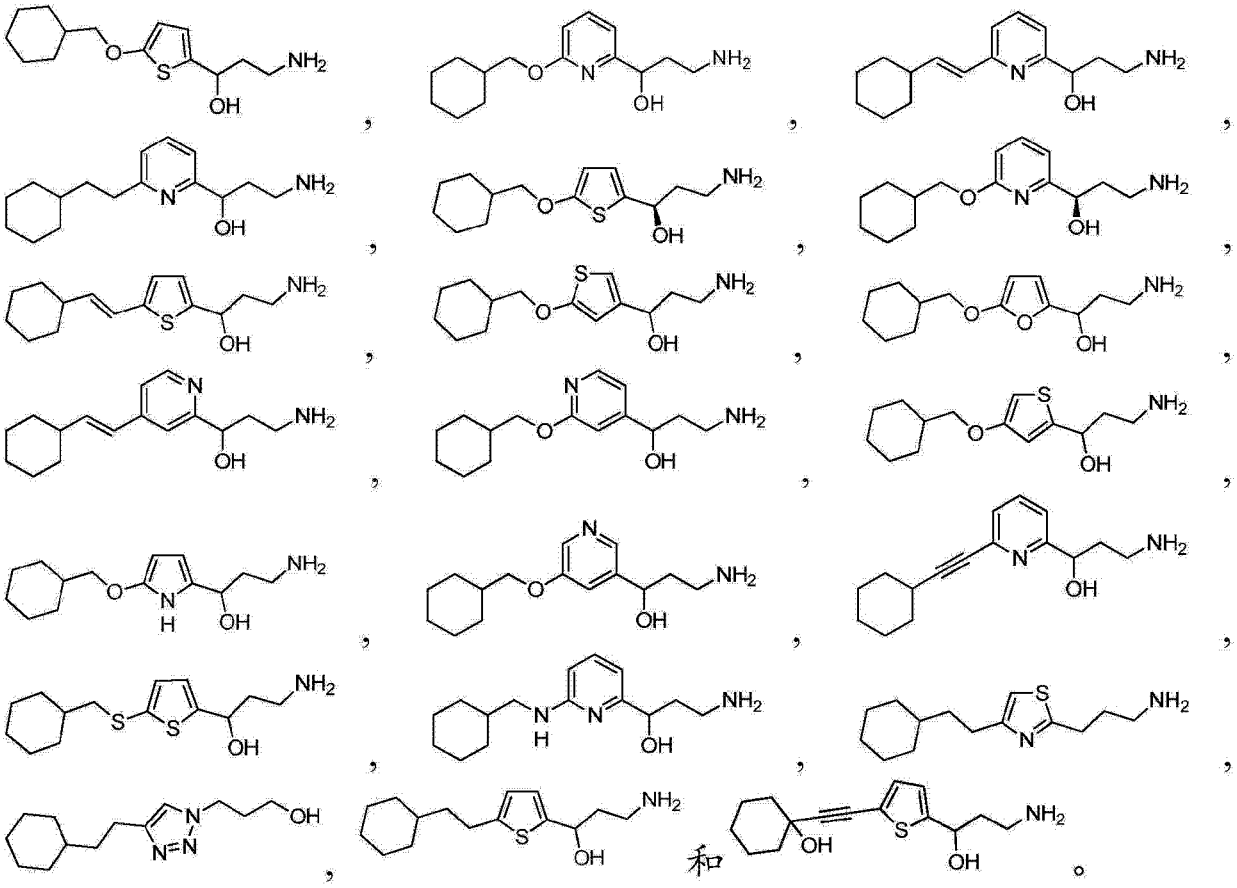
$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

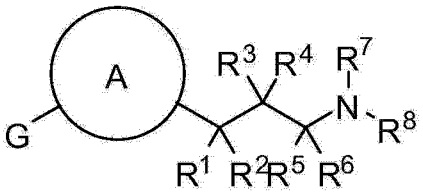
各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0005] 一个实施方案提供了一种化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：



[0006] 一个实施方案提供了一种药物组合物，其包含药学上可接受的载体和式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

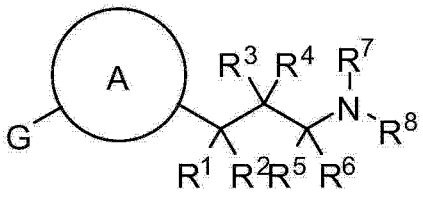
$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0007] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

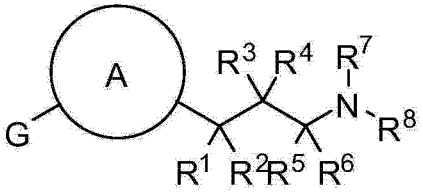
各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0008] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其中，该眼科疾病或病症为年龄相关性黄斑变性或斯塔加特氏黄斑营养不良。

[0009] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其中，该眼科疾病或病症选自视网膜脱落、出血性视网膜病、色素性视网膜炎、视锥 - 视杆营养不良、Sorsby 眼底营养不良、视神经病变、炎性视网膜病、糖尿病视网膜病变、糖尿病性斑丘疹病、视网膜血管闭塞、早产儿视网膜病、或缺血再灌注相关性视网膜损伤、增生性玻璃体视网膜病、视网膜营养性萎缩、遗传性视神经病、葡萄膜炎、视网膜损伤、与阿尔茨海默病相关的视网膜病症、与多发性硬化症相关的视网膜病症、与帕金森病相关的视网膜病症、与病毒感染相关的视网膜病症、与光暴露过度相关的视网膜病症、近视以及与 AIDS 相关的视网膜病症。

[0010] 一个实施方案提供了一种调节类视黄醇循环中的生色团通量的方法，该方法包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

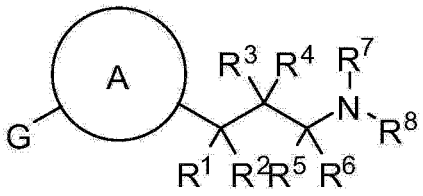
$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0011] 一个实施方案提供了一种抑制视网膜的视杆细胞的暗适应的方法，该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$

形成氧代基团；或者任选地，$R^1$和$R^3$一起形成直接键以提供双键；或者任选地，$R^1$和$R^3$一起形成直接键，且$R^2$和$R^4$一起形成直接键以提供三键；

$R^3$和$R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或-$NR^{10}R^{11}$；或者$R^3$和$R^4$一起形成氧代基团；

$R^5$和$R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或C-连接的杂环基；或者$R^5$和$R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者$R^5$和$R^6$一起形成亚氨基；

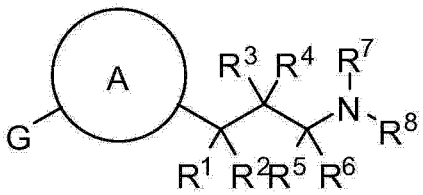
$R^7$和$R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^7$和$R^8$和与它们连接的氮原子一起形成N-杂环基；

各$R^9$独立地为氢或烷基；

各$R^{10}$和$R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者$R^{10}$和$R^{11}$和与它们连接的氮原子一起形成N-杂环基；且

各$R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0012] 一个实施方案提供了一种抑制视网膜的视杆细胞中的视紫质再生的方法，该方法包括使视网膜接触式(A)的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或N-氧化物：




式(A)

其中，

环A选自1,3-二取代的杂环；

G为-X-Y；

X选自-O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O-和-C($R^9$)$_2$-$NR^9$-；

Y选自$C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和$R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基；或者$R^1$和$R^2$形成氧代基团；或者任选地，$R^1$和$R^3$一起形成直接键以提供双键；或者任选地，$R^1$和$R^3$一起形成直接键，且$R^2$和$R^4$一起形成直接键以提供三键；

$R^3$和$R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或-$NR^{10}R^{11}$；或者$R^3$和$R^4$一起形成氧代基团；

$R^5$和$R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或C-连接的杂环基；或者$R^5$和$R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者$R^5$和$R^6$一起形成亚氨基；

$R^7$和$R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或$SO_2NR^{10}R^{11}$；或者

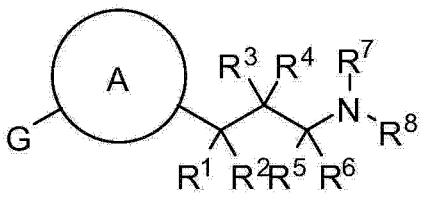
$R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0013] 一个实施方案提供了一种减轻受试者眼睛中的局部缺血的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1-C_5$烷基、氟代烷基、$-OR^9$或 $-NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

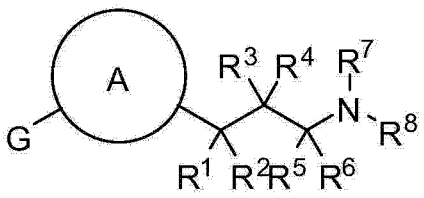
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0014] 一个实施方案提供了一种抑制受试者眼睛的视网膜中的新生血管形成的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：



式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

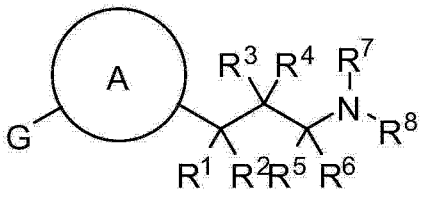
$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0015] 一个实施方案提供了一种抑制视网膜中的视网膜细胞变性的方法，该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：



式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

援引并入

[0016] 在本说明书中提到的所有的出版物、专利和专利申请均在此通过引用并入本文，其程度与将各个单独的出版物、专利或专利申请具体地且单独地指出将通过引用而并入的程度是相同的。

## 具体实施方式

[0017] 如本文和所附权利要求书中所使用的单数形式“一种”、“和”以及“该（所述）”包括复数的指示物，除非上下文明确指明不是这样。因此，例如，所提及的“一种药剂”包括多种这样的药剂，并且所提及的“该细胞”包括所提及的一种或多种细胞（或多个细胞）和本领域技术人员已知的其等效物，等等。当在此对诸如分子量的物理性质或诸如化学式的化学性质使用范围时，意在包括范围的所有组合和子组合以及其中的具体实施方案。当提及数字或数值范围时使用的术语“约”是指所提及的数字或数值范围为在实验可变性范围内（或者在统计实验误差范围内）的近似值，因而该数字或数值范围可以在所述数字或数值范围的 1％至 15％之间变化。术语“包含”（以及相关的术语，例如“包括”或“具有”或“含有”）并非旨在排除，在其它某些实施方案中，例如，本文描述的物质、组合物、方法或过程等的任意组合的实施方案可以“由所述特征组成”或“基本由所述特征组成”。

定义

[0018] 如在本说明书及所附权利要求书中所使用的，除非指出意思相反，否则下列术语具有以下所述的含义。

[0019] 如本文和所附权利要求书中所使用的单数形式“一种”、“和”以及“该（所述）”包

括复数的指示物，除非上下文明确指明不是这样。因此，例如，所提及的“一种化合物”包括多种这样的化合物，并且所提及的“该细胞”包括所提及的一种或多种细胞（或多个细胞）和本领域技术人员已知的其等效物，等等。当在此对诸如分子量的物理性质或诸如化学式的化学性质使用范围时，意在包括范围的所有组合和子组合以及其中的具体实施方案。当提及数字或数值范围时使用的术语“约”是指所提及的数字或数值范围为在实验可变性范围内（或者在统计实验误差范围内）的近似值，因而该数字或数值范围可以在所述数字或数值范围的 1％至 15％之间变化。术语“包含”（以及相关的术语，例如“包括”或“具有”或“含有”）并非旨在排除，在其它某些实施方案中，例如，本文描述的物质、组合物、方法或过程等的任意组合的实施方案可以“由所述特征组成”或“基本由所述特征组成”。

[0020] “氨基”是指 $-NH_2$基团。

[0021] “氰基”是指 -CN 基团。

[0022] “硝基”是指 $-NO_2$基团。

[0023] “氧杂”是指 -O- 基团。

[0024] “氧代基团”是指＝ O 基团。

[0025] “硫代基团”是指＝ S 基团。

[0026] “亚氨基”是指＝ N-H 基团。

[0027] “肼基”是指＝ $N-NH_2$基团。

[0028] “烷基”是指仅由碳和氢原子组成、不包含不饱和键并且具有 1-15 个碳原子的直链或支链烃链基团（例如，$C_1$-$C_{15}$烷基）。在某些实施方案中，烷基包含 1-13 个碳原子（例如，$C_1$-$C_{13}$烷基）。在某些实施方案中，烷基包含 1-8 个碳原子（例如，$C_1$-$C_8$烷基）。在其它一些实施方案中，烷基包含 1-5 个碳原子（例如，$C_1$-$C_5$烷基）。在其它一些实施方案中，烷基包含 1-4 个碳原子（例如，$C_1$-$C_4$烷基）。在其它一些实施方案中，烷基包含 1-3 个碳原子（例如，$C_1$-$C_3$烷基）。在其它一些实施方案中，烷基包含 1-2 个碳原子（例如，$C_1$-$C_2$烷基）。在其它一些实施方案中，烷基包含 1 个碳原子（例如，$C_1$烷基）。在其它一些实施方案中，烷基包含 5-15 个碳原子（例如，$C_5$-$C_{15}$烷基）。在其他一些实施方案中，烷基包含 5-8 个碳原子（例如，$C_5$-$C_8$烷基）。在其他一些实施方案中，烷基包含 2-5 个碳原子（例如，$C_2$-$C_5$烷基）。在其他一些实施方案中，烷基包含 3-5 个碳原子（例如，$C_3$-$C_5$烷基）。在其它一些实施方案中，烷基选自甲基 (Me)、乙基 (Et)、1- 丙基（正丙基）、1- 甲基乙基（异丙基）、1- 丁基（正丁基）、1- 甲基丙基（仲丁基）、2- 甲基丙基（异丁基）、1,1- 二甲基乙基（叔丁基）或正戊基。烷基通过单键连接在分子的其余部分上。除非在说明书中另有特别说明，烷基任选地被如下取代基中的一种或多种所取代：卤素、氰基、硝基、氧代基团、硫代基团、三甲基硅烷基、$-OR^a$、$-SR^a$、$-OC(O)-R^a$、$-N(R^a)_2$、$-C(O)R^a$、$-C(O)OR^a$、$-C(O)N(R^a)_2$、$-N(R^a)C(O)OR^a$、$-N(R^a)C(O)R^a$、$-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-S(O)_tOR^a$（其中，t 为 1 或 2）和 $-S(O)_tN(R^a)_2$（其中，t 为 1 或 2），其中各 $R^a$均独立地为氢、烷基、氟代烷基、碳环基、碳环基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基。

[0029] “烯基”是指仅由碳和氢原子组成、包含至少一个双键并且具有 2-12 个碳原子的直链或支链烃链基团。在某些实施方案中，烯基包含 2-8 个碳原子。在其它一些实施方案中，烯基包含 2-4 个碳原子。烯基通过单键连接在分子的其余部分上，例如，乙烯基 (ethenyl)（即，乙烯基 (vinyl)）、丙 -1- 烯基（即，烯丙基）、丁 -1- 烯基、戊 -1- 烯基、戊 -1,4- 二烯

基等。除非在说明书中另有特别说明，烯基基团任选地被如下取代基中的一种或多种所取代：卤素、氰基、硝基、氧代基团、硫代基团、三甲基硅烷基、$-OR^a$、$-SR^a$、$-OC(O)-R^a$、$-N(R^a)_2$、$-C(O)R^a$、$-C(O)OR^a$、$-C(O)N(R^a)_2$、$-N(R^a)C(O)OR^a$、$-N(R^a)C(O)R^a$、$-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-S(O)_tOR^a$（其中，t 为 1 或 2）和 $-S(O)_tN(R^a)_2$（其中，t 为 1 或 2），其中各 $R^a$ 均独立地为氢、烷基、氟代烷基、碳环基、碳环基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基。

[0030] “炔基”是指仅由碳和氢原子组成、包含至少一个三键并且具有 2-12 个碳原子的直链或支链烃链基团。在某些实施方案中，炔基包含 2-8 个碳原子。在其它一些实施方案中，炔基具有 2-4 个碳原子。炔基通过单键连接在分子的其余部分上，例如，乙炔基、丙炔基、丁炔基、戊炔基、己炔基等。除非在说明书中另有特别说明，炔基任选地被选自如下取代基中的一种或多种所取代：卤素、氰基、硝基、氧代基团、硫代基团、三甲基硅烷基、$-OR^a$、$-SR^a$、$-OC(O)-R^a$、$-N(R^a)_2$、$-C(O)R^a$、$-C(O)OR^a$、$-C(O)N(R^a)_2$、$-N(R^a)C(O)OR^a$、$-N(R^a)C(O)R^a$、$-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-S(O)_tOR^a$（其中，t 为 1 或 2）和 $-S(O)_tN(R^a)_2$（其中，t 为 1 或 2），其中各 $R^a$ 均独立地为氢、烷基、氟代烷基、碳环基、碳环基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基。

[0031] “亚烷基”或“亚烷基链”是指将分子的其余部分连接到一个基团上、仅由碳和氢组成、不包含不饱和性并且具有 1-12 个碳原子的直链或支链二价烃链，例如，亚甲基、亚乙基、亚丙基、亚正丁基等。亚烷基链通过单键连接在分子的其余部分上并通过单键连接在所述基团上。在一些实施方案中，亚烷基链连接到分子的其余部分上以及连接到所述基团上的连接点是通过该亚烷基链中的一个碳。在其它一些实施方案中，亚烷基链连接到分子的其余部分上以及连接到所述基团上的连接点是通过该亚烷基链内的任意两个碳。除非在说明书中另有特别说明，亚烷基链任选地被如下取代基中的一种或多种所取代：卤素、氰基、硝基、芳基、环烷基、杂环基、杂芳基、氧代基团、硫代基团、三甲基硅烷基、$-OR^a$、$-SR^a$、$-OC(O)-R^a$、$-N(R^a)_2$、$-C(O)R^a$、$-C(O)OR^a$、$-C(O)N(R^a)_2$、$-N(R^a)C(O)OR^a$、$-N(R^a)C(O)R^a$、$-N(R^a)S(O)tR^a$（其中，t 为 1 或 2）、$-S(O)tOR^a$（其中，t 为 1 或 2）和 $-S(O)tN(R^a)_2$（其中，t 为 1 或 2），其中各 $R^a$ 均独立地为氢、烷基、氟代烷基、碳环基、碳环基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基。

[0032] “亚烯基”或“亚烯基链”是指将分子的其余部分连接到一个基团上、仅由碳和氢组成、包含至少一个双键并具有 2-12 个碳原子的直链或支链的二价烃链，例如，亚乙烯基、亚丙烯基、亚正丁烯基等。亚烯基链通过双键或单键连接在分子的其余部分上，并通过双键或单键连接到所述基团上。在一些实施方案中，亚烯基链连接到分子的其余部分上以及连接到所述基团上的连接点是通过一个碳。在其它一些实施方案中，亚烯基链连接到分子的其余部分上以及连接到所述基团上的连接点是通过该链内的任意两个碳。除非在说明书中另有特别说明，亚烯基链任选地被如下取代基中的一种或多种所取代：卤素、氰基、硝基、芳基、环烷基、杂环基、杂芳基、氧代基团、硫代基团、三甲基硅烷基、$-OR^a$、$-SR^a$、$-OC(O)-R^a$、$-N(R^a)_2$、$-C(O)R^a$、$-C(O)OR^a$、$-C(O)N(R^a)_2$、$-N(R^a)C(O)OR^a$、$-N(R^a)C(O)R^a$、$-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-S(O)_tOR^a$（其中，t 为 1 或 2）和 $-S(O)_tN(R^a)_2$（其中，t 为 1 或 2），其中各 $R^a$ 均独立地为氢、烷基、氟代烷基、环烷基、环烷基烷基、芳基（任选地被一个或多个卤素基团所取代）、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基，并且除非另有说明，否则上述每

个取代基为未取代的。

[0033] “芳基”是指通过从环碳原子中除去氢原子而由芳香族单环或多环烃环体系衍生的基团。芳香族单环或多环烃环体系仅包含氢和选自 6-18 个碳原子的碳，其中，在环系中的至少一个环为完全不饱和的，即，其根据休克尔 (Hückel) 理论包含环状、离域的 (4n+2) π - 电子体系。芳基包括但不限于诸如苯基、芴基和萘基的基团。除非在说明书中另有特别说明，术语“芳基”或前缀“芳 -”（例如”芳烷基”）意在包括任选地被独立地选自如下基团的一种或多种取代基所取代的芳基：烷基、烯基、炔基、卤素、氟代烷基、氰基、硝基、任选地取代的芳基、任选地取代的芳烷基、任选地取代的芳烯基、任选地取代的芳炔基、任选地取代的碳环基、任选地取代的碳环基烷基、任选地取代的杂环基、任选地取代的杂环基烷基、任选地取代的杂芳基、任选地取代的杂芳基烷基、$-R^b-OR^a$、$-R^b-OC(O)-R^a$、$-R^b-N(R^a)_2$、$-R^b-C(O)R^a$、$-R^b-C(O)OR^a$、$-R^b-C(O)N(R^a)_2$、$-R^b-O-R^c-C(O)N(R^a)_2$、$-R^b-N(R^a)C(O)OR^a$、$-R^b-N(R^a)C(O)R^a$、$-R^b-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-R^b-S(O)_tOR^a$（其中，t 为 1 或 2）以及 $-R^b-S(O)_tN(R^a)_2$（其中，t 为 1 或 2），其中，各 $R^a$ 均独立地为氢、烷基、氟代烷基、环烷基、环烷基烷基、芳基（任选地被一个或多个卤素基团取代）、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基，各 $R^b$ 均独立地为直接键，或者直链或支链亚烷基或亚烯基链，且 $R^c$ 为直链或支链亚烷基或亚烯基链，并且其中，除非另有说明，否则上述每个取代基为未取代的。

[0034] “芳烷基”是指式 $-R^c-$ 芳基的基团，其中 $R^c$ 为如上所定义的亚烷基链，例如，苄基、二苯基甲基等。芳烷基的亚烷基链部分如以上对于亚烷基链所述任选地被取代。芳烷基的芳基部分如以上对于芳基所述任选地被取代。

[0035] “芳烯基”是指式 $-R^d-$ 芳基的基团，其中，$R^d$ 为如上所定义的亚烯基链。芳烯基的芳基部分如以上对于芳基所述任选地被取代。芳烯基的亚烯基链部分如以上对于亚烯基所述任选地被取代。

[0036] “芳炔基”是指式 $-R^e-$ 芳基的基团，其中，$R^e$ 为如上所定义的亚炔基链。芳炔基的芳基部分如以上对于芳基所述任选地被取代。芳炔基的亚炔基链部分如以上对于亚炔基链所述任选地被取代。

[0037] “碳环基”是指仅由碳和氢原子组成的、含有 3-15 个碳原子的稳定的非芳香族单环或多环烃基，其包括稠环或桥环体系。在某些实施方案中，碳环基包含 3-10 个碳原子。在其它一些实施方案中，碳环基包含 5-7 个碳原子。碳环基通过单键连接在分子的其余部分上。碳环基为饱和的（即，仅包含 C-C 单键）或者是不饱和的（即，包含一个或多个双键或三键）。完全饱和的碳环基也称作“环烷基”。单环环烷基的实例包括，例如，环丙基、环丁基、环戊基、环己基、环庚基和环辛基。不饱和的碳环基也称作“环烯基”。单环环烯基的实例包括，例如环戊烯基、环己烯基、环庚烯基和环辛烯基。多环碳环基基团包括，例如，金刚烷基、降冰片烷基（即，双环 [2.2.1] 庚烷基）、降冰片烯基、十氢萘基、7,7- 二甲基 - 双环 [2.2.1] 庚烷基等。除非在说明书中另有特别说明，术语“碳环基”意在包括任选地被独立地选自如下基团中的一种或多种取代基所取代的碳环基：烷基、烯基、炔基、卤素、氟代烷基、氧代基团、硫代基团、氰基、硝基、任选地取代的芳基、任选地取代的芳烷基、任选地取代的芳烯基、任选地取代的芳炔基、任选地取代的碳环基、任选地取代的碳环基烷基、任选地取代的杂环基、任选地取代的杂环基烷基、任选地取代的杂芳基、任选地取代的杂芳基烷基、$-R^b-OR^a$、$-R^b-SR^a$、$-R^b-OC(O)-R^a$、$-R^b-N(R^a)_2$、$-R^b-C(O)R^a$、$-R^b-C(O)OR^a$、$-R^b-C(O)N(R^a)_2$、$-R^b-O-R^c-C(O)$

$N(R^a)_2$、$-R^b-N(R^a)C(O)OR^a$、$-R^b-N(R^a)C(O)R^a$、$-R^b-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-R^b-S(O)_tOR^a$（其中，t 为 1 或 2）以及 $-R^b-S(O)_tN(R^a)_2$（其中，t 为 1 或 2），其中，各 $R^a$ 均独立地为氢、烷基、氟代烷基、环烷基、环烷基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基，各 $R^b$ 均独立地为直接键或者直链或支链亚烷基或亚烯基链，且 $R^c$ 为直链或支链亚烷基或亚烯基链，并且除非另有说明，上述每个取代基为未取代的。

[0038] “碳环基烷基”是指式 $-R^c-$ 碳环基的基团，其中，$R^c$ 为如上所定义的亚烷基链。亚烷基链和碳环基如上所定义地任选地被取代。

[0039] “卤代”或“卤素”是指溴、氯、氟或碘取代基。

[0040] “氟代烷基”是指被一个或多个如上所定义的氟基所取代的如上所定义的烷基，例如，三氟甲基、二氟甲基、2,2,2- 三氟乙基、1- 氟甲基 -2- 氟乙基等。氟代烷基的烷基部分如以上对于烷基所定义地任选地被取代。

[0041] “杂环基”是指包含 2-12 个碳原子和 1-6 个选自氮、氧和硫的杂原子的稳定的 3 元至 18 元非芳香环基团。除非在说明书中另有特别说明，杂环基为单环、双环、三环或四环环系，包括稠环或桥环体系。在杂环基中的杂原子任选地被氧化。如果存在一个或多个氮原子，其任选地被季铵化。杂环基为部分或者完全饱和的。杂环基通过环上的任意原子连接在分子的其余部分上。这样的杂环基的实例包括但不限于，二氧杂环戊烷基、噻吩基 [1,3] 二噻烷基、十氢异喹啉基、咪唑啉基、咪唑烷基、异噻唑烷基、异噁唑烷基、吗啉基、八氢吲哚基、八氢异吲哚基、2- 氧代哌嗪基、2- 氧代哌啶基、2- 氧代吡咯烷基、噁唑烷基、哌啶基、哌嗪基、4- 哌啶酮基、吡咯烷基、吡唑烷基、奎宁环基、噻唑烷基、四氢呋喃基、三噻烷基、四氢吡喃基、硫代吗啉基 (thiomorpholinyl)、硫杂吗啉基 (thiamorpholinyl)、1- 氧代 - 硫代吗啉基和 1,1- 二氧代 - 硫代吗啉基。除非在说明书中另有特别说明，术语“杂环基”意在包括任选地被选自如下基团的一种或多种取代基所取代的如上所定义的杂环基 :烷基、烯基、炔基、卤素、氟代烷基、氧代基团、硫代基团、氰基、硝基、任选地取代的芳基、任选地取代的芳烷基、任选地取代的芳烯基、任选地取代的芳炔基、任选地取代的碳环基、任选地取代的碳环基烷基、任选地取代的杂环基、任选地取代的杂环基烷基、任选地取代的杂芳基、任选地取代的杂芳基烷基、$-R^b-OR^a$、$-R^b-SR^a$、$-R^b-OC(O)-R^a$、$-R^b-N(R^a)_2$、$-R^b-C(O)R^a$、$-R^b-C(O)OR^a$、$-R^b-C(O)N(R^a)_2$、$-R^b-O-R^c-C(O)N(R^a)_2$、$-R^b-N(R^a)C(O)OR^a$、$-R^b-N(R^a)C(O)R^a$、$-R^b-N(R^a)S(O)_tR^a$（其中，t 为 1 或 2）、$-R^b-S(O)_tOR^a$（其中，t 为 1 或 2）和 $-R^b-S(O)_tN(R^a)_2$（其中，t 为 1 为 2），其中，各 $R^a$ 均独立地为氢、烷基、氟代烷基、环烷基、环烷基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基，各 $R^b$ 独立地为直接键或者直链或支链亚烷基或亚烯基链，并且 $R^c$ 为直链或支链亚烷基或亚烯基链，并且除非另有说明，上述各个取代基为未取代的。

[0042] “N- 杂环基”或“N- 连接的杂环基”是指包含至少一个氮的如上所定义的杂环基，并且其中杂环基连接到分子的其余部分上的连接点是通过杂环基中的氮原子。N- 杂环基如以上对于杂环基所述任选地被取代。这样的 N- 杂环基基团的实例包括但不限于，1- 吗啉基、1- 哌啶基、1- 哌嗪基、1- 吡咯烷基、吡唑烷基、咪唑啉基和咪唑烷基。

[0043] “C- 杂环基”或“C- 连接的杂环基”是指包含至少一个杂原子的如上所定义的杂环基，并且其中杂环基连接到分子的其余部分上的连接点是通过杂环基中的碳原子。C- 杂环基如以上对于杂环基所述任选地被取代。这样的 C- 杂环基的实例包括但不限于，2- 吗啉

基、2- 或 3- 或 4- 哌啶基、2- 哌嗪基、2- 或 3- 吡咯烷基等。

[0044] “杂环基烷基”是指式 -$R^c$- 杂环基的基团，其中，$R^c$为如上所定义的亚烷基链。如果杂环基为含氮的杂环基，则杂环基任选地在氮原子上连接到烷基基团上。杂环基烷基基团的亚烷基链如以上对于亚烷基链所定义地任选地被取代。杂环基烷基基团的杂环基部分如以上对于杂环基所定义地任选地被取代。

[0045] “杂芳基”是指由包含 2-17 个碳原子和 1-6 个选自氮、氧和硫的杂原子的 3 元至 18 元芳香环基团所衍生的基团。如本文所使用的，杂芳基为单环、双环、三环或四环环系，其中，环系中的至少一个环为完全不饱和的，即，其根据休克尔理论包含环状、离域的 (4n+2) π - 电子体系。杂芳基包括稠环或桥环体系。杂芳基基团中的杂原子任选地被氧化。如果存在一个或多个氮原子，其任选地被季铵化。杂芳基通过环上任意原子连接到分子的其余部分上。杂芳基的实例包括但不限于，氮杂䓬基 (azepinyl)、吖啶基、苯并咪唑基、苯并吲哚基、1,3- 苯并二氧杂环戊基、苯并呋喃基、苯并噁唑基、苯并 [d] 噻唑基、苯并噻二唑基、苯并 [b][1,4] 二氧杂䓬基、苯并 [b][1,4] 噁嗪基、1,4- 苯并二噁烷基、苯并萘并呋喃基、苯并噁唑基、苯并二氧杂环戊基、苯并二氧杂环己基、苯并吡喃基、苯并吡喃酮基、苯并呋喃基、苯并呋喃酮基、苯并噻吩基 (benzothiophenyl)、苯并噻吩并 [3,2-d] 嘧啶基、苯并三唑基、苯并 [4,6] 咪唑并 [1,2-a] 吡啶基、咔唑基、噌啉基、环戊并 [d] 嘧啶基、6,7- 二氢 -5H- 环戊并 [4,5] 噻吩并 [2,3-d] 嘧啶基、5,6- 二氢苯并 [h] 喹唑啉基、5,6- 二氢苯并 [h] 噌啉基、6,7- 二氢 -5H- 苯并 [6,7] 环庚并 [1,2-c] 哒嗪基、二苯并呋喃基、二苯并噻吩基、呋喃基、呋喃酮基、呋喃并 [3,2-c] 吡啶基、5,6,7,8,9,10- 六氢环辛并 [d] 嘧啶基、5,6,7,8,9,10- 六氢环辛并 [d] 哒嗪基、5,6,7,8,9,10- 六氢环辛并 [d] 吡啶基、异噻唑基、咪唑基、吲唑基、吲哚基、吲唑基、异吲哚基、二氢吲哚基、异二氢吲哚基、异喹啉基、吲嗪基、异噁唑基、5,8- 甲桥 -5,6,7,8- 四氢喹唑啉基、萘啶基、1,6- 萘啶酮基 (1,6-naphthyridinonyl)、噁二唑基、2- 氧氮杂䓬基、噁唑基、环氧乙烷基、5,6,6a,7,8,9,10,10a- 八氢苯并 [h] 喹唑啉基、1- 苯基 -1H- 吡咯基、吩嗪基、吩噻嗪基、吩噁嗪基、酞嗪基、蝶啶基、嘌呤基、吡咯基、吡唑基、吡唑并 [3,4-d] 嘧啶基、吡啶基、吡啶并 [3,2-d] 嘧啶基、吡啶并 [3,4-d] 嘧啶基、吡嗪基、嘧啶基、哒嗪基、吡咯基、喹唑啉基、喹喔啉基、喹啉基、异喹啉基、四氢喹啉基、5,6,7,8- 四氢喹唑啉基、5,6,7,8- 四氢苯并 [4,5] 噻吩并 [2,3-d] 嘧啶基、6,7,8,9- 四氢 -5H- 环庚并 [4,5] 噻吩并 [2,3-d] 嘧啶基、5,6,7,8- 四氢吡啶并 [4,5-c] 哒嗪基、噻唑基、噻二唑基、三唑基、四唑基、三嗪基、噻吩并 [2,3-d] 嘧啶基、噻吩并 [3,2-d] 嘧啶基、噻吩并 [2,3-c] 吡啶基和噻吩基 ( 即，噻吩基 (thienyl))。除非在说明书中另有特别说明，术语“杂芳基”意在包括任选地被选自如下基团的一种或多种取代基所取代的如上所定义的杂芳基基团 :烷基、烯基、炔基、卤素、氟代烷基、卤代烯基、卤代炔基、氧代基团、硫代基团、氰基、硝基、任选地取代的芳基、任选地取代的芳烷基、任选地取代的芳烯基、任选地取代的芳炔基、任选地取代的碳环基、任选地取代的碳环基烷基、任选地取代的杂环基、任选地取代的杂环基烷基、任选地取代的杂芳基、任选地取代的杂芳基烷基、-$R^b$-$OR^a$、-$R^b$-$SR^a$、-$R^b$-OC(O)-$R^a$、-$R^b$-$N(R^a)_2$、-$R^b$-C(O)$R^a$、-$R^b$-C(O)$OR^a$、-$R^b$-C(O)$N(R^a)_2$、-$R^b$-O-$R^c$-C(O)$N(R^a)_2$、-$R^b$-$N(R^a)$C(O)$OR^a$、-$R^b$-$N(R^a)$C(O)$R^a$、-$R^b$-$N(R^a)$$S(O)_tR^a$( 其中，t 为 1 或 2)、-$R^b$-$S(O)_tOR^a$( 其中，t 为 1 或 2) 和 -$R^b$-$S(O)_tN(R^a)_2$( 其中，t 为

1 为 2)，其中，各 $R^a$均独立地为氢、烷基、氟代烷基、环烷基、环烷基烷基、芳基、芳烷基、杂环基、杂环基烷基、杂芳基或杂芳基烷基，各 $R^b$均独立地为直接键或者直链或支链亚烷基或亚烯基链，且 $R^c$为直链或支链亚烷基或亚烯基链，并且除非另有说明，上述每个取代基为未取代的。

[0046] “N- 杂芳基”是指包含至少一个氮的如上所定义的杂芳基基团，并且其中杂芳基基团连接到分子的其余部分上的连接点是通过杂芳基基团中的氮原子。N- 杂芳基基团如以上对于杂芳基基团所述任选地被取代。

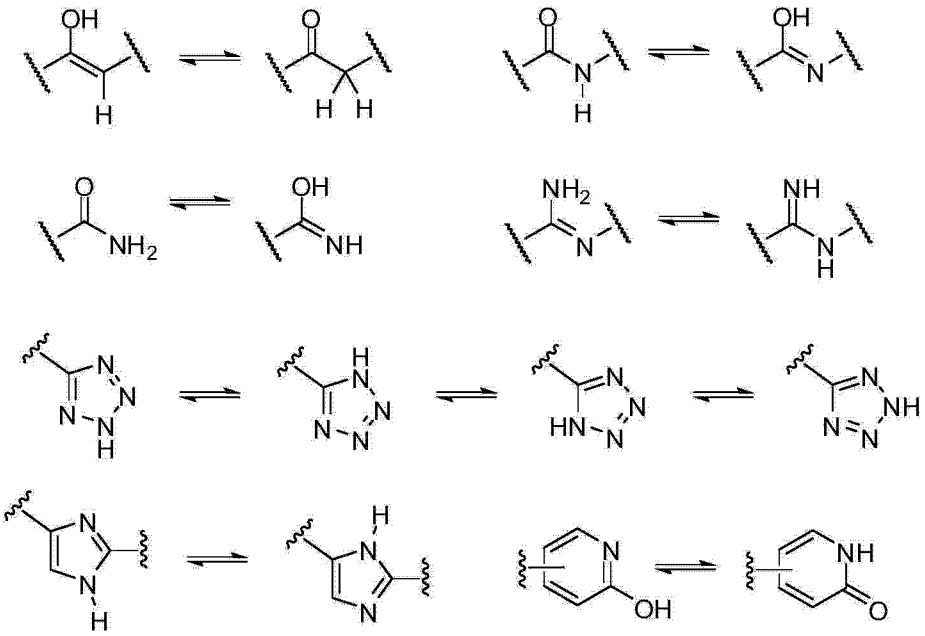
[0047] “C- 杂芳基”是指如上所定义的杂芳基，并且其中杂芳基基团连接到分子的其余部分上的连接点是通过杂芳基基团中的碳原子。C- 杂芳基如以上对于杂芳基基团所述任选地被取代。

[0048] “杂芳基烷基”是指式 -$R^c$- 杂芳基的基团，其中，$R^c$为如上所定义的亚烷基链。如果杂芳基为含氮杂芳基，则该杂芳基任选地在氮原子处连接到烷基基团上。杂芳基烷基基团的亚烷基链如以上对于亚烷基链所定义地任选地被取代。杂芳基烷基基团的杂芳基部分如以上对于杂芳基基团所定义地任选地被取代。

[0049] 在一些实施方案中，所述化合物或其药学上可接受的盐包含一个或多个非对称中心，因而产生对映异构体、非对映体和其它立体异构体形式，其根据绝对立体化学被定义为 (R)- 或 (S)-，或者对于氨基酸被定义为 (D)- 或 (L)-。当本文描述的化合物包含烯烃双键或其它几何非对称中心时，并且除非另有特别说明，化合物意欲包括 E 和 Z 几何异构体（例如，顺式或反式）。同样地，也意欲包括所有可能的异构体和它们的外消旋及光学纯形式，以及所有互变异构体形式。

[0050] “立体异构体”是指由通过相同键结合的相同原子组成但具有不同三维结构的化合物，这些结构不可互换。因此考虑了各种立体异构体及其混合物并且包括“对映异构体”，对映异构体是指其分子互为不可重叠的镜像的两种立体异构体。

[0051] 在一些实施方案中，本文提出的化合物作为互变异构体存在。“互变异构体”是指质子从分子上的一个原子转移到同一分子的另一个原子上，伴随有相邻双键的异构化。在可能发生互变异构化的键合排列中，将存在互变异构体的化学平衡。本文公开的化合物的所有互变异构形式都被考虑在内。互变异构体的确切比例取决于几个因素，包括温度、溶剂和 pH。互变异构互变的一些实例包括 ：



[0052] “任选的”或“任选地”是指在其后描述的事件或情况可以发生或者可以不发生，并且该描述包括当事件或情况发生时的情形和不发生时的情形。例如，“任选地取代的芳基”是指芳基可以被取代或者可以不被取代，并且该描述既包括被取代的芳基也包括没有取代的芳基。

[0053] “药学上可接受的盐”既包括酸加成盐也包括碱加成盐。本文描述的任意一种取代的杂环胺衍生物化合物的药学上可接受的盐意在包括任意的和所有的药学上合适的盐形式。本文所述化合物的优选的药学上可接受的盐为药学上可接受的酸加成盐和药学上可接受的碱加成盐。

[0054] “药学上可接受的酸加成盐”是指保留了生物有效性和游离碱的性质的那些盐，其在生物学上或其它方面不是不合需要的，并且其是用诸如盐酸、氢溴酸、硫酸、硝酸、磷酸、氢碘酸、氢氟酸、亚磷酸等无机酸形成的。也包括用如下有机酸形成的盐：例如脂肪族单羧酸和二羧酸、苯基取代的链烷酸、羟基链烷酸、链烷二酸、芳香酸、脂肪族和芳香族磺酸等，并且包括例如醋酸、三氟醋酸、丙酸、羟基乙酸、丙酮酸、草酸、马来酸、丙二酸、琥珀酸、富马酸、酒石酸、柠檬酸、苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、对甲苯磺酸、水杨酸等。因此，示例性的盐包括硫酸盐、焦硫酸盐、硫酸氢盐、亚硫酸盐、亚硫酸氢盐、硝酸盐、磷酸盐、磷酸单氢盐、磷酸二氢盐、偏磷酸盐、焦磷酸盐、氯化物、溴化物、碘化物、醋酸盐、三氟醋酸盐、丙酸盐、辛酸盐、异丁酸盐、草酸盐、丙二酸盐、琥珀酸盐、辛二酸盐、癸二酸盐、富马酸盐、马来酸盐、扁桃酸盐、苯甲酸盐、氯苯甲酸盐、甲基苯甲酸盐、二硝基苯甲酸盐、邻苯二甲酸盐、苯磺酸盐、甲苯磺酸盐、苯基醋酸盐、柠檬酸盐、乳酸盐、苹果酸盐、酒石酸盐、甲磺酸盐等。还考虑到氨基酸的盐如精氨酸盐、葡糖酸盐和半乳糖醛酸盐（参见，例如，Berge S.M. 等，“Pharmaceutical Salts”Journal of Pharmaceutical Science,66:1-19(1997)，其通过引用整体并入本文）。根据本领域熟练技术人员所熟知的方法和技术，通过使游离碱形式与足量的所需酸接触以产生盐，来制备碱性化合物的酸加成盐。

[0055] “药理学上可接受的碱加成盐”是指保留生物有效性和游离酸的性质的那些盐，其在生物学上或其它方面不是不合需要的。这些盐是通过向游离酸中加入无机碱或有机碱而

制备的。药学上可接受的碱加成盐可以用金属或胺如碱金属和碱土金属或有机胺来形成。源于无机碱的盐包括但不限于，钠、钾、锂、铵、钙、镁、铁、锌、铜、锰、铝的盐等。源于有机碱的盐包括但不限于下列有机碱的盐：伯胺、仲胺和叔胺；取代的胺（包括天然存在的取代的胺）；环胺和碱离子交换树脂，例如，异丙胺、三甲胺、二乙胺、三乙胺、三丙胺、乙醇胺、二乙醇胺、2- 二甲基氨基乙醇、2- 二乙基氨基乙醇、二环己基胺、赖氨酸、精氨酸、组氨酸、咖啡因、普鲁卡因、N,N- 二苄基乙二胺、氯普鲁卡因、海巴明 (hydrabamine)、胆碱、甜菜碱、乙二胺、亚乙基二苯胺、N- 甲基葡糖胺、葡糖胺、甲基葡糖胺、可可碱 (theobromine)、嘌呤、哌嗪、哌啶、N- 乙基哌啶、聚胺树脂等。参见 Berge 等，同上。

[0056] “非类视黄醇化合物”是指不属于类视黄醇的任何化合物。类视黄醇是具有含有三甲基环己烯基环和终止于极性末端基团的多烯链的二萜骨架的化合物。类视黄醇的实例包括视黄醛及衍生的亚胺 / 酰肼 / 肟、视黄醇及任意的衍生酯、视黄基胺及任意的衍生酰胺、视黄酸及任意衍生酯或酰胺。在一些实施方案中，非类视黄醇化合物任选地包含内部环状基团（例如，芳香基）。

[0057] 本文使用的“治疗”或“处理”或“减轻”或“改善”在本文中可以互换使用。这些术语是指用于获得包括但不限于治疗益处和 / 或预防益处的有益或所需结果的方法。“治疗益处”意指使正在治疗的潜在病症的消除或改善。同样地，治疗益处是通过与潜在病症相关的一种或多种生理学症状的消除或改善来实现的，从而在患者身上观察到改善，即使该患者仍然遭受潜在病症的折磨。至于预防益处，可以将所述组合物施用于具有发展成特定疾病的风险的患者，或者报告疾病的一种或多种生理学症状的患者，即使可能还没有对该疾病作出诊断。

[0058] “前药”是指在生理条件下或通过溶剂分解可以转化为本文描述的生物活性化合物的化合物。因此，术语“前药”是指药学上可接受的生物活性化合物的前体。当施用于受试者时，前药可以是无活性的，但是在体内转化为活性化合物，例如，通过水解。前药化合物通常在哺乳动物生物体内具有溶解性、组织相容性或延迟释放的优点（参见，例如，Bundgard,H.,Design of Prodrugs(1985),pp.7-9,21-24(Elsevier,Amsterdam)）。

[0059] 在 Higuchi,T. 等，"Pro drugs as Novel Delivery Systems,"A.C.S.Symposium Series,Vol.14 和 Bioreversible Carriers in Drug Design,ed.Edward B.Roche,American Pharmaceutical Association and Pergamon Press,1987 中均提供了对前药的论述，其全部内容均通过引用并入本文。

[0060] 术语“前药”也意在包括任何共价键合的载体，当将这种前药施用于哺乳动物受试者时，该载体在体内释放活性化合物。本文所述的活性化合物的前药可以如下制备：以这样一种方式修饰存在于活性化合物中的官能团，该方式使得该修饰通过常规操作或者在体内分裂为母体活性化合物。前药包括其中羟基、氨基或巯基键合到如下所述的任一基团上的化合物，当将活性化合物的前药施用于哺乳动物受试者时，该基团裂解，从而分别形成游离羟基、游离氨基或游离巯基。前药的实例包括但不限于，活性化合物中的醇或胺官能团的乙酸酯、甲酸酯和苯甲酸酯衍生物等。

[0061] 年龄相关性黄斑变性在美国影响到 1000 万至 1500 万患者，并且它是全世界老年人口中失明的首要原因。AMD 影响中央视觉，并导致视网膜中央部分中的感光细胞（称作黄斑）的丧失。黄斑变性可以被分成两类：干型和湿型。干型比湿型更常见；约 90％的年龄

相关性黄斑变性患者被诊断为干型。该疾病的湿型和地图状萎缩(geographic atrophy)(其为干型AMD的末期表型)导致最严重的视觉丧失。所有发展成湿型AMD的患者都被认为先前干型AMD已发展持续了很长一段时间。AMD的确切原因仍不清楚。干型AMD可由与黄斑视网膜色素上皮中的色素沉着相关的黄斑组织的老化和变薄引起。在湿型AMD中,新的血管在视网膜下生长,形成瘢痕组织,出血,并渗漏液体。上面的视网膜可被严重地损伤,从而在中央视觉中产生“盲”区。

[0062] 对于绝大多数患有干型黄斑变性的患者,仍然没有可用的有效治疗。因为干型黄斑变性早于湿型黄斑变性的发展,所以防止或延缓干型AMD的疾病进展的治疗性干预将有益于干型AMD患者,并且可降低湿型AMD的发病率。

[0063] 患者注意到的视力下降或者眼科医师在常规眼部检查中检测到的特有特征可为AMD的第一指征。在黄斑的视网膜色素上皮下的“玻璃疣”或膜状碎片的形成常常是AMD正在发展的第一体征。后期症状包括:直线的感知失真,以及在晚期病例中,在视觉中央出现模糊的暗区或没有视觉的区域;和/或可能存在色觉改变。

[0064] 不同形式的遗传连锁的黄斑变性也可能会发生在较年轻的患者中。对于其它黄斑病,疾病因素有遗传性、营养的、外伤性的、感染或者其它生态因素。

[0065] 青光眼是用来描述引起缓慢进行性视野丧失(通常无症状地)的一类疾病的概括性术语。症状的缺失可能导致青光眼的诊断延误直到疾病的终末期。在美国,估计有220万人患有青光眼,约120,000例失明可归因于这种情况。在日本,这种疾病尤其普遍,有400万报告病例。与美国和日本相比,在世界上的许多地方较难得到治疗,因此青光眼被列为全世界失明的首要原因。即使罹患青光眼的对象没有失明,他们的视力常常也严重受损。

[0066] 青光眼中周边视野的进行性丧失是由视网膜中的神经节细胞的死亡引起的。神经节细胞是连接眼睛与大脑的特定类型的投射神经元。青光眼通常伴有眼内压升高。目前的治疗包括使用降低眼内压的药物;然而,降低眼内压的当前方法常常不足以彻底终止疾病进展。神经节细胞被认为对压力敏感并且可在眼内压降低前经受永久变性。观察到正常眼压性青光眼的病例数的增加,在该疾病中,在没有观察到眼内压升高的情况下神经节细胞变性。目前的青光眼药物仅仅治疗眼内压,而对预防和逆转神经节细胞的变性是无效的。

[0067] 最近的报道提示,青光眼是一种神经变性疾病,除了特异性地影响视网膜神经元以外,它类似于脑部的阿尔茨海默病和帕金森病。眼睛的视网膜神经元源自大脑的间脑神经元。虽然视网膜神经元常常错误地被认为不是脑的一部分,但是视网膜细胞是中枢神经系统的关键组分,用于解释来自光感细胞的信号。

[0068] 阿尔茨海默病(AD)为老年人中最常见的痴呆类型。痴呆症为严重影响人进行日常活动的能力的脑功能障碍。仅在美国阿尔茨海默病就影响到四百万人。该疾病的特征为对记忆和其它精神功能至关重要的大脑区域中的神经细胞的丧失。目前可以获得的药物能够在相对有限的一段时间内缓解AD症状,但是还没有药物能治疗该疾病或者完全停止精神功能的进行性减退。近来的研究提示,在AD患者中,支撑神经元或神经细胞的神经胶质细胞可能存在缺陷,但是AD的病因仍然未知。患有AD的个体似乎具有更高的青光眼和年龄相关性黄斑变性的发病率,表明眼睛和大脑的这些神经变性疾病可能存在相似的发病机理。(参见Giasson等,Free Radic.Biol.Med.32:1264-75(2002);Johnson等,Proc.Natl.Acad.Sci.USA 99:11830-35(2002);Dentchev等,Mol.Vis.9:184-90(2003))。

[0069] 神经元细胞死亡是这些疾病的病理学的基础。遗憾的是，已经发现的能够提高视网膜神经元细胞存活（特别是感光细胞存活）的组合物和方法非常少。因此，存在以下需要：确定和开发可以用于治疗和预防在发病机理中以神经细胞死亡作为主要或相关因素的许多视网膜疾病和病症的组合物。

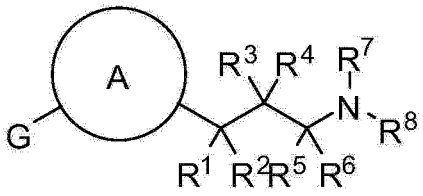
[0070] 在脊椎动物的感光细胞中，光子的发光导致 11- 顺式 - 亚视黄基生色团向全反式 - 亚视黄基的异构化作用，并从视觉视蛋白受体上解偶联。这种光致异构化触发视蛋白的构象变化，后者转而引起被称作光转导的生化反应链 (Filipek 等，Annu. Rev. Physiol. 65:851-79(2003))。视色素的再生需要生色团在通称为类视黄醇（视觉）循环的过程中转化回 11- 顺式 - 构象（参见，例如，McBee 等，Prog. Retin. Eye Res. 20:469-52(2001))。首先，生色团从视蛋白中释放出，并在光感受器中被视黄醇脱氢酶还原。产物全反式视黄醇在被称为视网膜体 (retinosomes) 的亚细胞结构中以不溶性脂肪酸酯的形式被捕获在邻近的视网膜色素上皮 (RPE) 中 (Imanishi 等，J. Cell Biol. 164:373-87(2004))。

[0071] 在斯塔加特病 (Allikmets 等，Nat. Genet. 15:236-46(1997))（一种与充当翻转酶的 ABCR 转运体中的突变有关的疾病）中，全反式视黄醛的积聚可以造成脂褐质色素 (A2E) 的形成，A2E 对视网膜色素上皮细胞具有毒性并导致进行性视网膜变性，因而导致视觉的丧失 (Mata 等，Proc. Natl. Acad. Sci. USA 97:7154-59(2000)；Weng 等，Cell 98:13-23(1999))。已经考虑用视黄醇脱氢酶 13- 顺式 -RA（异维 A 酸，Accutane®, Roche) 的抑制剂治疗患者作为可能防止或减缓 A2E 形成并且可能具有维持正常视力的保护性作用的疗法 (Radu 等，Proc. Natl. Acad. Sci. USA 100:4742-47(2003))。13- 顺式 -RA 已经用来通过抑制 11- 顺式 -RDH 减缓 11- 顺式 - 视黄醛的合成 (Law 等，Biochem. Biophys. Res. Commun. 161:825-9(1989))，但是它的使用也会引起明显的夜盲症。有人提出，13- 顺式 -RA 通过与 RPE65（一种对眼睛中的异构化过程而言必需的蛋白质）结合起到防止生色团再生的作用 (Gollapalli 等，Proc. Natl. Acad. Sci. USA 101:10030-35(2004))。Gollapalli 等报道，13- 顺式 -RA 阻断了 A2E 的形成，并且提示这种治疗可以抑制脂褐质聚积，从而延迟了斯塔加特病或者年龄相关性黄斑变性（这两种疾病都与视网膜色素相关的脂褐质聚积有关）中的丧失视觉的开始时间。然而，阻断类视黄醇循环并形成未有配体的视蛋白可能引起更严重的后果并使患者的预后变差（参见，例如，Van Hooser 等，J. Biol. Chem. 277:19173-82(2002)；Woodruff 等，Nat. Genet. 35:158-164(2003))。不能形成生色团可以导致进行性视网膜变性并且可以产生类似于利伯先天性黑矇 (LCA) 的表型，LCA 为一种非常罕见的、影响出生不久的婴儿的遗传病。

取代的杂环胺衍生物化合物

[0072] 本文描述了抑制类视黄醇循环的异构化步骤的取代的杂环胺衍生物化合物。这些化合物和包含这些化合物的组合物可用于抑制视网膜细胞的变性或用于增强视网膜细胞的存活。本文所述的化合物因此可用于治疗眼科疾病和病症，包括视网膜疾病和病症，例如年龄相关性黄斑变性和斯塔加特病。

[0073] 一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 -O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O- 和 -C($R^9$)$_2$-$NR^9$-；

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或 -$NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

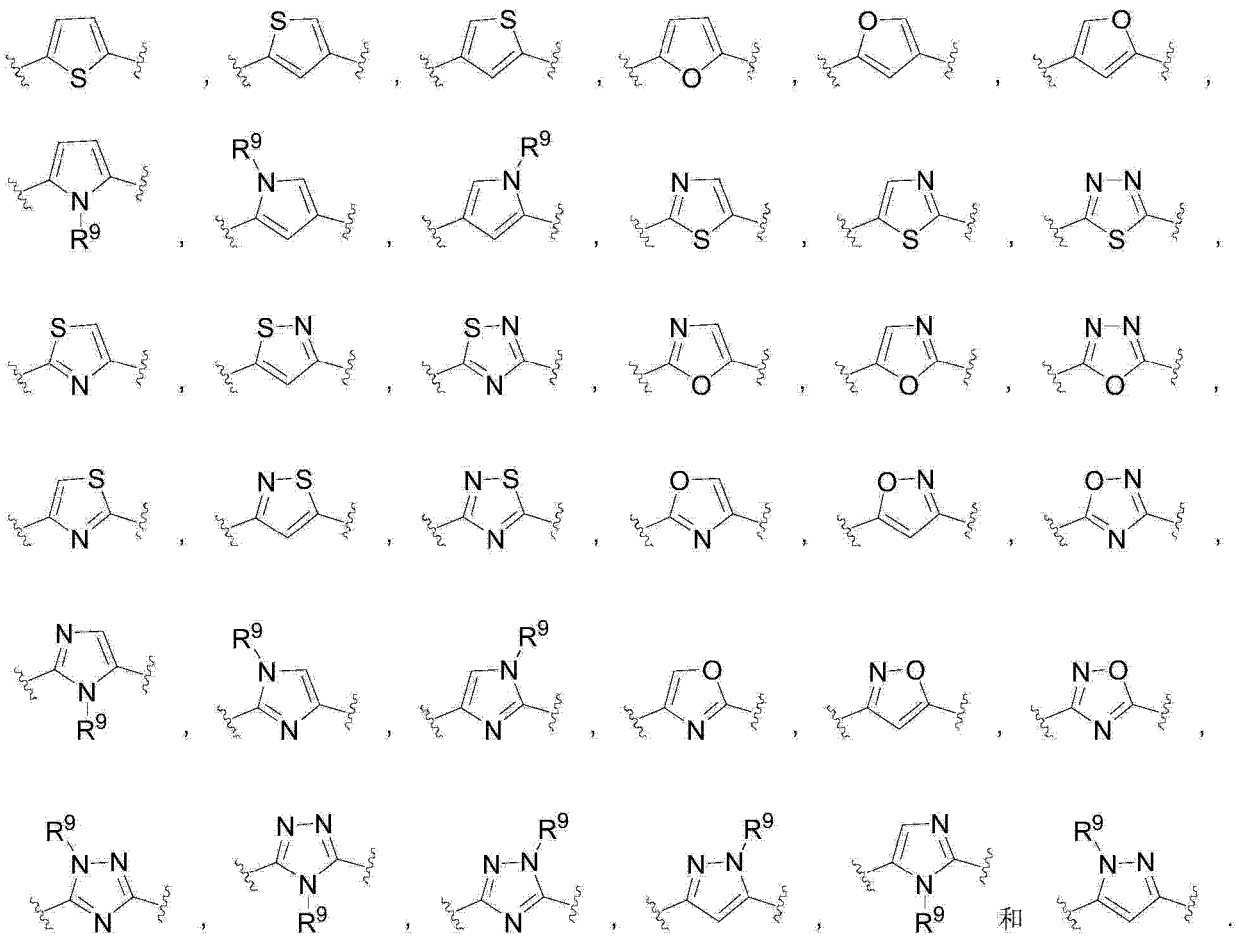
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

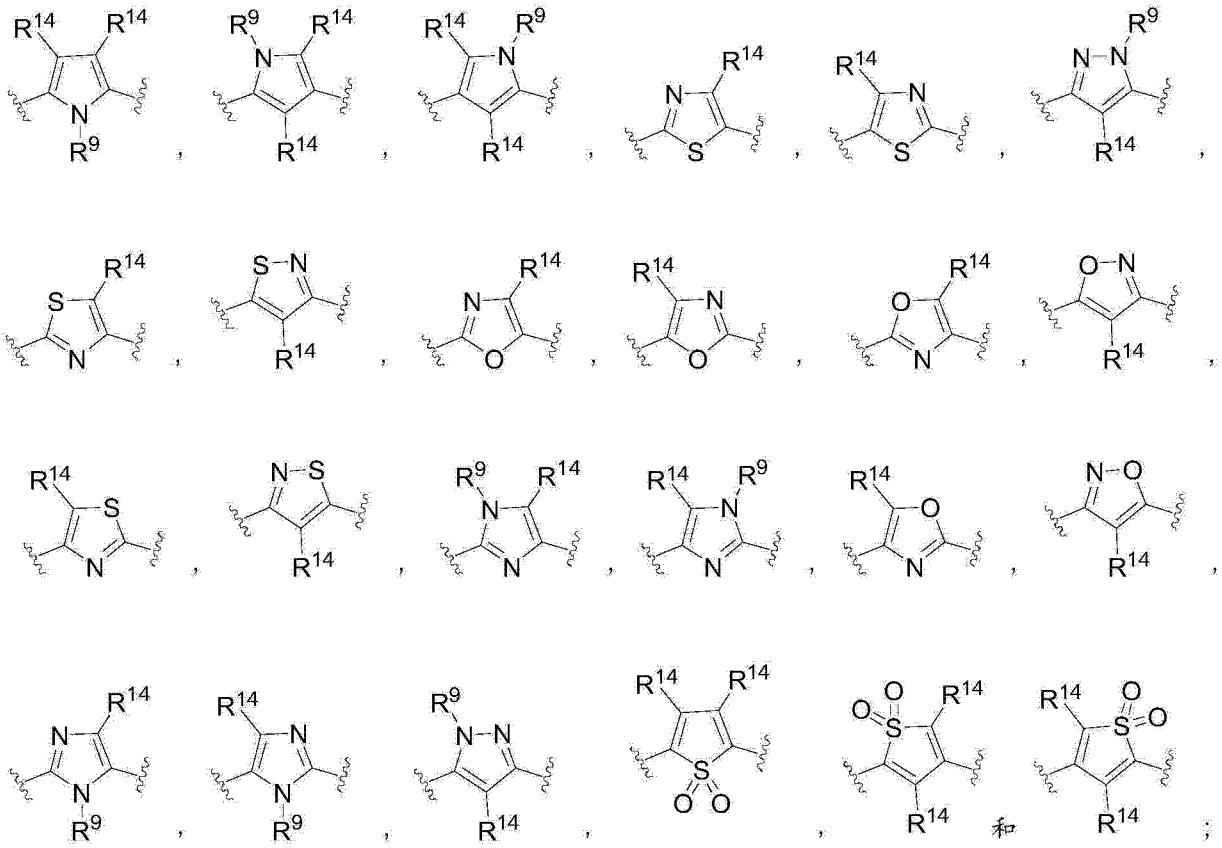
各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基

[0074] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

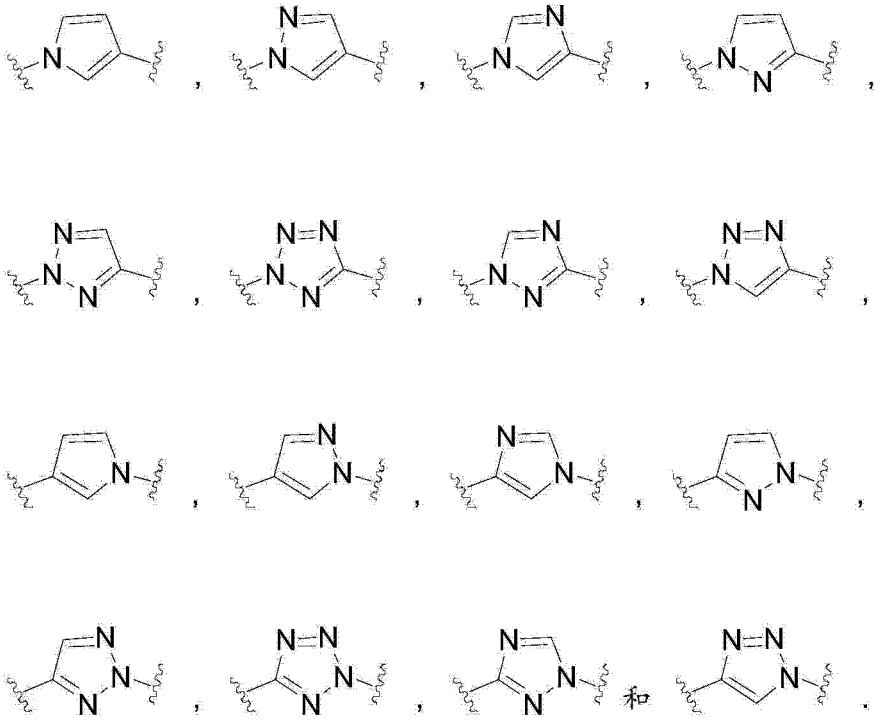


[0075] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

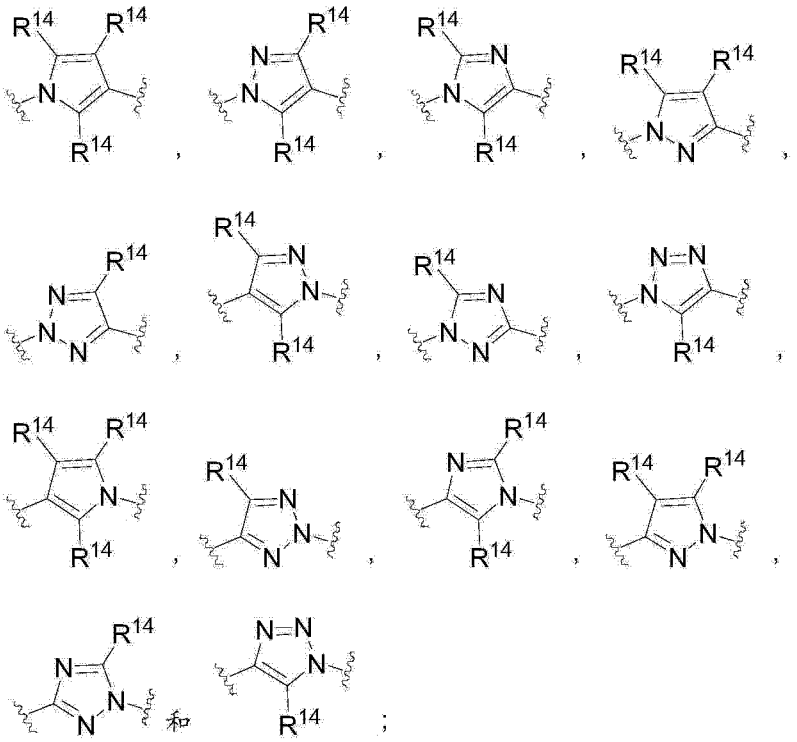


且各 $R^{14}$独立地选自氢、卤素、$OR^9$、烷基或氟代烷基。

[0076] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

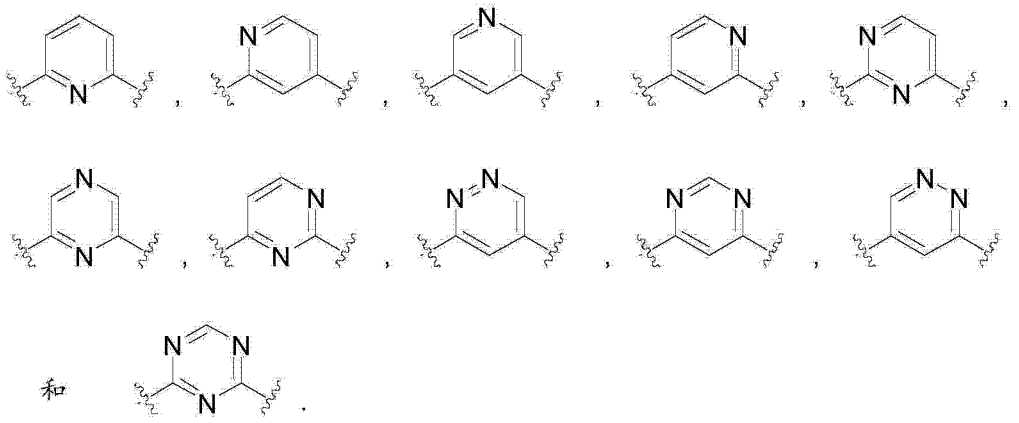


[0077] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

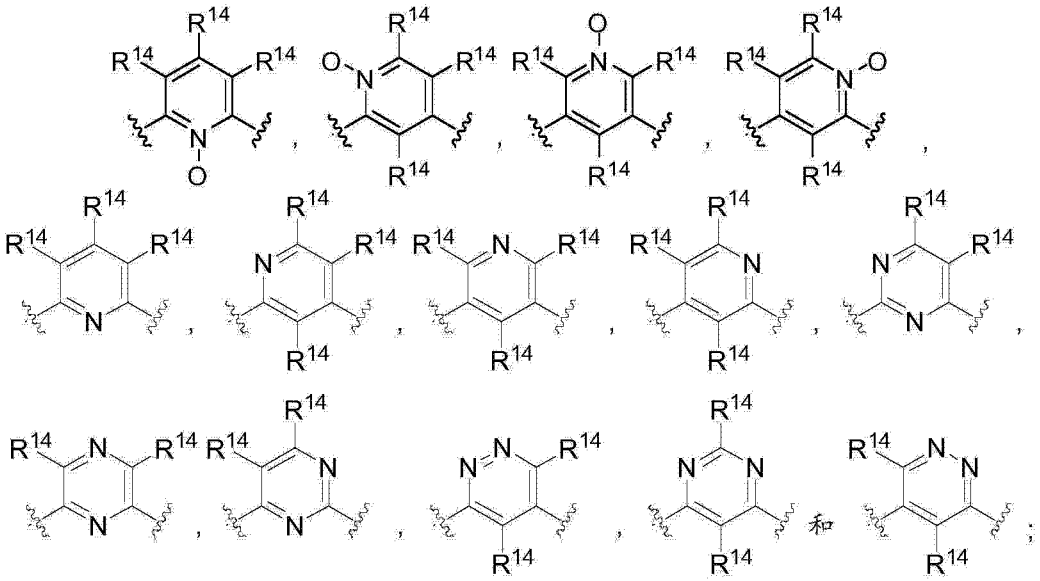


且各 $R^{14}$独立地选自氢、卤素、$OR^{9}$、烷基或氟代烷基。

[0078] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

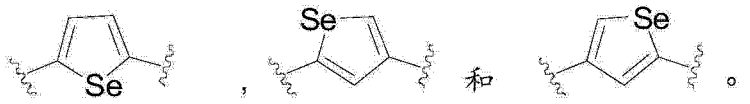


[0079] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

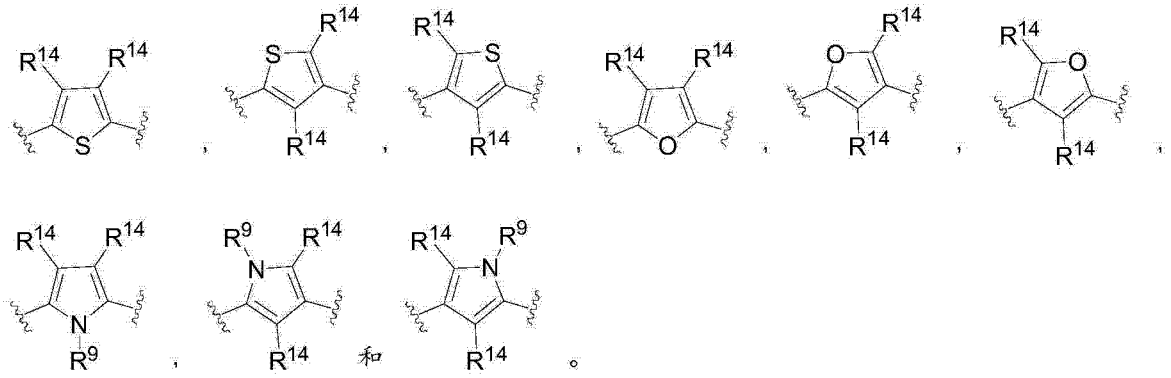


且各 $R^{14}$独立地选自氢、卤素、$OR^{9}$、烷基或氟代烷基。

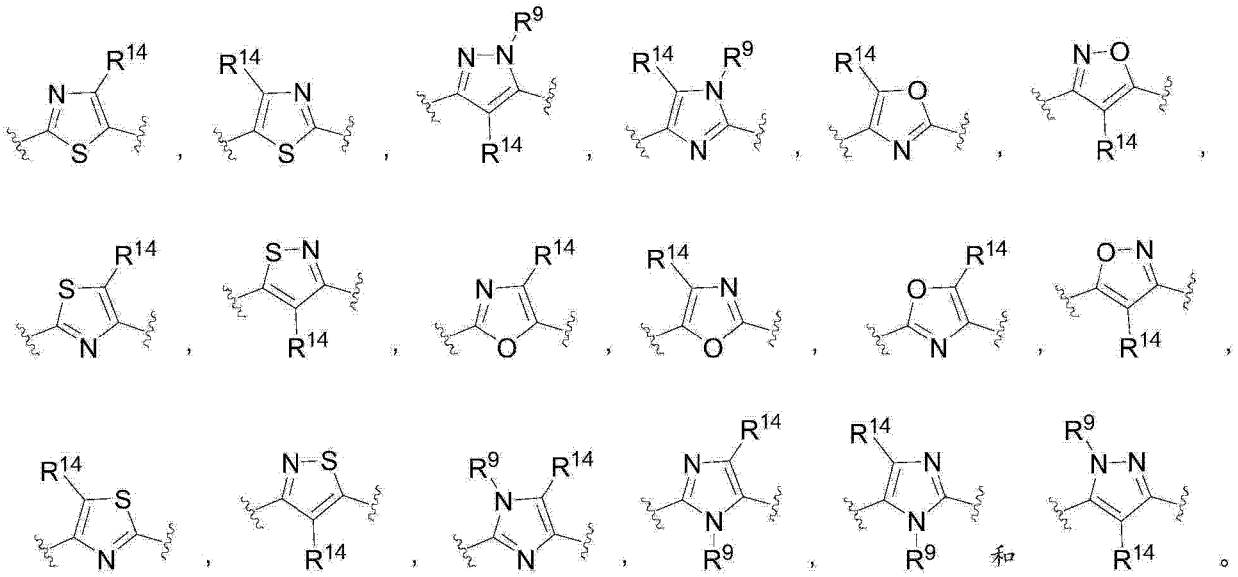
[0080] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



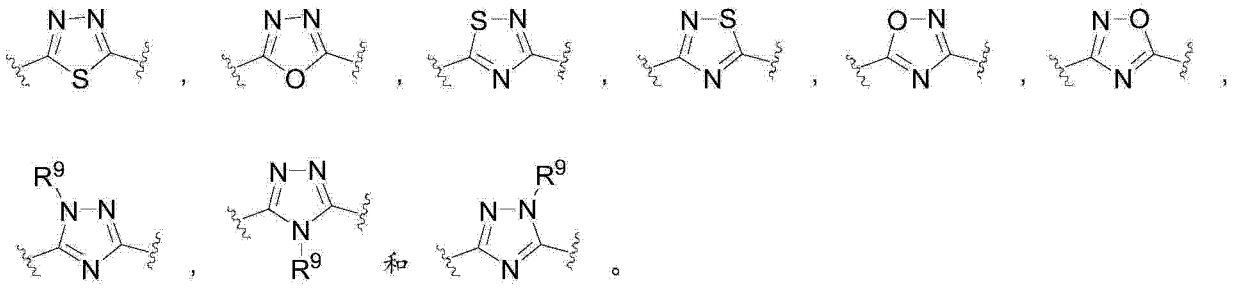
[0081] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



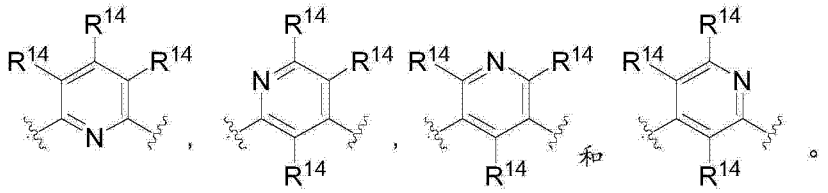
[0082] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



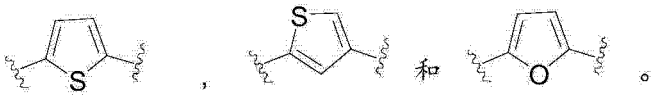
[0083] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



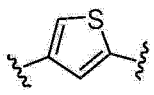
[0084] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



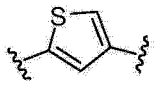
[0085] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



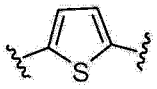
[0086] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



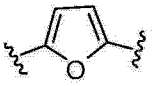
[0087] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



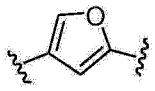
[0088] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



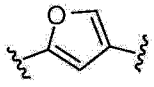
[0089] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



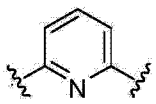
[0090] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



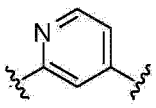
[0091] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



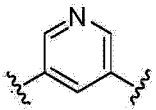
[0092] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



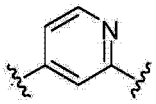
[0093] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



[0094] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



[0095] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为 ：



[0096] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为烷基、碳环基或杂环基。

[0097] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为烷基、碳环基或杂环基。

[0098] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者

$R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；且

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基。

[0099] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^{16}$和 $R^{17}$和与它们连接的碳原子一起形成碳环基或杂环基。

[0100] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成环丁基、环戊基、环己基、环庚基或环辛基，且 $R^{18}$为氢或羟基。

[0101] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成环戊基、环己基或环庚基，且 $R^{18}$为氢或羟基。

[0102] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^{16}$和 $R^{17}$各自独立地选自 $C_1$-$C_{13}$烷基；且 $R^{18}$为氢、羟基或烷氧基。

[0103] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 $-O-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$ 和 $-NR^9-S(O)_2-$。

[0104] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 $-C(R^9)_2-C(R^9)_2-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$。

[0105] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$。

[0106] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 为 $-C(R^9)_2-C(R^9)_2-$。

[0107] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 为 $-O-C(R^9)_2-$。

[0108] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^3$和 $R^4$均为氢。

[0109] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构

体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^5$ 和 $R^6$ 均为氢。

[0110] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^3$、$R^4$、$R^5$ 和 $R^6$ 均为氢。

[0111] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 均为氢。

[0112] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 为氢且 $R^2$ 为 -OH。

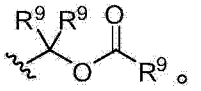
[0113] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 一起形成氧代基团。

[0114] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^7$ 和 $R^8$ 均为氢。

[0115] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^7$ 为氢且 $R^8$ 为 $-C(=O)R^{13}$ 或 $CO_2R^{13}$。

[0116] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^{13}$ 为烷基。

[0117] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^8$ 为 $CO_2R^{13}$ 且 $R^{13}$ 为



。

[0118] 在此考虑到以上对于各种变量所描述的基团的任意组合。在整个说明书中，基团及其取代基由本领域技术人员选择，以提供稳定的部分和化合物。

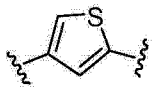
[0119] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中

Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$ 和 $R^{17}$ 各自独立地选自氢、$C_1$-$C_{13}$ 烷基、卤代或氟代烷基；或者 $R^{16}$ 和 $R^{17}$ 和与它们连接的碳原子一起形成碳环基或杂环基；

$R^{18}$ 选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



。

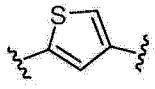
[0120] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$ 和 $R^{17}$ 各自独立地选自氢、$C_1$-$C_{13}$ 烷基、卤代或氟代烷基；或者 $R^{16}$ 和 $R^{17}$ 和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$ 选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$ ；且

环 A 为：



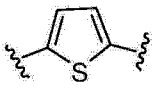
[0121] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$ ；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1-C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$ ；且

环 A 为：



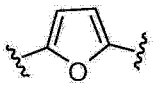
[0122] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$ ；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1-C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$ ；且

环 A 为：



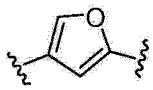
[0123] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$ ；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1-C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$ ；且

环 A 为：



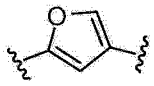
[0124] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$ ；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1-C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$ ；且

环 A 为：



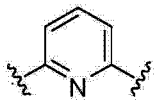
[0125] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



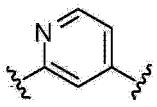
[0126] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



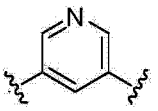
[0127] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



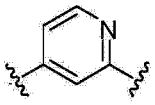
[0128] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0129] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

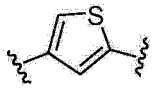
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0130] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

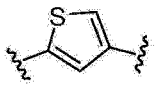
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0131] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

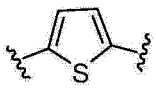
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0132] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构

体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

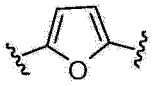
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0133] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

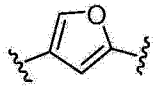
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0134] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

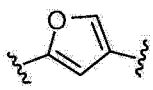
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0135] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

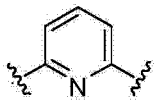
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0136] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

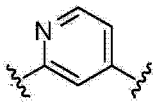
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0137] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

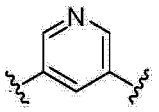
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：



[0138] 另一个实施方案提供了式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中，

$R^1$为氢，$R^2$为 -OH，$R^3$、$R^4$、$R^5$和 $R^6$均为氢；

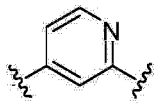
Y 为 $-C(R^{16})(R^{17})(R^{18})$；

$R^{16}$和 $R^{17}$各自独立地选自氢、$C_1$-$C_{13}$烷基、卤代或氟代烷基；或者 $R^{16}$和 $R^{17}$和与它们连接的碳一起形成碳环基或杂环基；

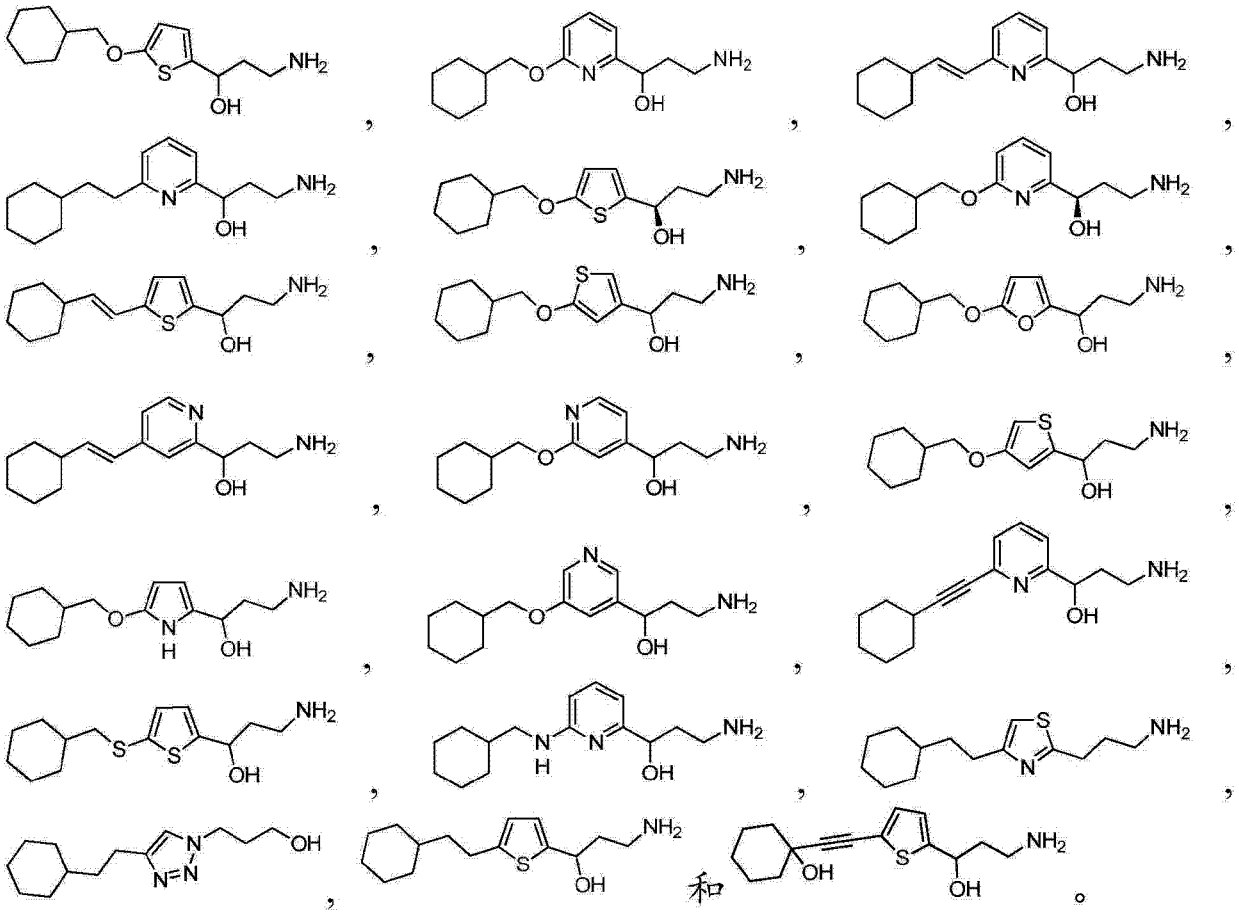
$R^{18}$选自氢、烷基、烷氧基、羟基、卤代或氟代烷基；

X 选自 $-O-C(R^9)_2-$ 或 $-C(R^9)_2-C(R^9)_2-$；且

环 A 为：

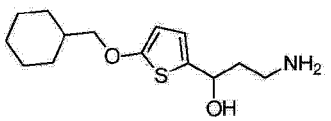
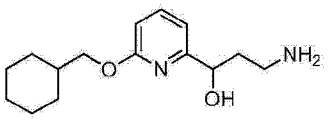
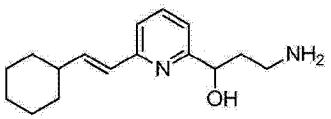
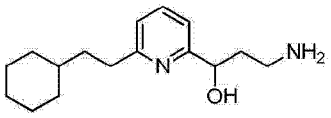
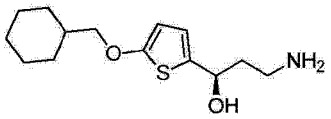


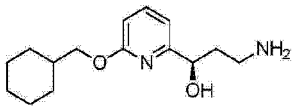
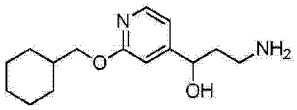
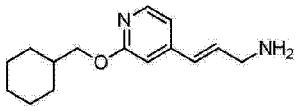
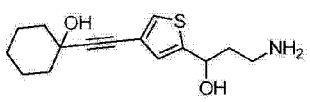
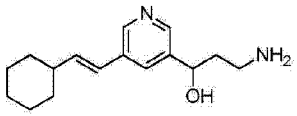
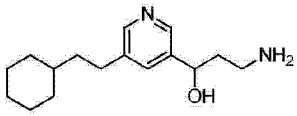
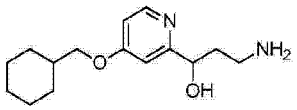
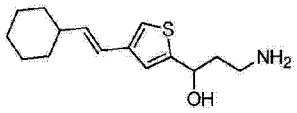
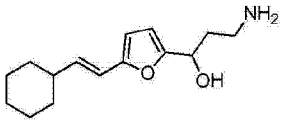
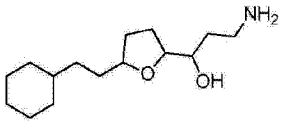
[0139] 一个实施方案提供了一种化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其选自：

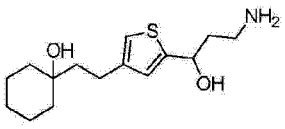
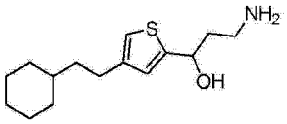
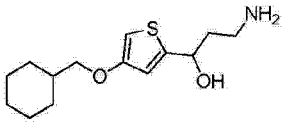
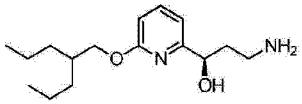
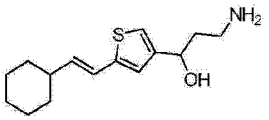
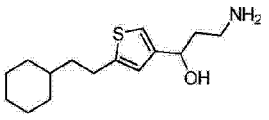
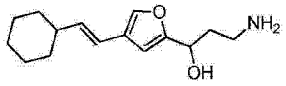
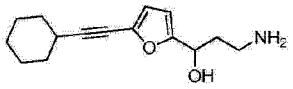
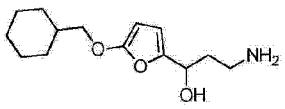
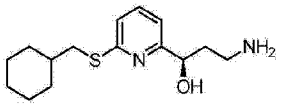


[0140] 在一些实施方案中，本文公开的式 (A) 的化合物具有表 1A 中提供的结构。

表 1A

| 合成实施例 | 结构 | 名称 |
|---|---|---|
| 1 |  | 3-氨基-1-(5-(环己基甲氧基)噻吩-2-基)丙-1-醇 |
| 2 |  | 3-氨基-1-(6-(环己基甲氧基)吡啶-2-基)丙-1-醇 |
| 3 |  | (*E*)-3-氨基-1-(6-(2-环己基乙烯基)吡啶-2-基)丙-1-醇 |
| 4 |  | 3-氨基-1-(6-(2-环己基乙基)吡啶-2-基)丙-1-醇 |
| 5 |  | (*R*)-3-氨基-1-(5-(环己基甲氧基)噻吩-2-基)丙-1-醇 |

| | | |
|---|---|---|
| 6 |  | (*R*)-3-氨基-1-(6-(环己基甲氧基)吡啶-2-基)丙-1-醇 |
| 7 |  | 3-氨基-1-(2-(环己基甲氧基)吡啶-4-基)丙-1-醇 |
| 8 |  | (*E*)-3-(2-(环己基甲氧基)吡啶-4-基)丙-2-烯-1-胺 |
| 9 |  | 1-((5-(3-氨基-1-羟丙基)噻吩-3-基)乙炔基)环己醇 |
| 10 |  | (*E*)-3-氨基-1-(5-(2-环己基乙烯基)吡啶-3-基)丙-1-醇 |
| 11 |  | 3-氨基-1-(5-(2-环己基乙基)吡啶-3-基)丙-1-醇 |
| 12 |  | 3-氨基-1-(4-(环己基甲氧基)吡啶-2-基)丙-1-醇 |
| 13 |  | (*E*)-3-氨基-1-(4-(2-环己基乙烯基)噻吩-2-基)丙-1-醇 |
| 14 |  | (E)-3-氨基-1-(5-(2-环己基乙烯基)呋喃-2-基)丙-1-醇 |
| 15 |  | 3-氨基-1-(5-(2-环己基乙基)四氢呋喃-2-基)丙-1-醇 |

| | | |
|---|---|---|
| 16 |  | 1-(2-(5-(3-氨基-1-羟丙基)噻吩-3-基)乙基)环己醇 |
| 17 |  | 3-氨基-1-(4-(2-环己基乙基)噻吩-2-基)丙-1-醇 |
| 18 |  | 3-氨基-1-(4-(环己基甲氧基)噻吩-2-基)丙-1-醇 |
| 19 |  | (*R*)-3-氨基-1-(6-((2-丙基戊基)氧基)吡啶-2-基)丙-1-醇 |
| 20 |  | (*E*)-3-氨基-1-(5-(2-环己基乙烯基)噻吩-3-基)丙-1-醇 |
| 21 |  | 3-氨基-1-(5-(2-环己基乙基)噻吩-3-基)丙-1-醇 |
| 22 |  | (*E*)-3-氨基-1-(4-(2-环己基乙烯基)呋喃-2-基)丙-1-醇 |
| 23 |  | 3-氨基-1-(5-(环己基乙炔基)呋喃-2-基)丙-1-醇 |
| 24 |  | 3-氨基-1-(5-(环己基甲氧基)呋喃-2-基)丙-1-醇 |
| 25 |  | (*R*)-3-氨基-1-(6-((环己基甲基)硫基)吡啶-2-基)丙-1-醇 |

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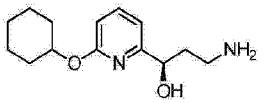
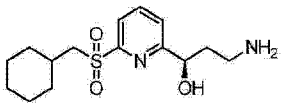
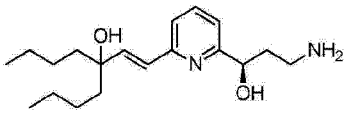
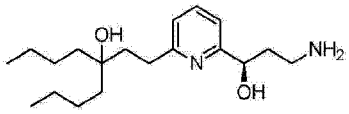
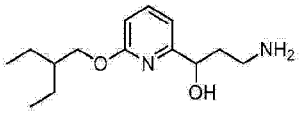
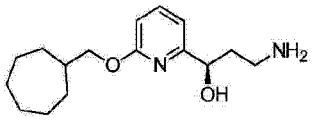
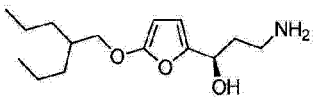
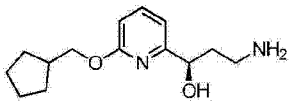
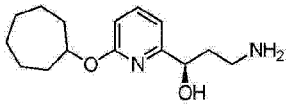
| 26 |  | (*R*)-3-氨基-1-(6-(环己基氧基)吡啶-2-基)丙-1-醇 |
| 27 |  | (*R*)-3-氨基-1-(6-((环己基甲基)磺酰基)吡啶-2-基)丙-1-醇 |
| 28 |  | (*R*,*E*)-5-(2-(6-(3-氨基-1-羟丙基)吡啶-2-基)乙烯基)壬-5-醇 |
| 29 |  | (*R*)-5-(2-(6-(3-氨基-1-羟丙基)吡啶-2-基)乙基)壬-5-醇 |
| 30 |  | 3-氨基-1-(6-(2-乙基丁氧基)吡啶-2-基)丙-1-醇 |
| 31 |  | (*R*)-3-氨基-1-(6-(环庚基甲氧基)吡啶-2-基)丙-1-醇 |
| 32 |  | (*R*)-3-氨基-1-(5-((2-丙基戊基)氧基)呋喃-2-基)丙-1-醇 |
| 33 |  | (*R*)-3-氨基-1-(6-(环戊基甲氧基)吡啶-2-基)丙-1-醇 |
| 34 |  | (*R*)-3-氨基-1-(6-(环庚基氧基)吡啶-2-基)丙-1-醇 |

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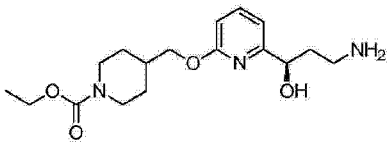
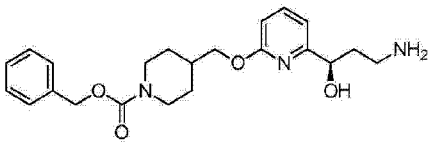
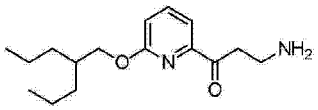
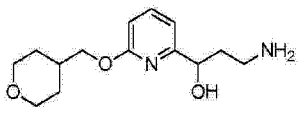
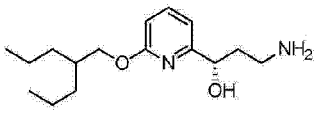
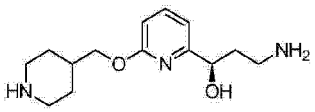
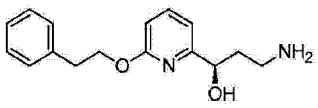
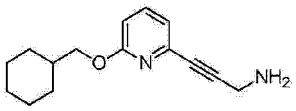
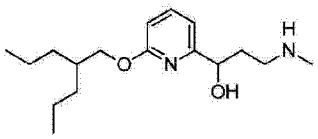
| 35 |  | (*R*)-4-(((6-(3- 氨 基 -1- 羟 丙 基 ) 吡 啶 -2- 基 ) 氧 基 ) 甲 基 ) 哌 啶 -1- 甲酸乙酯 |
| 36 |  | (*R*)-4-(((6-(3- 氨 基 -1- 羟 丙 基 ) 吡 啶 -2- 基 ) 氧 基 ) 甲 基 ) 哌 啶 -1- 甲酸苄酯 |
| 37 |  | 3- 氨 基 -1-(6-((2- 丙 基 戊 基 ) 氧 基 ) 吡 啶 -2- 基 ) 丙 -1- 酮 |
| 38 |  | 3- 氨 基 -1-(6-(( 四 氢 -2*H*- 吡 喃 -4- 基 ) 甲 氧 基 ) 吡 啶 -2- 基 ) 丙 -1- 醇 |
| 39 |  | (*S*)-3- 氨 基 -1-(6-((2- 丙 基 戊 基 ) 氧 基 ) 吡 啶 -2- 基 ) 丙 -1- 醇 |
| 40 |  | (*R*)-3- 氨 基 -1-(6-( 哌 啶 -4- 基 甲 氧 基 ) 吡 啶 -2- 基 ) 丙 -1- 醇 |
| 41 |  | (*R*)-3- 氨 基 -1-(6- 苯 乙 氧 基 吡 啶 -2- 基 ) 丙 -1- 醇 |
| 42 |  | 3-(6-( 环 己 基 甲 氧 基 ) 吡 啶 -2- 基 ) 丙 -2- 炔 -1- 胺 |
| 43 |  | 3-( 甲 基 氨 基 )-1-(6-((2- 丙 基 戊 基 ) 氧 基 ) 吡 啶 -2- 基 ) 丙 -1- 醇 |

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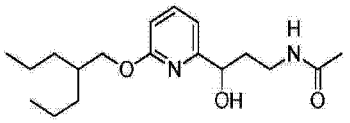
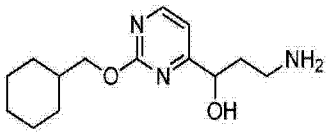
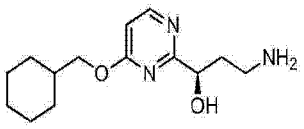
| 44 |  | *N*-(3-羟基-3-(6-((2-丙基戊基)氧基)吡啶-2-基)丙基)乙酰胺 |
| 45 |  | 3-氨基-1-(2-(环己基甲氧基)嘧啶-4-基)丙-1-醇 |
| 46 |  | (R)-3-氨基-1-(4-(环己基甲氧基)嘧啶-2-基)丙-1-醇 |

[0141] 在另一个实施方案中是选自下组的化合物：

3-氨基-1-(5-(环己基甲氧基)噻吩-2-基)丙-1-醇；

3-氨基-1-(6-(环己基甲氧基)吡啶-2-基)丙-1-醇；

(E)-3-氨基-1-(6-(2-环己基乙烯基)吡啶-2-基)丙-1-醇；

3-氨基-1-(6-(2-环己基乙基)吡啶-2-基)丙-1-醇；

(R)-3-氨基-1-(5-(环己基甲氧基)噻吩-2-基)丙-1-醇；

(R)-3-氨基-1-(6-(环己基甲氧基)吡啶-2-基)丙-1-醇；

3-氨基-1-(2-(环己基甲氧基)吡啶-4-基)丙-1-醇；

(E)-3-(2-(环己基甲氧基)吡啶-4-基)丙-2-烯-1-胺；

1-((5-(3-氨基-1-羟丙基)噻吩-3-基)乙炔基)环己醇；

(E)-3-氨基-1-(5-(2-环己基乙烯基)吡啶-3-基)丙-1-醇；

3-氨基-1-(5-(2-环己基乙基)吡啶-3-基)丙-1-醇；

3-氨基-1-(4-(环己基甲氧基)吡啶-2-基)丙-1-醇；

(E)-3-氨基-1-(4-(2-环己基乙烯基)噻吩-2-基)丙-1-醇；

(E)-3-氨基-1-(5-(2-环己基乙烯基)呋喃-2-基)丙-1-醇；

3-氨基-1-(5-(2-环己基乙基)四氢呋喃-2-基)丙-1-醇；

1-(2-(5-(3-氨基-1-羟丙基)噻吩-3-基)乙基)环己醇；

3-氨基-1-(4-(2-环己基乙基)噻吩-2-基)丙-1-醇；

3-氨基-1-(4-(环己基甲氧基)噻吩-2-基)丙-1-醇；

(R)-3-氨基-1-(6-((2-丙基戊基)氧基)吡啶-2-基)丙-1-醇；

(E)-3-氨基-1-(5-(2-环己基乙烯基)噻吩-3-基)丙-1-醇；

3-氨基-1-(5-(2-环己基乙基)噻吩-3-基)丙-1-醇；

(E)-3-氨基-1-(4-(2-环己基乙烯基)呋喃-2-基)丙-1-醇；

3-氨基-1-(5-(环己基乙炔基)呋喃-2-基)丙-1-醇；

3- 氨基 -1-(5-( 环己基甲氧基 ) 呋喃 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-(( 环己基甲基 ) 硫基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-( 环己基氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-(( 环己基甲基 ) 磺酰基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R,E)-5-(2-(6-(3- 氨基 -1- 羟丙基 ) 吡啶 -2- 基 ) 乙烯基 ) 壬 -5- 醇 ;

(R)-5-(2-(6-(3- 氨基 -1- 羟丙基 ) 吡啶 -2- 基 ) 乙基 ) 壬 -5- 醇 ;

3- 氨基 -1-(6-(2- 乙基丁氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-( 环庚基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(5-((2- 丙基戊基 ) 氧基 ) 呋喃 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-( 环戊基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-( 环庚基氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-4-(((6-(3- 氨基 -1- 羟丙基 ) 吡啶 -2- 基 ) 氧基 ) 甲基 ) 哌啶 -1- 甲酸乙酯 ;

(R)-4-(((6-(3- 氨基 -1- 羟丙基 ) 吡啶 -2- 基 ) 氧基 ) 甲基 ) 哌啶 -1- 甲酸苄酯 ;

3- 氨基 -1-(6-((2- 丙基戊基 ) 氧基 ) 吡啶 -2- 基 ) 丙 -1- 酮 ;

3- 氨基 -1-(6-(( 四氢 -2H- 吡喃 -4- 基 ) 甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(S)-3- 氨基 -1-(6-((2- 丙基戊基 ) 氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6-( 哌啶 -4- 基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

(R)-3- 氨基 -1-(6- 苯乙氧基吡啶 -2- 基 ) 丙 -1- 醇 ;

3-(6-( 环己基甲氧基 ) 吡啶 -2- 基 ) 丙 -2- 炔 -1- 胺 ;

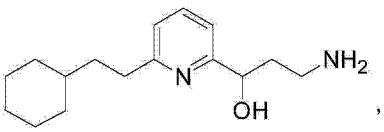
3-( 甲基氨基 )-1-(6-((2- 丙基戊基 ) 氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇 ;

N-(3- 羟基 -3-(6-((2- 丙基戊基 ) 氧基 ) 吡啶 -2- 基 ) 丙基 ) 乙酰胺 ;

3- 氨基 -1-(2-( 环己基甲氧基 ) 嘧啶 -4- 基 ) 丙 -1- 醇 ;和

(R)-3- 氨基 -1-(4-( 环己基甲氧基 ) 嘧啶 -2- 基 ) 丙 -1- 醇。

[0142] 在另一些实施方案中,式 (A) 的化合物选自 :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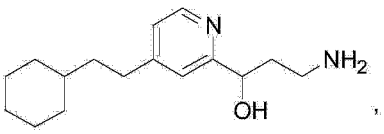
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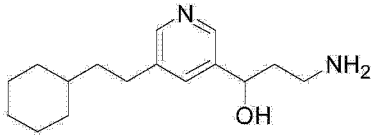
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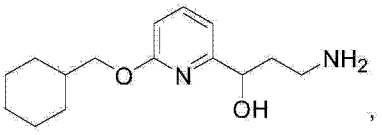
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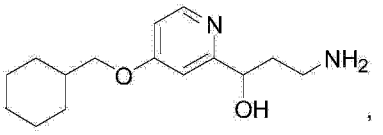
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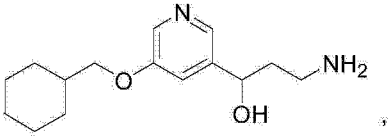
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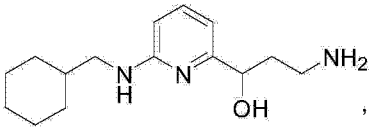
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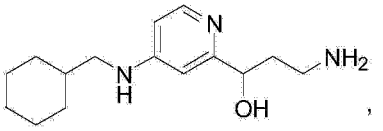
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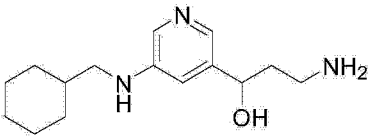
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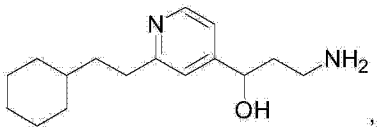
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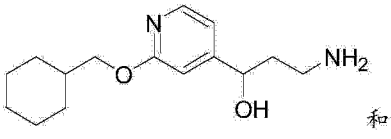
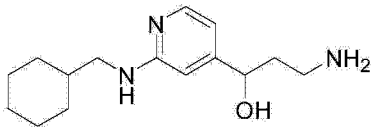
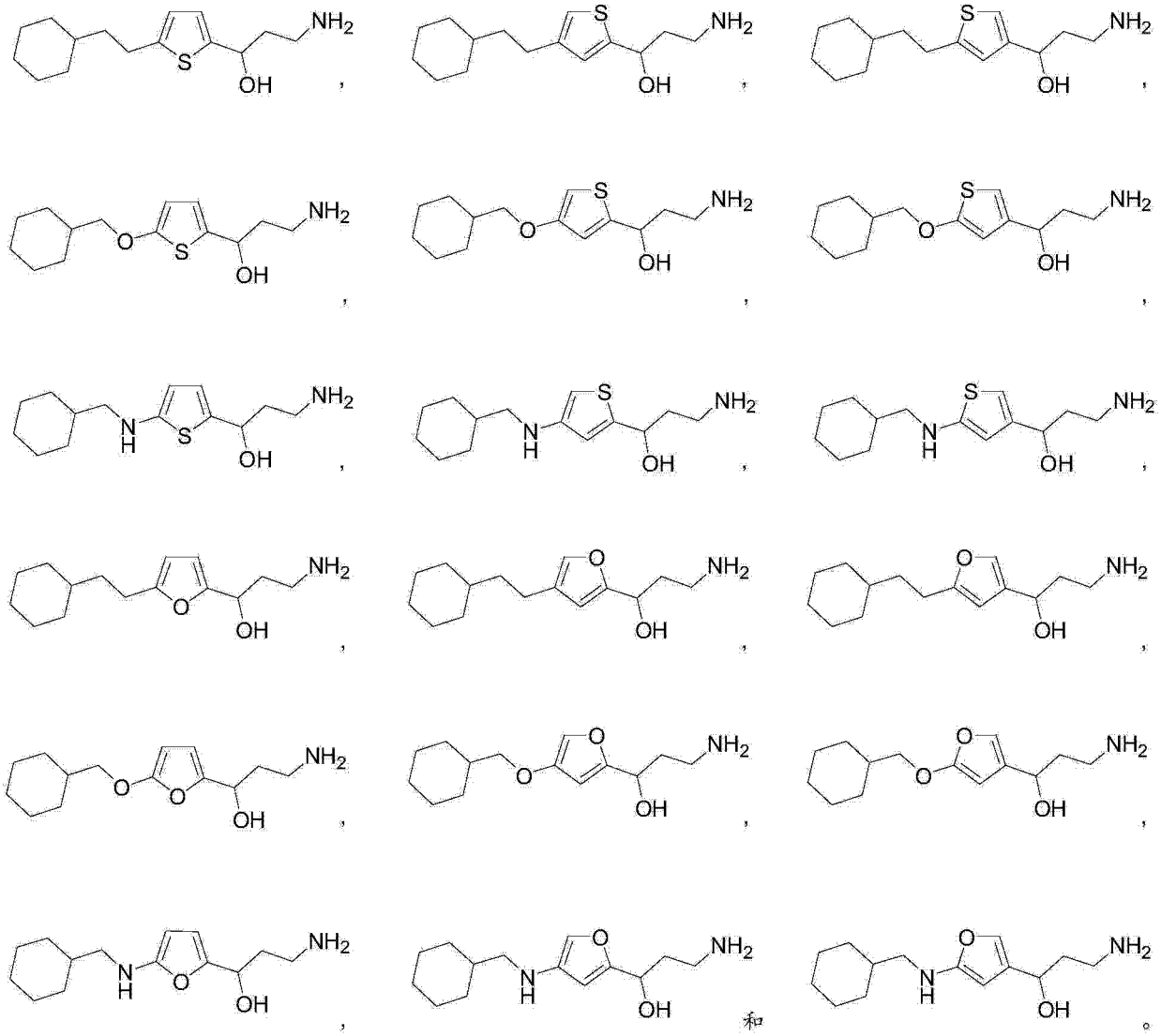
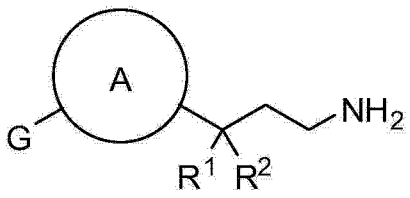

和

。

[0143] 在另一些实施方案中，式 (A) 的化合物选自：



[0144] 一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：



式(B)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

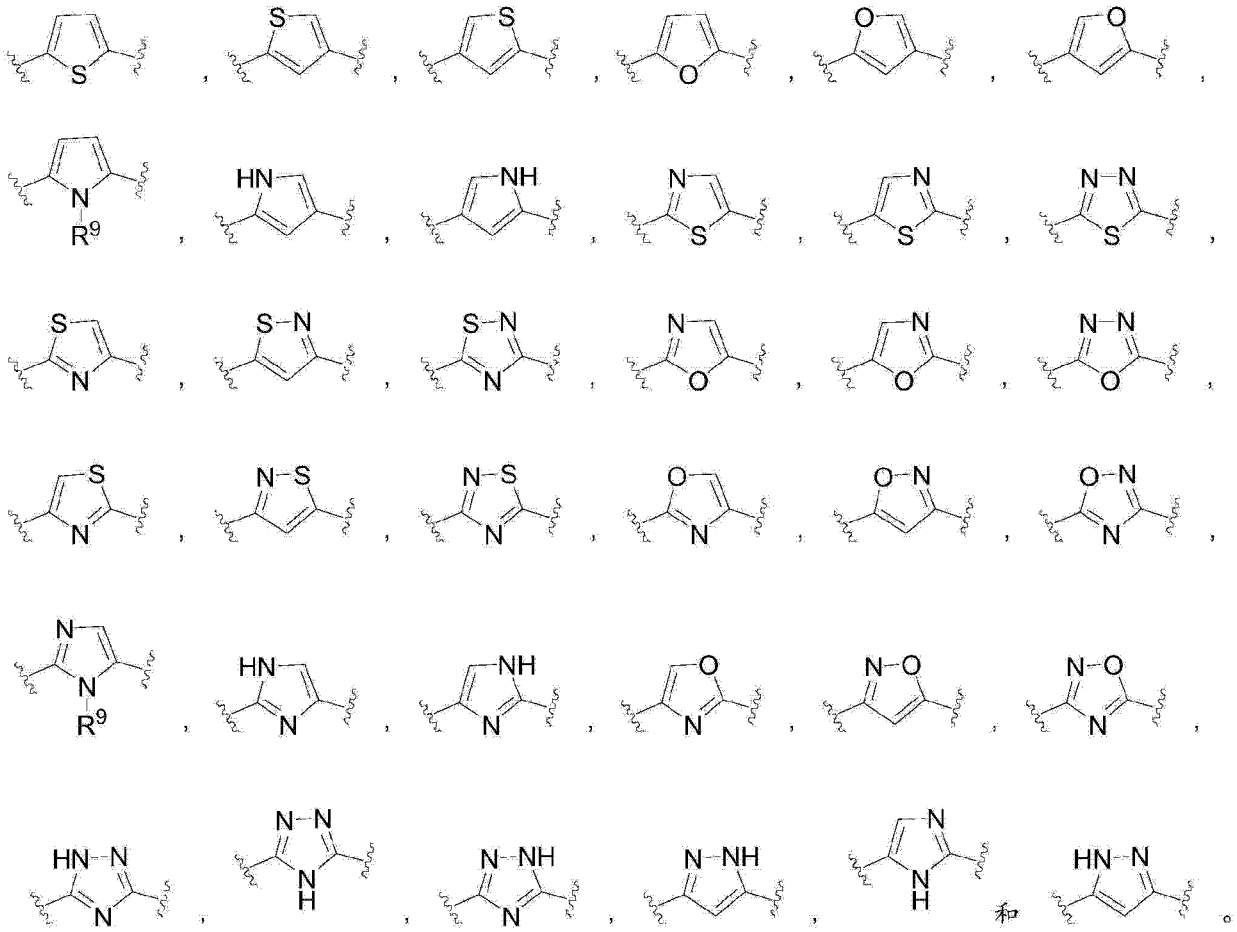
X 选自 -O-、-S-、-NH- 或 $-CH_2-$；

Y 选自碳环基或杂环基；且

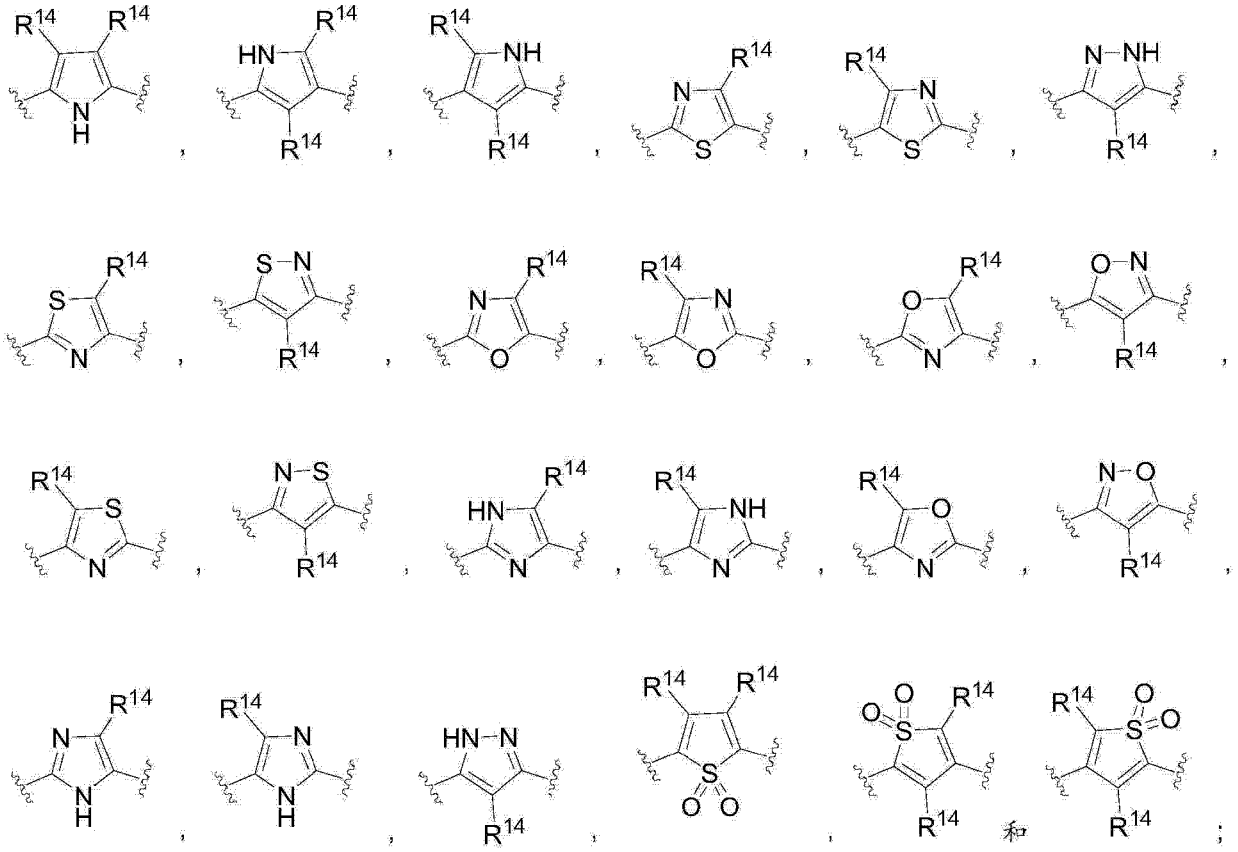
$R^1$和 $R^2$各自独立地选自氢或 -OH；或者 $R^1$和 $R^2$形成氧代基团。

[0145] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实

施方案中，提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

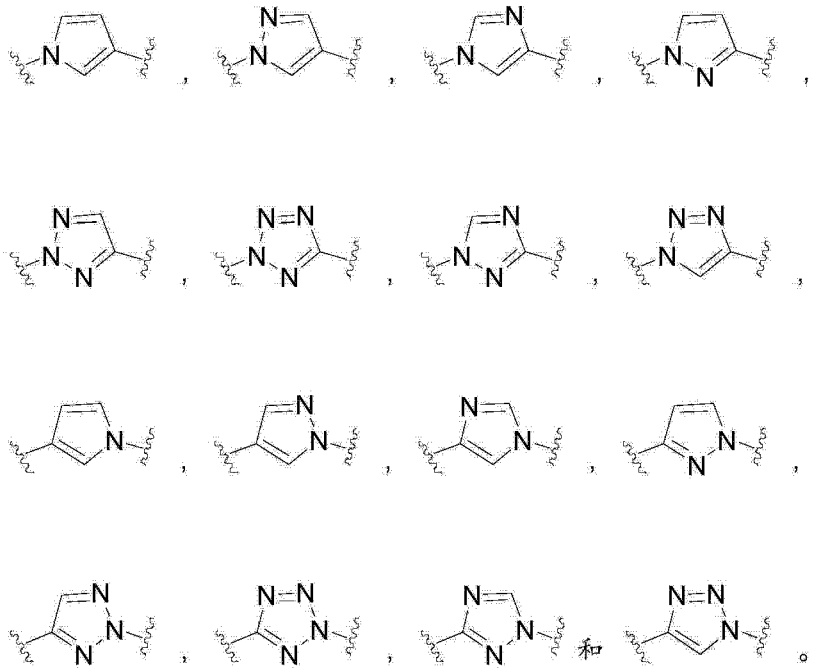


[0146] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

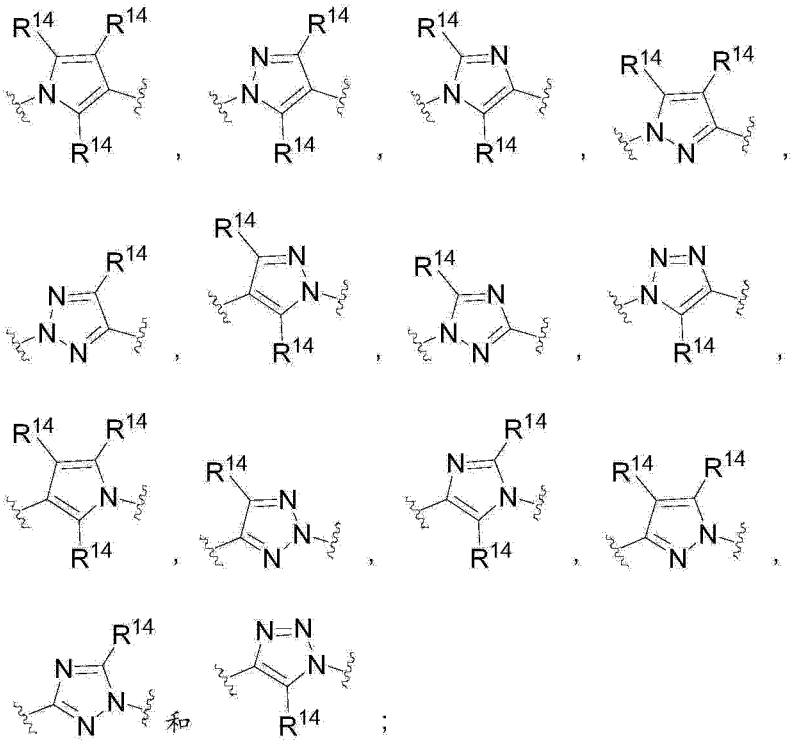


且各 $R^{14}$ 独立地选自氢、卤素、烷基或氟代烷基。

[0147] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

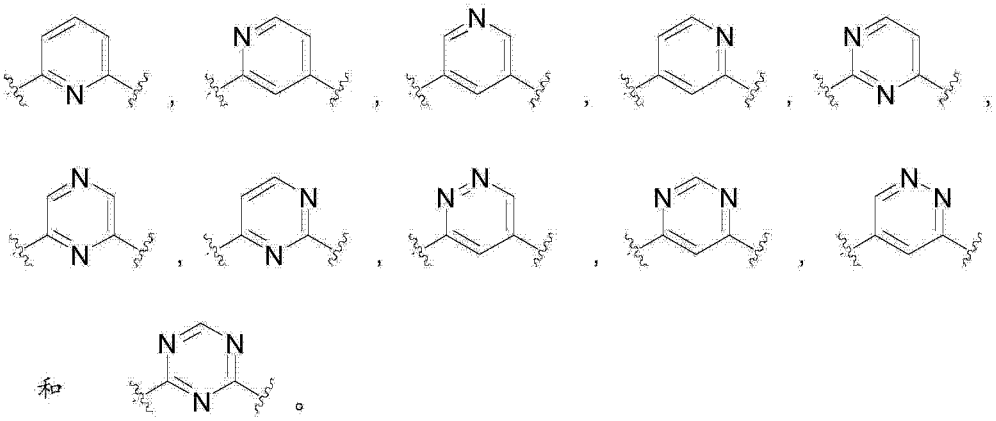


[0148] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

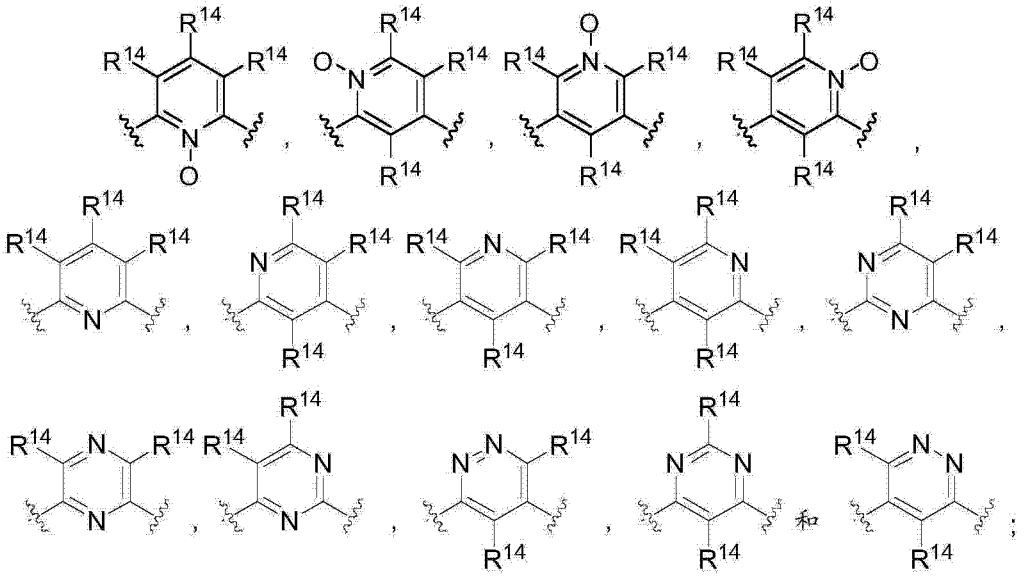


且各 $R^{14}$独立地选自氢、卤素、烷基或氟代烷基。

[0149] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

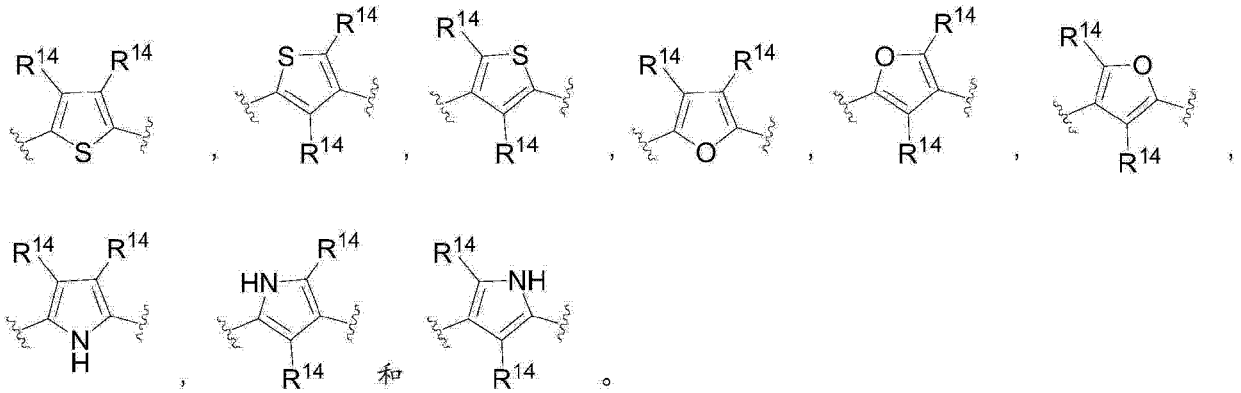


[0150] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

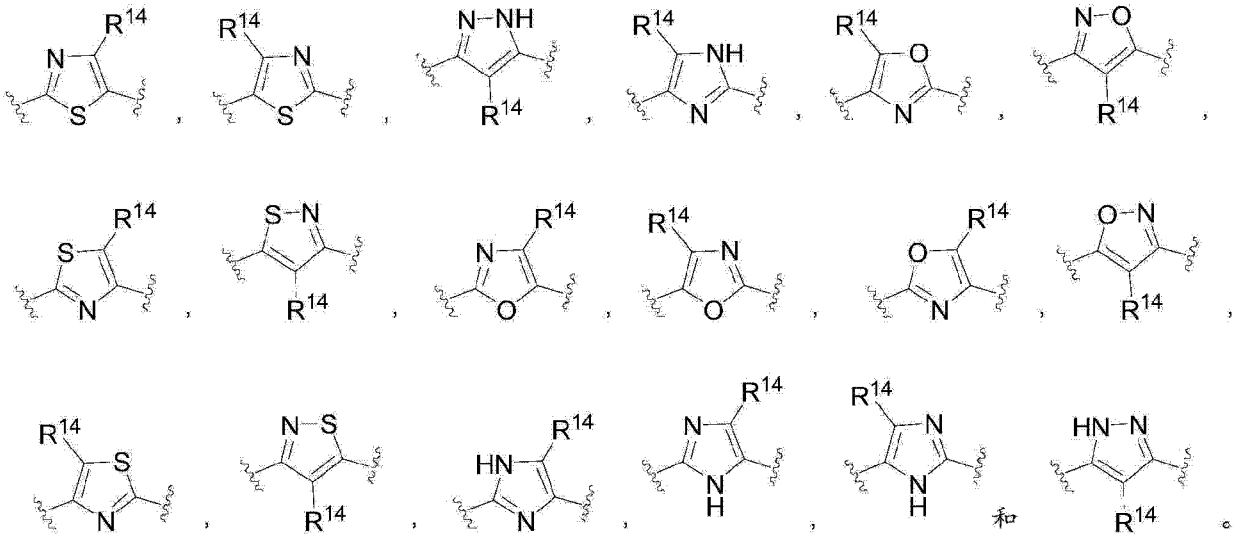


且各 $R^{14}$ 独立地选自氢、卤素、烷基或氟代烷基。

[0151] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

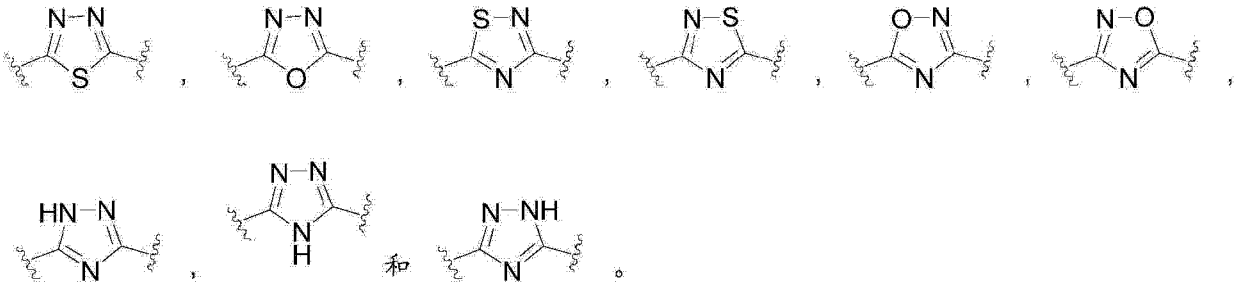


[0152] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：

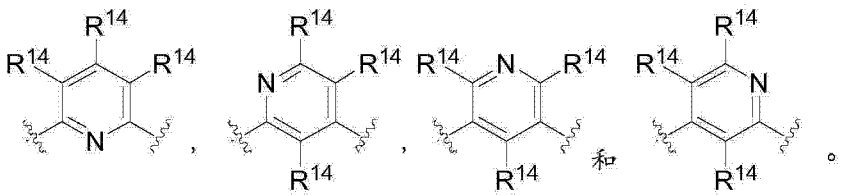


[0153] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构

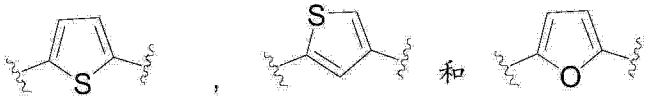
体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



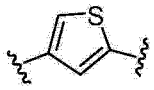
[0154] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



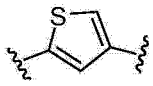
[0155] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 选自：



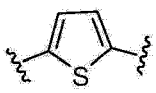
[0156] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



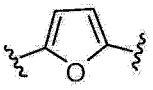
[0157] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



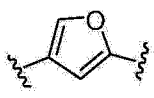
[0158] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



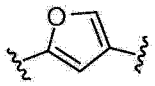
[0159] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



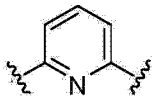
[0160] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



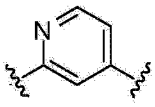
[0161] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



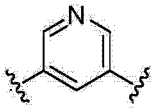
[0162] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



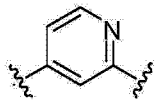
[0163] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



[0164] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



[0165] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中环 A 为：



[0166] 对于任何及所有实施方案，取代基选自所列出的替代基团的子集。例如，在一些实施方案中，提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 4 元、5 元、6 元或 7 元碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为环丁基、环戊基、环己基或环庚基。

[0167] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-。

[0168] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -S-。

[0169] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -NH-。

[0170] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 为 $-CH_2-$。

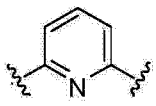
[0171] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，且 Y 为碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，且 Y 为 4 元、5 元、6 元或 7 元碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，且 Y 为环丁基、环戊基、环己基或环庚基。

[0172] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 均为氢。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 均为氢，X 选自 -O-，且 Y 为碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 均为氢，X 选自 -O-，且 Y 为 4 元、5 元、6 元或 7 元碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 均为氢，X 选自 -O-，且 Y 为环丁基、环戊基、环己基或环庚基。

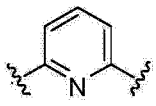
[0173] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 为氢且 $R^2$ 为 -OH。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 为氢且 $R^2$ 为 -OH，X 选自 -O-，且 Y 为碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 为氢且 $R^2$ 为 -OH，X 选自 -O-，且 Y 为 4 元、5 元、6 元或 7 元碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 为氢且 $R^2$ 为 -OH，X 选自 -O-，且 Y 为环丁基、环戊基、环己基或环庚基。

[0174] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 一起形成氧代基团。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 一起形成氧代基团，X 选自 -O-，且 Y 为碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 一起形成氧代基团，X 选自 -O-，且 Y 为 4 元、5 元、6 元或 7 元碳环基。另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 和 $R^2$ 一起形成氧代基团，X 选自 -O-，且 Y 为 4 元、5 元、6 元或 7 元碳环基。

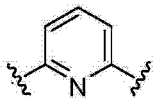
[0175] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，且环 A 为：



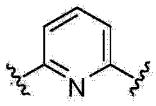
[0176] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为碳环基，且环 A 为：



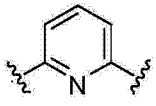
[0177] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为 4 元、5 元、6 元或 7 元碳环基，且环 A 为：



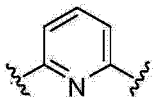
[0178] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 Y 为环丁基、环戊基、环己基或环庚基，且环 A 为：



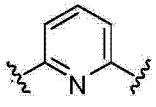
[0179] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，Y 为碳环基，且环 A 为：



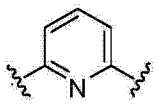
[0180] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，Y 为 4 元、5 元、6 元或 7 元碳环基，且环 A 为：



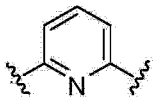
[0181] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 X 选自 -O-，Y 为环丁基、环戊基、环己基或环庚基，且环 A 为：



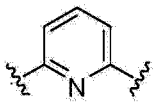
[0182] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中 $R^1$ 为氢，$R^2$ 为 -OH，X 选自 -O-，Y 为碳环基，且环 A 为：



[0183] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或N-氧化物，其中$R^1$为氢，$R^2$为 -OH，X选自 -O-，Y 为 4 元、5 元、6 元或 7 元碳环基，且环 A 为：



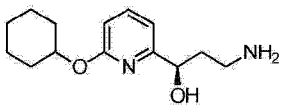
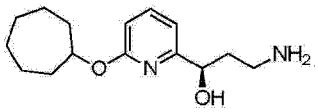
[0184] 另一个实施方案提供了式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或N-氧化物，其中$R^1$为氢，$R^2$为 -OH，X选自 -O-，Y 为环丁基、环戊基、环己基或环庚基，且环 A 为：



[0185] 在此考虑到以上对于各种变量所描述的基团的任意组合。在整个说明书中，基团及其取代基由本领域技术人员选择，以提供稳定的部分和化合物。

[0186] 在一些实施方案中，本文公开的式 (B) 的化合物具有表 1B 中提供的结构。

表 1B

| 合成实施例 | 结构 | 名称 |
|---|---|---|
| 26 |  | (*R*)-3-氨基-1-(6-(环己基氧基)吡啶-2-基)丙-1-醇 |
| 34 |  | (*R*)-3-氨基-1-(6-(环庚基氧基)吡啶-2-基)丙-1-醇 |

取代的杂环胺衍生物化合物的制备

[0187] 在本文描述的反应中所使用的化合物是从市售的化学品和/或从在化学文献中描述的化合物开始，根据本领域技术人员熟知的有机合成技术制备的。“市售的化学品”是从标准商业来源得到的，包括 Acros Organics(Pittsburgh PA)、Aldrich Chemical(Milwaukee WI，包括 Sigma Chemical 和 Fluka)、Apin Chemicals Ltd.(Milton Park UK)、Avocado Research(Lancashire U.K.)、BDH Inc.(Toronto,Canada)、Bionet(Cornwall,U.K.)、Chemservice Inc.(West Chester PA)、Crescent Chemical Co.(Hauppauge NY)、Eastman Organic Chemicals、Eastman Kodak Company(Rochester NY)、Fisher Scientific Co.(Pittsburgh PA)、Fisons Chemicals(Leicestershire UK)、Frontier Scientific(Logan UT)、ICN Biomedicals,Inc.(Costa Mesa CA)、Key

Organics(Cornwall U.K.)、Lancaster Synthesis(Windham NH)、Maybridge Chemical Co.Ltd.(Cornwall U.K.)、Parish Chemical Co.(Orem UT)、Pfaltz&Bauer,Inc.(Waterbury CN)、Polyorganix(Houston TX)、Pierce Chemical Co.(Rockford IL)、Riedel de Haen AG(Hanover,Germany)、Spectrum Quality Product,Inc.(New Brunswick,NJ)、TCI America(Portland OR)、Trans World Chemicals,Inc.(Rockville MD) 和 Wako Chemicals USA,Inc.(Richmond VA)。

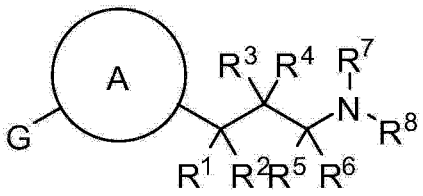
[0188] 通过各种参考书和数据库确认本领域普通技术人员已知的方法。详述了在本文所述化合物的制备中有用的反应物的合成或对描述这种制备的文章提供参考的合适的参考书和论文包括,例如,"Synthetic Organic Chemistry",John Wiley&Sons,Inc.,New York;S.R.Sandler 等,"Organic Functional Group Preparations,"2nd Ed.,Academic Press,New York,1983;H.O.House,"Modern Synthetic Reactions",2nd Ed.,W.A.Benjamin,Inc.Menlo Park,Calif.1972;T.L.Gilchrist,"Heterocyclic Chemistry",2nd Ed.,John Wiley&Sons,New York,1992;J.March,"Advanced Organic Chemistry:Reactions,Mechanisms and Structure",4th Ed.,Wiley-Interscience,New York,1992。详述了在本文所述化合物的制备中有用的反应物的合成或对描述了这种制备的文章提供参考的其它合适的参考书和论文包括,例如 Fuhrhop,J. 和 Penzlin G."Organic Synthesis:Concepts,Methods,Starting Materials",Second,Revised and Enlarged Edition(1994)John Wiley&Sons ISBN:3-527-29074-5;Hoffman,R.V."Organic Chemistry,An Intermediate Text"(1996)Oxford University Press,ISBN 0-19-509618-5;Larock,R.C."Comprehensive Organic Transformations:A Guide to Functional Group Preparations"2nd Edition(1999)Wiley-VCH,ISBN:0-471-19031-4;March,J."Advanced Organic Chemistry:Reactions,Mechanisms,and Structure"4th Edition(1992)John Wiley&Sons,ISBN:0-471-60180-2;Otera,J.(编 者)"Modern Carbonyl Chemistry"(2000)Wiley-VCH,ISBN:3-527-29871-1;Patai,S."Patai's 1992Guide to the Chemistry of Functional Groups"(1992)Interscience ISBN:0-471-93022-9;Quin,L.D. 等,"A Guide to Organophosphorus Chemistry"(2000)Wiley-Interscience,ISBN:0-471-31824-8;Solomons,T.W.G."Organic Chemistry"7th Edition(2000)John Wiley&Sons,ISBN:0-471-19095-0;Stowell,J.C.,"Intermediate Organic Chemistry"2nd Edition(1993)Wiley-Interscience,ISBN:0-471-57456-2;"Industrial Organic Chemicals:Starting Materials and Intermediates:An Ullmann's Encyclopedia"(1999)John Wiley&Sons,ISBN:3-527-29645-X,8 卷;"Organic Reactions"(1942-2000)John Wiley&Sons,55 卷; 和 "Chemistry of Functional Groups"John Wiley&Sons,73 卷。

[0189] 具体的和类似的反应物也可以通过由美国化学学会的化学文摘服务(Chemical Abstract Service of the American Chemical Society)提供的已知化学品索引进行确认,该服务在大多数公共图书馆和大学图书馆中可以获得,也可以通过在线数据库获得(可以联系美国化学学会,Washington,D.C. 获得更多信息)。已知的但尚无法在目录上商购获得的化学品可以由专门订制化学品合成机构制备,其中,许多标准化学药品供应机构(例如,上面列出的那些)提供订制合成服务。用于制备和选择本文描述的取代的杂

环胺衍生物化合物的药用盐的一份参考文献是 P. H. Stahl&C. G. Wermuth “Handbook of Pharmaceutical Salts”, Verlag Helvetica Chimica Acta, Zurich, 2002。

眼科疾病和病症的治疗

[0190] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3$-$C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1$-$C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0191] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其中，该眼科疾病或病症为年龄相关性黄斑变性或斯塔加特氏黄斑营养不良。

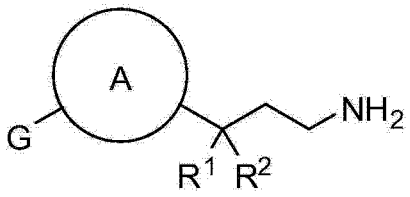
[0192] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其中，该眼科疾病或病症选自视网膜脱落、出血性视网膜病、色素性视网膜炎、视锥 - 视杆营养不良、Sorsby 眼底营养不良、视神经病变、炎性视网膜病、糖尿病视网膜病变、糖尿病性斑丘疹病、

视网膜血管闭塞、早产儿视网膜病、或缺血再灌注相关性视网膜损伤、增生性玻璃体视网膜病、视网膜营养性萎缩、遗传性视神经病、葡萄膜炎、视网膜损伤、与阿尔茨海默病相关的视网膜病症、与多发性硬化症相关的视网膜病症、与帕金森病相关的视网膜病症、与病毒感染相关的视网膜病症、与光暴露过度相关的视网膜病症、近视以及与 AIDS 相关的视网膜病症。

[0193] 另一实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其导致受试者眼睛中积聚的脂褐质色素的减少。

[0194] 另一实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其导致受试者眼睛中积聚的脂褐质色素的减少，其中，该脂褐质色素为 N- 亚视黄基 -N- 视黄基 - 乙醇胺 (A2E)。

[0195] 一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 ：




式(B)

其中，

环 A 选自 1,3- 二取代的杂环 ；

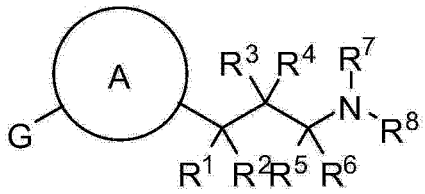
G 为 - X-Y ；

X 选自 - O-、-S-、-NH- 或 $-CH_2-$ ；

Y 选自碳环基或杂环基 ；且

$R^1$和 $R^2$各自独立地选自氢或 -OH ；或者 $R^1$和 $R^2$形成氧代基团。另一个实施方案提供了一种治疗受试者的眼科疾病或病症的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中所述眼科疾病或病症为年龄相关性黄斑变性或斯塔加特氏黄斑营养不良。

[0196] 一个实施方案提供了一种调节类视黄醇循环中的生色团通量的方法，该方法包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 ：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环 ；

G 为 -X-Y ;

X 选自 -O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O- 和 -C($R^9$)$_2$-$NR^9$- ;

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基 ;

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基 ;或者 $R^1$和 $R^2$形成氧代基团 ;或者任选地,$R^1$和 $R^3$一起形成直接键以提供双键 ;或者任选地,$R^1$和 $R^3$一起形成直接键,且 $R^2$和 $R^4$一起形成直接键以提供三键 ;

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或 -$NR^{10}R^{11}$;或者 $R^3$和 $R^4$一起形成氧代基团 ;

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基 ;或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基 ;或者 $R^5$和 $R^6$一起形成亚氨基 ;

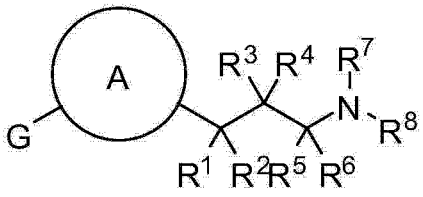
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基 ;

各 $R^9$独立地为氢或烷基 ;

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基 ;且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0197] 一个实施方案提供了一种抑制视网膜的视杆细胞的暗适应的方法,该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :




式(A)

其中,

环 A 选自 1,3- 二取代的杂环 ;

G 为 -X-Y ;

X 选自 -O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O- 和 -C($R^9$)$_2$-$NR^9$- ;

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基 ;

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基 ;或者 $R^1$和 $R^2$形成氧代基团 ;或者任选地,$R^1$和 $R^3$一起形成直接键以提供双键 ;或者任选地,$R^1$和 $R^3$一起

形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或 -$NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

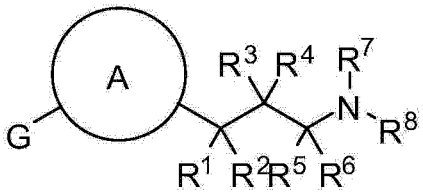
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0198] 一个实施方案提供了一种抑制视网膜的视杆细胞中的视紫质再生的方法，该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 -O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O- 和 -C($R^9$)$_2$-$NR^9$-；

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或 -$NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

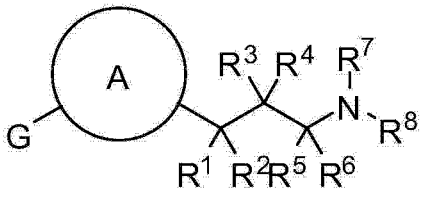
$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0199] 一个实施方案提供了一种减轻受试者眼睛中的局部缺血的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基；或者 $R^1$和 $R^2$形成氧代基团；或者任选地，$R^1$和 $R^3$一起形成直接键以提供双键；或者任选地，$R^1$和 $R^3$一起形成直接键，且 $R^2$和 $R^4$一起形成直接键以提供三键；

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、$-OR^9$或 $-NR^{10}R^{11}$；或者 $R^3$和 $R^4$一起形成氧代基团；

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

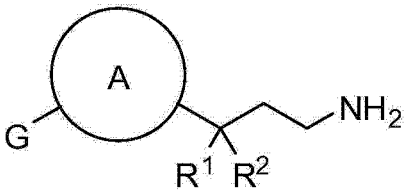
各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0200] 另一实施方案提供了一种减轻受试者眼睛中的局部缺血的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中该药物组合物在足以抑制视杆细胞的暗适应的条件和时间下施用，从而减轻眼睛中的局部缺血。

[0201] 一个实施方案提供了一种调节类视黄醇循环中的生色团通量的方法，该方法包括向受试者施用一种药物组合物，该药物组合物包含式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 ：




式(B)

其中，

环 A 选自 1,3- 二取代的杂环 ；

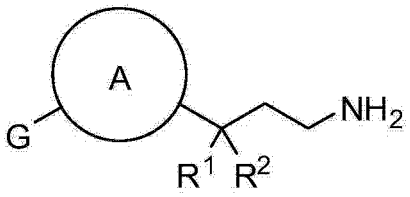
G 为 -X-Y ；

X 选自 -O-、-S-、-NH- 或 $-CH_2-$ ；

Y 选自碳环基或杂环基 ；且

$R^1$和 $R^2$各自独立地选自氢或 -OH ；或者 $R^1$和 $R^2$形成氧代基团。

[0202] 一个实施方案提供了一种抑制视网膜的视杆细胞的暗适应的方法，该方法包括使视网膜接触式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 ：




式(B)

其中，

环 A 选自 1,3- 二取代的杂环 ；

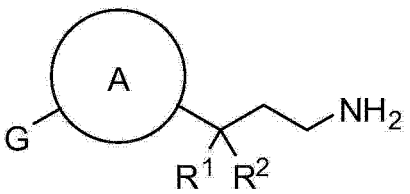
G 为 -X-Y ；

X 选自 -O-、-S-、-NH- 或 $-CH_2-$ ；

Y 选自碳环基或杂环基 ；且

$R^1$和 $R^2$各自独立地选自氢或 -OH ；或者 $R^1$和 $R^2$形成氧代基团。

[0203] 一个实施方案提供了一种抑制视网膜的视杆细胞中的视紫质再生的方法，该方法包括使视网膜接触式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 ：




式(B)

其中，

环 A 选自 1,3- 二取代的杂环 ;

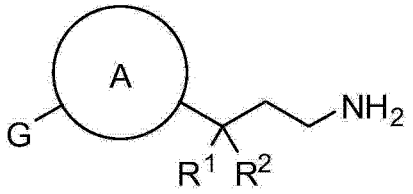
G 为 -X-Y ;

X 选自 -O-、-S-、-NH- 或 $-CH_2-$ ;

Y 选自碳环基或杂环基 ;且

$R^1$和 $R^2$各自独立地选自氢或 -OH ;或者 $R^1$和 $R^2$形成氧代基团。

[0204] 一个实施方案提供了一种减轻受试者眼睛中的局部缺血的方法,其包括向受试者施用一种药物组合物,该药物组合物包含式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :




式(B)

其中,

环 A 选自 1,3- 二取代的杂环 ;

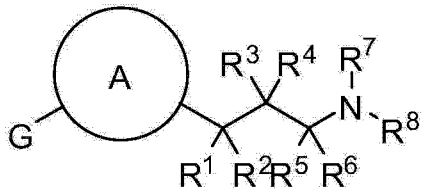
G 为 -X-Y ;

X 选自 -O-、-S-、-NH- 或 $-CH_2-$ ;

Y 选自碳环基或杂环基 ;且

$R^1$和 $R^2$各自独立地选自氢或 -OH ;或者 $R^1$和 $R^2$形成氧代基团。

[0205] 一个实施方案提供了一种抑制受试者眼睛的视网膜中的新生血管形成的方法,其包括向受试者施用一种药物组合物,该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :




式(A)

其中,

环 A 选自 1,3- 二取代的杂环 ;

G 为 -X-Y ;

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$ ;

Y 选自 $C_3-C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基 ;

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$或碳环基 ;或者 $R^1$和 $R^2$形成氧代基团 ;或者任选地,$R^1$和 $R^3$一起形成直接键以提供双键 ;或者任选地,$R^1$和 $R^3$一起形成直接键,且 $R^2$和 $R^4$一起形成直接键以提供三键 ;

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$和 $R^6$一起形成亚氨基；

$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基；

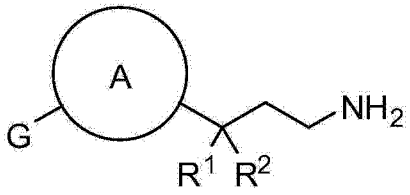
各 $R^9$独立地为氢或烷基；

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0206] 一个实施方案提供了一种抑制受试者眼睛的视网膜中的新生血管形成的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物，其中该药物组合物在足以抑制视杆细胞的暗适应的条件和时间下施用，从而抑制视网膜中的新生血管形成。

[0207] 一个实施方案提供了一种抑制受试者眼睛的视网膜中的新生血管形成的方法，其包括向受试者施用一种药物组合物，该药物组合物包含式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(B)

其中，

环 A 选自 1,3- 二取代的杂环；

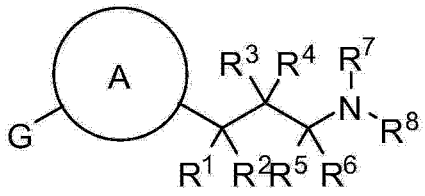
G 为 -X-Y；

X 选自 -O-、-S-、-NH- 或 $-CH_2-$；

Y 选自碳环基或杂环基；且

$R^1$和 $R^2$各自独立地选自氢或 -OH；或者 $R^1$和 $R^2$形成氧代基团。

[0208] 一个实施方案提供了一种抑制视网膜中的视网膜细胞变性的方法，该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y ;

X 选自 -O-C($R^9$)$_2$-、-O-C(=O)-、-S-C($R^9$)$_2$-、-S(O)-C($R^9$)$_2$-、-S(O)$_2$-C($R^9$)$_2$-、-$SO_2$($NR^9$)-、-$NR^9$-C($R^9$)$_2$-、-$NR^9$-C(=O)-、-$NR^9$-S(O)$_2$-、-C($R^9$)$_2$-C($R^9$)$_2$-、-C(=O)-C($R^9$)$_2$-、-C($R^9$)$_2$-C(=O)-、-C($R^9$)=C($R^9$)-、-C≡C-、-C(=O)-N($R^9$)-、-C(=O)-O-、-C($R^9$)$_2$-O- 和 -C($R^9$)$_2$-$NR^9$- ;

Y 选自 $C_3$-$C_{15}$烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基 ;

$R^1$和 $R^2$各自独立地选自氢、卤素、烷基、氟代烷基、-$OR^9$、-$NR^{10}R^{11}$或碳环基 ;或者 $R^1$和 $R^2$形成氧代基团 ;或者任选地,$R^1$和 $R^3$一起形成直接键以提供双键 ;或者任选地,$R^1$和 $R^3$一起形成直接键,且 $R^2$和 $R^4$一起形成直接键以提供三键 ;

$R^3$和 $R^4$各自独立地选自氢、卤素、$C_1$-$C_5$烷基、氟代烷基、-$OR^9$或 -$NR^{10}R^{11}$;或者 $R^3$和 $R^4$一起形成氧代基团 ;

$R^5$和 $R^6$各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基 ;或者 $R^5$和 $R^6$和与它们连接的碳原子一起形成碳环基或杂环基 ;或者 $R^5$和 $R^6$一起形成亚氨基 ;

$R^7$和 $R^8$各自独立地选自氢、烷基、碳环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^7$和 $R^8$和与它们连接的氮原子一起形成 N- 杂环基 ;

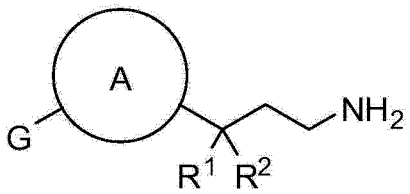
各 $R^9$独立地为氢或烷基 ;

各 $R^{10}$和 $R^{11}$独立地选自氢、烷基、碳环基、杂环基、-C(=O)$R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$或 $SO_2NR^{10}R^{11}$;或者 $R^{10}$和 $R^{11}$和与它们连接的氮原子一起形成 N- 杂环基 ;且

各 $R^{13}$独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0209] 一个实施方案提供了一种抑制视网膜中的视网膜细胞变性的方法,该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物,其中该视网膜细胞为视网膜神经元细胞。一个实施方案提供了一种抑制视网膜中的视网膜细胞变性的方法,该方法包括使视网膜接触式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物,其中该视网膜神经元细胞为感光细胞。

[0210] 一个实施方案提供了一种抑制视网膜中的视网膜细胞变性的方法,该方法包括使视网膜接触式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物 :




式(B)

其中,

环 A 选自 1,3- 二取代的杂环 ;

G 为 -X-Y ;

X 选自 -O-、-S-、-NH- 或 $-CH_2-$ ;

Y 选自碳环基或杂环基；且

$R^1$和 $R^2$各自独立地选自氢或 -OH；或者 $R^1$和 $R^2$形成氧代基团。

[0211] 本文详细描述的取代的杂环胺衍生物化合物，包括具有如式 (A) 或式 (B) 所示的结构及其子结构的化合物，以及本文所述的可用于治疗眼科疾病或病症的具体的取代的杂环胺化合物，抑制视觉循环中的一个或多个步骤，例如，通过抑制或阻断视觉循环反式 - 顺式异构酶（还包括视觉循环反式 - 顺式异构水解酶 (isomerohydrolase)）的功能性活动。本文描述的化合物抑制、阻断或者以某种方式干扰视觉循环中的异构化步骤。在具体的实施方案中，所述化合物抑制全反式视黄基酯的异构化；在某些实施方案中，该全反式视黄基酯为全反式 - 视黄醇的脂肪酸酯，并且该化合物抑制全反式 - 视黄醇向 11- 顺式 - 视黄醇的异构化。该化合物与至少一种视觉循环异构酶结合，或者以某种方式与之相互作用，并抑制其异构酶活性，该异构酶在本文中和在本领域内也被称作视黄醛异构酶或异构水解酶。该化合物阻断或抑制全反式 - 视黄基酯底物与异构酶的结合。可替代地，或此外，该化合物与异构酶的催化部位或区域结合，从而抑制该酶催化全反式 - 视黄基酯底物的异构化的能力。基于迄今为止的科学数据，认为至少一种催化全反式 - 视黄基酯的异构化的异构酶位于 RPE 细胞的细胞质中。如本文所述的，视觉循环的各个步骤、酶、底物、中间体和产物尚未阐明（参见，例如，Moiseyev 等，Proc. Natl. Acad. Sci. USA102:12413-18(2004)；Chen 等，Invest. Ophthalmol. Vis. Sci. 47:1177-84(2006)；Lamb 等，同上）。

[0212] 如本文和本领域所述，用于测定化合物对异构酶活性的影响的方法在体外进行 (Stecher 等，J Biol Chem 274:8577-85(1999)；另外参见 Golczak 等，Proc. Natl. Acad. Sci. USA 102:8162-67(2005))。从动物（例如，牛、猪、人）中分离的视网膜色素上皮 (RPE) 微粒体膜可以用作异构酶的来源。取代的杂环胺衍生物化合物抑制异构酶的能力也通过体内鼠异构酶试验来测定。已知眼睛短暂暴露于强光（视色素的“光漂白”，或简称为“漂白”）会使视网膜中几乎所有的 11- 顺式 - 视黄醛发生光致异构化。11- 顺式 - 视黄醛在漂白后的恢复可以用来评估体内异构酶的活性（参见，例如，Maeda 等，J. Neurochem 85:944-956(2003)；Van Hooser 等，J Biol Chem 277:19173-82,2002)。如前所述 (Haeseleer 等，Nat. Neurosci. 7:1079-87(2004)；Sugitomo 等，J. Toxicol. Sci. 22Suppl 2:315-25(1997)；Keating 等，Documenta Ophthalmologica 100:77-92(2000))，可以进行视网膜电流图 (ERG) 记录 (electroretinographic recording)。也参见 Deigner 等，Science, 244:968-971(1989)；Gollapalli 等，Biochim Biophys Acta. 1651:93-101(2003)；Parish, 等，Proc. Natl. Acad. Sci. USA 95:14609-13(1998)；Radu, 等，Proc Natl Acad Sci USA 101:5928-33(2004))。在某些实施方案中，如在本文所述的或者本领域公知的异构酶试验中所测定的，可用于治疗患有本文所述的任意一种眼科和视网膜疾病或病症的受试者或者具有患上述疾病的风险的受试者的化合物具有小于约 1μM 的 $IC_{50}$水平（异构酶活性的 50％受到抑制时的化合物浓度）；在其它一些实施方案中，测定的 $IC_{50}$水平小于约 10nM；在其它一些实施方案中，测定的 $IC_{50}$水平小于约 50nM；在其它某些实施方案中，测定的 $IC_{50}$水平小于约 100nM；在其它某些实施方案中，测定的 $IC_{50}$水平小于约 10μM；在其它一些实施方案中，测定的 $IC_{50}$水平小于约 50μM；在其它某些实施方案中，测定的 $IC_{50}$水平小于约 100μM 或约 500μM；在其它实施方案中，测定的 $IC_{50}$水平在约 1μM 至 10μM 之间；在其它实施方案中，测定的 IC50 水平在约 1nM 至 10nM 之间。

当施用于受试者时，如通过抑制导致产生 11- 顺式视黄醇的异构酶反应所确定的，一种或多种本发明的化合物显示出约 5mg/kg、5mg/kg 或更低的 $ED_{50}$ 值。在一些实施方案中，当施用于受试者时，本发明的化合物具有约 1mg/kg 的 $ED_{50}$ 值。在其它一些实施方案中，当施用于受试者时，本发明的化合物具有约 0.1mg/kg 的 $ED_{50}$ 值。可以在将该化合物或其药物组合物施用于受试者约 2 小时、4 小时、6 小时、8 小时或更长时间后测量 $ED_{50}$ 值。

[0213] 本文描述的化合物可用于治疗患有眼科疾病或病症（特别是诸如年龄相关性黄斑变性或斯塔加特氏黄斑营养不良的视网膜疾病或病症）的受试者。在一个实施方案中，本文描述的化合物抑制（即，阻止、减少、减缓、消除或最小化）眼睛中脂褐质色素和脂褐质有关的和 / 或相关的分子的积聚。在另一实施方案中，所述化合物抑制（即，阻止、减少、减缓、消除或最小化）眼睛中 N- 亚视黄基 -N- 视黄基乙醇胺 (A2E) 的积聚。所述眼科疾病至少部分地是由眼睛中的脂褐质色素的积聚和 / 或 A2E 的积聚导致的。因此，在某些实施方案中，提供了用于抑制或阻止脂褐质色素和 / 或 A2E 在受试者眼睛中的积聚的方法。这些方法包括向受试者施用包含药学上可接受的或合适的赋形剂（即，药学上可接受的或合适的载体）和本文详细描述的取代的杂环胺衍生物化合物的组合物，该化合物包括具有如式 (A) 或式 (B) 所示的结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物。

[0214] 视网膜色素上皮 (RPE) 细胞中的脂褐质色素积聚已与包括年龄相关性黄斑变性在内的致盲性视网膜疾病的进展相关联 (De Laey 等，Retina15:399-406(1995))。脂褐质颗粒为自发荧光的溶酶体残余体（也称作老年斑）。脂褐质的主要荧光物质为 A2E（一种发橙色光的荧光团），其为全反式视黄醛与磷脂酰乙醇胺 (2 :1 比例）形成的带正电荷的希夫碱缩合产物（参见，例如，Eldred 等，Nature 361:724-6(1993)；另参见 Sparrow, Proc. Natl. Acad. Sci. USA 100:4353-54(2003))。很多无法消化的脂褐质色素被认为起源于感光细胞；由于 RPE 内化了感光细胞每天排出的膜状碎屑，所以在 RPE 中发生沉积。据认为这种化合物的形成不是通过任何酶的催化而发生的，而是通过自发的循环反应形成 A2E。此外，A2E 具有一旦形成就耐受酶促降解的吡啶双类视黄醇 (pyridinium bisretinoid) 结构。脂褐质，因而 A2E，随着人眼的老化而积聚，而且也在被称作斯塔加特病的青少年形式的黄斑变性和几种其它先天性视网膜营养性萎缩中积聚。

[0215] A2E 可以通过几种不同的机制诱导对视网膜的损害。在低浓度时，A2E 抑制溶酶体中正常的蛋白水解作用 (Holz 等，Invest. Ophthalmol. Vis. Sci. 40:737-43(1999))。在更高的、充足的浓度下，A2E 可以起到带正电荷的亲溶酶体 (lysosomotropic) 去污剂的作用，溶解细胞膜，并可以改变溶酶体的功能，从线粒体中释放出凋亡前体蛋白，并最终杀死 RPE 细胞（参见，例如，Eldred 等，同上；Sparrow 等，Invest. Ophthalmol. Vis. Sci. 40:2988-95(1999)；Holz 等，同上；Finneman 等，Proc. Natl. Acad. Sci. USA99:3842-347(2002)；Suter 等，J. Biol. Chem. 275:39625-30(2000))。A2E 为光毒性的，并且在 RPE 细胞中引发蓝光诱导的细胞凋亡（参见，例如，Sparrow 等，Invest. Ophthalmol. Vis. Sci. 43:1222-27(2002))。当暴露于蓝光时，形成了损害包括 DNA 在内的细胞大分子的 A2E 的光氧化产物（例如，环氧化物）(Sparrow 等，J. Biol. Chem. 278(20):18207-13(2003))。A2E 自体产生单态氧，该单态氧与 A2E 反应以在碳 - 碳双键处生成环氧化物 (Sparrow 等，同上）。A2E 光致激发时产生的活性氧物质导致对细胞的氧

化性损伤，这通常会导致细胞死亡。已经描述了一种通过抑制A2E的直接前体全反式-视黄醛的生物合成而阻断A2E形成的间接方法（参见美国专利申请公开第2003/0032078号）。然而，其中描述的方法的实用性有限，因为全反式视黄醛的产生是视觉循环的重要组成部分。描述的其它疗法包括通过使用超氧化物歧化酶模拟物中和由氧化自由基物质引起的损伤（参见，例如，美国专利申请公开第2004/0116403号）和用带负电荷的磷脂抑制视网膜细胞中A2E诱导的细胞色素C氧化酶（参见，例如美国专利申请公开第2003/0050283号）。

[0216] 本文描述的取代的杂环胺衍生物化合物可以用于防止、降低、抑制或减少RPE中A2E及A2E相关的和/或衍生的分子的积聚（即，沉积）。不希望被理论所约束，由于RPE对感光细胞的完整性的维持十分关键，防止、降低或抑制对RPE的损害可以抑制视网膜神经元细胞（特别是感光细胞）的变性（即，提高细胞的存活或提高或延长细胞活力）。与A2E、A2E-相关的和/或衍生的分子特异性结合或相互作用或影响A2E的形成和积聚的化合物也可以降低、抑制、防止或减少导致视网膜神经元细胞（包括感光细胞）损伤、丧失或神经变性或者以某种方式降低视网膜神经元细胞活力的A2E或A2E相关的和/或衍生的分子的一种或多种毒性作用。这些毒性作用包括凋亡的诱导、单态氧的自体产生和氧活性种的产生；单态氧的自体产生以形成诱导DNA损伤的A2E-环氧化物，从而损伤细胞DNA并诱导细胞损伤；溶解细胞膜；改变溶酶体的功能；和实现凋亡前体蛋白从线粒体中的释放。

[0217] 在其它一些实施方案中，本文描述的化合物可以用于治疗其它眼科疾病或病症，例如，青光眼、视锥-视杆营养不良、视网膜脱落、出血性或高血压性视网膜病、色素性视网膜炎、视神经病、炎性视网膜病、增生性玻璃体视网膜病、遗传性视网膜营养性萎缩、视神经的外伤性损伤（例如由于物理损伤、过度光暴露或激光）、遗传性视神经病变、由于毒剂或由不良的药物反应或维生素缺乏导致的神经病变、Sorsby眼底营养不良、葡萄膜炎、与阿尔茨海默病相关的视网膜病症、与多发性硬化症相关的视网膜病症、与病毒感染（巨细胞病毒或单纯疱疹病毒）相关的视网膜病症、与帕金森病相关的视网膜病症、与AIDS相关的视网膜病症，或其它形式的进行性视网膜萎缩或变性。在另一个具体的实施方案中，所述疾病或病症由机械损伤、化学或药物诱导的损伤、热损伤、辐射损伤、光损伤、激光损伤引起。本发明的化合物可用于治疗遗传性和非遗传性视网膜营养性萎缩。这些方法也可用于预防由于环境因素导致的眼部损伤，例如光诱导的氧化性视网膜损伤、激光诱导的视网膜损伤、“闪光炸弹损伤”或“光炫”、屈光不正，包括但不限于近视（参见，例如Quinn GE等，Nature 1999；399：113-114；Zadnik K等，Nature 2000；404:143-144；Gwiazda J等Nature 2000；404:144）等。

[0218] 在其它一些实施方案中，本文提供了使用任意一种或多种如本文详细描述的取代的杂环胺衍生物化合物抑制视网膜中的新生血管形成（包括但不限于新生血管性青光眼）的方法，所述化合物包括具有如式(A)或式(B)所示的结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物。在某些其它实施方案中，提供了使用本文描述的化合物减轻视网膜中的缺氧的方法。这些方法包括向有需要的受试者施用包含药学上可接受的或合适的赋形剂（即，药学上可接受的或合适的载体）和本文详细描述的取代的杂环胺衍生物化合物的组合物，所述化合物包括具有如式(A)所示的结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物。

[0219] 仅仅作为解释说明而不被任何理论约束，以及如本文进一步详细讨论的，暗适应

的视杆光感受器导致非常高的代谢需求（即，能量消耗（ATP 消耗）和氧气消耗）。导致的缺氧可以引起和 / 或加剧视网膜变性，这种变性在视网膜脉管系统已经受损的情况下可能恶化，所述视网膜变性包括但不限于如下病状，例如糖尿病视网膜病变、黄斑水肿、糖尿病性斑丘疹病、视网膜血管闭塞（其包括视网膜静脉闭塞和视网膜动脉闭塞）、早产儿视网膜病、缺血再灌注相关性视网膜损伤以及湿型年龄相关性黄斑变性 (AMD)。此外，视网膜变性和缺氧可以导致新生血管形成，后者又可能使视网膜变性的程度恶化。在一些实施方案中，施用本文描述的调节视觉循环的取代的杂环胺衍生物化合物，以防止、抑制和 / 或延迟视杆细胞的暗适应，并且因此降低代谢的需求，从而减轻缺氧并抑制新生血管形成。

[0220] 作为背景，氧是用于保持哺乳动物的视网膜功能的关键代谢物，并且视网膜缺氧可能是许多以局部缺血作为要件的视网膜疾病和病症的因素。在大多数具有通向视网膜的双维管供应的哺乳动物（包括人）中，内部视网膜的氧合作用是通过视网膜内的微脉管系统实现的，与向 RPE 和光感受器供氧的脉络膜毛细管层相比，该微脉管系统是稀疏的。不同的维管供应网络穿过视网膜的厚度产生不均匀的氧张力 (Cringle 等，Invest. Ophthalmol. Vis. Sci. 43:1922-27(2002))。穿过视网膜层的氧的波动与不同的毛细血管密度和各种视网膜神经元和神经胶质的耗氧量差异都有关。

[0221] 局部的氧张力通过调节一系列包括例如血管内皮生长因子 (VEGF) 在内的血管活性物质可以显著地影响视网膜及其微脉管系统。（参见，例如，Werdich 等，Exp. Eye Res. 79:623(2004)；Arden 等，Br. J. Ophthalmol. 89:764(2005))。视杆光感受器被认为具有体内任何细胞的最高的代谢率（参见，例如，Arden 等，同上）。在暗适应过程中，视杆光感受器通过 cGMP 门控的钙通道恢复了它们的高细胞质钙水平，同时挤出钠离子和水。钠从细胞中的流出为 ATP 依赖性过程，使得与明视（即，光适应的）条件相比，在暗视（即，暗适应的）条件下视网膜神经元消耗估计可达 5 倍的氧。因而，在光感受器的特有暗适应过程中，高代谢需求导致在暗适应的视网膜中氧浓度局部显著降低 (Ahmed 等，Invest. Ophthalmol. Vis. Sci. 34:516(1993))。

[0222] 不被任何一种理论所约束，在患有例如视网膜中央静脉闭塞（其中视网膜脉管系统已经受到损伤）的疾病或病症的受试者的视网膜中，视网膜缺氧可能进一步加剧。缺氧的加剧可增加对危及视力的视网膜新生血管形成的易感性。新生血管形成是具有红细胞灌注的新的功能性微血管网络的形成，并且是视网膜变性病症的一个特征，所述视网膜变性病症包括但不限于，糖尿病视网膜病变、早产儿视网膜病、湿型 AMD 和视网膜中央静脉闭塞。防止或抑制视杆细胞的暗适应，从而降低能量的消耗和氧气的消耗（即，降低代谢的需求），可以抑制或减缓视网膜变性，和 / 或可以促进包括视杆细胞和视网膜色素上皮 (RPE) 细胞在内的视网膜细胞的再生，并且可以减轻缺氧并可以抑制新生血管形成。

[0223] 本文描述了用于抑制（即，以生物学上或统计学上显著的方式降低、防止、减缓或延缓）视网膜细胞（包括本文描述的视网膜神经元细胞和 RPE 细胞）的变性和 / 或用于降低（即，以生物学上或统计学上显著的方式防止或减缓、抑制、消除）视网膜局部缺血的方法。本文也提供了用于抑制（即，以生物学上或统计学上显著的方式降低、防止、减缓或延缓）眼睛中，特别是视网膜中的新生血管形成的方法。这些方法包括在可以防止、抑制或延缓视网膜中的视杆细胞的暗适应的条件和时间下用至少一种本文描述的取代的杂环胺衍生物化合物与视网膜接触，从而与视网膜细胞（包括视网膜神经元细胞，例如视杆细胞和

RPE 细胞）接触，所述化合物抑制至少一种视觉循环反式-顺式异构酶（其可以包括抑制全反式-视黄基酯的异构化）。如本文进一步详细描述的，在特定实施方案中，与视网膜接触的化合物与视网膜中的 RPE 细胞中的异构酶或酶复合物相互作用，并抑制、阻断或者以某种方式干扰该异构酶的催化活性。从而抑制或降低全反式-视黄基酯的异构化。将至少一种取代的杂环胺衍生物化合物（或包含至少一种化合物的组合物）施用于已经发展成和表现出眼科疾病或病症的受试者，或具有患上眼科疾病或病症的风险的受试者，或者表现出诸如新生血管形成或视网膜局部缺血的病状或者具有表现出这些病症的风险的受试者。

[0224] 作为背景，视觉循环（也称作类视黄醇循环）是指发生在眼睛的感光细胞和视网膜色素上皮 (RPE) 细胞中的 11-顺式和全反式形式的视黄醇 / 视黄醛之间的一系列由酶和光介导的转化。在脊椎动物的感光细胞中，光子引起 11-顺式-亚视黄基生色团向与视觉视蛋白受体偶合的全反式-亚视黄基的异构化。这种光致异构化触发视蛋白的构象变化，后者又引发被称作光转导的生化反应链 (Filipek 等，Annu. Rev. Physiol. 65:851-79(2003))。在光吸收和 11-顺式-视黄醛向全反式视黄醛的光致异构化之后，视觉生色团的再生是使光感受器恢复至其暗适应状态的关键步骤。视色素的再生需要将生色团转化回 11-顺式-构型（在 McBee 等，Prog. Retin Eye Res. 20:469-52(2001) 中综述）。生色团从视蛋白中释放并在光感受器中被视黄醇脱氢酶还原。在被称为视网膜体的亚细胞结构中，产物全反式视黄醇以不溶性脂肪酸酯的形式被捕获在邻近的视网膜色素上皮 (RPE) 中 (Imanishi 等，J. Cell Biol. 164:373-78(2004))。

[0225] 在视杆受体细胞的视觉循环中，视色素分子内的 11-顺式-视黄醛生色团（称作视紫质）吸收光的光子并被异构化成全反式构型，从而激活光转导级联。视紫质为一种 G 蛋白偶联受体 (GPCR)，其由七个通过细胞外和细胞质环相互连接的跨膜螺旋组成。当全反式形式的类视黄醇仍然与色素分子共价结合时，该色素被称作变视紫质，其以不同的形式存在（例如，变视紫质 I 和变视紫质 II）。全反式类视黄醇随后被水解，并且视色素为脱辅蛋白质视蛋白的形式，其在本领域内和在本文中也称作脱辅基视紫质。这种全反式类视黄醇被转运或者陪伴离开感光细胞并穿过细胞外间隙至 RPE 细胞中，其中类视黄醇转化为 11-顺式异构体。类视黄醇在 RPE 与感光细胞之间的移动被认为是通过各种细胞类型中的不同陪伴多肽实现的。参见 Lamb 等，Progress in Retinal and Eye Research 23:307-80(2004)。

[0226] 在光条件下，视紫质在三种形式（视紫质、变视紫质和脱辅基视紫质）间不断转变。当大部分的视色素为视紫质形式（即，与 11-顺式视黄醛结合）时，视杆细胞为“暗适应”状态。当视色素主要为变视紫质形式（即，与全反式视黄醛结合）时，感光细胞的状态被称作“光适应的”，并且当视色素为脱辅基视紫质（或视蛋白）并且不再具有结合的生色团时，感光细胞的状态被称作“视紫质耗竭的”。感光细胞的三种状态各自具有不同的能量需求，并且消耗不同水平的 ATP 和氧。在暗适应状态下，视紫质对阳离子通道不具有调节效应，该阳离子通道开放，导致阳离子 ($Na^+/K^+$和 $Ca^{2+}$) 的流入。为了在暗状态过程中使这些阳离子在细胞中保持适当的水平，感光细胞经由依赖 ATP 的泵向细胞外主动转运阳离子。因而这种“暗电流”的维持需要大量的能量，从而导致高代谢需求。在光适应状态下，变视紫质触发导致 GMP 水解的酶级联过程，该过程转而关闭感光细胞膜中的阳离子特异性通道。在视紫质耗竭的状态下，生色团从变视紫质水解以形成脱辅蛋白质视蛋白（脱辅基视紫质），其部分地调节阳离子通道，使得视杆细胞显示出比暗适应状态下的光感受器减弱的电流，

从而导致中度的代谢需求。

[0227] 在正常光的条件下，处于暗适应状态的视杆光感受器的发生率低，一般为 2％或更低，并且该细胞主要处于光适应或视紫质耗竭状态，与处于暗适应状态的细胞相比，其将总体上导致相对较低的代谢需求。然而，在晚上，由于不存在光适应和 RPE 细胞中的“暗”视觉循环的持续工作（其用 11- 顺式 - 视黄醛补充视杆细胞），暗适应的光感受器状态的相对发生率显著增加。这种向视杆光感受器的暗适应的转移导致代谢需求的增加（即，增加的 ATP 和氧的消耗），最终导致视网膜缺氧及随后血管发生的开始。因而，视网膜的大多数缺血性损伤发生在黑暗中，例如在晚上睡眠期间。

[0228] 不被任何理论所约束，在“暗”视觉循环期间的治疗性干预可以防止由暗适应视杆细胞中的高代谢活动引起的视网膜缺氧和新生血管形成。仅举一个例子，通过施用本文描述的任意一种化合物（其为异构酶抑制剂）改变“暗”视觉循环，可以减少或耗尽视紫质（即，11- 顺式视黄醛结合的），从而防止或抑制视杆光感受器的暗适应。这转而可以降低视网膜代谢需求，降低视网膜局部缺血和新生血管形成的夜间风险，从而抑制或减缓视网膜变性。

[0229] 在一个实施方案中，以统计学上或生物学上显著的方式例如阻止、减轻、抑制或以某种方式减弱视觉循环异构酶的催化活性的至少一种本文描述的化合物（即，本文详细描述的取代的杂环胺衍生物化合物，包括具有如式 (A) 或式 (B) 所示的结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物），防止、抑制或延缓视杆细胞的暗适应，从而抑制（即，以统计学上或生物学上显著的方式减轻、消除、防止、延缓其进展，或者减少）眼睛视网膜中的视网膜细胞的变性（或提高视网膜细胞的存活）。在另一实施方案中，该取代的杂环胺衍生物化合物防止或抑制视杆细胞的暗适应，从而降低局部缺血（即，以统计学上或生物学上以显著的方式减少、防止、抑制、减缓局部缺血的进展）。在又一实施方案中，本文描述的取代的杂环胺衍生物化合物防止视杆细胞的暗适应，从而抑制眼睛视网膜中的新生血管形成。因此，本文提供了抑制视网膜细胞变性、抑制受试者眼睛视网膜中的新生血管形成和减轻受试者眼睛中的局部缺血的方法，其中，这些方法包括在足以防止、抑制或延缓视杆细胞的暗适应的条件和时间下施用至少一种本文描述的取代的杂环胺衍生物化合物。因而这些方法和组合物可用于治疗眼科疾病或病症，包括但不限于糖尿病视网膜病变、糖尿病性斑丘疹病、视网膜血管闭塞、早产儿视网膜病或缺血再灌注相关性视网膜损伤。

[0230] 本文描述的取代的杂环胺衍生物化合物（即，本文详细描述的取代的杂环胺衍生物化合物，包括具有如式 (A) 或式 (B) 所示的结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物）防止（即，延缓、减缓、抑制或降低）视色素生色团的恢复，这防止或抑制或延缓了视黄醛的形成，并且提高了视黄基酯的水平，其扰乱了视觉循环，抑制了视紫质的再生，并且其防止、减缓、延缓或抑制了视杆细胞的暗适应。在某些实施方案中，当在所述化合物的存在下视杆细胞的暗适应被阻止时，暗适应基本得到阻止，并且与在不存在药剂的情况下视紫质耗竭的或光适应的细胞的数目或百分比相比，视紫质耗竭的或光适应的视杆细胞的数目或百分比增加。因此，在某些实施方案中，当视杆细胞的暗适应被阻止（即，基本被阻止）时，仅有至少 2％的视杆细胞为暗适应的，这类似于在正常光条件下处于暗适应状态的细胞的百分比或数目。在其它某些实施方案中，在施用所述药剂后，至

少 5-10％、10-20％、20-30％、30-40％、40-50％、50-60％或 60-70％的视杆细胞为暗适应的。在其它一些实施方案中，所述化合物起到延迟暗适应的作用，并且与不存在该化合物的情况下视杆细胞的暗适应相比，在该化合物的存在下，视杆细胞的暗适应延迟 30 分钟、1 小时、2 小时、3 小时或 4 小时。相比之下，当施用取代的杂环胺衍生物化合物以使得该化合物在光适应条件期间有效地抑制底物的异构化时，该化合物是以使暗适应的视杆细胞的百分比最小化的方式施用的，例如，仅仅 2％、5％、10％、20％或 25％的视杆细胞为暗适应的（参见，例如，美国专利申请公开第 2006/0069078 号；专利申请第 PCT/US2007/002330 号）。

[0231] 在存在至少一种取代的杂环胺衍生物化合物的视网膜中，至少部分地通过防止视黄醛的形成、降低视黄醛的水平和 / 或增加视黄基酯的水平，抑制视杆细胞中的视紫质的再生或者降低（即，以统计学上或生物学上显著的方式抑制、降低或减少）再生速率。为了测定视杆细胞中的视紫质再生的水平，在使化合物与视网膜接触前（即，施用药剂前）测定视紫质再生的水平（其也可被称作第一水平）。在经过足以使化合物与视网膜和视网膜中的细胞相互作用的时间后（即，在施用该化合物之后），测定视紫质再生的水平（其可以被称作第二水平）。与第一水平相比，第二水平的降低指示该化合物抑制视紫质的再生。可以在每个剂量后或在任意数目的剂量后测定视紫质产生的水平，并且在整个治疗方案中持续进行，以表征该药剂对视紫质再生的影响。

[0232] 在某些实施方案中，需要本文所述的治疗的受试者患有导致或引起视杆细胞在视网膜中再生视紫质的能力减弱的疾病或病症。例如，视紫质再生的抑制（或视紫质再生速率的降低）可能是糖尿病患者的症状。除了在施用本文描述的取代的杂环胺衍生物化合物之前和之后测定糖尿病受试者的视紫质再生的水平外，也通过比较在施用该化合物的第一受试者（或第一组或多个受试者）中与患有糖尿病但没有接受该药剂的第二受试者（或第二组或多个受试者）中的视紫质再生的抑制来表征该化合物的效果。

[0233] 在另一实施方案中，提供了一种防止或抑制视网膜中的视杆细胞（或者多个视杆细胞）的暗适应的方法，其包括：在足以使药剂与视网膜细胞（例如 RPE 细胞）中存在的异构酶之间发生相互作用的条件和时间下，使视网膜接触至少一种本文描述的取代的杂环胺衍生物化合物（即，本文详细描述的化合物，包括具有如式 (A) 或式 (B) 所示的结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物）。测定在所述化合物的存在下视杆细胞中的 11- 顺式 - 视黄醛的第一水平，并与在不存在所述化合物的情况下视杆细胞中的 11- 顺式 - 视黄醛的第二水平相比较。当 11- 顺式 - 视黄醛的第一水平小于 11- 顺式 - 视黄醛的第二水平时，指示视杆细胞的暗适应的防止或抑制。

[0234] 抑制视紫质的再生也包括与在不存在所述化合物的情况下（即，在施用该药剂之前）存在于 RPE 细胞中的 11- 顺式 - 视黄基酯的水平相比，在该化合物的存在下提高存在于 RPE 细胞中的 11- 顺式 - 视黄基酯的水平。使用双光子成像技术观察和分析 RPE 中的视网膜体结构，其结构被认为是用来存储视黄基酯（参见，例如，Imanishi 等，J.Cell Biol.164:373-83(2004)，Epub 2004 年 1 月 26 日）。可以在施用所述化合物之前测定视黄基酯的第一水平，并且可以在施用第一剂量或任何后续剂量之后测定视黄基酯的第二水平，其中，与第一水平相比，第二水平的增加指示所述化合物抑制视紫质的再生。

[0235] 根据本领域常用的方法采用梯度 HPLC 分析视黄基酯（参见，例如，Mata 等，Neuron 36:69-80(2002)；Trevino 等，J.Exp.Biol.208:4151-57(2005)）。为了测量

11-顺式和全反式视黄醛，在用等度 HPLC（参见，例如，Trevino 等，同上）分析之前通过甲醛法（参见，例如，Suzuki 等，Vis.Res.28:1061-70(1988)；Okajima 和 Pepperberg，Exp.Eye Res.65:331-40(1997)）或通过羟胺法（参见，例如，Groenendijk 等，Biochim.Biophys.Acta.617:430-38(1980)）提取类视黄醇。使用分光光度法监测类视黄醇（参见，例如，Maeda 等，J.Neurochem.85:944-956(2003)；Van Hooser 等，J.Biol.Chem.277:19173-82(2002)）。

[0236] 在用于治疗眼科疾病或病症、抑制视网膜细胞变性（或提高视网膜细胞存活）、抑制新生血管形成以及降低视网膜中局部缺血的本文描述的方法的另一实施方案中，防止或抑制视网膜中视杆细胞的暗适应包括增加感光细胞中的脱辅基视紫质（又称视蛋白）的水平。视色素的总水平接近视紫质和脱辅基视紫质的总量，并且总水平保持恒定。因此，防止、延缓或抑制视杆细胞的暗适应可以改变脱辅基视紫质与视紫质的比例。在特定实施方案中，与不存在药剂（例如，施用药剂之前）的比率相比，通过施用本文描述的取代的杂环胺衍生物化合物防止、延缓或抑制暗适应可以提高脱辅基视紫质水平与视紫质水平的比率。脱辅基视紫质与视紫质的比率的增加（即，统计学上或生物学上的显著增加）指示视紫质耗竭的视杆细胞的百分比或数目增加，并且暗适应的视杆细胞的百分比或数目减少。可以在整个治疗过程中测定脱辅基视紫质与视紫质的比率以监测药剂的效果。

[0237] 对化合物防止、延缓或抑制视杆细胞暗适应的能力的测定或表征可以在动物模型研究中测定。视紫质的水平和脱辅基视紫质与视紫质的比率可以在施用药剂之前测定（其可以分别称作第一水平或第一比率），然后在施用第一个或任意后续剂量的药剂后测定（其可以分别称作第二水平或第二比率），以确定或证明脱辅基视紫质的水平大于未接受该药剂的动物的视网膜中脱辅基视紫质的水平。可以根据本领域内常用的和本文提供的方法测定视杆细胞中的视紫质的水平（参见，例如，Yan 等 J.Biol.Chem.279:48189-96(2004)）。

[0238] 需要这种治疗的受试者为人或者为非人灵长类或其它动物（即，兽医用途），这些受试者已经发展出眼科疾病或病症的症状或者处于发展成眼科疾病或病症的风险中。非人灵长类和其它动物的实例包括但不限于农场动物、宠物和动物园动物（例如，马、牛、水牛、美洲驼、山羊、兔子、猫、狗、黑猩猩、猩猩、大猩猩、猴、象、熊、大型猫科动物等）。

[0239] 本文还提供了用于抑制（降低、减缓、防止）变性和提高视黄醛神经元细胞的存活（或延长细胞活力）的方法，其包括向受试者施用包含药学上可接受的载体和本文详细描述的取代的杂环胺衍生物化合物的组合物，所述化合物包括具有如式 (A) 或式 (B) 所示的任一结构及其子结构的化合物和本文描述的具体的取代的杂环胺衍生物化合物。视网膜神经元细胞包括感光细胞、双极细胞、水平细胞、神经节细胞和无长突细胞。在另一实施方案中，提供了提高成熟视网膜细胞如 RPE 细胞和米勒胶质细胞的存活或抑制其变性的方法。在其它一些实施方案中，提供了防止或抑制受试者眼睛中的光感受器变性的方法。一种防止或抑制光感受器变性的方法可包括用于恢复受试者眼睛中的光感受器功能的方法。这样的方法包括向受试者施用包含如本文所述的取代的杂环胺衍生物化合物和药学上可接受的载体（即赋形剂或辅料）的组合物。更具体而言，这些方法包括向受试者施用药学上可接受的赋形剂和本文所述的取代的杂环胺衍生物化合物，包括本文描述的具有如式 (A) 或式 (B) 所示的结构或其子结构的化合物。不希望被理论约束，本文所述的化合物可以抑制

眼睛中的类视黄醇循环（即，视觉循环）的异构化步骤和/或可以减慢类视黄醇循环的生色团通量。

[0240] 眼科疾病至少部分地可能是由眼睛中的脂褐质色素积聚和/或由N-亚视黄基-N-视黄基乙醇胺(A2E)的积聚引起的。因此，在某些实施方案中，提供了抑制或防止受试者眼睛中的脂褐质色素和/或A2E的积聚的方法。这些方法包括向受试者施用包含药学上可接受的载体和本文详细描述的取代的杂环胺衍生物化合物的组合物，所述化合物包括具有如式(A)所示的结构或其子结构的化合物。

[0241] 在一些实施方案中，将取代的杂环胺衍生物化合物施用于在眼睛中含有过量的类视黄醇（例如，过量的11-顺式-视黄醇或11-顺式-视黄醛）、过量的在全反式-视黄醛循环中的类视黄醇废物或中间体等的受试者。在施用本文描述的任意一种化合物的过程中或之后，可以使用本文描述的和在本领域内常用的方法确定受试者的一种或多种内源性类视黄醇的水平是否改变（以统计学上显著的或生物学上显著的方式增加或减少）。由蛋白质视蛋白和视黄醛（维生素A形式）组成的视紫质位于眼睛视网膜中的感光细胞的细胞膜中，并催化视觉中唯一的光敏感步骤。11-顺式-视黄醛生色团位于蛋白质的口袋中，并且当吸收光时异构化成全反式视黄醛。视黄醛的异构化导致视紫质形状的改变，这引发了产生由视神经传递至大脑的神经冲动的反应级联。

[0242] 例如，在美国专利申请公开第2005/0159662号（其公开内容通过引用整体并入本文）中公开了测定脊椎动物的眼睛中内源性类视黄醇水平以及这些类视黄醇的过量或不足的方法。测定受试者的内源性类视黄醇水平（其可用于确定这些类视黄醇的水平是否高于正常范围）的其它方法包括，例如，通过高压液相色谱法(HPLC)对来自受试者的生物样品中的类视黄醇进行的分析。例如，可以测定来自受试者的生物样品（其为血液样品（包括血清或血浆））中的类视黄醇水平。生物样品也可以包括玻璃体液、房水、眼内液、视网膜下积液或泪液。

[0243] 例如，血液样品可从受试者获得，而样品中不同的类视黄醇化合物和一种或多种类视黄醇化合物的水平可以通过正相高压液相色谱法(HPLC)（例如，用HP1100HPLC和Beckman，Ultrasphere-Si，4.6mm×250mm柱，使用10％乙酸乙酯/90％己烷，流速1.4毫升/分钟）分离和分析。类视黄醇可以通过例如采用二极管阵列检测器和HP Chemstation A.03.03软件在325nm处的检测进行检测。例如，通过比较样品中与来自正常受试者的样品中的类视黄醇概况（即定性的，例如具体化合物的身份，和定量的，例如每种具体化合物的水平），可以确定类视黄醇的过量。熟悉这类分析和技术的本领域技术人员将容易理解也包括适当的对照。

[0244] 如本文所使用的，内源性类视黄醇（如11-顺式-视黄醇或11-顺式-视黄醛）水平的增加或过量，是指内源性类视黄醇水平高于在相同物种的年轻脊椎动物的健康眼睛中发现的内源性类视黄醇水平。取代的杂环胺衍生物化合物的施用可以减少或消除对内源性类视黄醇的需求。在某些实施方案中，可以比较在向受试者施用任意一次或多次剂量的取代的杂环胺衍生物化合物之前或之后的内源性类视黄醇的水平，以确定该化合物对受试者中的内源性类视黄醇水平的影响。

[0245] 在另一实施方案中，本文描述的用于治疗眼科疾病或病症、抑制新生血管形成和减少视网膜的局部缺血的方法包括施用至少一种本文描述的取代的杂环胺衍生物化合物，

从而实现代谢需求降低，其包括实现视杆细胞中 ATP 消耗和氧消耗的降低。如本文所述，暗适应的视杆细胞中 ATP 和氧的消耗大于光适应或视紫质耗竭的视杆细胞中 ATP 和氧的消耗；因此，与暗适应的视杆细胞（例如在施用该化合物或与该化合物接触之前的细胞，或者从未暴露于该化合物的细胞）相比，在本文所述的方法中使用所述化合物减少了被防止、抑制或延迟暗适应的视杆细胞中的 ATP 消耗。

[0246] 本文描述的方法防止或抑制视杆细胞的暗适应，因而缓解视网膜的缺氧（即，以统计学或生物学上显著的方式缓解）。例如，在治疗方案开始之前，即，在化合物（或包含该化合物的如本文所述的组合物）的第一次给药之前，可以测定缺氧的水平（第一水平）。可以在第一次给药和 / 或任意第二次或后续的施药之后测定缺氧的水平（例如，第二水平）以监测及表征在整个治疗方案中的缺氧。与初次给药之前的缺氧水平相比，第二（或任意后续的）缺氧水平的降低（缓解）指示该化合物和治疗方案防止了视杆细胞的暗适应，并可以用于治疗眼科疾病和病症。氧的消耗、视网膜的氧合作用和 / 或视网膜的缺氧可以使用本领域常用的方法测定。例如，视网膜的氧合作用可以通过测量视网膜中的黄素蛋白的荧光来测定（参见，例如，美国专利第 4,569,354 号）。另一示例性的方法为视网膜血氧定量法，其测量靠近视神经盘的视网膜的大血管中的血氧饱和度。这样的方法可以用于在能够检测到视网膜血管结构变化之前确认和测定视网膜缺氧的程度。

[0247] 生物样品为来自受试者或生物源的血液样品（由其可以制备血清和血浆）、活检标本、体液（例如，玻璃体液、房水、眼内液、视网膜下液或泪液）、组织外植体、器官培养物或任何其它组织或细胞制品。样品可以进一步指组织或细胞制品，其中形态完整性或物理状态已经被破坏，例如通过解剖、分离、增溶、分级分离、均化、生物化学或化学提取、粉碎、冻干、超声处理或任何其它用于处理源自受试者或生物源的样品的方法。受试者或生物源可以为人或非人动物、原代细胞培养物（例如，视网膜细胞培养物）或适于培养的细胞系，包括但不限于，可以包含染色体整合的或附加型重组核酸序列的遗传工程细胞系、无限增殖的或可无限增殖的细胞系、体细胞杂合细胞系、分化的或可分化的细胞系、转化的细胞等。包括视网膜神经元细胞、RPE 细胞和米勒胶质细胞在内的成熟视网膜细胞可以存在于或分离自如本文所述的生物样品。例如，成熟视网膜细胞可以从原代细胞培养物或长期细胞培养物得到，或者可以存在于或分离自从受试者（人或非人动物）得到的生物样品。

视网膜细胞

[0248] 视网膜是位于眼睛中的玻璃体和脉络膜之间的神经组织的薄层。视网膜中的主要界标是中央凹、黄斑和视神经盘。视网膜在后极区附近最厚，并在周边附近变薄。黄斑位于视网膜后部，包含中央凹和小凹。小凹包含视最大视锥密度的区域，因此它提供视网膜中最高的视敏度。小凹包含在中央凹内，中央凹包含在黄斑内。

[0249] 视网膜的周边部分增加了视野。周边视网膜在睫状体之前延伸，且分为四个区：近周边（最后部）、中周边、远周边和锯齿缘（最前部）。锯齿缘表示视网膜的终止。

[0250] 在本领域中所理解的和本文处所使用的术语神经元（或神经细胞）表示从神经上皮细胞前体产生的细胞。成熟的神经元（即完全分化的细胞）显示出几种特异性的抗原标记物。按功能可将神经元分为四组：(1) 传入神经元（或感觉神经元），其将信息传送到大脑用于意识感知和运动协调；(2) 运动神经元，其将指令传递到肌肉和腺体；(3) 中间神经元，其负责局部环路；和 (4) 投射中间神经元，其将信息从大脑的一个区域传递到另一个区

域，因此具有长轴突。中间神经元处理大脑的特定子区域内的信息，并具有相对较短的轴突。神经元一般有四个确定的区域：细胞体（或胞体）；轴突；树突；和突触前末梢。树突主要负责从其它神经细胞传入信息。轴突携带从细胞体发起的到其它神经元或效应器官的电信号。在突触前末梢，神经元将信息传送到另一个细胞（突触后细胞），该细胞可能是另一个神经元、肌细胞或分泌细胞。

[0251] 视网膜由几种类型的神经元细胞组成。如本文所述，可通过此方法在体外培养的视网膜神经元细胞的类型包括感光细胞、神经节细胞和中间神经元，如双极细胞、水平细胞和无长突细胞。光感受器是特化的光反应性神经细胞，包括两大类：视杆和视锥。视杆与暗视或弱光视觉有关，而明视或亮光视觉起源于视锥。导致失明的许多神经变性疾病（例如AMD）会影响光感受器。

[0252] 从其细胞体延伸，光感受器具有两个形态上不同的区域：内节和外节。外节位于距感光细胞体最远处，并且包含将入射光能量转化成电脉冲（光转导）的视盘。外节由非常细小和脆弱的纤毛附到内节上。外节的大小和形状在视杆和视锥之间变化并且依赖于在视网膜中的位置。参见 Hogan，" Retina" in Histology of the Human Eye:an Atlas and Text Book(Hogan 等（编）.WB Saunders；Philadelphia,PA(1971))；Eye and Orbit,8th Ed.,Bron 等，(Chapman and Hall,1997)。

[0253] 神经节细胞是将信息从视网膜中间神经元（包括水平细胞、双极细胞、无长突细胞）传递到大脑的输出神经元。双极细胞根据其形态命名，并接收来自光感受器的输入，与无长突细胞连接，并将输出呈放射状地发送到神经节细胞。无长突细胞具有平行于视网膜平面的突起，并具有向神经节细胞的典型抑制性输出。无长突细胞常常根据神经递质或神经调质或肽（如钙网膜蛋白或钙结合蛋白）再细分，并彼此相互作用、与双极细胞相互作用，并与光感受器相互作用。双极细胞是视网膜中间神经元，其根据形态命名；双极细胞接收来自光感受器的输入，并将输入发送到神经节细胞。水平细胞调制和转化来自大量光感受器的视觉信息，并具有水平整合（而双极细胞通过视网膜呈放射状传递信息）。

[0254] 其它可能存在于本文所述视网膜细胞培养物中的视网膜细胞包括胶质细胞，如米勒胶质细胞和视网膜色素上皮细胞 (RPE)。胶质细胞包围着细胞体和轴突。胶质细胞不携带电脉冲，但有助于大脑正常功能的保持。米勒胶质细胞，其为视网膜内胶质细胞的主要类型，提供对视网膜的结构支持，并与视网膜代谢相关（例如，有助于离子浓度的调节、神经递质的降解及某些代谢物的去除（例如，参见 Kljavin 等，J.Neurosci.11:2985(1991))。米勒纤维（也称为视网膜支持纤维）是视网膜的支持神经胶质细胞，其贯穿视网膜的厚度，从内界膜通向视杆和视锥基部，本文它们形成一行连接复合体。

[0255] 视网膜色素上皮 (RPE) 细胞构成视网膜的最外层，其通过布鲁赫膜与富集血管的脉络膜分离。RPE 细胞是一类吞噬上皮细胞，具有一些巨噬细胞样功能，其直接位于视网膜光感受器下方。RPE 细胞的背面紧密并列于视杆的端部，并且当视盘从视杆外节脱落时它们被 RPE 细胞内化并消化。视椎的视盘发生类似的过程。RPE 细胞还产生、储存和转运有助于光感受器的正常功能和存活的多种因子。RPE 细胞的另一项功能是循环利用维生素 A，因为它在被称为视觉循环的光适应与暗适应的过程中，在光感受器和 RPE 之间移动。

[0256] 本文描述了示例性的体外长期细胞培养系统，该系统允许和促进成熟视网膜细胞（包括视网膜神经元）在培养物中存活至少 2-4 周、超过 2 个月或长达 6 个月。该细胞培养

系统可用于鉴别和表征取代的杂环胺衍生物化合物，该化合物可用于本文所述的治疗和/或预防眼科疾病或病症，或防止或抑制脂褐质和/或A2E在眼中积聚的方法。视网膜细胞从非胚胎、非致瘤性组织中分离，且没有通过任何方法（例如用致癌病毒转化或感染）进行无限增殖化。该细胞培养系统包括所有主要的视网膜神经元细胞类型（光感受器、双极细胞、水平细胞、无长突细胞和神经节细胞），也可包括其它成熟视网膜细胞，如视网膜色素上皮细胞和米勒胶质细胞。

[0257] 例如，血液样品可从受试者获得，而样品中不同的类视黄醇化合物和一种或多种类视黄醇化合物的水平可以通过正相高压液相色谱法(HPLC)（例如，用HP1100HPLC和Beckman，Ultrasphere-Si，4.6mm×250mm柱，使用10％乙酸乙酯/90％己烷，流速1.4毫升/分钟）进行分离和分析。类视黄醇可以通过例如采用二极管阵列检测器和HP Chemstation A.03.03软件在325nm处的检测进行检测。例如，通过比较样品中与来自正常受试者的样品中的类视黄醇概况（即定性的，例如具体化合物的身份，和定量的，例如每种具体化合物的水平），可以确定类视黄醇的过量。熟悉这类分析和技术的本领域技术人员将容易理解也包括适当的对照。

[0258] 如本文所使用的，内源性类视黄醇（如11-顺式-视黄醇或11-顺式-视黄醛）水平的增加或过量，是指内源性类视黄醇水平高于在相同物种的年轻脊椎动物的健康眼睛中发现的内源性类视黄醇水平。在一些实施方案中，取代的杂环胺衍生物化合物的施用将会减少或消除对内源性类视黄醇的需求。

用于确定化合物的疗效的体内及体外方法

[0259] 在一个实施方案中，提供了使用本文所述的化合物增强或延长视网膜细胞的存活（包括视网膜神经元细胞的存活和RPE细胞的存活）的方法。本文还提供了使用本文所述的化合物抑制或防止视网膜细胞变性的方法，该视网膜细胞包括视网膜神经元细胞（例如，感光细胞、无长突细胞、水平细胞、双极细胞和神经节细胞），和其它成熟的视网膜细胞，如视网膜色素上皮细胞和米勒胶质细胞。在某些实施方案中，这些方法包括施用本文描述的取代的杂环胺衍生物化合物。这种化合物可用于增强视网膜细胞的存活，包括感光细胞的存活和视网膜色素上皮细胞的存活，抑制或延缓视网膜细胞的变性，从而提高视网膜细胞活力，这可导致延缓或停止眼科疾病或病症或视网膜损伤的进展，这在本文中进行了描述。

[0260] 取代的杂环胺衍生物化合物对视网膜细胞存活（和/或视网膜细胞变性）的影响可通过使用细胞培养模型、动物模型和本文所述的和本领域技术人员使用的其它方法来确定。举例而言，并且非限制性的，这样的方法和试验包括以下文献中描述的方法和试验：Oglivie等，Exp.Neurol.161:675-856(2000)；美国专利第6,406,840号；WO 01/81551；WO 98/12303；美国专利申请第2002/0009713号；WO 00/40699；美国专利第6,117,675号；美国专利第5,736,516号；WO 99/29279；WO 01/83714；WO 01/42784；美国专利第6,183,735号；美国专利第6,090,624号；WO 01/09327；美国专利第5,641,750号；美国专利申请公开第2004/0147019号；和美国专利申请公开第2005/0059148号。

[0261] 本文描述的可用于治疗眼科疾病或病症（包括视网膜疾病或病症）的化合物抑制、阻断、削弱或者以某种方式干扰视觉循环（在本文中和在本领域中又称类视黄醇循环）中的一个或多个步骤。不希望被特定理论所约束，取代的杂环胺衍生物化合物抑制或阻断视觉循环中的异构化步骤，例如，通过抑制或阻断视觉循环反式-顺式异构酶的功能性活

动。本文描述的化合物直接或间接地抑制全反式视黄醇向 11- 顺式视黄醇的异构化。该化合物与视网膜细胞中的至少一种异构酶结合，或者以某种方式与之相互作用，并抑制其异构酶活性。本文所述的化合物也直接或间接地抑制或降低视觉循环中涉及的异构酶的活性。该化合物阻断或抑制异构酶与一种或多种底物（包括但不限于全反式视黄基酯底物或全反式视黄醇）结合的能力。可替代地，或此外，该化合物可以结合至异构酶的催化部位或区域，从而抑制该酶催化至少一种底物的异构化的能力。基于迄今为止的科学数据，认为在视觉循环中催化底物的异构化的至少一种异构酶位于 RPE 细胞的细胞质中。如本文所述，视觉循环的各个步骤、酶、底物、中间体和产物尚未阐明。然而，已经在 RPE 细胞中的细胞质中发现的、膜结合的、被称作 RPE65 的多肽被假定具有异构酶活性（在本领域中也曾称作具有异构水解酶活性）（参见，例如，Moiseyev 等，Proc.Natl.Acad.Sci.USA 102:12413-18(2004)；Chen 等，Invest.Ophthalmol.Vis.Sci.47:1177-84(2006)），本领域的其他技术人员认为 RPE65 主要起到全 - 反式 - 视黄基酯的陪伴分子的作用（参见，例如，Lamb 等，同上）。

[0262] 示例性的方法在本文中描述，并且由本领域技术人员实施，用于在本文所述的任一化合物的存在下确定视觉循环异构酶的酶活性水平。降低异构酶活性的化合物可用于治疗眼科疾病或病症。因此，本文提供了检测对异构酶活性的抑制的方法，该方法包括使包含异构酶的生物样品与本文所述的取代的杂环胺衍生物化合物接触（即混合、组合或以某种方式使所述化合物和异构酶相互作用），然后确定异构酶的酶活性水平。本领域技术人员将意识到，作为对照，可确定在不存在化合物的情况下或在已知不会改变异构酶的酶活性的化合物存在下异构酶活性的水平，并与在所述化合物存在下的活性水平相比较。在该化合物存在下的异构酶活性水平相比在该化合物不存在下的异构酶活性水平的降低表明，该化合物可用于治疗眼科疾病或病症，如年龄相关性黄斑变性或斯塔加特病。在该化合物存在下的异构酶活性水平相比该化合物不存在下的异构酶活性水平的降低表明，该化合物也可用于本文所述的抑制或预防暗适应、抑制新血管形成和缓解缺氧的方法中，从而可用于治疗眼科疾病或病症，例如，糖尿病视网膜病变、糖尿病性斑丘疹病、视网膜血管闭塞、早产儿视网膜病或缺血再灌注相关性视网膜损伤。

[0263] 本文所述的取代的杂环胺衍生物化合物通过抑制视紫质的再生而抑制或阻止视杆细胞的暗适应的能力通过体外试验和 / 或体内动物模型来确定。举例来说，再生的抑制在化学诱发糖尿病样状况的小鼠模型中或在糖尿病小鼠模型中确定（参见，例如，Phipps 等，Invest.Ophthalmol.Vis.Sci.47:3187-94(2006)；Ramsey 等，Invest.Ophthalmol.Vis.Sci.47:5116-24(2006)）。可以在施用药剂前测定（例如，通过分光光度分析）动物视网膜中视紫质的水平（第一水平）并与施用药剂后测定的动物视网膜中视紫质的水平（第二水平）相比较。与视紫质的第一水平相比视紫质的第二水平的减少表明，该药剂抑制了视紫质的再生。本领域技术人员可以容易地确定和实施用以确定视紫质的再生是否以统计学显著的或生物学显著的方式得到抑制的适当的对照和研究设计。

[0264] 用于确定或表征本文所述的任何一种化合物对哺乳动物（包括人）的暗适应和视杆细胞视紫质再生的影响的方法和技术，可以根据本文所描述和本领域中实践的程序来完成。例如，在黑暗中暴露于光（即光漂白）后的视觉刺激对时间的检测可在施用化合物第一剂量前和第一剂量和 / 或随后的任何剂量后的时间进行确定。第二种用于确定视杆

细胞暗适应的防止或抑制的方法包括对至少一个、至少两个、至少三个或更多个视网膜电流图组成部分的幅度的测量，其中包括例如，a 波和 b 波。参见，例如，Lamb 等，同上；Asi 等，Documenta Ophthalmologica 79:125-39(1992)。

[0265] 用本文所述的取代的杂环胺衍生物化合物抑制视紫质再生包括降低在 PRE 细胞中产生并存在的生色团 11-顺式-视黄醛的水平，因而降低感光细胞中存在的 11-顺式-视黄醛的水平。因此，当使该化合物在足以阻止视杆细胞的暗适应和抑制视杆细胞中视紫质的再生的适当条件和时间下接触视网膜时，该化合物引起视杆细胞中 11-顺式-视黄醛水平的降低（即，统计学显著的或生物学显著的降低）。也就是说，相比化合物的第一次和/或随后任何施用后感光细胞中 11-顺式-视黄醛的水平，施用该化合物前视杆细胞中 11-顺式-视黄醛的水平较高。可在施用该化合物前测定 11-顺式视黄醛的第一水平，并且可在施用第一剂量或随后的任何剂量后测定 11-顺式视黄醛的第二水平，以监测该化合物的效果。与第一水平相比第二水平的减少表明，该化合物抑制了视紫质的再生，从而抑制或阻止视杆细胞的暗适应。

[0266] 用于确定或表征取代的杂环胺衍生物化合物减轻视网膜缺氧的能力的示例性方法包括测定视网膜氧合水平，例如，通过磁共振成像 (MRI)，以测量氧压力的变化（参见，例如，Luan 等，Invest.Ophthalmol.Vis.Sci.47:320-28(2006)）。在本领域内还可以获得并常规实施用于确定或表征本文描述的化合物抑制视网膜细胞变性的能力的方法（见，例如，Wenzel 等，Prog.Retin.Eye Res.24:275-306(2005)）。

[0267] 动物模型可以用来表征和确定可用于治疗视网膜疾病和病症的化合物。Ambati 等人 (Nat.Med.9:1390-97(2003)；Epub 2003 年 10 月 19 日）已经描述了一种最近开发的可用于评估对黄斑变性的治疗的动物模型。该动物模型是仅有的极少数目前可用的示例性动物模型之一，所述动物模型可用于评价用于治疗（包括预防）视网膜疾病或病症的进展或发展的化合物或任何分子。编码 ATP 结合盒转运体的 ABCR 基因位于光感受器外节视盘边缘的动物模型可用于评估化合物的效果。ABCR 基因的突变与斯塔加特病相关，而 ABCR 的杂合突变与 AMD 相关。因此，已产生了 ABCR 功能部分或全部丧失的动物，并且其可用来表征本文所述的取代的杂环胺衍生物化合物。（参见，例如，Mata 等，Invest.Ophthalmol.Sci.42:1685-90(2001)；Weng 等，Cell 98:13-23(1999)；Mata 等，Proc.Natl.Acad.Sci.USA 97:7154-49(2000)；US 2003/0032078；美国专利第 6,713,300 号）。其它动物模型包括使用突变 ELOVL4 转基因小鼠来测定视紫质的积聚、电生理学和光感受器变性，或其预防或抑制（参见，例如，Karan 等，Proc.Natl.Acad.Sci.USA 102:4164-69(2005)）。

[0268] 本文所述的任意一种化合物的效果可以如 Luan 等所述在糖尿病视网膜病变动物模型中测定，或可以在正常的动物模型中测定，在该动物模型中，该动物已在存在和不存在本文所述的任意一种化合物的情况下进行了光适应或暗适应。另一测定药剂减轻视网膜缺氧的能力的示例性方法通过羟基探针的沉积测量视网膜缺氧（参见，例如，de Gooyer 等 Invest.Ophthalmol.Vis.Sci.47:5553-60(2006)）。这种技术可以在使用 Rho-/Rho- 敲除小鼠的动物模型（参见 de Gooyer 等，同上）中进行，其中在存在和不存在至少一种化合物的情况下向动物组施用至少一种本文所述的化合物，或可在正常的、野生型动物中进行，其中在存在和不存在至少一种化合物的情况下向动物组施用至少一种本文所述的化合物。其它动物模型包括用于测定光感受器功能的模型，如测量视网膜电流图 (ERG) 振荡电位的

大鼠模型（参见，例如，Liu 等，Invest.Ophthalmol.Vis.Sci.47:5447-52(2006)；Akula 等，Invest.Ophthalmol.Vis.Sci.48:4351-59(2007)；Liu 等，Invest.Ophthalmol.Vis.Sci.47:2639-47(2006)；Dembinska 等，Invest.Ophthalmol.Vis.Sci.43:2481-90(2002)；Penn 等，Invest.Ophthalmol.Vis.Sci.35:3429-35(1994)；Hancock 等，Invest.Ophthalmol.Vis.Sci.45:1002-1008(2004))。

[0269] 正如本文所述和在本领域内所知的，在体外进行用于测定化合物对异构酶活性的效果的方法 (Stecher 等，J Biol Chem 274:8577-85(1999)；另也参见 Golczak 等，Proc.Natl.Acad.Sci.USA 102:8162-67(2005))。从动物（例如，牛、猪、人）分离的视网膜色素上皮 (RPE) 微粒体膜用作异构酶的来源。取代的杂环胺衍生物化合物抑制异构酶的能力也通过体内鼠异构酶试验来测定。已知眼睛短暂暴露于强光（视色素的“光漂白”或简称为“漂白”）会使视网膜中几乎所有的 11- 顺式 - 视黄醛发生光致异构化。11- 顺式 - 视黄醛在漂白后的恢复可以用来评估体内异构酶的活性（参见，例如，Maeda 等，J.Neurochem 85:944-956(2003)；Van Hooser 等，J Biol Chem 277:19173-82,2002)。如前所述进行视网膜电流图 (ERG) 记录 (Haeseleer 等，Nat.Neurosci.7:1079-87(2004)；Sugitomo 等，J.Toxicol.Sci.22Suppl 2:315-25(1997)；Keating 等，Documenta Ophthalmologica100:77-92(2000))。也参见 Deigne 等，Science,244:968-971(1989)；Gollapalli 等，Biochim Biophys Acta.1651:93-101(2003)；Parish 等，Proc.Natl.Acad.Sci.USA 95:14609-13(1998)；Radu 等，Proc Natl Acad Sci USA 101:5928-33(2004))。

[0270] 细胞培养方法，如本文描述的方法，也可用于测定本文所述的化合物对视网膜神经元细胞存活的影响。示例性的细胞培养模型在本文中描述并在美国专利申请公开第 US2005-0059148 号和美国专利申请公开第 US2004-0147019 号（其通过引用整体并入本文）中详细描述，其可用于测定本文所述的取代的杂环胺衍生物化合物增强或延长神经元细胞（特别是视网膜神经元细胞和视网膜色素上皮细胞）存活的能力以及抑制、预防、减缓或者阻碍眼或视网膜或其视网膜细胞或 RPE 的变性的能力，并确定哪些化合物可用于治疗眼科疾病和病症。

[0271] 细胞培养模型包括成熟视网膜细胞的长期或扩展培养，该成熟视网膜细胞包括视网膜神经元细胞（例如，感光细胞、无长突细胞、神经节细胞、水平细胞和双极细胞）。细胞培养系统和生产细胞培养系统的方法提供感光细胞的扩展培养。细胞培养系统还可以包括视网膜色素上皮 (RPE) 细胞和米勒胶质细胞。

[0272] 视网膜细胞培养系统还可以包括细胞应激物。应激物的施加或存在以可用于研究在视网膜疾病或病症中观察到的疾病病理学的方式在体外影响成熟视网膜细胞，包括视网膜神经元细胞。该细胞培养模型提供了体外神经元细胞培养系统，该系统可用于对取代的杂环胺衍生物化合物的鉴定和生物测试，该化合物通常适用于治疗神经系统疾病或病症，且特别用于治疗眼睛和大脑的变性疾病。使来自包括视网膜神经元在内的成熟视网膜组织的原代、体外培养细胞在应激物的存在下维持一段较长时间的能力，使得能够检测细胞与细胞的相互作用，选择和分析刺激神经的化合物和材料，使用受控的细胞培养系统进行体外 CNS 和眼科试验，和分析对来自一致的视网膜细胞群体的单个细胞的影响。

[0273] 细胞培养系统和视网膜细胞应激模型包括培养的成熟视网膜细胞，视网膜神经元和视网膜细胞应激物，其可用于筛选和表征取代的杂环胺衍生物化合物，该化合物能够诱

导或刺激已被疾病破坏的 CNS 组织的再生。该细胞培养系统提供了成熟视网膜细胞培养物，它是成熟视网膜神经元细胞和非神经元视网膜细胞的混合物。该细胞培养系统包括所有主要的视网膜神经元细胞类型（光感受器、双极细胞、水平细胞、无长突细胞和神经节细胞），并且也可以包括其它成熟视网膜细胞，如 RPE 和米勒胶质细胞。通过将这些不同类型的细胞引入体外培养系统中，该系统基本上类似于“人造器官”，这更近似于视网膜的体内自然状态。

[0274] 一种或多种从视网膜组织中分离（收获）并且平板接种进行组织培养的成熟视网膜细胞类型的活力可维持较长的一段时间，例如，从 2 周到 6 个月。视网膜细胞的活力可根据本文所述的和本领域公知的方法来测定。总体上类似于神经元细胞，视网膜神经元细胞在体内不是活跃分裂细胞，因此视网膜神经元细胞的细胞分裂不一定指示活力。该细胞培养系统的优势是能够长时间地培养无长突细胞、光感受器以及相关的神经节投射神经元和其它成熟视网膜细胞，从而提供确定本文描述的取代的杂环胺衍生物化合物对于治疗视网膜疾病的有效性的机会。

[0275] 视网膜细胞或视网膜组织的生物源可以是哺乳动物（例如人、非人灵长类动物、有蹄类动物、啮齿类动物、犬、猪、牛或其它哺乳动物来源）、禽类或来自其它属。可以使用来自出生后非人灵长类动物、出生后猪或出生后鸡的包括视网膜神经元在内的视网膜细胞，但是任何成体或出生后视网膜组织可以适用于该视网膜细胞培养系统。

[0276] 在某些情况下，细胞培养系统可提供视网膜细胞的稳定的长期存活，而不包括从非视网膜组织衍生或分离或纯化的细胞。这样的细胞培养系统包含仅从眼睛的视网膜分离的细胞，因此基本上不含来自与视网膜分离的眼睛其它部分或区域（如睫状体、虹膜、脉络膜和玻璃体）的细胞类型。其它细胞培养方法包括添加非视网膜细胞，如睫状体细胞和 / 或干细胞（其可以是也可以不是视网膜干细胞）和 / 或其它纯化的胶质细胞。

[0277] 本文所述的体外视网膜细胞培养系统可作为生理学视网膜模型，其可用于表征视网膜的生理学方面。这个生理学视网膜模型也可用作更广泛的通用神经生物学模型。细胞应激物可以包括在该模型细胞培养系统中。如本文所述的为视网膜细胞应激物的细胞应激物不利地影响活力或减少细胞培养系统中一种或多种不同视网膜细胞类型（包括视网膜神经元细胞类型）的活力。本领域技术人员会很容易明白和理解，如本文所述，与在适当的对照细胞系统（例如，无细胞应激物的本文所述的细胞培养系统）培养的视网膜细胞相比，表现出降低的活力的视网膜细胞意味着视网膜细胞在细胞培养系统中存活的时间长度减少或降低（缩短的寿命）和 / 或视网膜细胞表现出生物或生化功能的下降、抑制或不利影响（例如代谢减少或异常；凋亡开始；等等）。降低的视网膜细胞活力可由以下现象来指示：细胞死亡；细胞结构或形态的改变或变化；凋亡的诱导和 / 或进展；视网膜神经元细胞神经变性（或神经元细胞损伤）的开始、增强和 / 或加速。

[0278] 测定细胞活力的方法和技术在本文详细描述，并且是本领域技术人员所熟悉的。这些测定细胞活力的方法和技术可用于监测细胞培养系统中视网膜细胞的健康和状态，以及用于测定本文所述的取代的杂环胺衍生物化合物改变（优选增加、延长、增强、改善）视网膜细胞或视网膜色素上皮细胞活力或视网膜细胞存活的能力。

[0279] 细胞培养系统中细胞应激物的添加可用于测定取代的杂环胺衍生物化合物除去、抑制、消除或减轻应激物影响的能力。视网膜细胞培养系统可以包括细胞应激物，该细胞应

激物是化学的（例如，A2E，香烟烟雾浓缩物）；生物的（例如，毒素暴露；β-淀粉样蛋白；脂多糖）；或非化学的，如物理应激物、环境应激物或机械力（例如，增加的压力或光暴露）（参见，例如，US 2005-0059148）。

[0280] 视网膜细胞应激物模型系统还可以包括细胞应激物，例如但不限于，可以作为疾病或病症的风险因子的应激物或可能有助于疾病或病症发展或进展的应激物，包括但不限于，不同波长和强度的光；A2E；暴露于香烟烟雾冷凝物；氧化应激（例如，与过氧化氢、硝普盐、Zn++或Fe++的存在或暴露有关的应激）；增加的压力（例如，大气压或流体静力压）、谷氨酸或谷氨酸激动剂（例如，N-甲基-D-天冬氨酸（NMDA）、α-氨基-3-羟基-5-甲基异噁唑-4-丙酸酯（AMPA）、红藻氨酸、使君子氨酸、鹅膏蕈氨酸、喹啉酸、天冬氨酸、反式-1-氨基环戊基-1,3-二羧酸酯（ACPD））；氨基酸（例如，天冬氨酸、L-半胱氨酸；β-N-甲基胺-L-丙氨酸）；重金属（如铅）；各种毒素（例如线粒体毒素（例如，丙二酸酯，3-硝基丙酸；鱼藤酮、氰化物）；MPTP（1-甲基-4-苯基-1,2,3,6-四氢吡啶），其代谢为其活性毒性代谢物MPP+（1-甲基-4-苯基吡啶））；6-羟基多巴胺；α-突触核蛋白；蛋白激酶C激活剂（如佛波醇肉豆蔻酸乙酸酯）；生物氨基刺激物（例如，甲基苯丙胺，MDMA（3-4亚甲基二氧基甲基苯丙胺））；或一种或多种应激物的组合。有用的视网膜细胞应激物包括模拟影响本文所述的任何一种或多种成熟视网膜细胞的神经变性疾病的应激物。慢性疾病模型特别重要，因为大多数神经变性疾病是慢性的。通过利用这一体外细胞培养系统，在长期疾病发展过程中最早发生的事件可能会因为允许长时间的细胞分析而得到鉴别。

[0281] 视网膜细胞应激物可以改变（即以统计学显著的方式增加或减少）视网膜细胞的活力，如通过改变视网膜细胞（包括视网膜神经元细胞和RPE细胞）的存活，或通过改变视网膜神经元细胞和/或RPE细胞的神经变性。优选地，视网膜细胞应激物不利地影响视网膜神经元细胞或RPE细胞，以使视网膜神经元细胞或RPE细胞的存活下降或受到不利影响（即在应激物的存在下细胞存活的时间长度减少）或细胞的神经变性（或神经细胞损伤）得到增加或加强。应激物可能只影响视网膜细胞培养物中的单一的视网膜细胞类型，或者应激物可能影响两种、三种、四种或更多不同的细胞类型。例如，应激物可以改变感光细胞的活力和存活而不影响其它所有主要的细胞类型（如神经节细胞、无长突细胞、水平细胞、双极细胞、RPE和米勒胶质细胞）。应激物可缩短视网膜细胞（在体内或体外）的存活时间，提高视网膜细胞的神经变性的速度或程度，或以一些其它方式不利地影响视网膜细胞的活力、形态、成熟或寿命。

[0282] 可针对一种或多种不同的视网膜细胞类型测定在细胞培养系统中细胞应激物对视网膜细胞活力的影响（在存在和不存在取代的杂环胺衍生物化合物的情况下）。细胞活力的测定可包括在视网膜细胞培养物制备后，在一段时间长度内以一定的间隔或在特定时间点评价视网膜细胞的结构和/或功能。一种或多种不同的视网膜细胞类型或一种或多种不同的视网膜神经元细胞类型的活力或长期存活可以根据一种或多种生化或生物参数来测定，该参数在观察到形态或结构变化之前指示减少的活力，例如凋亡或代谢功能的下降。

[0283] 当在本文所述的用于维持长期细胞培养的条件下将应激物添加到细胞培养物中时，化学、生物或物理细胞应激物可减少细胞培养系统中存在的一种或多种视网膜细胞类型的活力。或者，可以调节一种或多种培养条件，以使应激物对视网膜细胞的影响可以被更容易地观察到。例如，当细胞暴露于特定的细胞应激物时，细胞培养物中胎牛血清的浓度或

百分比可能会减少或消除（参见，例如，US2005-0059148）。或者，在为了维持细胞而含有特定浓度的血清的培养基中培养的视网膜细胞可突然暴露于不包含任何水平的血清的培养基。

[0284] 视网膜细胞培养物可暴露于细胞应激物一段时间，该时间被确定为降低一种或多种在视网膜细胞培养系统中的视网膜细胞类型的活力。这些细胞在从视网膜组织分离后，在平板接种视网膜细胞后可立即暴露于细胞应激物。或者，视网膜细胞培养物可在培养物建立或其后的任何时间以后暴露于应激物。当两种或更多种细胞应激物包含在视网膜细胞培养系统内时，在视网膜细胞系统培养过程中可同时且以同样长度的时间，或者分别以同样长度的时间或以不同长度的时间在不同时间点，将各个应激物添加到细胞培养系统中。取代的杂环胺衍生物化合物可在视网膜细胞培养物暴露于细胞应激物之前添加，可与细胞应激物同时添加，或者可在视网膜细胞培养物暴露于应激物之后添加。

[0285] 光感受器可通过使用与诸如视蛋白、外周蛋白等光感受器特异性蛋白质特异性结合的抗体来确定。通过使用泛神经元标记物，细胞培养物中的光感受器也可以被鉴别为免疫细胞化学标记的细胞的形态学子集，或者可以在活培养物的对比度增强的图像中在形态学上鉴别。外段可作为光感受器的附件在形态学上检测。

[0286] 包括光感受器在内的视网膜细胞也可以通过功能分析进行检测。例如，电生理学方法和技术可用于测量光感受器对光的反应。光感受器在对光的分级反应上显示出特别的动力学。钙敏感性染料也可用于检测含有活性光感受器的培养物内对光的分级反应。为分析应激诱导化合物或潜在的神经疗法，视网膜细胞培养物可以针对免疫细胞化学进行处理，并且光感受器和／或其它视网膜细胞可以使用显微照相和成像技术由手动或通过计算机软件进行计数。在本领域中已知的其它免疫测定（例如ELISA、免疫印迹法、流式细胞术）也可用于鉴别和表征本文所述的细胞培养模型系统的视网膜细胞和视网膜神经元细胞。

[0287] 视网膜细胞培养应激模型也可以用于鉴别由所关注的生物活性剂（如本文所述的取代的杂环胺衍生物化合物）引起的直接和间接的药理学剂效应。例如，在一种或多种视网膜细胞应激物的存在下加入到细胞培养系统中的生物活性剂可通过加强或减少其它细胞类型的存活的方式刺激一种细胞类型。细胞／细胞的相互作用和细胞／细胞外组分的相互作用可能在理解疾病和药物功能的机制上是重要的。例如，一种神经元细胞类型可以分泌影响另一种神经元细胞类型的生长或存活的营养因子（参见，例如，WO99/29279）。

[0288] 在另一实施方案中，将取代的杂环胺衍生物化合物引入到包含本文所述的视网膜细胞培养应激模型系统的筛选试验中，以确定化合物是否和／或在何种水平或程度上增加或延长多个视网膜细胞的活力（即以统计学显著的或生物学显著的方式增加）。本领域技术人员会很容易明白和理解，如本文所述，与在适当的对照细胞系统（例如，不存在该化合物的本文所述的细胞培养系统）中培养的视网膜细胞相比，表现出活力增强的视网膜细胞意味着视网膜细胞在细胞培养系统中存活的时间长度增加（增加的寿命）和／或视网膜细胞维持生物或生化功能（正常的代谢和细胞器功能、凋亡的缺乏，等等）。增加的视网膜细胞活力可由如下现象指示：延迟的细胞死亡或者减少的死亡或濒死细胞数目；结构和／或形态的维持；凋亡的缺乏或延迟启动；视网膜神经元细胞的神经变性的延迟、抑制、减缓进展和／或消除；或延迟或消除或阻止神经元细胞损伤的影响。确定视网膜细胞活力以及因此视网膜细胞是否展示出增加的活力的方法和技术在本文中更详细描述，并且对于本领域

的技术人员而言是已知的。

[0289] 在某些实施方案中，提供了一种用于确定取代的杂环胺衍生物化合物是否提高了感光细胞的存活的方法。一种方法包括在足以使视网膜神经元细胞与化合物之间相互作用的条件和时间下，使本文所述的视网膜细胞培养系统接触取代的杂环胺衍生物化合物。增强的存活（存活时间的延长）可根据本文所述的和本领域已知的方法进行测量，包括检测视紫质的表达。

[0290] 取代的杂环胺衍生物化合物提高视网膜细胞活力和/或增强、促进或延长细胞存活（即，延长包括视网膜神经元细胞在内的视网膜细胞存活的时间），和/或损害、抑制或妨碍作为本文所述应激的直接或间接结果的变性的能力，可通过本领域技术人员已知的多种方法中的任何一种来确定。例如，在存在和不存在化合物的情况下细胞形态学的变化可通过视觉检查来确定，如通过光学显微镜检查、共聚焦显微镜检查或本领域已知的其它显微镜检查。例如，细胞的存活也可以通过对活细胞和/或不存活的细胞进行计数来确定。免疫化学或免疫组织化学技术（如固定细胞染色或流式细胞术）可用于鉴别和评价细胞骨架结构（例如，通过使用细胞骨架蛋白质（如胶质纤维酸性蛋白、纤连蛋白、肌动蛋白、波形蛋白、微管蛋白等）特异性抗体）或评价本文所述的细胞标记物的表达。取代的杂环胺衍生物化合物对细胞完整性、形态学和/或存活的影响也可通过测定神经元细胞多肽如细胞骨架多肽的磷酸化状态来确定（参见，例如，Sharma 等，J.Biol.Chem.274:9600-06(1999)；Li 等，J.Neurosci.20:6055-62(2000)）。细胞存活或细胞死亡也可根据本文所述的和本领域已知的用于测量凋亡的方法（例如，膜联蛋白 V 结合、DNA 片段化测定、胱天蛋白酶活化、标记物分析，例如聚（ADP- 核糖）聚合酶（PARP）等）来确定。

[0291] 在脊椎动物的眼睛，例如，哺乳动物的眼睛中，A2E 的形成是一个光依赖性过程，并且其积聚导致眼睛中的一些不利影响。这包括视网膜色素上皮（RPE）膜的去稳定化，细胞对蓝光损伤的敏化和受损的磷脂降解。分子氧（环氧乙烷）氧化 A2E（和 A2E 相关分子）的产物显示出在培养的 RPE 细胞中诱导 DNA 损伤。所有这些因素导致视敏度度逐渐下降，并最终视力丧失。如果在视觉过程中减少视黄醛的形成是可能的，那么这种减少将导致眼睛中 A2E 的量的减少。不希望被理论所约束，A2E 积聚的减少可减少或延迟 RPE 和视网膜中的变性过程，因此可以减缓或防止在干型 AMD 和斯塔加特病中的视力丧失。

[0292] 在另一实施方案中，提供了治疗和/或预防变性疾病和病症（包括本文所述的视网膜神经变性疾病和眼科疾病，以及视网膜疾病和病症）的方法。需要这种治疗的受试者是人或非人灵长类动物或其它动物，这些受试者已经显现出视网膜变性疾病的症状，或有发展成视网膜变性疾病的风险。如本文所述，提供了通过向受试者施用包含药学上可接受的载体和取代的杂环胺衍生物化合物（例如，具有如式 (A) 或式 (B) 的结构及其子结构的化合物）的组合物来治疗（包括防止或预防）眼科疾病或病症的方法。如本文所述，提供了通过施用本文所述的包含取代的杂环胺衍生物化合物的药物组合物来提高神经元细胞（如包括感光细胞在内的视网膜神经元细胞）的存活和/或抑制视网膜神经元细胞变性的方法。

[0293] 在取代的杂环胺衍生物化合物存在下一种或多种视网膜细胞类型的增强的存活（或延长或增长的存活）表明，该化合物是用于治疗变性疾病的有效药剂，该疾病尤其是视网膜疾病或病症，并包括视网膜神经变性疾病或病症。细胞存活和增强的细胞存活可以根

据本文所述的和本领域技术人员已知的方法确定，包括活力测定和检测视网膜细胞标记蛋白的表达的试验。为了确定感光细胞增强的存活，可以检测视蛋白，例如，包括由视杆表达的视紫质蛋白质。

[0294] 在另一实施方案中，受试者正在接受针对斯塔加特病或斯塔加特氏黄斑变性的治疗。在与 ABCA4（也称为 ABCR）转运体突变有关的斯塔加特病中，已经提出全反式视黄醛的积聚是脂褐质色素 A2E 的形成的原因，A2E 对视网膜细胞具有毒性，并且导致视网膜变性，因此导致视力丧失。

[0295] 在又一个实施方案中，受试者正在接受针对年龄相关性黄斑变性 (AMD) 的治疗。在不同实施方案中，年龄相关性黄斑变性可为湿型或干型。在 AMD 中，视力丧失主要发生在疾病晚期的并发症导致新的血管在黄斑下生长或黄斑萎缩时。不打算被任何特定理论所约束，已经提出全反式视黄醛的积聚是脂褐质色素 N- 亚视黄基 -N- 视黄基乙醇胺 (A2E) 和 A2E 相关分子形成的原因，后者对 RPE 和视网膜细胞具有毒性，并且导致视网膜变性，最终导致视力丧失。

[0296] 本文所述的化合物和方法可以治疗、治愈、预防、改善其症状或减缓、抑制或停止其进展的视网膜神经变性疾病或病症，是导致或其特征为视网膜神经元细胞损失的疾病或病症，这是视力缺损的原因。这样的疾病或病症包括但不限于年龄相关性黄斑变性（包括干型和湿型黄斑变性）和斯塔加特氏黄斑营养不良。

[0297] 本文所述的年龄相关性黄斑变性是影响黄斑（视网膜中央区域）且导致中央视力下降和丧失的疾病。年龄相关性黄斑变性通常发生在 55 岁以上的个体中。年龄相关性黄斑变性的病因可能既包括环境影响也包括遗传因素（参见，例如，Lyengar 等，Am. J. Hum. Genet. 74:20-39(2004)(Epub 2003 年 12 月 19 日）；Kenealy 等，Mol. Vis. 10:57-61(2004)；Gorin 等，Mol. Vis. 5:29(1999)）。更罕见地，黄斑变性也发生在年轻个体中，包括儿童和婴儿，且通常，这些疾病是由基因突变引起的。青少年黄斑变性的类型包括斯塔加特病（参见，例如，Glazer 等，Ophthalmol. Clin. North Am. 15:93-100, viii(2002)；Weng 等，Cell 98:13-23(1999)）；多恩蜂巢状视网膜营养性萎缩（参见，例如，Kermani 等，Hum. Genet. 104:77-82(1999)）；Sorsby 眼底营养不良，Malattia Levintinese，眼底黄色斑点症和常染色体显性出血性黄斑营养不良（又参见 Seddon 等，Ophthalmology 108:2060-67(2001)；Yates 等，J. Med. Genet. 37:83-7(2000)；Jaakson 等，Hum. Mutat. 22:395-403(2003)）。RPE 的地图状萎缩是非新生血管性干型年龄相关性黄斑变性的晚期形式，并与脉络膜毛细管层、RPE 和视网膜的萎缩有关。

[0298] 斯塔加特氏黄斑变性是一种隐性遗传性疾病，是儿童的遗传性失明疾病。斯塔加特病的主要病理缺陷也是毒性脂褐质色素如 A2E 在视网膜色素上皮 (RPE) 细胞中的积聚。这种积聚似乎是在斯塔加特病患者中发现的光感受器死亡和重度视力丧失的原因。本文所述的化合物通过抑制视觉循环中的异构酶而减缓 11- 顺式 - 视黄醛 (11cRAL 或视黄醛）的合成和视紫质的再生。视紫质的光激活导致其全反式视黄醛的释放，全反式视黄醛构成了 A2E 生物合成的第一反应物。用取代的杂环胺衍生物化合物进行治疗抑制了脂褐质的积聚，从而延缓了斯塔加特病和 AMD 患者的视力丧失的发作，而没有将会阻碍用取代的杂环胺衍生物化合物治疗的毒性作用。本文所述的化合物用于对其它形式的与脂褐质积聚相关的视网膜或黄斑变性的有效治疗。

[0299] 向受试者施用取代的杂环胺衍生物化合物可以防止对视网膜细胞有毒性且引起视网膜变性的脂褐质色素 A2E(和 A2E 相关分子)的形成。在一些实施方案中,取代的杂环胺衍生物化合物的施用减少了废物(如脂褐质色素 A2E(和 A2E 相关分子))的产生,改善了 AMD(例如,干型)和斯塔加特病的发展,并减少或延缓了视力丧失(例如,脉络膜新生血管形成和/或脉络膜视网膜萎缩)。在以前的研究中,曾经向患者施用 13- 顺式 - 视黄酸(Accutane®或异维 A 酸 (Isotretinoin))(一种通常用于治疗痤疮的药物和 11- 顺式 - 视黄醇脱氢酶的抑制剂)以防止 RPE 中的 A2E 积聚。然而,这种建议疗法的主要缺点是 13- 顺式 - 视黄酸可以很容易异构化为全反式视黄酸。全反式视黄酸是一种非常强的致畸化合物,其会不利地影响细胞的增殖和发展。视黄酸还积聚在肝脏中并可能是肝脏疾病的促成因素。

[0300] 在另一些实施方案中,将取代的杂环胺衍生物化合物施用于受试者,如具有眼中 ABCA4 转运体突变的人。在一些实施方案中,将取代的杂环胺衍生物化合物施用于老年受试者。如本文所使用的,老年人受试者通常是至少 45 岁,或至少 50 岁,或至少 60 岁,或至少 65 岁。在与 ABCA4 转运体的突变有关的斯塔加特病中,已经提出全反式视黄醛的积聚是对视网膜细胞有毒性的并导致视网膜变性和最终视力丧失的脂褐质色素 A2E(和 A2E 相关分子)形成的原因。不希望被理论所约束,本文所述的取代的杂环胺衍生物化合物是在视觉循环中所涉及的异构酶的强抑制剂。用本文所述的取代的杂环胺衍生物化合物治疗患者阻止或减缓了 A2E(和 A2E 相关分子)的形成,并且对正常视力可能具有保护性质。

[0301] 在其它一些实施方案中,本文所述的一种或多种化合物用于治疗其它眼科疾病或病症,例如,青光眼、视网膜脱落、出血性视网膜病、色素性视网膜炎、炎性视网膜病、增生性玻璃体视网膜病、视网膜营养性萎缩、遗传性视神经病变、Sorsby 眼底营养不良、葡萄膜炎、视网膜损伤、视神经病变;以及与其它神经变性疾病相关的视网膜病症,该神经变性疾病如阿尔茨海默病、多发性硬化症、帕金森病或其它影响脑细胞的神经变性疾病;与病毒性感染或其它状况如 AIDS 有关的视网膜病症。视网膜病症还包括视网膜的光损害,这与增加的光暴露(即过度的光暴露)有关,例如,在手术过程中偶然的强烈的或激烈的光暴露;强烈的、激烈的或长期的日光暴露,如在沙漠或积雪地形;在战斗中,例如,在注视照明弹或爆炸或激光装置等时。视网膜疾病可为变性或非变性性质的。视网膜变性疾病的非限制例子包括年龄相关性黄斑变性和斯塔加特氏黄斑营养不良。非变性视网膜疾病的例子包括但不限于出血性视网膜病、色素性视网膜炎、视神经病变、炎性视网膜病、糖尿病视网膜病变、糖尿病性斑丘疹病、视网膜血管闭塞、早产儿视网膜病或缺血再灌注相关性视网膜损伤、增生性玻璃体视网膜病、视网膜营养性萎缩、遗传性视神经病变、Sorsby 眼底营养不良、葡萄膜炎、视网膜损伤、与阿尔茨海默病相关的视网膜病症、与多发性硬化症相关的视网膜病症、与帕金森病相关的视网膜病症、与病毒感染相关的视网膜病症、与过度光暴露相关的视网膜病症和与 AIDS 相关的视网膜病症。

[0302] 在其它一些实施方案中,至少一种本文所述的化合物用于治疗、治愈、预防、改善症状,或减缓、抑制或制止某些眼科疾病和病症的进展,所述眼科疾病和病症包括但不限于糖尿病视网膜病变、糖尿病性斑丘疹病、糖尿病性黄斑水肿、视网膜缺血、缺血再灌注相关性视网膜损伤和视网膜血管闭塞(包括静脉闭塞和动脉闭塞)。

[0303] 糖尿病视网膜病变是人类失明的主要原因,并且是糖尿病的一种并发症。当糖尿

病损害视网膜内部的血管时会出现糖尿病视网膜病变。非增生性视网膜病变是一种常见的、通常为轻度的形式，一般不会妨碍视力。异常仅限于视网膜，并且只有当涉及黄斑时，视力才会受到损伤。如果不治疗，视网膜病可进展为增生性视网膜病变，这是更为严重的糖尿病视网膜病变形式。当新的血管在视网膜中和其周围增生时，发生增生性视网膜病变。因此，可能发生向玻璃体内出血、视网膜水肿和 / 或视网膜脱落，从而导致失明。

[0304] 可使用本文所述的方法和组合物治疗的其它眼科疾病和病症包括与视网膜内缺血相关的、由视网膜内缺血加剧的或由其引起的疾病、病症和病状。视网膜缺血包括内视网膜和外视网膜的缺血。视网膜缺血可因脉络膜或视网膜血管疾病如中央或分支视网膜视力阻塞、胶原血管疾病和血小板减少性紫癜而发生。视网膜静脉周围炎和系统性红斑狼疮可见视网膜脉管炎和闭塞。

[0305] 视网膜缺血可能与视网膜血管闭塞有关。在美国，分支和中央视网膜静脉闭塞是糖尿病视网膜病变后第二大常见的视网膜血管疾病。约 7％至 10％的一只眼睛有视网膜静脉闭塞症的患者最终双侧染病。视野丧失通常因黄斑水肿、缺血或在血管内皮生长因子释放诱导的视盘或视网膜新血管形成后继发的玻璃体出血而发生。

[0306] 在视网膜动静脉通道交叉处（动脉和静脉有一个共同的外膜鞘的区域）的动脉硬化因交叉动脉而导致视网膜静脉壁的收缩。该收缩导致血栓形成和随后的静脉闭塞。阻断的静脉可导致在静脉流经区域的血 - 视网膜屏障崩溃后继发的黄斑水肿和出血、在静脉流中具有紊流的循环的中断、内皮损伤和局部缺血。临床上，缺血性视网膜区域出现被称为棉絮状渗出点的羽毛状白色斑块。

[0307] 具有丰富的缺血的分支视网膜静脉闭塞引起急性中央和旁中央视野损失，这与所累及的视网膜象限的位置相对应。由于缺血导致的视网膜新血管形成可能导致玻璃体出血以及亚急性或急性视力丧失。

[0308] 取决于是否存在普遍的视网膜缺血，可发生两种类型的视网膜中央静脉闭塞 :缺血型和非缺血型。即使在非缺血型中，黄斑仍可能缺血。大约 25％的视网膜中央静脉闭塞是缺血型的。视网膜中央静脉闭塞的诊断通常可以根据特征性检眼镜检查结果作出，其包括所有象限中的视网膜出血、扩张及扭曲的静脉和棉絮状渗出点。黄斑水肿和中心凹缺血可导致视力丧失。细胞外液增加组织间隙压，这可导致视网膜毛细血管闭合（即片状缺血性视网膜白化）或睫状视网膜动脉闭塞的区域。

[0309] 缺血性视网膜中央静脉闭塞患者更可能出现视力丧失的突发发作，并具有低于 20/200 的视敏度，相对传入性瞳孔缺陷，丰富的视网膜内出血，和荧光素血管造影术的广泛无灌注。缺血性视网膜中央静脉闭塞的自然史与不良后果相关 :最终，大约三分之二的患有缺血性视网膜中央静脉闭塞的患者将有眼睛新生血管形成，而三分之一的患者将有新生血管性青光眼。后一种病状是严重的青光眼类型，可导致快速视野和视力丧失、伴有继发性上皮侵蚀和易感细菌性角膜炎的角膜上皮水肿、严重的疼痛、恶心和呕吐，以及最终的眼球痨（没有光感的眼球萎缩）。

[0310] 如本文使用的，患者（或受试者）是任何哺乳动物，包括人，其可罹患神经变性疾病或症状，包括眼科疾病或病症，或可能无可检测的疾病。因此，可以向已有疾病的受试者施用治疗，或者治疗可以是预防性的，向具有发展为疾病或症状的风险的受试者施用。处理或治疗是指在损伤、病理或病状的治疗或改善中成功的任何指标，包括任何客观或主观的

参数，如消除；减轻；症状的消失或使损伤、病理或病状对患者而言是更可耐受的；减缓变性或衰退的速度；使变性的终点不太虚弱；或改善受试者的身体或精神健康。

[0311] 症状的治疗或缓和可以基于客观或主观的参数，包括身体检查的结果。因此，术语“治疗”包括本文所述的化合物或药剂的施用以治疗疼痛、痛觉过敏、异常性疼痛或疼痛性事件，以及防止或延迟、缓解或阻滞或抑制与疼痛、痛觉过敏、异常性疼痛、疼痛性事件或其它病症相关的症状或病状的发展。术语“疗效”是指受试者的疾病、该病的症状或该病的后遗症的减少、消除或预防。治疗还包括经过一段时间后测量（例如，几周或几个月内测量），恢复或改善脊椎动物视觉系统中视网膜神经元细胞的功能（包括光感受器功能），例如，如视敏度和视野测试等。治疗还包括稳定疾病进展（即减缓、减少或停止眼科疾病及相关症状的进展），以及最小化脊椎动物视觉系统的其它变性。治疗还包括预防，是指将取代的杂环胺衍生物化合物施用于受试者以防止脊椎动物受试者的视觉系统的变性或进一步的变性或者恶化或进一步的恶化，并防止或抑制疾病和/或相关症状的发展和后遗症。

[0312] 医疗和眼科领域技术人员用以确定和评价疾病状态和/或监测并评估治疗方案的各种方法和技术包括，例如，荧光素血管造影术、眼底照相术、脉络膜循环系统的吲哚青绿染料示踪、眼底检查法、光学相干断层扫描（OCT）和视敏度测试。

[0313] 荧光素血管造影术包括静脉注射荧光素染料，然后观察染料在循环通过眼睛时的任何渗漏。吲哚青绿染料的静脉注射也可用于确定眼内的血管是否受到损害，特别是在正好位于视网膜后的脉络膜循环系统中。眼底照相术可用于检查视神经、黄斑、血管、视网膜和玻璃体。微动脉瘤是糖尿病视网膜病变中的可见病变，其可以于疾病早期在眼底数字影像中检测到（参见，例如，美国专利申请公开第2007/0002275号）。检眼镜可用于检查视网膜和玻璃体。眼底检查法通常随瞳孔放大进行，以得到眼内的最佳查看。可使用两种类型的检眼镜：直接的和间接的。直接检眼镜通常用于查看视神经和中央视网膜。外围或整个视网膜可通过使用间接检眼镜查看。光学相干断层扫描（OCT）得到身体组织的高分辨率、高速、非侵入性横截面图像。OCT是非侵入性的，并提供对组织破坏早期微观指征的检测。

[0314] 受试者或患者是指任何施用本文所述的组合物的脊椎动物或哺乳动物患者或受试者。术语“脊椎动物”或“哺乳动物”包括人和非的灵长类动物，和实验动物如兔子、大鼠、小鼠和其它动物，如家养宠物（如猫，狗，马）、农场动物和动物园动物。需要用本文所述的方法治疗的受试者可按照在医疗领域公认的筛查方法进行鉴别，其用来确定与本文所述的眼科疾病或病状相关的风险因素或症状，或者确定受试者中现有的眼科疾病或病状的状态。这些以及其它常规方法允许临床医生选择需要使用本文所述的方法和制剂进行治疗的患者。

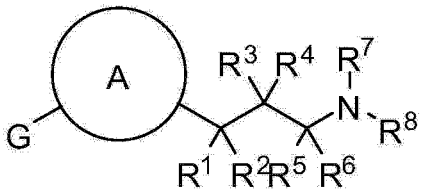
药物组合物

[0315] 在某些实施方案中，取代的杂环胺衍生物化合物作为纯化学品施用。在其它实施方案中，取代的杂环胺衍生物化合物与药学上合适的或可接受的载体（在本文中也称为药学上合适的（或可接受的）赋形剂，生理学上合适的（或可接受的）赋形剂，或者生理学上合适的（或可接受的）载体）组合，该载体基于所选择的给药途径和如以下文献中所述的标准制药实践进行选择，例如，Remington:The Science and Practice of Pharmacy (Gennaro,21$^{st}$ Ed.Mack Pub.Co.,Easton,PA(2005)，其公开内容通过引用整体并入本文。

[0316] 因此，本文提供了一种药物组合物，其包含一种或多种取代的杂环胺衍生物化合

物或其立体异构体、前药、药学上可接受的盐、水合物、溶剂化物、酸式盐水合物、N- 氧化物或同形结晶形式，以及一种或多种药学上可接受的载体，及任选地，其它治疗和 / 或预防性成分。如果载体（或赋形剂）与组合物的其它成分兼容且不对组合物的接受者（即，受试者）有害，则该载体就是可接受的或合适的。药学上可接受的或合适的组合物包括眼科合适的或可接受的组合物。

[0317] 一个实施方案提供了一种药物组合物，其包含药学上可接受的载体和式 (A) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(A)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 $-O-C(R^9)_2-$、$-O-C(=O)-$、$-S-C(R^9)_2-$、$-S(O)-C(R^9)_2-$、$-S(O)_2-C(R^9)_2-$、$-SO_2(NR^9)-$、$-NR^9-C(R^9)_2-$、$-NR^9-C(=O)-$、$-NR^9-S(O)_2-$、$-C(R^9)_2-C(R^9)_2-$、$-C(=O)-C(R^9)_2-$、$-C(R^9)_2-C(=O)-$、$-C(R^9)=C(R^9)-$、$-C\equiv C-$、$-C(=O)-N(R^9)-$、$-C(=O)-O-$、$-C(R^9)_2-O-$ 和 $-C(R^9)_2-NR^9-$；

Y 选自 $C_3-C_{15}$ 烷基、碳环基、碳环基烷基、杂环基、杂环基烷基、芳基或芳烷基；

$R^1$ 和 $R^2$ 各自独立地选自氢、卤素、烷基、氟代烷基、$-OR^9$、$-NR^{10}R^{11}$ 或碳环基；或者 $R^1$ 和 $R^2$ 形成氧代基团；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键以提供双键；或者任选地，$R^1$ 和 $R^3$ 一起形成直接键，且 $R^2$ 和 $R^4$ 一起形成直接键以提供三键；

$R^3$ 和 $R^4$ 各自独立地选自氢、卤素、$C_1-C_5$ 烷基、氟代烷基、$-OR^9$ 或 $-NR^{10}R^{11}$；或者 $R^3$ 和 $R^4$ 一起形成氧代基团；

$R^5$ 和 $R^6$ 各自独立地选自氢、烷基、烯基、氟代烷基、芳基、杂芳基、碳环基或 C- 连接的杂环基；或者 $R^5$ 和 $R^6$ 和与它们连接的碳原子一起形成碳环基或杂环基；或者 $R^5$ 和 $R^6$ 一起形成亚氨基；

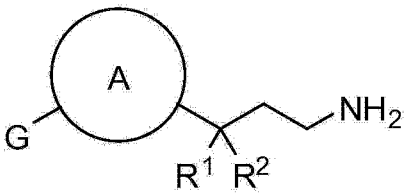
$R^7$ 和 $R^8$ 各自独立地选自氢、烷基、碳环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^7$ 和 $R^8$ 和与它们连接的氮原子一起形成 N- 杂环基；

各 $R^9$ 独立地为氢或烷基；

各 $R^{10}$ 和 $R^{11}$ 独立地选自氢、烷基、碳环基、杂环基、$-C(=O)R^{13}$、$SO_2R^{13}$、$CO_2R^{13}$ 或 $SO_2NR^{10}R^{11}$；或者 $R^{10}$ 和 $R^{11}$ 和与它们连接的氮原子一起形成 N- 杂环基；且

各 $R^{13}$ 独立地选自烷基、杂烷基、烯基、芳基、芳烷基、碳环基、杂芳基或杂环基。

[0318] 一个实施方案提供了一种药物组合物，其包含药学上可接受的载体和式 (B) 的化合物或其互变异构体、立体异构体、几何异构体或其药学上可接受的溶剂化物、水合物、盐或 N- 氧化物：




式(B)

其中，

环 A 选自 1,3- 二取代的杂环；

G 为 -X-Y；

X 选自 -O-、-S-、-NH- 或 $-CH_2-$；

Y 选自碳环基或杂环基；且

$R^1$和 $R^2$各自独立地选自氢或 -OH；或者 $R^1$和 $R^2$形成氧代基团。

[0319] 药物组合物（例如，用于口服或用于通过注射或组合装置递送，或用于作为滴眼剂施用）可以是液体或固体的形式。液体药物组合物可以包括，例如，以下一种或多种：无菌稀释剂如注射用水、盐水溶液（优选生理盐水）、林格氏溶液、等渗氯化钠、可作为溶剂或悬浮介质的不挥发性油、聚乙二醇、甘油、丙二醇或其它溶剂；抗菌剂；抗氧化剂；螯合剂；缓冲液和张度调节剂如氯化钠或右旋糖。肠胃外给药制剂可以封装在用玻璃或塑料制成的安瓿、一次性注射器或多剂量瓶中。生理盐水通常用作赋形剂，且可注射的药物组合物或经眼睛递送的组合物优选是无菌的。

[0320] 在某些实施方案中，所述化合物基本上是纯的，因为其含有少于约 5％或少于约 1％，或少于约 0.1％的其它有机小分子，例如，如在合成方法的一个或多个步骤中产生的污染性中间体或副产物。在其它一些实施方案中，施用一种或多种取代的杂环胺衍生物化合物的组合。

[0321] 在一些实施方案中，取代的杂环胺衍生物化合物通过任何适当的方式递送给受试者，该方式包括，例如，口服、肠胃外、眼内、静脉内、腹膜内、鼻内（或其它递送到例如鼻、咽喉和支气管的粘膜的方法），或通过向眼睛局部给药，或通过眼内或眼周装置。局部给药的方式包括，例如，滴眼剂、眼内注射或眼周注射。眼周注射通常涉及在结膜下或向 Tennon 间隙（覆盖眼睛的纤维组织下方）内注射合成的异构化抑制剂，即取代的杂环胺衍生物化合物。眼内注射通常涉及向玻璃体内注射取代的杂环胺衍生物化合物。在某些实施方案中，给药是非侵入性的，如通过滴眼剂或口服剂型，或作为联合装置。

[0322] 在一些实施方案中，使用药学上可接受的（合适的）载体或赋形剂以及本领域中常规使用的技术将取代的杂环胺衍生物化合物配制成用于给药。药学上可接受的或合适的载体包括眼科合适的或可接受的载体。载体根据取代的杂环胺衍生物化合物的溶解度进行选择。合适的眼科组合物包括那些可向眼睛局部施用的组合物，如通过滴眼剂、注射等施用的组合物。在滴眼剂的情况下，该制剂任选地还包括，例如，眼科相容的药剂，如，诸如氯化钠、浓缩甘油等的等渗剂；诸如磷酸钠、醋酸钠等缓冲剂；诸如聚氧乙烯脱水山梨糖醇单油酸酯（也称为聚山梨酯 80）、聚烃氧基硬脂酸酯 40、聚氧乙烯氢化蓖麻油等表面活性剂；诸如柠檬酸钠、依地酸钠等稳定剂；诸如苯扎氯铵、对羟基苯甲酸酯等防腐剂；及其它成分。防腐剂可以例如以约 0.001％到约 1.0％重量 / 体积的水平使用。该制剂的 pH 值通常在眼

科制剂可以接受的范围内，如在约 pH 4-8 的范围内。

[0323] 对于注射，取代的杂环胺衍生物化合物在注射级盐水溶液中、以可注射脂质体溶液、缓释聚合物体系等形式提供。眼内和眼周注射对本领域技术人员而言是已知的，并在许多出版物中有所描述，包括，例如，Spaeth,Ed.,Ophthalmic Surgery:Principles of Practice,W.B.Sanders Co.,Philadelphia,Pa.,85-87,1990。

[0324] 为了通过粘膜途径递送包含至少一种本文所述化合物的组合物，包括递送到鼻道、咽喉和气道，该组合物可以以气雾剂的形式递送。该化合物可以是用于粘膜内递送的液体或粉末形式。例如，该组合物可以通过具有诸如碳氢化合物推进剂（例如，丙烷、丁烷、异丁烯）等合适的推进剂的加压气雾剂容器递送。该组合物可通过诸如喷雾器或雾化器等非加压递送系统递送。

[0325] 合适的口服剂型包括，例如，片剂，丸剂，囊剂，或硬或软明胶、甲基纤维素或其它合适的易于在消化道中溶解的材料的胶囊。可使用合适的无毒固体载体，其包括，例如，制药级别的甘露醇、乳糖、淀粉、硬脂酸镁、糖精钠、滑石、纤维素、葡萄糖、蔗糖、碳酸镁等。（参见，例如，Remington:The Science and Practice of Pharmacy(Gennaro,21$^{st}$ Ed.Mack Pub.Co.,Easton,PA(2005))。

[0326] 在一些实施方案中，将本文所述的取代的杂环胺衍生物化合物配制成用于持续或缓慢释放。这样的组合物通常可使用众所周知的技术来制备，并通过例如口腔、眼周、眼内、直肠或皮下植入，或通过在期望的目标位置植入来施用。持续释放制剂可以包含分散在载体基质中和/或包含在由速率控制膜包围的储层中的药剂。在这类制剂内使用的赋形剂为生物相容性的，并且也可以是可生物降解的；优选地，该制剂提供相对恒定的活性成分释放水平。持续释放制剂中活性化合物的量取决于植入的位置、释放的速率和预期持续时间以及所要治疗或预防的病状的性质。

[0327] 通过眼部途径施用的药物或组合物的全身药物吸收对本领域技术人员而言是已知的（参见，例如，Lee 等，Int.J.Pharm.233:1-18(2002)）。在一个实施方案中，取代的杂环胺衍生物化合物通过眼睛局部递送方法递送（参见，例如，Curr.Drug Metab.4:213-22(2003)）。在一些实施方案中，该组合物为滴眼剂、油膏或软膏等形式，如水性滴眼剂、水性眼科悬浮液、非水性滴眼剂和非水性眼科悬浮液、凝胶、眼用软膏等。为了制备凝胶，可以使用例如聚羧乙烯聚合物、甲基纤维素、海藻酸钠、羟丙基纤维素、乙烯马来酸酐聚合物等。

[0328] 包含至少一种本文所述的取代的杂环胺衍生物化合物的组合物的剂量有所不同，这取决于患者（例如人）的病状（即疾病的阶段）、一般健康状况、年龄以及其它医疗领域技术人员用于确定剂量的因素。当该组合物用作滴眼剂时，例如，可以每日约 1 次至约 6 次应用每单位剂量一至数滴，优选 1 或 2 滴（每 1 滴约 50μl）。

[0329] 药物组合物可以按照由医疗领域技术人员所确定的适于所治疗（或预防）的疾病的方式施用。适当的剂量和合适的给药持续时间和频率将取决于如下因素：患者的状况、受试者疾病的种类和严重程度、有效成分的具体形式以及给药方法。一般而言，适当的剂量和治疗方案以足以提供治疗和/或预防益处（例如，改善的临床结果，如更频繁的完全或部分缓解，或更长的无病和/或总存活期，或症状严重程度的减轻）的量提供组合物。对于预防性应用，剂量应足以防止与视网膜神经元细胞的神经变性和/或其它成熟视网膜细胞如

RPE 细胞的变性相关的疾病，延缓其发病，或降低其严重程度。最佳剂量通常可利用试验模型和 / 或临床试验来确定。最佳剂量可取决于患者的身体质量、体重或血量。

[0330] 取代的杂环胺衍生物化合物的剂量根据受试者的临床状态、病状和年龄、剂型等适当选择。在滴眼剂的情况下，取代的杂环胺衍生物化合物例如以每单次剂量从约 0.01mg、约 0.1mg 或约 1mg 至约 25mg、至约 50mg、至约 90mg 施用。根据需要，滴眼剂每天施用一次或多次。在注射剂的情况下，合适的剂量为，例如，约 0.0001mg、约 0.001mg、约 0.01mg 或约 0.1mg 至约 10mg、至约 25mg、至约 50mg 或至约 90mg 的取代的杂环胺衍生物化合物，每周一次到七次。在其它实施方案，每周一次到七次施用约 1.0 到约 30mg 取代的杂环胺衍生物化合物。

[0331] 口服剂量通常是从 1.0 到 1000mg，每天一次到四次或更多次。示例性的口服剂量范围为 10 至 250mg，每天一至三次。如果组合物是液体制剂，则该组合物在每单位体积载体中包含特定质量或重量（例如，从 1.0 到 1000mg）的至少 0.1％的活性化合物，例如，从约 2％到约 60％。

[0332] 在某些实施方案中，至少一种本文所述的取代的杂环胺衍生物化合物在可以抑制或阻止视杆细胞的暗适应的条件和时间下施用。在某些实施方案中，在睡前至少 30 分钟（半小时）、60 分钟（一小时）、90 分钟（1.5 小时）或 120 分钟（2 小时）将该化合物施用于受试者。在某些实施方案中，在受试者晚上睡前施用该化合物。在其它一些实施方案中，通过将受试者置于移除光线的环境中，如将受试者置于黑暗的房间中或通过在受试者的眼睛上施加眼罩，可在白天或在正常光照条件下阻断或移除光刺激。当以这样的方式或通过本领域中考虑的其它手段移除光刺激时，可以在睡前施用该药剂。

[0333] 为了防止或抑制视杆细胞的暗适应而施用的化合物的剂量可以根据受试者的临床状态、病状和年龄、剂型等适当选择。在滴眼剂的情况下，化合物（或包含该化合物的组合物）可例如以每单次剂量从约 0.01mg、约 0.1mg 或约 1mg 至约 25mg、至约 50mg、至约 90mg 施用。在注射剂的情况下，合适的剂量为，例如，约 0.0001mg、约 0.001mg、约 0.01mg 或约 0.1mg 至约 10mg、至约 25mg、至约 50mg 或至约 90mg 的化合物，在睡前或对受试者移除所有光源前，每周施用一到七天之间的任意天数。在某些其它实施方案中，对于化合物通过滴眼剂或注射剂的给药，其剂量为 1-10mg（化合物）/kg（受试者的体重）（即，例如，对体重 80kg 的受试者，每剂量 80-800mg 总量）。在其它一些实施方案，每周一到七次施用约 1.0 到约 30mg 化合物。口服剂量通常是从约 1.0 到约 1000mg，施用每周一到七天之间的任意天数。示例性的口服剂量范围为约 10 至约 800mg，每天睡前一次。在其它一些实施方案中，该组合物通过玻璃体内给药的方式施用。

[0334] 还提供了本文所述的化合物和药物组合物的制备方法。包含药学上可接受的赋形剂或载体和至少一种本文所述的取代的杂环胺衍生物化合物的组合物如下制备：根据本文所述的或本领域中实践的任何一种方法合成该化合物，然后将该化合物与药学上可接受的载体一起配制。组合物的制剂将是适当的，并取决于几个因素，包括但不限于化合物的递送途径、剂量以及稳定性。

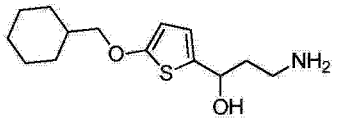
[0335] 在本公开内容的启示下，对于本领域技术人员，其它的实施方案和用途将是显而易见的。下面的实施例只是作为各种实施方案的示例来提供，而不得以任何方式解释为限制本发明。

实施例

I. 化学合成

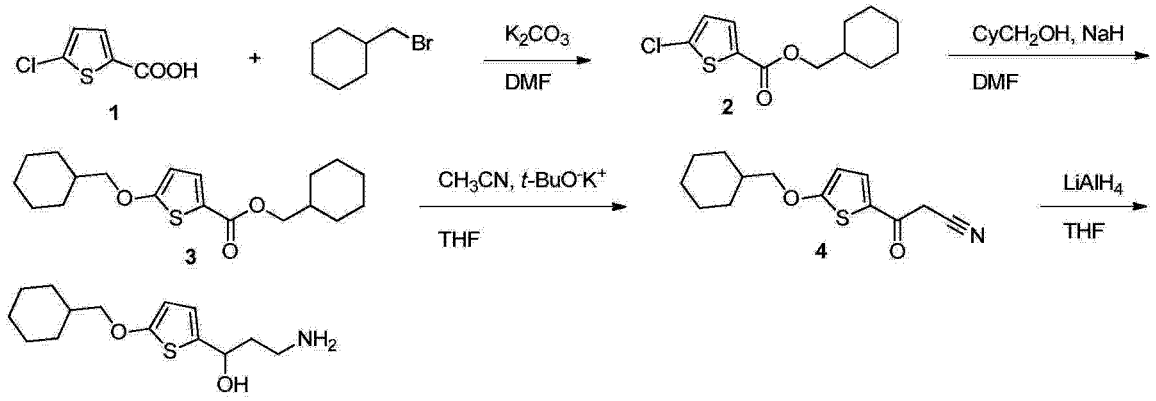
[0336] 除非另有说明，使用从商业供应商处得到的试剂和溶剂。无水溶剂和烘干的玻璃器皿用于对水分和 / 或氧敏感的合成转化。产率未经优化。反应时间是近似值并且未经优化。除非另有说明，快速柱层析和薄层层析 (TLC) 在硅胶上进行。质子和碳核磁共振谱用 VarianVnmrJ 400 得到，质子谱在 400MHz。波谱以 ppm(δ) 为单位给出，而耦合常数 J 以赫兹为单位报告。对于质子谱，使用溶剂峰作为参照峰。HPLC/LC-MS 采用以下方法进行：Agilent HP 1100 系统，在 Phenomenex Gemini 4.6x150mm5μ 柱上于 220nm 进行二极管阵列检测，流动相为含有 0.05% TFA 的 $CH_3CN$-$H_2O$(10% -70% 15min，70% -95% 2min，95% 3min，然后 10% 4min)，采用电喷射离子化 (ESI+) 模式进行质谱检测。

实施例 1-3- 氨基 -1-(5-( 环己基甲氧基 ) 噻吩 -2- 基 ) 丙 -1- 醇的制备



[0337] 3- 氨基 -1-(5-( 环己基甲氧基 ) 噻吩 -2- 基 ) 丙 -1- 醇按照流程 1 所示的方法制备。

流程 1



[0338] 步骤 1：将 5- 氯噻吩 -2- 甲酸 (3.01g，19.0mmol)、环己基甲基溴化物 (3.51g，19.8mmol) 和碳酸钾 (2.81g，20.33mmol) 的混合物在 Ar 下于 +85℃搅拌 3 天，并冷却至室温。反应混合物用水稀释并用己烷萃取三次。合并的有机层用无水 $MgSO_4$ 干燥并减压浓缩。通过快速层析纯化 (2% -15% EtOAc - 己烷梯度 ) 得到呈无色油的 5- 氯噻吩 -2- 甲酸环己基甲酯。产率 (4.76g，97% )；$^1H$ NMR(400MHz，$CDCl_3$) δ 7.56-7.60(m，1H)，6.90-6.94(m，1H)，4.08(d，J = 6.10Hz，2H)，1.64-1.82(m，6H)，1.10-1.34(m，3H)，0.97-1.10(m，2H)。

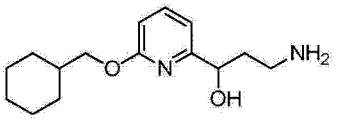
[0339] 步骤 2：在 Ar 下于室温下向搅拌的 NaH(0.19g，7.92mmol) 在无水 DMF(3mL) 中的悬浮液中加入环己基甲醇 (1.0mL，8.13mmol)。将混合物搅拌 5hr 然后加入氯化物 (2)(1.20g，4.64mmol)。将反应混合物在 +65℃下搅拌 1h，用 25% $NH_4Cl$ 水溶液猝灭，并用 MBTE 萃取两次。合并的有机层用盐水洗涤并减压浓缩。通过快速层析纯化 (1% -5% EtOAc - 己烷梯度 ) 得到呈浅黄色固体的醚 (3)。产率 (0.90g，58% )；$^1$HNMR(400MHz，DMSO-$d_6$) δ 7.49-7.53(m，1H)，6.38-6.43(m，1H)，3.98(d，J = 6.07Hz，2H)，3.94(d，J = 5.87Hz，2H)，1.56-1.80(m，12H)，1.17-1.28(m，6H)，0.90-1.16(m，4H)。

[0340] 步骤 3：在 Ar 下向 t-BuO$^-$K$^+$ 的冷 (-50℃ ) 溶液 (1M/THF，1.5mL，1.5mmol) 中加入

无水 $CH_3CN$(0.07mL,1.34mmol),将混合物搅拌 10min,之后添加酯 (3)(0.303g,0.90mmol) 在无水 THF(2mL) 中的溶液。将反应混合物在 Ar 下搅拌,同时在 3 小时内逐渐升温至 0℃,然后在冰浴上搅拌 1h。向反应混合物中加入 5% $NaHSO_4$水溶液,并用 EtOAc 萃取所得的混合物两次。合并的有机层用盐水洗涤。通过快速层析纯化 (5% -30% EtOAc - 己烷梯度) 得到呈白色固体的酮腈 (ketonitrile)(4)。产率 (0.12g,51%) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.75-7.79(m,1H),6.51-6.55(m,1H),4.52(s,2H),4.00(d,J = 6.10Hz,2H),1.58-1.80(m,6H),1.10-1.27(m,3H),0.96-1.08(m,2H)。

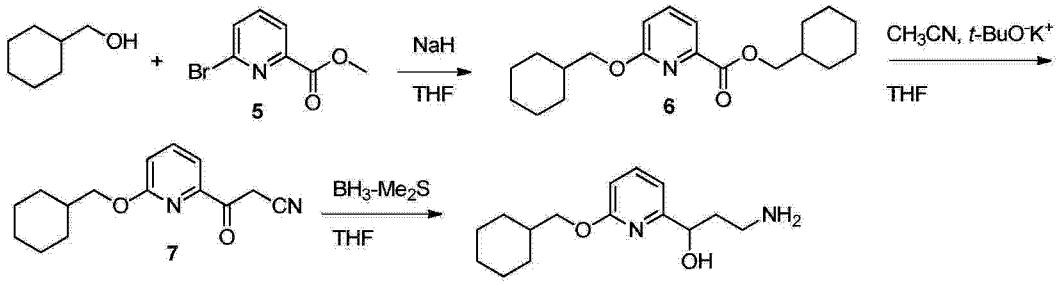
[0341] 步骤 4 :在 Ar 下向 0℃的酮腈 (4)(0.12g,0.456mmol) 在无水 THF(8mL) 中的溶液中加入 $LiAlH_4$的溶液 (1M/THF,0.7mL,0.7mmol)。将反应混合物在 0℃下搅拌 30min,并通过缓慢添加饱和 $Na_2SO_4$水溶液来猝灭。通过 Celite 过滤,随后减压浓缩和快速层析纯化 (2% -20% 7N $NH_3$/MeOH - $CH_2Cl_2$梯度),得到呈浅黄色固体的实施例 1。产率 (0.015g,12 % ) ;$^1H$ NMR(400MHz,$CD_3OD$) δ 6.54-6.59(m,1H),6.00-6.40(m,1H),4.77(t,J = 7.24Hz,1H),3.80(d,J = 5.87Hz,2H),2.86-2.77(m,2H),1.65-1.96(m,8H),1.18-1.36(m,3H),1.00-1.12(m,2H) ;RP-HPLC $t_R$= 10.12min ;ESI-MS m/z 252.2$[M-H_2O+H]^+$。

实施例 2-3- 氨基 -1-(6-( 环己基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇的制备




[0342] 3- 氨基 -1-(6-( 环己基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇按照流程 2 所示的方法制备。

流程 2



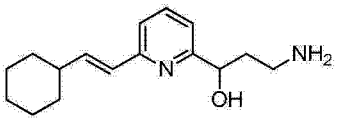

[0343] 步骤 1 :在室温下向环己基甲醇 (0.79g,6.90mmol) 的无水 THF(20mL) 溶液中加入 NaH(0.15g,6.90mmol)。将反应混合物在 60℃下搅拌 1 小时,然后加入 6- 溴吡啶甲酸甲酯 (5)(1.0g,4.60mmol)。将反应混合物在 60℃下搅拌 18 小时,冷却至室温,通过 Celite 过滤,并减压浓缩。通过快速层析纯化 (30% -50% EtOAc - 己烷梯度) 得到呈无色油的醚 (6)。产率 (0.60g,41%) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.83(t,J = 8.0Hz,1H),7.63(d,J = 8.0Hz,1H),7.03(d,J = 8.4Hz,1H),4.08(d,J = 6.0Hz,2H),3.79(d,J = 6.0Hz,2H),1.84-1.58(m,12H),0.88-1.26(m,10H)。

[0344] 步骤 2 :在 -35℃下向叔丁醇钾 (1M/THF,6.4mL,6.40mmol) 的 THF(20mL) 溶液中加入 $CH_3CN$(0.22g,5.46mmol)。将反应混合物在该温度下搅拌 15min,然后逐滴加入在 THF(15ml) 中的酯 (6)(0.6g,1.84mmol)。将反应混合物在 0℃下搅拌 1 小时,用乙酸 (0.42ml,6.4mmol) 猝灭,用饱和 $NH_4Cl$(30ml) 稀释。混合物用乙酸乙酯 (50ml) 萃取,用无水 $Na_2SO_4$干燥,并减压浓缩。通过快速层析纯化 (30% -50% EtOAc - 己烷梯度) 得到呈黄色油

的酮腈 (7)。产率 (0.20g,42%) ;$^1$H NMR(400MHz,$CDCl_3$) δ 7.12(t,J=8.0Hz,1H),7.67(d,J=7.2Hz,1H),6.99(d,J=8.0Hz,1H),4.26(s,2H),1.88-1.64(m,6H),1.08-1.02(m,5H)。

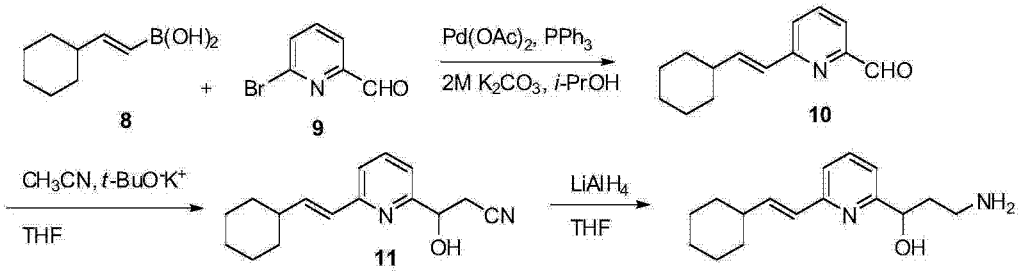
[0345] 步骤 3 :向搅拌的酮腈 (7)(0.2g,0.74mmol) 在无水 THF(20mL) 中的溶液中加入 $BH_3.Me_2S$(0.22g,2.96mmol)。将反应混合物在 60℃下搅拌 2 小时并在室温下搅拌 60 小时,用 3N HCl(pH=0) 猝灭。所得的混合物在室温下搅拌 12 小时,用水 (20ml) 和 MTBE(40ml) 稀释,并用浓 NaOH 调节 pH 至 14。将有机层分离,用 $Na_2SO_4$干燥并减压浓缩。通过快速层析纯化 (5%-20% 7N $NH_3$-MeOH-$CH_2Cl_2$梯度) 得到呈黄色油的实施例 2。产率 (0.05g,4%) :$^1$H NMR(400MHz,$CD_3OD$) δ 7.64(t,J=8.0Hz,1H),7.03(d,J=7.6Hz,1H),6.63(d,J=8.0Hz,1H),4.72-4.66(m,1H),4.06(d,J=6.4Hz,2H),2.86(t,J=6.1Hz,2H),1.92-1.68(m,8H),1.38-1.02(m,5H) ;RP-HPLC $t_R$=9.02min ;ESI-MS m/z 265.2$[M+H]^+$。

实施例 3-(E)-3- 氨基 -1-(6-(2- 环己基乙烯基) 吡啶 -2- 基) 丙 -1- 醇的制备




[0346] (E)-3- 氨基 -1-(6-(2- 环己基乙烯基) 吡啶 -2- 基) 丙 -1- 醇按照流程 3 所示的方法制备。

流程 3

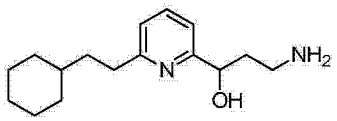



[0347] 步骤 1 :向氩气饱和的 (E)-(2- 环己基乙烯基) 硼酸 (8)(2.74g,16.0mmol)、6- 溴吡啶甲醛 (9)(3.0g,16mmol)、$Pd(OAc)_2$(0.04g,0.18mmol)、$K_2CO_3$(2M,在 i-PrOH 中,30mmol) 的混合物中加入 $PPh_3$(0.20g,0.76mmol)。将反应混合物在 $N_2$下于 70℃搅拌 20 小时,减压浓缩,并在 $H_2O$(80ml) 与乙酸乙酯 (80ml) 之间分配。有机层用无水 $Na_2SO_4$干燥并减压浓缩。通过快速层析纯化 (30%-50% EtOAc- 己烷梯度) 得到呈淡黄色油的烯烃 (10)。产率 (3.1g,90%) ;$^1$H NMR(400MHz,DMSO-$d_6$) δ 9.34(s,1H),7.93(t,J=7.6Hz,1H),7.71(d,J=8.4Hz,1H),7.69(d,J=8.4Hz,1H),7.86(dd,J=6.8,16.0Hz,1H),6.54(d,J=16Hz,1H),2.26-2.16(m,1H),1.84-1.58(m,5H),1.36-1.10(m,5H)。

[0348] 步骤 2 :在 -35℃下向叔丁醇钾 (1M,在 THF 中,15mL,15.0mmol) 的 THF(20mL) 溶液中加入 $CH_3CN$(0.56g,15.8mmol)。将反应混合物在该温度下搅拌 15min,然后逐滴加入在无水 THF(15ml) 中的醛 (10)(1.0g,4.6mmol)。将反应混合物在 -35℃下搅拌 30min,并用 $NH_4Cl$ 水溶液 (30ml) 猝灭,用乙酸乙酯 (50ml) 萃取,用无水 $Na_2SO_4$干燥并减压浓缩。通过快速层析纯化 (30%-50% EtOAc- 己烷梯度) 得到呈黄色油的羟基腈 (11)。产率 (0.55g,46%) ;$^1$H NMR(400MHz,$CDCl_3$) δ 7.37(t,J=7.6Hz,1H),7.34(d,J=7.6Hz,1H),7.28(d,J=7.6Hz,1H),6.73(dd,J=6.8,16.0Hz,1H),6.40(d,J=16Hz,1H),6.16-6.06(m,1H),4.90-4.80(m,1H),3.04-2.87(m,2H),2.21-2.08(m,1H),1.82-1.58(m,5H),1.36-1.10(m,5H)。

[0349] 步骤 3：在氩气流下于 0℃，向羟基腈 (11)(0.55g，2.15mmol) 的二乙醚 (20mL) 溶液中加入 $LiAlH_4$(1M，在 THF 中，2.6mL，2.6mmol)。将反应混合物在 0℃下搅拌 20min，通过缓慢添加饱和 $Na_2SO_4$ 猝灭并在室温下搅拌 2 小时。将有机层分离，用 $Na_2SO_4$ 干燥并减压浓缩。通过快速层析纯化 (5％ -20％ 7N $NH_3$-MeOH - $CH_2Cl_2$ 梯度 ) 得到呈淡黄色油的实施例 3。产率 (0.3g，54％ )；$^1H$ NMR(400MHz，$CD_3OD$) δ 7.71(t，J ＝ 7.6Hz，1H)，7.34-7.30(m，2H)，6.66(dd，J ＝ 16 和 6.8Hz，1H)，6.45(d，J ＝ 16Hz，1H)，6.16-6.06(m，1H)，4.78-4.76(m，1H)，2.24-2.16(m，2H)，2.21-2.08(m，1H)，2.04-1.66(m，5H)，1.44-1.16(m，5H)；RP-HPLC $t_R$ ＝ 6.54min；ESI-MS m/z 261.2$[M+H]^+$。

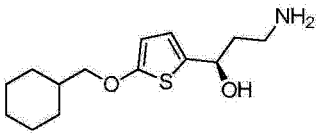
实施例 4-3- 氨基 -1-(6-(2- 环己基乙基 ) 吡啶 -2- 基 ) 丙 -1- 醇的制备




[0350] 3- 氨基 -1-(6-(2- 环己基乙基 ) 吡啶 -2- 基 ) 丙 -1- 醇按照以下所述的方法制备。

[0351] 步骤 1：向用氩气饱和的实施例 3(0.28g，1.22mmol) 在 MeOH(20mL) 中的溶液中加入 Pd/C(10％ wt，0.015g)。所得的混合物在 $H_2$(1atm) 下搅拌 20 小时。将反应混合物过滤，并将滤液减压浓缩。通过快速层析纯化 (5％ -20％ 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 得到呈淡黄色油的实施例 4。产率 (0.20g，71％ )；$^1H$ NMR(400MHz，$CD_3OD$) δ 7.71(t，J ＝ 7.6Hz，1H)，7.35(d，J ＝ 7.6Hz，1H)，7.13(d，J ＝ 8.0Hz，1H)，4.78-4.76(m，1H)，2.83-2.76(m，4H)，1.84-1.56(m，9H)，1.36-0.95(m，6H)；RP-HPLC $t_R$ ＝ 6.46min；ESI-MS m/z 263.2$[M+H]^+$。

实施例 5-(R)-3- 氨基 -1-(5-( 环己基甲氧基 ) 噻吩 -2- 基 ) 丙 -1- 醇的制备



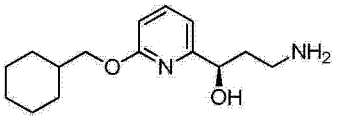

[0352] (R)-3- 氨基 -1-(5-( 环己基甲氧基 ) 噻吩 -2- 基 ) 丙 -1- 醇按照实施例 1 中和以下所述的方法制备。

[0353] 步骤 1：将 (1R，2R)-RuCl(TsDPEN)( 对伞花烃 )(6.3mg，0.01mmol) 加入脱气的 3-(5-( 环己基甲氧基 ) 噻吩 -2- 基 )-3- 氧代丙腈 (4)(0.27g，1.03mmol) 的 HCOOH:$Et_3N$(1:1，4.0M，在 EtOH 中 ) 溶液中，并将反应混合物在室温下搅拌 24hr。加入 $NH_4Cl$ 水溶液 (25％ )，并且用 MTBE 萃取该混合物两次。合并的有机层用盐水洗涤并减压浓缩。通过快速层析纯化得到呈灰白色固体的 (R)-3-(5-( 环己基甲氧基 ) 噻吩 -2- 基 )-3- 羟基丙腈，其直接用于下一步。产率 (0.21g，77％ )；$^1H$ NMR(400MHz，$CD_3OD$) δ 6.64-6.78(m，1H)，6.02-6.10(m，1H)，4.99-5.09(m，1H)，3.79-3.88(m，2H)，2.79-2.91(m，2H)，1.62-1.90(m，6H)，1.12-1.39(m，3H)，0.98-1.12(m，2H)。

[0354] 步骤 2：除使用 $Et_2O$ 作为溶剂外按照实施例 1 中使用的方法进行 (R)-3-(5-( 环己基甲氧基 ) 噻吩 -2- 基 )-3- 羟基丙腈的还原，在通过快速层析纯化 (4％ -20％ 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到呈无色油的实施例 5。产率 (0.0185g，9 ％ )；$^1H$ NMR(400MHz，$CD_3OD$) δ 6.54-6.59(m，1H)，6.00-6.40(m，1H)，4.77(t，J ＝

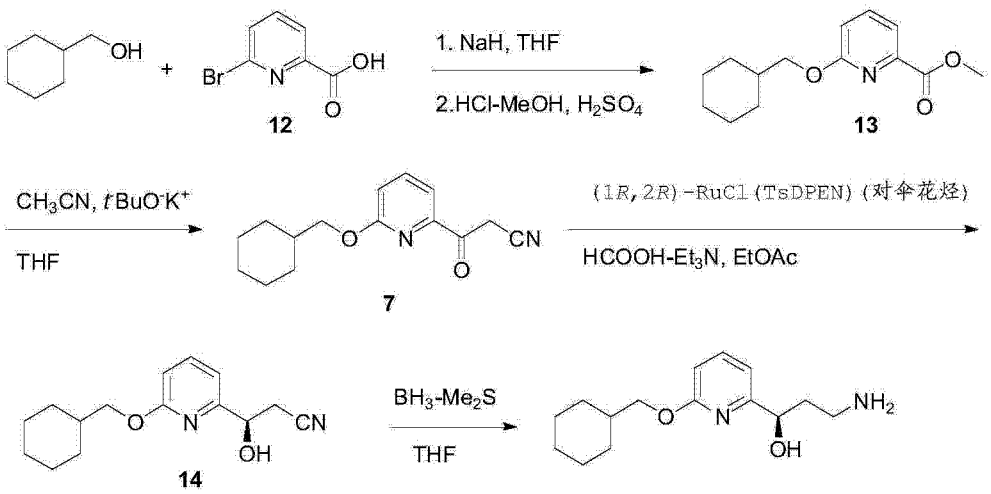
7.2Hz, 1H), 3.80(d, J = 5.9Hz, 2H), 2.86-2.77(m, 2H), 1.65-1.96(m, 8H), 1.18-1.36(m, 3H), 1.00-1.12(m, 2H) ;RP-HPLC $t_R$= 10.01min ;ESI-MS m/z 252.2$[M-H_2O+H]^+$。

实施例 6-(R)-3- 氨基 -1-(6-( 环己基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇的制备



[0355] (R)-3- 氨基 -1-(6-( 环己基甲氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇按照流程 4 所示的方法制备。.

流程 4.




[0356] 步骤 1 :在室温下向 6- 溴吡啶甲酸 (12)(1.0g,4.9mmol) 和环己基甲醇 (0.79g,6.90mmol) 在 THF(20mL) 中的悬浮液中加入 NaH(0.355g,15mmol)。将反应混合物在 60℃下搅拌 18 小时,然后减压浓缩。向残余物添加甲醇 (20ml),随后添加 1.25M HCl/MeOH(10ml) 和浓 $H_2SO_4$(1ml)。所得的混合物在 60℃下搅拌 18 小时,减压浓缩,在饱和 $NaHCO_3$(50ml) 与乙酸乙酯 (100ml) 之间分配。将有机层分离,用无水 $Na_2SO_4$干燥并减压浓缩。粗品 6-( 环己基甲氧基 ) 吡啶甲酸甲酯 (13) 无需纯化而用于下一反应。产率 (1.22g,定量 ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.84(t, J = 8.0Hz, 1H), 7.63(d, J = 8.0Hz, 1H), 7.03(d, J = 8.4Hz, 1H), 4.08(d, J = 6.0Hz, 2H), 3.84(s, 3H), 1.84-1.58(m, 6H), 0.88-1.26(m, 5H)。

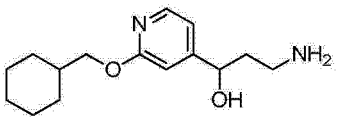
[0357] 步骤 2 :在 -35℃下向叔丁醇钾 (1M, 在 THF 中,11mL,11mmol) 的 THF(20mL) 溶液中加入 $CH_3CN$(0.41g,10mmol)。将反应混合物在该温度下搅拌 15min。向反应混合物中逐滴加入在 THF(15ml) 中的 6-( 环己基甲氧基 ) 吡啶甲酸甲酯 (4.9mmol)。将反应混合物在 0℃下搅拌 1 小时,并通过加入 HCl 水溶液 (1M,11ml,11mmol) 猝灭,用饱和 $NH_4Cl$ 水溶液 (30ml) 洗涤,用乙酸乙酯 (50ml) 萃取。合并的有机层用无水 $Na_2SO_4$干燥并减压浓缩。粗品酮腈 7 无需纯化而用于下一步。产率 (1.26g,定量 ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.90(t, J = 7.6Hz, 1H), 7.60(d, J = 7.6Hz, 1H), 7.13(d, J = 8.4Hz, 1H), 4.66(s, 2H), 4.15(d, J = 6.4Hz, 2H), 1.84-1.58(m, 6H), 0.88-1.26(m, 5H)。

[0358] 步骤 3 :向酮腈 7(4.9mmol) 在 EtOAc(5ml) 中的溶液中加入 HCOOH-$Et_3N$(4M) 的 EtOH(5mL) 溶液,随后加入三乙胺 (1ml) 和 (1R,2R)-RuCl(TsDPEN)( 对伞花烃 )(30mg,0.047mmol)。将混合物用氩气饱和,在室温下搅拌 18hr,通过加入 HCl 水溶液 (1N,11ml,11mmol) 猝灭,用饱和 $NH_4Cl$(30ml) 洗涤,用乙酸乙酯 (50ml) 萃取,用无水 $Na_2SO_4$干燥,并减

压浓缩。通过快速层析纯化（30％-50％ EtOAc- 己烷梯度）得到呈淡黄色油的 (R)-羟基腈 14。产率 (1.1g,87％)；$^1$H NMR(400MHz,$CD_3OD$) δ 7.66(t,J = 7.6Hz,1H),7.11(d,J = 7.6Hz,1H),6.67(d,J = 8.0Hz,1H),4.88(t,J = 5.2Hz,1H),4.09(d,J = 6.8Hz,2H),3.04-2.86(m,2H),1.88-1.66(m,6H),1.38-1.02(m,5H)。

[0359] 步骤 4：按照实施例 2 中使用的方法用 $BH_3$-$Me_2S$ 还原 (R)-羟基腈 14 得到呈无色油的实施例 6。产率 (1.0g,89％)；$^1$H NMR(400MHz,$CD_3OD$) δ 7.63(t,J = 7.6Hz,1H),7.02(d,J = 7.2Hz,1H),6.61(d,J = 8.0Hz,1H),4.69-4.66(m,1H),4.07(d,J = 6.4Hz,2H),2.79(t,J = 6.4Hz,2H),1.92-1.64(m,8H),1.38-1.02(m,5H)；RP-HPLC $t_R$ = 8.99min；ESI-MS m/z265.2$[M+H]^+$。

实施例 7-3-氨基-1-(2-(环己基甲氧基）吡啶-4-基）丙-1-醇的制备



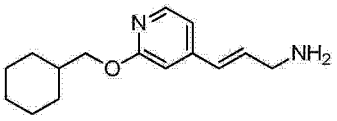

[0360] 3-氨基-1-(2-(环己基甲氧基）吡啶-4-基）丙-1-醇按照实施例 2 和 6 中描述的方法制备。

[0361] 步骤 1：按照实施例 6 中使用的方法使 2-溴异烟酸与环己基甲醇之间发生反应得到 2-(环己基甲氧基）异烟酸甲酯，其无需额外纯化而用于下一步。产率 (1.27g,定量)；$^1$H NMR(400MHz,DMSO-$d_6$) δ 8.31(d,J = 4.2Hz,1H),7.38-7.40(m,1H),7.17(s,1H),4.08(d,J = 6.4Hz,2H),3.86(s,3H),1.80-1.54(m,6H),1.30-0.96(m,5H)。

[0362] 步骤 2：按照实施例 2 中使用的方法向 2-(环己基甲氧基）异烟酸甲酯中加入 $CH_3CN$ 在快速层析纯化（50％-60％ EtOAc- 己烷梯度）后得到呈黄色油的 3-(2-(环己基甲氧基）吡啶-4-基)-3-氧代丙腈。产率 (0.65g,51％)；$^1$H NMR(400MHz,$CD_3OD$) δ 8.29(d,J = 5.2Hz,1H),7.34(d,J = 5.6Hz,1H),7.23(s,1H),4.13(d,J = 6.0Hz,2H),3.34-3.30(m,2H),1.88-1.64(m,6H),1.08-1.02(m,5H)。

[0363] 步骤 3：按照实施例 2 中使用的方法对 3-(2-(环己基甲氧基）吡啶-4-基)-3-氧代丙腈进行还原在快速层析纯化（5％-20％ 7N $NH_3$/MeOH-$CH_2Cl_2$ 梯度）后得到呈黄色油的实施例 7 和实施例 8（见下文）。产率 (0.16g,24％)；$^1$H NMR(400MHz,$CD_3OD$) δ 8.02-8.00(m,1H),6.92(d,J = 5.2Hz,1H),6.79(s,1H),4.76-4.71(m,1H),4.04-4.01(m,2H),2.78(t,J = 6.8Hz,2H),1.90-1.66(m,8H),1.40-1.02(m,5H)；RP-HPLC $t_R$ = 6.79min；ESI-MS m/z 265.2$[M+H]^+$。

实施例 8-(E)-3-(2-(环己基甲氧基）吡啶-4-基）丙-2-烯-1-胺的制备

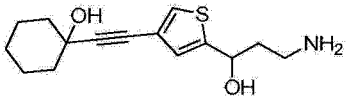



[0364] (E)-3-(2-(环己基甲氧基）吡啶-4-基）丙-2-烯-1-胺按照实施例 7 中描述的方法制备。

[0365] 步骤 1：按照实施例 7 中使用的方法制备实施例 8 并在步骤 3 层析过程中分离（见上文）。产率 (0.04g,6％)；$^1$H NMR(400MHz,$CD_3OD$) δ 7.98(d,J = 5.2Hz,1H),6.97(d,J = 5.6Hz,1H),6.73(s,1H),6.63-6.53(m,1H),6.47(d,J = 16Hz,1H),4.01(d,J =

5.6Hz,2H),3.41(d,J = 6.0Hz,2H),1.88-1.66(m,6H),1.38-1.02(m,5H);RP-HPLC $t_R$= 7.79min;ESI-MS m/z 247.2$[M+H]^+$。

实施例 9-1-((5-(3- 氨基 -1- 羟丙基 ) 噻吩 -3- 基 ) 乙炔基 ) 环己醇的制备




[0366] 1-((5-(3- 氨基 -1- 羟丙基 ) 噻吩 -3- 基 ) 乙炔基 ) 环己醇按照以下所述的方法制备。

[0367] 步骤 1 :按照实施例 2 中使用的方法向 4- 溴噻吩 -2- 甲醛中加入 $CH_3CN$ 得到呈浅棕色油的 3-(4- 溴噻吩 -2- 基 )-3- 羟基丙腈,其无需额外纯化而用于下一步。产率 (1.95g,80% )。

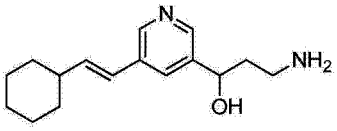
[0368] 步骤 2 :按照实施例 1 中使用的方法对 3-(4- 溴噻吩 -2- 基 )-3- 羟基丙腈进行 $LiAlH_4$ 还原在快速层析纯化 (2% -10% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到 3- 氨基 -1-(4- 溴噻吩 -2- 基 ) 丙 -1- 醇,其直接用于下一步。$^1H$ NMR(400MHz,$CD_3OD$) δ 7.26(d,J = 1.5Hz,1H),6.85-6.92(m,1H),4.94(t,J = 5.0Hz,1H),2.70-2.80(m,2H),1.86-1.94(m,2H)。

[0369] 步骤 3 :将 3- 氨基 -1-(4- 溴噻吩 -2- 基 ) 丙 -1- 醇和三氟乙酸乙酯 (2.0mL) 在 $CH_2Cl_2$(10mL) 中于室温下搅拌过夜。减压浓缩得到 N-(3-(4- 溴噻吩 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺,其无需额外纯化而用于下一步。产率 (0.77g,三步 28% );$^1H$ NMR(400MHz,DMSO-$d_6$) δ 9.36(br.s,1H),7.51(d,J = 1.5Hz,1H),6.90-7.00(m,1H),5.86(d,J = 5.0Hz,1H),4.75-4.83(m,1H),3.20-3.30(m,2H),1.80-1.94(m,$2_H$)。

[0370] 步骤 4 :通过 Ar 鼓泡 5min 对 N-(3-(4- 溴噻吩 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺 (0.77g,2.32mmol) 和 1- 乙炔基环己醇 (0.48g,3.87mmol) 在 $Et_3N$(10mL) 中的溶液进行脱气。向反应混合物中加入 CuI(0.0482g,0.253mmol) 和 $PdCl_2(Ph_3P)_2$(0.0874g,0.125mmol),并通过交替真空 /Ar 一次进行脱气。将反应混合物在 +80℃下搅拌过夜,在 EtOAc 与 $NH_4Cl$ 水溶液 (25% ) 之间分配。另外用 EtOAc 萃取水层,用盐水洗涤合并的有机层。减压浓缩,随后快速层析纯化 (10% -75% EtOAc - 己烷梯度 ),得到呈浅黄色油的 2,2,2- 三氟 -N-(3- 羟基 -3-(4-((1- 羟基环己基 ) 乙炔基 ) 噻吩 -2- 基 ) 丙基 ) 乙酰胺。产率 (0.52g,60% );$^1H$ NMR(400MHz,DMSO-$d_6$) δ 9.37(br.s,1H),7.52(d,J = 1.3Hz,1H),6.92(d,J = 1.3Hz,1H),5.78(d,J = 4.7Hz,1H),5.34(s,1H),4.74-4.81(m,1H),3.20-3.30(m,2H),1.84-1.91(m,2H),1.74-1.84(m,2H),1.56-1.65(m,2H),1.38-1.56(m,6H)。

[0371] 步骤 5 :将 2,2,2- 三氟 -N-(3- 羟基 -3-(4-((1- 羟基环己基 ) 乙炔基 ) 噻吩 -2- 基 ) 丙基 ) 乙酰胺 (0.52g,1.39mmol) 和 $K_2CO_3$(0.43g,3.11mmol) 在 MeOH:$H_2O$(3:1,16mL) 中的混合物在室温下搅拌过夜并减压浓缩。通过快速层析纯化 (7% -20% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 得到呈浅黄色油的实施例 9。产率 (0.105g,27% );$^1H$ NMR(400MHz,$CD_3OD$) δ 7.37(d,J = 1.5Hz,1H),6.94(s,1H),4.93(dd,J = 5.8,7.3Hz,1H),2.70-2.80(m,2H),1.86-2.00(m,4H),1.67-1.76(m,2H),1.52-1.67(m,5H),1.22-1.36(m,1H);RP-HPLC $t_R$= 6.98min;ESI-MS m/z 280.2$[M-H_2O+H]^+$。

实施例 10-(E)-3- 氨基 -1-(5-(2- 环己基乙烯基 ) 吡啶 -3- 基 ) 丙 -1- 醇的制备



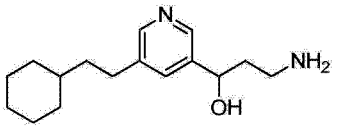
[0372] (E)-3-氨基-1-(5-(2-环己基乙烯基)吡啶-3-基)丙-1-醇按照实施例3中和以下所述的方法制备。

[0373] 步骤1:按照实施例3中使用的方法使(E)-(2-环己基乙烯基)硼酸与5-溴烟醛偶合得到呈黄色油的(E)-5-(2-环己基乙烯基)烟醛。产率(0.8g,69%);$^1$H NMR(400MHz,DMSO-$d_6$)δ10.08(s,1H),8.32(s,1H),8.75(s,1H),8.28(s,1H),6.51-6.38(m,2H),2.26-2.13(m,1H),1.88-1.58(m,5H),1.42-1.18(m,5H)。

[0374] 步骤2:按照实施例3中使用的方法向(E)-5-(2-环己基乙烯基)烟醛中加入$CH_3CN$得到呈黄色油的(E)-3-(5-(2-环己基乙烯基)吡啶-3-基)-3-羟基丙腈。产率(0.9g,95%);$^1$H NMR(400MHz,$CDCl_3$)δ8.43(s,1H),8.41(s,1H),7.93(s,1H),6.42(s,2H),5.05(t,J = 5.6Hz,1H),2.98-2.82(m,2H),2.24-2.12(m,1H),1.88-1.66(m,5H),1.42-1.18(m,5H)。

[0375] 步骤3:按照实施例3中使用的方法对(E)-3-(5-(2-环己基乙烯基)吡啶-3-基)-3-羟基丙腈进行$LiAlH_4$还原在快速层析纯化(10%-30% 7N $NH_3$/MeOH-$CH_2Cl_2$梯度)后得到呈浅黄色油的实施例10。产率(0.5g,59%);$^1$H NMR(400MHz,$CD_3OD$)δ8.37(d,J = 2.0Hz,1H),8.33(d,J = 1.5Hz,1H),7.85(t,J = 2.0Hz,1H),6.40-6.38(m,2H),4.84-4.76(m,1H),2.86-2.78(m,2H),2.24-2.08(m,1H),1.98-1.66(m,7H),1.44-1.28(m,5H);RP-HPLC $t_R$ = 6.23min;ESI-MS m/z 261.2$[M+H]^+$。

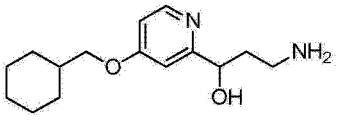
实施例11-3-氨基-1-(5-(2-环己基乙基)吡啶-3-基)丙-1-醇的制备



[0376] 3-氨基-1-(5-(2-环己基乙基)吡啶-3-基)丙-1-醇按照实施例10中和以下所述的方法制备。

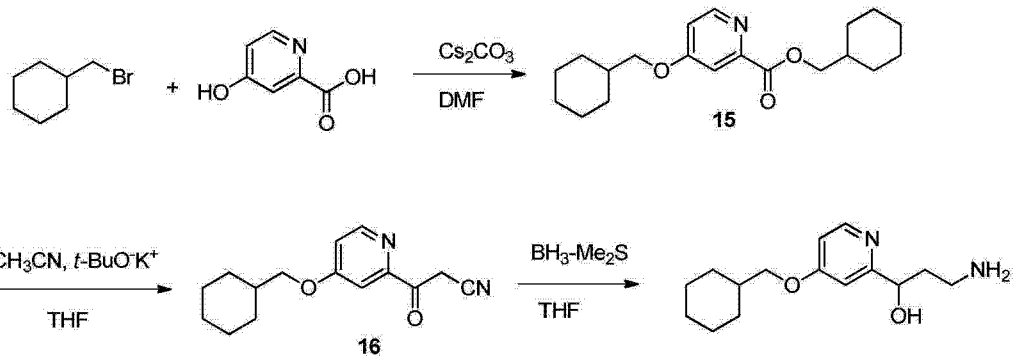
[0377] 步骤1:将(E)-3-氨基-1-(5-(2-环己基乙烯基)吡啶-3-基)丙-1-醇(0.40g,1.54mmol)、Pd/C(10% wt,30mg)在甲醇(20ml)中的溶液于氢气氛下于室温搅拌18hr。将反应混合物过滤并减压浓缩。将残余物通过快速层析纯化(20%-30% 7N $NH_3$/MeOH-$CH_2Cl_2$(梯度),得到呈淡黄色油的实施例11。产率(0.14g,34%);$^1$H NMR(400MHz,$CD_3OD$)δ8.30(s,1H),8.24(s,1H),7.50(s,1H),4.70-4.67(m,1H),2.64-2.60(m,4H),1.78-1.56(m,8H),1.50-1.38(m,2H),1.24-0.95(m,5H),0.98-0.82(m,2H);RP-HPLC $t_R$ = 6.28min;ESI-MS:m/z 263.2$[M+H]^+$。

实施例12-3-氨基-1-(4-(环己基甲氧基)吡啶-2-基)丙-1-醇的制备



[0378] 3-氨基-1-(4-(环己基甲氧基)吡啶-2-基)丙-1-醇按照流程5所示的方法制备。

流程 5.

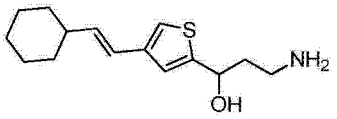



[0379] 步骤 1：向 4- 羟基吡啶甲酸 (1.0g,7.2mmol) 和 ( 溴甲基 ) 环己烷 (3.25g,18.4mmol) 在 DMF(30ml) 中的混合物中加入 $Cs_2CO_3$(11.8g,36.7mmol)。所得的混合物在 80℃下搅拌 18hr 并减压浓缩。向残余物添加 EtOAc(50ml)，超声处理，过滤，减压浓缩。通过快速层析纯化 (50% -75% EtOAc - 己烷梯度 ) 得到呈无色油的酯 15。产率 (0.66g,28% )；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 8.46(d,J = 4.9Hz,1H),7.46(d,J = 2.3Hz,1H),7.18(dd,J = 5.5,2.3Hz,1H),4.08(d,J = 6.2Hz,2H),3.92(d,J = 6.2Hz,2H),1.82-1.58(m,12H),1.28-1.00(m,10H)。

[0380] 步骤 2：按照实施例 2 中使用的方法向酯 15 中加入 $CH_3CN$ 得到呈黄色油的酮腈 16。产率 (0.30g,59% )；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 8.47(d,J = 4.9Hz,1H),7.46(d,J = 2.3Hz,1H),7.18(dd,J = 5.5,2.3Hz,1H),4.48(s,2H),3.94(d,J = 5.8Hz,2H),1.82-1.58(m,6H),1.28-1.02(m,5H)。

[0381] 步骤 3：按照实施例 2 中使用的方法用硼烷 - 二甲基硫醚还原 3-(4-( 环己基甲氧基 ) 吡啶 -2- 基 )-3- 氧代丙腈在快速层析纯化 (20% -30% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到呈黄色油的实施例 12。产率 (0.13g,43% )；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 8.22(d,J = 4.5Hz,1H),6.98(d,J = 2.3Hz,1H),6.76(dd,J = 5.9,2.8Hz,1H),4.62-4.58(m,1H),3.94(d,J = 5.8Hz,2H),2.72-2.58(m,2H),1.88-1.58(m,8H),1.40-1.02(m,5H)；RP-HPLC $t_R$ = 5.91min；ESI-MS m/z 265.2$[M+H]^+$。

实施例 13-(E)-3- 氨基 -1-(4-(2- 环己基乙烯基 ) 噻吩 -2- 基 ) 丙 -1- 醇的制备




[0382] (E)-3- 氨基 -1-(4-(2- 环己基乙烯基 ) 噻吩 -2- 基 ) 丙 -1- 醇按照实施例 3 中描述的方法制备。

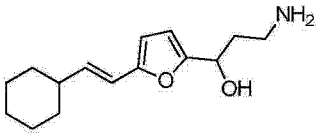
[0383] 步骤 1：按照实施例 3 中使用的方法使 (E)-(2- 环己基乙烯基 ) 硼酸与 4- 溴噻吩 -2- 甲醛偶合在快速层析纯化 (30% -40% EtOAc - 己烷梯度 ) 后得到呈黄色油的 (E)-4-(2- 环己基乙烯基 ) 噻吩 -2- 甲醛。产率 (1.2g,91% )；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 9.88(d,J = 1.6Hz,1H),8.15(d,J = 1.6Hz,1H),7.89(s,1H),6.37(d,J = 16.8Hz,1H),6.22(dd,J = 16.8,6.8Hz,1H),2.08-2.02(m,1H),1.80-1.58(m,5H),1.32-1.18(m,5H)。

[0384] 步骤 2：按照实施例 3 中使用的方法向 (E)-4-(2- 环己基乙烯基 ) 噻吩 -2- 甲

醛中加入 $CH_3CN$ 在快速层析纯化（10％ -50％ EtOAc - 己烷梯度）后得到呈黄色油的 (E)-3-(4-(2- 环己基乙烯基）噻吩 -2- 基）-3- 羟基丙腈。产率 (1.2g,84％）；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.19(s,1H),7.17(s,1H),6.27(d,J ＝ 16.8Hz,1H),6.29-6.26(m,1H),6.00(dd,J ＝ 16.0,6.4Hz,1H),5.05(q,J ＝ 5.6Hz,1H),3.0-2.86(m,2H),2.24-2.12(m,1H),1.78-1.56(m,5H),1.38-1.08(m,5H)。

[0385] 步骤 3：按照实施例 3 中使用的方法对 (E)-2-(4-(2- 环己基乙烯基）噻吩 -2- 基）-2- 羟基乙腈进行 $LiAlH_4$ 还原在快速层析纯化（20％ -30％ 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度）后得到呈浅黄色油的实施例 13。产率 (0.44g,36％）；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.19(s,1H),7.13(s,1H),6.25(d,J ＝ 16.8Hz,1H),5.98(dd,J ＝ 16.0,6.4Hz,1H),4.84(t,J ＝ 6.0Hz,1H),2.72-2.58(m,2H),2.24-2.08(m,1H),1.78-1.58(m,7H),1.38-1.02(m,5H)；RP-HPLC $t_R$ ＝ 10.49min；ESI-MS m/z 219.1.2$[M+H]^+$。

实施例 14-(E)-3- 氨基 -1-(5-(2- 环己基乙烯基）呋喃 -2- 基）丙 -1- 醇的制备




[0386] (E)-3- 氨基 -1-(5-(2- 环己基乙烯基）呋喃 -2- 基）丙 -1- 醇按照实施例 3 中和以下所述的方法制备。

[0387] 步骤 1：通过 Ar 鼓泡然后交替真空 /Ar 三次使 5- 溴呋喃 -2- 甲醛 (1.03g,5.89mmol)、乙烯基环己烷 (0.86g,7.80mmol)、P(o-Tol)$_3$(0.089g,0.29mmol)、Pd(OAc)$_2$(0.070g,0.31mmol) 和 $Et_3N$(2.0mL) 在无水 DMF(3.0mL) 中的混合物脱气。反应混合物在惰性气氛下于 +90℃加热 20hr，并冷却至室温。向反应混合物中加入 $NH_4Cl$ 水溶液，并用己烷和 EtOAc 萃取该混合物两次。合并的有机层用盐水洗涤，减压浓缩。通过快速层析纯化（3％ -8％ EtOAc - 己烷梯度）得到呈黄色油的 (E)-5-(2- 环己基乙烯基）呋喃 -2- 甲醛。产率 (0.40g,33％）；$^1H$ NMR(400MHz,$CDCl_3$) δ 9.53(s,1H),7.19(d,J ＝ 3.8Hz,1H),6.55(dd,J ＝ 7.0,16.1Hz,1H),6.34(d,J ＝ 3.5Hz,1H),6.19-6.26(m,1H),2.10-2.19(m,1H),1.52-1.92(m,6H),1.10-1.42(m,4H)。

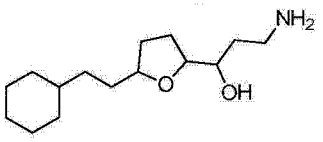
[0388] 步骤 2：按照实施例 3 中使用的方法向 (E)-5-(2- 环己基乙烯基）呋喃 -2- 甲醛中加入乙腈在快速层析纯化（10％ -50％ EtOAc - 己烷梯度）后得到呈黄色油的 (E)-3-(5-(2- 环己基乙烯基）呋喃 -2- 基）-3- 羟基丙腈。产率 (0.45g,94 ％）；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 6.32(d,J ＝ 2.9Hz,1H),6.23(d,J ＝ 3.5Hz,1H),6.15(m,1H),6.05(dd,J ＝ 3.9,17.6Hz,1H),4.76-4.87(m,1H),2.84-3.00(m,2H),2.02-2.14(m,1H),1.40-1.80(m,4H),1.02-1.36(m,6H)。

[0389] 步骤 3：除了使用 $Et_2O$ 作为溶剂外按照实施例 1 中使用的方法还原 (E)-3-(5-(2- 环己基乙烯基）呋喃 -2- 基）-3- 羟基丙腈在快速层析纯化（2％ -16％ 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度）后得到粗品 (E)-3- 氨基 -1-(5-(2- 环己基乙烯基）呋喃 -2- 基）丙 -1- 醇，其如下所述另外进行纯化。产率 (0.25g,55％）。

[0390] 步骤 4：将 (E)-3- 氨基 -1-(5-(2- 环己基乙烯基）呋喃 -2- 基）丙 -1- 醇 (0.25g,1.0mmol) 溶解在 $CH_2Cl_2$(5mL) 中，并加入三氟乙酸乙酯 (0.5mL)。将反应混合物在室温下搅拌 30min 并减压浓缩。通过快速层析纯化（10％ -50％ EtOAc - 己烷梯度）得到呈无色油

的 (E)-N-(3-(5-(2- 环己基乙烯基 ) 呋喃 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺。产率 (0.26g,75%)。将 (E)-N-(3-(5-(2- 环己基乙烯基 ) 呋喃 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺 (0.15g,0.434mmol) 溶解在 MeOH:$H_2O$(3:1,8mL) 中,并加入 $K_2CO_3$(0.13g,0.94mmol)。将反应混合物在室温下搅拌过夜并减压浓缩。快速层析纯化 (2% -16% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 得到呈浅黄色油的实施例 14。产率 (0.025g,23% ) ;$^1H$ NMR(400MHz,$CD_3OD$) δ 6.00-6.40(m,4H),4.64-4.74(m,1H),2.70-2.80(m,2H),2.01-2.14(m,1H),1.90-2.00(m,2H),1.50-1.80(m,5H),1.10-1.40(m,5H) ;RP-HPLC $t_R$= 10.06min ;ESI-MS m/z 232.2$[M-H_2O+H]^+$。

实施例 15-3- 氨基 -1-(5-(2- 环己基乙基 ) 四氢呋喃 -2- 基 ) 丙 -1- 醇的制备

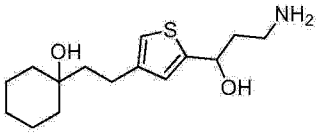



[0391] 3- 氨基 -1-(5-(2- 环己基乙基 ) 四氢呋喃 -2- 基 ) 丙 -1- 醇按照实施例 14 中和以下所述的方法制备。

[0392] 步骤 1 :通过交替真空 /$H_2$ 三次使 (E)-N-(3-(5-(2- 环己基乙烯基 ) 呋喃 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺 (0.11g,0.319mmol) 和 Pd/C(10% wt,0.037g) 在 EtOAc(10mL) 中的混合物脱气,然后在 $H_2$ 气氛下于室温搅拌 40hr,通过 Celite 过滤,并减压浓缩,得到 N-(3-(5-(2- 环己基乙基 ) 四氢呋喃 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺,其无需额外纯化而直接用于下一步。

[0393] 步骤 2 :按照实施例 14 中使用的方法对 N-(3-(5-(2- 环己基乙基 ) 四氢呋喃 -2- 基 )-3- 羟丙基 )-2,2,2- 三氟乙酰胺进行脱保护在快速层析纯化 (4% -16% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到呈无色油的实施例 15。产率 (0.033g,40% ) ;$^1H$ NMR(400MHz,$CD_3OD$) δ 3.62-3.84(m,2H),3.45-3.57(m,2H),2.71-2.88(m,2H),1.80-2.05(m,2H),1.39-1.80(m,10H),1.09-1.37(m,6H),0.87-0.99(m,2H) ;RP-HPLC $t_R$= 9.75min ;ESI-MS m/z256.3$[M+H]^+$。

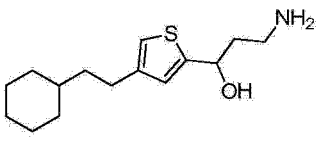
实施例 16-1-(2-(5-(3- 氨基 -1- 羟丙基 ) 噻吩 -3- 基 ) 乙基 ) 环己醇的制备




[0394] 1-(2-(5-(3- 氨基 -1- 羟丙基 ) 噻吩 -3- 基 ) 乙基 ) 环己醇按照实施例 11 中描述的方法制备。

[0395] 步骤 1 :除了使用 EtOH 作为溶剂外按照实施例 15 中使用的方法对实施例 9 进行氢化在通过 Celite 过滤并减压浓缩后得到呈无色油的实施例 16。产率 (0.055g,77% ) ;$^1H$ NMR(400MHz,$CD_3OD$) δ 6.88(s,1H),6.85(s,1H),4.91(dd,J = 5.8,7.8Hz,1H),2.68-2.80(m,2H),2.58-2.68(m,2H),1.86-2.05(m,2H),1.40-1.78(m,12H),1.2-1.4(m,1H) ;RP-HPLC $t_R$ = 7.25min ;ESI-MS m/z 284.2$[M+H]^+$。

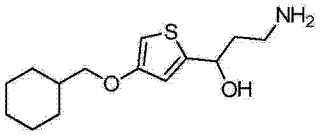
实施例 17-3- 氨基 -1-(4-(2- 环己基乙基 ) 噻吩 -2- 基 ) 丙 -1- 醇的制备



[0396] 3-氨基-1-(4-(2-环己基乙基)噻吩-2-基)丙-1-醇按照实施例11和13中描述的方法制备。

[0397] 按照实施例11中使用的方法对(E)-3-氨基-1-(4-(2-环己基乙烯基)噻吩-2-基)丙-1-醇(实施例13)进行氢化得到呈淡黄色油的实施例17。产率(0.3g,75%);$^1$H NMR(400MHz,DMSO-$d_6$) δ 6.89(s,1H),6.73(s,1H),4.82(t,J = 6.0Hz,1H),2.72-2.58(m,4H),1.78-1.56(m,9H),1.46-1.36(m,2H),1.24-1.06(m,5H),0.98-0.80(m,2H);RP-HPLC $t_R$= 10.85min;ESI-MS m/z 221.2[M+H]$^+$。

实施例18-3-氨基-1-(4-(环己基甲氧基)噻吩-2-基)丙-1-醇的制备



[0398] 3-氨基-1-(4-(环己基甲氧基)噻吩-2-基)丙-1-醇按照实施例1、2中和以下所述的方法制备。

[0399] 步骤1:在30min内,将草酰氯(1.4mL,16.1mmol)在无水$CH_2Cl_2$(10mL)中的溶液逐滴加入到4-溴噻吩-2-甲酸(3.08g,14.9mmol)和DMF(0.2mL)在无水$CH_2Cl_2$(40mL)中的溶液中。将反应混合物在室温下搅拌35min然后减压浓缩。向残余物添加$CH_2Cl_2$(30mL),随后添加环己基甲醇(1.9mL,15.44mmol)和$Et_3N$(2.5mL,17.94mmol)。将反应混合物在室温下搅拌过夜,并在EtOAc与25%$NH_4Cl$水溶液之间分配。有机层用盐水洗涤,减压浓缩,并通过快速层析纯化(2%-20% EtOAc-己烷梯度),得到呈无色油的4-溴噻吩-2-甲酸环己基甲酯,其直接用于下一步。产率(3.61g,80%)。

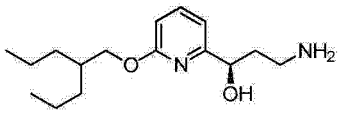
[0400] 步骤2:向NaH(0.080g,3.33mmol)在无水THF(5mL)中的悬浮液中加入环己基甲醇(0.50mL,4.06mmol)。然后向反应混合物中加入4-溴噻吩-2-甲酸环己基甲酯(0.56g,1.847mmol),随后加入CuI(0.34g,1.79mmol)。将反应混合物在室温下搅拌12天,然后加入$NH_4Cl$水溶液(25%)。水层用EtOAc萃取,合并的有机层用盐水洗涤,用无水$MgSO_4$干燥,并减压浓缩。快速层析纯化(2%-10% EtOAc-己烷梯度)得到呈无色油的4-(环己基甲氧基)噻吩-2-甲酸环己基甲酯。产率(0.17g,27%);$^1$H NMR(400MHz,$CD_3OD$) δ 7.35(d,J = 1.7Hz,1H),6.75(d,J = 1.7Hz,1H),4.07(d,J = 6.3Hz,2H),3.78(d,J = 6.3Hz,2H),1.65-1.90(m,12H),1.15-1.38(m,6H),1.00-1.15(m,4H)。

[0401] 步骤3:按照实施例1中使用的方法向4-(环己基甲氧基)噻吩-2-甲酸环己基甲酯中加入乙腈在快速层析纯化(5%-20% EtOAc-己烷梯度)后得到呈白色固体的3-(4-(环己基甲氧基)噻吩-2-基)-3-氧代丙腈。产率(0.084g,63%);$^1$H NMR(400MHz,$CDCl_3$) δ 7.38(d,J = 2Hz,1H),6.72(d,J = 1.5Hz,1H),3.93(s,2H),3.76(d,J = 5.9Hz,2H),1.67-1.86(m,6H),1.13-1.38(m,3H),0.95-1.13(m,2H)。

[0402] 步骤4:按照实施例2中使用的方法对3-(4-(环己基甲氧基)噻吩-2-基)-3-氧代丙腈进行硼烷-二甲基硫醚还原在快速层析纯化(2%-20% 7N $NH_3$/MeOH-$CH_2Cl_2$梯度)后得到呈无色油的实施例18。产率(0.037g,43%);$^1$H NMR(400MHz,$CD_3OD$) δ 6.62(dm J =

1Hz, 1H), 6.22(d, J = 1.4Hz, 1H), 4.85(m, 1H), 3.71(d, J = 6.3Hz, 2H), 2.71-2.78(m, 2H), 1.64-1.97(m, 8H), 1.15-1.37(m, 3H), 1.05-1.15(m, 2H) ;RP-HPLC $t_R$ = 9.63min ;ESI-MS m/z 223.1 $[C_{13}H_{18}OS_2 \cdot +H]^+$ 或 $[M-H_2O-CH_2NH_2+H]^+$。

实施例 19-(R)-3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇的制备




[0403] (R)-3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇按照实施例 6 中描述的方法制备。

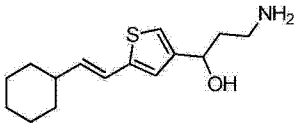
[0404] 步骤 1 :按照实施例 6 中使用的方法使 6- 溴吡啶甲酸与 2- 丙基戊 -1- 醇反应得到呈灰白色固体的 6-((2- 丙基戊基）氧基）吡啶甲酸甲酯，其无需进一步纯化而直接用于下一反应。产率 (1.29g，定量）；$^1$H NMR(400MHz, DMSO-$d_6$) δ 7.84(t, J = 8.3Hz, 1H), 7.63(d, J = 7.2Hz, 1H), 7.04(d, J = 8.4Hz, 1H), 4.18(d, J = 6.0Hz, 2H), 3.84(s, 3H), 1.84-1.58(m, 1H), 1.40-1.20(m, 8H), 0.91-0.80(m, 6H)。

[0405] 步骤 2 :按照实施例 6 中使用的方法向 6-((2- 丙基戊基）氧基）吡啶甲酸甲酯中加入 $CH_3CN$ 以定量产率得到固体 3- 氧代 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈，其无需进一步纯化而直接用于下一反应。

[0406] 步骤 3 :按照实施例 6 中使用的方法对 3- 氧代 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈进行手性还原得到呈灰白色固体的 (R)-3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈，其无需进一步纯化而直接用于下一反应。产率 (1.34g，定量）；$^1$H NMR(400MHz, DMSO-$d_6$) δ 7.69(t, J = 8.0Hz, 1H), 7.09(d, J = 6.8Hz, 1H), 6.68(d, J = 8.4Hz, 1H), 6.09(d, J = 5.2Hz, 1H), 4.80-4.75(m, 1H), 4.20-4.08(m, 2H), 3.01-2.81(m, 2H), 1.80-1.68(m, 1H), 1.40-1.21(m, 8H), 0.92-0.80(m, 6H)。

[0407] 步骤 4 :按照实施例 6 中使用的方法对 (R)-3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈进行还原得到呈无色油的实施例 19。产率 (0.5g，39％）；$^1$H NMR(400MHz, DMSO-$d_6$) δ 7.62(t, J = 8.0Hz, 1H), 7.02(d, J = 7.6Hz, 1H), 6.58(d, J = 8.0Hz, 1H), 4.56-4.52(m, 1H), 4.08-4.11(m, 2H), 3.18-3.44(br.m, 2H), 2.65-2.74(m, 2H), 1.78-1.84(m, 2H), 1.64-1.56(m, 1H), 1.38-1.20(m, 10H), 0.92-0.78(m, 6H) ;RP-HPLC $t_R$ = 10.56min ;ESI-MS m/z 281.3 $[M+H]^+$。

实施例 20-(E)-3- 氨基 -1-(5-(2- 环己基乙烯基）噻吩 -3- 基）丙 -1- 醇的制备




[0408] (E)-3- 氨基 -1-(5-(2- 环己基乙烯基）噻吩 -3- 基）丙 -1- 醇按照实施例 3 中描述的方法制备。

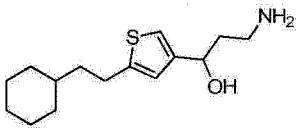
[0409] 步骤 1 :按照实施例 3 中使用的方法在四丁基溴化铵 (1.2g，3.72mmol) 的存在下使 (E)-(2- 环己基乙烯基）硼酸与 5- 氯噻吩 -3- 甲醛偶合在快速层析纯化 (10％ -50％ EtOAc- 己烷梯度）后得到呈黄色油的 (E)-5-(2- 环己基乙烯基）噻吩 -3- 甲醛。产率 (0.4g，53％）；$^1$H NMR(400MHz, DMSO-$d_6$) δ 9.77(s, 1H), 8.38(s, 1H), 7.29(s, 1H), 6.55(d, J

= 8.0Hz, 1H), 6.13(dd, J = 16.4, 6.8Hz, 1H), 2.08-2.02(m, 1H), 1.80-1.58(m, 5H), 1.38-1.08(m, 5H)。

[0410] 步骤 2：按照实施例 3 中使用的方法向 (E)-5-(2- 环己基乙烯基）噻吩 -3- 甲醛中加入 $CH_3CN$ 得到呈黄色油的 (E)-3-(5-(2- 环己基乙烯基）噻吩 -3- 基）-3- 羟基丙腈，其无需进一步纯化而用于下一步。产率 (0.47g，定量）。

[0411] 步骤 3：按照实施例 3 中使用的方法对 (E)-3-(5-(2- 环己基乙烯基）噻吩 -3- 基）-3- 羟基丙腈进行 $LiAlH_4$ 还原得到呈浅黄色油的实施例 20。产率 (0.2g，49％）；$^1H$ NMR(400MHz, DMSO-$d_6$) δ 6.99(s, 1H), 6.88(s, 1H), 6.45(d, J = 16.8Hz, 1H), 5.91(dd, J = 16.0, 6.8Hz, 1H), 4.60(t, J = 6.4Hz, 1H), 2.66-2.56(m, 2H), 2.18-2.08(m, 1H), 1.78-1.58(m, 7H), 1.38-1.02(m, 5H)；RP-HPLC $t_R$ = 10.62min；ESI-MS m/z 219.1 $[M+H]^+$。

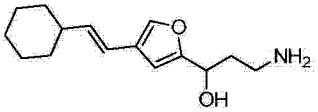
实施例 21-3- 氨基 -1-(5-(2- 环己基乙基）噻吩 -3- 基）丙 -1- 醇的制备




[0412] 3- 氨基 -1-(5-(2- 环己基乙基）噻吩 -3- 基）丙 -1- 醇按照 20 和 11 中描述的方法制备。

[0413] 步骤 1：按照实施例 11 中使用的方法对 (E)-3- 氨基 -1-(5-(2- 环己基乙烯基）噻吩 -3- 基）丙 -1- 醇进行氢化得到呈淡黄色油的实施例 21。产率 (0.08g，90％）；$^1H$ NMR(400MHz, DMSO-$d_6$) δ 6.99(s, 1H), 6.78(s, 1H), 4.72(t, J = 6.0Hz, 1H), 2.82-2.68(m, 4H), 1.98-1.82(m, 2H), 1.81-1.61(m, 6H), 1.58-1.46(m, 2H), 1.38-1.06(m, 3H), 0.98-0.80(m, 2H)；RP-HPLC $t_R$ = 10.78min；ESI-MS m/z 221.1 $[M+H]^+$。

实施例 22-(E)-3- 氨基 -1-(4-(2- 环己基乙烯基）呋喃 -2- 基）丙 -1- 醇的制备




[0414] (E)-3- 氨基 -1-(4-(2- 环己基乙烯基）呋喃 -2- 基）丙 -1- 醇按照实施例 1 和 3 中描述的方法制备。

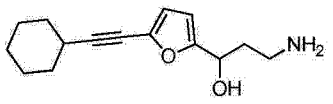
[0415] 步骤 1：按照实施例 3 中使用的方法在 (E)-(2- 环己基乙烯基）硼酸与 4- 溴呋喃 -2- 甲醛之间进行 Suzuki 偶合在快速层析纯化 (1％ -15％ EtOAc - 己烷梯度）后得到呈黄色油的 (E)-4-(2- 环己基乙烯基）呋喃 -2- 甲醛。产率 (0.18g，21％）。

[0416] 步骤 2：按照实施例 3 中使用的方法向 (E)-4-(2- 环己基乙烯基）呋喃 -2- 甲醛中添加乙腈在快速层析纯化 (10％ -50％ EtOAc - 己烷梯度）后得到呈浅黄色油的 (E)-3-(4-(2- 环己基乙烯基）呋喃 -2- 基）-3- 羟基丙腈。产率 (0.13g，60％）；$^1H$ NMR(400MHz, $CD_3OD$) δ 7.38(s, 1H), 6.53(s, 1H), 6.17(d, J = 16.1Hz, 1H), 5.90(dd, J = 6.9, 16.2Hz, 1H), 4.90(t, J = 6.3Hz, 1H), 2.84-2.97(m, 2H), 1.99-2.12(m, 1H), 1.63-1.81(m, 5H), 1.10-1.40(m, 5H)。

[0417] 步骤 3：按照实施例 1 中使用的方法对 (E)-3-(4-(2- 环己基乙烯基）呋喃 -2- 基）-3- 羟基丙腈进行 $LiAlH_4$ 还原在快速层析纯化 (2％ -20％ 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度）后得到呈无色油的实施例 22。产率 (0.07g，53％）；$^1H$

NMR(400MHz, $CD_3OD$) δ 7.34(s, 1H), 6.41(s, 1H), 6.17(d, J = 17.2Hz, 1H), 5.88(dd, J = 7.3, 16.1Hz, 1H), 4.67(t, J = 6.9Hz, 1H), 2.67-2.80(m, 2H), 2.00-2.109m, 1H), 1.90-2.00(m, 2H), 1.63-1.81(m, 5H), 1.10-1.40(m, 5H) ;RP-HPLC $t_R$= 10.42min ;ESI-MS m/z 232.2[M-$H_2O$+H]$^+$。

实施例 23-3- 氨基 -1-(5-( 环己基乙炔基 ) 呋喃 -2- 基 ) 丙 -1- 醇的制备




[0418] 3- 氨基 -1-(5-( 环己基乙炔基 ) 呋喃 -2- 基 ) 丙 -1- 醇按照实施例 1 中和以下所述的方法制备。

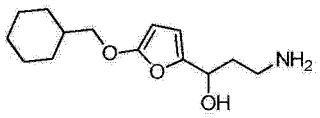
[0419] 步骤 1 :将 5- 溴呋喃 -2- 甲酸 (2.64g, 13.8mmol)、( 环己基甲基 ) 溴化物 (2.62g, 14.8mmol)、$K_2CO_3$(2.30g, 16.64mmol) 在无水 NMP 中的混合物在 Ar 下于 +70℃搅拌 8hr, 之后加入额外的 ( 环己基甲基 ) 溴化物 (1.55g, 8.75mmol)。继续搅拌过夜, 然后将反应混合物减压浓缩。使残余物在 $NaHCO_3$水溶液 (10％ ) 与己烷之间分配, 然后用己烷萃取水层。合并的有机层用盐水洗涤, 用无水 $MgSO_4$干燥, 并减压浓缩, 得到呈浅黄色油的 5- 溴呋喃 -2- 甲酸环己基甲酯。产率 (2.22g, 56％ ) ;$^1$H NMR(400MHz, $CDCl_3$) δ 7.10(d, J = 3.9Hz, 1H), 6.44(d, J = 3.4Hz, 1H), 4.10(d, J = 6.4Hz, 2H), 1.64-1.84(m, 6H), 1.12-1.34(m, 3H), 0.95-1.09(m, 2H)。

[0420] 步骤 2 :通过 Ar 鼓泡使 5- 溴呋喃 -2- 甲酸环己基甲酯 (0.63g, 2.19mmol) 和乙炔基环己烷 (0.32g, 2.96mmol) 在 $Et_3N$(10mL) 中的混合物脱气。加入 CuI(0.023g, 0.119mmol) 和 $PdCl_2(Ph_3P)_2$(0.0412g, 0.0587mmol), 并通过交替真空 /Ar 三次使反应混合物脱气。将反应混合物在 Ar 下于 +70℃搅拌过夜并减压浓缩。使残余物在己烷与 $NH_4Cl$ 水溶液 (25％ ) 之间分配, 并用己烷萃取水层两次。合并的有机层用盐水洗涤, 用活性炭处理, 并用无水 $MgSO_4$ 干燥。减压浓缩得到呈橙色固体的 5-( 环己基乙炔基 ) 呋喃 -2- 甲酸环己基甲酯, 其无需额外纯化而直接用于下一步。产率 (0.75g, 定量 ) ;$^1$H NMR(400MHz, $CDCl_3$) δ 7.10(d, J = 3.9Hz, 1H), 6.50(d, J = 3.9Hz, 1H), 4.10(d, J = 6.4Hz, 2H), 1.56-2.66(m, 1H), 1.63-1.84(m, 9H), 1.42-1.60(m, 4H), 1.10-1.40(m, 6H), 0.96-1.10(m, 2H)。

[0421] 步骤 3 :按照实施例 1 中使用的方法向 5-( 环己基乙炔基 ) 呋喃 -2- 甲酸环己基甲酯中添加乙腈在快速层析纯化 (10％ -75％ EtOAc- 己烷梯度 ) 后得到呈橙色固体的 3-(5-( 环己基乙炔基 ) 呋喃 -2- 基 )-3- 氧代丙腈, 其无需额外纯化而直接用于下一步。产率 (0.64g, 定量 )。

[0422] 步骤 4 :按照实施例 1 中使用的方法对 3-(5-( 环己基乙炔基 ) 呋喃 -2- 基 )-3- 氧代丙腈进行 $LiAlH_4$还原在快速层析纯化 (2％ -20％ 7N $NH_3$/MeOH- $CH_2Cl_2$梯度 ) 及随后的活性炭处理后得到呈浅黄色油的实施例 23。产率 (0.14g, 26％ ) ;$^1$H NMR(400MHz, $CD_3OD$) δ 6.39(d, J = 3.4Hz, 1H), 6.24(d, J = 3.9Hz, 1H), 4.68(t, J = 6.8Hz, 1H), 2.69-2.79(m, 2H), 2.56-2.64(m, 1H), 1.90-1.98(m, 2H), 1.81-1.90(m, 2H), 1.68-1.80(m, 2H), 1.28-1.68(m, 6H) ;RP-HPLC $t_R$= 9.95min ;ESI-MS m/z 230.2[M-$H_2O$+H]$^+$。

实施例 24-3- 氨基 -1-(5-( 环己基甲氧基 ) 呋喃 -2- 基 ) 丙 -1- 醇的制备



[0423] 3- 氨基 -1-(5-( 环己基甲氧基 ) 呋喃 -2- 基 ) 丙 -1- 醇按照实施例 1、23 中和以下所述的方法制备。

[0424] 步骤 1 :在 Ar 下将环己基甲醇 (1.60g,14.0mmol) 缓慢加入到冷却的 (0℃) 氢化钠 (0.30g,12.5mmol) 在无水 NMP(5mL) 中的悬浮液中。向反应混合物中加入 5- 溴呋喃 -2- 甲酸环己基甲酯 (1.79g,6.23mmol) 在无水 NMP(6mL) 中的溶液,并在室温下搅拌过夜。使反应混合物在 $NH_4Cl$ 水溶液 (25%) 与己烷之间分配。水层用己烷萃取,合并的有机层用盐水洗涤并减压浓缩。通过快速层析纯化 (2% -10% EtOAc - 己烷梯度 ) 得到呈无色油的 5-( 环己基甲氧基 ) 呋喃 -2- 甲酸环己基甲酯。产率 (1.05g,53%) ;$^1H$ NMR(400MHz,$CDCl_3$) δ 7.10(d,J = 3.4Hz,1H),5.27(d,J = 3.9Hz,1H),4.05(d,J = 6.4Hz,2H),3.91(d,J = 5.9Hz,2H),1.62-1.85(m,12H),1.10-1.33(m,6H),0.94-1.10(m,4H)。

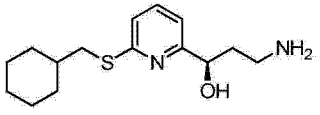
[0425] 步骤 2 :按照实施例 1 中使用的方法对 5-( 环己基甲氧基 ) 呋喃 -2- 甲酸环己基甲酯进行 $LiAlH_4$ 还原在快速层析纯化 (10% -50% EtOAc - 己烷梯度 ) 后得到作为与环己基甲醇的混合物的 (5-( 环己基甲氧基 ) 呋喃 -2- 基 ) 甲醇,其无需进一步纯化而用于下一步。产率 (0.75g,定量 ) ;$^1$HNMR(400MHz,DMSO-$d_6$) δ 6.09(d,J = 3.4Hz,1H),5.17(d,J = 2.9Hz,1H),4.98(t,J = 5.4Hz,1H),4.19(d,J = 5.9Hz,2H),3.77(d,J = 5.9Hz,2H),1.55-1.77(m,6H),1.05-1.25(m,3H),0.94-1.05(m,2H)。

[0426] 步骤 3 :将 (5-( 环己基甲氧基 ) 呋喃 -2- 基 ) 甲醇和环己基甲醇 (0.75g) 和 $MnO_2$(3.16g,36.3mmol) 在无水 $CH_2Cl_2$(16mL) 中的混合物在室温下搅拌 3 天。将反应混合物通过 Celite 过滤并减压浓缩。快速层析纯化 (10% -50% EtOAc - 己烷梯度 ) 得到呈浅黄色的 5-( 环己基甲氧基 ) 呋喃 -2- 甲醛,其含有环己基甲醇作为杂质。产率 (0.68g,99 % ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 9.20(s,1H),7.52(d,J = 3.8Hz,1H),5.79(d,J = 3.8Hz,1H),4.03(d,J = 5.8Hz,2H),1.55-1.80(m,6H),0.96-1.25(m,5H)。

[0427] 步骤 4 :按照实施例 3 中使用的方法向 5-( 环己基甲氧基 ) 呋喃 -2- 甲醛中添加乙腈在快速层析纯化 (10% -50% EtOAc - 己烷梯度 ) 及随后的活性炭处理后得到呈无色油的 3-(5-( 环己基甲氧基 ) 呋喃 -2- 基 )-3- 羟基丙腈,其直接用于下一步。产率 (0.56g,69%)。

[0428] 步骤 5 :按照实施例 1 中使用的方法对 3-(5-( 环己基甲氧基 ) 呋喃 -2- 基 )-3- 羟基丙腈进行 $LiAlH_4$ 还原在快速层析纯化 (2% -20% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到呈浅黄色油的实施例 24,其在静置时凝固。产率 (0.26g,46%) ;$^1H$ NMR(400MHz,$CD_3OD$) δ 6.11(d,J = 3.4Hz,1H),5.10(d,J = 3.4Hz,1H),4.56(t,J = 6.8Hz,1H),3.79(d,J = 6.3Hz,2H),2.65-2.77(m,2H),1.82-1.96(m,2H),1.66-1.82(m,6H),1.15-1.37(m,3H),1.00-1.13(m,2H) ;ESI-MS m/z 254.2$[M+H]^+$。

实施例 25-(R)-3- 氨基 -1-(6-(( 环己基甲基 ) 硫基 ) 吡啶 -2- 基 ) 丙 -1- 醇的制备



[0429] (R)-3- 氨基 -1-(6-(( 环己基甲基 ) 硫基 ) 吡啶 -2- 基 ) 丙 -1- 醇按照实施例 6

和以下所述的方法制备。

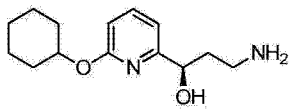
[0430] 步骤 1：通过 Ar 鼓泡使（溴甲基）环己烷 (0.95g,5.4mmol) 和 AcSK(0.65, 5.4mmol) 在 DMF 中的悬浮液脱气，并在 60℃下搅拌 4hr。然后向反应混合物中加入 $Cs_2CO_3$(3.1g,10.8mmol)，随后加入 MeOH(1ml) 和 6- 溴吡啶甲酸 (1.0g,4.9mmol)。在 70℃下继续搅拌 18hr。反应混合物通过 Celite 过滤并减压浓缩。向残余物添加甲醇 (20ml)，随后添加 1.25M HCl-MeOH(10ml) 和浓 $H_2SO_4$(1ml)。所得的混合物在 60℃下搅拌 18 小时，浓缩，在饱和 $NaHCO_3$(50ml) 与乙酸乙酯 (100ml) 之间分配。将有机层分离，用无水 $Na_2SO_4$ 干燥并减压浓缩。通过快速层析纯化 (30％ -50％ EtOAc - 己烷梯度）得到 6-((环己基甲基）硫基）吡啶甲酸甲酯。产率 (0.6g,46％）；$^1$H NMR(400MHz, $CDCl_3$) δ 7.76(d, J ＝ 8.0Hz, 1H), 7.58(t, J ＝ 8.0Hz, 1H), 7.31(d, J ＝ 8.0Hz, 1H), 3.96(s, 3H), 3.14(d, J ＝ 6.4Hz, 2H), 1.96-1.84(m, 2H), 1.78-1.58(m, 4H), 1.26-1.00(m, 5H)。

[0431] 步骤 2：按照实施例 6 中使用的方法向 6-((环己基甲基）硫基）吡啶甲酸甲酯中加入 $CH_3CN$ 得到呈黄色油的 3-(6-((环己基甲基）硫基）吡啶 -2- 基）-3- 氧代丙腈，其无需进一步纯化而用于下一步。产率 (0.63g，定量）。

[0432] 步骤 3：按照实施例 6 中描述的方法对 3-(6-((环己基甲基）硫基）吡啶 -2- 基）-3- 氧代丙腈进行手性还原得到呈黄色油的 (R)-3-(6-((环己基甲基）硫基）吡啶 -2- 基）-3- 羟基丙腈，其无需进一步纯化而用于下一步。产率 (0.63g，定量）。

[0433] 步骤 4：按照实施例 6 中描述的方法对 (R)-3-(6-((环己基甲基）硫基）吡啶 -2- 基）-3- 羟基丙腈进行还原在快速层析纯化 (15％ -20％ 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度）后得到呈无色油的实施例 25。产率 (0.3g,43％）；$^1$H NMR(400MHz, $CD_3OD$) δ 7.56(t, J ＝ 7.6Hz, 1H), 7.17(d, J ＝ 7.6Hz, 1H), 7.09(d, J ＝ 8.0Hz, 1H), 4.75-4.72(m, 1H), 3.04(d, J ＝ 7.2Hz, 2H), 2.80(t, J ＝ 7.6Hz, 2H), 2.03-1.98(m, 1H), 1.94-1.54(m, 7H), 1.30-0.99(m, 5H)；RP-HPLC $t_R$ ＝ 9.63min；ESI-MS m/z 281.2$[M+H]^+$。

实施例 26-(R)-3- 氨基 -1-(6-（环己基氧基）吡啶 -2- 基）丙 -1- 醇的制备




[0434] (R)-3- 氨基 -1-(6-（环己基氧基）吡啶 -2- 基）丙 -1- 醇按照实施例 6 中描述的方法制备。

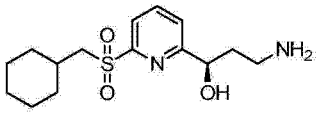
[0435] 步骤 1：按照实施例 6 中使用的方法使 6- 溴吡啶甲酸与环己醇反应得到呈黄色油的 6-（环己基氧基）吡啶甲酸甲酯，其无需额外纯化而用于下一步。产率 (1.15g，定量）。

[0436] 步骤 2：按照实施例 6 中描述的方法向 6-（环己基氧基）吡啶甲酸甲酯中添加 $CH_3CN$ 得到呈黄色油的 3-(6-（环己基氧基）吡啶 -2- 基）-3- 氧代丙腈，其无需进一步纯化而用于下一步。产率 (1.2g，定量）。

[0437] 步骤 3：按照实施例 6 中描述的方法对 3-(6-（环己基氧基）吡啶 -2- 基）-3- 氧代丙腈进行手性还原得到呈黄色油的 (R)-3-(6-（环己基氧基）吡啶 -2- 基）-3- 羟基丙腈，其无需进一步纯化而用于下一步。产率 (1.2g，定量）；$^1$H NMR(400MHz, DMSO-$d_6$) δ 7.77(t, J ＝ 7.6Hz, 1H), 7.06(d, J ＝ 7.6Hz, 1H), 6.63(d, J ＝ 8.4Hz, 1H), 6.07(d, J ＝ 5.2Hz, 1H), 5.02-4.92(m, 1H), 4.76(q, J ＝ 5.6Hz, 1H), 3.0-2.86(m, 2H), 2.0-1.06(m, 10H)。

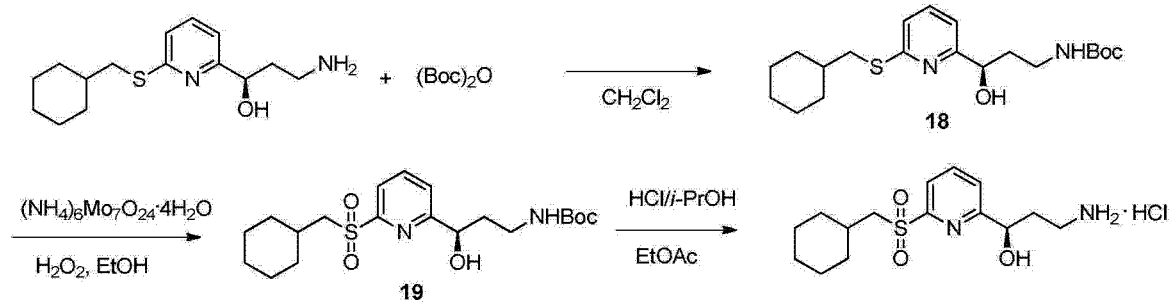
[0438] 步骤 4：按照实施例 6 中描述的方法对 (R)-3-(6-(环己基氧基)吡啶 -2- 基)-3- 羟基丙腈进行还原在快速层析纯化 (15％ -25％ 7N $NH_3$/MeOH - $CH_2Cl_2$梯度) 后得到呈无色油的实施例 26。产率 (0.4g,33％)；$^1H$ NMR(400MHz,$CD_3OD$) δ 7.61(t,J = 7.8Hz,1H),7.00(d,J = 7.6Hz,1H),6.58(d,J = 8.4Hz,1H),5.05-4.96(m,1H),4.40-4.28(m,1H),2.84(t,J = 6.8Hz,2H),2.08-1.74(m,6H),1.62-1.32(m,6H)；RP-HPLC $t_R$= 7.04min；ESI-MS m/z 251.2$[M+H]^+$。

实施例 27-(R)-3- 氨基 -1-(6-((环己基甲基)磺酰基)吡啶 -2- 基)丙 -1- 醇的制备



[0439] (R)-3- 氨基 -1-(6-((环己基甲基)磺酰基)吡啶 -2- 基)丙 -1- 醇按照流程 6 所示的方法制备。

流程 6.

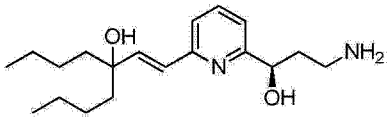



[0440] 步骤 1：将实施例 25(0.2g,0.71mmol) 和碳酸二叔丁酯 (0.17g,0.78mmol) 在 DCM(10ml) 中的混合物在室温下搅拌 18hr。减压浓缩得到呈淡黄色油的氨基甲酸酯 18，其无需进一步纯化而用于下一步。产率 (0.27g，定量)。

[0441] 步骤 2：向硫醚 18(0.27g,0.71mmol) 和四水合钼酸铵 (0.28g,0.22mmol) 在乙醇 (10ml) 中的混合物中加入过氧化氢 (1ml,30％)。将反应混合物在室温下搅拌 18hr，用水 (15ml) 稀释，减压浓缩。水层用 EtOAc(3x20ml) 萃取，合并的有机层用无水 $Na_2SO_4$干燥并减压浓缩。通过快速层析纯化 (60％ -75％ EtOAc - 己烷梯度) 得到呈无色油的砜 19。产率 (0.16g,55％)；$^1H$ NMR(400MHz,$CD_3OD$) δ 8.10(t,J = 7.6Hz,1H),7.95(d,J = 7.6Hz,1H),7.83(d,J = 7.6Hz,1H),4.84-4.81(m,1H),3.47-3.42(m,2H),3.30-3.12(m,2H),2.10-1.98(m,1H),1.94-1.54(m,7H),1.43(s,9H),1.30-0.99(m,5H)。

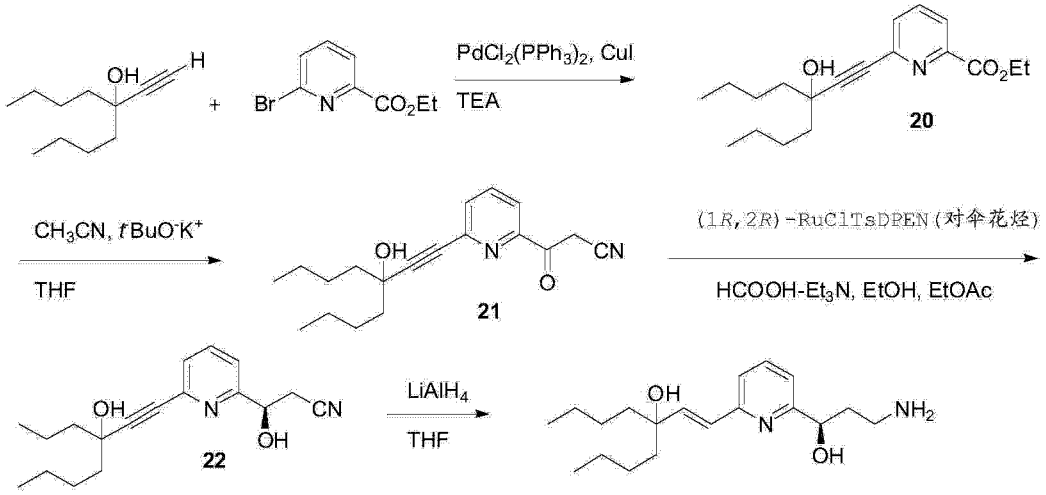
[0442] 步骤 3：将氨基甲酸酯 19(0.16g,0.39mmol) 和 HCl/i-PrOH(2.0ml,11mmol) 在 EtOAc(5ml) 中的混合物在室温下搅拌 18hr 并减压浓缩，得到呈无色油的实施例 27 盐酸盐。产率 (0.12g,88％)；$^1H$ NMR(400MHz,$CD_3OD$) δ 8.10(t,J = 6.8Hz,1H),7.95(d,J = 7.2Hz,1H),7.83(d,J = 8.0Hz,1H),4.94-4.86(m,1H),3.14-3.04(m,2H),2.24-2.14(m,1H),2.06-1.96(m,1H),1.94-1.54(m,7H),1.30-0.99(m,6H)；RP-HPLC $t_R$= 7.82min；ESI-MS:m/z 313.2$[M+H]^+$。

实施例 28-(R,E)-5-(2-(6-(3- 氨基 -1- 羟丙基)吡啶 -2- 基)乙烯基)壬 -5- 醇的制备



[0443] (R,E)-5-(2-(6-(3-氨基-1-羟丙基)吡啶-2-基)乙烯基)壬-5-醇按照流程7所示的方法制备。

流程7.



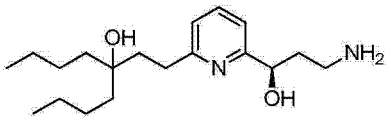

[0444] 步骤1:向5-乙炔基壬-5-醇(0.76g,5.0mmol)、6-溴吡啶甲酸乙酯(1.0g,5.0mmol)和$PdCl_2(PPh_3)_2$(0.1g,0.14mmol)在TEA(20ml)中的混合物中加入CuI(0.07g,0.37mmol)。反应混合物用氩气鼓泡,然后在+70℃下搅拌18hr,冷却至室温,用EtOAc(40ml)稀释,并通过Celite过滤。减压浓缩得到炔烃20,其无需进一步纯化而用于下一步。产率(1.59g,定量)。

[0445] 步骤2:按照实施例6中描述的方法向酯20中加入$CH_3CN$得到呈黄色油的酮腈21,其无需进一步纯化而用于下一步。产率(1.63g,定量)。

[0446] 步骤3:按照实施例6中使用的方法对酮腈21进行手性还原在通过快速层析纯化(35%-50%EtOAc-己烷梯度)后得到呈白色固体的(R)-羟基腈22。产率(1.20g,70%);$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.85(t,J = 8.0Hz,1H),7.49(d,J = 7.6Hz,1H),7.33(d,J = 8.0Hz,1H),4.88-4.82(m,1H),3.02-2.82(m,2H),1.66-1.52(m,4H),1.50-1.34(m,4H),1.32-1.22(m,4H),0.92-0.80(m,6H)。

[0447] 步骤4:按照实施例3中使用的方法对(R)-羟基腈22进行$LiAlH_4$还原在快速层析纯化(20%-30% 7N $NH_3$/MeOH-$CH_2Cl_2$梯度)后得到呈浅黄色油的实施例28。产率(0.23g,21%);$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.65(t,J = 7.80Hz,1H),7.26-7.20(m,2H),6.63(d,J = 16Hz,1H),6.50(d,J = 16Hz,1H),4.65-4.56(m,1H),2.72-2.58(m,2H),1.82-1.72(m,2H),1.50-1.38(m,4H),1.32-1.10(m,8H),0.86-0.76(m,6H);RP-HPLC $t_R$ = 7.62min;ESI-MS m/z 321.1$[M+H]^+$。

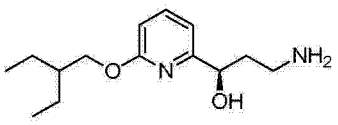
实施例29-(R)-5-(2-(6-(3-氨基-1-羟丙基)吡啶-2-基)乙基)壬-5-醇的制备



[0448] (R)-5-(2-(6-(3-氨基-1-羟丙基)吡啶-2-基)乙基)壬-5-醇按照实施例11和以下所述的方法制备。

[0449] 步骤1:按照实施例11中使用的方法对实施例28进行氢化得到呈浅黄色油的实施例29。产率(0.09g,90%);$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.60(t,J=7.80Hz,1H),7.24(d,J=8.0Hz,1H),7.04(d,J=8.0Hz,1H),4.65-4.56(m,1H),2.72-2.58(m,4H),1.84-1.68(m,2H),1.66-1.54(m,2H),1.36-1.26(m,4H),1.25-1.14(m,8H),0.88-0.78(m,6H);RP-HPLC $t_R$=7.50min;ESI-MS m/z 323.3[M+H]。

实施例30-(R)-3-氨基-1-(6-(2-乙基丁氧基)吡啶-2-基)丙-1-醇的制备



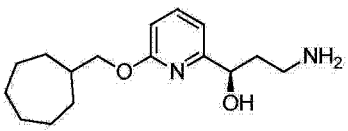

[0450] (R)-3-氨基-1-(6-(2-乙基丁氧基)吡啶-2-基)丙-1-醇按照实施例6中描述的方法制备。

[0451] 步骤1:按照实施例6中使用的方法使6-溴吡啶甲酸与2-乙基丁-1-醇反应得到呈黄色油的6-(2-乙基丁氧基)吡啶甲酸甲酯,其无需进一步纯化而用于下一步。产率(1.19g,定量);$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.83(t,J=8.0Hz,1H),7.62(d,J=7.6Hz,1H),7.02(d,J=8.0Hz,1H),4.18(d,J=6.0Hz,2H),3.82(s,3H),1.66-1.56(m,1H),1.42-1.32(m,4H),0.86(t,J=7.6Hz,6H)。

[0452] 步骤2:按照实施例6中描述的方法向6-(2-乙基丁氧基)吡啶甲酸甲酯中加入$CH_3CN$得到呈黄色油的3-(6-(2-乙基丁氧基)吡啶-2-基)-3-氧代丙腈,其无需进一步纯化而用于下一步。产率(1.2g,定量)。

[0453] 步骤3:按照实施例6中描述的方法对3-(6-(2-乙基丁氧基)吡啶-2-基)-3-氧代丙腈进行硼烷还原在快速层析纯化(25%-30% 7N $NH_3$/MeOH-$CH_2Cl_2$梯度)后得到呈无色油的实施例30。产率(0.11g,25%);$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.61(t,J=7.6Hz,1H),7.0(d,J=7.6Hz,1H),6.57(d,J=8.4Hz,1H),4.57-4.50(m,1H),4.15-4.06(m,2H),2.70-2.58(m,2H),1.84-1.76(m,1H),1.64-1.52(m,2H),1.42-1.28(m,4H),0.85(t,J=7.2Hz,6H);RP-HPLC $t_R$=8.51min;ESI-MS m/z 253.2$[M+H]^+$。

实施例31-(R)-3-氨基-1-(6-(环庚基甲氧基)吡啶-2-基)丙-1-醇的制备




[0454] (R)-3-氨基-1-(6-(环庚基甲氧基)吡啶-2-基)丙-1-醇按照实施例6中描述的方法制备。

[0455] 步骤1:按照实施例6中使用的方法使6-溴吡啶甲酸与环庚基甲醇反应得到呈黄色油的6-(环庚基甲氧基)吡啶甲酸甲酯,其无需进一步纯化而用于下一步。产率(2.0g,定量);$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.82(t,J=8.0Hz,1H),7.61(d,J=7.2Hz,1H),7.03(d,J=8.0Hz,1H),4.05(d,J=6.4Hz,2H),3.82(s,3H),1.99-1.01(m,13H)。

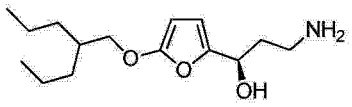
[0456] 步骤2:按照实施例6中使用的方法向6-(环庚基甲氧基)吡啶甲酸甲酯中加入$CH_3CN$得到呈黄色油的3-(6-(环庚基甲氧基)吡啶-2-基)-3-氧代丙腈,其无需进一步纯

化而用于下一步。产率 (2.12g,定量)。

[0457] 步骤 3 :按照实施例 6 中描述的方法对 3-(6-(环庚基甲氧基)吡啶 -2- 基)-3- 氧代丙腈进行手性还原在通过快速层析纯化 (30% -50% EtOAc - 己烷梯度)后得到呈黄色油的 (R)-3-(6-(环庚基甲氧基)吡啶 -2- 基)-3- 羟基丙腈。产率 (0.77g,36%) ;$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.67(t,J = 8.0Hz,1H),7.06(d,J = 7.4Hz,1H),6.66(d,J = 8.2Hz,1H),6.05(d,J = 5.0Hz,1H),4.78-4.70(m,1H),4.18-3.96(m,2H),3.01-2.82(m,2H),1.99-1.01(m,13H)。

[0458] 步骤 4 :按照实施例 1 中描述的方法对 (R)-3-(6-(环庚基甲氧基)吡啶 -2- 基)-3- 羟基丙腈进行 $LiAlH_4$ 还原在快速层析纯化 (20% -30% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度)后得到呈无色油的实施例 31。产率 (0.11g,25%) ;$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.60(t,J = 8.0Hz,1H),7.00(d,J = 6.8Hz,1H),6.67(d,J = 7.6Hz,1H),4.56-4.50(m,1H),4.02-3.98(m,2H),2.72-2.60(m,2H),1.92-1.6(m,15H) ;RP-HPLC $t_R$ = 9.59min ;ESI-MS m/z279.2$[M+H]^+$。

实施例 32-(R)-3- 氨基 -1-(5-((2- 丙基戊基)氧基)呋喃 -2- 基)丙 -1- 醇的制备




[0459] (R)-3- 氨基 -1-(5-((2- 丙基戊基)氧基)呋喃 -2- 基)丙 -1- 醇按照实施例 5、18 和以下所述的方法制备。

[0460] 步骤 1 :按照实施例 18 中使用的方法进行 5- 溴呋喃 -2- 甲酸与 2- 丙基戊 -1- 醇的酯化在快速层析纯化 (5% -20% EtOAc - 己烷梯度)后得到呈无色油的 5- 溴呋喃 -2- 甲酸 2- 丙基戊酯。产率 (4.85g,98%) ;$^1$H NMR(400MHz,$CDCl_3$) δ 7.07(d,J = 3.9Hz,1H),6.43(d,J = 3.4Hz,1H),4.18(d,J = 5.9Hz,2H),1.70-1.80(m,1H),1.25-1.40(m,8H),0.83-0.95(m,6H)。

[0461] 步骤 2 :除使用 NMP 作为溶剂、不使用 CuI 并且在 Ar 下于 +50℃加热反应混合物 1.5hr 外,按照实施例 18 中使用的方法使 2- 丙基戊 -1- 醇与 5- 溴呋喃 -2- 甲酸 2- 丙基戊酯之间进行反应在快速层析纯化 (2% -5% EtOAc - 己烷梯度)后得到呈无色油的 5-((2- 丙基戊基)氧基)呋喃 -2- 甲酸 2- 丙基戊酯。产率 (0.62g,48%) ;$^1$H NMR(400MHz,$CD_3OD$) δ 7.15(d,J = 3.9Hz,1H),5.47(d,J = 3.9Hz,1H),4.14(d,J = 5.9Hz,2H),4.06(d,J = 5.9Hz,2H),1.70-1.84(m,2H),1.28-1.44(m,16H),0.86-0.97(m,12H)。

[0462] 步骤 3 :将无水 MeOH(75mL) 中的 5-((2- 丙基戊基)氧基)呋喃 -2- 甲酸 2- 丙基戊酯 (0.62g,1.76mmol)、NaOMe(30%,在 MeOH 中,2mL) 在室温下搅拌过夜,然后减压浓缩。残余物在 $NH_4Cl$ 水溶液 (25%) 与己烷之间分配。有机层用盐水洗涤,用无水 $MgSO_4$ 干燥,减压浓缩。快速层析纯化 (5% -20% EtOAc - 己烷梯度)得到呈无色油的 5-((2- 丙基戊基)氧基)呋喃 -2- 甲酸甲酯。产率 (0.38g,85%) ;$^1$H NMR(400MHz,$CDCl_3$) δ 7.12(d,J = 4.0Hz,1H),5.27(d,J = 3.5Hz,1H),3.99(d,J = 5.9Hz,2H),3.03(s,3H),1.74-1.83(m,1H),1.20-1.40(8H),0.86-0.94(m,6H)。

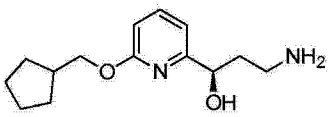
[0463] 步骤 4 :在惰性气氛下于 -75℃向 LiHMDS 溶液 (1M/THF,3.0mL,3.0mmol) 中加入无水 $CH_3CN$(0.15mL,2.87mmol)。并将反应混合物搅拌 5min。向反应混合物中加入 5-((2- 丙基戊基)氧基)呋喃 -2- 甲酸甲酯 (1.337mmol) 在无水 THF(7mL) 中的溶液,

并将反应混合物在惰性气氛下搅拌，同时缓慢升温至 0℃保持超过 75min。反应混合物在 $NaHSO_4$水溶液（10％）与 EtOAc 之间分配。有机层用盐水洗涤，减压浓缩。快速层析纯化（10％ -50％ EtOAc - 己烷梯度）得到呈灰白色固体的 3- 氧代 -3-(5-((2- 丙基戊基）氧基）呋喃 -2- 基）丙腈。产率（0.23g，66％）；$^1H$ NMR(400MHz, DMSO-$d_6$) δ 7.57(d, J = 3.8Hz, 1H), 5.78(d, J = 3.8Hz, 1H), 4.30(s, 2H), 4.08(d, J = 5.6Hz, 2H), 1.69-1.79(m, 1H), 1.23-1.35(m, 8H), 0.80-0.88(m, 6H)。

[0464] 步骤 5：按照实施例 5 中使用的方法对 3- 氧代 -3-(5-((2- 丙基戊基）氧基）呋喃 -2- 基）丙腈进行手性还原在快速层析纯化（20％ -100％ EtOAc - 己烷梯度）后得到呈黄色油的 (R)-3- 羟基 -3-(5-((2- 丙基戊基）氧基）呋喃 -2- 基）丙腈。产率（0.14g，61 ％）；$^1H$ NMR(400MHz, DMSO-$d_6$) δ 6.19(d, J = 2.4Hz, 1H), 5.86(d, J = 5.4Hz, 1H), 5.22(d, J = 3.4Hz, 1H), 4.67(q, J = 5.8Hz, 1H), 3.84(d, J = 5.4Hz, 2H), 2.77-2.91(m, 2H), 1.64-1.75(m, 1H), 1.20-1.35(m, 8H), 0.78-0.90(m, 6H)。

[0465] 步骤 6：按照实施例 1 中使用的方法对 (R)-3- 羟基 -3-(5-((2- 丙基戊基）氧基）呋喃 -2- 基）丙腈进行 $LiAlH_4$还原在快速层析纯化（2％ -20％ 7N $NH_3$/MeOH - $CH_2Cl_2$梯度）后得到呈无色油的实施例 32。产率（0.080g，61％）；$^1H$ NMR(400MHz, $CD_3OD$) δ .6.11(d, J = 2.9Hz, 1H), 5.11(d, J = 2.9Hz, 1H), 4.56(t, J = 6.9Hz, 1H), 3.88(d, J = 5.9Hz, 2H), 2.65-2.78(m, 2H), 1.88-1.96(m, 2H), 1.70-1.80(m, 1H), 1.30-1.44(m, 8H), .085-0.97(m, 6H)；ESI-MS 270.2m/z $[M+H]^+$。

实施例 33-(R)-3- 氨基 -1-(6-（环戊基甲氧基）吡啶 -2- 基）丙 -1- 醇的制备




[0466] (R)-3- 氨基 -1-(6-（环戊基甲氧基）吡啶 -2- 基）丙 -1- 醇按照实施例 6 中描述的方法制备。

[0467] 步骤 1：按照实施例 6 中使用的方法使 6- 溴吡啶甲酸与环戊基甲醇反应得到呈黄色油的 6-（环戊基甲氧基）吡啶甲酸甲酯，其无需进一步纯化而用于下一步。产率（1.1g，定量）；$^1H$ NMR(400MHz, DMSO-$d_6$) δ 7.83(t, J = 8.0Hz, 1H), 7.62(d, J = 7.2Hz, 1H), 7.03(d, J = 8.0Hz, 1H), 4.14(d, J = 6.4Hz, 2H), 3.82(s, 3H), 2.32-2.22(m, 1H), 1.80-1.62(m, 2H), 1.60-1.44(m, 4H), 1.38-1.21(m, 2H)。

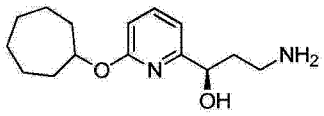
[0468] 步骤 2：按照实施例 6 中描述的方法向 6-（环戊基甲氧基）吡啶甲酸甲酯中加入 $CH_3CN$得到呈黄色油的 3-(6-（环戊基甲氧基）吡啶 -2- 基）-3- 氧代丙腈，其无需进一步纯化而用于下一步。产率（1.22g，定量）。

[0469] 步骤 3：按照实施例 6 中描述的方法对 3-(6-（环戊基甲氧基）吡啶 -2- 基）-3- 氧代丙腈进行手性还原得到呈黄色油的 (R)-3-(6-（环戊基甲氧基）吡啶 -2- 基）-3- 羟基丙腈，其无需进一步纯化而用于下一步。产率（1.22g，定量）；$^1H$ NMR(400MHz, DMSO-$d_6$) δ 7.68(t, J = 7.6Hz, 1H), 7.07(d, J = 7.6Hz, 1H), 6.66(d, J = 8.0Hz, 1H), 6.06(d, J = 5.6Hz, 1H), 4.78-4.72(m, 1H), 4.18-4.04(m, 2H), 3.01-2.82(m, 2H), 2.32-2.02(m, 1H), 1.78-1.62(m, 2H), 1.60-1.42(m, 4H), 1.36-1.21(m, 2H)。

[0470] 步骤 4：按照实施例 1 中描述的方法对 (R)-3-(6-（环戊基甲氧基）吡

啶 -2- 基 )-3- 羟基丙腈进行 $LiAlH_4$ 还原在快速层析纯化 (20 % -30 % 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到呈无色油的实施例 33。产率 (0.33g,24 % ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.60(t,J = 7.6Hz,1H),7.00(d,J = 6.8Hz,1H),6.56(d,J = 8.0Hz,1H),4.57-4.51(m,1H),4.10-4.04(m,2H),2.71-2.58(m,2H),2.30-2.02(m,1H),1.82-1.21(m,10H) ;RP-HPLC $t_R$ = 7.71min ;ESI-MS m/z 251.3$[M+H]^+$。

实施例 34-(R)-3- 氨基 -1-(6-( 环庚基氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇的制备




[0471] (R)-3- 氨基 -1-(6-( 环庚基氧基 ) 吡啶 -2- 基 ) 丙 -1- 醇按照实施例 6 中描述的方法制备。

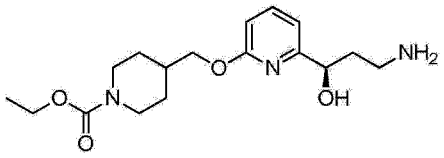
[0472] 步骤 1 :按照实施例 6 中使用的方法使 6- 溴吡啶甲酸与环庚醇反应得到呈黄色油的 6-( 环庚基氧基 ) 吡啶甲酸甲酯,其无需进一步纯化而用于下一步。产率 (1.24g,定量 ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.80(t,J = 8.0Hz,1H),7.58(d,J = 7.2Hz,1H),6.57(d,J = 8.8Hz,1H),5.25-5.15(m,1H),3.80(s,3H),2.0-1.82(m,2H),1.76-1.40(m,10H)。

[0473] 步骤 2 :按照实施例 6 中描述的方法向 6-( 环庚基氧基 ) 吡啶甲酸甲酯中加入 $CH_3CN$ 得到呈黄色油的 3-(6-( 环庚基氧基 ) 吡啶 -2- 基 )-3- 氧代丙腈,其无需进一步纯化而用于下一步。产率 (1.29g,定量 )。

[0474] 步骤 3 :按照实施例 6 中描述的方法对 3-(6-( 环庚基氧基 ) 吡啶 -2- 基 )-3- 氧代丙腈进行手性还原得到呈黄色油的 (R)-3-(6-( 环庚基氧基 ) 吡啶 -2- 基 )-3- 羟基丙腈,其无需进一步纯化而用于下一步。产率 (1.29g,定量 )。

[0475] 步骤 4 :按照实施例 1 中描述的方法对 (R)-3-(6-( 环庚基氧基 ) 吡啶 -2- 基 )-3- 羟基丙腈进行 $LiAlH_4$ 还原在快速层析纯化 (20 % -30 % 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度 ) 后得到呈无色油的实施例 34。产率 (0.19g,14 % ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.58(t,J = 8.0Hz,1H),6.97(d,J = 7.2Hz,1H),6.51(d,J = 8.0Hz,1H),5.16-5.08(m,1H),4.56-4.48(m,1H),2.72-2.56(m,2H),1.98-1.36(m,14H) ;RP-HPLC $t_R$= 7.98min ;ESI-MS m/z 265.2$[M+H]^+$。

实施例 35-(R)-4-(((6-(3- 氨基 -1- 羟丙基 ) 吡啶 -2- 基 ) 氧基 ) 甲基 ) 哌啶 -1- 甲酸乙酯的制备




[0476] (R)-4-(((6-(3- 氨基 -1- 羟丙基 ) 吡啶 -2- 基 ) 氧基 ) 甲基 ) 哌啶 -1- 甲酸乙酯按照实施例 6 和以下所述的方法制备。

[0477] 步骤 1 :按照实施例 6 中使用的方法使 6- 溴吡啶甲酸与哌啶 -4- 基甲醇反应得到呈黄色油的 6-( 哌啶 -4- 基甲氧基 ) 吡啶甲酸甲酯。产率 (0.3g,24 % ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.82(t,J = 8.0Hz,1H),7.62(d,J = 7.4Hz,1H),7.02(d,J = 8.0Hz,1H),4.08(d,J = 6.4Hz,2H),3.82(s,3H),2.98-2.86(m,2H),2.51-2.28(m,2H),1.84-1.71(m,1H),1.66-1.58(m,2H),1.20-1.06(m,24H)。

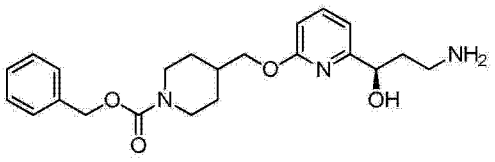
[0478] 步骤 2：在 0℃下向 6-(哌啶 -4- 基甲氧基）吡啶甲酸甲酯 (0.3g,1.2mmol)、$Et_3N$(0.2g,1.8mmol) 在 DCM(10ml) 中的混合物中加入氯甲酸乙酯 (0.2g,1.8mmol)。使反应升温至室温，用 1N HCl(20ml) 洗涤，用 $Na_2SO_4$ 干燥，并减压浓缩，得到 6-((1-( 乙氧羰基）哌啶 -4- 基）甲氧基）吡啶甲酸甲酯，其无需进一步纯化而用于下一步。产率 (0.38g，定量）。

[0479] 步骤 3：按照实施例 6 中描述的方法向 6-((1-( 乙氧羰基）哌啶 -4- 基）甲氧基）吡啶甲酸甲酯中加入 $CH_3CN$ 得到 4-(((6-(2- 氰基乙酰基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸乙酯的乙酸乙酯溶液，其无需进一步纯化而用于下一步。

[0480] 步骤 4：按照实施例 6 中描述的方法对 4-(((6-(2- 氰基乙酰基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸乙酯进行手性还原在快速层析纯化 (20％ -75％ EtOAc- 己烷梯度）后得到呈黄色油的 (R)-4-(((6-(2- 氰基 -1- 羟基乙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸乙酯。产率 (0.27g,81％）；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.67(t,J = 8.0Hz,1H),7.12(d,J = 7.2Hz,1H),6.68(d,J = 8.4Hz,1H),4.92-4.83(m,1H),4.21-4.04(m,6H),3.02-2.68(m,4H),2.04-1.98(m,1H),1.88-1.78(m,2H),1.38-1.21(m,5H)。

[0481] 步骤 5：将 (R)-4-(((6-(2- 氰基 -1- 羟基乙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸乙酯 (0.27g,0.81mmol)、海绵镍催化剂 A-4000(0.1g，Johnson Mathey) 在 7N $NH_3$/MeOH(20ml) 中的混合物在 Parr 氢化器中于 50psi 压强的 $H_2$ 下 50℃振摇 18hr，冷却至室温，过滤，减压浓缩。通过快速层析纯化 (20％ -30％ 7N $NH_3$/MeOH- $CH_2Cl_2$ 梯度）得到呈浅黄色油的实施例 35。产率 (0.26g,95％）；$^1H$ NMR(400MHz,$CD_3OD$) δ 7.64(t,J = 8.4Hz,1H),7.04(d,J = 8.4Hz,1H),6.63(d,J = 8.0Hz,1H),4.70-4.62(m,1H),4.18-4.08(m,6H),2.82-2.78(m,4H),2.08-1.81(m,5H),1.25-1.21(m,5H)；RP-HPLC $t_R$ = 6.99min；ESI-MS m/z 338.3$[M+H]^+$。

实施例 36-(R)-4-(((6-(3- 氨基 -1- 羟丙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯的制备




[0482] (R)-4-(((6-(3- 氨基 -1- 羟丙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯按照实施例 6 和 35 中描述的方法制备。

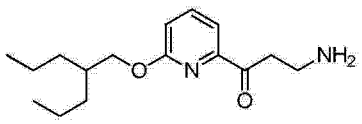
[0483] 步骤 1：按照实施例 35 中描述的方法使 6-( 哌啶 -4- 基甲氧基）吡啶甲酸甲酯与苄氧基氯甲酸酯反应在快速层析纯化 (30％ -50％ EtOAc- 己烷梯度）后得到 6-((1-(( 苄基氧基）羰基）哌啶 -4- 基）甲氧基）吡啶甲酸甲酯。产率 (1.5g,61％）；$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.84(t,J = 8.4Hz,1H),7.63(d,J = 8.0Hz,1H),7.36-7.24(m,5H),7.04(d,J = 8.0Hz,1H),5.04(s,2H),4.12(d,J = 6.8Hz,2H),4.07-3.96(m,4H),3.02(s,3H),2.01-1.81(m,1H),1.78-1.66(m,2H),1.21-1.12(m,2H)。

[0484] 步骤 2：按照实施例 6 中描述的方法向 6-((1-(( 苄基氧基）羰基）哌啶 -4- 基）甲氧基）吡啶甲酸酯中加入 $CH_3CN$ 得到 4-(((6-(2- 氰基乙酰基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯，其无需进一步纯化而用于下一步。产率 (1.53g，定量）。

[0485] 步骤 3：按照实施例 6 中描述的方法对 4-(((6-(2- 氰基乙酰基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯进行手性还原在快速层析纯化 (50％ -75％ EtOAc - 己烷梯度）后得到呈黄色油的 (R)-4-(((6-(2- 氰基 -1- 羟基乙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯。产率 (1.0g,65％）；$^1$H NMR(400MHz,$CD_3OD$) δ 7.66(t,J ＝ 8.0Hz,1H),7.36-7.25(m,5H),7.12(d,J ＝ 7.2Hz,1H),6.67(d,J ＝ 8.4Hz,1H),5.10(s,2H),4.87(t,J ＝ 6.0Hz,1H),4.21-4.10(m,4H),3.02-2.76(m,4H),2.06-1.98(m,1H),1.90-1.78(m,2H),1.36-1.20(m,2H)。

[0486] 步骤 4：按照实施例 2 中描述的方法对 (R)-4-(((6-(2- 氰基 -1- 羟基乙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯进行硼烷 - 二甲基硫醚还原在快速层析纯化 (30％ -40％ 7N $NH_3$/MeOH - $CH_2Cl_2$梯度）后得到呈无色油的实施例 36。产率 (0.27g,27 ％）；$^1$H NMR(400MHz,$CD_3OD$) δ 7.63(t,J ＝ 8.4Hz,1H),7.38-7.25(m,5H),7.03(d,J ＝ 7.2Hz,1H),6.62(d,J ＝ 8.0Hz,1H),5.10(s,2H),4.70-4.62(m,1H),4.21-4.10(m,4H),2.88-2.78(m,4H),2.02-1.70(m,5H),1.34-1.20(m,2H)；RP-HPLC $t_R$＝ 9.40min；ESI-MS m/z400.3$[M+H]^+$。

实施例 37-3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 酮的制备

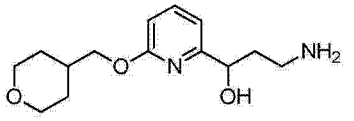


[0487] 3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 酮按照实施例 27 和以下使用的方法制备。

[0488] 步骤 1：按照实施例 27 中描述的方法使实施例 19 与碳酸二叔丁酯反应得到处于溶液中的 (R)-(3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）氨基甲酸叔丁酯，其用 PCC(0.16g,0.76mmol) 在室温下原位处理 18hr。反应混合物通过 Celite 过滤，减压浓缩，通过快速层析纯化 (50％ -75％ EtOAc - 己烷梯度），得到呈浅黄色油的 (3- 氧代 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）氨基甲酸叔丁酯，其无需进一步纯化。产率 (0.03g,21 ％）；$^1$H NMR(400MHz,$CD_3OD$) δ 7.80(t,J ＝ 8.4Hz,1H),7.58(d,J ＝ 7.2Hz,1H),6.97(d,J ＝ 8.0Hz,1H),4.31(d,J ＝ 5.6Hz,2H),3.48-3.40(m,2H),3.38-3.32(m,2H),1.91-1.84(m,1H),1.48-1.35(m,17H),0.92-0.82(m,6H)。

[0489] 步骤 2：按照实施例 27 中描述的方法对 (3- 氧代 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）氨基甲酸叔丁酯进行脱保护得到呈无色油的实施例 37 盐酸盐。产率 (0.01g,38 ％）；$^1$H NMR(400MHz,$CD_3OD$) δ 7.84(t,J ＝ 8.4Hz,1H),7.66(d,J ＝ 8.0Hz,1H),7.04(d,J ＝ 8.4Hz,1H),4.30(d,J ＝ 5.6Hz,2H),3.60(t,J ＝ 6.4Hz,2H),3.38-3.32(m,2H),1.92-1.82(m,1H),1.54-1.35(m,8H),0.92-0.82(m,6H)；RP-HPLC $t_R$＝ 11.33min；ESI-MS m/z 279.3$[M+H]^+$。

实施例 38-3- 氨基 -1-(6-((四氢 -2H- 吡喃 -4- 基）甲氧基）吡啶 -2- 基）丙 -1- 醇的制备



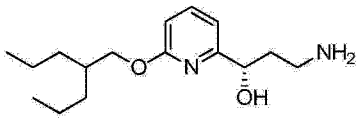
[0490] 3- 氨基 -1-(6-((四氢 -2H- 吡喃 -4- 基）甲氧基）吡啶 -2- 基）丙 -1- 醇按照实施例 2 和 6 中使用的方法制备。

[0491] 步骤 1 :按照实施例 6 中使用的方法使（四氢 -2H- 吡喃 -4- 基）甲醇与 NaH 反应随后加入 6- 溴吡啶甲酸 12,在与 HCl/MeOH 酯化后得到 6-((四氢 -2H- 吡喃 -4- 基）甲氧基）吡啶甲酸甲酯。

[0492] 步骤 2 :按照实施例 6 中使用的方法使 6-((四氢 -2H- 吡喃 -4- 基）甲氧基）吡啶甲酸甲酯与 $CH_3CN$ 之间反应得到 3- 氧代 -3-(6-((四氢 -2H- 吡喃 -4- 基）甲氧基）吡啶 -2- 基）丙腈。

[0493] 步骤 3 :按照实施例 2 中使用的方法用 $LiAlH_4$ 还原 3- 氧代 -3-(6-((四氢 -2H- 吡喃 -4- 基）甲氧基）吡啶 -2- 基）丙腈得到实施例 38。

实施例 39-(S)-3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇的制备

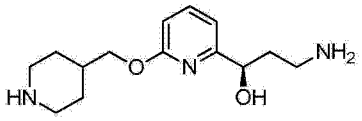



[0494] (S)-3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇按照实施例 6 中使用的方法制备。

[0495] 步骤 1 :使用 (1S,2S)-RuCl(TsDPEN)（对伞花烃）作为催化剂,按照实施例 6 中使用的方法对 3- 氧代 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈进行手性还原,得到呈灰白色固体的 (S)-3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈,其无需纯化而直接用于下一步。产率 (0.83g,定量）。

[0496] 步骤 2 :按照实施例 6 中使用的方法对 (S)-3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙腈进行还原,随后用 HCl-MeOH 处理,得到呈无色油的实施例 39。产 率 (0.25g,39 % ) ;$^1H$ NMR(400MHz,DMSO-$d_6$) δ 7.63(t,J = 8.4Hz,1H),7.03(d,J = 8.0Hz,1H),6.62(d,J = 7.6Hz,1H),4.70-4.66(m,1H),4.20-4.14(m,2H),2.82-2.78(m,2H),2.02-1.78(m,3H),1.44-1.38(m,8H),0.98-0.84(m,6H) ;RP-HPLC $t_R$= 10.38min ;ESI-MS m/z 281.2$[M+H]^+$。

实施例 40-(R)-3- 氨基 -1-(6-（哌啶 -4- 基甲氧基）吡啶 -2- 基）丙 -1- 醇的制备



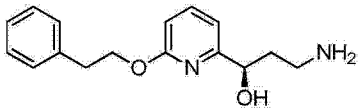

[0497] (R)-3- 氨基 -1-(6-（哌啶 -4- 基甲氧基）吡啶 -2- 基）丙 -1- 醇按照实施例 6 中和以下描述的方法制备。

[0498] 步骤 1 :按照实施例 27 中使用的方法使实施例 36 与碳酸二叔丁酯反应在快速层析纯化 (50％ -75％ EtOAc - 己烷梯度）后得到呈无色油的 (R)-4-(((6-(3-((叔丁氧基羰基）氨基）-1- 羟丙基）吡啶 -2- 基）氧基）甲基）哌啶 -1- 甲酸苄酯。产率 (0.3g,61 % ) ;$^1H$ NMR(400MHz,$CD_3OD$) δ 7.62(t,J = 8.4Hz,1H),7.36-7.28(m,5H),7.01(d,J = 7.6Hz,1H),6.61(d,J = 7.6Hz,1H),5.10(s,2H),4.64-4.57(m,1H),4.21-4.04(m,4H),3.22-3.08(m,2H),2.98-2.78(m,2H),2.08-1.98(m,1H),1.88-1.66(m,2H),1.42(s,9H),1.36-1.08(m,2H)。

[0499] 步骤 2 :按照实施例 11 中使用的方法通过氢化对 (R)-4-(((6-(3-((叔丁氧基羰基)氨基)-1- 羟丙基)吡啶 -2- 基)氧基)甲基)哌啶 -1- 甲酸苄酯进行脱保护得到呈无色油的 (R)-(3- 羟基 -3-(6-(哌啶 -4- 基甲氧基)吡啶 -2- 基)丙基)氨基甲酸叔丁酯。产率 (0.25g,定量) ;$^1$H NMR(400MHz,$CD_3OD$) δ 7.62(t,J = 8.4Hz,1H),7.02(d,J = 6.8Hz,1H),6.61(d,J = 7.6Hz,1H),4.64-4.58(m,1H),4.18-4.12(m,2H),3.10-3.06(m,2H),2.72-2.61(m,2H),2.06-1.84(m,3H),1.86-1.78(m,4H),1.45-1.20(m,11H) ;ESI-MS m/z366.3[M+H]$^+$。

[0500] 步骤 3 :除了使用 2M HCl-$Et_2O$ 和 $CH_2Cl_2$作为溶剂外,按照实施例 27 中描述的方法对 (R)-(3- 羟基 -3-(6-(哌啶 -4- 基甲氧基)吡啶 -2- 基)丙基)氨基甲酸叔丁酯进行脱保护得到呈无色油的实施例 40 盐酸盐。产率 (0.16g,86%) ;$^1$H NMR(400MHz,$CD_3OD$) δ 8.30(t,J = 8.0Hz,1H),7.47(d,J = 7.6Hz,1H),7.34(d,J = 8.8Hz,1H),5.06-5.03(m,1H),4.38(d,J = 6.4Hz,2H),3.52-3.44(m,2H),3.18-3.14(m,2H),3.10-3.04(m,2H),2.36-2.02(m,5H),1.78-1.64(m,2H) ;RP-HPLC $t_R$= 1.69min ;ESI-MS m/z 266.2[M+H]$^+$。

实施例 41-(R)-3- 氨基 -1-(6- 苯乙氧基吡啶 -2- 基)丙 -1- 醇的制备




[0501] (R)-3- 氨基 -1-(6- 苯乙氧基吡啶 -2- 基)丙 -1- 醇按照实施例 6 中描述的方法制备。

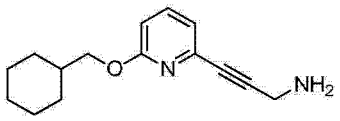
[0502] 步骤 1 :按照实施例 6 中使用的方法使 6- 溴吡啶甲酸与 2- 苯基乙醇反应得到呈黄色油的 6- 苯乙氧基吡啶甲酸甲酯,其无需进一步纯化而用于下一步。产率 (1.28g,定量) ;$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.85(t,J = 8.4Hz,1H),7.65(d,J = 8.4Hz,1H),7.15-7.35(m,5H),7.04(d,J = 8.0Hz,1H),4.48(t,J = 7.2Hz,2H),3.84(s,3H),3.04(t,J = 6.8Hz,2H)。

[0503] 步骤 2 :按照实施例 6 中描述的方法向 6- 苯乙氧基吡啶甲酸甲酯中加入 $CH_3CN$ 得到呈黄色油的 3- 氧代 -3-(6- 苯乙氧基吡啶 -2- 基)丙腈,其无需进一步纯化而用于下一步。产率 (1.33g,定量)。

[0504] 步骤 3 :按照实施例 6 中描述的方法对 3- 氧代 -3-(6- 苯乙氧基吡啶 -2- 基)丙腈进行手性还原在快速层析纯化 (40% -50% EtOAc - 己烷梯度) 后得到呈无色油的 (R)-3- 羟基 -3-(6- 苯乙氧基吡啶 -2- 基)丙腈。产率 (0.6g,45%) ;$^1$H NMR(400MHz,$CD_3OD$) δ 7.66(t,J = 8.0Hz,1H),7.30-7.15(m,5H),7.11(d,J = 8.0Hz,1H),6.65(d,J = 8.0Hz,1H),4.90-4.86(m,1H),4.55-4.51(m,2H),3.08-2.84(m,4H)。

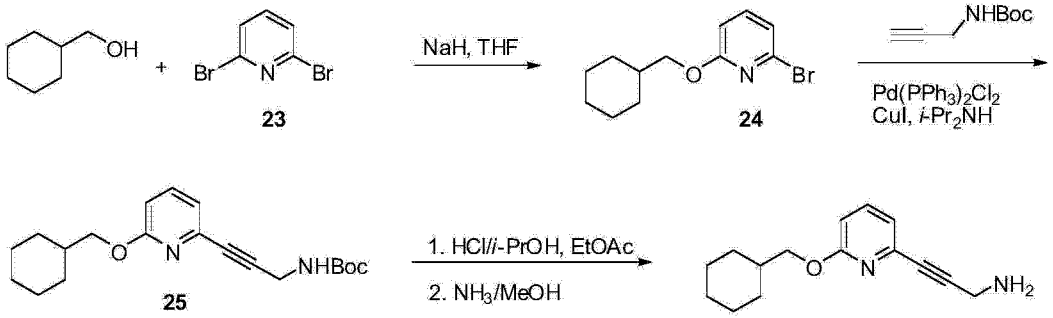
[0505] 步骤 4 :按照实施例 1 中描述的方法对 (R)-3- 羟基 -3-(6- 苯乙氧基吡啶 -2- 基)丙腈进行 $LiAlH_4$还原在快速层析纯化 (20% -30% 7N $NH_3$/MeOH - $CH_2Cl_2$梯度) 后得到呈无色油的实施例 41。产率 (0.13g,21%) ;$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.62(t,J = 8.0Hz,1H),7.28-7.16(m,5H),7.02(d,J = 8.0Hz,1H),6.60(d,J = 8.0Hz,1H),4.70-4.68(m,1H),4.78(t,J = 7.2Hz,2H),3.05(t,J = 7.2Hz,2H),2.78(t,J = 6.8Hz,2H),2.04-1.82(m,2H) ;RP-HPLC $t_R$= 7.83min ;ESI-MS m/z 273.2[M+H]$^+$。

实施例 42-3-(6-(环己基甲氧基)吡啶 -2- 基)丙 -2- 炔 -1- 胺的制备



[0506] 3-(6-(环己基甲氧基)吡啶-2-基)丙-2-炔-1-胺按照流程8所示的方法制备。

流程8.

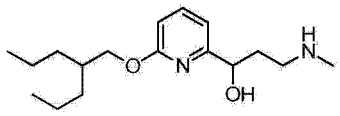



[0507] 步骤1:按照实施例6中使用的方法使2,6-二溴吡啶(23)与环己基甲醇反应得到呈黄色油的烷氧基吡啶24,其无需额外纯化而用于下一步。产率(1.34g,定量);$^1$H NMR(400MHz,DMSO-$d_6$)δ7.61(t,J = 8.0Hz,1H),7.17(d,J = 8.0Hz,1H),6.82(d,J = 8.4Hz,1H),4.00(d,J = 6.0Hz,2H),1.80-1.61(m,6H),1.24-0.98(m,5H)。

[0508] 步骤2:将2-溴吡啶24(0.68g,2.53mmol)、$Pd(PPh_3)_2Cl_2$(0.09g,0.12mmol)、CuI(0.03g,0.15mmol)在i-$Pr_2NH$(15ml)中的溶液用氮气饱和,并向反应混合物中加入丙-2-炔-1-基氨基甲酸叔丁酯(0.35g,2.25mmol)。所得的混合物在50℃下搅拌18hr,减压浓缩,在1N HCl(10ml)、$NH_4Cl$(30ml)和EtOAc(80ml)之间分配。有机层用$Na_2SO_4$干燥,减压浓缩,并通过快速层析纯化(50%-75% EtOAc-己烷梯度),得到呈浅黄色油的炔丙基吡啶25。产率(0.38g,44%);$^1$H NMR(400MHz,$CD_3OD$)δ7.59(t,J = 8.0Hz,1H),7.01(d,J = 7.2Hz,1H),6.72(d,J = 8.4Hz,1H),4.08-4.02(m,4H),1.88-1.66(m,6H),1.46(s,9H),1.38-1.02(m,5H)。

[0509] 步骤3:按照实施例27中使用的方法对氨基甲酸酯25进行氯化氢脱保护在快速层析纯化(15%-25% 7N $NH_3$/MeOH-$CH_2Cl_2$梯度)后得到呈黄色油的实施例42。产率(0.03g,27%);$^1$H NMR(400MHz,$CD_3OD$)δ7.62(t,J = 8.0Hz,1H),7.36(d,J = 7.6Hz,1H),6.64(d,J = 8.8Hz,1H),4.09(d,J = 6.4Hz,2H),3.54(s,2H),1.86-1.64(m,6H),1.28-1.02(m,5H);RP-HPLC $t_R$ = 10.42min;ESI-MS m/z 281.1$[M+H]^+$。

实施例43-3-(甲基氨基)-1-(6-((2-丙基戊基)氧基)吡啶-2-基)丙-1-醇的制备




[0510] 3-(甲基氨基)-1-(6-((2-丙基戊基)氧基)吡啶-2-基)丙-1-醇按照实施例6中描述的方法制备。

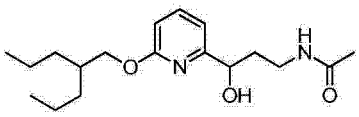
[0511] 步骤1:按照实施例6中使用的方法对3-氧代-3-(6-((2-丙基戊基)氧基)吡啶-2-基)丙腈进行还原在快速层析(20%-30% 7N $NH_3$/MeOH-$CH_2Cl_2$梯度)后得到呈无色

油的 3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇。产率 (0.16g,28%）；$^1$H NMR(400MHz,$CD_3OD$) δ 7.63(t,J＝8.4Hz,1H),7.03(d,J＝8.0Hz,1H),6.62(d,J＝8.0Hz,1H),4.70-4.67(m,1H),4.21-4.14(m,2H),2.82-2.78(m,2H),2.06-1.78(m,3H),1.48-1.28(m,8H),0.98-0.86(m,6H) ;ESI-MS m/z 281.2$[M+H]^+$。

[0512] 步骤 2 :按照实施例 27 中描述的方法使 3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇与碳酸二叔丁酯反应在快速层析纯化 (50% -75% EtOAc - 己烷梯度）后得到呈无色油的 (3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）氨基甲酸叔丁酯，其无需纯化而用于下一步。产率 (0.09g,41%）。

[0513] 步骤 3 :按照实施例 1 中描述的方法对 (3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）氨基甲酸叔丁酯进行 $LiAlH_4$ 还原在快速层析纯化 (30% -40% 7N $NH_3$/MeOH - $CH_2Cl_2$ 梯度）后得到呈无色油的实施例 43 ;产率 (0.04g,62%）；$^1$H NMR(400MHz,DMSO-$d_6$) δ 7.63(t,J ＝ 8.4Hz,1H),7.03(d,J ＝ 8.0Hz,1H),6.62(d,J ＝ 8.0Hz,1H),4.69-4.66(m,1H),4.18-4.16(m,2H),2.76-2.72(m,2H),2.40(s,3H),2.10-1.68(m,3H),1.46-1.26(m,8H),0.96-0.88(m,6H) ;RP-HPLC $t_R$＝ 10.66min ;ESI-MS m/z 295.3$[M+H]^+$。

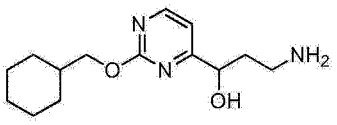
实施例 44-N-(3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）乙酰胺的制备



[0514] N-(3- 羟基 -3-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙基）乙酰胺按照实施例 43 中和以下使用的方法制备。

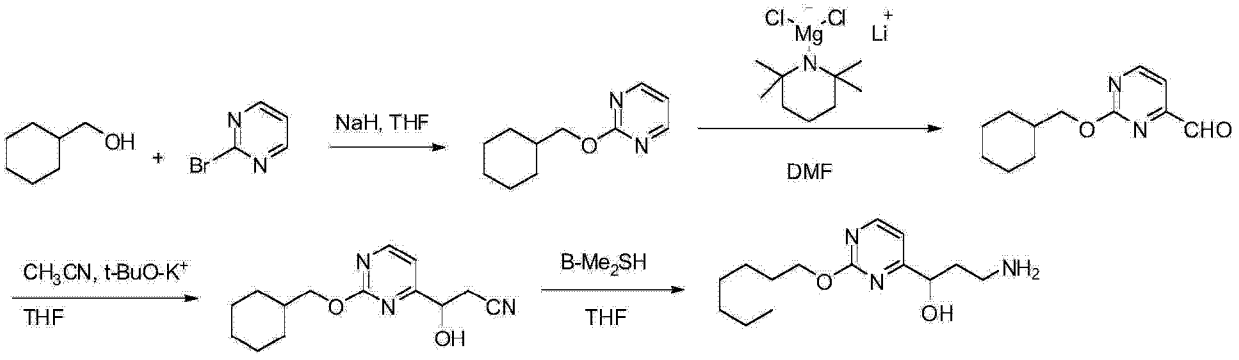
[0515] 步骤 1 :在叔碱如 $Et_3N$ 的存在下，在适当的溶剂中用 $Ac_2O$ 或 AcCl 对 3- 氨基 -1-(6-((2- 丙基戊基）氧基）吡啶 -2- 基）丙 -1- 醇进行乙酰化，得到实施例 44。

实施例 45-3- 氨基 -1-(2-( 环己基甲氧基）嘧啶 -4- 基）丙 -1- 醇的制备



[0516] 3- 氨基 -1-(2-( 环己基甲氧基）嘧啶 -4- 基）丙 -1- 醇按照实施例 6 中所述的和流程 9 中所示的方法制备。

流程 9.



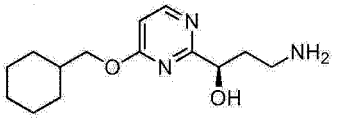
[0517] 步骤 1：将 NaH(1.1 当量）加入到 2- 溴嘧啶和环己基甲醇在 THF 中的等摩尔混合物中。将反应混合物在 +60℃下搅拌 18 小时，冷却至室温，在 $H_2O$ 与乙酸乙酯之间分配。分离有机部分，用无水 $Na_2SO_4$ 干燥，并减压浓缩，得到 2-（环己基甲氧基）嘧啶。

[0518] 步骤 2：在 -78℃下向 2-（环己基甲氧基）嘧啶在 THF 中的混合物中加入 Knochel-Hauser 试剂 (2,2,6,6- 四甲基哌啶基氯化镁氯化锂复合物），搅拌 15min，然后加入 DMF。将反应混合物在 -30℃下搅拌，用 $NH_4Cl$ 水溶液猝灭，用乙酸乙酯萃取。合并的有机层用无水 $Na_2SO_4$ 干燥并减压浓缩，得到 2-（环己基甲氧基）- 嘧啶 -4- 甲醛。

[0519] 步骤 3：按照实施例 6 中描述的方法向 2-（环己基甲氧基）嘧啶 -4- 甲醛中添加 $CH_3CN$ 得到 3-(2-（环己基甲氧基）嘧啶 -4- 基）-3- 羟基丙腈。

[0520] 步骤 4：按照实施例 2 中描述的方法用 $BH_3$-$Me_2S$ 还原 3-(2-（环己基甲氧基）嘧啶 -4- 基）-3- 羟基丙腈得到实施例 45。

实施例 46-(R)-3- 氨基 -1-(4-（环己基甲氧基）嘧啶 -2- 基）丙 -1- 醇的制备




[0521] (R)-3- 氨基 -1-(4-（环己基甲氧基）嘧啶 -2- 基）丙 -1- 醇按照实施例 6 中描述的方法制备。

[0522] 步骤 1：按照实施例 6 中描述的方法使环己基甲醇与 4- 溴嘧啶 -2- 甲酸反应得到 4-（环己基甲氧基）嘧啶 -2- 甲酸甲酯。

[0523] 步骤 2：按照实施例 6 中描述的方法向 4-（环己基甲氧基）嘧啶 -2- 甲酸甲酯中加入 $CH_3CN$ 得到 3-(4-（环己基甲氧基）嘧啶 -2- 基）-3- 氧代丙腈。

[0524] 步骤 3：按照实施例 6 中描述的方法对 3-(4-（环己基甲氧基）嘧啶 -2- 基）-3- 氧代丙腈进行手性还原得到 (R)-3-(4-（环己基甲氧基）嘧啶 -2- 基）-3- 羟基丙腈。

[0525] 步骤 4：按照实施例 2 中描述的方法用 $BH_3$-$Me_2S$ 还原 (R)-3-(4-（环己基甲氧基）嘧啶 -2- 基）-3- 羟基丙腈得到实施例 46。

II. 生物学评价

实施例 1 - 体外异构酶抑制

[0526] 确定了本文公开的化合物抑制视觉循环异构酶的活性的能力。具体而言，基本如 Golczak 等 .Proc.Natl.Acad.Sci.(2005)102,8162-8167 和 Imanishi 等 .J.Cell Biol.(2004),164,373-383 所述进行人体外异构酶试验。

人脱辅基细胞视黄醛结合蛋白 (CRALBP) 的分离

[0527] 根据标准分子生物学方法（参见 Crabb 等，Protein Science 7:746-57(1998)；Crabb 等，J.Biol.Chem.263:18688-92(1988)）克隆并表达重组人脱辅基细胞视黄醛结合蛋白 (CRALBP)。简言之，从铺满的 ARPE19 细胞（美国典型培养物保藏中心 (American Type Culture Collection)，Manassas，VA) 中制备总 RNA，使用寡聚 $(dT)_{12-18}$ 引物合成 cDNA，然后通过两个连续的聚合酶链反应扩增编码 CRALBP 的 DNA（参见 Crabb 等，J.Biol.Chem.263:18688-92(1988)；Intres 等，J.Biol.Chem.269:25411-18(1994)；GenBank 登录号 L34219.1)。根据制造商的方案 (nvitrogen Inc.，Carlsbad,CA；目录号 K4400-01) 将 PCR 产物亚克隆到 pTrcHis2-TOPO TA 载体中，然后根据标准核苷酸测序技术确定序

列。在 One Shot TOP 10 化学感受态大肠杆菌细胞 (Invitrogen) 中表达重组 6x 组氨酸标记的人 CRALBP，并且使用用于 HPLC 的镍 (Ni)Sepharose XK16-20 柱 (Amersham Bioscience,Pittsburgh,PA ;目录号 17-5268-02) 通过镍亲和层析从大肠杆菌细胞裂解物中分离重组多肽。用 10mM 1,3- 双 (( 三羟甲基 ) 甲氨基 ) 丙烷 (bis-tris-Propane)(BTP) 透析纯化的 6x 组氨酸标记的人 CRALBP，并通过 SDS-PAGE 进行分析。重组人 CRALBP 的分子量约为 39kDal。

异构酶试验

[0528] 将本文公开的化合物和对照化合物在乙醇中重建为 0.1M。制备每种化合物在乙醇中的 10 倍系列稀释液 ($10^{-2}$、$10^{-3}$、$10^{-4}$、$10^{-5}$、$10^{-6}$M)，用于在异构酶试验中进行分析。

[0529] 表达重组人 RPE65 和 LRAT 的 HEK293 细胞克隆的匀浆为视觉酶的来源，并使用外源性全反式 - 视黄醇 ( 约 20μM) 作为底物。加入重组人 CRALBP( 约 80μg/mL) 以增强 11- 顺式 - 视黄醛的形成。基于 200μL 的 Bis-Tris 磷酸盐缓冲液 (10mM,pH 7.2) 的反应混合物还含有 0.5% BSA 和 1mM NaPPi。在该试验中，反应一式两份在 37℃下进行 1 小时，并通过加入 300μL 甲醇终止反应。用庚烷提取反应混合物之后通过 HPLC 分析测定反应产物 11- 顺式 - 视黄醇的量。记录 HPLC 色谱中对应于 11- 顺式 - 视黄醇的峰面积单位 (PAU)，并通过 GraphPad Prism 分析浓度依赖性曲线来计算 $IC_{50}$ 值。对本文公开的化合物抑制异构化反应的能力进行定量，并确定其各自的 $IC_{50}$ 值。以下表 2 总结了如上所述测定的本文公开的各种化合物的 $IC_{50}$ 值。

表 2 人体外抑制数据

| $IC_{50}$ (μM) | 实施例编号 |
|---|---|
| ≤ 0.1 μM | 1、2、3、4、5、6、10、11、12、13、14、16、17、18、19、20、21、22、23、24、25、26、28、30、31、32、33、34、35、36、37、39、41、43 |
| >0.1 μM - ≤ 1 μM | 7、8、9、15、27、29 |
| >1 μM - ≤ 10 μM | 40 |
| >10 μM | |
| 无可检测的活性 | |

实施例 2 - 体内鼠异构酶测定

[0530] 通过体内鼠异构酶测定确定本文所述的化合物抑制异构酶的能力。已知眼睛短暂暴露于强光 ( 视色素的“光漂白”或简称为“漂白”) 会使视网膜中几乎所有的 11- 顺式 - 视黄醛发生光致异构化。11- 顺式 - 视黄醛在漂白后的恢复用来评估体内异构酶的活性。如较低的 11- 顺式 - 视黄醛肪水平所代表的延迟恢复指示了对异构化反应的抑制。基本上如 Golczak 等，Proc.Natl.Acad.Sci.USA 102:8162-67(2005) 所述进行操作。也参见 Deigner 等，Science,244:968-71(1989) ;Gollapalli 等，Biochim Biophys

Acta. 1651:93-101(2003) ;Parish 等 ,Proc. Natl. Acad. Sci. USA, 14609-13(1998) ;Radu 等,Proc Natl Acad Sci USA 101:5928-33(2004)。

[0531] 6 周龄的暗适应 CD-1(白化体)雄性小鼠经口强饲溶于 100μl 含有 10%乙醇的玉米油的化合物 (0.03-3mg/kg)(每组 5 只动物)。在黑暗中 2-24 小时后,将小鼠暴露于 5,000 勒克斯的白光下 10 分钟进行光漂白。让小鼠在黑暗中恢复 2 小时。然后通过吸入二氧化碳处死动物。从眼中提取类视黄醇并在各时间间隔评估 11- 顺式 - 视黄醛的再生。

眼类视黄醇的提取

[0532] 所有步骤都在具有最低限度的红光照明的黑暗中进行(根据需要采用低光暗室光和红光过滤的手电筒用于局部照明)(参见,例如,Maeda 等,J. Neurochem 85:944-956, 2003 ;Van Hooser 等,J Biol Chem 277:19173-82, 2002)。处死小鼠后,立即取出眼睛并将其置于液氮中贮存。

[0533] 将眼睛置于 500μL 双((三羟甲基)甲氨基)丙烷缓冲液 (10mM, pH ～ 7.3) 和 20μL 的 0.8M 羟胺 (pH ～ 7.3) 中。用小虹膜剪将眼睛切成小块,然后在试管中用机械匀浆器 (Polytron PT 1300D) 以 30000rpm 充分均化直到无可见组织残留。向每个试管中加入 500μL 甲醇和 500μL 庚烷。将试管附接到涡旋器 (vortexer) 上,以使内容物在室温下充分混合 15 分钟。通过在 4℃下以 13K rpm 离心 10 分钟而使有机相与水相分离。使用玻璃移液器从上层(有机相)移取 240μL 溶液并转移至 HPLC 小瓶内的清洁的 300μl 玻璃衬管中,并紧密地卷边封闭小瓶。

[0534] 在具有正相柱的 Agilent 1100HPLC 系统上分析样品 :SILICA(Beckman Coutlier, dp 5μm, 4.6mM x 250mM)。运行方法采用 1.5ml/min 的流速 ;溶剂组分为 15%的溶剂 1(1%异丙醇的乙酸乙酯溶液)和 85%的溶剂 2(100%己烷)。每个样品的加样体积为 100μl ;检测波长为 360nm。通过 Agilent Chemstation 软件计算并手工记录 11- 顺式视黄醛肟的曲线下面积。采用 Prizm 软件进行数据处理。

[0535] 处死完全暗适应的阳性对照小鼠(未施用化合物),并分析眼睛类视黄醇。处死光(漂白的)对照小鼠(未施用化合物),并在光处理后立即分离并分析类视黄醇。

[0536] 进行时间过程研究以测定测试化合物的异构酶抑制活性。雄性 Balb/c 小鼠 (4 只 / 组)经强饲口服接受测试化合物。然后在给药后 2、4、8、16 和 24 小时对动物进行“光漂白”(5000 勒克斯白光 10 分钟),并返回到黑暗中以使眼内 11- 顺式 - 视黄醛含量恢复。漂白后 2 小时处死小鼠,摘出眼,并通过 HPLC 分析类视黄醇含量。

[0537] 对恢复对照小鼠(仅用载体处理的)进行光处理,并且在处死并分析之前使之在黑暗中恢复 2 小时。光对照小鼠(仅用载体处理的)在光漂白后立即处死以进行分析。

[0538] 表 3 提供了本文公开的各种化合物在所示的剂量和时间点的体内鼠异构酶测定结果。

表 3 体内鼠异构酶测定数据

| 合成实施例 | 抑制, % | 剂量 (mg/kg) | 时间(小时) |
|---|---|---|---|
| 1 | 0 | 1 | 2 |
| 1 | 0 | 1 | 4 |

| | | | |
|---|---|---|---|
| 3 | 0 | 1 | 2 |
| 4 | 29.3±4.3 | 1 | 2 |
| 5 | 0 | 1 | 2 |
| 6 | 68.9±6.5 | 1 | 2 |
| 6 | 37.7±14.9 | 1 | 4 |
| 6 | 93.2±0.9 | 3 | 2 |
| 6 | 85.5±2.9 | 3 | 4 |
| 6 | 62.3±3.8 | 3 | 6 |
| 6 | 30.8±9.9 | 3 | 8 |
| 6 | 0 | 3 | 16 |
| 6 | 0 | 3 | 24 |
| 9 | 8.6±4.2 | 1 | 2 |
| 12 | 0 | 1 | 2 |
| 19 | 98.2±2.3 | 1 | 4 |
| 19 | 90.7±3.3 | 1 | 8 |

实施例 3 - 体内光损伤小鼠模型

[0539] 本实施例描述了本文公开的化合物在体内光损伤小鼠模型中的作用。

[0540] 眼睛暴露于强烈的白光可导致视网膜的光损伤。光处理后的损伤程度通过测定眼内细胞质组蛋白结合的 DNA 片段（单核小体和寡核小体）的含量来评估（参见，例如，Wenzel 等，Prog. Retin. Eye Res. 24:275-306(2005)）。

[0541] 给暗适应的雄性 Balb/c（白化体，10 只 / 组）小鼠强饲不同剂量 (0.03、0.1、0.3、1 和 3mg/kg) 的测试化合物或仅施用赋形剂。给药后六小时，对动物进行光处理 (8,000 勒克斯的白光持续 1 小时）。在黑暗中恢复 40 小时以后处死小鼠，并切下视网膜。按照制造商的操作说明进行细胞死亡检测 ELISA 测定 (ROCHE APPLIED SCIENCE, Cell Death Detection ELISA plus Kit)。测定视网膜内片段化 DNA 的含量以评估测试化合物的视网膜保护活性。

实施例 4 - 视网膜电流图 (ERG) 研究

[0542] ERG 实验使用两种性别的 16 周龄的 BALB/c 小鼠进行 (n = 5)。所有研究均包括对暗适应的（暗视，视杆主导的）和光适应的（明视，视锥主导的）ERG 响应的药效学评价。使用测试化合物进行实验。所有记录程序均按照相同的方案并使用相同的设备进行。汇总各个研究中的数据以生成概要图。

[0543] 在单次口服测试化合物（溶解于玉米油中）后 4 小时，将来自四个独立研究的结果合并起来以构建在测试化合物的给药与暗视 b- 波幅度的变化 (0.01cd.s/$m^2$) 之间的剂量 - 响应函数。

[0544] 基于在光适应条件下对 ERG b- 波强度 - 响应函数的记录和测量来评估对视锥系统的影响。在这样的研究中，通常评价两个参数：以微伏为单位测量的最大响应 ($V_{max}$)，和以 cd.s/$m^2$为单位测量的半饱和常数 (k)。

[0545] 将来自三个独立研究的结果合并起来以评估测试化合物单一给药对光适应 ERG 的影响（两种性别的 11-16 周龄 BALB/c 小鼠，n = 5)。

III. 剂型的制备

实施例 1：肠胃外组合物

[0546] 为了制备适于通过注射给药的肠胃外药物组合物，将 100mg 式 (A) 的化合物的水溶性盐溶解于无菌水中，然后与 10mL 0.9％无菌盐水混合。将混合物引入适合于通过注射给药的剂量单位形式中。

实施例 2：口服组合物

[0547] 为了制备用于口服递送的药物组合物，将 100mg 式 (A) 的化合物与 750mg 淀粉混合。将混合物引入适合于口服给药的口服剂量单位如硬明胶胶囊中。

实施例 3：舌下（硬锭剂）组合物

[0548] 为了制备用于颊部递送的药物组合物，如硬锭剂，将 100mg 式 (A) 的化合物与 420mg 糖粉、1.6mL 轻质玉米糖浆、2.4mL 蒸馏水和 0.42mL 薄荷提取物混合。将混合物轻轻掺混并倒入模具中以形成适合于颊部给药的锭剂。

实施例 4：快速崩解舌下片剂

[0549] 通过混合 48.5 重量％的式 (A) 化合物、44.5 重量％的微晶纤维素 (KG-802)、5 重量％的低取代羟丙基纤维素 (50μm) 和 2 重量％的硬脂酸镁制备快速崩解舌下片剂。通过直接压制 (AAPS PharmSciTech.2006；7(2)：E41) 制备片剂。压制片剂的总重量保持在 150mg。通过采用三维手动混合器（Inversina ®，Bioengineering AG，瑞士）混合该量的式 (A) 化合物与总量的微晶纤维素 (MCC) 和 2/3 量的低取代羟丙基纤维素 (L-HPC) 4.5 分钟来制备制剂。在混合结束前 30 秒加入所有硬脂酸镁 (MS) 和剩余的 1/3 量的 L-HPC。

实施例 5：吸入组合物

[0550] 为了制备用于吸入递送的药物组合物，将 20mg 式 (A) 的化合物与 50mg 无水柠檬酸和 100mL 0.9％氯化钠溶液混合。将混合物引入适合于吸入给药的吸入递送单元如喷雾器中。

实施例 6：直肠凝胶组合物

[0551] 为了制备用于直肠递送的药物组合物，将 100mg 式 (A) 的化合物与 2.5g 甲基纤维素 (1500mPa)、100mg 对羟基苯甲酸甲酯、5g 甘油和 100mL 纯化水混合。然后将所得的凝胶混合物引入适合于直肠给药的直肠递送单元如注射器中。

实施例 7：局部凝胶组合物

[0552] 为了制备局部凝胶药物组合物，将 100mg 式 (A) 的化合物与 1.75g 羟丙基纤维素、10mL 丙二醇、10mL 肉豆蔻酸异丙酯和 100mL 纯化醇 USP 混合。然后将所得的凝胶混合物引入适合于局部给药的容器如管中。实施例 8：眼科 (Ophthalmic) 溶液组合物

[0553] 为了制备眼科溶液药物组合物，将 100mg 式 (A) 的化合物与 0.9gNaCl 在 100mL 纯化水中混合，并使用 0.2 微米滤器过滤。然后将得到的等渗溶液引入适合眼部给药的眼科递送单元如滴眼剂容器中。

实施例 9 ：鼻喷雾溶液

[0554] 为了制备药物鼻喷雾溶液，将 10g 式 (A) 的化合物与 30mL 0.05M 磷酸盐缓冲溶液 (pH 4.4) 混合。将该溶液置于设计为每次施用递送 100μl 喷雾剂的鼻部给药器中。

VI. 临床试验

实施例 1 - 安全性和药效学效果的 1A 期研究

[0555] 进行单中心、随机化、双盲、安慰剂对照的、剂量递增 1A 期研究，以确定式 (A) 化合物如 3- 氨基 -1-(6-(2- 环己基乙基）吡啶 -2- 基）丙 -1- 醇（实施例 4) 的单一口服剂量的安全性和药效学效果，这通过暗适应视网膜电流图 (ERG) 进行测量。研究参与者为两种性别的健康志愿者，年龄 55-80 岁，体重 50 至 110kg。主要排除标准包括其他眼睛病状（例如，白内障、青光眼、葡萄膜炎、糖尿病视网膜病变、活动性结膜炎），之前 28 天内长期处方药物的变更，上一年内采用类视黄醇化合物的治疗，上周内采用枸橼酸西地那非、他达拉非或枸橼酸伐地那非的治疗，或采用安眠药、抗抑郁药、精神活性物质、洋地黄糖甙类、L-DOPA、氯喹、羟氯喹、全身皮质类固醇、局部抗青光眼药物或用于治疗湿型 AMD 的药物的伴随治疗。8 个群组以 5:1/ 药物 ：安慰剂随机化，并分配至 2mg、7mg、10mg、20mg、40mg、60mg 和 75mg 的剂量群组。确定随时间变化的血浆浓度。对所有剂量测定峰值血浆浓度 ($C_{max}$)、峰值血浆浓度时间 ($T_{max}$) 和平均终末清除半衰期 ($t_{1/2}$)。

[0556] 在给药前、给药后 4-6 小时（第 1 天 ERG)、给药后 24 小时（第 2 天 ERG)、第 4 天和第 7 天进行 ERG 研究。对于给予安慰剂的患者，监测 ERG 读数在幅度上的快速上升，使得到大约 20 分钟时其响应恢复 90％。对于给予式 (A) 测试化合物如 3- 氨基 -1-(6-(2- 环己基乙基）吡啶 -2- 基）丙 -1- 醇（实施例 4) 的患者，监测 ERG 读数的清楚的剂量相关的恢复速率减慢 ；即，恢复函数的斜率随剂量升高而变得较慢。

实施例 2 - 干型年龄相关性黄斑变性的治疗

[0557] 被诊断为干型年龄相关性黄斑变性的个体用 5mg 口服剂量的式 (A) 测试化合物如 3- 氨基 -1-(6-(2- 环己基乙基）吡啶 -2- 基）丙 -1- 醇（实施例 4) 进行治疗。在第 2、4、6、8、12、18、24 和 30 天，对个体进行视网膜电流图检查，以评价治疗反应，并且监测个体的延迟暗适应和全色盲的情况，以及全身性不良反应。

[0558] 当本文中对诸如分子量的物理性质或者诸如化学式的化学性质使用范围时，意在包括范围的所有组合和子组合以及其中的具体实施方案。

[0559] 本文描述的多种实施方案可以组合起来以得到进一步的实施方案。在本说明书中引用的和 / 或在申请数据表中列出的所有美国专利、美国专利申请公开、美国专利申请、国外专利、国外专利申请和非专利公开均通过引用整体并入本文。

[0560] 从以上所述将会理解，尽管出于说明的目的在此描述了具体的实施方案，但可以进行多种改变。本领域技术人员将会认识到或者仅利用常规实验就能够确定本文描述的具体实施方案的许多等效方案。下面的权利要求意在包括这样的等效方案。一般而言，在下面的权利要求中，所使用的术语不应该理解为将权利要求限制于说明书和权利要求书中公开的具体实施方案，而应将其理解为包括所有可能的实施方案以及这些权利要求的等效物

的全部范围。因此，权利要求不受公开内容的限制。

[0561] 尽管在本文中已经显示并描述了本发明的优选实施方案，但对本领域技术人员显而易见的是，这些实施方案仅作为示例来提供。在不偏离本发明的条件下，本领域技术人员现将会想到多种变化、改变和替代。应该理解，本文描述的本发明实施方案的多种替代方案可用于实践本发明。应当理解，意图以下列权利要求限定本发明的范围并由此涵盖这些权利要求的范围中的方法和结构及其等效物。

## Abstract

The present invention relates generally to compositions and methods for treating neurodegenerative diseases and disorders, particularly ophthalmic diseases and disorders. Provided herein are substituted heterocyclic amine derivative compound and pharmaceutical compositions comprising these compounds. The subject compositions are useful for treating and preventing ophthalmic diseases and disorders, including age-related macular degeneration (AMD) and Stargardt's Disease.