(54) Titre : COMPOSES ET METHODES POUR LE TRAITEMENT DE L'HYPERTENSION
(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF HYPERTENSION

Figure 8

- Vehicle
- Cpd 3b, 15 mg/kg
- Cpd 3, 15 mg/kg
- Cpd 3, 30 mg/kg

(57) Abrégé/Abstract:
Hydrogenated pyrido[4,3-b]indoles, pyrido [3, 4-b] indoles and azepino[4,5-b]indoles are described. The compounds may bind to and are adrenergic receptor α<sub>2</sub>B antagonists. The compounds may also bind to and antagonize adrenergic receptor α<sub>1</sub>B. The
commodities may find use in therapy, e.g., to (i) reduce blood pressure and/or (ii) promote renal blood flow and/or (iii) decrease or inhibit sodium reabsorption. The compounds may also be used to treat diseases or conditions that are, or are expected to be, responsive to a decrease in blood pressure. Use of the compounds to treat cardiovascular and renal disorders is particularly described.
Title: COMPOUNDS AND METHODS FOR TREATMENT OF HYPERTENSION

Abstract: Hydrogenated pyrido[4,3-b]indoles, pyrido[3,4-b] indoles and azaquinol[4,5-b]indoles are described. The compounds may bind to and are adrenergic receptor α₂b antagonists. The compounds may also bind to and antagonize adrenergic receptor α₁b. The compounds may find use in therapy, e.g., to (i) reduce blood pressure and/or (ii) promote renal blood flow and/or (iii) decrease or inhibit sodium reabsorption. The compounds may also be used to treat diseases or conditions that are, or are expected to be, responsive to a decrease in blood pressure. Use of the compounds to treat cardiovascular and renal disorders is particularly described.
DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D’UN TOME.

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:
COMPOUNDS AND METHODS FOR TREATMENT OF HYPERTENSION

CROSS-REFERENCE TO RELATED APPLICATIONS


BACKGROUND OF THE INVENTION

[0002] Hypertension is a serious condition that can damage vital organs, such as the heart and kidneys, and other parts of the body, such as the central nervous system. Individuals who have hypertension may have, or be at risk of developing, dangerous diseases such as coronary heart disease and kidney failure. Hypertension, which is the leading modifiable risk factor for cardiovascular disease mortality, causes more than 7 million deaths every year worldwide.

[0003] Hypertension is the most common chronic medical condition in developed countries as well as the most common indication for physician visits and prescription medication use. Hypertension affects more than 50 million individuals in the United States and over one billion individuals worldwide, and overall prevalence may continue to increase with the advancing age of the population.

[0004] Unfortunately, despite the importance of blood pressure control and the availability of multiple classes of antihypertensive agents, the treatment of hypertension remains suboptimal. Data from the most recent National Health and Nutrition Examination Survey demonstrate that only 34% of patients with hypertension have blood pressures at their therapeutic goal. Additionally, it was shown that the majority of patients with hypertension will require two or more antihypertensive agents to achieve their goal blood pressure. Even with optimal compliance with multiple antihypertensive agents of different classes, a significant fraction of patients will not be able to achieve their goal blood pressure. The overall prevalence of resistant hypertension, defined as elevated blood pressure in spite of the use of three or more
antihypertensive agents, is unknown, but small studies suggest that it ranges from 5%–16% in primary care settings to greater than 50% in nephrology clinics. Given data suggesting that increasing age and obesity are important risk factors for the development of resistant hypertension, it is expected that the overall prevalence of this condition is likely to increase due to demographic changes in the population.

[0005] Systolic blood pressure tends to increase with age and systolic hypertension is an important health issue, prominent in the elderly (Duprez, Am. J. Med. 121:179-184 (2008)). It has been suggested that this occurs as large vessels such as the aorta lose their elasticity with age and is less able to buffer the pulsative nature of cardiac output. There exists a need for a treatment for patients in such clinical setting, for example, patients with systolic hypertension accompanied with low diastolic pressure (Franklin et al. J. Hypertension 29:1101–1108 (2011)).

[0006] Metabolic syndrome is a cluster of disorders including obesity, hypertension, hypertriglyceridemia, hypercholesterolemia and elevated blood sugar. Individuals with this spectrum of disorders are at increased risk of diabetes, heart disease and stroke. Agents capable of treating more than one of these disorders are desirable.

[0007] Hypertensive emergencies are defined as severe elevations in blood pressure associated with resultant organ damage (i.e. pulmonary edema, renal impairment, visual impairment, intracranial hemorrhage, or encephalopathy). The treatment of hypertensive emergencies involves aggressive and controlled blood pressure lowering in a highly monitored intensive care setting using intravenous blood pressure lowering agents. Therapeutic agents and method of treatment is needed to gradually lower blood pressure and minimize damage of end organs such as the brain, kidney, heart, and eye.

[0008] The frequency of chronic kidney disease also continues to increase worldwide as does the prevalence of end-stage renal disease. Although chronic kidney disease is often caused by hypertension, other factors such as a decrease in renal blood flow and increase in sodium retention or reabsorption can lead to renal diseases. Increased age and diabetes can also contribute to renal disease. Especially the elderly, which are a growing segment of the world population, are at increased risk for renal disease. The presence of chronic kidney disease is also associated with a large increase in cardiovascular morbidity and mortality. Consequently, the identification and reduction of chronic kidney disease has become a vital public health priority.
[0009] Thus, there remains a need for new and useful agents that are capable of (i) reducing an individual’s blood pressure and/or (ii) promoting renal blood flow and/or (iii) inhibiting or decreasing sodium reabsorption.

BRIEF SUMMARY OF THE INVENTION

[0010] Hydrogenated pyrido[4,3-b]indoles, pyrido[3,4-b]indoles and azepino[4,5-b]indoles are described. Compositions and kits comprising the compounds are also provided, as are methods of using and making the compounds. Compounds provided herein may find use in treating a disease or condition that is, or is believed to be responsive to any one or more of: (i) a decrease in blood pressure; (ii) an increase in renal blood flow and (iii) a decrease or inhibition of sodium reabsorption. In one aspect, compounds provided herein are selective adrenergic receptor α2B antagonists that may find use in treating a disease or condition that is, or is believed to be responsive to any one or more of: (i) a decrease in blood pressure; (ii) an increase in renal blood flow and (iii) a decrease or inhibition of sodium reabsorption. Compounds provided may also find use in treating diseases and/or conditions such as hypertension, congestive heart failure or a renal disease or condition.

[0011] In another aspect, compounds that promote mitochondrial health and cellular viability are also described. The compounds provided herein are selective adrenergic receptor α2B antagonists that may find use in treating a disease or condition that is associated with dysfunction of mitochondria in a renal or cardiac cell. Compounds provided may also find use in treating diseases and/or conditions selected from the group consisting of acute renal failure, chronic renal failure, coronary ischemia, acute congestive heart failure, chronic congestive heart failure, coronary artery disease, sleep apnea, respiratory distress, hypertension, and peripheral vascular disease.

[0012] In one aspect, provided is a method of lowering blood pressure in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I):
or a salt, solvate or N-oxide thereof, wherein:

R\(^1\) is H; C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl, SO\(_2\)H, SR\(^{1a}\), S(O)R\(^{1a}\), SO\(_2\)R\(^{1a}\) and perhaloalkyl; C\(_3\)-C\(_8\) cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C\(_2\)-C\(_5\) alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or –C(O)O-C\(_1\)-C\(_5\) alkyl; or is taken together with R\(^{2a}\) or R\(^{3a}\) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety; or is taken together with R\(^{4a}\) or R\(^{5a}\), where present, to form an ethylene (-CH\(_2\)CH\(_2\)-) moiety or a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

R\(^{1a}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl;

R\(^{2a}\) is H; optionally substituted C\(_1\)-C\(_5\) alkyl; optionally substituted C\(_2\)-C\(_5\) alkenyl; or optionally substituted aryl; or is taken together with R\(^1\) or R\(^{5a}\), where present, to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety; or is taken together with R\(^{3a}\) to form an ethylene (-CH\(_2\)CH\(_2\)-) moiety or a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety; or is taken together with R\(^{4a}\), where present, to form a methylene (-CH\(_2\)-) moiety or an ethylene (-CH\(_2\)CH\(_2\)-) moiety;

R\(^{3a}\) is H; optionally substituted C\(_1\)-C\(_5\) alkyl; optionally substituted C\(_2\)-C\(_5\) alkenyl; or optionally substituted aryl; or is taken together with R\(^1\) or R\(^{4a}\), where present, to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety; or is taken together with R\(^{2a}\) to form an ethylene (-CH\(_2\)CH\(_2\)-) moiety or a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety; or is taken together with R\(^{5a}\), where present, to form a methylene (-CH\(_2\)-) moiety or an ethylene (-CH\(_2\)CH\(_2\)-) moiety;
R^{4a}, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R^{14a})R^{15a}; -C(O)N(R^{14a})R^{15a}; optionally substituted C_1-C_5 alkyl; optionally substituted C_2-C_5 alkenyl; or optionally substituted aryl; or is taken together with R^{3a} to form a propylene (-CH_2CH_2CH_2-) moiety or a butylene (-CH_2CH_2CH_2CH_2-) moiety; or is taken together with R^1 to form an ethylene (-CH_2CH_2-) moiety or a propylene (-CH_2CH_2CH_2-) moiety; or is taken together with R^{2a} to form a methylene (-CH_2-) moiety or an ethylene (-CH_2CH_2-) moiety; or is taken together with R^{5a}, where present, to form a methylene (-CH_2-) moiety;

R^{5a}, where present, is H H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R^{14a})R^{15a}; -C(O)N(R^{14a})R^{15a}; optionally substituted C_1-C_5 alkyl; optionally substituted C_2-C_5 alkenyl; or optionally substituted aryl; or is taken together with R^{2a} to form a propylene (-CH_2CH_2CH_2-) moiety or a butylene (-CH_2CH_2CH_2CH_2-) moiety; or is taken together with R^1 to form an ethylene (-CH_2CH_2-) moiety or a propylene (-CH_2CH_2CH_2-) moiety; or is taken together with R^{3a} to form a methylene (-CH_2-) moiety or an ethylene (-CH_2CH_2-) moiety; or is taken together with R^{4a}, where present, to form a methylene (-CH_2-) moiety;

each R^{2b} and R^{3b} is independently H, optionally substituted C_1-C_5 alkyl, optionally substituted C_2-C_5 alkenyl, or optionally substituted aryl;
each R^{4b} and R^{5b}, where present, is independently H, halo, optionally substituted C_1-C_5 alkyl, optionally substituted C_2-C_5 alkenyl, or optionally substituted aryl;
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;
each X^1, X^2, X and U is independently N or CR^6;
each R^6 is independently H; hydroxyl; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C_2-C_5 alkenyl; optionally substituted C_1-C_5 alkoxy; or optionally substituted –C(O)C_1-C_5 alkyl;

R^7 is H; halo; optionally substituted C_1-C_5 alkyl; or optionally substituted aryl; or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R^9 to form a C_3-C_5 alkyne when R^8 and R^{10} are taken together to form a bond;

R^8 is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carboxylalkoxy; N(R^{11})R^{12}; SR^{13}, S(O)R^{13}; SO_2R^{13}; -OC(O)N(R^{14})R^{15}; -C(O)N(R^{14})R^{15}; optionally substituted -OC(O)-aryl; optionally substituted -OC(O)-heteroaryl; -OC(O)C_1-C_6 alkyl optionally substituted with amino or carboxyl; or –OC_1-C_5 alkyl optionally substituted with carboxyl; or is taken together with R^7
and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R
\(^10\) to form a bond;

\[ R^9 \text{ is } H \text{ or optionally substituted } C_1-C_5 \text{ alkyl, or is taken together with } R^7 \text{ to form a } C_3-C_5 \text{ alkylene when } R^8 \text{ and } R^{10} \text{ are taken together to form a bond;} \]

\[ R^{10} \text{ is } H \text{ or optionally substituted } C_1-C_5 \text{ alkyl, or is taken together with } R^8 \text{ to form a bond;} \]

\[ \text{each } R^{11} \text{ and } R^{12} \text{ is independently } H \text{ or optionally substituted } C_1-C_5 \text{ alkyl, or } R^{11} \text{ and } R^{12} \text{ are taken together to form } C_3-C_5 \text{ alkylene;} \]

\[ R^{13} \text{ is } H \text{ or optionally substituted } C_1-C_5 \text{ alkyl;} \]

\[ \text{each } R^{14} \text{ and } R^{15} \text{ is independently } H \text{ or optionally substituted } C_1-C_5 \text{ alkyl; or } R^{14} \text{ and } R^{15} \text{ are taken together to form a } C_3-C_5 \text{ alkylene;} \]

\[ \text{each } R^{14a} \text{, and } R^{15a} \text{ is independently } H \text{ or optionally substituted } C_1-C_5 \text{ alkyl; and } Q \text{ is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.} \]

[0013] In some embodiments, the individual has high blood pressure. In other embodiments, the method reduces one or more of any of the following: systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and pulse pressure of the individual, following administration of the compound. In other embodiments, the method does not substantially increase heart rate of the individual. In yet other embodiments, the individual has one or more risk factors for developing high blood pressure.

[0014] Provided is also a method of (i) increasing renal blood flow, and/or (ii) decreasing sodium reabsorption, in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I) or any variations detailed herein. In some embodiments, the method results in one or more of any of the following: increase in renal blood flow, decrease in sodium reabsorption, increase in urine sodium content and/or increase in urine volume, reduction in edema, reduction in elevated blood urea nitrogen to creatinine (BUN/Cr) ratio, and decrease in creatinine levels.

[0015] In some embodiments, the individual has or is at risk of developing acute or chronic congestive heart failure, acute decompensated congestive heart failure, acute or chronic renal failure, or acute or chronic renal failure due to renal insufficiency.

[0016] Provided is also a method of treating a disease or condition that is responsive to any one or more of: (i) a decrease in blood pressure; (ii) an increase in renal blood flow; and (iii) a
decrease of sodium reabsorption, comprising administering to an individual in need thereof an effective amount of a compound of the formula (I) or any variations detailed herein. In some embodiments, the disease or condition is hypertension. In certain embodiments, the disease or condition is treatment-resistant hypertension, or hypertensive emergency. In yet other embodiments, the disease or condition is a cardiac or renal disease or condition.

[0017] In some embodiments, the compound used in the methods described above is a compound of formula (A-III):

![Chemical Structure](image)

(A-III)

or a salt, solvate or N-oxide thereof, wherein:

- $R^1$ is H; C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or -C(O)O-C$_1$-C$_5$ alkyl; or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{4a}$ or $R^{5a}$, where present, to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety;

- each $n$ and $m$ is 1, or $n$ is 0 and $m$ is 1, or $n$ is 1 and $m$ is 0;

- $R^{2a}$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^1$ or $R^{5a}$, where present, to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{3a}$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-)
moiety; or is taken together with R^{4a}, where present, to form a methylene (-CH\_2-) moiety or an ethylene (-CH\_2CH\_2-) moiety;

R^{3a} is H; optionally substituted C\_1-C\_5 alkyl; optionally substituted C\_2-C\_5 alkenyl; or optionally substituted aryl; or is taken together with R\(^1\) or R\(^{4a}\), where present, to form a propylene (-CH\_2CH\_2CH\_2-) moiety or a butylene (-CH\_2CH\_2CH\_2CH\_2-) moiety; or is taken together with R\(^{2a}\) to form an ethylene (-CH\_2CH\_2-) moiety or a propylene (-CH\_2CH\_2CH\_2-) moiety; or is taken together with R\(^{5a}\), where present, to form a methylene (-CH\_2-) moiety or an ethylene (-CH\_2CH\_2-) moiety;

R\(^{4a}\) is H; optionally substituted C\_1-C\_5 alkyl; optionally substituted C\_2-C\_5 alkenyl; or optionally substituted aryl; or is taken together with R\(^{3a}\) to form a propylene (-CH\_2CH\_2CH\_2-) moiety or a butylene (-CH\_2CH\_2CH\_2CH\_2-) moiety; or is taken together with R\(^1\) to form an ethylene (-CH\_2CH\_2-) moiety or a propylene (-CH\_2CH\_2CH\_2-) moiety; or is taken together with R\(^{2a}\) to form a methylene (-CH\_2-) moiety or an ethylene (-CH\_2CH\_2-) moiety; or is taken together with R\(^{5a}\), where present, to form a methylene (-CH\_2-) moiety;

R\(^{5a}\) is H; optionally substituted C\_1-C\_5 alkyl; optionally substituted C\_2-C\_5 alkenyl; or optionally substituted aryl; or is taken together with R\(^{2a}\) to form a propylene (-CH\_2CH\_2CH\_2-) moiety or a butylene (-CH\_2CH\_2CH\_2CH\_2-) moiety; or is taken together with R\(^1\) to form an ethylene (-CH\_2CH\_2-) moiety or a propylene (-CH\_2CH\_2CH\_2-) moiety; or is taken together with R\(^{3a}\) to form a methylene (-CH\_2-) moiety or an ethylene (-CH\_2CH\_2-) moiety; or is taken together with R\(^{4a}\), where present, to form a methylene (-CH\_2-) moiety;

each R\(^{2b}\), R\(^{3b}\), R\(^{4b}\) and R\(^{5b}\) is independently H, optionally substituted C\_1-C\_5 alkyl, optionally substituted C\_2-C\_5 alkenyl, or optionally substituted aryl;

X is N or CR\(^{6a}\);

t is 1, 2 or 3;

each R\(^6\) and R\(^{6a}\) is independently H; hydroxyl; halo; C\_1-C\_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C\_2-C\_5 alkenyl; optionally substituted C\_1-C\_5 alkoxy; or optionally substituted -C(O)C\_1-C\_5 alkyl;

R\(^7\) is H; halo; optionally substituted C\_1-C\_5 alkyl; or optionally substituted aryl; or is taken together with R\(^8\) and the carbon atom to which they are attached to form a dioxyline ring or a carbonyl moiety; or is taken together with R\(^9\) to form a C\_3-C\_5 alkylene when R\(^8\) and R\(^{10}\) are taken together to form a bond;
R^8 is H; halo; hydroxyl; N(R^{11})R^{12}; SR^{13}, S(O)R^{13}; SO_2R^{13}; -OC(O)N(R^{14})R^{15}; -OC(O)-aryl; -OC(O)-heteroaryl; or -OC(O)C_1-C_5 alkyl optionally substituted with amino; or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R^{10} to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl; or is taken together with R^7 to form a C_2-C_5 alkyylene when R^8 and R^{10} are taken together to form a bond;

R^{10} is H or optionally substituted C_1-C_5 alkyl; or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl; or R^{11} and R^{12} are taken together to form C_2-C_5 alkyylene;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_2-C_5 alkyylene; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino.

[0018] In some embodiments, the compound used in the methods described above is a compound of formula (A-III), wherein any one or more of provisions (1) to (34) apply:

(1) X is CR^{6a}, wherein each R^{6a} is independently H, halo or C_1-C_5 alkyl;
(2) each R^6 is independently H, halo or C_1-C_5 alkyl;
(3) X is N;
(4) R^1 is H or C_1-C_5 alkyl;
(5) R^{2a} and R^{3a} is H;
(6) R^7 is H or C_1-C_5 alkyl;
(8) R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl;
(9) R^7 is H or C_1-C_5 alkyl, and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl;
(10) R^7 is H, and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl;
(11) R^7 is C_1-C_5 alkyl, and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl;
(12) R^7 is H or C₁-C₅ alkyl, and R^8 is H or hydroxyl;
(13) R^7 is H or C₁-C₅ alkyl, and R^8 is hydroxyl;
(14) R^7 is H, and R^8 is hydroxyl;
(15) R^7 is methyl, and R^8 is hydroxyl;
(16) R^7 is H, and R^8 is NH₂;
(17) R^7 is H, and R^8 is -OC(O)C₁-C₅ alkyl;
(18) R^9 is H or C₁-C₅ alkyl;
(19) R^1⁰ is H or C₁-C₅ alkyl;
(20) each R^9 and R^1⁰ is H;
(21) one of R^9 and R^1⁰ is H and the other is C₁-C₅ alkyl;
(22) Q is: unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl;
unsubstituted phenyl; unsubstituted imidazolyl; unsubstituted triazolyl; pyridyl substituted with
1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-
substituted C₁-C₅ alkyl, carboxyl and –C(O)NR₁⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently
H or optionally substituted C₁-C₅ alkyl; pyrimidyl substituted with 1 to 3 substituents
independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅
alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally
substituted C₁-C₅ alkyl; pyrazinyl substituted with 1 to 3 substituents independently selected
form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –
C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅
alkyl; or phenyl substituted with 1 to 3 substituents independently selected form the group
consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷,
wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; imidazolyl
substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-
C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is
independently H or optionally substituted C₁-C₅ alkyl; or triazolyl substituted with 1 to 3
substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-
substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently
H or optionally substituted C₁-C₅ alkyl;
(23) X is CR⁶⁶, wherein R⁶⁶ is H, halo or C₁-C₅ alkyl; and each R⁶ is independently H,
halo or C₁-C₅ alkyl;
(24) wherein R¹ is H or C₁-C₅ alkyl, R⁷ is H or C₁-C₅ alkyl, and R⁸ is H, hydroxyl,
N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl;
(25) wherein R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, and R^{8} is H or hydroxyl;
(26) R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, and R^{8} is hydroxyl;
(27) wherein R^{1} is CH_{3}, R^{7} is H, R^{8} is hydroxyl, n is zero and m is 1;
(28) R^{1} is CH_{3}, R^{7} is methyl, R^{8} is hydroxyl, n is zero and m is 1;
(29) X is CR^{6a}, wherein R^{6a} is H, halo or C_{1}-C_{5} alkyl; each R^{6} is independently H, halo or C_{1}-C_{5} alkyl; R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; each R^{9} and R^{10} is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl;
(30) n is 0 and m is 1; R^{1} is H or CH_{3}; R^{7} is H or CH_{3}; and R^{8} is H or hydroxyl;
(31) X is N; R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; each R^{9} and R^{10} is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl;
(32) n is 0 and m is 1; R^{1} is H or CH_{3}; R^{7} is H or CH_{3}; and R^{8} is H or hydroxyl;
(33) n is 0 and m is 1; R^{1} is taken together with R^{2a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety; X is CR^{6a}, wherein R^{6a} is H, halo or C_{1}-C_{5} alkyl; each R^{6} is independently H, halo or C_{1}-C_{5} alkyl; R^{7} is H or C_{1}-C_{5} alkyl, R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; each R^{9} and R^{10} is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl; and
(34) R^{7} is H or CH_{3}; and R^{8} is H or hydroxyl.

[0019] In some embodiments, the compound used in the methods described herein is a compound of formula (A-III)A detailed herein, wherein any one or more of provisions (35) - (45) apply:

(35) X is CH;
(36) X is N;
(37) R^{1} is H or CH_{3};
(38) $R^{2a}$ is H or is taken together with $R^1$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety;
(39) each $R^6$ and $R^{6a}$ is independently H, halo or C$_1$-C$_5$ alkyl;
(40) $R^7$ is H or CH$_3$;
(41) $R^8$ is hydroxyl;
(42) Q is: unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl;
unsubstituted phenyl; pyridyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; pyrimidyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; pyrazinyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; or phenyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$;
(43) Q is: unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl;
unsubstituted phenyl; unsubstituted imidazolyl; unsubstituted triazolyl; pyridyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; pyrimidyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; pyrazinyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; or phenyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$;
(44) X is CH; $R^1$ is H or CH$_3$; each $R^6$ is independently H, halo or C$_1$-C$_5$ alkyl; $R^7$ is H or CH$_3$; $R^8$ is hydroxyl; and Q is unsubstituted pyridyl, or pyridyl substituted with halo, CH$_3$, CF$_3$, CONH$_2$, OH, or OCH$_3$; and
(45) $R^1$ is CH$_3$; $R^6$ is CH$_3$; and Q is unsubstituted pyridyl.

[0020] In some embodiments, the compound is an adrenergic receptor $\alpha_{2B}$ antagonist. In other embodiments, the compound is also an adrenergic receptor $\alpha_{1B}$ antagonist. In yet other embodiments, the compound is also an adrenergic receptor $\alpha_{1D}$ antagonist.

[0021] Further provided is a kit comprising (i) a compound of formula (I) or any variations detailed herein, or a pharmaceutically acceptable salt thereof, and (ii) instructions for use according to the method described above. Also provided is a kit comprising a compound of formula (A-IIIA) or any variations detailed herein, or a pharmaceutically acceptable salt thereof, and (ii) instructions for use according to the method described above.

[0022] Also provided is use of a compound detailed herein, such as a compound of formula (I) or any variations thereof, or a salt, solvate or N-oxide thereof, in lowering blood pressure, increasing renal blood flow, and/or decreasing or inhibiting sodium reabsorption. Further provided are uses of a compound detailed herein, such as a compound of formula (I) or any variations thereof, or a salt, solvate or N-oxide thereof, for the manufacturing of a medicament for the treatment of a disease or condition that is responsive to any one or more of: (i) a decrease
in blood pressure; (ii) an increase in renal blood flow; and (iii) a decrease of sodium reabsorption.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] Figure 1 illustrates the $\alpha_{2B}$ antagonist activity of Compound Nos. 3a and 3b in the cell-based Aequorin Assay. The word “Compound” may be abbreviated as “Cpd.” in the figures.

[0024] Figure 2 illustrates the $\alpha_{2B}$ antagonist activity of Compound No. 3b in the Aequorin Antagonist Activity Assay.

[0025] Figure 3 illustrates the binding activity of Compound No. 3b in the $\alpha_{2A}$ and $\alpha_{2B}$ receptor assays.

[0026] Figure 4 illustrates the inhibitory effects of Compound No. 3b in a human $\alpha_{2B}$ cell membrane-based GTPgS binding activity assay (24 nM cirazoline (EC80)).

[0027] Figure 5 illustrates the $\alpha_{1B}$ antagonist activity of Compound No. 3b in the Aequorin Antagonist Activity Assay.

[0028] Figure 6 illustrates the inhibitory effects of Compound No. 5b in a $\alpha_{2B}$ receptor in a cell-based activity assay.

[0029] Figure 7 illustrates the effects of Compound Nos. 3, 3b, 4a and 5b on Systolic Blood Pressure in a SHR model.

[0030] Figure 8 illustrates the effects of Compound Nos. 3 and 3b (SC Treatment) on Systolic Blood Pressure in a SHR model.

[0031] Figure 9 illustrates the effects of Compound No. 3b on Systolic Blood Pressure in SHR model (administration: 15 mg/kg SC vs. 20 mg/kg PO).

[0032] Figure 10 illustrates the effects of Compound Nos. 13b and 41a on Systolic Blood Pressure in a SHR model.

[0033] Figure 11 illustrates the effect of Compound No. 3b on Systolic Blood Pressure in a dexmedetomidine induced dog model of hypertension.

[0034] Figure 12 illustrates the effect of Compound No. 5b on Systolic Blood Pressure in a dexmedetomidine induced dog model of hypertension.

[0035] Figure 13 illustrates the effect of Compound No. 5b on Systolic Blood Pressure in a dexmedetomidine induced dog model of hypertension, with DEX challenge.

[0036] Figure 14 illustrates the effect of Compound No. 41a on Systolic Blood Pressure in a dexmedetomidine induced dog model of hypertension.
[0037] Figure 15 illustrates the effect of Compound No. 3b on Systolic Blood Pressure in a dexmedetomidine induced dog model of hypertension – chronic mode, day 1.

[0038] Figure 16 illustrates the effect of Compound No. 3b on Systolic Blood Pressure in a dexmedetomidine induced dog model of hypertension – chronic mode, day 2.

[0039] Figure 17A illustrates the mitochondrial effects of Compound Nos. 3b, 4a, 5b and 39a and dimebon when subjected to hydrogen peroxide toxicity. The word “Dimebon” may be abbreviated as “DMB” in the figures.

[0040] Figure 17B illustrates the mitochondrial effects of Compound Nos. 3b, 4a, 5b and 39a and dimebon when subjected to calcium overload toxicity.

[0041] Figures 18A and 18B illustrate the cytoprotective effects of Compound Nos. 3b, 4a, 5b and 39a and dimebon from α-Synuclein (α-syn) toxicity.

[0042] Figure 19 illustrates the effects of Compound No. 144b (10 mg/kg, i.v.) in SHR model on Systolic Blood Pressure (Change from baseline).

[0043] Figure 20 illustrates the effects of Compound No. 27a in SHR on Systolic Blood Pressure in an i.v. dose escalation model (Change from baseline).

[0044] Figure 21 illustrates the effects of Compound No. 176a in SHR on Systolic Blood Pressure in an i.v. dose escalation model (Change from baseline).

[0045] Figure 22 illustrates the effects of Compound No. 26a in SHR on Systolic Blood Pressure in an i.v. dose escalation model (Change from baseline).

[0046] Figure 23 illustrates the effect of Compound No. 129d (PO) on Systolic blood pressure in SHR rats.

[0047] Figure 24 illustrates the effect of Compound No. 129d (i.v., Bolus) on Systolic blood pressure in SHR rats.

[0048] Figure 25 illustrates the effect of Compound No. 129d (i.v., Escalating Doses) on Systolic blood pressure in SHR rats.

[0049] Figure 26 illustrates the dose-response effects of Compound No. 3b, clonidine and vehicle on mean arterial blood pressure, systolic blood pressure, diastolic blood pressure and heart rate in rabbits.

[0050] Figure 27 illustrates the time-course effect of Compound No. 3b at 3 mg/kg and vehicle on mean arterial blood pressure, systolic blood pressure, diastolic blood pressure and heart rate in rabbits.
[0051] Figure 28 illustrates Compound No. 129d in a human adrenergic $\alpha_{2A}$ receptor inverse agonist activity assay (using GTPgS binding functional assay).

DETAILED DESCRIPTION OF THE INVENTION

Definitions
[0052] Unless clearly indicated otherwise, the terms “a”, “an”, and the like, refer to one or more.
[0053] It is also understood and clearly conveyed by this disclosure that reference to “the compound” or “a compound” includes and refers to any compounds (e.g., selective adrenergic receptor $\alpha_{2B}$ antagonists) or pharmaceutically acceptable salt or other form thereof as described herein.
[0054] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.
[0055] Unless clearly indicated otherwise, “an individual” as used herein intends a mammal, including but not limited to a human. The invention may find use in both human medicine and in the veterinary context.
[0056] As used herein, an “at risk” individual is an individual who is at risk of developing a disease or condition. An individual “at risk” may or may not have a detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment methods described herein. “At risk” denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factor(s).
[0057] As used herein, “treatment” or “treating” is an approach for obtaining a beneficial or desired result, including clinical results.
[0058] As used herein, “delaying” development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease or condition.
[0059] As used herein, the term “effective amount” intends such amount of a compound of the invention which should be effective in a given therapeutic form. As is understood in the art, an effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any of the co-administered compounds may optionally be lowered due to the combined action (e.g., additive or synergistic effects) of the compounds.

[0060] As used herein, “unit dosage form” refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient, or compound which may be in a pharmaceutically acceptable carrier.

[0061] As used herein, by “pharmaceutically acceptable” is meant a material that is not biologically or otherwise undesirable, e.g., the material may be incorporated into a pharmaceutical composition administered to an individual without causing significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably thus in some embodiments met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0062] “Pharmaceutically acceptable salts” are those salts which retain at least some of the biological activity of the free (non-salt) compound and which can be administered as drugs or pharmaceuticals to an individual. Such salts, for example, include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, oxalic acid, propionic acid, succinic acid, maleic acid, tartaric acid and the like; (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth metal ion, or an aluminum ion; or coordinates with an organic base.

Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, and the like. Further examples of pharmaceutically acceptable salts include those listed in Berge et al., Pharmaceutical Salts, J.
Pharm. Sci. 1977 Jan;66(1):1-19. Pharmaceutically acceptable salts can be prepared in situ in the manufacturing process, or by separately reacting a purified compound of the invention in its free acid or base form with a suitable organic or inorganic base or acid, respectively, and isolating the salt thus formed during subsequent purification. It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms or crystal forms thereof, particularly solvates or polymorphs. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholytes are formed when the solvent is alcohol. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature may cause a single crystal form to dominate.

[0063] The term “excipient” as used herein includes an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound detailed herein, or a pharmaceutically acceptable salt thereof, as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., carbomers, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc = “directly compressible”), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g.,
aspartame, dextrose, fructose, sorbitol, sucrose, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

[0064] An inverse agonist is a compound that binds to a receptor and inhibits the activity of the receptor in the absence of an agonist. An inverse agonist requires that the receptor have some constitutive basal activity in the absence of an agonist. While an agonist increases activity of the receptor over basal level an inverse agonist reduces receptor activity below basal level.

[0065] “Alkyl” refers to and includes saturated linear, branched, or cyclic univalent hydrocarbon structures and combinations thereof. Particular alkyl groups are those having 1 to 20 carbon atoms (a “C<sub>1</sub>-C<sub>20</sub> alkyl”). More particular alkyl groups are those having 1 to 8 carbon atoms (a “C<sub>1</sub>-C<sub>8</sub> alkyl”). When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, “butyl” is meant to include n-butyl, sec-butyl, iso-butyl, tert-butyl and cyclobutyl; “propyl” includes n-propyl, iso-propyl and cyclopropyl. This term is exemplified by groups such as methyl, t-butyl, n-heptyl, octyl, cyclohexylmethyl, cyclopropyl and the like. Cycloalkyl is a subset of alkyl and can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantyl. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. A preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a saturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a “C<sub>3</sub>-C<sub>8</sub> cycloalkyl”). Examples of cycloalkyl groups include adamantyl, decahydronaphthalenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

[0066] “Alkylene” refers to the same residues as alkyl, but having bivalency. Examples of alkylene include methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>CH<sub>2</sub>-), propylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-), butylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-) and the like.

[0067] “Alkenyl” refers to an unsaturated hydrocarbon group having at least one site of olefinic unsaturation (i.e., having at least one moiety of the formula C=C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms. Examples of alkenyl include but are not limited to -CH<sub>2</sub>-CH=CH-CH<sub>3</sub> and -CH<sub>2</sub>-CH<sub>2</sub>-cyclohexenyl, where the ethyl group of the latter example can be attached to the cyclohexenyl moiety at any available position on the ring. Cycloalkenyl is a subset of alkenyl and can consist of one ring, such as cyclohexenyl, or multiple rings, such as norbornenyl. A more preferred cycloalkenyl is an unsaturated cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a “C<sub>3</sub>-C<sub>8</sub> cycloalkenyl”). Examples of
cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and the like.

[0068] “Alkynyl” refers to an unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (i.e., having at least one moiety of the formula C≡C) and preferably having from 2 to 10 carbon atoms and more preferably 2 to 8 carbon atoms and the like.

[0069] “Substituted alkyl” refers to an alkyl group having from 1 to 5 substituents including, but not limited to, substituents such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminocarbonyl, aminocarboxyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0070] “Substituted alkenyl” refers to alkenyl group having from 1 to 5 substituents including, but not limited to, substituents such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminocarbonyl, aminocarboxyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0071] “Substituted alkynyl” refers to alkynyl groups having from 1 to 5 substituents including, but not limited to, groups such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminocarbonyl, aminocarboxyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[0072] “Acyl” refers to the groups H-C(=O)-, alkyl-C(=O)-, substituted alkyl-C(=O)-, alkenyl-C(=O)-, substituted alkenyl-C(=O)-, cycloalkenyl-C(=O)-, substituted cycloalkenyl-C(=O)-, alkynyl-C(=O)-, substituted alkynyl-C(=O)-, aryl-C(=O)-, substituted aryl-C(=O)-, heteroaryl-C(=O)-, substituted
heteroaryl-C(O)-, heterocyclic-C(O)-, and substituted heterocyclic-C(O)-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0073] “Acyloxy” refers to the groups H-C(O)O-, alkyl-C(O)O-, substituted alkyl-C(O)O-, alkenyl-C(O)O-, substituted alkenyl-C(O)O-, alkynyl-C(O)O-, substituted alkynyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, substituted aryl-C(O)O-, heteroaryl-C(O)O-, substituted heteroaryl-C(O)O-, heterocyclic-C(O)O-, and substituted heterocyclic-C(O)O-, wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0074] “Heterocycle”, “heterocyclic”, or “heterocyclyl” refers to a saturated or an unsaturated non-aromatic group having a single ring or multiple condensed rings, and having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the rings can be aryl or heteroaryl. A heterocycle having more than one ring where at least one ring is aromatic may be connected to the parent structure at either a non-aromatic ring position or at an aromatic ring position. In one variation, a heterocycle having more than one ring where at least one ring is aromatic is connected to the parent structure at a non-aromatic ring position.

[0075] “Substituted heterocyclic” or “substituted heterocyclyl” refers to a heterocycle group which is substituted with from 1 to 3 substituents including, but not limited to, substituents such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylaminio, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alky, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylalkoxy and the like. In one variation, a substituted heterocycle is a heterocycle substituted with an additional ring, wherein the additional ring may be aromatic or non-aromatic.

[0076] “Aryl” or “Ar” refers to an unsaturated aromatic carbocyclic group having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl) which condensed rings may
or may not be aromatic. In one variation, the aryl group contains from 6 to 14 annular carbon atoms. An aryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, an aryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[H0077] “Heteroaryl” or “HetAr” refers to an unsaturated aromatic carbocyclic group having from 1 to 10 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur. A heteroaryl group may have a single ring (e.g., pyridyl, furyl) or multiple condensed rings (e.g., indolizyl, benzothienyl) which condensed rings may or may not be aromatic. A heteroaryl group having more than one ring where at least one ring is non-aromatic may be connected to the parent structure at either an aromatic ring position or at a non-aromatic ring position. In one variation, a heteroaryl group having more than one ring where at least one ring is non-aromatic is connected to the parent structure at an aromatic ring position.

[H0078] “Substituted aryl” refers to an aryl group having 1 to 5 substituents including, but not limited to, groups such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarboxyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[H0079] “Substituted heteroaryl” refers to a heteroaryl group having 1 to 5 substituents including, but not limited to, groups such as alkoxy, substituted alkoxy, acyl, acyloxy, carbonylalkoxy, acylamino, substituted or unsubstituted amino, aminoacyl, aminocarbonylamino, aminocarboxyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy and the like.

[H0080] “Aralkyl” refers to a residue in which an aryl moiety is attached to an alkyl residue and wherein the aralkyl group may be attached to the parent structure at either the aryl or the alkyl
residue. Preferably, an aralkyl is connected to the parent structure via the alkyl moiety. In one variation, an aralkyl is a fused ring system where at least one cycloalkyl moiety is fused with at least one aryl moiety. A “substituted aralkyl” refers to a residue in which an aryl moiety is attached to a substituted alkyl residue and wherein the aralkyl group may be attached to the parent structure at either the aryl or the alkyl residue. When an aralkyl is connected to the parent structure via the alkyl moiety, it may also be referred to as an “alkaryl”. More particular alkaryl groups are those having 1 to 3 carbon atoms in the alkyl moiety (a “C₁-C₃ alkaryl”).

“Alkoxy” refers to the group alkyl-O-, which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and the like. Similarly, alkenyloxy refers to the group “alkenyl-O-” and alkynylloxy refers to the group “alkynyl-O-”. “Substituted alkoxy” refers to the group substituted alkyl-O.

“Unsubstituted amino” refers to the group -NH₂.

“Substituted amino” refers to the group -NRₐRₐ wherein either (a) each Rₐ and Rₐ group is independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, provided that both Rₐ and Rₐ groups are not H; or (b) Rₐ and Rₐ are joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

“Acylamino” refers to the group -C(O)NRₐRₐ wherein Rₐ and Rₐ are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic or Rₐ and Rₐ groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

“Aminoacyl” refers to the group -NRₐC(O)Rₐ wherein each Rₐ and Rₐ group is independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic. Preferably, Rₐ is H or alkyl.

“Aminosulfonyle” refers to the groups -NRₐSO₂-alkyl, -NRₐSO₂-substituted alkyl, -NRₐSO₂-alkenyl, -NRₐSO₂-substituted alkenyl, -NRₐSO₂-alkynyl, -NRₐSO₂-substituted alkynyl, -NRₐSO₂-cycloalkyl, -NRₐSO₂-substituted cycloalkyl, -NRₐSO₂-aryls, -NRₐSO₂-substituted aryl, -NRₐSO₂-heteroaryl, -NRₐSO₂-substituted heteroaryl, -NRₐSO₂-heterocyclic, and -NRₐSO₂-
substituted heterocyclic, where R is H or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[S087] “Sulfonylamino” refers to the groups -SO₂NH₂, -SO₂NR-alkyl, -SO₂NR-substituted alkyl, -SO₂NR-alkenyl, -SO₂NR-substituted alkenyl, -SO₂NR-alkynyl, -SO₂NR-substituted alkynyl, -SO₂NR-aryl, -SO₂NR-substituted aryl, -SO₂NR-heteroaryl, -SO₂NR-substituted heteroaryl, -SO₂NR-heterocyclic, and -SO₂NR-substituted heterocyclic, where R is H or alkyl, or -SO₂NR₂, where the two R groups are taken together and with the nitrogen atom to which they are attached to form a heterocyclic or substituted heterocyclic ring.


[S089] “Aminocarbonylalkoxy” refers to the group –NRₐC(O)ORₐ where each Rₐ and Rₐ group is independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic.

[S090] “Carbonylalkylenealkoxy” refers to the group -(C(O)-(CH₂)ₙ-OR where R is a substituted or unsubstituted alkyl and n is an integer from 1 to 100, more preferably n is an integer from 1 to 10 or 1 to 5.

[S091] “Halo” or “halogen” refers to elements of the Group 17 series having atomic number 9 to 85. Preferred halo groups include the radicals of fluorine, chlorine, bromine and iodine. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, e.g., dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each H is replaced with a halo group is referred to as a “perhaloalkyl.” A preferred perhaloalkyl group is trifluoroalkyl (-CF₃). Similarly, “perhaloalkoxy” refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkoxy moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (-OCF₃).
“Carbonyl” refers to the group C=O.

“Cyano” refers to the group -CN.

“Oxo” refers to the moiety =O.

“Nitro” refers to the group -NO₂.

“Thioalkyl” refers to the groups -S-alkyl.

“Alkylsulfonylamino” refers to the groups -R¹SO₂NR₂R₃, where R₄ and R₅ are independently selected from the group consisting of H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, or the R₆ and R₇ groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring and R¹ is an alkyl group.

“Carbonylalkoxy” refers to as used herein refers to the groups –C(O)O-alkyl, –C(O)O-substituted alkyl, –C(O)O-aryl, –C(O)O-substituted aryl, –C(O)O-alkenyl, –C(O)O-substituted alkenyl, –C(O)O-alkynyl, –C(O)O-substituted alkynyl, –C(O)O-heteroaryl, –C(O)O-substituted heteroaryl, –C(O)O-heterocyclic or –C(O)O-substituted heterocyclic.

“Geminal” refers to the relationship between two moieties that are attached to the same atom. For example, in the residue -CH₂-CHR¹R², R¹ and R² are geminal and R¹ may be referred to as a geminal R group to R².

“Vicinal” refers to the relationship between two moieties that are attached to adjacent atoms. For example, in the residue –CHR¹-CH₂R², R¹ and R² are vicinal and R¹ may be referred to as a vicinal R group to R².

**Receptor Binding Profile**

In some embodiments, compounds that bind to and are antagonists of the adrenergic receptor α₂B, but which are not antagonists of the adrenergic receptor α₂A, and pharmaceutically acceptable salts thereof, are provided. The compounds may find use in therapy for decreasing blood pressure in an individual and in treating diseases or conditions which are responsive to (i) a decrease in blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption or sodium retention. Thus, an individual who has a disease or condition that is responsive to (i) a decrease in blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption or sodium retention will experience one or more beneficial or desirable results upon administration of a compound.
provided herein, or pharmaceutically acceptable salt thereof. In one aspect, the beneficial or desirable result is a reduction in the individual’s mean arterial blood pressure for a period of time following administration of the compound or pharmaceutically acceptable salt thereof. In another aspect, the beneficial or desirable result is a reduction in the individual’s systolic blood pressure for a period of time following administration of the compound or pharmaceutically acceptable salt thereof. In a further aspect, the beneficial or desirable result is an increase in renal blood flow (e.g., by altering the vascular tone of renal efferent and afferent arterioles) for a period of time following administration of the compound or pharmaceutically acceptable salt thereof. In another aspect, the beneficial or desirable result is a decrease or inhibition in sodium reabsorption (e.g., thereby exerting a natriuretic and diuretic effect) for a period of time following administration of the compound or pharmaceutically acceptable salt thereof. In another aspect, the beneficial or desirable result is an increase in urine sodium and/or urine volume for a period of time following administration of the compound or pharmaceutically acceptable salt thereof. In one variation, the compounds may find use in therapy in treating diseases or conditions which are responsive to (i) a decrease in blood pressure and (ii) an increase in renal blood flow. In one variation, the compounds may find use in therapy in treating diseases or conditions which are responsive to (i) a decrease in blood pressure and (ii) a decrease or inhibition of sodium reabsorption. In one variation, the compounds may find use in treating diseases or conditions which are responsive to (i) an increase in renal blood flow and (ii) a decrease or inhibition of sodium reabsorption. In one variation, the compounds may find use in therapy in treating diseases or conditions which are responsive to (i) a decrease in blood pressure and (ii) an increase in renal blood flow and (iii) a decrease or inhibition of sodium reabsorption.

[0102] Compounds that bind to and are antagonists of the adrenergic receptor α2B should reduce an individual’s blood pressure. However, compounds that antagonize the adrenergic receptor α2A in some instances may actually increase an individual’s blood pressure. Thus, compounds that antagonize the adrenergic receptor α2B but do not antagonize the adrenergic receptor α2A (compounds referred to herein as “selective adrenergic receptor α2B antagonists”) are desirable agents in therapy. Selective adrenergic receptor α2B antagonists find further use in therapy of cardiovascular and renal indications. The selective adrenergic receptor α2B antagonists provided herein (i) bind to and are antagonists of the adrenergic receptor α2B, and (ii) are not antagonists of the adrenergic receptor α2A.
[0103] The selective adrenergic receptor $\alpha_{2B}$ antagonists may in some variations also bind to and be agonists of the adrenergic receptor $\alpha_{2A}$. The selective adrenergic receptor $\alpha_{2B}$ antagonists may also be used in conjunction with other agents that are agonists of the adrenergic receptor $\alpha_{2A}$.

[0104] The selective adrenergic receptor $\alpha_{2B}$ antagonists may in some variations also bind to and be antagonists of the adrenergic receptor $\alpha_{1B}$. The selective adrenergic receptor $\alpha_{2B}$ antagonists may also be used in conjunction with other agents that are antagonists of the adrenergic receptor $\alpha_{1B}$.

[0105] The selective adrenergic receptor $\alpha_{2B}$ antagonists may in some variations also bind to and be antagonists of the adrenergic receptor $\alpha_{1D}$. The selective adrenergic receptor $\alpha_{2B}$ antagonists may also be used in conjunction with other agents that are antagonists of the adrenergic receptor $\alpha_{1D}$.

[0106] The selective adrenergic receptor $\alpha_{2B}$ antagonists may in some variations both (i) bind to and be agonists of the adrenergic receptor $\alpha_{2A}$ and (ii) bind to and be antagonists of the adrenergic receptor $\alpha_{1B}$ and/or $\alpha_{1D}$.

[0107] In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$ and (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and about 90%, between about 70% and about 90%, or between about 80% and about 100% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about any one of 30%, 25%, 20%, 15%, 10%, or 5%, or between about 0% and about 30%, between about 10% and about 30%, or between about 20% and about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.1 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$ and (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and about 90%, between about 70% and about 90%, between about 80% and about 90%,
or between about 80% and about 100% inhibition of $\alpha_{2B}$ ligand binding at 0.1 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about any one of 30%, 25%, 20%, 15%, 10%, or 5%, or between about 0% and about 30%, between about 10% and about 30%, or between about 20% and about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. It is understood and clearly conveyed herein that a selective adrenergic receptor $\alpha_{2B}$ antagonist can exhibit any of the adrenergic receptor $\alpha_{2A}$ binding profiles described herein in combination with any of the adrenergic receptor $\alpha_{2A}$ binding profiles described herein, as if each and every combination were listed separately. For example, a selective adrenergic receptor $\alpha_{2B}$ antagonist may exhibit (i) equal to or greater than about 65% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about 25% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$.

[0108] In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.03 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and about 90%, between about 70% and about 90%, or between about 80% and about 100% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about any one of 30%, 25%, 20%, 15%, 10%, or 5%, or between about 0% and about 30%, between about 10% and about 30%, or between about 20% and about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.03 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.1 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.03 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits (i) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and about 90%, between about 70% and about 90%, or between about 80% and about 100% inhibition of $\alpha_{2B}$ ligand binding at 0.1 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about any one of 30%, 25%, 20%, 15%, 10%, or 5%, or between about 0% and about 30%, between about 10% and about
30%, or between about 20% and about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.03 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$. It is understood and clearly conveyed herein that a selective adrenergic receptor $\alpha_{2B}$ antagonist can exhibit any of the adrenergic receptor $\alpha_{2B}$ binding profiles described herein in combination with any of the adrenergic receptor $\alpha_{2A}$ binding profiles described herein, as if each and every combination were listed separately. For example, a selective adrenergic receptor $\alpha_{2B}$ antagonist may exhibit (i) equal to or greater than about 65% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about 25% inhibition of $\alpha_{2A}$ ligand binding at 0.03 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$.

[0109] In another variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist has a Ki ratio of $\alpha_{2A}$ to $\alpha_{2B}$ that is greater than about any one of 5 or 15 or 50. Ki is the binding affinity from the Cheng-Prusoff equation: $\text{Ki} = \text{IC}_{50} / (1 + [S]\text{/Kd})$, wherein [S] is the concentration of the radioligand and Kd is dissociation constant (affinity) of the radioligand for the protein (Cheng, Y., Prusoff, W.H., Biochem. Pharmacol. 22:3099-3108, 1973). It is understood that the Ki ratio of $\alpha_{2A}$ to $\alpha_{2B}$ may be combined with any binding and/or other activity profile details described herein for selective adrenergic receptor $\alpha_{2B}$ antagonists the same as if each were specifically and individually listed. For example, in one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist may exhibit (i) equal to or greater than about 65% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, and (ii) equal to or less than about 25% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$; and a Ki ratio of $\alpha_{2A}$ to $\alpha_{2B}$ that is greater than about any one of 5 or 15 or 50.

[0110] The selective adrenergic receptor $\alpha_{2B}$ antagonists may in some variations also bind to and be antagonists of the adrenergic receptor $\alpha_{1B}$. In one variation, the selective adrenergic receptor $\alpha_{2B}$ antagonists may exhibit (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$, and (iii) equal to or greater than about 60% inhibition of $\alpha_{1B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{1B}$. In one variation, the selective adrenergic receptor $\alpha_{2B}$ antagonists may exhibit (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$, and (iii) equal to or greater than about any one of
60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and 90%, between about 70% and 90%, or between about 80% and about 100% inhibition of α1B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α1B. In one variation, the selective adrenergic receptor α2B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α2B ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α2B, (ii) equal to or less than about 30% inhibition of α2A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α2A, and (iii) equal to or greater than about 60% inhibition of α1B ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α1B. In one variation, the selective adrenergic receptor α2B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α2B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α2B, (ii) equal to or less than about 30% inhibition of α2A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α2A, and (iii) equal to or greater than about 60% inhibition of α1B ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α1B. In one variation, the selective adrenergic receptor α2B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α2B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α2B, (ii) equal to or less than about 30% inhibition of α2A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α2A, and (iii) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and 90%, between about 70% and 90%, or between about 80% and about 100% inhibition of α1B ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α1B. It is understood and clearly conveyed herein that a selective adrenergic receptor α2B antagonist can exhibit any of the adrenergic receptor α2B binding profiles described herein in combination with any of the adrenergic receptor α2A binding profiles described herein and any of the adrenergic receptor α1B binding profiles, as if each and every combination were listed separately. For example, a selective adrenergic receptor α2B antagonist may exhibit (i) equal to or greater than about 65% inhibition of α2B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α2B, (ii) equal to or less than about 25% inhibition of α2A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α2A, and (iii) equal to or greater than about 65% inhibition of α1B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α1B. The selective adrenergic receptor α2B antagonists may also be used in conjunction with other agents that antagonize the adrenergic receptor α1B. Administration in conjunction with another
compound includes administration in the same or different composition, either sequentially, simultaneously, or continuously.

[0111] The selective adrenergic receptor α₂B antagonists may in some variations also bind to and be antagonists of the adrenergic receptor α₁D. In one variation, the selective adrenergic receptor α₂B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₂B, (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α₂A, and (iii) equal to or greater than about 60% inhibition of α₁D ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₁D. In another variation, the selective adrenergic receptor α₂B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₂B, (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α₂A, (iii) equal to or greater than about 60% inhibition of α₁B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₁B and (iv) equal to or greater than about 60% inhibition of α₁D ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₁D. In one variation, the selective adrenergic receptor α₂B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₂B, (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α₂A, and (iii) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and 90%, between about 70% and 90%, or between about 80% and about 100% inhibition of α₁D and/or α₁B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₁D and/or α₁B. In one variation, the selective adrenergic receptor α₂B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α₂B, (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α₂A, and (iii) equal to or greater than about 60% inhibition of α₁B and/or α₁D ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α₁B and/or α₁D. In one variation, the selective adrenergic receptor α₂B antagonists may exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α₂B, (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α₂A, and (iii) equal to or greater than about 60%
inhibition of $\alpha_{1B}$ and/or $\alpha_{1D}$ ligand binding at 0.1 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{1B}$ and/or $\alpha_{1D}$. In one variation, the selective adrenergic receptor $\alpha_{2B}$ antagonists may exhibit (i) equal to or greater than about 60% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, (ii) equal to or less than about 30% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$, and (iii) equal to or greater than about any one of 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 60% and 90%, between about 70% and 90%, or between about 80% and about 100% inhibition of $\alpha_{1B}$ and/or $\alpha_{1D}$ ligand binding at 0.1 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{1B}$ and/or $\alpha_{1D}$. It is understood and clearly conveyed herein that a selective adrenergic receptor $\alpha_{2B}$ antagonist can exhibit any of the adrenergic receptor $\alpha_{2B}$ binding profiles described herein in combination with any of the adrenergic receptor $\alpha_{2A}$ binding profiles described herein and any of the adrenergic receptor $\alpha_{1B}$ and/or $\alpha_{1D}$ binding profiles, as if each and every combination were listed separately. For example, a selective adrenergic receptor $\alpha_{2B}$ antagonist may exhibit (i) equal to or greater than about 65% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{2B}$, (ii) equal to or less than about 25% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and absence of antagonist activity to adrenergic receptor $\alpha_{2A}$, and (iii) equal to or greater than about 65% inhibition of $\alpha_{1D}$ ligand binding at 0.03 $\mu$M and antagonist activity to adrenergic receptor $\alpha_{1D}$. The selective adrenergic receptor $\alpha_{2B}$ antagonists may also be used in conjunction with other agents that antagonize the adrenergic receptor $\alpha_{1D}$. Administration in conjunction with another compound includes administration in the same or different composition, either sequentially, simultaneously, or continuously.

[0112] In some instances, compounds provided herein bind to and are antagonists of adrenergic receptor $\alpha_{2B}$ and may also be antagonists for the adrenergic receptor $\alpha_{2A}$. In such instances, it is preferable that the compound is more potent at inhibiting the adrenergic receptor $\alpha_{2B}$ compared to the adrenergic receptor $\alpha_{2A}$. In one variation, the compound inhibit both the adrenergic receptor $\alpha_{2B}$ and the adrenergic receptor $\alpha_{2A}$, and wherein the compound has limited or no brain bioavailability and so cannot easily activate adrenergic $\alpha_{2A}$ receptors in the brain. In one variation, the compound inhibits both the adrenergic receptor $\alpha_{2B}$ and the adrenergic receptor $\alpha_{2A}$, and wherein the compound has brain bioavailability. In some other instances, compounds provided herein bind to and are antagonists of adrenergic receptor $\alpha_{2B}$ and may be inverse agonists for the adrenergic receptor $\alpha_{2A}$. In some embodiments, the compound (1) binds to and is an antagonist of adrenergic receptor $\alpha_{2B}$, and (2) binds to and is an antagonist and/or
inverse agonist of the adrenergic receptor $\alpha_{2A}$. In some embodiments, the compound (1) binds to and is an antagonist of adrenergic receptor $\alpha_{2B}$, (2) binds to and is an antagonist and/or inverse agonist of the adrenergic receptor $\alpha_{2A}$, and (3) binds to and is antagonist of the adrenergic receptor $\alpha_{1B}$ and/or the adrenergic receptor $\alpha_{1D}$. It is understood and clearly conveyed herein that an adrenergic receptor $\alpha_{2B}$ antagonist can exhibit any of the adrenergic receptor $\alpha_{2B}$ binding profiles (in terms of % inhibition at a given concentration and/or in terms of $K_i$) described herein in combination with any of the adrenergic receptor $\alpha_{1B}$ and/or $\alpha_{1D}$ binding profiles, as if each and every combination were listed separately.

[0113] The binding properties to adrenergic receptors of compounds disclosed herein may be assessed by methods known in the art, such as competitive binding assays. In one variation, compounds are assessed by the binding assays detailed herein. In one variation, inhibition of binding of a ligand to a receptor is measured by the assays described herein. In another variation, inhibition of binding of a ligand is measured in an assay known in the art.

*Functional Assay Profile*

[0114] Antagonist activity to the adrenergic receptor $\alpha_{2B}$ receptor may be assessed by methods known in the art, such as standard $\alpha_{2B}$ receptor cell membrane-based or intact cell-based activity assays. For example, the GTP$\gamma$S binding or Aequorin-based assays may be used. In one variation, the selective adrenergic receptor $\alpha_{2B}$ antagonists exhibit an IC$_{50}$ value equal to or less than about any one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC$_{80}$ of oxymetazoline (for Aequorin assay) or guanfacine (for GTP$\gamma$S assay)) in an $\alpha_{2B}$ antagonist assay. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay equal to or less than about 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC$_{80}$ of oxymetazoline (for Aequorin assay) or guanfacine (for GTP$\gamma$S assay)) in an $\alpha_{2B}$ antagonist assay. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of oxymetazoline corresponding to its EC$_{80}$ concentration as obtained by assay protocols described herein. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of oxymetazoline between about 50 nM and about 5000 nM. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay
equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of about 480 nM oxymetazoline. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of guanfacine between about 50 nM and about 5000 nM. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of about 500 nM guanfacine, which in a particular variation is 504 nM guanfacine.

[0115] The absence of antagonist activity to the adrenergic receptor $\alpha_{2A}$ may be assessed by methods known in the art, such as standard $\alpha_{2A}$ receptor intact cell-based activity assays. For example, the Aequorin-based assay may be used. It is understood and clearly conveyed that absence of antagonist activity to the adrenergic receptor $\alpha_{2A}$ intends activity that is sufficiently reduced, but not necessarily eliminated or undetectable, at the adrenergic receptor $\alpha_{2A}$. In one variation, a compound will exhibit an undetectable amount of antagonist activity to the adrenergic receptor $\alpha_{2A}$. In another variation, a compound will lack antagonist activity to the adrenergic receptor $\alpha_{2A}$ if it exhibits an IC$_{50}$ value in an $\alpha_{2A}$ antagonist assay that is greater than about any one of 50 nM, 100 nM or 200 nM at a given concentration of agonist (e.g., concentration corresponding to EC$_{80}$ of UK14304). In one variation, the adrenergic receptor $\alpha_{2A}$ exhibits an IC$_{50}$ value in an $\alpha_{2A}$ antagonist assay that is greater than about 200 nM at a given concentration of agonist (e.g., concentration corresponding to EC$_{80}$ of UK14304). In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2A}$ antagonist assay greater than about any one of 50 nM, 100 nM or 200 nM at a concentration of UK14304 corresponding to its EC$_{80}$ concentration as obtained by assay protocols described herein. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonist exhibits an IC$_{50}$ value in an $\alpha_{2A}$ antagonist assay greater than about any one of 50 nM, 100 nM or 200 nM at a concentration of UK14304 between about 0.4 nM and about 40 nM. In one variation, a selective adrenergic receptor $\alpha_{2B}$ antagonists exhibits an IC$_{50}$ value in an $\alpha_{2A}$ antagonist assay greater than about any one of 50 nM, 100 nM or 200 nM at a concentration of about 5 nM UK14304, which in a particular variation is 4.57 nM UK14304. Alternatively, a compound that does not bind the $\alpha_{2A}$ receptor will be neither an agonist nor antagonist of the $\alpha_{2A}$ receptor.

[0116] In some variations, regardless of IC$_{50}$ values obtained from $\alpha_{2B}$ and $\alpha_{2A}$ assays, a compound may nonetheless be a selective adrenergic receptor $\alpha_{2B}$ antagonist if it exhibits a Ki ratio of $\alpha_{2A}$ to $\alpha_{2B}$ that is higher than about any one of 5, 10, or 15. For example, where a
compound exhibits an IC_{50} value between about 50-100 nM in an \( \alpha_{2B} \) antagonist assay at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of oxymetazoline) and an IC_{50} value between about 50 and 100 nM in an \( \alpha_{2A} \) antagonist assay at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of UK14304), the compound is considered, in one variation, a selective adrenergic receptor \( \alpha_{2B} \) antagonist if it exhibits a Ki ratio of \( \alpha_{2A} \) to \( \alpha_{2B} \) higher than about any one of 5, 10, or 15.

[0117] Antagonist activity to adrenergic receptor \( \alpha_{1B} \) may be assessed by methods known in the art, such as standard \( \alpha_{1B} \) receptor intact cell-based activity assays, including the Aequorin-based assay. In one variation, a selective adrenergic receptor \( \alpha_{2B} \) antagonist will also antagonize the adrenergic receptor \( \alpha_{1B} \) and exhibit an IC_{50} value equal to or less than about any one of 100 nM or 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of cirazoline) in an adrenergic receptor \( \alpha_{1B} \) antagonist assay. In one variation, a selective adrenergic receptor \( \alpha_{2B} \) antagonist will also antagonize the adrenergic receptor \( \alpha_{1B} \) and exhibit an IC_{50} value equal or less than about 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of cirazoline) in an adrenergic receptor \( \alpha_{1B} \) antagonist assay. In one variation, the selective adrenergic receptor \( \alpha_{2B} \) antagonists exhibit an IC_{50} value in an \( \alpha_{1B} \) antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10nM at a concentration of cirazoline corresponding to its EC_{80} concentration as obtained by assay protocols described herein. In one variation, the selective adrenergic receptor \( \alpha_{2B} \) antagonists exhibit an IC_{50} value in an \( \alpha_{1B} \) antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of cirazoline between about 2.3 nM and about 230 nM. In one variation, the selective adrenergic receptor \( \alpha_{2B} \) antagonists exhibit an IC_{50} value in an \( \alpha_{1B} \) antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of about 25 nM cirazoline, which in a particular variation is 23.56 nM cirazoline.

[0118] Antagonist activity to adrenergic receptor \( \alpha_{1D} \) may be assessed by methods known in the art, such as standard \( \alpha_{1D} \) receptor intact cell-based activity assays, including the Aequorin-based assay. In one variation, a selective adrenergic receptor \( \alpha_{2B} \) antagonist will also antagonize the adrenergic receptor \( \alpha_{1D} \) and exhibit an IC_{50} value equal to or less than about any one of 100 nM or 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of cirazoline) in an adrenergic receptor \( \alpha_{1D} \) antagonist assay. In one variation, a selective adrenergic receptor \( \alpha_{2B} \) antagonist will also antagonize the adrenergic receptor \( \alpha_{1D} \) and exhibit an IC_{50} value equal or less than about 10 nM at a given concentration of agonist (e.g., concentration
corresponding to EC₈₀ of cirazoline) in an adrenergic receptor α₁D antagonist assay. In one variation, the selective adrenergic receptor α₂B antagonists exhibit an IC₅₀ value in an α₁D antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of cirazoline corresponding to its EC₈₀ concentration as obtained by assay protocols described herein. In one variation, the selective adrenergic receptor α₂B antagonists exhibit an IC₅₀ value in an α₁D antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of cirazoline between about 2.3 nM and about 230 nM. In one variation, the selective adrenergic receptor α₂B antagonists exhibit an IC₅₀ value in an α₁D antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of about 25 nM cirazoline, which in a particular variation is 23.56 nM cirazoline.

[0119] In one variation, the selective adrenergic receptor α₂B antagonists exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and an IC₅₀ value in an α₂B antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC₈₀ of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay)), and (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and an IC₅₀ value in an α₂A antagonist assay that is greater than about any one of 50 nM, 100 nM or 200 nM at a given concentration of agonist (e.g., concentration corresponding to EC₈₀ of UK14304). In some variations, the selective adrenergic receptor α₂B antagonists exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and an IC₅₀ value in an α₂B antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC₈₀ of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay)), and (ii) equal to or less than about 30% inhibition of α₂A ligand binding at 0.1 μM and an IC₅₀ value in an α₂A antagonist assay that is greater than about any one of 50 nM, 100 nM or 200 nM at a given concentration of agonist (e.g., concentration corresponding to EC₈₀ of UK14304), and (iii) equal to or greater than about 60% inhibition of α₁B ligand binding at 0.03 μM and an IC₅₀ value in an α₁B antagonist assay equal or less than about any one of 100 nM or 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC₈₀ of cirazoline). In some variations, the selective adrenergic receptor α₂B antagonists exhibit (i) equal to or greater than about 60% inhibition of α₂B ligand binding at 0.03 μM and an IC₅₀ value in an α₂B antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC₈₀ of oxymetazoline (for
Aequorin assay) or guanfacine (for GTPγS assay), and (ii) equal to or less than about 30% inhibition of α2A ligand binding at 0.1 μM and an IC_{50} value in an α2A antagonist assay that is greater than about any one of 50 nM, 100 nM or 200 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of UK14304), and (iii) equal to or greater than about 60% inhibition of α1D ligand binding at 0.03 μM and an IC_{50} value in an α1D antagonist assay equal or less than about any one of 100 nM or 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of cirazoline). In some variations, the selective adrenergic receptor α2B antagonists exhibit (i) equal to or greater than about 60% inhibition of α2B ligand binding at 0.03 μM and an IC_{50} value in an α2B antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay)), and (ii) equal to or less than about 30% inhibition of α2A ligand binding at 0.1 μM and an IC_{50} value in an α2A antagonist assay that is greater than about any one of 50 nM, 100 nM or 200 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of UK14304), (iii) equal to or greater than about 60% inhibition of α1B ligand binding at 0.03 μM and an IC_{50} value in an α1B antagonist assay equal or less than about any one of 100 nM or 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of cirazoline); and (iv) equal to or greater than about 60% inhibition of α1D ligand binding at 0.03 μM and an IC_{50} value in an α1D antagonist assay equal or less than about any one of 100 nM or 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of cirazoline).

[0120] In another variation, the selective adrenergic receptor α2B antagonists exhibit (i) equal to or greater than about 60% inhibition of α2B ligand binding at 0.03 μM and an IC_{50} value in an α2B antagonist assay equal to or less than any about one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay)), and (ii) binding to and agonist activity to adrenergic receptor α2A.

[0121] In another variation, the adrenergic receptor α2B antagonists exhibit (i) equal to or greater than about 60% inhibition of α2B ligand binding at 0.03 μM and an IC_{50} value in an α2B antagonist assay equal to or less than any about one of 100 nM, 30 nM or 10 nM at a given concentration of agonist (e.g., concentration corresponding to EC_{80} of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay)), and (ii) greater than or equal to about 30%
inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and IC$_{50}$ value in an adrenergic receptor $\alpha_{2A}$ antagonist assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of UK14304 (for Aequorin assay) corresponding to its EC$_{80}$ concentration obtained by assay protocols described herein.

[0122] It is understood and clearly conveyed herein that compounds provided herein, including selective adrenergic receptor $\alpha_{2B}$ antagonists provided herein can exhibit any of the binding profiles and any of the antagonist or agonist activity profiles detailed herein, the same as if each and every combination were individually listed. For example, in one variation, the selective adrenergic receptor $\alpha_{2B}$ antagonists exhibit (i) greater than about 65% inhibition of $\alpha_{2B}$ ligand binding at 0.03 $\mu$M and an IC$_{50}$ value in an $\alpha_{2B}$ antagonist assay equal to or less than about 10nM at a concentration of oxymetazoline corresponding to its EC$_{80}$ concentration as obtained by assay protocols described herein, and (ii) less than about 25% inhibition of $\alpha_{2A}$ ligand binding at 0.1 $\mu$M and an IC$_{50}$ value in an $\alpha_{2A}$ antagonist assay that is greater than 200nM at a concentration of UK14304 corresponding to its EC$_{80}$ concentration as obtained by assay protocols described herein, and (iii) equal to or greater than about 60% inhibition of $\alpha_{1B}$ ligand binding at 0.03 $\mu$M and an IC$_{50}$ value in an $\alpha_{1B}$ antagonist assay equal or less than 10 nM at a concentration of cirazoline corresponding to its EC$_{80}$ concentration as obtained by assay protocols described herein. In one aspect, such a compound will also exhibit a Ki ratio of $\alpha_{2A}$ to $\alpha_{2B}$ that is greater than about any one of 5 or 15 or 50.

Medical Use

[0123] Without being bound by theory, it is believed that the compounds provided herein are capable of (i) reducing blood pressure and/or (ii) promoting renal blood flow and/or (iii) decreasing or inhibiting sodium reabsorption. In some embodiments, the compounds are adrenergic receptor $\alpha_{2B}$ antagonists (e.g., selective adrenergic receptor $\alpha_{2B}$ antagonists). In some embodiments, it is believed that the selective adrenergic receptor $\alpha_{2B}$ antagonists provided herein are capable of (i) reducing blood pressure and/or (ii) promoting renal blood flow and/or (iii) decreasing or inhibiting sodium reabsorption without concomitantly antagonizing the $\alpha_{2A}$ receptor, which would reduce or potentially eliminate the beneficial blood pressure lowering and renal effects modulated by antagonizing $\alpha_{2B}$. Furthermore, the selective adrenergic receptor $\alpha_{2B}$ antagonists provided herein may be capable of decreasing blood pressure sensitivity to salt, decreasing sodium retention, decreasing vasoconstriction in small arteries and veins, increasing
insulin secretion, increasing basal metabolic rate, decreasing platelet aggregation and/or
enhancing mitochondrial function. However, in certain cases where the compound has strong
antagonist activities against adrenergic receptor α_{2B} and/or adrenergic receptor α_{1B}, some
antagonist activity against adrenergic receptor α_{2A} may be tolerated and even beneficial.

Compounds provided herein may be capable of mediating control of the renal function.
Adrenergic α_{2B} receptors are located within the kidney. Regard et al. (Cell 2008; 135:561) have
demonstrated that the gene for the adrenergic α_{2B} receptor is most abundantly expressed in the
kidney. Meister et al. (J. Pharmacol. Exp. Therapeutics 1994; 268:1605) have shown by in situ
hybridization that expression predominates in the medulla outer stripe with extensions into the
cortical S3 segment of the proximal tubules. Adrenergic α_{2B} receptor antagonists provided
herein may be capable of disrupting sodium reabsorption resulting in natriuresis and diuresis.
Methods to determine effects of adrenergic α_{2B} antagonists on renal function in a rabbit model of
hypertension have been described by Burke et al. (J Hypertens 29:945–952).

In addition to reducing blood pressure, compounds disclosed herein, including
adrenergic α_{2B} antagonists, are capable of a reduction in blood volume that might result from
diuresis and/or the movement of fluid from the vascular space to the extravascular space.
Reduction of blood volume results in increase in hematocrit levels which can be measured by
methods known in the art, for example, by estimation of erythrocyte volume fraction.
Characterization of the effect of α_{2B} antagonists on renal function are determined by measuring
urine volume, urine sodium and urine potassium using methods described by Burke et al.
(Effects of chronic sympatho-inhibition on renal excretory function in renovascular hypertension
(2011).

The compounds detailed herein are expected to find use in therapy, particularly in
cardiac and renal diseases and conditions, in addition to hypertension and other conditions in
which a (i) reduction in blood pressure and/or (ii) increase in renal blood flow and/or (iii)
decrease in sodium reabsorption would be beneficial. In the methods provided herein, an
effective amount of a compound detailed herein is administered to an individual. Methods of
using compounds as described herein to (i) reduce blood pressure and/or (ii) promote renal blood
flow and/or (iii) decrease or inhibit sodium reabsorption in an individual in need thereof are
provided. The compounds may also find use in treating a disease or condition that is, or is
expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an
increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption. The individual may be a human who has been diagnosed with or is suspected of having high blood pressure or a disease or condition that is, or is expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption. The individual may be a human who exhibits one or more symptoms associated with high blood pressure or a disease or condition that is, or is expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption. The individual may be a human who is genetically or otherwise predisposed to developing high blood pressure or a disease or condition that is, or is expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption. In one variation, the compounds may find use in treating metabolic syndrome. In some embodiments, the compounds are adrenergic receptor α_2B antagonists. In one variation, the adrenergic receptor α_2B antagonists are selective adrenergic receptor α_2B antagonists. In one variation, a compound that is an adrenergic receptor α_2B antagonist also showing adrenergic receptor α_2A antagonist and/or inverse agonist activity may find use reducing blood pressure in an individual with hypertension who is also suffering from obesity, type-2 diabetes and/or metabolic syndrome. Thus, provided is a method for lowering blood pressure in hypertensive patients with a disease or condition that is responsive to treatment using an antagonist or inverse agonist of adrenergic receptor α_2A, such as obesity and/or type-2 diabetes and/or metabolic syndrome.

[0127] Compounds detailed herein may be used in a method of treating a disease or condition that is responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption. For example, the compounds may find use in treating hypertension, including treatment-resistant hypertension. In some embodiments, the compounds may be used in a method of treating hypertension in an individual not suffering from obesity or type-2 diabetes. In some embodiments, the compounds are adrenergic receptor α_2B antagonists. In some embodiments, the compounds are selective adrenergic receptor α_2B antagonists.

[0128] In one aspect, the disease or indication is a cardiac or renal disease or indication for which (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption would be, or would be expected to
be, beneficial. Such cardiac indications include, but are not limited to, heart failure, such as compensated heart failure, decompensated heart failure, acute decompensated congestive heart failure and chronic congestive heart failure, coronary heart disease, cardiac arrhythmias, myocardial ischemia, and hypertrophy. Such renal indications include, but are not limited to, renal failure such as chronic renal failure, acute renal failure and endstage renal failure, renal ischemia and chronic kidney disease. Other indications for which (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption would be, or would be expected to be, beneficial include but are not limited to sleep apnea and ischemic attacks.

**[0129]** Compounds detailed herein may also ameliorate symptoms of a disease or condition that have a cardiac or renal component in which (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption would be, or would be expected to be, beneficial. For example, the compounds may reduce elevated blood pressure, improve shortness of breath, reduce tachycardia, reduce edema, reduce elevated blood urea nitrogen to creatinine (BUN/Cr) ratio, improve creatinine levels, improve the ability to lie flat, reduce the incidence or severity of high blood pressure, reduce the risk and/or number of acute cardiac events (e.g., acute decompensation or myocardial infarction) an individual experiences over a period of time (e.g., one year, 2 years, 5 years, etc.), reduce the incidence of acute heart failure an individual experiences over a period of time (e.g., one year, 2 years, 5 years, etc.), reduce the severity and/or incidence of pulmonary congestion and/or reduce the risk of stroke, reduce shortness of breath and/or tachycardia in individuals after myocardial infarction, improve left ventricular ejection fraction (LVEF) post infarct and/or lower weight and blood pressure in obese individuals (e.g., men and women) with pre-hypertension. In some embodiments, the compounds are adrenergic receptor \( \alpha_{2B} \) antagonists. In some embodiments, the compounds are selective adrenergic receptor \( \alpha_{2B} \) antagonists.

**[0130]** Compounds detailed herein (such as the adrenergic receptor \( \alpha_{2B} \) antagonists detailed herein) may find use in the treatment of hypertensive emergencies. Provided is a method of treating hypertensive emergencies, comprising administering intravenously an effective amount of an adrenergic receptor \( \alpha_{2B} \) antagonist to an individual in need thereof. In some embodiments, the method comprises administering intravenously an effective amount of an adrenergic receptor \( \alpha_{2B} \) antagonist to an individual in need thereof in a highly monitored intensive care setting, wherein the administration results in aggressive and controlled blood pressure lowering in the
individual. In some embodiments, intravenous administration of an adrenergic receptor $\alpha_{2B}$ antagonist in an individual results in gradually lowering of blood pressure in the individual and minimizing damage of end organs such as the brain, kidney, heart, and eye. Particularly useful in the treatment of hypertensive emergencies or crisis are parenteral formulations of an adrenergic receptor $\alpha_{2B}$ antagonist detailed herein. In one variation, the compound is an adrenergic receptor $\alpha_{2B}$ antagonist. In some variations, the compound is a selective adrenergic receptor $\alpha_{2B}$ antagonist. In one variation, the adrenergic receptor $\alpha_{2B}$ antagonist also exhibits adrenergic receptor $\alpha_{2A}$ antagonist and/or inverse agonist activity.

[0131] In one variation, a method of decreasing the severity and/or incidence of shortness of breath, tachycardia, edema, and/or the inability to lie flat is provided, comprising administering an effective amount of a compound detailed herein to an individual who has or is suspected of having heart failure (e.g., compensated heart failure and decompensated heart failure). In another variation, a method of decreasing the severity and/or incidence of elevated BUN/Cr, and/or edema is provided comprising administering an effective amount of a compound detailed herein to an individual who has or is suspected of having renal failure (e.g., acute or chronic renal failure). In another variation, a method of reducing blood pressure in an individual is provided comprising administering an effective amount of a compound detailed herein to an individual who has or is suspected of having hypertension (e.g., treatment-resistant hypertension). In another variation, a method of decreasing the severity and/or incidence of shortness of breath, tachycardia, and/or improving LVEF post infarct in an individual is provided comprising administering an effective amount of a compound detailed herein to an individual who has experienced myocardial infarction (e.g., an individual who has recently experienced myocardial infarction such as within 30 minutes, 1, 3, 6, 12, or 24 hours of treatment). In some of the variations, the adrenergic receptor $\alpha_{2B}$ antagonist is a selective adrenergic receptor $\alpha_{2B}$ antagonist. In some of the variations, the adrenergic receptor $\alpha_{2B}$ antagonist also exhibits antagonist activity for the adrenergic receptor $\alpha_{2A}$. In some embodiments, the compounds are adrenergic receptor $\alpha_{2B}$ antagonists. In some embodiments, the compounds are selective adrenergic receptor $\alpha_{2B}$ antagonists.

[0132] In one variation, provided is method for lowering the blood pressure in an individual in need thereof comprising administering to the individual a compound described herein, or a pharmaceutically acceptable salt thereof. Administration of an adrenergic receptor $\alpha_{2B}$ antagonist detailed herein lowers the blood pressure in the individual from a level considered
above the desired level for such individual. The blood pressure lowering therapy such as administration of compounds detailed herein is intended to help hypertensive individuals reach their blood pressure goals defined by their individual cardiovascular risk factors. For example, for otherwise healthy individuals without diabetes or known cardiovascular disease, goal blood pressure is less than about 140/90 mmHg; for patients with known cardiovascular disease (e.g., prior myocardial infarction, peripheral vascular disease) goal blood pressure is less than about 130-135/85 mmHg; for patients with diabetes, goal blood pressure is less than about 130/80 mmHg.

[0133] In one variation, compounds provided herein may have any one or more of the following beneficial effects on an individual: (1) reduce arterial blood pressure (e.g., in an individual with hypertension, certain forms of heart failure and/or renal failure); (2) reduce pulse pressure (e.g., in an individual with hypertension, certain forms of heart failure and/or renal failure); (3) tachycardia-preserved baroreceptor activity (e.g., in an individual whose systolic blood pressure is expected to or does fall in response to an \( \alpha_{2B} \) antagonist), which may suggest a lack of orthostatic hypotension; and (4) bradycardia- reduced cardiac work load and added reduction on blood pressure reduction by further reducing cardiac output (e.g., in an individual who has been administered a therapy that is an \( \alpha_{2B} \) and \( \alpha_{1B} \) mixed antagonist).

[0134] In another variation, compounds provided herein may exert their therapeutic effect with no or reduced side-effects, such as when compared to other therapies used in the treatment of the same or similar indication. In one aspect, compounds provided herein exhibit no or reduced side effects upon administration to an individual, wherein the side effects may be any one or more of: (i) reduced libido, (ii) orthostatic hypotension, (iii) muscle weakness, (iv) fatigue, (v) erectile dysfunction, (vi) constipation, (vii) depression, (viii) dizziness, (ix) dry mouth, (x) impaired thinking, (xi) weight gain, (xii) persistent cough, (xiii) chest pain, (xiv) headache, (xv) fluid retention, (xvi) racing pulse, and (xvii) emesis.

[0135] In one aspect, compounds are provided that do not bind appreciably any one or more of the histamine, dopamine and serotonin receptors. In any of the methods detailed herein, in one variation the individual does not have a cognitive disorder, psychotic disorder, neurotransmitter-mediated disorder and/or neuronal disorder. As used herein, the term “cognitive disorders” refers to and intends diseases and conditions that are believed to involve or be associated with or do involve or are associated with progressive loss of structure and/or function of neurons, including death of neurons, and where a central feature of the disorder may be the impairment of
cognition (e.g., memory, attention, perception and/or thinking). These disorders include pathogen-induced cognitive dysfunction, e.g., HIV associated cognitive dysfunction and Lyme disease associated cognitive dysfunction. Examples of cognitive disorders include Alzheimer’s Disease, Huntington’s Disease, Parkinson’s Disease, schizophrenia, amyotrophic lateral sclerosis (ALS), autism, mild cognitive impairment (MCI), stroke, traumatic brain injury (TBI) and age-associated memory impairment (AAMI). As used herein, the term “psychotic disorders” refers to and intends mental diseases or conditions that are believed to cause or do cause abnormal thinking and perceptions. Psychotic disorders are characterized by a loss of reality which may be accompanied by delusions, hallucinations (perceptions in a conscious and awake state in the absence of external stimuli which have qualities of real perception, in that they are vivid, substantial, and located in external objective space), personality changes and/or disorganized thinking. Other common symptoms include unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out the activities of daily living. Exemplary psychotic disorders are schizophrenia, bipolar disorders, psychosis, anxiety and depression. As used herein, the term “neurotransmitter-mediated disorders” refers to and intends diseases or conditions that are believed to involve or be associated with or do involve or are associated with abnormal levels of neurotransmitters such as histamine, serotonin, dopamine, norepinephrine or impaired function of aminergic G protein-coupled receptors. Exemplary neurotransmitter-mediated disorders include spinal cord injury, diabetic neuropathy, allergic diseases and diseases involving geroprotective activity such as age-associated hair loss (alopecia), age-associated weight loss and age-associated vision disturbances (cataracts). Abnormal neurotransmitter levels are associated with a wide variety of diseases and conditions including, but not limited to Alzheimer’s disease, Parkinson’s Disease, autism, Guillain-Barré syndrome, mild cognitive impairment, schizophrenia, anxiety, multiple sclerosis, stroke, traumatic brain injury, spinal cord injury, diabetic neuropathy, fibromyalgia, bipolar disorders, psychosis, depression and a variety of allergic diseases. As used herein, the term “neuronal disorders” refers to and intends diseases or conditions that are believed to involve, or be associated with, or do involve or are associated with neuronal cell death and/or impaired neuronal function or decreased neuronal function. Exemplary neuronal indications include neurodegenerative diseases and disorders such as Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis (ALS), Parkinson’s disease, canine cognitive dysfunction syndrome (CCDS), Lewy body disease, Menkes disease, Wilson disease, Creutzfeldt-Jakob disease, Fahr disease, an acute or chronic disorder involving
cerebral circulation, such as ischemic or hemorrhagic stroke or other cerebral hemorrhagic insult, age-associated memory impairment (AAMI), mild cognitive impairment (MCI), injury-related mild cognitive impairment (MCI), post-concussion syndrome, post-traumatic stress disorder, adjuvant chemotherapy, traumatic brain injury (TBI), neuronal death mediated ocular disorder, macular degeneration, age-related macular degeneration, autism, including autism spectrum disorder, Asperger syndrome, and Rett syndrome, an avulsion injury, a spinal cord injury, myasthenia gravis, Guillain-Barré syndrome, multiple sclerosis, diabetic neuropathy, fibromyalgia, neuropathy associated with spinal cord injury, schizophrenia, bipolar disorder, psychosis, anxiety or depression.

[0136] Individuals who have high blood pressure, or a disease or condition that is, or is expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption may benefit from the compounds detailed herein, including the adrenergic receptor $\alpha_{2B}$ antagonists (e.g., the selective adrenergic receptor $\alpha_{2B}$ antagonist) detailed herein.

[0137] An individual who does not have high blood pressure or a disease or condition that is, or is expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption may nevertheless benefit from the compounds detailed herein if the individual has one or more risk factors for high blood pressure, or a disease or condition that is, or is expected to be, responsive to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption. Risk factors for developing high blood pressure may include gender, race, ethnicity, age, family history, weight and/or lifestyle. For example, African-Americans, men (particularly if over age 45), woman over age 55, anyone over age 60, pre-hypertension individuals (individuals with a blood pressure of 120-130/80-89 mmHg), individuals who are overweight or obese, individuals with sleep apnea (such as obstructive sleep apnea), individuals who smoke, individuals who have a high salt diet, individuals who have a low potassium diet, individuals with chronic heavy alcohol use, individuals with a sedentary lifestyle, individuals with moderate to high stress, individuals with compromised renal function or renal failure and individuals with close relatives who have high blood pressure are each at an increased risk of developing high blood pressure themselves, or diseases or conditions associated with high blood pressure. Individuals with more than one such risk factor are particularly susceptible to developing high blood pressure. Risk factors for
developing kidney disease may include diabetes, high blood pressure (hypertension), cardiovascular diseases, smoking, obesity, high cholesterol, a family history of kidney disease, and/or age 65 or older. Members of certain ethnic groups are also at higher risk for kidney disease including people of Aboriginal, Asian, south Asian, Pacific Island, African/Caribbean, American Indian and Hispanic origin.

Cell viability and mitochondrial health

[0138] Methods of promoting cellular viability by promoting mitochondrial health are provided, the methods comprising contacting the cell with a compound detailed herein. The methods are applicable to various cells, such as neuronal and non-neuronal cells. In one variation, the cell is a non-neuronal cell, such as a renal or cardiac cell (e.g., myocardial muscle cell). In one aspect, methods of promoting cellular viability are provided wherein the cell is one whose viability would be, or would be expected to be, promoted by nutrient influx and/or oxygenation. Methods of promoting cellular viability in a cell experiencing, or exhibiting symptoms of, mitochondrial stress are also provided.

[0139] Methods of treating a disease or condition that is, or is expected to be, responsive to promoting mitochondrial health and cell viability are also described, the methods comprising administering to an individual in need thereof an effective amount of a compound provided herein. In one variation, the disease or condition is one which is associated with dysfunction of mitochondria in a non-neuronal cell. In a particular variation, the disease or condition is one which is associated with dysfunction of mitochondria in a renal or cardiac cell (e.g., myocardial muscle cell). In another variation, the disease or condition is one which would benefit from cellular (e.g., renal or cardiac) nutrient influx and/or oxygenation.

[0140] Thus, individuals who have a disease or condition that is associated with, or believed to be associated with, mitochondrial dysfunction may benefit from the compounds detailed herein, or pharmaceutically acceptable salts thereof. An individual who has a disease or condition that is associated with mitochondrial dysfunction should experience one or more beneficial or desirable results upon administration of an effective amount of a compound provided herein, or pharmaceutically acceptable salt thereof. In one aspect, the beneficial or desirable result is an increase in nutrient influx and/or oxygenation of a cell. In another aspect, the beneficial or desirable result is a reduction in the number and/or severity of symptoms associated with a disease or condition that is associated with mitochondrial dysfunction.
In one variation, a method of treating a renal or cardiac condition is provided, comprising administering to an individual in need thereof a compound as detailed herein. Such conditions include, but are not limited to, renal failure, such as acute renal failure and chronic renal failure, coronary (e.g., myocardial) ischemia, heart failure, such as acute and chronic congestive heart failure (including the muscle fatigue associated with these conditions), and coronary artery disease. Methods of treating other diseases and conditions are also described, such as methods of treating sleep apnea, acute respiratory distress syndrome (adult and infant) and peripheral vascular disease. The compounds as provided herein may also be used in a method of delaying the onset and/or development of a disease or condition associated with mitochondrial dysfunction, comprising administering a compound as provided herein, or a pharmaceutical salt thereof, to an individual who is at risk of developing a disease or condition associated with mitochondrial dysfunction.

Compounds that do not bind appreciably to neurotransmitter receptors but nevertheless enhance mitochondrial function, e.g., when administered to cells in the setting of mitochondrial stress (e.g., excess intracellular calcium), may be used in the methods herein to promote cell survival. In one aspect, the compounds exhibit the ability to enhance mitochondrial function by protecting against cell death mediated by mitochondrial dysfunction in an assay detailed herein. Thus, it is understood and clearly conveyed that enhancing mitochondrial function includes protecting a cell against cell death mediated by mitochondrial dysfunction. The compounds may also be assessed in assays known in the art.

It is understood and clearly conveyed that the binding and activity profiles detailed herein (e.g., in the disclosure above) in one variation apply to the formulae provided herein (e.g., the formulae for use in the methods). In one aspect, selective adrenergic receptor \( \alpha_{2B} \) antagonists are of the formula (I), (A-I), (A-IIA), (A-IIIB, (A-IIC), (A-IID), (A-IIA-1), (A-IIIB-1), (A-IIC-1), (A-IID-1), (A-IIIA), (A-IIIB, (A-IIC), (A-IID), (A-IIIE), (A-IIIE-1), (A-IIIE-2), (A-IIIE-3), (A-IIIE-4), (A-IIIE-5), (A-IIIE-6), (A-IIIE-7), (A-IIIE-8), (A-IIIF), (A-IIIF-1), (A-IIIF-2), (A-IIIF-3), (A-IIIF-4), (A-IIIF), (A-IIIG-1), (A-IIIG-2), (A-IIIG-3), (A-IIIG-4), (A-IIIG-5), (A-IIIG-6), (A-IIIH-1), (A-IIIH-2), (A-IIIH-3), (A-IIIH-4), (A-IIIA'), (A-IV), (A-V), (A-VI), (A-VIIA), (A-VIIIB), (A-VIIC), (A-VIID), (A-VIIE), (A-VIIF), (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), (A-VIIIA-7), (A-IXA), (A-IXB), (A-IXC), (A-IXD), (B-I), (B-IA), (B-IB), (B-IC), (B-ID), (C-I), (C-IA), (C-IB), (C-IA-1), (C-IA-2), (C-IA-3), (C-IA-4), (C-IA-5), (C-IA-6), (C-IA-7), (C-IB), (C-IB-1), (C-IB-2), (C-IB-3), (C-IC-1), (C-II), (C-IIA), (C-IIIB), (C-IIIA), (C-
IIIB), (C-IIIC), (C-IIID), (C-IIIE), (C-IIIF), (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), (C-IVG), (C-V), (C-VB), (D-I), (D-IIA), (D-IIIB), (D-IIA-1), (D-IIA-2), (D-IIIA), (D-IIIB), (E-I), (E-IIA), (E-IIIB), (F-I), (F-IIA), (F-IIIB), (F-IIA-1), (F-IIA-2), (G-I), (G-IIA), (G-IIIB), (G-IIIA-1), (G-IIIA-2), (H-I), (H-IB), (H-IC), (H-ID), (H-IIA-1), (H-IIB-1), (H-IC-1), (H-ID-1), (H-IE-1), (H-IF-1), (J), (J-IA), (J-IB), (J-IC), (J-ID), (J-IIA-1), (J-IIB-1), (J-IC-1), (J-ID-1), (K-I), (K-IB), (K-IC), (K-ID), (K-IE) or (K-IF), or any variations detailed herein.

Compounds of the Invention

[0144] Compounds according to the invention are detailed herein, including in the Brief Summary of the Invention and elsewhere. The invention includes the use of all of the compounds described herein, including any and all stereoisomers, including geometric isomers (cis/trans or E/Z isomers), tautomers, salts, N-oxides, and solvates of the compounds described herein, as well as methods of making such compounds.

[0145] In one aspect, provided is a compound of formula (I):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

\[ R^1 \text{ is } H; \ C_1-C_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, carboxyl, } SO_2H, SR, S(OR)R, SO_2R \text{ and perhaloalkyl; } C_3-C_8 \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, carboxyl and perhaloalkyl; } C_2-C_5 \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, carboxyl and perhaloalkyl; or } -C(O)O-C_1-C_5 \text{ alkyl; or is taken together with } R^{2a} \text{ or } R^{3a} \text{ to form a propylene } (-CH_2CH_2CH_2-) \text{ moiety or a butylene } (-CH_2CH_2CH_2CH_2-) \]
moiety; or is taken together with $R_{4a}^a$ or $R_{5a}^a$, where present, to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety;

$R_{1a}^a$ is H or optionally substituted C$_1$-C$_5$ alkyl;

$R_{2a}^a$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R_{1}^1$ or $R_{5a}^a$, where present, to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{3a}^a$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{4a}^a$, where present, to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety;

$R_{3a}^a$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R_{1}^1$ or $R_{4a}^a$, where present, to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{2a}^a$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{5a}^a$, where present, to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety;

$R_{4a}^a$, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R$_{14a}^{14a}$)R$_{15a}^{15a}$; -CO(O)N(R$_{14a}^{14a}$)R$_{15a}^{15a}$; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R_{3a}^a$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{1}^1$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{2a}^a$ to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety; or is taken together with $R_{5a}^a$, where present, to form a methylene (-CH$_2$-) moiety;

$R_{5a}^a$, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R$_{14a}^{14a}$)R$_{15a}^{15a}$; -CO(O)N(R$_{14a}^{14a}$)R$_{15a}^{15a}$; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R_{2a}^a$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{1}^1$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R_{3a}^a$ to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety; or is taken together with $R_{4a}^a$, where present, to form a methylene (-CH$_2$-) moiety;

each $R_{2b}^b$ and $R_{3b}^b$ is independently H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted C$_2$-C$_5$ alkenyl, or optionally substituted aryl;
each R\(^{4b}\) and R\(^{5b}\), where present, is independently H, halo, optionally substituted C\(_1\)-C\(_5\) alkyl, optionally substituted C\(_2\)-C\(_5\) alkenyl, or optionally substituted aryl;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

each X\(^1\), X\(^2\), X and U is independently N or CR\(^6\);

each R\(^6\) is independently H; hydroxyl; halo; C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C\(_2\)-C\(_5\) alkenyl; optionally substituted C\(_1\)-C\(_5\) alkoxy; or optionally substituted –C(O)C\(_1\)-C\(_5\) alky;

R\(^7\) is H; halo; optionally substituted C\(_1\)-C\(_5\) alkyl; or optionally substituted aryl; or is taken together with R\(^8\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R\(^9\) to form a C\(_3\)-C\(_5\) alkylene when R\(^8\) and R\(^{10}\) are taken together to form a bond;

R\(^8\) is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carbonylalkoxy; N(R\(^{11}\))R\(^{12}\); SR\(^{13}\), S(O)R\(^{13}\); SO\(_2\)R\(^{13}\); -OC(O)N(R\(^{14}\))R\(^{15}\); -C(O)N(R\(^{14}\))R\(^{15}\); optionally substituted -OC(O)-aryl;

optionally substituted -OC(O)-heteroaryl; -OC(O)C\(_1\)-C\(_6\) alkyl optionally substituted with amino or carboxyl; or -OC\(_1\)-C\(_5\) alkyl optionally substituted with carboxyl; or is taken together with R\(^7\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R\(^{10}\) to form a bond;

R\(^9\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl, or is taken together with R\(^7\) to form a C\(_3\)-C\(_5\) alkylene when R\(^8\) and R\(^{10}\) are taken together to form a bond;

R\(^{10}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl, or is taken together with R\(^8\) to form a bond;

each R\(^{11}\) and R\(^{12}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl, or R\(^{11}\) and R\(^{12}\) are taken together to form C\(_3\)-C\(_5\) alkylene;

R\(^{13}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl;

each R\(^{14}\) and R\(^{15}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; or R\(^{14}\) and R\(^{15}\) are taken together to form a C\(_3\)-C\(_5\) alkylene;

each R\(^{14a}\), and R\(^{15a}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; and

Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.
[0146] It should be understood that when two substituents are taken together to form a bond, an additional bond is formed. For example, as shown below, when R^x and R^w are taken together to form a bond, an additional bond is formed such that R^x and R^z is a double bond.

[0147] In some variations, one of X^1, X^2, X and U is N, and the other three of X^1, X^2, X and U are independently CR^6. In other variations, two of X^1, X^2, X and U is N, and the other two of X^1, X^2, X and U are independently CR^6. In yet other variations, each X^1, X^2, X and U is independently CR^6.

[0148] In some variations, R^1 is H, optionally substituted C_1-C_5 alkyl, or optionally substituted C_3-C_8 cycloalkyl, wherein the C_1-C_5 alkyl or the C_3-C_8 cycloalkyl is independently unsubstituted or substituted with hydroxy. In some variations, R^1 is unsubstituted C_2-C_5 alkenyl. In other variations, the C_1-C_5 alkyl is substituted with SO_2H. In some variations, R^1 is methyl, ethyl, n-propyl, or i-propyl. In some variations, R^1 is CF_3, or CH_2CF_3. In some variations R^1 is H. In some variations, R^1 is hydroxyethyl, hydroxypropyl, or hydroxybutyl. In some variations, R^1 is cyclobutyl, or cyclopropyl. In some variations, R^1 is CH_2CH_2SO_2H. In some variations, R^1 is CH_2CH=CH_2.

[0149] In some variations, R'^4a is halo; hydroxy; cyano; carboxyl; -OC(O)N(R'^4a)R'^15a; -C(O)N(R'^4a)R'^15a; optionally substituted C_1-C_5 alkyl. In some embodiments, R'^4a is optionally substituted C_1-C_5 alkyl. In other embodiments, R'^4a is monohaloalkyl, dihaloalkyl, or perhaloalkyl. In one embodiment, R'^4a is CF_3, CHF_2, or CH_2F. In another embodiment, R'^4a is CCl_3, CHCl_2, or CH_2Cl. In some variations, R'^4a is halo. In some variations, R'^4a and R'^4b are each halo. In certain variations, each R'^4a and R'^4b is fluoro or chloro. In one variation, each R'^4a and R'^4b is fluoro. In one variation, each R'^4a and R'^4b is chloro.

[0150] In some variations, R'^5a is halo; hydroxy; cyano; carboxyl; -OC(O)N(R'^4a)R'^15a; -C(O)N(R'^4a)R'^15a; optionally substituted C_1-C_5 alkyl. In some embodiments, R'^5a is optionally substituted C_1-C_5 alkyl. In other embodiments, R'^5a is monohaloalkyl, dihaloalkyl, or perhaloalkyl. In one embodiment, R'^5a is CF_3, CHF_2, or CH_2F. In another embodiment, R'^5a is CCl_3, CHCl_2, or CH_2Cl. In some variations, R'^5a is halo. In some variations, R'^5a and R'^5b are
each halo. In certain variations, each $R^{5a}$ and $R^{5b}$ is fluoro or chloro. In one variation, each $R^{5a}$ and $R^{5b}$ is fluoro. In one variation, each $R^{5a}$ and $R^{5b}$ is chloro.

[0151] In some variations, $R^7$ is a $C_1$-$C_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, $-N(R^{7a})(R^{7b})$, $-C(O)N(R^{7a})(R^{7b})$, $-C(O)OR^{7a}$, and $-C(O)R^{7a}$. In other variations, $R^7$ is an optionally substituted $C_3$-$C_8$ cycloalkyl. In some variations, $R^8$ is hydroxyl or NH$_2$. In some variations, $R^8$ is $OC(O)C_1$-$C_5$ alkyl optionally substituted with amino or carboxyl. In some variations, $R^8$ is taken together with $R^{10}$ to form a bond. In some variations, $R^9$ is H or CH$_3$. In some variations, in $R^{10}$ is H or CH$_3$. In some variations, each $R^9$ and $R^{10}$ is H. In some variations, $R^{10}$ is an optionally substituted $C_3$-$C_8$ cycloalkyl. In other variations, $R^{11}$ or $R^{12}$ is an optionally substituted $C_3$-$C_8$ cycloalkyl.

[0152] In some variations, Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, $C_1$-$C_5$ alkyl, $C_3$-$C_8$ cycloalkyl, halo-substituted $C_1$-$C_5$ alkyl, halo-substituted $C_3$-$C_8$ cycloalkyl, $C_1$-$C_5$ alkoxy, $C_3$-$C_8$ cycloalkoxy, cyano, carboxyl, aminoacycyl, $N(R^{16})(R^{17})$, $-C(O)OR^{18}$, $SR^{18}$, $S(O)R^{18}$ and $SO_2R^{18}$; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, $C_1$-$C_5$ alkyl, $C_3$-$C_8$ cycloalkyl, halo-substituted $C_1$-$C_5$ alkyl, halo-substituted $C_3$-$C_8$ cycloalkyl, $C_1$-$C_5$ alkoxy, $C_3$-$C_8$ cycloalkoxy, cyano, carboxyl, aminoacycyl, $N(R^{16})(R^{17})$, $-C(O)OR^{18}$, $SR^{18}$, $S(O)R^{18}$ and $SO_2R^{18}$, wherein each $R^{16}$ and $R^{17}$ is independently H or optionally substituted $C_1$-$C_5$ alkyl, or $R^{16}$ and $R^{17}$ are taken together to form $C_3$-$C_5$ alkylene, and wherein $R^{18}$ is an optionally substituted $C_1$-$C_5$ alkyl.

[0153] In one embodiment of the compound of formula (I):

$R^1$ is H; $C_1$-$C_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; $C_3$-$C_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; $C_2$-$C_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; or $-C(O)O-C_1$-$C_5$ alkyl, or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene (-$CH_2$-$CH_2$-$CH_2$-) moiety or a butylene (-$CH_2$-$CH_2$-$CH_2$-$CH_2$-) moiety;

$R^{2a}$ is H, optionally substituted $C_1$-$C_5$ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with $R^1$ to form a propylene (-$CH_2$-$CH_2$-$CH_2$-) moiety or a butylene (-$CH_2$-$CH_2$-$CH_2$-$CH_2$-) moiety;
R\textsuperscript{3a} is H, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R\textsuperscript{1} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{4a} is selected from the group consisting of halo, hydroxyl, cyano, carboxyl, -OC(O)N(R\textsuperscript{14a})R\textsuperscript{15a}, -C(O)N(R\textsuperscript{14a})R\textsuperscript{15a}, and optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;

each R\textsuperscript{2b} and R\textsuperscript{3b} is independently H;

R\textsuperscript{4b} is H, halo, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;

n is 0 and m is 1;

each X\textsuperscript{1}, X\textsuperscript{2}, and U is CH;

X is independently N or CR\textsuperscript{6a};

each R\textsuperscript{6} and R\textsuperscript{6a} is independently H; hydroxyl; halo; C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C\textsubscript{2}-C\textsubscript{5} alkenyl; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkoxy; or optionally substituted -C(O)C\textsubscript{1}-C\textsubscript{5} alkyl;

R\textsuperscript{7} is H; halo; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; or optionally substituted aryl; or is taken together with R\textsuperscript{8} and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R\textsuperscript{9} to form a C\textsubscript{3}-C\textsubscript{5} alkylene when R\textsuperscript{8} and R\textsuperscript{10} are taken together to form a bond;

R\textsuperscript{8} is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carbonylalkoxy; N(R\textsuperscript{11})R\textsuperscript{12}; SR\textsuperscript{13}, S(O)R\textsuperscript{13}; SO\textsubscript{2}R\textsuperscript{13}; -OC(O)N(R\textsuperscript{14})R\textsuperscript{15}; -C(O)N(R\textsuperscript{14})R\textsuperscript{15}; optionally substituted -OC(O)-aryl;

optionally substituted -OC(O)-heteroaryl; -OC(O)C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted with amino or carboxyl; or -OC\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with carboxyl; or is taken together with R\textsuperscript{7} and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R\textsuperscript{10} to form a bond;

R\textsuperscript{9} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{7} to form a C\textsubscript{3}-C\textsubscript{5} alkylene when R\textsuperscript{8} and R\textsuperscript{10} are taken together to form a bond;

R\textsuperscript{10} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{8} to form a bond;

each R\textsuperscript{11} and R\textsuperscript{12} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or R\textsuperscript{11} and R\textsuperscript{12} are taken together to form C\textsubscript{3}-C\textsubscript{5} alkylene;

R\textsuperscript{13} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;
each R^{14} and R^{15} is independently H or optionally substituted C_{1-5} alkyl; or R^{14} and R^{15} are taken together to form a C_{7-9} alkyne; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1-5} alkyl, C_{3-6} cycloalkyl, halo-substituted C_{1-5} alkyl, halo-substituted C_{3-6} cycloalkyl, C_{1-5} alkoxy, C_{3-6} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0154] In some embodiments, R^{3a} is an optionally substituted C_{1-5} alkyl. In certain embodiments, R^{4a} is a monohaloalkyl, a dihaloalkyl, or perhaloalkyl. In some variations, R^{4a} is halo, hydroxyl, and cyano. In some variations, R^{4a} is halo. In some variations, R^{4a} and R^{4b} are each halo. In certain variations, each R^{4a} and R^{4b} is fluoro or chloro. In one variation, each R^{4a} and R^{4b} is fluoro.

[0155] In certain embodiments, with respect to the compounds of formula (I), X is CR^6, R^8 is –OC(O)C_{1-5} alkyl substituted with carboxyl, and the compound is Compound No. 25, 54, 130, 146, 147, 338, II-15, II-16, or II-19.

[0156] In certain embodiments, with respect to the compounds of formula (I), R^8 is azido, and the compound is Compound No. II-261, II-266, II-276, II-298, V-1, V-2, V-3, V-21, V-22, or V-23.

[0157] In one embodiment, the compound is of formula (A-I):

![Chemical Structure](image)

(A-I)

or a salt, solvate or N-oxide thereof, wherein:

R^1 is H, C_{1-5} alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C_{2-5} alkenyl, or –C(O)OR^{11};

each R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a} and R^{5b} is independently H or optionally substituted C_{1-5} alkyl;
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

or \( R^1 \) and \( R^{2a} \), or \( R^1 \) and \( R^{3a} \), or \( R^{2a} \) and \( R^{5a} \), or \( R^{3a} \) and \( R^{4a} \), where present, are taken together to form a propylene (-\( \text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (-\( \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety,

or \( R^1 \) and \( R^{4a} \), or \( R^1 \) and \( R^{5a} \), or \( R^{2a} \) and \( R^{3a} \), where present, are taken together to form an ethylene (-\( \text{CH}_2\text{CH}_2\)-) moiety or a propylene (-\( \text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety,

or \( R^{2a} \) and \( R^{4a} \), or \( R^{3a} \) and \( R^{5a} \), where present, are taken together to form a methylene (-\( \text{CH}_2\)-) moiety or an ethylene (-\( \text{CH}_2\text{CH}_2\)-) moiety,

or \( R^{4a} \) and \( R^{5a} \), where present, are taken together to form a methylene (-\( \text{CH}_2\)-) moiety;

\( X \) is N or CR\(^6a\);

each \( R^6 \) and \( R^{6a} \) is independently H, halogen, C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 halogen atoms, hydroxyl, optionally substituted C\(_1\)-C\(_5\) alkoxy or optionally substituted -C(O)C\(_1\)-C\(_5\) alkyl;

each \( R^7 \), \( R^9 \) and \( R^{10} \) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl;

\( R^8 \) is H, hydroxyl, N(R\(^{11}\))R\(^{12}\), SR\(^{13}\), S(O)R\(^{13}\), SO\(_2\)R\(^{13}\), or -OC(O)C\(_1\)-C\(_5\) alkyl optionally substituted with amino;

or \( R^7 \) and \( R^8 \) are taken together with the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

or \( R^{10} \) and \( R^8 \) are taken together to form a bond;

or \( R^9 \) and \( R^7 \) are taken together to form an alkylene bridge of 3-5 carbon atoms when \( R^{10} \) and \( R^8 \) are taken together to form a bond;

each \( R^{11} \), \( R^{12} \) and \( R^{13} \) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; and

\( Q \) is aryl or heteroaryl optionally substituted with 1 to 3 substituents including halogen, C\(_1\)-C\(_5\) alkyl or cycloalkyl, halo-substituted C\(_1\)-C\(_5\) alkyl or cycloalkyl, C\(_1\)-C\(_5\) alkoxy or cycloalkoxy, -CN or -C(O)N(R\(^a\))R\(^b\) where each \( R^a \) and \( R^b \) is independently H or C\(_1\)-C\(_5\) alkyl.

**[0158]** In another embodiment, the compound is of the formula (A-IIA), (A-IIB), (A-IIIC) or (A-IIID):
or a salt, solvate or N-oxide thereof, wherein:

R<sup>1</sup> is H, C<sub>1</sub>-C<sub>5</sub> alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, or -C(O)OR<sup>11</sup>;

each R<sup>2a</sup>, R<sup>2a</sup> or R<sup>5a</sup> is independently H or optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl;

or R<sup>1</sup> and R<sup>2a</sup>, or R<sup>1</sup> and R<sup>3a</sup> are taken together to form a propylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-) moiety or a butylene (-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-) moiety;

X is N or CR<sup>6a</sup>;

each R<sup>6</sup> and R<sup>6a</sup> is independently H, halogen, C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with 1 to 3 halogen atoms, hydroxyl, optionally substituted C<sub>1</sub>-C<sub>5</sub> alkoxy or optionally substituted -C(O)C<sub>1</sub>-C<sub>5</sub> alkyl;

each R<sup>7</sup>, R<sup>9</sup> and R<sup>10</sup> is independently H or optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl;

R<sup>8</sup> is H, hydroxyl, N(R<sup>11</sup>)R<sup>12</sup>, SR<sup>12</sup>, S(O)R<sup>12</sup>, SO<sub>2</sub>R<sup>12</sup>, or -OC(O)C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with amino;

or R<sup>7</sup> and R<sup>8</sup> are taken together with the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

or R<sup>10</sup> and R<sup>8</sup> are taken together to form a bond;
or R⁹ and R⁷ are taken together to form an alkylene bridge of 3 to 5 carbon atoms when
R¹⁰ and R⁸ are taken together to form a bond;

each R¹¹, R¹² and R¹³ is independently H or optionally substituted C₁-C₅ alkyl; and

Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents including halogen,
C₁-C₅ alkyl or cycloalkyl, halo-substituted C₁-C₅ alkyl or cycloalkyl, C₁-C₅ alkoxy or
cycloalkoxy, -CN, -CO₂H or -(O)nR²b, wherein each R²a and R²b is independently H or C₁-C₅ alkyl.

[0159] In some embodiments, the compound is of formula (A-IIA). In some variations, X is
CR⁶a, wherein R⁶a is H. In some variations, R⁶ is H. In other variations, R¹ is H or CH₃. In yet
other variations, R⁷ is H or CH₃. In yet other variations, R⁸ is hydroxyl. In yet other variations,
Q is optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted
pyrazinyl, or optionally substituted phenyl.

[0160] In some embodiments, the compound is of formula (A-IIB). In some variations, X is
CR⁶a, wherein R⁶a is H. In some variations, R⁶ is H. In other variations, R¹ is H or CH₃. In yet
other variations, R⁷ is H or CH₃. In yet other variations, R⁸ is hydroxyl. In yet other variations,
Q is optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted
pyrazinyl, or optionally substituted phenyl.

[0161] In one embodiment, the compound is of formula (A-IA):

or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or
hydroxyl, C₂-C₅ alkenyl, or -C(O)OR¹¹;

each R²a, R²b, R³a, R³b, R⁴a, R⁴b, R⁵a and R⁵b is independently H or optionally substituted
C₁-C₅ alkyl;
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;
or \( R^1 \) and \( R^{2a} \), or \( R^1 \) and \( R^{3a} \), or \( R^{2a} \) and \( R^{5a} \), or \( R^{3a} \) and \( R^{4a} \), where present, are taken
together to form a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety,
or \( R^1 \) and \( R^{4a} \), or \( R^1 \) and \( R^{5a} \), or \( R^{2a} \) and \( R^{3a} \), where present, are taken together to form an
ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety or a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety,
or \( R^{2a} \) and \( R^{4a} \), or \( R^{3a} \) and \( R^{5a} \), where present, are taken together to form a methylene
(\(-\text{CH}_2\)-) moiety or an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety,
or \( R^{4a} \) and \( R^{5a} \), where present, are taken together to form a methylene (\(-\text{CH}_2\)-) moiety;
\( X \) is \( N \) or \( \text{CR}^{6a} \);
each \( R^6 \) and \( R^{6a} \) is independently \( H \), halogen, \( \text{C}_1-\text{C}_5 \) alkyl optionally substituted with 1 to
3 halogen atoms, hydroxyl, optionally substituted \( \text{C}_1-\text{C}_5 \) alkoxy or optionally substituted -
\( \text{C(O)C}_1-\text{C}_5 \) alkyl;
each \( R^7 \), \( R^9 \) and \( R^{10} \) is independently \( H \) or optionally substituted \( \text{C}_1-\text{C}_5 \) alkyl;
\( R^8 \) is \( \text{N(R}^{11}\text{)}\text{R}^{12}, \text{SR}^{13}, \text{S(O)R}^{13}, \text{SO}_2\text{R}^{13}, \) or \(-\text{OC(O)C}_1-\text{C}_5 \) alkyl optionally substituted
with amino;
each \( R^{11}, R^{12} \) and \( R^{13} \) is independently \( H \) or optionally substituted \( \text{C}_1-\text{C}_5 \) alkyl; and
\( Q \) is aryl or heteroaryl optionally substituted with 1 to 3 substituents including halogen,
\( \text{C}_1-\text{C}_5 \) alkyl or cycloalkyl, halo-substituted \( \text{C}_1-\text{C}_5 \) alkyl or cycloalkyl, \( \text{C}_1-\text{C}_5 \) alkoxy or
cycloalkoxy, \(-\text{CN}, -\text{CO}_2\text{H} \) or \(-\text{C(O)N(R}^b\text{)R}^b \), wherein each \( R^a \) and \( R^b \) is independently \( H \) or \( \text{C}_1-\text{C}_5 \) alkyl.

[0162] In one aspect, the present invention provides compounds according to formula (A-IB),
(A-IC) or (A-ID):
wherein \( Q, R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, R^7, R^8, m, \) and \( n \) are as described for formula (A-I), above; and each \( X^1, U, X^2 \) and \( X \) is independently CR^6.

[0163] In certain embodiments, with respect to the compounds of formula (A-IB), \( R^7 \) is optionally substituted cycloalkyl; \( R^8 \) is OH; \( R^3 \) is methyl; \( n = 0 \); each of \( R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^9 \), and \( R^{10} \) is H; each \( R^{2a} \) and \( R^{4a} \) is H; or \( R^{2a} \) taken together with \( R^{4a} \), when present, to form an ethylene (-CH\(_2\)CH\(_2\)-) moiety; each \( X^1, X^2 \) and \( X \) is CH, U is CR^6, and \( R^6 \) is methyl or chloro; and \( Q \) is other than unsubstituted phenyl, phenyl substituted with F, or unsubstituted pyridyl.

[0164] In certain embodiments, with respect to the compounds of formula (A-IB), \( R^7 \) is C\(_1\)-C\(_5\) alkyl substituted with acylamino. In one embodiment, \( R^7 \) is CH\(_2\)-CON(H)CH\(_3\); \( R^1 \) is methyl or ethyl; \( n = 0 \); each of \( R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^9 \) and \( R^{10} \) is H; each \( R^{2a} \) and \( R^{4a} \) is H; or \( R^{2a} \) taken together with \( R^{4a} \), when present, to form an ethylene (-CH\(_2\)CH\(_2\)-) moiety; each \( X^1, X^2 \) and \( X \) is CH, U is CR^6, and \( R^6 \) is methyl or chloro; and \( Q \) is other than phenyl substituted with fluoro, chloro, methoxy, or difluoro, unsubstituted pyridyl, pyridyl substituted with methyl, or unsubstituted pyrimidinyl.
[0165] In certain embodiments, with respect to the compounds of formula (A-IB), R^7 is C\textsubscript{1}-C\textsubscript{5} alkyl substituted with -C(O)OR\textsuperscript{7a}, wherein R\textsuperscript{7a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; R\textsuperscript{1} is methyl or ethyl; n is 0; each of R\textsuperscript{2b}, R\textsuperscript{3a}, R\textsuperscript{3b} and R\textsuperscript{4b} is H; each R\textsuperscript{2a} and R\textsuperscript{4a} is H; or R\textsuperscript{2a} taken together with R\textsuperscript{4a}, when present, to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; each X\textsuperscript{1}, X\textsuperscript{2} and X is CH, U is CR\textsuperscript{6}, and R\textsuperscript{6} is methyl or chloro; and Q is other than phenyl substituted with fluoro, chloro, methoxy, or difluoro, unsubstituted pyridyl, pyridyl substituted with methyl, or unsubstituted pyrimidinyl.

[0166] In certain embodiments, with respect to the compounds of formula (A-IB), R\textsuperscript{7} is C\textsubscript{1}-C\textsubscript{5} alkyl substituted with 1 to 3 halo; R\textsuperscript{7} is CF\textsubscript{3}; R\textsuperscript{8} is OH; R\textsuperscript{1} is methyl; n is 0.; each of R\textsuperscript{2b}, R\textsuperscript{3a}, R\textsuperscript{3b} and R\textsuperscript{4b} is H; each R\textsuperscript{2a} and R\textsuperscript{4a} is H; or R\textsuperscript{2a} taken together with R\textsuperscript{4a}, when present, to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; each X\textsuperscript{1}, X\textsuperscript{2} and X is CH, U is CR\textsuperscript{6}, and R\textsuperscript{6} is methyl; and Q is other than phenyl substituted with fluoro.

[0167] In certain embodiments, with respect to the compounds of formula (A-IB), R\textsuperscript{7} is optionally substituted phenyl; R\textsuperscript{8} is OH; R\textsuperscript{1} is methyl or ethyl; n is 0; each of R\textsuperscript{2b}, R\textsuperscript{3a}, R\textsuperscript{3b} and R\textsuperscript{4b} is H; each R\textsuperscript{2a} and R\textsuperscript{4a} is H; or R\textsuperscript{2a} taken together with R\textsuperscript{4a}, when present, to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; each X\textsuperscript{1}, X\textsuperscript{2} and X is CH, U is CR\textsuperscript{6}, and R\textsuperscript{6} is methyl or chloro; and Q is other than unsubstituted phenyl, phenyl substituted with fluoro or unsubstituted pyridyl.

[0168] In certain embodiments, with respect to the compounds of formula (A-IB), R\textsuperscript{8} is halo. In one embodiment, R\textsuperscript{8} is fluoro or chloro; R\textsuperscript{1} is methyl, ethyl, isopropyl, or cyclopropyl; n is 0; each of R\textsuperscript{2b}, R\textsuperscript{3a}, R\textsuperscript{3b} and R\textsuperscript{4b} is H; each R\textsuperscript{2a} and R\textsuperscript{4a} is H; or R\textsuperscript{2a} taken together with R\textsuperscript{4a}, when present, to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; R\textsuperscript{7} is H or methyl; each X\textsuperscript{1}, X\textsuperscript{2} and X is CH, U is CR\textsuperscript{6}, and R\textsuperscript{6} is methyl or chloro; and Q is other than unsubstituted phenyl, phenyl substituted with methoxy, chloro, fluoro, difluoro, unsubstituted pyridyl, pyridyl substituted with methyl, or unsubstituted pyrimidinyl.

[0169] In certain embodiments, with respect to the compounds of formula (A-IB), R\textsuperscript{8} is -C(O)N(R\textsuperscript{14})R\textsuperscript{15}; and each R\textsuperscript{14} and R\textsuperscript{15} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; or R\textsuperscript{14} and R\textsuperscript{15} are taken together to form a C\textsubscript{3}-C\textsubscript{5} alkylene; R\textsuperscript{1} is methyl; n is 0; each of R\textsuperscript{2b}, R\textsuperscript{3a}, R\textsuperscript{3b} and R\textsuperscript{4b} is H; each R\textsuperscript{2a} and R\textsuperscript{4a} is H; or R\textsuperscript{2a} taken together with R\textsuperscript{4a}, when present, to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; each X\textsuperscript{1}, X\textsuperscript{2} and X is CH, U is CR\textsuperscript{6}, and R\textsuperscript{6} is methyl; and Q is other than cyclobutyl.

[0170] In certain embodiments, with respect to the compounds of formula (A-IB), R\textsuperscript{8} is -OC(O)N(R\textsuperscript{14})R\textsuperscript{15}, -OC(O)-aryl, -OC(O)-heteroaryl, -OC(O)C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted...
with amino, –OC(O)C₁-C₅ alkyl substituted with carboxyl, or –OC₁-C₅ alkyl optionally substituted with carboxyl; and each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl, or R¹⁴ and R¹⁵ are taken together to form a C₂-C₅ alkyne.

[0171] In certain embodiments, with respect to the compounds of formula (A-IC), Q is optionally substituted 5-membered heteroaryl; n is 0; R⁷ is fluoro or methyl; R¹ is methyl; each of R²a, R²b, R³a, R³b, R⁴a and R⁴b is H; each X¹, X² and X is CH, U is CR⁶, and R⁶ is methyl or chloro; and Q is other than unsubstituted thienyl or unsubstituted thiazolyl.

[0172] In certain embodiments, with respect to the compounds of formula (A-IC), Q is optionally substituted pyridyl, each of R²a, R²b, R³a, R³b, R⁴a and R⁴b is H; each X¹, X² and X is CH, U is CR⁶, and R⁶ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted C₁-C₅ alkoxy; and Q is other than unsubstituted pyridyl, or pyridyl substituted with methyl, chloro, bromo, methoxy, or dimethyl.

[0173] In certain embodiments, with respect to the compounds of formula (A-IC), Q is optionally substituted pyrimidinyl; R¹ is methyl; each of R²a, R²b, R³a, R³b, R⁴a and R⁴b is H, each X¹, X² and X is CH, U is CR⁶, and R⁶ is methyl or chloro; and Q is other than unsubstituted pyrimidin-4-yl, pyrimidin-4-yl substituted with methyl, unsubstituted pyrimidin-5-yl, or pyrimidin-5-yl substituted with methyl.

[0174] In certain embodiments, with respect to the compounds of formula (A-ID), each of R²b, R³a, R³b, R⁴b, R⁵a and R⁵b is H; each R²a and R⁴a is H; or R²a taken together with R⁴a, where present, an ethylene (-CH₂CH₂-) moiety; U is CR⁶, and R⁶ is selected from the group consisting of CF₃, methyl, Cl, CONHCH₃, COOH, COOCH₃, H and F; then R¹ is other than methyl.

[0175] In certain embodiments, with respect to the compounds of formula (A-ID), each of R²b, R³a, R³b, R⁴b, R⁵a and R⁵b is H; each R²a and R⁴a is H; or R²a taken together with R⁴a, where present, an ethylene (-CH₂CH₂-) moiety; X is CR⁶, and R⁶ is F; then R¹ is other than methyl.

[0176] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), n is 0. In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), n is 1. In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), m is 0. In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), m is 1.

[0177] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), each R²a, R²b, R³a, R³b, R⁴a, R⁴b, R⁵a, and R⁵b is H.
[0178] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), \( R^{2a} \) together with \( R^1 \) form a butylene or propylene moiety.

[0179] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), \( R^{2a} \) together with \( R^{3a} \) form a propylene or ethylene moiety.

[0180] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), \( R^{2a} \) together with \( R^{1a} \) form a propylene or ethylene moiety.

[0181] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), \( R^{5a} \) together with \( R^{3a} \) form a methylene or ethylene moiety.

[0182] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), \( R^{2a} \) together with \( R^{1a} \) form a methylene or ethylene moiety.

[0183] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), \( R^{3a} \) together with \( R^1 \) form a butylene or propylene moiety.

[0184] In one embodiment, the present invention provides compounds according to formula (A-IE):

\[
\text{(A-IE)}
\]

wherein \( X^1, U, X^2, X, Q, R^1, R^6, R^7 \) and \( R^8 \) are as described for formula (A-IB).

[0185] In another embodiment, the compound is of the formula (A-IIA-1), (A-IIB-1), (A-IIC-1) or (A-IIID-1):

\[
\begin{align*}
\text{(A-IIA-1)} & , \\
\text{(A-IIB-1)} & ,
\end{align*}
\]
or a salt, solvate or N-oxide thereof, wherein:

- $R^1$ is H, C$_1$-C$_5$ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C$_2$-C$_5$ alkenyl, or $-\text{C(O)OR}^{11}$;
- each $R^{2a}$, $R^{3a}$ or $R^{5a}$ is independently H or optionally substituted C$_1$-C$_5$ alkyl;
- or $R^1$ and $R^{2a}$, or $R^1$ and $R^{3a}$ are taken together to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety;
- $X$ is N or CR$_6^a$;
- each $R^6$ and $R^{6a}$ is independently H, halogen, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 halogen atoms, hydroxyl, optionally substituted C$_1$-C$_5$ alkoxy or optionally substituted -C(O)C$_1$-C$_5$ alkyl;
- each $R^7$, $R^9$ and $R^{10}$ is independently H or optionally substituted C$_1$-C$_5$ alkyl;
- $R^8$ is H, azido, hydroxyl, N(R$^{11}$)R$^{12}$, SR$^{13}$, S(O)R$^{13}$, SO$_2$R$^{13}$, or -OC(O)C$_1$-C$_5$ alkyl optionally substituted with amino;
- each $R^{11}$, $R^{12}$ and $R^{13}$ is independently H or optionally substituted C$_1$-C$_5$ alkyl; and
- $Q$ is aryl or heteroaryl optionally substituted with 1 to 3 substituents including halogen, C$_1$-C$_5$ alkyl or cycloalkyl, halo-substituted C$_1$-C$_5$ alkyl or cycloalkyl, C$_1$-C$_5$ alkoxy or cycloalkoxy, -CN or -C(O)N(R$^a$)R$^b$ where each $R^a$ and $R^b$ is independently H or C$_1$-C$_5$ alkyl.

[0186] In one variation, each $R^6$ and $R^{6a}$ is independently H, CH$_3$ or Cl.

[0187] In one variation, $R^8$ is H, hydroxyl, N(R$^{11}$)R$^{12}$, SR$^{13}$, S(O)R$^{13}$, SO$_2$R$^{13}$, or -OC(O)C$_1$-C$_5$ alkyl optionally substituted with amino, where $R^{11}$, $R^{12}$ and $R^{13}$ are each independently H or optionally substituted C$_1$-C$_5$ alkyl. In a particular variation, $R^8$ is H, OH, NH$_2$, -OC(O)CH(NH$_2$)-CH$_3$, -OC(O)CH(NH$_2$)-CH(CH$_3$)$_2$, and -OC(O)CH(NH$_2$)-CH$_3$-CH(CH$_3$)$_2$.

[0188] In one variation, $R^{10}$ and $R^8$ are taken together to form a bond.
[0189] In one variation, $R^{10}$ and $R^8$ are taken together to form a bond, and $R^7$ and $R^9$ are taken together to form an alkylene bridge of 3 to 5 carbon atoms.

[0190] In one embodiment, the compound is of formula (A-IIA-1). In some variations, X is CR$_6^6$, wherein $R^6_a$ is H. In other variations, $R^6$ is H. In other variations, $R^1$ is H or CH$_3$. In yet other variations, $R^7$ is H or CH$_3$. In yet other variations, $R^8$ is hydroxyl or NH$_2$. In yet other variations, Q is optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyrazinyl, or optionally substituted phenyl.

[0191] In another embodiment, the compound is of formula (A-IID-1). In some variations, X is CR$_6^6$, wherein $R^6$ is H. In other variations, $R^1$ is H or CH$_3$. In yet other variations, $R^7$ is H or CH$_3$. In yet other variations, $R^8$ is hydroxyl or NH$_2$. In yet other variations, Q is optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyrazinyl, or optionally substituted phenyl.

[0192] In another embodiment, the compound is of formula (A-III):

![Chemical Structure Image]

(A-III)

or a salt, solvate or N-oxide thereof, wherein:

$R^1$ is H; C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or –C(O)O-C$_1$-C$_3$ alkyl; or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{4a}$ or $R^{5a}$, where present, to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety;
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

R\textsuperscript{2a} is H; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{1} or R\textsuperscript{5a}, where present, to form a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{3a} to form an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{4a}, where present, to form a methylene (-\text{CH\textsubscript{2}-) moiety or an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{3a} is H; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{1} or R\textsuperscript{4a}, where present, to form a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{2a} to form an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{5a}, where present, to form a methylene (-\text{CH\textsubscript{2}-) moiety or an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{4a} is H; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{3a} to form a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{1} to form an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{2a} to form a methylene (-\text{CH\textsubscript{2}-) moiety or an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{5a}, where present, to form a methylene (-\text{CH\textsubscript{2}-) moiety;

R\textsuperscript{5a} is H; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{2a} to form a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{1} to form an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-\text{CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{3a} to form a methylene (-\text{CH\textsubscript{2}-) moiety or an ethylene (-\text{CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{4a}, where present, to form a methylene (-\text{CH\textsubscript{2}-) moiety;

each R\textsuperscript{2b}, R\textsuperscript{3b}, R\textsuperscript{4b} and R\textsuperscript{5b} is independently H, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl, or optionally substituted aryl;

X is N or CR\textsuperscript{6a};

t is 1, 2 or 3;

each R\textsuperscript{6} and R\textsuperscript{6a} is independently H; hydroxyl; halo; C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl,
carboxyl and perhaloalkyl; C₂-C₅ alkenyl; optionally substituted C₁-C₅ alkoxy; or optionally substituted –C(O)C₁-C₅ alkyl;

R⁷ is H; halo; optionally substituted C₁-C₅ alkyl; or optionally substituted aryl; or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R⁹ to form a C₃-C₅ alkylene when R⁸ and R¹⁰ are taken together to form a bond;

R⁸ is H; halo; hydroxyl; N(R¹¹)R¹²; SR¹³, S(O)R¹³; SO₂R¹³; -OC(O)N(R¹⁴)R¹⁵; -OC(O)-aryl; -OC(O)-heteroaryl; or -OC(O)C₁-C₅ alkyl optionally substituted with amino; or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R¹⁰ to form a bond;

R⁹ is H or optionally substituted C₁-C₅ alkyl; or is taken together with R⁷ to form a C₃-C₅ alkylene when R⁸ and R¹⁰ are taken together to form a bond;

R¹⁰ is H or optionally substituted C₁-C₅ alkyl; or is taken together with R⁸ to form a bond;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl; or R¹¹ and R¹² are taken together to form C₃-C₅ alkylene;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkylene; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino.

[0193] In some variations, Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with halo, CH₃, CF₃, or OCH₃; or heteroaryl substituted with halo, CH₃, CF₃, or OCH₃. In other variations, Q is unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; pyridyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; pyrimidyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; or phenyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃.
In one variation, the compound is of the formula (A-III), wherein Q, X, m, n, t, R\(^1\), R\(^{2a}\), R\(^{2b}\), R\(^3\), R\(^4\), R\(^5\), R\(^6\), R\(^{6a}\), R\(^{11}\), R\(^{12}\), R\(^{13}\), R\(^{14}\) and R\(^{15}\) are as defined for the formula (A-III), R\(^7\) is H, halo, optionally substituted C\(_1\)-C\(_5\) alkyl, R\(^8\) is H, halo, hydroxyl, N(R\(^{11}\))R\(^{12}\), SR\(^{13}\), S(O)R\(^{13}\), SO\(_2\)R\(^{13}\), -OC(O)N(R\(^{14}\))R\(^{15}\), or -OC(O)C\(_1\)-C\(_5\) alkyl optionally substituted with amino, and each R\(^9\) and R\(^{10}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; or a salt, solvate or N-oxide thereof.

In some variations of the compound of the formula (A-III), R\(^1\) is C\(_1\)-C\(_5\) alkyl (e.g., methyl), each R\(^{2a}\) and R\(^3\) is H, R\(^6\) is methyl or chloro, and X is CR\(^{6a}\) where R\(^{6a}\) is methyl or chloro. In some of these variations, t is 1, 2 or 3. In some of these variations, R\(^7\) is H or C\(_1\)-C\(_5\) alkyl (e.g., methyl) and R\(^8\) is H or hydroxyl. In some of these variations, each R\(^7\) and R\(^8\) is H. In some of these variations, R\(^{11}\) is H or C\(_1\)-C\(_5\) alkyl (e.g., methyl) and R\(^{12}\) is H. In some of these variations, each R\(^9\) and R\(^{10}\) is H. In some of these variations, each R\(^7\), R\(^8\), R\(^9\) and R\(^{10}\) is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3- pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluoro phenyl). In some of these variations, Q is 4- fluorophenyl. In some of these variations, Q is phenyl substituted with -C(O)NR\(^{16}\)R\(^{17}\), wherein each R\(^{16}\) and R\(^{17}\) is H. In some of these variations, Q is 4-carbamoylphenyl.

In some variations, X is CR\(^{6a}\), wherein R\(^{6a}\) is H, halo or C\(_1\)-C\(_5\) alkyl; and each R\(^6\) is independently H, halo or C\(_1\)-C\(_5\) alkyl. In other variations, X is N. In some variations, R\(^1\) is H or C\(_1\)-C\(_5\) alkyl. In some variations, R\(^7\) is H or C\(_1\)-C\(_5\) alkyl, and R\(^8\) is H, hydroxyl, N(R\(^{11}\))R\(^{12}\) or -OC(O)C\(_1\)-C\(_5\) alkyl. In other variations, R\(^7\) is H or C\(_1\)-C\(_5\) alkyl, and R\(^8\) is H or hydroxyl. In yet other variations, R\(^7\) is H or C\(_1\)-C\(_5\) alkyl, and R\(^8\) is hydroxyl. In yet other variations, R\(^7\) is H, R\(^8\) is hydroxyl, n is zero and m is 1. In certain variations, R\(^7\) is methyl, R\(^8\) is hydroxyl, n is zero and m is 1.

In some variations, Q is unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; unsubstituted imidazolyl; unsubstituted triazolyl; pyridyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C\(_1\)-C\(_5\) alkyl, halo-substituted C\(_1\)-C\(_5\) alkyl, carboxyl and -C(O)NR\(^{16}\)R\(^{17}\), wherein each R\(^{16}\) and R\(^{17}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; pyrimidyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C\(_1\)-C\(_5\) alkyl, halo-
substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; pyrazinyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; imidazolyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; or triazolyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl.

[0198] In certain variations, X is CR⁶⁻, wherein R⁶⁻ is H, halo or C₁-C₅ alkyl; each R⁶ is independently H, halo or C₁-C₅ alkyl; R⁷ is H or C₁-C₅ alkyl; R⁸ is H, hydroxyl, N(R¹¹⁻)R¹²⁻ or -OC(O)C₁-C₅ alkyl; each R⁹ and R¹⁰ is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl. In some variations, n is 0 and m is 1; R⁷ is H or CH₃; and R⁸ is H or hydroxyl.

[0199] In yet other variations, X is N; R⁷ is H or C₁-C₅ alkyl; R⁸ is H, hydroxyl, N(R¹¹⁻)R¹²⁻ or -OC(O)C₁-C₅ alkyl; each R⁹ and R¹⁰ is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl. In some variations, n is 0 and m is 1; R⁷ is H or CH₃; and R⁸ is H or hydroxyl.

[0200] In some variations, n is 0 and m is 1; R¹ is taken together with R²⁻ to form a propylene (–CH₂CH₂CH₂–) moiety; X is CR⁶⁻, wherein R⁶⁻ is H, halo or C₁-C₅ alkyl; each R⁶ is independently H, halo or C₁-C₅ alkyl; R⁷ is H or C₁-C₅ alkyl; R⁸ is H, hydroxyl, N(R¹¹⁻)R¹²⁻ or -OC(O)C₁-C₅ alkyl; each R⁹ and R¹⁰ is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl; or triazolyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and –C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl.
independently H or optionally substituted C₁-C₅ alkyl. In some variations, R⁷ is H or CH₃; and R⁸ is H or hydroxyl.

[0201] In some variations, the compound is Compound No. 3a, 3b, 39a, 4a, 5b, 13b, 14a, 41a, 74a, 26a, 26b, 27a, 29b, 31a, 127a, 129d, 134b, 144b, 148#1, 173a, 174a, 150a, 176a, IV-210a, 151a, II-4b, II-132b, 148b, 141b, 154b, II-135b, II-138, II-139, II-140, II-244a, II-7, II-146a, II-152a, II-227c, II-220, II-148a, II-13a, II-212a, II-260a or II-260b.

[0202] In one aspect, compounds provided herein used in the methods described above is a compound of formula (A-III), wherein any one or more of the following conditions applies: (1) X is CR⁶⁺, wherein each R⁶⁺ is independently H, halo or C₁-C₅ alkyl; (2) each R⁶⁻ is independently H, halo or C₁-C₅ alkyl; (3) X is N; (4) R¹ is H or C₁-C₅ alkyl; (5) R³⁺ and R³⁻ is H; (6) R⁷ is H or C₁-C₅ alkyl; (8) R⁸ is H, hydroxyl, N(R¹¹)R¹² or -OC(O)C₁-C₅ alkyl; (9) R⁷ is H or C₁-C₅ alkyl, and R⁸ is H, hydroxyl, N(R¹¹)R¹² or -OC(O)C₁-C₅ alkyl; (10) R⁷ is H, and R⁸ is H, hydroxyl, N(R¹¹)R¹² or -OC(O)C₁-C₅ alkyl; (11) R⁷ is C₁-C₅ alkyl, and R⁸ is H, hydroxyl, N(R¹¹)R¹² or -OC(O)C₁-C₅ alkyl; (12) R⁷ is H or C₁-C₅ alkyl, and R⁸ is H or hydroxyl; (13) R⁷ is H or C₁-C₅ alkyl, and R⁸ is hydroxyl; (14) R⁷ is H, and R⁸ is hydroxyl; (15) R⁷ is methyl, and R⁸ is hydroxyl; (16) R⁷ is H, and R⁸ is NH₂; (17) R⁷ is H, and R⁸ is -OC(O)C₁-C₅ alkyl; (18) R⁷ is H or C₁-C₅ alkyl; (19) R¹⁰ is H or C₁-C₅ alkyl; (20) each R⁹ and R¹⁰ is H; (21) one of R⁹ and R¹⁰ is H and the other is C₁-C₅ alkyl; (22) Q is: unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; unsubstituted imidazolyl; unsubstituted triazolyl; pyridyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and -C(O)NR¹⁰⁻R¹¹, wherein each R¹⁰ and R¹¹ is independently H or optionally substituted C₁-C₅ alkyl; pyrimidyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and -C(O)NR¹⁰⁻R¹¹, wherein each R¹⁰ and R¹¹ is independently H or optionally substituted C₁-C₅ alkyl; pyrazinyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and -C(O)NR¹⁰⁻R¹¹, wherein each R¹⁰ and R¹¹ is independently H or optionally substituted C₁-C₅ alkyl; or phenyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and -C(O)NR¹⁰⁻R¹¹, wherein each R¹⁰ and R¹¹ is independently H or optionally substituted C₁-C₅ alkyl; imidazolyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and -C(O)NR¹⁰⁻R¹¹.
wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl; or triazolyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl; (23) X is CR^{6a}, wherein R^{6a} is H, halo or C_{1}-C_{5} alkyl; and each R^{6} is independently H, halo or C_{1}-C_{5} alkyl; (24) wherein R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, and R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; (25) wherein R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, and R^{8} is H or hydroxyl; (26) R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, and R^{8} is hydroxyl; (27) wherein R^{1} is CH_{3}, R^{7} is H, R^{8} is hydroxyl, n is zero and m is 1; (28) R^{1} is CH_{3}, R^{7} is methyl, R^{8} is hydroxyl, n is zero and m is 1; (29) X is CR^{6a}, wherein R^{6a} is H, halo or C_{1}-C_{5} alkyl; each R^{6} is independently H, halo or C_{1}-C_{5} alkyl; R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; each R^{9} and R^{10} is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl; (30) n is 0 and m is 1; R^{1} is H or CH_{3}; R^{7} is H or CH_{3}; and R^{8} is H or hydroxyl; (31) X is N; R^{1} is H or C_{1}-C_{5} alkyl, R^{7} is H or C_{1}-C_{5} alkyl, R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; each R^{9} and R^{10} is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl; (32) n is 0 and m is 1; R^{1} is H or CH_{3}; R^{7} is H or CH_{3}; and R^{8} is H or hydroxyl; (33) n is 0 and m is 1; R^{1} is taken together with R^{2a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety; X is CR^{6a}, wherein R^{6a} is H, halo or C_{1}-C_{5} alkyl; each R^{6} is independently H, halo or C_{1}-C_{5} alkyl; R^{7} is H or C_{1}-C_{5} alkyl, R^{8} is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_{1}-C_{5} alkyl; each R^{9} and R^{10} is hydrogen; and Q is unsubstituted pyridyl; or pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, halo-substituted C_{1}-C_{5} alkyl, carboxyl and –C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_{1}-C_{5} alkyl; (34) R^{7} is H or CH_{3}; and R^{8} is H or hydroxyl.

[0203] In another embodiment, the compound of formula (A-III) has the formula (A-IIIA):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H; C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₃-C₅ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; or -C(O)O-C₁-C₅ alkyl, or is taken together with R²ₐ or R³ₐ to form a propylene (-CH₂CH₃CH₂-) moiety or a butylene (-CH₂CH₃CH₂CH₂-) moiety;

R²ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₃CH₂-) moiety or a butylene (-CH₂CH₃CH₂CH₂-) moiety;

R³ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₃CH₂-) moiety or a butylene (-CH₂CH₃CH₂CH₂-) moiety;

X is N or CR₆ₐ;

each R⁶ and R₆ₐ is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted –C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R⁹ to form a C₃-C₅ alkylene when R⁸ and R¹⁰ are taken together to form a bond;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken
together with $R^7$ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with $R^{10}$ to form a bond;

$R^9$ is $H$ or optionally substituted C$_1$-C$_5$ alkyl, or is taken together with $R^7$ to form a C$_3$-C$_5$ alkylene when $R^8$ and $R^{10}$ are taken together to form a bond;

$R^{10}$ is $H$ or optionally substituted C$_1$-C$_5$ alkyl, or is taken together with $R^8$ to form a bond;

each $R^{11}$ and $R^{12}$ is independently $H$ or optionally substituted C$_1$-C$_5$ alkyl, or $R^{11}$ and $R^{12}$ are taken together to form C$_3$-C$_5$ alkylene;

$R^{13}$ is $H$ or optionally substituted C$_1$-C$_5$ alkyl;

each $R^{14}$ and $R^{15}$ is independently $H$ or optionally substituted C$_1$-C$_5$ alkyl, or $R^{14}$ and $R^{15}$ are taken together to form a C$_3$-C$_5$ alkylene; and

$Q$ is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C$_1$-C$_5$ alkyl, C$_3$-C$_8$ cycloalkyl, halo-substituted C$_1$-C$_5$ alkyl, halo-substituted C$_3$-C$_8$ cycloalkyl, C$_1$-C$_5$ alkoxy, C$_3$-C$_8$ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C$_1$-C$_5$ alkyl, C$_3$-C$_8$ cycloalkyl, halo-substituted C$_1$-C$_5$ alkyl, halo-substituted C$_3$-C$_8$ cycloalkyl, C$_1$-C$_5$ alkoxy, C$_3$-C$_8$ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0204] In some variations, $Q$ is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with halo, CH$_3$, CF$_3$, or OCH$_3$; or heteroaryl substituted with halo, CH$_3$, CF$_3$, or OCH$_3$. In other variations, $Q$ is unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; pyridyl substituted with halo, CH$_3$, CF$_3$, or OCH$_3$; pyrimidyl substituted with halo, CH$_3$, CF$_3$, or OCH$_3$; pyrazinyl substituted with halo, CH$_3$, CF$_3$, or OCH$_3$; or phenyl substituted with halo, CH$_3$, CF$_3$, or OCH$_3$.

[0205] In one variation, the compound is of the formula (A-III A), wherein $Q$, X, $R^1$, $R^{2a}$, $R^{3a}$, $R^6$, $R^{6a}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$ and $R^{15}$ are as defined for the formula (A-III A); $R^7$ is $H$, halo, optionally substituted C$_1$-C$_5$ alkyl; $R^8$ is $H$, halo, hydroxyl, N($R^{11}$)R$_{12}$, SR$_{13}$, S($O$)R$_{13}$, SO$_2$R$_{13}$, OCO($O$)N($R^{14}$)R$_{15}$, or -OC($O$)C$_1$-C$_5$ alkyl optionally substituted with amino; and each $R^9$ and $R^{10}$ is independently $H$ or optionally substituted C$_1$-C$_5$ alkyl.

[0206] In some variations of the compound of the formula (A-III A), each $R^{2a}$ and $R^{3a}$ is $H$. In some variations, $R^1$ is C$_1$-C$_5$ alkyl (e.g., methyl). In some variations, each $R^6$ and $R^{6a}$ is independently halo (e.g., chloro) or C$_1$-C$_5$ alkyl (e.g., methyl). In some variations, each $R^6$ and
R^6a is independently halo (e.g., chloro or fluoro). In some variations, each R^6 or R^6a is chloro. In some variations, each R^6 and R^6a is independently C_1-C_5 alkyl (e.g., methyl). In some variations, X is CR^6a, wherein R^6a is H or halo. In some variations, X is CR^6a, wherein R^6a is H. In some variations, X is CR^6a, wherein R^6a is chloro. In some variations, X is CR^6a, wherein R^6a is halo (e.g., chloro or fluoro). In some variations, R^6 is H or halo. In some variations, R^6 is H. In some variations, R^6 is chloro. In some variations, R^6 is halo (e.g., chloro or fluoro). In some variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl). In some variations, X is N. In some variations, R^7 is H. In some variations, R^7 is C_1-C_5 alkyl (e.g., methyl). In some variations, R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl. In some variations, R^8 is H or hydroxyl. In some variations, R^8 is N(R^{11})R^{12} where each R^{11} and R^{12} is H. In some variations, R^8 is -OC(O)C_1-C_5 alkyl (e.g., -OC(O)-t-butyl). In some variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl) and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl. In some variations, R^7 is H; and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl. In some variations, R^7 is C_1-C_5 alkyl (e.g., methyl); and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl. In some variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl); and R^8 is H or hydroxyl. In some variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl); and R^8 is hydroxyl. In some variations, R^7 is H; and R^8 is hydroxyl. In some variations, R^7 is methyl; and R^8 is hydroxyl. In some variations, R^7 is H; and R^8 is N(R^{11})R^{12}, wherein each R^{11} and R^{12} is H. In some variations, R^7 is H; and R^8 is -OC(O)C_1-C_5 alkyl (e.g., -OC(O)-t-butyl). In some variations, R^9 is H or C_1-C_5 alkyl (e.g., methyl). In some variations, R^10 is H or C_1-C_5 alkyl (e.g., methyl). In some variations, each R^9 and R^10 is H. In some variations, one of R^9 and R^10 is H and the other of R^9 and R^10 is C_1-C_5 alkyl (e.g., methyl). In some variations, Q is an unsubstituted heteroaryl (e.g., pyridyl). In some variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some variations, Q is 3-pyridyl or 4-pyridyl. In some variations, Q is heteroaryl substituted with a substituent selected form the group consisting of halo (e.g., fluoro or chloro), C_1-C_5 alkyl (e.g., methyl), halo-substituted C_1-C_5 alkyl (e.g., CF_3) and carboxyl. In some variations, Q is heteroaryl substituted with halo (e.g., fluoro or chloro) or C_1-C_5 alkyl (e.g., methyl). In some variations, Q is heteroaryl substituted with C_1-C_5 alkyl (e.g., methyl). In some variations, Q is a pyridyl optionally substituted with a methyl where the pyridyl group may be attached to the parent structure at any position and the methyl group may be attached to the pyridyl group at any open position (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some variations, Q is phenyl substituted with a substituent selected form the group.
consisting of halo (e.g., fluoro or chloro), C₁-C₅ alkyl (e.g., methyl), halo-substituted C₁-C₅ alkyl (e.g., CF₃), carboxyl and −C(O)NR¹⁶R¹⁷ where each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl. In some variations, Q is phenyl substituted with a halo group (e.g., fluoro-phenyl). In some variations, Q is 4-fluorophenyl. In some variations, Q is phenyl substituted with −C(O)NR¹⁶R¹⁷ where each R¹⁶ and R¹⁷ is H.

[0207] In some variations of the compound of the formula (A-III A), R¹ is C₁-C₅ alkyl (e.g., methyl), each R²ᵃ and R³ᵃ is H, R⁶ is methyl or chloro, and X is CH. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl) and R⁸ is hydroxyl. In some of these variations, R⁷ is H and R⁸ is hydroxyl. In some of these variations, R⁷ is methyl and R⁸ is hydroxyl. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl) and R¹⁰ is H. In some of these variations, each R⁹ and R¹⁰ is H. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl), R⁸ is hydroxyl, and each R⁹ and R¹⁰ is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3-pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, phenyl substituted with a halo group (e.g., fluoro-phenyl). In some of these variations, Q is 4-fluorophenyl. In some of these variations, Q is phenyl substituted with −C(O)NR¹⁶R¹⁷ where each R¹⁶ and R¹⁷ is H. In some of these variations, Q is 4-carbamoylphenyl.

[0208] In some variations of the compound of the formula (A-III A), R¹ is C₁-C₅ alkyl (e.g., methyl), each R²ᵃ and R³ᵃ is H, R⁶ is methyl or chloro, and X is CH. In some variations, R⁷ is H and R⁸ is N(R¹¹)R¹², wherein each R¹¹ and R¹² is H. In some variations, R⁷ is H and R⁸ is −OC(O)C₁-C₅ alkyl (e.g., −OC(O)-t-butyl). In some of these variations, R⁹ is H or C₁-C₅ alkyl (e.g., methyl); and R¹⁰ is H. In some of these variations, each R⁹ and R¹⁰ is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3-pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluoro-phenyl). In some of these variations, Q is 4-fluorophenyl. In some of these variations, Q is phenyl substituted with −C(O)NR¹⁶R¹⁷ wherein each R¹⁶ and R¹⁷ is H. In some of these variations, Q is 4-carbamoylphenyl.
[0209] In some variations of the compound of the formula (A-IIIA), R¹ and R²⁺ are taken together to form a propylene (-CH₂CH₂CH₂-) moiety and R³⁺ is H. In some of these variations, X is N. In some of these variations, X is CH. In some of these variations, R⁶ is C₁-C₅ alkyl (e.g., methyl) or halo (e.g., chloro). In some of these variations, R⁶ is methyl or chloro. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl) and R⁸ is H or hydroxyl. In some of these variations, R⁷ is H and R⁸ is hydroxyl. In some of these variations, R⁷ is methyl and R⁸ is hydroxyl. In some of these variations, each R⁷ and R⁸ is H. In some of these variations, R⁹ is H or C₁-C₅ alkyl (e.g., methyl) and R¹⁰ is H. In some of these variations, each R⁹ and R¹⁰ is H. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl), R⁸ is H or hydroxyl, and each R⁹ and R¹⁰ is H. In some of these variations, each R⁷, R⁸, R⁹ and R¹⁰ is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3- pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-fluorophenyl. In some of these variations, Q is phenyl substituted with -C(O)NR¹⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is H. In some of these variations, Q is 4-carbamoylphenyl.

[0210] In some variations, X is CH. In other variations, X is N. In yet other variations, R¹ is H or CH₃. In yet other variations, R²⁺ is H or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety. In some variations, each R⁶ and R⁶⁺ is independently H, halo or C₁-C₅ alkyl. In yet other variations, R⁷ is H or CH₃. In one variation, R⁸ is hydroxyl.

[0211] In some variations, Q is: unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; unsubstituted imidazolyl; unsubstituted triazolyl; pyridyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; pyrimidyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; pyrazinyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; or phenyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃.

[0212] In some variations, X is CH; each R⁶ is independently H, halo or C₁-C₅ alkyl; R⁷ is H or CH₃; R⁸ is hydroxyl; and Q is unsubstituted pyridyl, or pyridyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃.

[0213] In some variations, the compound is Compound No. 3a, 3b, 39a, 4a, 5b, 74a, 26a, 26b, 27a, 29b, 31a, 127a, 129d, 134b, 144b, 148#1, 173a, 174a, 150a, 176a, IV-210a, 151a, II-4b, II-
In another embodiment, the compound of formula (A-III) has the formula (A-IIIB):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

- \( R^1 \) is H, C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C\(_3\)-C\(_8\) cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C\(_2\)-C\(_5\) alkenyl optionally substituted with 1 - 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or \(-\text{O(O)}\)-C\(_1\)-C\(_5\) alkyl, or is taken together with \( R^{2a} \) or \( R^{2a} \) to form a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety;

- \( R^{2a} \) is H, optionally substituted C\(_1\)-C\(_5\) alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with \( R^1 \) to form a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety;

- \( R^{3a} \) is H, optionally substituted C\(_1\)-C\(_5\) alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with \( R^1 \) to form a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety;

- \( X \) is N or CR\(^6a\);

- each \( R^6 \) and \( R^{6a} \) is independently H, hydroxyl, halo, C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C\(_1\)-C\(_5\) alkoxy or optionally substituted \(-\text{O(O)}\)-C\(_1\)-C\(_5\) alkyl;

- \( R^7 \) is H, halo, optionally substituted C\(_1\)-C\(_5\) alkyl, or optionally substituted aryl, or is taken together with \( R^8 \) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with \( R^9 \) to form a C\(_3\)-C\(_5\) alkylene when \( R^8 \) and \( R^{10} \) are taken together to form a bond;
R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R^{10} to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^7 to form a C_3-C_5 alkyne when R^8 and R^{10} are taken together to form a bond;

R^{10} is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkyne;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl, or R^{14} and R^{15} are taken together to form a C_3-C_5 alkyne; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0215] In some variations, Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with halo, CH_3, CF_3, or OCH_3; or heteroaryl substituted with halo, CH_3, CF_3, or OCH_3. In other variations, Q is unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; pyridyl substituted with halo, CH_3, CF_3, CONH_2, OH, or OCH_3; pyrimidyl substituted with halo, CH_3, CF_3, CONH_2, OH, or OCH_3; pyrazinyl substituted with halo, CH_3, CF_3, CONH_2, OH, or OCH_3; or phenyl substituted with halo, CH_3, CF_3, CONH_2, OH, or OCH_3.

[0216] In some variations of the compound of the formula (A-IIIB), R^1 is C_1-C_5 alkyl (e.g., methyl), each R^{2a} and R^{3a} is H, R^6 is methyl or chloro, and X is CH. In some of these variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl) and R^8 is hydroxyl. In some of these variations, R^7 is H and R^8 is hydroxyl. In some of these variations, R^2 is methyl and R^8 is hydroxyl. In some of these variations, R^2 is methyl and R^8 is hydroxyl. In some of these variations, each R^9 and R^{10} is H. In some of these variations, each R^9 and R^{10} is H. In some of these variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl), R^8 is
hydroxyl, and each $R^9$ and $R^{10}$ is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3-pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-fluorophenyl.

[0217] In another embodiment, the compound of formula (A-III) has the formula (A-IICC):

![Chemical Structure](image)

(A-IICC)

, or a salt, solvate or N-oxide thereof, wherein:

$R^1$ is H, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_2$-C$_5$ alkenyl optionally substituted with 1 – 3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C$_1$-C$_5$ alkyl, or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety;

$R^{2a}$ is H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with $R^1$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety;

$R^{3a}$ is H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with $R^1$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety;

$R^{5a}$ is H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR$_6$;
each R⁶ and R⁶a is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted –C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R⁹ to form a C₃-C₅ alkylene when R⁸ and R¹⁰ are taken together to form a bond;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R¹⁰ to form a bond;

R⁹ is H or optionally substituted C₁-C₅ alkyl, or is taken together with R⁷ to form a C₃-C₅ alkylene when R⁸ and R¹⁰ are taken together to form a bond;

R¹⁰ is H or optionally substituted C₁-C₅ alkyl, or is taken together with R⁸ to form a bond;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl, or R¹¹ and R¹² are taken together to form C₃-C₅ alkylene;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl, or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkylene; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₅-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0218] In some variations, Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with halo, CH₃, CF₃, or OCH₃; or heteroaryl substituted with halo, CH₃, CF₃, or OCH₃. In other variations, Q is unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; pyridyl substituted with halo, CH₃, CF₃, or OCH₃; pyrimidyl substituted
with halo, CH₃, CF₃, or OCH₃; pyrazinyl substituted with halo, CH₃, CF₃, or OCH₃; or phenyl substituted with halo, CH₃, CF₃, or OCH₃.

[0219] In one variation, the compound is of the formula (A-IIIC), wherein Q, X, R¹, R²a, R³a, R⁵a, R⁶, R⁶a, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ are as defined for the formula (A-IIIC), R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, or -OC(O)C₅⁻C₅ alkyl optionally substituted with amino, and each R⁹ and R¹⁰ is independently H or optionally substituted C₁-C₅ alkyl; or a salt, solvate or N-oxide thereof.

[0220] In another embodiment, the compound of formula (A-III) has the formula (A-IIID):

![Chemical Structure](A-IIID)

or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₆ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R²a or R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R²a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R³a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

X is N or CR⁶a;
each R^6 and R'^6 is independently H, hydroxyl, halo, C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C_1-C_5 alkoxy or optionally substituted –C(O)C_1-C_5 alkyl;

R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R^9 to form a C_3-C_5 alkylene when R^8 and R^10 are taken together to form a bond;

R^8 is H, halo, hydroxyl, N(R'^11)R'^12, SR'^13, S(O)R'^13, SO_2R'^13, -OC(O)N(R'^14)R'^15, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R^10 to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^7 to form a C_3-C_5 alkylene when R^8 and R^10 are taken together to form a bond;

R^10 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^8 to form a bond;

each R'^11 and R'^12 is independently H or optionally substituted C_1-C_5 alkyl, or R'^11 and R'^12 are taken together to form C_3-C_5 alkylene;

R'^13 is H or optionally substituted C_1-C_5 alkyl;

each R'^14 and R'^15 is independently H or optionally substituted C_1-C_5 alkyl, or R'^14 and R'^15 are taken together to form a C_3-C_5 alkylene; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0221] In some variations, Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with halo, CH_3, CF_3, or OCH_3; or heteroaryl substituted with halo, CH_3, CF_3, or OCH_3. In other variations, Q is unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; pyridyl substituted with halo, CH_3, CF_3, CONH_2, OH, or OCH_3; pyrimidyl
substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; pyrazinyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; or phenyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃.

In one variation, the compound is of the formula (A-IIID), wherein Q, X, R¹, R²a, R³a, R⁶, R⁶a, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ are as defined for the formula (A-IIID), R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, and each R⁹ and R¹⁰ is independently H or optionally substituted C₁-C₅ alkyl; or a salt, solvate or N-oxide thereof.

In some variations of the compound of the formula (A-IIID), R¹ is C₁-C₅ alkyl (e.g., methyl), each R²a and R³a is H, R⁶ is methyl or chloro, and X is CH. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl) and R⁸ is H or hydroxyl. In some of these variations, R⁷ is H and R⁸ is hydroxyl. In some of these variations, R⁷ is methyl and R⁸ is hydroxyl. In some of these variations, R⁹ is H or C₁-C₅ alkyl (e.g., methyl) and R¹⁰ is H. In some of these variations, each R⁹ and R¹⁰ is H. In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl), R⁸ is hydroxyl, and each R⁹ and R¹⁰ is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3-pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-fluorophenyl.

In certain embodiments, with respect to the compounds of formula (IIIID), X is CH, R⁷ is H or methyl, R⁸ is H or OH, Q is phenyl, unsubstituted or substituted with F, Cl, or methoxy; and R⁶ is other than methyl or chloro.

In another embodiment, the compound of formula (A-III) has the formula (A-IIIE):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H; C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₅-C₆ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl; or is taken together with R²a or R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R²a is H; optionally substituted C₁-C₅ alkyl; optionally substituted alkenyl; or optionally substituted aryl; or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R³a is H; optionally substituted C₁-C₅ alkyl; optionally substituted alkenyl; or optionally substituted aryl; or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

each R²b and R³b is independently H or optionally substituted C₁-C₅ alkyl;

R⁶ is H; hydroxyl; halo; C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R⁷ is H; halo; optionally substituted C₁-C₅ alkyl; or optionally substituted aryl; or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R⁸ is H; halo; hydroxyl; N(R¹¹)R¹²; SR¹³; S(O)R¹³; SO₂R¹³; -OC(O)N(R¹⁴)R¹⁵; -OC(O)-aryl; -OC(O)-heteroaryl; or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl, or R¹¹ and R¹² are taken together to form C₂-C₅ alkyne;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkyne; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy,
cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0226] In some variations of the compound of formula (A-IIIIE), R¹ is C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl. In certain variations, R¹ is C₁-C₅ alkyl substituted with a hydroxyl. In other variations, R¹ is methyl. In yet other variations, R¹ is H.

[0227] In some variations of the compound of formula (A-IIIIE), R⁶ is halo, C₁-C₅ alkyl, or perhaloalkyl. In certain variations, R⁵ is methyl or isopropyl. In other variations of the compound of formula (A-IIIIE), each R²a, R²b, R³a and R³b is H. In yet other variations of the compound of formula (A-IIIIE), R⁷ is an optionally substituted H or an unsubstituted C₁-C₅ alkyl, and R⁸ is hydroxyl. In certain variations, R⁷ is methyl, and R⁸ is hydroxyl.

[0228] In yet other variations of the compound of formula (A-IIIIE), Q is cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; aryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino. In other variations, Q is an optionally substituted pyridyl, an optionally substituted pyrimidyl, an optionally substituted pyrazinyl, or an optionally substituted phenyl, wherein each of the pyridyl, pyrimidyl, pyrazinyl and phenyl is independently unsubstituted or substituted with 1 to 3 substituents independently selected from halo, carboxyl, alkoxy and C₁-C₅ alkyl. In one variation, Q is an unsubstituted pyridyl. In another variation, Q is an unsubstituted pyrimidyl. In yet another variation, Q is an unsubstituted pyrazinyl. In yet another variation, Q is an unsubstituted phenyl. In yet another variation, Q is a phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo or C₁-C₅ alkyl. In one variation, Q is fluoro-phenyl.
In another embodiment, the compound is of the formula (A-IIIIE-1), (A-IIIIE-2), (A-IIIIE-3) or (A-IIIIE-4):

\[ \text{or a salt, solvate or N-oxide thereof, wherein:} \]

\[ R^1 \text{ is H, } C_1-C_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, } C_3-C_8 \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, } C_2-C_5 \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or } -\text{C(O)O-C}_1-C_5 \text{ alkyl;} \]

\[ R^6 \text{ is H, hydroxyl, halo, } C_1-C_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted } C_1-C_5 \text{ alkoxy or optionally substituted } -\text{C(O)C}_1-C_5 \text{ alkyl;} \]
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkyne;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkyne; and

each Y^1, Y^2, Y^3, Y^4 and Y^5 is independently N or CR^4 such that no more than two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3.

[0230] In some variations of the compound of the formula (A-IIIE-1), (A-IIIE-2), (A-IIIE-3) or (A-IIIE-4), one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the other four of Y^1, Y^2, Y^3, Y^4 and Y^5 are independently CR^4, and wherein R^4 is H, halo, CH_3, CF_3, or OCH_3. In other variations, Y^5 is CH, and each Y^1, Y^2, Y^3 and Y^4 is independently N or CR^4 such that two of Y^1, Y^2, Y^3 and Y^4 are N, and wherein R^4 is H, halo, CH_3, CF_3, or OCH_3. In some variations, R^4 is halo. In other variations, R^4 is CH_3. In one embodiment, R^4 is F. In another embodiment, R^4 is Cl. In some embodiments, any two of Y^1, Y^2, Y^3, Y^4 and Y^5 are CR^4, and each R^4 is independently Cl or F. In one embodiment, each R^4 is Cl. In another embodiment, each R^4 is F.

[0231] In some embodiments, the compound is of formula (A-IIIE-1), when each R^7 and R^8 is H; R^1 is H or methyl; R^6 is methyl or chloro; each Y^1, Y^2, Y^4 and Y^5 is CR^4, and Y^3 is CH, CF, or CCl; then at least one of Y^1, Y^2, Y^4 and Y^5 is other than CH.

[0232] In certain embodiments, with respect to the compounds of formula (A-IIIE-1), the compound is Compound No. 214.

[0233] In some embodiments, the compound is of formula (A-IIIE-2). In some variations, X is CH. In other variations, R^1 is H or CH_3. In yet other variations, R^7 is H or CH_3. In yet other variations, R^6 is hydroxyl. In some variations, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N, and the other four of Y^1, Y^2, Y^3, Y^4 and Y^5 are independently CR^4 (e.g., optionally substituted pyridyl). In other variations, two of Y^1, Y^2, Y^3, Y^4 and Y^5 is N, and the other three of Y^1, Y^2, Y^3, Y^4 and Y^5
are independently CR^4 (e.g., optionally substituted pyrimidyl or optionally substituted pyrazinyl). In yet other variations, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4 (e.g., optionally substituted phenyl). In certain variations, R^4 is H, halo, CH_3, CF_3, or OCH_3. In one embodiment, R^4 is F. In another embodiment, R^4 is Cl. In some embodiments, any two of Y^1, Y^2, Y^3, Y^4 and Y^5 are CR^4, wherein each R^4 is independently Cl or F. In one embodiment, each R^4 is Cl. In another embodiment, each R^4 is F.

[0234] In some embodiments, the compound is of formula (A-III-E-2), R^7 is optionally substituted cycloalkyl, R^8 is OH, R^1 is methyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4 wherein at least one R^4 is other than H or fluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H.

[0235] In some embodiments, the compound is of formula (A-III-E-2), R^7 is C_1-C_5 alkyl, substituted with acylamo, R^8 is CH_2-C(O)NHCH_3, R^1 is methyl or ethyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H, fluoro, chloro, methoxy, or difluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H or methyl. In another embodiment, two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N and the rest are independently CR^4, wherein at least one R^4 is other than H.

[0236] In some embodiments, the compound is of formula (A-III-E-2), R^7 is C_1-C_5 alkyl, substituted with -C(O)OR^7, R^7 is H or optionally substituted C_1-C_5 alkyl, R^1 is methyl or ethyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H, fluoro, chloro, methoxy, or difluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H, or methyl. In another embodiment, two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N and the rest are independently CR^4, wherein at least one R^4 is other than H.

[0237] In some embodiments, the compound is of formula (A-III-E-2), R^7 is C_1-C_5 alkyl, substituted with 1-3 halo, R^7 is CF_3, R^8 is OH, R^1 is methyl, R^6 is methyl, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H or fluoro.

[0238] In some embodiments, the compound is of formula (A-III-E-2), R^7 is optionally substituted phenyl, R^8 is OH, R^1 is methyl or ethyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H, or fluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H.
In some embodiments, the compound is of formula (A-IIE-2), R^8 is halo. In one embodiment, R^2 is fluoro or chloro, R^1 is methyl, ethyl, isopropyl, or cyclopropyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H, fluoro, chloro, methoxy, or difluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H, or methyl. In another embodiment, two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N and the rest are independently CR^4, wherein at least one R^4 is other than H.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), each R^7 and R^8 is H, and the compound is Compound No. 60, 61, 84-86, 89, 91, 117, 180, 184, 200, 201, 202, 204, 206-210, 213, 217-19, 297-299, 317, 319-320, or 332.

In certain embodiments, with respect to the compounds of formula (I), each R^7 and R^8 is H, and the compound is Compound No. II-39 or II-40.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. 30, 52, 66, 67, 139, 142, 183, or 203.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. II-88 or II-192.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^3, Y^4 and Y^5 is CR^4, Y^2 is N, and the compound is Compound No. 7, 21, 51, 59, 62, 140, or 144.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^3, Y^4 and Y^5 is CR^4, Y^2 is N, and the compound is Compound No. II-57, II-92, II-94, II-190 or II-191.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^3, Y^4 and Y^5 is CR^4, Y^2 is N, and the compound is Compound No. III-1.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^2, Y^4 and Y^5 is CR^4, Y^3 is N, and the compound is Compound No. 3, 4, 6, 11, 23, 49, 63, 69-72, 81, 133, or 135.

In certain embodiments, with respect to the compounds of formula (A-IIE-2), R^7 is H, R^8 is OH, each Y^1, Y^2, Y^3 and Y^5 is CR^4, Y^2 is N, and the compound is Compound No. II-60, II-63, II-64, II-65, II-67, II-68, II-75, II-83, II-84, II-90, II-93, or II-97.
[0249] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y², Y³, Y⁴ and Y⁵ is CR⁴, and the compound is Compound No. 90, 98, or 254.

[0250] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y², Y³, Y⁴ and Y⁵ is CR⁴, and the compound is Compound No. II-36, 47, 163, 189, 194 to 203, or II-205.

[0251] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y², Y³, Y⁴ and Y⁵ is CR⁴, and the compound is Compound No. III-36, III-47, III-50, or III-51.

[0252] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y², Y⁴ and Y⁵ is CR⁴, Y³ is N, and the compound is Compound No. 1, 2, or 253.

[0253] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y², Y⁴ and Y⁵ is CR⁴, Y³ is N, and the compound is Compound No. II-58, II-168, II-172, II-173, II-181, II-182, or III-49.

[0254] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y², Y⁴ and Y⁵ is CR⁴, Y² is N, and the compound is Compound No. 5, 29, 31, 56, 64, 93, 143, 169, 174, or 179.

[0255] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is OH, each Y¹, Y³, Y⁴ and Y⁵ is CR⁴, Y² is N, and the compound is Compound No. II-80, 105, 118, 123, 124, 136, 141, 145, 148, 154, 193, 220, 269, II-280, or III-48.

[0256] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁸ is N(R¹¹)R¹², and the compound is Compound No. 27, 149 to 152, or 157.

[0257] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁸ is N(R¹¹)R¹², and the compound is Compound No. II-1, II-8 to II-14, or II-260.

[0258] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is other than H or methyl, R⁸ is OH, and the compound is Compound No. 33 to 35, 223, or 263.

[0259] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is other than H or methyl, R⁸ is OH, and the compound is Compound No. II-160, II-162, II-166, II-167, II-174, II-186, II-206, II-255, II-257, II-259, II-264, II-265, II-278, or III-52.

[0260] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R⁷ is methyl, R⁸ is H, and the compound is Compound No. 255, 288, or 289.
[0261] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R\(^7\) is substituted C\(_1\)-C\(_5\) alkyl, R\(^8\) is H, and the compound is Compound No. II-216 to II-218, II-221 to II-231, II-232, or III-224 to III-253.

[0262] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), the compound is Compound No. 25, 54, 68, 83, 94, 102, 130, 141, 146, 147, 260, or 338.


[0264] In some embodiments, the compound is of formula (A-IIIE-3), when each R\(^7\) and R\(^8\) is H; R\(^1\) is methyl; R\(^6\) is chloro; each Y\(^1\), Y\(^2\), Y\(^4\) and Y\(^5\) is CR\(^4\), and Y\(^3\) is CH, CF, or CCl; then at least one of Y\(^1\), Y\(^2\), Y\(^4\) and Y\(^5\) is other than CH.

[0265] In certain embodiments, with respect to the compounds of formula (A-IIIE-3), the compound is Compound No. 40, 53, 65, 119, 215, 315, II-169, or II-184.

[0266] In some embodiments, the compound is of formula (A-IIIE-4), when each R\(^7\) and R\(^8\) is H, or R\(^7\) taken together with R\(^8\) form a -CH\(_2\) moiety, R\(^1\) is methyl; R\(^6\) is F, Cl, CF\(_3\), ethenyl, or propenyl; each Y\(^1\), Y\(^2\), Y\(^4\) and Y\(^5\) is CR\(^4\), and Y\(^3\) is CH, CF or CCl; then at least one of Y\(^1\), Y\(^2\), Y\(^4\) and Y\(^5\) is other than CH.

[0267] In certain embodiments, with respect to the compounds of formula (A-IIIE-4), the compound is Compound No. 32, 44, 45, 48, 57, 82, 216, II-170, or II-183.

[0268] In another embodiment, the compound is of the formula (A-IIIE-5), (A-IIIE-6), (A-IIIE-7) or (A-IIIE-8):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₅ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl;

R⁶ is H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R¹⁰ to form a bond;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl, or R¹¹ and R¹² are taken together to form C₃-C₅ alkyne;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkyne;

Q is
wherein

each $Z^1$, $Z^2$, $Z^3$, and $Z^4$ is independently N or CR$^4$ such that no more than two of
$Z^1$, $Z^2$, $Z^3$, and $Z^4$ are N, wherein R$^4$ is H, halo, CH$_3$, CF$_3$, or OCH$_3$;

each $Z^5$ and $Z^{10}$ is independently O, S or NR$^{4a}$, wherein R$^{4a}$ is H or CH$_3$; and

each $Z^6$, $Z^7$, $Z^8$, $Z^9$, $Z^{11}$, and $Z^{12}$ is independently N or CR$^4$, wherein R$^3$ is H, halo,
CH$_3$, CF$_3$, or OCH$_3$.

[0269] In other embodiments, the compound is of formula (A-III-E-6). In other variations, R$^1$ is H or CH$_3$. In yet other variations, R$^7$ is H or CH$_3$. In yet other variations, R$^8$ is hydroxyl.

[0270] In some variations, Q is

In some variations, R^4 is H, halo, CH₃, CF₃, or OCH₃.

[0271] In some variations of the compound of formula (A-IIIE-1), (A-IIIE-2), (A-IIIE-3), (A-IIIE-4), (A-IIIE-5), (A-IIIE-6), (A-IIIE-7) or (A-IIIE-8), R^1 is C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl. In certain variations, R^1 is C₁-C₅ alkyl substituted with a hydroxyl. In other variations, R^1 is methyl. In some variations, R^6 is halo, C₁-C₅ alkyl or perhaloalkyl. In certain variations, R^6 is methyl or isopropyl. In yet other variations of the compound of formula (A-IIIE-1), (A-IIIE-2), (A-IIIE-3), (A-IIIE-4), (A-IIIE-5), (A-IIIE-6), (A-IIIE-7) or (A-IIIE-8), R^7 is an optionally substituted or an unsubstituted C₁-C₅ alkyl, and R^8 is hydroxyl. In certain variations, R^7 is methyl, and R^8 is hydroxyl.

[0272] In some embodiments, the compound is of formula (A-IIIE-6), when each R^7 and R^8 is H, R^6 is H, methyl, Cl, F, CF₃, or methoxy; then R^1 is other than methyl or cyclopropyl.

[0273] In certain embodiments, with respect to the compounds of formula (A-IIIE-6), the compound is Compound No. 131, 307, 308, 318, 326, II-106, or II-142.

[0274] In another embodiment, the compound is of the formula (A-IIIF):
or a salt, solvate or N-oxide thereof, wherein:

R\(^1\) is H, C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C\(_3\)-C\(_8\) cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C\(_2\)-C\(_5\) alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C\(_1\)-C\(_5\) alkyl, or is taken together with R\(^2\) or R\(^3\) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

R\(^2\) is H, optionally substituted C\(_1\)-C\(_3\) alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R\(^1\) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

R\(^3\) is H, optionally substituted C\(_1\)-C\(_3\) alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R\(^1\) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

each R\(^2\)b and R\(^3\)b is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl;

R\(^6\) is H, hydroxyl, halo, C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C\(_1\)-C\(_5\) alkoxy or optionally substituted -C(O)C\(_1\)-C\(_5\) alkyl;

R\(^7\) is H, halo, optionally substituted C\(_1\)-C\(_5\) alkyl, or optionally substituted aryl, or is taken together with R\(^8\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R\(^8\) is H, halo, hydroxyl, N(R\(^{11}\))R\(^{12}\), SR\(^{13}\), S(O)R\(^{13}\), SO\(_2\)R\(^{13}\), -OC(O)N(R\(^{14}\))R\(^{15}\), -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C\(_1\)-C\(_5\) alkyl optionally substituted with amino, or is taken
together with \(R^7\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each \(R^{11}\) and \(R^{12}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl, or \(R^{11}\) and \(R^{12}\) are taken together to form C\(_3\)-C\(_5\) alkyne;

\(R^{13}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl;

each \(R^{14}\) and \(R^{15}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; or \(R^{14}\) and \(R^{15}\) are taken together to form a C\(_3\)-C\(_5\) alkyne; and

\(Q\) is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\(_1\)-C\(_5\) alkyl, C\(_3\)-C\(_8\) cycloalkyl, halo-substituted C\(_1\)-C\(_5\) alkyl, halo-substituted C\(_3\)-C\(_8\) cycloalkyl, C\(_1\)-C\(_5\) alkoxy, C\(_3\)-C\(_8\) cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\(_1\)-C\(_5\) alkyl, C\(_3\)-C\(_8\) cycloalkyl, halo-substituted C\(_1\)-C\(_5\) alkyl, halo-substituted C\(_3\)-C\(_8\) cycloalkyl, C\(_1\)-C\(_5\) alkoxy, C\(_3\)-C\(_8\) cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino.

[0275] In another embodiment, the compound is of the formula (A-IIIIF-1), (A-IIIIF-2), (A-IIIIF-3) or (A-IIIIF-4):
or a salt, solvate or N-oxide thereof, wherein:

R₁ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₆ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl;

R₆ is H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R₇ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R₈ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R₈ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R₇ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl, or R¹¹ and R¹² are taken together to form C₃-C₅ alkylene;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkylene; and
each Y¹, Y², Y³, Y⁴ and Y⁵ is independently N or CR⁴ such that no more than two of Y¹, Y², Y³, Y⁴ and Y⁵ are N, wherein R⁴ is H, halo, CH₃, CF₃, or OCH₃.

[0276] In some variations, one of Y¹, Y², Y³, Y⁴ and Y⁵ is N and the other four of Y¹, Y², Y³, Y⁴ and Y⁵ are independently CR⁴, and wherein R⁴ is H, halo, CH₃, CF₃, or OCH₃. In other variations, Y⁵ is CH, and each Y¹, Y², Y³ and Y⁴ is independently N or CR⁴ such that two of Y¹, Y², Y³ and Y⁴ are N, and wherein R⁴ is H, halo, CH₃, CF₃, or OCH₃. In some variations, R⁴ is halo. In other variations, R⁴ is CH₃. In one embodiment, R⁴ is F. In another embodiment, R⁴ is Cl. In some embodiments, any two of Y¹, Y², Y³, Y⁴ and Y⁵ are CR⁴, and each R⁴ is independently Cl or F. In one embodiment, each R⁴ is Cl. In another embodiment, each R⁴ is F.

[0277] In some embodiments, the compound is of formula (A-IIIF-1), when R⁷ is methyl, R⁸ is OH, R¹ is methyl, R⁶ is chloro; then Y³ is other than N.

[0278] In some embodiments, the compound is of formula (A-IIIF-2), when each Y¹, Y², Y³, Y⁴ and Y⁵ is independently CR⁴; and R¹ is methyl, ethyl, iso-propyl, or cyclopropyl; then R⁶ is other than Cl or methyl.

[0279] In some embodiments, the compound is of formula (A-IIIF-2), R² is optionally substituted cycloalkyl, R⁷ is OH, R¹ is methyl, R⁶ is methyl or chloro, each Y¹, Y², Y³, Y⁴ and Y⁵ is CR⁴, wherein at least one R⁴ is other than H or fluoro. In another embodiment, one of Y¹, Y², Y³, Y⁴ and Y⁵ is N and the rest are independently CR⁴, wherein at least one R⁴ is other than H.

[0280] In some embodiments, the compound is of formula (A-IIIF-2), R² is C₁-C₅ alkyl, substituted with acylamino. In one embodiment, R² is CH₂-CON(H)CH₃, R¹ is methyl or ethyl, R⁶ is methyl or chloro, each Y¹, Y², Y³, Y⁴ and Y⁵ is CR⁴, wherein at least one R⁴ is other than H, fluoro, chloro, methoxy, or difluoro. In another embodiment, one of Y¹, Y², Y³, Y⁴ and Y⁵ is N and the rest are independently CR⁴, wherein at least one R⁴ is other than H, or methyl. In another embodiment, two of Y¹, Y², Y³, Y⁴ and Y⁵ are N and the rest are independently CR⁴, wherein at least one R⁴ is other than H.

[0281] In some embodiments, the compound is of formula (A-IIIF-2), R² is C₁-C₅ alkyl, substituted with -C(O)OR⁷a, R⁷a is H or optionally substituted C₁-C₅ alkyl, R¹ is methyl or ethyl, R⁶ is methyl or chloro, each Y¹, Y², Y³, Y⁴ and Y⁵ is CR⁴, wherein at least one R⁴ is other than H, fluoro, chloro, methoxy, or difluoro. In another embodiment, one of Y¹, Y², Y³, Y⁴ and Y⁵ is N and the rest are independently CR⁴, wherein at least one R⁴ is other than H, or methyl. In another embodiment, two of Y¹, Y², Y³, Y⁴ and Y⁵ are N and the rest are independently CR⁴, wherein at least one R⁴ is other than H.
In some embodiments, the compound is of formula (A-IIIF-2), R^7 is C_{1-3} alkyl, substituted with 1-3 halo, R^7 is CF_3, R^8 is OH, R^1 is methyl, R^6 is methyl, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H or fluoro.

In some embodiments, the compound is of formula (A-IIIF-2), R^7 is optionally substituted phenyl, R^8 is OH, R^1 is methyl or ethyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H, or fluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H.

In some embodiments, the compound is of formula (A-IIIF-2), and R^8 is halo. In one embodiment, R^8 is fluoro or chloro, R^1 is methyl, ethyl, isopropyl, or cyclopropyl, R^6 is methyl or chloro, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, wherein at least one R^4 is other than H, fluoro, chloro, methoxy, or difluoro. In another embodiment, one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the rest are independently CR^4, wherein at least one R^4 is other than H, or methyl. In another embodiment, two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N and the rest are independently CR^4, wherein at least one R^4 is other than H.

In certain embodiments, with respect to the compounds of formula (A-IIIF-2), R^8 is OH, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. 18 or 20.

In certain embodiments, with respect to the compounds of formula (A-IIIF-2), R^8 is OH, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. II-20, II-48, II-49, II-52, II-53, II-55, II-156, II-157, or II-158.

In certain embodiments, with respect to the compounds of formula (A-IIIF-2), R^8 is OH, each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. III-6, III-7, III-8, III-64-68, III-74, III-78, III-92, III-95 to III-97, or III-98.

In certain embodiments, with respect to the compounds of formula (A-IIIF-2), each Y^1, Y^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. III-189-191, III-196, III-256 to III-257, or III-258.

In certain embodiments, with respect to the compounds of formula (A-IIIF-2), R^8 is OH, each Y^1, Y^3, Y^4 and Y^5 is CR^4, Y^2 is N, and the compound is Compound No. 14, 28, 43, 128, 196, II-87, or III-93.

In certain embodiments, with respect to the compounds of formula (I) or (A-IIIF-2), each Y^1, Y^3, Y^4 and Y^5 is CR^4, Y^2 is N, and the compound is Compound No. II-249, III-192, or III-194.
[0291] In certain embodiments, with respect to the compounds of formula (I) or (A-IIIF-2), \( R^8 \)
is OH, each \( Y^1, Y^2, Y^4 \) and \( Y^5 \) is CR\(^4\), \( Y^3 \) is N, and the compound is Compound No. 8, 19, 41, III-69, III-75 to III-82, III-87 to III-88, III-90, or III-94.

[0292] In certain embodiments, with respect to the compounds of formula (A-IIIF-2), each \( Y^1, Y^2, Y^4 \) and \( Y^5 \) is CR\(^4\), \( Y^3 \) is N, and the compound is Compound No. 153, III-187, III-188, III-195 or III-197.

[0293] In some embodiments, the compound is of formula (A-IIIF-3), when each \( R^7 \) and \( R^8 \) is H; \( R^1 \) is methyl; \( R^6 \) is chloro; each \( Y^1, Y^2, Y^4 \) and \( Y^5 \) is CR\(^4\), and \( Y^3 \) is CH, CF or CCl; then at least one of \( Y^1, Y^2, Y^4 \) and \( Y^5 \) is other than CH.

[0294] In some embodiments, the compound is of formula (A-IIIF-4), when each \( R^7 \) and \( R^8 \) is H, or \( R^7 \) taken together with \( R^8 \) form a -CH\(_2\) moiety, \( R^1 \) is methyl, \( R^6 \) is F, Cl, CF\(_3\), ethenyl, or propenyl; each \( Y^1, Y^2, Y^4 \) and \( Y^5 \) is CR\(^4\), and \( Y^3 \) is CH, CF or CCl; then at least one of \( Y^1, Y^2, Y^4 \) and \( Y^5 \) is other than CH.

[0295] In some embodiments, the compound is of formula (A-IIIF-3), when \( R^7 \) is H or methyl; \( R^8 \) is OH; \( R^6 \) is chloro or iso-propyl; \( Y^2 \) or \( Y^3 \) is N; then \( R^1 \) is other than methyl.

[0296] In certain embodiments, with respect to the compounds of formula (A-IIIF-3), the compound is Compound No. III-4, III-71, or III-90.

[0297] In some embodiments, the compound is of formula (A-IIIF-4), when \( R^7 \) is H or methyl, \( R^8 \) is OH, \( R^1 \) is methyl, \( R^6 \) is Cl, F, or methoxy; then \( Y^3 \) is other than N.

[0298] In certain embodiments, with respect to the compounds of formula (A-IIIF-4), the compound is Compound No. III-5, III-70, III-72, or III-89.

[0299] In another embodiment, the compound is of the formula (A-IIIG-1), (A-IIIG-2) or (A-IIIG-3);
or a salt, solvate or N-oxide thereof, wherein:

R⁷ is H, C₁₋₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃₋₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂₋₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₃₋₅ alkyl;

R⁶ is H, hydroxyl, halo, C₁₋₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁₋₅ alkoxy or optionally substituted -C(O)C₁₋₅ alkyl;

R⁷ is H, halo, optionally substituted C₁₋₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁₋₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R¹¹ and R¹² is independently H or optionally substituted C₁₋₅ alkyl, or R¹¹ and R¹² are taken together to form C₃₋₅ alkylene;

R¹³ is H or optionally substituted C₁₋₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁₋₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃₋₅ alkylene; and
each \( Y^1, Y^2, Y^3, Y^4 \) and \( Y^5 \) is independently N or CR\(^4\) such that no more than two of \( Y^1, Y^2, Y^3 \) and \( Y^4 \) and \( Y^5 \) are N, wherein \( R^4 \) is H, halo, CH\(_3\), CF\(_3\), or OCH\(_3\).

[0300] In some embodiments, the compound is of the formula (A-IIIG-2). In some variations, \( R^1 \) is H or CH\(_3\). In other variations, \( R^7 \) is H or CH\(_3\). In yet other variations, \( R^8 \) is hydroxyl or NH\(_2\). In yet other variations, each \( R^7 \) and \( R^8 \) is H. In yet other variations, one of \( Y^1, Y^2, Y^3, Y^4 \) and \( Y^5 \) is N and the other four of \( Y^1, Y^2, Y^3, Y^4 \) and \( Y^5 \) are independently CR\(^4\), and wherein \( R^4 \) is H, halo, CH\(_3\), CF\(_3\), or OCH\(_3\). In other variations, \( Y^5 \) is CH and each \( Y^1, Y^2, Y^3 \) and \( Y^4 \) is independently N or CR\(^4\) such that two of \( Y^1, Y^2, Y^3 \) and \( Y^4 \) are N, and wherein \( R^4 \) is H, halo, CH\(_3\), CF\(_3\), or OCH\(_3\). In some variations, \( R^4 \) is halo. In other variations, \( R^4 \) is CH\(_3\). In one embodiment, \( R^3 \) is F. In another embodiment, \( R^4 \) is Cl. In some embodiments, any two of \( Y^1, Y^2, Y^3, Y^4 \) and \( Y^5 \) are CR\(^4\), and each \( R^4 \) is independently Cl or F. In one embodiment, each \( R^4 \) is Cl. In another embodiment, each \( R^4 \) is F.

[0301] In some embodiments, the compound is of the formula (A-IIIG-1), (A-IIIG-2), or (A-IIIG-3), \( R^6 \) is H, \( R^1 \) is methyl, each of \( R^7 \) and \( R^8 \) is H, each \( Y^1, Y^2, Y^3, Y^4 \) and \( Y^5 \) is CR\(^4\) wherein at least one \( R^4 \) is other than H.

[0302] In certain embodiments, with respect to the compounds of formula (A-IIIG-2), \( R^8 \) is OH, and the compound is Compound No. 55, 136, 138, 145, II-99, II-100, II-108, II-109, II-111, or II-114.

[0303] In certain embodiments, with respect to the compounds of formula (A-IIIG-2), the compound is Compound No. 156, 159, II-110, II-119, II-240, or V-2.

[0304] In another embodiment, the compound is of the formula (A-IIIH):

\[
\begin{align*}
\text{(A-IIIH)}
\end{align*}
\]

or a salt, solvate or N-oxide thereof, wherein:
R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₃-C₅ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl;

R⁶ is H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R⁸ is H, halo, hydroxyl, N(R¹¹)R², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl, or R¹¹ and R¹² are taken together to form C₃-C₅ alkyne;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkyne; and

each Y¹, Y², Y³, Y⁴ and Y⁵ is independently N or CR³ such that no more than two of Y¹, Y², Y³, Y⁴ and Y⁵ are N, wherein R⁴ is H, halo, CH₃, CF₃, or OCH₃.

[0305] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. 13, 15, 92, 154, 172, 221, or 339.

[0306] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. II-22, II-24 to II-35, II-37, II-38, II-41 to II-46, II-51, II-134, II-135, II-155, II-159, II-246, or II-289.

[0307] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. III-9-46, III-209 to III-220, III-320 to III-351, or III-352.

[0308] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. V-21.
In another embodiment, the compound is of the formula (A-IIIH-1), (A-IIIH-2), (A-IIIH-3) or (A-IIIH-4):

or a salt, solvate or N-oxide thereof, wherein:

$R^1$ is H, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 independently substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C$_1$-C$_5$ alkyl;

$R^6$ is H, hydroxyl, halo, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C$_1$-C$_5$ alkoxy or optionally substituted –C(O)C$_1$-C$_5$ alkyl;
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkylene;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene; and

each Y^1, Y^2, Y^3, Y^4 and Y^5 is independently N or CR^4 such that no more than two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3.

[0310] In some variations, R^1 is H or CH_3. In other variations, R^7 is H or CH_3. In yet other variations, R^8 is hydroxyl or NH_2. In yet other variations, each R^7 and R^8 is H. In some variations, each Y^1, Y^2, Y^3, Y^4 and Y^5 is independently N or CR^4 such that no more than two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3. one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the other four of Y^1, Y^2, Y^3, Y^4 and Y^5 are independently CR^4, and wherein R^4 is H, halo, CH_3, CF_3, or OCH_3. In other variations, Y^5 is CH, and each Y^1, Y^2, Y^3 and Y^4 is independently N or CR^4 such that two of Y^1, Y^2, Y^3 and Y^4 are N, and wherein R^4 is H, halo, CH_3, CF_3, or OCH_3. In some variations, R^4 is halo. In other variations, R^4 is CH_3. In one embodiment, R^4 is F. In another embodiment, R^4 is Cl. In some embodiments, any two of Y^1, Y^2, Y^3, Y^4 and Y^5 are CR^4, and each R^4 is independently Cl or F. In one embodiment, each R^4 is Cl. In another embodiment, each R^4 is F.

[0311] In certain embodiments, with respect to the compounds of formula (A-IHII-2), R^6 is methyl or chloro, R^7 is H or methyl, R^8 is H or OH, Y^1 or Y^2 is independently C-H, C-F, C-Cl, or C-methoxy, and Y^3 is other than CH, CF, CCl, or C-OCH_3.

[0312] In certain embodiments, with respect to the compounds of formula (A-IIHII-2), R^6 is Cl or methyl, R^7 is methyl, R^8 is hydroxyl, and the compound is Compound No. 221.
[0313] In certain embodiments, with respect to the compounds of formula (A-IIIH-2), R<sup>6</sup> is Cl or methyl, R<sup>7</sup> is methyl, R<sup>8</sup> is hydroxyl, and the compound is Compound No. II-24, II-25, or II-26.

[0314] In certain embodiments, with respect to the compounds of formula (A-IIIH-2), R<sup>6</sup> is Cl or methyl, R<sup>7</sup> is methyl, R<sup>8</sup> is hydroxyl, and the compound is Compound No. III-11 to III-20, III-22, III-26 to III-38, or III-44 to III-46.

[0315] In one aspect, provided is a compound of formula (A-IIIIA'):

![Chemical Structure](image)

(A-III'A')

or a salt, solvate or N-oxide thereof, wherein:

- X, R<sup>1</sup>, R<sup>3a</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> and Q are as defined for formula (A-IIIIA),
- R<sup>4a</sup> is selected from the group consisting of hydrogen; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R<sup>14a</sup>)R<sup>15a</sup>; and -C(O)N(R<sup>14a</sup>)R<sup>15a</sup>;
- R<sup>4b</sup> is selected from the group consisting of hydrogen, halo, and optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl;

[0316] In one embodiment, when R<sup>4b</sup> is hydrogen, R<sup>4a</sup> is other than hydrogen. In some variations, R<sup>4a</sup> is halo. In some variations, R<sup>4a</sup> is chloro. In some variations, R<sup>4a</sup> is fluoro. In some variations, each R<sup>4a</sup> and R<sup>4b</sup> is halo.

[0317] In one aspect, provided is a compound of formula (A-IV):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 – 3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R²ᵃ or R³ᵃ to form a propylene (⁻CH₂CH₂CH₂⁻) moiety or a butylene (⁻CH₂CH₂CH₂CH₂⁻) moiety, or is taken together with R⁴ᵃ or R⁵ᵃ, where present, to form an ethylene (⁻CH₂CH₂⁻) moiety or a propylene (⁻CH₂CH₂CH₂⁻) moiety;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

R²ᵃ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ or R⁵ᵃ, where present, to form a propylene (⁻CH₂CH₂CH₂⁻) moiety or a butylene (⁻CH₂CH₂CH₂CH₂⁻) moiety, or is taken together with R³ᵃ to form an ethylene (⁻CH₂CH₂⁻) moiety or a propylene (⁻CH₂CH₂CH₂⁻) moiety, taken together with R⁴ᵃ, where present, to form a methylene (⁻CH₂⁻) moiety or an ethylene (⁻CH₂CH₂⁻) moiety;

R³ᵃ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ or R⁴ᵃ, where present, to form a propylene (⁻CH₂CH₂CH₂⁻) moiety or a butylene (⁻CH₂CH₂CH₂CH₂⁻) moiety, or is taken together with R²ᵃ to form an ethylene (⁻CH₂CH₂⁻) moiety or a propylene (⁻CH₂CH₂CH₂⁻) moiety, taken together with R⁵ᵃ, where present, to form a methylene (⁻CH₂⁻) moiety or an ethylene (⁻CH₂CH₂⁻) moiety;

R⁴ᵃ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R³ᵃ to form a propylene (⁻CH₂CH₂CH₂⁻) moiety or a butylene (⁻CH₂CH₂CH₂CH₂⁻) moiety, or is taken together with R⁴ⁱ to form an ethylene (⁻
CH₂CH₂-) moiety or a propylene (CH₂CH₂CH₂-) moiety, or is taken together with R²a to form a
methylene (CH₂-) moiety or an ethylene (CH₂CH₂-) moiety, or is taken together with R⁵a,
where present, to form a methylene (CH₂-) moiety;

R⁵a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally
substituted aryl, or is taken together with R²a to form a propylene (CH₂CH₂CH₂-) moiety or a
butylene (CH₂CH₂CH₂CH₂-) moiety, or is taken together with R¹ to form an ethylene
(CH₂CH₂-) moiety or a propylene (CH₂CH₂CH₂-) moiety, or is taken together with R³a to form
a methylene (CH₂-) moiety or an ethylene (CH₂CH₂-) moiety, or is taken together with R⁴a,
where present, to form a methylene (CH₂-) moiety;

each R²b, R³b, R⁴b and R⁵b is independently H, optionally substituted C₁-C₅ alkyl,
optionally substituted alkenyl or optionally substituted aryl;

X is N or CR⁶a;

each R⁶ and R⁶a is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted
with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl,
optionally substituted C₁-C₅ alkoxy or optionally substituted –C(O)C₁-C₅ alkyl; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents
independently selected from the group consisting of halo, C₁-C₅ alkyl, C₅-C₈ cycloalkyl, halo-
substituted C₁-C₅ alkyl, halo-substituted C₇-C₈ cycloalkyl, C₁-C₅ alkoxy, C₅-C₈ cycloalkoxy,
cyano, carboxylic, aminoacyl and acylamino.

[0318] In one variation, the compound is of the formula (A-IV), wherein m, n and R¹ are as
defined for the formula (A-IV);

R²a is H or optionally substituted C₁-C₅ alkyl, or is taken together with R¹ or R⁵a, where
present, to form a propylene (CH₂CH₂CH₂-) moiety or a butylene (CH₂CH₂CH₂CH₂-) moiety,
or is taken together with R³a to form an ethylene (CH₂CH₂-) moiety or a propylene
(CH₂CH₂CH₂-) moiety, taken together with R⁴a, where present, to form a methylene (CH₂-) moiety or an ethylene (CH₂CH₂-) moiety;

R²a is H or optionally substituted C₁-C₅ alkyl, or is taken together with R¹ or R⁴a, where
present, to form a propylene (CH₂CH₂CH₂-) moiety or a butylene (CH₂CH₂CH₂CH₂-) moiety,
or is taken together with R²a to form an ethylene (CH₂CH₂-) moiety or a propylene
(CH₂CH₂CH₂-) moiety, taken together with R⁵a, where present, to form a methylene (CH₂-) moiety or an ethylene (CH₂CH₂-) moiety;
R\textsuperscript{4a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{3a} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{4} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{2a} to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{5a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety;

R\textsuperscript{5a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{2a} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{4} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{3a} to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{4a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety;

each R\textsuperscript{2b}, R\textsuperscript{3b}, R\textsuperscript{4b} and R\textsuperscript{5b} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;

X is N or CR\textsuperscript{6a};

each R\textsuperscript{6} and R\textsuperscript{6a} is independently H, hydroxyl, halogen, C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with 1 to 3 halogen atoms, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkoxy or optionally substituted -C(=O)C\textsubscript{1}-C\textsubscript{5} alkyl;

Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\textsubscript{1}-C\textsubscript{5} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl, halo-substituted C\textsubscript{1}-C\textsubscript{5} alkyl, halo-substituted C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{1}-C\textsubscript{5} alkoxy, C\textsubscript{3}-C\textsubscript{8} cycloalkoxy, cyano, carboxyl, -NHC(=O)CH\textsubscript{3} and -C(=O)NR\textsuperscript{16}R\textsuperscript{17}; and

each R\textsuperscript{16} and R\textsuperscript{17} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl.

[0319] In one embodiment, the compound is of formula (A-IV), each of R\textsuperscript{2b}, R\textsuperscript{3a}, R\textsuperscript{3b}, R\textsuperscript{4b}, R\textsuperscript{5a} and R\textsuperscript{5b} is H; each R\textsuperscript{2a} and R\textsuperscript{4a} is H, or R\textsuperscript{2a} is taken together with R\textsuperscript{4a}, when present, to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; each R\textsuperscript{6} and R\textsuperscript{6a} is independently CF\textsubscript{3}, methyl, Cl, CONHCH\textsubscript{3}, COOH, COOCH\textsubscript{3}, or F; X is CR\textsuperscript{6}; and R\textsuperscript{1} is other than methyl. In another embodiment, X is CR\textsuperscript{6}, R\textsuperscript{6} is F; and R\textsuperscript{1} is other than methyl.

[0320] In one aspect, provided is a compound of formula (A-V):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl,
cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C₂-C₅ alkenyl, or
-C(OR)OR¹, or is taken together with R²⁺ or R³⁺ to form a propylene (-CH₂CH₂CH₂-) moiety or a
butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R⁴⁺ or R⁵⁺, where present, to
form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

R²⁺ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally
substituted aryl, or is taken together with R¹ or R⁵⁺, where present, to form a propylene
(-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R³⁺
to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety, taken together
with R⁴⁺, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety;

R³⁺ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally
substituted aryl, or is taken together with R¹ or R⁴⁺, where present, to form a propylene
(-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R²⁺
to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety, taken together
with R⁵⁺, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety;

R⁴⁺ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally
substituted aryl, or is taken together with R³⁺ to form a propylene (-CH₂CH₂CH₂-) moiety or a
butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R¹ to form an ethylene
(-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety, or is taken together with R²⁺ to form
a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety, or is taken together with R⁵⁺,
where present, to form a methylene (-CH₂-) moiety;
R^{5a} is H, optionally substituted C_{1}-C_{5} alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^{2a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{1} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{3a} to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety, or is taken together with R^{4a}, where present, to form a methylene (-CH_{2}-) moiety;

each R^{2b}, R^{3b}, R^{4b} and R^{5b} is independently H, optionally substituted C_{1}-C_{5} alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR^{6a};

each R^{6} and R^{6a} is independently H, hydroxyl, halo, C_{1}-C_{5} alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C_{1}-C_{5} alkoxy or optionally substituted –C(O)C_{1}-C_{5} alkyl;

s is 0 or 1;

each R^{9} and R^{10}, where present, is independently H or optionally substituted C_{1}-C_{5} alkyl;

R^{18} is H or optionally substituted C_{1}-C_{5} alkyl, and \(\text{cis-}\) indicates the presence of either an (E) or (Z) double bond configuration; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1}-C_{5} alkyl, C_{3}-C_{8} cycloalkyl, halo-substituted C_{1}-C_{5} alkyl, halo-substituted C_{3}-C_{8} cycloalkyl, C_{1}-C_{5} alkoxy, C_{3}-C_{8} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0321] In one variation, the compound is of the formula (A-V), wherein m, n and R^{1} are as defined for the formula (A-V);

R^{2a} is H or optionally substituted C_{1}-C_{5} alkyl, or is taken together with R^{1} or R^{5a}, where present, to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{3a} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, taken together with R^{4a}, where present, to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety;

R^{3a} is H or optionally substituted C_{1}-C_{5} alkyl, or is taken together with R^{1} or R^{4a}, where present, to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{2a} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, taken together with R^{5a}, where present, to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety;
R^{4a} is H or optionally substituted C_{1-5} alkyl, or is taken together with R^{3a} to form a propylene (-CH\_2CH\_2CH\_2-) moiety or a butylene (-CH\_2CH\_2CH\_2CH\_2-) moiety, or is taken together with R^{1} to form an ethylene (-CH\_2CH\_2-) moiety or a propylene (-CH\_2CH\_2CH\_2-) moiety, or is taken together with R^{2a} to form a methylene (-CH\_2-) moiety or an ethylene (-CH\_2CH\_2-) moiety, or is taken together with R^{5a}, where present, to form a methylene (-CH\_2-) moiety;

R^{5a} is H or optionally substituted C_{1-5} alkyl, or is taken together with R^{2a} to form a propylene (-CH\_2CH\_2CH\_2-) moiety or a butylene (-CH\_2CH\_2CH\_2CH\_2-) moiety, or is taken together with R^{1} to form an ethylene (-CH\_2CH\_2-) moiety or a propylene (-CH\_2CH\_2CH\_2-) moiety, or is taken together with R^{2a} to form a methylene (-CH\_2-) moiety or an ethylene (-CH\_2CH\_2-) moiety, or is taken together with R^{1a}, where present, to form a methylene (-CH\_2-) moiety;

each R^{2b}, R^{3b}, R^{4b} and R^{5b} is independently H or optionally substituted C_{1-5} alkyl;

X is N or CR^{6a};

each R^{6} and R^{6a} is independently H, hydroxyl, halogen, C_{1-5} alkyl optionally substituted with 1-3 halogen atoms, optionally substituted C_{1-5} alkoxy or optionally substituted -C(O)C_{1-5} alkyl;

s is 0 or 1;

each R^{9} and R^{10}, where present, is independently H or optionally substituted C_{1-5} alkyl;

R^{18} is H or optionally substituted C_{1-5} alkyl, and \( =\) indicates the presence of either an (E) or (Z) double bond configuration;

Q is aryl or heteroaryl optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_{1-5} alkyl, C_{3-8} cycloalkyl, halo-substituted C_{1-5} alkyl, halo-substituted C_{3-8} cycloalkyl, C_{1-5} alkoxy, C_{3-8} cycloalkoxy, cyano, carboxyl, -NHC(O)CH\_3 and -C(O)NR^{16}R^{17}; and

each R^{16} and R^{17} is independently H or optionally substituted C_{1-5} alkyl.

[0322] In certain embodiments, with respect to the compounds of formula (A-V), the compound is Compound No. 116, 121, or 132.

[0323] In one aspect, provided is a compound of formula (A-VI):
or a salt, solvate or N-oxide thereof, wherein:

R^1 is H, C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C_3-C_6 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C_2-C_5 alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C_1-C_5 alkyl, or is taken together with R^{2a} or R^{3a} to form a propylene (-CH_2CH_2CH_2-) moiety or a butylene (-CH_2CH_2CH_2CH_2-) moiety, or is taken together with R^{4a} or R^{5a}, where present, to form an ethylene (-CH_2CH_2-) moiety or a propylene (-CH_2CH_2CH_2-) moiety;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

R^{2a} is H, optionally substituted C_1-C_5 alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^1 or R^5a, where present, to form a propylene (-CH_2CH_2CH_2-) moiety or a butylene (-CH_2CH_2CH_2CH_2-) moiety, or is taken together with R^{3a} to form an ethylene (-CH_2CH_2-) moiety or a propylene (-CH_2CH_2CH_2-) moiety, taken together with R^{4a}, where present, to form a methylene (-CH_2-) moiety or an ethylene (-CH_2CH_2-) moiety;

R^{3a} is H, optionally substituted C_1-C_5 alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^1 or R^{4a}, where present, to form a propylene (-CH_2CH_2CH_2-) moiety or a butylene (-CH_2CH_2CH_2CH_2-) moiety, or is taken together with R^{2a} to form an ethylene (-CH_2CH_2-) moiety or a propylene (-CH_2CH_2CH_2-) moiety, taken together with R^5a, where present, to form a methylene (-CH_2-) moiety or an ethylene (-CH_2CH_2-) moiety;

R^{4a} is H, optionally substituted C_1-C_5 alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^{3a} to form a propylene (-CH_2CH_2CH_2-) moiety or a butylene (-CH_2CH_2CH_2CH_2-) moiety, or is taken together with R^1 to form an ethylene
(-CH₂CH₂⁻) moiety or a propylene (-CH₂CH₂CH₂⁻) moiety, or is taken together with R²ᵃ to form a methylene (-CH₂⁻) moiety or an ethylene (-CH₂CH₂⁻) moiety, or is taken together with R⁵ᵃ, where present, to form a methylene (-CH₂⁻) moiety;

R⁵ᵃ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R²ᵃ to form a propylene (-CH₂CH₂CH₂⁻) moiety or a butylene (-CH₂CH₂CH₂CH₂⁻) moiety, or is taken together with R¹ to form an ethylene (-CH₂CH₂⁻) moiety or a propylene (-CH₂CH₂CH₂⁻) moiety, or is taken together with R³ᵃ to form a methylene (-CH₂⁻) moiety or an ethylene (-CH₂CH₂⁻) moiety, or is taken together with R⁴ᵃ, where present, to form a methylene (-CH₂⁻) moiety;

each R²ᵇ, R³ᵇ, R⁴ᵇ and R⁵ᵇ is independently H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR⁶ᵃ;

each R⁶ and R⁶ᵃ is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted –C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R⁹, where present, to form a C₃-C₅ alkylene when R⁸ and R¹⁰ are taken together to form a bond;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R¹⁰, where present, to form a bond;

s is 0 or 1;

each R⁹ and R¹⁰, where present, is independently H or optionally substituted C₁-C₅ alkyl;

each R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl;

and

Q is acylamino, carbonylalkoxy, acyloxy, aminoacyl, aminocarbonylalkoxy or aminoaryl.

[0324] In one variation, the compound is of the formula (A-VI), wherein m, n, Q and R¹ are as defined for the formula (A-VI);
R\textsuperscript{2a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{1} or R\textsuperscript{5a}, where present, to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{3a} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, taken together with R\textsuperscript{4a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{3a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{1} or R\textsuperscript{4a}, where present, to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{2a} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, taken together with R\textsuperscript{4a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{4a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{3a} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{1} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{2a} to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{5a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety;

R\textsuperscript{5a} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{2a} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{1} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{3a} to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety, or is taken together with R\textsuperscript{4a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety;

each R\textsuperscript{2b}, R\textsuperscript{3b}, R\textsuperscript{4b} and R\textsuperscript{5b} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;

X is N or CR\textsuperscript{6a};

each R\textsuperscript{6} and R\textsuperscript{6a} is independently H, hydroxyl, halogen, C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with 1-3 halogen atoms, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkoxy or optionally substituted -C(O)C\textsubscript{1}-C\textsubscript{5} alkyl;

R\textsuperscript{7} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;

R\textsuperscript{8} is H, halo, hydroxyl, N(R\textsuperscript{11})R\textsuperscript{12}, SR\textsuperscript{13}, S(O)R\textsuperscript{13}, SO\textsubscript{2}R\textsuperscript{13}, -OC(O)NH(R\textsuperscript{14})R\textsuperscript{15}, or -OC(O)C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with amino;

s is 0 or 1;

each R\textsuperscript{9} and R\textsuperscript{10}, where present, is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; and

each R\textsuperscript{11}, R\textsuperscript{12}, R\textsuperscript{13}, R\textsuperscript{14} and R\textsuperscript{15} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl.
[0325] In another embodiment, the compound is of formula (A-VIIA), (A-VIIB), (A-VIIC), (A-VIID), (A-VIIE) or (A-VIIF):

or a salt, solvate or N-oxide thereof, wherein:

R<sup>1</sup>, where present, is H, C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C<sub>1</sub>-C<sub>5</sub> alkyl;

each X<sup>1</sup>, X<sup>2</sup>, X and U is independently N or CR<sup>6</sup>;

each R<sup>6</sup> is independently H, hydroxyl, halo, C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C<sub>1</sub>-C<sub>5</sub> alkoxy or optionally substituted –C(O)C<sub>1</sub>-C<sub>5</sub> alkyl;
R\(^7\) is H, halo, optionally substituted C\(_1\)-C\(_5\) alkyl, or optionally substituted aryl, or is taken together with R\(^8\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R\(^8\) is H, halo, hydroxyl, N(R\(^{11}\))R\(^{12}\), SR\(^{13}\), S(O)R\(^{13}\), SO\(_2\)R\(^{13}\), -OC(O)N(R\(^{14}\))R\(^{15}\), -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C\(_1\)-C\(_5\) alkyl optionally substituted with amino, or is taken together with R\(^7\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R\(^{11}\) and R\(^{12}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl, or R\(^{11}\) and R\(^{12}\) are taken together to form C\(_3\)-C\(_5\) alkyiene;

R\(^{13}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl;

each R\(^{14}\) and R\(^{15}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; or R\(^{14}\) and R\(^{15}\) are taken together to form a C\(_3\)-C\(_5\) alkyiene; and

each Y\(^1\), Y\(^2\), Y\(^3\), Y\(^4\) and Y\(^5\) is independently N or CR\(^4\) such that no more than two of Y\(^1\), Y\(^2\), Y\(^3\), Y\(^4\) and Y\(^5\) are N, wherein R\(^4\) is H, halo, CH\(_3\), CF\(_3\), or OCH\(_3\).

**[0326]** In certain embodiments, with respect to the compounds of formula (A-VII A), R\(^8\) is OH, and the compound is Compound No. II-107, II-164, II-165, III-2, III-102-107, III-114, III-131, III-135, III-137, or III-138.

**[0327]** In certain embodiments, with respect to the compounds of formula (A-VII A), each X\(^1\), X\(^2\), X and U is independently CR\(^6\); and the compound is Compound No. 211, III-100, III-200-202, III-207, III-289 to III-296, III-307, III-309, III-316, III-318, or III-319.

**[0328]** In certain embodiments, with respect to the compounds of formula (A-VII A), each X\(^1\), X\(^2\), X and U is independently CR\(^6\); each Y\(^1\), Y\(^3\), Y\(^4\) and Y\(^5\) is independently CR\(^4\); Y\(^2\) is N, and the compound is Compound No. III-132, III-133, III-203, III-205, III-294, III-299, III-303, III-306, III-312, or III-315.

**[0329]** In certain embodiments, with respect to the compounds of formula (A-VII A), each X\(^1\), X\(^2\), X and U is independently CR\(^6\); each Y\(^1\), Y\(^2\), Y\(^4\) and Y\(^5\) is independently CR\(^4\); Y\(^3\) is N, and the compound is Compound No. 73, 154, II-66, III-101, III-108 to III-113, III-115 to III-121, III-125 to III-130, III-134, III-138, III-198, III-199, III-206 to III-208, III-297, III-298, III-301, III-302, III-305, III-308, III-311, III-314, or III-317.

**[0330]** In certain embodiments, with respect to the compounds of formula (A-VII A), each X\(^1\), X\(^2\), and X is CR\(^6\); U is N, and the compound is Compound No. III-2.
[0331] In certain embodiments, with respect to the compounds of formula (A-VIIIB), each $X^1$, $X^2$, $X$ and $U$ is independently CR$^6$, $R^8$ is OH, and the compound is Compound No. III-59.

[0332] In certain embodiments, with respect to the compounds of formula (A-VIIIC), each $X^1$, $X^2$, $X$ and $U$ is independently CR$^6$, $R^8$ is OH, each $Y^1$, $Y^2$, $Y^4$ and $Y^5$ is independently CR$^4$, $Y^3$ is N, and the compound is Compound No. 36, 38, or II-69.

[0333] In certain embodiments, with respect to the compounds of formula (A-VIID), each $X^1$, $X^2$, $X$ and $U$ is independently CR$^6$, $R^8$ is OH, and the compound is Compound No. III-58.

[0334] In certain embodiments, with respect to the compounds of formula (A-VIIIE), each $X^1$, $X^2$, $X$ and $U$ is independently CR$^6$, $R^8$ is OH, and the compound is Compound No. III-60.

[0335] In certain embodiments, with respect to the compounds of formula (A-VIIIE), each $X^1$, $X^2$, $X$ and $U$ is independently CR$^6$, $R^8$ is OH, and the compound is Compound No. III-56.

[0336] In another embodiment, the compound is of formula (A-VIIIA) or (A-VIIIB):

\[
\text{(A-VIIIA)} \quad \text{or} \quad \text{(A-VIIIB)},
\]

or a salt, solvate or N-oxide thereof, wherein:

$R^1$ is H, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C$_1$-C$_5$ alkyl;

- each $X^1$, $X^2$, $X$ and $U$ is independently N or CR$^6$;

- each $R^6$ is independently H, hydroxyl, halo, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C$_1$-C$_5$ alkoxy or optionally substituted -C(O)C$_1$-C$_5$ alkyl;
R^7 is H, halo, optionally substituted C_1-C_6 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxane ring or a carbonyl moiety;

R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxane ring or a carbonyl moiety;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkyne;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkyne; and

Q is aryl or heteroaryl, wherein the aryl or heteroaryl is independently optionally substituted with 1 to 3 substituents including halogen, C_1-C_5 alkyl or cycloalkyl, halo-substituted C_1-C_5 alkyl or cycloalkyl, C_1-C_5 alkoxy or cycloalkoxy, -CN or -C(O)N(R^a)R^b, and wherein each R^a and R^b is independently H or C_1-C_5 alkyl.

[0337] In some variations of the compounds of formula (A-VIIIA) or (A-VIIIB), one of X^1, X^2, X and U is N, and the other three of X^1, X^2, X and U is CR^6. In other variations, two of X^1, X^2, X and U is N, and the other two of X^1, X^2, X and U is CR^6. In some variations, R^7 is a C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, -N(R^{7a})(R^{7b}), -C(O)N(R^{7a})(R^{7b}), -C(O)OR^{7a}, -C(O)R^{7a}. In other variations, R^7 is an optionally substituted C_3-C_8 cycloalkyl. In some variations, R^{10} is an optionally substituted C_3-C_8 cycloalkyl. In other variations, R^{11} or R^{12} is an optionally substituted C_3-C_8 cycloalkyl. In some variations, Q is optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted pyrazinyl, or optionally substituted phenyl.

[0338] In some variations of the compounds of formula (A-VIIIA), X^1 is N; each X^2 and X is CR^6, wherein each R^6 is H; U is CR^6, wherein each R^6 is H or methyl; R^1 is methyl; each R^7 and R^8 is H; and Q is other than unsubstituted pyridyl, or pyridyl substituted with methyl or CF_3.

[0339] In some variations of the compounds of formula (A-VIIIA), U is N, each X^1, X^2 and X is CR^6, wherein each R^6 is H; R^1 is methyl; R^7 is H or methyl; R^8 is H, OH or methyl; and Q is other than unsubstituted phenyl, phenyl substituted with chloro, unsubstituted pyridyl, or pyridyl substituted with methyl or CF_3.
[0340] In some variations of the compounds of formula (A-VIIIA), X² is N, each X¹ and X is CR⁶, wherein each R⁶ is H; U is CR⁶, wherein R⁶ is H or methyl; R¹ is methyl; each of R⁷ and R⁸ is H; and Q is other than unsubstituted phenyl, unsubstituted pyridyl, or pyridyl substituted with CF₃.

[0341] In some variations of the compounds of formula (A-VIIIA), X is N, each X¹, U and X² is CR⁶, wherein each R⁶ is H; R¹ is methyl; each of R⁷ and R⁸ is H; and Q is other than unsubstituted phenyl.

[0342] In some variations of the compounds of formula (A-VIIIA), each X and U is N, each X¹ and X² is CR⁶, wherein each R⁶ is H; R¹ is methyl; each of R⁷ and R⁸ is H; and Q is other than unsubstituted phenyl.

[0343] In some variations of the compounds of formula (A-VIIIA), the compound is according to formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7):

(A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3),

(A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or
or a salt, solvate or N-oxide thereof, wherein Q, R¹, R⁶, R⁷, and R⁸, are as described for formula (A-VIIIA), and each X¹, U, X², or X (where present) is independently CR⁶.

[0344] In one embodiment, the compound is according to formula (A-VIIIA-1), each X¹, U and X² is CR⁶, wherein each R⁶ is H; R¹ is methyl; each of R⁷ and R⁸ is H; and Q is other than unsubstituted phenyl.

[0345] In one embodiment, the compound is according to formula (A-VIIIA-2), each X¹ and X is CR⁶, wherein each R⁶ is H; U is CR⁶, wherein R⁶ is H or methyl; R¹ is methyl; each of R⁷ and R⁸ is H; and Q is other than unsubstituted phenyl, unsubstituted pyridyl, or pyridyl substituted with CF₃.

[0346] In one embodiment, the compound is according to formula (A-VIIIA-3), each X¹, X² and X is CR⁶, wherein each R⁶ is H; R¹ is methyl; R⁷ is H or methyl; R⁸ is H, OH or methyl; and Q is other than unsubstituted phenyl, phenyl substituted with chloro, unsubstituted pyridyl, or pyridyl substituted with methyl or CF₃.

[0347] In one embodiment, the compound is according to formula (A-VIIIA-4), each X² and X is CR⁶, wherein each R⁶ is H; U is CR⁶, wherein R⁶ is H or methyl; R¹ is methyl; each R⁷ and R⁸ is H; and Q is other than unsubstituted pyridyl, or pyridyl substituted with methyl or CF₃.

[0348] In one embodiment, the compound is according to formula (A-VIIIA-5), each X¹ and X² is CR⁶, wherein each R⁶ is H; R¹ is methyl; each of R⁷ and R⁸ is H; and Q is other than unsubstituted phenyl.

[0349] In one embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), each X¹, U, X², or X (where present) is independently CR⁶, and each R⁶ is H. In another embodiment, each R⁶ is independently selected from H, C₁-C₅ alkyl, and halo C₁-C₅ alkyl. In certain embodiments, each R⁶ is independently selected from H, methyl, ethyl, fluoro, chloro, CH₂F, and CF₃.
In one embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-4), (A-VIIIA-6), or (A-VIIIA-7), each X₁, X₂, or X (where present) is CH, U is CR₆, and R₆ is selected from H, C₁-C₅ alkyl, and halo C₁-C₅ alkyl. In certain embodiments, each R₆ is independently selected from methyl, ethyl, fluoro, chloro, CH₂F, and CF₃.

In one embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), each R⁷ and R⁸ is H. In another embodiment, R⁷ is H or methyl, and R⁸ is H, OH or methyl.

In one embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is optionally substituted phenyl.

In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is phenyl substituted with C₁-C₅ alkyl, halo, halo C₁-C₅ alkyl, or C₁-C₅ alkoxy.

In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is phenyl substituted with methyl, ethyl, fluoro, chloro, methoxy, or CF₃.

In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is optionally substituted pyridyl, or optionally substituted pyrimidinyl.

In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is pyridyl substituted with C₁-C₅ alkyl, halo, halo or C₁-C₅ alkyl.

In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is pyridyl substituted with methyl, ethyl, fluoro, chloro, or CF₃.

In one embodiment, provided are compounds of formula (A-IXA), (A-IXB), (A-IXC) or (A-IXD):
wherein U, Q, R¹, R⁶, R⁷, and R⁸ are as described for formula (A-I).

[0359] In certain embodiments, R⁸ is azido. In certain embodiments, R⁸ is N(R¹₁₁)R¹₂. In certain embodiments, each R¹₁¹ and R¹₁² is independently H or optionally substituted C₁-C₅ alkyl, or R¹₁¹ and R¹₁² are taken together to form C₃-C₅ alkyne. In certain embodiments, R⁷ is H or methyl, R⁸ is azido, or N(R¹₁₁)R¹₁₂, and each R¹₁¹ and R¹₁² is independently H or optionally substituted C₁-C₅ alkyl, or R¹₁¹ and R¹₁² are taken together to form C₃-C₅ alkyne. In certain embodiments, R⁸ is SR¹₃, S(O)R¹₃, or SO₂R¹₃; and R¹₃ is independently H or optionally substituted C₁-C₅ alkyl. In one embodiment, R¹₃ is methyl, ethyl, i-propyl, n-propyl, n-butyl, or i-butyl. In certain embodiments, R⁷ is C₁-C₅ alkyl, substituted with amino or substituted amino. In certain embodiments, R⁷ is C₁-C₅ alkyl, substituted with OH or optionally substituted C₁-C₅ alkoxy. In certain embodiments, R⁷ is C₁-C₅ alkyl, substituted with -C(O)N(R⁷ₐ)R⁷ₐ; and each R⁷ₐ and R⁷ₐ is independently H or optionally substituted C₁-C₅ alkyl, or R⁷ₐ and R⁷ₐ are taken together to form C₃-C₅ alkyne. In certain embodiments, R⁷ is C₁-C₅ alkyl, substituted with acyl.
[0360] In certain embodiments, \( R^8 \) is halo. In one embodiment, with respect to the compounds of formula (A-IXB) or (A-IXC), when \( R^8 \) is fluoro or chloro, \( R^1 \) is methyl, ethyl, \( i \)-propyl, or cyclopropyl, \( R^2 \) is H or methyl, \( U \) is CR\(^6\), and \( R^6 \) is methyl or chloro, then Q is other than unsubstituted phenyl, phenyl substituted with methoxy, chloro, fluoro, difluoro, unsubstituted pyridyl, pyridyl substituted with methyl, or unsubstituted pyrimidinyl.

[0361] In certain embodiments, \( R^7 \) is optionally substituted cycloalkyl. In one embodiment, with respect to the compounds of formula (A-IXB) or (A-IXC), when \( R^7 \) is optionally substituted cycloalkyl, \( R^8 \) is OH, \( R^1 \) is methyl, \( U \) is CR\(^6\), and \( R^6 \) is methyl or chloro, then Q is other than unsubstituted phenyl, phenyl substituted with fluoro, or unsubstituted pyridyl. In one embodiment, \( R^7 \) is optionally substituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. In certain embodiments, \( R^7 \) is C\(_1\)-C\(_5\) alkyl, substituted with acylamino.

[0362] In one embodiment, with respect to the compounds of formula (A-IXB) or (A-IXC), when \( R^7 \) is CH\(_2\)-CON(H)CH\(_3\), \( R^1 \) is methyl or ethyl, \( U \) is CR\(^6\), and \( R^6 \) is methyl or chloro, then Q is other than phenyl substituted with fluoro, chloro, methoxy, or difluoro, unsubstituted pyridyl, pyridyl substituted with methyl, or unsubstituted pyrimidinyl.

[0363] In certain embodiments, \( R^7 \) is C\(_1\)-C\(_5\) alkyl, substituted with -C(O)OR\(^7_a\), and \( R^7_a \) is H or optionally substituted C\(_1\)-C\(_5\) alkyl.

[0364] In one embodiment, \( R^7 \) is C\(_1\)-C\(_5\) alkyl, substituted with -C(O)OR\(^7_a\), \( R^7_a \) is H or optionally substituted C\(_1\)-C\(_3\) alkyl, \( R^1 \) is methyl or ethyl, \( U \) is CR\(^6\), and \( R^6 \) is methyl or chloro; and Q is other than phenyl substituted with F, chloro, methoxy, or difluoro, unsubstituted pyridyl, pyridyl substituted with methyl, or unsubstituted pyrimidinyl.

[0365] In certain embodiments, \( R^7 \) is C\(_1\)-C\(_5\) alkyl, substituted with 1-3 halo.

[0366] In one embodiment, with respect to the compounds of formula (A-IXB), \( R^7 \) is CF\(_3\), \( R^8 \) is OH, \( R^1 \) is methyl, \( U \) is CR\(^6\), and \( R^6 \) is methyl; and Q is other than phenyl substituted with fluoro. In one particular embodiment, \( R^7 \) is CF\(_3\).

[0367] In certain embodiments, \( R^8 \) is -C(O)N(R\(^{14}\))R\(^{15}\); and each R\(^{14}\) and R\(^{15}\) is independently H or optionally substituted C\(_1\)-C\(_3\) alkyl, or R\(^{14}\) and R\(^{15}\) are taken together to form a C\(_3\)-C\(_5\) alkenylene.

[0368] In one particular embodiment, \( R^8 \) is -C(O)N(R\(^{14}\))R\(^{15}\); and each R\(^{14}\) and R\(^{15}\) is independently H or methyl, \( R^1 \) is methyl, \( U \) is CR\(^6\), and \( R^6 \) is methyl; and Q is other than cyclobutyl.
In certain embodiments, $R^8$ is $-\text{OC(O)}N(R^{14})R^{15}$, $-\text{OC(O)}$-aryl, $-\text{OC(O)}$-heteroaryl, $-\text{OC(O)}C_1-C_5$ alkyl optionally substituted with amino, $-\text{OC(O)}C_1-C_5$ alkyl substituted with carboxyl, or $-\text{OC}_1-C_5$ alkyl optionally substituted with carboxyl; and each $R^{14}$ and $R^{15}$ is independently H or optionally substituted $C_1-C_5$ alkyl, or $R^{14}$ and $R^{15}$ are taken together to form a $C_3-C_5$ alkylene.

In certain embodiments, $R^7$ is optionally substituted phenyl. In one particular embodiment, $R^7$ is optionally substituted phenyl, $R^8$ is OH, $R^1$ is methyl or ethyl, $U$ is $\text{CR}^6$, and $R^6$ is methyl or chloro; and Q is other than unsubstituted phenyl, phenyl substituted with fluoro or unsubstituted pyridyl.

In certain embodiments, $R^8$ is OH. In some embodiments, $R^8$ is OH, and $R^7$ is other than H, or $C_1-C_4$ alkyl.

In some embodiments, compounds of the formula (B-I) are provided:

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

$R^1$ is H, $C_1-C_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, $C_3-C_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, $C_2-C_5$ alkenyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or $-\text{C(O)}O-C_1-C_5$ alkyl, or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety, or is taken together with $R^{4a}$ or $R^{5a}$, where present, to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety;

each $n$ and $m$ is 1, or $n$ is 0 and $m$ is 1, or $n$ is 1 and $m$ is 0;
R^{2a} is H, optionally substituted C_{1-5} alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^1 or R^{5a}, where present, to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{2a} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, taken together with R^{4a}, where present, to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety;

R^{3a} is H, optionally substituted C_{1-5} alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^1 or R^{4a}, where present, to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{2a} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, taken together with R^{5a}, where present, to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety;

R^{4a} is H, optionally substituted C_{1-5} alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^{3a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{1} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{2a} to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety, or is taken together with R^{5a}, where present, to form a methylene (-CH_{2}-) moiety;

R^{5a} is H, optionally substituted C_{1-5} alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R^{2a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{1} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety, or is taken together with R^{3a} to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety, or is taken together with R^{4a}, where present, to form a methylene (-CH_{2}-) moiety;

each R^{2b}, R^{3b}, R^{4b} and R^{5b} is independently H, optionally substituted C_{1-5} alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR^{6a};

t is 1, 2 or 3;

each R^{6} and R^{6a} is independently H, hydroxyl, halo, C_{1-5} alkyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C_{1-5} alkoxy or optionally substituted -C(O)C_{1-5} alkyl;

R^{7} is H, halo, optionally substituted C_{1-5} alkyl, or optionally substituted aryl;

R^{8} is azido, acylamino, carboxyl, carbonylalkoxy, -OC(O)C_{1-5} alkyl substituted with carboxyl, or -OC_{1-5} alkyl optionally substituted with carboxyl;
each R⁹ and R¹⁰ is independently H or optionally substituted C₁-C₅ alkyl; and
Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1-3 substituents
independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-
substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy,
cyano, carboxyl, aminoacryl and acylamino.

[0373] In one variation, Q, X, m, n, t, R¹, R²a, R²b, R³a, R³b, R⁴a, R⁴b, R⁵a, R⁵b, R⁶, R⁶a, R⁷, R⁹
and R¹⁰ are as defined for the formula (B-I), and R⁸ is azido, acylamino, –OC(O)C₁-C₅ alkyl
substituted with carboxyl, or –OC₁-C₅ alkyl substituted with carboxyl, or a salt, solvate or N-
oxide thereof. In another variation, Q, X, m, n, t, R¹, R²a, R²b, R³a, R³b, R⁴a, R⁴b, R⁵a, R⁵b, R⁶, R⁶a, R⁷, R⁹ and R¹⁰ are as defined for the formula (B-I), and R⁸ is carboxyl, or carbonylalkoxy,
or a salt, solvate or N-oxide thereof.

[0374] In one variation, Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1-3
substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈
cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈
cycloalkoxy, cyano, carboxyl, -NHC(O)CH₃ and –C(O)NR¹¹R¹₂ where each R¹¹ and R¹² is
independently H or optionally substituted C₁-C₅ alkyl.

[0375] In some variations, R¹ is C₁-C₅ alkyl (e.g., methyl), each R²a and R³a is H, R⁶ is methyl
or chloro, and X is CR⁶a where R⁶a is methyl or chloro. In some of these variations, t is 1, 2 or 3.
In some of these variations, R⁷ is H or C₁-C₅ alkyl (e.g., methyl). In some of these variations, R⁷
is H. In some of these variations, R⁹ is H or C₁-C₅ alkyl (e.g., methyl) and R¹₀ is H. In some of
these variations, each R⁹ and R¹₀ is H. In some of these variations, each R⁷, R⁹ and R¹₀ is H.
In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the
parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these
variations, Q is 3- pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a
methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is
phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-
fluorophenyl. In some of these variations, Q is phenyl substituted with –C(O)NR¹¹R¹₂ where
each R¹¹ and R¹₂ is H. In some of these variations, Q is 4-carbamoylphenyl.

[0376] In another embodiment, the compound of formula (B-I) has the formula (B-IA):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R²ₐ or R³ₐ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R²ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R³ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

X is N or CR₆ₐ;

each R⁶ and R₆ₐ is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)O-C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl;

R⁸ is azido, acylamino, carboxyl, carbonylalkoxy, -OC(O)C₁-C₅ alkyl substituted with carboxyl or -OC₁-C₅ alkyl optionally substituted with carboxyl;

each R⁹ and R¹₀ is independently H or optionally substituted C₁-C₅ alkyl; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-
substituted C_{1-5} alkyl, halo-substituted C_{3-8} cycloalkyl, C_{1-5} alkoxy, C_{3-8} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

**[0377]** In one variation, the compound is of the formula (B-IA), wherein Q, X, R^1, R^{2a}, R^{3a}, R^6, R^{6a}, R^7, R^9 and R^{10} are as defined for the formula (B-IA), and R^8 is azido, acylamino, \(-OC(O)C_1-C_5\) alkyl substituted with carboxyl, or \(-OC_1-C_5\) alkyl substituted with carboxyl, or a salt, solvate or N-oxide thereof. In another variation, Q, X, R^1, R^{2a}, R^{3a}, R^6, R^{6a}, R^7, R^9 and R^{10} are as defined for the formula (B-IA), and R^8 is carboxyl, or carbonylalkoxy.

**[0378]** In some variations of the compound of the formula (B-IA), each R^{2a} and R^{3a} is H. In some variations, R^1 is C_1-C_5 alkyl (e.g., methyl). In some variations, each R^6 and R^{6a} is independently halo (e.g., chloro) or C_1-C_5 alkyl (e.g., methyl). In some variations, each R^6 and R^{6a} is independently halo (e.g., chloro or fluoro). In some variations, R^6 and R^{6a} is chloro. In some variations, each R^6 and R^{6a} is independently C_1-C_5 alkyl (e.g., methyl). In some variations, X is CR^{6a} where R^{6a} is H or halo. In some variations, X is CR^{6a} where R^{6a} is H. In some variations, X is CR^{6a} where R^{6a} is chloro. In some variations, X is CR^{6a} where R^{6a} is halo (e.g., chloro or fluoro). In some variations, R^6 is H or halo. In some variations, R^6 is H. In some variations, R^6 is chloro. In some variations, R^6 is halo (e.g., chloro or fluoro). In some variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl). In some variations, X is N. In some variations, R^7 is H. In some variations, R^7 is C_1-C_5 alkyl (e.g., methyl). In some variations, R^8 is azido. In some variations, R^8 is carboxyl, \(-OC(O)C_1-C_5\) alkyl substituted with carboxyl, or \(-OC_1-C_5\) alkyl optionally substituted with carboxyl. In some variations, R^8 is acylamino. In some variations, R^7 is H or C_1-C_5 alkyl (e.g., methyl) and R^8 is azido, acylamino, \(-OC(O)C_1-C_5\) alkyl substituted with carboxyl or \(-OC_1-C_5\) alkyl optionally substituted with carboxyl. In some variations, R^7 is H and R^8 is azido, acylamino, \(-OC(O)C_1-C_5\) alkyl substituted with carboxyl or \(-OC_1-C_5\) alkyl optionally substituted with carboxyl. In some variations, R^9 is H or C_1-C_5 alkyl (e.g., methyl). In some variations, R^{10} is H or C_1-C_5 alkyl (e.g., methyl). In some variations, each R^9 and R^{10} is H. In some variations, one of R^9 and R^{10} is H and the other is C_1-C_5 alkyl (e.g., methyl). In some variations, Q is an unsubstituted heteroaryl (e.g., pyridyl). In some variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some variations, Q is 3- pyridyl or 4-pyridyl. In some variations, Q is heteroaryl substituted with a substituent selected from the group consisting of halo (e.g., fluoro or chloro), C_1-C_5 alkyl (e.g., methyl), halo-substituted C_1-C_5 alkyl (e.g., CF_3) and carboxyl. In some variations, Q is heteroaryl substituted with halo (e.g., fluoro or chloro) or...
C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl). In some variations, Q is heteroaryl substituted with C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl). In some variations, Q is a pyridyl optionally substituted with a methyl where the pyridyl group may be attached to the parent structure at any position and the methyl group may be attached to the pyridyl group at any open position (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some variations, Q is phenyl substituted with a substituent selected from the group consisting of halo (e.g., fluoro or chloro), C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl), halo-substituted C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., CF<sub>3</sub>), carboxyl and –C(O)NR<sup>11</sup>R<sup>12</sup> where each R<sup>11</sup> and R<sup>12</sup> is independently H or optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl. In some variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some variations, Q is 4-fluorophenyl. In some variations, Q is phenyl substituted with –C(O)NR<sup>11</sup>R<sup>12</sup> where each R<sup>11</sup> and R<sup>12</sup> is H.

[0379] In some variations of the compound of the formula (B-IA), R<sup>1</sup> is C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl), each R<sup>2a</sup> and R<sup>3a</sup> is H, R<sup>6</sup> is methyl or chloro, and X is CH. In some of these variations, R<sup>7</sup> is H or C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl) and R<sup>8</sup> is azido. In some of these variations, R<sup>7</sup> is H and R<sup>8</sup> is azido, acylamino, –OC(O)C<sub>1</sub>-C<sub>5</sub> alkyl substituted with carboxyl or –OC<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with carboxyl. In some of these variations, R<sup>7</sup> is methyl and R<sup>8</sup> is azido, acylamino, –OC(O)C<sub>1</sub>-C<sub>5</sub> alkyl substituted with carboxyl or –OC<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with carboxyl. In some of these variations, R<sup>9</sup> is H or C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl) and R<sup>10</sup> is H. In some of these variations, each R<sup>9</sup> and R<sup>10</sup> is H. In some of these variations, R<sup>7</sup> is H or C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl), R<sup>8</sup> is azido, and each R<sup>9</sup> and R<sup>10</sup> is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3-pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-fluorophenyl. In some of these variations, Q is phenyl substituted with –C(O)NR<sup>11</sup>R<sup>12</sup> where each R<sup>11</sup> and R<sup>12</sup> is H. In some of these variations, Q is 4-carbamoylphenyl.

[0380] In some variations of the compound of the formula (B-IA), R<sup>1</sup> is C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl), each R<sup>2a</sup> and R<sup>3a</sup> is H, R<sup>6</sup> is methyl or chloro, and X is CH. In some variations, R<sup>7</sup> is H and R<sup>8</sup> is azido, acylamino, –OC(O)C<sub>1</sub>-C<sub>5</sub> alkyl substituted with carboxyl or –OC<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with carboxyl. In some variations, R<sup>7</sup> is H and R<sup>8</sup> is azido, acylamino, –OC(O)C<sub>1</sub>-C<sub>5</sub> alkyl substituted with carboxyl or –OC<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with carboxyl. In some of these variations, R<sup>9</sup> is H or C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl) and R<sup>10</sup> is H. In some of these variations, Q is heteroaryl substituted with C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl). In some variations, Q is a pyridyl optionally substituted with a methyl where the pyridyl group may be attached to the parent structure at any position and the methyl group may be attached to the pyridyl group at any open position (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some variations, Q is phenyl substituted with a substituent selected from the group consisting of halo (e.g., fluoro or chloro), C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., methyl), halo-substituted C<sub>1</sub>-C<sub>5</sub> alkyl (e.g., CF<sub>3</sub>), carboxyl and –C(O)NR<sup>11</sup>R<sup>12</sup> where each R<sup>11</sup> and R<sup>12</sup> is independently H or optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl. In some variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some variations, Q is 4-fluorophenyl. In some variations, Q is phenyl substituted with –C(O)NR<sup>11</sup>R<sup>12</sup> where each R<sup>11</sup> and R<sup>12</sup> is H.
some of these variations, each $R^9$ and $R^{10}$ is $H$. In some of these variations, $Q$ is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, $Q$ is 3- pyridyl or 4-pyridyl. In some of these variations, $Q$ is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, $Q$ is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, $Q$ is 4-fluorophenyl. In some of these variations, $Q$ is phenyl substituted with $-C(O)NR^{11}R^{12}$ where each $R^{11}$ and $R^{12}$ is $H$. In some of these variations, $Q$ is 4-carbamoylphenyl.

[0381] In some variations of the compound of the formula (B-IA), $R^1$ and $R^{2a}$ are taken together to form a propylene (−CH$_2$CH$_2$CH$_2$−) moiety and $R^{3a}$ is $H$. In some of these variations, $X$ is $N$. In some of these variations, $X$ is $CH$. In some of these variations, $R^6$ is C$_{1-5}$ alkyl (e.g., methyl) or halo (e.g., chloro). In some of these variations, $R^6$ is methyl or chloro. In some of these variations, $R^7$ is H or C$_{1-5}$ alkyl (e.g., methyl) and $R^8$ is azido, acylamino, $-OC(O)C_{1-5}$ alkyl substituted with carboxyl or $-OC_{1-5}$ alkyl optionally substituted with carboxyl. In some of these variations, $R^7$ is H and $R^8$ is azido, acylamino, $-OC(O)C_{1-5}$ alkyl substituted with carboxyl or $-OC_{1-5}$ alkyl optionally substituted with carboxyl. In some of these variations, $R^7$ is methyl and $R^8$ is azido, acylamino, $-OC(O)C_{1-5}$ alkyl substituted with carboxyl or $-OC_{1-5}$ alkyl optionally substituted with carboxyl. In some of these variations, $R^9$ is H or C$_{1-5}$ alkyl (e.g., methyl) and $R^{10}$ is $H$. In some of these variations, each $R^9$ and $R^{10}$ is $H$. In some of these variations, $R^7$ is H or C$_{1-5}$ alkyl (e.g., methyl), $R^8$ is azido, and each $R^9$ and $R^{10}$ is $H$. In some of these variations, $Q$ is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, $Q$ is 3- pyridyl or 4-pyridyl. In some of these variations, $Q$ is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, $Q$ is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, $Q$ is phenyl substituted with $-C(O)NR^{11}R^{12}$ where each $R^{11}$ and $R^{12}$ is $H$. In some of these variations, $Q$ is 4-carbamoylphenyl.

[0382] In certain embodiments, with respect to the compounds of formula (B-IA), $X$ is CR$^6$, $R^8$ is azido, and the compound is Compound No. II-261, II-266, II-276, II-298, V-1, V-3, V-22, or V23.
In certain embodiments, with respect to the compounds of formula (B-IA), X is CR$^6$, R$^8$ is acylamino, carboxyl, or carbonylalkoxy, and the compound is Compound No. II-258, II-262, II-263, or II-277.

In certain embodiments, with respect to the compounds of formula (B-IA), X is CR$^6$, R$^8$ is $-OC(O)C_1-C_5$ alkyl substituted with carboxyl, and the compound is Compound No. V-18.

In certain embodiments, with respect to the compounds of formula (B-IA), X is CR$^6$, R$^8$ is $-OC_1-C_5$ alkyl optionally substituted with carboxyl, and the compound is Compound No. II-256, II-274, II-281, V-14 or V-15.

In another embodiment, the compound of formula (B-I) has the formula (B-IB):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

- R$^1$ is H, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_3$-C$_5$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_2$-C$_5$ alkenyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C$_1$-C$_5$ alkyl, or is taken together with R$^{2a}$ or R$^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_3$CH$_2$CH$_2$-) moiety;

- R$^{2a}$ is H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R$^1$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_3$CH$_2$CH$_2$-) moiety;

- R$^{3a}$ is H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R$^1$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_3$CH$_2$CH$_2$-) moiety;

- X is N or CR$^{6a}$;
each \( R^6 \) and \( R^{6a} \) is independently H, hydroxyl, halo, C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C\(_1\)-C\(_3\) alkoxy or optionally substituted –C(O)C\(_1\)-C\(_5\) alkyl;

\( R^7 \) is H, halo, optionally substituted C\(_1\)-C\(_5\) alkyl, or optionally substituted aryl;

\( R^8 \) is azido, acylamino, carboxyl, carbonylalkoxy, –OC(O)C\(_1\)-C\(_5\) alkyl substituted with carboxyl, or –OC\(_1\)-C\(_5\) alkyl optionally substituted with carboxyl;

each \( R^9 \) and \( R^{10} \) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\(_1\)-C\(_5\) alkyl, C\(_3\)-C\(_8\) cycloalkyl, halo-substituted C\(_1\)-C\(_5\) alkyl, halo-substituted C\(_3\)-C\(_8\) cycloalkyl, C\(_1\)-C\(_5\) alkoxy, C\(_3\)-C\(_8\) cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0387] In one variation, the compound is of the formula (B-IB), wherein Q, X, \( R^1 \), \( R^{2a} \), \( R^{3a} \), \( R^6 \), \( R^{6a} \), \( R^7 \), \( R^9 \) and \( R^{10} \) are as defined for the formula (B-IB), and \( R^8 \) is azido, acylamino, –OC(O)C\(_1\)-C\(_5\) alkyl substituted with carboxyl, or –OC\(_1\)-C\(_5\) alkyl substituted with carboxyl, or a salt, solvate or N-oxide thereof. In another variation, Q, X, \( R^1 \), \( R^{2a} \), \( R^{3a} \), \( R^6 \), \( R^{6a} \), \( R^7 \), \( R^9 \) and \( R^{10} \) are as defined for the formula (B-IB), and \( R^8 \) is carboxyl, or carbonylalkoxy.

[0388] In some variations of the compound of the formula (B-IB), \( R^1 \) is C\(_1\)-C\(_5\) alkyl (e.g., methyl), each \( R^{2a} \) and \( R^{3a} \) is H, \( R^6 \) is methyl or chloro, and X is CH. In some of these variations, \( R^7 \) is H or C\(_1\)-C\(_5\) alkyl (e.g., methyl) and \( R^8 \) is azido. In some of these variations, \( R^7 \) is H and \( R^8 \) is azido, acylamino, –OC(O)C\(_1\)-C\(_5\) alkyl substituted with carboxyl or –OC\(_1\)-C\(_5\) alkyl optionally substituted with carboxyl. In some of these variations, \( R^7 \) is methyl and \( R^8 \) is azido, acylamino, –OC(O)C\(_1\)-C\(_5\) alkyl substituted with carboxyl or –OC\(_1\)-C\(_5\) alkyl optionally substituted with carboxyl. In some of these variations, \( R^9 \) is H or C\(_1\)-C\(_5\) alkyl (e.g., methyl) and \( R^{10} \) is H. In some of these variations, each \( R^9 \) and \( R^{10} \) is H. In some of these variations, \( R^7 \) is H or C\(_1\)-C\(_5\) alkyl (e.g., methyl), \( R^8 \) is azido, acylamino, –OC(O)C\(_1\)-C\(_5\) alkyl substituted with carboxyl or –OC\(_1\)-C\(_5\) alkyl substituted with carboxyl, and each \( R^9 \) and \( R^{10} \) is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3-pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-fluorophenyl.

[0389] In another embodiment, the compound of formula (B-I) has the formula (B-IC):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₆ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R²a or R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R²a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R³a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R⁵a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR⁶a;

each R⁶ and R⁶a is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl;

R⁸ is azido, acylamino, carboxyl, carbonylalkoxy, -OC(O)C₁-C₅ alkyl substituted with carboxyl or -OC₁-C₅ alkyl optionally substituted with carboxyl;

each R⁹ and R¹₀ is independently H or optionally substituted C₁-C₅ alkyl; and
Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0390] In one variation, the compound is of the formula (B-IC), wherein Q, X, R¹, R²a, R³a, R⁵a, R⁶, R⁶a, R⁷, R⁹ and R¹⁰ are as defined for the formula (B-IC), and R⁸ is azido, acylamino, –OC(O)C₁-C₅ alkyl substituted with carboxyl, or –OC₁-C₅ alkyl substituted with carboxyl, or a salt, solvate or N-oxide thereof. In another variation, Q, X, R¹, R²a, R³a, R⁵a, R⁶, R⁶a, R⁷, R⁹ and R¹⁰ are as defined for the formula (B-IC), and R⁸ is carboxyl, or carbonylalkoxy.

[0391] In another embodiment, the compound of formula (B-I) has the formula (B-ID):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R²a or R³a to form a propylene (–CH₂CH₂CH₂–) moiety or a butylene (–CH₂CH₂CH₂CH₂–) moiety;

R²a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (–CH₂CH₂CH₂–) moiety or a butylene (–CH₂CH₂CH₂CH₂–) moiety;

R³a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (–CH₂CH₂CH₂–) moiety or a butylene (–CH₂CH₂CH₂CH₂–) moiety;

X is N or CR⁶a;
each R⁶ and R⁶a is independently H; hydroxyl; halo; C¹⁻C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; optionally substituted C₁⁻C₃ alkoxy; or optionally substituted –C(O)C₁⁻C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁⁻C₅ alkyl, or optionally substituted aryl;

R⁸ is azido, acylamino, carboxyl, carbonylalkoxy, –OC(O)C₁⁻C₅ alkyl substituted with carboxyl, or –OC₁⁻C₅ alkyl optionally substituted with carboxyl;

each R⁹ and R¹⁰ is independently H or optionally substituted C₁⁻C₅ alkyl; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁⁻C₅ alkyl, C₃⁻C₈ cycloalkyl, halo-substituted C₁⁻C₅ alkyl, halo-substituted C₃⁻C₈ cycloalkyl, C₁⁻C₅ alkoxy, C₃⁻C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

[0392] In one variation, the compound is of the formula (B-ID), wherein Q, X, R¹, R²a, R³a, R⁶ and R⁶a are as defined for the formula (B-ID), R⁷ is H, halo, or optionally substituted C₁⁻C₅ alkyl; R⁸ is azido, acylamino, –OC(O)C₁⁻C₅ alkyl substituted with carboxyl or –OC₁⁻C₅ alkyl substituted with carboxyl; and each R⁹ and R¹⁰ is independently H or optionally substituted C₁⁻C₅ alkyl, or a salt, solvate or N-oxide thereof.

[0393] In some variations of the compound of the formula (B-ID), R¹ is C₁⁻C₅ alkyl (e.g., methyl), each R²a and R³a is H, R⁶ is methyl or chloro, and X is CH. In some of these variations, R⁷ is H or C₁⁻C₅ alkyl (e.g., methyl) and R⁸ is azido, acylamino, –OC(O)C₁⁻C₅ alkyl substituted with carboxyl or –OC₁⁻C₅ alkyl optionally substituted with carboxyl. In some of these variations, R⁷ is H and R⁸ is azido, acylamino, –OC(O)C₁⁻C₅ alkyl substituted with carboxyl or -OC₁⁻C₅ alkyl optionally substituted with carboxyl. In some of these variations, R⁷ is methyl and R⁸ is azido, acylamino, –OC(O)C₁⁻C₅ alkyl substituted with carboxyl or –OC₁⁻C₅ alkyl optionally substituted with carboxyl. In some of these variations, R⁷ is H or C₁⁻C₅ alkyl (e.g., methyl) and R¹⁰ is H. In some of these variations, each R⁹ and R¹⁰ is H. In some of these variations, Q is an unsubstituted pyridyl group which may be attached to the parent structure at any position (e.g., 2-pyridyl, 3-pyridyl or 4-pyridyl). In some of these variations, Q is 3- pyridyl or 4-pyridyl. In some of these variations, Q is pyridyl substituted a methyl (e.g., 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, Q is phenyl substituted with a halo group (e.g., fluorophenyl). In some of these variations, Q is 4-fluorophenyl.
In one particular embodiment, the compound is of the formula (B-IA), (B-IB), (B-IC) or (B-ID), or a salt, solvate or N-oxide thereof, wherein:

- $R^1$ is $H$, $C_1$-$C_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo and hydroxyl, $C_3$-$C_6$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo and hydroxyl, $C_2$-$C_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo and hydroxyl, or $-C(O)O-C_1$-$C_5$ alkyl;
- each $R^{2a}$, $R^{3a}$ or $R^{6a}$ (where applicable) is independently $H$ or optionally substituted $C_1$-$C_5$ alkyl;
- or $R^1$ and $R^{2a}$, or $R^1$ and $R^{3a}$ are taken together to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) moiety;
- $X$ is $N$ or $CR^{6a}$;
- each $R^6$ and $R^{6a}$ is independently $H$; halogen; $C_1$-$C_5$ alkyl optionally substituted with 1 to 3 substituents selected from halogen atoms and hydroxyl; optionally substituted $C_1$-$C_5$ alkoxy; or optionally substituted $-C(O)C_1$-$C_5$ alkyl;
- each $R^7$, $R^9$ and $R^{10}$ is independently $H$ or optionally substituted $C_1$-$C_5$ alkyl;
- $R^8$ is azido, acylamino, $-OC(O)C_1$-$C_5$ alkyl substituted with carboxyl or $-OC_1$-$C_5$ alkyl optionally substituted with carboxyl; and
- $Q$ is aryl or heteroaryl optionally substituted with 1 to 3 substituents including halogen, $C_1$-$C_5$ alkyl or cycloalkyl, halo-substituted $C_1$-$C_5$ alkyl or cycloalkyl, $C_1$-$C_5$ alkoxy or cycloalkoxy, $-CN$, $-CO_2H$ or $-C(O)N(R^a)R^b$ where each $R^a$ and $R^b$ is independently $H$ or $C_1$-$C_5$ alkyl.

In certain embodiments of the compounds of any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), $R^1$ is $H$, $C_1$-$C_5$ alkyl (e.g., methyl) or $-C(O)OR^{11}$ where $R^{11}$ is $C_1$-$C_5$ alkyl. It is understood that any descriptions of $R^1$ may be combined with any descriptions of other moieties (e.g., $X$, $R^6$, $R^{6a}$, $R^7$, $R^8$, $R^9$, $R^{10}$ and $Q$) the same as if each and every combination were specifically and individually listed.

In certain embodiments of the compounds of any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), each $R^6$ and $R^{6a}$ is independently $H$, $CH_3$ or $Cl$. It is understood that any descriptions of $R^6$ or $R^{6a}$ may be combined with any descriptions of other moieties (e.g., $X$, $R^1$, $R^7$, $R^8$, $R^9$, $R^{10}$ and $Q$) the same as if each and every combination were specifically and individually listed.
[0397] In certain embodiments of the compounds of any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), X is N. In certain embodiments of the compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), X is CR₆₅. In some of these embodiments, R₆₅ is H, CH₃ or Cl. It is understood that any descriptions of X, R⁶ and R₆₅ may be combined with any descriptions of other moieties (e.g., R¹, R⁷, R⁸, R⁹, R¹⁰ and Q) the same as if each and every combination were specifically and individually listed.

[0398] In certain embodiments of the compounds any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), R⁸ is azido. In another variation, R⁸ is carboxyl. In another variation, R⁸ is carbonylalkoxy. In another variation, R⁸ is –OC(O)C₅C₅ alkyl substituted with carboxyl (e.g., -OC(O)CH₂CO₂H, -OC(O)CH₂CH₂CO₂H, or -OC(O)CH₂CH₃CH₂CO₂H). In one variation, R⁸ is –OC₁-C₅ alkyl optionally substituted with carboxyl. In another variation, R⁸ is –OC₁-C₅ alkyl substituted with carboxyl (e.g., -OCH₂CO₂H, -OCH₂CH₂CO₂H, or -OCH₂CH₃CH₂CO₂H). In yet another variation, R⁸ is –OC₁-C₅ alkyl. In another variation, R⁸ is acylamino of the formula -C(O)NR₁³R₁⁴ where each R₁³ and R₁⁴ is independently H or optionally substituted C₁-C₅ alkyl (e.g., -C(O)NH₂, -C(O)NHCH₃ or -C(O)N(CH₂)₂). In some variations, R⁸ is acylamino of the formula -C(O)NR₁³R₁⁴ where R₁³ and R₁⁴ are joined with the nitrogen to which they are attached to form a heterocycle (e.g., -C(O)-pyrrolidinyl). It is understood that any descriptions of R⁸ may be combined with any descriptions of other moieties (e.g., X, R¹, R⁶, R₆₅, R⁷, R⁸, R¹⁰ and Q) the same as if each and every combination were specifically and individually listed.

[0399] In certain embodiments of the compounds of any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), Q is aryl or heteroaryl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo (e.g., fluoro or chloro), C₁-C₅ alkyl (e.g., methyl), halo-substituted C₁-C₅ alkyl (e.g., CF₃), carboxyl and –C(O)NR¹¹R¹². In some variations, Q is unsubstituted heteroaryl. In some variations, Q is aryl or heteroaryl substituted with a substituent selected from the group consisting of halo (e.g., fluoro or chloro), C₁-C₅ alkyl (e.g., methyl), halo-substituted C₁-C₅ alkyl (e.g., CF₃), carboxyl and –C(O)NR¹¹R¹². In some variations, Q is aryl or heteroaryl optionally substituted with 2 substituents independently selected from the group consisting of halo (e.g., fluoro or chloro), C₁-C₅ alkyl (e.g., methyl), halo-substituted C₁-C₅ alkyl (e.g., CF₃), carboxyl and –C(O)NR¹¹R¹². In some variations, Q is aryl or heteroaryl optionally
substituted with 3 substituents independently selected from the group consisting of halo (e.g., fluoro or chloro), C1-C5 alkyl (e.g., methyl), halo-substituted C1-C5 alkyl (e.g., CF3), carboxyl and \(-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}\) (e.g., \(-\text{C}(\text{O})\text{NH}_2\)). It is understood that any descriptions of Q may be combined with any descriptions of other moieties (e.g., \(X, R^1, R^6, R^{6a}, R^7, R^8, R^9\) and \(R^{10}\)) the same as if each and every combination were specifically and individually listed.

[0400] In certain embodiments, with respect to the compounds of formula (B-ID), the compound is Compound No. V-21.

[0401] In some embodiments, compounds of the formula (C-I) are provided:

![Chemical Structure](image)

(C-I)

or a salt, solvate or N-oxide thereof, wherein:

\(R^6\) is H; halo; C1-C5 alkyl optionally substituted with 1 to 3 substituents independently selected from halogen atoms or hydroxyl; C2-C5 alkenyl; or \(-\text{C}(\text{O})\text{OR}^{11}\); or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C2-C5 alkenyl, or \(-\text{C}(\text{O})\text{OR}^{11}\);

\(R^7\) is H or optionally substituted C1-C5 alkyl;

\(R^8\) is H, hydroxyl, \(-\text{OC}(\text{O})\text{C}1\text{-C}5\) alkyl optionally substituted with amino, N\((R^{11})\text{R}^{12}\), \(\text{SR}^{13}\), \(\text{S}(\text{O})\text{R}^{13}\) or \(\text{SO}_2\text{R}^{13}\);

each \(R^{11}\), \(R^{12}\) and \(R^{13}\) is independently H or optionally substituted C1-C5 alkyl;

each \(X^1, X^2\) and \(X\) is N or CH such that no more than two of \(X^1, X^2\) and \(X\) are N;

each \(Y^1, Y^2, Y^3\) and \(Y^4\) is N or CR4 such that no more than two of \(Y^1, Y^2, Y^3\) and \(Y^4\) are N, and wherein \(R^3\) is H, halo, CH3, CF3, or OCH3; and

\(n\) is 0 or 1.
In one variation of formula (C-I), one or more of the following apply (i) \( n \) is 1; (ii) \( R^6 \) is other than Cl when \( n \) is 0, each \( R^7 \) and \( R^8 \) is H, each \( X^1, X^2, X, Y^1, Y^2 \) and \( Y^4 \) is CH and \( Y^3 \) is CF; (iii) \( R^6 \) is other than H when \( n \) is 0 and (iv) \( R^6 \) is other than CH\(_3\) when \( n \) is 0, each \( R^7 \) and \( R^8 \) is H, each \( X^1, X^2, Y^1 \) and \( Y^4 \) is CH; each \( X \) and \( Y^2 \) is N and \( Y^3 \) is CCH\(_3\). In one such variation, \( R^6 \) is a fluoro-containing moiety, such as –CF\(_3\), –CHF\(_2\), –CH\(_2\)F, or –CH\(_2\)F. In another variation, compounds of the formula (C-I) are provided, wherein the compounds are other than compounds (A)-(G) in Table A.

In one variation, compounds of formula (C-I) are embraced, provided that at least one of \( X^1, X^2 \) and \( X \) is CH. In another variation, at least two of \( X^1, X^2 \) and \( X \) is CH. In one aspect, when at least one or when at least two of \( X^1, X^2 \) and \( X \) is CH, one or more of the following apply (i) \( n \) is 1 and (ii) \( R^6 \) is other than H, Cl or CH\(_3\). In another variation, when \( X^2 \) is N then \( X \) is CH. In another variation, when \( X^2 \) is CH then \( X \) is N. In one aspect, when \( X^2 \) is CH and \( X \) is N, then one or more of the following apply (i) \( n \) is 1 and (ii) \( R^6 \) is other than H or CH\(_3\).

In another variation of formula (C-I), \( R^6 \) is halo, CH\(_3\), CH\(_2\)F, CHF\(_2\), CF\(_3\) or CD\(_2\).

In another variation of formula (C-I), \( R^7 \) is \( H \) or CH\(_3\). In one variation, \( R^7 \) is H, CH\(_3\), CF\(_3\), CH\(_2\)F, CHF\(_2\) or CH\(_2\)OH.

In another variation of formula (C-I), \( R^8 \) is H or OH. In one variation, \( R^8 \) is -OC(O)C\(_1\)-C\(_5\) alkyl optionally substituted with amino, N(R\(^{11}\))R\(^{12}\), SR\(^{13}\), S(O)R\(^{13}\) or SO\(_2\)R\(^{13}\). In one variation, \( R^8 \) is N(R\(^{11}\))R\(^{12}\). In one variation, \( R^8 \) is SR\(^{13}\), S(O)R\(^{13}\) or SO\(_2\)R\(^{13}\).

In another variation of formula (C-I), at least one of \( Y^1, Y^2, Y^3 \) and \( Y^4 \) is N. In another variation, \( Y^1 \) and \( Y^3 \) are each N. In another variation, \( Y^2 \) and \( Y^4 \) are each N. In another variation, \( Y^1 \) and \( Y^4 \) are each N.

In another variation of formula (C-I), \( Y^1, Y^2 \) and \( Y^4 \) are each H, and \( Y^3 \) is CR\(^4\), wherein \( R^4 \) is halo, CH\(_3\), CF\(_3\) or OCH\(_3\).

In another variation of formula (C-I), \( R^6 \) is F, Cl, Br, CD\(_3\) or CH\(_2\)F; \( X^1, X^2 \) and \( X \) are each N or CH; \( Y^2 \) and \( Y^3 \) are each N or CR\(^4\), wherein \( R^4 \) is CH\(_3\) or CF\(_3\); \( R^8 \) is H or hydroxyl, and \( n \) is 0 or 1. In another variation, of formula (C-I), \( R^6 \) is F, Cl, Br, CD\(_3\) or CH\(_2\)F; \( R^7 \) is H, CH\(_3\), CF\(_3\), CH\(_2\)F, CHF\(_2\) or CH\(_2\)OH; \( X^1, X^2 \) and \( X \) are each N or CH; \( Y^2 \) and \( Y^3 \) are each N or CR\(^4\), wherein \( R^4 \) is CH\(_3\) or CF\(_3\); \( R^8 \) is H or hydroxyl, and \( n \) is 0 or 1. In one such variation, \( Y^1 \) and \( Y^4 \) are both CH.

In certain embodiments, with respect to the compounds of formula (C-I), \( n \) is 0, \( R^6 \) is Cl, \( R^7 \) and \( R^8 \) are both H, each \( X^1, X^2, X, Y^1, Y^2 \) and \( Y^4 \) is CH and \( Y^3 \) is other than CF.
In one embodiment, the compound is of formula (C-IA) or (C-IB):

wherein $R^6$, $R^7$, $R^8$, $X^1$, $X^2$, $X$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are as described for formula (C-I). In one variation of formula (C-IA), one or more of the following apply (i) $R^6$ is other than Cl when n is 0, each $R^7$ and $R^8$ is H, each $X^1$, $X^2$, $X$, $Y^1$, $Y^2$ and $Y^4$ is CH and $Y^3$ is CF; (ii) $R^6$ is other than H when n is 0 and (iii) $R^6$ is other than CH$_3$ when n is 0, each $R^7$ and $R^8$ is H, each $X^1$, $X^2$, $Y^1$ and $Y^4$ is CH; each X and $Y^2$ is N and $Y^3$ is CCH$_3$. In one such variation, $R^6$ is a fluoro-containing moiety, such as –CH$_2$F. In another variation, compounds of the formula (C-IA) and (C-IB) are provided, wherein the compounds are other than compounds (A)-(G) in Table A.

In certain embodiments, with respect to the compounds of formula (C-IA), $X^1$ is N, and the compound is Compound No. IV-3, IV-29 to IV-38, IV-109 to IV-118, IV-151, IV-152, IV-154 to IV-158, or IV-230 to IV-238.

In certain embodiments, with respect to the compounds of formula (C-IA), $X^2$ is N, and the compound is Compound No. II-5 or II-275.

In certain embodiments, with respect to the compounds of formula (C-IB), X is N, and the compound is Compound No. IV-8, IV-49 to IV-58, IV-169 to IV-177, or IV-178.

In certain embodiments, with respect to the compounds of formula (C-IB), $X^1$ is N, and the compound is Compound No. IV-69 to IV-78, IV-189 to IV-197, or IV-198.

In certain embodiments, with respect to the compounds of formula (C-IB), each of X, $X^1$, and $X^2$ is independently is CR, and the compound is Compound No. 47.

In specific variations, compounds of formula (C-IA) have the structure:
or a salt or solvate thereof, wherein $R^6$, $X^1$, $X^2$, $X$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (C-I).

[0418] In certain embodiments, with respect to the compounds of formula (C-IA-1), each of $X$, $X^1$, and $X^2$ is independently is CR$^6$, and the compound is Compound No. 197.

[0419] In certain embodiments, with respect to the compounds of formula (C-IA-1), each of $X$, $X^1$, and $X^2$ is independently is CR$^6$, and the compound is No. Compound II-290, IV-6, or IV-7.

[0420] In certain embodiments, with respect to the compounds of formula (C-IA-1), $X$ is N, and the compound is Compound No. 74, 134, or 336.

[0421] In certain embodiments, with respect to the compounds of formula (C-IA-1), $X$ is N, and the compound is Compound No. II-238, II-243 to II-245, II-268, or II-297.

[0422] In certain embodiments, with respect to the compounds of formula (C-IA-1), $X$ is N, and the compound is Compound No. IV-2, IV-4, IV-9, IV-11 to IV-18, IV-89, IV-93 to IV-97, or IV-98.

[0423] In certain embodiments, with respect to the compounds of formula (C-IA-1), $X^1$ is N, and the compound is Compound No. IV-29 to IV-38, IV-109 to IV-117, or IV-118 (Table IV).

[0424] In certain embodiments, with respect to the compounds of formula (C-IA-2), the compound is Compound No. II-129, II-168, or II-198.

[0425] In certain embodiments, with respect to the compounds of formula (C-IA-2), the compound is Compound No. IV-129 to IV-133, IV-149 to IV-152, IV-154 to IV-158, IV-209, IV-211 to IV-216, IV-219, IV-221, IV-229, IV-230, IV-232, IV-234, IV-236, IV-239, IV-241, IV-242, or IV-244 (Table IV).

[0426] In certain embodiments, with respect to the compounds of formula (C-IA-3), each of $X$, $X^1$, and $X^2$ is independently is CR$^6$, and the compound is Compound No. 176.
In certain embodiments, with respect to the compounds of formula (C-IA-3), each of X, X₁, and X₂ is independently is CR₆, and the compound is Compound No. II-121, II-127, II-128, II-130, II-291, II-294, or IV-7.

In certain embodiments, with respect to the compounds of formula (C-IA-3), X is N, and the compound is Compound No. 26 or 148.

In certain embodiments, with respect to the compounds of formula (C-IA-3), X is N, and the compound is Compound No. II-149.

In certain embodiments, with respect to the compounds of formula (C-IA-3), X is N, and the compound is Compound No. IV-134 to IV-138, IV-210, IV-217, or IV-218.

In certain embodiments, with respect to the compounds of formula (C-IA-3), X₁ is N, and the compound is Compound No. II-17.

In certain embodiments, with respect to the compounds of formula (C-IA-3), X₁ is N, and the compound is Compound No. IV-231, IV-233, IV-235, IV-237, or IV-238.

In other variations, compounds of formula (C-IA) have the structure:

or a salt or solvate thereof, wherein R⁶, R⁷, R⁸, Y¹, Y², Y³, and Y⁴ are defined as for formula (C-I). In one variation, R⁷ and R⁸ are both H.

In certain embodiments, with respect to the compounds of formula (C-IA-4), each Y¹, Y², Y³ and Y⁴ is independently CR⁴; and the compound is Compound No. II-120, II-121, II-266, II-271, or II-279.

In certain embodiments, with respect to the compounds of formula (C-IA-4), each Y¹, Y², Y³ and Y⁴ is independently CR⁴; and the compound is Compound No. IV-6, IV-7, or IV-9.
In certain embodiments, with respect to the compounds of formula (C-IA-4), one of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. 129, 168, 197, or 198.

In certain embodiments, with respect to the compounds of formula (C-IA-4), one of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. II-125, II-127, II-128, II-130, II-131, II-281, II-282, II-284, II-290, II-291, or II-293.

In certain embodiments, with respect to the compounds of formula (C-IA-4), one of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. IV-4, IV-5, IV-15, or IV-18.

In certain embodiments, with respect to the compounds of formula (C-IA-4), two of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. 176.

In certain embodiments, with respect to the compounds of formula (C-IA-4), two of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. II-6, II-7, II-261, II-276, or II-294.

In certain embodiments, with respect to the compounds of formula (C-IA-5), each $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is independently CR$^4$; and the compound is Compound No. 336.

In certain embodiments, with respect to the compounds of formula (C-IA-5), each $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is independently CR$^4$; and the compound is Compound No. II-149. In certain embodiments, with respect to the compounds of formula (C-IA-5), each $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is independently CR$^4$; and the compound is Compound No. II-149a, II-149b, II-149c, or II-149d.

In certain embodiments, with respect to the compounds of formula (C-IA-5), each $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is independently CR$^4$; and the compound is Compound No. IV-1, IV-9, IV-11 to IV-18, IV-129, IV-130 to IV-137, or IV-138.

In certain embodiments, with respect to the compounds of formula (C-IA-5), one or two of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. 26, 74, 134, 137, or 148.

In certain embodiments, with respect to the compounds of formula (C-IA-5), one or two of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is N, and the rest of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are independently CR$^4$; and the compound is Compound No. II-79, II-238, II-243, II-244, II-245, II-268, or II-297.
[0446] In certain embodiments, with respect to the compounds of formula (C-I-A-5), one or two of \( Y^1 \), \( Y^2 \), \( Y^3 \) and \( Y^4 \) is N, and the rest of \( Y^1 \), \( Y^2 \), \( Y^3 \) and \( Y^4 \) are independently CR\(^4\); and the compound is Compound No. IV-2, IV-4, IV-89, IV-91, IV-93 to IV-98, IV-209, IV-210, IV-211, IV-213 to IV-217, or IV-218.

[0447] In other variations, compounds of formula (C-I-A) have the structure:

![Chemical Structure](image)

(C-I-A-6)

or a salt or solvate thereof, wherein \( X \) is C or N; and \( R^6 \), \( Y^1 \), \( Y^2 \), \( Y^3 \) and \( Y^4 \) are defined as for formula (C-I).

[0448] In certain embodiments, with respect to the compounds of formula (C-I-A-6), the compound is Compound No. 129, 168, or 198.

[0449] In certain embodiments, with respect to the compounds of formula (C-I-A-6), the compound is Compound No. II-79, II-120, II-125, II-131, or II-293.

[0450] In certain embodiments, with respect to the compounds of formula (C-I-A-6), the compound is Compound No. IV-129 to IV-133, IV-209, IV-211, IV-213 to IV-215, or IV-216.

[0451] In other variations, compounds of formula (C-I-A) have the structure:
or a salt or solvate thereof, wherein $R^6$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (C-I).

[0452] In certain embodiments, with respect to the compounds of formula (C-I-A-7); the compound is Compound No. 74, 134, 137, or 336.

[0453] In certain embodiments, with respect to the compounds of formula (C-I-A-7); the compound is Compound No. II-238, II-243, II-244, II-245, or II-297.

[0454] In certain embodiments, with respect to the compounds of formula (C-I-A-7); the compound is Compound No. IV-2, IV-4, IV-9, IV-11, IV-13 to IV18, IV-89, IV-91, IV-93 to IV-97, or IV-98.

[0455] In one variation of formula (C-I-A-1) one or more of the following apply: (i) $R^6$ is other than Cl when each $X^1$, $X^2$, $X$, $Y^1$, $Y^2$ and $Y^4$ is CH and $Y^3$ is CF; (ii) $R^6$ is other than H when each $X^1$, $X^2$, $X$, $Y^1$, $Y^2$ and $Y^4$ is CH and $Y^3$ is CF; (iii) $R^6$ is other than H when each $X^1$, $X^2$, $Y^1$ and $Y^4$ is CH; each X and $Y^2$ is N and $Y^3$ is CCH$_3$; and (iv) $R^6$ is other than CH$_3$ when each $X^1$, $X^2$, $Y^1$ and $Y^4$ is CH; each X and $Y^2$ is N and $Y^3$ is CCH$_3$.

[0456] In one variation of formula (C-I-A-2), $R^6$ is other than H when each $X^1$, $X^2$, $Y^1$, $Y^2$ and $Y^4$ is CH; each X and $Y^3$ is N.

[0457] In one variation of formula (C-I-A-3), $R^6$ is other than H when each $X^1$, $X^2$, $X$, $Y^1$, $Y^2$ and $Y^4$ is CH and $Y^3$ is N.

[0458] In certain embodiments, with respect to the compounds of formula (C-I-A), (C-I-A-1), (C-I-A-3), or (C-I-A-7), n is 0, $R^6$ is Cl, $R^7$ and $R^8$ are both H, each $X^1$, $X^2$, $X$, $Y^1$, $Y^2$ and $Y^4$ is CH and $Y^3$ is other than CF.

[0459] In specific variations, compounds of formula (C-I-B) have the structure:
or a salt or solvate thereof, wherein $R^6$, $X^1$, $X^2$, $X$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (C-I).

[0460] In certain embodiments, with respect to the compounds of formula (C-IB-1); the compound is Compound No. IV-8, IV-49 to IV-87, or IV-88.

[0461] In certain embodiments, with respect to the compounds of formula (C-IB-2); the compound is Compound No. 47.

[0462] In certain embodiments, with respect to the compounds of formula (C-IB-2); the compound is Compound No. IV-179 to IV-188, IV-199 to IV-207, or IV-208.

[0463] In certain embodiments, with respect to the compounds of formula (C-IB-3); the compound is Compound No. IV-169 to IV-178, IV-190 to IV-197, or IV-198.

[0464] In one embodiment, the compound is of formula (C-IC-1):

or a salt or solvate thereof, wherein $R^6$, $X^1$, $X^2$, $X$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (C-I).
In one embodiment, the compound is of formula (C-II):

wherein $R^6$, $R^7$, $R^8$, $X^1$, $X^2$, $X$, $Y^2$ and $Y^3$ are as described for formula (C-I). In one variation of formula (C-II), one or more of the following apply (i) $n$ is 1 and (ii) $R^6$ is other than Cl when $n$ is 0, each $R^7$ and $R^8$ is H, each $X^1$, $X^2$, $X$, $Y^1$, $Y^2$ and $Y^4$ is CH and $Y^3$ is CF; (iii) $R^6$ is other than H when $n$ is 0 and (iv) $R^6$ is other than CH$_3$ when $n$ is 0, each $R^7$ and $R^8$ is H, each $X^1$, $X^2$, $Y^1$ and $Y^4$ is CH; each $X$ and $Y^2$ is N and $Y^3$ is CCH$_3$. In one such variation, $R^6$ is a fluoro-containing moiety, such as –CH$_2$F. In another variation, compounds of the formula (C-II) are provided, wherein the compounds are other than compounds (A)-(G) in Table A.

In one embodiment, the compound is of formula (C-IIA) or (C-IIB):

wherein $R^6$, $R^7$, $R^8$, $X^1$, $X^2$, $X$, $Y^2$, and $Y^3$ are as described for formula (C-I). In one variation of formula (C-IIA), one or more of the following apply (i) $R^6$ is other than Cl when $n$ is 0, each $R^7$ and $R^8$ is H, each $X^1$, $X^2$, $X$, $Y^2$ is CH and $Y^3$ is CF; (ii) $R^6$ is other than H when $n$ is 0 and (iii) $R^6$ is other than CH$_3$ when $n$ is 0, each $R^7$ and $R^8$ is H, each $X^1$ and $X^2$ is CH; each $X$ and $Y^2$ is N and $Y^3$ is CCH$_3$. In one variation, the compound of formula (C-IIA) is selected from
Compounds (A)-(G), presented in Table A. In another variation, the compound of formula (C-IIA) is other than Compounds (A)-(G) in Table A. It is understood that each of compounds (A)-(G) may exist as individual isomers, e.g., isomer A1 and isomer A2 for compound A.

Table A: Representative Compounds of formula (C-IIA)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R^6</th>
<th>R'</th>
<th>R^8</th>
<th>X^1</th>
<th>X^2</th>
<th>X</th>
<th>Y^2</th>
<th>Y^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
<td>CF</td>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
</tr>
<tr>
<td>C</td>
<td>H</td>
<td>CH₃</td>
<td>OH</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
<td>CH</td>
<td>N</td>
</tr>
<tr>
<td>D</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>CH</td>
<td>CH</td>
<td>N</td>
<td>N</td>
<td>CCH₃</td>
</tr>
<tr>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>CH</td>
<td>CH</td>
<td>N</td>
<td>N</td>
<td>CCH₃</td>
</tr>
<tr>
<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH</td>
<td>CH</td>
<td>N</td>
<td>N</td>
<td>CCF₃</td>
</tr>
<tr>
<td>G</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>CH</td>
<td>CH</td>
<td>N</td>
<td>CH</td>
<td>N</td>
</tr>
</tbody>
</table>

In one embodiment, the compound is of formulae (C-III A)-(C-IIIF):

wherein R^6, R^7, R^8, X^1, X^2, X, Y^2, Y^3 and n are as described for formula (C-I). In one variation, the compound is of formula (C-III A), (C-IIIB), (C-IIIC), (C-IIID), (C-IIIE) or (C-IIIF), wherein n is 0. In one variation compound is of formulae (C-III A), (C-IIIB), (C-IIIC), (C-IIID), (C-IIIE) or (C-IIIF), wherein n is 0, and wherein one or more of the following provisions apply: (i) R^6 is other than Cl when n is 0, each R^7 and R^8 is H, each X^1, X^2, X, Y^1, Y^2 and Y^3 is CH. and Y^3 is
CF; (ii) \( R^6 \) is other than H when \( n \) is 0 and (iii) \( R^6 \) is other than CH\(_3\) when \( n \) is 0, each \( R^7 \) and \( R^8 \) is H, each \( X^1, X^2, Y^1 \) and \( Y^4 \) is CH; each \( X \) and \( Y^2 \) is N and \( Y^3 \) is CCH\(_3\). In another variation, the compound is of formulae (C-IIIA), (C-IIIB), (C-IIIC), (C-IIID), (CIII-E) or (C-IIIF), wherein \( n \) is 1.

[0469] In another embodiment the compound is according to formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG):
or a salt, solvate or N-oxide thereof, wherein:

n is 0 or 1;

each X¹, U, X², or X, where present, is independently CR⁶;

R⁶ is H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹², SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₃-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacetyl and acylamino.

[0470] In one embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), each X¹, U, X², or X is independently CR⁶, and each R⁶ is H. In another embodiment, each R⁶ is independently selected from H, C₁-C₅ alkyl, and halo C₁-C₅ alkyl. In certain embodiments, each R⁶ is independently selected from H, methyl, ethyl, fluoro, chloro, CH₂F, and CF₃.

[0471] In one embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVD), (C-IVF) or (C-IVG), each X¹, X² and X (where present) is CR⁶, wherein R⁶ is H; U is CR⁶, wherein R⁶ is selected from H, C₁-C₅ alkyl and halo C₁-C₅ alkyl. In certain embodiments, each R⁶ is independently selected from methyl, ethyl, fluoro, chloro, CH₂F, and CF₃.

[0472] In one embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG), each R⁷ and R⁸ is H. In another embodiment, R⁷ is H or methyl, and R⁸ is H, OH or methyl.

[0473] In certain embodiments, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG), R⁷ is H; and R⁸ is OH, NH₂, CF₃ or methyl.
[0474] In one embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG), Q is optionally substituted phenyl.

[0475] In another embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG), Q is phenyl substituted with C₁-C₅ alkyl, halo, halo C₁-C₅ alkyl or C₁-C₅ alkoxy.

[0476] In another embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), Q is phenyl substituted with methyl, ethyl, fluoro, chloro, methoxy or CF₃. In certain embodiments, Q is phenyl substituted with 4-methyl, 4-ethyl, 4-fluoro, 4-chloro, 4-methoxy, or 4-CF₃.

[0477] In another embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), Q is optionally substituted pyridyl, or optionally substituted pyrimidinyl.

[0478] In another embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), Q is pyridyl substituted with C₁-C₅ alkyl, halo, halo or C₁-C₅ alkyl.

[0479] In another embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), Q is pyridyl substituted with methyl, ethyl, fluoro, chloro, or CF₃.

[0480] In one embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), n is 0. In another embodiment, n is 1.

[0481] In certain embodiments, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG), the compound is any one of compounds listed in Table IV. In another embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), or (C-IVG), the compound is any one of compounds listed in Table IV, provided that the compound is other than Compound No. IV-2, IV-4, IV-5, IV-6, or IV-7.

[0482] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 0, Q is optionally substituted 4-pyridyl, and the compound is Compound No. II-79, II-89, II-209, or II-244.

[0483] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 0, Q is optionally substituted 3-pyridyl, and the compound is Compound No. 26, 74, 134, 137, 148, II-238, II-243, II-268, II-297, IV-2, IV-4, IV-97 to IV-98, IV-210, IV-217, or IV-218.
[0484] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 0, Q is optionally substituted 2-pyridyl, and the compound is Compound No. IV-91, IV-95, IV-96, IV-211, IV-215, or IV-216.

[0485] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 0, Q is optionally substituted pyrimidyl, and the compound is Compound No. IV-93 or IV-213.

[0486] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 0, Q is optionally substituted pyrazinyl, and the compound is Compound No. II-245, IV-94, or IV-214.

[0487] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 0, Q is optionally substituted phenyl, and the compound is Compound No. 336, II-149, IV-1, IV-9, IV-11 to IV-18, IV-129 to IV-137, or IV-138.

[0488] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 1, Q is optionally substituted phenyl, and the compound is Compound No. IV-49 to IV-58, or IV-178.

[0489] In certain embodiments, with respect to the compounds of formula (C-IVA), n is 1, Q is optionally substituted 3-pyridyl, and the compound is Compound No. IV-8.

[0490] In certain embodiments, with respect to the compounds of formula (C-IVB), n is 0, and the compound is Compound No. II-5 or II-275.

[0491] In certain embodiments, with respect to the compounds of formula (C-IVD), n is 0, and the compound is Compound IV-3, IV-29 to IV-38, IV-109 to IV-118, IV-149 to IV-158, IV-229 to IV-237, or IV-238.

[0492] In certain embodiments, with respect to the compounds of formula (C-IVD), n is 1, and the compound is Compound No. IV-69 to IV-78, IV-189 to IV-197, or IV-198.

[0493] In certain embodiments, with respect to the compounds of formula (C-IVF), the compound is Compound No. IV-19 to IV-21, IV-25 to IV-28, IV-59 to IV-68, IV-100 to IV-108, IV-139 to IV-148, IV-179 to IV-188, IV-219 to IV-227 or IV-228.

[0494] In certain embodiments, with respect to the compounds of formula (C-IVG), the compound is Compound No. IV-10, IV-39 to IV-48, IV-79 to IV-88, IV-90, IV-92, IV-119 to IV-128, IV-159 to IV-168, IV-199 to VI-208, IV-212, IV-239 to IV-243, or IV-244.

[0495] In one embodiment, compounds of formula (C-VA) or (C-VB) are provided:
or a salt, solvate or N-oxide thereof, wherein:

each $X^1$, $X^2$, $X$ and $U$ is independently $N$ or $CR^6$;

each $R^6$ is independently $H$, hydroxyl, halo, $C_1$-$C_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted $C_1$-$C_5$ alkoxy or optionally substituted $-C(O)C_1$-$C_5$ alkyl;

$R^7$ is $H$, halo, optionally substituted $C_1$-$C_5$ alkyl, or optionally substituted aryl, or is taken together with $R^8$ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

$R^8$ is $H$, halo, hydroxyl, $N(R^{11})R^{12}$, $SR^{13}$, $S(O)R^{13}$, $SO_2R^{13}$, $-OC(O)N(R^{14})R^{15}$, $-OC(O)$-aryl, $-OC(O)$-heteroaryl, or $-OC(O)C_1$-$C_5$ alkyl optionally substituted with amino, or is taken together with $R^7$ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

$Q$ is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, $C_1$-$C_5$ alkyl, $C_1$-$C_5$ cycloalkyl, halo-substituted $C_1$-$C_5$ alkyl, halo-substituted $C_7$-$C_8$ cycloalkyl, $C_1$-$C_5$ alkoxy, $C_7$-$C_8$ cycloalkoxy, cyano, carboxyl, $-NHC(O)CH_3$ and $-C(O)NR^{16}R^{17}$; and

each $R^{16}$ and $R^{17}$ is independently $H$ or optionally substituted $C_1$-$C_5$ alkyl.

[0496] In some embodiments, compounds of the formula (D-1) are provided:
or a salt, solvate or N-oxide thereof, wherein:

R⁶ is H, halo, C₁-C₅ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C₂-C₅ alkenyl, or −C(O)OR¹¹;

R⁷ is H or optionally substituted C₁-C₅ alkyl;

R⁸ is H, hydroxyl, −OC(O)C₁-C₅ alkyl optionally substituted with amino, N(R¹¹)R¹²,
SR¹³, S(O)R¹³ or SO₂R¹³;

    each R¹¹, R¹² and R¹³ is independently H or optionally substituted C₁-C₅ alkyl;
    each X¹, X² and X is N or CH such that no more than two of X¹, X² and X are N;
    each Y¹, Y², Y³ and Y⁴ is N or CR⁴ such that no more than two of Y¹, Y², Y³ and Y⁴ are
N, and wherein R⁴ is H, halo, CH₃, CF₃, or OCH₃; and
    n is 0 or 1.

[0497] In one variation, the compound is of formula (D-IIA) or (D-IIB):

or a salt or solvate thereof, wherein R⁶, X¹, X², X, Y² and Y³ are defined as for formula (D-I).
[0498] In other variations, compounds of formula (D-IIA) have the structure:

```
(D-IIA-1)
```

or a salt or solvate thereof, wherein R^6, R^7, R^8, Y^1, Y^2, Y^3 and Y^4 are defined as for formula (D-I).

[0499] In certain embodiments, with respect to the compounds of formula (D-IIIB), the compound is Compound No. 75.

[0500] In certain embodiments, with respect to the compounds of formula (D-IIA-1), the compound is Compound No. 76, III-122, III-356, III-358, or III-359.

[0501] In certain embodiments, with respect to the compounds of formula (D-IIA-2), the compound is Compound No. 37, II-86, II-234, II-235, II-236, or II-239.

[0502] In one embodiment, compounds of formula (D-IIIa) or (D-IIIb) are provided:

```
(D-IIIa)
```

or a salt, solvate or N-oxide thereof, wherein:

- each X^1, X^2, X and U is independently N or CR^6;
- each R^6 is independently H, hydroxyl, halo, C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C_1-C_5 alkoxy or optionally substituted –C(O)C_1-C_5 alkyl;

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R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, -NHC(O)CH_3 and -C(O)NR^{16}R^{17}; and

each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

[0503] In certain embodiments, with respect to the compounds of formula (D-IIIA), each X^1, U, X^2, and X is independently CR^6, and the compound is Compound 75, or 76 (Table I); or III-122, III-125, III-126, III-131, III-134, III-135, III-203, III-207, III-208, III-301, III-305, III-314, III-356, III-358, or III-359..

[0504] In certain embodiments, with respect to the compounds of formula (D-IIIA), each X^1, U, and X^2 is independently CR^6, X is N, and the compound is Compound No. 37, II-86, II-234, II-235, II-236, or II-239.

[0505] In certain embodiments, with respect to the compounds of formula (D-IIIB), the compound is Compound No. III-54, III-353, or III-354.

[0506] In some embodiments, compounds of the formula (E-I) are provided:
or a salt, solvate or N-oxide thereof, wherein:

\[ R^1 \text{ is } H, \text{C}_1-\text{C}_5 \text{ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or} \]
\[ \text{hydroxyl, C}_2-\text{C}_5 \text{ alkenyl, or } -\text{C}(\text{O})\text{OR}^{11}; \]
\[ R^6 \text{ is } H, \text{halo, C}_1-\text{C}_5 \text{ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or} \]
\[ \text{hydroxyl, C}_2-\text{C}_5 \text{ alkenyl, or } -\text{C}(\text{O})\text{OR}^{11}; \]
\[ R^7 \text{ is } H \text{ or optionally substituted C}_1-\text{C}_5 \text{ alkyl;} \]
\[ R^8 \text{ is } H, \text{hydroxyl, } -\text{OC}(\text{O})\text{C}_1-\text{C}_5 \text{ alkyl optionally substituted with amino, N(R}^{11}\text{)R}^{12}, \]
\[ \text{SR}^{13}, \text{S(O)R}^{13} \text{ or } \text{SO}_2\text{R}^{13}; \]
\[ \text{each } R^{11}, R^{12} \text{ and } R^{13} \text{ is independently } H \text{ or optionally substituted C}_1-\text{C}_5 \text{ alkyl;} \]
\[ \text{each } X^1, X^2 \text{ and } X \text{ is } N \text{ or CH such that no more than two of } X^1, X^2 \text{ and } X \text{ are } N; \]
\[ \text{each } Y^1, Y^2, Y^3 \text{ and } Y^4 \text{ is } N \text{ or } \text{CR}^4 \text{ such that no more than two of } Y^1, Y^2, Y^3 \text{ and } Y^4 \text{ are } \]
\[ N, \text{and wherein } R^4 \text{ is } H, \text{halo, CH}_3, \text{CF}_3, \text{or OCH}_3; \text{ and} \]
\[ n \text{ is 0 or 1.} \]

[0507] In one variation, the compound is of formula (E-IIA) or (E-IIB):

or a salt or solvate thereof, wherein R\(^1\), R\(^6\), X\(^1\), X\(^2\), X, Y\(^2\) and Y\(^3\) are defined as for formula (E-I).

[0508] In other variations, compounds of formula (E-IIA) have the structure:
or a salt or solvate thereof, wherein $R^1$, $R^6$, $R^7$, $R^8$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (E-I).

[0509] In certain embodiments, with respect to the compounds of formula (E-IIA), the compound is Compound No. III-61.

[0510] In some embodiments, compounds of the formula (F-I) are provided:

or a salt, solvate or N-oxide thereof, wherein:

$R^6$ is H, halo, C$_1$-C$_5$ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C$_2$-C$_5$ alkenyl, or -C(O)OR$^{11}$;

$R^7$ is H or optionally substituted C$_1$-C$_5$ alkyl;

$R^8$ is H, hydroxyl, -OC(O)C$_1$-C$_5$ alkyl optionally substituted with amino, N($R^{11}$)$R^{12}$, SR$^{13}$, S(O)R$^{13}$ or SO$_2$R$^{13}$;

each $R^{11}$, $R^{12}$ and $R^{13}$ is independently H or optionally substituted C$_1$-C$_5$ alkyl;
each $X^1$, $X^2$ and $X$ is N or CH such that no more than two of $X^1$, $X^2$ and $X$ are N;
 each $Y^1$, $Y^2$, $Y^3$ and $Y^4$ is N or CR$^4$ such that no more than two of $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are
N, and wherein $R^4$ is H, halo, CH$_3$, CF$_3$, or OCH$_3$; and
n is 0 or 1.

[0511] In one variation, the compound is of formula (F-IIA) or (F-IIB):

![Diagram](image)

(F-IIA) or (F-IIB)

or a salt or solvate thereof, wherein $R^6$, $X^1$, $X^2$, $X$, $Y^2$ and $Y^3$ are defined as for formula (F-I).

[0512] In other variations, compounds of formula (F-IIA) have the structure:

![Diagram](image)

(F-IIA-1) or (F-IIA-2)

or a salt or solvate thereof, wherein $R^6$, $R^7$, $R^8$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (F-I).

[0513] In certain embodiments, with respect to the compounds of formula (F-IIA), the
compound is Compound No. III-54, III-353, or III-354.

[0514] In some embodiments, compounds of the formula (G-I) are provided:
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C₂-C₅ alkenyl, or –C(O)OR¹¹;

R⁶ is H, halo, C₁-C₅ alkyl or cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C₂-C₅ alkenyl, or –C(O)OR¹¹;

R⁷ is H or optionally substituted C₁-C₅ alkyl;

R⁸ is H, hydroxyl, -OC(O)C₁-C₅ alkyl optionally substituted with amino, N(R¹¹)R¹², SR¹³, S(O)R¹³ or SO₂R¹³;

each R¹¹, R¹² and R¹³ is independently H or optionally substituted C₁-C₅ alkyl;

each X¹, X² and X is N or CH such that no more than two of X¹, X² and X are N;

each Y¹, Y², Y³ and Y⁴ is N or CR⁴ such that no more than two of Y¹, Y², Y³ and Y⁴ are N, and wherein R⁴ is H, halo, CH₃, CF₃, or OCH₃; and

n is 0 or 1.

[0515] In one variation, the compound is of formula (G-IIA) or (G-IIB):
or a salt or solvate thereof, wherein $R^1$, $R^6$, $X^1$, $X^2$, $X$, $Y^2$ and $Y^3$ are defined as for formula (G-I).

[0516] In other variations, compounds of formula (G-IIA) have the structure:

or a salt or solvate thereof, wherein $R^6$, $R^7$, $R^8$, $Y^1$, $Y^2$, $Y^3$ and $Y^4$ are defined as for formula (G-I).

[0517] In certain embodiments, with respect to the compounds of formula (G-I), $n$ is 0, $R^8$ is OH, and the compound is Compound No. III-57.

[0518] In one embodiment, compounds of formula (H-IA), (H-IB), (H-IC) or (H-ID) are provided:
or a salt, solvate or N-oxide thereof, wherein:

each \( X^1, X^2, X \) and \( U \) is independently \( N \) or \( CR^6 \);

\( R^1 \) is \( H, C_1-C_5 \) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, \( C_3-C_8 \) cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, \( C_2-C_5 \) alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or \(-C(O)O-C_1-C_5 \) alkyl;

each \( R^6 \) is independently \( H, \) hydroxyl, halo, \( C_1-C_5 \) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted \( C_1-C_5 \) alkoxy or optionally substituted \(-C(O)C_1-C_5 \) alkyl;

\( R^7 \) is \( H, \) halo, optionally substituted \( C_1-C_5 \) alkyl, or optionally substituted aryl;

\( Q \) is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, \( C_1-C_5 \) alkyl, \( C_3-C_8 \) cycloalkyl, halo-substituted \( C_1-C_5 \) alkyl, halo-substituted \( C_3-C_8 \) cycloalkyl, \( C_1-C_5 \) alkoxy, \( C_3-C_8 \) cycloalkoxy, cyano, carboxyl, \( -NHC(O)CH_3 \) and \(-C(O)NR^{16}R^{17} \); and

each \( R^{16} \) and \( R^{17} \) is independently \( H \) or optionally substituted \( C_1-C_5 \) alkyl.
In certain embodiments, with respect to the compounds of formula (H-IA), (H-IB), (H-IC), or (H-ID), each $X^1$, $X^2$ and $X$ is independently CR$^6$; wherein each R$^1$ is independently halo, C$_1$-C$_5$-alkyl, halo C$_1$-C$_5$-alkyl, perhalo C$_1$-C$_5$-alkyl, or C$_1$-C$_5$-alkoxy. In certain embodiments, each $X^1$, $X^2$ and $X$ is independently CR$^6$; wherein each R$^6$ is independently fluoro, chloro, methyl, ethyl, CF$_3$, or methoxy. In certain embodiments, U is CR$^6$, wherein R$^6$ is CF$_3$, methyl, chloro, CONHCH$_3$, COOH, COOCH$_3$, H, or fluoro; provided that R$^1$ is other than methyl.

In one embodiment, compounds of formula (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1) are provided:

or a salt, solvate or N-oxide thereof, wherein:

U is N or CR$^6$;

R$^1$ is H, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C$_1$-C$_5$ alkyl;

R$^6$ is independently H, hydroxyl, halo, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C$_1$-C$_5$ alkoxy or optionally substituted –C(O)C$_1$-C$_5$ alkyl;
R^7 is H, halo, optionally substituted C1-C5 alkyl, or optionally substituted aryl;
Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C1-C5 alkyl, C5-C8 cycloalkyl, halo-substituted C1-C5 alkyl, halo-substituted C3-C8 cycloalkyl, C1-C5 alkoxy, C3-C8 cycloalkoxy, cyano, carboxy, -NHC(O)CH3 and -C(O)NR16R17, and each R16 and R17 is independently H or optionally substituted C1-C5 alkyl.

[0521] In certain embodiments, with respect to the compounds of formula (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1), Q is an optionally substituted 5-membered heteroaryl; R^2 is F or methyl; R^1 is methyl; each X^1, X^2 and X (when present) is CR^6, wherein each R^6 is H; U is CR^6, wherein R^6 is methyl or Cl; and Q is other than unsubstituted thienyl or unsubstituted thiazolyl.

[0522] In certain embodiments, with respect to the compounds of (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1), Q is optionally substituted pyridyl; each X^1, X^2 and X (when present) is CR^6, wherein each R^6 is H; U is CR^6, wherein R^6 is H, halo, optionally substituted C1-C5 alkyl, or optionally substituted C1-C5 alkoxy; and Q is other than unsubstituted pyridyl, or pyridyl substituted with methyl, Cl, Br, OCH3, or di-methyl.

[0523] In certain embodiments, with respect to the compounds of formula (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1), Q is optionally substituted pyrimidinyl; R^1 is methyl; each X^1, X^2 and X (when present) is CR^6, wherein each R^6 is H; U is CR^6, wherein R^6 is methyl or Cl; and Q is other than unsubstituted pyrimidin-4-yl, pyrimidin-4-yl substituted with methyl, unsubstituted pyrimidin-5-yl, or pyrimidin-5-yl substituted with methyl.

[0524] In certain embodiments, with respect to the compounds of formula (H-IA-1), the compound is Compound No. 99, 106, 222, 226-230, 232-235, 238, 240-241, 244-249, or 251.

[0525] In certain embodiments, with respect to the compounds of formula (H-IB-1), the compound is Compound No. 224 or 239.

[0526] In certain embodiments, with respect to the compounds of formula (H-IC-1), Q is optionally substituted pyridyl, and the compound is Compound No. 78, 79, 100, 103, 105, 111, 112, 122, 124, 125, 126, 185, 186, 188, 250, 257, 259, 266, 269, 312, 329, or 331.

[0527] In certain embodiments, with respect to the compounds of formula (H-IC-1), Q is optionally substituted pyrimidyl, and the compound is Compound No. 101, 187, or 279.
[0528] In certain embodiments, with respect to the compounds of formula (H-IC-1), Q is optionally substituted pyridyl, and the compound is Compound No. II-2, II-3, II-59, II-76, II-77, II-96, or II-101.

[0529] In certain embodiments, with respect to the compounds of formula (H-IC-1), Q is optionally substituted 5-membered heteroaryl, and the compound is Compound No. 78, 108-110, 110, 115, 189, 273, 275, 277, 278, 285, or 287.

[0530] In certain embodiments, with respect to the compounds of formula (H-IC-1), Q is optionally substituted 9-membered heteroaryl, and the compound is Compound No. 282, 283, 284, 290, or 293.

[0531] In certain embodiments, with respect to the compounds of formula (H-IC-1), Q is optionally substituted quinolinyl or isoquinolinyl, and the compound is Compound No. 292, 311, 316, or 323.

[0532] In certain embodiments, with respect to the compounds of formula (H-IC), X is N, and the compound is Compound No. 78, 124, or 335.

[0533] In certain embodiments, with respect to the compounds of formula (H-IE-1), the compound is Compound No. 193 or 194. In certain embodiments, with respect to the compounds of formula (H-IE-1), the compound is Compound No. 193a, 193b, 194a, or 194b.

[0534] In certain embodiments, with respect to the compounds of formula (H-IF-1), the compound is Compound No. 199. In certain embodiments, with respect to the compounds of formula (H-IF-1), the compound is Compound No. 199a or 199b.

[0535] In certain embodiments, with respect to the compounds of formula (H-IIB-1), the compound is Compound No. 333.

[0536] In certain embodiments, with respect to the compounds of formula (H-IIC-1), the compound is Compound No. 242, 256, 264, 313, 321, 328, 330, or 334.

[0537] In certain embodiments, with respect to the compounds of formula (H-IID-1), the compound is Compound No. 95.

[0538] In certain embodiments, with respect to the compounds of formula (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1) U is CR₅, and R⁶ is CF₃, methyl, chloro, -CONHCH₃, -COOH, -COOCH₃, H, or fluoro; and R¹ is other than methyl.

[0539] In certain embodiments, with respect to the compounds of formula (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1), R⁷ is H, halo, or C₁-C₅ alkyl substituted with halo. In one embodiment, R⁷ is H, methyl, or CF₃.
In another aspect, provided is a compound of formula (J):

wherein:

$R^1$ is H; $C_1$-$C_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl, $SO_3H$, $SR^{1a}$, $S(O)R^{1a}$, $SO_2R^{1a}$ and perhaloalkyl; $C_3$-$C_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; $C_2$-$C_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or $-C(O)O-C_1$-$C_5$ alkyl; or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) moiety; or is taken together with $R^{4a}$ or $R^{5a}$, where present, to form an ethylene ($-CH_2CH_2-$) moiety or a propylene ($-CH_2CH_2CH_2-$) moiety;

$R^{1a}$ is H or optionally substituted $C_1$-$C_5$ alkyl;

$R^{2a}$ is H; optionally substituted $C_1$-$C_5$ alkyl; optionally substituted $C_2$-$C_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^1$ or $R^{5a}$, where present, to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) moiety; or is taken together with $R^{3a}$ to form an ethylene ($-CH_2CH_2-$) moiety or a propylene ($-CH_2CH_2CH_2-$) moiety; or is taken together with $R^{4a}$, where present, to form a methylene ($-CH_2-$) moiety or an ethylene ($-CH_2CH_2-$) moiety;

$R^{3a}$ is H; optionally substituted $C_1$-$C_5$ alkyl; optionally substituted $C_2$-$C_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^1$ or $R^{4a}$, where present, to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) moiety; or is taken together with $R^{2a}$ to form an ethylene ($-CH_2CH_2-$) moiety or a propylene ($-CH_2CH_2CH_2-$) moiety;
moiety; or is taken together with $R^{5a}$, where present, to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety;

- $R^{4a}$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^1$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{2a}$ to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety; or is taken together with $R^{5a}$, where present, to form a methylene (-CH$_2$-) moiety;

- $R^{5a}$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^{2a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^1$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{3a}$ to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety; or is taken together with $R^{4a}$, where present, to form a methylene (-CH$_2$-) moiety;

- each $R^{2b}$, $R^{3b}$, $R^{4b}$ and $R^{5b}$ is independently H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted C$_2$-C$_5$ alkenyl, or optionally substituted aryl;

- each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

- each $X^1$, $X^2$, $X$ and $U$ is independently N or CR$_6$;

- each $R^6$ is independently H; hydroxyl; halo; C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_2$-C$_5$ alkenyl; optionally substituted C$_1$-C$_5$ alkoxy; or optionally substituted –C(O)C$_1$-C$_5$ alkyl;

- Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

[0541] In one embodiment, compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID):
or a salt, solvate or N-oxide thereof, wherein:

each $X^1$, $X^2$, $X$ and $U$ is independently N or CR$^6$;

$R^1$ is H, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_3$-C$_8$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C$_1$-C$_5$ alkyl;

each $R^6$ is independently H, hydroxyl, halo, C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C$_1$-C$_5$ alkoxy or optionally substituted –C(O)C$_1$-C$_5$ alkyl;

$Q$ is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C$_1$-C$_5$ alkyl, C$_3$-C$_8$ cycloalkyl, halo-substituted C$_1$-C$_5$ alkyl, halo-substituted C$_3$-C$_8$ cycloalkyl, C$_1$-C$_5$ alkoxy, C$_3$-C$_8$ cycloalkoxy, cyano, carboxyl, -NHC(O)CH$_3$ and -C(O)NR$_{16}^6$R$^{17}$; and

each $R_{16}^6$ and $R_{17}^6$ is independently H or optionally substituted C$_1$-C$_5$ alkyl.

[0542] In certain embodiments, with respect to the compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID), each $X^1$, $X^2$ and $X$ is independently CR$^6$; wherein each $R^6$ is independently halo, C$_1$-C$_5$-alkyl, halo C$_1$-C$_5$-alkyl, perhalo C$_1$-C$_5$-alkyl, or C$_1$-C$_5$-alkoxy. In certain embodiments, each $X^1$, $X^2$ and $X$ is independently CR$^6$; wherein each $R^6$ is independently fluoro, chloro, methyl, ethyl, CF$_3$, or methoxy. In certain embodiments, $U$ is CR$^6$, wherein $R^6$ is CF$_3$, methyl, chloro, CONHCH$_3$, COOH, COOCH$_3$, H, or fluoro; provided that $R^1$ is other than methyl.

[0543] In certain embodiments, with respect to the compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID), $X$ is CR$^6$, wherein $R^6$ is fluoro; and $R^1$ is other than methyl.
In one embodiment, compound is according to formula (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1) are provided:

\[
\begin{align*}
\text{(J-IA-1)} & : \quad \text{U is N or CR}^6; \\
\text{R}^1 & \text{ is } H, \text{ C}_1-\text{C}_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C}_3-\text{C}_8 \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C}_2-\text{C}_5 \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-}\text{C}_1-\text{C}_5 \text{ alkyl; } \\
\text{Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C}_1-\text{C}_5 \text{ alkyl, C}_3-\text{C}_8 \text{ cycloalkyl, halo-substituted C}_1-\text{C}_5 \text{ alkyl, halo-substituted C}_3-\text{C}_8 \text{ cycloalkyl, C}_1-\text{C}_5 \text{ alkoxy, C}_3-\text{C}_8 \text{ cycloalkoxy, cyano, carboxyl, -NHC(O)CH}_3 \text{ and -C(O)NR}^{16}\text{R}^{17}; \text{ and } \\
\text{each R}^{16} \text{ and R}^{17} & \text{ is independently H or optionally substituted C}_1-\text{C}_5 \text{ alkyl.}
\end{align*}
\]
[0545] In another embodiment, the compound is of the formula (K-IA), (K-IB), (K-IC) or (K-ID):

![Chemical structures]

(K-IA) , (K-IB) , (K-IC) or (K-ID)

or a salt, solvate or N-oxide thereof, wherein:

- X is N or CH;
- R^6 is Cl, CF_3, or methyl;
- R^7 is independently H or methyl;
- R^8 is H; azido; F; OH; NH_2; N(CH_3)H; N(CH_3)_2; NH-cyclopropyl; or NH-cyclobutyl;
- OC(O)N(CH_3)_2; or 3,3-dimethyl-2-hydroxybutyl; and
- Q is unsubstituted 3-pyridyl; 3-pyridyl substituted with methyl, Cl, or CONH_2;
- unsubstituted 4-pyridyl; 4-pyridyl substituted with OH; unsubstituted pyrazinyl; unsubstituted imidazolyl; or unsubstituted triazolyl.

[0546] In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); R^7 is H, and R^8 is OH. In one embodiment, the compound is Compound 3, 4, 13, 39, 41, 129, or 144 (Table I); or II-132, II-138, II-139, or II-140 (Table II).
In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); \( R^7 \) is methyl, and \( R^8 \) is OH. In one embodiment, the compound is Compound 5, 14, 26, 29, 31, 148, 173, 174, or 176 (Table I); or II-148 (Table II).

In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); \( R^8 \) is NH$_2$, N(CH$_3$)$_2$H, N(CH$_3$)$_2$, NH-cyclopropyl, or NH-cyclobutyl. In one embodiment, the compound is Compound 27, 150, 151, or 154 (Table I); or II-4, II-7, II-13, or II-260 (Table II).

In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); each \( R^7 \) and \( R^8 \) is H. In one embodiment, the compound is Compound 74, 134, or II-244 (Table I and II).

In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); \( R^7 \) Me, and \( R^8 \) is F. In one embodiment, the compound is Compound II-212 (Table II).

In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); \( R^8 \) is -OC(O)N(CH$_3$)$_2$. In one embodiment, the compound is Compound 141.

In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); \( R^7 \) is 3,3-dimethyl-2-hydroxybutyl. In one embodiment, the compound is Compound II-227 (Table II).

In another embodiment, the compound is of the formula (K-IE), or (K-IF):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

\( R^6 \) is Cl, or methyl;

\( R^7 \) is H or methyl;

\( R^8 \) is OH; N(CH$_3$)$_2$; or OC(O)-t-Bu;

and
Q is phenyl substituted with F; unsubstituted 3-pyridyl; 3-pyridyl substituted with methyl; unsubstituted 4-pyridyl; or unsubstituted pyrazinyl.

[0554] In certain embodiments, with respect to the compounds of formula (K-IE), or (K-IF); R⁷ is H, and R⁸ is OH. In one embodiment, the compound is Compound 129 (Table I); or II-131 (Table II).

[0555] In certain embodiments, with respect to the compounds of formula (K-IE), or (K-IF); R⁷ is methyl, and R⁸ is OH. In one embodiment, the compound is II-121, II-127, II-128, or II-130 (Table II).

[0556] In certain embodiments, with respect to the compounds of formula (K-IE), or (K-IF), R⁸ is N(CH₃)₂. In one embodiment, the compound is Compound II-6 (Table II).

[0557] In certain embodiments, with respect to the compounds of formula (K-IE), or (K-IF); R⁸ is OC(O)-t-Bu. In one embodiment, the compound is Compound 130 (Table I).

[0558] In one embodiment, the compound is Compound II-123 (Table II).

[0559] In one embodiment, the compound is Compound 325 (Table I).

[0560] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and R¹ is methyl.

[0561] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and R⁵ is methyl, chloro, or trifluoromethyl.

[0562] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and R⁷ is H, methyl, cyclopropyl, cyclobutyl, or 3,3-dimethyl-2-hydroxybutyl.

[0563] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and R⁸ is H, F, OH, -N(CH₃)₂, or -OC(O)N(CH₃)₂.

[0564] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and Y² is N. In one embodiment, Y² is N, and one of Y¹, Y³, or Y⁴ is methyl.

[0565] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and Y³ is N. In one embodiment, Y³ is N, and one of Y¹, Y², or Y⁴ is methyl.
In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), and each of Y¹ and Y⁴ is N.

In certain embodiments, with respect to the compounds of formula (A-IIIE-6), and Q is triazolyl, or imidazolyl.

In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), R⁷ is H, R⁸ is OH, and the compound is Compound No. 3, 4, 13, 39, 41, 127, 144, II-132, II-138, II-139, or II-140.

In certain embodiments, with respect to the compounds of formula (I), (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), R⁷ is methyl, R⁸ is OH, and the compound is Compound No. 5, 14, 26, 29, 31, 148, 173, 174, 176, II-148, II-151, II-152, or II-220.

In certain embodiments, with respect to the compounds of formula (I), (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), R⁸ is NH₂, N(CH₃)H, N(CH₃)₂, NH-cyclopropyl, or NH-cyclobutyl, and the compound is Compound No. 27, 150, 151, 154, II-4, II-7, II-13, or II-260.

In certain embodiments, with respect to the compounds of formula (I), (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), each R⁷ and R⁸ is H, and the compound is Compound No. 74, 134, or II-244.

In certain embodiments, with respect to the compounds of formula (I), (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), R⁷ Me, and R⁸ is F, and the compound is Compound No. II-212.

In certain embodiments, with respect to the compounds of formula (I), (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), or (C-IA-5), R⁸ is -OC(O)N(CH₃)₂, and the compound is Compound No. 141.

In certain embodiments, with respect to the compounds of formula (A-IIIE-2), (A-IIIE-6), (A-IIIF-2), (A-IIIG-2), (A-IIIH-2), (C-IA-4), and R⁷ is 3,3-dimethyl-2-hydroxybutyl, and the compound is Compound No. II-227.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is optionally substituted phenyl.
In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is phenyl substituted with C₁-C₅ alkyl, halo, halo C₁-C₅ alkyl, or C₁-C₅ alkoxy.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is phenyl substituted with methyl, ethyl, F, Cl, OCH₃, or CF₃.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is optionally substituted pyridyl, or optionally substituted pyrimidinyl.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (H-IIIB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is pyridyl substituted with C₁-C₅ alkyl, halo, halo or C₁-C₅ alkyl.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is pyridyl substituted with methyl, ethyl, F, Cl, or CF₃.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), R¹ is H; unsubstituted C₁-C₅ alkyl; C₁-C₅ alkyl substituted with OH or SO₂H; cycloalkyl; or C₂-C₅ alkenyl.

In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIIB), (C-VA), (C-VB), (D-III), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), R¹ is H; unsubstituted C₁-C₅ alkyl; C₁-C₅ alkyl substituted with up to three halogen atoms; cycloalkyl; or C₂-C₅ alkenyl.
[0583] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIII), (A-VIIIIB), (C-VA), (C-VB), (D-IIIA), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), R^1 is methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, cyclobutyl, cyclopropyl, CF_3, CH_2CF_3 or CH_2CH_2-SO_2H.

[0584] In one particular embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIII), (A-VIIIIB), (C-VA), (C-VB), (D-IIIA), (D-IIIB), (H-IA), (H-IB), (H-IC) or (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (J-IA), (J-IB), (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), R^1 is methyl.

[0585] In one embodiment, with respect to the compounds of formula (I); R^4 is F. In another embodiment, each R^4 and R^6 is F. In a particular embodiment, the compound is Compound II-267 or II-280.

[0586] In certain embodiments, with respect to the compounds of formula (A-IIIE-2); when R^1 is methyl, R^4 is F, R^6 is H, R^6 is Cl, each R^7 and R^8 is H, and Y^3 is C-CF_3; then Y^2 is other than N.

[0587] In certain embodiments, with respect to the compounds of formula (A-IIIE-2); when R^1 is methyl, each R^4 and R^6 is F, H, R^6 is methyl, each R^7 and R^8 is H, and Y^3 is C-CH_3; then Y^2 is other than N.

[0588] In certain embodiments, with respect to the compounds of formula (A-IIIE-2); when R^1 is methyl, each R^4 and R^6 is F, H, R^6 is Cl or methyl, each R^7 and R^8 is H, and Y^3 is C-F; then Y^2 is other than CH.

[0589] In one embodiment, the invention relates to Compound No. 87, and uses thereof. In another embodiment, the invention relates to Compound No. 88, and uses thereof. In yet another embodiment, the invention relates to Compound No. 120, and uses thereof. In a further embodiment, the invention relates to Compound No. 324, and uses thereof.

[0590] In one embodiment, the invention relates to Compound No. 338, and uses thereof. In another embodiment, the invention relates to Compound No. II-1, and uses thereof.

[0591] In one embodiment, the invention relates to Compounds 25a, 25b, 27a, 27b, 54a and 54b, and uses thereof. In another embodiment, the invention relates to Compounds 25, 25a, 25b, 27, 27a, 27b, 54a, 54b, 130a, 130b, 141, 147 and 149-160, and uses thereof.
[0592] In another embodiment, the invention relates to Compounds 3a-5a, 3b-5b, 6, 7a-9a, 7b-9b, 8-9, 39, 51, 55, 63-68, 70-73, 77-82, 91-92, 10a-31a, 10b-31b, 37c-37d, 39a-59a, 39b-59b, 69a-b, 74a-b, 75a-d and 76a-d, and uses thereof.

[0593] In another embodiment, the invention relates to Compounds 6, 9-12, 14, 16-21, 23-25, 27-28, 39-40, 42, 44-45, 48-49, 51-59, 63-72, 75-82, 108-122, 124-126, 128-131, 133-176; 1a-25a, 27a-31a, 36a-45a, 48a-49a, 51a-59a, 62a-67a, 69a-73a, 75a-76a, 81a-82a, 93a, 95a-98a, 102a, 127a-128a, 130a-131a, 133a, 135a-136a, 138a-179a; 1b-25b, 27b-31b, 36b-45b, 48b-49b, 51b-59b, 62b-67b, 69b-73b, 75b-76b, 81b-82b, 93b, 95b-98b, 102b, 127b-128b, 130b-131b, 133b, 135b-136b, 138b-179b; 36c-h, 37c-d, 38c-h, 70c-d, 73c-h, 75c-d, 76c-d, 95c-d, 97c-d, 127c-d, 148c-d, 155c-h, 161c-d, 162c-d, 163c-d, 164c-d, 168c-d, 176c-d and 177c-d, and uses thereof.

[0594] In another embodiment, the invention relates to Compounds 3, 3b, 4a, 5b and 39a. In another embodiment, the invention relates to Compounds 3, 3a, 3b, 5a, 5b, 13b, 14a, 15b, 26a, 26b, 27a, 29a, 31a, 74a, 93a, 127a, 130a, 130b, 133b, 134b, 137a, 139a, 141, 144b, 147, 150a and 154, and uses thereof.

[0595] In another embodiment, the invention relates to Compound Nos. 3, 39, 4, 5, 13, 14, 41, 74, 26, 27, 29, 31, 127, 129, 134, 144, 148, 173, 174, 150, 176, IV-210, 151, II-4, II-132, 141, 154, II-135, II-138, II-139, II-140, V-22, II-244, II-7, II-146, II-151, II-152, II-227, II-220, II-148, IV-13, II-212, IB-260 and II-260b, and uses thereof. In another embodiment, the invention relates to Compound Nos. 3a, 3b, 39a, 4a, 5b, 13b, 14a, 41a, 74a, 26a, 26b, 27a, 29b, 31a, 127a, 129d, 134b, 144b, 148#1, 173a, 174a, 150a, 176a, IV-210a, 151a, II-4b, II-132b, 148b, 141b, 154b, II-135b, II-138, II-139, II-140, V-22, II-244a, II-7, II-146a, II-151b, II-152a, II-227c, II-220, II-148a, II-13a, II-212a, II-260a and II-260b, and uses thereof.

[0596] In one embodiment, the invention relates to Compound Nos. 3a, 3b, 4a, 4b, 5a, 5b, 6, 7a, 7b, 8a, 8b, 9, 9a, 9b, 10, 10a, 11, 11a, 11b, 12, 12a, 12b, 13b, 13b, 14, 14a, 14b, 15a, 15b, 16, 16a, 16b, 17, 17a, 17b, 18, 18a, 18b, 19, 19a, 19b, 20, 20a, 20b, 21, 21a, 21b, 22a, 22b, 23, 23a, 23b, 24, 24a, 24b, 25, 25a, 25b, 26, 26a, 26b, 26c, 26d, 27, 27a, 27b, 28, 28a, 28b, 29a, 29b, 30a, 30b, 31a, 31b, 36, 37, 37c, 37d, 39, 39a, 39b, 40, 40a, 40b, 41, 41a, 41b, 42, 42a, 42b, 43a, 43b, 44, 44a, 44b, 45, 45a, 45b, 47a, 47b, 47c, 47d, 48a, 48b, 49a, 49b, 51, 51a, 51b, 52, 52a, 52b, 53, 53a, 53b, 54, 54a, 54b, 55, 55a, 55b, 56, 56a, 56b, 57, 57a, 57b, 58, 58a, 58b, 59, 59a, 59b, 63, 63a, 63b, 64, 65, 66, 67, 68, 69, 69a, 69b, 70, 71, 72, 75, 75a, 75b, 75c, 75d, 76, 76a, 76b, 76c, 76d, 77, 78, 79, 80, 81, 82, 90a, 90b, 108, 109, 110, 111, 112, 113, 114, 115,
In another embodiment, the invention relates to Compounds described in Table 1, and uses thereof. In another embodiment, the invention relates to one or more of the Compounds described in Table 2, and uses thereof.

In another embodiment, the invention relates to one or more of the Compounds described in Table 3, and uses thereof.

In another embodiment, the invention relates to one or more of the Compounds described in Table 4, and uses thereof.

In another embodiment, the invention relates to one or more of the Compounds described in Table 5, and uses thereof.

In one embodiment, the invention embraces compounds detailed herein provided that the compound is other than dimebon and metabolites of dimebon. In another embodiment, the invention embraces dimebon or a salt thereof for uses detailed herein. In another embodiment, the invention embraces a dimebon metabolite or salt thereof for uses detailed herein, such as use in therapy, *e.g.*, to (i) reduce blood pressure and/or (ii) promote renal blood flow and/or (iii) decrease or inhibit sodium reabsorption.

The embodiments and variations described herein are suitable for compounds of any formulae detailed herein, where applicable.

Representative examples of compounds detailed herein, including intermediates and final compounds according to the invention are depicted in the tables below. It is understood that in one aspect, any of the compounds may be used in the methods detailed herein, including, where applicable, intermediate compounds that may be isolated and administered to an individual.

The compounds depicted herein may be present as salts even if salts are not depicted and it is understood that the invention embraces all salts and solvates of the compounds depicted
here, as well as the non-salt and non-solvate form of the compound, as is well understood by the skilled artisan. In some embodiments, the salts of the compounds of the invention are pharmaceutically acceptable salts. Where one or more tertiary amine moiety is present in the compound, the N-oxides are also provided and described.

[0605] Where tautomeric forms may be present for any of the compounds described herein, each and every tautomeric form is intended even though only one or some of the tautomeric forms may be explicitly depicted. For example, when a 2-hydroxypyridyl moiety is depicted, the corresponding 2-pyridone tautomer is also intended. The tautomeric forms specifically depicted may or may not be the predominant forms in solution or when used according to the methods described herein.

[0606] The invention also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms of the compounds described. The structure or name is intended to embrace all possible stereoisomers of a compound depicted, and each unique stereoisomer has a compound number bearing a suffix “a”, “b”, etc. All forms of the compounds are also embraced by the invention, such as crystalline or non-crystalline forms of the compounds. Compositions comprising a compound of the invention are also intended, such as a composition of substantially pure compound, including a specific stereochemical form thereof, or a composition comprising mixtures of compounds of the invention in any ratio, including two or more stereochemical forms, such as in a racemic or non-racemic mixture.

[0607] Pharmaceutical compositions of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

[0608] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In one variation, "substantially pure" intends a composition that contains no more than 35% impurity, wherein the impurity
denotes a compound other than the compound comprising the majority of the composition or a salt thereof. Taking compound 1 as an example, a composition of substantially pure compound 1 intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than compound 1 or a salt thereof. In one variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 20% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 10% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 5% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 3% impurity. In still another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 1% impurity. In a further variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 0.5% impurity. In yet other variations, a composition of substantially pure compound means that the composition contains no more than 15% or preferably no more than 10% or more preferably no more than 5% or even more preferably no more than 3% and most preferably no more than 1% impurity, which impurity may be the compound in a different stereochemical form. For instance, a composition of substantially pure (S) compound means that the composition contains no more than 15% or no more than 10% or no more than 5% or no more than 3% or no more than 1% of the (R) form of the compound.

[0609] In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

[0610] Kits comprising a compound of the invention, or a salt or solvate thereof, and suitable packaging are provided. In one embodiment, a kit further comprises instructions for use. In one
aspect, a kit comprises a compound of the invention, or a salt or solvate thereof, and instructions for use of the compounds in the treatment of a disease or condition for which a reduction in blood pressure and/or promoting renal blood flow and/or inhibiting or decreasing sodium reabsorption is expected to be or is beneficial.

[0611] Articles of manufacture comprising a compound of the invention, or a salt or solvate thereof, in a suitable container are provided. The container may be a vial, jar, ampoule, preloaded syringe, i.v. bag, and the like.

[0612] In one aspect, a compounds detailed herein as provided herein exhibits the ability to cross the blood-brain barrier. In another aspect, a compounds detailed herein as provided herein is not able to cross the blood-brain barrier. In one aspect, a compounds detailed herein as provided herein exerts its therapeutic effect in the brain only. In one aspect, a compounds detailed herein as provided herein exerts its therapeutic effect in the periphery only. In one aspect, a compounds detailed herein as provided herein exerts its therapeutic effect both in the brain and peripherally. In some embodiments, the adrenergic receptor α2B antagonist is a selective adrenergic receptor α2B antagonist. In some embodiments, the adrenergic receptor α2B antagonist also exhibits adrenergic receptor α2A antagonist and/or inverse agonist activity.

[0613] Blood brain barrier permeability can be measured in rodents or dog by administering the compound orally or intravenously, recovering a blood and brain tissue sample at different time points and comparing how much compound is in each sample. Blood fraction is typically processed to plasma for determination of compound content. Brain exposure can be described from the ratio of brain to plasma levels of drug. In one variation, a compound that poorly crosses the blood brain barrier has a brain to plasma ratio of compound of about 0.1 or less. In another variation, the compound has a brain to plasma ratio of about 0.2 or less, about 0.3 or less, about 0.4 or less, about 0.5 or less, about 0.8 or less, or about 1.0 or less.

[0614] Preferably, the compounds detailed herein are orally bioavailable. However, the compounds may also be formulated for parenteral (e.g., intravenous) administration. In some settings, parenteral administration of an adrenergic receptor α2B antagonists (e.g., selective adrenergic receptor α2B antagonist) may be desired. For example, intra-renal delivery may offer treatment options for acute and chronic renal failure, end stage renal failure and acute decompensated congestive heart failure. Parenteral formulation may be preferred in the treatment of hypertensive urgency and emergency. In some embodiments, the adrenergic receptor α2B antagonist is a selective adrenergic receptor α2B antagonist. In some embodiments,
the adrenergic receptor \( \alpha_{2B} \) antagonist also exhibits adrenergic receptor \( \alpha_{2A} \) antagonist and/or inverse agonist activity.

[0615] One or several compounds described herein can be used in the preparation of a medicament by combining the compound or compounds as an active ingredient with a pharmacologically acceptable carrier, which are known in the art. Depending on the therapeutic form of the medication, the carrier may be in various forms. In one variation, the manufacture of a medicament is for use in any of the methods disclosed herein, e.g., reducing the blood pressure of an individual, promoting renal blood flow and/or decreasing or inhibiting sodium reabsorption.

[0616] Methods as provided herein may comprise administering to an individual a pharmacological composition that contains an effective amount of a compound and a pharmaceutically acceptable carrier. The effective amount of the compound may in one aspect be a dose of between about 0.01 and about 100 mg.

[0617] The compound may be formulated for any available delivery route, including an oral, mucosal (e.g., nasal, sublingual, vaginal, buccal or rectal), parenteral (e.g., intramuscular, subcutaneous or intravenous), topical or transdermal delivery form. A compound may be formulated with suitable carriers to provide delivery forms that include, but are not limited to, tablets, caplets, capsules (such as hard gelatin capsules or soft elastic gelatin capsules), cachets, troches, lozenges, gums, dispersions, suppositories, ointments, cataplasms (poultices), pastes, powders, dressings, creams, solutions, patches, aerosols (e.g., nasal spray or inhalers), gels, suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions or water-in-oil liquid emulsions), solutions and elixirs.

[0618] One or several compounds described herein can be used in the preparation of a formulation, such as a pharmaceutical formulation, by combining the compound or compounds as an active ingredient with a pharmaceutically acceptable carrier, such as those mentioned above. Depending on the therapeutic form of the system (e.g., transdermal patch vs. oral tablet), the carrier may be in various forms. In addition, pharmaceutical formulations may contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes, adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants. Formulations comprising the compound may also contain other substances which have valuable therapeutic properties. Pharmaceutical formulations may be prepared by known pharmaceutical methods. Suitable formulations can be found, e.g., in Remington’s Pharmaceutical Sciences,
Mack Publishing Company, Philadelphia, PA, 20th ed. (2000), which is incorporated herein by
reference.

[0619] Compounds as described herein may be administered to individuals in a form of
generally accepted oral compositions, such as tablets, coated tablets, gel capsules in a hard or in
soft shell, emulsions or suspensions. Examples of carriers, which may be used for the
preparation of such compositions, are lactose, corn starch or its derivatives, talc, stearate or its
salts, etc. Acceptable carriers for gel capsules with soft shell are, for instance, plant oils, wax,
fats, semisolid and liquid poly-ols, and so on. In addition, pharmaceutical formulations may
contain preservatives, solubilizers, stabilizers, re-wetting agents, emulgators, sweeteners, dyes,
adjusters, salts for the adjustment of osmotic pressure, buffers, coating agents or antioxidants.

[0620] Any of the compounds described herein can be formulated in a tablet in any dosage
form described, for example, a compound as described herein or a pharmaceutically acceptable
salt thereof can be formulated as a 10 mg tablet.

[0621] The compound may be administered to an individual in accordance with an effective
dosing regimen for a desired period of time or duration, such as at least about one month, at least
about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or
longer, which in some variations may be for the duration of the individual’s life. In one
variation, the compound is administered on a daily or intermittent schedule. The compound can
be administered to an individual continuously (for example, at least once daily) over a period of
time. The dosing frequency can also be less than once daily, e.g., about a once weekly dosing.
The dosing frequency can be more than once daily, e.g., twice or three times daily. The dosing
frequency can also be intermittent (e.g., once daily dosing for 7 days followed by no doses for 7
days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6
months or more). Any of the dosing frequencies can employ any of the compounds described
herein together with any of the dosages described herein.

[0622] Compositions comprising a compound provided herein are also described. In one
variation, the composition comprises a compound and a pharmaceutically acceptable carrier or
excipient. In another variation, a composition of substantially pure compound is provided.

[0623] The invention further provides kits for carrying out the methods of the invention,
which comprises one or more compounds described herein or a pharmacological composition
comprising a compound described herein. The kits may employ any of the compounds disclosed
herein. In one variation, the kit employs a compound described herein or a pharmaceutically
acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for any one or more of the following uses: treating, preventing, and/or delaying the onset and/or development of hypertension and/or a disease or condition which is responsive, or expected to be responsive, to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption.

[0624] Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

[0625] The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein (e.g., hypertension) to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

[0626] The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

[0627] The invention also provides compositions (including pharmacological compositions) as described herein for the use in treating, preventing, and/or delaying the onset and/or development of hypertension and/or a disease or condition which is responsive, or expected to be responsive, to (i) a reduction in an individual’s blood pressure and/or (ii) an increase in renal blood flow and/or (iii) a decrease or inhibition of sodium reabsorption and other methods described herein. In certain embodiments, the composition comprises a pharmaceutical formulation which is present in a unit dosage form. As used herein, the term “unit dosage form” refers to a formulation that contains a predetermined dose of a compound as disclosed herein and
optionally a second pharmaceutically active compound useful for treatment of a disease or condition detailed herein (e.g., hypertension).

For compounds bearing one or more chiral centers, each unique stereoisomer has a compound number bearing a suffix “a”, “b”, etc. As examples, racemic compound V-1, bearing one chiral center, can be resolved into its individual enantiomers V-1a and V-1b.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{N} & \quad \text{N}\text{H}_3 \\
\text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{Enantiomers } V-1a \text{ and } V-1b \\
* & \quad \text{chiral center}
\end{align*}
\]

Similarly, racemic compound V-4, bearing two chiral centers, can be resolved into its individual diastereomers V-4a, V-4b, V-4c and V-4d.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{N} & \quad \text{N}\text{H}_3 \\
\text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{Diastereomers } V-4a, V-4b, V-4c \text{ and } V-4d \\
* & \quad \text{chiral center}
\end{align*}
\]

Representative compounds of the invention are shown in Tables 1-5.
Table 1. Representative Compounds of the Invention

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**Compounds:**

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- 146, 146a, 146b
- 147, 147a, 147b
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Table 3. Representative Compounds of the Invention.
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- CO$_2$H

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- CONHCH$_3$

**III-285**
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- CONHCH$_3$

**III-287**
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- CONHCH$_3$

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### Table 4. Representative Compounds of the Invention

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IV-161a, IV-161b, IV-161c, IV-161d

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IV-164a, IV-164b, IV-164c, IV-164d
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IV-216
IV-216a, IV-216b, IV-216c, IV-216d

IV-217
IV-217a, IV-217b, IV-217c, IV-217d

IV-218
IV-218a, IV-218b, IV-218c, IV-218d

IV-219
IV-219a, IV-219b, IV-219c, IV-219d

IV-220
IV-220a, IV-220b, IV-220c, IV-220d

IV-221
IV-221a, IV-221b, IV-221c, IV-221d

IV-222
IV-222a, IV-222b, IV-222c, IV-222d

IV-223
IV-223a, IV-223b, IV-223c, IV-223d

IV-224
IV-224a, IV-224b, IV-224c, IV-224d
Table 5. Representative Compounds of the Invention

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**General Synthetic Methods**

[0635] The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

[0636] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, e.g., a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid
Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

**[0637]** Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

**General Protocol for Chiral Preparative HPLC Separation of Racemic Compounds**

**[0638]** For chiral separations, samples were dissolved in MeOH and EtOH according to the solubility of sample and filtered through 0.22μ PTFE filters. The columns used were CHIRALPAK-AD; 20*250mm, 10μ and CHIRALCEL-ODH; 20*250mm, 5μ. A flow rate of 12 mL/min -17 mL/min was used according to the resolution. Alkanes such as n-Pentane, Hexane and Heptane (40% - 95%) and alcohols such as EtOH, Isopropyl alcohol and t-Butanol (5% - 60%) were used as mobile phase. In some cases alcohol combinations i.e. (EtOH + MeOH), (EtOH + IPA), (IPA + MeOH), (t-Butanol + MeOH), (t-Butanol + EtOH) were used instead of a single alcohol. Diethyl amine (up to 0.3%) was used as modifier in the mobile phase.

*Example H1: General method for the chiral HPLC separation and characterization of compounds that were synthesized initially as a mixture of enantiomers:*

**[0639]** Crude or in some cases partially purified (normal or reverse phase HPLC) mixtures of enantiomers were analyzed by analytical chiral HPLC methods. Once adequate separation was achieved, larger quantities of the mixtures were separated using preparative scale columns as shown below for Compound Nos. 138a and 138b. Separation was followed by removal of solvents on a rotary evaporator to accomplish the isolation of the individual single enantiomers. In some cases where appropriate, after removal of solvent, the samples were lyophilized. After isolation, each individual enantiomer was further analyzed by analytical (reverse phase and chiral) HPLC, LCMS and NMR. When final products were converted to salts, final characterization of the compounds was carried out after conversion to the salt for each enantiomer.

**[0640]** Analytical Chiral HPLC of Compound Nos. 138a and 138b.

- Column: Chiralcel OD-H; Column ID: 4.6*250mm, 5μ.
  - Compound No. 138b - 13.660 min.
Chiral Preparative Data of Compound Nos. 138a and 138b.
Column: Chiralcel OD-H. Column ID: 20*250mm, 5μ. Mobile Phase: Hexane: (EtOH:MeOH 80:20) - 95:5. Flow rate: 15 mL/min. Solubility: 30 mg/mL in MeOH.

Example H2: General method for the chiral HPLC separation and characterization of compounds that were synthesized initially as a mixture of diastereomers:
Crude or in some cases partially purified (normal or reverse phase HPLC) mixtures of diastereomers were analyzed by analytical chiral HPLC methods. Once adequate separation was achieved, larger quantities of the mixtures were separated using preparative scale columns as shown below for Compound Nos. II-149a-d. Separation was followed by removal of solvents on a rotary evaporator to accomplish the isolation of the individual single diastereomers. In some cases where appropriate, after removal of solvent, the samples were lyophilized. Once each individual diastereomer was isolated they were further analyzed by analytical (reverse phase and chiral) HPLC, LCMS and NMR. When final products were converted to salts, final characterization of the compounds was carried out after conversion to the salt for each diastereomer.

Analytical Chiral HPLC Data of Compound Nos. II-149a-d.

Chiral Preparative Data of Compound Nos. II-149a-d.
Column: Chiral PAK-AD-H. Column ID: 20*250mm, 5μ. Mobile Phase: Hexane (0.2% diethylamine):Isopropanol - 93:7. Flow rate: 15 mL/min. Solubility: 40 mg/mL in MeOH.
The following abbreviations are used herein: thin layer chromatography (TLC); hour (h); minute (min); second (sec); ethanol (EtOH); dimethylsulfoxide (DMSO); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); tetrahydrofuran (THF); Normal(N); aqueous (aq.); methanol (MeOH); dichloromethane (DCM); ethyl acetate (EtOAc); Retention factor (Rf); room temperature (RT).
Compounds detailed herein may be prepared by those of skill in the art by referral to General Methods and Examples described in published PCT applications WO2009/055828 (see e.g., General Methods 1-24 and Examples 1-325), WO2010/127177 (General Methods 1-3 and
Examples 1-58), WO2009/120720 (General Methods 1-15C and Examples 1-134), WO2009/120717 (General Methods 1-17 and Examples 1-134), WO2010/051501 (General Methods 1-10 and Examples 1-450) and WO2010/051503 (General Methods 1-15 and Examples 1-111), WO2011/019417 (General Methods 1-9 and Examples 1-10), WO2011/038164 (General Methods 1-19), WO2011/038162 (General Methods 1-21 and Examples 1-6), WO2011/038163 (General Methods 1-19 and Examples 1-49) and WO2011/038161 (General Methods 1-15B and Examples 1-22). The PCT publications described above are incorporated herein by reference in their entireties. Particular examples of each of the General Methods and Examples are provided in the Examples below.

*General Method 1*

![Reaction Scheme]

[0647] In certain examples of formula (I) provided herein, and as similarly described in the publications presented above, alcohols of the type C can be prepared by treating appropriately functionalized carboline A with functionalized epoxide B, in the presence of a base. A selection of bases effective for this reaction will be apparent to those skilled in the art, such as for example, sodium hydride, sodium tert-butoxide, potassium tert-butoxide, lithium tert-butoxide, lithium diisopropylamide, lithium hexamethyldisilazide, sodium ethoxide, sodium methoxide, and the like. In some instances, one or more of the bases may be used interchangeably; for example, other bases such as sodium tert-butoxide, potassium tert-butoxide, lithium tert-butoxide, lithium diisopropylamide, lithium hexamethyldisilazide, sodium ethoxide or sodium methoxide may be substituted where sodium hydride is specifically described. It is understood that modifications to the specific materials shown are intended, e.g., where Compound B can be a heteroaryl group such as pyridyl, and Compound A can comprise structures such as pyrido[3,4-b]indoles, azepto[4,5-b]indoles, and indolizino[7,8-b]indoles, and the like.

[0648] The following Examples are provided to illustrate but not to limit the invention.
All references disclosed herein are incorporated herein by reference in their entireties.

EXAMPLES

Example 1: Preparation of Compound Nos. 1, 1a and 1b

Sodium hydride (1-3 equiv.) was added to a solution of 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.0 equiv.) in DMF and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 4-(2-methyloxiran-2-yl)pyridine (2-7.5 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and followed by brine, dried over anhydrous sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/hexane) using a gradient of 5 to 15% MeOH/EtOAc to yield the free base. The pure compound was converted to its oxalate salt. The analytical sample was prepared by dissolving free base in THF and treatment with 1 equiv. of oxalic acid dihydrate. $^1$H NMR (CDCl$_3$, oxalate salt) δ (ppm): 8.42 (d, 2H), 7.35-7.20 (m, 3H), 7.00-6.90 (m, 2H), 4.10 (q, 2H), 3.50 (q, 2H), 2.95-2.68 (m, 4H), 2.42(s, 3H), 1.55 (s, 3H). Separation by chiral HPLC provides enantiomers 1a and 1b.

Example 2: Preparation of Compound Nos. 2, 2a and 2b

Sodium hydride (1-3 equiv.) was added to a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (1.0 equiv.) in DMF, and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 4-(2-methyloxiran-2-yl)pyridine (2-7.5 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and followed by brine, dried over anhydrous sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/hexane) using a gradient of 5 to 15% MeOH/EtOAc to yield the free base. The pure compound was converted to its oxalate salt. The analytical sample was prepared by dissolving free base in THF and treatment with 1 equiv. of oxalic acid dihydrate. $^1$H NMR
(CD$_3$OD, oxalate salt) $\delta$ (ppm): 8.38 (d, 2H), 7.50 (d, 2H), 7.15 (s, 1H), 7.06 (d, 1H), 6.86 (d, 1H), 4.45 (m, 2H), 4.31 (m, 1H), 4.22 (m, 1H), 3.61 (m, 2H), 3.19 (m, 1H), 3.06 (s, 3H), 2.78 (m, 2H), 2.35 (s, 3H), 1.60 (s, 3H). Separation by chiral HPLC provides enantiomers 2a and 2b.

**Example 3: Preparation of Compound Nos. 3, 3a and 3b**

Sodium hydride (2.4 g, 100 mmol) was washed with hexane and dried under vacuum. To this was added DMF (15 mL) and cooled to 0 °C. Then to this was added 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (4 g, 20 mmol) and the mixture stirred at 0 °C for 30 min. Then 4-oxiranyl-pyridine (2.90 g, 23.96 mmol) was dissolved in 5 mL DMF and added dropwise to the mixture, which was then left stirred at RT overnight. The reaction was monitored by TLC. The reaction mixture was poured into ice water and extracted with EtOAc (3x). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The resultant solid material was washed with hexane and crystallized from EtOH and ether. $^1$H NMR (DMSO-d$_6$, HCl salt) $\delta$ (ppm): 8.70 (d, 2H), 7.70 (d, 2H), 7.38 (m, 1H), 7.20 (s, 1H), 6.90 (d, 1H), 5.05 (m, 1H), 4.58 (m, 1H), 4.30 (m, 1H), 4.20 (m, 2H), 3.70 (m, 2H), 3.20 (m, 4H), 2.90 (s, 1H), 2.38 (s, 3H). Separation by chiral HPLC provided enantiomers 3a and 3b. Optical rotations: Compound 3a; (-)31.32 (c 1, Chloroform, 94.1% HPLC purity); Compound 3b, (+)28.24 (c 1, Chloroform, 98.05% HPLC purity).

**Example 4: Preparation of Compound Nos. 4, 4a, and 4b**

Sodium hydride (2.72 g, 113.33 mmol) was washed with hexane and dried under vacuum. To this was added DMF (15 mL) and the mixture cooled to 0 °C. 8-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (5 g, 22.72 mmol) was added and the mixture stirred at 0 °C for 30 min, followed by 4-oxiranyl-pyridine (3.3 g, 27.27 mmol) dissolved in 5 mL DMF added dropwise. The reaction mixture was stirred at RT overnight. The reaction was monitored by TLC. The reaction mixture was poured into ice water and the product extracted into EtOAc (3x). The combined organic layers were washed with water, dried over anhydrous sodium sulfate and concentrated. The resultant solid material was washed with hexane and crystallized from EtOH and ether. $^1$H NMR (CD$_3$OD, HCl salt) $\delta$ (ppm): 8.80 (d, 2H), 8.18 (d, 2H), 7.50 (s, 1H), 7.30 (m, 1H), 7.10 (d, 1H), 5.30 (m, 1H), 4.70 (m, 1H), 4.50 (m, 1H), 4.40 (m, 2H), 3.90 (m, 1H), 3.60 (m, 2H), 3.40 (m, 2H), 3.10 (s, 3H). Separation by chiral HPLC provided enantiomers 4a and 4b. Optical rotations: Compound 4a, (+)47.31 (c 0.58, Chloroform, 96.26% HPLC purity); Compound 4b, (-)43.75 (c 0.55, Chloroform, 98.59% HPLC purity).

**Example 5: Preparation of Compound Nos. 5, 5a and 5b**
[0654] To a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (290 mg, 1.4 mmol) in DMF (6 mL) was added sodium hydride (38 mg, 1.6 mmol) and the solution was stirred at 120 °C for 1h. The reaction mixture was cooled to 0 °C and 3-(2-methyloxiran-2-yl)pyridine (400 mg, 2.96 mmol) was added dropwise over a period of 5 min. The reaction mixture was stirred at 120 °C for 2h, quenched with ice-water (15 mL) and extracted with EtOAc (60 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography (5-15% MeOH/EtOAc) to yield 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-(pyridin-3-yl)propan-2-ol. Separation by chiral HPLC provided enantiomers 5a and 5b. 1H NMR (CDCl3, freebase) δ (ppm): 8.79 (s, 1H), 8.42 (d, 1H), 7.56 (d, 1H), 7.04 (s, 1H), 6.9 (m, 2H), 6.8 (d, 1H), 4.17 (dd, 2H), 3.42 (s, 2H), 2.8 (t, 2H), 2.62 (t, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 1.61 (s, 3H). Optical rotations: Compound 5a, (-)-39.27 (c 0.43, Chloroform, 99.69% HPLC purity); Compound 5b, (+)-58.97 (c 0.58, Chloroform, 99.49% HPLC purity).

Example 6: Preparation of Compound Nos. 6, 6a and 6b

[0655] To a solution of 2-methyl-8-(trifluoromethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 3.937 mmol) in DMF (10 mL) was added sodium hydride (472 mg, 11.81 mmol) in portions at RT. After stirring at RT for 15 min, the suspension was allowed to cool to 0 °C and 4-(oxiran-2-yl) pyridine (762 mg, 6.299 mmol) was added dropwise into the reaction mixture, which was stirred at RT overnight. The reaction mixture was poured into ice-cooled water and extracted with EtOAc (3x50 mL). The organic layer was washed with water (2x50 mL), dried over anhydrous sodium sulfate and concentrated. The solid obtained was recrystallized in DCM-diethyl ether to yield 2-(2-methyl-8-(trifluoromethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl) ethanol. 1H NMR (CDCl3, freebase) δ (ppm): 8.59 (d, 2H), 7.4 (s, 1H), 7.39 (d, 1H), 7.3 (d, 1H), 7.19 (d, 2H), 4.68 (m, 1H), 4.1 (m, 2H), 3.4 (dd, 2H), 2.82 (m, 1H), 2.74 (bs, 2H), 2.6 (m, 1H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers 6a and 6b.

Example 7: Preparation of Compound Nos. 7, 7a and 7b

[0656] Chloro carboline (500 mg, 2.27 mmol) was taken in DMF. NaH (180 mg, 4.5 mmol) was added at RT and stirred for 10-15 min. Neat epoxide (450 mg, 3.7 mmol) was added dropwise at RT. The reaction was stirred at RT for 4 h and the reaction was monitored by LCMS. After completion, the reaction mixture was poured on ice water and extracted with EtOAc, dried and concentrated. The residue was purified by HPLC. 465 mg of product as a
white solid (TFA salt). TLC: 5% MeOH-DCM, Rf 0.1 was observed. $^1$H NMR (CD$_3$OD, TFA salt) δ (ppm): 8.80 (s, 2H), 8.40 (s, 1H), 7.9 (t, 1H), 7.40 (s, 1H), 7.20 (d, 1H), 7.0 (d, 1H), 5.25 (bs, 1H), 4.7 (d, 1H), 4.4 (m, 2H), 4.3 (d, 1H), 3.9 (bs, 1H), 3.5 (bs, 1H), 3.3 (m, 2H), 3.10 (s, 3H). Separation by chiral HPLC provided enantiomers 7a and 7b. Optical rotations: Compound 7a, (-)-21.05 (c 0.52, Chloroform, 89.7% HPLC purity); Compound 7b, (+)-6.85 (c 0.69, Chloroform, 95.74% HPLC purity).

**Example 8: Preparation of Compound Nos. 8, 8a and 8b**

[0657] To a solution of 2,6-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (1.0 g, 5.00 mmol) in DMF (20 mL) was added sodium hydride (600 mg, 15 mmol), the suspension stirred at RT for 10 min. A solution of 4-(oxiran-2-yl) pyridine (1.21 g, 10 mmol) in DMF (5 mL) was added slowly into the reaction mixture which was stirred at RT overnight. The progress of reaction was monitored by TLC and LCMS. The reaction mass was poured into ice cold water (200 mL) slowly and extracted with EtOAc (3x200 mL). The organic layer was washed with water (4x300 mL), dried over anhydrous sodium sulfate and concentrated. The residue obtained was washed with hexane (2x15 mL) and triturated with diethyl ether (50 mL) to yield the desired product. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.62 (d, 2H), 7.31 (d, 2H), 7.28 (s, 1H), 7.21 (d, 1H), 7.02 (d, 1H), 5.05 (m, 1H), 4.14 (dd, 1H), 4.078 (dd, 1H), 3.74 (d, 1H), 3.37 (d, 1H), 2.83 (m, 3H), 2.72 (m, 1H), 2.51 (s, 3H), 2.46 (s, 3H). Separation by chiral HPLC provided enantiomers 8a and 8b.

**Example 9: Preparation of Compound Nos. 9, 9a and 9b**

[0658] 2-(2- Allyl-8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyrindin-3-yl-ethanol (1.0 g, 2.8 mmol) was dissolved in DCM and the solution was purged with nitrogen for 5 min. 1,3-Dimethylbarbituric acid (1.34 g, 8.6 mmol) and Pd(PPh$_3$)$_4$ (66.5 mg, 0.056 mmol) were added and the reaction mixture was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was basified with saturated aqueous potassium carbonate, and extracted with EtOAc (3x50 mL). The combined organic layer was washed with saturated aqueous potassium carbonate (6x20 mL), dried over anhydrous sodium sulfate and concentrated. The crude product was purified by reverse phase chromatography to obtain 50 mg of 2-(8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyrindin-3-yl-ethanol. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.47 (s, 1H), 8.41 (d, 1H), 7.59 (d, 1H), 7.19 (m, 3H), 7.10 (s, 1H), 7.00 (d, 1H), 5.0 (t, 1H), 4.10 q (d, 2H), 3.92 q (d, 2H), 3.10 (m, 2H), 2.90 (m, 2H), 2.47 (m,
1H), 2.42 (s, 3H). This racemate was separated by chiral semi-preparative HPLC to obtain enantiomers 9a and 9b.

**Example 10: Preparation of Compound Nos. 10, 10a and 10b**

2-(2- Allyl-8-chloro-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (4.0 g, 10.87 mmol) was dissolved in DCM (350 mL) and nitrogen was purged for 10 min into the reaction mixture. 1,3-Dimethyl barbituric acid (5.08 g, 32.62 mmol) and Pd(PPh3)4 (251 mg, 0.217 mmol) was added and stirred for 2 h at RT. After consumption of starting material, the reaction mixture was diluted with saturated potassium carbonate (200 mL) and extracted with DCM (2x100mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated, and the crude mixture crystallized in MeOH (5 mL) and ether (50 mL) to obtain 2.2 g of 2-(8-chloro-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. 1H NMR (CDCl3, freebase) δ (ppm): 8.58 (d, 2H), 7.37 (s, 1H), 7.25 (d, 2H), 7.23 (d, 1H), 7.13 (d, 1H), 5.0 (t, 1H), 4.15 (d, 2H), 3.99 (s, 2H), 3.19 (m, 2H), 2.81 (m, 1H), 2.53 (m, 1H). Separation by chiral HPLC provided enantiomers 10a and 10b. Optical rotations: Compound 10a, (−)34.60 (c 0.55, Chloroform, 99.16% HPLC purity); Compound 10b, (+)31.78 (c 0.53, Chloroform, 92.71% HPLC purity).

**Example 11: Preparation of Compound Nos. 11, 11a and 11b**

3-[8-Chloro-5-(2-hydroxy-2-pyridin-4-yl-ethyl)-1,3,4,5-tetrahydro-pyrido[4, 3-b]indol-2-yl]-propionic acid methyl ester (200 mg, 0.484 mmol) was dissolved in dry THF (5 mL), and cooled to −78 °C. Methyl magnesium chloride (0.2 mL, 1.93 mmol) was added dropwise and stirred for 15 min and allowed to RT and stirred for 2 h. After consumption of starting material, 2 mL MeOH was added into the reaction, which was then concentrated, and the residue diluted with water (20 mL) and extracted with EtOAc (3×30 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated, and the crude product purified by reverse phase chromatography to obtain 50 mg of 4-[8-chloro-5-(2-hydroxy-2-pyridin-4-yl-ethyl)-1,3,4,5-tetrahydro-pyrido[4, 3-b]indol-2-yl]-2-methyl-butan-2-ol. 1H NMR (CDCl3, freebase) δ (ppm): 8.48 (d, 2H), 7.35 (s, 1H), 7.18 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H), 4.90 (t, 1H), 4.05 (m, 2H), 3.68 (m, 2H), 2.87 (m, 3H), 2.79 (m, 2H), 2.49 (m, 1H), 1.72 (t, 2H), 1.24 (s, 6H). Separation by chiral HPLC provided enantiomers 11a and 11b. Optical rotations: Compound 11a, (−)25.66 (c 0.56, Chloroform, 96.42% HPLC purity); Compound 11b, (+)24.07 (c 0.56, Chloroform, 98.39% HPLC purity).

**Example 12: Preparation of Compound Nos. 12, 12a and 12b**
[0661] 1-(6-Allyl-3-chloro-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-2-pyridin-4-yl-propan-2-ol (260 mg, 0.680 mmol) was dissolved in DCM (7 mL) and N₂ was purged into the reaction mixture. 1,3-Dimethyl barbituric acid (318 mg, 2.04 mmol) and Pd(PPh₃)₄ (15 mg, 0.013 mmol) was added and the mixture stirred for 45 min at RT. After consumption of starting material, the reaction mixture was diluted with saturated potassium carbonate and extracted with DCM (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated, and the crude product was purified by reverse phase chromatography to obtain 100 mg of 1-(3-chloro-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-2-pyridin-4-yl-propan-2-ol. ¹H NMR (CDCl₃, freebase) δ (ppm): 8.51 (d, 2H), 8.14 (s, 1H), 7.67 (s, 1H), 7.33 (d, 2H), 4.39 (d, 1H), 4.36 (d, 1H), 3.93 q (d, 2H), 3.16 (m, 2H), 2.62 (m, 1H), 2.40 (m, 1H), 1.57 (s, 3H).

Separation by chiral HPLC provided enantiomers 12a and 12b. Optical rotations: Compound 12a, (+)121.78 (c 0.53, Chloroform, 97.32% HPLC purity); Compound 12b, (-)118.34 (c 0.54, Chloroform, 99.01% HPLC purity).

Example 13: Preparation of Compound Nos. 13, 13a and 13b

[0662] 3,9-Dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (300 mg, 1.40 mmol) was taken into DMF (6 mL). To a solution of sodium hydride (50%) (100 mg, 4.22 mmol) was added in portions at RT and stirred at RT for 10 min. A solution of 4-(oxiran-2-yl)pyridine (254 mg, 2.11 mmol) in DMF (1 mL) was added dropwise for 10 min. and stirred for 14 h at RT. The reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice water, extracted in ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by reverse phase chromatography to get pure product 2-(3,9-dimethyl-2,3,4,5-tetrahydroazepino[4,5-b]indol-6(1H)-yl)-1-(pyridin-4-yl)ethanol as the TFA salt (250 mg). Separation by chiral HPLC provided enantiomers 13a and 13b. Optical rotations: Compound 13a, (-)5.03 (c 0.56, Chloroform, 99.17% HPLC purity); Compound 13b, (+)5.70 (c 0.56, Chloroform, 99.35% HPLC purity).

Example 14: Preparation of Compound Nos. 14, 14a and 14b

[0663] 2,6-Dimethyl-2,3,4,9-tetrahydro-1H-β-carboline (1 g, 5 mmol) was dissolved in 15 mL DMF and stirred for 10 min at 0 °C. Sodium hydride (600 mg, 15 mmol) was added portionwise at RT and stirred for 10 min. 3-(2-Methyl-oxiranyl)-pyridine (1.01 g, 7.5 mmol) was added dropwise at the same temperature and the mixture stirred for 12 h at RT. The reaction was monitored by TLC & LCMS. After consumption of starting material, the reaction mixture was
quenched with ice water and extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (4x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated and the residue was crystallized in EtOH and ether to obtain 375 mg of 1-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-2-pyridin-3-yl-propan-2-ol. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, freebase) \(\delta\) (ppm): 8.76 (d, 1H), 8.55 (dd, 1H), 7.703 (d, 1H), 7.24 (s, 1H), 7.23 (dd, 1H), 7.15 (d, 1H), 6.95 (d, 1H), 4.13 (d, 1H), 4.08 (d, 1H), 3.38 (dd, 2H), 2.79 (q, 2H), 2.74 (q, 2H), 2.46 (s, 3H), 2.43 (s, 3H), 1.64 (s, 3H). Separation by chiral HPLC provided enantiomers 14a and 14b. Optical rotations: Compound 14a, (+)-31.28 (c 0.58, Chloroform, 96.04% HPLC purity); Compound 14b, (-)-27.23 (c 0.57, Chloroform, 96.09% HPLC purity).

Example 15: Preparation of Compound Nos. 15, 15a and 15b

[0664] 9-Chloro-3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (300 mg, 1.27 mmol) was taken into DMF (6 mL). Sodium hydride (50%) (92 mg, 3.83 mmol) was added in portions at RT and the mixture was stirred at RT for 10 min. A solution of 4-(oxiran-2-yl)pyridine (232 mg, 1.9 mmol) in DMF (1 mL) was added dropwise for 10 min and stirred for 14 h at RT. The reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice water, extracted in ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by reverse phase chromatography to get pure product 2-(9-chloro-3-methyl-2,3,4,5-tetrahydroazepino[4,5-b]indol-6(1H)-yl)-1-(pyridin-4-yl)ethanol as the TFA salt (230 mg). \textsuperscript{1}HNMR (DMSO-d\textsubscript{6}, TFA salt) \(\delta\) (ppm): 8.65 (m, 2H), 7.80-7.45 (m, 3H), 7.40 (m, 1H), 7.0 (m, 1H), 6.0 (m, 1H), 4.95 (m, 1H), 4.40 (m, 2H), 3.40 (m, 3H), 3.20 (m, 4H), 2.92 (s, 3H). Separation by chiral HPLC provided enantiomers 15a and 15b.

Example 16: Preparation of Compound Nos. 16, 16a and 16b

[0665] 2, 6-Dimethyl-2, 3, 4, 9-tetrahydro-1H-β-carboline (500 mg, 2.5 mmol) was dissolved in 20 mL DMF and stirred for 10 min at RT. Sodium hydride (180 mg, 7.5 mmol) was added portionwise at RT and the mixture stirred for 10min. 2-(2-Methyl-oxiranyl)-pyridine (472 mg, 3.5 mmol) was added dropwise at the same temperature and stirred for 12 h at RT. The reaction was monitored by TLC & LCMS. After consumption of starting material, the reaction mixture was quenched with ice water and extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated and the residue was crystallized in hexane to obtain 115 mg of 1-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-2-pyridin-2-yl-propan-2-ol. \textsuperscript{1}HNMR (CDCl\textsubscript{3},
freebase) $\delta$ (ppm): 8.51 (d, 1H), 7.65 (t, 1H), 7.29 (d, 1H), 7.22 (d, 1H), 7.20 (s, 1H), 6.95 (d, 1H), 6.85 (d, 1H), 4.9 (bs, 1H), 4.18 (s, 2H), 3.21 (dd, 2H), 2.77 (m, 2H), 2.69 (m, 2H), 2.42 (d, 6H), 1.63 (s, 3H). Separation by chiral HPLC provided enantiomers 16a and 16b. Optical rotations: Compound 16a, (-)-5.77 (c 0.52, Chloroform, 98.11% HPLC purity); Compound 16b, (+)-5.85 (c 0.51, Chloroform, 98.06% HPLC purity).

**Example 17: Preparation of Compound Nos. 17, 17a and 17b**

6,8,8-Trimethyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene (100 mg, 0.465 mmol) was dissolved in DMF (2 mL) and sodium hydride (56 mg, 1.39 mmol) was added portionwise under nitrogen. 4-Oxiranyl-pyridine (113 mg, 0.933 mmol) was added dropwise at RT and stirred for 12 h. After consumption of starting material (by monitoring TLC and LCMS), the reaction mixture was poured into ice water and extracted with EtOAc (2x25 mL). The combined organic layer was washed with water (5x10mL), the organic layer was dried over anhydrous sodium sulfate and concentrated, and the crude product purified by reverse phase chromatography to obtain 15 mg of 1-pyridin-4-yl-2-(6,8,8-trimethyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-ethanol. $^1$HNMR (CDCl$_3$, freebase) $\delta$ (ppm): 8.63 (d, 2H), 8.22 (d, 1H), 7.75 (d, 1H), 7.45 (d, 2H), 7.09 (dd, 1H), 5.17 (d, 1H), 4.53 (dd, 1H), 4.47 (d, 1H), 3.71 (d, 1H), 3.44 (d, 1H), 2.5 (s, 3H), 2.49 (d, 1H), 2.44 (d, 1H), 1.47 (s, 3H), 1.32 (s, 3H). Separation by chiral HPLC provided enantiomers 17a and 17b. Optical rotations: Compound 17a, (+)-50.54 (c 0.56, Chloroform, 99.31% HPLC purity); Compound 17b, (-)-51.38 (c 0.55, Chloroform, 95.62% HPLC purity).

**Example 18: Preparation of Compound Nos. 18, 18a and 18b**

2,6-Dimethyl-2,3,4,9-tetrahydro-1H-β-carboline (500 mg, 2.5 mmol) was dissolved in 5 mL DMF and sodium hydride (250 mg, 6.24 mmol) was added portionwise at 0 °C and the mixture stirred for 10 min. 2-(4-Fluoro-phenyl)-oxirane (450 mg, 3.26 mmol) was added dropwise at the same temperature and stirred for 12 h at RT. The reaction was monitored by TLC & LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water. The resultant solid was filtered and washed with water (100 mL) and hexane (100 mL), and the crude product was crystallized in EtOH:hexane (5:95 ratio) to obtain 300 mg of 2-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carboline-9-yl)-1-(4-fluoro-phenyl)-ethanol. $^1$H NMR (CDCl$_3$, Free base) $\delta$ (ppm): 7.30 (m, 2H), 7.20 (d, 1H), 7.05 (m, 3H), 7.0 (d, 1H), 5.0 (t, 1H), 4.05 (d, 2H), 3.62 (d, 1H), 3.30 (d, 1H), 2.80 (m, 3H), 2.70 (m, 1H), 2.50 (s, 3H), 2.44 (s, 3H). Separation by chiral HPLC provided enantiomers 18a and 18b. Optical rotations: Compound
18a, (-)-6.97 (c 0.56, Chloroform, 89.35% HPLC purity); Compound 18b, (+)-13.03 (c 0.51, Chloroform, 99.51% HPLC purity).

**Example 19: Preparation of Compound Nos. 19, 19a and 19b**

2,6-Dimethyl-2,3,4,9-tetrahydro-1H-β-carboline (500 mg, 2.5 mmol) was dissolved in 10 mL DMF and stirred for 10 min at 0 °C. Sodium hydride (300mg, 7.5mmol) was added portionwise at RT and stirred for 10 min. 4-(2-Methyl-oxiranyl)-pyridine (472 mg, 3.5 mmol) was added dropwise at the same temperature and stirred for 4 h at RT. The reaction was monitored by TLC & LCMS. After consumption of starting material, the reaction mixture was quenched with ice water and extracted with EtOAc (2x60 mL). The combined organic layer was washed with water (5x75 mL), dried over anhydrous sodium sulfate and concentrated and the residue was crystallized in EtOH and hexane to obtain 175 mg of 1-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-2-pyridin-4-yl-propan-2-ol. $^1$H NMR (CDCl$_3$, Freebase) δ (ppm): 8.58 (d, 2H), 7.40 (d, 2H), 7.25 (s, 1H), 7.16 (d, 1H), 6.92 (d, 1H), 4.18-4.0 (dd, 2H), 3.50-3.38 (dd, 2H), 2.80 (m, 2H), 2.70 (m, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 1.58 (s, 3H). Separation by chiral HPLC provided enantiomers 19a and 19b. Optical rotations: Compound 19a, (+)-22.35 (c 0.58, Chloroform, 98.36% HPLC purity); Compound 19b, (-)-22.43 (c 0.55, Chloroform, 99.09% HPLC purity).

**Example 20: Preparation of Compound Nos. 20, 20a and 20b**

2,6-Dimethyl-2,3,4,9-tetrahydro-1H-β-carboline (1.0 g, 5.0 mmol) was dissolved in 15 mL DMF and sodium hydride (600 mg, 15 mmol) was added portionwise at 0 °C and stirred for 10 min. 2-(4-Methoxy-phenyl)-oxirane (900mg, 6.0mmol) was added dropwise at the same temperature and stirred for 12 h at RT. The reaction was monitored by TLC & LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water and filtered through a Celite bed. A cake of compound was formed which was dissolved in MeOH and DCM. This was again filtered through a Celite bed and the filtrate concentrated. The solid thus obtained was crystallized in ether & hexane to get 600 mg of 2-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-1-(4-methoxy-phenyl)-ethanol. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 7.27 (m, 3H), 7.24 (d, 1H), 7.00 (d, 1H), 6.98 (d, 2H), 4.98 (t, 1H), 4.09 (d, 2H), 3.81 (s, 3H), 3.67 (d, 1H), 3.32 (d, 1H), 2.79 (m, 3H), 2.7 (m, 1H), 2.49 (s, 3H), 2.45 (s, 3H). Separation by chiral HPLC provided enantiomers 20a and 20b. Optical rotations: Compound 20a, (-)-10.20 (c 0.58, Chloroform, 99.61% HPLC purity); Compound 20b, (+)-10.00 (c 0.59, Chloroform, 96.54% HPLC purity).
Example 21: Preparation of Compound Nos. 21, 21a and 21b

[0670] 2-(8-Methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5 (2H)-yl)-1-(pyridin-3-yl) ethanol (1.6 g) was dissolved in acetone (40 mL) followed by the addition of potassium carbonate (2.16 g) and 2-bromoethanol (1.29 g). The reaction mixture was heated at 80 °C for 2 h. The reaction was monitored by TLC and LCMS. The reaction mixture was cooled to RT and evaporated under reduced pressure. The residue was diluted with water and extracted with DCM, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to obtain crude product. The crude product was purified by reverse phase column chromatography to obtain desired product. 1H NMR (CDCl3, freebase) δ (ppm): 8.33 (d, 1H), 8.24 (s, 1H), 7.56 (d, 1H), 7.16 (m, 2H), 7.11 (s, 1H), 6.99 (d, 1H), 4.82 (dd, 1H), 4.03 (dd, 1H), 3.98 (dd, 1H), 3.75 (d, 1H), 3.70 (m, 2H), 3.64 (d, 1H), 2.90 (m, 3H), 2.74 (m, 2H), 2.5 (dd, 1H), 2.44 (s, 3H). Separation by chiral HPLC provided enantiomers 21a and 21b. Optical rotations: Compound 21a, (-)-12.41 (c 0.56, Chloroform, 97.75% HPLC purity); Compound 21b, (+)-12.71 (c 0.56, Chloroform, 97.37% HPLC purity).

Example 22: Preparation of Compound Nos. 22, 22a and 22b

[0671] Sodium hydride (54 mg, 2.2 mmol) was dissolved in N,N-dimethylformamide (7.5 mL) and stirred for 10 min. 2,6-Dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (150 mg, 0.75 mmol) was added to the solution and stirred for 10 min, followed by addition of 2-(oxiran-2-yl)pyridine (133 mg, 1.1 mmol) and stirred overnight at RT. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice water, extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by reverse phase chromatography to get pure title compound as the TFA salt (27 mg). 1H NMR (DMSO) δ (ppm): 10.30-10.10 (m, 1H), 8.70-8.55 (m, 1H), 7.95-7.50 (m, 2H), 7.45-7.05 (m, 2H), 7.00-6.75 (m, 2H), 4.95-4.70 (m, 1H), 4.60-4.40 (m, 2H), 4.20-3.60 (m, 4H), 3.55-3.35 (m, 2H), 3.00 (s, 3H), 2.38 (s, 3H). Separation by chiral HPLC provided enantiomers 22a and 22b. Optical rotations: Compound 22a, (-)-58.57 (c 0.57, Chloroform, 98.5% HPLC purity); Compound 22b, (+)-31.73 (c 0.52, Chloroform, 96.24% HPLC purity).

Example 23: Preparation of Compound Nos. 23, 23a and 23b

[0672] To a stirred solution of 2-(2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4, 3-b]indol-8-yl) propan-2-ol (942 mg, 3.86 mmol) in DMF (5 mL) was added sodium hydride (60%, 464 mg, 11.58 mmol). After stirring for 10 min, the reaction mixture was cooled to 0 °C and a solution
of 4-(oxiran-2-yl) pyridine (700 mg, 5.8 mmol) in DMF (2 mL) was added. The reaction mixture was allowed to warm to RT and stirring was continued for 16 h. The progress of reaction was monitored by LCMS and NMR. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was crystallized from ether to yield 2-(2,3,4,5-tetrahydro-5-(2-hydroxy-2-(pyridin-4-yl) ethyl)-2-methyl-1H-pyrido[4, 3-b]indol-8-yl) propan-2-ol (500 mg) as yellow solid. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.37 (d, 2H), 7.36 (s, 1H), 7.20 (d, 1H), 7.11 (d, 2H), 7.04 (d, 1H), 4.82 (t, 1H), 4.05 (d, 2H), 3.49 (d, 1H), 3.4 (d, 1H), 2.9 (m, 1H), 2.85 (m, 1H), 2.64 (m, 2H), 2.40 (s, 3H), 1.65 (s, 6H). Separation by chiral HPLC provided enantiomers 23a and 23b. Optical rotations: Compound 23a, (-)52.54 (c 0.55, Chloroform, 95.4% HPLC purity); Compound 23b, (+)29.08 (c 0.56, Chloroform, 98.94% HPLC purity).

**Example 24: Preparation of Compound Nos. 24, 24a and 24b**

To a solution of carboline (320 mg, 1.49 mmol) in DMF (4 mL) was added sodium hydride (169 mg, 4.23 mmol). After stirring for 5 min, a solution of 3-(2-methyloxiran-2-yl) pyridine (285 mg, 2.11 mmol) in DMF was added to the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, concentrated and residue obtained was submitted for reverse phase HPLC purification. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.72 (s, 1H), 8.52 (d, 1H), 7.69 (d, 1H), 7.21 (m, 3H), 6.95 (d, 1H), 4.21 (q, 2H), 4.00 (s, 2H), 3.11 (t, 2H), 2.48 (m, 2H), 2.43 (s, 3H), 1.65 (s, 3H). Separation by chiral HPLC provided enantiomers 24a and 24b. Optical rotations: Compound 24a, (+)25.89 (c 0.58, Chloroform, 96.39% HPLC purity); Compound 24b, (-)26.65 (c 0.56, Chloroform, 93.46% HPLC purity).

**Example 25: Preparation of Compound Nos. 25, 25a and 25b**

To an ice-cooled stirred solution of the Boc protected ester (75 mg) in DCM (1 mL) was added cold 20% TFA-DCM solution (5 mL). After stirring for 30 min at 0 °C, the reaction mixture was stirred at RT for 2 h. The solvent was removed under reduced pressure to yield title compound as the TFA salt. HPLC provided enantiomers 25a and 25b. Compound No. 25a: $^1$H NMR (CD$_2$OD, Di-TFA salt) δ (ppm): 8.74 (t, 2H), 7.84 (t, 2H), 7.29 (s, 1H), 7.03 (t, 1H), 6.4 (m, 1H), 4.66 (m, 3H), 4.32 (d, 1H), 3.98 (m, 2H), 3.5 (m, 1H), 3.2 (m, 1H), 3.11 (s, 3H), 3.06 (m, 1H), 2.4 (s, 3H), 2.38 (m, 1H), 0.95 (d, 3H), 0.91 (d,3H). Compound No. 25b: $^1$H NMR (CD$_2$OD, Di-TFA salt) δ (ppm): 8.806 (d, 2H), 8.05 (t, 2H), 7.63 (t, 1H), 7.03 (d, 1H), 6.35 (s,
Example 26: Preparation of Compound Nos. 26, 26a, 26b, 26c and 26d

To a stirred solution of 6-aza-8-methyl tetracyclic carboline (320 mg, 1.4 mmol) in DMF (4 mL) was added sodium hydride (169 mg, 4.2 mmol). After stirring for 5 min, a solution of 3-(2-methyloxiran-2-yl) pyridine (285 mg, 2.14 mmol) in DMF (1 mL) was added and the reaction mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield title compound (574 mg). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.64 (s, 1H), 8.42 (d, 1H), 8.03 (s, 1H), 7.7 (d, 1H), 7.53 (s, 1H), 7.14 (dd, 1H), 4.45 (d, 1H), 4.26 (d, 2H), 4.14 (t, 1H), 3.25 (d, 1H), 3.01 (m, 1H), 2.84 (m, 1H), 2.63 (q, 1H), 2.46 (m, 2H), 2.42 (s, 3H), 2.34 (m, 1H), 1.85 (m, 2H), 1.68 (m, 1H), 1.64 (s, 3H). Separation by chiral HPLC provided enantiomers 26a, 26b 26c and 26d.

Example 27: Preparation of Compound Nos. 27, 27a and 27b

To a solution of 5-(2-azido-2-(pyridin-4-yl) ethyl)-2,3,4,5-tetrahydro-2, 8-dimethyl-1H-pyrido[4, 3-b]indole (2.4 g, 6.93 mmol) in EtOH-water (25-2.5 mL) were added zinc dust (1.8 g, 27.7 mmol) and ammonium chloride (1.5 g, 27.74 mmol) and the reaction mixture stirred at 80 °C for 45 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was basified with aq. ammonia and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and evaporated to yield 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl) ethanamine (1.2 g). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.56 (d, 2H), 7.28 (d, 2H), 7.21 (m, 2H), 7.00 (d, 1H), 4.48 (t, 1H), 4.08 (m, 2H), 3.65 (q, 2H), 2.83 (m, 2H), 2.72 (m, 1H), 2.56 (m, 1H), 2.53 (s, 3H), 2.44 (s, 3H). Separation by chiral HPLC provided enantiomers 27a and 27b.

Example 28: Preparation of Compound Nos. 28, 28a and 28b

To a stirred solution of 6-chloro-2,3,4,9-tetrahydro-2-methyl-1H-pyrido[3,4-b]indole (550 mg, 2.5 mmol) in DMF (5 mL) was added sodium hydride (300 mg, 7.5 mmol). After stirring for 5 min, a solution of 3-(2-methyloxiran-2-yl) pyridine (506 mg, 3.75 mmol) in DMF (1 mL) was added and the reaction mixture stirred at RT for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under
reduced pressure. The solid was crystallized from ether to yield the title compound (300 mg). \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 8.68 (s, 1H), 8.49 (d, 1H), 7.54 (d, 1H), 7.32 (s, 1H), 7.0 (t, 1H), 6.94 (s, 1H), 4.10 (d, 1H), 4.04 (d, 1H), 3.59 (d, 1H), 3.34 (d, 1H), 2.65 (m, 4H), 2.42 (s, 3H), 1.63 (s, 3H). Separation by chiral HPLC provided enantiomers 28a and 28b. Optical rotations: Compound 28a, (+)26.78 (c 0.54, Chloroform, 98.11% HPLC purity); Compound 28b, (-)20.39 (c 0.59, Chloroform, 93.42% HPLC purity).

Example 29: Preparation of Compound Nos. 29, 29a and 29b

[0678] A mixture of compound 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (1.5 g, 7.5 mmol, 1 equiv.) and NaH (252 mg, 10.5 mmol, 1.4 equiv.) in DMF (30 mL) were heated to 120 °C for 1 h. The reaction mixture was cooled to RT and 2-methyl-5-(2-methyloxiran-2-yl)pyridine (2.46 g, 16.5 mmol, 2.2 equiv.) in DMF (17 mL) was added dropwise over 12 min. The temperature was again raised to 120 °C and stirred for 3 h. The reaction mixture was cooled to RT and water (5 mL) was added, diluted with EtOAc (700 mL) and the organic layer was washed with water (3x100 mL) and then with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The compound was purified by column chromatography over 230-400 mesh silica gel using a gradient of 10-20% MeOH in EtOAc. Yield: 2.3 g (87%). \(^1\)H NMR (DMSO-d6, oxalate salt) \(\delta\) (ppm): 8.52 (bs, 1H), 7.73-7.71 (d, 1H), 7.31-7.29 (d, 1H), 7.17-7.15 (m, 2H), 6.88-6.86 (d, 1H), 4.34 (bs, 2H), 4.24-4.40 (dd, 2H), 3.47 (bs, 2H), 2.98 (bs, 2H), 2.91 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H), 1.48 (s, 3H). Separation by chiral HPLC provided enantiomers 29a and 29b.

Example 30: Preparation of Compound Nos. 30, 30a and 30b

[0679] Activated magnesium turnings (480 mg, 20 g/atom) and 2-3 crystals of iodine were stirred under anhydrous conditions. The excess of iodine was removed by heating with a heat gun. The magnesium turnings were now yellow in color. To this was added diethyl ether (15 mL) at 0 °C and stirred for 15 min. (until the color of the magnesium becomes white). To this was added cyclopentyl bromide (480 mg, 20 g/atom) dropwise with constant stirring. The reaction mixture was stirred until a dark grey-colored solution was obtained. Into a separate flask was placed the starting material 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (168 mg, 5 mmol) in THF under anhydrous conditions. The solution of the prepared cyclopentylmagnesium bromide (5 mL) was added dropwise. After addition, the mixture was allowed to come to RT and stirred at RT for 2 h. The reaction was monitored by TLC and NMR. The reaction was quenched with ice water and the product extracted into
EtOAc. The organic extracts were concentrated and the residue purified by silica gel column chromatography (#100-200 mesh) using 0-3% MeOH:DCM as eluent. (Note: The desired compound was not formed but reduction of keto group occurred to yield the hydroxy compound). $^1$H NMR (DMSO-d$_6$, oxalate salt) δ (ppm): 7.55 (m, 3H), 7.18 (m, 3H), 6.95 (d, 1H), 4.85 (s, 1H), 4.30 (m, 2H), 4.15 (m, 2H), 3.60 (m, 2H), 3.10 (m, 3H), 2.90 (s, 3H), 2.40 (s, 3H). Separation by chiral HPLC provided enantiomers 30a and 30b.

**Example 31: Preparation of Compound Nos. 31, 31a and 31b**

Sodium hydride (1-3 equiv.) was added to a solution of 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.0 equiv.) in DMF, and heated to 120 °C for 1 h with stirring. The reaction mixture was cooled to 0 °C and 3-(2-methyloxiran-2-yl)pyridine (2-7.5 equiv.) was added dropwise over 5 min. The temperature was raised to 120 °C and stirred for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and followed by brine, dried over anhydrous sodium sulfate and concentrated under vacuum to provide the crude product. The product was purified by flash column chromatography over silica gel (230-400 mesh, deactivated with 1% triethylamine/hexane) using a gradient of 5 to 15% MeOH/EtOAc to yield the free base. The pure compound was converted to its oxalate salt. The analytical sample was prepared by dissolving free base in THF and treatment with 1 equiv. of oxalic acid dihydrate. $^1$H NMR (CD$_3$OD, oxalate salt) δ (ppm): 8.43 (s, 1H), 8.34 (d, 1H), 7.87 (d, 1H), 7.37 (s, 1H), 7.30 (m, 1H), 6.97 (m, 1H), 6.93 (d, 1H), 4.48 (m, 2H), 4.32 (m, 2H), 3.71 (m, 2H), 3.12 (s, 3H), 2.81 (m, 2H), 1.70 (s, 3H). Separation by chiral HPLC provided enantiomers 31a and 31b.

**Example 32: Preparation of Compound Nos. 32, 32a and 32b**

8-flask was charged with 6-chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 4.5 mmol) in DMF (10 mL) and stirred for 5 min. To this was added NaH (60% in hexane) (220 mg, 6.8 mmol) and stirred at RT for 10 min., followed by 4-(2-methyloxiran-2-yl)pyridine (1.08 g, 9 mmol) and stirred at RT for 16 h. The progress of reaction was monitored by TLC. The mixture was poured into ice water and filtered. The filtrate was washed with water and concentrated. The residue was recrystallized from ether to get pure product. $^1$H NMR (DMSO-d$_6$, HCl salt) δ (ppm): 8.70 (d, 2H), 7.90 (d, 2H), 7.40 (m, 1H), 7.0 (m, 2H), 6.0 (m, 1H), 4.80 (m, 1H), 4.60 (m, 2H), 4.25 (m, 2H), 3.80 (m, 2H), 2.90 (s, 3H), 1.60 (s, 3H). Separation by chiral HPLC provided enantiomers 32a and 32b.
Example 33: Preparation of Compound Nos. 33, 33a and 33b

[0682] 8-Chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1.3 g, 5 mmol) was dissolved in DMF (10 mL) and stirred for 5 min. Sodium hydride (709 mg, 17.7 mmol) was then added to it portionwise under nitrogen. This was followed by addition of 2-butyl-2-(4-fluorophenyl)oxirane (3.4 g, 17.7 mmol) at RT and the reaction mixture was stirred for 18 h. After completion of reaction, the reaction mixture was poured into ice water and the product extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product which was purified by silica gel (#100-200 mesh) column chromatography using 1% MeOH in DCM as eluent. The pure compound was converted into the oxalate salt. $^1$HNMR (CDCl$_3$, Oxalate salt) $\delta$ (ppm): 7.30 (m, 3H), 7.10 (d, 1H), 6.95 (m, 3H), 4.20 (m, 1H), 4.0 (m, 1H), 3.62 (m, 2H), 2.70 (m, 3H), 2.50 (s, 3H), 2.20 (m, 1H), 2.0 (m, 1H), 1.80 (m, 1H), 1.22 (m, 3H), 1.0 (m, 1H), 0.80 (t, 3H). Separation by chiral HPLC provided enantiomers 33a and 33b.

Example 34: Preparation of Compound Nos. 34, 34a and 34b

[0683] 2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethanone (168 mg, 5 mmol) was dissolved in 10 mL anhydrous THF. Ethyl magnesium bromide (1.5 mL, 0.0015 mol) was then added dropwise at RT under nitrogen. The reaction mixture was stirred at RT for 2 h. The reaction was monitored by LCMS. On completion of the reaction, water (3 mL) was added to the reaction mixture and the product extracted with EtOAc (3x). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and the solvent evaporated under reduced pressure to obtain the crude product, which was purified by HPLC. The pure compound was isolated as the TFA salt. $^1$HNMR (CD$_3$OD, TFA salt) $\delta$ (ppm): 7.38 (m, 2H), 7.18 (d, 1H), 7.10 (m, 1H), 7.0 (m, 2H), 6.85 (d, 1H), 4.60 (m, 1H), 4.30 (m, 2H), 3.75 (m, 1H), 3.42 (m, 1H), 3.10 (s, 3H), 2.90 (m, 2H), 2.42 (d, 1H), 2.38 (s, 3H), 2.20 (m, 1H), 1.80 (m, 2H), 0.8 (t, 3H). Separation by chiral HPLC provided enantiomers 34a and 34b.

Example 35: Preparation of Compound Nos. 35, 35a and 35b

[0684] A flask was charged with sodium hydride (0.640 g, 50-60%) in dry DMF (10 mL) at 0 °C and to this was added 2,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole (0.8 g). The mixture was stirred at RT for 30 min and then 4-(2-ethylxiran-2-yl)pyridine (0.834g) dissolved in DMF (2 mL) was added, which was stirred at RT for 12 h. The reaction mixture was diluted with ice-water and extracted with EtOAc (3x30 mL). The combined organic layers
were washed with brine, dried over anhydrous sodium sulfate and evaporated. The crude product was triturated with diethyl ether to obtain the desired compound. $^1$H NMR (DMSO, Oxalate salt) $\delta$ (ppm): 8.45 (d, 2H), 7.42 (d, 2H), 7.30 (d, 1H), 7.10 (s, 1H), 6.82 (d, 1H), 4.30 (d, 1H), 4.18 (d, 1H), 3.60 (s, 2H), 3.50 (m, 2H), 3.38 (m, 1H), 3.0 (m, 2H), 2.90 (s, 3H), 3.32 (s, 3H), 2.10 (m, 1H), 0.6 (t, 3H). Separation by chiral HPLC provided enantiomers 35a and 35b.

**Example 36: Preparation of Compound Nos. 36, 36a-36d**

[0685] To a solution of 1-ethyl-7-methyl-3,4,5,10-tetrahydro-1H-2,5-methanoazepino[3,4-b]indole (1000 mg, 4.17 mmol) in DMF (10 mL) was added sodium hydride (500 mg, 12.498 mmol) portionwise. After stirring at RT for 5 min, 4-(oxiran-2-yl)pyridine (630 mg, 5.00 mmol) was added dropwise into the reaction mixture, which was stirred at RT overnight. The reaction mixture was quenched with ice-water and the solid mass was filtered. The residue was washed with water (2x10 mL), hexane (2x50 mL) and purified by reverse phase HPLC to yield the title compound. Separation by chiral HPLC provided enantiomers 36a and 36b.

**Example 37: Preparation of Compound Nos. 37, 37a, 37c and 37d**

[0686] To a solution of 2,3,4,9,10,10a-hexahydro-1H-3a, 8, 9-triaza-cyclopenta[b]fluorene (1 g, 0.0046 mol) in DMF (20 mL) was added NaH (60%, 0.552 g, 0.0138 mol) portionwise followed by 4-(oxiran-2-yl) pyridine (0.709 g, 0.0056 mol). The reaction mixture was stirred at RT overnight. The progress of reaction mixture was monitored by LCMS. The reaction mixture was quenched with ice cold water (300 mL) and extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (10x100 mL) followed by brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography followed by reverse phase HPLC to obtain the desired compound. $^1$H NMR (CDCl$_3$, freebase) $\delta$ (ppm): 8.56 (d, 2H), 8.21 (d, 1H), 7.74 (d, 1H), 7.32 (d, 2H), 7.06 (dd, 1H), 5.16 (dd, 1H), 4.44 (dd, 1H), 4.31 (dd, 1H), 4.2 (d, 1H), 3.32 (m, 2H), 2.85 (d, 1H), 2.5 (m, 1H), 2.39 (q, 2H), 2.11 (m, 1H), 1.93 (m, 2H). Separation by chiral HPLC provided enantiomers 37a, 37b, 37c and 37d.

**Example 38: Preparation of Compound Nos. 38, 38a-38h**

[0687] To a solution of 1,7-dimethyl-3,4,5,10-tetrahydro-1H-2,5-methanoazepino[3,4-b]indole (1 g, 4.42 mmol) in DMF (10 mL) was added sodium hydride (530 mg,13.24 mmol) portionwise under nitrogen. After stirring for 10 min at 0 °C, 4-oxiranyl-pyridine (1.07 g, 8.84 mmol) was added dropwise at 0 °C into the reaction mixture and stirring continued for 12 h at RT. After completion, the reaction mixture was poured into ice water and extracted with EtOAc (2x100
mL). The combined organic layers were washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated to obtain 1.2 g of product. \(^1\)H NMR (CD\(_2\)OD, Formate salt) \(\delta\) (ppm): 8.42 (d, 2H), 7.8 (d, 2H), 7.22 (s, 1H), 6.78 (t, 2H), 5.67 (q, 1H), 5.4 (m, 1H), 4.77 (dd, 1H), 4.4 (dd, 1H), 3.82 (d, 1H), 3.7-3.8 (m, 3H), 3.6 (d, 1H), 2.4 (m, 1H), 2.3 (s, 3H), 2.18 (m, 1H), 1.97 (d, 3H). Separation by chiral HPLC provided enantiomers 38a and 38b.

**Example 39: Preparation of Compound Nos. 39, 39a and 39b**

2-(2-allyl-8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (740mg, 2.132 mmol) was dissolved in 40 mL DCM, and purged with nitrogen for 5 min. Pd(PPh\(_3\))\(_4\) (50 mg, 0.0432 mmol) and 1,3-dimethylbarbituric acid (998 mg, 6.397 mmol) were added and the reaction mixture was stirred at RT for 30 min. The reaction mixture was diluted with saturated aqueous potassium carbonate (20 mL) solution and extracted with DCM (2x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography over neutral alumina (eluent 50 % MeOH in DCM) to obtain 400 mg of 2-(8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. \(^1\)H NMR (CD\(_2\)OD, freebase) \(\delta\) (ppm) : 8.71 (d, 2H), 8.04 (d, 2H), 7.22 (s, 1H), 7.13 (d, 1H), 6.94 (d, 1H), 5.33 (t, 1H), 4.42 (m, 4H), 3.63 (t, 2H), 3.28 d (t, 1H), 3.22 (m 1H), 2.38 (s, 3H). This racemate was separated by chiral semi-preparative HPLC to obtain enantiomers 39a and 39b.

**Example 40: Preparation of Compound Nos. 40, 40a and 40b**

To a solution of 2-methyl-7-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1H-pyrido[4, 3-b]indole (500 mg, 1.96 mmol) in DMF (5 mL) was added sodium hydride (60%, 236 mg, 5.9 mmol) at RT under N\(_2\). After stirring for 10 min, a solution of 3-(oxiran-2-yl) pyridine (356 mg, 2.9 mmol) in DMF (1 mL) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC, LCMS and NMR. After completion, the reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to obtain the desired compounds 40a and 40b.

**Example 41: Preparation of Compound Nos. 41, 41a and 41b**

To a solution of 6-chloro-2-methyl-2, 3, 4, 9-tetrahydro-1H-pyrido[3, 4-b]indole (1.0 g, 4.55 mmol) in DMF (20 mL), sodium hydride (546 mg, 13.65 mmol) was added and the suspension stirred at RT for 10 min. A solution of 4-(oxiran-2-yl) pyridine (1.10 g, 9.1 mmol) in
DMF (5 mL) was added slowly into the reaction mixture, which was stirred at RT overnight. The progress of reaction was monitored by TLC and LCMS. The reaction mass was poured into ice cold water (200 mL) slowly and extracted with EtOAc (3x200 mL). The organic layer was washed with water (4x300 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography using 7% MeOH-DCM as eluent. The residue obtain was triturated with diethyl ether (20 mL) to yield the desired product. \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 8.42-8.58 (d, 2H), 7.4 (s, 1H), 7.26 (d, 2H), 7.15 (d, 1H), 7.11 (d, 1H), 4.9 (dd, 1H), 4.08 (dd, 1H), 4.04 (dd, 1H), 3.73 (d, 1H), 3.48 (s, 1H), 3.3 (d, 1H), 2.69 (m, 1H), 2.68 (m, 3H), 2.45 (s, 3H). Separation by chiral HPLC provided enantiomers 41a and 41b.

Example 42: Preparation of Compound Nos. 42, 42a and 42b

**[0691]** 1-(2-Allyl-8-chloro-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-2-pyrimidin-4-yl-propan-2-ol (300 mg, 0.785 mmol) was dissolved in DCM (6 mL) and \(N_2\) was purged for 5 min into the reaction mixture. 1,3-Dimethylbarbituricacid (367 mg, 2.356 mmol) and Pd(PPh\(_3\))\(_4\) (18mg, 0.0157 mmol) was added and the mixture stirred for 1 h at RT. After consumption of starting material, the reaction mixture was diluted with saturated potassium carbonate (50 mL) and extracted with DCM (2x40 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated, crude was purified by reverse phase chromatography to obtain 97 mg of 1-(8-chloro-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyrimidin-4-yl-propan-2-ol. \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 9.13 (s, 1H), 8.45 (d, 1H), 7.31 (d, 1H), 7.25 (s, 1H), 6.94 (s, 2H), 4.3 (q, 2H), 3.93 (q, 2H), 3.13 (m, 2H), 2.78 (d, 1H), 2.57 (d, 1H), 1.6 (s, 3H). Separation by chiral HPLC provided enantiomers 42a and 42b.

Example 43: Preparation of Compound Nos. 43, 43a and 43b

**[0692]** To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1 g, 5 mmol) in 10 mL DMF, was added sodium hydride (600 mg, 15 mmol) portionwise under nitrogen at 0 °C and stirred for 10 min. 3-Oxiranyl-pyridine (908 mg, 15.0 mmol) was added dropwise under nitrogen and the reaction mixture stirred at RT for 12 h. After the complete conversion of starting material (TLC and LCMS), the reaction mixture was poured in ice-cold water and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate, and concentrated. The crude mixture was purified by reverse phase chromatography to obtain 290 mg of 2-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-1-pyridin-3-yl-ethanol. \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 8.62 (s, 1H), 8.57 (d,
1H), 7.67 (d, 1H), 7.3 (m, 2H), 7.19 (d, 1H), 7.01 (d, 1H), 5.09 (t, 1H), 4.13 (m, 2H), 3.70 (d, 1H), 3.36 (d, 1H), 2.79 (m, 3H), 2.703 (m, 1H), 2.5 (s, 3H), 2.45 (s, 3H). Separation by chiral HPLC provided enantiomers 43a and 43b.

Example 44: Preparation of Compound Nos. 44, 44a and 44b

Sodium hydride (60%) (555 mg, 13.88 mmol) was added portionwise to a solution of 6-methoxy-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4, 3-b]indole (1.0 g, 4.629 mmol) in DMF (10 mL) and stirred at RT for 15 min, the suspension was allowed to cool at 0 °C. 4-(Oxiran-2-yl) pyridine (896 mg, 7.407 mmol) was added dropwise and reaction mixture was stirred at RT for 48 h. The reaction mixture was poured in to ice-cooled water and extracted with EtOAc (3x50 mL), and the organic layer was washed with water (2x50mL), dried over anhydrous sodium sulfate and concentrated in vacuo, afforded crude was purified by reverse phase HPLC to afford 2-(6-methoxy-2-methyl-3,4-dihydro-1H-pyrido[4, 3-b]indol-5(2H)-yl)-1-(pyridin-4-yl) ethanol (165 mg) as the formate salt. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.60 (d, 2H), 7.31 (d, 2H), 7.02 (m, 2H), 6.66 (d, 1H), 5.08 (dd, 1H), 4.66 (dd, 1H), 4.12 (dd, 1H), 3.99 (s, 3H), 3.60 (d, 1H), 3.56 (d, 1H), 2.9 (m, 1H), 2.81 (m, 1H), 2.72 (m, 1H), 2.64 (m, 1H), 2.55 (s, 3H). Separation by chiral HPLC provided enantiomers 44a and 44b.

Example 45: Preparation of Compound Nos. 45, 45a and 45b

To a stirred solution of 6-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4, 3-b]indole (1 g, 4.54 mmol) in DMF (8 mL) was added sodium hydride (60%, 545 mg, 13.6 mmol). After stirring for 10 min, a solution of 4-(oxiran-2-yl) pyridine (825 mg, 6.8 mmol) in DMF (2 mL) was added into the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was poured into ice-cold water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.54 (d, 2H), 7.31 (d, 2H), 7.19 (d, 1H), 7.11 (d, 1H), 7.01 (t, 1H), 5.04 (dd, 1H), 4.81 (dd, 1H), 3.99 (dd, 1H), 3.27 (dd, 2H), 3.11 (m, 1H), 2.84 (m, 1H), 2.51 (m, 2H), 2.32 (s, 3H). Separation by chiral HPLC provided enantiomers 45a and 45b.

Example 46: Preparation of Compound Nos. 47, 47a, 47b, 47c and 47d

To a solution of 11-methyl-1,2,3,4,6,7,8,12c-octahydro-indolo[3,2-a]quinolizine (800 mg, 3.33 mmol) in 12 mL DMF was added sodium hydride (400 mg, 13.2 mmol) under nitrogen at RT and stirred for 20 min. 4-Oxiranyl-pyridine (685 mg, 5.66mmol) was added dropwise under nitrogen and the reaction mixture stirred at RT for 18 h. After complete conversion of starting material (TLC and LCMS), the reaction mixture was poured in ice-cold water and
extracted with EtOAc (3x80 mL). The combined organic layer was washed with water (5x50mL), dried over anhydrous sodium sulfate, concentrated and the crude product was recrystallized in EtOH (1 mL) and ether (50 mL) to obtain 700 mg of desired product. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.53 (d, 2H), 7.36 (s, 1H), 7.21 (d, 2H), 7.12 (d, 1H), 6.94 (d, 1H), 4.99 (t, 1H), 4.1 (m, 2H), 3.35 (d, 1H), 3.13 (t, 1H), 3.0 (m, 2H), 2.63 (d, 1H), 2.56 (m, 1H), 2.46 (s, 3H), 2.4 (d, 1H), 1.8 (d, 1H), 1.7 (m, 1H), 1.5 (m, 2H). Separation by chiral HPLC provided enantiomers 47a 47b, 47c and 47d.

**Example 47: Preparation of Compound Nos. 48, 48a and 48b**

To a stirred solution of 6-bromo-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (1 g, 3.77 mmol) in DMF (8 mL) was added sodium hydride (60%, 452 mg, 11.32 mmol). After stirring for 10 min, a solution of 4-(oxiran-2-yl) pyridine (684 mg, 5.66 mmol) in DMF (2 mL) was added into the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was poured into ice-cold water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in DCM and pure product precipitated out as a white solid. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.57 (d, 2H), 7.36 (d, 2H), 7.33 (d, 1H), 7.27 (d, 1H), 6.95 (t, 1H), 5.17 (dd, 1H), 4.96 (dd, 1H), 4.04 (dd, 1H), 3.34 (dd, 2H), 3.1 (m, 1H), 2.85 (m, 1H), 2.55 (m, 2H), 2.38 (s, 3H). Separation by chiral HPLC provided enantiomers 48a and 48b.

**Example 48: Preparation of Compound Nos. 49, 49a and 49b**

To a stirred solution of 1-(2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indol-8-yl) ethanone (80 mg, 0.35 mmol) in DMF (2 mL) was added sodium hydride (60%, 42 mg, 1.05 mmol). After stirring for 10 min, a solution of 4-(oxiran-2-yl) pyridine (62 mg, 0.51 mmol) in DMF (1 mL) was added into the reaction mixture, and stirred at RT for 4 h. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtain was purified by crystallization with ether to yield 1-(2,3,4,5-tetrahydro-5-(2-hydroxy-2-(pyridin-4-yl)ethyl)-2-methyl-1H-pyrido[4, 3-b]indol-8-yl) ethanone (6 mg). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.5 (d, 2H), 7.95 (s, 1H), 7.73 (d, 1H), 7.26 (d, 2H), 7.12 (d, 1H), 4.78 (t, 1H), 4.8 (d, 2H), 3.49 (m, 2H), 2.90 (m, 1H), 2.8 (q, 2H), 2.79 (s, 3H), 2.6 (m, 1H), 2.37 (s, 3H). Separation by chiral HPLC provided enantiomers 49a and 49b.

**Example 49: Preparation of Compound Nos. 51, 51a and 51b**
2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 5.0 mmol) was dissolved in DMF (8 mL). Sodium hydride (600 mg, 15 mmol) was added portionwise under nitrogen at 0 °C. 2-Methoxy-5-oxiranyl-pyridine (1.130 g, 7.5 mmol) was diluted in DMF (2 mL) and was added dropwise under nitrogen atmosphere and the reaction mixture stirred at RT for 3 h. By monitoring TLC & NMR after consumption of starting material, the reaction mixture was then quenched with ice water and extracted with EtOAc (3×40 mL). The combined organic layer was washed with water (4×30 mL) and dried over anhydrous sodium sulfate and concentrated to obtain 1.0 g of 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-(6-methoxy-pyridin-3-yl)-ethanol. 1H NMR (CDCl₃, freebase) δ (ppm): 8.11 (s, 1H), 7.55 (d, 1H), 7.18 (s, 1H), 7.16 (d, 1H), 6.98 (d, 1H), 6.72 (s, 1H), 4.98 (t, 1H), 4.11 (m, 2H), 3.93 (s, 3H), 3.60 (q, 2H), 2.88 (d, 1H), 2.78 (m, 2H), 2.69 (d, 1H), 2.51 (s, 3H), 2.44 (s, 3H).

Separation by chiral HPLC provided enantiomers 51a and 51b.

Example 50: Preparation of Compound Nos. 52, 52a and 52b

To a stirred solution of 2,3,4,5-tetrahydro-2, 8-dimethyl-1H-pyrido[4,3-b]indole (250 mg, 1.25 mmol) in DMF (5 mL) was added sodium hydride (60%, 150 mg, 3.75 mmol). After stirring for 10 min, a solution of ethyl 4-(oxiran-2-yl) benzoate (480 mg, 2.5 mmol) in DMF (1 mL) was added to the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, evaporated and residue was purified by reverse phase HPLC. 1H NMR (CDCl₃, freebase) δ (ppm): 7.28 (m, 4H), 7.12 (s, 1H), 7.04 (d, 1H), 6.88 (d, 1H), 4.91 (t, 1H), 4.09 (d, 2H), 3.58 (q, 2H), 3.1 (s, 3H), 2.92 (s, 3H), 2.87 (m, 1H), 2.80 (m, 2H), 2.68 (d, 1H), 2.47 (s, 3H), 2.41 (s, 3H). Separation by chiral HPLC provided enantiomers 52a and 52b.

Example 51: Preparation of Compound Nos. 53, 53a and 53b

To a stirred solution of 7-chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.5 g, 2.265 mmol) in anhydrous DMF was added sodium hydride (271 mg, 3 eq.) portionwise followed by 4-(oxiran-2-yl) pyridine (548 mg, 4.5 mmol) at RT. The reaction mixture was stirred for 12 h. The reaction mixture was quenched with ice water and extracted with EtOAc, the organic layer washed with water, dried on anhydrous sodium sulfate, concentrated under vacuum to obtain crude product that was triturated with diethyl ether to obtain 2-(7-chloro-2-methyl-3, 4-dihydro-1H-pyrido[4, 3-b]indol-5 (2H)-yl)-1-(pyridin-4-yl) ethanol as solid. 1H NMR (CDCl₃, freebase) δ (ppm): 8.53 (d, 2H), 7.2 (m, 3H), 7.14 (d, 1H), 7.05 (d, 1H), 4.82 (t,
1H), 4.03 (d, 2H), 3.4 (q, 2H), 2.85 (m, 1H), 2.76 (m, 1H), 2.64 (m, 2H), 2.37(s, 3H).
Separation by chiral HPLC provided enantiomers 53a and 53b.

**Example 52: Preparation of Compound Nos. 54, 54a and 54b**

To a solution of 2-(1,2,3,4-tetrahydro-2, 8-dimethylpyrido[4, 3-b]indol-5-yl)-1-(pyridin-4-yl) ethanol (500 mg, 1.55 mmol) and isobutyric acid (274 mg, 3.1 mmol) in DCM (100 mL) were added EDC.HCl (657 mg, 3.4 mmol), DMAP (19 mg, 0.16 mmol) and TEA (346 mg, 3.4 mmol). The reaction mixture was stirred at RT for 16 h and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4% MeOH-DCM) followed by reverse phase purification to yield 2-(1,2,3,4-tetrahydro-2, 8-dimethylpyrido[4, 3-b]indol-5-yl)-1-(pyridin-4-yl) ethyl isobutyrate (310 mg). 1H NMR (CDCl₃, freebase) δ (ppm): 8.53 (d, 2H), 7.2 (d, 1H), 7.18 (s, 1H), 7.04 (d, 2H), 6.97 (d, 1H), 5.98 (t, 1H), 4.4 (dd, 1H), 4.14 (dd, 1H), 3.64 (q, 2H), 2.73 (m, 2H), 2.6 (m, 1H), 2.49 (s, 3H), 2.43 (s, 3H), 2.37 (m, 1H), 1.15 (d, 3H), 1.09 (d, 3H). Separation by chiral HPLC provided enantiomers 54a and 54b.

**Example 53: Preparation of Compound Nos. 55, 55a and 55b**

3,6-Dimethyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene (250mg, 1.243 mmol) was dissolved in DMF (3 mL) and cooled to 0 °C. Sodium hydride (149 mg, 3.729 mmol) was added portionwise and the mixture stirred at the same temperature for 10 min. 4-Oxiranyl-pyridine (240 mg, 1.990 mmol) was diluted in DMF (1 mL) and added dropwise in the reaction mixture at 0 °C. The reaction mixture was stirred at RT for 12 h. The desired product was detected by LCMS. The reaction mixture was poured in ice cold water and extracted with EtOAc (3x25mL). The combined organic layer was washed with water (5x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography to obtain 18 mg of 2-(3,6-dimethyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluorene-9-yl)-1-pyridin-4-yl-ethanol. 1H NMR (CDCl₃, freebase) δ (ppm): 8.48 (d, 2H), 7.95 (s, 1H), 7.43 (s, 1H), 7.18 (d, 2H) 5.06 (d, 1H), 4.37 (d, 1H), 4.24 (dd, 1H), 3.45 (q, 2H), 2.29 (t, 2H), 2.55 (t, 2H), 2.45 (s, 3H), 2.38 (s, 3H). Separation by chiral HPLC provided enantiomers 55a and 55b.

**Example 54: Preparation of Compound Nos. 56, 56a and 56b**

To a solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethanol (900 mg, 4.5 mmol) in DMF (4 mL) was added sodium hydride (540 mg, 13.5 mmol). After stirring for 10 min at RT, a solution of 3-(2-methyloxiran-2-yl) pyridine-N-oxide
(1 g, 6.75 mmol) was added to the reaction mixture, and stirred at RT for 16 h. The reaction mixture was cooled to 0 °C, quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The residue was triturated with ether to yield the title compound as yellow solid (220 mg). \[^1\text{H NMR (CD}_2\text{OD, freebase) } \delta (\text{ppm}): 8.27 (s, 1H), 8.12 (d, 1H), 7.58 (d, 1H), 7.32 (t, 1H), 7.07 (s, 1H), 6.94 (d, 1H), 6.79 (d, 1H) 4.14 (q, 2H), 3.63 (s, 2H), 2.88 (m, 1H), 2.82 (s, 2H), 2.79 (m, 1H), 2.51 (s, 3H), 2.331 (s, 3H), 1.62 (s, 3H). Separation by chiral HPLC provided enantiomers 56a and 56b.

Example 55: Preparation of Compound Nos. 57, 57a and 57b

[0704] 6-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1 g, 4.5 mmol) was dissolved in 15 mL DMF and stirred for 5 min at RT. Sodium hydride (540 mg, 13.5 mmol) was added portionwise at RT under nitrogen. 3-(2-Methyl-oxiranyl)-pyridine (800 mg, 5.9 mmol) was diluted in 5 mL DMF and added dropwise at the same temperature and stirred for 16 h at RT. The reaction was monitored by TLC & LCMS. After consumption of starting material, the reaction mixture was quenched with ice water (30 mL) and filtered. The residue was crystallized in EtOH (1 mL) and ether (40 mL) and purified by reverse phase chromatography to obtain 620 mg of 6-Chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol. \[^1\text{H NMR (CDCl}_3, \text{ freebase) } \delta (\text{ppm}): 8.77 (s, 1H), 8.5 (d, 1H), 8.45 (s, 1H), 7.71 b(s, 1H), 7.17 b(s, 1H), 7.06 (d, 1H), 6.97 (t, 1H), 5.12 b(s, 1H), 4.3 b(s, 1H), 3.78 (m, 1H), 3.62 (m, 1H), 3.14 (m, 1H), 2.63 (m, 2H), 2.57 (s, 3H), 2.5 b(s, 2H), 1.53 (s, 3H). Separation by chiral HPLC provided enantiomers 57a and 57b.

Example 56: Preparation of Compound Nos. 58, 58a and 58b

[0705] To a degassed solution of 2-(6-allyl-3-methyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-1-pyridin-4-yl-ethanol (300 mg, 0.862 mmol) and 1,3 dimethyl barbituric acid (403 mg, 2.586 mmol) in DCM (7 mL) was added and Pd(PPh\textsubscript{3})\textsubscript{4} (20 mg, 0.0172 mmol) and the reaction mixture stirred at RT for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with 20% aq potassium carbonate solution and extracted with DCM (3x25 mL). The combined organic layer was washed with 20% aq potassium carbonate solution, dried over anhydrous sodium sulfate and concentrated to yield 2-(3-methyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-1-pyridin-4-yl-ethanol. \[^1\text{H NMR (CDCl}_3, \text{ freebase) } \delta (\text{ppm}): 8.5 (d, 2H), 8.03 (s, 1H), 7.51 (s, 1H), 7.22 (d, 2H) 5.14 (d, 1H), 4.4 (dd, 1H), 4.27 (dd, 1H), 3.93 (q,
2H), 3.13 (m, 2H), 2.54 (dd, 1H), 2.42 (s, 3H), 2.3 (dd, 1H). Separation by chiral HPLC provided enantiomers 58a and 58b.

Example 57: Preparation of Compound Nos. 59, 59a and 59b

[0706] To a solution of 2-methyl-8-(trifluoromethyl)-2, 3, 4, 5-tetrahydro-1H-pyrido[4, 3-b]indole (200 mg, 0.78 mmol) in DMF (3 mL) was added sodium hydride (60%, 94 mg, 2.3 mmol) at RT under N₂. After stirring for 10 min, a solution of 3-(oxiran-2-yl) pyridine (142 mg, 1.17 mmol) in DMF (1 mL) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC, LCMS and NMR. After completion, the reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to obtain the desired compounds.

59a: ¹H NMR (CDCl₃, freebase) δ (ppm): 8.51 (s, 1H), 8.35 (d, 1H), 7.51 (s, 1H), 7.42 (d, 1H), 7.32 (d, 1H), 7.21 (d, 1H), 7.07 (t, 1H), 4.94 (t, 1H), 4.20 (dd, 1H), 4.09 (dd, 1H), 3.49 (q, 2H), 2.9 (d, 1H), 2.76 (m, 3H), 2.41 (s, 3H). 59b: ¹H NMR (CDCl₃, freebase) δ (ppm): 8.51 (s, 1H), 8.35 (d, 1H), 7.51 (s, 1H), 7.42 (d, 1H), 7.32 (d, 1H), 7.21 (d, 1H), 7.07 (t, 1H), 4.94 (t, 1H), 4.20 (dd, 1H), 4.09 (dd, 1H), 3.49 (q, 2H), 2.9 (d, 1H), 2.76 (m, 3H), 2.41 (s, 3H). Separation by chiral HPLC provided enantiomers 59a and 59b. Optical rotations: Compound 59a, (-)16.42 (c 0.54, Chloroform, 99.96% HPLC purity); Compound 59b, (+)11.20 (c 0.54, Chloroform, 99.01% HPLC purity).

Example 58: Preparation of Compound No. 60

[0707] To a solution of 8-chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.2 g, 0.9 mmol) in N-methyl-2-pyrolidone (1.5 mL) was added powdered potassium hydroxide (0.507 g, 9.0 mmol). The reaction mixture was stirred for 10 min at RT. 3-Vinyl pyridine (0.3 g, 2.8 mmol) was added and the reaction mixture was stirred at 100 °C for 18 h. After consumption of starting material (TLC), the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (eluent 8% MeOH: DCM) followed by preparative TLC to obtain the desired compound as a yellow oil (0.032 g, 11% yield). ¹H NMR (DMSO, Oxalate salt) δ (ppm): 8.4 (d, 1H), 8.3 (s, 1H), 7.57 (d, 2H), 7.49 (d, 1H), 7.26 (m, 1H), 7.10 (d, 1H), 4.45 (m, 4H), 3.5 (bs, 2H), 3.0 (t, 2H), 2.95 (m, 2H), 2.90 (s, 3H).
Example 59: Preparation of Compound No. 61

To a solution of 2, 8-dimethyl-2, 3, 4, 5-tetrahydro-1H-pyrido[4, 3-b]indole (0.1 g, 0.49 mmol) in N-methyl-2-pyrrolidone (0.5 mL) was added powdered potassium hydroxide (0.274 g, 4.9 mmol) and the reaction mixture was stirred for 10 min at RT. 3-Vinyl pyridine (0.26 g, 2.49 mmol) was added and stirring was continued for further 18 h at 100 °C. After consumption of starting material (TLC), the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent 7% MeOH: DCM) followed by preparative TLC, to obtain desired compound as yellow oil (0.040 g, 26% yield). 1H NMR (DMSO, Oxalate salt) δ (ppm): 8.4 (s, 1H), 8.3 (s, 1H), 7.55 (s, 2H), 7.35 (d, 1H), 7.25 (bs, 1H), 7.2 (s, 1H), 4.35 (bs, 4H), 3.5 (bs, 2H), 3.0 (m, 2H), 2.9 (m, 5H), 2.45 (s, 3H).

Example 60: Preparation of Compound Nos. 62, 62a and 62b

Carboline (500 mg, 2.5 mmol) was dissolved in DMF (5 mL). To this solution was added NaH (60%, 180 mg, 4.5 mmol) at RT and the reaction mixture was stirred for 10-15 min. after which 3-(oxiran-2-yl)pyridine (450 mg, 3.7 mmol) was added. The reaction mixture was stirred at RT for 4 h and the reaction was monitored by LCMS. After completion, the reaction mixture was poured on ice water and extracted with EtOAc. The organic layer was dried on sodium sulfate and concentrated under reduced pressure. The residue was purified by HPLC to obtain 420 mg of product as a white solid (TFA salt). TLC (silica gel) 5:95 MeOH:DCM, Rf 0.1 was observed. 1H NMR (CD3OD, TFA salt) δ (ppm): 8.60 (d, 2H), 8.20 (bs, 1H), 7.85 (bs, 1H), 7.20 (s, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 5.2 (bs, 1H), 4.8 (d, 2H), 4.4 (m, 4H), 3.9 (bs, 1H), 3.60 (bs, 2H), 3.10 (s, 3H), 2.40 (s, 3H). Separation by chiral HPLC provides enantiomers 62a and 62b.

Example 61: Preparation of Compound Nos. 63, 63a and 63b

2-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (200 mg, 0.62 mmol) was dissolved in 10 mL DCM and m-CPBA (128 mg, 0.74 mmol) was diluted in DCM and added dropwise at RT. After consumption of starting material by monitoring TLC & LCMS reaction mixture was complete, the mixture was concentrated and the crude product was purified by reverse phase chromatography, to obtain 120 mg of 2-(2,8-dimethyl-2-oxy-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. Separation by chiral HPLC provided enantiomers 63a and 63b. 63a: 1H NMR (CD3OD, TFA salt) δ (ppm):
8.56 (d, 2H), 7.9 (t, 2H), 7.22 (s, 1H), 7.2 (d, 1H), 7.0 (d, 1H), 5.23 (dd, 1H), 5.08 (d, 1H), 5.0 (d, 1H), 4.4 (m, 2H), 4.2 (d, 2H), 3.68 (s, 3H), 3.44 (m, 1H), 3.3 (m, 1H), 2.4 (s, 3H). 63b: $^1$H NMR (CD$_3$OD, Free base) δ (ppm): 8.44 d (2H), 7.38 d (2H), 7.24 d (1H), 7.25 s (1H), 7.00 d (1H), 5.07 t (1H), 4.77 d (1H), 4.56 d (1H), 4.27 m (2H), 3.86 t (2H), 3.39 m (1H), 3.34 s (3H), 2.82 d t (1H), 2.4 s (3H).

**Example 62: Preparation of Compound Nos. 64, 64a and 64b**

[0711] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.5 mmol) was dissolved in 5 mL DMF and stirred for 10 min at RT. Sodium hydride (300 mg, 7.5 mmol) was added portionwise at 0 °C and the reaction mixture was stirred for 10 min. 2-Methoxy-5-(2-methyl-oxiranyl)-pyridine (566 mg, 3.75 mmol) was diluted in DMF (2 mL) and added dropwise at the same temperature and stirred for 12 h. After consumption of starting material, the reaction mixture was quenched with ice water and extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (7x30 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography over silica gel (eluent: 15% MeOH in DCM) and further crystallized in ether-hexane to obtain 190 mg of 1-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-(6-methoxy-pyridin-3-yl)-propan-2-ol. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.22 (s, 1H), 7.5 (d, 1H), 7.1 (s, 1H), 7.0 (d, 1H), 6.83 (d, 1H), 6.5 (d, 1H), 4.1 (m, 2H), 3.91 (s, 3H), 3.5 (m, 2H), 2.63-2.81 (m, 4H), 2.41 (s, 3H), 2.39 (s, 3H), 1.58 (s, 3H). Separation by chiral HPLC provides enantiomers 64a and 64b.

**Example 63: Preparation of Compound Nos. 65, 65a and 65b**

[0712] 10 g, 3.937 mmol) in DMF (5 mL) was added NaH (472 mg, 11.81 mmol) in portions at 0 °C. After stirring the reaction mixture at 0 °C for 15 min, a solution of 4-(oxiran-2-yl)pyridine (714 mg, 5.90 mmol) in DMF (1 mL) was dropwise added into the reaction mixture at the same temperature and stirring was continued at RT overnight. The progress of reaction was monitored by TLC, LCMS and NMR. After consumption of starting material, ice water was added into the reaction mixture and the product was extracted with EtOAc (3x50 mL). The organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography to yield 2-(2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1 g, 3.937 mmol) in DMF (5 mL) was added NaH (472 mg, 11.81 mmol) in portions at 0 °C. After stirring the reaction mixture at 0 °C for 15 min, a solution of 4-(oxiran-2-yl)pyridine (714 mg, 5.90 mmol) in DMF (1 mL) was dropwise added into the reaction mixture at the same temperature and stirring was continued at RT overnight. The progress of reaction was monitored by TLC, LCMS and NMR. After consumption of starting material, ice water was added into the reaction mixture and the product was extracted with EtOAc (3x50 mL). The organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography to yield 2-(2-methyl-7-(trifluoromethyl)-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethanol. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.54 (d, 2H), 7.5 (s, 1H), 7.37 (d, 1H), 7.3 (d, 1H), 7.18 (d,
2H), 4.78 (m, 1H), 4.17 (m, 2H), 3.5 (m, 2H), 2.8 (m, 1H), 2.7 (m, 2H), 2.63 (m, 1H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers 65a and 65b.

Example 64: Preparation of Compound Nos. 66, 66a and 66b

To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.2 g, 6.0 mmol) in 6 mL DMF, was added sodium hydride (720 mg, 12 mmol) under nitrogen at 0 °C and stirred for 5 min. 2-(3,4-Dimethoxy-phenyl)-oxirane (2.16 g, 18 mmol) was diluted in DMF (2 mL) and added dropwise to the reaction mixture under nitrogen atmosphere. The reaction mixture was stirred at RT for 5 h. After consumption of starting material (TLC and LCMS), the reaction mixture was poured in ice-cold water and extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (5x30 mL) and dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (silica gel 100-200 mesh, eluent: 6 % MeOH in DCM) to obtain 590 mg of 1-(3,4-dimethoxy-phenyl)-2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethanol. 1H NMR (CDCl3, freebase) δ (ppm): 7.19 (m, 2H), 6.0 (s, 2H), 6.83 (m, 2H), 6.78 (s, 1H), 4.98 (t, 1H), 4.1 (m, 2H), 4.83 (s, 3H), 4.8 (s, 3H), 3.6 (dd, 2H), 2.68-2.88 (m, 3H), 2.53 (m, 1H), 2.5 (s, 3H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers 66a and 66b.

Example 65: Preparation of Compound Nos. 67, 67a and 67b

To a solution of 4-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-hydroxy-ethyl]-benzoic acid ethyl ester (800 mg, 2.04 mmol) in 5 mL EtOH was added sodium hydroxide (327 mg, 8.17 mmol, in 5 mL water) and heated to 65 °C. After complete conversion of starting material (TLC and LCMS), the EtOH and water were removed under reduced pressure. The crude product was passed through HPLC to yield 600 mg of 4-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-1-hydroxy-ethyl]-benzoic acid. 1H NMR (DMSO, freebase) δ (ppm): 7.79 (d, 2H), 7.29 (s, 1H), 7.17 (d, 2H), 7.09 (s, 1H), 6.88 (d, 1H), 5.5 b(s, 1H), 4.82 (t, 1H), 4.12 (dd, 1H), 4.06 (dd, 1H), 3.44 (s, 2H), 3.16 (s, 2H), 2.71 (d, 1H), 2.56 (m, 2H), 2.36 s (7H). Separation by chiral HPLC provides enantiomers 67a and 67b.

Example 66: Preparation of Compound No. 68

To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (145 mg, 0.72 mmol) in DMF (2 mL) was added sodium hydride (87 mg, 2.1 mmol). After stirring for 10 min at RT, a solution of 4-(oxiran-2-yl) pyridine-N-oxide (149 mg, 1.08 mmol) was added into the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was cooled to 0 °C, quenched with ice water and extracted with EtOAc. The organic layer was washed with water,
dried over anhydrous sodium sulfate and evaporated. The residue was triturated with ether to yield the title compound (20 mg). \(^1\)H NMR (CDCl\(_3\), Free base) \(\delta\) (ppm): 8.2 (d, 2H), 7.71 (d, 2H), 7.25 (d, 1H), 6.99 (s, 2H), 5.22 (s, 2H), 3.64 (s, 2H), 2.85 (t, 2H), 2.7 (t, 2H), 2.56 (s, 3H), 2.42 (s, 3H).

Example 67: Preparation of Compound Nos. 69, 69a and 69b

[0716] To a solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4, 3-b]indol-5-yl)-1-(pyridin-4-yl) ethanol (450 mg, 2.25 mmol) in DMF (2 mL) was added sodium hydride (270 mg, 6.75 mmol). After stirring for 10 min at RT, a solution of 4-(oxiran-2-yl) pyridine-N-oxide (462 mg, 3.37 mmol) was added into the reaction mixture, and stirred at RT for 16 h. The reaction mixture was cooled to 0 °C, quenched with ice water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The aqueous layer was also lyophilized to get crude product, which was submitted for reverse phase HPLC purification. (The organic layer had the keto compound, and the aqueous layer had the hydroxy compound). \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 7.83 (d, 2H), 7.04 (s, 1H), 6.91 (m, 4H), 4.72 (t, 1H), 4.01 (dd, 1H), 3.9 (m, 1H), 3.65 (m, 1H), 3.46 (d, 1H), 3.4 (d, 1H), 2.77 (m, 1H), 2.6 (m, 1H), 2.4 (m, 1H), 2.39 (s, 6H). Separation by chiral HPLC provided enantiomers 69a and 69b.

Example 68: Preparation of Compound Nos. 70, 70a, 70b, 70c and 70d

[0717] To an ice-cooled stirred solution of 1-(2,3,4,5-tetrahydro-5-(2-hydroxy-2-(pyridin-4-yl) ethyl)-2-methyl-1H-pyrido[4, 3-b]indol-8-yl) ethanone (600 mg, 1.72 mmol) in anhydrous THF (10 mL) was portionwise added LAH (163 mg, 4.3 mmol) and stirred at 0 °C for 30 min. The reaction mixture was quenched by adding water, 15% NaOH and again water. The reaction mixture was filtered, and the filtrate was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield the title compound. \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 8.45 (d, 2H), 7.3 (d, 1H), 7.19 (d, 2H), 7.14 (m, 2H), 4.9 (m, 2H), 4.09 (m, 2H), 3.82 (dd, 1H), 3.7 (dd, 1H), 3.07 (m, 2H), 2.9 (m, 1H), 2.7 (d, 1H), 2.57 (s, 3H), 1.51 (d, 3H). Separation by chiral HPLC provides enantiomers 70a, 70b, 70c and 70d.

Example 69: Preparation of Compound Nos. 71, 71a and 71b

[0718] 2,4,4,8-Tetramethyl-2,3,4,5-tetrahydro-1H-pyrido[4, 3-b]indole (1.0gm, 4.385mmol) was dissolved in DMF (8 mL) and sodium hydride (0.526 g, 13.15 mmol) was added portionwise under nitrogen. 4-Oxiranyl-pyridine (0.9 g, 7.45mmol) was diluted in DMF (2 mL) and added dropwise at RT and stirred for 4 h. After consumption of starting material (by
monitoring TLC & LCMS), the reaction mixture was poured into ice water, product was precipitated and filtered, and the residue was washed with water & hexane, dried under reduced pressure and crystallized in EtOH (10 mL) and diethyl ether (50 mL) to obtain 900 mg of 1-pyridin-4-yl-2-(2,4,4,8-tetramethyl-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-ethanol. 1H NMR (CDCl3, freebase) δ (ppm): 8.62 (d, 2H), 7.37 (d, 2H), 7.31 (d, 1H), 7.19 (s, 1H), 7.01 (d, 1H), 5.22 (t, 1H), 4.32 (d, 1H), 3.6 (d, 1H), 3.48 (d, 1H), 2.65 (s, 1H), 2.44 (s, 3H), 1.47 (s, 3H), 1.28 (s, 3H). Separation by chiral HPLC provides enantiomers 71a and 71b.

Example 70: Preparation of Compound Nos. 72, 72a and 72b

To a stirred solution of 2-(1,2,3,4-tetrahydro-8-methylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethanol (300 mg, 0.977 mmol) and triethyl amine (0.18 mL, 1.27 mmol) in DCM (6 mL) was added ethyl chloroformate (138 mg, 1.27 mmol), and the reaction mixture stirred at RT for 2 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with DCM and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography (MeOH-DCM) to yield ethyl 3, 4-dihydro-5-(2-hydroxy-2-(pyridin-4-yl) ethyl)-8-methyl-1H-pyrido[4, 3-b]indole-2 (5H)-carboxylate (170 mg). 1H NMR (CDCl3, freebase) δ (ppm): 8.4 (d, 2H), 7.21 (m, 4H), 7.0 (d, 1H), 5.03 (t, 1H), 4.6 (m, 2H), 4.21 (m, 4H), 3.78 (m, 2H), 3.6 (m, 1H), 2.75 (m, 1H), 2.4 (s, 3H), 1.28 (t, 3H). Separation by chiral HPLC provides enantiomers 72a and 72b.

Example 71: Preparation of Compound Nos. 73, 73a-73d

To a solution of carboline (1 g, 4.4 mmol) in 10 mL DMF, was added sodium hydride (528 mg, 13.2 mmol) under nitrogen at RT and stirred for 5 min. 4-Oxiranyl-pyridine (803 mg, 6.6 mmol) was diluted in DMF and added dropwise under nitrogen and the reaction mixture stirred at RT for 16 h. After the complete conversion of starting material (TLC and LCMS), the reaction mixture was poured in ice-cold water and extracted with EtOAc (3x40 mL). The combined organic layer was washed with water (6x30 mL) and dried over anhydrous sodium sulfate, concentrated and crude was crystallized in EtOH in ether to obtain 1.2 g of desired product. 1H NMR (CDCl3, freebase) δ (ppm): 8.59 (d, 1H), 8.58 (d, 1H), 7.38 (d, 1H), 7.24 (d, 1H), 7.20 (d, 1H), 7.08 (d, 1H), 7.0 (d, 1H), 5.0 (m, 1H), 4.62 (dd, 1H), 4.18 (m, 2H), 4.0 (m, 1H), 2.70 (m, 2H), 2.58 (m, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.10 (m, 1H), 1.70 (m, 1H). Separation by chiral HPLC provides enantiomers 73a-73d.

Example 72: Preparation of Compound Nos. 74, 74a and 74b
[0721] To a solution of 10-methyl-2,3,5,6,7,11c-hexahydro-1H-pyrido[3',2':4,5]pyrrolo[2,3-g]indolizine (110 mg, 0.484 mmol) in DMF (1 mL) was added a suspension of NaH (60.0 mg, 1.45 mmol) in DMF (1 mL). After stirring for 5 min at RT, a solution of 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (423 mg, 1.45 mmol) in DMF (1 mL) was added dropwise into the reaction mixture and stirring continued for another 2 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x25 mL). The organic layer was washed with water (3x20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by reverse phase HPLC to yield 10-methyl-7-(2-(6-methylpyridin-3-yl)ethyl)-2,3,5,6,7,11c-hexahydro-1H-pyrido[3',2':4,5]pyrrolo[2,3-g]indolizine. 1H NMR (CD3OD, Tri-HCl salt) δ (ppm): 8.7 (s, 1H), 8.4 (d, 1H), 8.25 (s, 2H), 7.8 (d, 1H), 5.1 (m, 1H), 4.8-4.6 (m, 2H), 3.9-3.7 (m, 3H), 3.4 (m, 2H), 3.4-3.2 (m, 2H), 2.9-2.7 (m, 2H), 2.8 (s, 3H), 2.5 (s, 3H), 2.3-2.15 (m, 3H). Separation by chiral HPLC provided enantiomers 74a and 74b.

Example 73: Preparation of Compound Nos. 75, 75a, 75b, 75c and 75d

[0722] To a solution of 2-methyl-6,7,8,9,10,12-hexahydro-5H,6aH-indolol[2,3-b]quinolizine (1.0 g, 4.16 mmol) in 15 mL DMF, was added sodium hydride (500 mg, 12.49 mmol) under nitrogen at RT and stirred for 20 min. 4-Oxirany1-pyridine (857 mg, 7.08 mmol) was added dropwise under nitrogen and the reaction mixture stirred at RT for 18 h. After the complete conversion of starting material (TLC and LCMS), the reaction mixture was poured in ice-cold water and extracted with EtOAc (3x80 mL). The combined organic layer was washed with water (5x50 mL) and dried over anhydrous sodium sulfate, concentrated and crude was crystallized in EtOH (1 mL) and ether (40 mL) to obtain 800 mg of desired product. 1H NMR (CDCl3, freebase) δ (ppm): 8.54 (d, 2H), 7.22 (d, 2H), 7.102 (s, 1H), 7.00 (d, 1H), 6.92 (d, 1H), 4.78 (t, 1H), 4.02 (m, 2H), 3.81 (d, 1H), 3.26 (d, 1H), 2.99 (d, 1H), 2.7 (dd, 1H), 2.5 (d, 1H), 2.43 (s, 3H), 2.23 (m, 2H), 1.89 (d, 1H), 1.81 (d, 1H), 1.69 (m, 2H), 1.5 (q, 1H), 1.35 (t, 1H). This racemate was separated by semi-preparative chiral HPLC separation to give enantiomers 75a, 75b, 75c and 75d.

Example 74: Preparation of Compound Nos. 76, 76a, 76b, 76c and 76d

[0723] To a solution of 7-methyl-2,3,5,10,11,11a-hexahydro-1H-indolizino[7,6-b]indole (200 mg, 0.88 mmol) in DMF (2 mL) was added NaH (106 mg, 2.65 mmol). After stirring for 5 min, a solution of 4-(oxirany1-2-yl) pyridine (161 mg, 1.32 mmol) in DMF was added into the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was quenched with ice-water.
and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, concentrated and the residue obtained was purified by reverse phase HPLC to yield the title compound. 76a: $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.6 (d, 2H), 7.26 (d, 2H), 7.21 (s, 1H), 7.15 (d, 1H), 7.0 (d, 1H), 5.0 (dd, 1H), 4.2 (m, 3H), 3.29 (m, 2H), 2.7 (s, 2H), 2.42 (s, 3H), 2.4 (q, 1H), 2.1 (m, 1H), 2.0 (m, 1H), 1.85 (m, 1H), 1.62 (m, 2H). 76b: $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.53 (d, 2H), 7.24 (d, 2H), 7.17 (s, 1H), 7.14 (d, 1H), 6.97 (d, 1H), 4.95 (d, 1H), 4.10 (m, 3H), 3.28 (m, 2H), 3.0 (d, 1H), 2.49 (m, 2H), 2.44 (s, 3H), 2.37 (q, 1H), 2.11 (m, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.63 (m, 1H). 76c: $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.5 (d, 2H), 7.17 (d, 2H), 7.06 (s, 1H), 6.97 (d, 1H), 6.9 (d, 1H), 4.76 (t, 1H), 4.0 (m, 2H), 3.9 (d, 1H), 3.19 (d, 1H), 3.13 (t, 1H), 2.67 (q, 2H), 2.42 (s, 3H), 2.39 (m, 1H), 2.28 (q, 1H), 2.08 (t, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.64 (m, 1H). 76d: $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.53 (d, 2H), 7.24 (d, 2H), 7.17 (s, 1H), 7.14 (d, 1H), 6.97 (d, 1H), 4.95 (d, 1H), 4.10 (m, 3H), 3.28 (m, 2H), 3.0 (d, 1H), 2.49 (m, 2H), 2.44 (s, 3H), 2.37 (q, 1H), 2.11 (m, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.63 (m, 1H).

**Example 75: Preparation of Compound No. 77**

**[0724]** A solution of 5-(2-bromocyclopent-1-enyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4, 3-b]indole (100 mg, 0.29 mmol), 1H-pyrazole-4-boronic acid (75 mg, 0.580 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-DME (4 mL)-water (2 mL) was purged with nitrogen. Pd(PPh$_3$)$_4$ (16 mg, 0.0147 mmol) was added and the reaction mixture was heated at 90 °C for 45 min. The reaction mixture concentrated under vacuum, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum to obtain crude which was purified by reverse phase HPLC to yield 5-(2-(1H-pyrazol-4-yl)cyclopent-1-enyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4, 3-b]indole. $^1$H NMR (CD$_3$OD, TFA salt) δ (ppm): 7.38 (s, 1H), 7.0 (m, 2H), 6.4 (m, 2H), 4.7 (m, 1H), 4.4 (m, 1H), 3.78 (m, 1H), 3.42 (m, 1H), 3.11 (m, 4H), 2.6-3.0 (m, 5H), 2.4 (s, 3H), 2.2 (m, 2H).

**Example 76: Preparation of Compound No. 78**

**[0725]** To a degassed solution of 3,6-dimethyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene (201 mg, 1.00 mmol), potassium phosphate (466 mg, 2.20 mmol), L-proline (19 mg, 0.10 mmol) and copper iodide (23 mg, 0.20 mmol) in DMF (2 mL) was added 4-(2-bromo-1-methyl-vinyl)pyridine (424 mg, 2.00 mmol). The reaction mixture was stirred at 120 °C for 20 h. The progress of reaction was monitored by TLC and LCMS. The reaction was monitored by TLC.
and LCMS. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x10 mL). The organic layer was washed with water (3x20 mL), followed by brine (25 mL), dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by reverse phase HPLC. $^1$H NMR (CD$_3$OD, TFA salt) δ (ppm): 9.0 (s, 1H), 8.8 (d, 1H), 8.2 (s, 1H), 8.0 (t, 2H), 7.3 (s, 1H), 4.8 (bs, 1H), 4.4 (bs, 1H), 3.9 (bs, 1H), 3.6 (bs, 1H), 3.2 (bs, 2H), 3.18 (s, 3H), 2.8 (s, 3H), 2.5 (s, 3H), 2.06 (s, 3H).

Example 77: Preparation of Compound No. 79

[0726] 2-Allyl-8-methyl-5-(2-(pyridin-4-yl)vinyl)-2,3,4,5-tetrahydro-1H-pyrido[4, 3-b]indole (50 mg, 0.151 mmol) was dissolved in DCM (2mL), which was degassed with nitrogen for 15 min. To this was added Pd(PPh$_3$)$_4$ (4 mg, 0.002 mmol) followed by 1, 3-dimethyl barbituric acid (71 mg, 0.454 mmol). The reaction mixture was again degassed by nitrogen for 15 min. The resultant mixture was stirred at RT for 1 h. DCM was evaporated in vacuo. EtOAc (20 mL) was added to reaction mixture and was washed with saturated potassium carbonate solution (3x1 mL). The organic layer was dried over anhydrous sodium sulfate, evaporated in vacuo and purified by reverse phase HPLC to obtain 2 mg of 8-methyl-5-(2-(pyridin-4-yl) vinyl)-2,3,4,5-tetrahydro-1H-pyrido[4, 3-b]indole. $^1$H NMR (CD$_3$OD, Free base): δ (ppm): 8.45 (d, 2H), 8.0 (d, 1H), 7.7 (d, 1H), 7.58 (d, 2H), 7.3 (s, 1H), 7.19 (d, 1H), 6.8 (d, 1H), 4.29 (s, 2H), 3.42 (m, 2H), 3.2 (m, 2H), 2.4 (s, 3H).

Example 78: Preparation of Compound No. 80

[0727] To a degassed solution of trifluoro-methanesulfonic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-methyl-vinylester (200 mg, 0.515 mmol), potassium carbonate (214 mg, 1.550 mmol) and 4-(4,4,5,5-tetramethyl-1,3, 2)dioxaborolan-2-yl)-1H-pyrazole (150 mg, 0.773 mmol) in DME: water (2: 1mL) was added Pd(PPh$_3$)$_4$ (30 mg, 0.025 mmol) and the reaction mixture stirred at 90 °C for 1.5 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (2x25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography followed by reverse phase HPLC to yield the desired product. $^1$H NMR (CD$_3$OD, TFA salt) δ (ppm): 7.3 (s, 1H), 7.08 (d, 1H), 7.0 (d, 1H), 6.92 (s, 2H), 6.5 (s, 1H), 4.76 (d, 1H), 4.39 (d, 1H), 3.75 (m, 1H), 3.43 (m, 1H), 3.05 (s, 3H), 2.9 (m, 2H), 2.41 (s, 3H), 2.25 (s, 3H).

Example 79: Preparation of Compound Nos. 81, 81a and 81b

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[0728] To a solution of 8-isopropyl-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 4.38 mmol) in DMF (20 mL) was added sodium hydride (526 mg, 13.14 mmol) and the suspension was stirred at RT for 10 min. A solution of 4-(oxiran-2-yl) pyridine (1.0 g, 8.26 mmol) in DMF (5 mL) was added dropwise, and stirring was continued overnight. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice cold water (200 mL) and extracted with EtOAc (3x200 mL). The organic layer was washed with water (4x300 mL), dried over anhydrous sodium sulfate and concentrated. The residue obtained was triturated with diethyl ether (200 mL) to yield the desired product. \( ^1H \) NMR (CDCl\(_3\), freebase) \( \delta \) (ppm): 8.58 (d, 2H), 7.21 (d, 2H), 7.18 (d, 2H), 7.03 (d, 1H), 4.81 (t, 1H), 4.05 (d, 2H), 3.55 (dd, 2H), 3.0 (q, 1H), 2.82 (m, 1H), 2.7 (m, 2H), 2.6 (m, 1H), 2.4 (s, 3H), 1.3 (d, 6H). Separation by chiral HPLC provides enantiomers 81a and 81b.

**Example 80: Preparation of Compound Nos. 82, 82a and 82b**

[0729] To a solution of 2,6-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 5.00 mmol) in DMF (10 mL) was added sodium hydride (600 mg, 15 mmol) under nitrogen atmosphere at 0 \( ^\circ \)C and stirred for 10 min. 4-(Oxiran-2-yl)pyridine (1.08 g, 8.92 mmol) was added dropwise under nitrogen atmosphere. The reaction mixture was stirred at RT for 12 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured in ice-cold water and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was crystallized with diethyl ether to yield 2-(2,6-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. \( ^1H \) NMR (CDCl\(_3\), freebase) \( \delta \) (ppm): 8.58 (d, 2H), 7.23 (m, 3H), 7.0 (t, 1H), 6.9 (d, 1H), 4.81 (t, 1H), 4.3-4.4 (m, 2H), 3.5 (dd, 2H), 3.0 (m, 1H), 2.8 (m, 1H), 2.75 (s, 3H), 2.7 (m, 1H), 2.6 (m, 1H), 2.43 (s, 3H). Separation by chiral HPLC provides enantiomers 82a and 82b.

**Example 81: Preparation of Compound No. 83**

[0730] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (2 g, 10 mmol) was dissolved in 20 mL of DMF. The resulting solution was cooled in an ice-water bath and sodium hydride (840 mg, 4.2 mmol) was added under nitrogen atmosphere. 2-Bromomethyl-2-phenyl[1,3]dioxolane (2.43 g, 10 mmol) was added and the reaction mixture was heated at 100 \( ^\circ \)C overnight. Water was added and the product was extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced
pressure. The residue was purified by silica gel chromatography eluting with 0-5% MeOH:DCM.

Example 82

[0731] Compound Nos. 84, 85, 86, 89, 90, 90a, 90b and 91 were synthesized as described in PCT publication WO-2009/055828; see, for example, synthetic procedures 20, 23, 87, 178 and 274.

Example 83

[0732] Compound Nos. 87 and 88 were synthesized as described in PCT publication WO-2009/094668; see, for example, synthetic procedures 71 and 72.

Example 84

[0733] Compound Nos. 95, 95a-b, 97 and 97a-b were synthesized as described in PCT publication WO-2009/120720; see, for example, synthetic procedures 109 and 115.

Example 85

[0734] Compound Nos. 96 and 96a-b were synthesized as described in PCT publication WO-2009/120717; see, for example, synthetic procedure 131.

Example 86

[0735] Compound Nos. 93, 93a-b, 98, 98a-b, 100, 101, 103, 105, 107 and 132 were synthesized as described in PCT publication WO-2010/051501; see, for example, synthetic procedures 45, 131, 199, 241, 273, 329, 341, 354 and 401.

Example 87

[0736] Compound Nos. 92, 99 and 106 were synthesized as described in PCT publication WO-2010/051503; see, for example, synthetic procedures 41, 147 and 168.

Example 88

[0737] Compound No. 94 was synthesized as described in PCT publication WO-2010/127177; see, for example, synthetic procedure 6.

Example 89

[0738] Compound Nos. 102 and 102a-b were synthesized as described in PCT publication WO-2011/019417; see, for example, synthetic procedure 9.

Example 90: Preparation of Compound No. 108

[0739] To a degassed solution of [(E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl]trifluoromethanesulfonate] (50 mg, 0.128 mmol), potassium carbonate (17.8 mg, 0.1287 mmol) and 1-methyl-1H-pyrazole-5-boronic acid pinacol ester (53.5 mg,
0.2574 mmol) in DME-water (2 mL:1 mL) was added Pd(PPh₃)₄ (7.4 mg, 0.0064) and the reaction mixture was heated to reflux for 2.5 h. The reaction mixture was cooled to RT and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 7.58 (d, 1H), 7.26 (d, 1H), 7.18 (m, 2H), 6.93 (s, 1H), 6.45 (s, 1H), 4.78 (d, 1H), 4.39 (d, 1H), 4.02 (s, 3H), 3.86 (m, 1H), 3.59 (m, 1H), 3.23 (m, 1H), 3.18 (m, 4H), 2.42 (s, 3H), 1.87 (s, 3H).

**Example 91: Preparation of Compound No. 109**

To a degassed solution of [(E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate] (100 mg, 0.257 mmol), 1-methylpyrazole-4-boronic acid pinacol ester (108 mg, 0.515 mmol) and potassium carbonate (36 mg, 0.257 mmol) in DME-water (4:2 mL) was added Pd(PPh₃)₄ (15 mg, 0.0128) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 7.92 (s, 1H), 7.89 (s, 1H), 7.26 (s, 1H), 7.16 (m, 2H), 6.98 (s, 1H), 4.78 (d, 1H), 4.37 (d, 1H), 3.85 (s, 3H), 3.82 (m, 1H), 3.58 (m, 1H), 3.18 (s, 3H), 3.13 (m, 2H), 2.43 (s, 3H), 1.82 (s, 3H).

**Example 92: Preparation of Compound No. 110**

To a degassed solution of [(E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate] (100 mg, 0.257 mmol), 3,5-dimethylisoxazole-4-boronic acid pinacol ester (115 mg, 0.515 mmol) and potassium carbonate (36 mg, 0.257 mmol) in DME-water (4:2 mL) was added Pd(PPh₃)₄ (15 mg, 0.0128) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 7.27 (s, 1H), 7.17 (m, 2H), 6.61 (s, 1H), 4.78 (d, 1H), 4.39 (d, 1H), 3.83 (m, 1H), 3.60 (m, 1H), 3.02-3.23 (m, 5H), 2.31-2.60 (m, 9H), 1.81 (s, 3H).

**Example 93: Preparation of Compound No. 111**
[0742] To a solution of [(E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate] (100 mg), potassium carbonate (36 mg), and 2-acetamidopyridine-5-boronic acid pinacol ester (135 mg) in DME-water (4:2 mL) was added Pd(PPh₃)₄ (15 mg) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 7.91 (s, 1H), 7.68 (d, 1H), 7.58 (d, 1H), 7.21 (s, 1H), 7.10 (d, 1H), 6.98 (d, 1H), 6.91 (s, 1H), 4.61 (d, 1H), 4.30 (d, 1H), 3.71 (m, 1H), 3.40 (m, 1H), 3.07 (s, 3H), 2.90 (m, 2H), 2.38 (m, 6H), 2.16 (s, 3H).

Example 94: Preparation of Compound No. 112

[0743] To a solution of [(E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate] (100 mg), potassium carbonate (36 mg), and 2-acetamidopyridine-5-boronic acid pinacol ester (135 mg) in DME-water (4:2 mL) was added Pd(PPh₃)₄ (15 mg) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 8.58 (s, 1H), 8.35 (d, 1H), 7.96 (d, 1H), 7.30 (s, 1H), 7.11 (m, 3H), 4.37 (d, 1H), 4.40 (d, 1H), 3.83 (m, 1H), 3.58 (m, 1H), 3.12 (m, 5H), 2.42 (s, 3H), 2.21 (s, 3H), 2.0 (s, 3H).

Example 95: Preparation of Compound No. 113

[0744] To a degassed solution of [(E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate] (100 mg, 0.257 mmol), potassium carbonate (36 mg, 0.257 mmol) and naphthalene-1-boronic acid (88 mg, 0.515 mmol) in DME-water (4:2 mL) was added Pd(PPh₃)₄ (15 mg, 0.0128 mmol) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, TFA salt) δ (ppm): 8.18 (d, 1H), 7.84-7.98 (m, 2H), 7.51-7.62 (m, 4H), 7.38 (m, 2H), 7.18 (d, 1H), 6.78 (s, 1H), 4.67 (m, 1H), 4.42 (m, 1H), 3.81 (m, 1H), 3.63 (m, 1H), 3.24 (m, 1H), 3.21 (s, 3H), 3.19 (m, 1H), 2.47 (s, 3H), 2.12 (s, 3H).
Example 96: Preparation of Compound No. 114

[0745] To a degassed solution of 5-(2-bromocyclopent-1-ethyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (120 mg, 0.348 mmol), 4-pyridineboronic acid (85 mg, 0.69 mmol) and potassium carbonate (144 mg, 1.04 mmol) in DME-water (4:2 mL) was added Pd(PPh₃)₄ (20 mg, 0.0174 mmol) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₂OD, TFA salt) δ (ppm): 8.52 (d, 2H), 7.40 (m, 2H), 7.36 (s, 1H), 6.92-7.15 (m, 2H), 4.78 (d, 1H), 4.40 (d, 1H), 3.80 (m, 1H), 3.51 (m, 1H), 3.20 (m, 6H), 2.80-3.00 (m, 3H), 2.41 (s, 3H), 2.37 (m, 2H).

Example 97: Preparation of Compound No. 115

[0746] To a degassed solution of (E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol), potassium carbonate (110 mg, 0.77 mmol) and 1H-pyrazole-4-boronic acid (60 mg, 0.540 mmol) in DME-water (2:1 mL) was added Pd(PPh₃)₄ (20 mg, 0.017 mmol) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₂OD, TFA salt) δ (ppm): 8.0 (s, 2H), 7.27 (s, 1H), 7.0-7.11 (m, 3H), 4.7 (d, 1H), 4.37 (d, 1H), 3.82 (m, 1H), 3.56 (m, 1H), 3.01-3.22 (m, 5H), 2.41 (s, 3H), 1.80 (s, 3H).

Example 98: Preparation of Compound No. 116

[0747] To a de-aerated solution of 8-chloro-5-(2-chloroallyl)-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (200 mg, 0.680 mmol) and potassium carbonate (281 mg, 2.039 mmol) in 1,2-dimethoxyethane-water (2:1) were added pyridine-4-boronic acid (167.2 mg, 1.36 mmol) and Pd(PPh₃)₄ (53 mg, 0.045 mmol). The reaction mixture was stirred at 90 °C for 45 min. The reaction mixture was concentrated under reduced pressure to dryness. The residue obtained was dissolved in EtOAc (50 mL) and washed with water (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC. ¹H NMR (CDCl₃, freebase) δ (ppm): 8.6 (d, 2H),
7.4 (s, 1H), 7.3 (d, 2H), 7.1 (s, 2H), 5.57 (s, 1H), 4.98 (s, 2H), 4.58 (s, 1H), 3.82 (s, 2H), 3.05 (t, 2H), 2.82 (t, 2H), 2.6 (s, 3H).

Example 99: Preparation of Compound No. 117
[0748] To a degassed solution of 5-(5-fluoro-pyridin-3-ylethynyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (60 mg, 0.188 mmol) in MeOH (3 mL) were added 10% dry Pd-C (35 mg) and ammonium formate (59 mg, 0.940 mmol). The reaction mixture was stirred at 75 °C for 1 h. The reaction mass was filtered through Celite and the filtrate concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC to yield 5-[2-(5-fluoro-pyridin-3-yl)-ethyl]-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. \(^1\)H NMR (CD\(_3\)OD, TFA salt) δ (ppm): 8.3 (s, 1H), 7.9 (s, 1H), 7.38 (d, 1H), 7.21 (s, 1H), 7.2 (d, 1H), 7.0 (d, 1H), 4.62 (d, 1H), 4.4 (t, 2H), 4.3 (d, 1H), 3.78 (m, 1H), 3.4 (m, 1H), 3.18 (t, 2H), 3.1 (s, 3H), 2.9 (m, 1H), 2.8 (m, 1H), 2.4 (s, 3H).

Example 100: Preparation of Compound No. 118
[0749] A mixture of 5-ethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (300 mg, 1.33 mmol), 1H-imidazole (182 mg, 2.66 mmol), TBAF.3H\(_2\)O (1.2 g, 3.80 mmol) and dichloro bis(triphenylphosphine) palladium (II) (47 mg, 0.06 mmol) was heated at 85 °C for 30 min. The reaction mixture was cooled to RT, diluted with water and extracted with EtOAc (3x25 mL). The organic layer was washed with water (3x25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (100-200 mesh) eluting with 4% MeOH-DCM to yield 90 mg of 5-(1-imidazol-1-yl-vinyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. The free base was converted into the di-HCl salt by treatment with ethanolic HCl. \(^1\)H NMR (CD\(_3\)OD, Di-HCl salt) δ (ppm): 9.21 (s, 1H), 7.78 (d, 2H), 7.38 (s, 1H), 7.1 (d, 1H), 6.92 (d, 1H), 6.21 (d, 1H), 5.75 (d, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.83 (m, 1H), 3.6 (m, 1H), 3.18 (m, 5H), 2.4 (s, 3H).

Example 101: Preparation of Compound No. 119
[0750] To a solution of 2-methyl-7-trifluoromethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.393 mmol) in DMF (2 mL) were added sodium hydride (60 mg, 1.17 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (300 mg, 0.98 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1 h. The reaction mixture was cooled to RT and quenched with water and extracted with EtOAc (3x10 mL). The organic layer was washed with water (10 mL x 2), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC. \(^1\)H NMR
(CD$_3$OD, TFA salt) δ (ppm): 8.21 (s, 1H), 8.07 (d, 1H), 7.6 (dd, 2H), 7.28 (m, 2H), 4.78 (d, 1H), 4.6 (t, 2H), 4.4 (d, 1H), 3.9 (m, 1H), 3.6 (m, 1H), 3.2-3.4 (m, 4H), 3.18 (s, 3H), 2.6 (s, 3H).

**Example 102: Preparation of Compound No. 120**

To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (200 mg, 1.00 mmol) and 2-aminopyridine (188 mg, 2.00 mmol) in DCM (2 mL) was added powdered KOH (392 mg, 7.00 mmol), and the reaction mixture was stirred at 85 °C for 2 h. The progress of reaction was monitored by TLC and LCMS. DCM was removed under reduced pressure. Water was added to the residue and extracted with EtOAc (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to afford crude material, which was purified by reverse phase HPLC to yield 2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-ylmethyl)-pyridin-2-yl-amine. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.1 (d, 1H), 7.38 (m, 2H), 7.18 (s, 1H), 7.0 (d, 1H), 6.6 (t, 1H), 6.3 (d, 1H), 5.57 (s, 2H), 5.26 (bs, 1H), 3.8 (s, 2H), 3.1 (t, 2H), 3.0 (t, 2H), 2.6 (s, 3H), 2.4 (s, 3H).

**Example 103: Preparation of Compound No. 121**

To a de-aerated solution of 5-(2-chloroallyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (150 mg, 0.547 mmol) and potassium carbonate (226 mg, 1.64 mmol) in 1,2-dimethoxyethane-water (2:1) were added pyridine-4-boronic acid (135 mg, 1.09 mmol) and Pd(PPh$_3$)$_4$ (44 mg, 0.0383 mmol). The reaction mixture was stirred at 90 °C for 45 min. The reaction mixture was cooled to RT and concentrated under reduced pressure to dryness. The residue obtained was dissolved in EtOAc (50 mL) and washed with water (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC as a TFA salt. $^1$H NMR (CD$_3$OD, TFA salt) δ (ppm): 8.8 (d, 2H), 8.2 (d, 2H), 7.3 (m, 2H), 7.05 (d, 1H), 6.0 (s, 1H), 5.3 (d, 2H), 4.8 (s, 1H), 4.7 (d, 1H), 4.37 (d, 1H), 3.86 (m, 1H), 3.6 (m, 1H), 3.17 (m, 2H), 3.1 (s, 3H), 2.43 (s, 3H).

**Example 104: Preparation of Compound No. 122**

To a degassed solution of (E,Z)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) and potassium carbonate (110 mg, 0.796 mmol), in DME (2 mL) and water (1 mL) were added Pd(PPh$_3$)$_4$ (20 mg, 0.017 mmol) and N-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinamide (135 mg, 0.514 mmol) and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue...
was diluted with water and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. $^1$H NMR (CD$_2$OD, TFA salt) δ (ppm): 8.9 (s, 1H), 8.1-8.21 (m, 2H), 7.3 (s, 1H), 7.19 (s, 1H), 7.1 (m, 2H), 4.76 (d, 1H), 4.4 (d, 1H), 3.82 (bs, 1H), 3.6 (bs, 1H), 3.2 (m, 2H), 3.17 (s, 3H), 3.0 (s, 3H), 2.42 (s, 3H), 2.0 (s, 3H).

**Example 105: Preparation of Compound No. 124**

[0754] To a degassed solution of 3,6-dimethyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene (201 mg, 1.00 mmol), potassium phosphate (466 mg, 2.20 mmol), L-proline (19 mg, 0.10 mmol) and copper iodide (23 mg, 0.20 mmol) in DMF (2 mL) was added 4-(2-bromo-1-methyl-vinyl)-pyridine (396 mg, 2.00 mmol). The reaction mixture was stirred at 120 °C for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x 10 mL). The organic layer was washed with water (3x 20 mL), followed by brine (25 mL), dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by reverse phase HPLC. $^1$H NMR (CD$_2$OD, TFA salt) δ (ppm): 8.8 (bs, 2H), 8.22 (d, 2H), 8.18 (s, 1H), 7.8 (s, 1H), 7.6 (s, 1H), 4.76 (bs, 1H), 4.4 (bs, 1H), 3.82 (bs, 1H), 3.6 (bs, 1H), 3.21 (bs, 2H), 3.1 (s, 3H), 2.42 (s, 3H), 2.1 (s, 3H).

**Example 106: Preparation of Compound No. 125**

[0755] To a stirred solution of (E)-5-(2-(6-(methoxymethyl)pyridin-3-yl)prop-1-en-1-yl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (90 mg, 0.249 mmol) in dry DCM (3 mL) was dropwise addition of solution of BBr$_3$ (0.3 mL, 1.745 mmol) in dry DCM (2 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 2 h. The solvent was removed under reduced pressure. The residue was basified with saturated sodium bicarbonate solution and extracted with DCM (3x 20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC to yield (E)-(5-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl)pyridin-2-yl)methanol as the TFA salt. $^1$H NMR (CD$_2$OD, TFA salt) δ (ppm): 8.9 (s, 1H), 8.77 (d, 1H), 8.0 (d, 1H), 7.4 (s, 1H), 7.3 (s, 1H), 7.17 (d, 1H), 7.1 (d, 1H), 5.1 (d, 1H), 5.0 (s, 2H), 4.6 (d, 1H), 4.1 (m, 2H), 3.17 (s, 3H), 3.1 (bs, 2H), 2.42 (s, 3H), 2.1 (s, 3H).

**Example 107: Preparation of Compound No. 126**

[0756] To a degassed solution of (Z)-2,8-dimethyl-5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-en-1-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3b]indole (271 mg, 0.742 mmol), 5-bromo-2-(methoxymethyl)pyridine (100 mg, 0.495) and potassium carbonate (204 mg,
1.485 mmol) in DME-water (2:1 mL) and was added Pd(PPh₃)₄ (40.0 mg, 0.034 mmol), and the reaction mixture was heated to reflux for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ¹H NMR (CD₃OD, Di-HCl salt) δ (ppm): 9.0 (s, 1H), 8.84 (d, 1H), 8.05 (d, 1H), 7.42 (s, 1H), 7.3 (s, 1H), 7.15 (d, 1H), 7.1 (d, 1H), 4.9 (s, 2H), 4.78 (d, 1H), 4.4 (d, 1H), 3.82 (bs, 1H), 3.6 (s, 3H), 3.58 (bs, 1H), 3.2 (bs, 2H), 3.1 (s, 3H), 2.43 (s, 3H), 2.1 (s, 3H).

Example 108: Preparation of Compound Nos. 127 and 127a-d.

To an ice-cooled stirred suspension of 4-bromopyridine hydrochloride salt (1.0 g, 5.1 mmol) in THF (5 mL) was added isopropyl magnesium chloride (2M in THF, 5 mL, 10.3 mmol) and stirred the reaction at RT for 30 min. A solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)propanal (300 mg, 1.17 mmol) in THF (3 mL) was added into the brown colored reaction mixture, which was stirred at RT for 1.5 h. The progress of reaction was monitored by TLC and LCMS (45 % conversion). The reaction mixture was cooled to 0 °C and quenched with cold saturated ammonium chloride solution (till effervescence stops) and added water, stirred at RT for 15 min and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was purified by reverse phase HPLC. The product was further purified, and enantiomers separated, by chiral preparative HPLC. ¹H NMR (CDCl₃, freebase) δ (ppm): 8.20 (d, 2H), 7.1 (s, 1H), 7.06 (s, 1H), 6.86 (d, 1H), 6.8 (s, 2H), 4.85 (s, 1H), 4.2 (s, 1H), 3.49 (d, 1H), 3.39 (d, 1H), 2.61 (d, 2H), 2.41 (d, 3H), 2.33 (s, 3H), 1.56 (s, 3H). Separation by chiral HPLC provided diastereomers 127a-d.

Example 109: Preparation of Compound Nos. 128 and 128a-b.

A solution of tert-butyl 9-(2-hydroxy-2-(pyridin-3-yl)propyl)-6-methyl-3,4-dihydro-1H-pyrido[3,4-b]indole-2(9H)-carboxylate (350 mg) in 3M aqueous HCl solution (10 mL) was stirred at RT for 1 h. The progress of reaction was monitored with TLC and LCMS. The reaction mixture was lyophilized and the solid obtained was washed with diethyl ether (2x30 mL), dried to yield the title compound. The product was further purified, and enantiomers separated, by chiral preparative HPLC. ¹H NMR (CD₃OD, HCl salt) δ (ppm): 8.67 (d, 1H), 8.6 (d, 1H), 8.54 (s, 1H), 7.9 (t, 1H), 7.2 (s, 1H), 6.8 (d, 1H), 6.7 (s, 1H), 4.98 (d, 1H), 4.6 (d, 1H), 4.4 (q, 2H), 3.62 (t, 2H), 3.07 (m, 2H), 2.32 (s, 3H), 1.8 (s, 3H). Separation by chiral HPLC provided enantiomers 128a and 128b.
Example 110: Preparation of Compound Nos. 129 and 129a-d.

To a solution of 9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (100 mg, 0.442 mmol) in DMF (2 mL) was added sodium hydride (60%, 53 mg, 1.32 mmol, ) at 0 °C. After stirring for 5 min, 4-oxiranyl-pyridine (81 mg, 0.669 mmol) was added at 0 °C and the mixture stirred at RT for 12 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice-cold water and extracted with EtOAc (2x25 mL). The combined organic layer was washed with water (5x25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to compound 129 (90 mg), which was separated by chiral prep HPLC to give compounds 129a, 129b, 129c and 129d. Compound 129a: $^1$HNMR (CDCl₃, freebase) δ (ppm): 8.58 (d, 2H), 7.25 (m, 4H), 7.04 (d, 1H), 5.08 (t, 1H), 4.3 (bs, 1H), 4.18 (d, 2H), 3.3 (d, 1H), 3.07 (m, 2H), 2.85 (m, 2H), 2.6 (m, 1H), 2.42 (m, 1H), 2.4 (s, 3H), 2.01 (m, 3H), 1.82 (m, 1H). Compound 129b: $^1$HNMR (CDCl₃, freebase) δ (ppm): 8.55 (d, 2H), 7.25 (m, 4H), 7.0 (d, 1H), 5.0 (t, 1H), 4.3 (bs, 1H), 4.19 (m, 2H), 3.32 (d, 1H), 3.0 (m, 4H), 2.5 (m, 2H), 2.45 (s, 3H), 2.0 (m, 2H), 1.9 (m, 1H). Compound 129c: $^1$HNMR (CDCl₃, freebase) δ (ppm): 8.6 (d, 2H), 7.25 (m, 4H), 7.0 (d, 1H), 5.05 (t, 1H), 4.2 (m, 2H), 3.9 (t, 1H), 3.3 (m, 1H), 2.91 (m, 2H), 2.8 (t, 1H), 2.7 (q, 1H), 2.43 (s, 3H), 2.4 (m, 2H), 1.9 (m, 3H). Compound 129d: $^1$HNMR (CDCl₃, freebase) δ (ppm): 8.58 (d, 2H), 7.25 (m, 4H), 7.04 (d, 1H), 5.08 (t, 1H), 4.3 (bs, 1H), 4.18 (d, 2H), 3.3 (d, 1H), 3.07 (m, 2H), 2.85 (m, 2H), 2.6 (m, 1H), 2.42 (m, 1H), 2.4 (s, 3H), 2.01 (m, 3H), 1.82 (m, 1H).

Example 111: Preparation of Compound Nos. 130 and 130a-b.

To an ice-cooled stirred solution of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]jindol-5(2H)-yl)-1-(pyridin-4-yl)ethanol (50 g, 155.76 mmol) in DMF (300 mL) was added NaH (60%, 12.5 g, 312.5 mmol). After stirring at RT for 15 min, pivaloyl chloride (37.38 g, 311.5 mmol) was added dropwise into the reaction mixture, which was stirred at RT for 1 h. The reaction was quenched with EtOH and diluted with ice water. The product was extracted with EtOAc, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was passed through a silica gel filter column to remove excess pivaloyl chloride and yield title compound as yellow solid (22.3 g). The product was further purified by chiral preparative HPLC. $^1$H NMR (CDCl₃, freebase) δ (ppm): 8.54 (d, 2H), 7.21 (d, 1H), 7.2 (s, 1H), 7.0 (d ,2H), 6.95 (d, 1H), 6.0 (t, 1H), 4.4 (dd, 1H), 4.1 (dd, 1H), 3.62 (q, 2H), 2.7 (m ,3H), 2.52 (s, 3H), 2.41 (s, 3H), 2.3 (m, 1H), 1.19 (s, 9H).
Example 112: Preparation of Compound Nos. 131 and 131a-b.

To solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (160 mg, 0.8 mmol) in DMF (3 mL) was added NaH (60%, 96 mg, 2.4 mmol). After stirring for 5 min at RT, 1-methyl-4-(oxiran-2-yl)-1H-pyrazole (150 mg, 1.2 mmol) was added into the reaction mixture, which was stirred at RT for 26 h. The progress of reaction was monitored by TLC, NMR and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (EtOH-Hex) to yield 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(1-methyl-1H-pyrazol-4-yl)ethanol. The product was further purified by chiral HPLC separation. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 7.46 (s, 1H), 7.2 (s, 1H), 7.19 (s, 1H), 7.15 (d, 1H), 6.98 (d, 1H), 5.0 (t, 1H), 4.2 (d, 2H), 3.82 (s, 3H), 3.6 (s, 2H), 2.9 (m, 1H), 2.8 (m, 2H), 2.7 (m, 1H), 2.5 (s, 3H), 2.42 (s, 3H).

Example 113: Preparation of Compound Nos. 133 and 133a-b.

To a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (100 mg, 0.5 mmol) in DMF (2 mL) was added NaH (60 mg, 1.5 mmol). After stirring for 10 min at RT, a solution of 3-methyl-4-(oxiran-2-yl)pyridine (100 mg, 0.75 mmol) in DMF (1 mL) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC, LCMS and NMR. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.42 (d, 1H), 8.30 (s, 1H), 7.50 (d, 1H), 7.10 (m, 2H), 6.95 (d, 1H), 5.10 (m, 1H), 4.05 (m, 2H), 3.50 (s, 2H), 2.95-2.60 (m, 4H), 2.42 (s, 6H), 2.20 (s, 3H). Separation by chiral HPLC provided enantiomers 133a and 133b.

Example 114: Preparation of Compound Nos. 134 and 134a-b.

A mixture of 9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6,7-triaza-cyclopenta[c]fluorene (100 mg, 0.44 mmol), 3-vinyl-pyridine (185 mg, 1.762 mmol), tetrabutylammonium bromide (425 mg, 1.32 mmol) and 50% NaOH solution (6 mL) was stirred at 100 °C for 18 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2x50 mL). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column...
chromatography to yield 9-methyl-6-(2-pyridin-3-yl-ethyl)-2,3,4,5,6,10c-hexahydro-1H-3a,6,7-triaza-cyclopenta[c]fluorene (58 mg). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.41 (d, 1H), 8.27 (s, 1H), 8.07 (s, 1H), 7.58 (s, 1H), 7.2 (d, 1H), 7.1 (dd, 1H), 4.4 (m, 2 H), 3.99 (bs, 1H), 3.2 (dd, 1H), 3.17 (t, 2H), 2.84-2.7 (m, 3H), 2.5 (m, 1H), 2.41 (s, 3H), 2.2 (dd, 1H), 1.9 (m, 4H). Separation by chiral HPLC provided enantiomers 134a and 134b.

**Example 115: Preparation of Compound Nos. 135 and 135a-b.**

[0764] To a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (400 mg, 1.61 mmol) in DMF (5 mL) was added NaH (240 mg, 6.0 mmol). After stirring at RT for 15 min, 3-chloro-4-(oxiran-2-yl)pyridine (620 mg, 4.0 mmol) was added into the reaction mixture, which was stirred at RT for 8 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc (3x50 mL). The organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was crystallized from ether to yield title compound (430 mg) which was separated by chiral preparative HPLC to obtain 135a and 135b. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.4 (s, 1H), 8.21 (d, 1H), 7.39 (d, 1H), 7.1 (d, 1H), 6.97 (s, 1H), 6.88 (d, 1H), 5.7 (bs, 1H), 5.19 (d, 1H), 4.21 (d, 1H), 3.89 (dd, 1H), 3.23 (dd, 2H), 2.86 (m, 2H), 2.67 (m, 2H), 2.45 (s, 3H), 2.29 (s, 3H).

**Example 116: Preparation of Compound Nos. 136 and 136a-b.**

[0765] To a solution of aza carboline (500 mg, 2.48 mmol) in DMF (5 mL) was added NaH (298 mg, 7.46 mmol). After stirring at RT for 10 min, 2-(4-fluorophenyl)oxirane (515 mg, 3.73 mmol) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice water and extracted with EtOAc. The organic layer was washed thoroughly with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was recrystallized from ether and further separated by chiral preparative HPLC to obtain 136a and 136b. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.02 (s, 1H), 7.5 (s, 1H), 7.23 (m, 2H), 7.0 (t, 2H), 6.6 (bs, 1H), 5.11 (d, 1H), 4.3 (d, 1H), 4.24 (dd, 1H), 3.56 (dd, 2H), 2.74 (m, 2H), 2.6 (m, 1H), 2.49 (s, 3H), 2.44 (m, 1H), 2.41 (s, 3H).

**Example 117: Preparation of Compound Nos. 137 and 137a-b.**

[0766] To a solution of 9-chloro-2,3,4,5,6,10c-hexahydro-1H-3a,6,7-tri-azacyclopenta[c]fluorene (400 mg, 1.61 mmol) in DMF (5 mL) was added sodium hydride (195 mg, 4.87 mmol). After stirring for 10 min at RT, 2-(6-methylpyridin-3-yl)ethyl 4-
methylbenzenesulfonate (1.08 g, 3.71 mmol) was added into the reaction mixture, which was stirred at RT for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography followed by reverse phase HPLC to yield the title compound. Separation by chiral HPLC provided enantiomers 133a and 133b. $^1$H NMR (CDCl$_3$, freebase) $\delta$ (ppm): 8.2 (s, 1H), 8.19 (s, 1H), 7.7 (s, 1H), 7.1 (d, 1H), 7.0 (d, 1H), 4.38 (m, 2H), 3.8 (bs, 1H), 3.03 (t, 2H), 2.8 (m, 2H), 2.7 (m, 1H), 2.4 (m, 1H), 2.5 (s, 3H), 2.38 (m, 1H), 2.12 (dd, 1H), 1.8 (m, 4H). Separation by chiral HPLC provided enantiomers 137a and 137b.

Example 118: Preparation of Compound Nos. 138 and 138a-b.

[0767] To a solution of dimethyl-aza carboline (693 mg, 3.4 mmol) in DMF (5 mL) was added NaH (413 mg, 10.3 mmol, 60%). After stirring at RT for 10 min, 2-(4-fluorophenyl)-2-methyloxirane (1.0 g, 6.8 mmol) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified through reverse phase HPLC to obtain the racemate which was separated by chiral preparative HPLC to obtain 138a and 138b. $^1$H NMR (CDCl$_3$, freebase) $\delta$ (ppm): 8.01 (s, 1H), 7.49 (s, 1H), 7.24 (m, 2H), 6.95 (t, 2H), 4.27 (dd, 2H), 3.62 (d, 1H), 3.5 (d, 1H), 2.8 (m, 3H), 2.49 (s, 3H), 2.45 (m, 1H), 2.4 (s, 3H), 1.53 (s, 3H).

Example 119: Preparation of Compound Nos. 139 and 139a-b.

[0768] A solution of 4-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-hydroxy-ethyl]-benzoic acid ethyl ester (90 mg, 0.229 mmol) in 25% ammonium hydroxide solution (5 mL) was stirred at 120 °C for 1 h. The progress of reaction was monitored by NMR and LCMS. The reaction mixture was cooled to RT, diluted with water and extracted with EtOAc (3x30mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 4-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-hydroxy-ethyl]-benzamide (3 mg) which was separated by chiral preparative HPLC to obtain 139a and 139b. $^1$H NMR (CD$_3$OD, TFA salt) $\delta$ (ppm): 7.18 (t, 2H), 7.4 (d, 1H), 7.31 (d, 2H), 7.23 (s, 1H), 7.03 (t, 1H), 336
5.08 (t, 1H), 4.64 (dd, 1H), 4.33 (m, 2H), 4.21 (dd, 1H), 3.71 (t, 1H), 3.45 (bs, 1H), 3.12 (m, 1H), 3.09 (d, 3H), 2.6 (d, 1H), 2.41 (s, 3H).

Example 120: Preparation of Compound Nos. 140 and 140a-b.

[0769] To a degassed solution of 1-(6-bromo-pyridin-3-yl)-2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethanol (1 g, 2.5 mmol) in DMF (10 mL) were added Pd(PPh₃)$_4$ (0.173 g, 0.15 mmol) and zinc cyanide (585 mg, 5.0 mmol) and the reaction mixture was stirred at 150 °C for 2 h. The reaction mixture was cooled to RT, diluted with EtOAc (250 mL) and filtered. The filtrate was washed with water (3×100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield 5-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-hydroxy-ethyl]-pyridine-2-carbonitrile (350 mg). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.55 (s, 1H), 7.38 (d, 1H), 7.23 (d, 1H), 6.93 (s, 1H), 6.81 (s, 1H), 6.74 (s, 1H), 4.96 (m, 1H), 4.11 (dd, 2H), 3.29 (dd, 2H), 2.95 (m, 1H), 2.88 (m, 1H), 2.86 (m, 2H), 2.5 (s, 6H). Separation by chiral HPLC provided enantiomers 140a and 140b.

Example 121: Preparation of Compound Nos. 141 and 141a-b.

[0770] To a solution of 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyrind-4-yl-ethanol (2.0 g, 9.04 mmol) in DMF (20 mL) was added sodium hydride (1.0 g, 25 mmol). After stirring at RT for 20 min, a solution of N,N-dimethyl carbamoyl chloride (1.9 g, 17.7 mmol) in DMF (5 mL) was added dropwise into the reaction mixture, which was stirred at RT for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice water (400 mL) and extracted with EtOAc (3×200 mL). The organic layer was washed with water (3×300 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5-7% MeOH in DCM) to yield N,N-dimethyl-carbamic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyrindin-4-yl-ethyl ester (100 mg). $^1$H NMR (CD$_3$OD, freebase) δ (ppm): 8.5 (d, 2H), 7.34 (d, 2H), 7.31 (d, 1H), 7.21 (s, 1H), 7.00 (d, 1H), 5.96 (t, 1H), 4.53 (dd, 1H), 4.45 (dd, 1H), 3.49 (t, 2H), 2.98 (m, 2H), 2.95 (m, 5H), 2.92 (s, 3H), 2.77 (s, 3H), 2.39 (s, 3H). Separation by chiral HPLC provided enantiomers 141a and 141b.

Example 122: Preparation of Compound Nos. 142 and 142a-b.

[0771] To an ice-cooled stirred solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (2.6 g, 13.24 mmol) in DMF (12 mL) was added sodium hydride (1.6 g, 39.72 mmol, 60%). After stirring at 0 °C for 10 min, 4-(oxiran-2-yl)benzonitrile (2.4 g, 16.55 mmol) was
added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was re-crystallized from ether (2.5 g) followed by chiral separation. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 7.55 (d, 2H), 1.76 (d, 2H), 7.11 (s, 1H), 7.04 (d, 1H), 6.91 (d, 1H), 5.01 (m, 1H), 4.1 (dd, 2H), 3.52 (dd, 2H), 2.79 (m, 2H), 2.67 (m, 2H), 2.46 (s, 3H), 2.43 (s, 3H).

**Example 123: Preparation of Compound Nos. 143 and 143a-b.**

A solution of 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (290 mg, 1.31 mmol) and sodium hydride (38 mg, 1.6 mmol) in DMF (6 mL) was stirred at 120 °C for 1 h. The reaction mixture was cooled to 0 °C and 2-(trifluoromethyl)-5-(2-methylxiran-2-yl)pyridine (400 mg, 1.97 mmol) was added dropwise into the reaction mixture, which was stirred at 120 °C for 2 h. The reaction mixture was cooled to RT and partitioned between EtOAc (60 mL) and water (15mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (1x20 mL). The combined organic layer was washed with water, followed by brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to yield title compound. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.79 (s, 1H), 7.21 (bs, 1H), 6.97 (s, 1H), 6.79 (d, 1H), 6.42 (bs, 2H), 4.15 (d,1H), 4.05 (d, 1H), 3.2 (m, 3H), 2.99 (s, 1H), 2.74 (t, 1H), 2.56 (t, 1H), 2.45 (s, 3H), 1.75 (s, 3H). Separation by chiral HPLC provided enantiomers 143a and 143b.

**Example 124: Preparation of Compound Nos. 144 and 144a-b.**

To a solution of 5-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-hydroxy-ethyl]-pyridine-2-carbonitrile (1.5 g, 4.3 mmol) in tert-butanol (30 mL) was added crushed KOH (728 mg, 13 mmol) and the reaction mixture was stirred at 80 °C for 1 h. The progress of reaction was monitored by LCMS. The reaction mixture was concentrated. The residue was diluted with water (50 mL) and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (2x100 mL), dried over anhydrous sodium sulfate and concentrated. The crude material was purified by reverse phase HPLC to yield 5-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-hydroxy-ethyl]-pyridine-2-carboxylic acid amide (200 mg). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.45 (d, 1H), 8.12 (t, 1H), 7.78 (s, 2H), 7.05 (m, 2H), 6.94 (t, 1H), 5.57 (bs,1H), 5.03 (m, 1H), 4.13 (s, 2H), 3.63 (m, 2H), 2.79
(m, 2H), 2.78 (bs 1H), 2.66 (d, 1H), 2.53 (d, 3H), 2.42 (s, 3H). Separation by chiral HPLC provided enantiomers 144a and 144b.

Example 125: Preparation of Compound Nos. 145 and 145a-b.

[0774] To an ice-cooled stirred solution of aza dimethyl-carboline (1.8 g, 8.9 mmol) in DMF (10 mL) was added sodium hydride (1.0 g, 26.86 mmol, 60%). After stirring at 0 °C for 10 min, 4-(oxiran-2-yl)benzonitrile (2.6 g, 17.9 mmol) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was re-crystallized from EtOH (825 mg). $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.03 (s, 1H), 7.58 (d, 2H), 7.51 (s, 1H), 7.39 (d, 2H), 7.1 (s 1H), 5.19 (m, 1H), 4.4 (dd, 1H), 4.26 (dd, 1H), 3.55 (dd, 2H), 2.75 (m, 1H), 2.64 (m 1H), 2.49 (s, 3H), 2.42 (s, 3H), 2.38 (m, 1H). Separation by chiral HPLC provides enantiomers 133a and 133b.

Example 126: Preparation of Compound Nos. 146 and 146a-b.

[0775] To a solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-(pyridin-3-yl)propan-2-ol (1.0 g, 2.98 mmol) in DMF (10 mL) was added sodium hydride (60%, 0.36 g, 8.95 mmol). After stirring at RT for 10 min, isobutyryl chloride (0.95 g, 8.95 mmol) was added dropwise into the reaction mixture, which was stirred at RT for 15 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched with water (5 mL), basified with sat. aq. sodium bicarbonate and extracted with EtOAc (3x50 mL). The organic layer was washed with water (3x50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-6% MeOH-DCM) to yield the title compound (186.3 mg), which was resolved by chiral preparative HPLC. $^1$H NMR (CDCl$_3$, freebase) δ (ppm): 8.5 (dd, 1H), 8.42 (s, 1H), 7.24 (d, 1H), 7.16 (m, 3H), 6.93 (d 1H), 4.26 (dd, 2H), 3.65 (dd, 2H), 2.7 (m, 1H), 2.55 (m, 3H), 2.56 (m, 1H), 2.49 (s 3H), 2.43 (s, 3H), 2.0 (m, 1H), 1.98 (s, 3H), 1.1 (m, 6H).

Example 127: Preparation of Compound Nos. 147 and 147a-b.

[0776] To a solution of isonicotinic acid (200 mg, 1.626 mmol) in DMF (10mL) was added potassium carbonate (560 mg, 4.065 mmol) and stirred the solution at 80 °C for 30 min. Methanesulfonic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl ester (455 mg, 1.138 mmol) was added portionwise into the reaction mixture, which was stirred at 80 °C 30 min. The progress of reaction was monitored by LCMS and TLC. The
reaction mixture was cooled to RT, diluted with water (30 mL) and extracted with EtOAc (2x50 mL). The combined organic layer was washed with water (4x50 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield isonicotinic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethylester (30 mg). 1H NMR (CDCl3, freebase) δ (ppm): 8.79 (d, 2H), 8.58 (d, 2H), 7.77 (d, 2H), 7.23 (d, 1H), 7.18 (s, 1H), 7.12 (d, 2H), 7.0 (d, 1H), 6.24 (t, 1H), 4.54 (dd, 1H), 4.35 (dd, 1H), 3.68 (s, 2H), 2.76 (t, 2H), 2.61 (m, 1H), 2.51 (s, 3H), 2.43 (s, 3H), 2.43 (m, 1H).

Separation by chiral HPLC provided enantiomers 147a and 147b.

Example 128: Preparation of Compound Nos. 148 and 148a-d.

[0777] To a solution of 8-aza-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (500 mg, 2.2 mmol) in DMF (5 mL) was added sodium hydride (264 mg, 6.6 mmol). After stirring for 5 min at RT, 2-methyl-5-(2-methyloxiran-2-yl)pyridine (656 mg, 4.4 mmol) was added into the reaction mixture, which was stirred at RT for 16 h. The progress of reaction was monitored by LCMS. The reaction mixture was quenched with ice-water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield title compound, which was resolved by chiral preparative HPLC. 1H NMR (CDCl3, freebase) δ (ppm): 8.48 (s, 1H), 8.03 (s, 1H), 7.55 (d, 1H), 7.53 (s, 1H), 6.98 (d, 1H), 4.41 (d, 1H), 4.23 (d, 1H), 3.22 (m, 2H), 3.0 (m, 1H), 2.8 (m, 1H), 2.6 (m, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.34 (m, 1H), 1.88 (m, 2H), 1.63 (s, 3H), 1.58 (m, 1H).

Example 129: Preparation of Compound Nos. 149 and 149a-b.

[0778] 5-(2-Azido-2-(pyridin-3-yl)propyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Crude) (500 mg, 1.4 mmol) was dissolved in EtOH (4 mL) and water (1 mL). Ammonium chloride (243 mg, 4.5 mmol) followed by zinc dust (293 mg, 4.5 mmol) were added to the reaction mixture and heated at 80 °C for 1 h. The reaction mixture was concentrated to dryness, basified with aqueous ammonia solution and extracted with EtOAc (150 mL). The organic layer was dried over sodium sulfate, evaporated in vacuo and purified by reverse phase HPLC to afford 2 mg of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-amine. 1H NMR (CD3OD, freebase): δ (ppm): 8.39 s (1H), 8.3 d (1H), 7.72 d (1H), 7.32 t (1H), 7.11 s (1H), 6.91 d (1H), 6.8 d (1H), 4.18 dd (2H), 3.61 dd (2H), 2.7 m (2H), 2.46 s (3H), 2.35 s (3H), 2.26 m (2H). Chiral HPLC provided enantiomers 149a and 149b.

Example 130: Preparation of Compound Nos. 150 and 150a-b.
A solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethyl methanesulfonate (250 mg, 0.62 mmol) in dimethyl amine (3 mL, 40% in water) was stirred at 90 °C for 16 h. The progress of reaction was monitored by LCMS. The reaction mixture was lyophilized and crude material was purified by reverse phase HPLC. The racemate was further separated into optically active forms by chiral preparative HPLC. \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 8.4 (d, 2H), 7.16 (s, 1H), 7.0 (d, 1H), 6.96 (m, 3H), 4.58 (dd, 1H), 4.0 (m, 1H), 3.62 (d, 1H), 3.58 (m, 1H), 3.4 (dd, 1H), 2.7 (t, 2H), 2.6 (t, 2H), 2.42 (s, 3H), 2.4 (s, 3H), 2.3 (s, 6H).

**Example 131: Preparation of Compound Nos. 151 and 151a-b.**

A solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethyl methanesulfonate (250 mg, 0.62 mmol) in methyl amine (3 mL, 40% in water) was stirred at 90 °C for 12 h. The progress of reaction was monitored by LCMS. The reaction mixture was extracted with EtOAc. The organic layer was dried and concentrated to get the crude product, which was purified by reverse phase HPLC to obtain the 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-N-methyl-1-(pyridin-4-yl)ethanamine. \(^1\)H NMR (CDCl\(_3\), freebase): \(\delta\) (ppm): 8.59 d (2H), 7.3 d (2H), 7.29 d (1H), 7.23 s (1H), 7.03 d (1H), 4.19 m (1H), 4.03 m (2H), 3.66 dd (2H), 2.8 m (3H), 2.6 m (1H), 2.55 s (3H), 2.47 s (3H), 2.18 s (3H). Chiral HPLC provided enantiomers 151a and 151b.

**Example 132: Preparation of Compound Nos. 152 and 152a-b.**

A solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethyl methanesulfonate (250 mg, 0.62 mmol) in pyrrolidine (2.5 mL) was irradiated in microwave at 90 °C for 1 h. The progress of reaction was monitored by LCMS. The volatiles were removed under reduced pressure. The residue was diluted with water and extracted with DCM. The organic layer was dried and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC. The racemate was further separated into optically active forms by chiral preparative HPLC. \(^1\)H NMR (CDCl\(_3\), freebase) \(\delta\) (ppm): 8.39 (d, 2H), 7.16 (s, 1H), 7.0 (d, 1H), 6.97 (m, 3H), 4.6 (dd, 1H), 4.0 (m, 1H), 3.79 (d, 1H), 3.6 (d, 1H), 3.57 (dd, 1H), 2.7-2.6 (m, 4H), 2.46-2.4 (m, 10H), 1.82 (m, 4H).

**Example 133: Preparation of Compound Nos. 153 and 153a-b.**

To a solution of 9-(2-azido-2-(pyridin-4-yl)ethyl)-2,6-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (800 mg, 2.3 mmol) in ethanol-water (9 mL:1 mL) were added zinc dust (600 mg, 9.2 mmol) and ammonium chloride (490 mg, 9.2 mmol) and the reaction mixture
stirred at 85 °C for 45 min. The reaction mixture was filtered and the filtrate concentrated. The residue was basified with aqueous ammonia and extracted with EtOAc (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC to yield 2-(2,6-dimethyl-3,4-dihydro-1H-pyrido[3,4-b]indol-9(2H)-yl)-1-(pyridin-4-yl)ethanamine (25 mg). The racemate can be further separated into the optically active forms by chiral preparative HPLC. \( \text{H NMR (CD}_{3}\text{OD, TFA salt)} \delta (\text{ppm}): 8.6 \text{ (s, 2H)}, 7.62 \text{ (bs, 2H)}, 7.23 \text{ (s, 1H)}, 7.0 \text{ (d, 1H)}, 6.98 \text{ (d, 1H)}, 4.9 \text{ (m, 1H)}, 4.8-4.58 \text{ (m, 3H)}, 4.0 \text{ (bs, 1H)}, 3.8 \text{ (bs, 1H)}, 3.6-3.4 \text{ (m, 2H)}, 3.1 \text{ (bs, 4H), 2.38 (s, 3H)}. \)

**Example 134: Preparation of Compound Nos. 154 and 154a-b.**

**[0783]** To a solution of 6-(2-azido-2-(pyridin-4-yl)ethyl)-3,9-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (188 mg, 0.522 mmol) in ethanol-water (9 mL:1 mL), zinc dust (135 mg, 2.08 mmol) and ammonium chloride (110 mg, 2.08 mmol) were added and the reaction mixture was stirred at 85 °C for 45 min. The reaction mixture was filtered and the filtrate concentrated. The residue was basified with aqueous ammonia and extracted with EtOAc (2x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by reverse phase HPLC to yield 2-(3,9-dimethyl-2,3,4,5-tetrahydroazepino[4,5-b]indol-6(1H)-yl)-1-(pyridin-4-yl)ethanamine (45 mg). The racemate can be further separated into the optically active forms by chiral preparative HPLC. \( \text{H NMR (CD}_{3}\text{OD, TFA salt)} \delta (\text{ppm}): 8.6 \text{ (d, 2H)}, 7.6 \text{ (d, 2H)}, 7.22 \text{ (s, 1H)}, 7.0 \text{ (s, 1H)}, 6.9 \text{ (s, 1H)}, 4.9 \text{ (m, 3H)}, 4.8 \text{ (m, 1H)}, 4.7 \text{ (m, 1H)}, 3.8-3.6 \text{ (m, 2H)}, 3.2 \text{ (m, 2H)}, 3.18-2.97 \text{ (m, 4H)}, 2.8 \text{ (bs, 1H)}, 2.38 \text{ (s, 3H)}. \)

**Example 135: Preparation of Compound Nos. 155 and 155a-d.**

**[0784]** The azide compound (350 mg, 0.940 mmol) was dissolved in EtOH-water (10 mL: 1 mL). Zinc dust (244 mg, 3.763 mmol) and ammonium chloride (199 mg, 3.763 mmol) were added and the mixture was heated at 85 °C for 45 min. After consumption of starting material, the reaction mixture was filtered through Celite and filtrate was concentrated to obtain the residue. The residue was basified with aq ammonia and extracted with EtOAc (2x70 mL). The combined organic layer was dried over sodium sulfate and concentrated to obtain the crude product, which was crystallized in diethyl ether to obtain 150 mg of desired product. \( \text{H NMR (CDCl}_{3}, \text{ freebase)} \delta (\text{ppm): 8.55 d (2H), 7.29 d (2H), 7.25 d (1H), 7.2 s (1H), 7.02 d (1H), 4.77} \)
m (2H), 4.49 t (1H), 4.1 m (1H), 4.08 m (2H), 3.51 m (1H), 2.7 dd (1H), 2.46 s (3H), 2.25 s (3H), 2.2 m (1H), 1.86 t (1H), 1.44 t (1H). Chiral HPLC provided enantiomers 155a and 155b.

**Example 136: Preparation of Compound Nos. 156 and 156a-b.**

[0785] To a solution of 5-(2-azido-2-(pyridin-4-yl)ethyl)-2,8-dimethyl-6-aza-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (160 mg, 0.461 mmol) in EtOH:water (4:0.4 mL) were added zinc dust (119.8 mg, 1.84 mmol) and ammonium chloride (99.59 mg, 1.84 mmol) and the reaction mixture was stirred at 80 °C for 1 h. The progress of reaction was monitored by NMR. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was basified with aqueous ammonia and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield the title compound. The racemate can be further separated into the optically active forms by chiral preparative HPLC. \(^1\)H NMR (CD\(_3\)OD, TFA salt) \(\delta\) (ppm): 8.8 (m, 2H), 8.19 (s, 1H), 7.9 (m, 2H), 7.7 (s, 1H), 5.3 (m, 1H), 4.8 (m, 2H), 4.63 (d, 1H), 4.25 (d, 1H), 3.85 (m, 1H), 3.5 (m, 1H), 3.2 (m, 2H), 3.17 (s, 3H), 2.4 (s, 3H).

**Example 137: Preparation of Compound Nos. 157 and 157a-b.**

[0786] To a solution of 5-[1-aminophenyl]-2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethyl]-pyridine-2-carbonitrile (400 mg, 1.15 mmol) in tert-butanol (20 mL) was added crushed KOH (194 mg, 3.47 mmol) and the reaction mixture was stirred at 80 °C for 1 h. The progress of reaction was monitored by LCMS. The reaction mixture was concentrated to dryness. The residue was diluted with water (50 mL) and extracted with EtOAc (2x100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 5-[1-aminophenyl]-2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethyl]-pyridine-2-carboxylic acid amide (70 mg). The racemate can be further separated into the optically active forms by chiral preparative HPLC. \(^1\)H NMR (CDCl\(_3\), free base) \(\delta\) (ppm): 8.5 (s, 1H), 8.2 (d, 1H), 7.9 (d, 1H), 7.2 (m, 2H), 7.0 (d, 1H), 5.6 (bs, 1H), 4.6 (t, 1H), 4.1 (d, 2H), 3.7 (q, 2H), 2.9 (t, 2H), 2.8 (m, 1H), 2.6 (m, 1H), 2.58 (s, 3H), 2.42 (s, 3H).

**Example 138: Preparation of Compound Nos. 158 and 158a-b.**

[0787] To a solution of 5-(2-azido-2-(pyridin-4-yl)ethyl)-8-methyl-6-aza-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (730 mg, 2.19 mmol) in EtOH:H\(_2\)O (15:1.5 mL) were added zinc dust (570 mg, 8.76 mmol) and ammonium chloride (473.5 mg, 8.76 mmol) and the reaction mixture was stirred at 80 °C for 1 h. The progress of reaction was monitored by NMR. The mixture was
filtered and the filtrate concentrated under reduced pressure. The residue was basified with aqueous ammonia and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield the title compound. The racemate can be further separated into the optically active forms by chiral preparative HPLC. $^1$H NMR (CDCl$_3$, free base) δ (ppm): 8.5 (d, 2H), 8.08 (s, 1H), 7.5 (s, 1H), 7.21 (d, 2H), 4.6 (t, 1H), 4.3 (dd, 1H), 4.2 (dd, 1H), 4.0 (s, 2H), 3.1 (m, 2H), 2.6 (d, 1H), 2.4 (s, 3H), 2.3 (d, 1H).

Example 139: Preparation of Compound Nos. 159 and 159a-b.

[0788] To a degassed solution of 4-(1-azido-2-(6-aza-2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethyl)benzonitrile (240 mg) in EtOAc:EtOH (7:7 mL) was added 10% Pd-C (100 mg), and hydrogen gas was bubbled into the reaction mixture with stirring at RT for 5 h. The progress of reaction was monitored by LCMS. The reaction mass was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified through reverse phase HPLC to yield the racemate (200 mg), which was separated by chiral preparative HPLC. $^1$H NMR (CDCl$_3$, free base) δ (ppm): 8.05 (s, 1H), 7.6 (d, 2H), 7.43 (m, 3H), 4.6 (t, 1H), 4.23 (dd, 2H), 3.7 (dd, 2H), 2.9 (m, 1H), 2.8 (m, 2H), 2.6 (s, 3H), 2.5 (m, 1H), 2.4 (s, 3H).

Example 140: Preparation of Compound Nos. 160 and 160a-b.

[0789] To a degassed solution of 4-(1-azido-2-(6-aza-8-methyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)ethyl)benzonitrile (219 mg) in EtOAc:EtOH (7:7 mL) was added 10% Pd-C (100 mg), and hydrogen gas was bubbled into the reaction mixture with stirring at RT for 5 h. The progress of reaction was monitored by LCMS. The reaction mass was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified through reverse phase HPLC to yield the racemate, which was separated by chiral preparative HPLC. $^1$H NMR (CDCl$_3$, free base) δ (ppm): 8.1 (s, 1H), 7.6 (d, 2H), 7.47 (m, 3H), 4.6 (t, 1H), 4.2 (m, 2H), 4.18 (s, 2H), 3.21 (bm, 1H), 2.8 (bm, 1H), 2.7-2.6 (m, 2H), 2.6 (s, 3H).

Example 141:

[0790] Compound Nos. 161, 161a-d, 162, 162a-d, 163, 163a-d, 164, 164a-d, 165, 165a-b, 166, 166a-b, 167, 167a-b, 171 and 171a-b can be prepared in analogous fashion to Compound Nos. 3 and 3a-b, using appropriately functionalized aromatic-tethered oxiranes as reagents. Compound Nos. 173, 174, 175 and 176 were prepared in analogous fashion to Compound Nos. 3 and 3a-b,
using appropriately functionalized aromatic-tethered oxiranes as reagents. Chiral HPLC provided, respectively, Compound Nos. 173a-b, 174a-b, 175a-b and 176a-d.

Example 142: Preparation of Compound Nos. 168 and 168a-d.

[0791] To a solution of 4-[1-hydroxy-2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-ethyl]-pyridine-2-carbonitrile (68 mg, 0.18 mmol) in 1 mL THF was added NaOH (21 mg, 0.52 mmol) i.e. 0.5 mL 1M NaOH solution and was heated at 80 °C for overnight. The reaction was monitored with LCMS. The solvent was removed under reduced pressure to obtain the crude product that was purified by reverse phase HPLC to obtain pure product as the TFA salt (8 mg). 1H NMR (CD3OD, TFA salt): δ (ppm): 8.55 t (1H), 7.95 d (1H), 7.61 d (1H), 7.25 s (1H), 7.2 dd (1H), 7.01 dd (1H), 5.16 m (1H), 5.03 m (1H), 4.36 m (2H), 3.61 m (3H), 3.3 m (1H), 2.7 m (2H), 2.4 d (3H), 2.2 m (3H). Chiral HPLC provides diastereomers 168a-d.

Example 143: Preparation of Compound Nos. 169 and 169a-b.

[0792] A solution of 5-(1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-hydroxypropan-2-yl)pyridine-2-carbonitrile (1.6 g) in ethanol (4 mL) and 10 N NaOH (15 mL) was stirred at 100 °C for 45 min. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was lyophilized and purified with reverse phase HPLC to obtain the 5-(1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-hydroxypropan-2-yl)pyridine-2-carboxylic acid. 1H NMR (CD3OD, TFA salt): δ (ppm): 8.6 d (1H), 8.1 s (1H), 8.0 d (1H), 7.19 d (1H), 6.9 d (1H), 6.8 d (1H), 4.7 dd (1H), 4.37 m (2H), 4.3 m (1H), 3.8 m (1H), 3.52 m (2H), 3.15 m (1H), 3.1 s (3H), 2.38 s (3H), 1.7 d (3H). Chiral HPLC provides enantiomers 169a and 169b.

Example 144: Preparation of Compound Nos. 170 and 170a-b.

[0793] These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 5-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)nictinate as starting material. Separation by chiral HPLC provides enantiomers 170a-b.

Example 145: Preparation of Compound Nos. 177 and 177a-d.

[0794] These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 4-(1-hydroxy-2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)ethyl)nictinate as starting material. Separation by chiral HPLC provides diastereomers 177a-d.
Example 146: Preparation of Compound Nos. 178 and 178a-b.

These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 3-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)picolinate as starting material. Separation by chiral HPLC provides enantiomers 178a-b.

Example 147: Preparation of Compound Nos. 179 and 179a-b.

3-(1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)isonicotinonitrile (200 mg, 0.554 mmol) was dissolved in ethanol and an aqueous solution of sodium hydroxide was added and heated at 100 °C for 1 h. The reaction was monitored by LCMS. After completion of reaction, solvent was removed under reduced pressure and the crude product was purified by reverse phase HPLC (8 mg). 1H NMR (CD3OD, freebase): 9.3 s (1H), 8.42 s (1H), 8.3 s (1H), 7.4 d (1H), 7.1 s (1H), 6.8 d (1H), 4.4 s (2H), 4.2 m (2H), 3.58 m (2H), 3.55 m (1H), 3.3 m (1H), 3.1 s (3H), 2.4 s (3H), 1.54 s (3H). Chiral separation provides enantiomers 179a and 179b.

Example 148: Preparation of Compound Nos. 46 and 46a-b.

These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 3-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)picolinate as starting material. Separation by chiral HPLC provides enantiomers 46a-b.

Example 149: Preparation of Compound Nos. 50 and 50a-d.

These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 4-(1-ethoxy-2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)ethyl)nicotinate as starting material. Separation by chiral HPLC provides diastereomers 50a-d.

Example 150: Preparation of Compound Nos. 104 and 104a-b.

These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 4-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-hydroxy-3-(pyridin-3-yl)butanoate as starting material. Separation by chiral HPLC provides enantiomers 104a-b.

Example 151: Preparation of Compound Nos. 123 and 123a-b.

These compounds can be prepared in analogous fashion to Compound Nos. 67 and 67a-b, using ethyl 5-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-
hydroxypropan-2-yl)nicotinate as starting material. Separation by chiral HPLC provides enantiomers 123a-b.

Example 152: Preparation of Compound No. 180.

[0801] 2,3,4,5-Tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (200 mg, 1 mmol), 4-methylstyrene (239 mg, 2.3 mmol) and NaH (120 mg, 60% dispersion in oil, 3 mmol) were heated in DMSO (4 mL) at 120 °C overnight (16h) after which methanol was added and the contents were concentrated to dryness. The resulting crude product was purified by reverse-phase chromatography (C-18, 500 mm × 50 mm, Mobile Phase A= 0.05% TFA in water, B= 0.05% TFA in acetonitrile, Gradient: 10% B to 80% B in 30 min, injection vol: 5 mL) and/or silica gel (230-400 mesh) chromatography eluting with methanol-dichloromethane gradient to obtain 20 mg (6.2% yield) of 2,3,4,5-tetrahydro-2,8-dimethyl-5-(4-methylphenethyl)-1H-pyrido[4,3-b]indole as a trifluoroacetate salt. ¹H NMR (CDCl₃, TFA salt) δ (ppm): 13.3 (bs, 1H), 7.4-7.0 (m, 5H), 6.80-6.70 (d, 2H), 4.7-4.6 (d, 1H), 4.40-4.22 (m, 1H), 4.20-4.10 (m, 1H), 4.10-4.0 (d, 1H), 3.5-3.4 (t, 1H), 3.20-3.17 (t, 1H), 3.0 (t, 2H), 2.80 (s, 3H), 2.7-2.61 (m, 1H), 2.40 (s, 3H), 2.23 (s, 3H), 2.2-2.1 (m, 1H).

Example 153: Preparation of Compound No. 181.

[0802] 2,3,4,5-Tetrahydro-2-methyl-5-(4-methylphenethyl)-1H-pyrido[4,3-b]indole was prepared from 2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (200 mg, 1.07 mmol), 4-methylstyrene (1.41 mL, 10.7 mmol) and NaH (250 mg, 60% dispersion in oil, 6.25 mmol) in DMF (6 mL) at 200 °C for 16h to obtain 7 mg of 2,3,4,5-tetrahydro-2-methyl-5-(4-methylphenethyl)-1H-pyrido[4,3-b]indole after purification. ¹H NMR (CDCl₃, TFA salt) δ (ppm): 7.45-7.40 (d, 2H), 7.25-7.16 (m, 2H), 7.1-6.9 (d, 2H), 6.8-6.7 (d, 2H), 4.7 (d, 1H), 4.4-4.3 (m, 1H), 4.20-4.03 (m, 2H), 3.55-3.40 (m, 1H), 3.22-3.10 (m, 1H), 3.09-2.90 (m, 2H), 2.83 (s, 3H), 2.65 (m, 1H), 2.35 (s, 3H), 2.2 (m, 1H).

Example 154: Preparation of Compound No. 182.

[0803] 2,3,4,5-Tetrahydro-2-methyl-5-phenethyl-1H-pyrido[4,3-b]indole was prepared from 2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (200 mg, 1.07), styrene (1.23 mL mmol, 10.65) and NaH (250 mg, 6.25 mmol) in DMF (6 mL) at 200 °C for 16h to obtain 15 mg of 2,3,4,5-tetrahydro-2-methyl-5-phenethyl-1H-pyrido[4,3-b]indole after purification. ¹H NMR (CDCl₃, TFA salt) δ (ppm): 7.5-7.10 (m, 7H), 6.9-6.8 (m, 2H), 4.6 (d, 1H), 4.30-4.19 (m, 2H), 4.05 (d, 1H), 3.62-3.40 (m, 1H), 3.20-3.0 (m, 3H), 2.9 (s, 3H), 2.7-2.6 (t, 1H), 2.2-2.1 (t, 1H).
Example 155: Preparation of Compound Nos. 183 and 183a-b.

[0804] 3, 4, 5-Tetrahydro-2,8-dimethyl-1H-pyrido[4, 3-b]indole (2.2 g, 11 mmol, 1 equiv.), 4-
methylstyrene oxide (5.8 g, 44 mmol, 4 equiv.) and NaH (1.3 g, 32.5 mmol, 2.95eq) were heated
in DMF (70 mL) at 120 °C for 16 h (overnight). The contents were quenched by MeOH and
evaporated to dryness. The resulting crude product was purified by silica gel chromatography
(230-400 mesh) using EtOAc-hexane gradient to obtain 1.3 g of racemic 2-(1,2,3,4-tetrahydro-2,
8-dimethylpyrido[4, 3-b]indol-5-yl)-1-p-tolylethanol. The free base was converted into its
hydrochloride salt by treatment of ethanolic HCl. \(^1\)H NMR (DMSO-d6, HCl salt) δ (ppm):
10.30 (s, 1H), 7.42-7.0 (m, 7H), 5.6 (m, 1H), 4.90-4.80 (m, 1H), 4.60-4.55 (d, 1H), 4.30-4.00 (m,
3H), 3.70 (s, 1H), 3.4 (m, 1H), 3.22-3.10 (d, 1H), 3.00-2.90 (m, 3H), 2.80-2.60 (d, 1H), 2.40 (s,
3H), 2.30 (s, 3H). Separation by chiral HPLC provided enantiomers 183a and 183b.

Example 156: Preparation of Compound No. 184.

[0805] 5-(4-Chlorophenethyl)-2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole was
prepared from 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (500 mg, 2.5 mmol), 4-
chlorostyrene (3.18 mL, 25 mmol) and NaH (300 mg, 7.5 mmol) in DMF (10 mL) at 180 °C
overnight (16h) to obtain 15 mg of 5-(4-chlorophenethyl)-2,3,4,5-tetrahydro-2,8-dimethyl-1H-
pyrido[4,3-b]indole after purification. \(^1\)H NMR (CDCl3, TFA salt) δ (ppm): 7.30-7.08 (m, 5H),
6.85-6.78 (d, 2H), 4.70-4.60 (d, 1H), 4.40-4.20 (m, 1H), 4.20-4.0 (m, 2H), 3.65-3.50 (m,
1H), 3.10-3.00 (m, 3H), 2.85 (s, 3H), 2.80 (m, 1H), 2.45 (s, 3H), 2.2 (m, 1H).

Example 157: Preparation of Compound No. 185.

[0806] 1-(8-Chloro-1,2,3,4-tetrahydro-2-methylpyrido[4,3-b]indol-5-yl)-2-(pyridin-4-
yl)propan-2-ol (1 equiv.) was refluxed with 25% sulfuric acid for 2h. The reaction mixture was
cooled to 5 °C with an ice-water bath. KOH (15% aq. solution) was added dropwise to the
reaction mixture until pH 9-10 was achieved. The reaction mixture was extracted with EtOAc.
The combined organic layers were washed with water followed by brine, dried over anhydrous
sodium sulfate and evaporated under vacuum. The crude product was purified by column
chromatography over silica gel (100-200 mesh) using a gradient of MeOH-EtOAc (0-10%) to
obtain a mixture of 8-chloro-2,3,4,5-tetrahydro-2-methyl-5-(E)-2-(pyridin-4-yl)prop-1-enyl-
1H-pyrido[4,3-b]indole and 8-chloro-2,3,4,5-tetrahydro-2-methyl-5-(2-(pyridin-4-yl)allyl)-1H-
pyrido[4,3-b]indole, which were separated by HPLC. \(^1\)H NMR (DMSO, Oxalate Salt) δ (ppm):
8.60 (d, 2H), 7.62 (m, 3H), 7.40 (s, 1H), 7.30 (d, 1H), 7.20 (d, 1H), 4.40 (m, 2H), 3.10 (m, 4H),
2.99 (s, 3H), 1.90 (s, 3H).
Example 158: Preparation of Compound No. 186.

1-(1,2,3,4-Tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-(6-methylpyridin-3-yl)propan-2-ol (1 equiv.) was refluxed with 25% sulfuric acid for 2h. The reaction mixture was cooled to 5 °C with an ice-water bath. KOH (15% aq. solution) was added dropwise to the reaction mixture until pH 9-10 was achieved. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with water followed by brine, dried over anhydrous sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography over silica gel (100-200 mesh) using a gradient of MeOH-EtOAc (0-10%) to obtain a mixture of 2,3,4,5-tetrahydro-2,8-dimethyl-5- ((E)-2-(6-methylpyridin-3-yl)prop-1-enyl)-1H-pyrido[4,3-b]indole and 2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)allyl)-1H-pyrido[4,3-b]indole, which were separated by HPLC. 1HNMR (CD3OD, TFA salt) δ (ppm) 8.90 (s, 1H), 8.60 (d, 1H), 7.80 (d, 1H), 7.30 (d, 2H), 7.16 (d, 1H), 7.10 (d, 1H), 4.78 (m, 1H), 4.40 (m, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 3.20 (m, 2H), 3.16 (s, 3H), 3.80 (s, 3H), 2.42 (s, 3H), 2.05 (s, 3H).

Example 159: Preparation of Compound No. 187.

To a solution of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) in DME (4 mL) was added Pd(PPh3)4 (15 mg, 0.0128 mmol) and the solution was purged with nitrogen for 5 min. Potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 2-(dimethylamino)- pyrimidine-5-boronic acid pinacol ester (128 mg, 0.515 mmol) were added, the reaction mixture was purged with nitrogen and refluxed for 45 min. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered. The filtrate was concentrated under reduced pressure and purified by reverse phase HPLC to obtain the desired product as its TFA salt. 1H NMR (CD3OD, TFA salt) δ (ppm): 8.78 (s, 2H), 7.31 (s, 1H), 7.10 (m, 3H), 4.78 (d, 1H), 4.38 (d, 1H), 3.82 (m, 1H), 3.59 (m, 1H), 3.38 (s, 6H), 3.10 (m, 5H), 2.41 (s, 3H), 1.97 (s, 3H).

Example 160: Preparation of Compound No. 188.

5-(1-Bromoprop-1-en-2-yl)-2-methylpyridine (254 mg, 1.2 mmol) was dissolved in DMF (2 mL) and potassium phosphate (424 mg, 2 mmol), copper(I) iodide (19 mg, 0.1 mmol) and L-proline (23 mg, 0.2 mmol) were added, followed by 2,3,4,5-tetrahydro-2,6,8-trimethyl-1H-pyrido[4,3-b]indole (214 mg, 1 mmol). The reaction mixture was purged with nitrogen and heated at 140 °C overnight. The reaction mixture was cooled to RT, diluted with ice water and
DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D’UN TOME.

CECI EST LE TOME 1 DE 2
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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:
CLAIMS

What is claimed is:

1. A method of lowering blood pressure in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I):

   ![Chemical Structure](image)

   (I)

or a salt, solvate or N-oxide thereof, wherein:

   R<sup>1</sup> is H; C<sub>1</sub>-C<sub>5</sub> alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl, SO<sub>3</sub>H, SR<sup>1a</sup>, S(O)R<sup>1a</sup>, SO<sub>2</sub>R<sup>1a</sup> and perhaloalkyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C<sub>2</sub>-C<sub>5</sub> alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or --C(O)O-C<sub>1</sub>-C<sub>5</sub> alkyl; or is taken together with R<sup>2a</sup> or R<sup>3a</sup> to form a propylene (--CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>--) moiety or a butylene (--CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>--) moiety; or is taken together with R<sup>4a</sup> or R<sup>5a</sup>, where present, to form an ethylene (--CH<sub>2</sub>CH<sub>2</sub>--) moiety or a propylene (--CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>--) moiety;

   R<sup>1a</sup> is H or optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl;

   R<sup>2a</sup> is H; optionally substituted C<sub>1</sub>-C<sub>5</sub> alkyl; optionally substituted C<sub>2</sub>-C<sub>5</sub> alkenyl; or optionally substituted aryl; or is taken together with R<sup>1</sup> or R<sup>5a</sup>, where present, to form a propylene (--CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>--) moiety or a butylene (--CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>--) moiety; or is taken together with R<sup>3a</sup> to form an ethylene (--CH<sub>2</sub>CH<sub>2</sub>--) moiety or a propylene (--CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>--) moiety;
moiety; or is taken together with $R^{4a}$, where present, to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety;

$R^{3a}$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^1$ or $R^{4a}$, where present, to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{2a}$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{5a}$, where present, to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety;

$R^{4a}$, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R$^{14a}$)R$^{15a}$; -C(O)N(R$^{14a}$)R$^{15a}$; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^1$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{2a}$ to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety; or is taken together with $R^{5a}$, where present, to form a methylene (-CH$_2$-) moiety;

$R^{5a}$, where present, is H H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R$^{14a}$)R$^{15a}$; -C(O)N(R$^{14a}$)R$^{15a}$; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^{2a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^1$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{3a}$ to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety; or is taken together with $R^{4a}$, where present, to form a methylene (-CH$_2$-) moiety;

each $R^{2b}$ and $R^{2b}$ is independently H, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted C$_2$-C$_5$ alkenyl, or optionally substituted aryl;

each $R^{4b}$ and $R^{4b}$, where present, is independently H, halo, optionally substituted C$_1$-C$_5$ alkyl, optionally substituted C$_2$-C$_5$ alkenyl, or optionally substituted aryl;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

each $X_1$, $X_2$, X and U is independently N or CR$_5$;

each $R^6$ is independently H; hydroxyl; halo; C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_2$-C$_5$ alkenyl; optionally substituted C$_1$-C$_5$ alkoxy; or optionally substituted –C(O)C$_1$-C$_5$ alkyl;
R^7 is H; halo; optionally substituted C_1-C_5 alkyl; or optionally substituted aryl; or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiet; or is taken together with R^9 to form a C_3-C_5 alkylene when R^8 and R^{10} are taken together to form a bond;

R^8 is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carbonylalkoxy; N(R^{11})R^{12}; SR^{13}, S(O)R^{13}; SO_2R^{13}; -OC(O)N(R^{14})R^{15}; -C(O)NR^{14})R^{15}; optionally substituted -OC(O)-aryl; optionally substituted -OC(O)-heteroaryl; -OC(O)C_1-C_6 alkyl optionally substituted with amino or carboxyl; or -OC_1-C_5 alkyl optionally substituted with carboxyl; or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiet; or is taken together with R^{10} to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^7 to form a C_3-C_5 alkylene when R^8 and R^{10} are taken together to form a bond;

R^{10} is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkylene;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene;

each R^{14a}, and R^{15a} is independently H or optionally substituted C_1-C_5 alkyl; and
Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

2. The method of claim 1, wherein the individual has high blood pressure.

3. The method of claim 2, wherein the method reduces systolic blood pressure of the individual.

4. The method of claim 2, wherein the method reduces diastolic blood pressure of the individual.
5. The method of claim 2, wherein the method reduces (i) mean arterial blood pressure, or (ii) pulse pressure, of the individual.

6. The method of any one of claims 3 to 5, wherein the method does not substantially increase heart rate of the individual.

7. The method of any one of claims 1 to 6, wherein the individual has one or more risk factors for developing high blood pressure.

8. A method of (i) increasing renal blood flow, and/or (ii) decreasing sodium reabsorption, in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

R\(^1\) is H; C\(_1\)-C\(_5\) alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl, SO\(_3\)H, SR\(^{1a}\), S(O)R\(^{1a}\), SO\(_2\)R\(^{1a}\) and perhaloalkyl; C\(_2\)-C\(_8\) cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C\(_2\)-C\(_5\) alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or –C(O)O-C\(_1\)-C\(_5\) alkyl; or is taken together with R\(^{2a}\) or R\(^{3a}\) to form a propylene (–CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (–CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety; or is taken together with R\(^{4a}\) or R\(^{5a}\), where present, to form an ethylene (–CH\(_2\)CH\(_2\)-) moiety or a propylene (–CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

R\(^{1a}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl;
R^{2a} is H; optionally substituted C_{1-6} alkyl; optionally substituted C_{2-5} alkenyl; or optionally substituted aryl; or is taken together with R^1 or R^{5a}, where present, to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{3a} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{4a}, where present, to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety;

R^{3a} is H; optionally substituted C_{1-6} alkyl; optionally substituted C_{2-5} alkenyl; or optionally substituted aryl; or is taken together with R^1 or R^{4a}, where present, to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{2a} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{5a}, where present, to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety;

R^{4a}, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R^{14a})R^{15a}, -C(O)N(R^{14a})R^{15a}; optionally substituted C_{1-5} alkyl; optionally substituted C_{2-5} alkenyl; or optionally substituted aryl; or is taken together with R^{3a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{1} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{2a} to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety; or is taken together with R^{5a}, where present, to form a methylene (-CH_{2}-) moiety;

R^{5a}, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R^{14a})R^{15a}, -C(O)N(R^{14a})R^{15a}; optionally substituted C_{1-5} alkyl; optionally substituted C_{2-5} alkenyl; or optionally substituted aryl; or is taken together with R^{2a} to form a propylene (-CH_{2}CH_{2}CH_{2}-) moiety or a butylene (-CH_{2}CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{1} to form an ethylene (-CH_{2}CH_{2}-) moiety or a propylene (-CH_{2}CH_{2}CH_{2}-) moiety; or is taken together with R^{3a} to form a methylene (-CH_{2}-) moiety or an ethylene (-CH_{2}CH_{2}-) moiety; or is taken together with R^{4a}, where present, to form a methylene (-CH_{2}-) moiety;

each R^{2b} and R^{3b} is independently H, optionally substituted C_{1-5} alkyl, optionally substituted C_{2-5} alkenyl, or optionally substituted aryl;

each R^{4b} and R^{5b}, where present, is independently H, halo, optionally substituted C_{1-5} alkyl, optionally substituted C_{2-5} alkenyl, or optionally substituted aryl;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;
each X^1, X^2, X and U is independently N or CR^6;
each R^6 is independently H; hydroxyl; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C_2-C_5 alkenyl; optionally substituted C_1-C_5 alkoxy; or optionally substituted – \text{C(O)}C_1-C_5 alkyl;

R^7 is H; halo; optionally substituted C_1-C_5 alkyl; or optionally substituted aryl; or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R^9 to form a C_3-C_5 alkyne when R^8 and R^10 are taken together to form a bond;

R^8 is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carbonylalkoxy; N(R^{11})R^{12}; SR^{13}, S(O)R^{13}; SO_2R^{13}; -OC(O)N(R^{14})R^{15}; -C(O)N(R^{14})R^{15}; optionally substituted -OC(O)-aryl; optionally substituted -OC(O)-heteroaryl; -OC(O)C_1-C_6 alkyl optionally substituted with amino or carboxyl; or –OC_1-C_5 alkyl optionally substituted with carboxyl; or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R^10 to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^7 to form a C_3-C_5 alkyne when R^8 and R^10 are taken together to form a bond;

R^10 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkyne;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkyne;

each R^{14a}, and R^{15a} is independently H or optionally substituted C_1-C_5 alkyl; and

Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

9. The method of claim 8, wherein the method results in increase in renal blood flow.

10. The method of claim 8, wherein the method results in decrease in sodium reabsorption.
11. The method of claim 9 or 10, wherein the method results in increase in urine sodium content and/or increase in urine volume.

12. The method of claim 9 or 10, wherein the method results in any one or more of: (i) reducing edema, (ii) reducing elevated blood urea nitrogen to creatinine (BUN/Cr) ratio, and (iii) decreasing creatinine levels.

13. The method of any one of claims 1 to 12, wherein the individual has or is at risk of developing acute or chronic congestive heart failure, acute decompensated congestive heart failure, acute or chronic renal failure, or acute or chronic renal failure due to renal insufficiency.

14. A method of treating a disease or condition that is responsive to any one or more of: (i) a decrease in blood pressure; (ii) an increase in renal blood flow; and (iii) a decrease of sodium reabsorption, comprising administering to an individual in need thereof an effective amount of a compound of the formula (I):

\[
\text{\text{R}}^1 \text{H; C}_1\text{-C}_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl, SO}_3\text{H, SR}^{\text{\text{I}}}\text{, S(O)R}^{\text{\text{I}}}\text{, SO}_2\text{R}^{\text{\text{I}}}\text{ and perhaloalkyl; C}_5\text{-C}_8 \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C}_2\text{-C}_5 \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or } \text{C}(\text{O})\text{H-C}_1\text{-C}_5 \text{ alkyl; or is taken together with}}
\]
R²a or R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety; or is taken together with R⁴a or R⁵a, where present, to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety;

R¹a is H or optionally substituted C₁-C₅ alkyl;

R²a is H; optionally substituted C₁-C₅ alkyl; optionally substituted C₂-C₅ alkenyl; or optionally substituted aryl; or is taken together with R¹ or R⁵a, where present, to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety; or is taken together with R³a to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety; or is taken together with R⁴a, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety;

R³a is H; optionally substituted C₁-C₅ alkyl; optionally substituted C₂-C₅ alkenyl; or optionally substituted aryl; or is taken together with R¹ or R⁴a, where present, to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety; or is taken together with R²a to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety; or is taken together with R⁵a, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety;

R⁴a, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)NR¹⁴aR¹⁵a; -C(O)NR¹⁴aR¹⁵a; optionally substituted C₁-C₅ alkyl; optionally substituted C₂-C₅ alkenyl; or optionally substituted aryl; or is taken together with R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety; or is taken together with R¹ to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety; or is taken together with R⁵a, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety; or is taken together with R⁴a, where present, to form a methylene (-CH₂-) moiety;

R⁵a, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)NR¹⁴aR¹⁵a; -C(O)NR¹⁴aR¹⁵a; optionally substituted C₁-C₅ alkyl; optionally substituted C₂-C₅ alkenyl; or optionally substituted aryl; or is taken together with R²a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety; or is taken together with R¹ to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety; or is taken together with R⁵a, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety; or is taken together with R⁴a, where present, to form a methylene (-CH₂-) moiety;

Each R²b and R³b is independently H, optionally substituted C₁-C₅ alkyl, optionally substituted C₂-C₅ alkenyl, or optionally substituted aryl.
each R^{4b} and R^{5b}, where present, is independently H, halo, optionally substituted C_1-C_5 alkyl, optionally substituted C_2-C_5 alkenyl, or optionally substituted aryl;
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;
each X^1, X^2, X and U is independently N or CR^6;
each R^6 is independently H; hydroxyl; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C_2-C_5 alkenyl; optionally substituted C_1-C_5 alkoxy; or optionally substituted –C(O)C_1-C_5 alkyl;

R^7 is H; halo; optionally substituted C_1-C_5 alkyl; or optionally substituted aryl; or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R^3 to form a C_3-C_5 alkylene when R^8 and R^{10} are taken together to form a bond;

R^8 is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carbonylalkoxy; N(R^{11})R^{12}; SR^{13}, S(O)R^{13}; SO_2R^{13}; -OC(O)N(R^{14})R^{15}; -C(O)N(R^{14})R^{15}; optionally substituted -OC(O)-aryl; optionally substituted -OC(O)-heteroaryl; -OC(O)C_1-C_6 alkyl optionally substituted with amino or carboxyl; or –OC_1-C_5 alkyl optionally substituted with carboxyl; or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R^{10} to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^7 to form a C_3-C_5 alkylene when R^8 and R^{10} are taken together to form a bond;

R^{10} is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkylene;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene;

each R^{14a} and R^{15a} is independently H or optionally substituted C_1-C_5 alkyl; and Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

15. The method of claim 14, wherein the disease or condition is hypertension.
16. The method of claim 15, wherein the disease or condition is treatment-resistant hypertension.

17. The method of claim 14, wherein the disease or condition is hypertensive emergency.

18. The method of claim 14, wherein the disease or condition is a cardiac or renal disease or condition.

19. The method of any one of claims 1-18, wherein one of $X^1$, $X^2$, $X$ and $U$ is N, and the other three of $X^1$, $X^2$, $X$ and $U$ are independently CR$^6$.

20. The method of any one of claims 1-18, wherein two of $X^1$, $X^2$, $X$ and $U$ is N, and the other two of $X^1$, $X^2$, $X$ and $U$ are independently CR$^6$.

21. The method of any one of claims 1-18, wherein each $X^1$, $X^2$, $X$ and $U$ is independently CR$^6$.

22. The method of any one of claims 1-21, wherein Q is:

   unsubstituted aryl;

   unsubstituted heteroaryl;

   aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, $C_1$-$C_5$ alkyl, $C_3$-$C_8$ cycloalkyl, halo-substituted $C_1$-$C_5$ alkyl, halo-substituted $C_3$-$C_8$ cycloalkyl, $C_1$-$C_5$ alkoxy, $C_3$-$C_8$ cycloalkoxy, cyano, carboxyl, aminoacyl, $N(R^{16})(R^{17})$, -C(O)OR$^{18}$, SR$^{18}$, S(O)R$^{18}$ and SO$_2$R$^{18}$; or

   heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, $C_1$-$C_5$ alkyl, $C_3$-$C_8$ cycloalkyl, halo-substituted $C_1$-$C_5$ alkyl, halo-substituted $C_3$-$C_8$ cycloalkyl, $C_1$-$C_5$ alkoxy, $C_3$-$C_8$ cycloalkoxy, cyano, carboxyl, aminoacyl, $N(R^{16})(R^{17})$, -C(O)OR$^{18}$, SR$^{18}$, S(O)R$^{18}$ and SO$_2$R$^{18}$,

   wherein each $R^{16}$ and $R^{17}$ is independently H or optionally substituted $C_1$-$C_5$ alkyl, or $R^{16}$ and $R^{17}$ are taken together to form $C_3$-$C_5$ alkylene, and

   wherein $R^{18}$ is an optionally substituted $C_1$-$C_5$ alkyl.
23. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (A-III):

![Chemical Structure](image)

(A-III)

or a salt, solvate or N-oxide thereof, wherein:

- $R^1$ is H; C$_1$-C$_5$ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_3$-C$_6$ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C$_2$-C$_5$ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or $-$C(O)O-C$_1$-C$_5$ alkyl; or is taken together with $R^{2a}$ or $R^{3a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{4a}$ or $R^{5a}$, where present, to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety;

- each $n$ and $m$ is 1, or $n$ is 0 and $m$ is 1, or $n$ is 1 and $m$ is 0;

- $R^{2a}$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^1$ or $R^{5a}$, where present, to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{3a}$ to form an ethylene (-CH$_2$CH$_2$-) moiety or a propylene (-CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{4a}$, where present, to form a methylene (-CH$_2$-) moiety or an ethylene (-CH$_2$CH$_2$-) moiety;

- $R^{3a}$ is H; optionally substituted C$_1$-C$_5$ alkyl; optionally substituted C$_2$-C$_5$ alkenyl; or optionally substituted aryl; or is taken together with $R^1$ or $R^{4a}$, where present, to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken together with $R^{5a}$ to form a propylene (-CH$_2$CH$_2$CH$_2$-) moiety or a butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-) moiety; or is taken
together with \( R^{2a} \) to form an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety or a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^{5a} \), where present, to form a methylene (\(-\text{CH}_2\)-) moiety or an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety;

\( R^{4a} \) is H; optionally substituted \( \text{C}_1-\text{C}_5 \) alkyl; optionally substituted \( \text{C}_2-\text{C}_5 \) alkenyl; or optionally substituted aryl; or is taken together with \( R^{3a} \) to form a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^1 \) to form an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety or a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^{2a} \) to form a methylene (\(-\text{CH}_2\)-) moiety or an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^{5a} \), where present, to form a methylene (\(-\text{CH}_2\)-) moiety;

\( R^{5a} \) is H; optionally substituted \( \text{C}_1-\text{C}_5 \) alkyl; optionally substituted \( \text{C}_2-\text{C}_5 \) alkenyl; or optionally substituted aryl; or is taken together with \( R^{2a} \) to form a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety or a butylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^1 \) to form an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety or a propylene (\(-\text{CH}_2\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^{3a} \) to form a methylene (\(-\text{CH}_2\)-) moiety or an ethylene (\(-\text{CH}_2\text{CH}_2\)-) moiety; or is taken together with \( R^{4a} \), where present, to form a methylene (\(-\text{CH}_2\)-) moiety;

each \( R^{2b}, R^{3b}, R^{4b} \) and \( R^{5b} \) is independently H, optionally substituted \( \text{C}_1-\text{C}_5 \) alkyl, optionally substituted \( \text{C}_2-\text{C}_5 \) alkenyl, or optionally substituted aryl;

\( X \) is \( \text{N} \) or \( \text{CR}^{6a} \);  
\( t \) is 1, 2 or 3;

each \( R^6 \) and \( R^{6a} \) is independently H; hydroxyl; halo; \( \text{C}_1-\text{C}_5 \) alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; \( \text{C}_2-\text{C}_5 \) alkenyl; optionally substituted \( \text{C}_1-\text{C}_5 \) alkoxy; or optionally substituted \(-\text{C}(\text{O})\text{C}_1-\text{C}_5 \) alkyl;

\( R^7 \) is H; halo; optionally substituted \( \text{C}_1-\text{C}_5 \) alkyl; or optionally substituted aryl; or is taken together with \( R^8 \) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with \( R^9 \) to form a \( \text{C}_2-\text{C}_5 \) alkylene when \( R^8 \) and \( R^{10} \) are taken together to form a bond;

\( R^8 \) is H; halo; hydroxyl; \( \text{N}(\text{R}^{11})\text{R}^{12} \); \( \text{SR}^{13} \); \( \text{S}(\text{O})\text{R}^{13} \); \( \text{SO}_2\text{R}^{13} \); \( -\text{OC}(\text{O})\text{N}(\text{R}^{14})\text{R}^{15} \); \( -\text{OC}(\text{O})\)-aryl; \( -\text{OC}(\text{O})\)-heteroaryl; or \( -\text{OC}(\text{O})\text{C}_1-\text{C}_5 \) alkyl optionally substituted with amino; or is taken together with \( R^7 \) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with \( R^{10} \) to form a bond;

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R^9 is H or optionally substituted C_1-C_5 alkyl; or is taken together with R^7 to form a C_3-C_5 alkyne when R^8 and R^{10} are taken together to form a bond;

R^{10} is H or optionally substituted C_1-C_5 alkyl; or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl; or R^{11} and R^{12} are taken together to form C_3-C_5 alkyne;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkyne; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

24. The method of claim 23, wherein X is CR^6a, wherein each R^6a is independently H, halo or C_1-C_5 alkyl.

25. The method of claim 24, wherein R^6a is H.

26. The method of any one of claims 23 to 25, wherein each R^6 is independently H, halo or C_1-C_5 alkyl.

27. The method of claim 23, wherein X is N.

28. The method of any one of claims 23-27, wherein R^1 is H or C_1-C_5 alkyl.

29. The method of any one of claims 23-28, wherein each R^{2a} and R^{3a} is H.

30. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl.

31. The method of any one of claims 23-30, wherein, R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl.
32. The method of claim 31, wherein R^8 is hydroxyl.

33. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl, and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl.

34. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl.

35. The method of any one of claims 23-29, wherein R^7 is C_1-C_5 alkyl, and R^8 is H, hydroxyl, N(R^{11})R^{12} or -OC(O)C_1-C_5 alkyl.

36. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl, and R^8 is H or hydroxyl.

37. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl, and R^8 is hydroxyl.

38. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is hydroxyl.

39. The method of any one of claims 23-29, wherein R^7 is methyl, and R^8 is hydroxyl.

40. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is NH_2.

41. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is -OC(O)C_1-C_5 alkyl.

42. The method of any one of claims 23-41, wherein R^9 is H or C_1-C_5 alkyl.

43. The method of any one of claims 23-42, wherein R^{10} is H or C_1-C_5 alkyl.

44. The method of any one of claims 23-41, wherein each R^9 and R^{10} is H.
45. The method of any one of claims 23-41, wherein one of R^9 and R^{10} is H and the other is C_1-C_5 alkyl.

46. The method of any one of claims 23-45, wherein Q is:

- unsubstituted pyridyl;
- unsubstituted pyrimidyl;
- unsubstituted pyrazinyl;
- unsubstituted phenyl;
- unsubstituted imidazolyl;
- unsubstituted triazolyl;

  pyridyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and -C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl;

  pyrimidyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and -C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl;

  pyrazinyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and -C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl;

  phenyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and -C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl;

  imidazolyl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and -C(O)NR^{16}R^{17}, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl; or
triazolyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, carboxyl and -C(O)NR₁⁶R¹⁷, wherein each R¹⁶ and R¹⁷ is independently H or optionally substituted C₁-C₅ alkyl.

47. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (A-III A):

![Chemical Structure](image)

(A-III A)

or a salt, solvate or N-oxide thereof, wherein:

R¹ is H; C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₃-C₆ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; or -C(O)O-C₁-C₅ alkyl, or is taken together with R²a or R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety:

R²a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R³a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

X is N or CR⁶a;

each R⁶ and R⁶a is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R^9 to form a C_3-C_5 alkylene when R^8 and R^10 are taken together to form a bond;

R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, (OC(O))N(R^{14})R^{15}, (OC(O))-aryl, -(OC(O))-heteroaryl, or -(OC(O))C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R^10 to form a bond;

R^9 is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^7 to form a C_3-C_5 alkylene when R^8 and R^10 are taken together to form a bond;

R^{10} is H or optionally substituted C_1-C_5 alkyl, or is taken together with R^8 to form a bond;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkylene;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl, or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

48. The method of claim 47, wherein X is CH.

49. The method of claim 47, wherein X is N.

50. The method of any one of claims 47-49, wherein R^1 is H or CH_3.

51. The method of any one of claims 47-50, wherein R^{2a} is H or is taken together with R^1 to form a propylene (CH_2CH_2CH_2-) moiety.
52. The method of any one of claims 47-51, wherein R^{3a} is H.

53. The method of any one of claims 47-52, wherein each R^6 and R'^{6a} is independently H, halo or C_{1-5} alkyl.

54. The method of any one of claims 47-53, wherein R^7 is H or CH₃.

55. The method of any one of claims 47-54, wherein R^8 is hydroxyl.

56. The method of any one of claims 47-55, wherein Q is:

- unsubstituted pyridyl;
- unsubstituted pyrimidyl;
- unsubstituted pyrazinyl;
- unsubstituted phenyl;
- unsubstituted imidazolyl;
- unsubstituted triazolyl;
- pyridyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃;
- pyrimidyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃;
- pyrazinyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; or
- phenyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃.

57. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (A-IIID):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R²a or R³a to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R²a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

R³a is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety;

X is N or CR⁶a;

each R⁶ and R⁶a is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted -C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl, or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R⁹ to form a C₃-C₅ alkylenne when R⁸ and R¹₀ are taken together to form a bond;

R⁸ is H, halo, hydroxyl, N(R¹¹)R¹₂, SR¹³, S(O)R¹³, SO₂R¹³, -OC(O)N(R¹⁴)R¹⁵, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C₁-C₅ alkyl optionally substituted with amino, or is taken
together with R\textsuperscript{7} and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R\textsuperscript{10} to form a bond;

R\textsuperscript{9} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{7} to form a C\textsubscript{3}-C\textsubscript{5} alkylene when R\textsuperscript{8} and R\textsuperscript{10} are taken together to form a bond;

R\textsuperscript{10} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or is taken together with R\textsuperscript{8} to form a bond;

each R\textsuperscript{11} and R\textsuperscript{12} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or R\textsuperscript{11} and R\textsuperscript{12} are taken together to form C\textsubscript{3}-C\textsubscript{5} alkylene;

R\textsuperscript{13} is H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl;

each R\textsuperscript{14} and R\textsuperscript{15} is independently H or optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, or R\textsuperscript{14} and R\textsuperscript{15} are taken together to form a C\textsubscript{3}-C\textsubscript{5} alkylene; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\textsubscript{1}-C\textsubscript{5} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl, halo-substituted C\textsubscript{1}-C\textsubscript{5} alkyl, halo-substituted C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{1}-C\textsubscript{5} alkoxy, C\textsubscript{3}-C\textsubscript{8} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\textsubscript{1}-C\textsubscript{5} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl, halo-substituted C\textsubscript{1}-C\textsubscript{5} alkyl, halo-substituted C\textsubscript{3}-C\textsubscript{8} cycloalkyl, C\textsubscript{1}-C\textsubscript{5} alkoxy, C\textsubscript{3}-C\textsubscript{8} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

58. The method of claim 57, wherein X is CH.

59. The method of claim 57 or 58, wherein R\textsuperscript{1} is H or CH\textsubscript{3}.

60. The method of any one of claims 57-59, wherein each R\textsuperscript{6} and R\textsuperscript{6a} is independently H, halo or C\textsubscript{1}-C\textsubscript{5} alkyl.

61. The method of any one of claims 57-60, wherein R\textsuperscript{7} is H or CH\textsubscript{3}.

62. The method of any one of claims 57-61, wherein R\textsuperscript{8} is hydroxyl.

63. The method of any one of claims 57-62, wherein Q is:

unsubstituted pyridyl;

unsubstituted pyrimidyl;
unsubstituted pyrazinyl;
unsubstituted phenyl;
unsubstituted imidazolyl;
unsubstituted triazolyl;
pyridyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃;
pyrimidyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃;
pyrazinyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃; or
phenyl substituted with halo, CH₃, CF₃, CONH₂, OH, or OCH₃.

64. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (A-IIIE-2):

![Chemical Structure](image)

or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl;
R^6 is H, hydroxyl, halo, C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C_1-C_5 alkoxy or optionally substituted -C(O)C_1-C_5 alkyl;

R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

R^8 is H, halo, hydroxyl, N(R^{11})R^{12}, SR^{13}, S(O)R^{13}, SO_2R^{13}, -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkyne;

R^{13} is H or optionally substituted C_1-C_5 alkyl;

each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkyne; and

each Y^1, Y^2, Y^3, Y^4 and Y^5 is independently N or CR^4 such that no more than two of Y^1, Y^2, Y^3, Y^4 and Y^5 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3.

65. The method of claim 64, wherein one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the other four of Y^1, Y^2, Y^3, Y^4 and Y^5 are independently CR^4.

66. The method of claim 64, wherein Y^5 is CH, and each Y^1, Y^2, Y^3 and Y^4 is independently N or CR^4 such that two of Y^1, Y^2, Y^3 and Y^4 are N.

67. The method of any one of claims 64-66, wherein each R^4 is independently H, halo, CH_3, CF_3, or OCH_3.

68. The method of any one of claims 64-67, wherein R^1 is H or CH_3.

69. The method of any one of claims 64-68, wherein R^6 is CH_3 or chloro.

70. The method of any one of claims 64-69, wherein R^7 is H or CH_3.

71. The method of any one of claims 64-70, wherein R^8 is hydroxyl.
72. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (A-IIIIE-6):

\[
\begin{align*}
R^6 & \text{ is H, hydroxyl, halo, C}_1\text{-C}_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C}_3\text{-C}_8 \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C}_2\text{-C}_5 \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C}_1\text{-C}_5 \text{ alkyl;} \\
R^6 & \text{ is H, hydroxyl, halo, C}_1\text{-C}_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C}_1\text{-C}_5 \text{ alkoxy or optionally substituted -C(O)C}_1\text{-C}_5 \text{ alkyl;} \\
R^7 & \text{ is H, halo, optionally substituted C}_1\text{-C}_5 \text{ alkyl, or optionally substituted aryl, or is taken together with R}^8 \text{ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;} \\
R^8 & \text{ is H, halo, hydroxyl, N(R}^{11})R^{12}, \text{ SR}^{13}, \text{ S(O)R}^{13}, \text{ SO}_2R^{13}, -\text{OC(O)N(R}^{14})R^{15}, -\text{OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C}_1\text{-C}_5 \text{ alkyl optionally substituted with amino, or is taken together with R}^7 \text{ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R}^{10} \text{ to form a bond;} \\
\text{each R}^{11} \text{ and R}^{12} & \text{ is independently H or optionally substituted C}_1\text{-C}_5 \text{ alkyl, or R}^{11} \text{ and R}^{12} \text{ are taken together to form C}_3\text{-C}_5 \text{ alkylene;} \\
R^{13} & \text{ is H or optionally substituted C}_1\text{-C}_5 \text{ alkyl;} \\
\text{each R}^{14} \text{ and R}^{15} & \text{ is independently H or optionally substituted C}_1\text{-C}_5 \text{ alkyl; or R}^{14} \text{ and R}^{15} \text{ are taken together to form a C}_3\text{-C}_5 \text{ alkylene;} \\
\end{align*}
\]

or a salt, solvate or N-oxide thereof, wherein:

\[
\begin{align*}
R^6 & \text{ is H, hydroxyl, halo, C}_1\text{-C}_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C}_3\text{-C}_8 \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C}_2\text{-C}_5 \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C}_1\text{-C}_5 \text{ alkyl;} \\
R^6 & \text{ is H, hydroxyl, halo, C}_1\text{-C}_5 \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C}_1\text{-C}_5 \text{ alkoxy or optionally substituted -C(O)C}_1\text{-C}_5 \text{ alkyl;} \\
R^7 & \text{ is H, halo, optionally substituted C}_1\text{-C}_5 \text{ alkyl, or optionally substituted aryl, or is taken together with R}^8 \text{ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;} \\
R^8 & \text{ is H, halo, hydroxyl, N(R}^{11})R^{12}, \text{ SR}^{13}, \text{ S(O)R}^{13}, \text{ SO}_2R^{13}, -\text{OC(O)N(R}^{14})R^{15}, -\text{OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C}_1\text{-C}_5 \text{ alkyl optionally substituted with amino, or is taken together with R}^7 \text{ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R}^{10} \text{ to form a bond;} \\
\text{each R}^{11} \text{ and R}^{12} & \text{ is independently H or optionally substituted C}_1\text{-C}_5 \text{ alkyl, or R}^{11} \text{ and R}^{12} \text{ are taken together to form C}_3\text{-C}_5 \text{ alkylene;} \\
R^{13} & \text{ is H or optionally substituted C}_1\text{-C}_5 \text{ alkyl;} \\
\text{each R}^{14} \text{ and R}^{15} & \text{ is independently H or optionally substituted C}_1\text{-C}_5 \text{ alkyl; or R}^{14} \text{ and R}^{15} \text{ are taken together to form a C}_3\text{-C}_5 \text{ alkylene;} \\
\end{align*}
\]

499
Q is

\[
\begin{align*}
\text{Z}^4 &\quad \text{Z}^1, \\
\text{Z}^3 &\quad \text{Z}^2, \\
\text{Z}^5 &\quad \text{Z}^6, \\
\text{Z}^{12} &\quad \text{Z}^9, \\
\text{Z}^{11} &\quad \text{Z}^{10},
\end{align*}
\]

wherein

- each $\text{Z}^1$, $\text{Z}^2$, $\text{Z}^3$ and $\text{Z}^4$ is independently N or CR$^4$ such that no more than two of $\text{Z}^1$, $\text{Z}^2$, $\text{Z}^3$ and $\text{Z}^4$ are N, wherein R$^4$ is H, halo, CH$_3$, CF$_3$, or OCH$_3$;
- each $\text{Z}^5$ and $\text{Z}^{10}$ is independently O, S or NR$^{4a}$, wherein R$^{4a}$ is H or CH$_3$; and
- each $\text{Z}^6$, $\text{Z}^7$, $\text{Z}^8$, $\text{Z}^9$, $\text{Z}^{11}$ and $\text{Z}^{12}$ is independently N or CR$^4$ wherein R$^4$ is H, halo, CH$_3$, CF$_3$, or OCH$_3$.

73. The method of claim 72, wherein Q is selected from the group consisting of:

\[
\begin{align*}
\text{R}^4 &\quad \text{N} &\quad \text{R}^{4a}, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^4, \\
\text{R}^4 &\quad \text{N} &\quad \text{O}, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^{4a}, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^4, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^4, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^{4a}, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^4, \\
\text{R}^4 &\quad \text{N} &\quad \text{R}^4.
\end{align*}
\]
74. The method of claim 72 or 73, wherein R\(^1\) is H or CH\(_3\).

75. The method of any one of claims 72-74, wherein R\(^6\) is CH\(_3\) or chloro.

76. The method of any one of claims 72-75, wherein R\(^7\) is H or CH\(_3\).

77. The method of any one of claims 72-76, wherein R\(^8\) is hydroxyl.

78. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (C-IA):

\[
\text{(C-IA)}
\]

or a salt, solvate or N-oxide thereof, wherein:
R^6 is H; halo; C_{1-5} alkyl optionally substituted with 1 to 3 substitutents independently selected from halogen atoms and hydroxyl; C_{2-5} alkenyl; or -C(OR)^11;

R^7 is H or optionally substituted C_{1-5} alkyl;

R^8 is H; hydroxyl; or -OC(O)C_{1-5} alkyl optionally substituted with amino; N(R^11)R^{12};

SR^{13}, S(O)R^{13}, or SO_2R^{13};

each R^11, R^{12} and R^{13} is independently H or optionally substituted C_{1-5} alkyl;

each X^1, X^2 and X is N or CH such that no more than two of X^1, X^2 and X are N; and

each Y^1, Y^2, Y^3 and Y^4 is N or CR^4 such that no more than two of Y^1, Y^2, Y^3 and Y^4 are N, and wherein each R^4 is independently H, halo, CH_3, CF_3, or OCH_3.

79. The method of claim 78, wherein each of X^1, X^2 and X is CH.

80. The method of claim 78 or 79, wherein R^6 is CH_3 or chloro.

81. The method of any one of claims 78-80, wherein R^7 and R^8 are H.

82. The method of any one of claims 78-81, wherein one of Y^1, Y^2, Y^3 and Y^4 is N and the remaining three of Y^1, Y^2, Y^3 and Y^4 are CR^4, and wherein each R^4 is independently H, halo, CH_3, CF_3, or OCH_3.

83. The method of any one of claims 78-82, wherein each of Y^1, Y^3 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^2 is N.

84. The method of any one of claims 78-82, wherein each of Y^1, Y^2 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^3 is N.

85. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (D-IIA-1), (E-IIA-1), (E-IIA-2), (F-IIA-1), (F-IIA-2), (G-IIA-1), or (G-IIA-2):
or a salt, solvate or N-oxide thereof, wherein:
R⁶ is H; halo; C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halogen atoms and hydroxyl; C₃-C₈ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halogen atoms and hydroxyl; C₂-C₅ alkenyl; or – C(Ø)OR¹¹;

R⁷ is H or optionally substituted C₁-C₅ alkyl;

R⁸ is H; hydroxyl; or -OC(Ø)C₁-C₅ alkyl optionally substituted with amino, N(R¹¹)R¹², SR¹³, S(Ø)R¹³ or SO₂R¹³;

each R¹¹, R¹² and R¹³ is independently H or optionally substituted C₁-C₅ alkyl; and each Y¹, Y², Y³ and Y⁴ is N or CR⁴ such that no more than two of Y¹, Y², Y³ and Y⁴ are N, and wherein R³ is H, halo, CH₃, CF₃, or OCH₃.

86. The method of claim 85, wherein R⁶ is unsubstituted C₁-C₅ alkyl or halo.

87. The method of claim 85 or 86, wherein R⁷ and R⁸ are H.

88. The method of any one of claims 85-87, wherein one of Y¹, Y², Y³ and Y⁴ is N and the remaining three of Y¹, Y², Y³ and Y⁴ are CR⁴, and wherein each R⁴ is independently H, halo, CH₃, CF₃, or OCH₃.

89. The method of any one of claims 85-88, wherein each of Y¹, Y³ and Y⁴ is independently CR⁴, wherein R⁴ is H or CH₃, and Y² is N.

90. The method of any one of claims 85-88, wherein each of Y¹, Y² and Y⁴ is independently CR⁴, wherein R⁴ is H or CH₃, and Y² is N.

91. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (B-I):
or a salt, solvate or N-oxide thereof, wherein:

R¹ is H, C₁-C₅ alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₃-C₆ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C₂-C₅ alkenyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, or -C(O)O-C₁-C₅ alkyl, or is taken together with R₂ₐ or R₃ₐ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R₃ₐ or R₅ₐ, where present, to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

R₂ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ or R₅ₐ, where present, to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R₃ₐ to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety, taken together with R₄ₐ, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety;

R₃ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R¹ or R₄ₐ, where present, to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R₂ₐ to form an ethylene (-CH₂CH₂-) moiety or a propylene (-CH₂CH₂CH₂-) moiety, taken together with R₅ₐ, where present, to form a methylene (-CH₂-) moiety or an ethylene (-CH₂CH₂-) moiety;

R₄ₐ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R₃ₐ to form a propylene (-CH₂CH₂CH₂-) moiety or a butylene (-CH₂CH₂CH₂CH₂-) moiety, or is taken together with R¹ to form an ethylene
(-CH₂CH₂⁻) moiety or a propylene (-CH₂CH₂CH₂⁻) moiety, or is taken together with R²⁸ to form a methylene (-CH₂⁻) moiety or an ethylene (-CH₂CH₂⁻) moiety, or is taken together with R⁵₅, where present, to form a methylene (-CH₂⁻) moiety;

R⁵₅ is H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with R²⁸ to form a propylene (-CH₂CH₂CH₂⁻) moiety or a butylene (-CH₂CH₂CH₂CH₂⁻) moiety, or is taken together with R¹ to form an ethylene (-CH₂CH₂⁻) moiety or a propylene (-CH₂CH₂CH₂⁻) moiety, or is taken together with R³ to form a methylene (-CH₂⁻) moiety or an ethylene (-CH₂CH₂⁻) moiety, or is taken together with R⁴, where present, to form a methylene (-CH₂⁻) moiety;

each R²ᵇ, R³ᵇ, R⁴ᵇ and R⁵ᵇ is independently H, optionally substituted C₁-C₅ alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR⁶₅;

t is 1, 2 or 3;

each R⁶ and R⁶₅ is independently H, hydroxyl, halo, C₁-C₅ alkyl optionally substituted with 1-3 substituents selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted C₁-C₅ alkoxy or optionally substituted –C(O)C₁-C₅ alkyl;

R⁷ is H, halo, optionally substituted C₁-C₅ alkyl, or optionally substituted aryl;

R⁸ is azido, acylamino, carboxyl, carbonylalkoxy, –OC(O)C₁-C₅ alkyl substituted with carboxyl, or –OC₁-C₅ alkyl optionally substituted with carboxyl;

each R⁹ and R¹⁰ is independently H or optionally substituted C₁-C₅ alkyl; and

Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C₁-C₅ alkyl, C₅-C₈ cycloalkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₃-C₈ cycloalkyl, C₁-C₅ alkoxy, C₃-C₈ cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

92. The method of claim 91, wherein X is CR⁶₅, wherein each R⁶₅ is independently H, halo or C₁-C₅ alkyl.

93. The method of claim 91 or 92, wherein each R⁶ is independently H, halo or C₁-C₅ alkyl.

94. The method of claim 91, wherein X is N.
95. The method of any one of claims 91-94, wherein R^1 is H or C_{1-5} alkyl.

96. The method of any one of claims 91-95, wherein each R^{2a} and R^{3a} is H.

97. The method of any one of claims 91-96, wherein R^7 is H or optionally substituted C_{1-5} alkyl.

98. The method of any one of claims 91-97, wherein, R^8 is azido.

99. The method of any one of claims 91-98, wherein R^9 is H or C_{1-5} alkyl.

100. The method of any one of claims 91-99, wherein R^{10} is H or C_{1-5} alkyl.

101. The method of any one of claims 91-100, wherein Q is:

unsubstituted aryl;

unsubstituted heteroaryl;

aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1-5} alkyl, C_{3-8} cycloalkyl, halo-substituted C_{1-5} alkyl, halo-substituted C_{3-8} cycloalkyl, C_{1-5} alkoxy, C_{3-8} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or

heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_{1-5} alkyl, C_{3-8} cycloalkyl, halo-substituted C_{1-5} alkyl, halo-substituted C_{3-8} cycloalkyl, C_{1-5} alkoxy, C_{3-8} cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino.

102. The method of any one of claims 1-18, wherein the compound is selected from Table I, Table II, Table III, Table IV or Table V; or a salt, solvate or N-oxide thereof.

103. The method of any one of claims 1-18, wherein the compound is Compound No. 1 to 343, II-1 to II-265, III-1 to III-368, IV-1 to IV-244 or V-1 to V-23; or a salt, solvate or N-oxide thereof.
104. The method of any one of claims 1-18, wherein the compound is selected from the group consisting of Compound Nos. 3a, 3b, 39a, 4a, 5b, 13b, 14a, 41a, 74a, 26a, 26b, 27a, 29b, 31a, 127a, 129d, 134b, 14b, 148#1, 173a, 174a, 150a, 176a, IV-210a, 151a, II-4b, II-132b, 148b, 141b, 154b, II-135b, II-138, II-139, II-140, V-22, II-244a, II-7, II-146a, II-151b, II-152a, II-227c, II-220, II-148a, II-13a, II-212a, II-260a and II-260b; or a salt, solvate or N-oxide thereof.

105. The method of any one of claims 1-18, wherein the compound is selected from the group consisting of Compound Nos. 3a, 3b, 4a, 4b, 5a, 5b, 6, 7a, 7b, 8a, 8b, 9, 9a, 9b, 10, 10a, 10b, 11, 11a, 11b, 12, 12a, 12b, 13a, 13b, 14, 14a, 14b, 15a, 15b, 16, 16a, 16b, 17, 17a, 17b, 18, 18a, 18b, 19, 19a, 19b, 20, 20a, 20b, 21, 21a, 21b, 22a, 22b, 23, 23a, 23b, 24, 24a, 24b, 25, 25a, 25b, 26, 26a, 26b, 26c, 26d, 27, 27a, 27b, 28, 28a, 28b, 29a, 29b, 30a, 30b, 31a, 31b, 36, 37, 37c, 37d, 39a, 39b, 40, 40a, 40b, 41, 41a, 41b, 42, 42a, 42b, 43a, 43b, 44, 44a, 44b, 45, 45a, 45b, 47a, 47b, 47c, 47d, 48a, 48b, 49a, 49b, 51, 51a, 51b, 52, 52a, 52b, 53, 53a, 53b, 54, 54a, 54b, 55, 55a, 55b, 56, 56a, 56b, 57, 57a, 57b, 58, 58a, 58b, 59, 59a, 59b, 63, 63a, 63b, 64, 65, 66, 67, 68, 69, 69a, 69b, 70, 71, 72, 75, 75a, 75b, 75c, 75d, 76, 76a, 76b, 76c, 76d, 77, 78, 79, 80, 81, 82, 90a, 90b, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 124, 125, 126, 127a, 127b, 128a, 128b, 129a, 129b, 129c, 129d, 130a, 130b, 131a, 131b, 133a, 133b, 134a, 134b, 135a, 135b, 136a, 136b, 137a, 137b, 138a, 138b, 139, 139a, 139b, 140, 140a, 140b, 141, 141a, 141b, 142, 142a, 142b, 143, 143a, 143b, 144, 144a, 144b, 145, 146, 146a, 146b, 147, 147a, 147b, 148, 148a, 148b, 148c, 148d, 149, 149a, 149b, 150, 150a, 150b, 151, 151a, 151b, 152, 152a, 152b, 153, 154, 154a, 154b, 155, 155a, 155b, 156, 157, 158, 159, 159a, 159b, 160, 160a, 160b, 168, 169, 170, 171, 172a, 172b, 173, 173a, 173b, 174, 174a, 174b, 175, 175a, 175b, 176, 176a, 176b, 177, 178, 179, 189, 190, 191, 193a, 193b, 194a, 194b, 196, 196a, 196b, 197, 197a, 197b, 198, 198a, 198b, 198c, 198d, 199a, 199b, 203a, 203b, 203c, 211a, 211b, 221a, 221b, 223a, 223b, 225a, 225b, 231a, 231b, 253a, 253b, 255a, 255b, 257a, 257b, 269, 270, 271, 272a, 272b, 273, 274, 274a, 274b, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288a, 288b, 289a, 289b, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 314a, 314b, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 336a, 336b, 338, 338a, 338b, 339a, 339b, II-1a, II-1b, II-2, II-3, II-4a, II-4b, II-5, II-6a, II-6b, II-7, II-7a, II-7b, II-8,

106. The method of any one of claims 1 to 105, wherein the compound is an adrenergic receptor \( \alpha_{2B} \) antagonist.
107. The method of claim 106, wherein the compound is also an adrenergic receptor $\alpha_{1B}$ antagonist.

108. The method of claims 106 or 107, wherein the compound is also an adrenergic receptor $\alpha_{1D}$ antagonist.

109. A kit comprising (i) a compound of formula (I)

\[
\begin{align*}
\text{R}^1 & \text{ is H; C}_{1-5} \text{ alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl, SO}_2\text{H, SR}^{1a}, \text{S(O)R}^{1a}, \text{SO}_2\text{R}^{1a} \text{ and perhaloalkyl; C}_{5-8} \text{ cycloalkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C}_{2-5} \text{ alkenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; or -C(O)O-C}_{1-5} \text{ alkyl; or is taken together with R}^{2a} \text{ or R}^{2a} \text{ to form a propylene (-CH}_2\text{CH}_2\text{CH}_2-) moiety or a butylene (-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-) moiety; or is taken together with R}^{4a} \text{ or R}^{5a} \text{, where present, to form an ethylene (-CH}_2\text{CH}_2-) moiety or a propylene (-CH}_2\text{CH}_2\text{CH}_2-) moiety;}
\text{R}^{1a} & \text{ is H or optionally substituted C}_{1-5} \text{ alkyl;}
\text{R}^{2a} & \text{ is H; optionally substituted C}_{1-5} \text{ alkyl; optionally substituted C}_{2-5} \text{ alkenyl; or optionally substituted aryl; or is taken together with R}^1 \text{ or R}^{5a}, \text{ where present, to form a propylene (-CH}_2\text{CH}_2\text{CH}_2-) moiety or a butylene (-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-) moiety; or is taken together with R}^{3a} \text{ to form an ethylene (-CH}_2\text{CH}_2-) moiety or a propylene (-CH}_2\text{CH}_2\text{CH}_2-) moiety;}
\end{align*}
\]
moiety; or is taken together with R\textsuperscript{4a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{3a} is H; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{1} or R\textsuperscript{4a}, where present, to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{2a} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{5a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety;

R\textsuperscript{4a}, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R\textsuperscript{14a})R\textsuperscript{15a}; -C(O)N(R\textsuperscript{14a})R\textsuperscript{15a}, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{3a} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{1} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{2a} to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{5a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety;

R\textsuperscript{5a}, where present, is H; halo; hydroxyl; cyano; carboxyl; -OC(O)N(R\textsuperscript{14a})R\textsuperscript{15a}; -C(O)N(R\textsuperscript{14a})R\textsuperscript{15a}, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl; optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl; or optionally substituted aryl; or is taken together with R\textsuperscript{3a} to form a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety or a butylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{1} to form an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety or a propylene (-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{2a} to form a methylene (-CH\textsubscript{2}-) moiety or an ethylene (-CH\textsubscript{2}CH\textsubscript{2}-) moiety; or is taken together with R\textsuperscript{4a}, where present, to form a methylene (-CH\textsubscript{2}-) moiety;

each R\textsuperscript{2b} and R\textsuperscript{3b} is independently H, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl, or optionally substituted aryl;

each R\textsuperscript{4b} and R\textsuperscript{5b}, where present, is independently H, halo, optionally substituted C\textsubscript{1}-C\textsubscript{5} alkyl, optionally substituted C\textsubscript{2}-C\textsubscript{5} alkenyl, or optionally substituted aryl;

each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

each X\textsuperscript{1}, X\textsuperscript{2}, X and U is independently N or CR\textsuperscript{6};

each R\textsuperscript{6} is independently H; hydroxyl; halo; C\textsubscript{1}-C\textsubscript{5} alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C\textsubscript{2}-C\textsubscript{5} alkenyl; optionally substituted C\textsubscript{1}-C\textsubscript{5} alkoxy; or optionally substituted –C(O)C\textsubscript{1}-C\textsubscript{5} alkyl;
R⁷ is H; halo; optionally substituted C₁-C₅ alkyl; or optionally substituted aryl; or is taken together with R⁸ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R⁹ to form a C₃-C₅ alkyne when R⁸ and R¹⁰ are taken together to form a bond;

R⁸ is H; halo; hydroxyl; azido; aminoacyl, carboxyl; carbonylalkoxy; N(R¹¹)R¹²; SR¹³, S(O)R¹³; SO₂R¹³; -OC(O)N(R¹⁴)R¹⁵; -C(O)N(R¹⁴)R¹⁵; optionally substituted -OC(O)-aryl; optionally substituted -OC(O)-heteroaryl; -OC(O)C₁-C₆ alkyl optionally substituted with amino or carboxyl; or -OC₁-C₅ alkyl optionally substituted with carboxyl; or is taken together with R⁷ and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety; or is taken together with R¹⁰ to form a bond;

R⁹ is H or optionally substituted C₁-C₅ alkyl, or is taken together with R⁷ to form a C₃-C₅ alkyne when R⁸ and R¹⁰ are taken together to form a bond;

R¹⁰ is H or optionally substituted C₁-C₅ alkyl, or is taken together with R⁸ to form a bond;

each R¹¹ and R¹² is independently H or optionally substituted C₁-C₅ alkyl, or R¹¹ and R¹² are taken together to form C₃-C₅ alkyne;

R¹³ is H or optionally substituted C₁-C₅ alkyl;

each R¹⁴ and R¹⁵ is independently H or optionally substituted C₁-C₅ alkyl; or R¹⁴ and R¹⁵ are taken together to form a C₃-C₅ alkyne;

each R¹⁴a, and R¹⁵a is independently H or optionally substituted C₁-C₅ alkyl; and

Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl,

or a pharmaceutically acceptable salt thereof, and (ii) instructions for use according to the method of any one of claims 1-18.

110. A kit comprising (i) a compound of formula (A-IIIa):
wherein:

\( R^1 \) is H; \( C_1\text{-}C_5 \) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; \( C_3\text{-}C_6 \) cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; \( C_2\text{-}C_5 \) alkenyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl; or -C(O)O-C\(_1\text{-}C_5\) alkyl, or is taken together with \( R^{2a} \) or \( R^{3a} \) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

\( R^{2a} \) is H, optionally substituted \( C_1\text{-}C_3 \) alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with \( R^1 \) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

\( R^{3a} \) is H, optionally substituted \( C_1\text{-}C_5 \) alkyl, optionally substituted alkenyl or optionally substituted aryl, or is taken together with \( R^1 \) to form a propylene (-CH\(_2\)CH\(_2\)CH\(_2\)-) moiety or a butylene (-CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)-) moiety;

\( X \) is N or CR\(^{6a}\);

each \( R^6 \) and \( R^{6a} \) is independently H, hydroxyl, halo, \( C_1\text{-}C_5 \) alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, optionally substituted \( C_1\text{-}C_5 \) alkoxy or optionally substituted -C(O)C\(_1\text{-}C_5\) alkyl;

\( R^7 \) is H, halo, optionally substituted \( C_1\text{-}C_4 \) alkyl, or optionally substituted aryl, or is taken together with \( R^8 \) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with \( R^9 \) to form a C\(_3\text{-}C_5\) alkylene when \( R^8 \) and \( R^{10} \) are taken together to form a bond;

\( R^8 \) is H, halo, hydroxyl, N(R\(^{11} \))R\(^{12} \), SR\(^{13} \), S(O)R\(^{13} \), SO\(_3\)R\(^{13} \), -OC(O)N(R\(^{14} \))R\(^{15} \), -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C\(_1\text{-}C_5\) alkyl optionally substituted with amino, or is taken
together with R\(^7\) and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety, or is taken together with R\(^{10}\) to form a bond;

R\(^9\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl, or is taken together with R\(^7\) to form a C\(_3\)-C\(_5\) alkylen when R\(^8\) and R\(^{10}\) are taken together to form a bond;

R\(^{10}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl, or is taken together with R\(^8\) to form a bond;

each R\(^{11}\) and R\(^{12}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl, or R\(^{11}\) and R\(^{12}\) are taken together to form C\(_3\)-C\(_5\) alkylen;

R\(^{13}\) is H or optionally substituted C\(_1\)-C\(_5\) alkyl;

each R\(^{14}\) and R\(^{15}\) is independently H or optionally substituted C\(_1\)-C\(_5\) alkyl, or R\(^{14}\) and R\(^{15}\) are taken together to form a C\(_3\)-C\(_5\) alkylen; and

Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\(_1\)-C\(_5\) alkyl, C\(_3\)-C\(_8\) cycloalkyl, halo-substituted C\(_1\)-C\(_5\) alkyl, halo-substituted C\(_3\)-C\(_8\) cycloalkyl, C\(_1\)-C\(_5\) alkoxy, C\(_3\)-C\(_8\) cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C\(_1\)-C\(_5\) alkyl, C\(_3\)-C\(_8\) cycloalkyl, halo-substituted C\(_1\)-C\(_5\) alkyl, halo-substituted C\(_3\)-C\(_8\) cycloalkyl, C\(_1\)-C\(_5\) alkoxy, C\(_3\)-C\(_8\) cycloalkoxy, cyano, carboxyl, aminoacyl and acylamino,

or a pharmaceutically acceptable salt thereof, and (ii) instructions for use according to the method of any one of claims 47-56.

111. A compound selected from the group consisting of Compound No. 6, 9 to 12, 14, 16 to 21, 23 to 28, 39 to 42, 44 to 59, 63 to 72, 75 to 82, 104, 108 to 131, 133 to 171, 173 to 179, 187 to 193, 195 to 198, 220, 269 to 271, 273 to 287, 290 to 38, 340 to 343, II-1 to II-265, III-1 to III-368, IV-1, IV-3, IV-8 to IV-244, or V-1 to V-23, or a salt thereof.

112. A pharmaceutical composition comprising a compound of claim 111, and a pharmaceutically acceptable carrier.

113. A kit comprising (i) a compound of claim 111 or a pharmaceutically acceptable salt thereof, and (ii) instructions for use in a disease or condition that is responsive to a decrease in blood pressure.
114. The kit of claim 113, wherein the disease or condition is selected from the group consisting of hypertension, acute decompensated congestive heart failure, chronic congestive heart failure, coronary heart disease, cardiac arrhythmias, myocardial ischemia, hypertrophy, endstage renal failure, renal ischemia, acute renal failure and chronic kidney disease.
Figure 7

Systolic Pressure Change from Baseline (mmHg)

Time (minutes)
Figure 9

- Vehicle
- Cpd 3b, 15 mg/kg, SC
- Cpd 3b, 20 mg/kg, PO

Systolic Pressure: Change from Baseline (mmHg)

Time (minutes)
Figure 11

18 mg/kg Cpd3b

Dexmedetomidine 5 μg/kg, IV

6 mg/kg Cpd3b

Vehicle or Cpd3b, PO

0 mg/kg Cpd3b
Figure 18A

Cell Viability (MTS Reduction)

- dox  - dox  DMB  Cpd3b  Cpd3a  Cpd4a  Cpd5b

0.1 nM
Figure 18B

Cell Viability (MTS Reduction)

10 nM

+ dox  - dox  DMB  Cpd3b  Cpd39a  Cpd4a  Cpd5b
Figure 19

- Vehicle
- Cpd 144b, 10 mg/kg/hv

Systolic Pressure, Change from baseline (mmHg)

Time (minutes)
Figure 21

Graph showing the change in systolic blood pressure (Baseline mmHg) over time (minutes) with different doses of Cpd 176a. The graph indicates a decrease in blood pressure with increasing dose levels of 1, 3, 10, and 30 mg/kg.
Figure 28

Plot showing the relationship between ligand concentration and activation.

Log [Ligand], M

% Activation

EC₅₀ = 14.09 nM

129d