(19) DANMARK

(10) DK/EP 3244891 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 31/4196 (2006.01)* *A 61 P 25/28 (2006.01)* *C 07 D 251/00 (2006.01)* *C 07 D 339/06 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2022-10-24**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2022-07-20**

(86) Europæisk ansøgning nr.: **16737944.5**

(86) Europæisk indleveringsdag: **2016-01-15**

(87) Den europæiske ansøgnings publiceringsdag: **2017-11-22**

(86) International ansøgning nr.: **US2016013553**

(87) Internationalt publikationsnr.: **WO2016115434**

(30) Prioritet: **2015-01-16 US 201562104547 P** **2015-06-16 US 201562180380 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **The General Hospital Corporation, 55 Fruit Street, Boston, MA 02114, USA**
The United States of America, as represented by The Secretary, Department of Health and Human Services, National Institutes of Health , Office of Technology Transfer , 6011 Executive Boulevard , Suite 325 , MSC 7660, Bethesda, MD 20852-7660, USA

(72) Opfinder: **SLAUGENHAUPT, Susan, A., 10 Quail Run, Hingham, MA 02043, USA**
JOHNSON, Graham, 3 Lakeside Drive, Sanbornton, NH 03269, USA
PAQUETTE, William, D., 108 Gay Lane, Amsterdam, NY 12010, USA
ZHANG, Wei, 9 Remmington Road, Schenectady, NY 12303, USA
MARUGAN, Juan, 16500 Apache Lane, Gaithersburg, MD 20878, USA

(74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**

(54) Benævnelse: **FORBINDELSER TIL FORBEDRING AF MRNA-SPLEJSNING**

(56) Fremdragne publikationer:
WO-A1-2010/038060
WO-A1-2010/090764
WO-A1-2011/041655
WO-A1-2015/005491
WO-A2-2005/033290
WO-A2-2008/006547
US-A- 3 037 980
US-A1- 2005 153 989
US-A1- 2007 191 293
US-A1- 2014 330 006

Fortsættes ...

US-B2- 8 729 025
RIVKIN A ET AL: "Purine derivatives as potent @?-secretase modulators", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 20, no. 7, 1 April 2010 (2010-04-01), pages 2279-2282, XP026971060, ISSN: 0960-894X [retrieved on 2010-02-06]
DATABASE PUBCHEM [Online] XP055467498 Retrieved from NCBI Database accession no. SID 163507406

DESCRIPTION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This invention claims the benefit of United States Provisional Application Nos. 62/104,547, filed January 16, 2015, and 62/180,380, filed June 16, 2015.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with Government support under Grant No. U01NS078025, awarded by the National Institutes of Health. The Government has certain rights in the invention.

TECHNICAL FIELD

[0003] The present disclosure relates to compounds for treating disorders associated with misspliced mRNA, and more particularly to kinetin derivatives for treating familial dysautonomia in a patient in need thereof.

BACKGROUND

[0004] Familial dysautonomia (FD) (MIM#2239001), also known as Riley Day syndrome or hereditary sensory and autonomic neuropathy III (HSAN-III), is the best-known and most common member of a group of congenital sensory and autonomic neuropathies (HSAN) characterized by widespread sensory and variable autonomic dysfunction. FD affects neuronal development and is associated with progressive neuronal degeneration. Multiple systems are impacted resulting in a markedly reduced quality of life and premature death. FD is caused by mutations in the *IKBKAP* gene and all cases described to date involve an intron 20 mutation that results in a unique pattern of tissue-specific exon skipping.

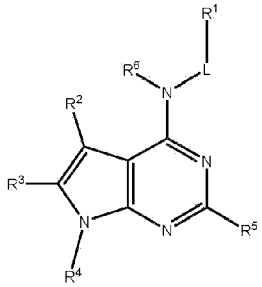
[0005] See also, for example, Shetty et al. Human Molecular Genetics, 2011, 20(21):4093-4101; Axelrod et al. Pediatric Research, 2011, 70(5):480-483; Gold-von Simson et al. Pediatric Research, 2009, 65(3):341-346; Yoshida et al. PNAS, 2015, 112(9):2764-2769; and International Patent Application Nos. WO2005/033290, WO 2015/005491, WO 2010/118367, and WO 2014/124458.

[0006] It is appreciated that certain features of the disclosure, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single

embodiment. Conversely, various features of the disclosure which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

SUMMARY

[0007] The present invention provides compounds of Formula (Ia):

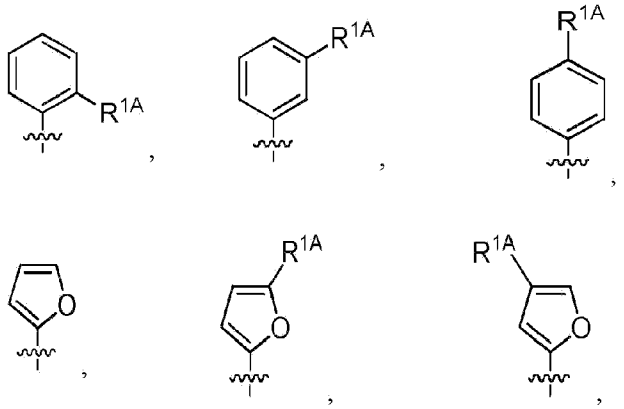


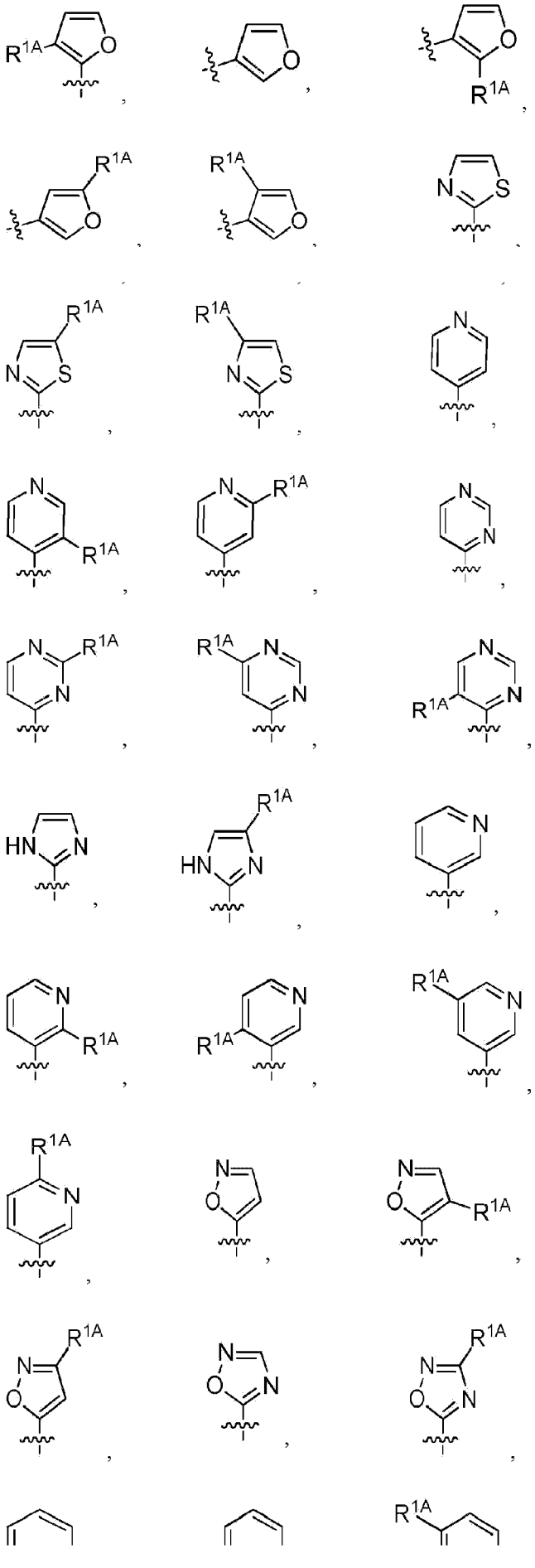
Ia

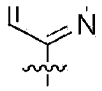
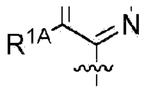
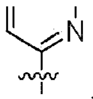
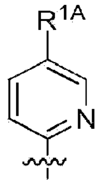
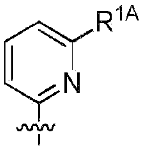
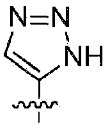
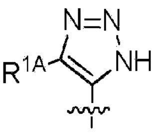
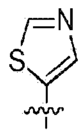
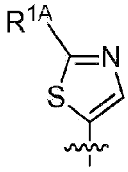
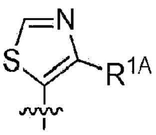
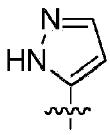
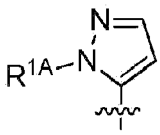
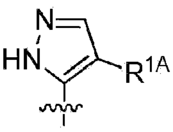
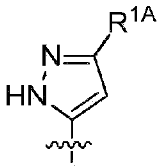
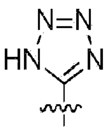
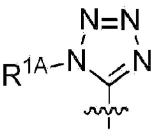
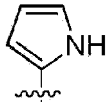
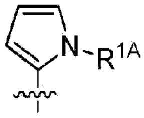
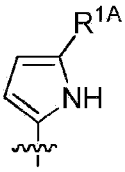
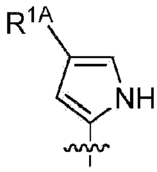
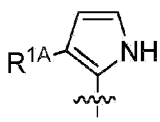
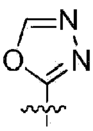
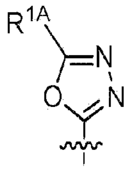
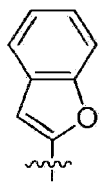
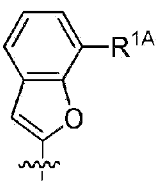
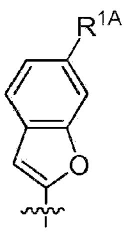
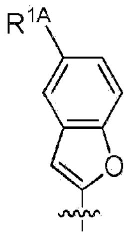
or a pharmaceutically acceptable salt thereof according to claim .

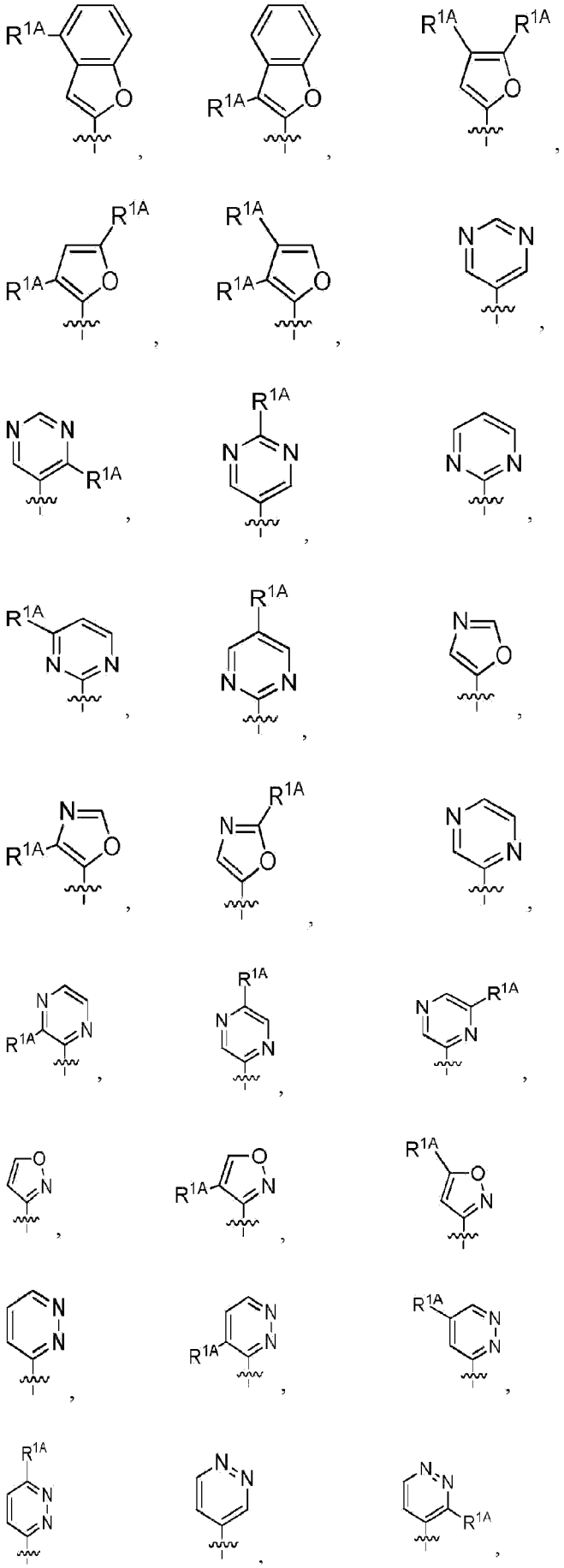
[0008] In some embodiments, L is C_{1-6} alkylene optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, L is unsubstituted C_{1-6} alkylene. In some embodiments, L is unsubstituted methylene or unsubstituted ethylene.

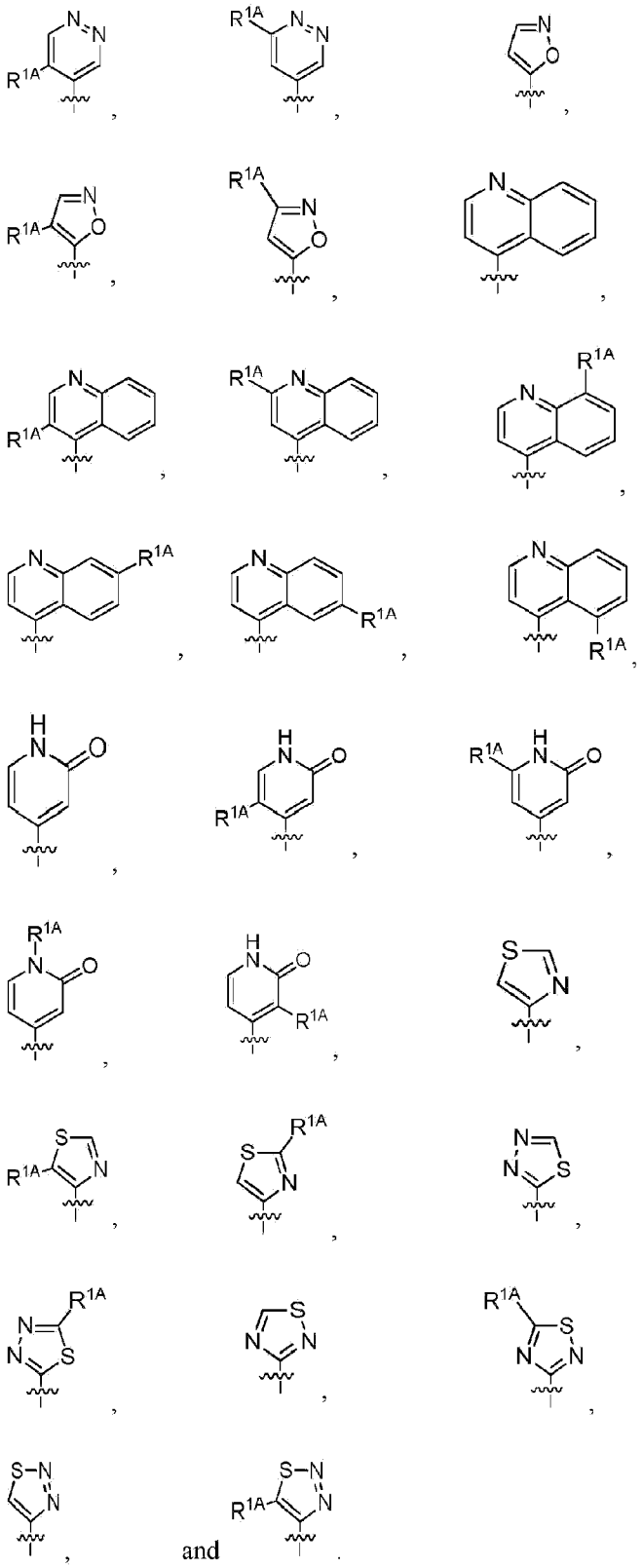
[0009] In some embodiments, R^1 is selected from the group consisting of C_{6-10} aryl, and 5-6 membered heteroaryl, each optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups. In some embodiments, R^1 is 2-benzofuranyl or 4-quinolinyl, each optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups. In some embodiments, R^1 is selected from the group consisting of 2-benzofuranyl, 4-quinolinyl, phenyl, and a 5-6 membered heteroaryl, each optionally substituted by 1 or 2 independently selected R^{1A} groups. In some embodiments, R^1 is selected from the group consisting of 2-benzofuranyl, 4-quinolinyl, and a 5-6 membered heteroaryl, each optionally substituted by 1 or 2 independently selected R^{1A} groups. In some embodiments, R^1 is selected from the group consisting of:





 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,
 ,



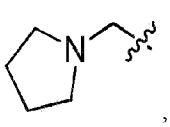
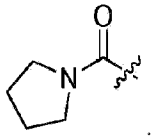


[0010] In some embodiments, each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH. In some embodiments, each

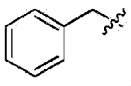
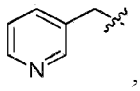
R^{1A} is independently selected from the group consisting of CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, and -C(=O)OH.

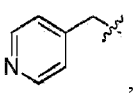
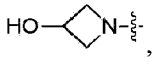
[0011] In some embodiments, R^1 is selected from the group consisting of unsubstituted phenyl, and an unsubstituted 5-6 membered heteroaryl.

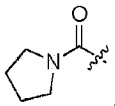
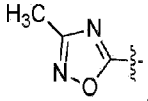
[0012] In some embodiments, R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^2 is selected from the group consisting of H, oxo, chloro, fluoro, bromo, CN, methyl, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, NH_2, $-NHCH_3$, $-N(CH_3)_2$, phenyl, 4-pyridinyl, $C(=O)OCH_3$, $C(=O)NH_2$, $C(=O)NHCH_3$,

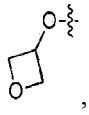
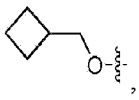
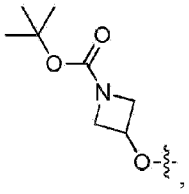
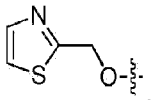
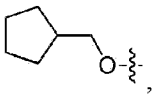
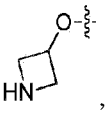
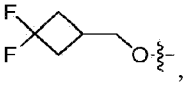
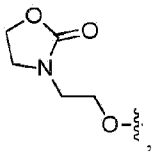
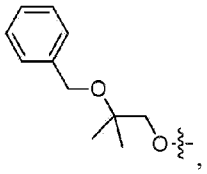
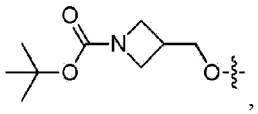
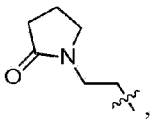
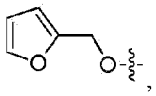
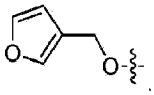

, and 
.

[0013] In some embodiments, R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{d3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^3 is selected from the group consisting of H, azido, CN, methyl, cyclopropyl, cyclobutyl, phenyl, 3-pyridinyl, N-morpholino, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, $-OCH_2CH_2OH$, $-OCH_2CH_2CH_2OH$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2CH_2OCH_3$, $-ONHCH_3$, $-OCH_2CHF_2$, $-OCH_2CF_3$, $-OCH_2CH_2CF_3$, $-OCH_2CHF_2CH_3$, $-OCH_2CH_2NHC(=O)CH_3$, cyclobutoxy, $-OCH_2CH_2$-O-phenyl, $-SCH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2OH$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-NHCH_2CH_2OH$, $-C(=O)NHCH_2CH_2OH$, $-OC(=O)CH_3$, $-OCH_2$-azetidinyl, $-OCH_2$-oxetanyl,

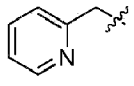
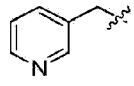
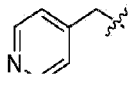
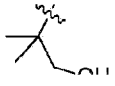

, 
,

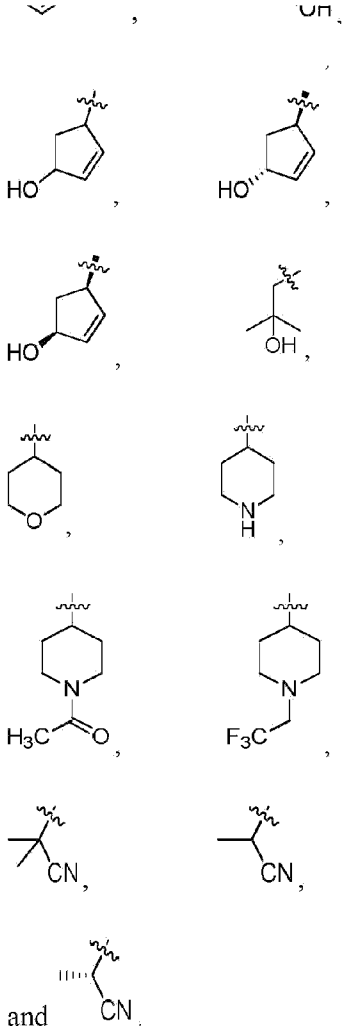

, 
,


, 
,













and 

[0014] In some embodiments, R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^4 is selected from the group consisting of H, halo, methyl, $-CH_2CH_2F$, $-CH_2CH_2CF_3$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2C(=O)OH$, $-CH_2C(=O)NH(CH_3)$,$-CH_2C(=O)N(CH_3)_2$, $-CH_2CH_2NHC(=O)CH_3$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$,



[0015] In some embodiments, R^5 is halo.

[0016] In some embodiments, R^5 is chloro or fluoro.

[0017] In some embodiments, R^6 is H.

[0018] In some embodiments:

L is unsubstituted C_{1-6}alkylene;

R^1 is selected from the group consisting of 2-benzofuranyl, 4-quinolinyl, C_{6-10} aryl, 5-6 membered heteroaryl, optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{d3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R5 is halo;

R^6 is H.

[0019] In some embodiments:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of 2-furanyl, 4-quinolinyl, C_{6-10} aryl, and 5-6 membered heteroaryl, optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{d3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered

heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0020] In some embodiments:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of 2-furanyl, 4-quinolinyl, phenyl, and 5-6 membered heteroaryl, each optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{d3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0021] In some embodiments:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of 2-furanyl, 4-quinolinyl, phenyl, and 5-6 membered heteroaryl, each optionally substituted by 1 or 2 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{d3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H;

[0022] In some embodiments:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of unsubstituted 2-furanyl, unsubstituted 4-quinolinyl, unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

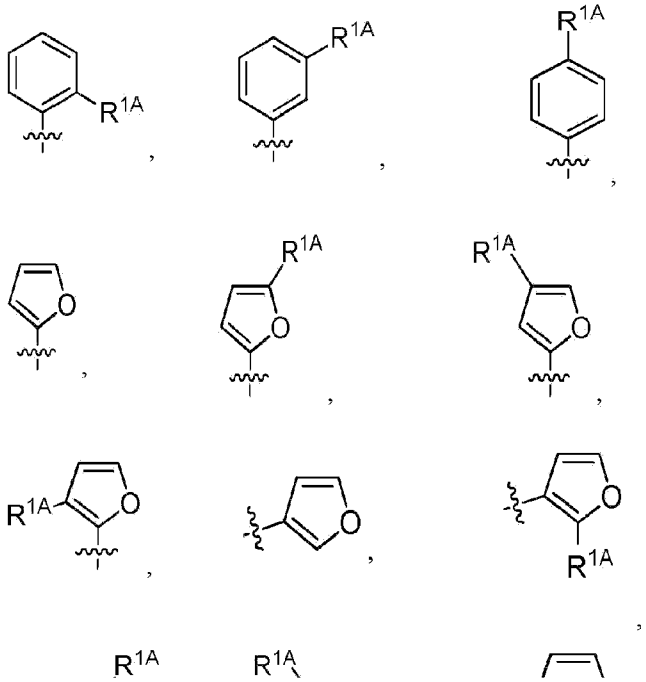
R^5 is halo;

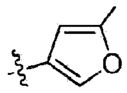
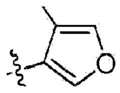
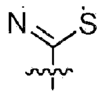
R^6 is H.

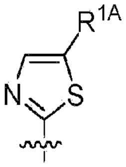
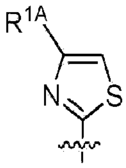
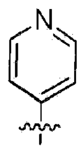
[0023] In some embodiments:

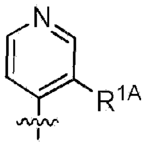
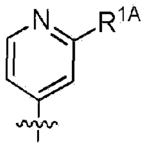
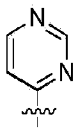
L is unsubstituted methylene or unsubstituted ethylene;

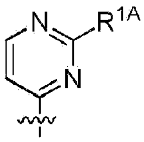
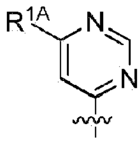
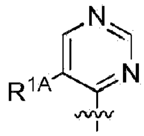
R^1 is selected from the group consisting of:

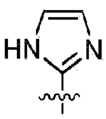
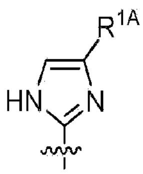
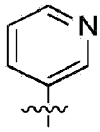


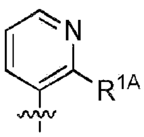
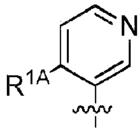
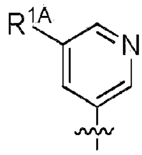
 ,  ,  ,

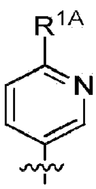
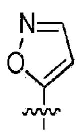
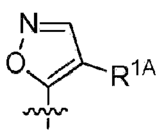
 ,  ,  ,

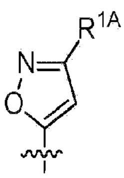
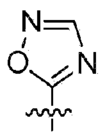
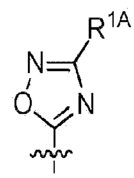
 ,  ,  ,

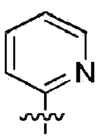
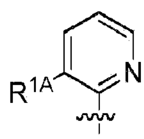
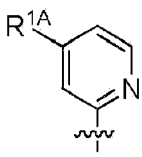
 ,  ,  ,

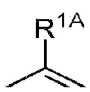
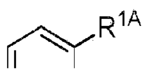
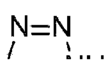
 ,  ,  ,

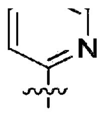
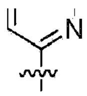
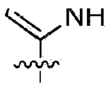
 ,  ,  ,

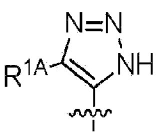
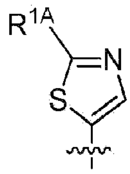
 ,  ,  ,

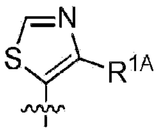
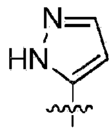
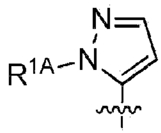
 ,  ,  ,

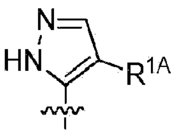
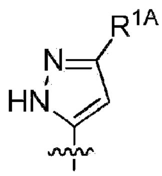
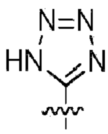
 ,  ,  ,

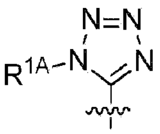
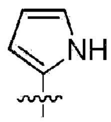
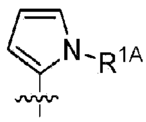
  

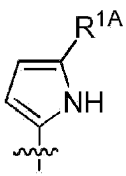
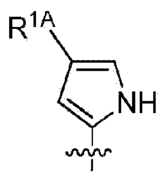
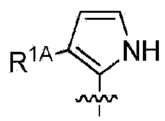
 ,  ,  ,

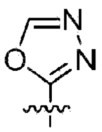
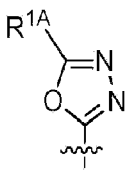
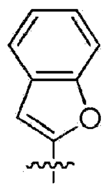
 ,  ,  ,

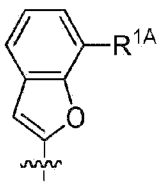
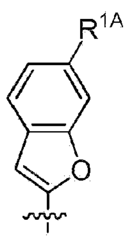
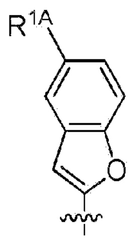
 ,  ,  ,

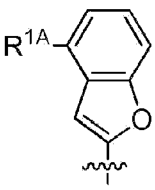
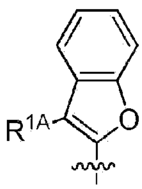
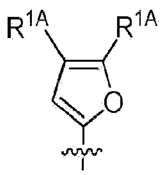
 ,  ,  ,

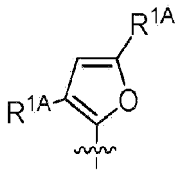
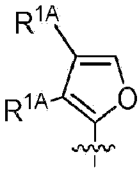
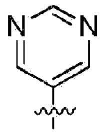
 ,  ,  ,

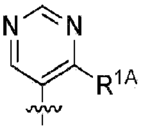
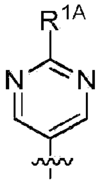
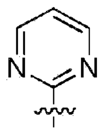
 ,  ,  ,

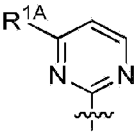
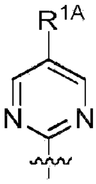
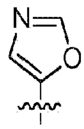
 ,  ,  ,

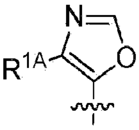
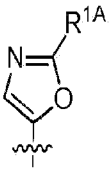
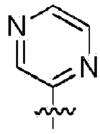
 ,  ,  ,

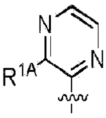
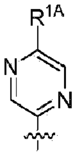
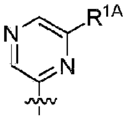
 ,  ,  ,

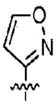
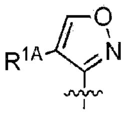
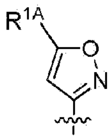
 ,  ,  ,

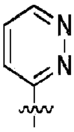
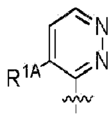
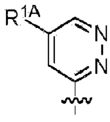
 ,  ,  ,

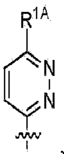
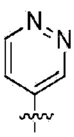
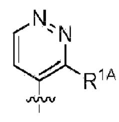
 ,  ,  ,

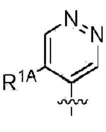
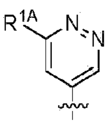
 ,  ,  ,

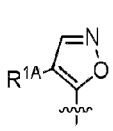
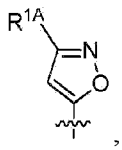
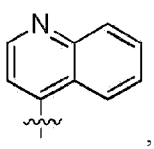
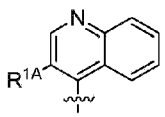
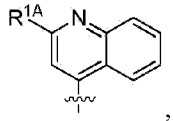
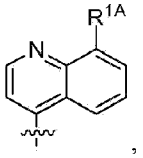
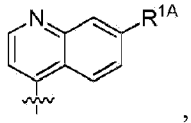
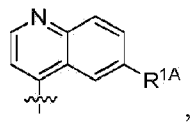
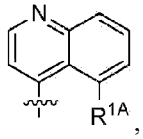
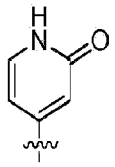
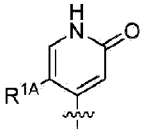
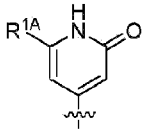
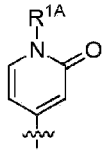
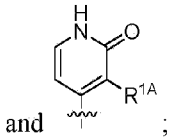
 ,  ,  ,

 ,  , 

 ,  ,  ,

 ,  ,  ,

 ,  ,  ,


,

,

,

,

,

,

,

,

,

,

,

,

,

and
;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{d3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0024] In some embodiments, the compound of Formula (Ia) is selected from the group of compounds provided in Table A, or a pharmaceutically acceptable salt thereof.

[0025] The present invention further provides a pharmaceutical composition comprising a compound provided herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

[0026] The present invention further provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in treating a disease associated with one or more mRNA splicing defects.

[0027] In some embodiments, the disease associated with one or more mRNA splicing defects comprises a disease of the central nervous system. In some embodiments, disease associated with one or more mRNA splicing defects is a disease of the central nervous system. In some embodiments, the compounds for use include delivering the compound to the central nervous system.

[0028] In some embodiments, the disease associated with one or more mRNA splicing defects is selected from the group consisting of amyotrophic lateral sclerosis (ALS), atypical cystic fibrosis, autism, autism spectrum disorders, Charcot-Marie-Tooth disease, CHARGE syndrome, dementia, epilepsy, epileptic encephalopathy, familial dysautonomia (FD), familial isolated growth hormone deficiency type II (IGHD II), Frasier syndrome, frontotemporal dementia and Parkinson's linked to Chromosome 17 (FTDP-17), Huntington's disease, Marfan syndrome, mental retardation, Menkes Disease (MD), muscular dystrophies, myopathies, myotonic dystrophy type 1 (DM1), myotonic dystrophy type 2 (DM2), neurofibromatosis 1 (NF1, von Recklinghausen NF; peripheral NF), occipital horn syndrome, Parkinson's disease, retinoblastoma, schizophrenia, tuberous sclerosis, and the gene-associated diseases listed in Table 1. In some embodiments, the disease associated with one or more mRNA splicing defects is selected from the group consisting of familial dysautonomia and neurofibromatosis 1. In some embodiments, the disease associated with one or more mRNA splicing defects is familial dysautonomia. In some embodiments, the disease associated with one or more mRNA splicing defects is neurofibromatosis 1. In some embodiments, the disease associated with one or more mRNA splicing defects is a disease listed in Table 1.

[0029] In some embodiments, the one or more mRNA splicing defects is associated with one or more genes comprising at least one exon comprising the nucleotide sequence CAA. In some embodiments, the one or more mRNA splicing defects is associated with one gene comprising at least one exon comprising the nucleotide sequence CAA. In some embodiments, the one or more mRNA splicing defects is associated with one or more genes selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1,

PGAP1, SLC9A9, SLC35A3, CACNA1S, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD7.

[0030] In some embodiments, the one or more mRNA splicing defects is associated with one gene selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1, PGAP1, SLC9A9, SLC35A3, CACNA1S, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD7. In some embodiments, the one or more genes is selected from the group provided in Table 1. In some embodiments, the gene is selected from the group provided in Table 1. In some embodiments, the gene is associated with a condition listed in Table 1 as associated with a gene provided therein.

[0031] The present invention further provides, a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in improving mRNA splicing of a gene (e.g., a gene in a cell), comprising contacting a cell expressing the gene with a compound provided herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the gene is selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1, PGAP1, SLC9A9, SLC35A3, CACNA1S, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD7. In some embodiments, the gene is selected from the group provided in Table 1. In some embodiments, the contacting the cell is performed in vitro. In some embodiments, the contacting the cell is performed in vivo. In some embodiments, the compound of the invention, or a pharmaceutically acceptable salt thereof, for use in improving mRNA splicing in a gene comprises improving exon inclusion.

[0032] The present invention further provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in improving mRNA splicing in a cell, wherein the improving comprises improving mRNA splicing in a gene.

[0033] The present invention further provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in improving mRNA splicing in a cell, wherein the improving comprises improving mRNA splicing in a gene selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1, PGAP1, SLC9A9, SLC35A3, CACNA1S, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD7. In some embodiments, the gene is selected from the

group provided in Table 1. In some embodiments, the contacting the cell is performed in vitro. In some embodiments, the contacting the cell is performed in vivo. In some embodiments, the compound of the invention for use in improving mRNA splicing in a gene comprises improving exon inclusion.

[0034] In some embodiments, the compounds for use described herein can include assaying mRNA splicing in a cell in the presence of a compound as provided herein, and detecting an improvement in mRNA splicing (e.g., increasing the rate of exon inclusion) in the cell.

[0035] In some embodiments, the compounds of the invention, or a pharmaceutically acceptable salt thereof, for use described herein are practiced on a cell or a subject who has a genetic mutation that causes an mRNA splicing defect, i.e., impaired or abnormal mRNA splicing that differs from mRNA splicing in a wild-type cell. The compounds of the invention, or a pharmaceutically acceptable salt thereof, for use can include identifying a subject who has such a genetic mutation and/or identifying a subject who has a condition associated with an mRNA splicing defect as described herein or known in the art.

[0036] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only In case of conflict, the present specification, including definitions, will control.

DESCRIPTION OF DRAWINGS

[0037]

FIG. 1A shows percent exon 20 inclusion in C57Bl6-FD mouse liver after administration of compound (**100**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day; and administration of kinetin at 400 mg/kg/day.

FIG. 1B shows percent exon 20 inclusion in C57Bl6-FD mouse liver after administration of compound (**230**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 1C shows percent exon 20 inclusion in C57Bl6-FD mouse liver after administration of compound (**270**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 2A shows percent exon 20 inclusion in C57Bl6-FD mouse heart after administration of compound (**100**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day; and administration of kinetin at 400 mg/kg/day.

FIG. 2B shows percent exon 20 inclusion in C57Bl6-FD mouse heart after administration of compound (**230**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 2C shows percent exon 20 inclusion in C57Bl6-FD mouse heart after administration of compound (**270**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 3A shows percent exon 20 inclusion in C57Bl6-FD mouse kidney after administration of compound (**100**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day; and administration of kinetin at 400 mg/kg/day.

FIG. 3B shows percent exon 20 inclusion in C57Bl6-FD mouse kidney after administration of compound (**230**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 3C shows percent exon 20 inclusion in C57Bl6-FD mouse kidney after administration of compound (**270**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 4A shows percent exon 20 inclusion in C57Bl6-FD mouse brain after administration of compound (**100**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day; and administration of kinetin at 400 mg/kg/day.

FIG. 4B shows percent exon 20 inclusion in C57Bl6-FD mouse brain after administration of compound (**230**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 4C shows percent exon 20 inclusion in C57Bl6-FD mouse brain after administration of compound (**270**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 5 shows percent exon 20 inclusion in C57Bl6-FD mouse trigeminal nerve after administration of compound (**270**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

FIG. 6 shows percent exon 20 inclusion in C57Bl6-FD mouse sciatic nerve after administration of compound (**270**) at 10 mg/kg/day; 30 mg/kg/day; and 60 mg/kg/day.

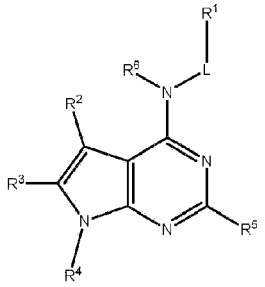
FIG. 7 shows results of a Western Blot on familial dysautonomia (FD) human fibroblast treated for five days with representative compounds (**230**), (**302**), (**270**), and (**100**).

DETAILED DESCRIPTION

[0038] Mutations that alter mRNA splicing have been estimated to account for as many as 20-30% of all disease-causing mutations, and studies have demonstrated that alternatively spliced isoforms are highly prevalent in the brain. These data collectively suggest that defects in alternative splicing may be a driver of neurodegenerative disease. Oral administration of kinetin (N^6-furfuryladenine) in mice (400 mg/kg/day for 7 days) has been shown to improve IKBKAP splicing in vivo in certain tissues, including the brain. Further, preliminary testing in human patients and carriers of familial dysautonomia led to increased normal IKBKAP mRNA in peripheral blood in humans (see e.g., U.S. Patent No. 8,729,025 and U.S. Patent No. 7,737,110). However, high doses were necessary to achieve splicing changes. Accordingly, the present invention provides compounds useful for therapeutically targeting mRNA splicing

mechanisms.

[0039] The present invention provides compounds of Formula (Ia):

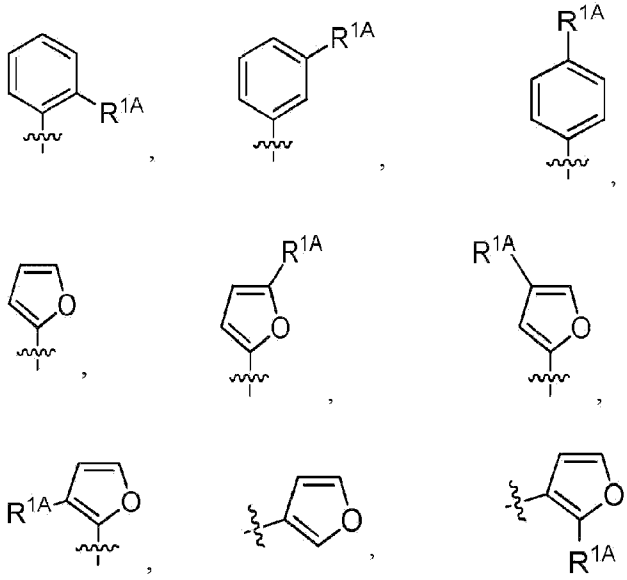


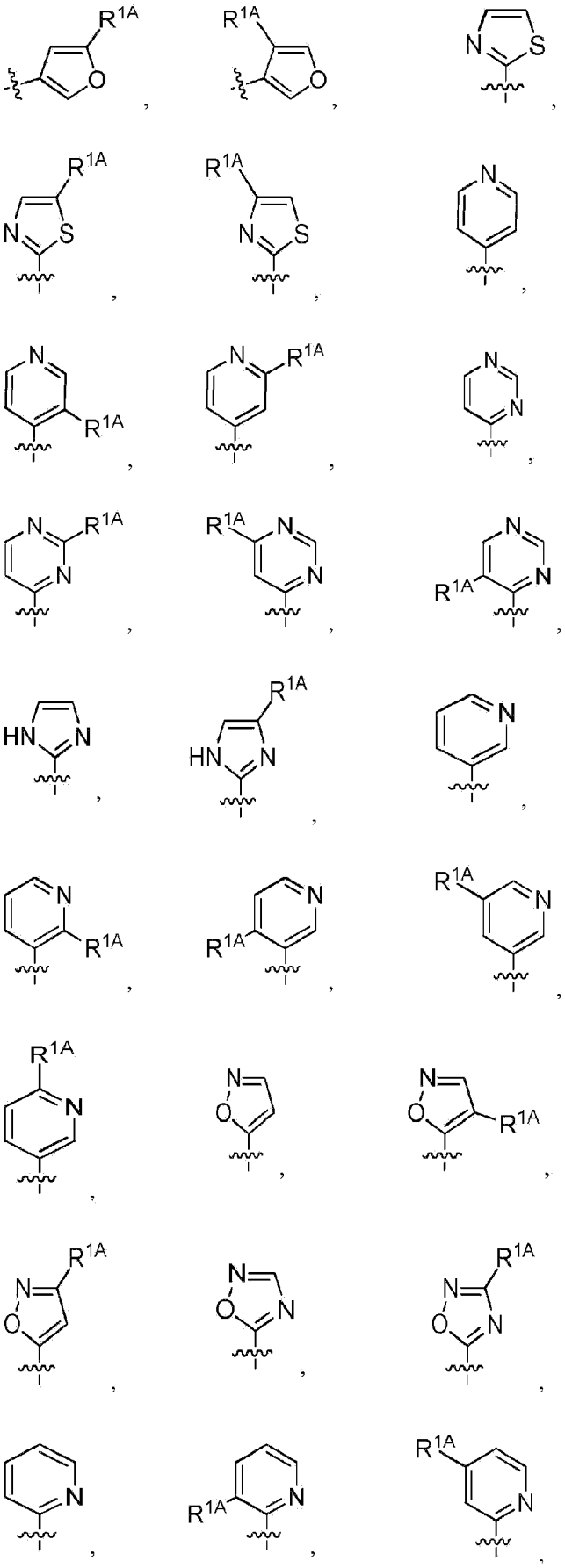
(Ia)

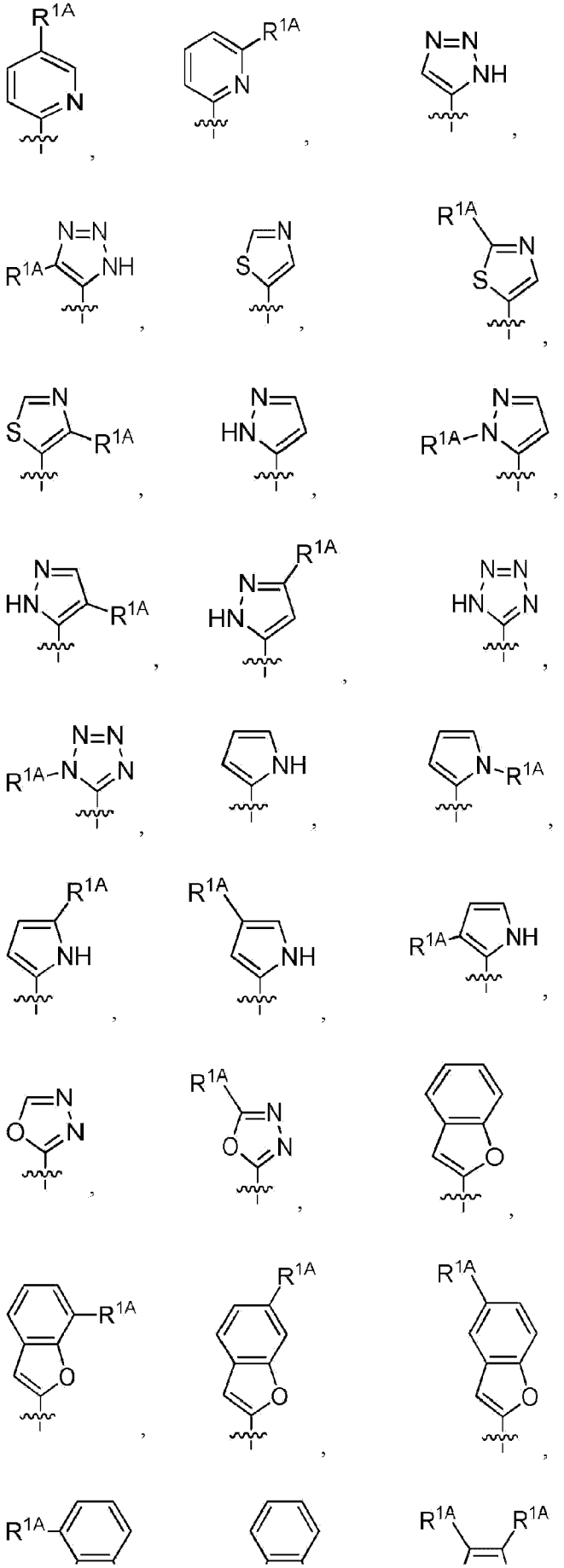
or a pharmaceutically acceptable salt thereof according to claim 1.

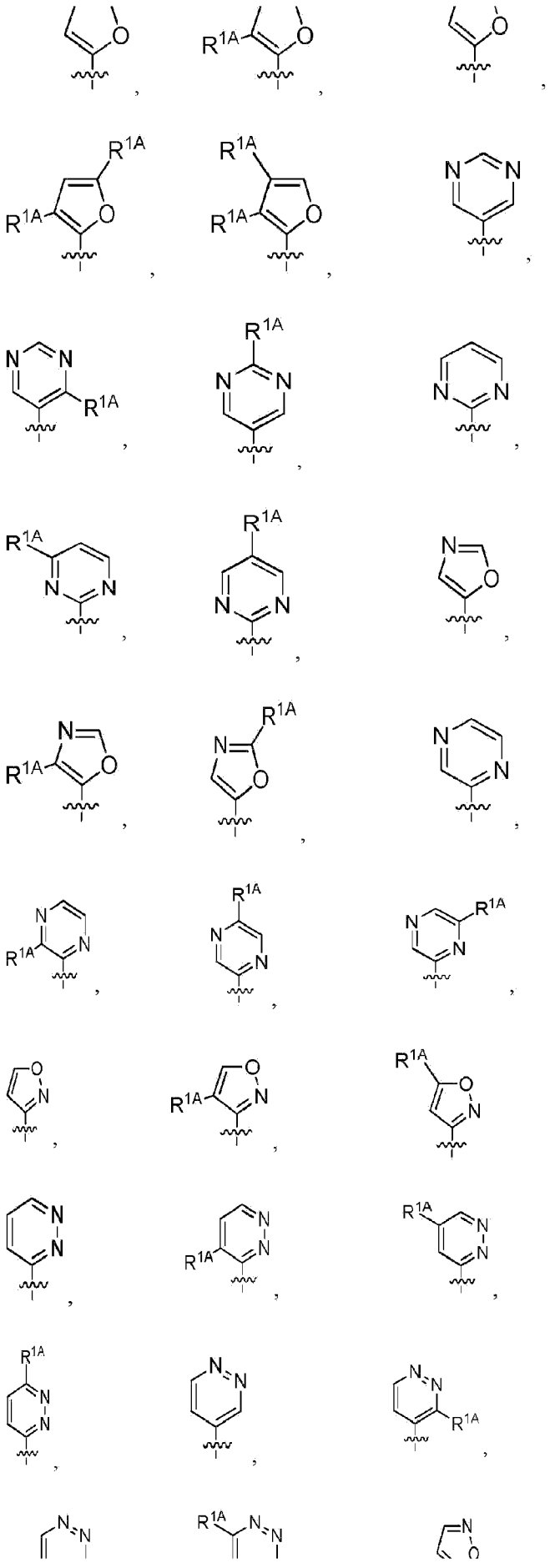
[0040] In some embodiments, L is C_{1-6} alkylene optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, L is unsubstituted C_{1-6} alkylene. In some embodiments, L is unsubstituted methylene or unsubstituted ethylene.

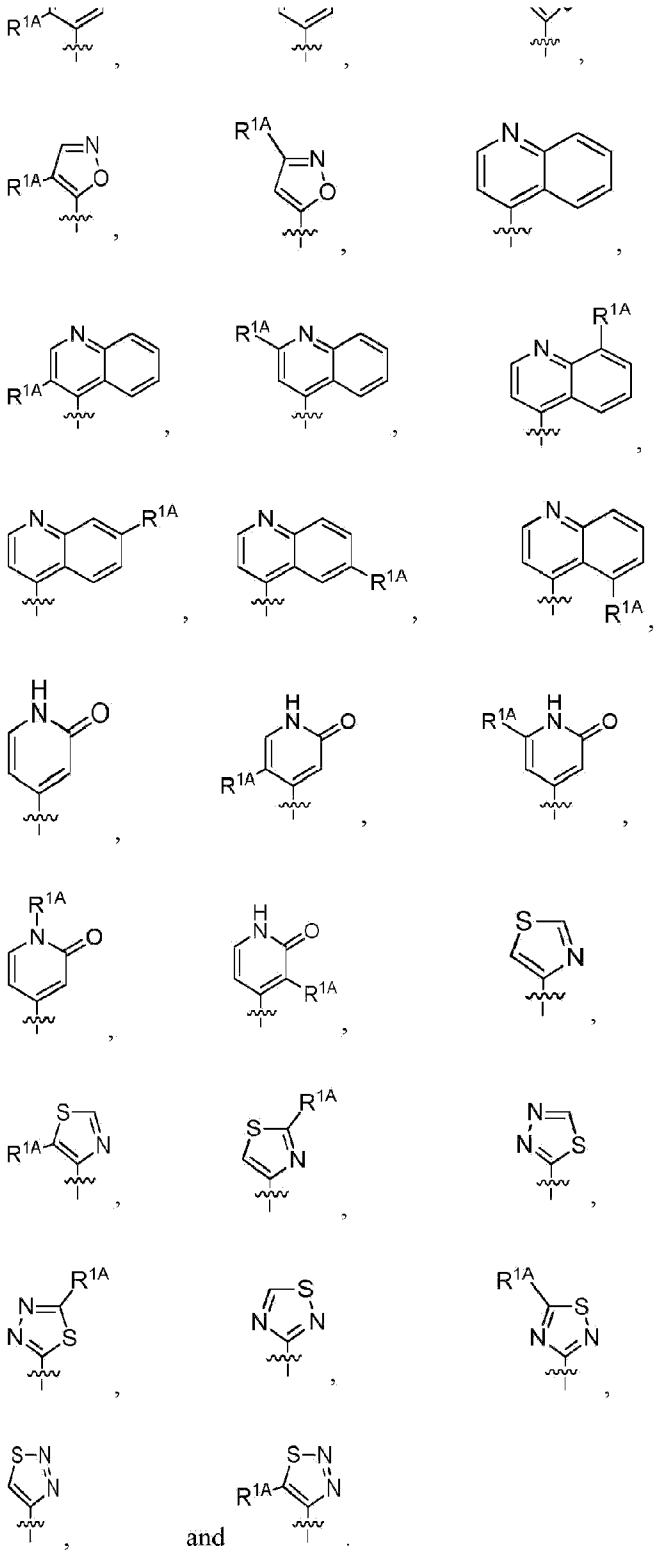
[0041] In some embodiments, R^1 is selected from the group consisting of C_{6-10} aryl, and 5-6 membered heteroaryl, each optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups. In some embodiments, R^1 is 2-benzofuranyl or 4-quinolinyl, each optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups. In some embodiments, R^1 is selected from the group consisting of 2-benzofuranyl, 4-quinolinyl, phenyl, and a 5-6 membered heteroaryl, each optionally substituted by 1 or 2 independently selected R^{1A} groups. In some embodiments, R^1 is selected from the group consisting of unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl, and unsubstituted 5-6 membered heterocycloalkyl. In some embodiments, R^1 is selected from the group consisting of 2-benzofuranyl, 4-quinolinyl, and a 5-6 membered heteroaryl, each optionally substituted by 1 or 2 independently selected R^{1A} groups. In some embodiments, R^1 is selected from the group consisting of:





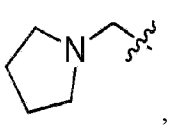
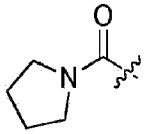




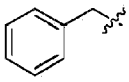
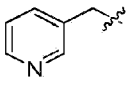


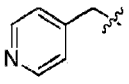
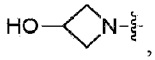
[0042] In some embodiments, each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH. In some embodiments, each R^{1A} is independently selected from the group consisting of CN, fluoro, chloro, methyl, trifluoromethyl, methoxy, and -C(=O)OH.

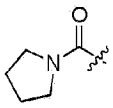
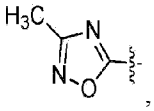
[0043] In some embodiments, R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^2 is selected from the group consisting of H, oxo, chloro, fluoro, bromo, CN, methyl, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, NH_2, $-NHCH_3$, $-N(CH_3)_2$, phenyl, 4-pyridinyl, $C(=O)OCH_3$, $C(=O)NH_2$, $C(=O)NHCH_3$,

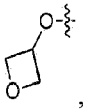
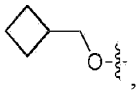

, and 
.

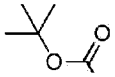
[0044] In some embodiments, R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^3 is $-OR^{a3}$. In some embodiments, R^3 is selected from the group consisting of H, azido, CN, methyl, cyclopropyl, cyclobutyl, phenyl, 3-pyridinyl, N-morpholino, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, $-OCH_2CH_2OH$, $-OCH_2CH_2CH_2OH$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2CH_2OCH_3$, $-ONHCH_3$, $-OCH_2CHF_2$, $-OCH_2CF_3$, $-OCH_2CH_2CF_3$, $-OCH_2CHF_2CH_3$, $-OCH_2CH_2NHC(=O)CH_3$, cyclobutoxy, $-OCH_2CH_2$-O-phenyl, $-SCH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2OH$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-NHCH_2CH_2OH$, $-C(=O)NHCH_2CH_2OH$, $-OC(=O)CH_3$, $-OCH_2$-azetidinyl, $-OCH_2$-oxetanyl,

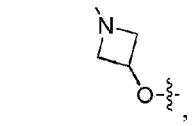
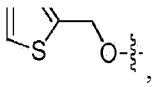
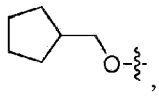
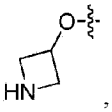
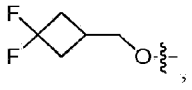
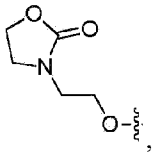
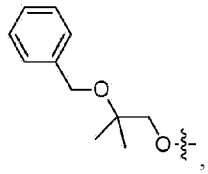
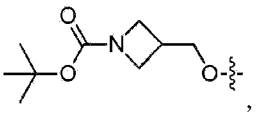
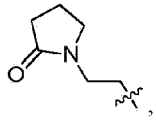
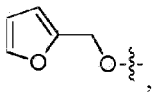
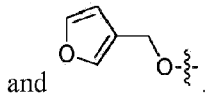

, 
,


, 
,

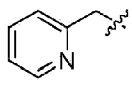
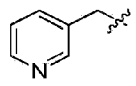
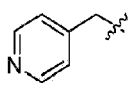
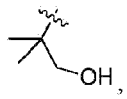
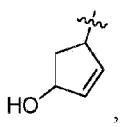
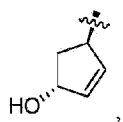

, 
,

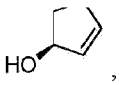

, 
,

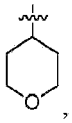
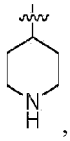
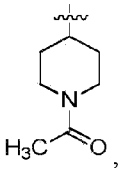
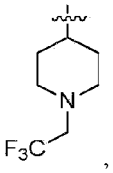
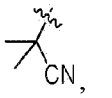


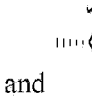












and

[0045] In some embodiments, R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups. In some embodiments, R^4 is selected from the group consisting of H, halo, methyl, $-CH_2CH_2F$, $-CH_2CH_2CF_3$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2C(=O)OH$, $-CH_2C(=O)NH(CH_3)$,$-CH_2C(=O)N(CH_3)_2$, $-CH_2CH_2NHC(=O)CH_3$, $-CH_2CH_2NHCH_3$, $-CH_2CH_2N(CH_3)_2$,





and

[0046] In some embodiments, R^5 is halo.

[0047] In some embodiments, R^5 is chloro or fluoro. In some embodiments, R^5 is chloro. In some embodiments, R^5 is fluoro.

[0048] In some embodiments, R^6 is H or C_{1-6} alkyl. In some embodiments, R^6 is H. In some embodiments, R^6 is C_{1-6} alkyl. In some embodiments, R^6 is C_{1-6} haloalkyl. In some embodiments, R^6 is C_{1-6} hydroxyalkyl. In some embodiments, R^6 is C_{1-6} alkoxy.

[0049] In some embodiments:

L is unsubstituted C_{1-6} alkylene;

R^1 is selected from the group consisting of 2-benzofuranyl, 4-quinolinyl, C_{6-10} aryl, and 5-6 membered heteroaryl, optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$,

wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0050] In some embodiments:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of 2-furanyl, 4-quinolinyl, C_{6-10} aryl, and 5-6 membered heteroaryl, optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0051] In some embodiments:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of 2-furanyl, 4-quinolinyl, phenyl, and 5-6 membered heteroaryl, each optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b3}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0052] In some embodiments,:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of 2-furanyl, 4-quinolinyl, phenyl, and 5-6 membered heteroaryl, each optionally substituted by 1 or 2 independently selected R^{1A} groups;

each R^{1A} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and -C(=O)OH;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is halo;

R^6 is H.

[0053] In some embodiments,:

L is unsubstituted methylene or unsubstituted ethylene;

R^1 is selected from the group consisting of unsubstituted 2-furanyl, unsubstituted 4-quinolinyl, unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{a2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by

1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

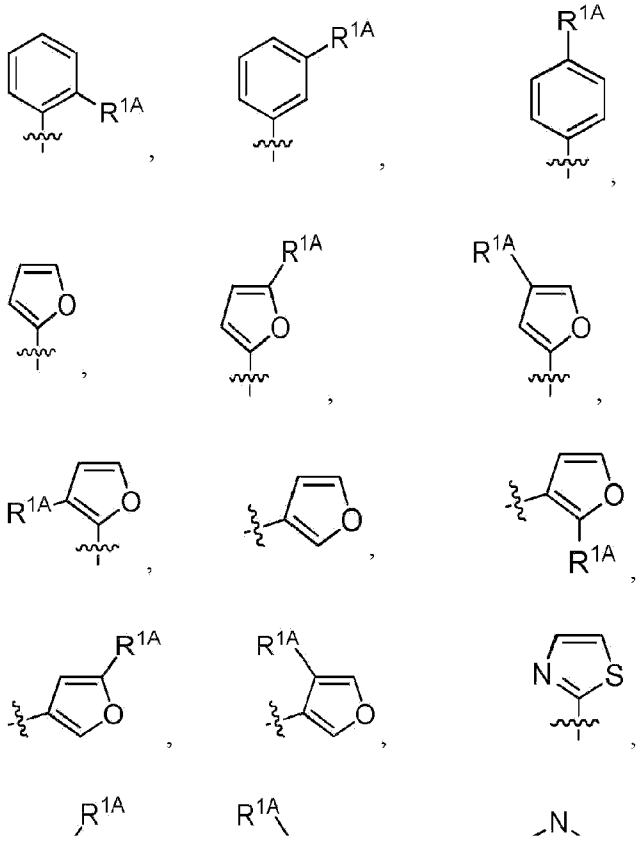
R^5 is halo;

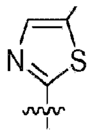
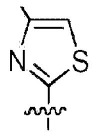
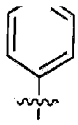
R^6 is H.

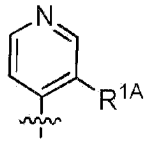
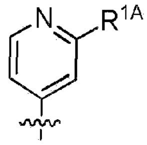
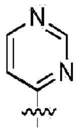
[0054] In some embodiments:

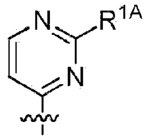
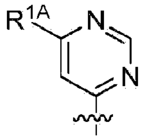
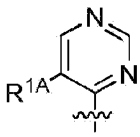
L is unsubstituted methylene or unsubstituted ethylene;

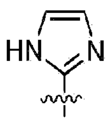
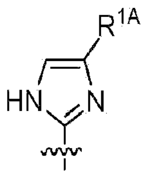
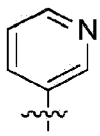
R^1 is selected from the group consisting of:

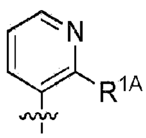
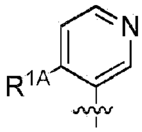
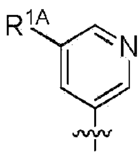


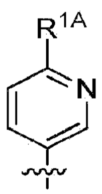
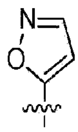
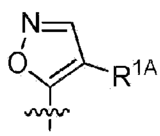
 ,  ,  ,

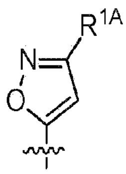
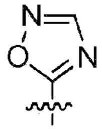
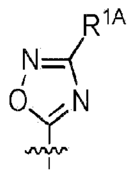
 ,  ,  ,

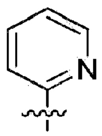
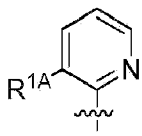
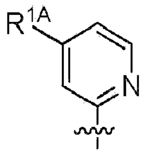
 ,  ,  ,

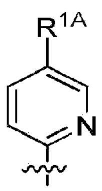
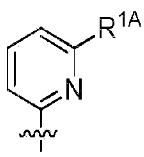
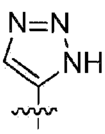
 ,  ,  ,

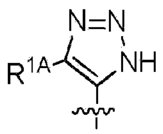
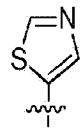
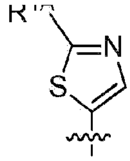
 ,  ,  ,

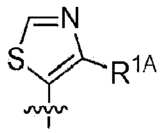
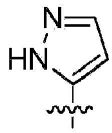
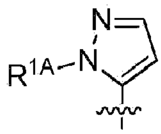
 ,  ,  ,

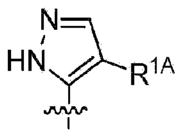
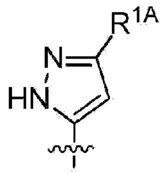
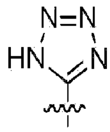
 ,  ,  ,

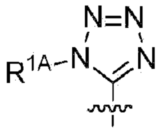
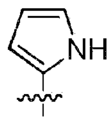
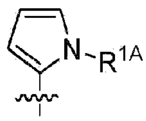
 ,  ,  ,

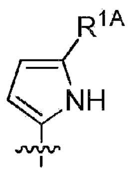
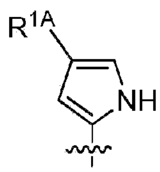
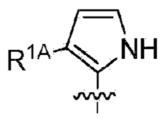
 ,  ,  ,

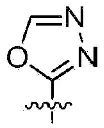
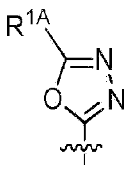
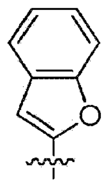
 ,  ,  ,

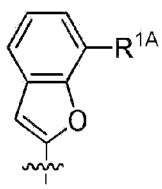
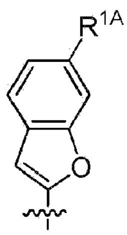
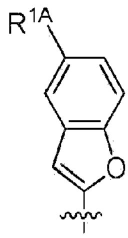
 ,  ,  ,

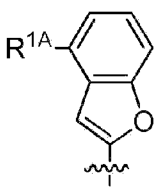
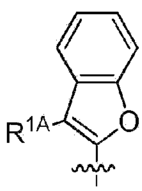
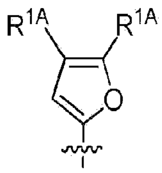
 ,  ,  ,

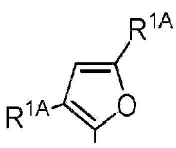
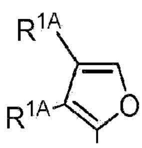
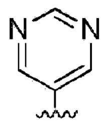
 ,  ,  ,

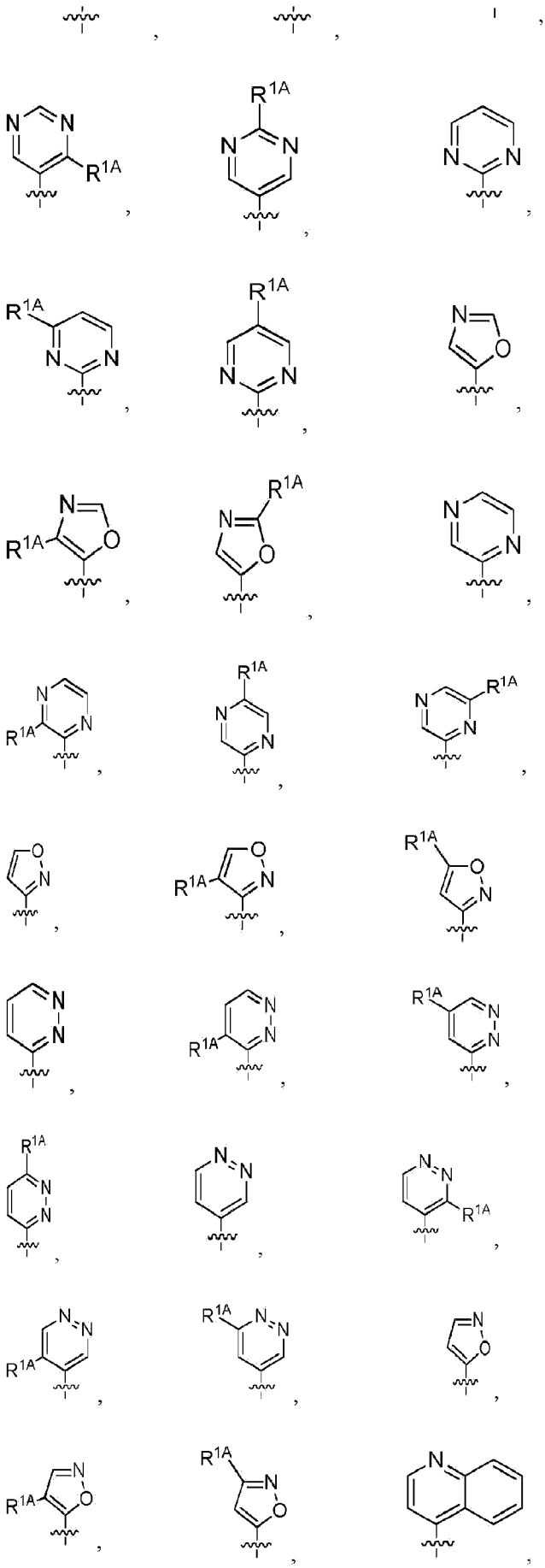
 ,  ,  ,

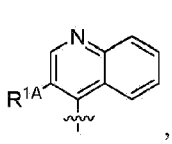
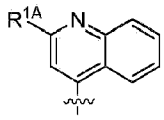
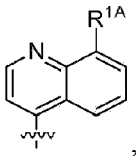
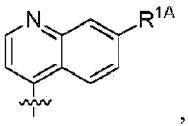
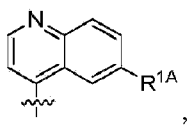
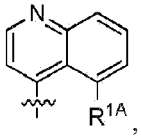
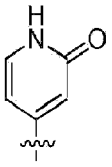
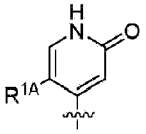
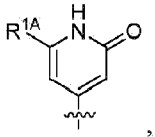
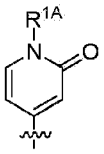
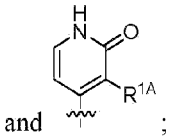
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,




,

,

,

,

,

,

,

,

,

,

and
;

R^2 is selected from the group consisting of H, oxo, halo, CN, C_{1-6} alkyl, OR^{a2}, $NR^{c2}R^{d2}$, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, $C(=O)OR^{b2}$, and $C(=O)NR^{c2}R^{d2}$, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^3 is selected from the group consisting of H, oxo, azido, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, 5-6 membered heteroaryl, 5-6 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^4 is selected from the group consisting of H, oxo, azido, halo, CN, C_{1-6} alkyl, OR^{a4}, $NR^{c4}R^{d4}$, and 4-10 membered heterocycloalkyl, wherein the C_{1-6} alkyl and 4-10 membered heterocycloalkyl are each optionally substituted by 1, 2, 3, or 4 independently selected R^{20} groups;

R^5 is selected from the group consisting of H, halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, OR^{a5}, SR^{a5}, $NR^{c5}R^{d5}$, C_{3-6} cycloalkyl, C_{6-10} aryl, and 5-6 membered heteroaryl;

R^6 is H.

[0055] In some embodiments, L is selected from the group consisting of an unsubstituted C_{1-6} alkylene, an unsubstituted C_{2-6} alkenylene, and a C_{2-6} alkynylene. In some embodiments, L is selected from the group consisting of an unsubstituted C_{1-6} alkylene, an unsubstituted C_{2-6} alkenylene, and a C_{2-6} alkynylene. In some embodiments, L is an unsubstituted C_{1-6} alkylene. In some embodiments, L is an unsubstituted methylene or an unsubstituted ethylene. In some embodiments, L is an unsubstituted methylene.

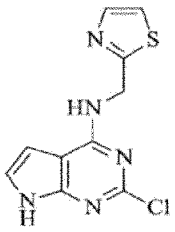
[0056] In some embodiments, R^1 is a 5-6 membered heteroaryl optionally substituted by 1, 2, 3, or 4 independently selected R^{1A} groups. In some embodiments, R^1 is an unsubstituted 5-6 membered heteroaryl.

[0057] In some embodiments, R^2, R^3, and R^4 are each independently selected from H and C_{1-6} alkyl. In some embodiments, R^2, R^3, and R^4 are each H.

[0058] In some embodiments, R^5 is halo. In some embodiments, R^5 is chloro or fluoro. In some embodiments, R^5 is chloro.

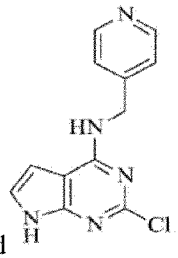
[0059] In some embodiments, R^6 is H or C_{1-6} alkyl. In some embodiments, R^6 is H.

[0060] In some embodiments, the compound of Formula (Ia) is selected from the group consisting of:



(107)

and

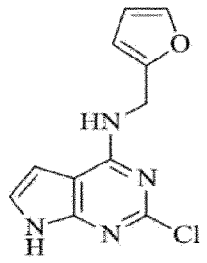


(100)

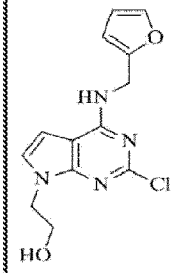
or a pharmaceutically acceptable salt thereof.

[0061] In some embodiments, the compound of Formula (Ia) is selected from the group of compounds provided in Table A, or a pharmaceutically acceptable salt thereof.

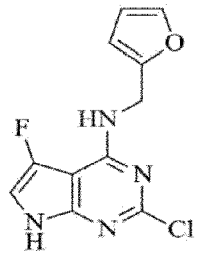
Table A.



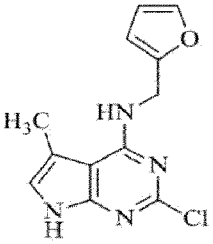
(55)



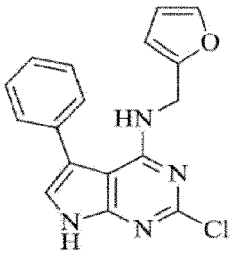
(77)



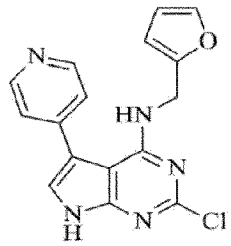
(81)

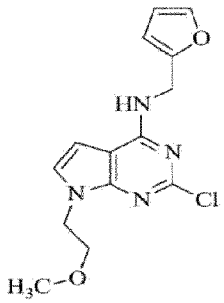
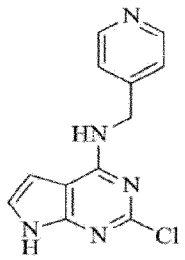
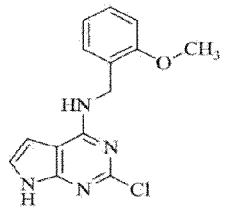
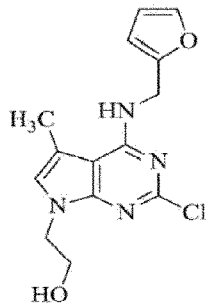
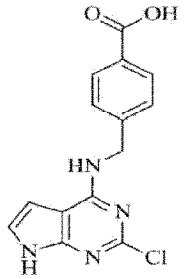
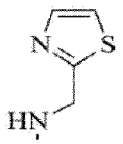
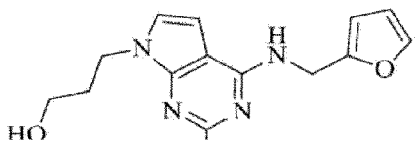


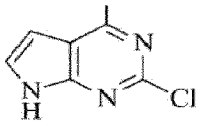
(84)



(86)

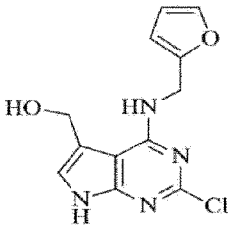


(89)	
	 (94)
	 (100)
 (101)	
 (105)	 (106)
	

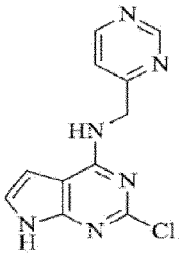


(107)

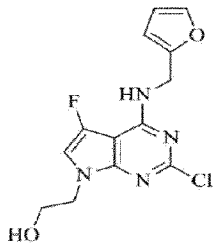
(108)



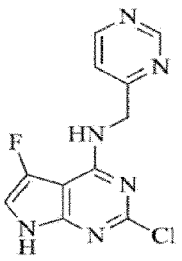
(109)



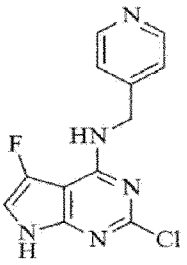
(110)



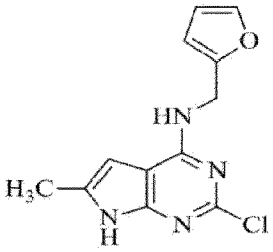
(111)



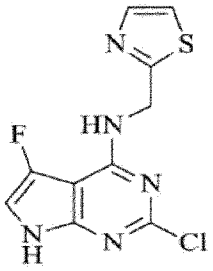
(112)



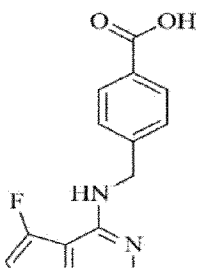
(114)

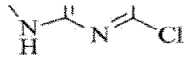


(115)

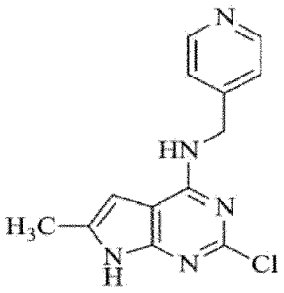


(116)

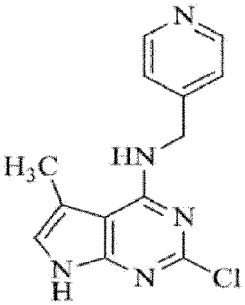




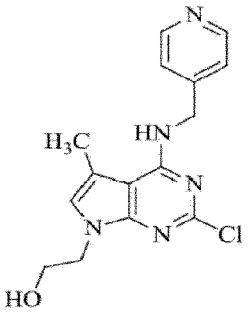
(117)



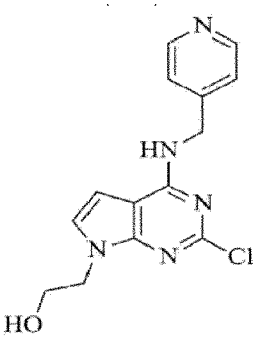
(119)



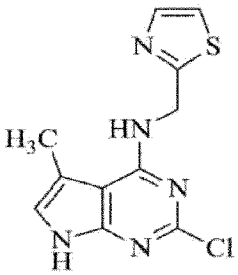
(120)



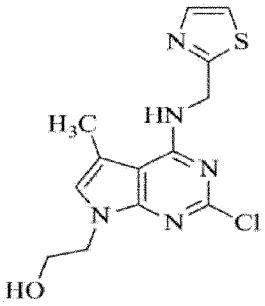
(121)



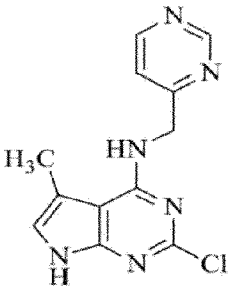
(122)



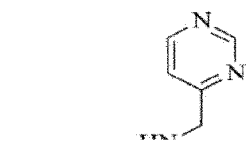
(123)

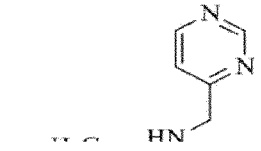


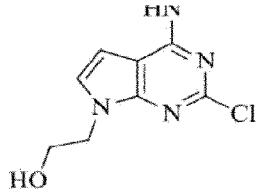
(125)



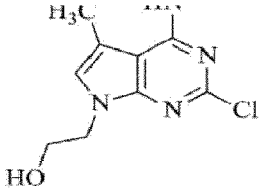
(126)



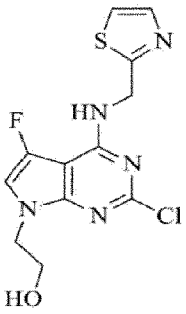




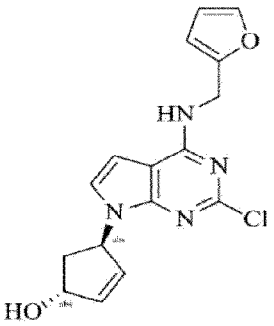
(127)



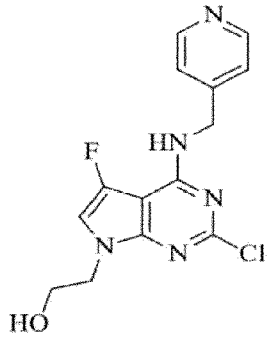
(128)



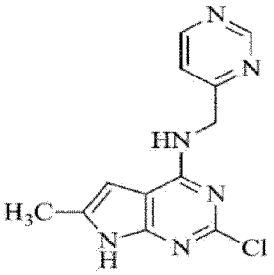
(130)



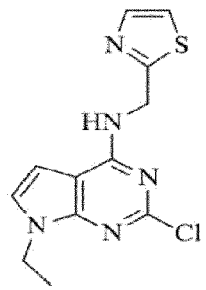
(132)

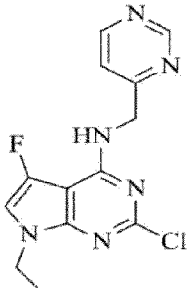


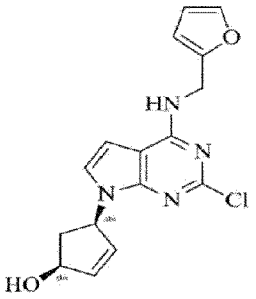
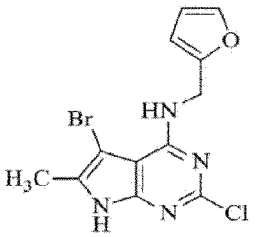
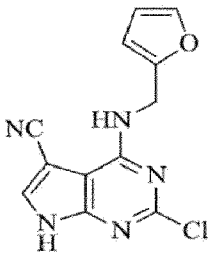
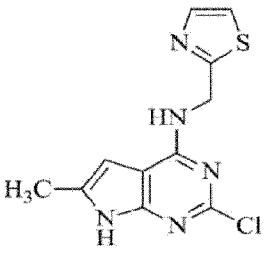
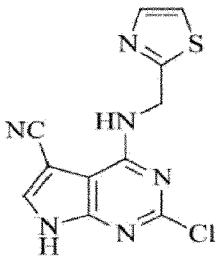
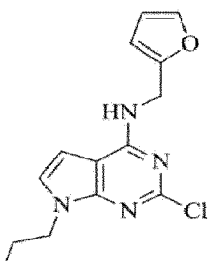
(135)

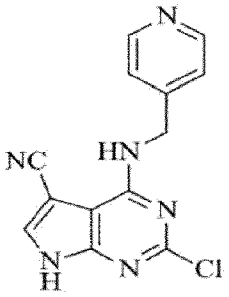
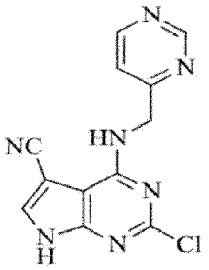
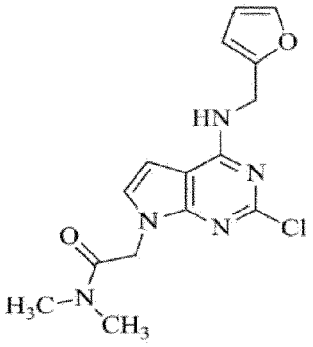
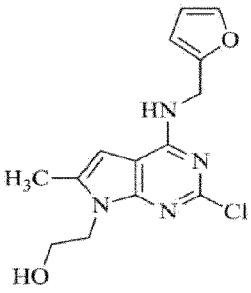
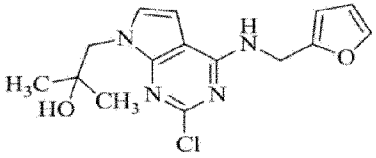
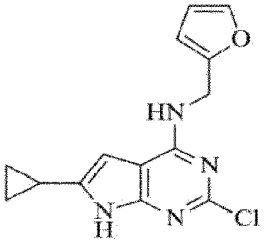
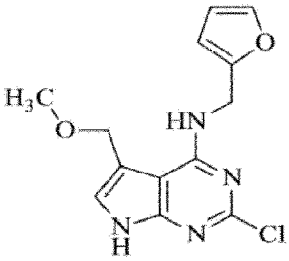
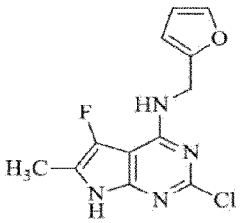
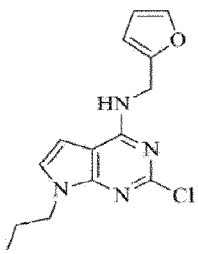


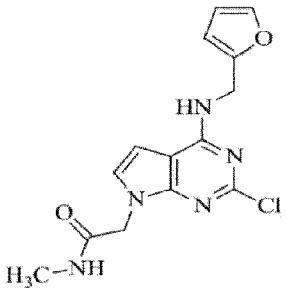
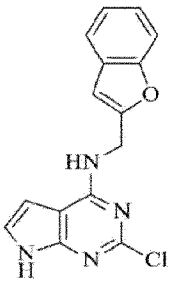
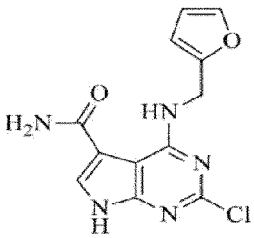
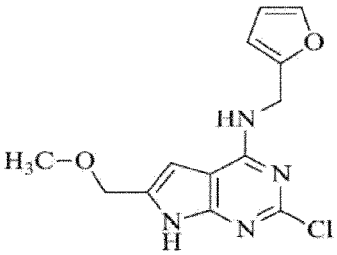
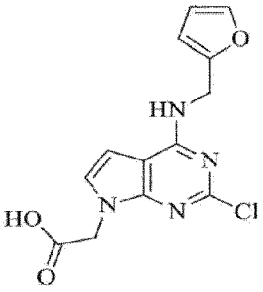
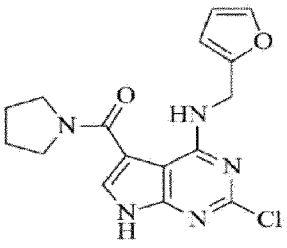
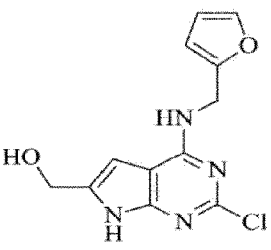
(136)

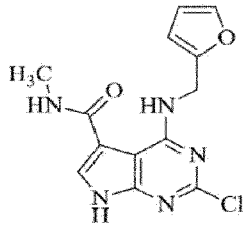
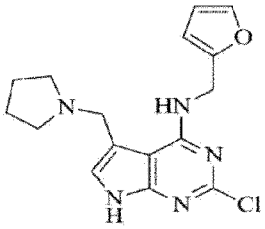
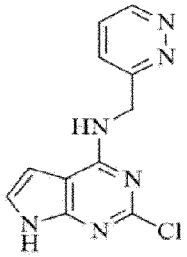
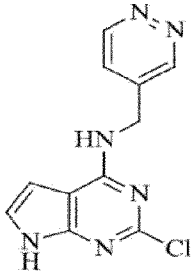
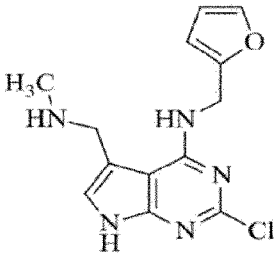
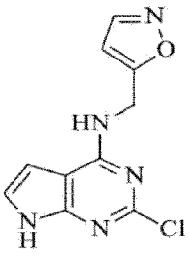
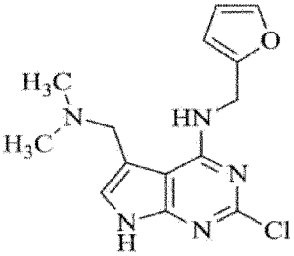


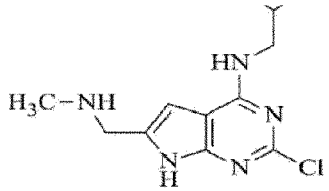


 (137)	 (138)
 (139)	
 (143)	
 (145)	
 (147)	 (148)
	

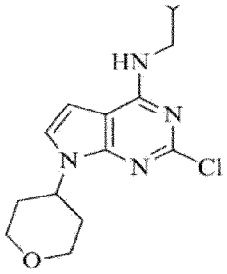
	F **(150)**
 **(151)**	 **(152)**
 **(153)**	 **(154)**
 **(155)**	 **(156)**
	 **(158)**
	

(159)	 (160)
 (161)	
 (163)	
 (165)	 (166)
 (167)	 (168)
	

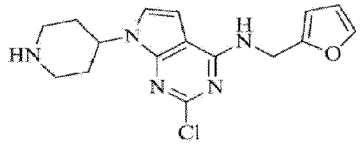
	(170)
	 (172)
 (173)	 (174)
	 (176)
 (177)	 (178)
	 (180)
	



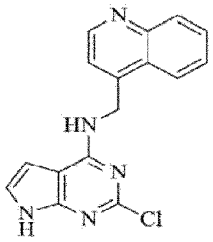
(181)



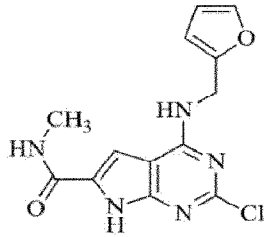
(182)



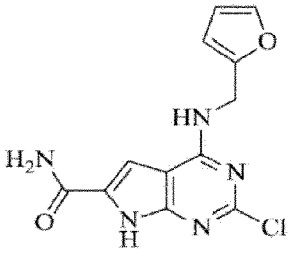
(183)



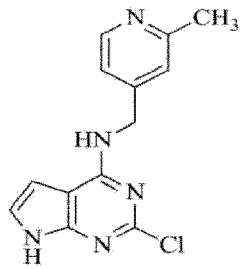
(186)



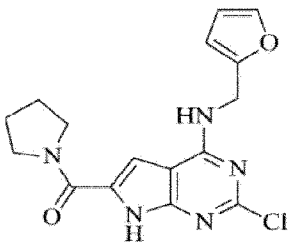
(187)



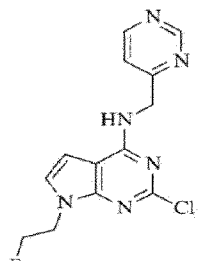
(188)

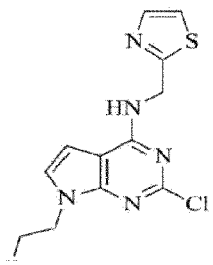


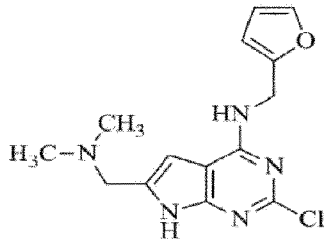
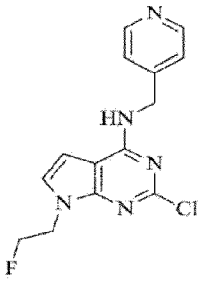
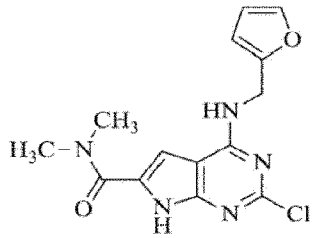
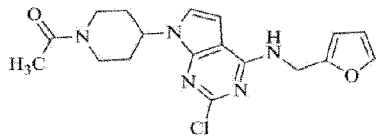
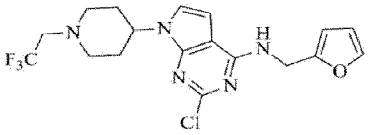
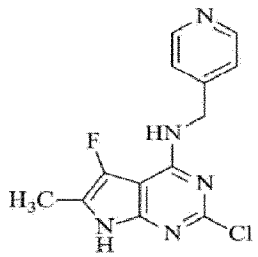
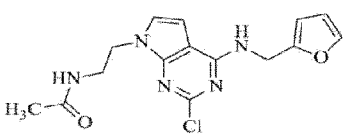
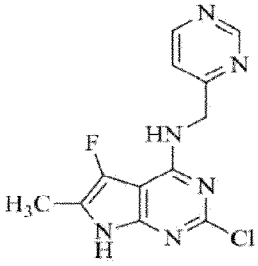
(189)

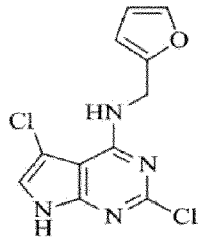
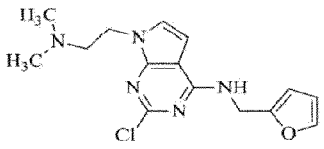
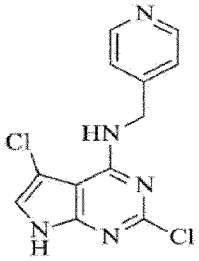
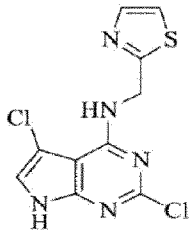
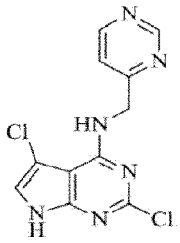
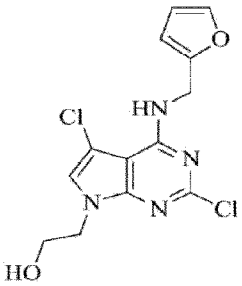
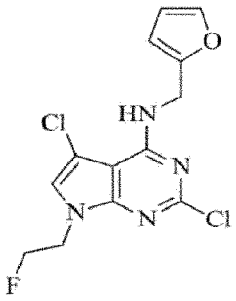
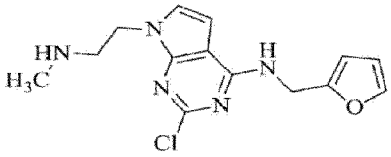
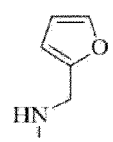
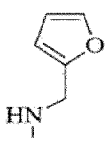


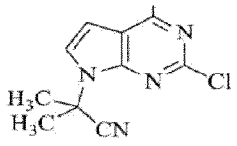
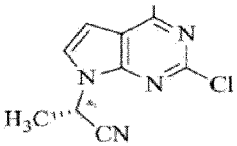
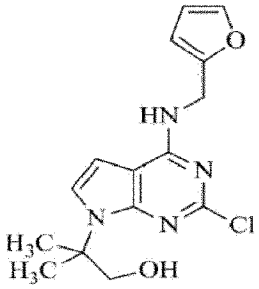
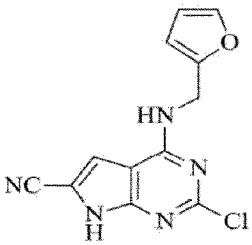
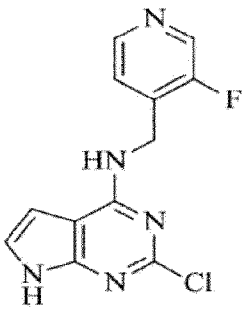
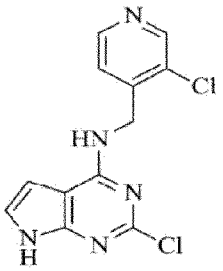
(190)

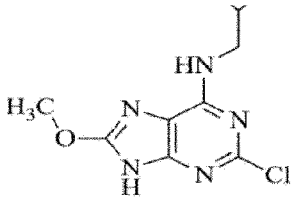
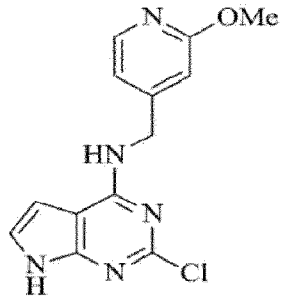
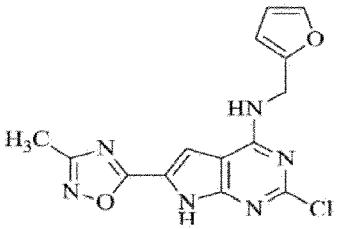
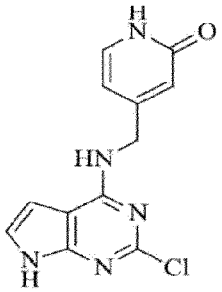
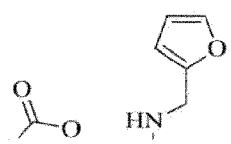


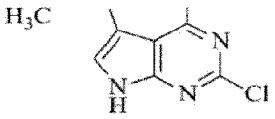
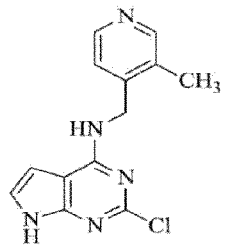
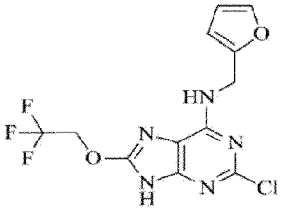


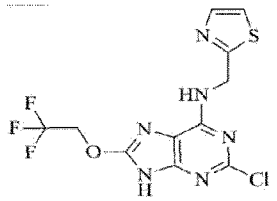
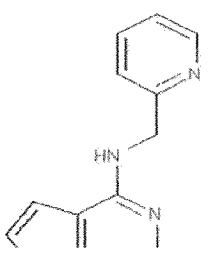
F **(191)**	F **(192)**
 **(193)**	 **(194)**
 **(195)**	
 **(197)**	
	 **(200)**
 **(201)**	
 **(203)**	

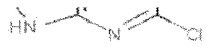
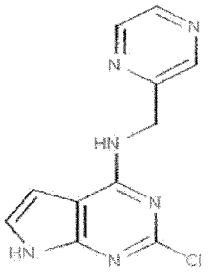
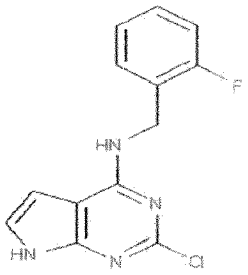
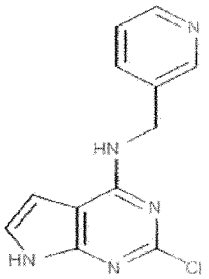
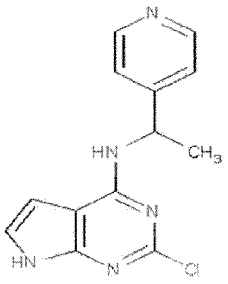
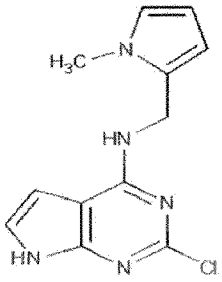
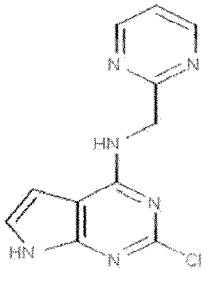
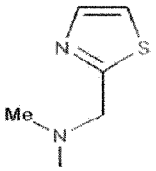
	(204)
 (205)	 (206)
 (207)	 (208)
	 (210)
 (211)	 (212)
 (213)	
	

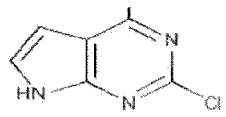
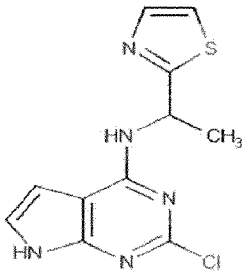
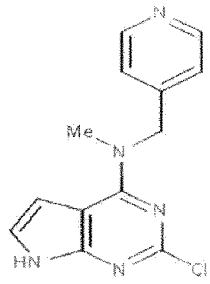
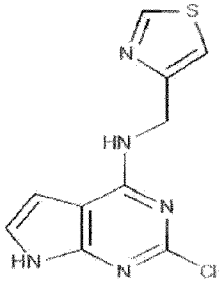
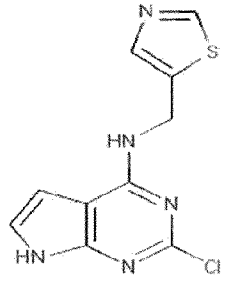
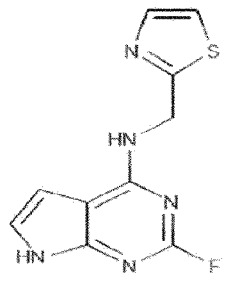
 (215)	 (216)
 (219)	
 (223)	
	 (226)
	 (228)
	

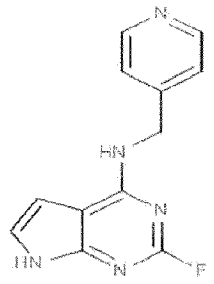
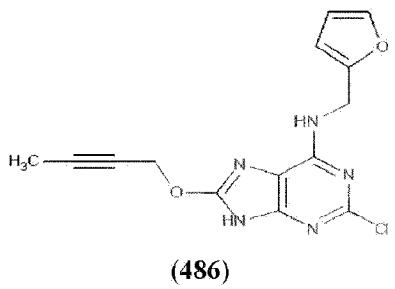
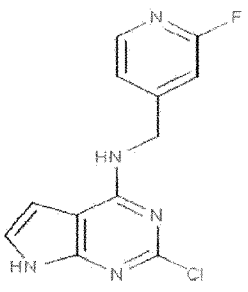
	 Reference Compound (**230**)
 (**237**)	
	 (**246**)
	 (**248**)
	

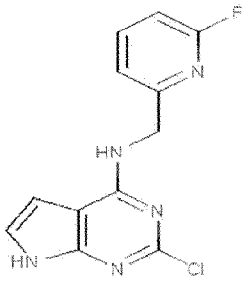
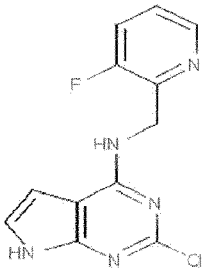
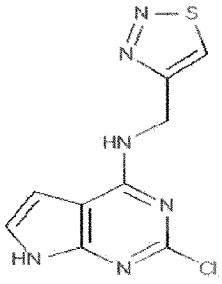
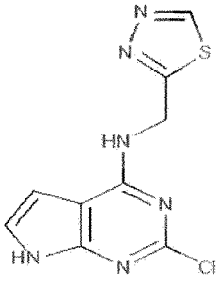
	 (252)
 (263)	
	 Reference Compound (270)

	 Reference Compound (**302**)
	

 (350)	
	 (353)
 (354)	 (355)
	 (359)
 (360)	 (361)
	

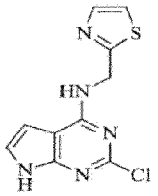
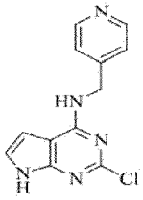
	 (363)
 (364)	
	 (369)
 (372)	 (373)
	 (379)

 (380)	
 (486)	 (487)

 (494)	 (495)
 (498)	
	 (501)

[0062] In some embodiments, the compound of Formula (Ia) is selected from the group of compounds provided in Table A-2, or a pharmaceutically acceptable salt thereof.

Table A-2.

	 (107), and
 (100)	

General Definitions

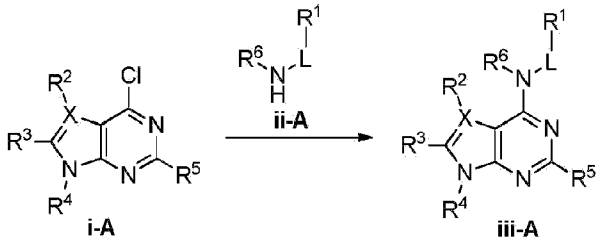
[0063] The following abbreviations may be used herein: ADME (Absorption, Distribution, Metabolism, and Excretion); aq. (aqueous); n-BuOH (n-butanol); calc. (calculated); d (doublet); dd (doublet of doublets); DBTCE (dibromotetrachloroethane); DCM (dichloromethane); DIPEA (*N,N*-diisopropylethylamine); DMA (dimethylacetamide); DMEM (Dulbecco's Modified Eagle's Media); DMF (*N,N*-dimethylformamide); eq. or equiv. (equivalents); Et (ethyl); EtOAc (ethyl acetate); EtOH (ethanol); FD (familial dysautonomia); g (gram(s)); h (hour(s)); HPLC (high performance liquid chromatography); Hz (hertz); IPA (isopropyl alcohol); *J* (coupling constant); KOH (potassium hydroxide); LCMS (liquid chromatography - mass spectrometry); LDA (lithium diisopropylamide); m (multiplet); M (molar); Me (methyl); MeI (methyl iodide); MeCN (acetonitrile); MeOH (methanol); mg (milligram(s)); min. (minutes(s)); mL (milliliter(s)); mmol (millimole(s)); MS (Mass spectrometry); Na_2SO_4 (sodium sulfate); nM (nanomolar); NMR (nuclear magnetic resonance spectroscopy); PBS (phosphate buffered saline); t (triplet or tertiary); TEA (triethylamine); THF (tetrahydrofuran); TLC (thin layer chromatography); µg (microgram(s)); µL (microliter(s)); µM (micromolar); wt % (weight percent).

Synthesis

[0064] As will be appreciated, the compounds provided herein, including salts thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

[0065] The compounds of Formula (I) can be prepared, for example, using a process as illustrated in Scheme I. A mixture of the desired chloropyrrolopyrimidine or purine **i-A**, desired aminomethyl heterocycle or appropriately substituted aryl or benzyl amine **ii-A**, and amine base (e.g. triethylamine or diisopropylethylamine) in an appropriate solvent (e.g., 1,4-dioxane) are stirred at 50-150 °C in a sealed tube to afford a compound **iii-A.**

Scheme I



[0066] It will be appreciated by one skilled in the art that the processes described herein are not the exclusive means by which compounds provided herein may be synthesized and that a broad repertoire of synthetic organic reactions is available to be potentially employed in synthesizing compounds provided herein. The person skilled in the art knows how to select and implement appropriate synthetic routes. Suitable synthetic methods of starting materials, intermediates and products may be identified by reference to the literature, including reference sources such as: Advances in Heterocyclic Chemistry, Vols. 1-107 (Elsevier, 1963-2012); Journal of Heterocyclic Chemistry Vols. 1-49 (Journal of Heterocyclic Chemistry, 1964-2012); Carreira, et al. (Ed.) Science of Synthesis, Vols. 1-48 (2001-2010) and Knowledge Updates KU2010/1-4; 2011/1-4; 2012/1-2 (Thieme, 2001-2012); Katritzky, et al. (Ed.) Comprehensive Organic Functional Group Transformations, (Pergamon Press, 1996); Katritzky et al. (Ed.); Comprehensive Organic Functional Group Transformations II (Elsevier, 2nd Edition, 2004); Katritzky et al. (Ed.), Comprehensive Heterocyclic Chemistry (Pergamon Press, 1984); Katritzky et al., Comprehensive Heterocyclic Chemistry II, (Pergamon Press, 1996); Smith et al., March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Ed. (Wiley, 2007); Trost et al. (Ed.), Comprehensive Organic Synthesis (Pergamon Press, 1991).

[0067] The reactions for preparing compounds described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, (e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature). A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

[0068] Preparation of compounds described herein can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The

chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., Wiley & Sons, Inc., New York (1999).

[0069] Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC), liquid chromatography-mass spectroscopy (LCMS), or thin layer chromatography (TLC). Compounds can be purified by those skilled in the art by a variety of methods, including high performance liquid chromatography (HPLC) and normal phase silica chromatography.

[0070] At various places in the present specification, divalent linking substituents are described. It is specifically intended that each divalent linking substituent include both the forward and backward forms of the linking substituent. For example, -NR(CR'R")$_n$-includes both -NR(CR'R")$_n$- and -(CR'R")$_n$NR-. Where the structure clearly requires a linking group, the Markush variables listed for that group are understood to be linking groups.

[0071] The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

[0072] As used herein, the phrase "optionally substituted" means unsubstituted or substituted. As used herein, the term "substituted" means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

[0073] Throughout the definitions, the term "C_{n-m}" indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C_{1-4}, or C_{1-6}.

[0074] As used herein, the term "C_{n-m} alkyl", employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, or 1,2,2-trimethylpropyl. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms.

[0075] As used herein, "C_{n-m} alkenyl" refers to an alkyl group having one or more double carbon-carbon bonds and having n to m carbons. Example alkenyl groups include, ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl, or sec-butenyl. In some embodiments, the alkenyl moiety

contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

[0076] As used herein, "C_{n-m} alkynyl" refers to an alkyl group having one or more triple carbon-carbon bonds and having n to m carbons. Example alkynyl groups include, but are not limited to, ethynyl, propyn-1-yl, or propyn-2-yl. In some embodiments, the alkynyl moiety contains 2 to 6, 2 to 4, or 2 to 3 carbon atoms.

[0077] As used herein, the term "C_{n-m} alkylene", employed alone or in combination with other terms, refers to a divalent alkyl linking group having n to m carbons. Examples of alkylene groups include, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, butan-1,3-diyl, butan-1,2-diyl, 2-methyl-propan-1,3-diyl, and the like. In some embodiments, the alkylene moiety contains 2 to 6, 2 to 4, 2 to 3, 1 to 6, 1 to 4, or 1 to 2 carbon atoms.

[0078] As used herein, the term "C_{n-m} alkoxy", employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), or *tert*-butoxy. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0079] As used herein, the term "C_{n-m} aryloxy", employed alone or in combination with other tersm, refers to a group of formula -O-aryl, wherein the aryl group has n to m carbon atoms. Example aryloxy group include, phenoxy and naphthyloxy.

[0080] As used herein, the term "C_{n-m} alkylamino" refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0081] As used herein, the term "C_{n-m} alkoxycarbonyl" refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0082] As used herein, the term "C_{n-m} alkylcarbonyl" refers to a group of formula -C(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0083] As used herein, the term "C_{n-m} alkylcarbonylamino" refers to a group of formula -NHC(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0084] As used herein, the term "C_{n-m} alkylsulfonylamino" refers to a group of formula -$NHS(O)_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0085] As used herein, the term "aminosulfonyl" refers to a group of formula -$S(O)_2NH_2$.

[0086] As used herein, the term "C_{n-m} alkylaminosulfonyl" refers to a group of formula -$S(O)_2NH$(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0087] As used herein, the term "di(C_{n-m} alkyl)aminosulfonyl" refers to a group of formula -$S(O)_2N$(alkyl)$_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0088] As used herein, the term "aminosulfonylamino" refers to a group of formula -$NHS(O)_2NH_2$.

[0089] As used herein, the term "C_{n-m} alkylaminosulfonylamino" refers to a group of formula -$NHS(O)_2NH$(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0090] As used herein, the term "di(C_{n-m} alkyl)aminosulfonylamino" refers to a group of formula -$NHS(O)_2N$(alkyl)$_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0091] As used herein, the term "aminocarbonylamino", employed alone or in combination with other terms, refers to a group of formula -$NHC(O)NH_2$.

[0092] As used herein, the term "C_{n-m} alkylaminocarbonylamino" refers to a group of formula -$NHC(O)NH$(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0093] As used herein, the term "di(C_{n-m} alkyl)aminocarbonylamino" refers to a group of formula -$NHC(O)N$(alkyl)$_2$, wherein each alkyl group independently has n to m carbon atoms. In some embodiments, each alkyl group has, independently, 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0094] As used herein, the term "C_{n-m} alkylcarbamyl" refers to a group of formula -C(O)-NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0095] As used herein, the term "C_{n-m} alkylcarbamoyl" refers to a group of formula -$OC(O)NH$(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0096] As used herein, the term "thio" refers to a group of formula -SH.

[0097] As used herein, the term "C_{n-m} alkylsulfinyl" refers to a group of formula -S(O)-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0098] As used herein, the term "C_{n-m} alkylsulfonyl" refers to a group of formula -$S(O)_2$-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0099] As used herein, the term "amino" refers to a group of formula -NH_2.

[0100] As used herein, the term "aryl," employed alone or in combination with other terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings). The term "C_{n-m} aryl" refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to about 20 carbon atoms, from 6 to about 15 carbon atoms, or from 6 to about 10 carbon atoms. In some embodiments, the aryl group is a substituted or unsubstituted phenyl.

[0101] As used herein, the term "carbamyl" to a group of formula -C(O)NH_2.

[0102] As used herein, the term "carbonyl", employed alone or in combination with other terms, refers to a -C(=O)- group, which may also be written as C(O).

[0103] As used herein, the term "carbamoyl" refers to a group of formula -OC(O)NH_2.

[0104] As used herein, the term "cyano-C_{1-3} alkyl" refers to a group of formula -(C_{1-3} alkylene)-CN.

[0105] As used herein, the term "HO-C_{1-3} alkyl" refers to a group of formula -(C_{1-3} alkylene)-OH.

[0106] As used herein, the term "di(C_{n-m}-alkyl)amino" refers to a group of formula - N(alkyl)$_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0107] As used herein, the term "di(C_{n-m}-alkyl)carbamyl" refers to a group of formula -C(O)N(alkyl)$_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0108] As used herein, the term "di(C_{n-m}-alkyl)carbamoyl" refers to a group of formula - -OC(O)N(alkyl)$_2$, wherein the two alkyl groups each has, independently, n to m carbon atoms. In

some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0109] As used herein, "halo" refers to F, Cl, Br, or I. In some embodiments, a halo is F, Cl, Br, or I. In some embodiments, a halo is F, Cl, or Br. In some embodiments, a halo is Cl. In some embodiments, a halo is F.

[0110] As used herein, "C_{n-m} haloalkoxy" refers to a group of formula -O-haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF_3. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0111] As used herein, the term "C_{n-m} haloalkyl", employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where "s" is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

[0112] As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and/or alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons (C_{3-10}). Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O) or C(S)). Cycloalkyl groups also include cycloalkylidenes. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl, or adamantyl. In some embodiments, the cycloalkyl has 6-10 ring-forming carbon atoms. In some embodiments, cycloalkyl is adamantyl. Also included in the definition of cycloalkyl are moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, and cyclohexane.

[0113] A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring.

[0114] As used herein, "heteroaryl" refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen, and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl has 5-10 ring atoms and 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl has 5-6 ring atoms and 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some

embodiments, the heteroaryl is a five-membered or six-membereted heteroaryl ring. A five-membered heteroaryl ring is a heteroaryl with a ring having five ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl. A six-membered heteroaryl ring is a heteroaryl with a ring having six ring atoms wherein one or more (e.g., 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

[0115] As used herein, "heterocycloalkyl" refers to non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N, or S. Included in heterocycloalkyl are monocyclic 4-, 5-, 6-, and 7-membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles. Example heterocycloalkyl groups include pyrrolidin-2-on-yl, 1,3-isoxazolidin-2-on-yl, pyranyl, tetrahydropyranyl, oxetanyl, azetidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, and benzazapene. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O), S(O), C(S), or $S(O)_2$). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, etc. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl has 4-10, 4-7 or 4-6 ring atoms with 1 or 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members.

[0116] At certain places, the definitions or embodiments refer to specific rings (e.g., a furan ring, a pyridine ring

[0117] Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For example, an azetidine ring may be attached at any position of the ring, whereas a pyridin-3-yl ring is attached at the 3-position.

[0118] The term "compound" as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

[0119] Compounds provided herein also include tautomeric forms. Tautomeric forms result

from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone - enol pairs, amide - imidic acid pairs, lactam - lactim pairs, enamine - imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

[0120] All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g. hydrates and solvates) or can be isolated.

[0121] In some embodiments, preparation of compounds can involve the addition of acids or bases to affect, for example, catalysis of a desired reaction or formation of salt forms such as acid addition salts.

[0122] Example acids can be inorganic or organic acids and include, but are not limited to, strong and weak acids. Some example acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, *p*-toluenesulfonic acid, 4-nitrobenzoic acid, methanesulfonic acid, benzenesulfonic acid, trifluoroacetic acid, and nitric acid. Some weak acids include acetic acid, propionic acid, butanoic acid, benzoic acid, tartaric acid, pyroglutamic acid, gulonic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, and decanoic acid. Also included are organic diacids such as malonic, fumaric and maleic acid.

[0123] Example bases include lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, and sodium bicarbonate. Some example strong bases include hydroxide, alkoxides, metal amides, metal hydrides, metal dialkylamides and arylamines, wherein; alkoxides include lithium, sodium and potassium salts of methyl, ethyl and t-butyl oxides; metal amides include sodium amide, potassium amide and lithium amide; metal hydrides include sodium hydride, potassium hydride and lithium hydride; and metal dialkylamides include lithium, sodium, and potassium salts of methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *tert*-butyl, trimethylsilyl and cyclohexyl substituted amides.

[0124] In some embodiments, the compounds provided herein, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds provided herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds provided herein, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[0125] The expressions, "ambient temperature" and "room temperature" or "rt" as used herein,

are understood in the art, and refer generally to a temperature, e.g. a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

[0126] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0127] The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (MeCN) are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Science, 66, 2 (1977). Conventional methods for preparing salt forms are described, for example, in Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Wiley-VCH, 2002.

Medical Use

[0128] Provided herein are compounds for use in treating a disease in a subject in need thereof. As used herein, the term "subject," refers to any animal, including mammals. For example, mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human. In some embodiments, the compound for use comprises administering to the subject a therapeutically effective amount of a compound provided herein (e.g., a compound of Formula (Ia)), or a pharmaceutically acceptable salt thereof. In some embodiments, the disease is a disease associated with one or more mRNA splicing defects.

[0129] The present invention further provides a compound for use in treating a disease associated with one or more mRNA splicing defects in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound provided herein

(i.e., a compound of Formula (Ia)). In some embodiments, the disease associated with the one or more mRNA splicing defects is a disease of the central nervous system.

[0130] In some embodiments of the compound for use provided herein, the compound is selected from the group of compounds provided in Table A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is selected from the group of compounds provided in Table A-2, or a pharmaceutically acceptable salt thereof.

[0131] Example diseases of the central nervous system include, but are not limited to, Alzehimer's disease, amyotrophic lateral sclerosis (ALS), attention deficit/hyperactivity disorder (ADHD), atypical cystic fibrosis, autism, autism spectrum disorders, Bell's Palsy, bipolar disorder, catalepsy, Cerebal Palsy, Charcot-Marie-Tooth disease, Charge syndrome, depression, dementia, epilepsy, epileptic encephalopathy, encephalitis, familial dysautomonia (FD), familial isolated growth hormone deficiency type II (IGHD II), Frasier syndrome, frontotemporal dementia and Parkinson's linked to Chromosome 17 (FTDP-17), Huntington's disease, locked-in syndrome, major depressive disorder, Marfan syndrome, meningitis, mental retardation, Menkes Disease (MD), migraine, multiple sclerosis (MS), muscular dystrophies (e.g., Duchenne Muscular Dystrophy, Becker Muscular Dystrophy, Ullrich congenital muscular dystrophy, Asphyxiating thoracic dystrophy, Fukuyama Muscular dystrophy, Spinal muscular atrophy with respiratory distress 1, Congenital Muscular dystrophy 1A, Muscular dystrophy with epidermolysis bullosa, Facioscapulohumeral-like muscular dystrophy), myopathies (e.g., Bethlem myopathy, Collagen VI myopathy, Myotubular myopathy, Nemaline myopathy, Proximal myopathy and learning difficulties, Desmin related Myopathy and Congenital Myopathy with cores), neurofibromatosis 1 (NF1, von Recklinghausen NF; peripheral NF), neurofibromatosis 2 (NF2), occipital horn syndrome, Parkinson's disease, retinoblastoma, Rett syndrome, schizophrenia, tropical spastic paraparesis, Tourette's syndrome, and tuberous sclerosis. In some embodiments, the disease associated with one or more mRNA splicing defects is a disease listed in Table 1.

[0132] In some embodiments, the disease associated with one or more mRNA splicing defects is selected from the group consisting of amyotrophic lateral sclerosis (ALS), atypical cystic fibrosis, autism, autism spectrum disorders, Charcot-Marie-Tooth disease, Charge syndrome, dementia, epilepsy, epileptic encephalopathy, familial dysautonomia (FD), familial isolated growth hormone deficiency type II (IGHD II), Frasier syndrome, frontotemporal dementia and Parkinson's linked to Chromosome 17 (FTDP-17), Huntington's disease, Marfan syndrome, mental retardation, Menkes Disease (MD), muscular dystrophies (e.g., Duchenne Muscular Dystrophy, Becker Muscular Dystrophy, Ullrich congenital muscular dystrophy, Asphyxiating thoracic dystrophy, Fukuyama Muscular dystrophy, Spinal muscular atrophy with respiratory distress 1, Congenital Muscular dystrophy 1A, Muscular dystrophy with epidermolysis bullosa, Facioscapulohumeral-like muscular dystrophy), myopathies (e.g., Bethlem myopathy, Collagen VI myopathy, Myotubular myopathy, Nemaline myopathy, Proximal myopathy and learning difficulties, Desmin related Myopathy and Congenital Myopathy with cores), myotonic dystrophy type 1 (DM1), myotonic dystrophy type 2 (DM2), neurofibromatosis 1 (NF1, von Recklinghausen NF; peripheral NF), occipital horn syndrome, Parkinson's disease,

retinoblastoma, schizophrenia, and tuberous sclerosis.

[0133] In some embodiments, the disease associated with one or more mRNA splicing defects is a disease listed in Table 1; for example, bilateral temporooccipital polymicrogyria; amyotrophic lateral sclerosis; Charcot-Marie-Tooth disease; Yunis-Varon syndrome; juvenile onset Parkinson disease 19; juvenile-onset neurodegeneration with brain iron accumulation; Parkinson disease 8; autosomal recessive spastic paraplegia 43; periventricular heterotopia with microcephaly; X linked mental retardation 46; Coach syndrome; Joubert syndrome 9; Meckel syndrome 6; X linked mental retardation syndromic 15, Cabezas type; X linked mental retardation syndromic, Claes-Jensen type; autosomal dominant mental retardation 1; X linked mental retardation, with cerebellar hypoplasia and distinctive facial appearance; autosomal recessive mental retardation 42; arthrogryposis; hypokalemic periodic paralysis, type 1; malignant hyperthermia susceptibility 5; susceptibility to thyrotoxic periodic paralysis 1; Angelman syndrome-like; early infantile epileptic encephalopathy; Fragile X syndrome; Fragile X-tremor/ataxia syndrome; premature ovarian failure 1; Cornelia de Lange syndrome 5; Wilson-Turner syndrome; Angelman syndrome; neonatal severe encephalopathy; X-linked syndromic, Lubs type mental retardation; X-linked syndromic mental retardation 13; Rett syndrome; preserved speech variant Rett syndrome; X-linked autism susceptibility 3; cerebral creatine deficiency syndrome 1; autosomal dominant mental retardation 5; childhood onset epileptic encephalopathy; epilepsy; Dravet syndrome; primary erythermalgia; familial febrile seizures 3B; autosomal recessive HSAN2D; paroxysmal extreme pain disorder/small fiber neuropathy; Dravet syndrome modifier of epileptic encephalopathy; early infantile 4 and 18; dilated cardiomyopathy 3B; Bethlem myopathy; short-rib thoracic dysplasia 3 with or without polydactyly cardiomyopathy, dilated, 1X; neuronopathy type VI; epidermolysis bullosa simplex with pyloric atresia; epidermolysis bullosa simplex, Ogna type; King-Denborough syndrome; minicore myopathy with external ophthalmoplegia; congnenital neuromuscular disease with uniform type 1 fiber; malignant hyperthermia susceptibility 1; Taylor balloon cell type focal cortical dysplasia; lymphangioleiomyomatosis; tuberous sclerosis-1; somatic lymphangioleiomyomatosis; tuberous sclerosis-2; acromicric dysplasia; ascending and dissection aortic aneurysm; familial ectopia lentis; Mass syndrome; stiff skin syndrome; dominant Weill-Marchesani syndrome 2; somatic bladder cancer; somatic osteosarcoma; retinoblastoma; small cell lung cancer; somatic Charge syndrome; hypogonadotropic hypogonadism 5 with or without anosmia; and, idiopathic scoliosis 3.

[0134] In some embodiments, the disease associated with one or more mRNA splicing defects is selected from familial dysautonomia and neurofibromatosis 1. In some embodiments, the disease associated with one or more mRNA splicing defects is familial dysautonomia. In some embodiments, the disease associated with one or more mRNA splicing defects is neurofibromatosis 1.

[0135] In some embodiments, the one or more mRNA splicing defects is associated with one or more genes comprising at least one exon comprising the nucleotide sequence CAA. In some embodiments, the one or more genes comprising at least one exon comprising the nucleotide sequence CAA is associated with a disease of the central nervous system. In some

embodiments, the one or more genes comprising at least one exon comprising the nucleotide sequence CAA is selected from the group provided in Table 1.

Table 1.

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein (IKBKAP)	NG_008788.1	Dysautonomia, familial	Anderson et al., Am. J. Hum. Genet. 68: 753-758, 2001; Slaugenhaup et al. Am. J., Hum. Genet. 68: 598-605, 2001
SAC domain-containing inositol phosphatase 3 (FIG4)	NG_007977.1	Polymicrogyria, bilateral temporooccipital, Amyotrophic lateral sclerosis 11, Charcot-Marie-Tooth disease, type 4J, Yunis-Varon syndrome	Chow et al Nature 448: 68-72, 2007; Chow et al., Am. J. Hum. Genet. 84: 85-88, 2009; Campeau et al., Am. J. Hum. Genet. 92: 781-791, 2013; Baulac et al., Neurology 82: 1068-1075,2014
DNAJ/HSP40 homology subfamily C member 6 (DNAJC6)	NG_033843.1	Parkinson disease 19, juvenile-onset	Edvardson et al., PLoS One 7: e36458, 2012; Koroglu et al., Parkinsonism Relat. Disord. 19: 320-324, 2013
WD40 repeat-containing protein 45 (WDR45)	NG_033004.1	Neurodegeneration with brain iron accumulation 5	Haack et al., Am. J. Hum. Genet. 91: 1144-1149, 2012; Saitsu et al., Nature Genet. 45: 445-449, 2013.
Leucine-rich repeat kinase 2 (LRRK2)	NG_011709.1	Parkinson disease 8	Zimprich et al., Neuron 44: 601-607, 2004; Tan et al., Hum. Mutat. 31: 561-568, 2010
Leucine-rich repeat- and sterile alpha motif-containing 1	NG_032008.1	Charcot-Marie-Toothe disease, axonal, type 2P	Guernsey et al., PLOS Genet. 6: e1001081, 2010; Nicolaou et al.,

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
(LRSAM1)			Europ. J. Hum. Genet. 21: 190-194,2013
SET-binding factor 2 (SBF2)	NG_008074.1	Charcot-Marie-Tooth disease, type 4B2	Senderek et al., Hum. Molec. Genet. 12: 349-356, 2003; Azzedine et al., Am. J. Hum. Genet. 72: 1141-1153, 2003
Chromosome 10 open reading frame 12 (C19orf12)	NG_031970.1	Spastic paraplegia 43, autosomal recessive; Neurodegeneration with brain iron accumulation 4	Hogarth et al., Neurology 80: 268-275, 2013; Meilleur et al., Neurogenetics 11: 313-318, 2010
ADP-ribosylation factor guanine nucleotide-exchange factor 2 (brefeldin A-inhibited) (ARFGEF2)	NG_011490.1	Periventricular heterotopia with microcephaly	Banne et al., J. Med. Genet. 50: 772-775, 2013
RHO guanine nucleotide exchange factor 6(ARHGEF6)	NG_008873.1	Mental retardation, X-linked 46	Yntema et al., J. Med. Genet. 35: 801-805, 1998; Kutsche et al., Nature Genet. 26: 247-250, 2000
Coiled-coil and C2 domain-containing protein 2A (CC2D2A)	NG_013035.1	COACH syndrome; Joubert syndrome 9; Meckel syndrome 6	Noor et al., DNA Res. 7: 65-73, 2000; Tallila et al., Am. J. Hum. Genet. 82: 1361-1367, 2008; Doherty et al., J. Med. Genet. 47: 8-21,2010
Chromodomain helicase DNA-binding protein 8 (CHD8)	NG_021249.1	Autism, susceptibility	O'Roak et al., Science 338: 1619-1622,2012
Cullin 4b (CUL4B)	NG_009388.1	Mental retardation, X-linked, syndromic 15	Tarpey et al., Nature Genet. 41:

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
		(Cabezas type)	535-543, 2009
Lysine-specific demethylase 5C (KDM5C)	NG_008085.1	Mental retardation, X-linked, syndromic, Claes-Jensen type	Jensen et al., Am. J. Hum. Genet. 76: 227-236, 2005
Methyl-CpG-binding domain protein 5 (MBD5)	NG_017003.1	Mental retardation, autosomal dominant 1	Wagenstaller et al., Am. J. Hum. Genet. 81: 768-779, 2007
Oligophrenin1 (OPHN1)	NG_008960.1	Mental retardation, X-linked, with cerebellar hypoplasia and distinctive facial appearance	Zanni et al., Neurology 65: 1364-1369,2005
Post-GPI attachment to proteins 1 (PGAP1)	NC_000002.12 Range: 196833004..196926995	Mental retardation, autosomal recessive 42	Murakami et al., PLoS Genet. 10: e1004320, 2014
Solute carrier family 9 (sodium/hydrogen exchanger) member 9 (SLC9A9)	NG_017077.1	Autism susceptibility	Morrow et al., Science 321: 218-223,2008
Solute carrier family 35 (UDP-N-acetylglucosamine transporter) member 3 (SLC35A3)	NG_033857.1	Arthrogryposis, mental retardation, and seizures	Edvardson et al., J. Med. Genet. 50: 733-739, 2013.
Calcium channel, voltage-dependent, L Type, alpha-IS subunit (CACNA1S)	NG_009816.1	Hypokalemic periodic paralysis, type 1; Malignant hyperthermia susceptibility 5; Thyrotoxic periodic paralysis, susceptibility to, 1	Ptacek et al., Cell 77: 863-868, 1994; Monnier et al., Am. J. Hum. Genet. 60: 1316-1325, 1997; Kung et al., J. Clin. Endocr. Metab. 89: 1340-1345, 2004
Cyclin-dependent kinase-like 5 (CDKL5)	NG_008475.1	Angelman syndrome-like; Epileptic encephalopathy, early infantile, 2	Van Esch et al., Am. J. Med. Genet. 143A: 364-369,2007; Nemos et al., Clin. Genet. 76: 357-371,2009.
Fragile X mental	NG_007529.1	Fragile X syndrome;	Devys et al.,

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
retardation protein (FMR1)		Fragile X tremor/ataxia syndrome; Premature ovarian failure 1	Nature Genet. 4: 335-340, 1993; Allingham-Hawkins et al., Am. J. Med. Genet. 83: 322-325, 1999; Leehey et al., Arch. Neurol. 60: 117-121, 2003
Histone deacetylase 8 (HDAC8)	NG_015851.1	Cornelia de Lange syndrome 5; Wilson-Turner syndrome	Harakalova et al., J. Med. Genet. 49: 539-543, 2012; Deardorff et al., Nature 489: 313-317, 2012
Methyl-CpG-binding protein 2 (MECP2)	NG_007107.2	Angelman syndrome; Encephalopathy, neonatal severe; Mental retardation, X-linked syndromic, Lubs type; Mental retardation, X-linked, syndromic 13; Rett syndrome; Rett syndrome, preserved speech variant; Autism susceptibility, X-linked 3	Wan et al., Hum. Molec. Genet. 10: 1085-1092, 2001; Xiang et al., J. Med. Genet. 37: 250-255, 2000; Meloni et al., Am. J. Hum. Genet. 67: 982-985, 2000; Watson et al., J. Med. Genet. 38: 224-228, 2001; Carney et al., Pediat. Neurol. 28: 205-211, 2003
Solute carrier family 6 (neurotransmitter transporter creatine) member 8(SLC6A8)	NG_012016.1	Cerebral creatine deficiency syndrome 1	Salomons et al., Am. J. Hum. Genet. 68: 1497-1500, 2001
Synaptic RAS-GTPase-activating protein 1 (SYNGAP1)	NG_016137.1	Mental retardation, autosomal dominant 5	Hamdan et al., Biol. Psychiat. 69: 898-901, 2011
Chromodomain helicase DNA-binding protein 2 (CHD2)	NG_012826.1	Epileptic encephalopathy, childhood-onset	Carvill et al., Nature Genet. 45: 825-830, 2013
Cholinergic receptor, neuronal	NG_011931.1	Epilepsy, nocturnal frontal lobe, 1; Nicotine	Steinlein et al., Nature Genet. 11:

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
nicotinic, alpha polypeptide 4 (CHRNA4)		addiction, susceptibility to	201-203, 1995; Li et al., Hum. Molec. Genet. 14: 1211-1219, 2005
DEP domain-containing protein 5 (DEPDC5)	NG_034067.1	Epilepsy, familial focal, with variable foci	Dibbens et al., Nature Genet. 45: 546-551, 2013
Golgi SNAP receptor complex member 2 (GOSR2)	NG_031806.1	Epilepsy , progressive myoclonic 6	Corbett et al., Am. J. Hum. Genet. 88: 657-663, 2011
Glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2A (GRIN2A)	NG_011812.1	Epilepsy, focal, with speech disorder and with or without mental retardation	Carvill et al., Nature Genet. 45: 1073-1076, 2013
Sodium channel, neuronal type 1, alpha subunit (SCN1A)	NG_011906.1	Dravet syndrome; Epilepsy , generalized, with febrile seizures plus, type 2; Febrile seizures, familial, 3A; Migraine, familial hemiplegic, 3	Baulac et al., Am. J. Hum. Genet. 65: 1078-1085, 1999; Claes et al., Am. J. Hum. Genet. 68: 1327-1332, 2001; Ohmori et al., Biochem. Biophys. Res. Commun. 295: 17-23, 2002
Sodium channel, voltage-gated, type IX, alpha subunit (SCN9A)	NG_012798.1	Epilepsy , generalized, with febrile seizures plus, type 7; Erythermalgia, primary; Febrile seizures, familial, 3B; HSAN2D, autosomal recessive; Paroxysmal extreme pain disorder, Small fiber neuropathy; Dravet syndrome, modifier of	Yang et al., J. Med. Genet. 41: 171-174, 2004; Faber et al., Ann. Neurol. 71: 26-39,2012; Goldberg etal., Clin. Genet. 71: 311-319, 2007; Catterall et al., Neuron 52: 743-749, 2006; Singh et al., PLoS Genet. 5: e1000649, 2009
Syntaxin-binding protein 1 (STXBP1)	NG_016623.1	Epileptic encephalopathy, early infantile, 4	Saitsu et al., Nature Genet. 40: 782-788, 2008
Seizure threshold 2 (SZT2)	NG_029091.1	Epileptic encephalopathy, early	Basel-Vanagaite et al., Am. J. Hum.

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
		infantile, 18	Genet. 93: 524-529, 2013
Dystrophin (DMD)	NG_012232.1	Becker muscular dystrophy; Cardiomyopathy, dilated, 3B; Duchenne muscular dystrophy	Gurvich et al., Hum. Mutat. 30: 633-640, 2009; Muntoni et al., Am. J. Hum. Genet. 56: 151-157, 1995; Daoud et al., Hum. Molec. Genet. 18: 3779-3794, 2009
Collagen type VI, alpha-3 (COL6A3)	NG_008676.1	Bethlem myopathy; Ullrich congenital muscular dystrophy	Demir et al., Am. J. Hum. Genet. 70: 1446-1458, 2002; Lampe et al., J. Med. Genet. 42: 108-120, 2005
Dynein, cytoplasmic 2 heavy chain 1 (DYNC2H1)	NG_016423.1	Short-rib thoracic dysplasia 3 with or without polydactyly	Dagoneau et al., Am. J. Hum. Genet. 84: 706-711, 2009
Fukutin (FKTN)	NG_008754.1	Cardiomyopathy, dilated, IX; Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A4, B4 and C4	Taniguchi-Ikeda et al., 478: 127-131,2011
Immunoglobin 2 MU-binding protein2 (IGHMBP2)	NG_007976.1	Charcot-Marie-Tooth disease, axonal, type 2S; Neuronopathy, distal hereditary motor, type VI	Grohmann et al., Nature Genet. 29: 75-77, 2001; Cottenie et al., Am. J. Hum. Genet. 95: 590-601, 2014
Laminin alpha-2 (LAMA2)	NG_008678.1	Muscular dystrophy, congenital merosin-deficient; Muscular dystrophy, congenital, due to partial LAMA2 deficiency	Tezak et al., Hum. Mutat. 21: 103-111, 2003; Oliveira et al., Clin. Genet. 74: 502-512, 2008
Myotubularin 1 (MTM1)	NG_008199.1	Myotubular myopathy, X-linked	Tanner et al., Hum. Mutat. 11: 62-68, 1998
Nebulin (NEB)	NG_009382.2	Nemaline myopathy 2,	Donner et al.,

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
		autosomal recessive	Europ. J. Hum. Genet. 12: 744-751, 2004; Lehtokari et al., Hum. Mutat. 27: 946-956, 2006
Plectin (PLEC)	NG_012492.1	Epidermolysis bullosa simplex with pyloric atresia; Epidermolysis bullosa simplex, Ogna type; Muscular dystrophy with epidermolysis bullosa simplex; Muscular dystrophy, limb-girdle, type 2Q	Pulkkinen et al., Hum. Molec. Genet. 5: 1539-1546, 1996; Pfendner et al., J. Invest. Derm. 124: 111-115, 2005
Mitochondrial calcium uptake protein 1 (MICU1)	NG_033179.1	Myopathy with extrapyramidal signs	Logan et al., Nature Genet. 46: 188-193, 2014
Structural maintenance of chromosomes flexible hinge domain-containing protein 1 (SMCHD1)	NG_031972.1	Fascioscapulohumeral muscular dystrophy 2, digenic	Lemmers et al., Nature Genet. 44: 1370-1374, 2012
Desmin (DES)	NG_008043.1	Muscular dystrophy, limb-girdle, type 2R; Cardiomyopathy, dilated, 1I; Myopathy, myofibrillar, 1; Scapuloperoneal syndrome, neurogenic, Kaeser type	Dalakas et al., New Eng. J. Med. 342: 770-780,2000; Li et al., Circulation 100: 461-464, 1999; Walter et al., Brain 130: 1485-1496, 2007; Cetin et al., J. Med. Genet. 50: 437-443, 2013
Ryanodine receptor 1 (RYR1)	NG_008866.1	Central core disease; King-Denborough syndrome; Minicore myopathy with external ophthalmoplegia; Neuromuscular disease, congenital, with uniform type 1 fiber; Malignant	Sambuughin et al., Am. J. Hum. Genet. 69: 204-208, 2001; Tilgen et al., Hum. Molec. Genet. 10: 2879-2887, 2001; Monnier et al., Hum. Molec.

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
		hyperthermia susceptibility 1	Genet. 12: 1171-1178, 2003; D'Arcy et al., Neurology 71: 776-777, 2008
Hamartin(TSC1)	NG_012386.1	Focal cortical dysplasia, Taylor balloon cell type; Lymphangioleiomyomatosis; Tuberous sclerosis-1	Iyer et al., Science 338: 222, 2012; Becker et al., Ann. Neurol. 52: 29-37,2002; Jones et al., Hum. Molec. Genet. 6: 2155-2161, 1997
Tuberin (TSC2)	NG_005895.1	Lymphangioleiomyomatosis, somatic; Tuberous sclerosis-2	Carbonara et al., Genes Chromosomes Cancer 15: 18-25, 1996; Carsillo et al., Proc. Nat. Acad. Sci. 97: 6085-6090, 2000
Fibrillin 1 (FBN1)	NG_008805.2	Acromicric dysplasia; Aortic aneurysm, ascending, and dissection; Ectopia lentis, familial; Marfan syndrome; MASS syndrome; Stiff skin syndrome; Weill-Marchesani syndrome 2, dominant	Dietz et al., Nature 352: 337-339, 1991; Faivre et al., J. Med. Genet. 40: 34-36, 2003; Loeys et al., Sci. Transl. Med. 2: 23ra20, 2010; Le Goff et al., Am. J. Hum. Genet. 89: 7-14, 2011
Retinoblastoma 1 (RB1)	NG_009009.1	Bladder cancer, somatic; Osteosarcoma, somatic; Retinoblastoma; Retinoblastoma, trilateral; Small cell cancer of the lung, somatic	Yandell et al., New Eng. J. Med. 321: 1689-1695, 1989; Harbour et al., Science 241: 353-357, 1988
Chromodomain helicase DNA-binding protein 7 (CHD7)	NG_007009.1	CHARGE syndrome; Hypogonadotropic hypogonadism 5 with or without anosmia; Scoliosis, idiopathic 3	Lalani et al., Am. J. Hum. Genet. 78: 303-314, 2006; Kim et al., Am. J. Hum. Genet. 83:

Human Gene Name	GeneBank Acc. No. for Human Gene	Associated Diseases	References
			511-519, 2008; Gao et al., Am. J. Hum. Genet. 80: 957-965, 2007; Felix et al., Am. J. Med. Genet. 140A: 2110-2114, 2006; Pleasance et al., Nature 463: 184-190, 2010

[0136] In some embodiments, the one or more mRNA splicing defects is associated with one or more genes selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1, PGAP1, SLC9A9, SLC35A3, CACNA1S, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD7. In some embodiments, the one or more mRNA splicing defects is associated with one or more genes selected from the group provided in Table 1; in some embodiments, the mRNA splicing defect causes or contributes to a disease listed in Table 1.

[0137] The present invention further provides a compound for use in improving mRNA splicing of a gene, e.g., in a cell or a subject, e.g., in a cell or a subject who has an mRNA splicing defect, e.g., a genetic mutation associated with an mRNA splicing defect or a disease associated with an mRNA splicing defect. In some embodiments, the gene comprises at least one exon comprising the nucleotide sequence CAA. In some embodiments, the compound for use in improving mRNA splicing of a gene comprises contacting the gene (e.g., in a cell or subject expressing the gene) with a compound provided herein (e.g., a compound of Formula (Ia)). In some embodiments, the compound for use in improving mRNA splicing of a gene comprises contacting a gene (e.g., a cell expressing a gene) selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1, PGAP1, SLC9A9, SLC35A3, CACNA1S, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD7 with a compound provided herein (e.g., a compound of Formula (Ia)); in some embodiments, the cell has an mRNA splicing defect in processing transcripts from the gene, e.g., the cell has a mutation that causes a mRNA splicing defect in processing transcripts from the gene. In some embodiments, the compound for use in improving mRNA splicing of a gene comprises improving exon inclusion (e.g., wherein the

mRNA splicing defect results in aberrant exon exclusion when compared to a wild-type cell or mRNA).

[0138] In some embodiments, the compound for use in improving mRNA splicing of a gene comprises improving exon inclusion, wherein the gene is selected from the group consisting of BMP2K, ABI2, IKBKAP, FIG4, DNAJC6, WDR45, LRRK2, LRSAM1, SBF2, C19orf12, ARFGEF2, ARHGEF6, CC2D2A, CHD8, CUL4B, KDM5C, MBD5, OPHN1, PGAP1, SLC9A9, SLC35A3, CACNAIS, CDKL5, FMR1, HDAC8, MECP2, SLC6A8, SYNGAP1, CHD2, CHRNA4, DEPDC5, GOSR2, GRIN2A, SCN1A, SCN9A, STXBP1, SZT2, DMD, COL6A3, DYNC2H1, FKTN, IGHMBP2, LAMA2, MTM1, NEB, PLEC, MICU1, SMCHD1, DES, RYR1, TSC1, TSC2, FBN1, RB1, and CHD. In some embodiments, the compound for use in improving mRNA splicing of a gene comprises improving exon inclusion, wherein the gene is selected from the group provided in Table 1.

[0139] In some embodiments, contacting the gene is performed in vitro. In some embodiments, contacting the gene is performed in vivo, e.g., in a subject who has a disease described herein and/or listed in Table 1.

[0140] In some embodiments, the compound (i.e., a compound of Formula (Ia)) for use described herein may be used in combination with one or more of the compounds provided and described in the present disclosure.

[0141] As used herein, the expression "EC_k" refers to the compound concentration at which the maximum kinetin efficacy (200 μM) is reached.

[0142] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. In some embodiments, the dosage of the compound, or a pharmaceutically acceptable salt thereof, administered to a subject or individual is about 1 mg to about 2 g, about 1 mg to about 1000 mg, about 1 mg to about 500 mg, about 1 mg to about 100 mg, about 1 mg to 50 mg, or about 50 mg to about 500 mg.

[0143] As used herein, the term "treating" or "treatment" refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease or reducing or alleviating one or more symptoms of the disease.

[0144] Also provided herein are compound for use in increasing *IKAP* protein expression, the use comprising administering an effective amount of a compound provide herein, (*i.e.*, a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof), to the patient. For example, such uses include increasing *IKAP* protein expression in serum samples from the patient. Further provided herein are compound for use in increasing the mean percentage of *IKAP* protein expression in a patient in need thereof, the use comprising administering an effective amount of a compound provided herein *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, to the patient.

[0145] Also provided herein are compound for use in increasing *IKAP* protein expression in a cell *(e.g., ex vivo* or *in vivo),* the use comprising contacting the cell with a therapeutically effective amount of a compound provided herein, *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof). In some embodiments the use is an *in vitro* use . In some embodiments, the use is an *in vivo* use . In some embodiments, the amount *IKAP* protein expression is increased in a cell selected from the group consisting of a lung cell, a muscle cell, a liver cell, a heart cell, a brain cell, a kidney cell, and a nerve cell *(e.g.,* a sciatic nerve cell or a trigeminal nerve cell), or any combination thereof. In some embodiments thereof, the amount *of IKAP* protein expression is increased in the plasma.

[0146] Also provided herein are compound for use in increasing *IKAP* protein level in a patient in need thereof, the use comprising administering an effective amount of a compound provide herein, *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof), to the patient. For example, such uses include increasing *IKAP* protein level in serum samples from the patient. Further provided herein are uses for increasing the mean percentage of *IKAP* protein level in a patient in need thereof, the use comprising administering an effective amount of a compound provided herein *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, to the patient.

[0147] Also provided herein are compound for use in increasing *IKAP* protein level in a cell *(e.g., ex vivo* or *in vivo),* the use comprising contacting the cell with a therapeutically effective amount of a compound provided herein, *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof). In some embodiments the use is an *in vitro* use . In some embodiments, the use is an *in vivo* use . In some embodiments, the amount *IKAP* protein level is increased in a cell selected from the group consisting of a lung cell, a muscle cell, a liver cell, a heart cell, a brain cell, a kidney cell, and a nerve cell *(e.g.,* a sciatic nerve cell or a trigeminal nerve cell), or any combination thereof. In some embodiments thereof, the amount of *IKAP* protein level is increased in the plasma.

[0148] Also provided herein are compound for use in increasing WT *IKBKAP* mRNA in a patient in need thereof, the use comprising administering an effective amount of a compound provide herein, *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof), to the patient. For example, such uses include increasing WT *IKBKAP* mRNA concentration in serum samples from the patient. Further provided herein are uses for

increasing the mean percentage exon inclusion (i.e. the percentage of correctly spliced or WT *IKBKAP* mRNA) in a patient in need thereof, the use comprising administering an effective amount of a compound provided herein (*i.e.*, a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof, to the patient.

[0149] In some embodiments, WT *IKBKAP* mRNA can be measured in the serum, for example, in blood samples obtained from the patient prior to administration of a compound as provided herein and in blood samples obtained from the patient following administration of a compound as provided herein. In some embodiments, the blood samples obtained from the patient following administration are obtained after one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, ten days, fourteen days, twenty-one days, twenty-eight days, and/or thirty days of administration of the compound as provided herein. See, for example, F.B. Axelrod et al., Pediatr Res (2011) 70(5): 480-483; and R.S. Shetty et al., Human Molecular Genetics (2011) 20(21): 4093-4101.

[0150] Further provided herein is a compound for use in increasing WT *IKBKAP* mRNA in a cell, the use comprising contacting the cell with a therapeutically effective amount of a compound provided herein *(i.e.,* a compound of Formula (Ia)). The amount of WT *IKBKAP* mRNA in the treated cell is increased relative to a cell in a subject not administered a compound provided herein. The compound for use in increasing the amount of WT *IKBKAP* mRNA in a cell may be performed by contacting the cell with a compound provided herein *(i.e.,* a compound of Formula (Ia), or a pharmaceutically acceptable salt form thereof), *in vitro,* thereby increasing the amount WT *IKBKAP* mRNA of a cell *in vitro.* Uses of such an *in vitro* use of increasing the amount of WT *IKBKAP* mRNA include, but are not limited to, use in a screening assay (for example, wherein a compound provided herein is used as a positive control or standard compared to a compound or compounds of unknown activity or potency in increasing the amount WT *IKBKAP* mRNA). In some embodiments, the amount of WT *IKBKAP* mRNA is increased in a cell selected from the group consisting of a lung cell, a muscle cell, a liver cell, a heart cell, a brain cell, a kidney cell, and a nerve cell *(e.g.,* a sciatic nerve cell or a trigeminal nerve cell), or any combination thereof. In some embodiments thereof, the amount of WT *IKBKAP* mRNA is increased in the plasma.

[0151] The compound for use in increasing WT *IKBKAP* mRNA in a cell may be performed, for example, by contacting a cell, *(e.g.,* a lung cell, a muscle cell, a liver cell, a heart cell, a brain cell, a kidney cell, or a nerve cell), with a compound provided herein (*i.e.* a compound of Formula (Ia), or a pharmaceutically acceptable salt thereof), *in vivo,* thereby increasing the amount of WT *IKBKAP* mRNA in a subject *in vivo.* The contacting is achieved by causing a compound provided herein, or a pharmaceutically acceptable salt form thereof, to be present in a subject in an amount effective to achieve an increase in the amount of WT *IKBKAP* mRNA. This may be achieved, for example, by administering an effective amount of a compound provided herein, or a pharmaceutically acceptable salt form thereof, to a subject. Uses of such an *in vivo* use of increasing the amount of WT *IKBKAP* mRNA include, but are not limited to, use in uses of treating a disease or condition, wherein an increase in the amount of WT *IKBKAP* mRNA is beneficial. In some embodiments thereof, the amount of WT *IKBKAP* mRNA

is increased in a cell selected from the group consisting of a lung cell, a muscle cell, a liver cell, a heart cell, a brain cell, a kidney cell, and a nerve cell *(e.g.,* a sciatic nerve cell or a trigeminal nerve cell), or any combination thereof, for example in a patient suffering from a disease or disorder provided herein (*e.g.*, familial dysautonomia or neurofibromatosis 1). The use is preferably performed by administering an effective amount of a compound provided herein, or a pharmaceutically acceptable salt form thereof, to a subject who is suffering from familial dysautonomia or neurofibromatosis 1.

Combination Therapies

[0152] In some embodiments, one or more of the compounds provided herein may be administered to a subject in need thereof in combination with at least one additional pharmaceutical agent. In some embodiments, the additional pharmaceutical agent is a compound provided herein (e.g., a compound of Formula (Ia)).

[0153] Additional examples of suitable additional pharmaceutical agents for use in combination with the compounds of the present invention for treatment of the diseases provided herein include, but are not limited to, antioxidants, anti-inflammatory agents, steroids, immunosuppressants, or other agents such as therapeutic antibodies. In some embodiments, the compounds provided herein may be administered to a subject in need thereof in combination with at least one additional pharmaceutical agent for the treatment of familial dysautonomia. In some embodiments, the additional pharmaceutical agent is phosphatidylserine.

Pharmaceutical Compositions and Formulations

[0154] When employed as pharmaceuticals, the compounds provided herein can be administered in the form of pharmaceutical compositions; thus, the uses described herein can include administering the pharmaceutical compositions. These compositions can be prepared as described herein or elsewhere, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral, or parenteral. Parenteral administration may include, but is not limited to intravenous, intraarterial, subcutaneous, intraperitoneal, intramuscular injection or infusion; or intracranial, (e.g., intrathecal, intraocular, or intraventricular) administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. In some embodiments, the compounds provided herein are suitable for oral and parenteral administration. In some embodiments, the compounds provided herein are suitable for oral administration. In some embodiments, the compounds provided herein are suitable for

parenteral administration. In some embodiments, the compounds provided herein are suitable for intravenous administration. In some embodiments, the compounds provided herein are suitable for transdermal administration (e.g., administration using a patch or microneedle). Pharmaceutical compositions for topical administration may include transdermal patches (e.g., normal or electrostimulated), ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

[0155] Also provided are pharmaceutical compositions which contain, as the active ingredient, a compound provided herein (e.g., a compound of Formula (Ia)), or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

[0156] Some examples of suitable excipients include, without limitation, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include, without limitation, lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; flavoring agents, or combinations thereof.

[0157] The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered and the schedule of administration will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual subject, or the severity of the subject's symptoms.

Kits

[0158] Also described herein are kits including a compound provided herein, more particularly to a compound of Formula (Ia) , or a pharmaceutically acceptable salt thereof. In some embodiments, a kit can include one or more delivery systems, *e.g.*, for a compound provided herein, or a pharmaceutically acceptable salt thereof, and directions for use of the kit (*e.g.*, instructions for treating a subject). In some embodiments, a kit can include a compound provided herein, or a pharmaceutically acceptable salt thereof, and one or more additional

agents as provided herein.

[0159] In some embodiments, the compound is selected from the group of compounds provided in Table A, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is selected from the group of compounds provided in Table A-2, or a pharmaceutically acceptable salt thereof.

[0160] In some embodiments, the kit can include one or more compounds or additional pharmaceutical agents as provided herein, or a pharmaceutically acceptable salt thereof, and a label that indicates that the contents are to be administered to a subject resistant to a standard of care agent or adjuvant used for the treatment of familial dysautonomia or neurofibromatosis 1. In some embodiments, the additional pharmaceutical agent is phosphatidylserine. In another embodiment, the kit can include a compound provided herein, or a pharmaceutically acceptable salt thereof, and a label that indicates that the contents are to be administered to a subject with cells expressing abnormal WT *IKBKAP* mRNA splicing. In another embodiment, the kit can include one or more compounds or additional pharmaceutical agents as provided herein, or a pharmaceutically acceptable salt thereof, and a label that indicates that the contents are to be administered to a subject having a disease of the central nervous system resulting from abnormal mRNA splicing. In another embodiment, the kit can include one or more compounds or additional pharmaceutical agents as provided herein, or a pharmaceutically acceptable salt thereof, and a label that indicates that the contents are to be administered to a subject having familial dysautonomia or neurofibromatosis 1. In some embodiments, a kit can include one or more compounds as provided herein, or a pharmaceutically acceptable salt thereof, and a label that indicates that the contents are to be administered with one or more additional pharmaceutical agents as provided herein.

EXAMPLES

[0161] The invention is further described in the following examples.

General Methods

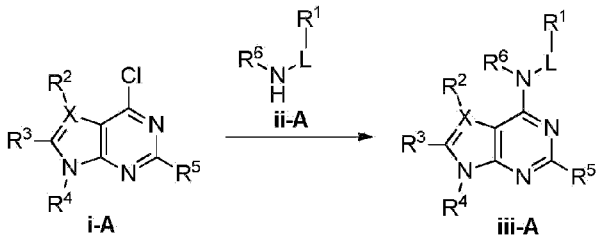
[0162] All reactions were performed under a dry atmosphere of nitrogen unless otherwise specified. Indicated reaction temperatures refer to the reaction bath, while room temperature (rt) is noted as 25 °C. Commercial grade reagents and anhydrous solvents were used as received from vendors and no attempts were made to purify or dry these components further. Removal of solvents under reduced pressure was accomplished with a Buchi rotary evaporator at approximately 28 mm Hg pressure using a Teflon-linked KNF vacuum pump. Thin layer chromatography was performed using 1" × 3" AnalTech No. 02521 silica gel plates with fluorescent indicator. Visualization of TLC plates was made by observation with either short wave UV light (254 nm lamp), 10% phosphomolybdic acid in ethanol or in iodine vapors.

Preparative thin layer chromatography was performed using Analtech, 20 × 20 cm, 1000 micron preparative TLC plates. Flash column chromatography was carried out using a Teledyne Isco CombiFlash Companion Unit with RediSep®Rf silica gel columns. If needed, products were purified by reverse phase chromatography, using a Teledyne Isco CombiFlash Companion Unit with RediSep®Gold C18 reverse phase column. Proton NMR spectra were obtained either on 300 MHz Bruker Nuclear Magnetic Resonance Spectrometer or 500 MHz Bruker Nuclear Magnetic Resonance Spectrometer and chemical shifts Bruker Nuclear Magnetic Resonance Spectrometer and chemical shifts (δ are reported in parts per million (ppm) and coupling constant (*J*) values are given in Hz, with the following spectral pattern designations: s, singlet; d, doublet; t, triplet, q, quartet; dd, doublet of doublets; m, multiplet; br, broad. Tetramethylsilane was used as an internal reference. Melting points are uncorrected and were obtained using a MEL-TEMP Electrothermal melting point apparatus. Mass spectroscopic analyses were performed using positive mode electron spray ionization (ESI) on a Varian ProStar LC-MS with a 1200L quadrapole mass spectrometer. High pressure liquid chromatography (HPLC) purity analysis was performed using a Varian Pro Star HPLC system with a binary solvent system A and B using a gradient elusion [A, H_2O with 0.1% trifluoroacetic acid (TFA); B, CH_3CN with 0.1% TFA] and flow rate = 1 mL/min, with UV detection at 254 nm. All final compounds were purified to ≥95% purity by the Varian Pro Star HPLC system using the following methods:

1. A) Phenomenex Luna C18(2) column (4.60 × 250 mm); mobile phase, A = H_2O with 0.1% TFA and B = CH_3CN with 0.1% TFA; gradient: 10-100% B (0.0-20.0 min); UV detection at 254 nm.
2. B) Phenomenex Luna C18(2) column (4.60 × 250 mm); mobile phase, A = H_2O with 0.1% TFA and B = CH_3CN with 0.1% TFA; gradient: 10-95% B (0.0-10.0 min); hold 95% B (6.0 min); UV detection at 254 nm.

Example 1. General Procedure A

[0163]

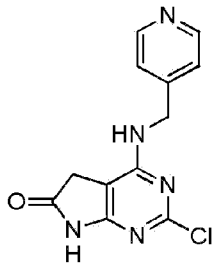


[0164] A mixture of the desired pyrrolopyrimidine or purine **i-A** (1 equiv), desired aminomethyl heterocycle or benzylamine **ii-A** (1.1 equiv), and triethylamine (NEt_3) or diisopropylethylamine

(DIPEA) (1.5-3.5 equiv) in a suitable solvent (*e.g.*, 1,4-dioxane, THF, EtOH, n-BuOH) was stirred at 50-150 °C in a reaction flask or sealed tube until the reaction was complete by LC-MS and/or TLC analysis. Following completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic extract was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (typical eluents included, for example, a mixture of hexanes and EtOAc, or a mixture of CH_2Cl_2 and MeOH, or an 80:18:2 mixture of CH_2Cl_2/CH_3OH/concentrated NH_4OH) to afford the desired product **iii-A.** The product structures prepared according to General Procedure **A** were confirmed by ^1H NMR and/or by mass analysis.

Example 18. 2-chloro-4-((pyridin-4-ylmethyl)amino)-5H-pyrrolo [2,3-d] pyrimidin-6(7H)-one

[0165]



(257)

[0166] A mixture of 2,4-dichloro-5H-pyrrolo[2,3-d]pyrimidin-6(7H)-one (29.5 mg, 0.145 mmol), 4-(aminomethyl)pyridine (18.6 mg, 0.172 mmol) and DIPEA (0.04 mL, 0.23 mmol) in 1,4-dioxane (1.2 mL) was heated in a sealed tube at 60 °C for 6.5 h, then cooled to room temperature. The mixture was immediately concentrated and the crude residue was purified by chromatography on silica gel (gradient 0-100% CMA in dichloromethane). The isolated product was dissolved in acetonitrile/water, frozen and lyophilized to afford the title compound (5.0 mg, 93%) as an off-white solid: ESI MS $[M+H]^+$ *m/z* 276; ^1H NMR (300 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 8.48 (dd, *J* = 1.6, 4.4 Hz, 2H), 8.09 (br s, 1H), 7.26 (d, *J* = 5.7 Hz, 2H), 4.47 (d, *J* = 6.2 Hz, 2H), 3.41 (s, 2H).

[0167] Table 2 shows a list of representative compounds that were prepared using the methods described herein and characterized via mass spectrometry.

Table 2.

Cpd No.	m/z	Cpd No.	m/z	Cpd No.	m/z
		(143)	341		

Cpd No.	m/z	Cpd No.	m/z	Cpd No.	m/z
		(145)	272		
		(147)	305		
		(148)	291		
		(150)	295		
		(151)	285		
		(152)	284		
		(153)	334		
		(154)	307		
		(155)	321		
		(156)	289		
		(158)	293		
		(159)	281		
		(160)	345		
		(161)	320		
		(163)	299		
		(165)	292		
		(166)	293		
		(167)	307		
		(168)	346		
		(170)	279		
		(172)	306		
		(173)	332		
		(174)	261		
		(176)	261		
		(177)	292		
		(178)	250	(350)	260
		(180)	306		

Cpd No.	m/z	Cpd No.	m/z	Cpd No.	m/z
		(181)	292	(353)	261
		(182)	333	(354)	277
		(183)	332	(355)	260
		(186)	307		
		(187)	306	(359)	274
		(188)	275	(360)	262
		(188)	292	(361)	261
		(189)	274		
		(190)	346	(363)	280
		(191)	307	(364)	280
		(192)	312		
		(193)	306		
		(194)	306		
		(195)	320		
		(197)	374	(369)	274
(55)	249				
		(200)	414	(372)	266
		(201)	292	(373)	266
		(203)	334		
		(204)	293		
		(205)	283		
		(206)	320		
		(207)	294	(379)	250
		(208)	300	(380)	244
		(210)	295		
		(211)	327		
		(212)	329		
		(213)	306		
		(215)	316		
		(216)	302		

Cpd No.	m/z	Cpd No.	m/z	Cpd No.	m/z
		(219)	321		
		(221)	336		
		(223)	272		
(77)	293				
		(226)	278		
		(228)	294		
(81)	267				
(84)	263				
(86)	325				
(89)	326				
		(237)	290		
(94)	307				
(100)	260	(246)	331		
(101)	289				
		(248)	276		
(105)	307				
(106)	303	(252)	307		
(107)	266				
(108)	307				

Cpd No.	m/z	Cpd No.	m/z	Cpd No.	m/z
(109)	279				
(110)	261				
(111)	311				
(112)	279				
(114)	278	(263)	274		
(115)	263				
(116)	284				
(117)	321				
(119)	274			(487)	278
(120)	274				
(121)	318				
(122)	304				
(123)	280				
(125)	324				
(126)	275			(494)	278
(127)	305			(495)	278
(128)	319				
(130)	326			(498)	267
(132)	331				
				(501)	267
(135)	322				
(136)	300				
(136)	275				
(137)	308				
(138)	323				
(139)	331				

Cpd No.	m/z	Cpd No.	m/z	Cpd No.	m/z

Example 44. Primary Splicing Assay

[0168] The primary splicing assay was carried out using human embryonic kidney 293T (HEK293T) routinely maintained in Dulbecco's Modified Eagle's media (DMEM) (GIBCO ref. 11995-065). The media was supplemented with 2 mM L-glutamine, 1% penicillin/streptomycin and 10% fetal bovine serum (SIGMA cat. 12306C). Splicing analysis was made possible by using an FD (familial dysautomonia) *IKBKAP* minigene which contained exon 19 through exon 21, including intervening introns, and also the T->C Thymine to cytosine transition located 6 base-pairs from the end of *IKBKAP* exon 20; See SEQ ID NO:3 for the complete sequence of plasmid pcDNA3.1/V5HisTOPO with Renilla-Familial Dysautonomia minigene-Firefly. Firefly luciferase (SEQ ID NO:14) was utilized as a splicing reporter, located downstream of exon 21, and Renilla luciferase (SEQ ID NO:13) was used as a control, located upstream of exon 19. The sequence of exon 19 is presented as SEQ ID NO:7; the Intron between Exon 19 and Exon 20 is SEQ ID NO:8; exon 20 is SEQ ID NO:9; the intron between Exon 19 and Exon 20 is SEQ ID NO:10; exon 21 is SEQ ID NO:11, and the spliced sequence of exons 19-20-21 is SEQ ID NO:12. HEK293T cells were plated in a 6-well plate 24 hours prior to transfection. Transfection was carried out using a mixture of Opti-MEM (GIBCO ref. 31985), *IKBKAP* minigene, and Fugene HD (PROMEGA ref. E2311), incubated in DMEM media containing HEK293T cells at 37 °C. The ratio of Opti-MEM, minigene, and Fugene was kept at approximately 9:1.5:1, with a total volume of 150 µL of transfection mixture applied per well.

[0169] After 4 hours of transfection, the cells were then plated in a 96-well plate coated with poly-L-lysine (SIGMA cat.P4707) for treatment scheduled 24 hours later. Treatment with compounds was performed at 8 concentrations, each diluted in PBS with a final DMSO concentration of 0.5%. After 24 hours of treatment, cells were washed in the poly-L-lysine coated 96-well plate using PBS and subsequently harvested using Passive Lysis Buffer (Promega cat.E196). Cell lysate was transferred to a black and white 96-well plate and analyzed for splicing correction using a Glomax luminometer (PROMEGA GloMax® 96 Microplate Luminometer w/Dual Injectors cat.E6521) and Promega Dual Glo Firefly and Stop and Glo Renilla reagents (Cat.E196). The compound's ability to correct splicing and promote exon 20 inclusion was marked by an increase in Firefly signal. Renilla signal, which is independent of exon 20 inclusion, was used to correct for cell number. Using the ratio of Firefly to Renilla signal, a dose response curve was produced, which referenced kinetin and DMSO Firefly/Renilla ratios as positive and negative controls, respectively.

[0170] Table 3 shows EC_k data for representative compounds (Cpd #) tested in the Primary Assay and Table 4 shows the max efficacy (E_{max}, %) for representative compounds (Cpd #) tested in the Primary Assay.

Table 3.

Cpd #	EC_k (μM)		Cpd #	EC_k (μM)		Cpd #	EC_k (μM)
			(205)	6.41			
			(207)	75.80			
			(208)	107.00			
			(210)	69.20			
			(211)	7.73			
(55)	1.71						
			(226)	1.80			
(77)	1-10 (RT-PCR)[b]						
(81)	3.08		**(228)**	15.65			
(84)	1-10 (RT-PCR)[a]						
(94)	10-31.6 (RT-PCR)[a]						
(100)	2.18						
(105)	10.36/ Firefly only[c]						
(107)	4.58/ Firefly only[c]						
(109)	12.16/ Firefly only[c]						
(110)	4.92/ Firefly only[c]						
(111)	9.3 / Firefly only[c]						
(112)	5.33/ Firefly only[c]						
(114)	6.59/ Firefly only[c]						
(115)	5.92					**(372)**	3.71
(116)	31.80						

Cpd #	EC_k (μM)		Cpd #	EC_k (μM)		Cpd #	EC_k (μM)
(119)	11.20					**(380)**	4.38
(120)	2.75						
(121)	17.30						
(122)	5.65						
(123)	4.90		**(263)**	27.40			
(125)	6.52						
(126)	4.73						
(127)	5.45						
(128)	15.45						
(130)	8.90						
(135)	9.06						
(136)	7.52						
(137)	7.25						
(138)	12.75						
(150)	1-10 (RT-PCR)[a]						
(154)	22.25						
(155)	22.25[a]					**(487)**	6.1
(156)	15.80						
(158)	13.40						
(159)	1-10 (RT-PCR)[a]						
(170)	49.55						
(181)	8.40						
(188)	11.70						

Cpd #	EC_k (μM)		Cpd #	EC_k (μM)		Cpd #	EC_k (μM)
(191)	5.92						
(192)	7.13						
(194)	4.49						

[a] Firefly inhibitor
[b] Renilla interference
[c] Renilla interference / Firefly only

Table 4.

Cpd #	E_{max} (%)		Cpd #	E_{max} (%)		Cpd #	E_{max} (%)
			(190)	68			
			(191)	231			
			(192)	210			
			(194)	241			
			(195)	81			
			(196)	7			
			(197)	14			
			(200)	11			
			(201)	27			
			(203)	27.00[a]			
			(204)	27			
			(205)	27			
			(206)	27			
			(207)	109			
			(208)	83			
			(209)	176			
			(210)	104			
			(211)	204			
			(212)	71			
			(213)	36			
(55)	173		**(214)**	197		**(350)**	49.5

Cpd #	E_{max} (%)		Cpd #	E_{max} (%)		Cpd #	E_{max} (%)
			(216)	16			
			(217)	151			
			(218)	154		**(353)**	78
			(220)	153		**(354)**	57.5
			(221)	86		**(355)**	26
			(222)	146			
			(223)	95		**(359)**	31.5
						(360)	12.3
						(361)	9.8
			(226)	191			
(77)	321 (RT-PCR)[b]					**(363)**	53.2
			(228)	152		**(364)**	18.2
(84)	250.6 (RT-PCR)[a]						
(86)	29						
						(369)	57.8
(89)	21						
						(372)	125.5
			(237)	21		**(373)**	25.1
(94)	180.1 (RT-PCR)[a]						
(100)	235						
						(379)	95
						(380)	108
(105)	134.5 / Firefly only[c]						
(106)	14		**(246)**	22			
(107)	183.5/ Firefly only[c]						
(108)	172 (RT-PCR)[a]		**(248)**	10			
(109)	128/ Firefly only[c]						

Cpd #	E_{max} (%)		Cpd #	E_{max} (%)		Cpd #	E_{max} (%)
(110)	193 / Firefly only[c]						
(111)	191 / Firefly only[c]						
(112)	110.85 / Firefly only[c]		**(252)**	43			
(114)	174/ Firefly only[c]						
(115)	174						
(116)	112						
(117)	23						
(119)	114						
(120)	166						
(121)	189						
(122)	256						
(123)	92		**(263)**	105			
(125)	225						
(126)	155						
(127)	264						
(128)	155						
(130)	201						
(132)	67.7 (RT-PCR)[a]						
(135)	194						
(136)	143						
(137)	214						
(138)	174						
(139)	52.2 (RT-PCR)[a]						
(143)	24						

Cpd #	E_{max} (%)		Cpd #	E_{max} (%)		Cpd #	E_{max} (%)
(145)	59						
(147)	80						
(148)	62						
(150)	320 (RT-PCR)[a]						
(151)	73						
(152)	35						
(153)	20						
(154)	151						
(155)	151[a]						
(156)	73						
(158)	20						
(159)	228[a]						
(160)	85						
(161)	65					**(487)**	114.2
(163)	35						
(164)	68						
(165)	59						
(166)	80						
(167)	37						
(168)	54					**(494)**	14.1
(170)	92					**(495)**	13.9
(172)	61						
(173)	30					**(498)**	37.7
(174)	37						
(176)	48					**(501)**	18.1
(177)	60						
(178)	76						
(180)	28						
(181)	122						

Cpd #	E_{max} (%)		Cpd #	E_{max} (%)		Cpd #	E_{max} (%)
(182)	20						
(186)	17						
(187)	111						
(188)	145						
(189)	33						

[a] Firefly inhibitor
[b] Renilla interference
[c] Renilla interference / Firefly only

Example 45. Secondary Assay

[0171] Compounds with an EC_K < 2 µM in the primary assay (see Example 44) were used in a secondary assay to treat FD fibroblast. The splicing analysis of *IKBKAP* in the FD fibroblast was used to validate the results of the most potent compounds obtained with the primary assay *in vitro.* FD fibroblasts GM04663 were purchased from the Coriell Cell Repository and were grown in Dulbecco's Modified Eagle's media (DMEM) (GIBCO ref.11995-065). The media was supplemented with 2 mM L-glutamine, 1% penicillin/streptomycin and 10% fetal bovine serum (SIGMA cat.12306C). Cells were plated in 6-wells and were treated 24 hours after plating. Compounds are added to the media using two different concentrations (0.08 µM and 0.8 µM). Cells were also treated with Kinetin 200 µM and DMSO 0.5%. Test compounds and kinetin were diluted in PBS with a final DMSO concentration of 0.5%. After 24 hours of treatment total RNA wasa extracted using QIAzol (QUIAGEN cat.79306) following the manufacture's protocol. Reverse Transcription (RT) was then performed using 0.5 µg of total RNA, oligo(dT), random primers, and Superscript III (INVITROGEN cat.18080-044) reverse transcriptase according to manufacturer's protocol. For splicing assessment, semi-quantitave PCR was used with cDNA equivalents of 75 ng of starting RNA in a 20 µL reaction mixture, with the use of Go Taq Green Master Mix (PROMEGA ref.M712C) and specific primers that recognize exon 19 (EXON19F: CCT GAG CAG CAA TCA TGT G; SEQ ID NO:1) and exon23 (EXON23R: TAC ATG GTC TTC GTG ACA TC; SEQ ID NO:2) of *IKBKAP.* The PCR reaction wasa carried out for 35 cycles (94 °C for 30 seconds; 58 °C for 30 seconds; 72 °C for 30 seconds) in a C1000 ThermoCycler (BIORAD). The PCR products were separated in a 1.5% agarose (INVITROGEN ref. 16500) gel stained with Ethidium Bromide (SIGMA E1501). The bands were visualized with UV light using the AlphaImager 2200 (ALPHA INNOTECH). *IKBKAP* wild type band is 363 base pairs (bp) and *IKBKAP* mutant band is 289 bp due to exon20 skipping. Relative band intensity was determined by evaluating the integrated density values as determined by ImageJ software. Splicing correction was measured as the ratio of wild type transcript to total transcript (mutant

plus wild type). These values were normalized using the splicing correction values of Kinetin and DMSO treated samples as positive and negative controls. The results were used to confirm the data obtained with the primary assay and to discriminate compounds based on their potency *in vitro.*

[0172] Table 5 shows % exon inclusion data (normalized) for representative compounds at various concentrations (μM) using the secondary assay.

Table 5.

Compound No.	**Concentration (μM)**	**%exon Inclusion Normalized**	**Standard Deviation**
Kinetin	200	100	8.20
(100)	0.8	62.10	17.72
(100)	0.08	22.62	6.28
Kinetin	200	100	3.66

Compound No.	Concentration (μM)	%exon Inclusion Normalized	Standard Deviation
(372)	0.08	13.41	4.12
(372)	0.8	48.69	9.13
(107)	0.8	93.24	3.63
(107)	0.08	25.64	2.46

Example 46. ***In vivo*** **Familial Dysautonomia Mouse Model**

Compound (100)

[0173] Compound (**100**) was administered by oral gavage for eight days at 60 mg/kg/day, 30 mg/kg/day and 10 mg/kg/day to the mouse transgenic familial dysautonomia (FD) model. Every dosing group and the control group (vehicle) consisted of 6 mice. The mice were given food and water *ad libitum,* and changes in body weights were monitored on a daily basis. On the eighth day the mice were dosed for the last time and after 1 hour the mice were sacrificed and dissected. Plasma, liver, kidney, heart and brain were collected. The splicing analysis was performed in all tissues and confirmed the presence of (**100**) in the plasma. Compound (**100**) improved splicing in kidney, heart, and liver at all doses tested (doses = 10, 30 and 60 mg/kg/day). In liver, compound (**100**) at 30 mg/kg/day reached the same level of correction observed with Kinetin treatment at 400mg/kg/day. In heart, compound (**100**) at 10 mg/kg/day improved splicing better than Kinetin at 400mg/kg/day. In kidney, there were no significant changes in splicing after treatment with kinetin at 400mg/kg/day whereas improvments were observed using compound (**100**) even at 10mg/kg/day. Compound (**100**) was evident in the brain and corrected splicing at 30 and 60 mg/kg whereas there was no significant change observed in the brain after 8 days of treatment with kinetin 400mg/kg/day.

[0174] In liver, it was shown that the treatment with compound (**100**) at 30 mg/kg/day increased the level of the IKAP protein whereas there were no significant changes after treatment with kinetin at 400 mg/kg/day.

Reference Compounds (230) and (270)

[0175] The following solutions were prepared daily: Compound (**230**) in 10% DMA/45% PEG 300/12% EtOH/33% sterile water; and Compound (**270**) in 10% DMA/45% PEG 300/12% EtOH/33% sterile water.

[0176] Six transgenic mice for each dose (60, mg/kg/day; 30 mg/kg/day; and 10 mg/kg/day) were fed using a 20 Gauge feeding needle (Fine Science Tools Inc., CA, USA) for a period of 8 days. Six transgenic mice were fed daily with 10% DMA/45% PEG 300/12% EtOH/33% sterile water solution for the same duration. The mice were given food and water *ad libitum,* and changes in body weights were monitored on a daily basis. On the eighth day the mice were dosed for the last time and after 1 hour were sacrificed and dissected. Plasma, lungs, muscle, liver, heart, brain, kidney, sciatic nerve, and trigeminal nerve were collected. Splicing was evaluating by RT-PCT and IKAP protein was evaluated using Western Blotting.

Results

[0177] The data shown in FIGs. 1A-6 for representative compounds (**100**), (**230**) and (**270**) demonstrate that the compounds are useful for improving inclusion of exon 20.

Example 47. Protein isolation and western blot analysis

[0178] Protein extracts were obtained by homogenizing liver or cell pellets in RIPA buffer (Tris-HCl 50 mM, pH 7.4; NaCl 150 mM; NP-40 1%; Sodium deoxycholate 0.5%; SDS 0.1%) containing protease inhibitor cocktail (Sigma), DTT (100 µM) and PMSF (100 µM). Insoluble debris were discarded after centrifugation and protein concentration was determined using Pierce® 400 BCA Protein Assay Kit (Thermo Scientific). 50 µg of protein was separated on NuPage 4-12% Bis - Tris Gel (Invitrogen) and transferred into nitrocellulose membrane (Thermo Scientific). Membrane was blocked in 5% non-fat milk for one hour at room temperature and incubated overnight at 4°C with rabbit polyclonal antibody against the C-terminus region of the human IKAP protein (Anaspec, 1:2000) or mouse monoclonal antibody against human IKAP protein (Sigma, 1:2000) and with the rabbit polyclonal antibody against actin (Sigma, 1:2000).

[0179] Membranes were washed and incubated with secondary antibodies for 1 hour at room temperature. Protein bands were visualized by chemiluminescence (Pierce® 407 ECL Western 408 Blotting Substrate, Thermo Scientific) followed by exposure to autoradiographic film. *IKAP* levels in FD fibroblasts were compared with the level of protein found in heterozygote (HET) fibroblasts, as shown in FIG. 7.

SEQUENCE LISTING

[0180]

<110> The General Hospital Corporation

<120> Compounds for Improving mRNA Splicing

<130> 40978-0010WO1

<150> US 62/104,547
<151> 2015-01-16

<150> US 62/180,380
<151> 2015-06-16

<160> 14

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> EXON19 Forward primer

<400> 1
cctgagcagc aatcatgtg 19

<210> 2
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> EXON23 Reverse primer

<400> 2
tacatggtct tcgtgacatc 20

<210> 3
<211> 9801
<212> DNA
<213> Artificial Sequence

<220>

<223> pcDNA3.1/V5HisTOPO with Renilla-Familial Dysautonomia-Firefly

<400> 3

```
gacggatcgg gagatctccc gatcccctat ggtcgactct cagtacaatc tgctctgatg 60
ccgcatagtt aagccagtat ctgctccctg cttgtgtgtt ggaggtcgct gagtagtgcg 120
cgagcaaaat ttaagctaca acaaggcaag gcttgaccga caattgcatg aagaatctgc 180
ttagggttag gcgttttgcg ctgcttcgcg atgtacgggc cagatatacg cgttgacatt 240
gattattgac tagttattaa tagtaatcaa ttacggggtc attagttcat agcccatata 300
tggagttccg cgttacataa cttacggtaa atggcccgcc tggctgaccg cccaacgacc 360
cccgcccatt gacgtcaata atgacgtatg ttcccatagt aacgccaata gggactttcc 420
attgacgtca atgggtggac tatttacggt aaactgccca cttggcagta catcaagtgt 480
atcatatgcc aagtacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt 540
atgcccagta catgacctta tgggactttc ctacttggca gtacatctac gtattagtca 600
tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg 660
actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc 720

aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg 780
gtaggcgtgt acggtgggag gtctatataa gcagagctct ctggctaact agagaaccca 840
ctgcttactg gcttatcgaa attaatacga ctcactatag ggagacccaa gctggctagt 900
taagcttggt accgagctcg gatccggtac tgttggtaaa gccaccatgg cttccaaggt 960
gtacgacccc gagcaacgca aacgcatgat cactgggcct cagtggtggg ctcgctgcaa 1020
gcaaatgaac gtgctggact ccttcatcaa ctactatgat tccgagaagc acgccgagaa 1080
cgccgtgatt tttctgcatg gtaacgctgc ctccagctac ctgtggaggc acgtcgtgcc 1140
tcacatcgag cccgtggcta gatgcatcat ccctgatctg atcggaatgg gtaagtccgg 1200
caagagcggg aatggctcat atcgcctcct ggatcactac aagtacctca ccgcttggtt 1260
cgagctgctg aaccttccaa agaaaatcat ctttgtgggc cacgactggg gggcttgtct 1320
ggcctttcac tactcctacg agcaccaaga caagatcaag gccatcgtcc atgctgagag 1380
tgtcgtggac gtgatcgagt cctgggacga gtggcctgac atcgaggagg atatcgccct 1440
gatcaagagc gaagagggcg agaaaatggt gcttgagaat aacttcttcg tcgagaccat 1500
gctcccaagc aagatcatgc ggaaactgga gcctgaggag ttcgctgcct acctggagcc 1560
attcaaggag aagggcgagg ttagacggcc taccctctcc tggcctcgcg agatccctct 1620
cgttaaggga ggcaagcccg acgtcgtcca gattgtccgc aactacaacg cctaccttcg 1680
ggccagcgac gatctgccta agatgttcat cgagtccgac cctgggttct tttccaacgc 1740
tattgtcgag ggagctaaga agttccctaa caccgagttc gtgaaggtga agggcctcca 1800
cttcagccag gaggacgctc cagatgaaat gggtaagtac atcaagagct tcgtggagcg 1860
cgtgctgaag aacgagcagg gatccactag tccaatgtgg tggaattgcc cttcattaca 1920
ggccggcctg agcagcaatc atgtgtccca tggggaagtt ctgcggaaag tggagagggg 1980
ttcacggatt gtcactgttg tgccccagga cacaaagctt gtattacagg taagctggtt 2040
tttcagacaa gatagatagt ctgattgtca ttcagccaag taccaagcat aattcttgca 2100
ggttgtattt taggctttct tattctttgt atcgtttatt gtaaaccttt ccttgatagt 2160
tttctgttag ctttattcaa aggagtgttg atacaggctg tgaccataag gctcaaagcg 2220
aaacttttct tgaaagtcaa gataaatata gagaacaaca agattctgct aaaagtgtgc 2280
tgattttaga gagttgtggt aattctctgt gaagagttag gtaaaatggt gtatcctggc 2340
tatttaaatg ttttctactt aattaaaaat gttactgctt taatttattt aagatgccaa 2400
ggggaaactt agaagttgtt catcatcgag ccctggtttt agctcagatt cggaagtggt 2460
tggacaagta agcgccattg tactgtttgc gactagttag cttgtgattt atgtgtgaag 2520
acaataagta ttttattaca atttcgagaa cttaaaatta tgaaaagccc tcattaccta 2580
tatcatcaat cagattctta gaggctcttt ttttttttt taacttttt actttaatgc 2640
agtattttgt agtggagatt cctagcagaa agaatcgtga cactcatcat ataaaggagg 2700
gcttctctta acctgaggga acacatgtgg gttttaggtg gcctgtgaac ccagggagat 2760
tgtacacacc aaaccttgtc tttgtgtatt tattcaagta gaaagcccac agctttcaat 2820
agatttacag cggggcctat gacccagaaa agcctgagct actcttgtga aggaaatgac 2880
tgattttctg aacctatttg gaggaaactt tgtattggaa agatctatac taatgttttg 2940
tttaaaaagt agacctgaat tccatgatga ttttctttgt ttttttttg agacagagtc 3000
ttgctctgtc acccaggctg gagtacagtg gcgcaatctc ggcttactgc aacctctgcc 3060
ttctgggttc aagcaatcct cccacttcag cctcccgcat agctaggatt acaggtgtgc 3120
accacgcctg gctaattttt ttttttgtat tttcagtaga gacagggttt caccatgttg 3180
gccaggctgg tctcaaactc ctgacctcaa gtgttctgcc cacctcggcc tcccaaagtg 3240
ctaggattac aggtgtgaac caccgtgccc gggcttctgt aatgattttc tgttgtatgt 3300
atgtgaagat gtagttctca gacagtcatg atgactaaat tacacctttt aagaaggtaa 3360
atgaatgtgg tacctgattt ttttattctg taatttcaga gtagaaatcc agtgatagca 3420
gcttggcatt ggggctgtaa tctgattata actggtttgt atcataatga aaatatgctg 3480
ggcccatgga gctcagtttt tgtgaatatc ttttctattc tttctctgtc ttctcacaga 3540
cttatgttta aagaggcatt tgaatgcatg agaaagctga gaatcaatct caatctgatt 3600
tatgatcata accctaagct ggaagatgcc aaaaacatta agaagggccc agcgccattc 3660
tacccactcg aagacgggac cgccggcgag cagctgcaca aagccatgaa gcgctacgcc 3720
ctggtgcccg gcaccatcgc ctttaccgac gcacatatcg aggtggacat tacctacgcc 3780
gagtacttcg agatgagcgt tcggctggca gaagctatga agcgctatgg gctgaataca 3840
aaccatcgga tcgtggtgtg cagcgagaat agcttgcagt tcttcatgcc cgtgttgggt 3900
gccctgttca tcggtgtggc tgtggcccca gctaacgaca tctacaacga gcgcgagctg 3960
ctgaacagca tgggcatcag ccagcccacc gtcgtattcg tgagcaagaa agggctgcaa 4020
aagatcctca acgtgcaaaa gaagctaccg atcatacaaa agatcatcat catggatagc 4080
aagaccgact accagggctt ccaaagcatg tacacgttcg tgacttccca tttgccaccc 4140
```

ggcttcaacg agtacgactt cgtgcccgag agcttcgacc gggacaaaac catcgccctg 4200
atcatgaaca gtagtggcag taccggattg cccaagggcg tagccctacc gcaccgcacc 4260
gcttgtgtcc gattcagtca tgcccgcgac cccatcttcg gcaaccagat catccccgac 4320
accgctatcc tcagcgtggt gccatttcac cacggcttcg gcatgttcac cacgctgggc 4380
tacttgatct gcggctttcg ggtcgtgctc atgtaccgct tcgaggagga gctattcttg 4440
cgcagcttgc aagactataa gattcaatct gccctgctgg tgcccacact atttagcttc 4500

ttcgctaaga gcactctcat cgacaagtac gacctaagca acttgcacga gatcgccagc 4560
ggcggggcgc cgctcagcaa ggaggtaggt gaggccgtgg ccaaacgctt ccacctacca 4620
ggcatccgcc agggctacgg cctgacagaa acaaccagcg ccattctgat caccccccgaa 4680
ggggacgaca agcctggcgc agtaggcaag gtggtgccct tcttcgaggc taaggtggtg 4740
gacttggaca ccggtaagac actgggtgtg aaccagcgcg gcgagctgtg cgtccgtggc 4800
cccatgatca tgagcggcta cgttaacaac cccgaggcta caaacgctct catcgacaag 4860
gacggctggc tgcacagcgg cgacatcgcc tactgggacg aggacgagca cttcttcatc 4920
gtggaccggc tgaagagcct gatcaaatac aagggctacc aggtagcccc agccgaactg 4980
gagagcatcc tgctgcaaca ccccaacatc ttcgacgccg gggtcgccgg cctgcccgac 5040
gacgatgccg gcgagctgcc cgccgcagtc gtcgtgctgg aacacggtaa aaccatgacc 5100
gagaaggaga tcgtggacta tgtggccagc caggttacaa ccgccaagaa gctgcgcggt 5160
ggtgttgtgt tcgtggacga ggtgcctaaa ggactgaccg gcaagttgga cgcccgcaag 5220
atccgcgaga ttctcattaa ggccaagaag ggcggcaaga tcgccgtgta ataattctag 5280
agggcccgcg gttcgaaggt aagcctatcc ctaaccctct cctcggtctc gattctacgc 5340
gtaccggtca tcatcaccat caccattgag tttaaacccg ctgatcagcc tcgactgtgc 5400
cttctagttg ccagccatct gttgtttgcc cctccccccgt gccttccttg accctggaag 5460
gtgccactcc cactgtcctt tcctaataaa atgaggaaat tgcatcgcat tgtctgagta 5520
ggtgtcattc tattctgggg ggtggggtgg ggcaggacag caaggggggag gattgggaag 5580
acaatagcag gcatgctggg gatgcggtgg gctctatggc ttctgaggcg gaaagaacca 5640
gctggggctc taggggggtat ccccacgcgc cctgtagcgg cgcattaagc gcggcgggtg 5700
tggtggttac gcgcagcgtg accgctacac ttgccagcgc cctagcgccc gctcctttcg 5760
ctttcttccc ttcctttctc gccacgttcg ccggctttcc ccgtcaagct ctaaatcggg 5820
gcatcccttt agggttccga tttagtgctt tacggcacct cgaccccaaa aaacttgatt 5880
agggtgatgg ttcacgtagt gggccatcgc cctgatagac ggtttttcgc cctttgacgt 5940
tggagtccac gttctttaat agtggactct tgttccaaac tggaacaaca ctcaacccta 6000
tctcggtcta ttcttttgat ttataaggga ttttggggat ttcggcctat tggttaaaaa 6060
atgagctgat ttaacaaaaa tttaacgcga attaattctg tggaatgtgt gtcagttagg 6120
gtgtggaaag tccccaggct ccccaggcag gcagaagtat gcaaagcatg catctcaatt 6180
agtcagcaac caggtgtgga aagtccccag gctccccagc aggcagaagt atgcaaagca 6240
tgcatctcaa ttagtcagca accatagtcc cgcccctaac tccgcccatc ccgcccctaa 6300
ctccgcccag ttccgcccat tctccgcccc atggctgact aatttttttt atttatgcag 6360
aggccgaggc cgcctctgcc tctgagctat tccagaagta gtgaggaggc ttttttggag 6420
gcctaggctt ttgcaaaaag ctcccgggag cttgtatatc cattttcgga tctgatcaag 6480
agacaggatg aggatcgttt cgcatgattg aacaagatgg attgcacgca ggttctccgg 6540
ccgcttgggt ggagaggcta ttcggctatg actgggcaca acagacaatc ggctgctctg 6600
atgccgccgt gttccggctg tcagcgcagg ggcgcccggt tcttttgtc aagaccgacc 6660
tgtccggtgc cctgaatgaa ctgcaggacg aggcagcgcg gctatcgtgg ctggccacga 6720
cgggcgttcc ttgcgcagct gtgctcgacg ttgtcactga agcgggaagg gactggctgc 6780
tattgggcga agtgccgggg caggatctcc tgtcatctca ccttgctcct gccgagaaag 6840
tatccatcat ggctgatgca atgcggcggc tgcatacgct tgatccggct acctgcccat 6900
tcgaccacca agcgaaacat cgcatcgagc gagcacgtac tcggatggaa gccggtcttg 6960
tcgatcagga tgatctggac gaagagcatc aggggctcgc gccagccgaa ctgttcgcca 7020
ggctcaaggc gcgcatgccc gacggcgagg atctcgtcgt gacccatggc gatgcctgct 7080
tgccgaatat catggtggaa aatggccgct tttctggatt catcgactgt ggccggctgg 7140
gtgtggcgga ccgctatcag gacatagcgt tggctacccg tgatattgct gaagagcttg 7200
gcggcgaatg ggctgaccgc ttcctcgtgc tttacggtat cgccgctccc gattcgcagc 7260
gcatcgcctt ctatcgcctt cttgacgagt tcttctgagc gggactctgg ggttcgcgaa 7320
atgaccgacc aagcgacgcc caacctgcca tcacgagatt tcgattccac cgccgccttc 7380
tatgaaaggt tgggcttcgg aatcgttttc cgggacgccg gctggatgat cctccagcgc 7440
ggggatctca tgctggagtt cttcgcccac cccaacttgt ttattgcagc ttataatggt 7500
tacaaataaa gcaatagcat cacaaatttc acaaataaag catttttttc actgcattct 7560
agttgtggtt tgtccaaact catcaatgta tcttatcatg tctgtatacc gtcgacctct 7620
agctagagct tggcgtaatc atggtcatag ctgtttcctg tgtgaaattg ttatccgctc 7680
acaattccac acaacatacg agccggaagc ataaagtgta aagcctgggg tgcctaatga 7740
gtgagctaac tcacattaat tgcgttgcgc tcactgcccg ctttccagtc gggaaacctg 7800
tcgtgccagc tgcattaatg aatcggccaa cgcgcgggga gaggcggttt gcgtattggg 7860
cgctcttccg cttcctcgct cactgactcg ctgcgctcgg tcgttcggct gcggcgagcg 7920
gtatcagctc actcaaaggc ggtaatacgg ttatccacag aatcagggga taacgcagga 7980
aagaacatgt gagcaaaagg ccagcaaaag gccaggaacc gtaaaaaggc cgcgttgctg 8040
gcgtttttcc ataggctccg cccccctgac gagcatcaca aaaatcgacg ctcaagtcag 8100
aggtggcgaa acccgacagg actataaaga taccaggcgt ttccccctgg aagctccctc 8160
gtgcgctctc ctgttccgac cctgccgctt accggatacc tgtccgcctt tctcccttcg 8220
ggaagcgtgg cgctttctca atgctcacgc tgtaggtatc tcagttcggt gtaggtcgtt 8280

cgctccaagc tgggctgtgt gcacgaaccc cccgttcagc ccgaccgctg cgccttatcc 8340
ggtaactatc gtcttgagtc caacccggta agacacgact tatcgccact ggcagcagcc 8400
actggtaaca ggattagcag agcgaggtat gtaggcggtg ctacagagtt cttgaagtgg 8460
tggcctaact acggctacac tagaaggaca gtatttggta tctgcgctct gctgaagcca 8520

```
gttaccttcg gaaaaagagt tggtagctct tgatccggca aacaaaccac cgctggtagc 8580
ggtggttttt ttgtttgcaa gcagcagatt acgcgcagaa aaaaaggatc tcaagaagat 8640
cctttgatct tttctacggg gtctgacgct cagtggaacg aaaactcacg ttaagggatt 8700
ttggtcatga gattatcaaa aaggatcttc acctagatcc ttttaaatta aaaatgaagt 8760
tttaaatcaa tctaaagtat atatgagtaa acttggtctg acagttacca atgcttaatc 8820
agtgaggcac ctatctcagc gatctgtcta tttcgttcat ccatagttgc ctgactcccc 8880
gtcgtgtaga taactacgat acgggagggc ttaccatctg gccccagtgc tgcaatgata 8940
ccgcgagacc cacgctcacc ggctccagat ttatcagcaa taaaccagcc agccggaagg 9000
gccgagcgca gaagtggtcc tgcaacttta tccgcctcca tccagtctat taattgttgc 9060
cgggaagcta gagtaagtag ttcgccagtt aatagtttgc gcaacgttgt tgccattgct 9120
acaggcatcg tggtgtcacg ctcgtcgttt ggtatggctt cattcagctc cggttcccaa 9180
cgatcaaggc gagttacatg atcccccatg ttgtgcaaaa aagcggttag ctccttcggt 9240
cctccgatcg ttgtcagaag taagttggcc gcagtgttat cactcatggt tatggcagca 9300
ctgcataatt ctcttactgt catgccatcc gtaagatgct tttctgtgac tggtgagtac 9360
tcaaccaagt cattctgaga atagtgtatg cggcgaccga gttgctcttg cccggcgtca 9420
atacgggata ataccgcgcc acatagcaga actttaaaag tgctcatcat tggaaaacgt 9480
tcttcggggc gaaaactctc aaggatctta ccgctgttga gatccagttc gatgtaaccc 9540
actcgtgcac ccaactgatc ttcagcatct tttactttca ccagcgtttc tgggtgagca 9600
aaaacaggaa ggcaaaatgc cgcaaaaaag ggaataaggg cgacacggaa atgttgaata 9660
ctcatactct tccttttttca atattattga agcatttatc agggttattg tctcatgagc 9720
ggatacatat ttgaatgtat ttagaaaaat aaacaaatag gggttccgcg cacatttccc 9780
cgaaaagtgc cacctgacgt c                                          9801
```

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> T7 promoter/priming site

<400> 4

taatacgact cactataggg 20

<210> 5

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer (Luciferase) 146Rev

<400> 5

ctcggcgtag gtaatgtcc 19

<210> 6

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer (Luciferase) 146Rev On Sequence

<400> 6

ggacattacc tacgccgag 19

<210> 7

<211> 116

<212> DNA

<213> Homo sapiens

<220>

<223> Exon 19

<400> 7

cattacaggc cggcctgagc agcaatcatg tgtcccatgg ggaagttctg cggaaagtgg 60
agaggggttc acggattgtc actgttgtgc cccaggacac aaagcttgta ttacag 116

<210> 8

<211> 363

<212> DNA

<213> Homo sapiens

<220>

<223> Intron between Exon 19 and Exon 20

<400> 8

taagctggtt tttcagacaa gatagatagt ctgattgtca ttcagccaag taccaagcat 60
aattcttgca ggttgtattt taggctttct tattctttgt atcgtttatt gtaaaccttt 120
ccttgatagt tttctgttag ctttattcaa aggagtgttg atacaggctg tgaccataag 180
gctcaaagcg aaacttttct tgaaagtcaa gataaatata gagaacaaca agattctgct 240
aaaagtgtgc tgattttaga gagttgtggt aattctctgt gaagagttag gtaaaatggt 300
gtatcctggc tatttaaatg ttttctactt aattaaaaat gttactgctt taatttattt 360
aag 363

<210> 9

<211> 74

<212> DNA

<213> Homo sapiens

<220>

<223> Exon 20

<400> 9

atgccaaggg gaaacttaga agttgttcat catcgagccc tggttttagc tcagattcgg 60
aagtggttgg acaa 74

<210> 10

<211> 1072

<212> DNA

<213> Homo sapiens

<220>

<223> Intron between Exon 20 and Exon 21

<400> 10

gtaagcgcca ttgtactgtt tgcgactagt tagcttgtga tttatgtgtg aagacaataa 60
gtattttatt acaatttcga gaacttaaaa ttatgaaaag ccctcattac ctatatcatc 120
aatcagattc ttagaggctc ttttttttt ttttaacttt tttactttaa tgcagtattt 180
tgtagtggag attcctagca gaaagaatcg tgacactcat catataaagg agggcttctc 240
ttaacctgag ggaacacatg tgggttttag gtggcctgtg aacccaggga gattgtacac 300

```
accaaacctt gtctttgtgt atttattcaa gtagaaagcc cacagctttc aatagattta 360
cagcggggcc tatgacccag aaaagcctga gctactcttg tgaaggaaat gactgatttt 420
ctgaacctat ttggaggaaa ctttgtattg gaaagatcta tactaatgtt ttgtttaaaa 480
agtagacctg aattccatga tgattttctt tgtttttttt ttgagacaga gtcttgctct 540
gtcacccagg ctggagtaca gtggcgcaat ctcggcttac tgcaacctct gccttctggg 600
ttcaagcaat cctcccactt cagcctcccg catagctagg attacaggtg tgcaccacgc 660
ctggctaatt ttttttttg tattttcagt agagacaggg tttcaccatg ttggccaggc 720
tggtctcaaa ctcctgacct caagtgttct gcccacctcg gcctcccaaa gtgctaggat 780
tacaggtgtg aaccaccgtg cccgggcttc tgtaatgatt ttctgttgta tgtatgtgaa 840
gatgtagttc tcagacagtc atgatgacta aattacacct tttaagaagg taaatgaatg 900
tggtacctga ttttttttatt ctgtaatttc agagtagaaa tccagtgata gcagcttggc 960
attggggctg taatctgatt ataactggtt tgtatcataa tgaaaatatg ctgggcccat 1020

ggagctcagt ttttgtgaat atcttttcta ttctttctct gtcttctcac ag         1072
```

<210> 11

<211> 79

<212> DNA

<213> Homo sapiens

<220>

<223> Exon 21

<400> 11

```
acttatgttt aaagaggcat ttgaatgcat gagaaagctg agaatcaatc tcaatctgat 60
ttatgatcat aaccctaag                                              79
```

<210> 12

<211> 269

<212> DNA

<213> Homo sapiens

<220>

<223> Exons 19-20-21

<400> 12

```
cattacaggc cggcctgagc agcaatcatg tgtcccatgg ggaagttctg cggaaagtgg 60
agaggggttc acggattgtc actgttgtgc cccaggacac aaagcttgta ttacagatgc 120
caaggggaaa cttagaagtt gttcatcatc gagccctggt tttagctcag attcggaagt 180
ggttggacaa acttatgttt aaagaggcat ttgaatgcat gagaaagctg agaatcaatc 240
tcaatctgat ttatgatcat aaccctaag                                  269
```

<210> 13

<211> 939

<212> DNA

<213> Renilla reniformis

<220>

<223> RENILLA LUCIFERASE

<400> 13

```
atggcttcca aggtgtacga ccccgagcaa cgcaaacgca tgatcactgg gcctcagtgg 60
tgggctcgct gcaagcaaat gaacgtgctg gactccttca tcaactacta tgattccgag 120
aagcacgccg agaacgccgt gatttttctg catggtaacg ctgcctccag ctacctgtgg 180
aggcacgtcg tgcctcacat cgagcccgtg gctagatgca tcatccctga tctgatcgga 240
atgggtaagt ccggcaagag cgggaatggc tcatatcgcc tcctggatca ctacaagtac 300
ctcaccgctt ggttcgagct gctgaacctt ccaaagaaaa tcatctttgt gggccacgac 360
tgggggcctt gtctggcctt tcactactcc tacgagcacc aagacaagat caaggccatc 420
```

```
gtccatgctg agagtgtcgt ggacgtgatc gagtcctggg acgagtggcc tgacatcgag 480
gaggatatcg ccctgatcaa gagcgaagag ggcgagaaaa tggtgcttga gaataacttc 540
ttcgtcgaga ccatgctccc aagcaagatc atgcggaaac tggagcctga ggagttcgct 600
gcctacctgg agccattcaa ggagaagggc gaggttagac ggcctaccct ctcctggcct 660
cgcgagatcc ctctcgttaa gggaggcaag cccgacgtcg tccagattgt ccgcaactac 720
aacgcctacc ttcgggccag cgacgatctg cctaagatgt tcatcgagtc cgaccctggg 780
ttcttttcca acgctattgt cgagggagct aagaagttcc ctaacaccga gttcgtgaag 840
gtgaagggcc tccacttcag ccaggaggac gctccagatg aaatgggtaa gtacatcaag 900
agcttcgtgg agcgcgtgct gaagaacgag cagggatcc                        939
```

<210> 14

<211> 1653

<212> DNA

<213> Artificial Sequence

<220>

<223> FIREFLY LUCIFERASE (with Mutation ATG-CTG base 3619)

<400> 14

```
ctggaagatg ccaaaaacat taagaagggc ccagcgccat tctacccact cgaagacggg 60
accgccggcg agcagctgca caaagccatg aagcgctacg ccctggtgcc cggcaccatc 120
gcctttaccg acgcacatat cgaggtggac attacctacg ccgagtactt cgagatgagc 180
gttcggctgg cagaagctat gaagcgctat gggctgaata caaaccatcg gatcgtggtg 240
tgcagcgaga atagcttgca gttcttcatg cccgtgttgg gtgccctgtt catcggtgtg 300
gctgtggccc cagctaacga catctacaac gagcgcgagc tgctgaacag catgggcatc 360
agccagccca ccgtcgtatt cgtgagcaag aaagggctgc aaaagatcct caacgtgcaa 420
aagaagctac cgatcataca aaagatcatc atcatggata gcaagaccga ctaccagggc 480
ttccaaagca tgtacacctt cgtgacttcc catttgccac ccggcttcaa cgagtacgac 540
ttcgtgcccg agagcttcga ccgggacaaa accatcgccc tgatcatgaa cagtagtggc 600
agtaccggat tgcccaaggg cgtagcccta ccgcaccgca ccgcttgtgt ccgattcagt 660
catgcccgcg accccatctt cggcaaccag atcatccccg acaccgctat cctcagcgtg 720
gtgccatttc accacggctt cggcatgttc accacgctgg gctacttgat ctgcggcttt 780
cgggtcgtgc tcatgtaccg cttcgaggag gagctattct tgcgcagctt gcaagactat 840
aagattcaat ctgccctgct ggtgcccaca ctatttagct tcttcgctaa gagcactctc 900
atcgacaagt acgacctaag caacttgcac gagatcgcca gcggcgggga gccgctcagc 960
aaggaggtag gtgaggccgt ggccaaacgc ttccacctac caggcatccg ccagggctac 1020
ggcctgacag aaacaaccag cgccattctg atcacccccg aaggggacga caagcctggc 1080
gcagtaggca aggtggtgcc cttcttcgag gctaaggtgg tggacttgga caccggtaag 1140
acactgggtg tgaaccagcg cggcgagctg tgcgtccgtg gccccatgat catgagcggc 1200
tacgttaaca accccgaggc tacaaacgct ctcatcgaca aggacggctg gctgcacagc 1260
ggcgacatcg cctactggga cgaggacgag cacttcttca tcgtggaccg gctgaagagc 1320
ctgatcaaat acaagggcta ccaggtagcc ccagccgaac tggagagcat cctgctgcaa 1380
caccccaaca tcttcgacgc cggggtcgcc ggcctgcccg acgacgatgc cggcgagctg 1440
cccgccgcag tcgtcgtgct ggaacacggt aaaaccatga ccgagaagga gatcgtggac 1500
tatgtggcca gccaggttac aaccgccaag aagctgcgcg gtggtgttgt gttcgtggac 1560
gaggtgccta aaggactgac cggcaagttg gacgcccgca agatccgcga gattctcatt 1620
aaggccaaga agggcggcaa gatcgccgtg taa                             1653
```

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in

compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US62104547 [0001]
- US62180380B [0001] [0180]
- WO2005033290A [0005]
- WO2015005491A [0005]
- WO2010118367A [0005]
- WO2014124458A [0005]
- US8729025B [0038]
- US7737110B [0038]
- WO409780010A [0180]
- US62104547B [0180]

Non-patent literature cited in the description

- **SHETTY et al.**Human Molecular Genetics, 2011, vol. 20, 214093-4101 [0005]
- **AXELROD et al.**Pediatric Research, 2011, vol. 70, 5480-483 [0005]
- **GOLD-VON SIMSON et al.**Pediatric Research, 2009, vol. 65, 3341-346 [0005]
- **YOSHIDA et al.**PNAS, 2015, vol. 112, 92764-2769 [0005]
- Advances in Heterocyclic ChemistryElsevier19630000vol. 1-107, [0066]
- Journal of Heterocyclic Chemistry, vol. 1-49, [0066]
- Journal of Heterocyclic Chemistry, 1964, [0066]
- Science of Synthesis20010000vol. 1-48, [0066]
- Knowledge Updates KU, 2010, [0066]
- Thieme, 2001, [0066]
- Comprehensive Organic Functional Group TransformationsPergamon Press19960000 [0066]
- Comprehensive Organic Functional Group Transformations IIElsevier20040000 [0066]
- Comprehensive Heterocyclic ChemistryPergamon Press19840000 [0066]
- **KATRITZKY et al.**Comprehensive Heterocyclic Chemistry IIPergamon Press19960000 [0066]
- **SMITH et al.**March's Advanced Organic Chemistry: Reactions, Mechanisms, and StructureWiley20070000 [0066]
- Comprehensive Organic SynthesisPergamon Press19910000 [0066]
- **P. G. M. WUTS**Protective Groups in Organic SynthesisWiley & Sons,

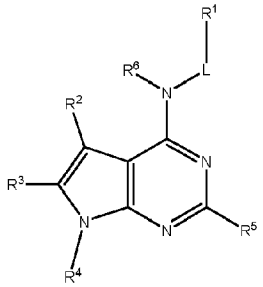
Inc.19990000 [0068]
- Remington's Pharmaceutical SciencesMack Publishing Company198500001418- [0127]
- Journal of Pharmaceutical Science, 1977, vol. 66, 2- [0127]
- Handbook of Pharmaceutical Salts: Properties, Selection, and UseWiley-VCH20020000 [0127]
- **ANDERSON et al.**Am. J. Hum. Genet., 2001, vol. 68, 753-758 [0135]
- **SLAUGENHAUP et al.**Am. J., Hum. Genet., 2001, vol. 68, 598-605 [0135]
- **CHOW et al.**Nature, 2007, vol. 448, 68-72 [0135]
- **CHOW et al.**Am. J. Hum. Genet., 2009, vol. 84, 85-88 [0135]
- **CAMPEAU et al.**Am. J. Hum. Genet., 2013, vol. 92, 781-791 [0135]
- **BAULAC et al.**Neurology, 2014, vol. 82, 1068-1075 [0135]
- **EDVARDSON et al.**PLoS One, 2012, vol. 7, e36458- [0135]
- **KOROGLU et al.**Parkinsonism Relat. Disord., 2013, vol. 19, 320-324 [0135]
- **HAACK et al.**Am. J. Hum. Genet., 2012, vol. 91, 1144-1149 [0135]
- **SAITSU et al.**Nature Genet, 2013, vol. 45, 445-449 [0135]
- **ZIMPRICH et al.**Neuron, 2004, vol. 44, 601-607 [0135]
- **TAN et al.**Hum. Mutat., 2010, vol. 31, 561-568 [0135]
- **GUERNSEY et al.**PLOS Genet, 2010, vol. 6, e1001081- [0135]
- **NICOLAOU et al.**Europ. J. Hum. Genet., 2013, vol. 21, 190-194 [0135]
- **SENDEREK et al.**Hum. Molec. Genet., 2003, vol. 12, 349-356 [0135]
- **AZZEDINE et al.**Am. J. Hum. Genet., 2003, vol. 72, 1141-1153 [0135]
- **HOGARTH et al.**Neurology, 2013, vol. 80, 268-275 [0135]
- **MEILLEUR et al.**Neurogenetics, 2010, vol. 11, 313-318 [0135]
- **BANNE et al.**J. Med. Genet., 2013, vol. 50, 772-775 [0135]
- **YNTEMA et al.**J. Med. Genet., 1998, vol. 35, 801-805 [0135]
- **KUTSCHE et al.**Nature Genet, 2000, vol. 26, 247-250 [0135]
- **NOOR et al.**DNA Res, 2000, vol. 7, 65-73 [0135]
- **TALLILA et al.**Am. J. Hum. Genet., 2008, vol. 82, 1361-1367 [0135]
- **DOHERTY et al.**J. Med. Genet., 2010, vol. 47, 8-21 [0135]
- **O'ROAK et al.**Science, 2012, vol. 338, 1619-1622 [0135]
- **TARPEY et al.**Nature Genet, 2009, vol. 41, 535-543 [0135]
- **JENSEN et al.**Am. J. Hum. Genet., 2005, vol. 76, 227-236 [0135]
- **WAGENSTALLER et al.**Am. J. Hum. Genet., 2007, vol. 81, 768-779 [0135]
- **ZANNI et al.**Neurology, 2005, vol. 65, 1364-1369 [0135]
- **MURAKAMI et al.**PLoS Genet, 2014, vol. 10, e1004320- [0135]
- **MORROW et al.**Science, 2008, vol. 321, 218-223 [0135]
- **EDVARDSON et al.**J. Med. Genet., 2013, vol. 50, 733-739 [0135]
- **PTACEK et al.**Cell, 1994, vol. 77, 863-868 [0135]
- **MONNIER et al.**Am. J. Hum. Genet., 1997, vol. 60, 1316-1325 [0135]
- **KUNG et al.**J. Clin. Endocr. Metab., 2004, vol. 89, 1340-1345 [0135]
- **VAN ESCH et al.**Am. J. Med. Genet., 2007, vol. 143A, 364-369 [0135]
- **NEMOS et al.**Clin. Genet., 2009, vol. 76, 357-371 [0135]
- **DEVYS et al.**Nature Genet, 1993, vol. 4, 335-340 [0135]
- **ALLINGHAM-HAWKINS et al.**Am. J. Med. Genet., 1999, vol. 83, 322-325 [0135]

- **LEEHEY et al.**Arch. Neurol., 2003, vol. 60, 117-121 [0135]
- **HARAKALOVA et al.**J. Med. Genet., 2012, vol. 49, 539-543 [0135]
- **DEARDORFF et al.**Nature, 2012, vol. 489, 313-317 [0135]
- **WAN et al.**Hum. Molec. Genet., 2001, vol. 10, 1085-1092 [0135]
- **XIANG et al.**J. Med. Genet., 2000, vol. 37, 250-255 [0135]
- **MELONI et al.**Am. J. Hum. Genet., 2000, vol. 67, 982-985 [0135]
- **WATSON et al.**J. Med. Genet., 2001, vol. 38, 224-228 [0135]
- **CARNEY et al.**Pediat. Neurol., 2003, vol. 28, 205-211 [0135]
- **SALOMONS et al.**Am. J. Hum. Genet., 2001, vol. 68, 1497-1500 [0135]
- **HAMDAN et al.**Biol. Psychiat., 2011, vol. 69, 898-901 [0135]
- **CARVILL et al.**Nature Genet, 2013, vol. 45, 825-830 [0135]
- **STEINLEIN et al.**Nature Genet, 1995, vol. 11, 201-203 [0135]
- **LI et al.**Hum. Molec. Genet., 2005, vol. 14, 1211-1219 [0135]
- **DIBBENS et al.**Nature Genet, 2013, vol. 45, 546-551 [0135]
- **CORBETT et al.**Am. J. Hum. Genet., 2011, vol. 88, 657-663 [0135]
- **CARVILL et al.**Nature Genet, 2013, vol. 45, 1073-1076 [0135]
- **BAULAC et al.**Am. J. Hum. Genet., 1999, vol. 65, 1078-1085 [0135]
- **CLAES et al.**Am. J. Hum. Genet., 2001, vol. 68, 1327-1332 [0135]
- **OHMORI et al.**Biochem. Biophys. Res. Commun., 2002, vol. 295, 17-23 [0135]
- **YANG et al.**J. Med. Genet., 2004, vol. 41, 171-174 [0135]
- **FABER et al.**Ann. Neurol., 2012, vol. 71, 26-39 [0135]
- **GOLDBERG et al.**Clin. Genet., 2007, vol. 71, 311-319 [0135]
- **CATTERALL et al.**Neuron, 2006, vol. 52, 743-749 [0135]
- **SINGH et al.**PLoS Genet, 2009, vol. 5, e1000649- [0135]
- **SAITSU et al.**Nature Genet, 2008, vol. 40, 782-788 [0135]
- **BASEL-VANAGAITE et al.**Am. J. Hum. Genet., 2013, vol. 93, 524-529 [0135]
- **GURVICH et al.**Hum. Mutat., 2009, vol. 30, 633-640 [0135]
- **MUNTONI et al.**Am. J. Hum. Genet., 1995, vol. 56, 151-157 [0135]
- **DAOUD et al.**Hum. Molec. Genet., 2009, vol. 18, 3779-3794 [0135]
- **DEMIR et al.**Am. J. Hum. Genet., 2002, vol. 70, 1446-1458 [0135]
- **LAMPE et al.**J. Med. Genet., 2005, vol. 42, 108-120 [0135]
- **DAGONEAU et al.**Am. J. Hum. Genet., 2009, vol. 84, 706-711 [0135]
- **GROHMANN et al.**Nature Genet, 2001, vol. 29, 75-77 [0135]
- **COTTENIE et al.**Am. J. Hum. Genet., 2014, vol. 95, 590-601 [0135]
- **TEZAK et al.**Hum. Mutat., 2003, vol. 21, [0135]
- **OLIVEIRA et al.**Clin. Genet., 2008, vol. 74, 502-512 [0135]
- **TANNER et al.**Hum. Mutat., 1998, vol. 11, 62-68 [0135]
- **DONNER et al.**Europ. J. Hum. Genet., 2004, vol. 12, 744-751 [0135]
- **LEHTOKARI et al.**Hum. Mutat., 2006, vol. 27, 946-956 [0135]
- **PULKKINEN et al.**Hum. Molec. Genet., 1996, vol. 5, 1539-1546 [0135]
- **PFENDNER et al.**J. Invest. Derm., 2005, vol. 124, 111-115 [0135]
- **LOGAN et al.**Nature Genet, 2014, vol. 46, 188-193 [0135]
- **LEMMERS et al.**Nature Genet, 2012, vol. 44, 1370-1374 [0135]
- **DALAKAS et al.**New Eng. J. Med., 2000, vol. 342, 770-780 [0135]

- **LI et al.**Circulation, 1999, vol. 100, 461-464 [0135]
- **WALTER et al.**Brain, 2007, vol. 130, 1485-1496 [0135]
- **CETIN et al.**J. Med. Genet., 2013, vol. 50, 437-443 [0135]
- **SAMBUUGHIN et al.**Am. J. Hum. Genet., 2001, vol. 69, 204-208 [0135]
- **TILGEN et al.**Hum. Molec. Genet., 2001, vol. 10, 2879-2887 [0135]
- **MONNIER et al.**Hum. Molec. Genet., 2003, vol. 12, 1171-1178 [0135]
- **D'ARCY et al.**Neurology, 2008, vol. 71, 776-777 [0135]
- **IYER et al.**Science, 2012, vol. 338, 222- [0135]
- **BECKER et al.**Ann. Neurol., 2002, vol. 52, 29-37 [0135]
- **JONES et al.**Hum. Molec. Genet., 1997, vol. 6, 2155-2161 [0135]
- **CARBONARA et al.**Genes Chromosomes Cancer, 1996, vol. 15, 18-25 [0135]
- **CARSILLO et al.**Proc. Nat. Acad. Sci., 2000, vol. 97, 6085-6090 [0135]
- **DIETZ et al.**Nature, 1991, vol. 352, 337-339 [0135]
- **FAIVRE et al.**J. Med. Genet., 2003, vol. 40, 34-36 [0135]
- **LOEYS et al.**Sci. Transl. Med., 2010, vol. 2, 23-20 [0135]
- **LE GOFF et al.**Am. J. Hum. Genet., 2011, vol. 89, 7-14 [0135]
- **YANDELL et al.**New Eng. J. Med., 1989, vol. 321, 1689-1695 [0135]
- **HARBOUR et al.**Science, 1988, vol. 241, 353-357 [0135]
- **LALANI et al.**Am. J. Hum. Genet., 2006, vol. 78, 303-314 [0135]
- **KIM et al.**Am. J. Hum. Genet., 2008, vol. 83, 511-519 [0135]
- **GAO et al.**Am. J. Hum. Genet., 2007, vol. 80, 957-965 [0135]
- **FELIX et al.**Am. J. Med. Genet., 2006, vol. 140A, 2110-2114 [0135]
- **PLEASANCE et al.**Nature, 2010, vol. 463, 184-190 [0135]
- **F.B. AXELROD et al.**Pediatr Res, 2011, vol. 70, 5480-483 [0149]
- **R.S. SHETTY et al.**Human Molecular Genetics, 2011, vol. 20, 214093-4101 [0149]

Patentkrav

1. Forbindelse med formel (Ia)



Ia

eller et farmaceutisk acceptabelt salt deraf, hvor:
L er valgt fra gruppen, der består af C_{1-6}alkylen, C_{2-6}alkenylen og C_{2-6}alkynylen, hvor C_{1-6}alkylen, C_{2-6}alkenylen og C_{2-6}alkynylen hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;
R^1 er valgt fra gruppen, der består af en C_{6-10}aryl, 2-benzofuranyl, 4-quinolinyl og en 5-6-leddet heteroaryl, der hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{1A}-grupper;
hver R^{1A} er valgt uafhængigt blandt halogen, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy, $-C(=O)OH$, $-C(=O)C_{1-6}$alkyl, $-C(=O)C_{1-6}$halogenalkyl og $-C(=O)C_{1-6}$alkoxy;
R^2 er valgt fra gruppen, der består af H, oxo, azido, halogen, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{6-10}aryl, en 5-10-leddet heteroaryl, en 4-10-leddet heterocycloalkyl, OR^{a2}, $C(=O)R^{b2}$, $C(=O)OR^{b2}$, $NR^{c2}R^{d2}$, $C(=O)NR^{c2}R^{d2}$, $-OC(=O)NR^{c2}R^{d2}$, $NR^{c2}C(=O)R^{b2}$, $NR^{c2}C(=O)OR^{b2}$, $NR^{c2}C(=O)NR^{c2}R^{d2}$, $NR^{c2}S(=O)_2R^{b2}$, $NR^{c2}S(=O)_2NR^{c2}R^{d2}$, $S(O)NR^{c2}R^{d2}$ og $S(O)_2NR^{c2}R^{d2}$, hvor C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, den 5-10-leddede heteroaryl og 4-10-leddede heterocycloalkyl hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;
R^3 er valgt fra gruppen, der består af H, oxo, azido, halogen, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{6-10}aryl, en 5-10-leddet heteroaryl, en 4-10-leddet heterocycloalkyl, OR^{a3}, SR^{a3}, $C(=O)R^{b3}$, $C(=O)OR^{b3}$, $NR^{c3}R^{d3}$, $C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, $-OC(=O)NR^{c3}R^{d3}$, $NR^{c3}C(=O)R^{b3}$, $NR^{c3}C(=O)OR^{b3}$, $NR^{c3}C(=O)NR^{c3}R^{d3}$, $NR^{c3}S(=O)_2R^{b3}$, $NR^{c3}S(=O)_2NR^{c3}R^{d3}$, $S(O)NR^{c3}R^{d3}$ og $S(O)_2NR^{c3}R^{d3}$, hvor C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-}

$_{10}$aryl, den 5-10-leddede heteroaryl og 4-10-leddede heterocycloalkyl hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;

R^4 er valgt fra gruppen, der består af H, oxo, azido, halogen, CN, NO_2, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, C_{6-10}aryl, en 5-10-leddet heteroaryl, en 4-10-leddet heterocycloalkyl, OR^{a4}, $C(=O)R^{b4}$, $C(=O)OR^{b4}$, $NR^{c4}R^{d4}$, $C(=O)NR^{c4}R^{d4}$, $-OC(=O)NR^{c4}R^{d4}$, $NR^{c4}C(=O)R^{b4}$, $NR^{c4}C(=O)OR^{b4}$, $NR^{c4}C(=O)NR^{c4}R^{d4}$, $NR^{c4}S(=O)_2R^{b4}$, $NR^{c4}S(=O)_2NR^{c4}R^{d4}$, $S(O)NR^{c4}R^{d4}$ og $S(O)_2NR^{c4}R^{d4}$, hvor C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, den 5-10-leddede heteroaryl og 4-10-leddede heterocycloalkyl hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;

R^5 er halogen;

R^6 er valgt fra gruppen, der består af H, C_{1-6}alkyl, C_{1-6}halogenalkyl, C_{1-6}hydroxyalkyl og C_{1-6}alkoxy;

hver R^{a2}, R^{b2}, R^{c2}, R^{d2}, R^{a3}, R^{b3}, R^{c3}, R^{d3}, R^{a4}, R^{b4}, R^{c4} og R^{d4} er valgt uafhængigt fra gruppen, der består af H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}hydroxyalkyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy, $-(C_{1-6}$alkylen$)-C_{1-6}$alkoxy, C_{3-10}cycloalkyl, $-(C_{1-6}$alkylen$)-C_{3-10}$cycloalkyl, C_{6-10}aryl, en 5-10-leddet heteroaryl, en 4-10-leddet heterocycloalkyl, hvor C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-10}cycloalkyl, $-(C_{1-6}$alkylen$)-C_{3-10}$cycloalkyl, C_{6-10}aryl, den 5-10-leddede heteroaryl og 4-10-leddede heterocycloalkyl hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;

eller R^{c2} og R^{d2} sammen med N-atomet, hvortil de er bundet, danner en 5-10-leddet heteroaryl- eller 4-10-leddet heterocycloalkylring, der hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;

eller R^{c3} og R^{d3} sammen med N-atomet, hvortil de er bundet, danner en 5-10-leddet heteroaryl- eller 4-10-leddet heterocycloalkylring, der hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;

eller R^{c4} og R^{d4} sammen med N-atomet, hvortil de er bundet, danner en 5-10-leddet heteroaryl- eller 4-10-leddet heterocycloalkylring, der hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper;

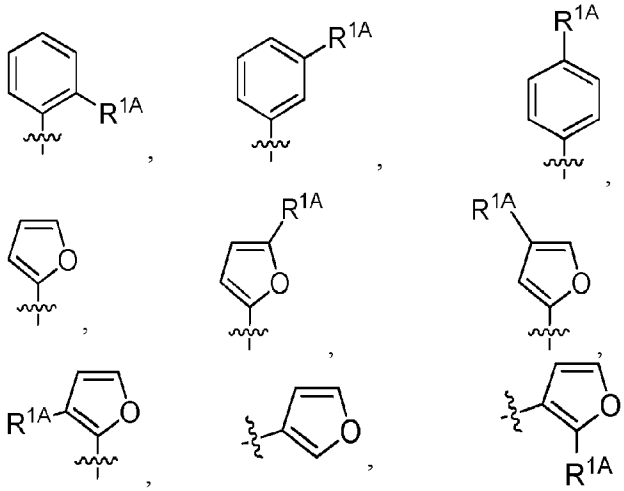
hver R^{20} er valgt uafhængigt fra gruppen, der består af OH, SH,

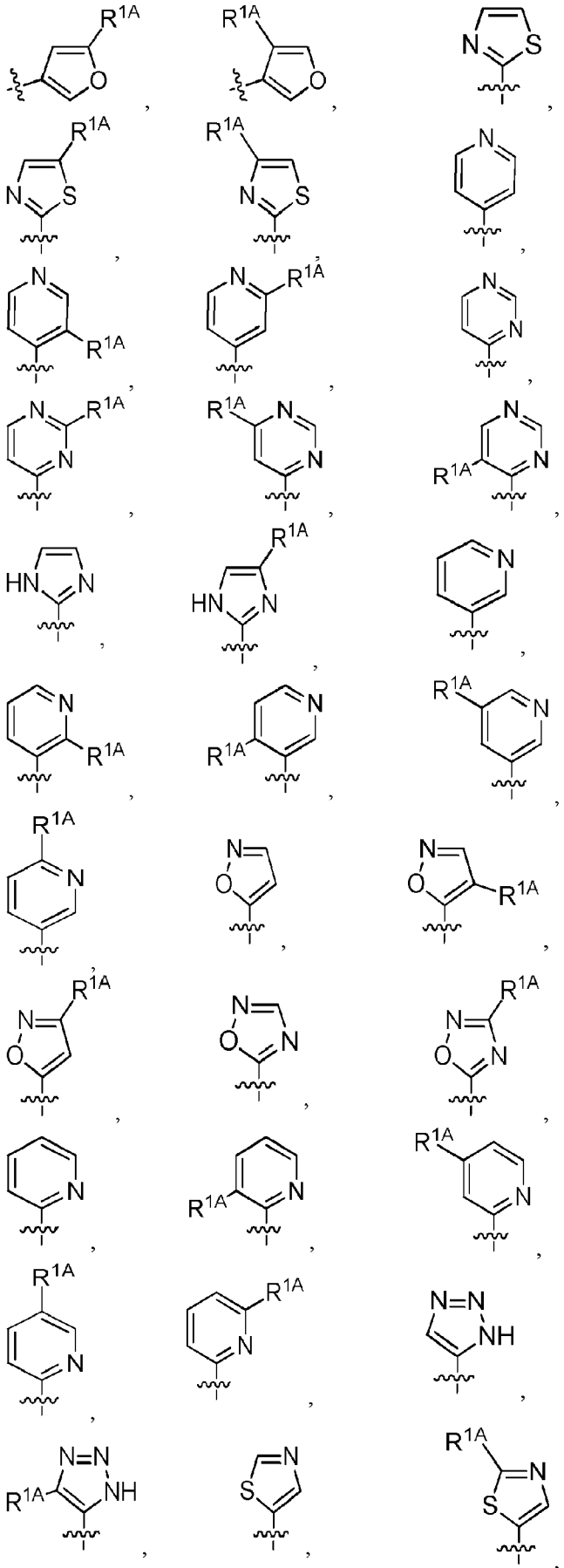
CN, NO_2, halogen, oxo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}halogenalkyl, C_{1-4}cyanoalkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, -(C_{1-4}alkyl)-(C_{1-4}alkoxy), -(C_{1-4}alkoxy)-(C_{1-4}alkoxy), C_{1-4}halogenalkoxy, C_{3-6}cycloalkyl, phenyl, en 5-6-leddet heteroaryl, en 5-6-leddet heterocycloalkyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, carbamyl, C_{1-4}alkylcarbamyl, di(C_{1-4}alkyl)carbamyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylcarbonyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylcarbonylamino, C_{1-4}alkylsulfonylamino, aminosulfonyl, C_{1-4}alkylaminosulfonyl, di(C_{1-4}alkyl)aminosulfonyl, aminosulfonylamino, C_{1-4}alkylaminosulfonylamino, di(C_{1-4}alkyl)aminosulfonylamino, aminocarbonylamino, C_{1-4}alkylaminocarbonylamino og di(C_{1-4}alkyl)aminocarbonylamino.

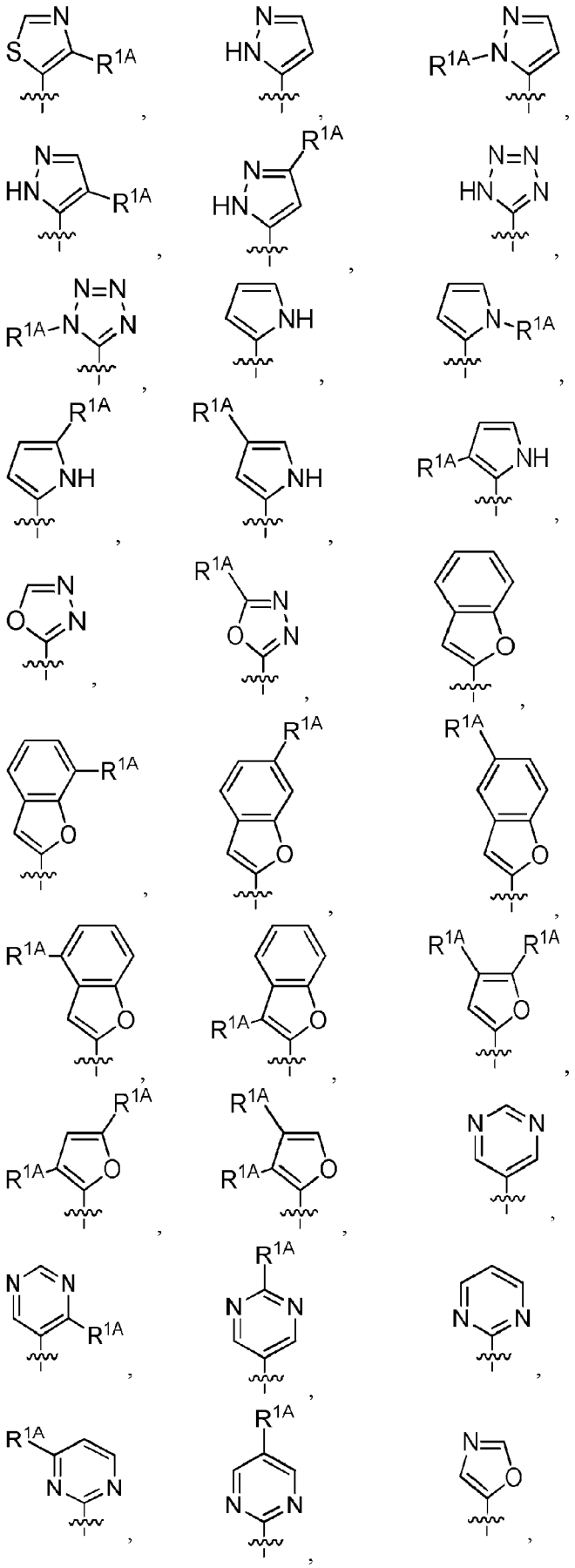
2. Forbindelse ifølge krav 1 eller et farmaceutisk acceptabelt salt deraf, hvor L er usubstitueret C_{1-6}alkylen eller C_{1-6}alkylen, der eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper.

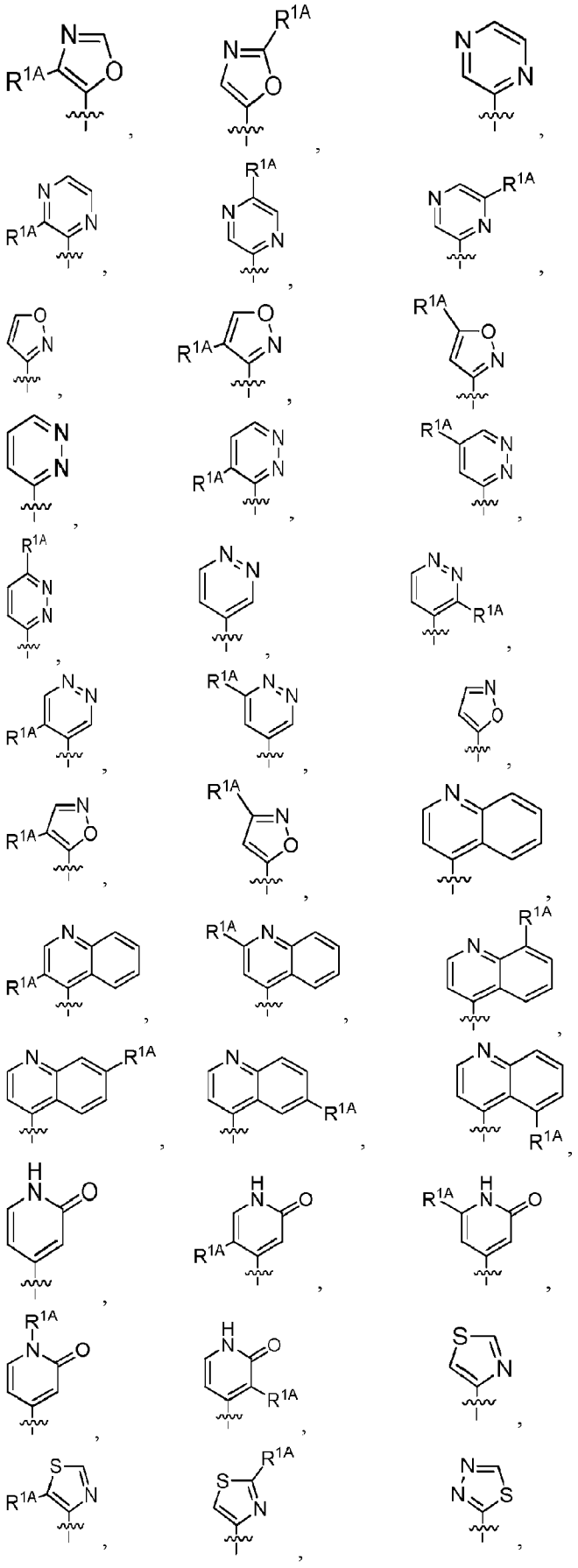
3. Forbindelse ifølge et hvilket som helst af kravene 1 eller 2 eller et farmaceutisk acceptabelt salt deraf, hvor R^1 er valgt fra gruppen, der består af C_{6-10}aryl og en 5-6-leddet heteroaryl, der hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{1A}-grupper.

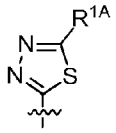
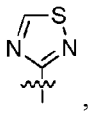
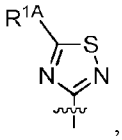
4. Forbindelse ifølge et hvilket som helst af kravene 1 til 3 eller et farmaceutisk acceptabelt salt deraf, hvor R^1 er valgt fra gruppen, der består af:

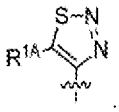









,

,

,

,
og

.

5. Forbindelse ifølge et hvilket som helst af kravene 1 til 4 eller et farmaceutisk acceptabelt salt deraf, hvor R^{1A} er valgt fra gruppen, der består af halogen, CN, C_{1-6}alkyl, C_{1-6}halogenalkyl, C_{1-6}alkoxy og -C(=O)OH.

6. Forbindelse ifølge et hvilket som helst af kravene 1 til 5, hvor R^2 er H eller C_{1-6}alkyl.

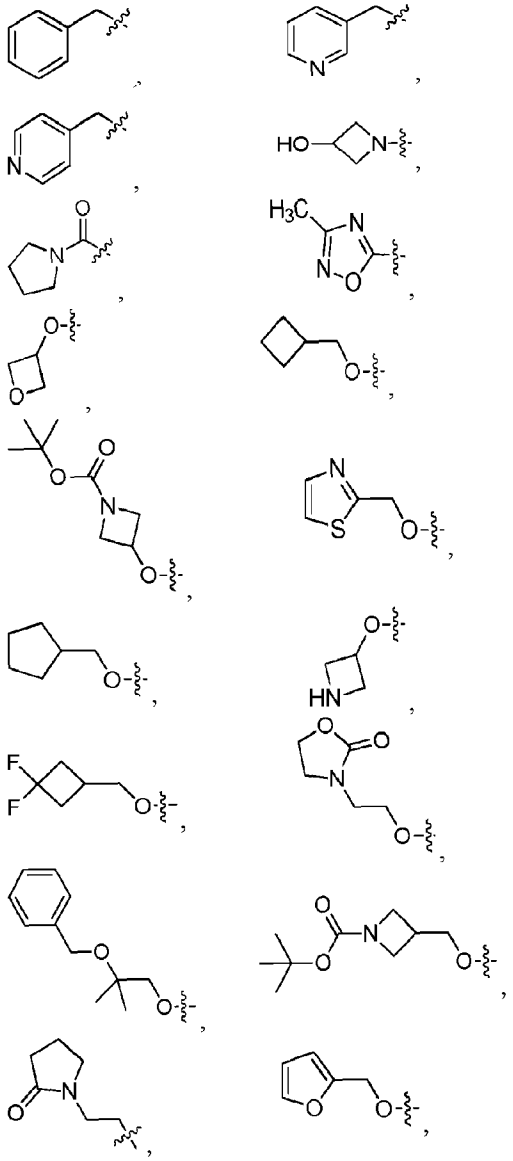
7. Forbindelse ifølge et hvilket som helst af kravene 1 til 6 eller et farmaceutisk acceptabelt salt deraf, hvor R^4 er H eller C_{1-6}alkyl, hvor C_{1-6}alkyl eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper.

8. Forbindelse ifølge et hvilket som helst af kravene 1 til 7 eller et farmaceutisk acceptabelt salt deraf, hvor R^6 er H eller C_{1-6}alkyl.

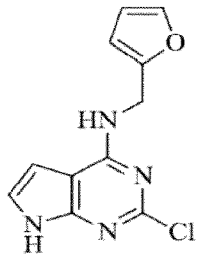
9. Forbindelse ifølge et hvilket som helst af kravene 1 til 8 eller et farmaceutisk acceptabelt salt deraf, hvor R^3 er valgt fra gruppen, der består af H, oxo, azido, CN, C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, en 5-6-leddet heteroaryl, en 5-6-leddet heterocycloalkyl, OR^{a3}, SR^{a3}, $NR^{c3}R^{d3}$, $C(=O)OR^{b3}$, $-C(=O)NR^{c3}R^{d3}$, $-OC(=O)R^{b3}$, hvor C_{1-6}alkyl, C_{3-6}cycloalkyl, phenyl, den 5-6-leddede heteroaryl, den 5-6-leddede heterocycloalkyl hver eventuelt er substitueret med 1, 2, 3 eller 4 uafhængigt valgte R^{20}-grupper.

10. Forbindelse ifølge et hvilket som helst af kravene 1 til 9 eller et farmaceutisk acceptabelt salt deraf, hvor R^3 er valgt fra gruppen, der består af H, azido, CN, methyl, cyclopropyl, cyclobutyl, phenyl, 3-pyridinyl, N-morpholino, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, $-OCH_2CH_2OH$, $-OCH_2CH_2CH_2OH$, $-OCH_2CH_2OCH_3$, $-OCH_2CH_2CH_2OCH_3$, $-ONHCH_3$, $-OCH_2CHF_2$, $-OCH_2CF_3$, -

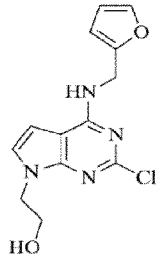
$OCH_2CH_2CF_3$, $-OCH_2CHF_2CH_3$, $-OCH_2CH_2NHC(=O)CH_3$, cyclobutoxy, $-OCH_2CH_2$-O-phenyl, $-SCH_3$, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-NHCH_2CH_2CH_2OH$, $-CH_2OCH_3$, $-CH_2OH$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-NHCH_2CH_2OH$, $-C(=O)NHCH_2CH_2OH$, $-OC(=O)CH_3$, $-OCH_2$-azetidinyl, $-OCH_2$-oxetanyl,



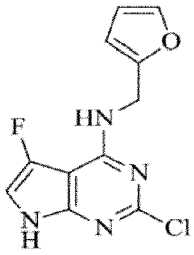
11. Forbindelse ifølge krav 1, som er valgt blandt:



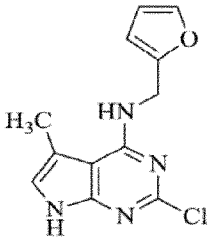
(55)



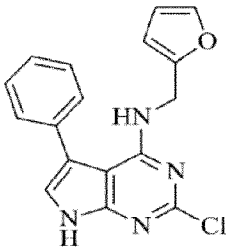
(77)



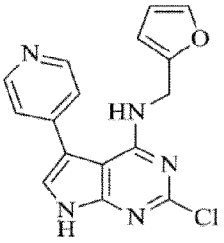
(81)



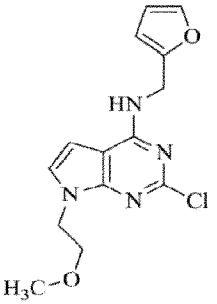
(84)



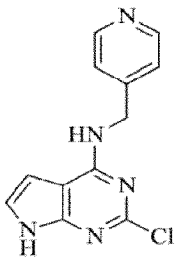
(86)



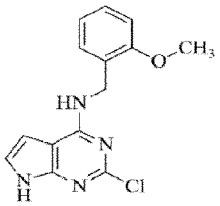
(89)



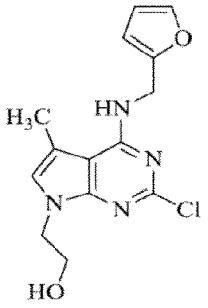
(94)



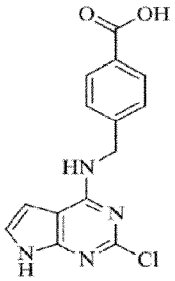
(100)



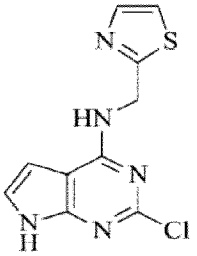
(101)



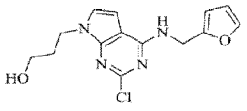
(105)



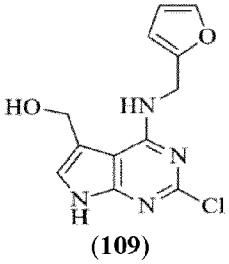
(106)



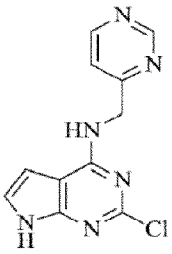
(107)



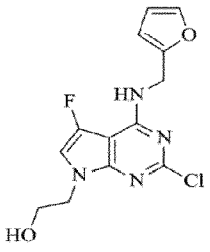
(108)



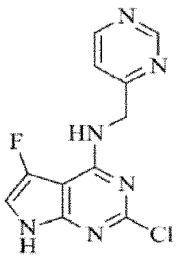
(109)



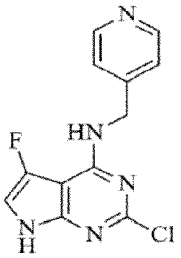
(110)



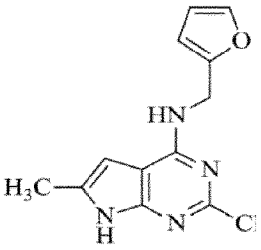
(111)



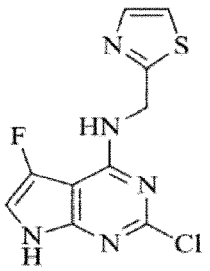
(112)



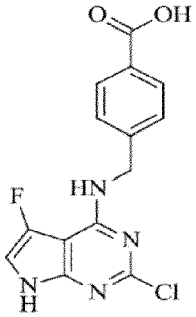
(114)



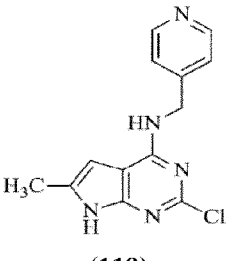
(115)



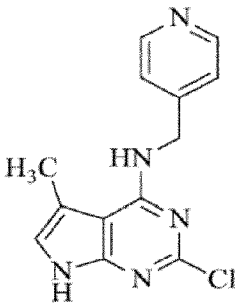
(116)



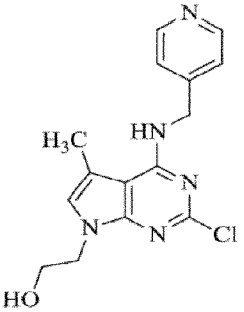
(117)



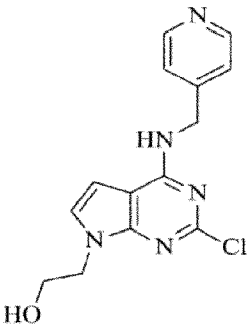
(119)



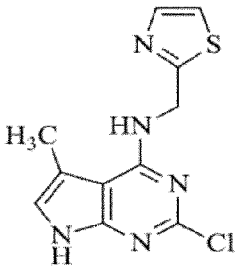
(120)



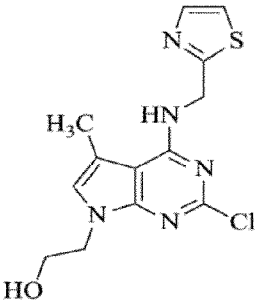
(121)



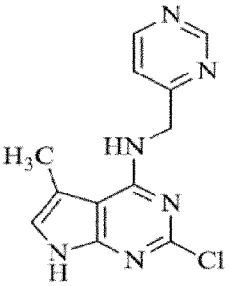
(122)



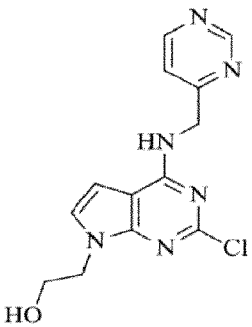
(123)



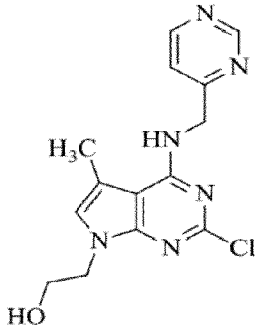
(125)



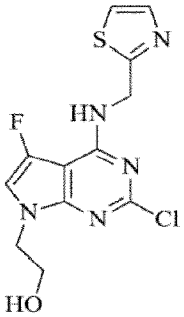
(126)



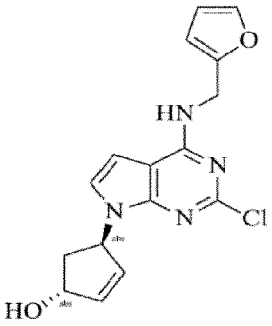
(127)



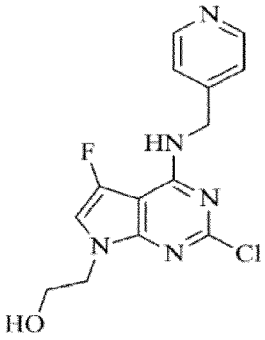
(128)



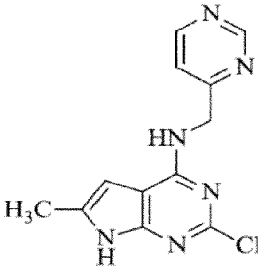
(130)



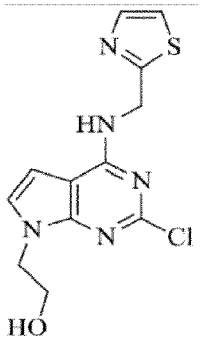
(132)



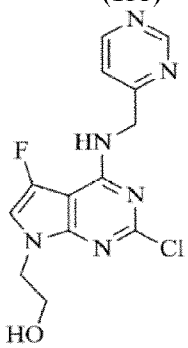
(135)



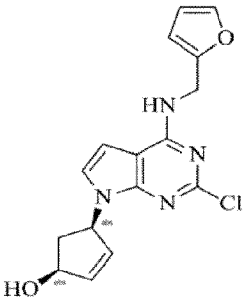
(136)



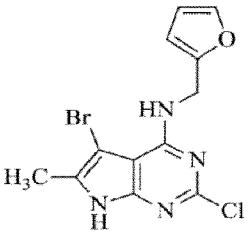
(137)



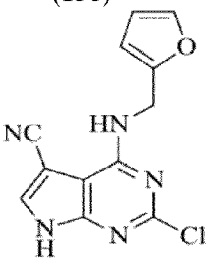
(138)



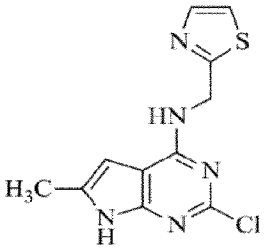
(139)



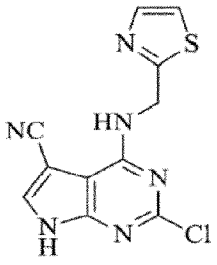
(143)



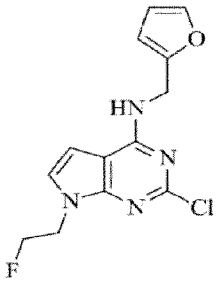
(145)



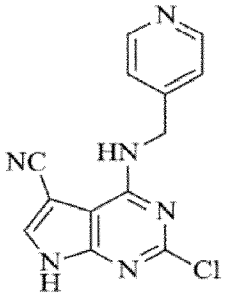
(147)



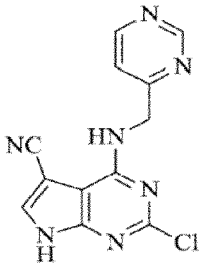
(148)



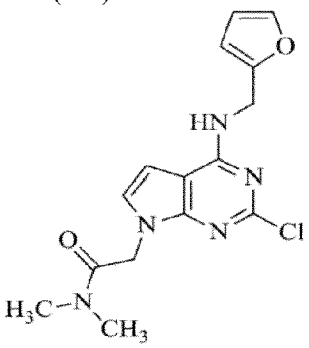
(150)



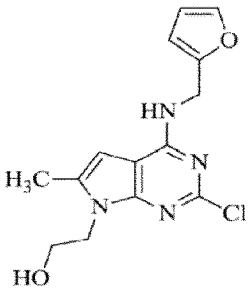
(151)



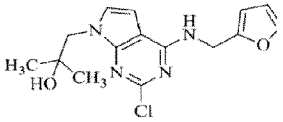
(152)



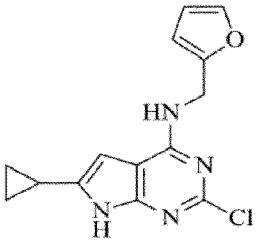
(153)



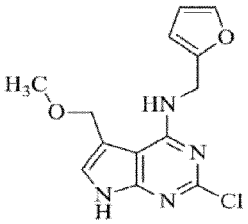
(154)



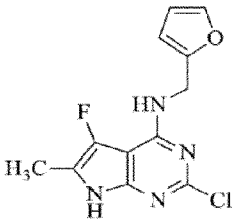
(155)



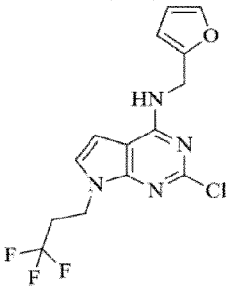
(156)



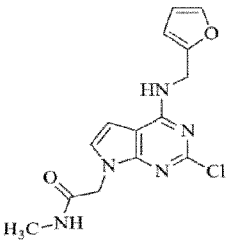
(158)



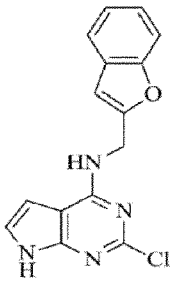
(159)



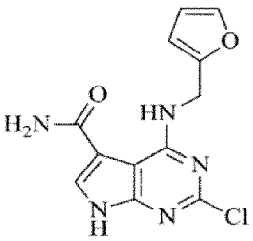
(160)



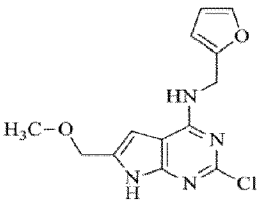
(161)



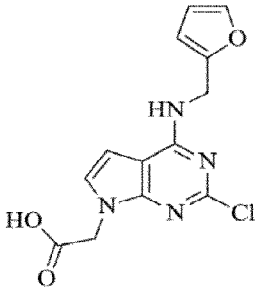
(163)



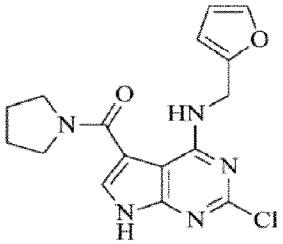
(165)



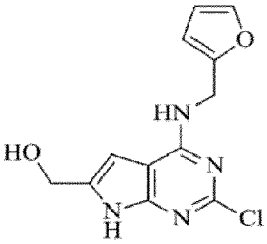
(166)



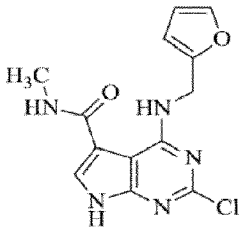
(167)



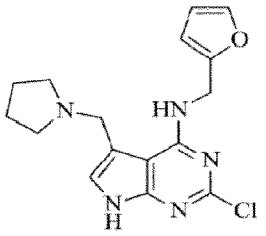
(168)



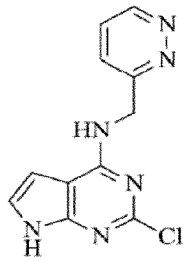
(170)



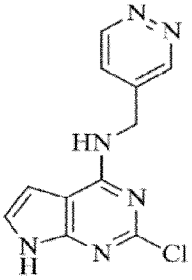
(172)



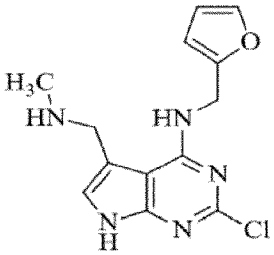
(173)



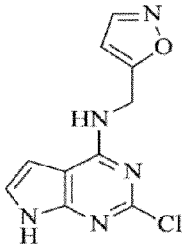
(174)



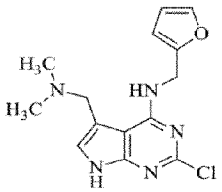
(176)



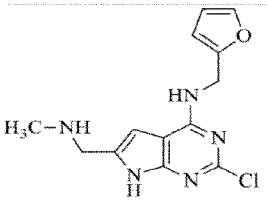
(177)



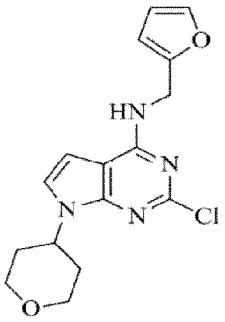
(178)



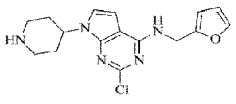
(180)



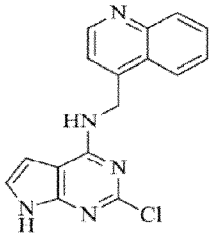
(181)



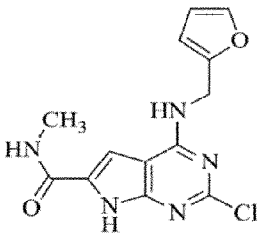
(182)



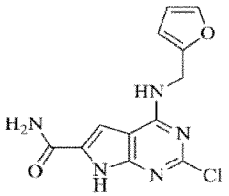
(183)



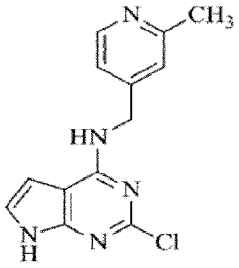
(186)



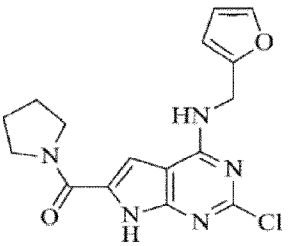
(187)



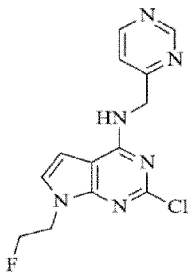
(188)



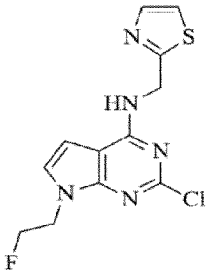
(189)



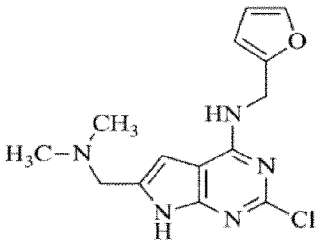
(190)



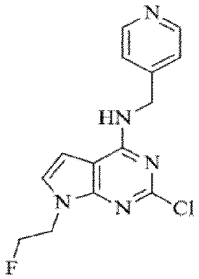
(191)



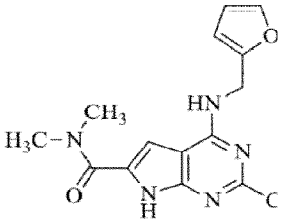
(192)



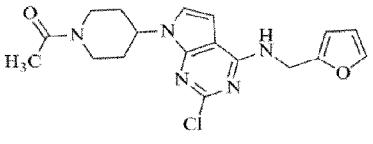
(193)



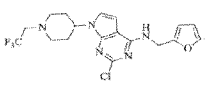
(194)



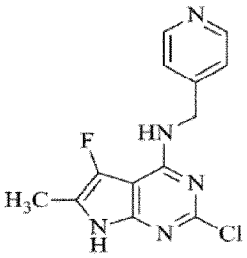
(195)



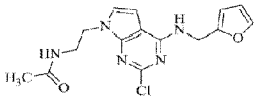
(197)



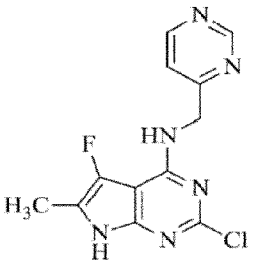
(200)



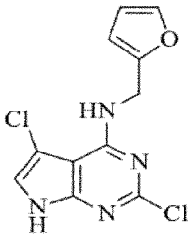
(201)



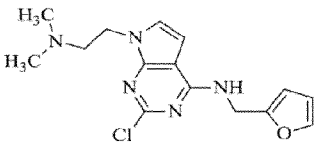
(203)



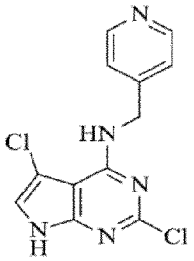
(204)



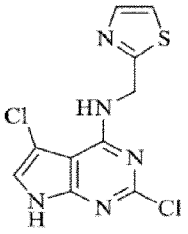
(205)



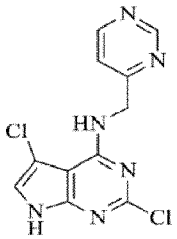
(206)



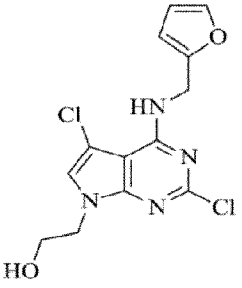
(207)



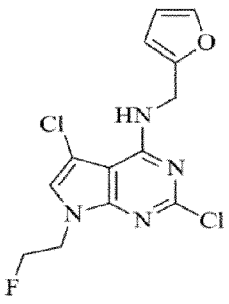
(208)



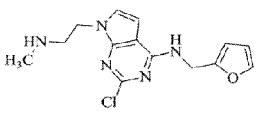
(210)



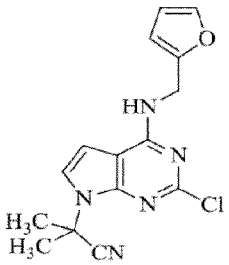
(211)



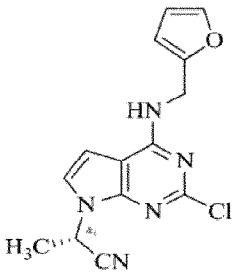
(212)



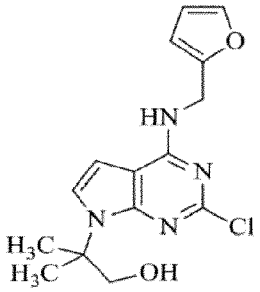
(213)



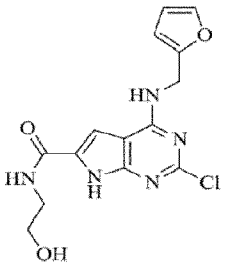
(215)



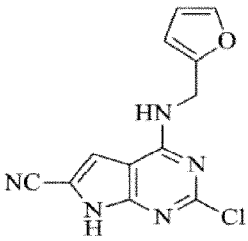
(216)



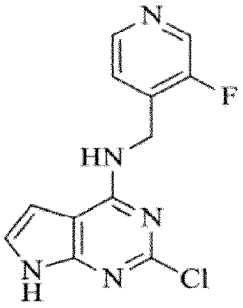
(219)



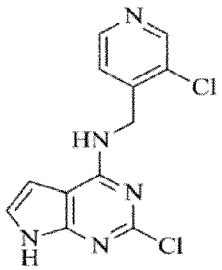
(221)



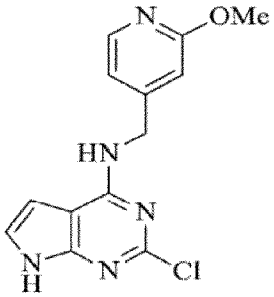
(223)



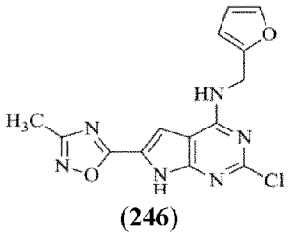
(226)



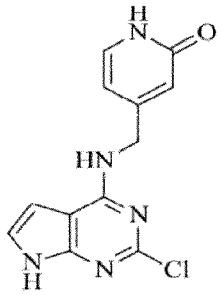
(228)



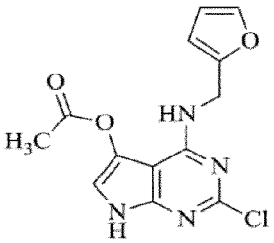
(237)



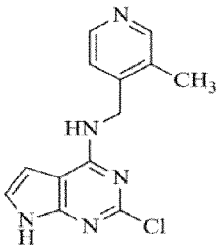
(246)



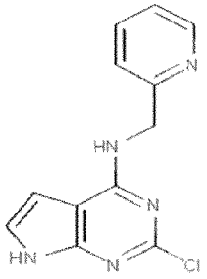
(248)



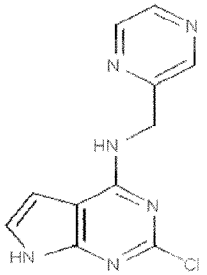
(252)



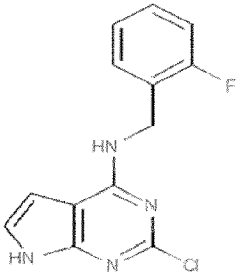
(263)



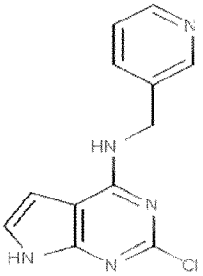
(350)



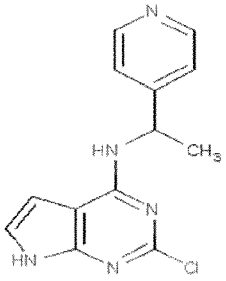
(353)



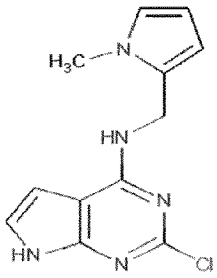
(354)



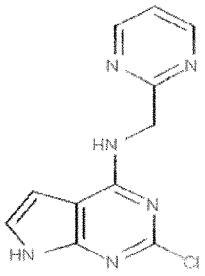
(355)



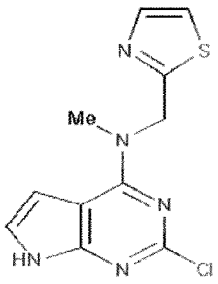
(359)



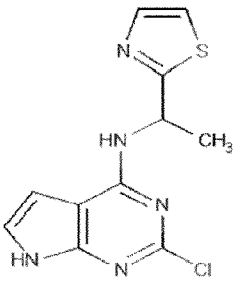
(360)



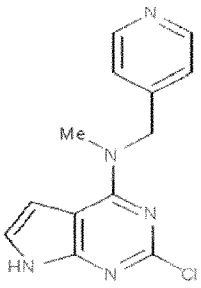
(361)



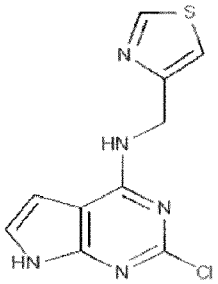
(363)



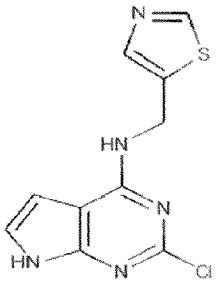
(364)



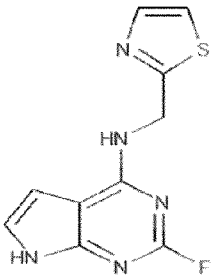
(369)



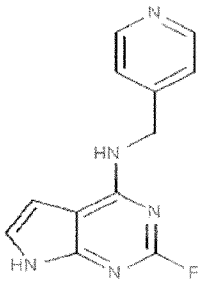
(372)



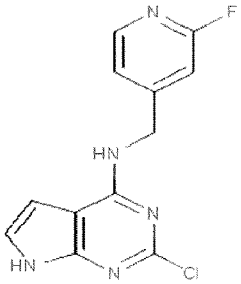
(373)



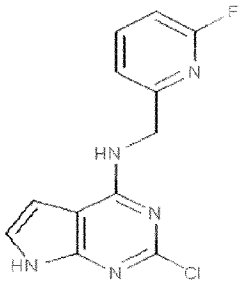
(379)



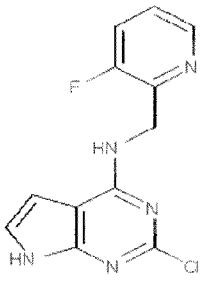
(380)



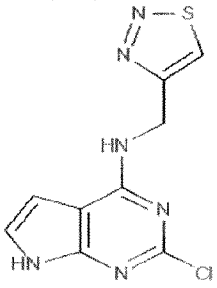
(487)



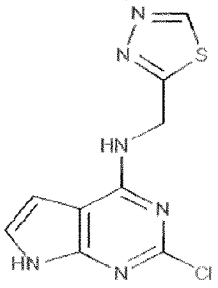
(494)



(495)



(498)



(501)

eller et farmaceutisk acceptabelt salt deraf.

12. Farmaceutisk sammensætning, som omfatter en forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller et

farmaceutisk acceptabelt salt deraf og mindst ét farmaceutisk acceptabelt bæremateriale.

13. Forbindelse ifølge et hvilket som helst af kravene 1 til 11 eller et farmaceutisk acceptabelt salt deraf eller farmaceutisk sammensætning ifølge krav 12 til anvendelse til behandling af familiær dysautonomi.