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(71) Applicant(s)
Medivation Technologies, Inc.

(72) Inventor(s)
Protter, Andrew Asher;Chakravarty, Sarvajit;Jain, Rajendra Parasmal;Green, Michael John

(74) Agent / Attorney
Pizzeys Patent and Trade Mark Attorneys Pty Ltd, GPO Box 1374, BRISBANE, QLD, 4001

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(71) Applicant *(for all designated States except US)*: **MEDIVATION TECHNOLOGIES, INC.** [US/US]; 201 Spear Street, 3rd Floor, San Francisco, CA 94105 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PROTTER, Andrew, Asher** [US/US]; 185 North California Avenue, Palo Alto, CA 94301 (US). **CHAKRAVARTY, Sarvajit** [US/US]; 1888 Miramonte Avenue, Mountain View, CA 94040 (US). **JAIN, Rajendra, Parasmal** [IN/IN]; E-202, Sapphire Park, Park Street Phase II, Wakad, Pune 411 057 (IN). **GREEN, Michael, John** [US/US]; 400 Balboa Boulevard, Half Moon Bay, CA 94019 (US).

(74) Agents: **TIAN, Zong-Qiang Bill** et al.; Morrison & Foerster LLP, 775 Page Mill Road, Palo Alto, CA 94304-1018 (US).

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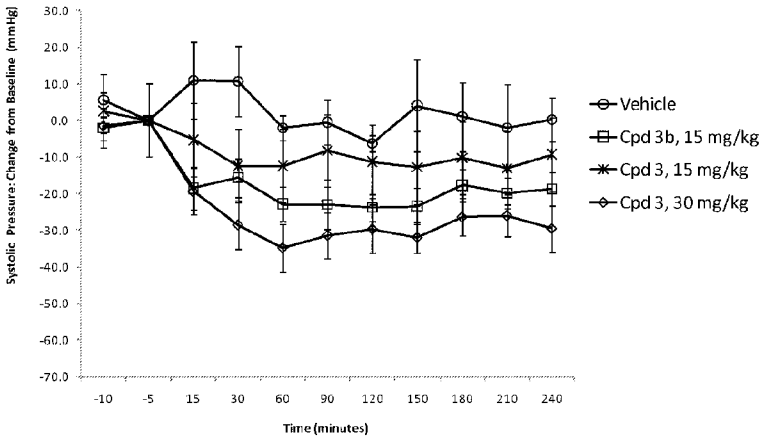
(54) **Title**: COMPOUNDS AND METHODS FOR TREATMENT OF HYPERTENSION

Figure 8



(57) **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_{2B} antagonists. The compounds may also bind to and antagonize adrenergic receptor α_{1B}. 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.

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COMPOUNDS AND METHODS FOR TREATMENT OF HYPERTENSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/444,642 filed February 18, 2011, U.S. Provisional Patent Application No. 61/444,655 filed February 18, 2011, U.S. Provisional Patent Application No. 61/444,659 filed February 18, 2011, U.S. Provisional Patent Application No. 61/469,664 filed March 30, 2011, U.S. Provisional Patent Application No. 61/529,745 filed August 31, 2011, U.S. Provisional Patent Application No. 61/529,816 filed August 31, 2011, U.S. Provisional Patent Application No. 61/562,927 filed November 22, 2011 and U.S. Provisional Patent Application No. 61/562,938 filed November 22, 2011, the disclosures of each of which are incorporated herein by reference in their entireties.

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, hypertrigleridemia, 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.

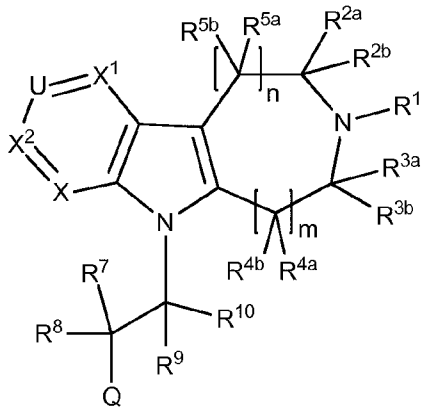
[0009] Thus, there remains a need for new and useful agents that are capable of (i) reducing an individual's blood pressure and/or (ii) promoting renal blood flow and/or (iii) inhibiting or decreasing sodium reabsorption.

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 α_{2B} 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 α_{2B} 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):



(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_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; 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}, 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 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.

[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.

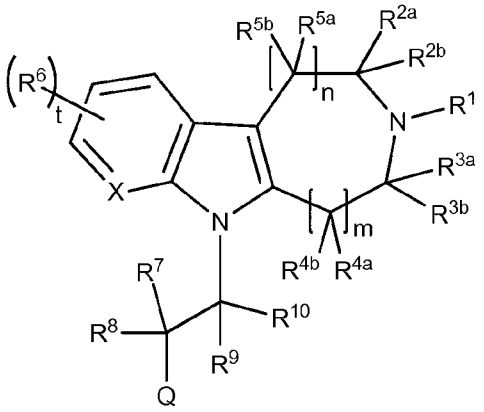
[0014] Provided is also a method of (i) increasing renal blood flow, and/or (ii) decreasing sodium reabsorption, in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I) or any variations detailed herein. In some embodiments, the 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 chonic 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):



(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 (-$CH_2CH_2CH_2$-) 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 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; 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 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.

[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 C_1-C_5 alkyl, and R^8 is H or hydroxyl;

(13) R^7 is H or C_1-C_5 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 NH_2;

(17) R^7 is H, and R^8 is -$OC(O)C_1$-C_5 alkyl;

(18) R^9 is H or C_1-C_5 alkyl;

(19) R^{10} is H or C_1-C_5 alkyl;

(20) each R^9 and R^{10} is H;

(21) one of R^9 and R^{10} is H and the other is C_1-C_5 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, 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 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 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; or phenyl 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; imidazolyl 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; or triazolyl 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;

(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 (-$CH_2CH_2CH_2$-) 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-IIIA) 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 (-$CH_2CH_2CH_2$-) 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 α_{2B} antagonist. In other embodiments, the compound is also an adrenergic receptor α_{1B} antagonist. In yet other embodiments, the compound is also an adrenergic receptor α_{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 α_{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 α_{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 α_{2A} and α_{2B} receptor assays.

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

[0027] Figure 5 illustrates the α_{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 α_{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 illustates 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 α_{2A} receptor inverse agonist activity assay (using GTPg35S 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 α_{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 alcoholates 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 dc, sorbitol, sucrose dc, 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_1-C_{20} alkyl"). More particular alkyl groups are those having 1 to 8 carbon atoms (a "C_1-C_8 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_3-C_8 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_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), butylene (-$CH_2CH_2CH_2CH_2$-) 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_2-CH=CH-CH_3 and –CH_2-CH_2-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 cyclohexyl, 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_3-C_8 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, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, 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, aminoacyl, aminocarbonylamino, aminocarbonyloxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, cyano, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, substituted or unsubstituted alkyl, 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, aminoacyl, aminocarbonylamino, aminocarbonyloxy, 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 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)-, cycloalkyl-C(O)-, substituted cycloalkyl-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, aminocarbonylamino, aminocarbonyloxy, 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 aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo, carbonylalkylenealkoxy 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.

[0077] "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.*, indolizinyl, 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.

[0078] "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, aminocarbonyloxy, 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.

[0079] "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, aminocarbonyloxy, 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.

[0080] "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 "C_1-C_3 alkaryl").

[0081] "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 alkynyloxy refers to the group "alkynyl-O-". "Substituted alkoxy" refers to the group substituted alkyl-O.

[0082] "Unsubstituted amino" refers to the group $-NH_2$.

[0083] "Substituted amino" refers to the group $-NR_aR_b$, where either (a) each R_a and R_b 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 R_a and R_b groups are not H; or (b) R_a and R_b are joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

[0084] "Acylamino" refers to the group $-C(O)NR_aR_b$ where R_a and R_b 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 R_a and R_b groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring.

[0085] "Aminoacyl" refers to the group $-NR_aC(O)R_b$ where each R_a and R_b 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, R_a is H or alkyl.

[0086] "Aminosulfonyl" refers to the groups $-NRSO_2$-alkyl, $-NRSO_2$ substituted alkyl, $-NRSO_2$-alkenyl, $-NRSO_2$-substituted alkenyl, $-NRSO_2$-alkynyl, $-NRSO_2$-substituted alkynyl, $-NRSO_2$-cycloalkyl, $-NRSO_2$-substituted cycloalkyl, $-NRSO_2$-aryl, $-NRSO_2$-substituted aryl, $-NRSO_2$-heteroaryl, $-NRSO_2$-substituted heteroaryl, $-NRSO_2$-heterocyclic, and $-NRSO_2$-

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.

[0087] "Sulfonylamino" refers to the groups $-SO_2NH_2$, $-SO_2NR$-alkyl, $-SO_2NR$-substituted alkyl, $-SO_2NR$-alkenyl, $-SO_2NR$-substituted alkenyl, $-SO_2NR$-alkynyl, $-SO_2NR$-substituted alkynyl, $-SO_2NR$-aryl, $-SO_2NR$-substituted aryl, $-SO_2NR$-heteroaryl, $-SO_2NR$-substituted heteroaryl, $-SO_2NR$-heterocyclic, and $-SO_2NR$-substituted heterocyclic, where R is H or alkyl, or $-SO_2NR_2$, 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.

[0088] "Sulfonyl" refers to the groups $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-alkenyl, $-SO_2$-substituted alkenyl, $-SO_2$-alkynyl, $-SO_2$-substituted alkynyl, $-SO_2$-aryl, $-SO_2$-substituted aryl, $-SO_2$-aralkyl, $-SO_2$-substituted aralkyl, $-SO_2$-heteroaryl, $-SO_2$-substituted heteroaryl, $-SO_2$-heterocyclic, and $-SO_2$-substituted heterocyclic.

[0089] "Aminocarbonylalkoxy" refers to the group $-NR_aC(O)OR_b$ where each R_a and R_b 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 heterocyclyl.

[0090] "Carbonylalkylenealkoxy" refers to the group $-C(O)-(CH_2)_n-OR$ 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.

[0091] "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 ($-CF_3$). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy ($-OCF_3$).

[0092] "Carbonyl" refers to the group C=O.

[0093] "Cyano" refers to the group -CN.

[0094] "Oxo" refers to the moiety =O.

[0095] "Nitro" refers to the group -NO_2.

[0096] "Thioalkyl" refers to the groups -S-alkyl.

[0097] "Alkylsulfonylamino" refers to the groups -$R^1SO_2NR_aR_b$ where R_a and R_b 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 R_a and R_b groups can be joined together with the nitrogen atom to form a heterocyclic or substituted heterocyclic ring and R^1 is an alkyl group.

[0098] "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.

[0099] "Geminal" refers to the relationship between two moieties that are attached to the same atom. For example, in the residue -CH_2-CHR^1R^2, R^1 and R^2 are geminal and R^1 may be referred to as a geminal R group to R^2.

[0100] "Vicinal" refers to the relationship between two moieties that are attached to adjacent atoms. For example, in the residue –CHR^1-CH_2R^2, R^1 and R^2 are vicinal and R^1 may be referred to as a vicinal R group to R^2.

Receptor Binding Profile

[0101] In some embodiments, compounds that bind to and are antagonists of the adrenergic receptor α_{2B}, but which are not antagonists of the adrenergic receptor α_{2A}, 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 my 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 α_{2B} should reduce an individual's blood pressure. However, compounds that antagonize the adrenergic receptor α_{2A} in some instances may actually increase an individual's blood pressure. Thus, compounds that antagonize the adrenergic receptor α_{2B} but do not antagonize the adrenergic receptor α_{2A} (compounds referred to herein as "selective adrenergic receptor α_{2B} antagonists") are desirable agents in therapy. Selective adrenergic receptor α_{2B} antagonists find further use in therapy of cardiovascular and renal indications. The selective adrenergic receptor α_{2B} antagonists provided herein (i) bind to and are antagonists of the adrenergic receptor α_{2B}, and (ii) are not antagonists of the adrenergic receptor α_{2A}.

[0103] The selective adrenergic receptor α_{2B} antagonists may in some variations also bind to and be agonists of the adrenergic receptor α_{2A}. The selective adrenergic receptor α_{2B} antagonists may also be used in conjunction with other agents that are agonists of the adrenergic receptor α_{2A}.

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

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

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

[0107] In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B} and (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}. In one variation, a selective adrenergic receptor α_{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 α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{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 α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}. In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B} and (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}. In one variation, a selective adrenergic receptor α_{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 α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{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 α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}. It is understood and clearly conveyed herein that a selective adrenergic receptor α_{2B} antagonist can exhibit any of the adrenergic receptor α_{2B} binding profiles described herein in combination with any of the adrenergic receptor α_{2A} binding profiles described herein, as if each and every combination were listed separately. For example, a selective adrenergic receptor α_{2B} antagonist may exhibit (i) equal to or greater than about 65% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, and (ii) equal to or less than about 25% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}.

[0108] In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B} and (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.03 μM and absence of antagonist activity to adrenergic receptor α_{2A}. In one variation, a selective adrenergic receptor α_{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 α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{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 α_{2A} ligand binding at 0.03 μM and absence of antagonist activity to adrenergic receptor α_{2A}. In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B} and (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.03 μM and absence of antagonist activity to adrenergic receptor α_{2A}. In one variation, a selective adrenergic receptor α_{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 α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{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 α_{2A} ligand binding at 0.03 μM and absence of antagonist activity to adrenergic receptor α_{2A}. It is understood and clearly conveyed herein that a selective adrenergic receptor α_{2B} antagonist can exhibit any of the adrenergic receptor α_{2B} binding profiles described herein in combination with any of the adrenergic receptor α_{2A} binding profiles described herein, as if each and every combination were listed separately. For example, a selective adrenergic receptor α_{2B} antagonist may exhibit (i) equal to or greater than about 65% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, and (ii) equal to or less than about 25% inhibition of α_{2A} ligand binding at 0.03 μM and absence of antagonist activity to adrenergic receptor α_{2A}.

[0109] In another variation, a selective adrenergic receptor α_{2B} antagonist has a Ki ratio of α_{2A} to α_{2B} that is greater than about any one of 5 or 15 or 50. Ki is the binding affinity from the Cheng-Prusoff equation: Ki= IC_{50}/(1+[S]/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 α_{2A} to α_{2B} may be combined with any binding and/or other activity profile details described herein for selective adrenergic receptor α_{2B} antagonists the same as if each were specifically and individually listed. For example, in one variation, a selective adrenergic receptor α_{2B} antagonist may exhibit (i) equal to or greater than about 65% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, and (ii) equal to or less than about 25% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}; and a Ki ratio of α_{2A} to α_{2B} that is greater than about any one of 5 or 15 or 50.

[0110] The selective adrenergic receptor α_{2B} antagonists may in some variations also bind to and be antagonists of the adrenergic receptor α_{1B}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 60% inhibition of α_{1B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1B}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{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 α_{1B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1B}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 60% inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 60% inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{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 α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}. It is understood and clearly conveyed herein that a selective adrenergic receptor α_{2B} antagonist can exhibit any of the adrenergic receptor α_{2B} binding profiles described herein in combination with any of the adrenergic receptor α_{2A} binding profiles described herein and any of the adrenergic receptor α_{1B} binding profiles, as if each and every combination were listed separately. For example, a selective adrenergic receptor α_{2B} antagonist may exhibit (i) equal to or greater than about 65% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 25% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 65% inhibition of α_{1B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1B}. The selective adrenergic receptor α_{2B} antagonists may also be used in conjunction with other agents that antagonize the adrenergic receptor α_{1B}. Administration in conjunction with another

compound includes administration in the same or different composition, either sequentially, simultaneously, or continuously.

[0111] The selective adrenergic receptor α_{2B} antagonists may in some variations also bind to and be antagonists of the adrenergic receptor α_{1D}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 60% inhibition of α_{1D} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1D}. In another variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, (iii) equal to or greater than about 60% inhibition of α_{1B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1B} and (iv) equal to or greater than about 60% inhibition of α_{1D} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1D}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{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 α_{1D} and/or α_{1B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1D} and/or α_{1B}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 60% inhibition of α_{1B} and/or α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B} and/or α_{1D}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 60%

inhibition of α_{1B} and/or α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B} and/or α_{1D}. In one variation, the selective adrenergic receptor α_{2B} antagonists may exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 30% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{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 α_{1B} and/or α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B} and/or α_{1D}. It is understood and clearly conveyed herein that a selective adrenergic receptor α_{2B} antagonist can exhibit any of the adrenergic receptor α_{2B} binding profiles described herein in combination with any of the adrenergic receptor α_{2A} binding profiles described herein and any of the adrenergic receptor α_{1B} and/or α_{1D} binding profiles, as if each and every combination were listed separately. For example, a selective adrenergic receptor α_{2B} antagonist may exhibit (i) equal to or greater than about 65% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, (ii) equal to or less than about 25% inhibition of α_{2A} ligand binding at 0.1 μM and absence of antagonist activity to adrenergic receptor α_{2A}, and (iii) equal to or greater than about 65% inhibition of α_{1D} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1D}. The selective adrenergic receptor α_{2B} antagonists may also be used in conjunction with other agents that antagonize the adrenergic receptor α_{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 α_{2B} and may also be antagonists for the adrenergic receptor α_{2A}. In such instances, it is preferable that the compound is more potent at inhibiting the adrenergic receptor α_{2B} compared to the adrenergic receptor α_{2A}. In one variation, the compound inhibit both the adrenergic receptor α_{2B} and the adrenergic receptor α_{2A}, and wherein the compound has limited or no brain bioavailability and so cannot easily activate adrenergic α_{2A} receptors in the brain. In one variation, the compound inhibits both the adrenergic receptor α_{2B} and the adrenergic receptor α_{2A}, and wherein the compound has brain bioavailability. In some other instances, compounds provided herein bind to and are antagonists of adrenergic receptor α_{2B} and may be inverse agonists for the adrenergic receptor α_{2A}. In some embodiments, the compound (1) binds to and is an antagonist of adrenergic receptor α_{2B}, and (2) binds to and is an antagonist and/or

inverse agonist of the adrenergic receptor α_{2A}. In some embodiments, the compound (1) binds to and is an antagonist of adrenergic receptor α_{2B}, (2) binds to and is an antagonist and/or inverse agonist of the adrenergic receptor α_{2A}, and (3) binds to and is antagonist of the adrenergic receptor α_{1B} and/or the adrenergic receptor α_{1D}. It is understood and clearly conveyed herein that an adrenergic receptor α_{2B} antagonist can exhibit any of the adrenergic receptor α_{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 α_{1B} and/or α_{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 α_{2B} receptor may be assessed by methods known in the art, such as standard α_{2B} receptor cell membrane-based or intact cell-based activity assays. For example, the GTPγS binding or Aequorin-based assays may be used. In one variation, the selective adrenergic receptor α_{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 GTPγS assay)) in an α_{2B} antagonist assay. In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits an IC_{50} value in an α_{2B} antagonist assay equal to or less than about 10nM at a given concentration of agonist (*e.g.*, concentration corresponding to EC_{80} of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay)) in an α_{2B} antagonist assay. In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits an IC_{50} value in an α_{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 α_{2B} antagonist exhibits an IC_{50} value in an α_{2B} antagonist assay equal to or less than about any one of 100nM, 30nM or 10nM at a concentration of oxymetazoline between about 50 nM and about 5000 nM. In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits an IC_{50} value in an α_{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 α_{2B} antagonist exhibits an IC_{50} value in an α_{2B} antagonist assay equal to or less than about any one of 100nM, 30nM or 10nM at a concentration of guanfacine between about 50 nM and about 5000 nM. In one variation, a selective adrenergic receptor α_{2B} antagonist exhibits an IC_{50} value in an α_{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 α_{2A} may be assessed by methods known in the art, such as standard α_{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 α_{2A} intends activity that is sufficiently reduced, but not necessarily eliminated or undetectable, at the adrenergic receptor α_{2A}. In one variation, a compound will exhibit an undetectable amount of antagonist activity to the adrenergic receptor α_{2A}. In another variation, a compound will lack antagonist activity to the adrenergic receptor α_{2A} if it exhibits an IC_{50} value in an α_{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 α_{2A} exhibits an IC_{50} value in an α_{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 α_{2B} antagonist exhibits an IC_{50} value in an α_{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 α_{2B} antagonist exhibits an IC_{50} value in an α_{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 α_{2B} antagonists exhibits an IC_{50} value in an α_{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 α_{2A} receptor will be neither an agonist nor antagonist of the α_{2A} receptor.

[0116] In some variations, regardless of IC_{50} values obtained from α_{2B} and α_{2A} assays, a compound may nonetheless be a selective adrenergic receptor α_{2B} antagonist if it exhibits a Ki ratio of α_{2A} to α_{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 α_{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 α_{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 α_{2B} antagonist if it exhibits a Ki ratio of α_{2A} to α_{2B} higher than about any one of 5, 10, or 15.

[0117] Antagonist activity to adrenergic receptor α_{1B} may be assessed by methods known in the art, such as standard α_{1B} receptor intact cell-based activity assays, including the Aequorin-based assay. In one variation, a selective adrenergic receptor α_{2B} antagonist will also antagonize the adrenergic receptor α_{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 α_{1B} antagonist assay. In one variation, a selective adrenergic receptor α_{2B} antagonist will also antagonize the adrenergic receptor α_{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 α_{1B} antagonist assay. In one variation, the selective adrenergic receptor α_{2B} antagonists exhibit an IC_{50} value in an α_{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 α_{2B} antagonists exhibit an IC_{50} value in an α_{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 α_{2B} antagonists exhibit an IC_{50} value in an α_{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 α_{1D} may be assessed by methods known in the art, such as standard α_{1D} receptor intact cell-based activity assays, including the Aequorin-based assay. In one variation, a selective adrenergic receptor α_{2B} antagonist will also antagonize the adrenergic receptor α_{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 α_{1D} antagonist assay. In one variation, a selective adrenergic receptor α_{2B} antagonist will also antagonize the adrenergic receptor α_{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 EC_{80} of cirazoline) in an adrenergic receptor α_{1D} antagonist assay. In one variation, the selective adrenergic receptor α_{2B} antagonists exhibit an IC_{50} value in an α_{1D} 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 α_{2B} antagonists exhibit an IC_{50} value in an α_{1D} 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 α_{2B} antagonists exhibit an IC_{50} value in an α_{1D} 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 α_{2B} antagonists exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{2B} antagonist assay equal to or less than about any one of 100nM, 30nM or 10nM 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 α_{2A} ligand binding at 0.1 μM and an IC_{50} value in an α_{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 some variations, the selective adrenergic receptor α_{2B} antagonists exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{2B} 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 α_{2A} ligand binding at 0.1 μM and an IC_{50} value in an α_{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), and (iii) equal to or greater than about 60% inhibition of α_{1B} ligand binding at 0.03 μM and an IC_{50} value in an α_{1B} 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 α_{2B} antagonists exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{2B} 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 α_{2A} ligand binding at 0.1 μM and an IC_{50} value in an α_{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), and (iii) equal to or greater than about 60% inhibition of α_{1D} ligand binding at 0.03 μM and an IC_{50} value in an α_{1D} 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 α_{2B} antagonists exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{2B} 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 α_{2A} ligand binding at 0.1 μM and an IC_{50} value in an α_{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), (iii) equal to or greater than about 60% inhibition of α_{1B} ligand binding at 0.03 μM and an IC_{50} value in an α_{1B} 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 α_{1D} ligand binding at 0.03 μM and an IC_{50} value in an α_{1D} 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 α_{2B} antagonists exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{2B} 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 α_{2A}.

[0121] In another variation, the adrenergic receptor α_{2B} antagonists exhibit (i) equal to or greater than about 60% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{2B} 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 α_{2A} ligand binding at 0.1 μM and IC_{50} value in an adrenergic receptor α_{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 α_{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 α_{2B} antagonists exhibit (i) greater than about 65% inhibition of α_{2B} ligand binding at 0.03 μM and an IC_{50} value in an α_{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 α_{2A} ligand binding at 0.1 μM and an IC_{50} value in an α_{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 α_{1B} ligand binding at 0.03 μM and an IC_{50} value in an α_{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 α_{2A} to α_{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 α_{2B} antagonists (e.g., selective adrenergic receptor α_{2B} antagonists). In some embodiments, it is believed that the selective adrenergic receptor α_{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 α_{2A} receptor, which would reduce or potentially eliminate the beneficial blood pressure lowering and renal effects modulated by antagonizing α_{2B}. Furthermore, the selective adrenergic receptor α_{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.

[0124] 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 hypbridization that expression predominates in the medulla outer stripe with extensions into the cortical S3 segment of the proximal tubules. Adrenergic α_{2B} receptorantagonists provided hereinmay 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).

[0125] 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 diueresis 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 Sandra L. Burke, Roger G. Evans and Geoffrey A. Head. Journal of Hypertens 29:945–952 (2011).

[0126] 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 α_{2B} antagonists. In some embodiments, the compounds are selective adrenergic receptor α_{2B} antagonists.

[0130] Compounds detailed herein (such as the adrenergic receptor α_{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 α_{2B} antagonist to an individual in need thereof. In some embodiments, the method comprises administering intravenously an effective amount of an adrenergic receptor α_{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 α_{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 α_{2B} antagonist detailed herein. In one variation, the compound is an adrenergic receptor α_{2B} antagonist. In some variations, the compound is a selective adrenergic receptor α_{2B} antagonist. In one variation, the adrenergic receptor α_{2B} antagonist also exhibits adrenergic receptor α_{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 α_{2B} antagonist is a selective adrenergic receptor α_{2B} antagonist. In some of the variations, the adrenergic receptor α_{2B} antagonist also exhibits antagonist activity for the adrenergic receptor α_{2A}. In some embodiments, the compounds are adrenergic receptor α_{2B} antagonists. In some embodiments, the compounds are selective adrenergic receptor α_{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 α_{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 α_{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 α_{2B} and α_{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 α_{2B} antagonists (e.g., the selective adrenergic receptor α_{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.

[0141] 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.

[0142] 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.

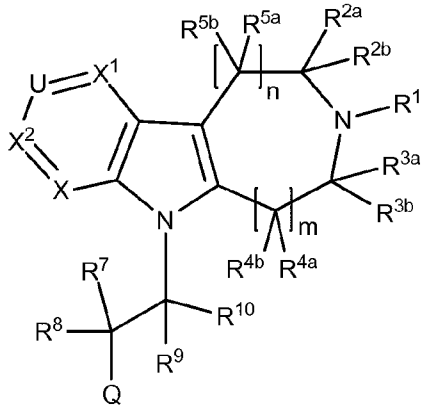
[0143] It is understood and clearly conveyed that the binding and activity profiles detailed herein (*e.g.*, in the disclosure above) in one variation apply to the formulae provided herein (*e.g.*, the formulae for use in the methods). In one aspect, selective adrenergic receptor α_{2B} antagonists are of the formula (I), (A-I), (A-IIA), (A-IIB), (A-IIC), (A-IID), (A-IIA-1), (A-IIB-1), (A-IIC-1), (A-IID-1), (A-III), (A-IIIA), (A-IIIB), (A-IIIC), (A-IIID), (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-IIIG-1), (A-IIIG-2), (A-IIIG-3), (A-IIIH), (A-IIIH-1), (A-IIIH-2), (A-IIIH-3), (A-IIIH-4), (A-IIIA'), (A-IV), (A-V), (A-VI), (A-VIIA), (A-VIIB), (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-IIB), (C-IIIA), (C-

IIIB), (C-IIIC), (C-IIID), (CIII-E), (C-IIIF), (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF), (C-IVG), (C-VA), (C-VB), (D-I), (D-IIA), (D-IIB), (D-IIA-1), (D-IIA-2), (D-IIIA), (D-IIIB), (E-I), (E-IIA), (E-IIB), (F-I), (F-IIA), (F-IIB), (F-IIA-1), (F-IIA-2), (G-I), (G-IIA), (G-IIB), (G-IIA-1), (G-IIA-2), (H-IA), (H-IB), (H-IC), (H-ID), (H-IA-1), (H-IB-1), (H-IC-1), (H-ID-1), (H-IE-1), (H-IF-1), (J), (J-IA), (J-IB), (J-IC), (J-ID), (J-IA-1), (J-IB-1), (J-IC-1), (J-ID-1), (K-IA), (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):



(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_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; 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}, 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; 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 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;

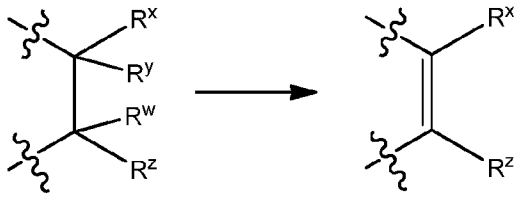
R^{13} is H or optionally substituted C_1-C_5 alkyl;

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.

[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^y 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 hydroxyl. 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_3H. 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_2-SO_3H. In some variations, R^1 is $CH_2CH{=}CH_2$.

[0149] In some variations, R^{4a} is 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. 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; hydroxyl; cyano; carboxyl; $-OC(O)N(R^{14a})R^{15a}$; $-C(O)N(R^{14a})R^{15a}$; 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, aminoacyl, $N(R^{16})(R^{17})$, -$C(O)OR^{18}$, 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, aminoacyl, $N(R^{16})(R^{17})$, -$C(O)OR^{18}$, 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 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) moiety;

R^{4a} is selected from the group consisting of halo, hydroxyl, cyano, carboxyl, $-OC(O)N(R^{14a})R^{15a}$, $-C(O)N(R^{14a})R^{15a}$, and optionally substituted C_1-C_5 alkyl;

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

R^{4b} is H, halo, optionally substituted C_1-C_5 alkyl;

n is 0 and m is 1;

each X^1, X^2, and U is CH;

X is independently 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 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 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; and

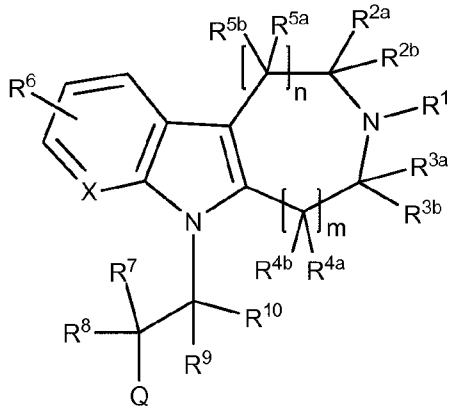
Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl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

[0154] In some embodiments, R^{4a} is an optionally substituted C_1-C_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 $-OC(O)C_1$-C_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):



(A-I)

,

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 $-C(O)OR^{11}$;

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-C_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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 ($-CH_2CH_2-$) moiety or a propylene ($-CH_2CH_2CH_2-$) moiety,

or R^{2a} and R^{4a}, or R^{3a} and R^{5a}, where present, are taken together to form a methylene ($-CH_2-$) moiety or an ethylene ($-CH_2CH_2-$) moiety,

or R^{4a} and R^{5a}, where present, are taken together to form a methylene ($-CH_2-$) 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_2R^{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;

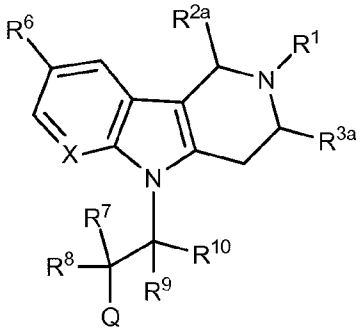
or R^{10} and R^8 are taken together to form a bond;

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;

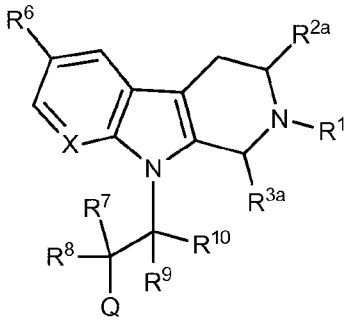
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl; and

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.

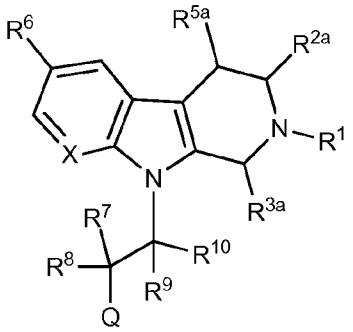
[0158] In another embodiment, the compound is of the formula (A-IIA), (A-IIB), (A-IIC) or (A-IID):



(A-IIA)

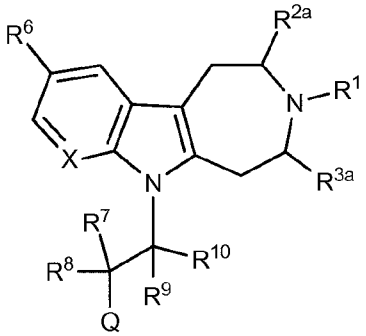


(A-IIB)



(A-IIC)

or



(A-IID)

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 $-C(O)OR^{11}$;

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 ($-CH_2CH_2CH_2-$) 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 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_2R^{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 to 5 carbon atoms when R^{10} and R^8 are taken together to form a bond;

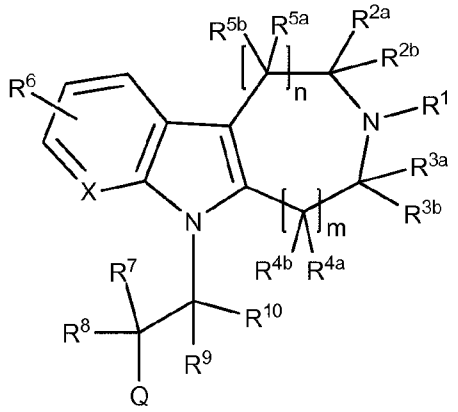
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl; and

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, $-CO_2H$ or $-C(O)N(R^a)R^b$, wherein each R^a and R^b is independently H or C_1-C_5 alkyl.

[0159] In some embodiments, the compound is of formula (A-IIA). In some variations, X is CR^{6a}, wherein R^{6a} is H. In some 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. 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 CR^{6a}, wherein R^{6a} is H. In some 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. 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):



(A-IA)

,

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 $-C(O)OR^{11}$;

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-C_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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 ($-CH_2CH_2-$) moiety or a propylene ($-CH_2CH_2CH_2-$) moiety,

or R^{2a} and R^{4a}, or R^{3a} and R^{5a}, where present, are taken together to form a methylene ($-CH_2-$) moiety or an ethylene ($-CH_2CH_2-$) moiety,

or R^{4a} and R^{5a}, where present, are taken together to form a methylene ($-CH_2-$) 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;

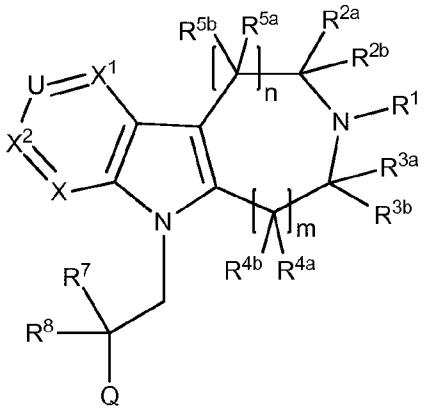
each R^7, R^9 and R^{10} is independently H or optionally substituted C_1-C_5 alkyl;

R^8 is $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, or $-OC(O)C_1$-C_5 alkyl optionally substituted with amino;

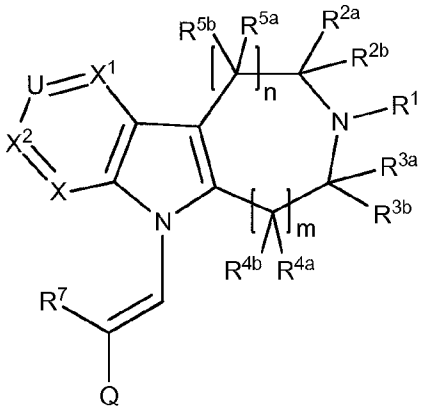
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl; and

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, $-CO_2H$ or $-C(O)N(R^a)R^b$, wherein each R^a and R^b is independently H or C_1-C_5 alkyl.

[0162] In one aspect, the present invention provides compounds according to formula (A-IB), (A-IC) or (A-ID):

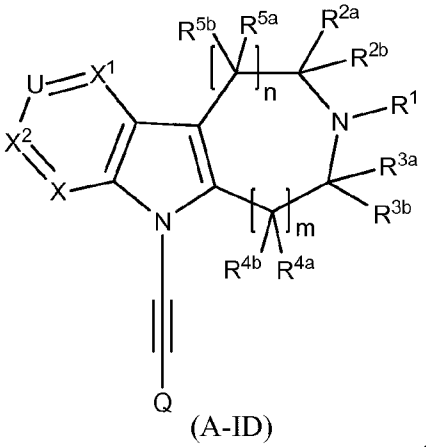


(A-IB)



(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^1 is methyl; n is 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 ($-CH_2CH_2-$) 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 is 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 ($-CH_2CH_2-$) 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_1-C_5 alkyl substituted with -C(O)OR^{7a}, wherein R^{7a} is H or optionally substituted C_1-C_5 alkyl; R^1 is methyl or ethyl; n is 0; each of R^{2b}, R^{3a}, R^{3b} and R^{4b} 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_2CH_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.

[0166] In certain embodiments, with respect to the compounds of formula (A-IB), R^7 is C_1-C_5 alkyl substituted with 1 to 3 halo; R^7 is CF_3' R^8 is OH; R^1 is methyl; n is 0,; each of R^{2b}, R^{3a}, R^{3b} and R^{4b} 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_2CH_2-) moiety; each X^1, X^2 and X is CH, U is CR^6, and R^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^7 is optionally substituted phenyl; R^8 is OH; R^1 is methyl or ethyl; n is 0; each of R^{2b}, R^{3a}, R^{3b} and R^{4b} 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_2CH_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 fluoro or unsubstituted pyridyl.

[0168] In certain embodiments, with respect to the compounds of formula (A-IB), R^8 is halo. In one embodiment, R^8 is fluoro or chloro; R^1 is methyl, ethyl, isopropyl, or cyclopropyl; n is 0; each of R^{2b}, R^{3a}, R^{3b} and R^{4b} 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_2CH_2-) moiety; R^7 is H or methyl; 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 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^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_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene; R^1 is methyl; n is 0; each of R^{2b}, R^{3a}, R^{3b} and R^{4b} 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_2CH_2-) moiety; each X^1, X^2 and X is CH, U is CR^6, and R^6 is methyl; and Q is other than cyclobutyl.

[0170] In certain embodiments, with respect to the compounds of formula (A-IB), R^8 is -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, -OC(O)C_1-C_5 alkyl optionally substituted

with amino, $-OC(O)C_1$-C_5 alkyl substituted with carboxyl, or $-OC_1$-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.

[0171] In certain embodiments, with respect to the compounds of formula (A-IC), Q is optionally substituted 5-membered heteroaryl; n is 0; R^7 is fluoro or methyl; R^1 is methyl; each of R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} and R^{4b} is H; 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 thienyl or unsubstituted thiazolyl.

[0172] In certain embodiments, with respect to the compounds of formula (A-IC), Q is optionally substituted pyridyl, each of R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} andR^{4b} is H; each X^1, X^2 and X is CH, U is CR^6, and R^6 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted C_1-C_5 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; R^1 is methyl; each of R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} and R^{4b} is H; 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 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 R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^{5a} and R^{5b} is H; each R^{2a} and R^{4a} is H; or R^{2a} taken together with R^{4a}, where present, an ethylene ($-CH_2CH_2-$) moiety; U is CR^6, and R^6 is selected from the group consisting of CF_3, methyl, Cl, $CONHCH_3$, COOH, $COOCH_3$, H and F; then R^1 is other than methyl.

[0175] In certain embodiments, with respect to the compounds of formula (A-ID), each of R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^{5a} and R^{5b} is H; each R^{2a} and R^{4a} is H; or R^{2a} taken together with R^{4a}, where present, an ethylene ($-CH_2CH_2-$) moiety; X is CR^6, and R^6 is F; then R^1 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 R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, and R^{5b} 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.

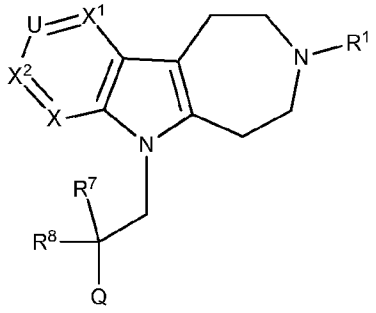
[0180] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), R^{2a} together with R^{4a} form a propylene or ethylene moiety.

[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^{4a} 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.

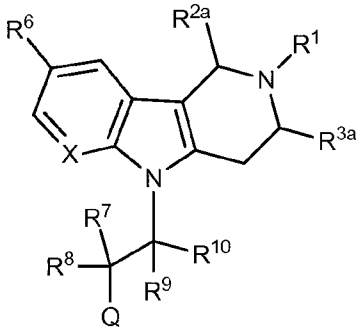
[0184] In one embodiment, the present invention provides compounds according to formula (A-IE):



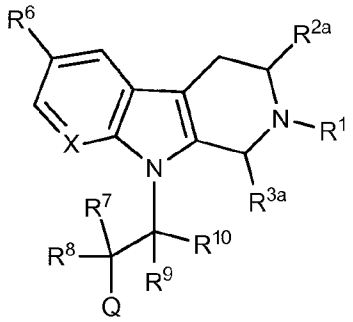
(A-IE)

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

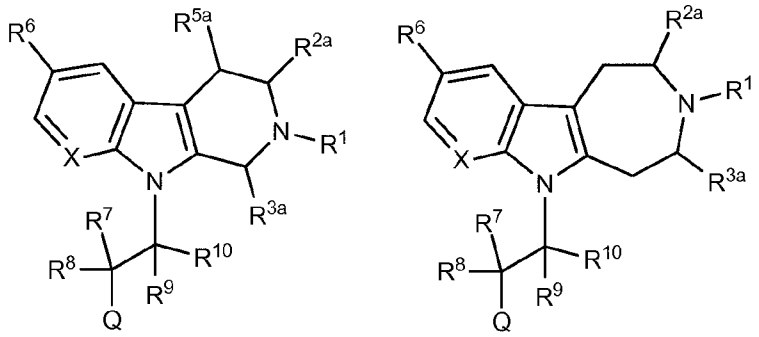
[0185] In another embodiment, the compound is of the formula (A-IIA-1), (A-IIB-1), (A-IIC-1) or (A-IID-1):



(A-IIA-1)



(A-IIB-1)



(A-IIC-1) or (A-IID-1)

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 –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 (-$CH_2CH_2CH_2$-) 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 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_2R^{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_2R^{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)$_2$.

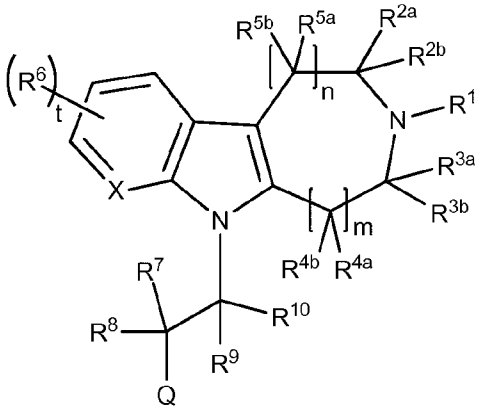
[0188] In one variation, R^{10} and R^8 are taken together to form a bond.

[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^{6a}, wherein R^{6a} 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, 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):



(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 (-$CH_2CH_2CH_2$-) 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 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; 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 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.

[0193] 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.

[0194] In one variation, the compound is of the formula (A-III), wherein Q, X, m, n, t, R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, 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_2R^{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.

[0195] 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^{3a} 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^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, 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.*, fluorophenyl). 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.

[0196] 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.

[0197] 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 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 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; phenyl 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; imidazolyl 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; or triazolyl 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.

[0198] In certain variations, 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. In some variations, n is 0 and m is 1; R^7 is H or CH_3; and R^8 is H or hydroxyl.

[0199] In yet other variations, X is N; 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. In some variations, n is 0 and m is 1; R^7 is H or CH_3; and R^8 is H or hydroxyl.

[0200] In some variations, n is 0 and m is 1; R^1 is taken together with R^{2a} to form a propylene (-$CH_2CH_2CH_2$-) 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

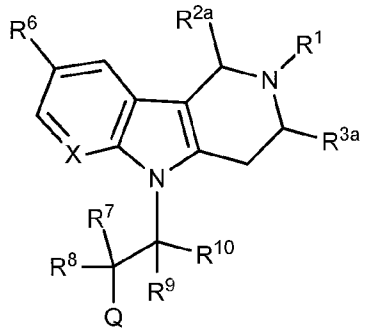
independently H or optionally substituted C_1-C_5 alkyl. In some variations, R^7 is H or CH_3; and R^8 is H or hydroxyl.

[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 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 C_1-C_5 alkyl, and R^8 is H or hydroxyl; (13) R^7 is H or C_1-C_5 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 NH_2; (17) R^7 is H, and R^8 is -$OC(O)C_1$-C_5 alkyl; (18) R^9 is H or C_1-C_5 alkyl; (19) R^{10} is H or C_1-C_5 alkyl; (20) each R^9 and R^{10} is H; (21) one of R^9 and R^{10} is H and the other is C_1-C_5 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, 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 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 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; or phenyl 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; imidazolyl 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; or triazolyl 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; (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 ($-CH_2CH_2CH_2-$) 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):



(A-IIIA)

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^{2a} or R^{3a} to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 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, 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.

[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-IIIA), 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-IIIA); 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_2R^{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.

[0206] In some variations of the compound of the formula (A-IIIA), 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), C_1-C_5 alkyl (*e.g.*, methyl), halo-substituted C_1-C_5 alkyl (*e.g.*, CF_3), carboxyl and $-C(O)NR^{16}R^{17}$ where each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 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 $-C(O)NR^{16}R^{17}$ where each R^{16} and R^{17} is H.

[0207] In some variations of the compound of the formula (A-IIIA), 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^7 is methyl and R^8 is hydroxyl. 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 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, 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 $-C(O)NR^{16}R^{17}$ where each R^{16} and R^{17} is H. In some of these variations, Q is 4-carbamoylphenyl.

[0208] In some variations of the compound of the formula (A-IIIA), 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 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 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, R^8 is NH_2, 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. 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.

[0209] In some variations of the compound of the formula (A-IIIA), R^1 and R^{2a} are taken together to form a propylene (-$CH_2CH_2CH_2$-) 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-C_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-C_5 alkyl (*e.g.*, methyl) and R^8 is H or hydroxyl. In some of these variations, R^7 is H and R^8 is hydroxyl. In some of these variations, R^7 is methyl and R^8 is hydroxyl. In some of these variations, each R^7 and R^8 is H. 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 H or hydroxyl, and 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.*, fluorophenyl). 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.

[0210] In some variations, X is CH. In other variations, X is N. In yet other variations, R^1 is H or CH_3. In yet other variations, R^{2a} is H or is taken together with R^1 to form a propylene (-$CH_2CH_2CH_2$-) moiety. In some variations, each R^6 and R^{6a} is independently H, halo or C_1-C_5 alkyl. In yet other variations, R^7 is H or CH_3. In one variation, R^8 is hydroxyl.

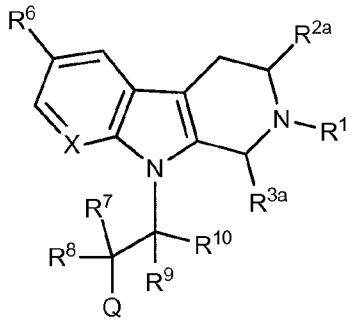
[0211] In some variations, Q is: unsubstituted pyridyl; unsubstituted pyrimidyl; unsubstituted pyrazinyl; unsubstituted phenyl; unsubstituted imidazolyl; unsubstituted triazolyl; pyridyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3; pyrimidyl substituted with halo, CH_3, CF_3, $CONH_2$, 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.

[0212] In some variations, X is CH; 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.

[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-

132b, 148b, 141b, II-135b, II-138, II-139, II-140, 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.

[0214] In another embodiment, the compound of formula (A-III) has the formula (A-IIIB):



(A-IIIB)

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 -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;

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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 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, 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

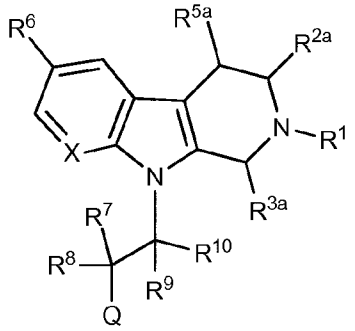
Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl,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

[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^7 is methyl and R^8 is hydroxyl. 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

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-IIIC):



(A-IIIC) ,

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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) moiety;

R^{5a} is H, optionally substituted C_1-C_5 alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR^{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;

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

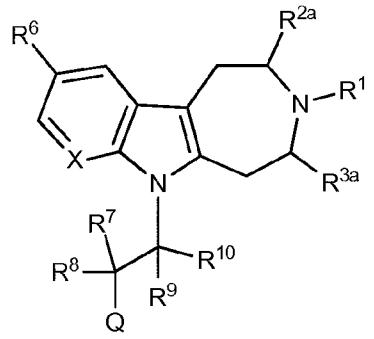
Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl,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

[0218] 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.

[0219] In one variation, the compound is of the formula (A-IIIC), wherein Q, X, R^1, R^{2a}, R^{3a}, R^{5a}, R^6, R^{6a}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are as defined for the formula (A-IIIC), 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_2R^{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.

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



(A-IIID) ,

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^{2a} or R^{3a} to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 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, 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

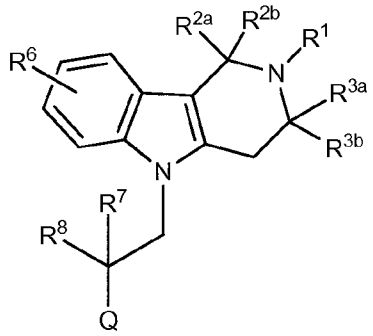
substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3; pyrazinyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3; or phenyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3.

[0222] In one variation, the compound is of the formula (A-IIID), 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-IIID), 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_2R^{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.

[0223] In some variations of the compound of the formula (A-IIID), 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 H or hydroxyl. In some of these variations, R^7 is H and R^8 is hydroxyl. In some of these variations, R^7 is methyl and R^8 is hydroxyl. 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 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.

[0224] In certain embodiments, with respect to the compounds of formula (IIID), X is CH, R^7 is H or methyl, R^8 is H or OH, Q is phenyl, unsubstituted or substituted with F, Cl, or methoxy; and R^6 is other than methyl or chloro.

[0225] In another embodiment, the compound of formula (A-III) has the formula (A-IIIE):



(A-IIIE)

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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^{2a} or R^{3a} to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) moiety;

each R^{2b} and R^{3b} 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_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

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,

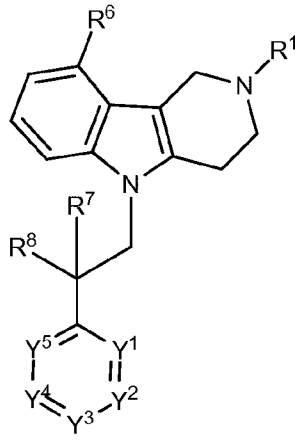
cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl,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

[0226] In some variations of the compound of formula (A-IIIE), R^1 is C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl. In certain variations, R^1 is C_1-C_5 alkyl substituted with a hydroxyl. In other variations, R^1 is methyl. In yet other variations, R^1 is H.

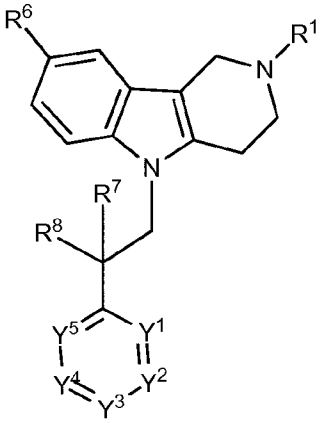
[0227] In some variations of the compound of formula (A-IIIE), R^6 is halo, C_1-C_5 alkyl, or perhaloalkyl. In certain variations, R^6 is methyl or isopropyl. In other variations of the compound of formula (A-IIIE), each R^{2a}, R^{2b}, R^{3a} and R^{3b} is H. In yet other variations of the compound of formula (A-IIIE), R^7 is an optionally substituted H or an unsubstituted C_1-C_5 alkyl, and R^8 is hydroxyl. In certain variations, R^7 is methyl, and R^8 is hydroxyl.

[0228] In yet other variations of the compound of formula (A-IIIE), Q is cycloalkyl 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; aryl 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; 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. 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, pryazinyl and phenyl is independently unsubstituted or substituted with 1 to 3 substituents independently selected from halo, carboxyl, alkoxy and C_1-C_5 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 C_1-C_5 alkyl. In one variation, Q is fluoro-phenyl.

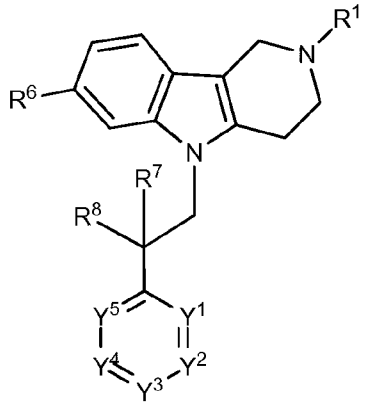
[0229] In another embodiment, the compound is of the formula (A-IIIE-1), (A-IIIE-2), (A-IIIE-3) or (A-IIIE-4):



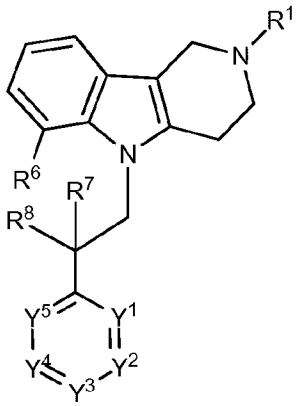
(A-IIIE-1),



(A-IIIE-2),



(A-IIIE-3) or



(A-IIIE-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 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 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.

[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^8 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-IIIE-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-IIIE-2), R^7 is C_1-C_5 alkyl, substituted with acylamino, R^8 is CH_2-$CON(H)CH_3$, 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-IIIE-2), R^7 is C_1-C_5 alkyl, substituted with -$C(O)OR^{7a}$, R^{7a} 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-IIIE-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-IIIE-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.

[0239] In some embodiments, the compound is of formula (A-IIIE-2), 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.

[0240] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0241] 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.

[0242] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0243] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0244] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0245] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0246] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0247] In certain embodiments, with respect to the compounds of formula (A-IIIE-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.

[0248] In certain embodiments, with respect to the compounds of formula (A-IIIE-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), R^7 is methyl, 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. 90, 98, or 254.

[0250] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R^7 is methyl, 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-36, 47, 163, 189, 194 to 203, or II-205.

[0251] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R^7 is methyl, 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-36, III-47, III-50, or III-51.

[0252] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R^7 is methyl, 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. 1, 2, or 253.

[0253] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), R^7 is methyl, 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. 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), R^7 is methyl, 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. 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), R^7 is methyl, 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-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), R^8 is $N(R^{11})R^{12}$, 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), R^8 is $N(R^{11})R^{12}$, 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), R^7 is other than H or methyl, R^8 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), R^7 is other than H or methyl, R^8 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), R^7 is methyl, R^8 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.

[0263] In certain embodiments, with respect to the compounds of formula (A-IIIE-2), the compound is Compound No. II-15, II-16, II-19, II-207- II-213, II-256, II-258, II-262, II-263, II-274, II-277, II- 295, II-296, II-299, or V-14.

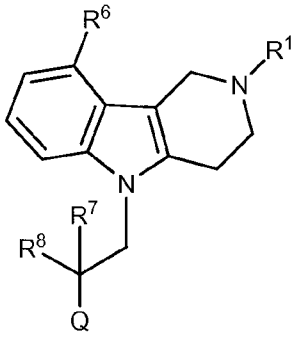
[0264] In some embodiments, the compound is of formula (A-IIIE-3), when each R^7 and R^8 is H; R^1 is methyl; R^6 is chloro; each Y^1, Y^2, Y^4 and Y^5 is CR^4, and Y^3 is CH, CF, or CCl; then at least one of Y^1, Y^2, Y^4 and Y^5 is other than CH.

[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.

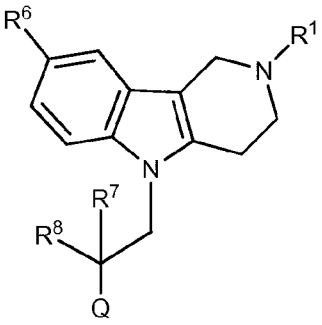
[0266] In some embodiments, the compound is of formula (A-IIIE-4), when each R^7 and R^8 is H, or R^7 taken together with R^8 form a -CH_2 moiety, R^1 is methyl; R^6 is F, Cl, CF_3, ethenyl, or propenyl; each Y^1, Y^2, Y^4 and Y^5 is CR^4, and Y^3 is CH, CF or CCl; then at least one of Y^1, Y^2, Y^4 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.

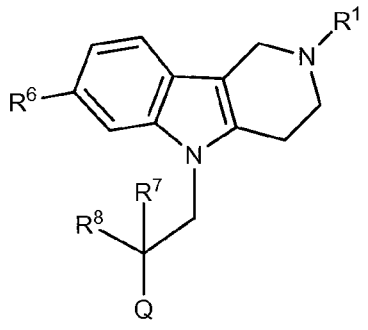
[0268] In another embodiment, the compound is of the formula (A-IIIE-5), (A-IIIE-6), (A-IIIE-7) or (A-IIIE-8):



(A-IIIE-5)

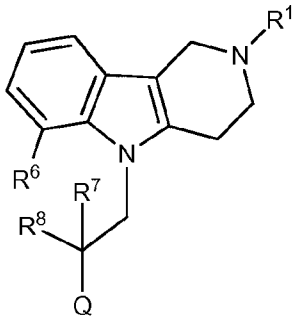


(A-IIIE-6)



(A-IIIE-7)

or



(A-IIIE-8)

,

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;

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;

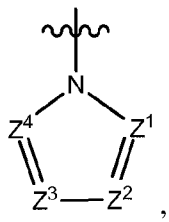
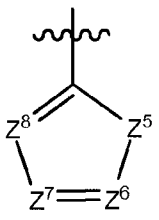
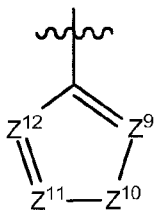
R^8 is H, halo, hydroxyl, $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, $-OC(O)N(R^{14})R^{15}$, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a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

Q is

wherein

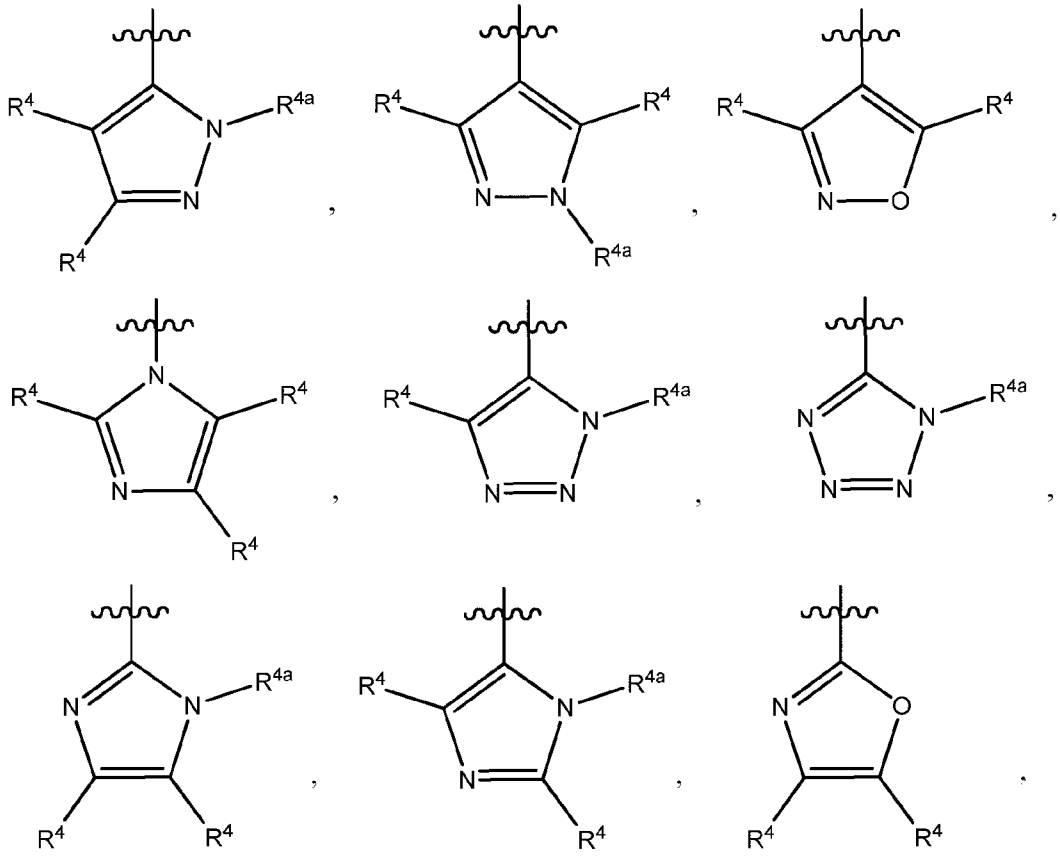
each Z^1, Z^2, Z^3 and Z^4 is independently N or CR^4 such that no more than two of Z^1, Z^2, Z^3 and Z^4 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3;

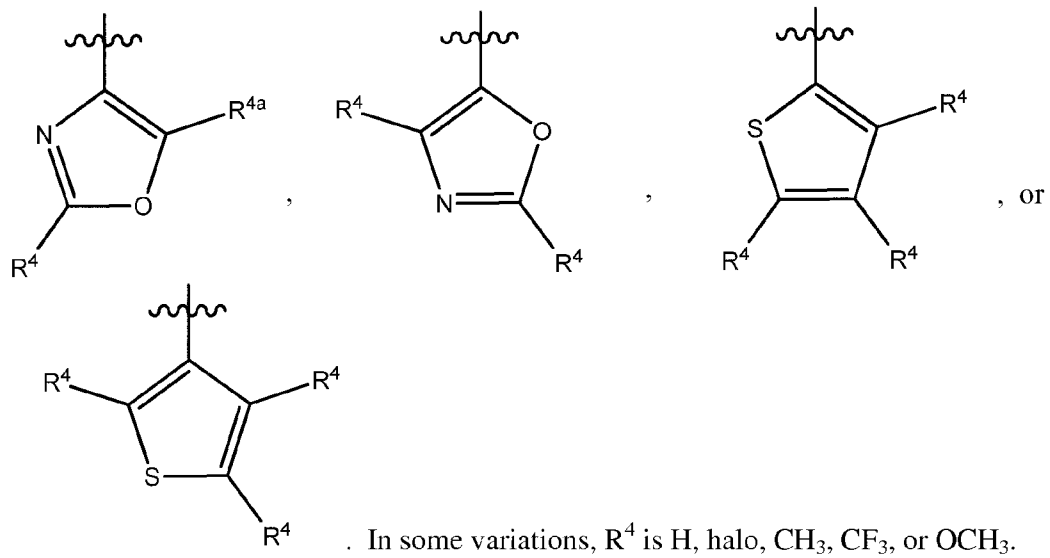
each Z^5 and Z^{10} is independently O, S or NR^{4a}, wherein R^{4a} is H or CH_3; and

each Z^6, Z^7, Z^8, Z^9, Z^{11} and Z^{12} is independently N or CR^4, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3.

[0269] In other embodiments, the compound is of formula (A-IIIE-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





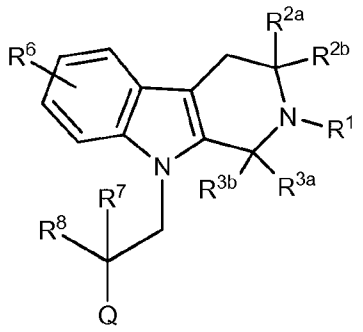
. In some variations, R^4 is H, halo, CH_3, CF_3, or OCH_3.

[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 C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl. In certain variations, R^1 is C_1-C_5 alkyl substituted with a hydroxyl. In other variations, R^1 is methyl. In some variations, R^6 is halo, C_1-C_5 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 C_1-C_5 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, CF_3, 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):



(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^{2a} or R^{3a} to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) moiety;

each R^{2b} and R^{3b} 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_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;

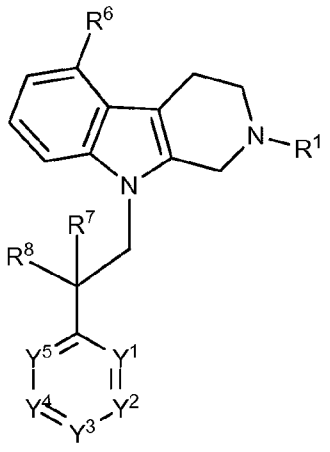
each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkylene;

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

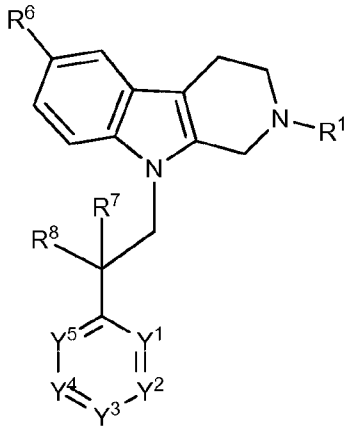
each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene; and

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.

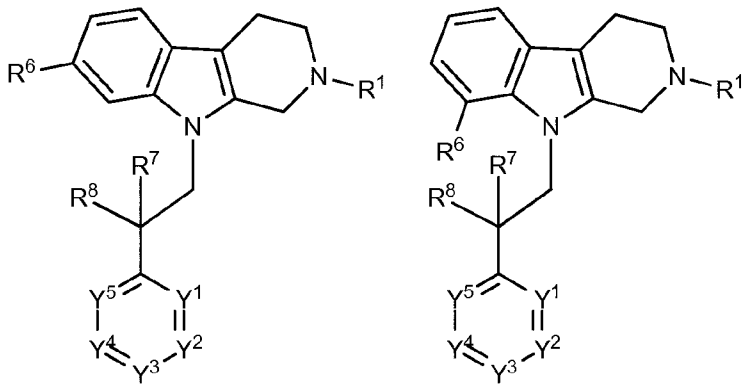
[0275] In another embodiment, the compound is of the formula (A-IIIF-1), (A-IIIF-2), (A-IIIF-3) or (A-IIIF-4):



(A-IIIF-1)



(A-IIIF-2)



(A-IIIF-3) or (A-IIIF-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 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 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.

[0276] 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, 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.

[0277] In some embodiments, the compound is of formula (A-IIIF-1), when R^7 is methyl, R^8 is OH, R^1 is methyl, R^6 is chloro; then Y^3 is other than N.

[0278] In some embodiments, the compound is of formula (A-IIIF-2), when each Y^1, Y^2, Y^3, Y^4 and Y^5 is independently CR^4; and R^1 is methyl, ethyl, iso-propyl, or cyclopropyl; then R^6 is other than Cl or methyl.

[0279] In some embodiments, the compound is of formula (A-IIIF-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.

[0280] In some embodiments, the compound is of formula (A-IIIF-2), 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, 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.

[0281] In some embodiments, the compound is of formula (A-IIIF-2), R^7 is C_1-C_5 alkyl, substituted with -C(O)OR^{7a}, R^{7a} 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.

[0282] In some embodiments, the compound is of formula (A-IIIF-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.

[0283] 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.

[0284] 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.

[0285] 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.

[0286] 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.

[0287] 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.

[0288] 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.

[0289] 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.

[0290] 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.

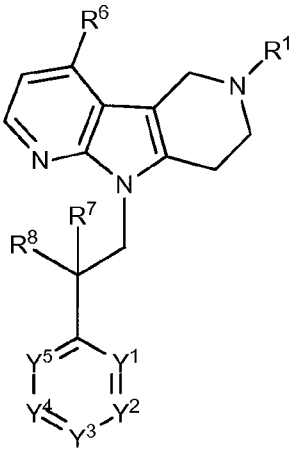
[0295] In some embodiments, the compound is of formula (A-IIIF-3), when R^7 is H or methyl; R^8 is OH; R^6 is chloro or iso-propyl; Y^2 or Y^3 is N; then R^1 is other than methyl.

[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):


(A-IIIG-1)

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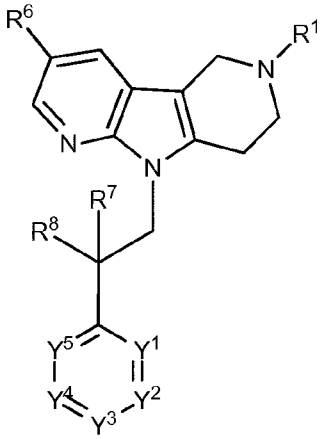
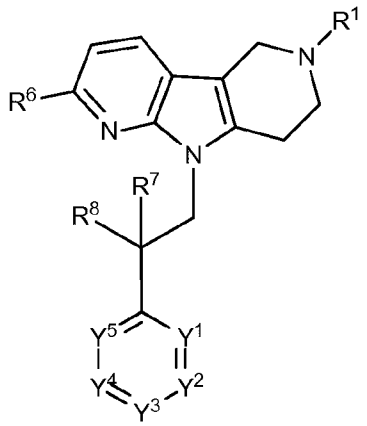

(A-IIIG-2)

or


(A-IIIG-3)

,

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;

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.

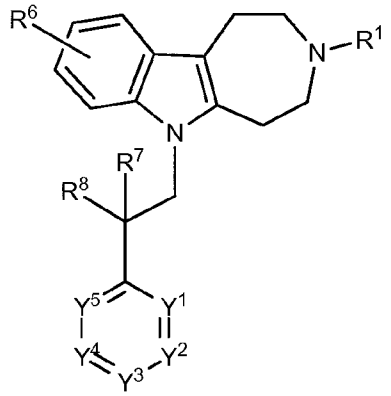
[0300] In some embodiments, the compound is of the formula (A-IIIG-2). In some variations, R^1 is H or CH_3. In other variations, R^7 is H or CH_3. In yet other variations, R^8 is hydroxyl or NH_2. In yet other variations, each R^7 and R^8 is H. In yet other variations, one of Y^1, Y^2, Y^3, Y^4 and 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^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.

[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):



(A-IIIH)

,

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;

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.

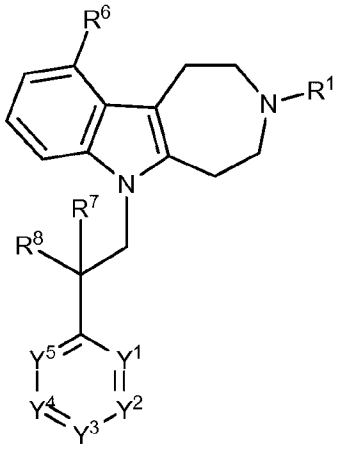
[0305] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. 13, 15, 92, 154, 172, 221, or 339.

[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.

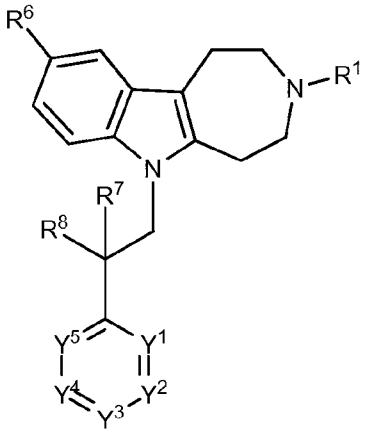
[0307] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. III-9-46, III-209 to III-220, III-320 to III-351, or III-352.

[0308] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. V-21.

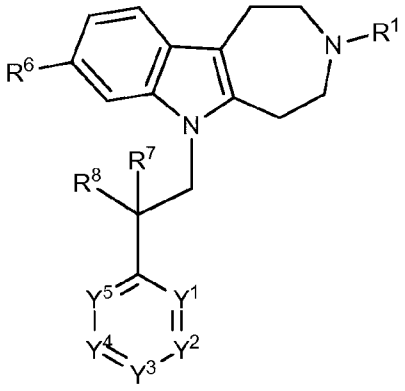
[0309] In another embodiment, the compound is of the formula (A-IIIH-1), (A-IIIH-2), (A-IIIH-3) or (A-IIIH-4):



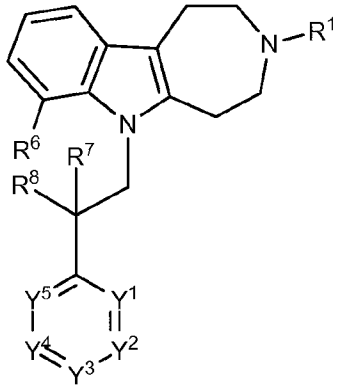
(A-IIIH-1) ,



(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.

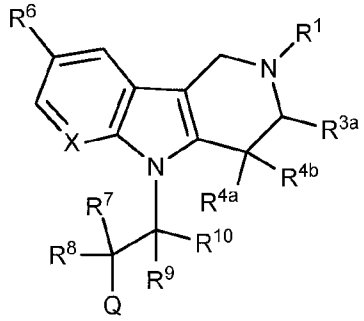
[0311] In certain embodiments, with respect to the compounds of formula (A-IIIH-2), R^6 is methyl or chloro, R^7 is H or methyl, R^8 is H or OH, Y^1 or Y^2 is independently C-H, C-F, C-Cl, or C-methoxy, and Y^3 is other than CH, CF, CCl, or C-OCH_3.

[0312] In certain embodiments, with respect to the compounds of formula (A-IIIH-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^6 is Cl or methyl, R^7 is methyl, R^8 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^6 is Cl or methyl, R^7 is methyl, R^8 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 compoud of formula (A-IIIA'):



(A-IIIA')

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

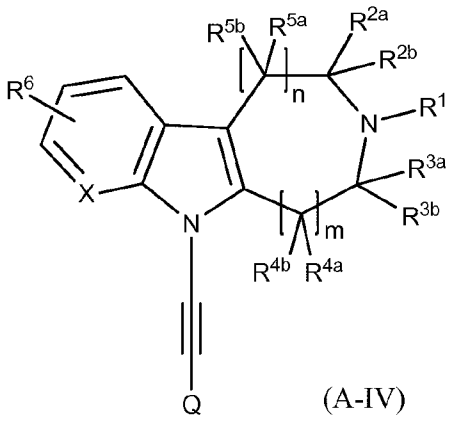
X, R^1, R^{3a}, R^6, R^7, R^8, R^9, R^{10} and Q are as defined for formula (A-IIIA),

R^{4a} is selected from the group consisting of hydrogen; halo; hydroxyl; cyano; carboxyl; -$OC(O)N(R^{14a})R^{15a}$; and -$C(O)N(R^{14a})R^{15a}$;

R^{4b} is selected from the group consisting of hydrogen, halo, and optionally substituted C_1-C_5 alkyl;

[0316] In one embodiment, when R^{4b} is hydrogen, R^{4a} is other than hydrogen. In some variations, R^{4a} is halo. In some variations, R^{4a} is chloro. In some variations, R^{4a} is fluoro. In some variations, each R^{4a} and R^{4b} is halo.

[0317] In one aspect, provided is a compound of formula (A-IV):



(A-IV)

,

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 (-$CH_2CH_2CH_2$-) 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 (-

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 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 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; 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.

[0318] In one variation, the compound is of the formula (A-IV), wherein m, n and R^1 are as defined for the formula (A-IV);

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 (-$CH_2CH_2CH_2$-) 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 or optionally substituted C_1-C_5 alkyl, or is taken together with R^1 or R^{4a}, where present, to form a propylene (-$CH_2CH_2CH_2$-) 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 or optionally substituted C_1-C_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-C_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^{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 or optionally substituted C_1-C_5 alkyl;

X is N or CR^{6a};

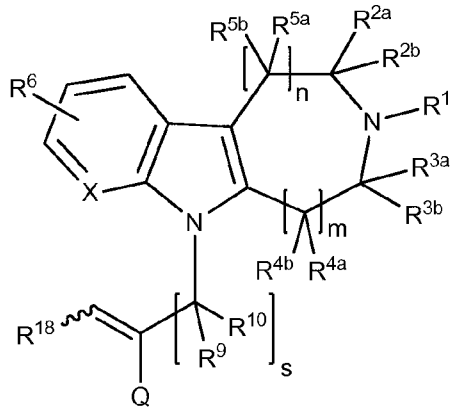
each R^6 and R^{6a} is independently H, hydroxyl, halogen, C_1-C_5 alkyl optionally substituted with 1 to 3 halogen atoms, optionally substituted C_1-C_5 alkoxy or optionally substituted -$C(O)C_1$-C_5 alkyl;

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 $-C(O)NR^{16}R^{17}$; and

each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

[0319] In one embodiment, the compound is of formula (A-IV), each of R^{2b}, R^{3a}, R^{3b}, R^{4b}, R^{5a} and R^{5b} is H; each R^{2a} and R^{4a} is H, or R^{2a} is taken together with R^{4a}, when present, to form an ethylene ($-CH_2CH_2-$) moiety; each R^6 and R^{6a} is independently CF_3, methyl, Cl, $CONHCH_3$, COOH, $COOCH_3$, or F; X is CR^6; and R^1 is other than methyl. In another embodiment, X is CR^6, R^6 is F; and R^1 is other than methyl.

[0320] In one aspect, provided is a compound of formula (A-V):



(A-V)

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

R^1 is H, C_1-C_5 alkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, cycloalkyl optionally substituted with 1 to 3 halogen atoms or hydroxyl, C_2-C_5 alkenyl, or $-C(O)OR^{11}$, 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 ($-CH_2CH_2-$) 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 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 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 ∿∿∿ 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 ($-CH_2CH_2CH_2-$) 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 or optionally substituted C_1-C_5 alkyl, or is taken together with R^1 or R^{4a}, where present, to form a propylene ($-CH_2CH_2CH_2-$) 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 or optionally substituted C_1-C_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-C_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^{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 or optionally substituted C_1-C_5 alkyl;

X is N or CR^{6a};

each R^6 and R^{6a} is independently H, hydroxyl, halogen, C_1-C_5 alkyl optionally substituted with 1-3 halogen atoms, 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;

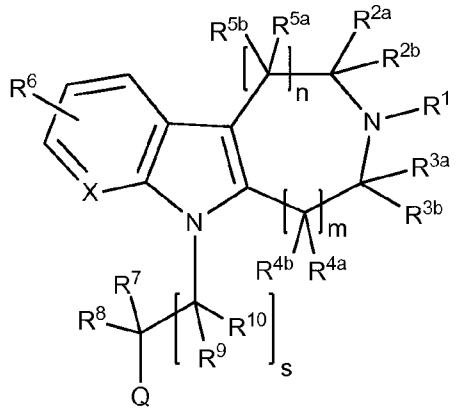
R^{18} is H or optionally substituted C_1-C_5 alkyl, and ∿∿∿ indicates the presence of either an (*E*) or (*Z*) double bond configuration;

Q is aryl or heteroaryl optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_1-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.

[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):



(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_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 ($-CH_2CH_2CH_2-$) 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

($-CH_2CH_2-$) 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 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 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;

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, where present, 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}, where present, to form a bond;

s is 0 or 1;

each R^9 and R^{10}, where present, is independently H or optionally substituted C_1-C_5 alkyl;

each R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 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 R^1 are as defined for the formula (A-VI);

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 (-$CH_2CH_2CH_2$-) 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 or optionally substituted C_1-C_5 alkyl, or is taken together with R^1 or R^{4a}, where present, to form a propylene (-$CH_2CH_2CH_2$-) 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 or optionally substituted C_1-C_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-C_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^{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 or optionally substituted C_1-C_5 alkyl;

X is N or CR^{6a};

each R^6 and R^{6a} is independently H, hydroxyl, halogen, C_1-C_5 alkyl optionally substituted with 1-3 halogen atoms, optionally substituted C_1-C_5 alkoxy or optionally substituted -C(O)C_1-C_5 alkyl;

R^7 is H or optionally substituted C_1-C_5 alkyl;

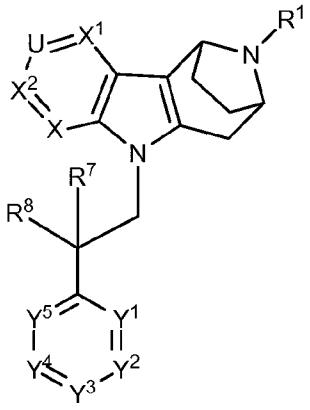
R^8 is H, halo, hydroxyl, $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, -$OC(O)N(R^{14})R^{15}$, or -$OC(O)C_1$-C_5 alkyl optionally substituted with amino;

s is 0 or 1;

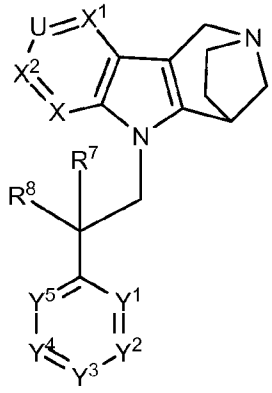
each R^9 and R^{10}, where present, is independently H or optionally substituted C_1-C_5 alkyl; and

each R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl.

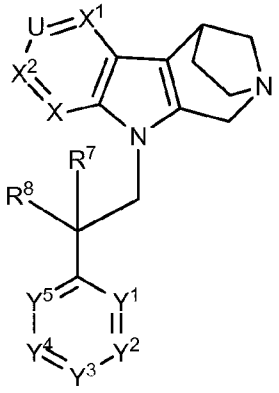
[0325] In another embodiment, the compound is of formula (A-VIIA), (A-VIIB), (A-VIIC), (A-VIID), (A-VIIE) or (A-VIIF):



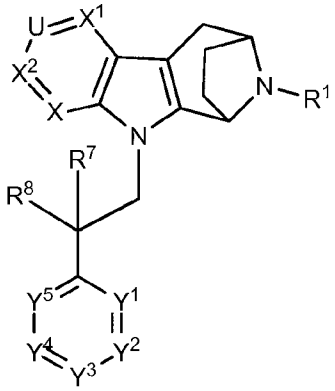
(A-VIIA)



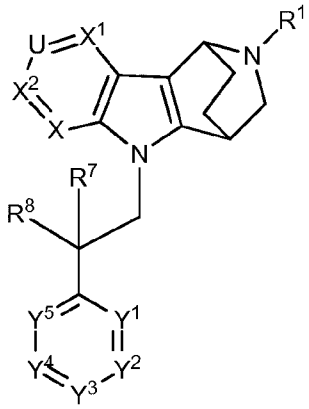
(A-VIIB)



(A-VIIC)

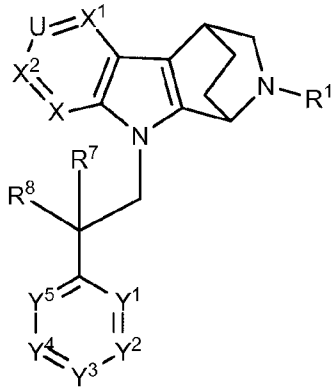


(A-VIID)



(A-VIIE)

or



(A-VIIF)

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

R^1, where present,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_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.

[0326] In certain embodiments, with respect to the compounds of formula (A-VIIA), 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-VIIA), 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-VIIA), 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-VIIA), 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-VIIA), 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-VIIB), each X^1, X^2, X and U is independently CR^6, R^8 is OH, and the compound is Compound No. III-59.

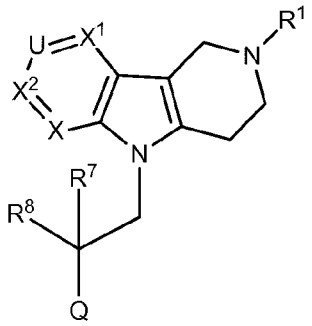
[0332] In certain embodiments, with respect to the compounds of formula (A-VIIC), each X^1, X^2, X and U is independently CR^6, R^8 is OH, each Y^1, Y^2, Y^4 and Y^5 is independently CR^4, Y^3 is N, and the compound is Compound No. 36, 38, or II-69.

[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-VIIE), each X^1, X^2, X and U is independently CR^6, R^8 is OH, and the compound is Compound No. III-60.

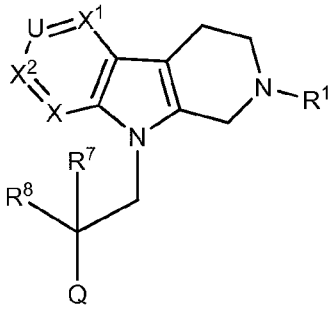
[0335] In certain embodiments, with respect to the compounds of formula (A-VIIE), each X^1, X^2, X and U is independently CR^6, R^8 is OH, and the compound is Compound No. III-56.

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



(A-VIIIA)

or



(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_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

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.

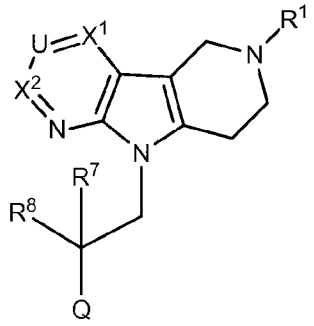
[0339] In some variations of the compounds of formula (A-VIIIA), U is N, each X^1, X^2 and X is CR^6, wherein each R^6 is H; R^1 is methyl; R^7 is H or methyl; R^8 is H, OH or methyl; and Q is other than unsubstituted phenyl, phenyl substituted with chloro, unsubstituted pyridyl, or pyridyl substituted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

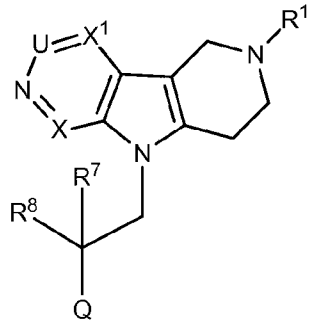
[0340] In some variations of the compounds of formula (A-VIIIA), X^2 is N, each X^2 and X is CR^6, wherein each R^6 is H; U is CR^6, wherein R^6 is H or methyl; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl, unsubstituted pyridyl, or pyridyl substituted with CF_3.

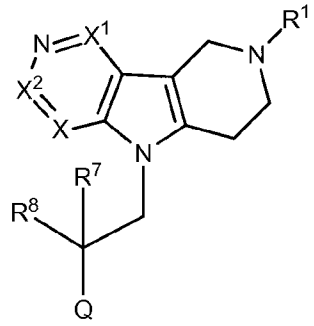
[0341] In some variations of the compounds of formula (A-VIIIA), X is N, each X^1, U and X^2 is CR^6, wherein each R^6 is H; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl.

[0342] In some variations of the compounds of formula (A-VIIIA), each X and U is N, each X^1 and X^2 is CR^6, wherein each R^6 is H; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl.

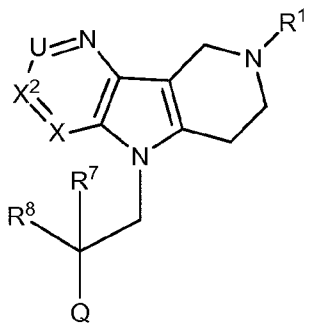
[0343] In some variations of the compounds of formula (A-VIIIA), the compound is according to formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7):

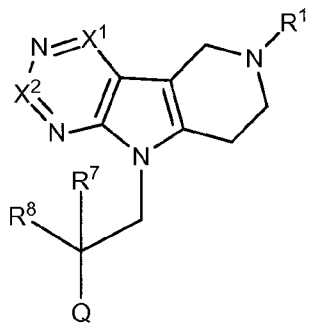


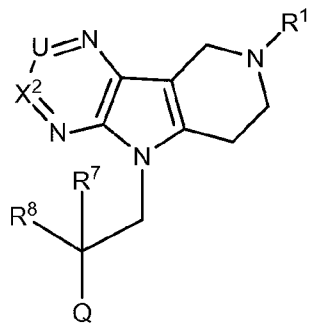
(A-VIIIA-1), 

(A-VIIIA-2), 

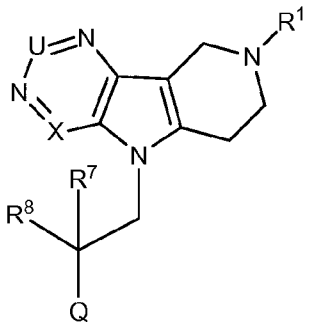
(A-VIIIA-3),



(A-VIIIA-4), 

(A-VIIIA-5), 

(A-VIIIA-6), or



(A-VIIIA-7)

or a salt, solvate or N-oxide thereof, wherein Q, R^1, R^6, R^7, and R^8, are as described for formula (A-VIIIA), and each X^1, U, X^2, or X (where present) is independently CR^6.

[0344] In one embodiment, the compound is according to formula (A-VIIIA-1), each X^1, U and X^2 is CR^6, wherein each R^6 is H; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl.

[0345] In one embodiment, the compound is according to formula (A-VIIIA-2), each X^1 and X is CR^6, wherein each R^6 is H; U is CR^6, wherein R^6 is H or methyl; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl, unsubstituted pyridyl, or pyridyl substituted with CF_3.

[0346] In one embodiment, the compound is according to formula (A-VIIIA-3), 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.

[0347] In one embodiment, the compound is according to formula (A-VIIIA-4), each X^2 and X is CR^6, wherein each R^6 is H; U is CR^6, wherein 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.

[0348] In one embodiment, the compound is according to formula (A-VIIIA-5), each X^1 and X^2 is CR^6, wherein each R^6 is H; R^1 is methyl; each of R^7 and R^8 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 X^1, U, X^2, or X (where present) is independently CR^6, and each R^6 is H. In another embodiment, each R^6 is independently selected from H, C_1-C_5 alkyl, and halo C_1-C_5 alkyl. In certain embodiments, each R^6 is independently selected from H, methyl, ethyl, fluoro, chloro, CH_2F, and CF_3.

[0350] 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 X^1, X^2, or X (where present) is CH, U is CR^6, and R^6 is selected from H, C_1-C_5 alkyl, and halo C_1-C_5 alkyl. In certain embodiments, each R^6 is independently selected from methyl, ethyl, fluoro, chloro, CH_2F, and CF_3.

[0351] 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 R^7 and R^8 is H. In another embodiment, R^7 is H or methyl, and R^8 is H, OH or methyl.

[0352] 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.

[0353] 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 C_1-C_5 alkyl, halo, halo C_1-C_5 alkyl, or C_1-C_5 alkoxy.

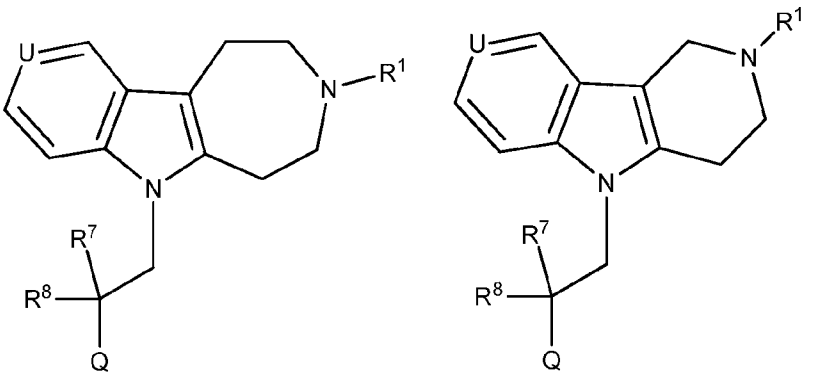
[0354] In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is phenyl substituted with methyl, ethyl, fluoro, chloro, methoxy, or CF_3.

[0355] 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.

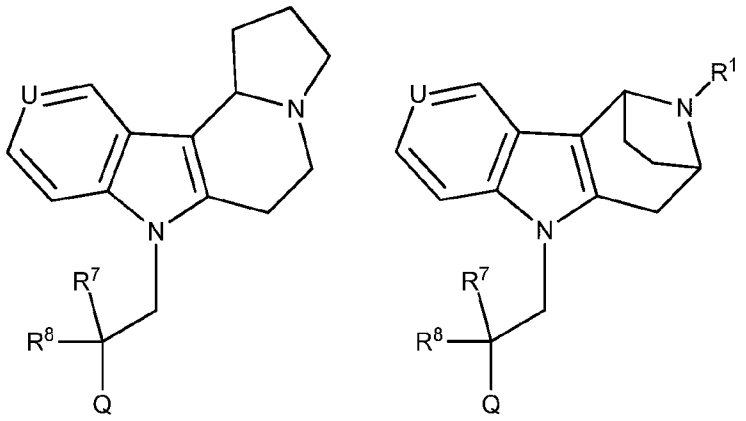
[0356] In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is pyridyl substituted with C_1-C_5 alkyl, halo, halo or C_1-C_5 alkyl.

[0357] 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 CF_3.

[0358] In one embodiment, provided are compounds of formula (A-IXA), (A-IXB), (A-IXC) or (A-IXD):



(A-IXA) , (A-IXB) ,



(A-IXC) or (A-IXD)

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

[0359] In certain embodiments, R^8 is azido. In certain embodiments, R^8 is $N(R^{11})R^{12}$. In certain embodiments, 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. In certain embodiments, R^7 is H or methyl, R^8 is azido, or $N(R^{11})R^{12}$, and 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. In certain embodiments, R^8 is SR^{13}, $S(O)R^{13}$, or SO_2R^{13}; and R^{13} is independently H or optionally substituted C_1-C_5 alkyl. In one embodiment, R^{13} is methyl, ethyl, *i*-propyl, *n*-propyl, *n*-butyl, or *t*-butyl. In certain embodiments, R^7 is C_1-C_5 alkyl, substituted with amino or substituted amino. In certain embodiments, R^7 is C_1-C_5 alkyl, substituted with OH or optionally substituted C_1-C_5 alkoxy. In certain embodiments, R^7 is C_1-C_5 alkyl, substituted with $-C(O)N(R^{7a})R^{7b}$; and each R^{7a} and R^{7b} is independently H or optionally substituted C_1-C_5 alkyl, or R^{7a} and R^{7b} are taken together to form C_3-C_5 alkylene. In certain embodiments, R^7 is C_1-C_5 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^7 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^{7a}, and R^{7a} 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^{7a}, R^{7a} is H or optionally substituted C_1-C_5 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_5 alkyl, or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene.

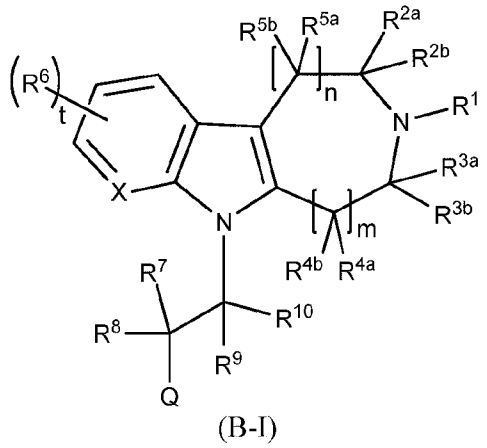
[0368] In one particular embodiment, R^8 is -C(O)N(R^{14})R^{15}; and each R^{14} and R^{15} is independently H or methyl, R^1 is methyl, U is CR^6, and R^6 is methyl; and Q is other than cyclobutyl.

[0369] In certain embodiments, R^8 is -OC(O)N(R^{14})R^{15}, -OC(O)-aryl, -OC(O)-heteroaryl, -OC(O)C_1-C_5 alkyl optionally substituted with amino, –OC(O)C_1-C_5 alkyl substituted with carboxyl, or –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.

[0370] 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 CR^6, and R^6 is methyl or chloro; and Q is other than unsubstituted phenyl, phenyl substituted with fluoro or unsubstituted pyridyl.

[0371] 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.

[0372] In some embodiments, compounds of the formula (B-I) are provided:



(B-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 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 (-$CH_2CH_2CH_2$-) 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 ($-CH_2CH_2-$) 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 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 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 1-3 substituents 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;

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

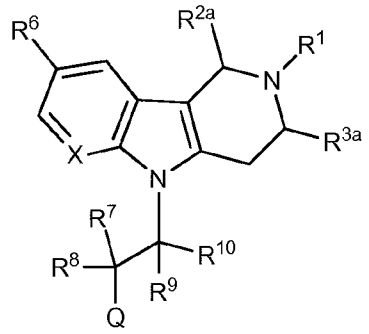
Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl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

[0373] In one variation, Q, X, m, n, t, R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, R^{6a}, R^7, R^9 and R^{10} are as defined for the formula (B-I), 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, m, n, t, R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a}, R^{4b}, R^{5a}, R^{5b}, R^6, R^{6a}, R^7, R^9 and R^{10} are as defined for the formula (B-I), and R^8 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, 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)$NR^{11}R^{12}$ where each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl.

[0375] In some variations, 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 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). In some of these variations, R^7 is H. 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, each R^7, 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.

[0376] In another embodiment, the compound of formula (B-I) has the formula (B-IA):



(B-IA)

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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 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, 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;

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.

[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 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), C_1-C_5 alkyl (*e.g.*, methyl), halo-substituted C_1-C_5 alkyl (*e.g.*, CF_3), carboxyl and $-C(O)NR^{11}R^{12}$ where each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 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 $-C(O)NR^{11}R^{12}$ where each R^{11} and R^{12} is H.

[0379] In some variations of the compound of the formula (B-IA), 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, 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, 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.

[0380] In some variations of the compound of the formula (B-IA), 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 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^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^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, 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 ($-CH_2CH_2CH_2-$) 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-C_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-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 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, 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. 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.

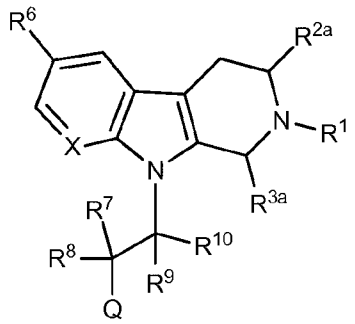
[0382] In certain embodiments, with respect to the compounds of formula (B-IA), X is CR^6, R^8 is azido, and the compound is Compound No. II-261, II-266, II-276, II-298, V-1, V-3, V-22, or V23.

[0383] 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.

[0384] 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.

[0385] 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.

[0386] In another embodiment, the compound of formula (B-I) has the formula (B-IB):



(B-IB)

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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 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, 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;

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;

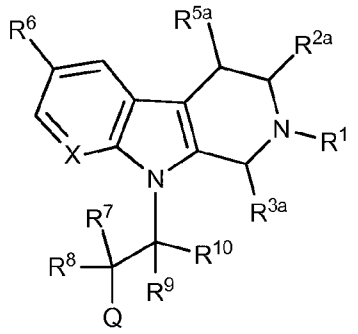
each R^9 and R^{10} is independently H or optionally substituted C_1-C_5 alkyl; and

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):



(B-IC)

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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) moiety;

R^{5a} is H, optionally substituted C_1-C_5 alkyl, optionally substituted alkenyl or optionally substituted aryl;

X is N or CR^{6a};

each R^6 and R^{6a} is independently H, hydroxyl, halo, C_1-C_5 alkyl optionally substituted with 1-3 substituents 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;

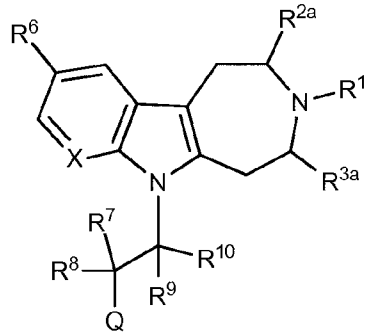
R^8 is azido, acylamino, carboxyl, carbonylalkoxy, –OC(O)C_1-C_5 alkyl substituted with carboxyl or –OC_1-C_5 alkyl optionally substituted with carboxyl;

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 1-3 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.

[0390] In one variation, the compound is of the formula (B-IC), wherein Q, X, R^1, R^{2a}, R^{3a}, R^{5a}, R^6, R^{6a}, R^7, R^9 and R^{10} are as defined for the formula (B-IC), 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^{5a}, R^6, R^{6a}, R^7, R^9 and R^{10} are as defined for the formula (B-IC), and R^8 is carboxyl, or carbonylalkoxy.

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



(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, 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 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; 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;

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.

[0392] In one variation, the compound is of the formula (B-ID), wherein Q, X, R^1, R^{2a}, R^{3a}, R^6 and R^{6a} are as defined for the formula (B-ID), R^7 is H, halo, 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 substituted with carboxyl; 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.

[0393] In some variations of the compound of the formula (B-ID), 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, 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 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, 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.

[0394] 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_8 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^{5a} (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.

[0395] 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.

[0396] 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 CR^{6a}. In some of these embodiments, R^{6a} is H, CH_3 or Cl. It is understood that any descriptions of X, R^6 and R^{6a} may be combined with any descriptions of other moieties (*e.g.*, 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.

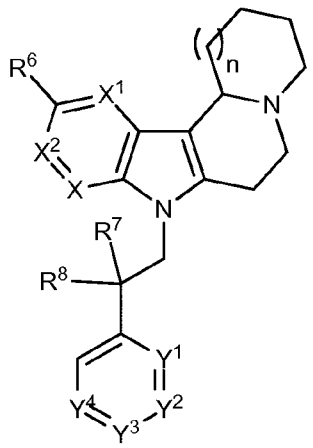
[0398] In certain embodiments of the compounds any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), R^8 is azido. In another variation, R^8 is carboxyl. In another variation, R^8 is carbonylalkoxy. In another variation, R^8 is $-OC(O)C_1$-C_5 alkyl substituted with carboxyl (*e.g.*, $-OC(O)CH_2CO_2H$, $-OC(O)CH_2CH_2CO_2H$, or $-OC(O)CH_2CH_2CH_2CO_2H$). In one variation, R^8 is $-OC_1$-C_5 alkyl optionally substituted with carboxyl. In another variation, R^8 is $-OC_1$-C_5 alkyl substituted with carboxyl (e.g., $-OCH_2CO_2H$, $-OCH_2CH_2CO_2H$, or $-OCH_2CH_2CH_2CO_2H$). In yet another variation, R^8 is $-OC_1$-C_5 alkyl. In another variation, R^8 is acylamino of the formula $-C(O)NR^{13}R^{14}$ where each R^{13} and R^{14} is independently H or optionally substituted C_1-C_5 alkyl (*e.g.*, $-C(O)NH_2$, $-C(O)NHCH_3$ or $-C(O)N(CH_3)_2$). In some variations, R^8 is acylamino of the formula $-C(O)NR^{13}R^{14}$ where R^{13} and R^{14} 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 R^8 may be combined with any descriptions of other moieties (*e.g.*, X, R^1, R^6, R^{6a}, R^7, R^9, R^{10} 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 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), carboxyl and $-C(O)NR^{11}R^{12}$. In some variations, Q is unsubstituted heteroaryl. In some variations, Q is aryl or 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), carboxyl and $-C(O)NR^{11}R^{12}$. In some variations, Q is aryl or heteroaryl optionally substituted with 2 substituents independently 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), carboxyl and $-C(O)NR^{11}R^{12}$. In some variations, Q is aryl or heteroaryl optionally

substituted with 3 substituents independently 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), carboxyl and $-C(O)NR^{11}R^{12}$ (*e.g.*, $-C(O)NH_2$). 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:



(C-I)

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

R^6 is H; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halogen atoms or hydroxyl; C_2-C_5 alkenyl; or $-C(O)OR^{11}$; 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_2R^{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.

[0402] 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 $-CF_3$, $-CHF_2$, $-CH_2F$, or $-CH_2F$. In another variation, compounds of the formula (C-I) are provided, wherein the compounds are other than compounds (A)-(G) in Table A.

[0403] 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.

[0404] In another variation of formula (C-I), R^6 is halo, CH_3, CH_2F, CHF_2, CF_3 or CD_3.

[0405] 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_2F, CHF_2 or CH_2OH.

[0406] 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_2R^{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_2R^{13}.

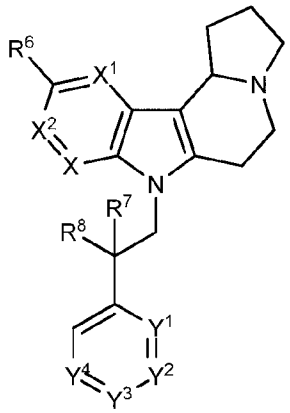
[0407] In another variation of formula (C-I), at least one of Y^1, Y^2, Y^3 and Y^4 is N. In another variation, Y^1 and Y^3 are each N. In another variation, Y^2 and Y^4 are each N. In another variation, Y^1 and Y^4 are each N.

[0408] 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.

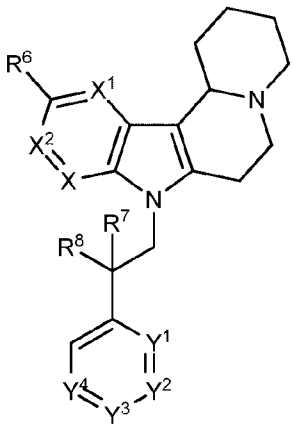
[0409] In another variation of formula (C-I), R^6 is F, Cl, Br, CD_3 or CH_2F; X^1, X^2 and X are each N or CH; Y^2 and Y^3 are each N or CR^4, wherein R^4 is CH_3 or CF_3; R^8 is H or hydroxyl; and n is 0 or 1. In another variation, of formula (C-I), R^6 is F, Cl, Br, CD_3 or CH_2F; R^7 is H, CH_3, CF_3, CH_2F, CHF_2 or CH_2OH; 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.

[0410] 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.

[0411] In one embodiment, the compound is of formula (C-IA) or (C-IB):



(C-IA)



(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 $-CH_2F$. 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.

[0412] 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.

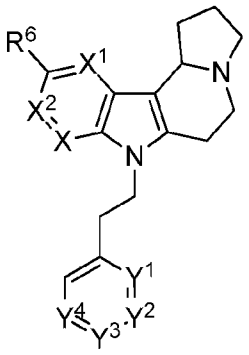
[0413] In certain embodiments, with respect to the compounds of formula (C-IA), X^2 is N, and the compound is Compound No. II-5 or II-275.

[0414] 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.

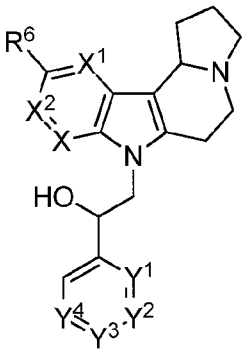
[0415] In certain embodiments, with respect to the compounds of formula (C-IB), X^1 is N, and the compound is Compound No. IV-69 to IV-78, IV-189 to IV-197, or IV-198.

[0416] In certain embodiments, with respect to the compounds of formula (C-IB), each of X, X^1, and X^2 is independently is CR^6, and the compound is Compound No. 47.

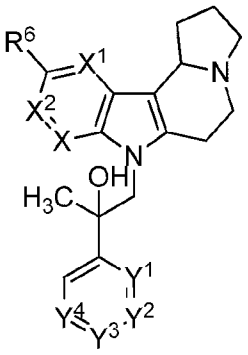
[0417] In specific variations, compounds of formula (C-IA) have the structure:



(C-IA-1)



(C-IA-2)



(C-IA-3)

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.

[0427] 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. II-121, II-127, II-128, II-130, II-291, II-294, or IV-7.

[0428] 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.

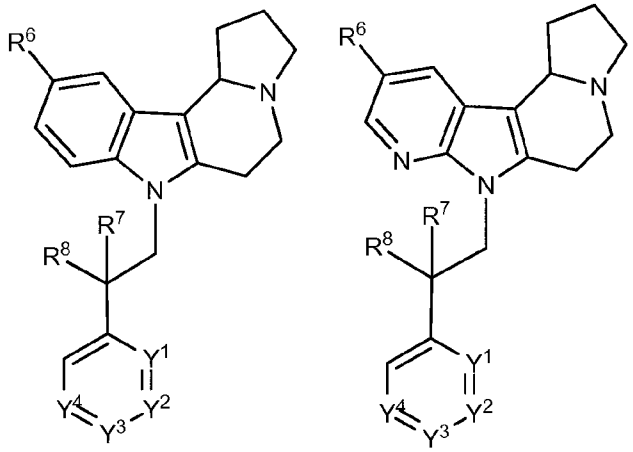
[0429] In certain embodiments, with respect to the compounds of formula (C-IA-3), X is N, and the compound is Compound No. II-149.

[0430] 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.

[0431] In certain embodiments, with respect to the compounds of formula (C-IA-3), X^1 is N, and the compound is Compound No. II-17.

[0432] In certain embodiments, with respect to the compounds of formula (C-IA-3), X^1 is N, and the compound is Compound No. IV-231, IV-233, IV-235, IV-237, or IV-238.

[0433] In other variations, compounds of formula (C-IA) have the structure:



(C-IA-4) or (C-IA-5)

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 (C-I). In one variation, R^7 and R^8 are both H.

[0434] In certain embodiments, with respect to the compounds of formula (C-IA-4), each Y^1, Y^2, Y^3 and Y^4 is independently CR^4; and the compound is Compound No. II-120, II-121, II-266, II-271, or II-279.

[0435] In certain embodiments, with respect to the compounds of formula (C-IA-4), each Y^1, Y^2, Y^3 and Y^4 is independently CR^4; and the compound is Compound No. IV-6, IV-7, or IV-9.

[0436] 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.

[0437] 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.

[0438] 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.

[0439] 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.

[0440] 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.

[0441] 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.

[0442] 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.

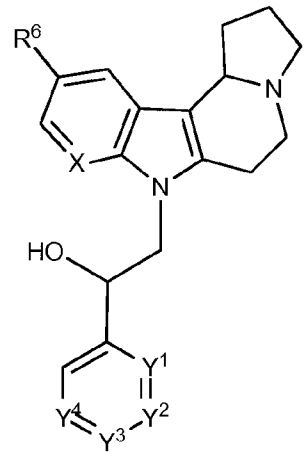
[0443] In certain embodiments, with respect to the compounds of formula (C-IA-5), each Y^1, Y^2, Y^3 and Y^4 is independently CR^4; and the compound is Compound No. IV-1, IV-9, IV-11 to IV-18, IV-129, IV-130 to IV-137, or IV-138.

[0444] 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.

[0445] 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-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. 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-IA) have the structure:



(C-IA-6)

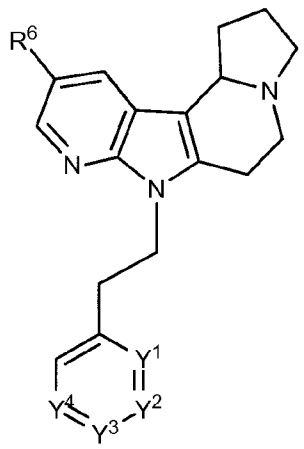
or a salt or solvate thereof, wherein X is C or N; and R^6, Y^1, Y^2, Y^3 and Y^4 are defined as for formula (C-I).

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

[0449] In certain embodiments, with respect to the compounds of formula (C-IA-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-IA-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-IA) have the structure:



(C-IA-7)

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-IA-7); the compound is Compound No. 74, 134, 137, or 336.

[0453] In certain embodiments, with respect to the compounds of formula (C-IA-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-IA-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.

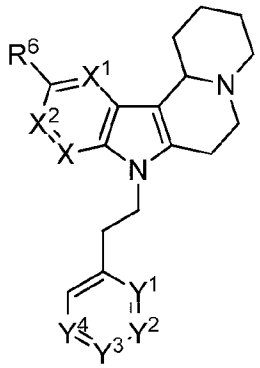
[0455] In one variation of formula (C-IA-1) one or more of the following apply: (i) R^6 is other than Cl when each X^1, X^2, X, Y^1, Y^2 and Y^4 is CH and Y^3 is CF; (ii) R^6 is other than H when each X^1, X^2, X, Y^1, Y^2 and Y^4 is CH and Y^3 is CF; (iii) R^6 is other than H when each X^1, X^2, Y^1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

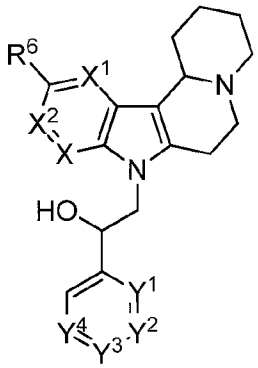
[0457] In one variation of formula (C-IA-3), R^6 is other than H when each X^1, X^2, X, Y^1, Y^2 and Y^4 is CH and Y^3 is N.

[0458] In certain embodiments, with respect to the compounds of formula (C-IA), (C-IA-1), (C-IA-3), or (C-IA-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.

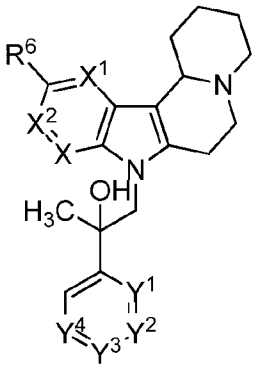
[0459] In specific variations, compounds of formula (C-IB) have the structure:



(C-IB-1)



(C-IB-2)



(C-IB-3)

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).

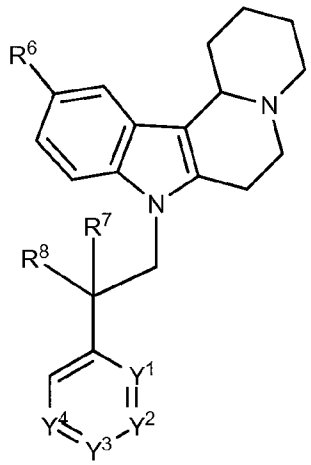
[0460] In certain embodiments, with respect to the compounds of formula (C-IB-1); the compound is Compound No. IV-8, IV-49 to IV-87, or IV-88.

[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.

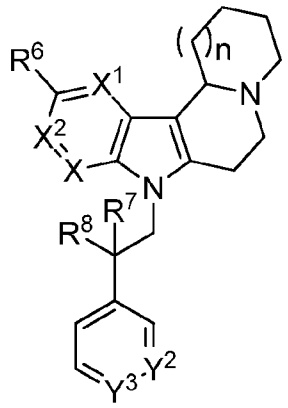
[0464] In one embodiment, the compound is of formula (C-IC-1):



(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).

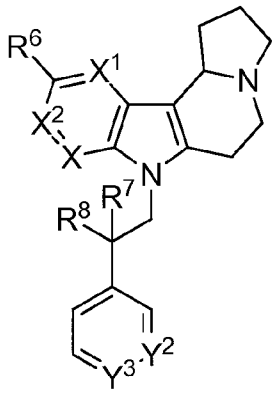
[0465] In one embodiment, the compound is of formula (C-II):



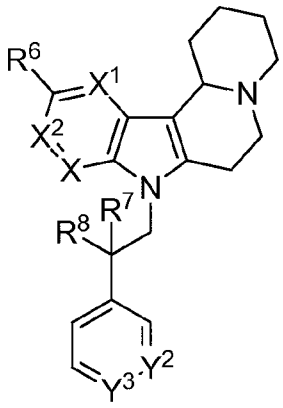
(C-II)

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 $-CH_2F$. In another variation, compounds of the formula (C-II) are provided, wherein the compounds are other than compounds (A)-(G) in Table A.

[0466] In one embodiment, the compound is of formula (C-IIA) or (C-IIB):



(C-IIA)



(C-IIB)

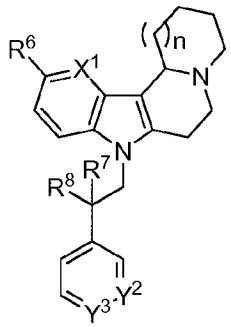
wherein R^6, R^7, R^8, X^1, X^2, X, Y^2, and Y^3 are as described for formula (C-I). In one variation of formula (C-IIA), one or more of the following apply (i) R^6 is other than Cl when n is 0, each R^7 and R^8 is H, each X^1, X^2, X, Y^2 is CH and Y^3 is CF; (ii) R^6 is other than H when n is 0 and (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

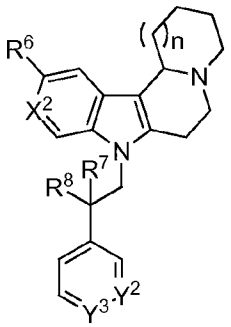
Compounds (A)-(G), presented in Table A. In another variation, the compound of formula (C-IIA) is other than Compounds (A)-(G) in Table A. It is understood that each of compounds (A)-(G) may exist as individual isomers, *e.g.*, isomer A1 and isomer A2 for compound A.

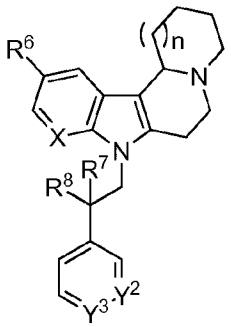
[0467] Table A: Representative Compounds of formula (C-IIA)

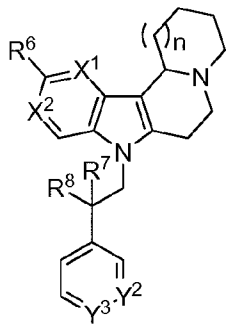
Compound	R^6	R^7	R^8	X^1	X^2	X	Y^2	Y^3
A	Cl	H	H	CH	CH	CH	CH	CF
B	H	H	H	CH	CH	CH	CH	CH
C	H	CH_3	OH	CH	CH	CH	CH	N
D	CH_3	H	H	CH	CH	N	N	CCH_3
E	H	H	H	CH	CH	N	N	CCH_3
F	H	H	H	CH	CH	N	N	CCF_3
G	H	H	OH	CH	CH	N	CH	N

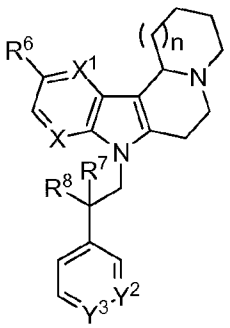
[0468] In one embodiment, the compound is of formulae (C-IIIA)-(C-IIIF):

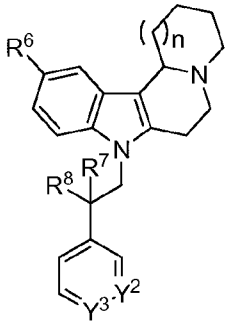

(C-IIIA)


(C-IIIB)


C-(IIIC)


(C-IIID)

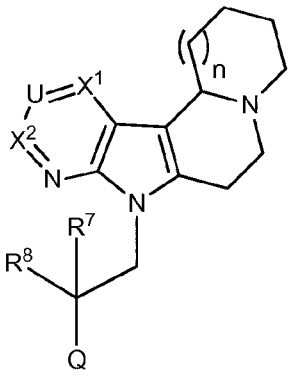

(C-IIIE)


(C-IIIF)

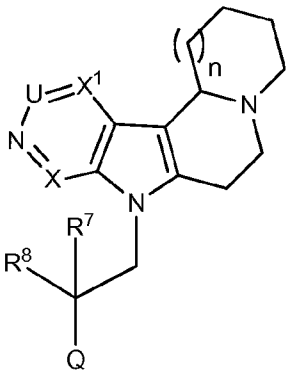
wherein R^6, R^7, R^8, X^1, X^2, X, Y^2, Y^3 and n are as described for formula (C-I). In one variation, the compound is of formula (C-IIIA), (C-IIIB), (C-IIIC), (C-IIID), (CIII-E) or (C-IIIF), wherein n is 0. In one variation compound is of formulae (C-IIIA), (C-IIIB), (C-IIIC), (C-IIID), (CIII-E) or (C-IIIF), wherein n is 0, and whereinone 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^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 another variation, the compound is of formulae (C-IIIA), (C-IIIB), (C-IIIC), (C-IIID), (CIII-E) or (C-IIIF), wherein n is 1.

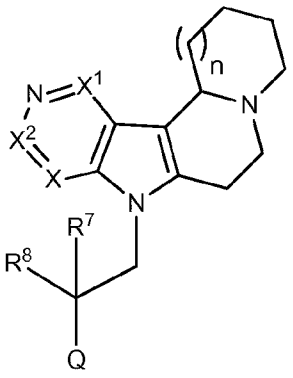
[0469] In another embodiment the compound is according to formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG):



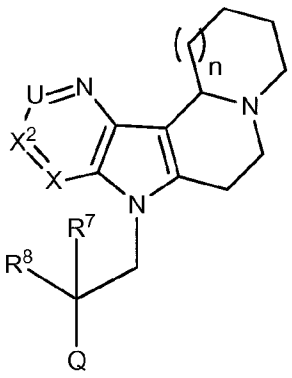
(C-IVA) ,



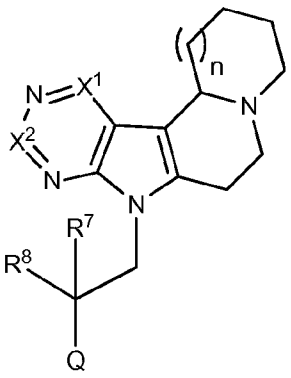
(C-IVB) ,



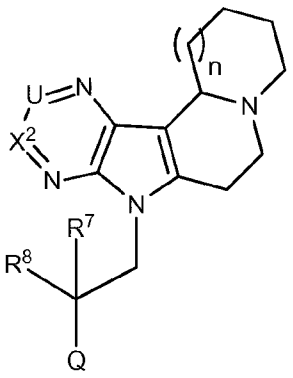
(C-IVC) ,



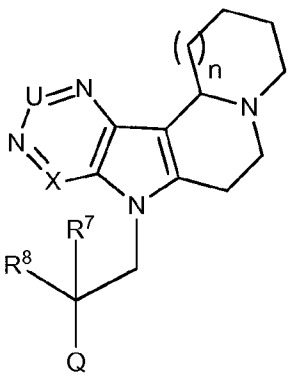
(C-IVD) ,



(C-IVE) ,



(C-IVF) ,



or (C-IVG) ,

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

n is 0 or 1;

each X^1, U, X^2, or X, where present, is independently CR^6;

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; 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.

[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 X^1, U, X^2, or X is independently CR^6, and each R^6 is H. In another embodiment, each R^6 is independently selected from H, C_1-C_5 alkyl, and halo C_1-C_5 alkyl. In certain embodiments, each R^6 is independently selected from H, methyl, ethyl, fluoro, chloro, CH_2F, and CF_3.

[0471] In one embodiment, with respect to the compounds of formula (C-IVA), (C-IVB), (C-IVD), (C-IVF) or (C-IVG), each X^1, X^2 and X (where present) is CR^6, wherein R^6 is H; , U is CR^6, wherein R^6 is selected from H, C_1-C_5 alkyl and halo C_1-C_5 alkyl. In certain embodiments, each R^6 is independently selected from methyl, ethyl, fluoro, chloro, CH_2F, and CF_3.

[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 R^7 and R^8 is H. In another embodiment, R^7 is H or methyl, and R^8 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), R^7 is H; and R^8 is OH, NH_2, CF_3 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 C_1-C_5 alkyl, halo, halo C_1-C_5 alkyl or C_1-C_5 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 CF_3. In certain embodiments, Q is phenyl substituted with 4-methyl, 4-ethyl, 4-fluoro, 4-chloro, 4-methoxy, or 4-CF_3.

[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 C_1-C_5 alkyl, halo, halo or C_1-C_5 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 CF_3.

[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.

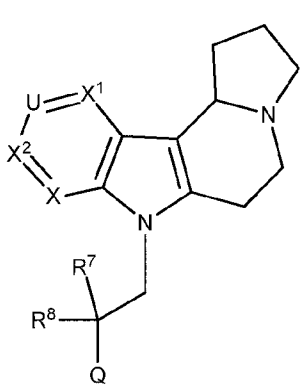
[0491] In certain embodiments, with respect to the compounds of formula (C-IVD), n is 0, and the compound is Compound IV-3, IV-29 to IV-38, IV-109 to IV-118, IV-149 to IV-158, IV-229 to IV-237, or IV-238.

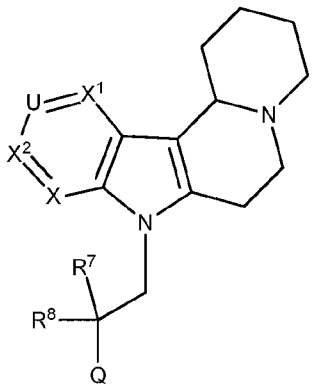
[0492] In certain embodiments, with respect to the compounds of formula (C-IVD), n is 1, and the compound is Compound No. IV-69 to IV-78, IV-189 to IV-197, or IV-198.

[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:



(C-VA) , or  (C-VB) ,

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;

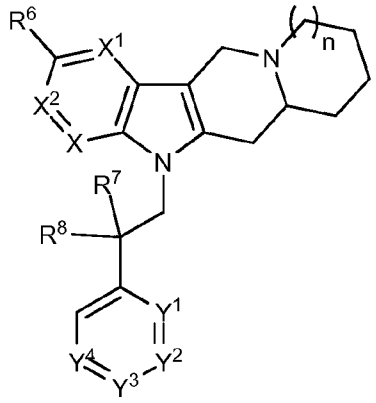
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

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_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.

[0496] In some embodiments, compounds of the formula (D-I) are provided:



(D-I)

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_2R^{13};

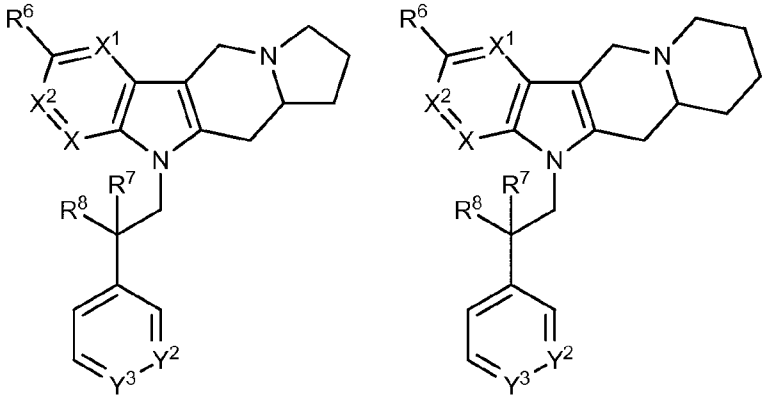
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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.

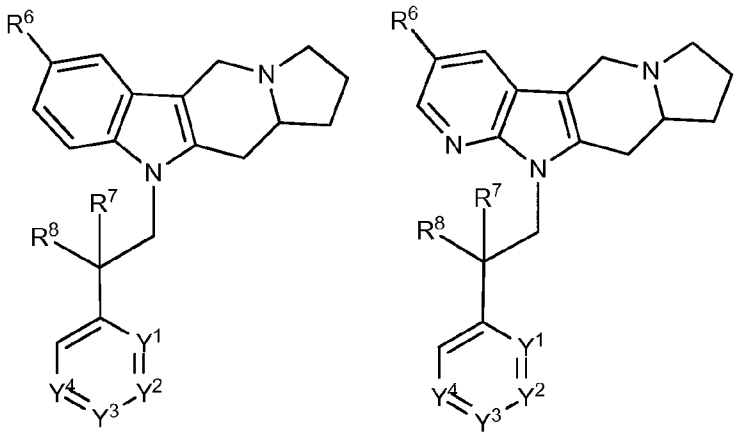
[0497] In one variation, the compound is of formula (D-IIA) or (D-IIB):



(D-IIA) or (D-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 (D-I).

[0498] In other variations, compounds of formula (D-IIA) have the structure:



(D-IIA-1) or (D-IIA-2)

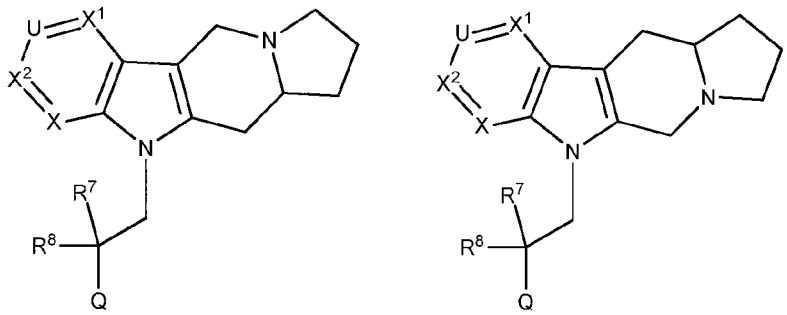
or a salt or solvate thereof, wherein R^6, R^7, R^8, Y^1,Y^2, Y^3 and Y^4 are defined as for formula (D-I).

[0499] In certain embodiments, with respect to the compounds of formula (D-IIB), 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 (D-IIIB)

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_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

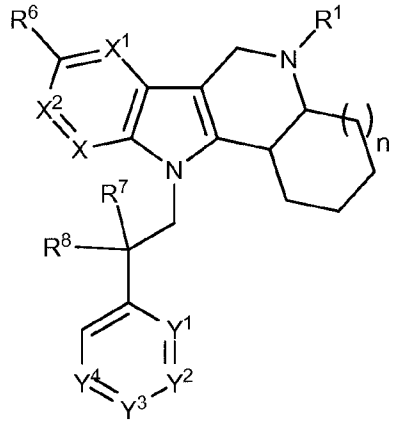
each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

[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:



(E-I)

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 $-C(O)OR^{11}$;

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_2R^{13};

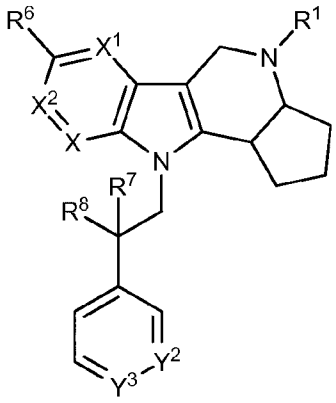
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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

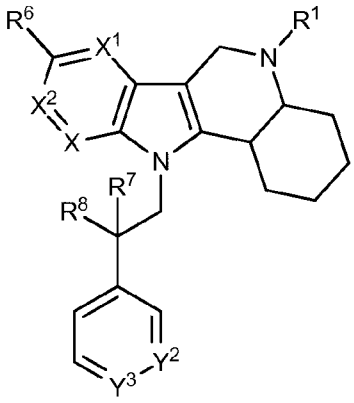
n is 0 or 1.

[0507] In one variation, the compound is of formula (E-IIA) or (E-IIB):



(E-IIA)

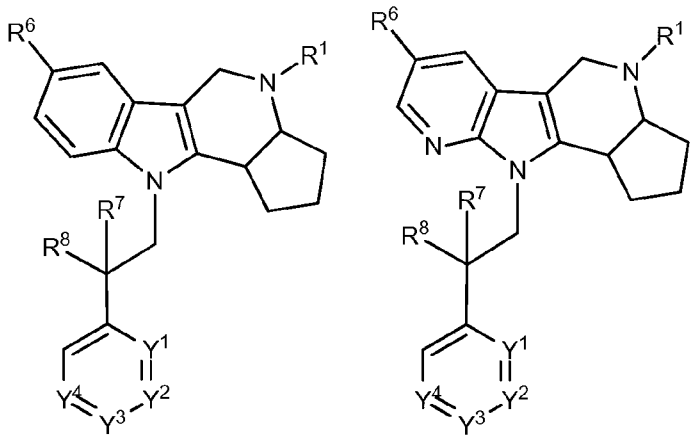
or



(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:

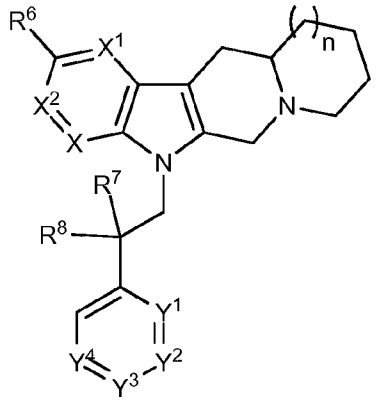


(E-IIA-1) or (E-IIA-2)

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:



(F-I)

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_2R^{13};

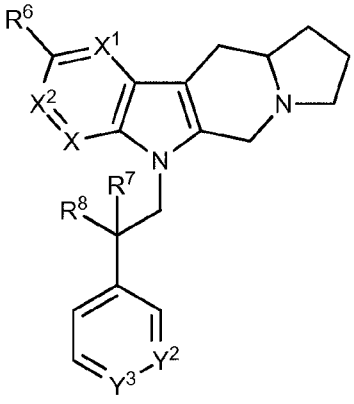
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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

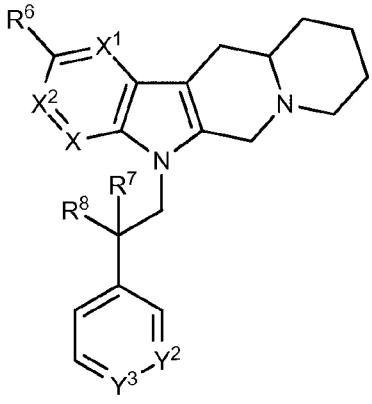
n is 0 or 1.

[0511] In one variation, the compound is of formula (F-IIA) or (F-IIB):



(F-IIA)

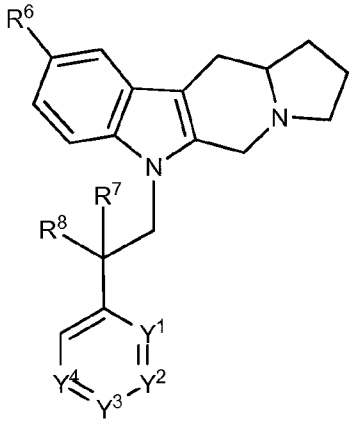
or



(F-IIB)

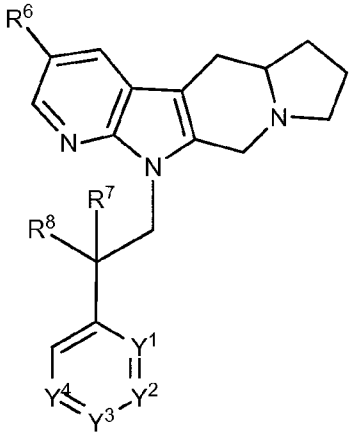
or a salt or solvate thereof, wherein R^6, X^1, X^2, X, Y^2 and Y^3 are defined as for formula (F-I).

[0512] In other variations, compounds of formula (F-IIA) have the structure:



(F-IIA-1)

or

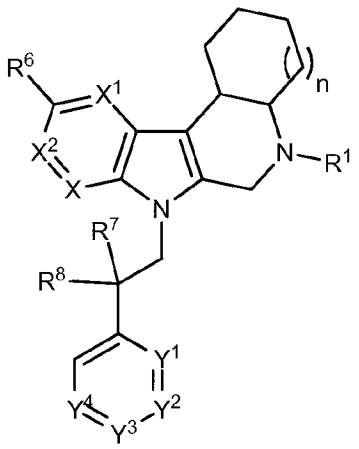


(F-IIA-2)

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:



(G-I)

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 $-C(O)OR^{11}$;

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_2R^{13};

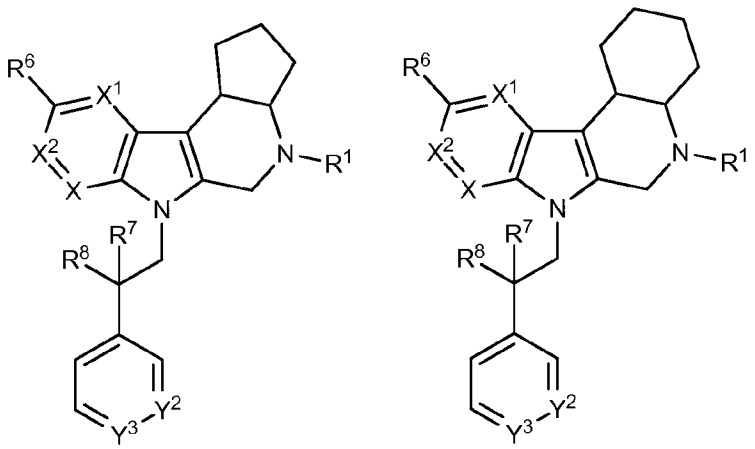
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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.

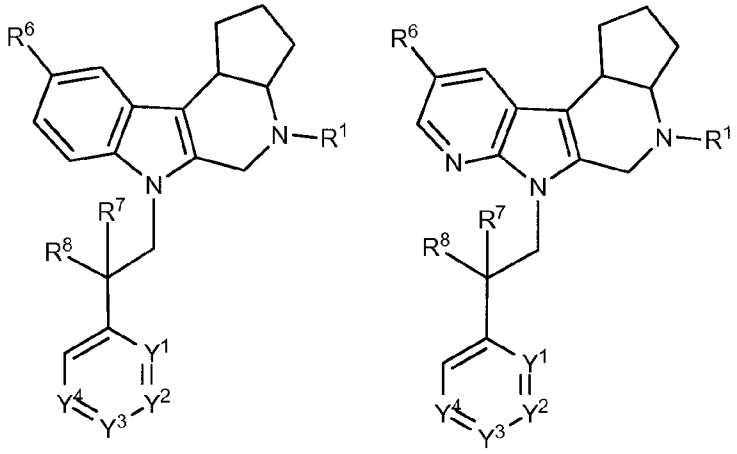
[0515] In one variation, the compound is of formula (G-IIA) or (G-IIB):



(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:

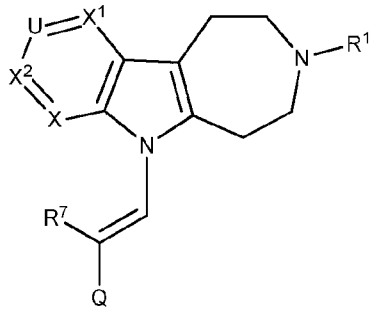


(G-IIA-1) or (G-IIA-2)

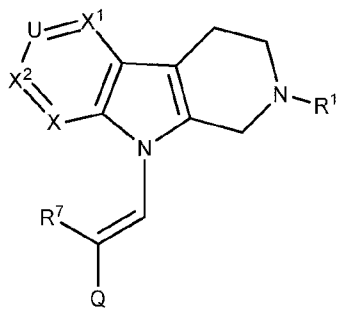
or a salt or solvate thereof, wherein R^6, R^7, R^8 , Y^1, Y^2, Y^3 and Y^4 are defined as for formula (G-I).

[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.

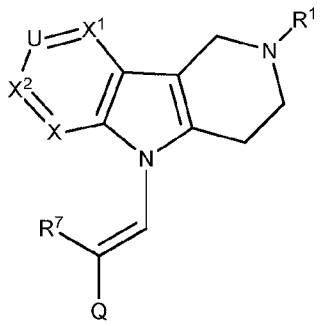
[0518] In one embodiment, compounds of formula (H-IA), (H-IB), (H-IC) or (H-ID) are provided:



(H-IA)

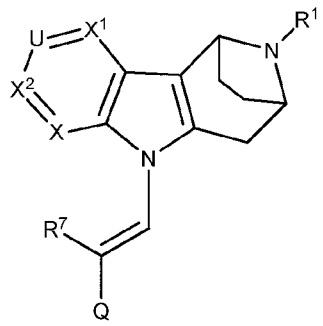


(H-IB)



(H-IC)

or



(H-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;

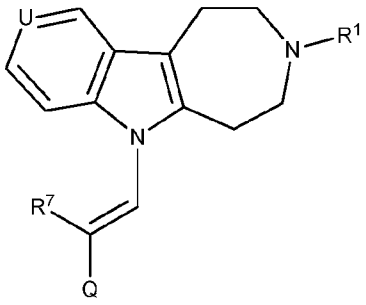
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl;

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

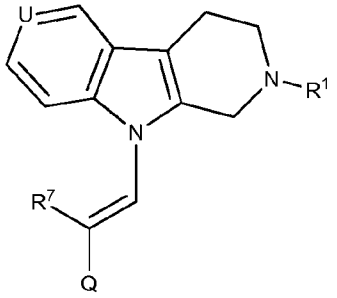
each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

[0519] 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^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.

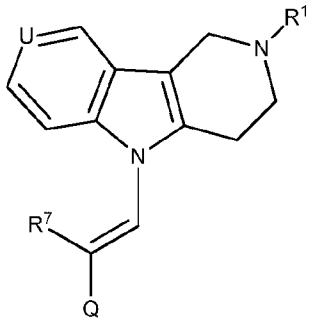
[0520] In one embodiment, compounds of formula (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1) are provided:



(H-IA-1)

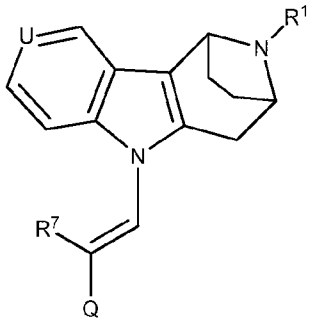


(H-IB-1)



(H-IC-1)

or



(H-ID-1)

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 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.

[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^7 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 C_1-C_5 alkyl, or optionally substituted C_1-C_5 alkoxy; and Q is other than unsubstituted pyridyl, or pyridyl substituted with methyl, Cl, Br, OCH_3, 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.

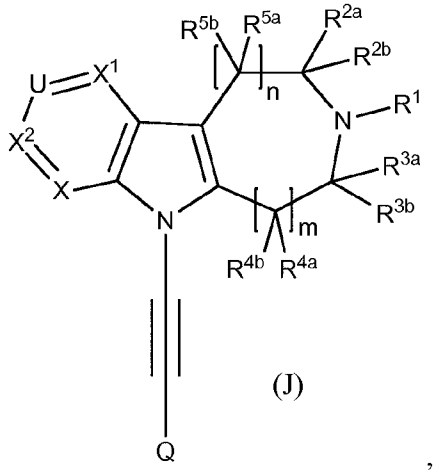
[0536] In certain embodiments, with respect to the compounds of formula (H-IIC-1), the compound is Compound No. 242, 256, 264, 313, 321, 328, 330, or 334.

[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 CR^6, and R^6 is CF_3, methyl, chloro, $-CONHCH_3$, -COOH, $-COOCH_3$, H, or fluoro; and R^1 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), R^7 is H, halo, or C_1-C_5 alkyl substituted with halo. In one embodiment, R^7 is H, methyl, or CF_3.

[0540] In another aspect, provided is a compound of formula (J):



(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; 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;

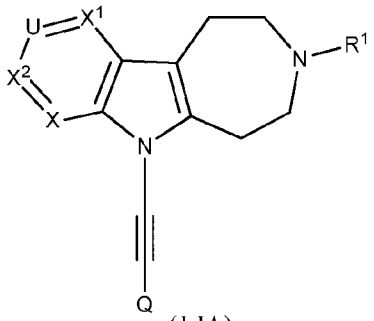
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

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

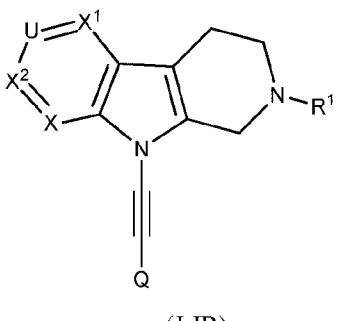
each R^6 is independently H; hydroxyl; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C_2-C_5 alkenyl; optionally substituted C_1-C_5 alkoxy; or optionally substituted $-C(O)C_1$-C_5 alkyl;

Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

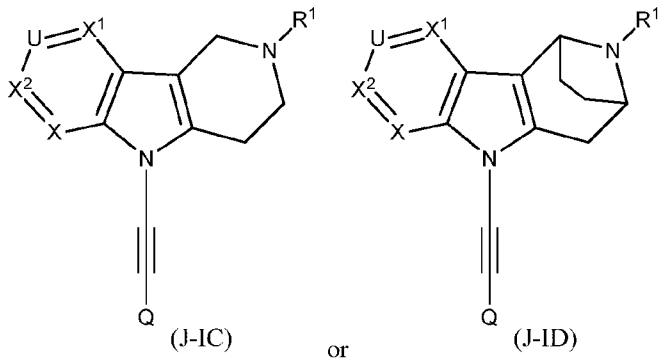
[0541] In one embodiment, compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID):



(J-IA)



(J-IB)



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;

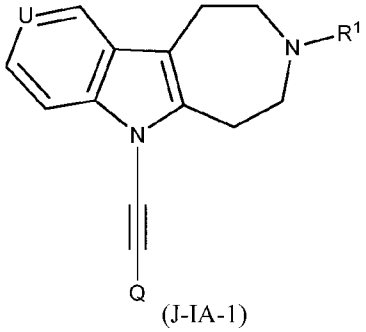
Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, -NHC(O)CH_3 and –C(O)$NR^{16}R^{17}$; and

each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

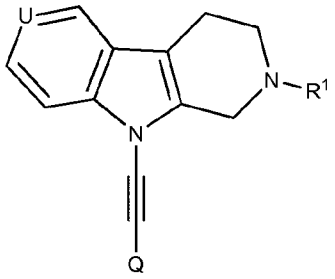
[0542] In certain embodiments, with respect to the compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID), each X^1, X^2 and X is independently CR^6; wherein each R^6 is independently halo, C_1-C_5-alkyl, halo C_1-C_5-alkyl, perhalo C_1-C_5-alkyl, or C_1-C_5-alkoxy. In certain embodiments, each X^1, X^2 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.

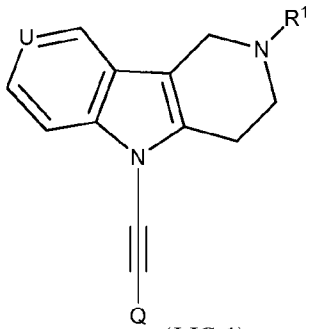
[0544] In one embodiment, compound is according to formula (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1) are provided:



(J-IA-1)

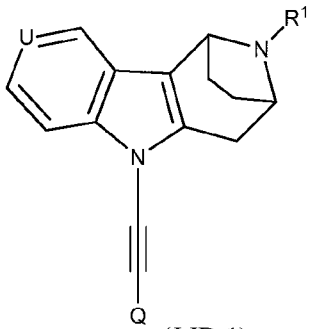


(J-IB-1)



(J-IC-1)

or



(J-ID-1)

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

U is N or CR^6;

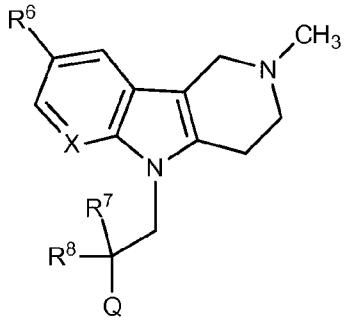
R^1 is H, C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C_3-C_8 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C_2-C_5 alkenyl optionally 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;

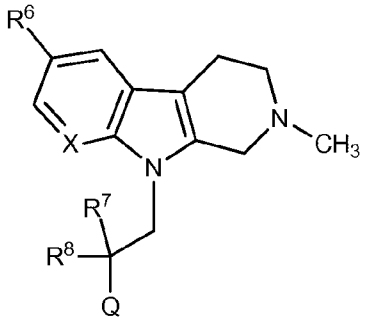
Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, -NHC(O)CH_3 and –C(O)$NR^{16}R^{17}$; and

each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

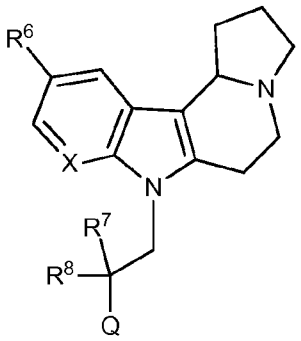
[0545] In another embodiment, the compound is of the formula (K-IA), (K-IB), (K-IC) or (K-ID):



(K-IA)

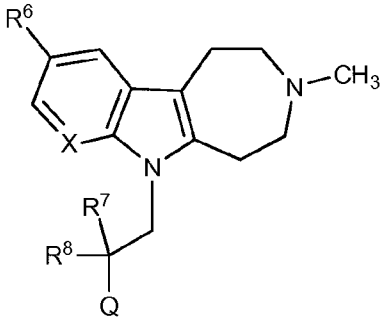


(K-IB)



(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).

[0547] 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).

[0548] In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); R^8 is NH_2, $N(CH_3)H$, $N(CH_3)_2$, 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).

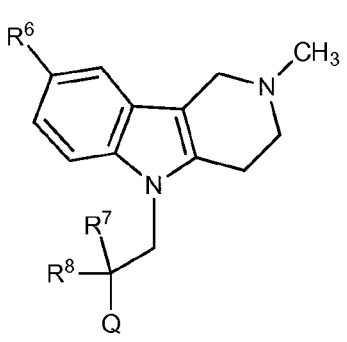
[0549] In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); each R^7 and R^8 is H. In one embodiment, the compound is Compound 74, 134, or II-244 (Table I and II).

[0550] 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).

[0551] 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.

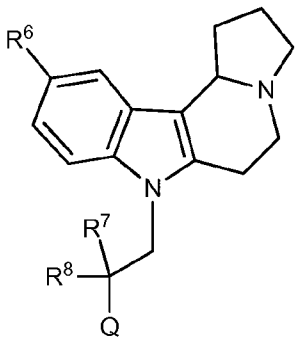
[0552] In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); R^7 is 3,3-dimethyl-2-hydroxybutyl. In one embodiment, the compound is Compound II-227 (Table II).

[0553] In another embodiment, the compound is of the formula (K-IE), or (K-IF):



(K-IE)

or



(K-IF)

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); R^7 is H, and R^8 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); R^7 is methyl, and R^8 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 $N(CH_3)_2$. 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); R^8 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 R^1 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 R^6 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 R^7 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 R^8 is H, F, OH, $-N(CH_3)_2$,or $-OC(O)N(CH_3)_2$.

[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 Y^2 is N. In one embodiment, Y^2 is N, and one of Y^1, Y^3, or Y^4 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 Y^3 is N. In one embodiment, Y^3 is N, and one of Y^1, Y^2, or Y^4 is methyl.

[0566] 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 Y^1 and Y^4 is N.

[0567] In certain embodiments, with respect to the compounds of formula (A-IIIE-6), and Q is triazolyl, or imidazolyl.

[0568] 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), R^7 is H, R^8 is OH, and the compound is Compound No. 3, 4, 13, 39, 41, 127, 144, II-132, II-138, II-139, or II-140.

[0569] 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), R^7 is methyl, R^8 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.

[0570] 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), R^8 is NH_2, $N(CH_3)H$, $N(CH_3)_2$, NH-cyclopropyl, or NH-cyclobutyl, and the compound is Compound No. 27, 150, 151, 154, II-4, II-7, II-13, or II-260.

[0571] 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 R^7 and R^8 is H, and the compound is Compound No. 74, 134, or II-244.

[0572] 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), R^7 Me, and R^8 is F, and the compound is Compound No. II-212.

[0573] 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), R^8 is $-OC(O)N(CH_3)_2$, and the compound is Compound No. 141.

[0574] 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 R^7 is 3,3-dimethyl-2-hydroxybutyl, and the compound is Compound No. II-227.

[0575] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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), Q is optionally substituted phenyl.

[0576] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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), Q is phenyl substituted with C_1-C_5 alkyl, halo, halo C_1-C_5 alkyl, or C_1-C_5 alkoxy.

[0577] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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), Q is phenyl substituted with methyl, ethyl, F, Cl, OCH_3, or CF_3.

[0578] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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), Q is optionally substituted pyridyl, or optionally substituted pyrimidinyl.

[0579] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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), (H-IIB, (J-IC) or (J-ID), (J-IA-1), (J-IB-1), (J-IC-1) or (J-ID-1), Q is pyridyl substituted with C_1-C_5 alkyl, halo, halo or C_1-C_5 alkyl.

[0580] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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 -1), Q is pyridyl substituted with methyl, ethyl, F, Cl, or CF_3.

[0581] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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 H; unsubstituted C_1-C_5alkyl; C_1-C_5 alkyl substituted with OH or SO_3H; cycloalkyl; or C_2-C_5 alkenyl.

[0582] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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 H; unsubstituted C_1-C_5alkyl; C_1-C_5 alkyl substituted with up to three halogen atoms; cycloalkyl; or C_2-C_5 alkenyl.

[0583] In one embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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_3H.

[0584] In one particular embodiment, with respect to the compounds of formula (A-IB), (A-IC), (A-ID), (A-IE), (A-VIIIA), (A-VIIIB), (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^{4a} is F. In another embodiment, each R^{4a} and R^{4b} 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^{4a} is F, R^{4b} 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^{4a} and R^{4b} 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^{4a} and R^{4b} 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, 5, 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, II-13, II-212, II-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, 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, 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, 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, 127, 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, 193, 193a, 193b, 194a, 194b, 196, 196a, 196b, 197, 197a, 197b, 198, 198a, 198b, 198c, 198d, 199a, 199b, 203a, 203b, 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, II-9, II-10, II-11, II-11a, II-11b, II-12, II-12a, II-12b, II-13, II-13a, II-13b, II-14a, II-14b, II-15a, II-15b, II-16a, II-16b, II-17, II-18, II-19, II-39, II-40, II-49a, II-49b, II-57a, II-57b, II-58, II-59, II-60, II-61, II-62, II-63, II-64, II-65, II-67, II-68, II-70, II-71, II-75, II-76, II-77, II-78, II-80, II-81, II-82, II-83, II-84, II-88, II-89, II-90, II-91, II-92, II-93a, II-93b, II-94a, II-94b, II-95a, II-95b, II-96, II-97, II-98a, II-98b, II-99a, II-99b, II-100a, II-100b, II-101, II-102, II-103, II-104, II-105, II-106a, II-106b, II-108a, II-108b, II-109a, II-109b, II-110, II-111, II-112a, II-112b, II-113a, II-113b, II-114a, II-114b, II-115a, II-115b, II-115c, II-115d, II-116, II-117, II-118a, II-118b, II-119, II-120a, II-120b, II-121a, II-121b, II-122, II-123a, II-123b, II-124a, II-124b, II-125a, II-125b, II-125c, II-125d, II-126, II-127a, II-127b, II-128a, II-128b, II-129, II-130, II-130a, II-130b, II-131, II-132a, II-132b, II-133, II-134a, II-134b, II-135a, II-135b, II-136a, II-136b, II-137, II-138, II-139, II-140, II-141, II-142, II-143, II-144, II-145, II-146a, II-146b, II-146c, II-146d, II-147a, II-147b, II-147c, II-147d, II-148, II-148a, II-148b, II-149a, II-149b, II-149c, II-149d, II-150, II-151a, II-151b, II-152a, II-152b, II-152c, II-152d, II-153, II-154, II-209, II-210, II-211, II-212, II-212a, II-212b, II-213, II-215, II-220, II-221, II-222, II-223, II-224, II-224a, II-224b, II-225, II-226, II-227a, II-227b, II-227c, II-227d, II-229, II-230, II-231, II-232, II-240, II-241, II-242, II-243, II-244a, II-244b, II-245, II-246, II-247, II-248, II-249, II-250, II-251, II-252, II-253, II-255a, II-255b, II-256, II-257, II-258, II-259, II-260a, II-260b, II-261, II-261a, II-261b, II-262, II-263, II-

264, II-265a, II-265b, II-266, II-267, II-268, II-269, II-270, II-271, II-272, II-273, II-274, II-275, II-276, II-277, II-278, II-279, II-280, II-281, II-282a, II-282b, II-282c, II-282d, II-283, II-284, II-285, II-286, II-287, II-288, II-289, II-290a, II-290b, II-291a, II-291b, II-291c, II-291d, II-292, II-293a, II-293b, II-293c, II-293d, II-294a, II-294b, II-294c, II-294d, II-295, II-296a, II-296b, II-297, II-298, II-299, IV-8, IV-8a, IV-8b, IV-93a, IV-93b, IV-209a, IV-209b, IV-209c, IV-209d, IV-210a, IV-210b, IV-210c, IV-210d, V-1, V-1a, V-1b, V-2, V-2a, V-2b, V-3, V-3a, V-3b, V-14, V-14a, V-14b, V-15, V-15a, V-15b, V-15c, V-15d, V-18, V-18a, V-18b, V-18c, V-18d, V-21, V-21a, V-21b, V-22, V-22a, V-22b, V-23, V-23a and V-23b.

[0597] 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.

[0598] In another embodiment, the invention relates to one or more of the Compounds described in Table 3, and uses thereof.

[0599] In another embodiment, the invention relates to one or more of the Compounds described in Table 4, and uses thereof.

[0600] In another embodiment, the invention relates to one or more of the Compounds described in Table 5, and uses thereof.

[0601] 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.

[0602] The embodiments and variations described herein are suitable for compounds of any formulae detailed herein, where applicable.

[0603] 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.

[0604] 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 diasteriomeric 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 or 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 or 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 or no more than 5% impurity. In another variation, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or 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 or 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 or 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 α_{2B} antagonist is a selective adrenergic receptor α_{2B} antagonist. In some embodiments, the adrenergic receptor α_{2B} antagonist also exhibits adrenergic receptor α_{2A} 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 varioation, 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 α_{2B} antagonists (e.g., selective adrenergic receptor α_{2B} 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 α_{2B} antagonist is a selective adrenergic receptor α_{2B} antagonist. In some embodiments,

the adrenergic receptor α_{2B} antagonist also exhibits adrenergic receptor α_{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.

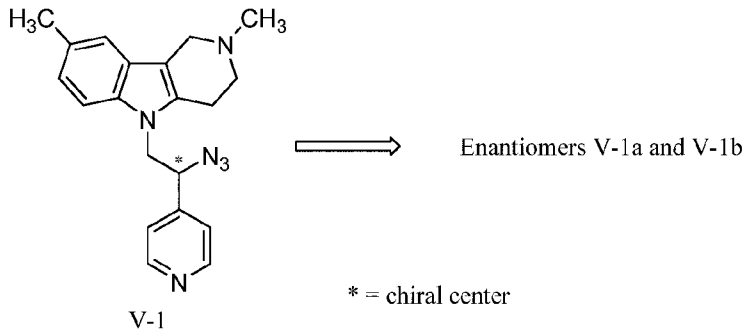
[0625] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein (e.g., 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

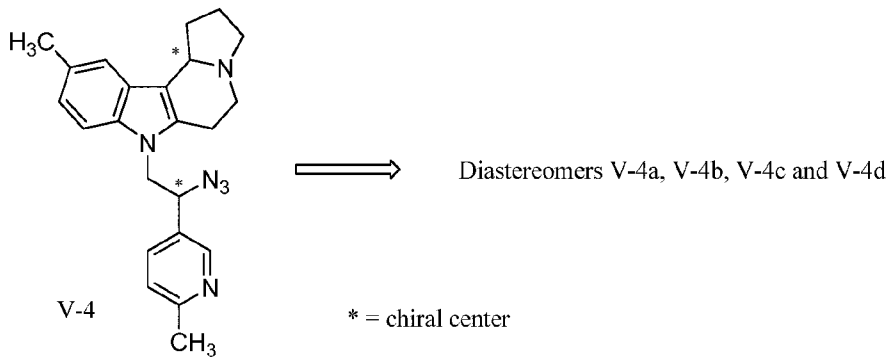
optionally a second pharmaceutically active compound useful for treatment of a disease or condition detailed herein (e.g., hypertension).

[0628] 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.



V-1

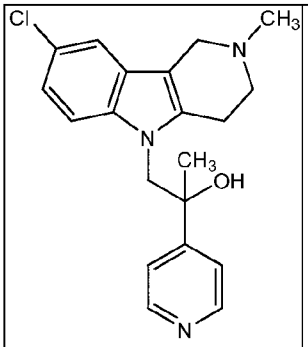
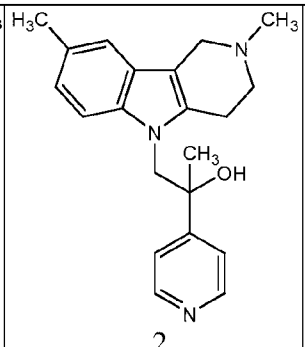
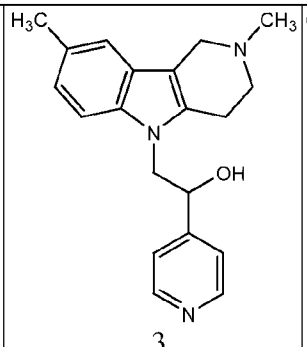
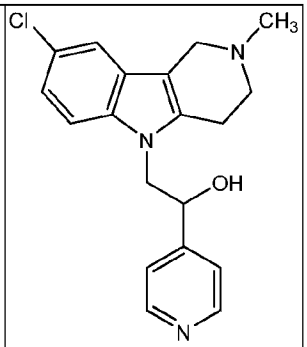
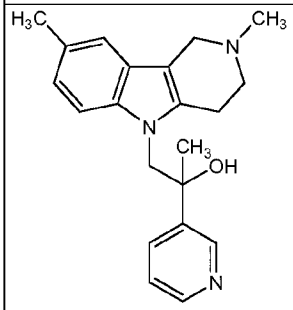
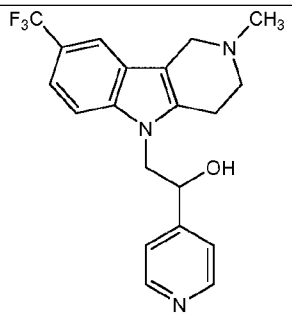
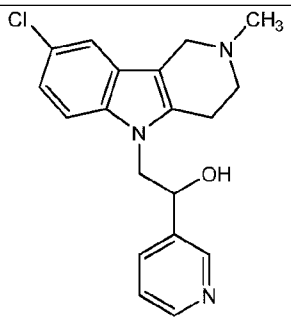
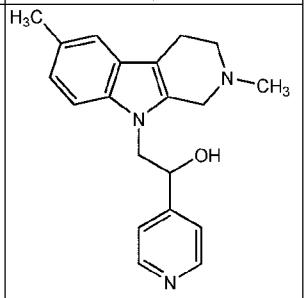
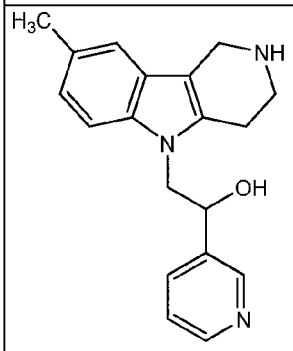
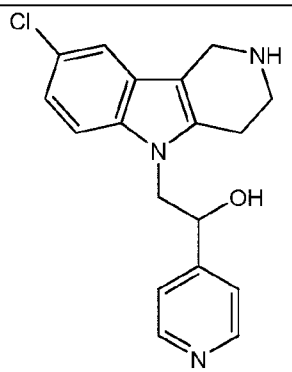
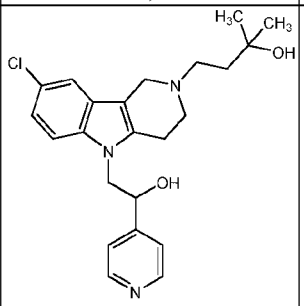
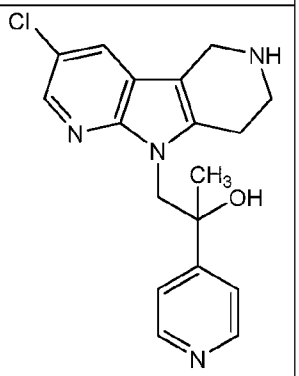
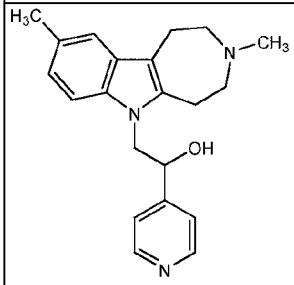
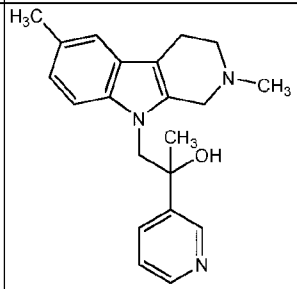
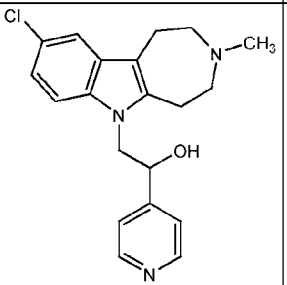
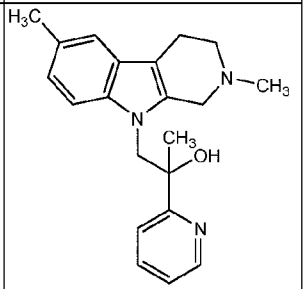
Similarly, racemic compound V-4, bearing two chiral centers, can be resolved into its individual diastereomers V-4a, V-4b, V-4c and V-4d.

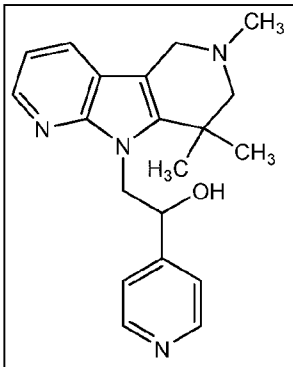
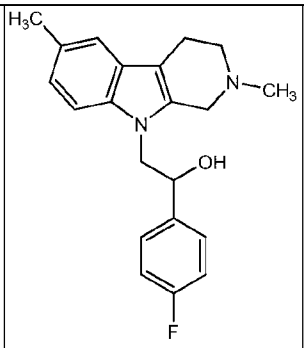
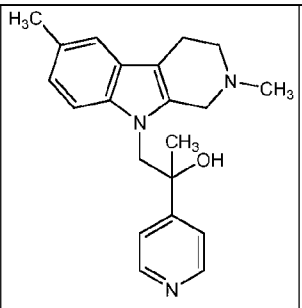
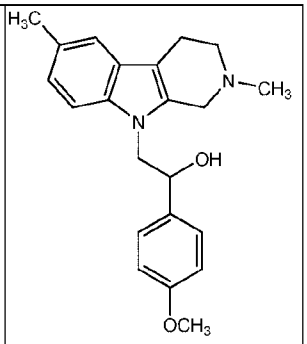
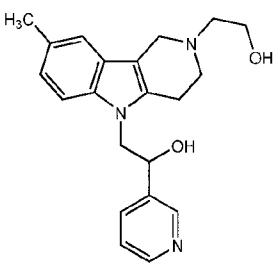
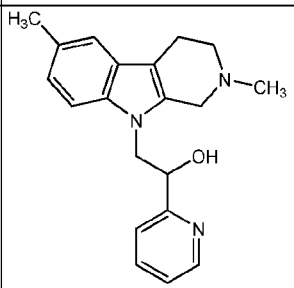
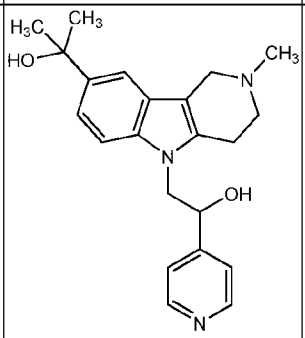
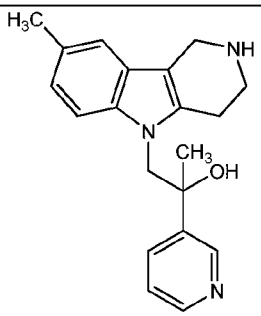
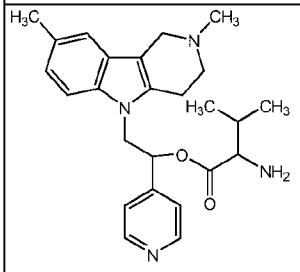
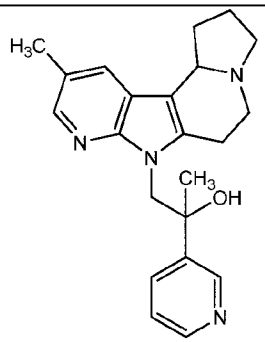
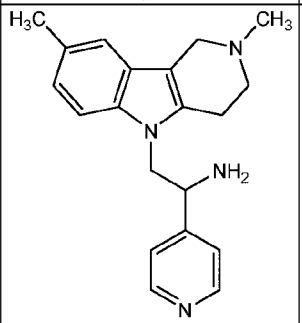
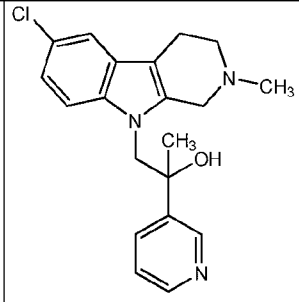


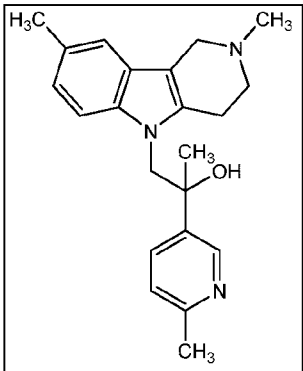
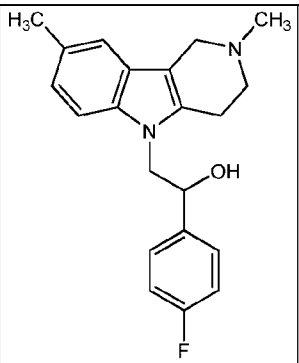
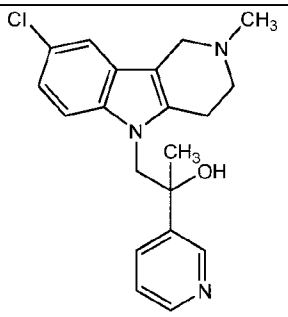
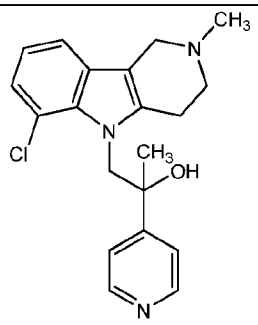
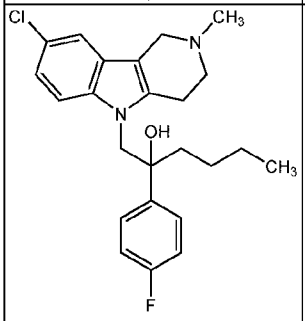
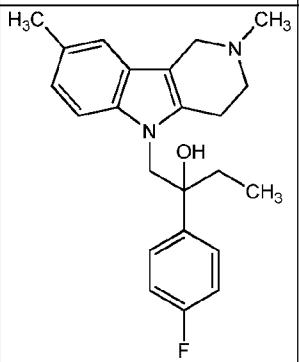
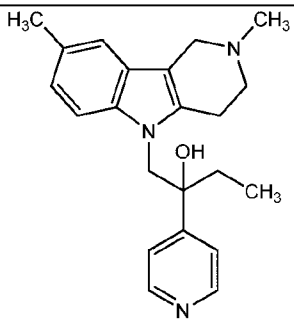
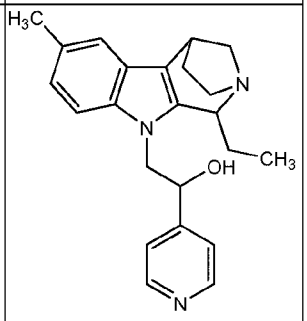
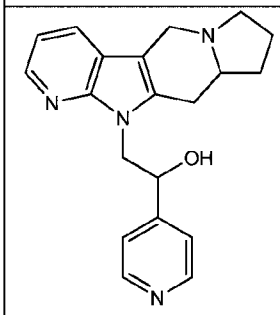
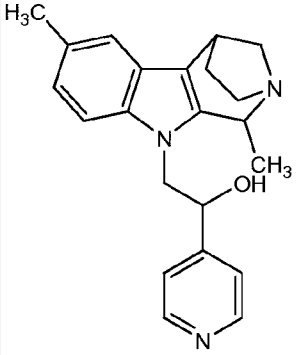
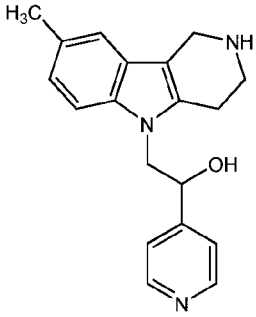
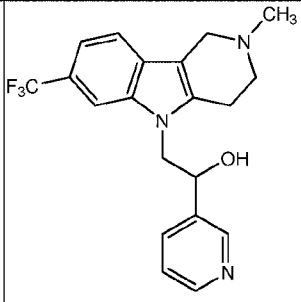
V-4

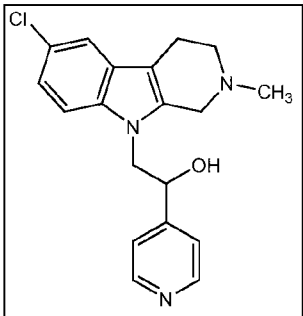
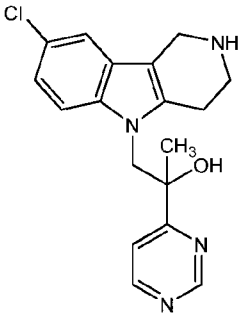
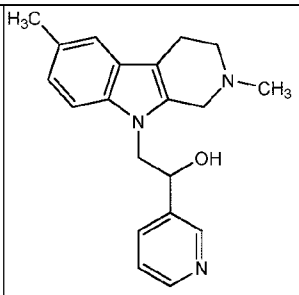
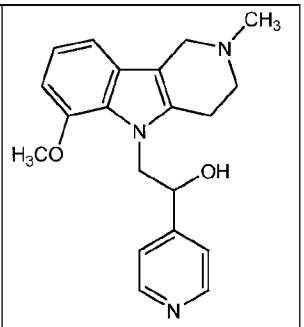
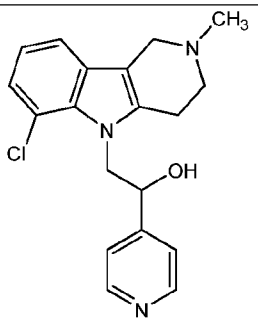
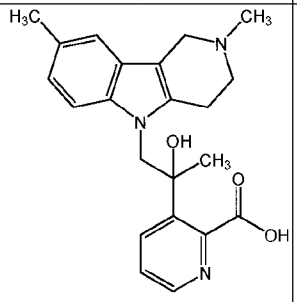
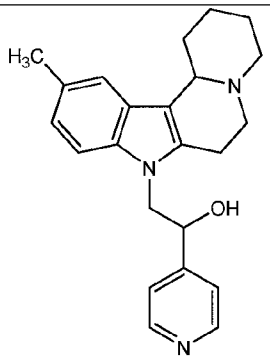
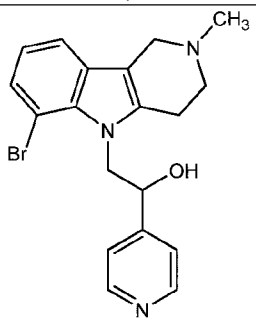
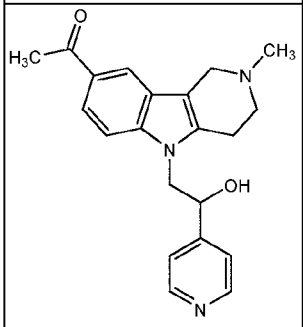
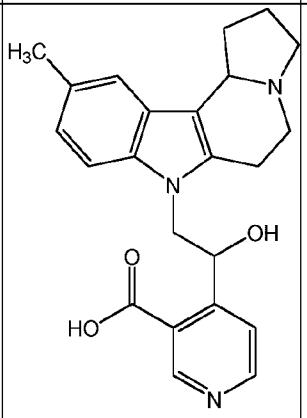
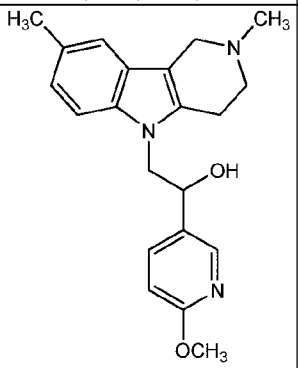
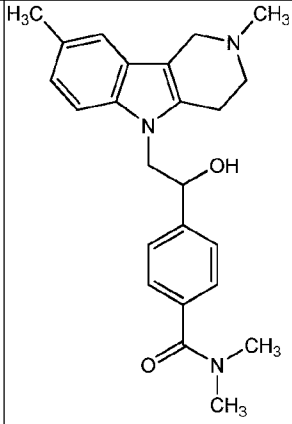
[0629] Representative compounds of the invention are shown in Tables 1-5.

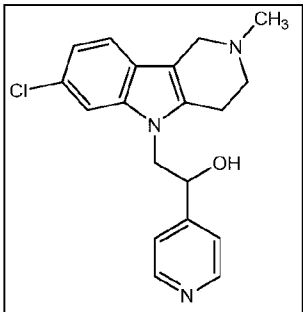
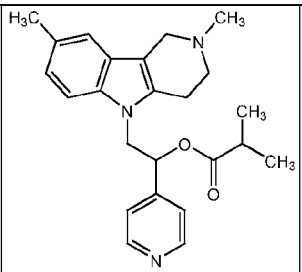
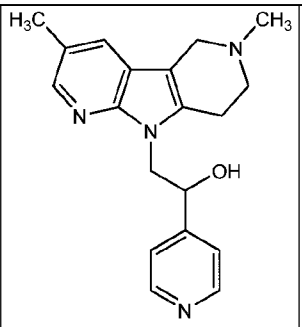
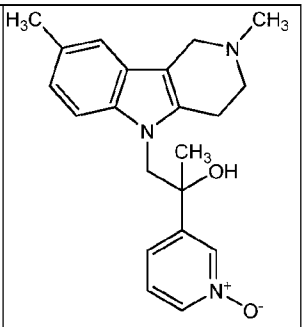
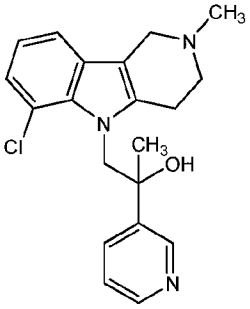
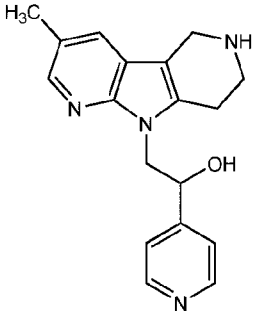
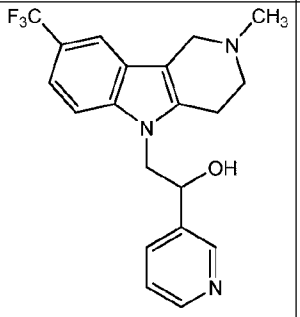
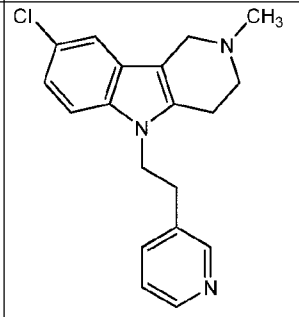
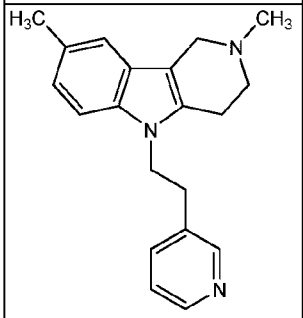
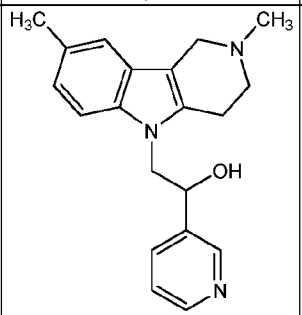
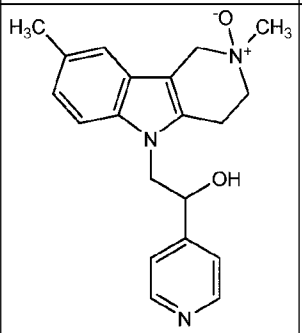
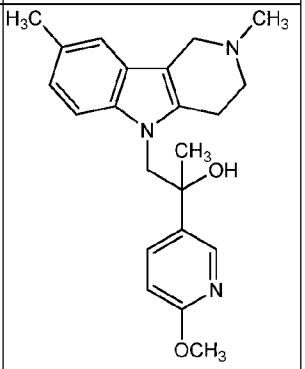
[0630] Table 1. Representative Compounds of the Invention

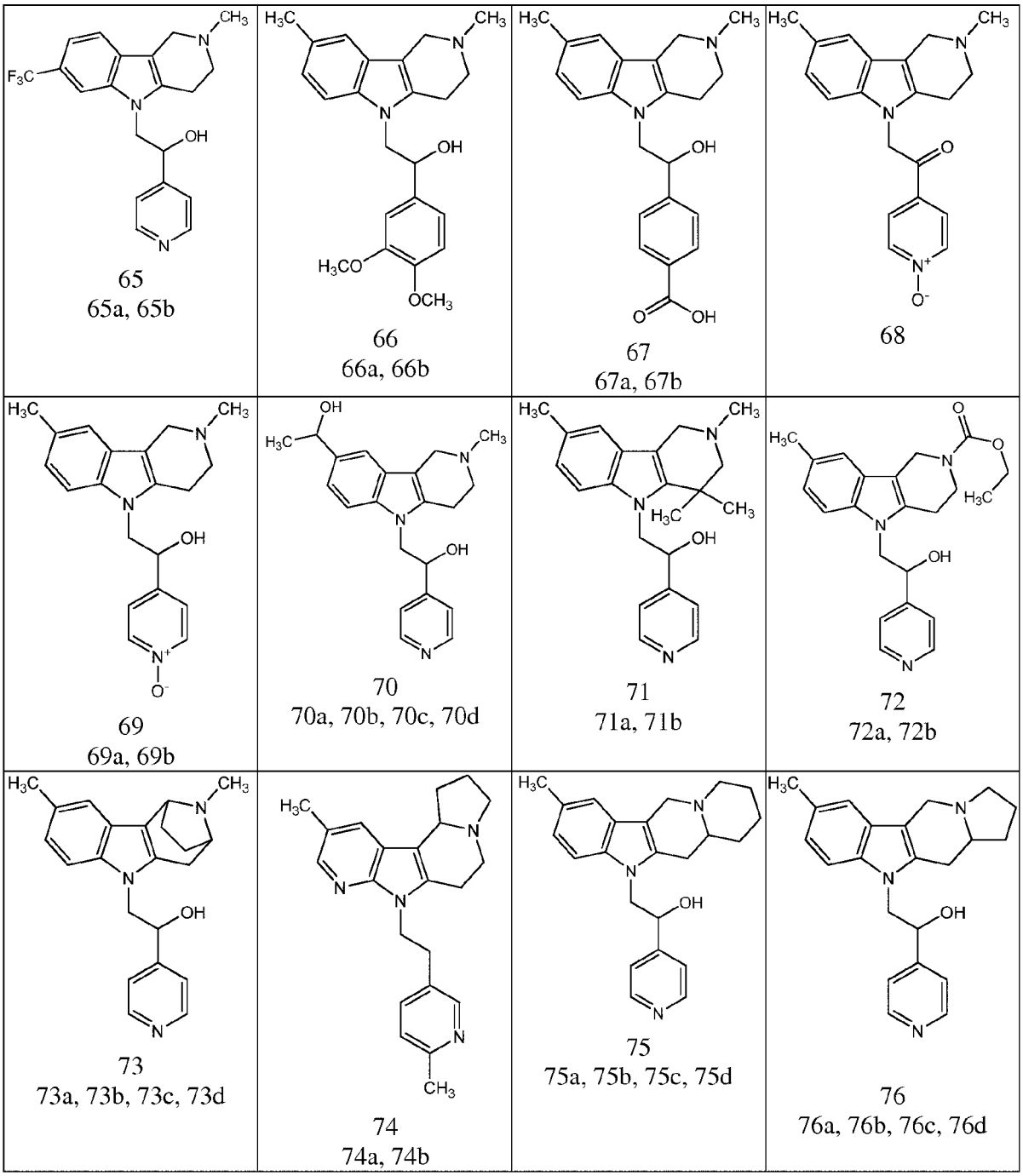
 1 1a, 1b	 2 2a, 2b	 3 3a,3b	 4 4a, 4b
 5 5a, 5b	 6 6a, 6b	 7 7a, 7b	 8 8a, 8b
 9 9a, 9b	 10 10a, 10b	 11 11a, 11b	 12 12a, 12b
 13 13a, 13b	 14 14a, 14b	 15 15a, 15b	 16 16a, 16b

 17 17a, 17b	 18 18a, 18b	 19 19a, 19b	 20 20a, 20b
 21 21a, 21b	 22 22a, 22b	 23 23a, 23b	 24 24a, 24b
 25 25a, 25b, 25c, 25d	 26 26a, 26b, 26c, 26d	 27 27a, 27b	 28 28a, 28b

 29 29a, 29b	 30 30a, 30b	 31 31a, 31b	 32 32a, 32b
 33 33a, 33b	 34 34a, 34b	 35 35a, 35b	 36 36a, 36b, 36c, 36d
 37 37a, 37b 37c, 37d	 38 38a, 38b, 38c, 38d, 38e, 38f, 38g, 38h	 39 39a, 39b	 40 40a, 40b

 41 41a, 41b	 42 42a, 42b	 43 43a, 43b	 44 44a, 44b
 45 45a, 45b	 46 46a, 46b	 47 47a,47b, 47c, 47d	 48 48a, 48b
 49 49a, 49b	 50 50a, 50b, 50c, 50d	 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	 60
 61	 62 62a, 62b	 63 63a, 63b	 64 64a, 64b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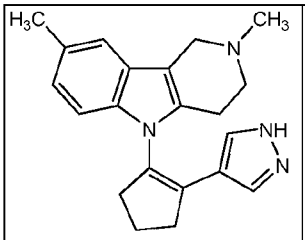
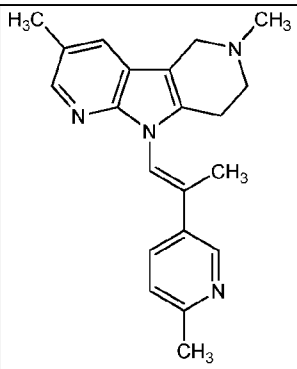
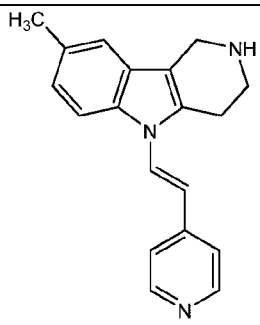
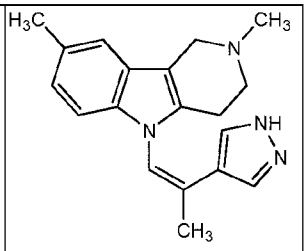
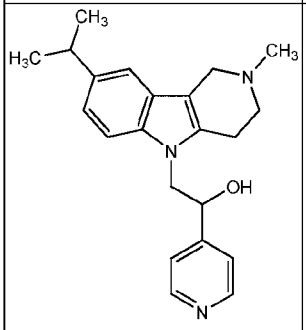
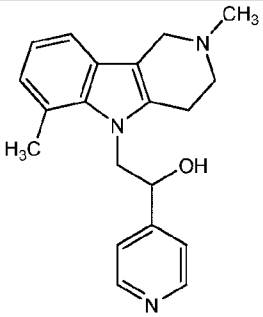
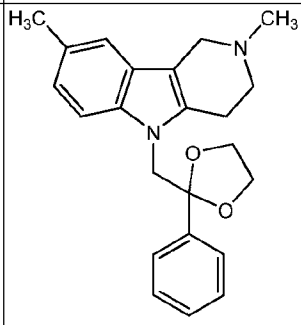
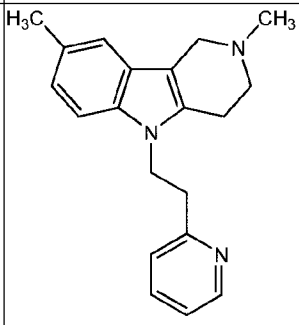
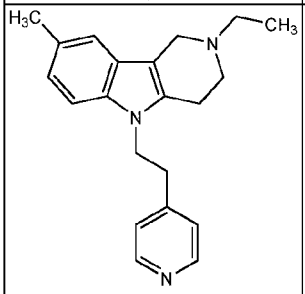
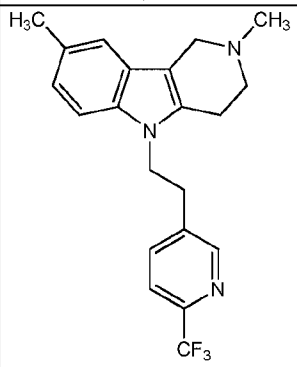
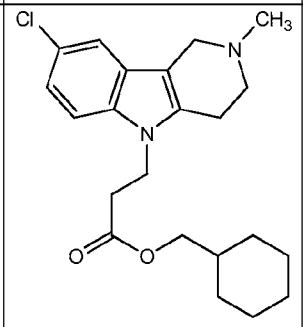
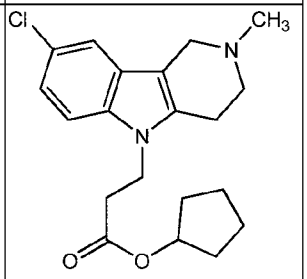
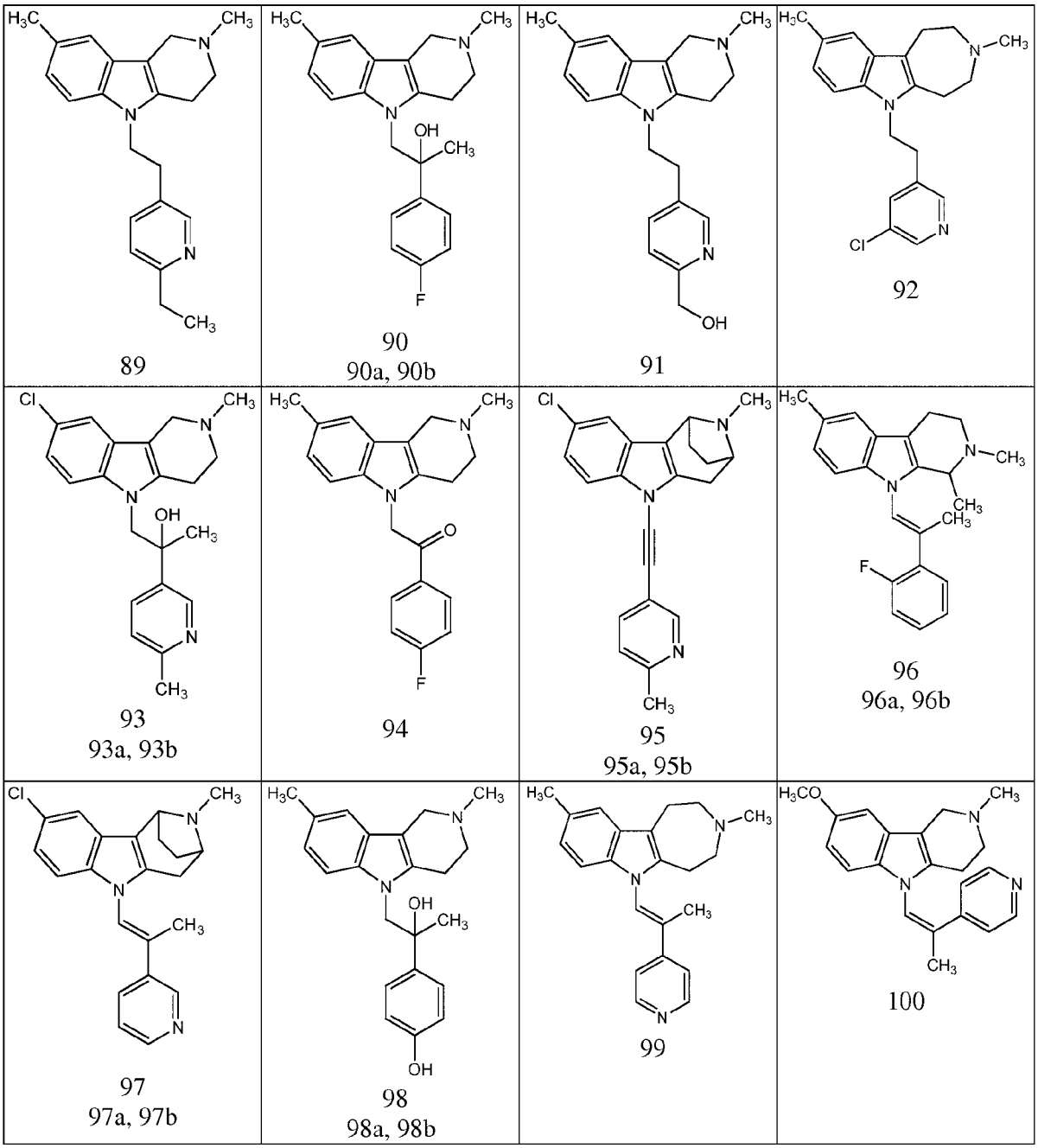
 77	 78	 79	 80
 81 81a, 81b	 82 82a, 82b	 83	 84
 85	 86	 87	 88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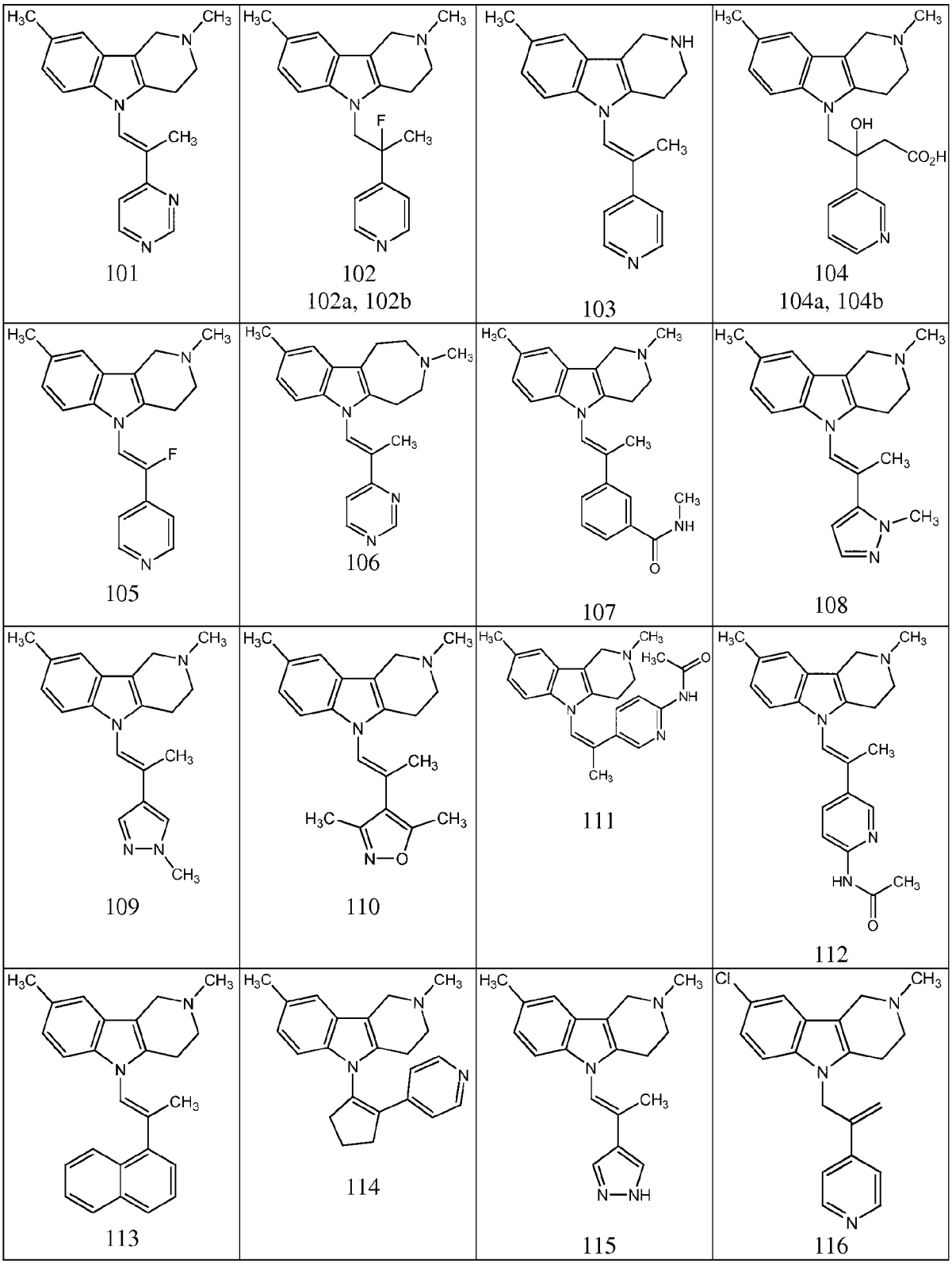
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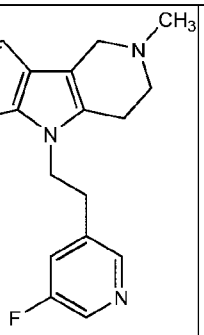
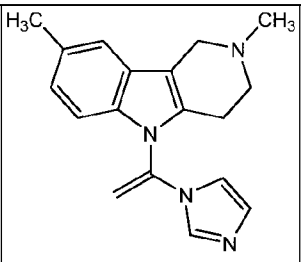
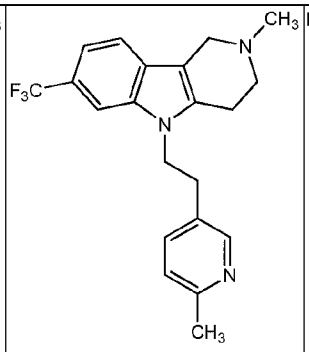
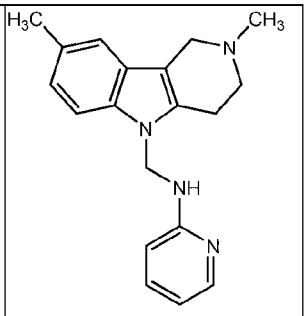
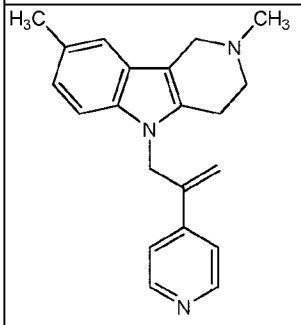
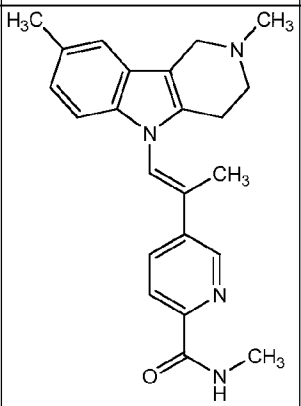
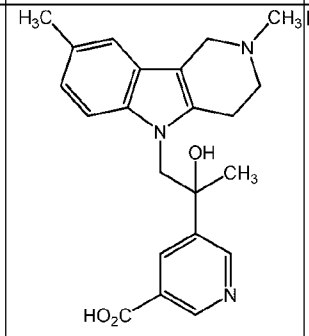
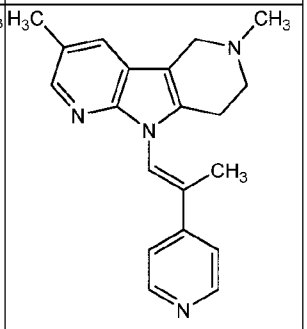
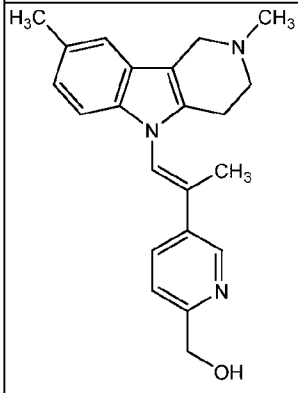
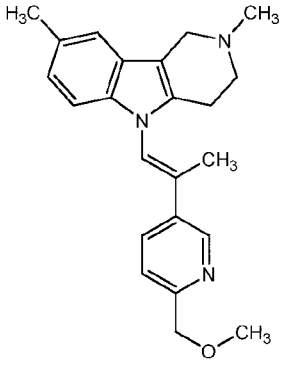
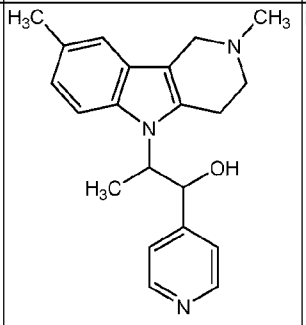
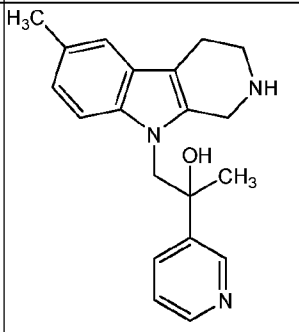
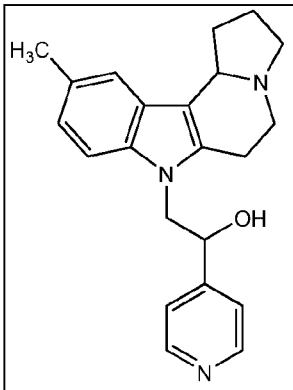
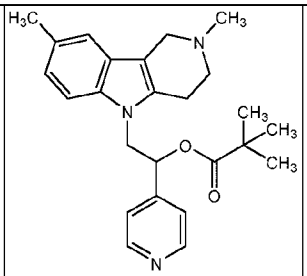
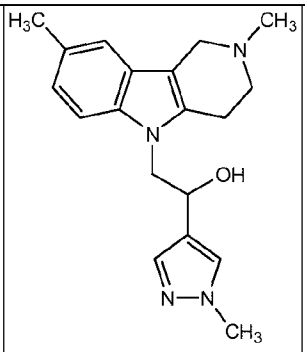
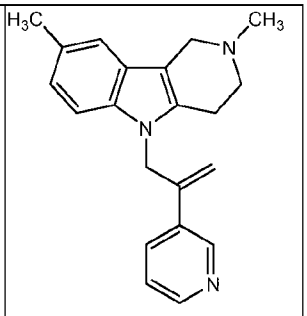
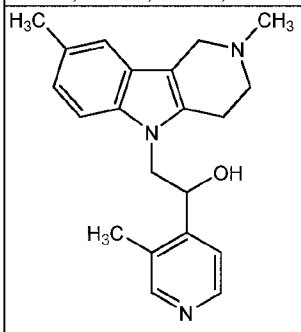
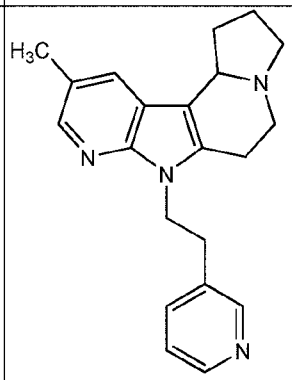
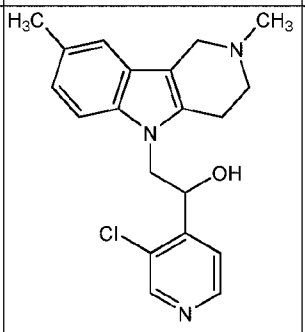
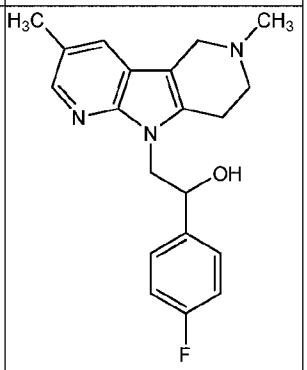
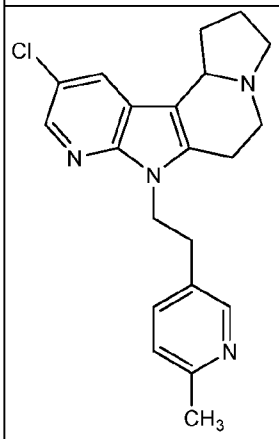
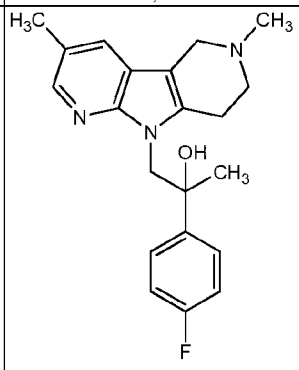
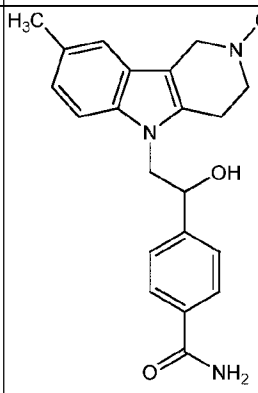
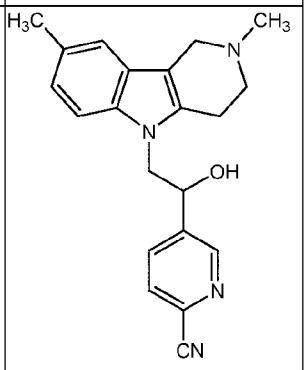
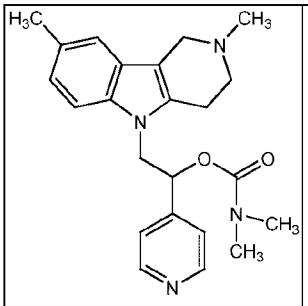
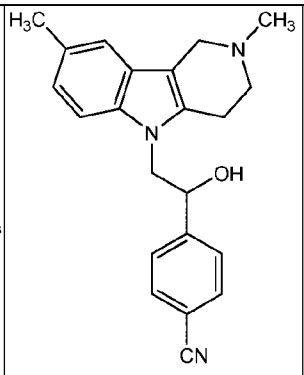
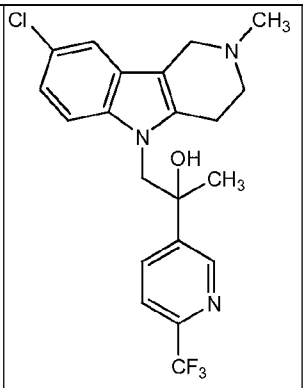
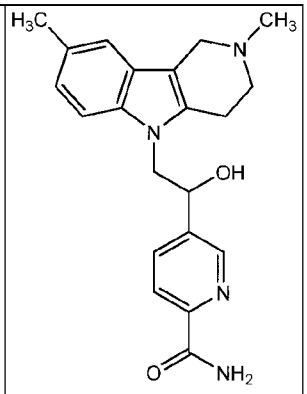
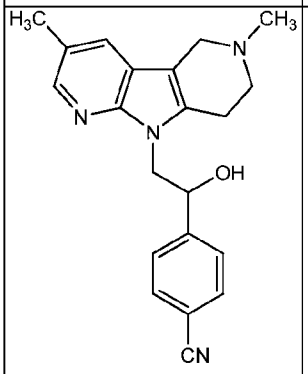
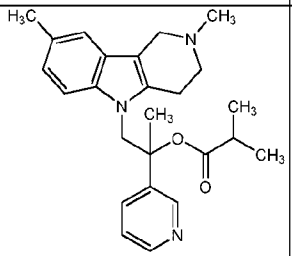
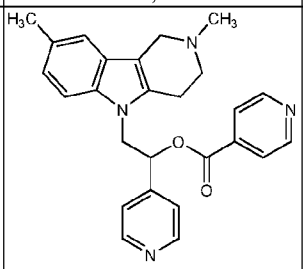
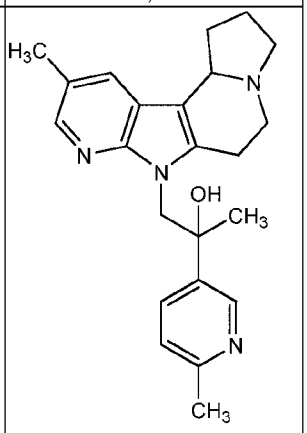
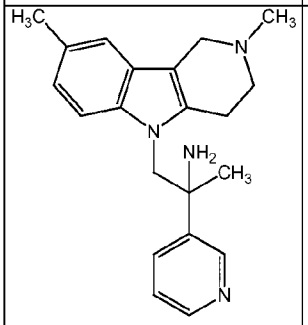
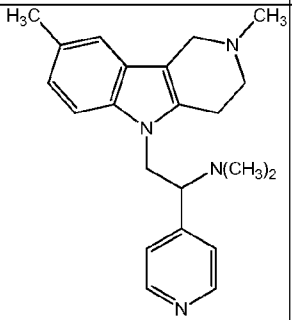
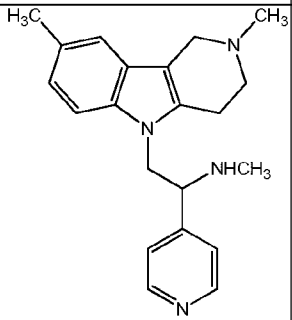
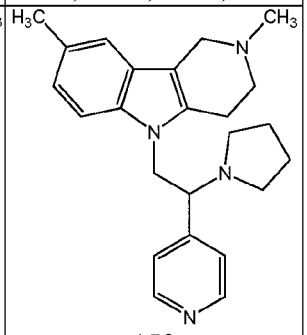
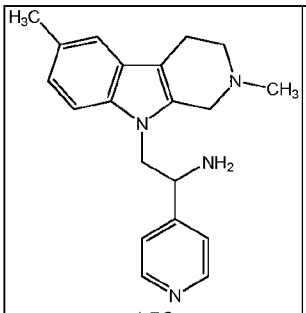
 117	 118	 119	 120
 121	 122	 123 123a, 123b	 124
 125	 126	 127 127a, 127b, 127c, 127d	 128 128a, 128b

 129 129a, 129b, 129c, 129d	 130 130a, 130b	 131 131a, 131b	 132
 133 133a, 133b	 134 134a, 134b	 135 135a, 135b	 136 136a, 136b
 137 137a, 137b	 138 138a, 138b	 139 139a, 139b	 140 140a, 140b

 141 141a, 141b	 142 142, 142b	 143 143a, 143b	 144 144a, 144b
 145 145a, 145b	 146 146a, 146b	 147 147a, 147b	 148 148a, 148b, 148a, 148d
 149 149a, 149b	 150 150a, 150b	 151 151a, 151b	 152 152a, 152b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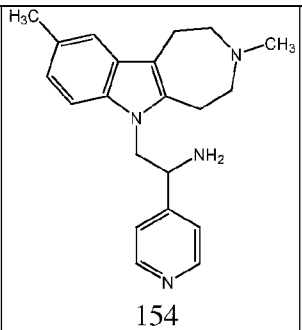
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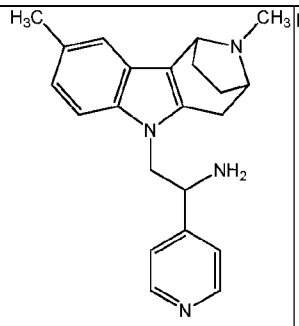
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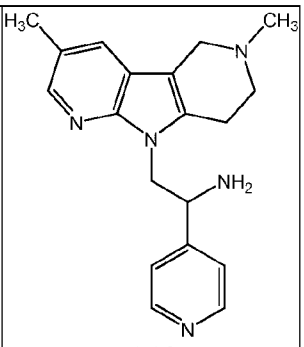
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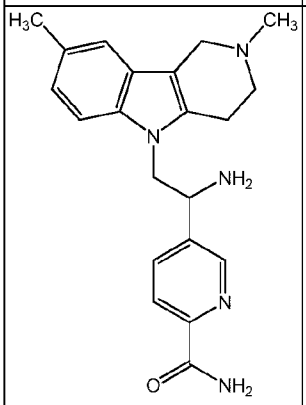
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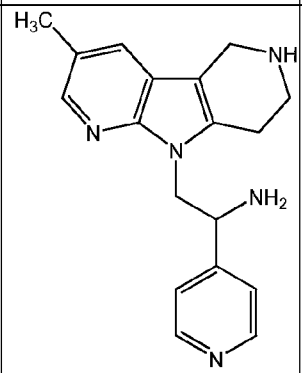
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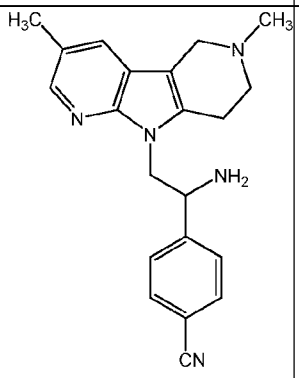
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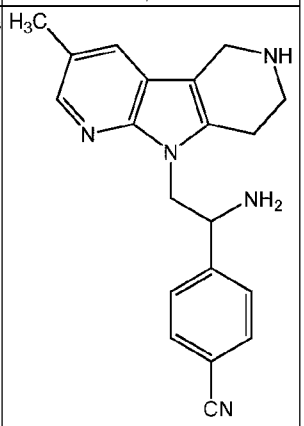
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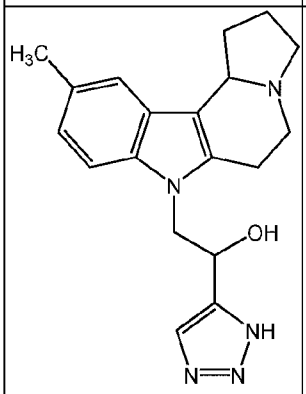
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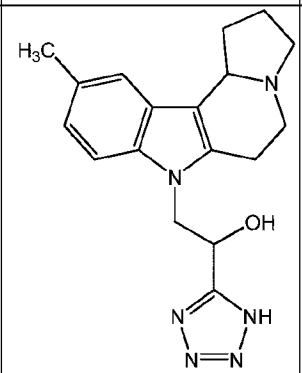
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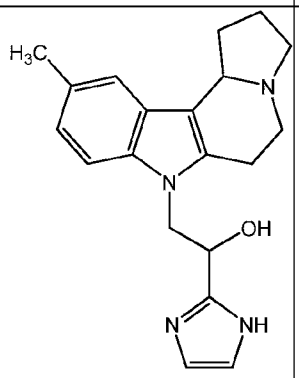
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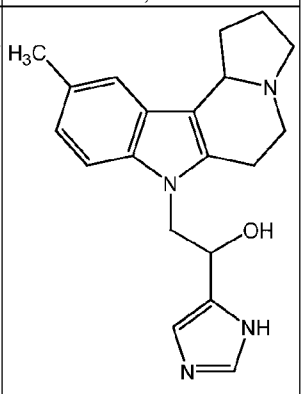
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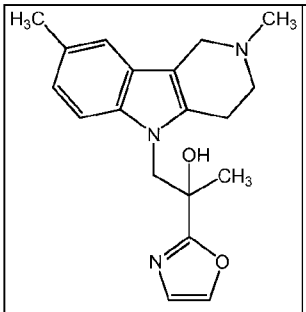
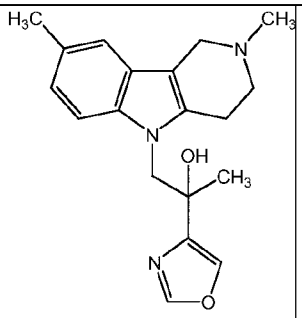
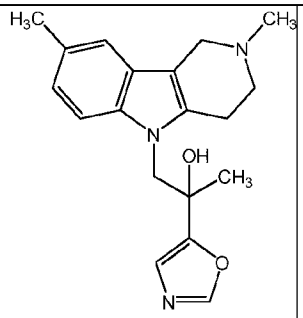
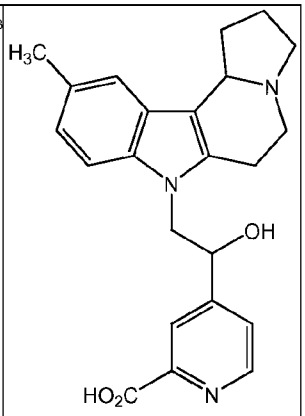
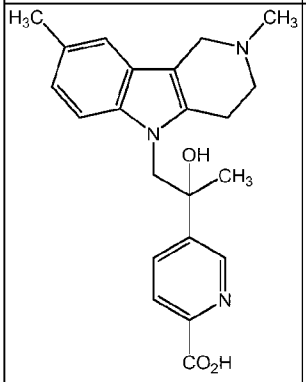
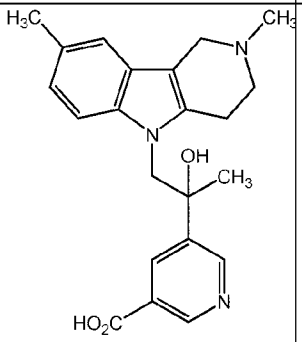
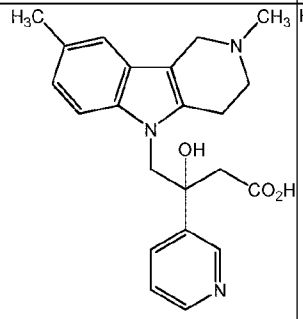
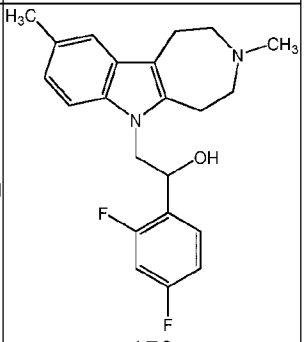
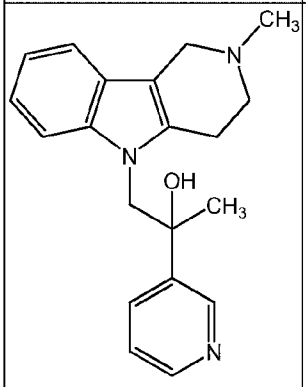
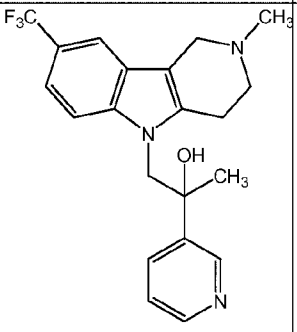
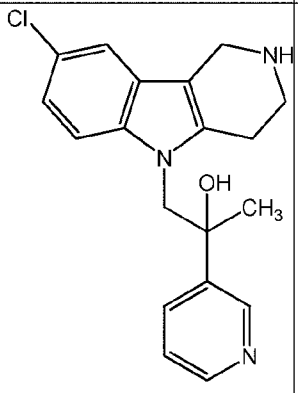
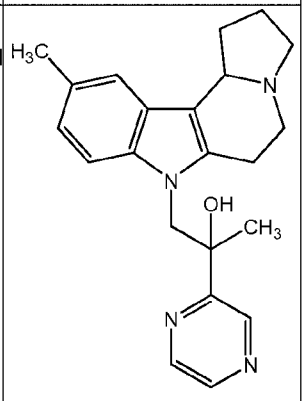
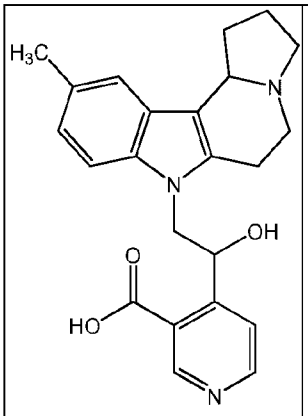
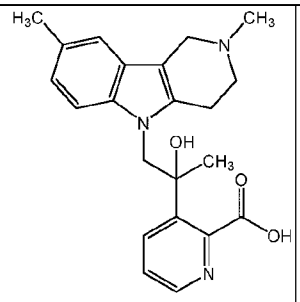
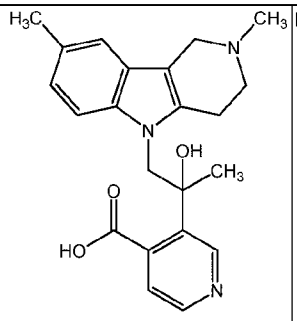
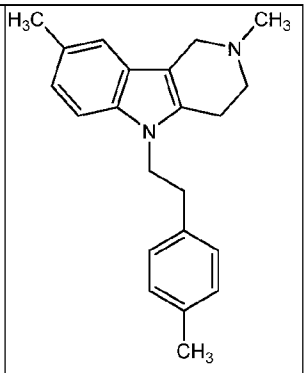
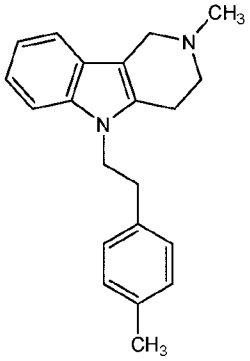
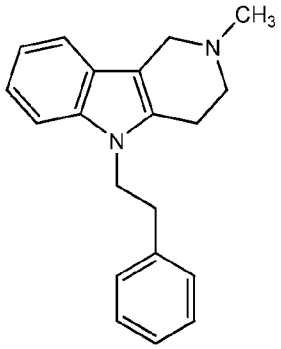
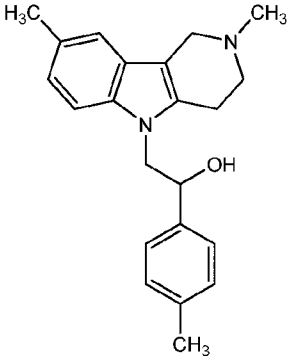
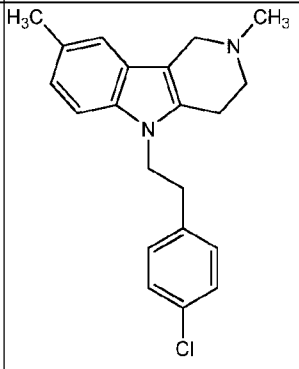
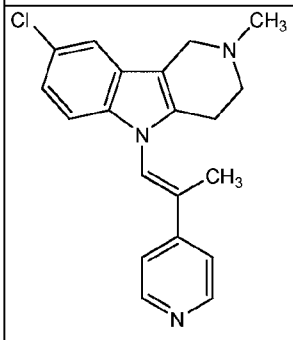
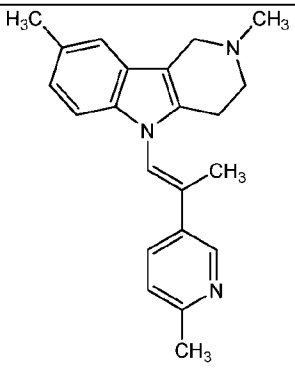
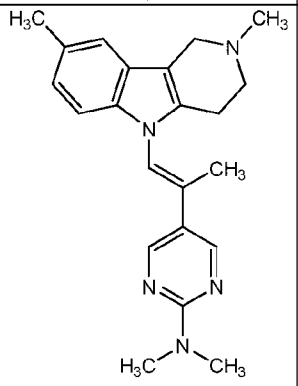
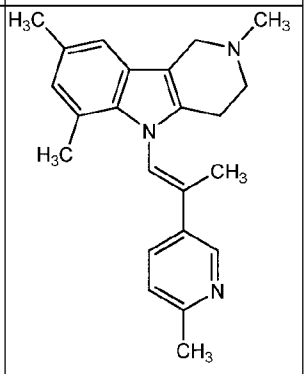
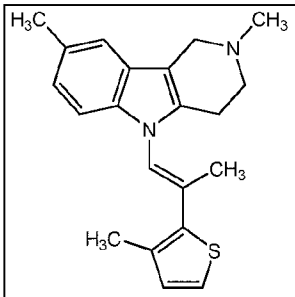
 165 165a, 165b	 166 166a, 166b	 167 167a, 167b	 168 168a, 168b, 168c, 168d
 169 169a, 169b	 170 170a, 170b	 171 171a, 171b	 172 172a, 172b
 173 173a, 173b	 174 174a, 174b	 175 175a, 175b	 176 176a, 176b, 176c, 176d

 177 177a, 177b, 177c, 177d	 178 178a, 178b	 179 179a, 179b	 180
 181	 182	 183 183a, 183b	 184
 185	 186	 187	 188



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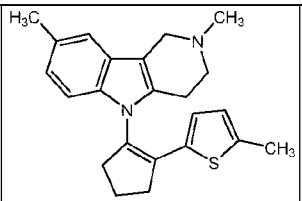

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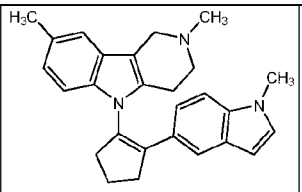

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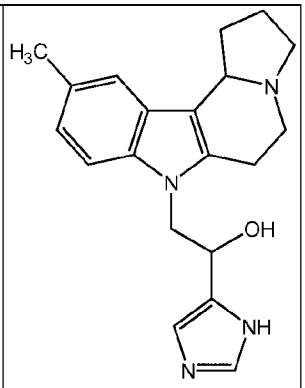

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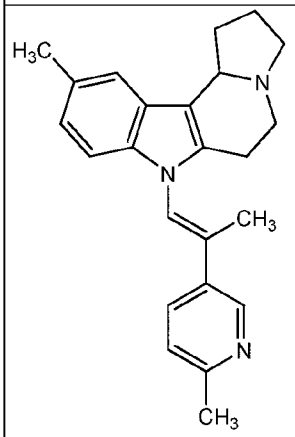

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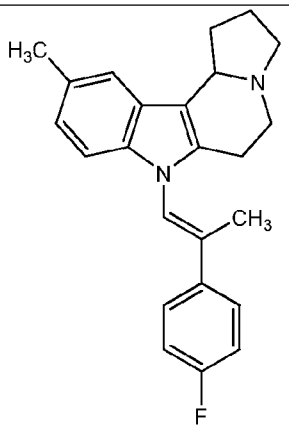

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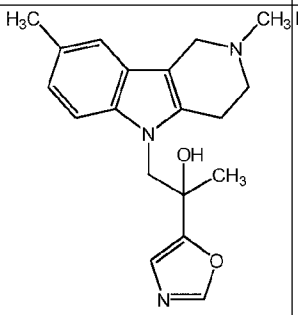

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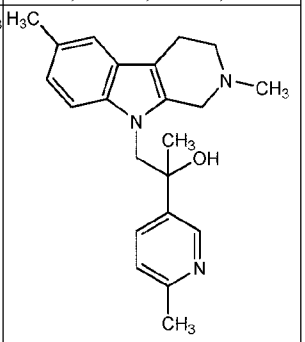

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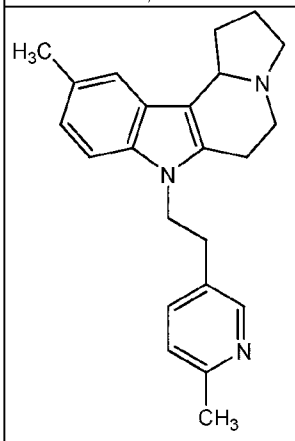

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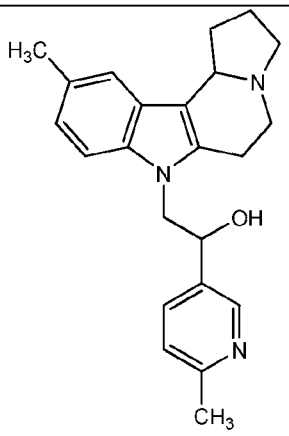

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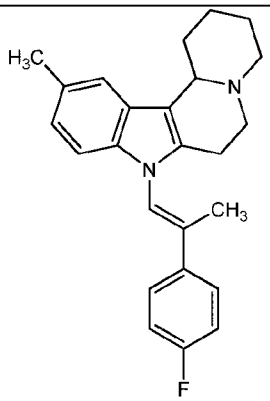

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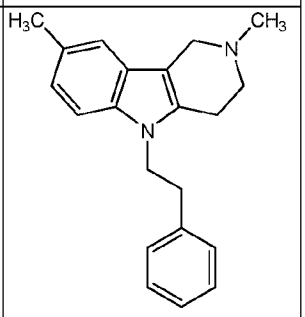

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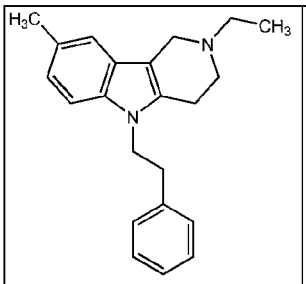
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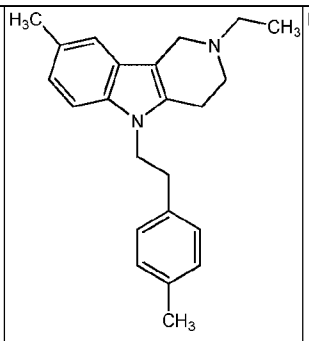
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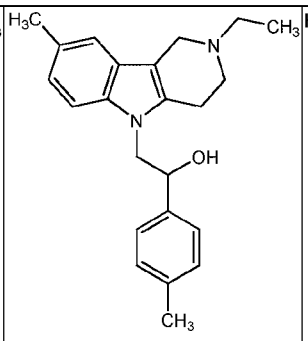
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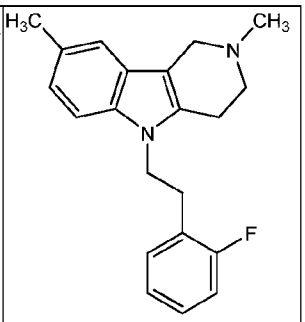
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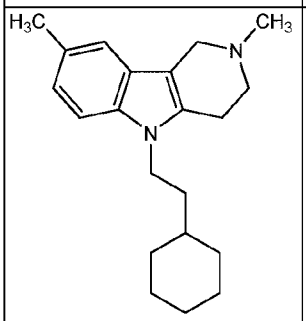
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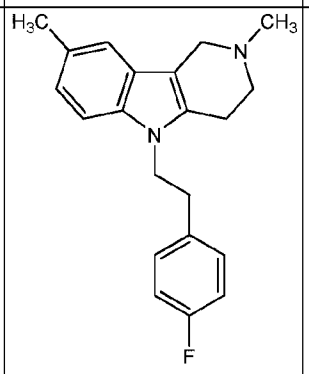
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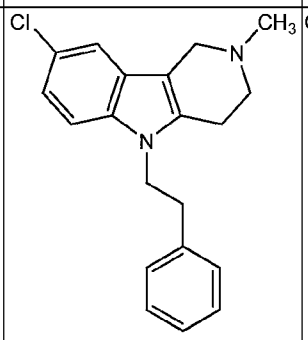
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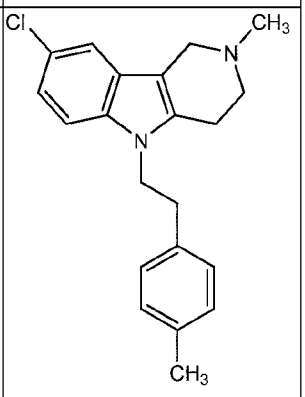
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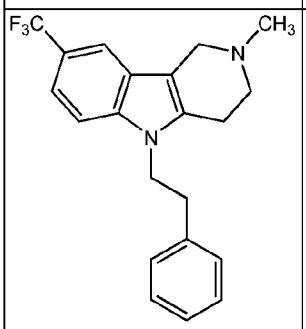
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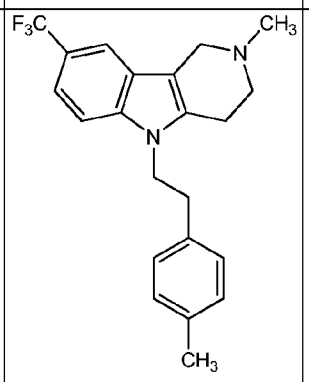
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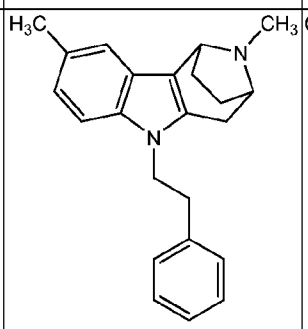
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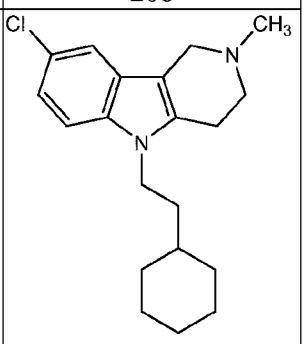
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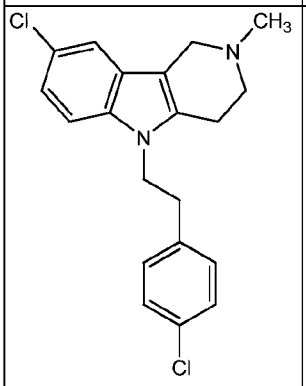
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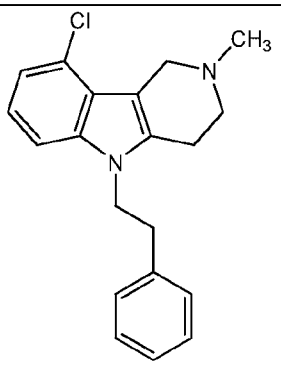
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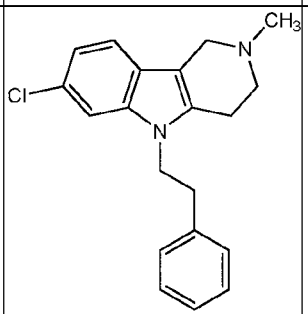
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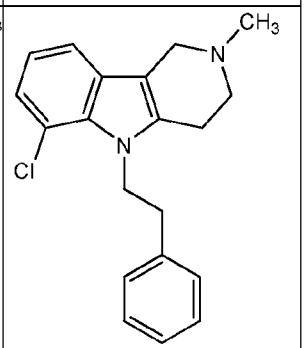
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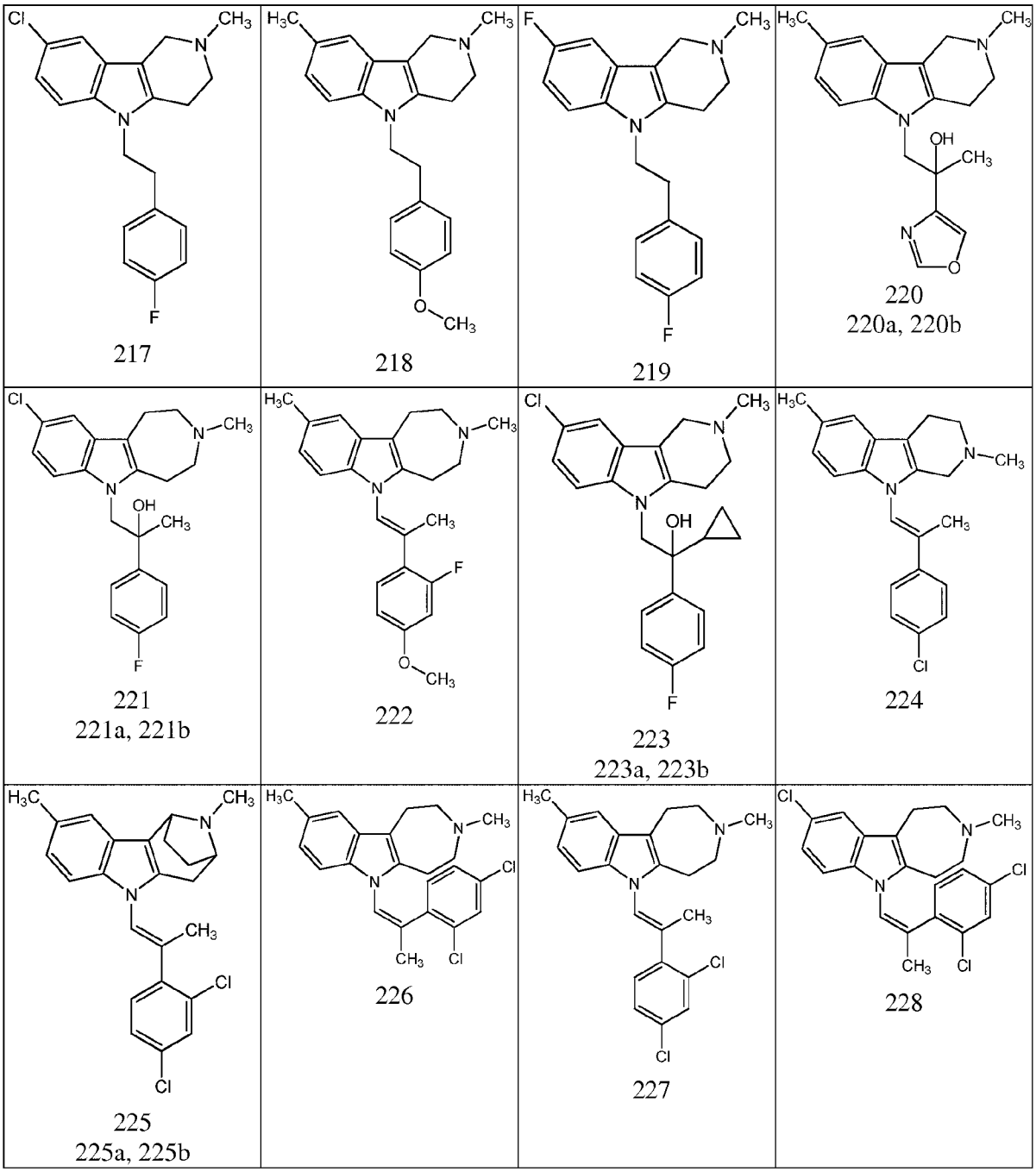
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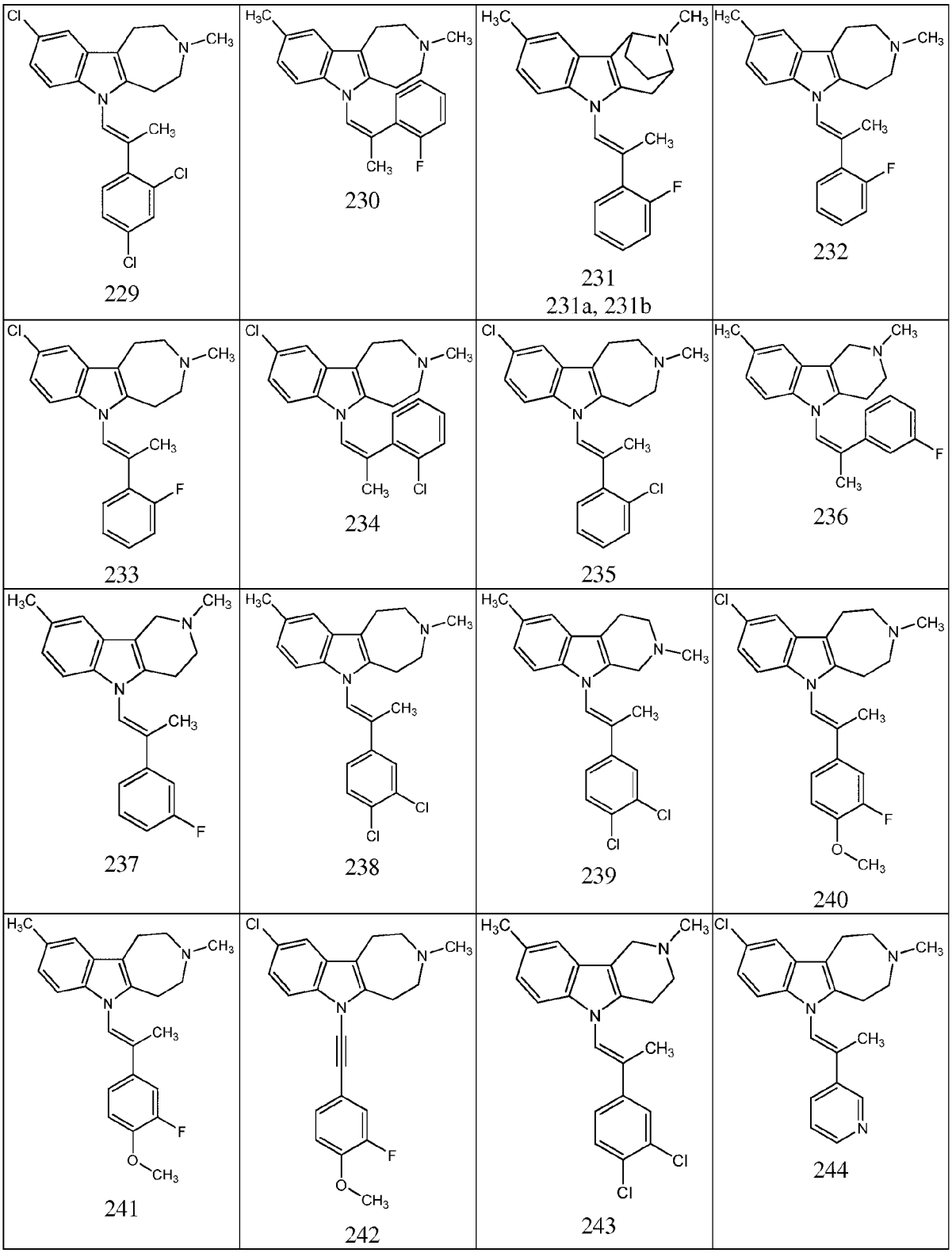
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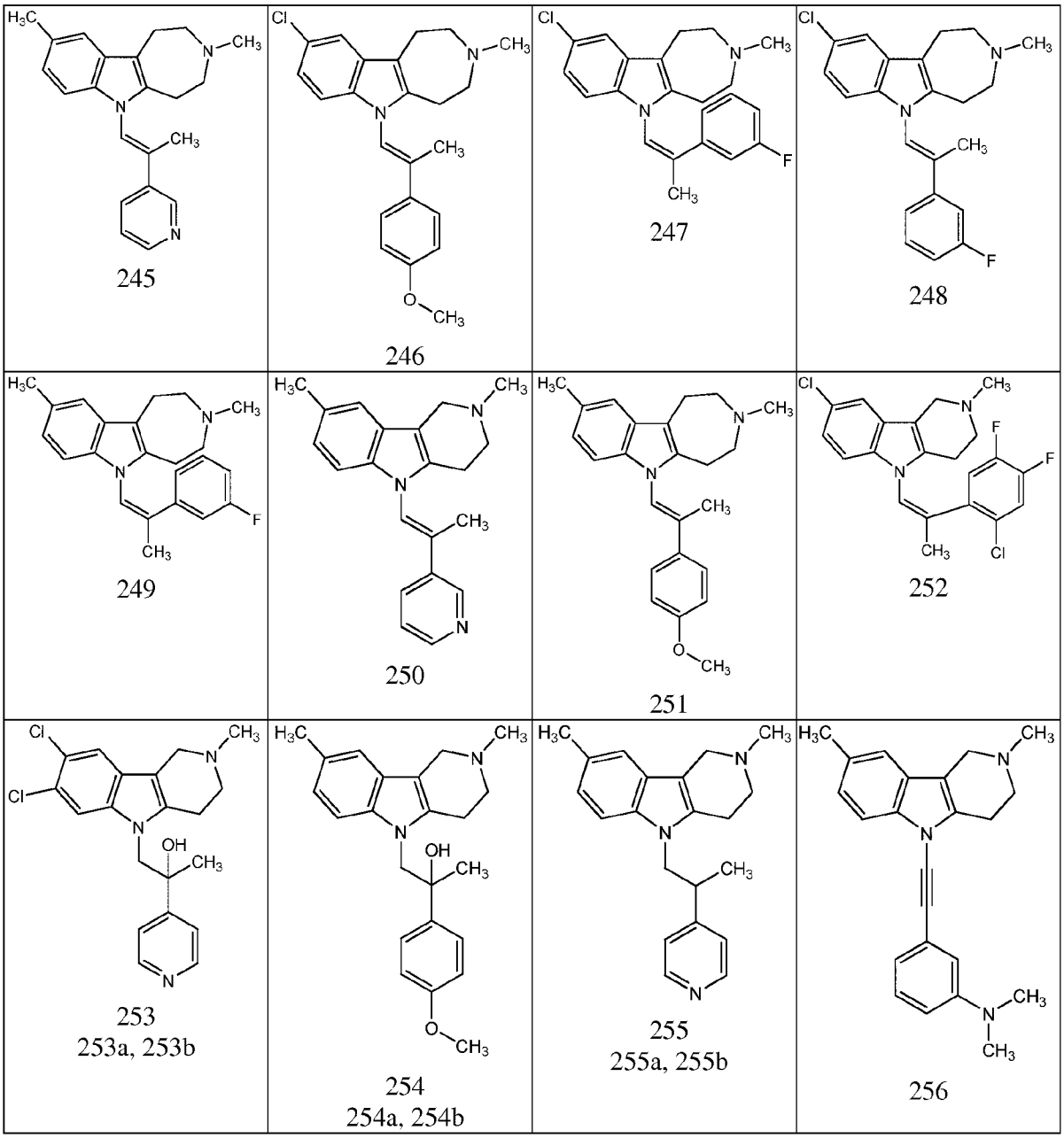
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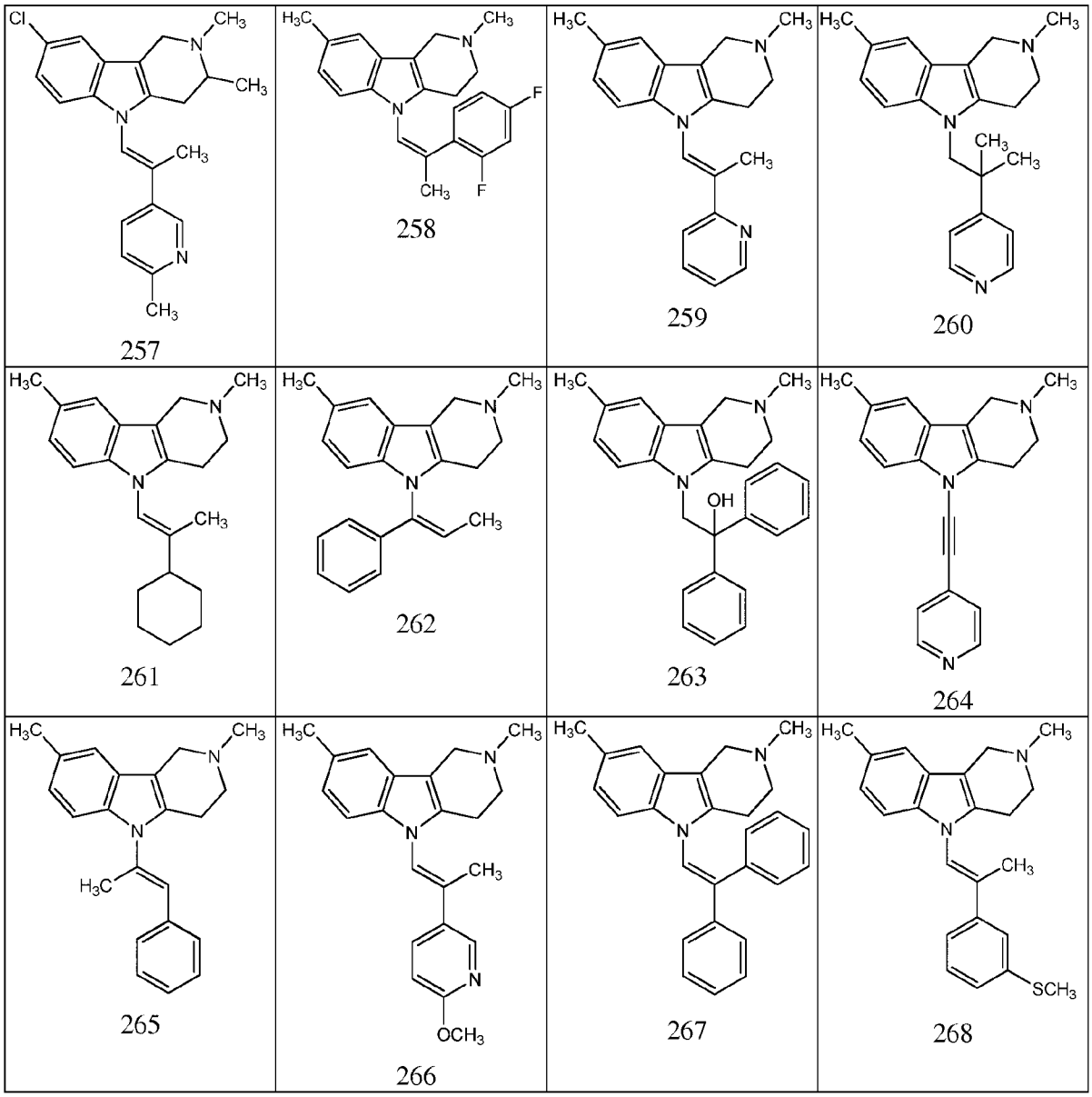
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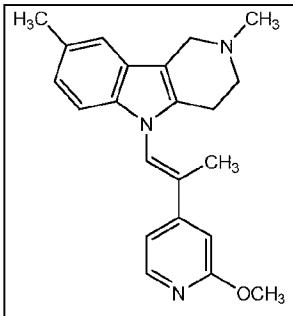
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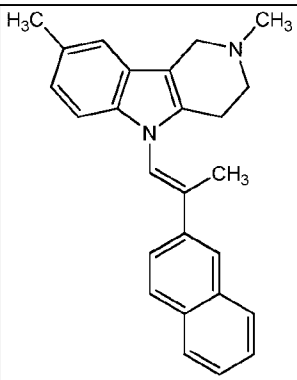
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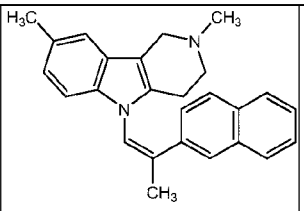
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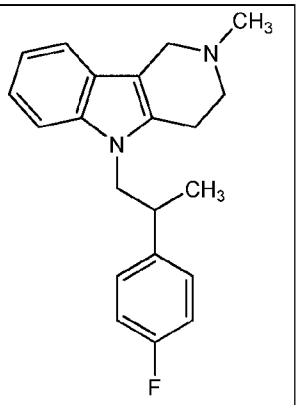
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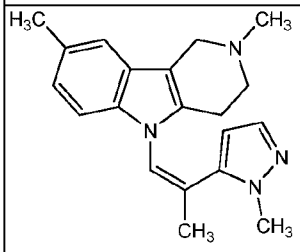
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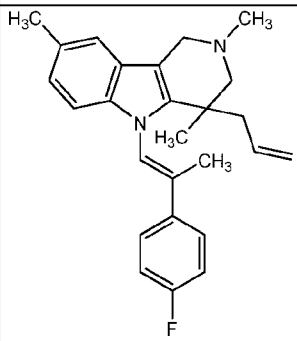
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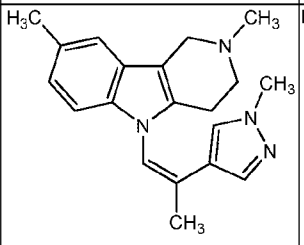
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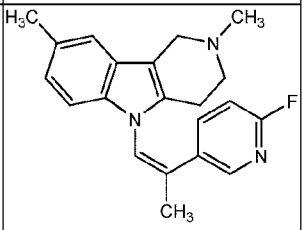
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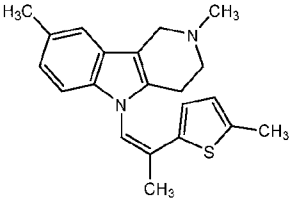
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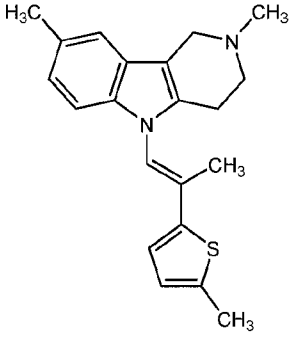
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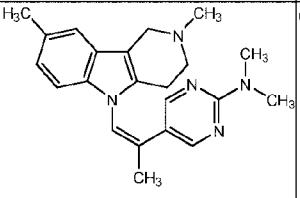
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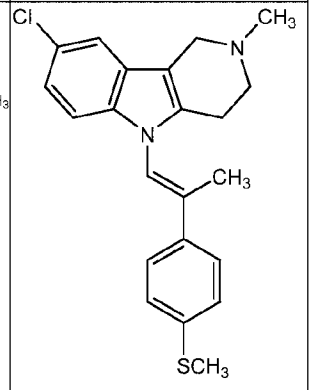
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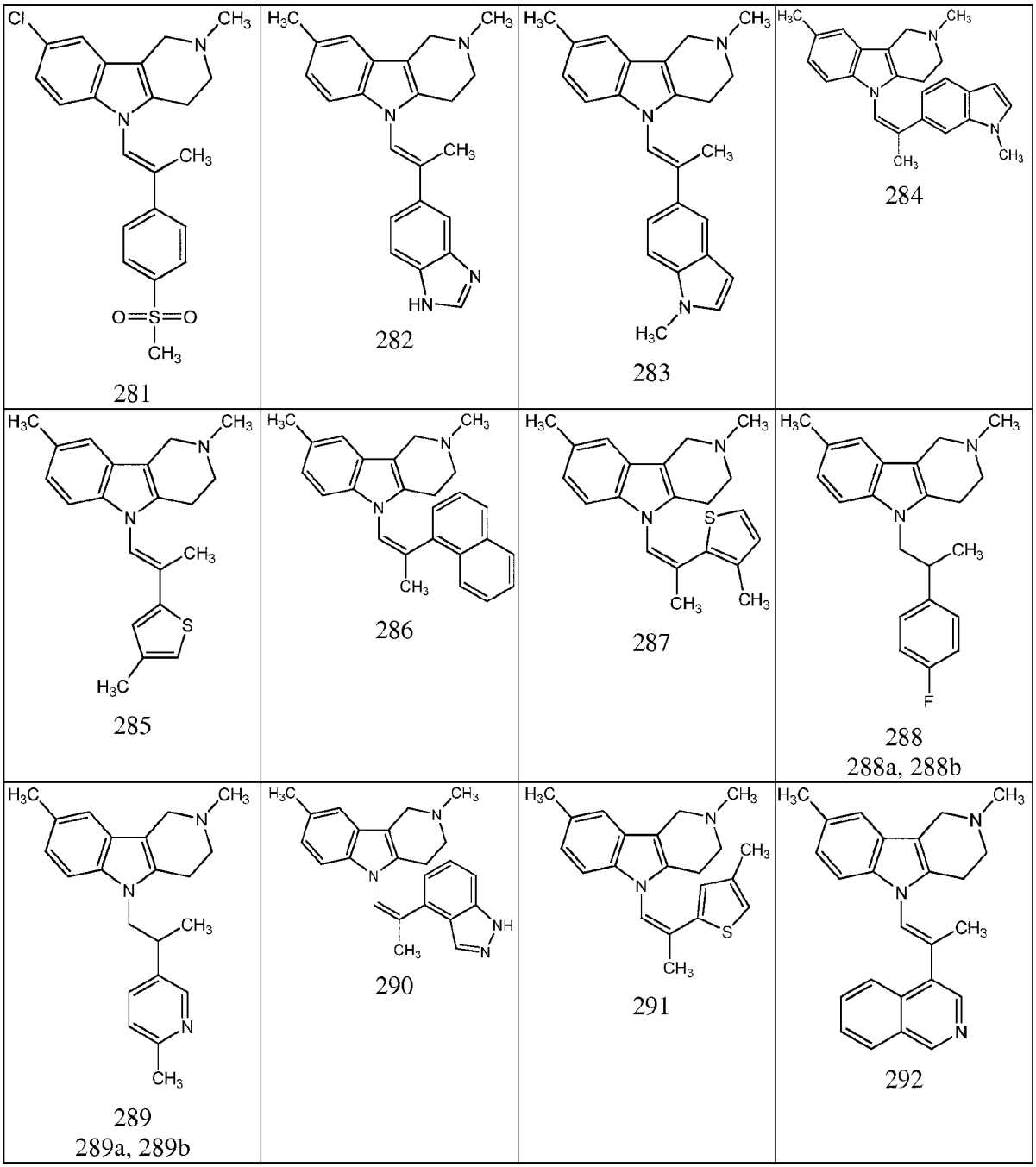
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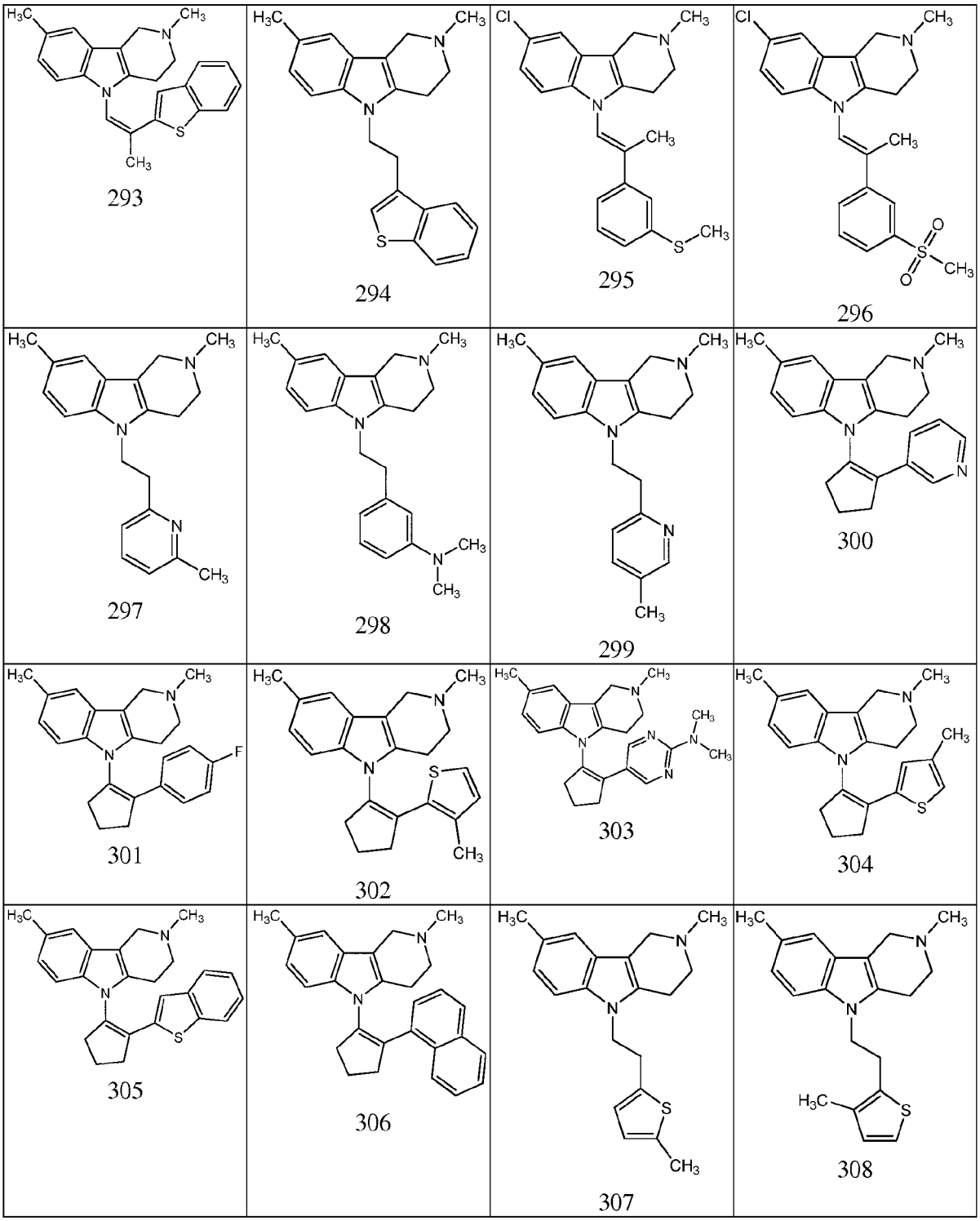
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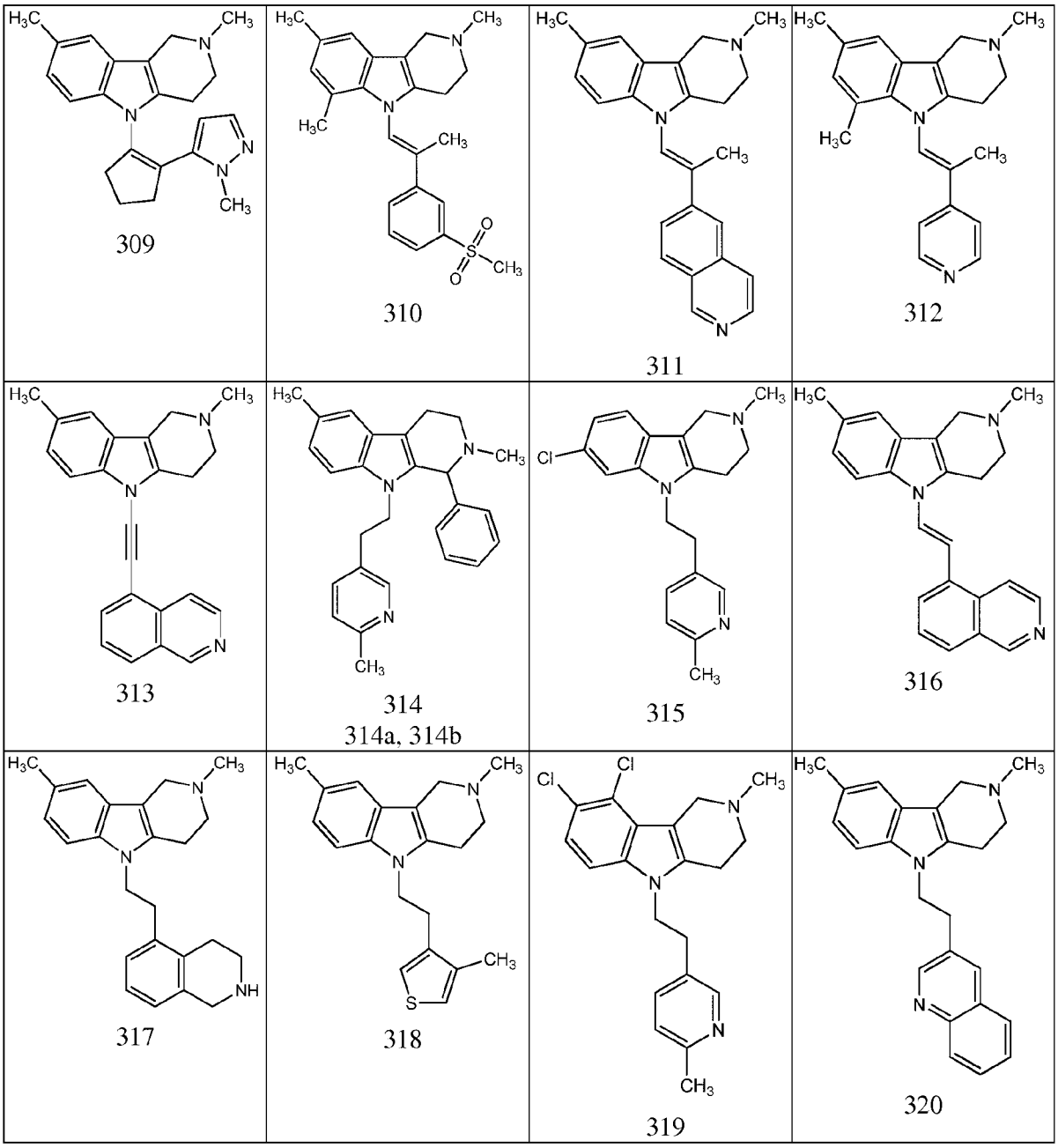
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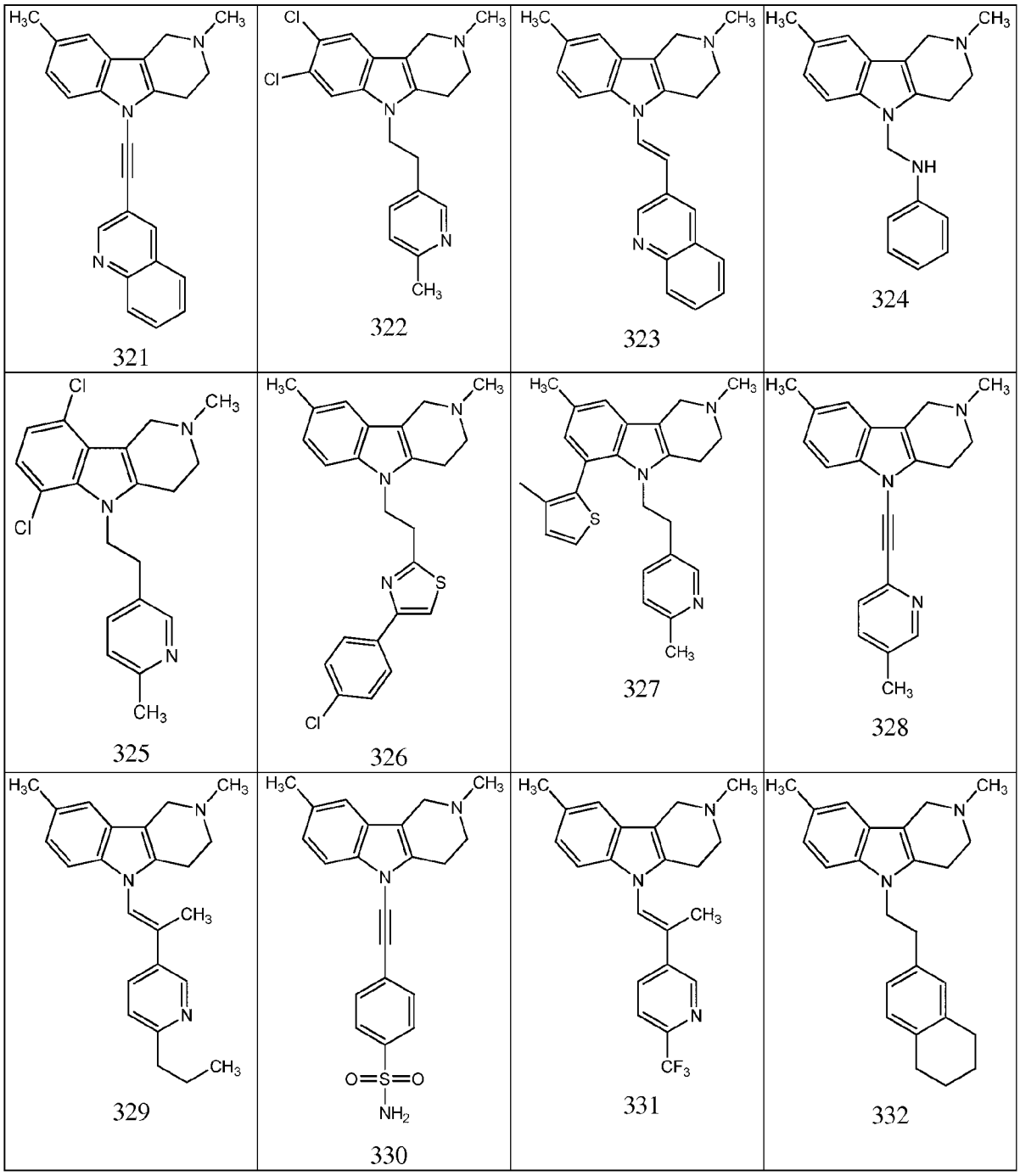
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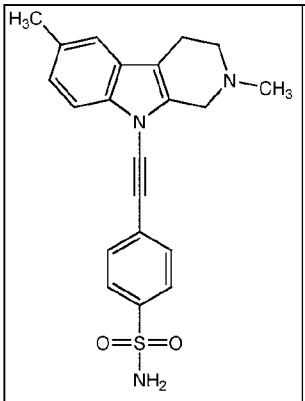
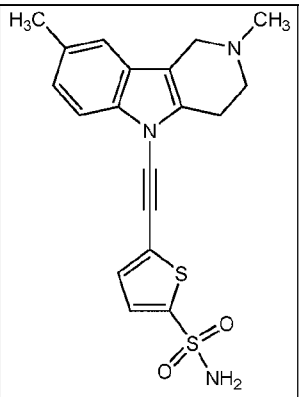
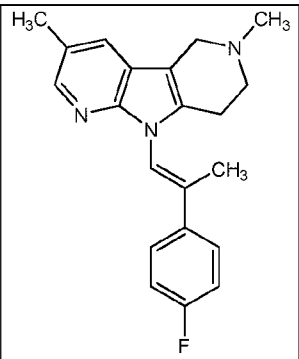
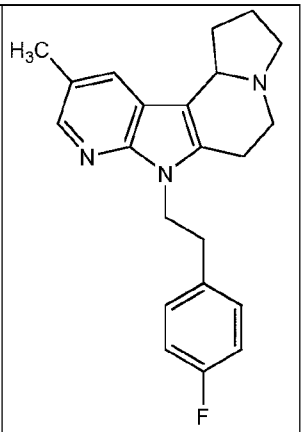
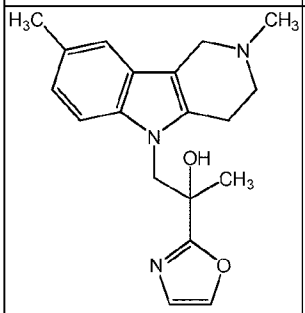
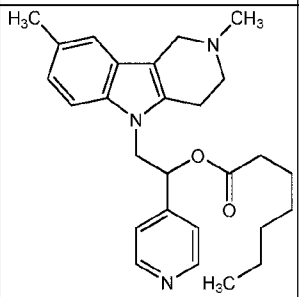
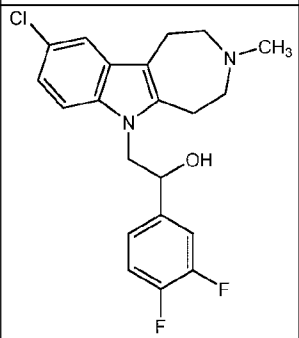
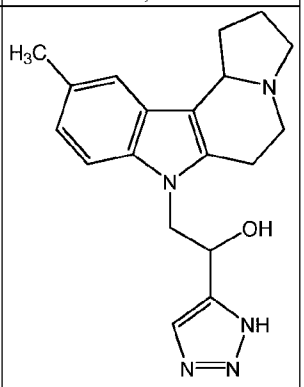
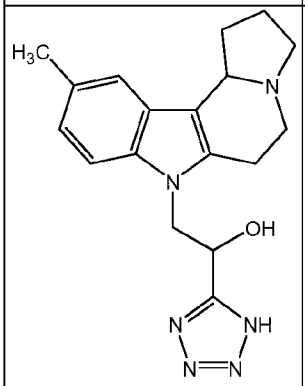
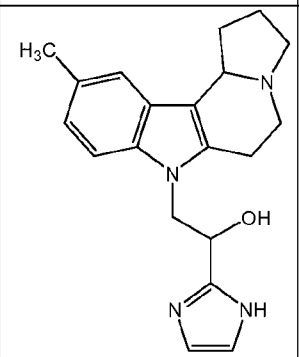
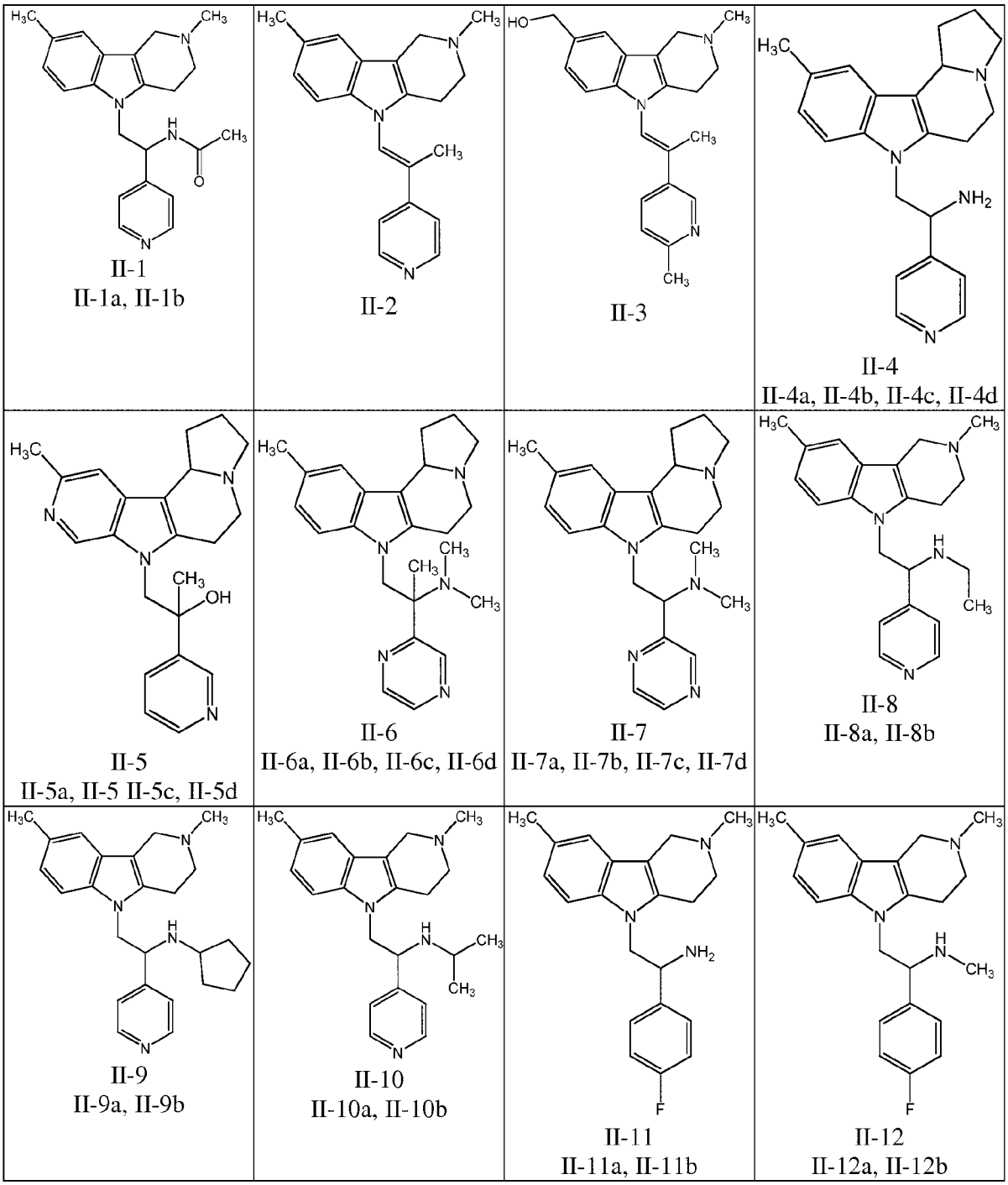
 333	 334	 335	 336 336a, 336b
 337 337a, 337b	 338 338a, 338b	 339 339a, 339b	 340 340a, 340b, 340c, 340d
 341 341a, 341b, 341c, 341d	 342 342a, 342b, 342c, 342d		

[0631] Table 2. Representative Compounds of the Invention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II-1a, II-1b
II-2
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II-4
II-4a, II-4b, II-4c, II-4d
II-5
II-5a, II-5 II-5c, II-5d
II-6
II-6a, II-6b, II-6c, II-6d
II-7
II-7a, II-7b, II-7c, II-7d
II-8
II-8a, II-8b
II-9
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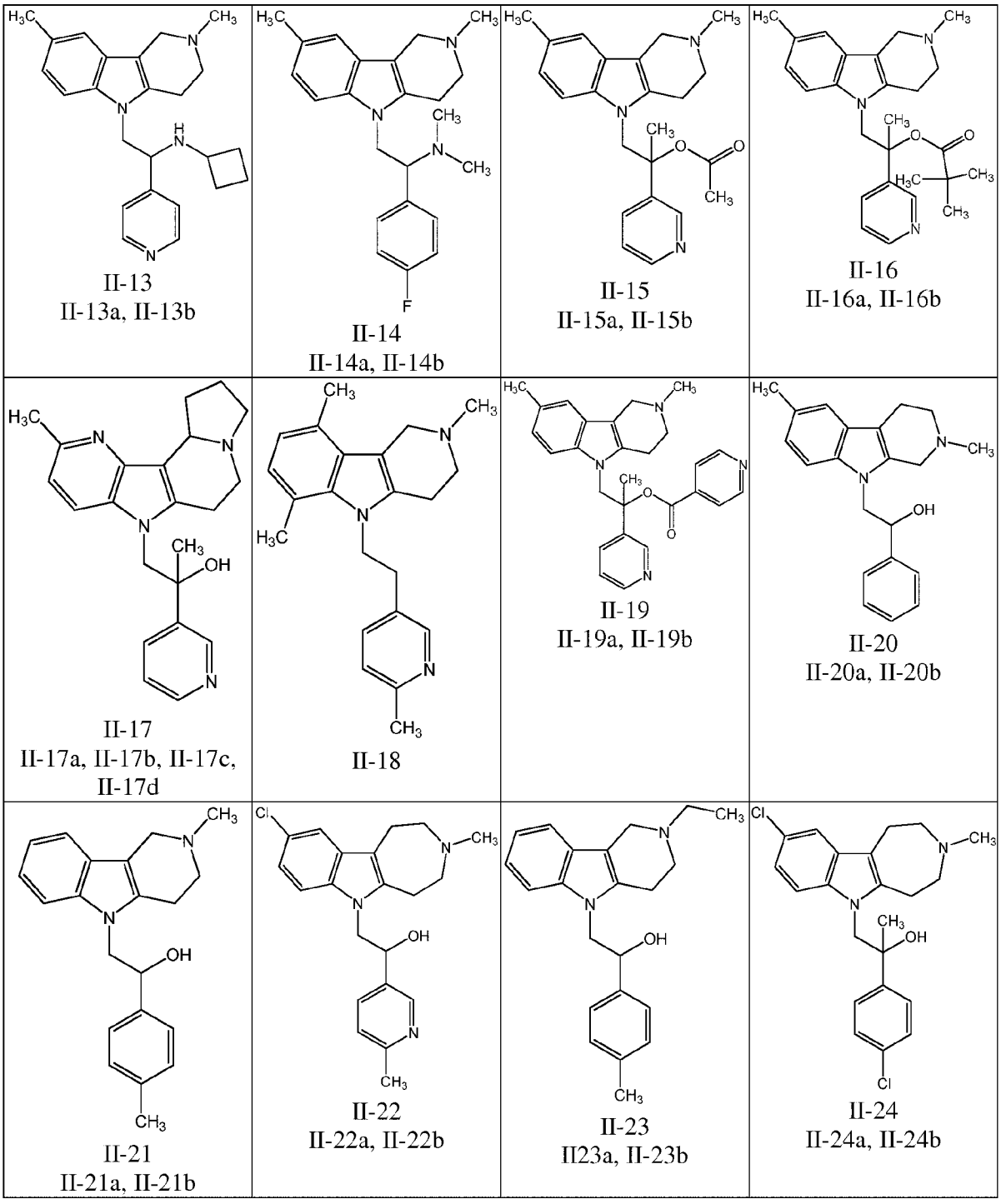
II-11
II-11a, II-11b
II-12
II-12a, II-12b



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II-13a, II-13b

II-14
II-14a, II-14b

II-15
II-15a, II-15b

II-16
II-16a, II-16b

II-17
II-17a, II-17b, II-17c, II-17d

II-18

II-19
II-19a, II-19b

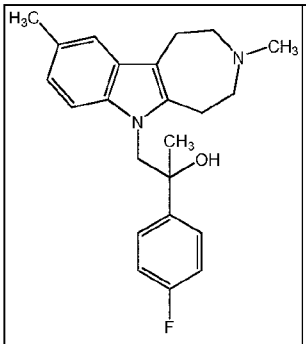
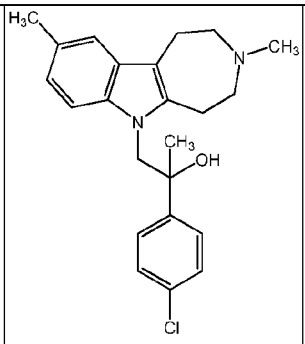
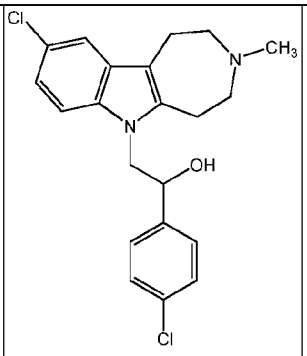
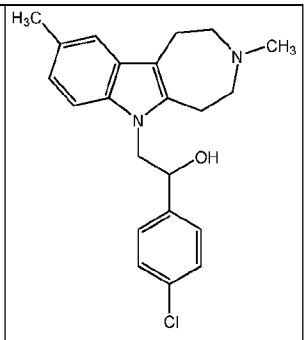
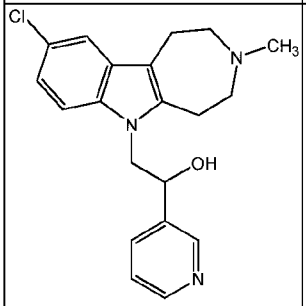
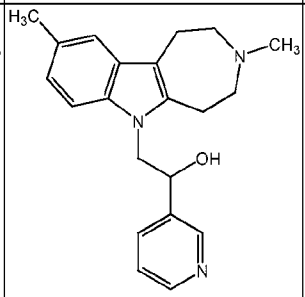
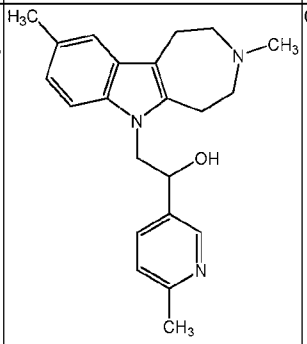
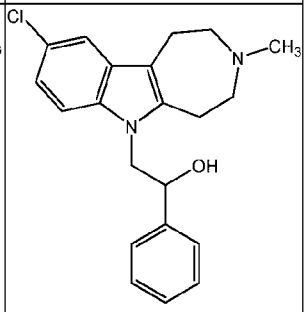
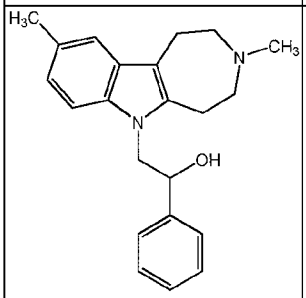
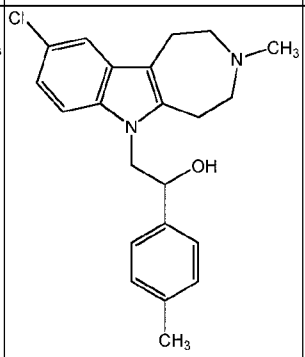
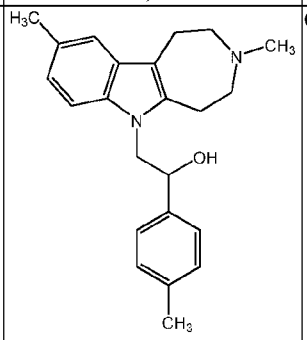
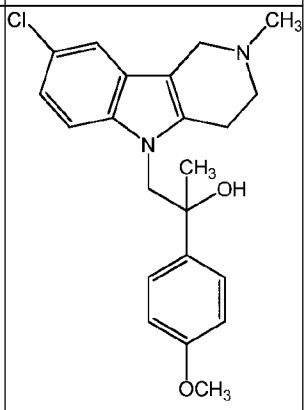
II-20
II-20a, II-20b

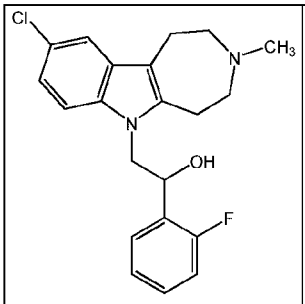
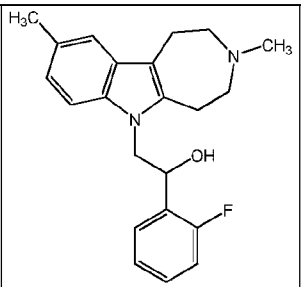
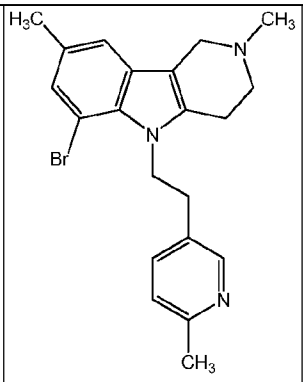
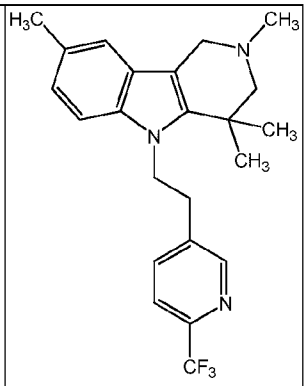
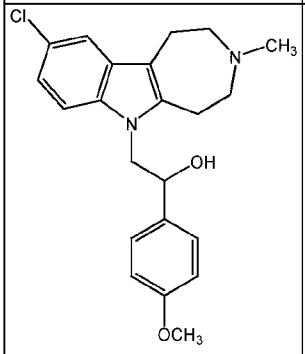
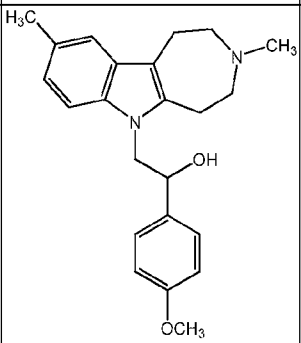
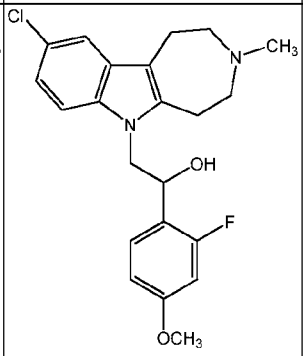
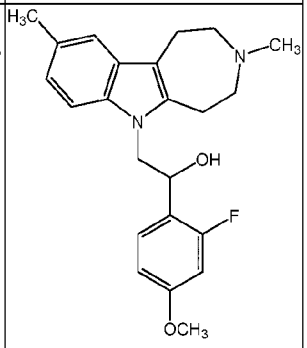
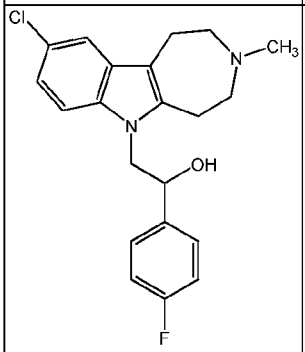
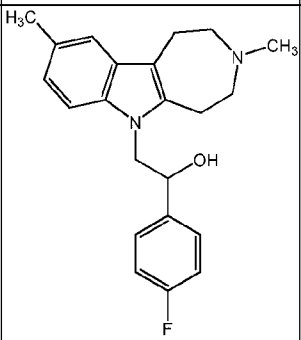
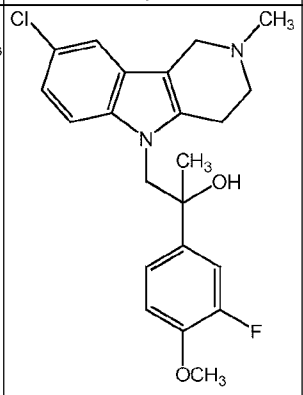
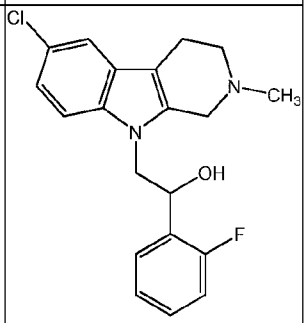
II-21
II-21a, II-21b

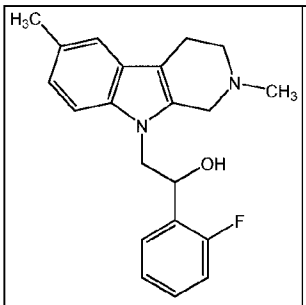
II-22
II-22a, II-22b

II-23
II23a, II-23b

II-24
II-24a, II-24b

 II-25 II-25a, II-25b	 II-26 II-26a, II-26b	 II-27 II-27a, II-27b	 II-28 II-28a, II-28b
 II-29 II-29a, II-29b	 II-30 II-30a, II-30b	 II-31 II-31a, II-31b	 II-32 II-32a, II-32b
 II-33 II-33a, II-33b	 II-34 II-34a, II-34b	 II-35 II-35a, II-35b	 II-36 II-36a, II-36b

 II-37 II-37a, II-37b	 II-38 II-38a, II-38b	 II-39	 II-40
 II-41 II-41a, II-41b	 II-42 II-42a, II-42b	 II-43 II-43a, II-43b	 II-44 II-44a, II-44b
 II-45 II-45a, II-45b	 II-46 II-46a, II-46b	 II-47 II-47a, II-47b	 II-48 II-48a, II-48b



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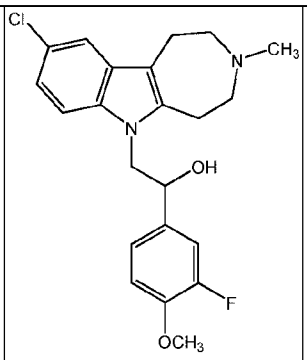
II-49a, II-49b



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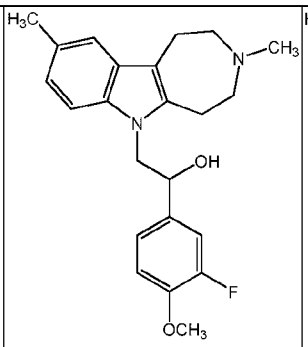
II-50a, II-50b



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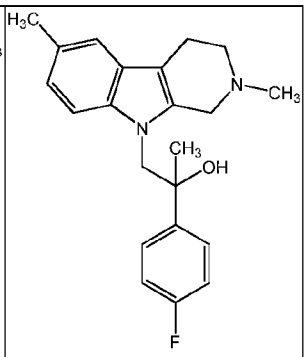
II-51a, II-51b



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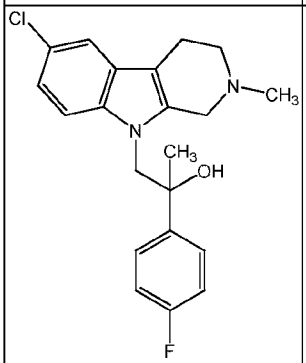
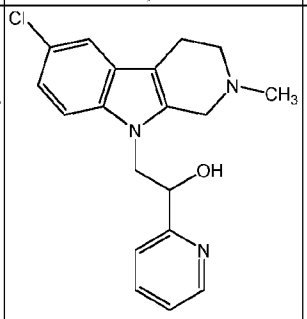
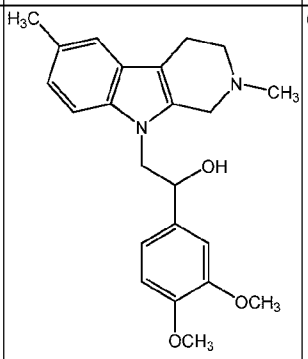


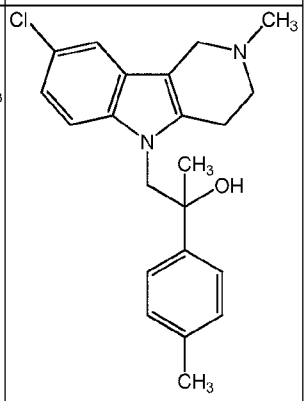
II-53
II-53a, II-53b



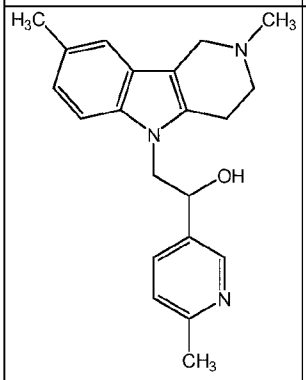
II-54
II-54a, II-54b



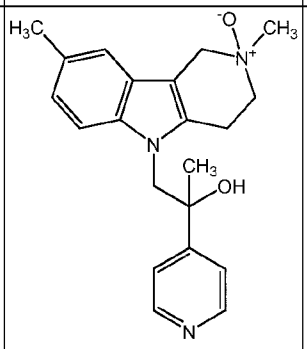
II-55
II-55a, II-55b



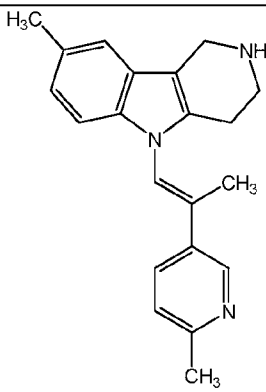
II-56
II-56a, II-56b



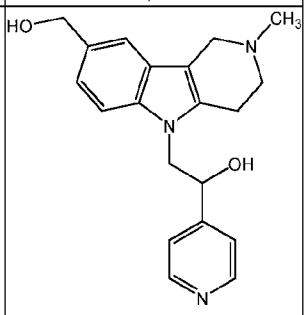
II-57
II-57a, II-57b



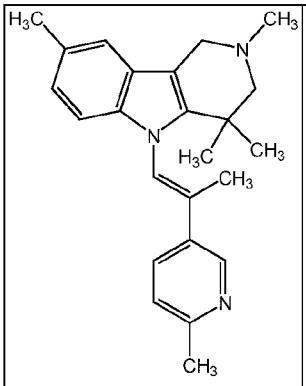
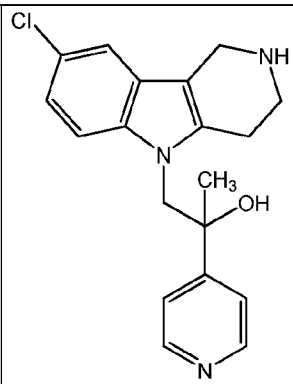
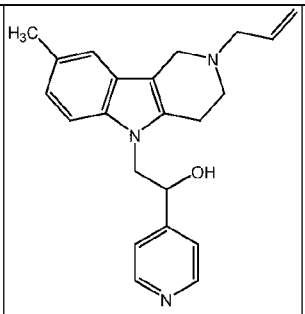
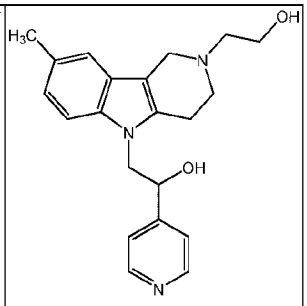
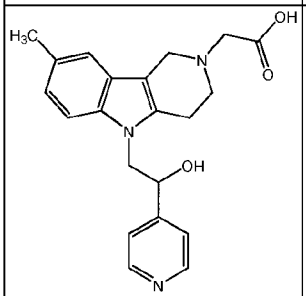
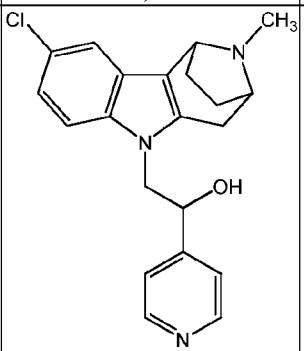
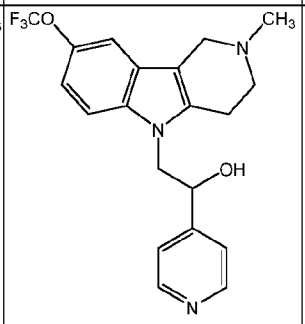
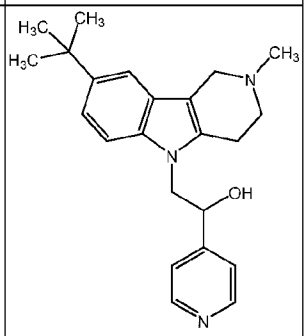
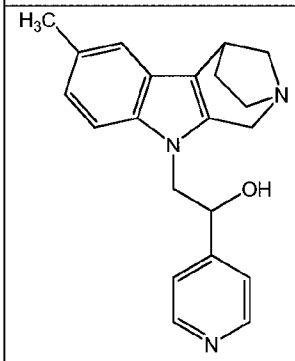
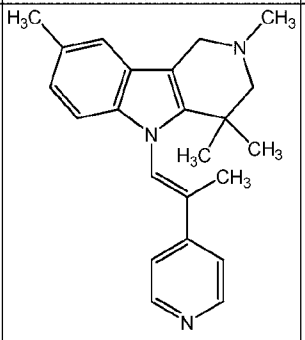
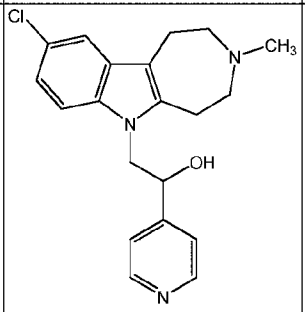
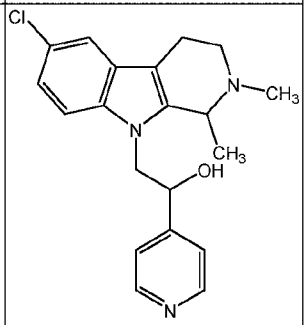
II-58
II-58a, II-58b

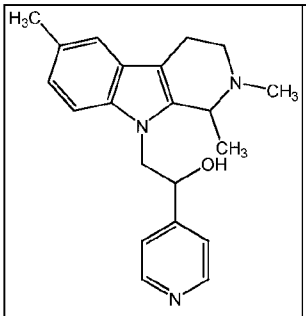
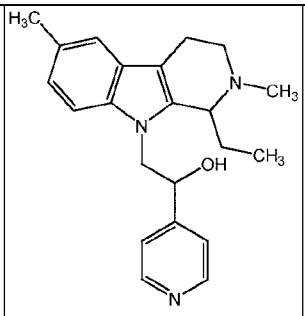
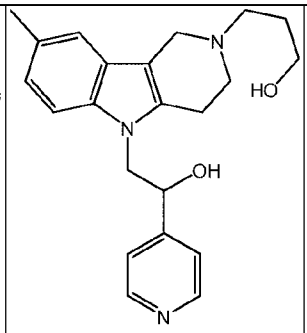
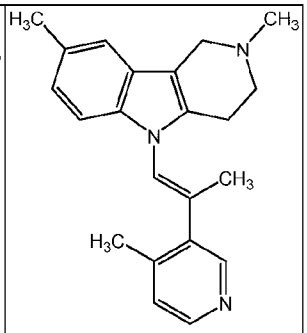
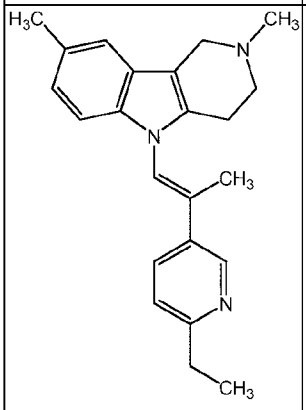
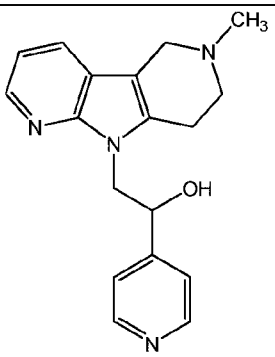
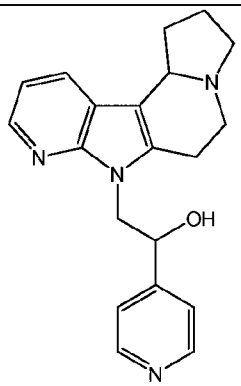
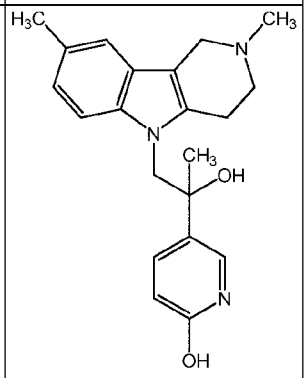
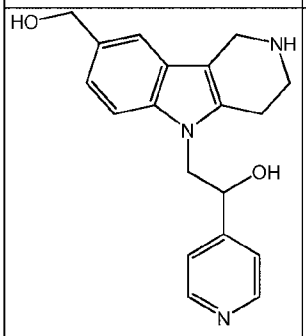
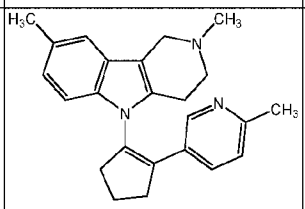
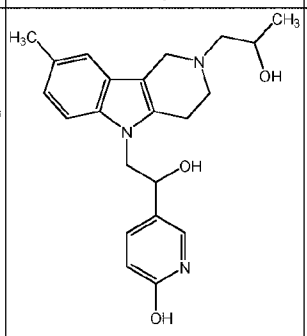
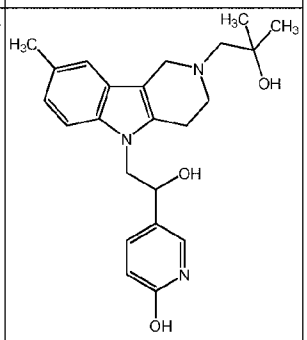


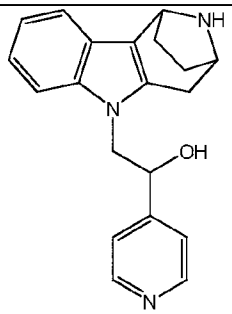
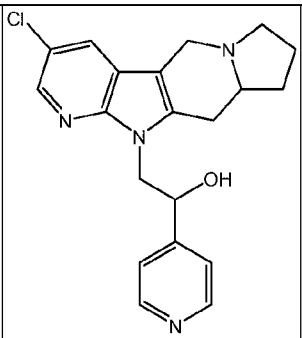
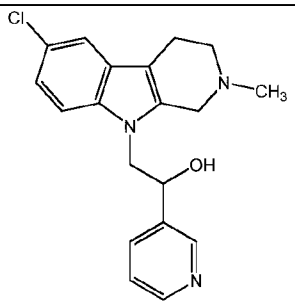
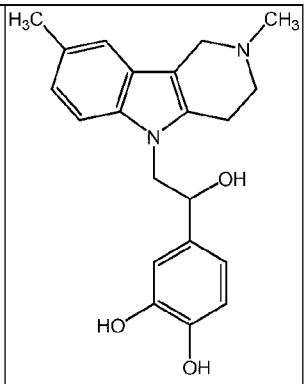
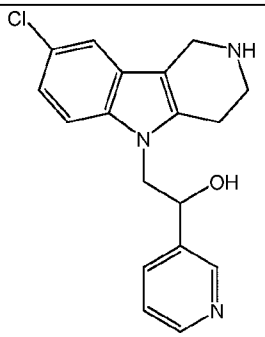
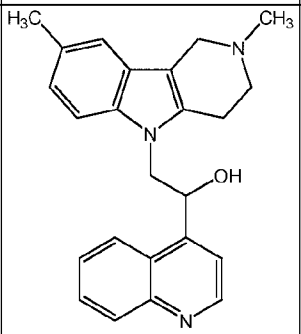
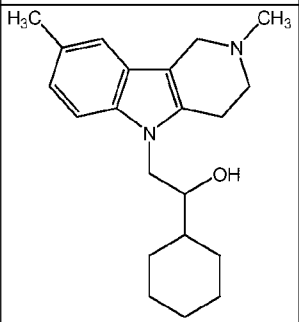
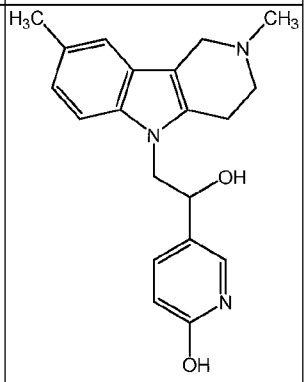
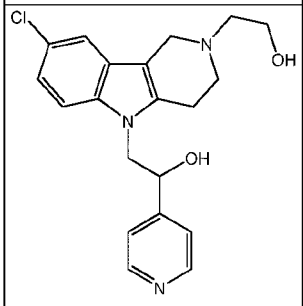
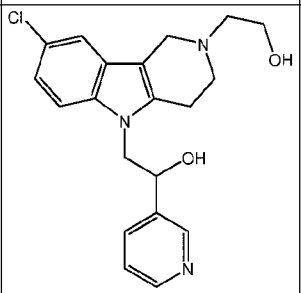
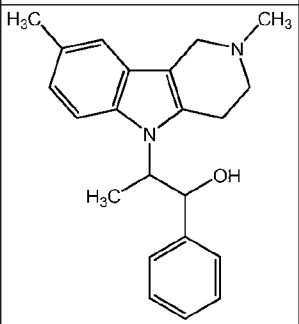
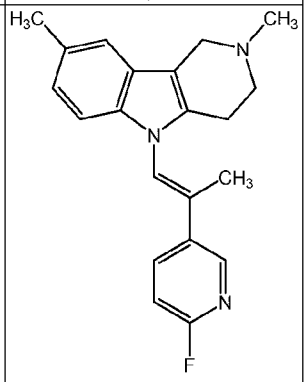
II-59

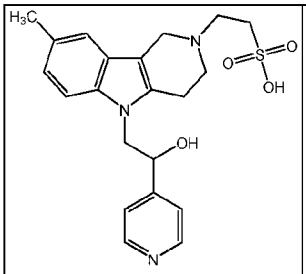
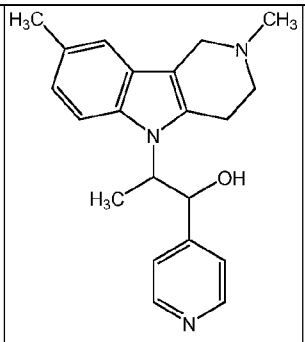
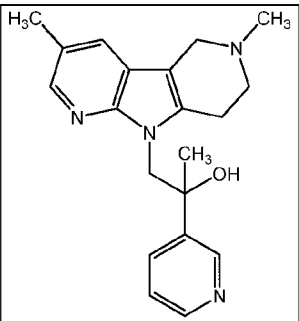
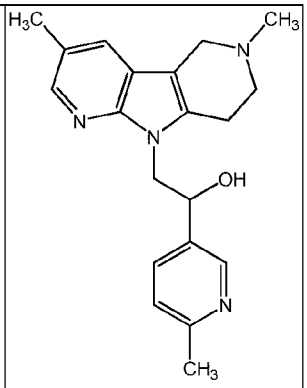
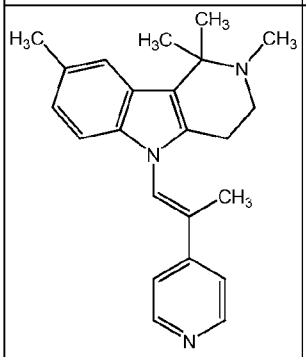
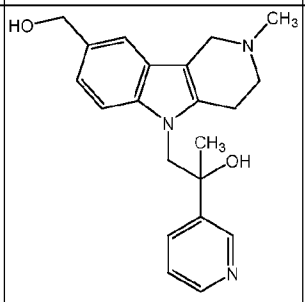
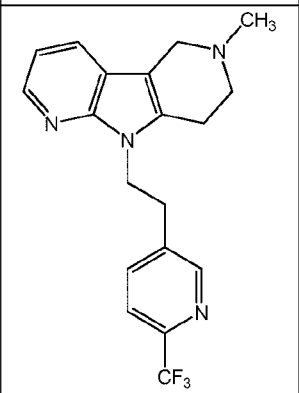
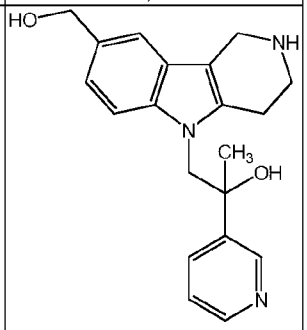
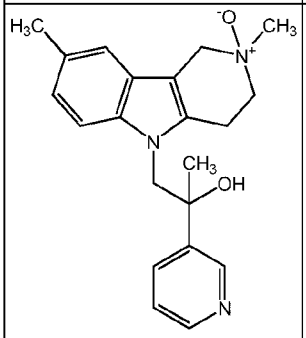
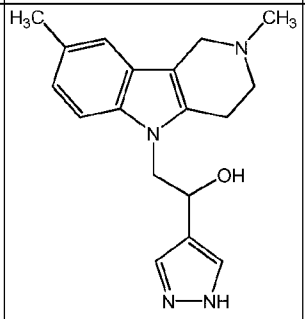
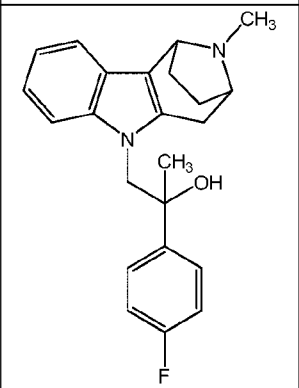
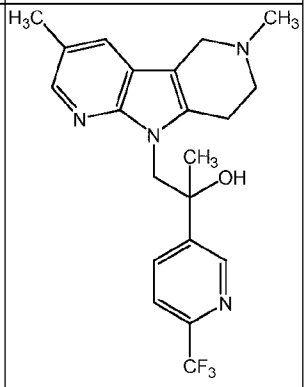


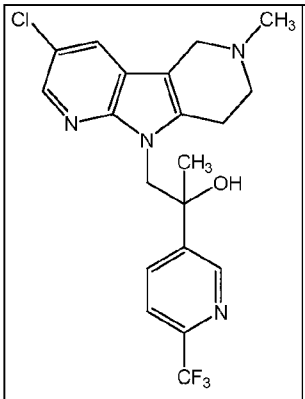
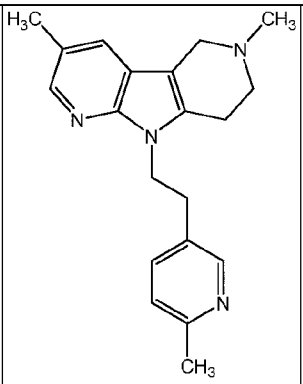
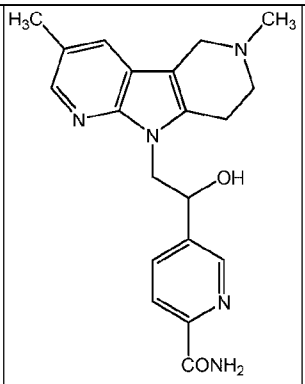
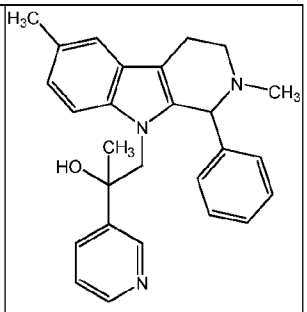
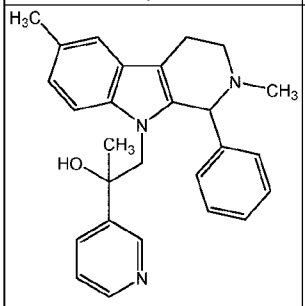
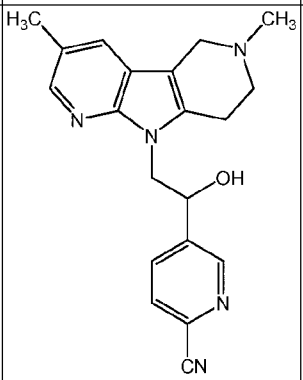
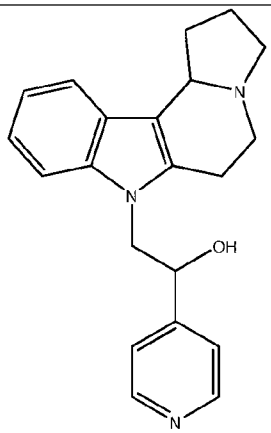
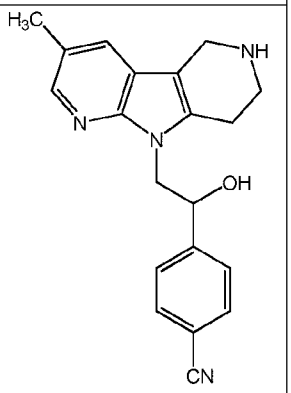
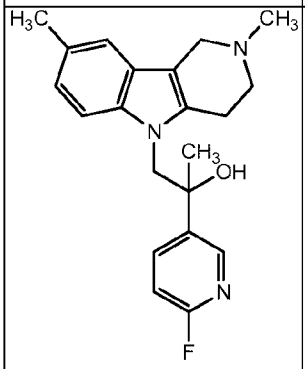
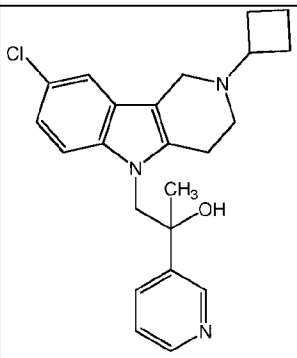
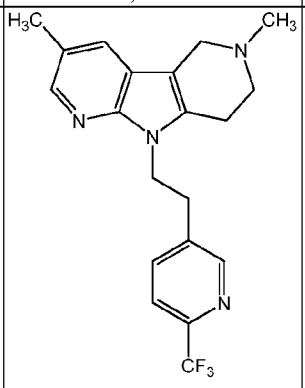
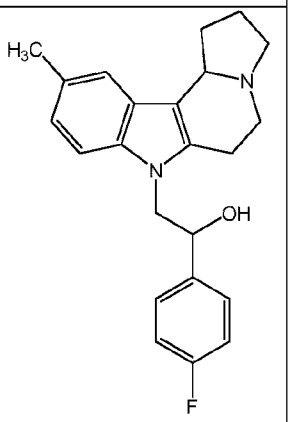
II-60
II-60a, II-60b

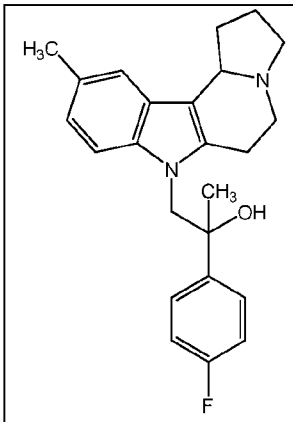
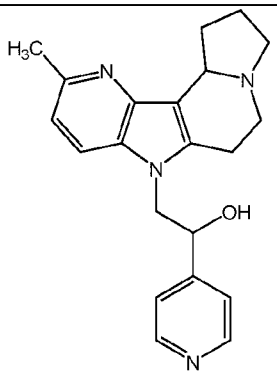
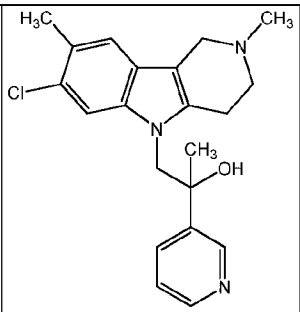
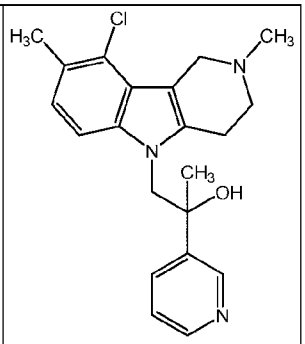
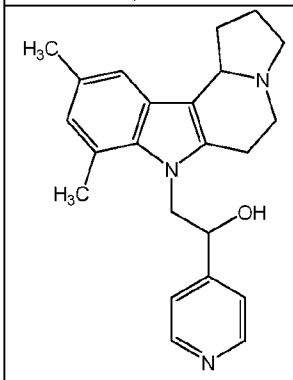
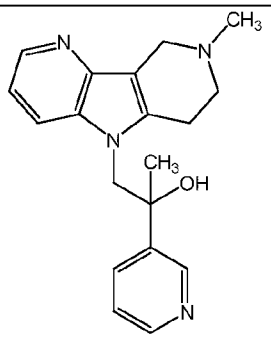
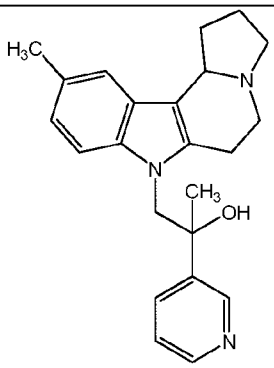
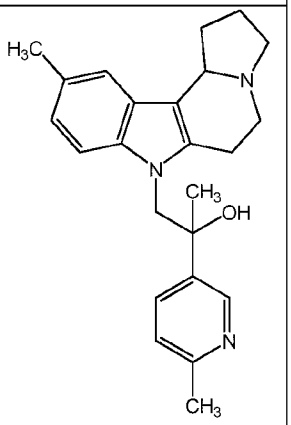
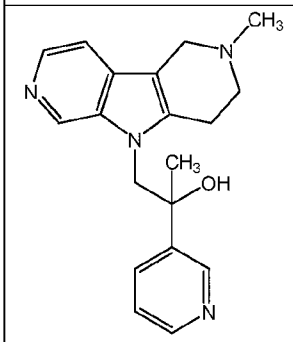
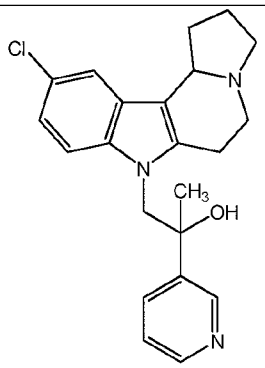
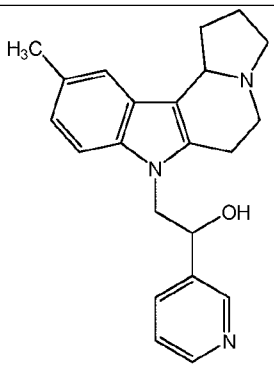
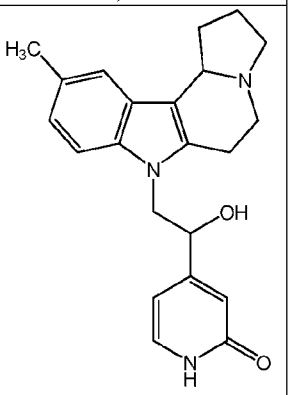
 II-61	 II-62 II-62a, II-62b	 II-63 II-63a, II-63b	 II-64 II-64a, II-64b
 II-65 II-65a, II-65b	 II-66 II-66a, II-66b	 II-67 II-67a, II-67b	 II-68 II-68a, II-68b
 II-69 II-69a, II-69b, II-69c, II-69d	 II-70	 II-71 II-71a, II-71b	 II-72 II-72a, II-72b, II-72c, II-72d

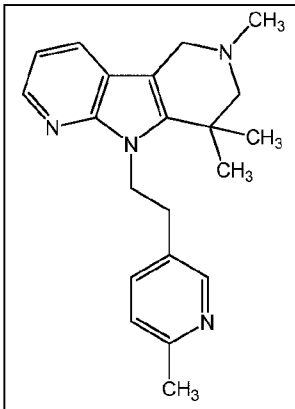
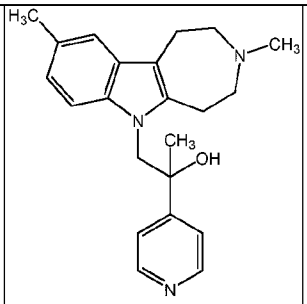
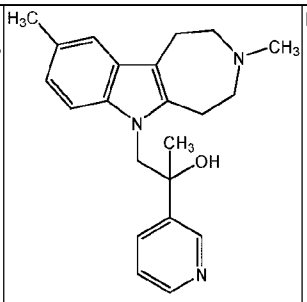
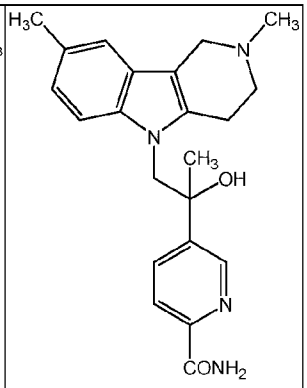
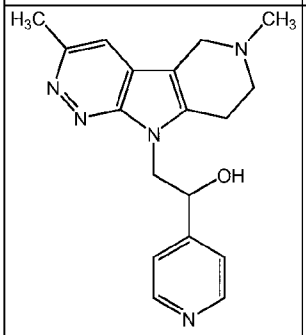
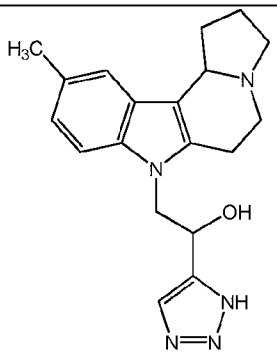
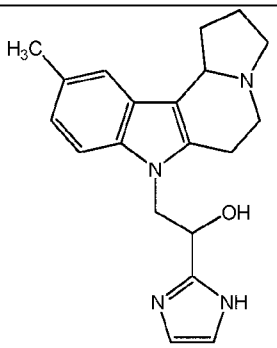
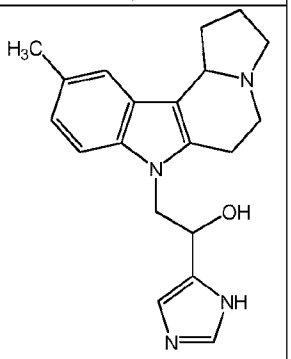
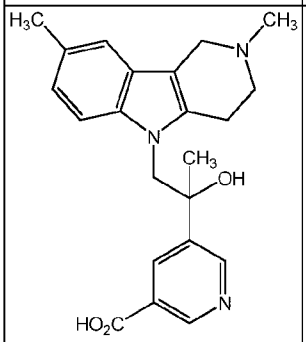
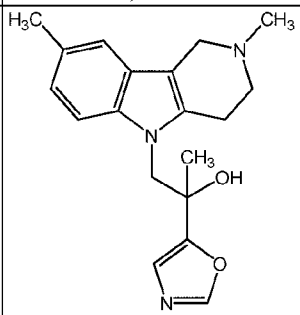
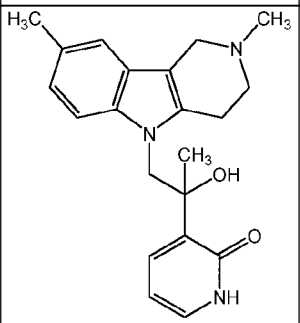
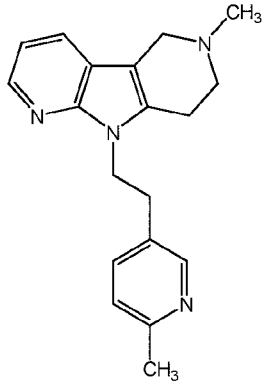
 II-73 II-73a, II-73b, II-73c, II-73d	 II-74 II-74a, II-74b, II-74c, II-74d	 II-75 II-75a, II-75b	 II-76
 II-77	 II-78 II-78a, II-78b	 II-79 II-79a, II-79b, II-79c, II-79d	 II-80 II-80a, II-80b
 II-81 II-81a, II-81b	 II-82	 II-83 II-83a, II-83b, II-83c, II-83d	 II-84 II-84a, II-84b

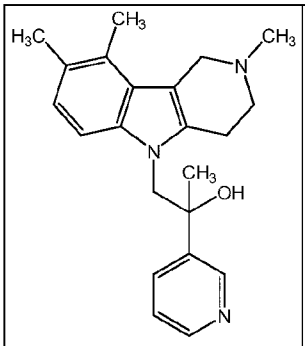
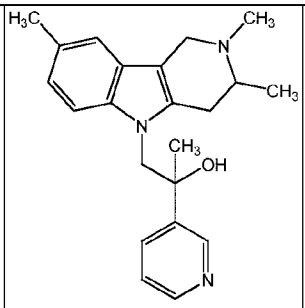
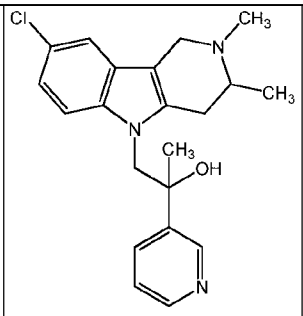
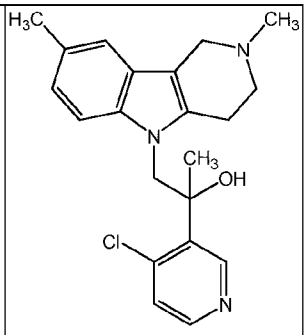
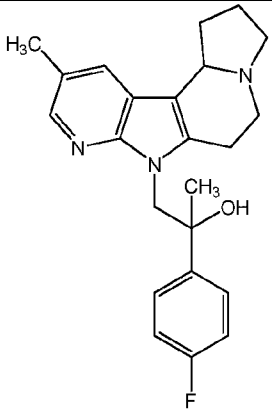
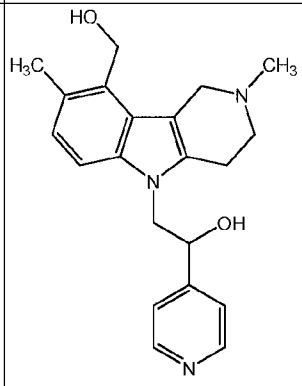
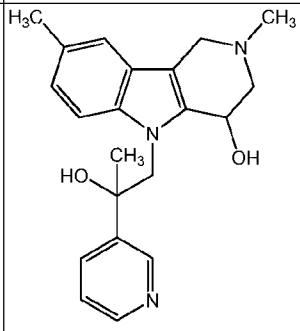
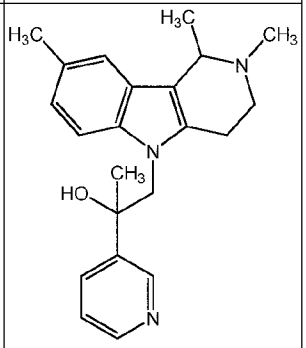
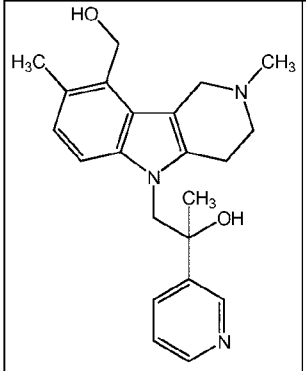
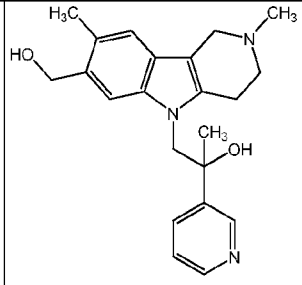
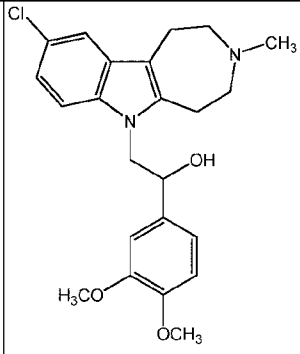
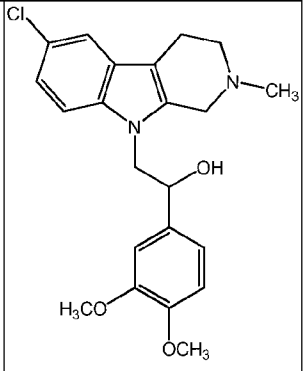
 II-85 II-85a, II-85b, II-85c, II-85d	 II-86 II-86a, II-86b, II-86c, II-86d	 II-87 II-87a, II-87b	 II-88 II-88a, II-88b
 II-89 II-89a, II-89b	 II-90 II-90a, II-90b	 II-91 II-91a, II-91b	 II-92 II-92a, II-92b
 II-93 II-93a, II-93b	 II-94 II-94a, II-94b	 II-95 II-95a, II-95b, II-95c, II-95d	 II-96

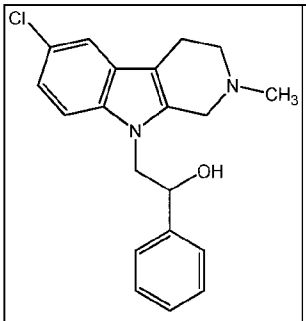
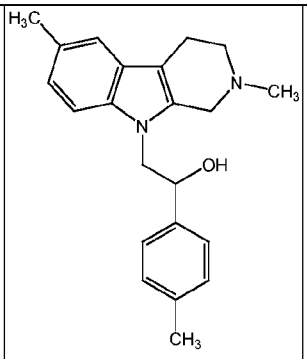
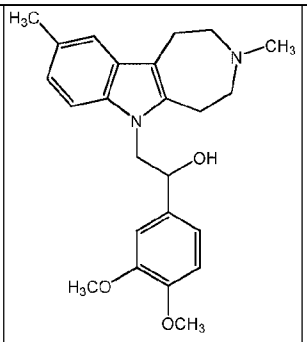
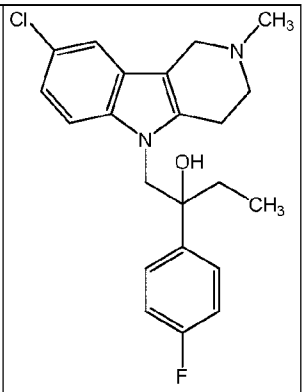
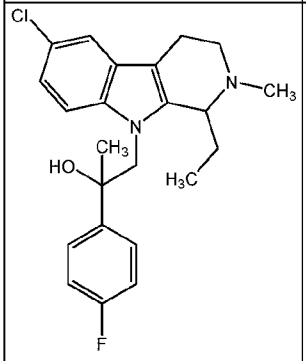
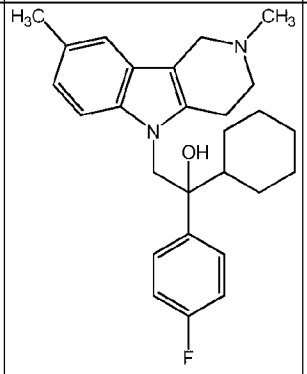
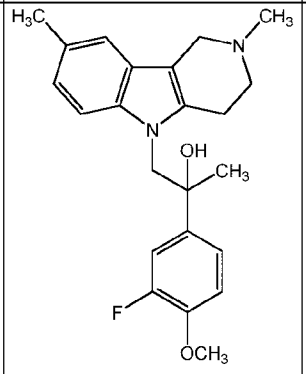
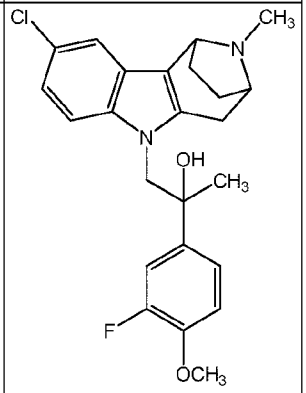
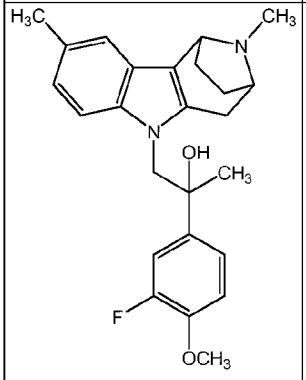
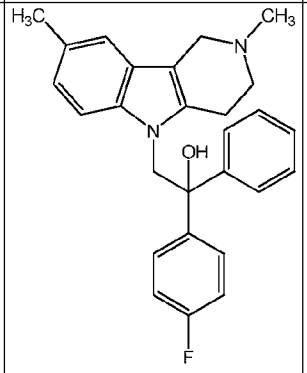
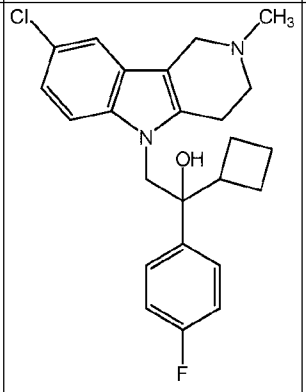
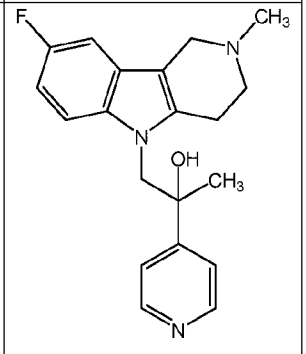
 II-97 II-97a, II-97b	 II-98 II-98a, II-98b, II-98c, II-98d	 II-99 II-99a, II-99b	 II-100 II-100a, II-100b
 II-101	 II-102 II-102a, II-102b	 II-103	 II-104 II-104a, II-104b
 II-105 II-105a, II-105b	 II-106 II-106a, II-106b	 II-107 II-107a, II-107b, II-107c, II-107d	 II-108 II-108a, II-108b

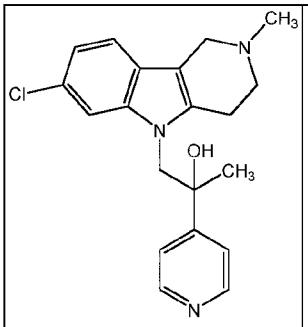
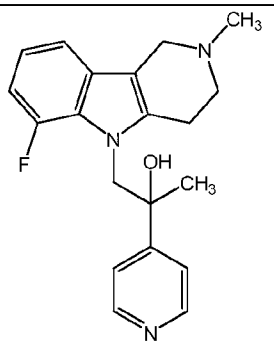
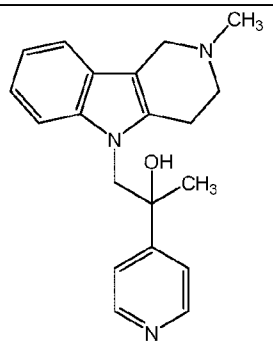
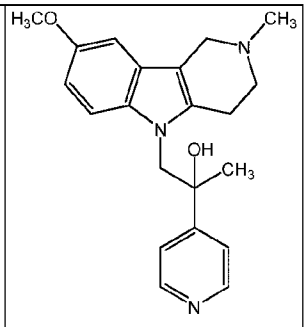
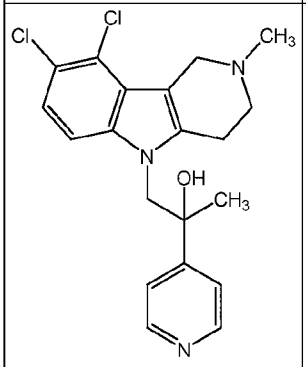
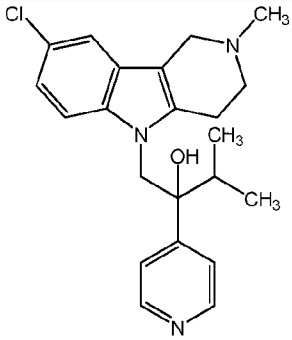
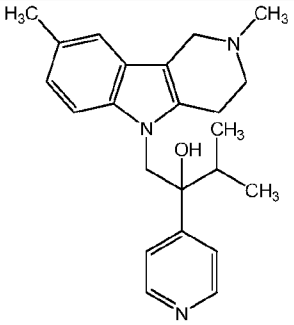
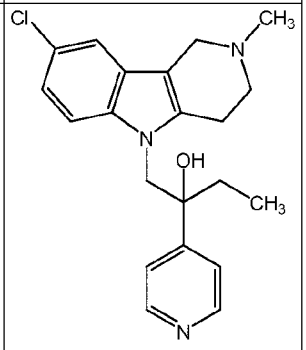
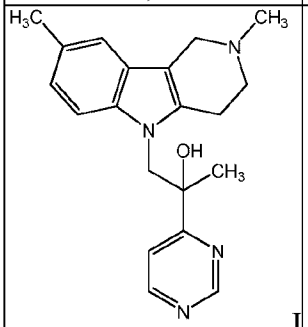
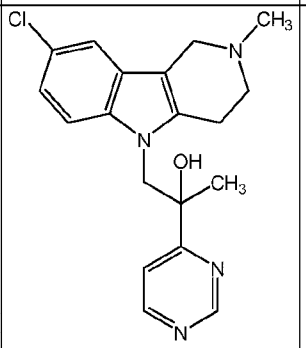
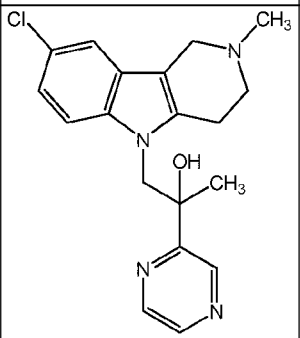
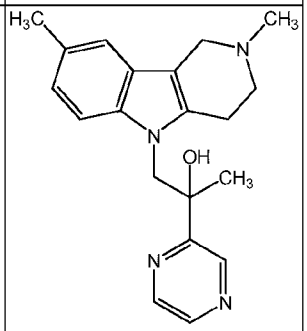
 II-109 II-109a, II-109b	 II-110	 II-111 II-111a, II-111b	 II-112 II-112a, II-112b, II-112c, II-112d
 II-113 II-113a, II-113b, II-113c, II-113d	 II-114 II-114a, II-114b	 II-115 II-115a, II-115b, II-115c, II-115d	 II-116 II-116a, II-116b
 II-117 II-117a, II-117b	 II-118 II-118a, II-118b	 II-119	 II-120 II-120a, II-120b, II-120c, II-120d

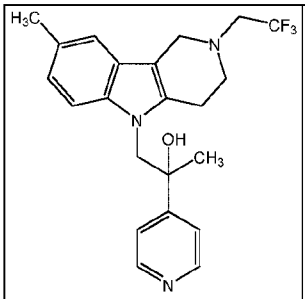
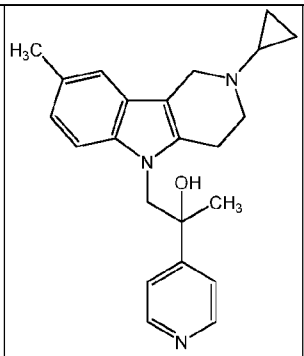
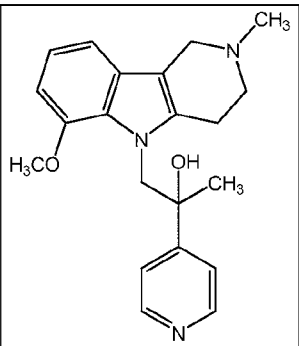
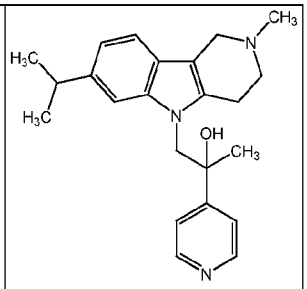
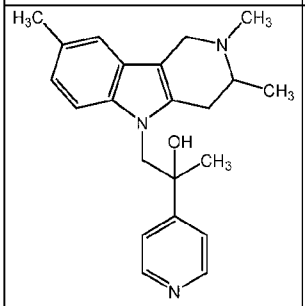
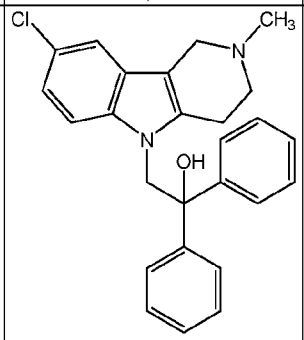
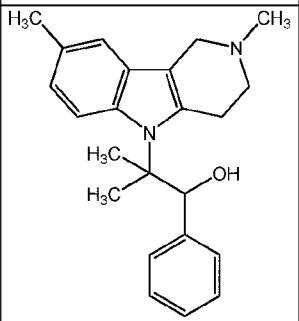
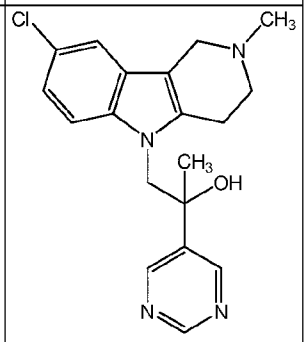
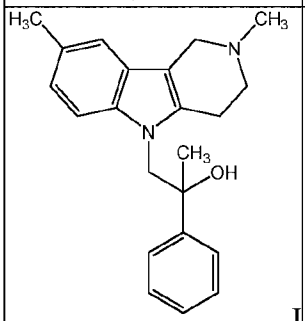
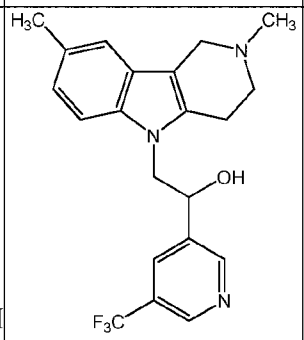
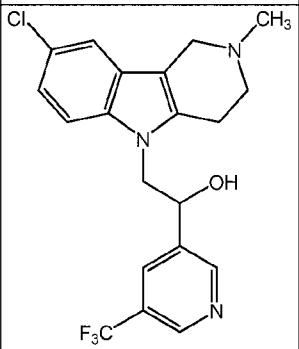
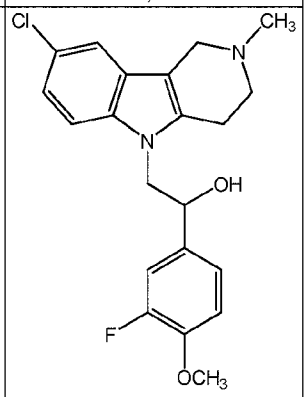
 II-121 II-121a, II-121b, II-121c, II-121d	 II-122 II-122a, II-122b, II-122c, II-122d	 II-123 II-123a, II-123b	 II-124 II-124a, II-124b
 II-125 II-125a, II-125b, II-125c, II-125d	 II-126 II-126a, II-126b	 II-127 II-127a, II-127b, II-127c, II-127d	 II-128 II-128a, II-128b, II-128c, II-128d
 II-129 II-129a, II-129b	 II-130 II-130a, II-130b, II-130c, II-130d	 II-131 II-131a, II-131b, II-131c, II-131d	 II-132 II-132a, II-132b, II-132c, II-132d

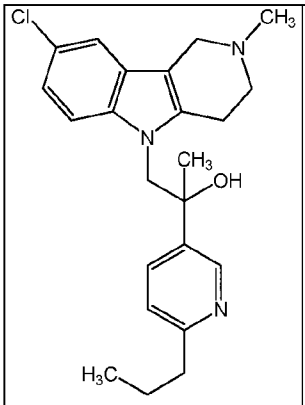
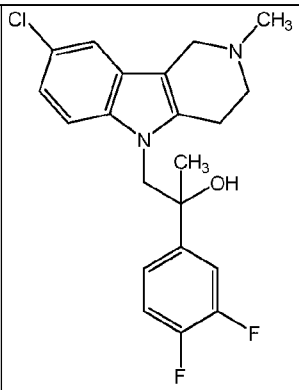
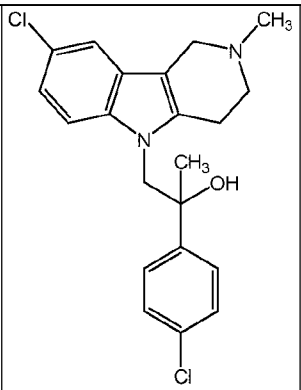
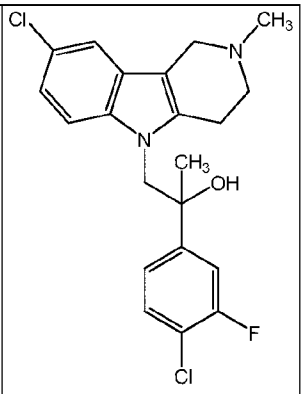
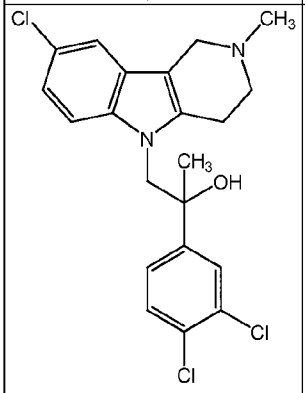
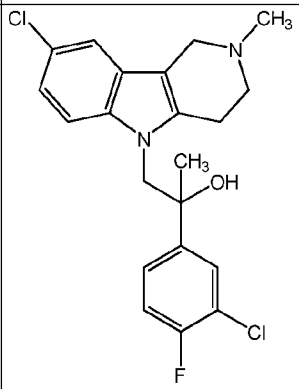
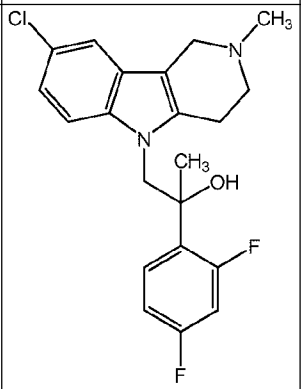
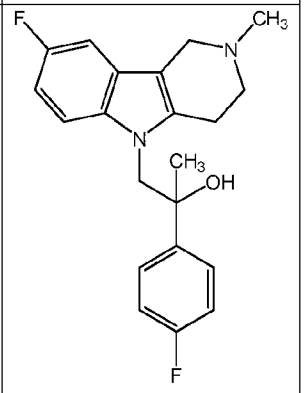
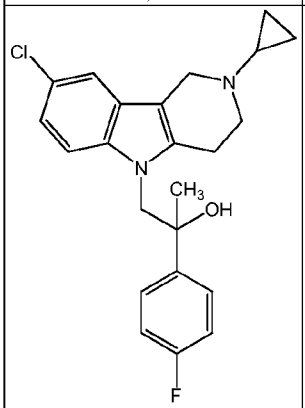
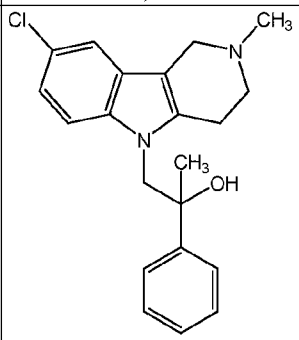
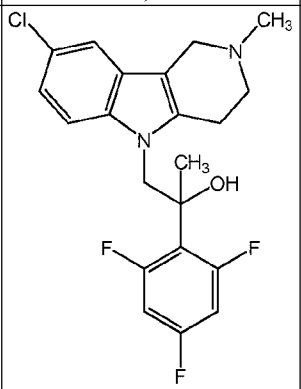
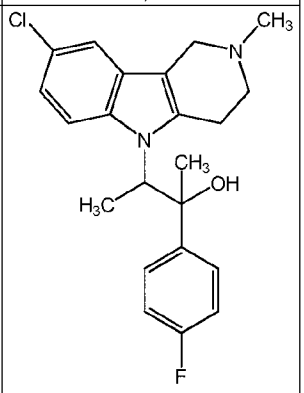
 II-133	 II-134 II-134a, II-134b	 II-135 II-135a, II-135b	 II-136 II-136a, II-136b
 II-137 II-137a, II-137b	 II-138 II-138a, II-138b, II-138c, II-138d	 II-139 II-139a, II-139b, II-139c, II-139d	 II-140 II-140a, II-140b, II-140c, II-140d
 II-141 II-141a, II-141b	 II-142 II-142a, II-142b	 II-143 II-143a, II-143b	 II-144

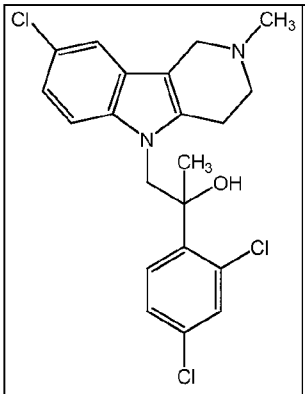
 II-145 II-145a, II-145b	 II-146 II-146a, II-146b, II-146c, II-147d	 II-147 II-147a, II-147b, II-147c, II-147d	 II-148 II-148a, II-148b
 II-149 II-149a, II-149b, II-149c, II-149d	 II-150 II-150a, II-150b, II-150c, II-150d	 II-151 II-151a, II-151b, II-151c, II-151d	 II-152 II-152a, II-152b, II-152c, II-152d
 II-153 II-153a, II-153b	 II-154 II-154a, II-154b	 II-155 II-155a, II-155b	 II-156 II-156a, II-156b

 II-157 II-157a, II-157b	 II-158 II-158a, II-158b	 II-159 II-159a, II-159b	 II-160 II-160a, II-160b
 II-161 II-161a, II-161b, II-161c, II-161d	 II-162 II-162a, II-162b	 II-163 II-163a, II-163b	 II-164 II-164a, II-164b, II-164c, II-164d
 II-165 II-165a, II-165b, II-165c, II-165d	 II-166 II-166a, II-166b	 II-167 II-167a, II-167b	 II-168 II-168a, II-168b

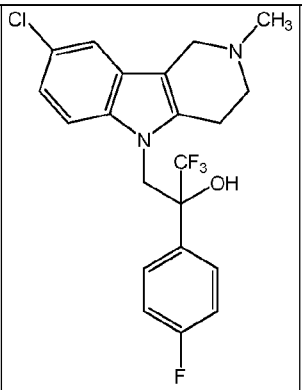
 II-169 II-169a, II-169b	 II-170 II-170a, II-170b	 II-171 II-171a, II-171b	 II-172 II-172a, II-172b
 II-173 II-173a, II-173b	 II-174 II-174a, II-174b	 II-175 II-175a, II-175b	 II-176 II-176a, II-176b
 I-177 II-177a, II-177b	 II-178 II-178a, II-178b	 II-179 II-179a, II-179b	 II-180 II-180a, II-180b

 II-181 II-181a, II-181b	 II-182 II-182a, II-182b	 II-183 II-183a, II-183b	 II-184 II-184a, II-184b
 II-185 II-185a, II-185b, II-185c, II-185d	 II-186	 II-187 II-187a, II-187b	 II-188 II-188a, II-188b
 I-189 II-189a, II-189b	 II-190 II-190a, II-190b	 II-191 II-191a, II-191b	 II-192 II-192a, II-192b

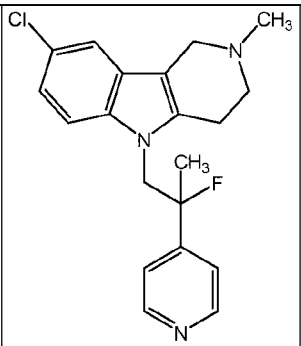
 II-193 II-193a, II-193b	 II-194 II-194a, II-194b	 II-195 II-195a, II-195b	 II-196 II-196a, II-196b
 II-197 II-197a, II-197b	 II-198 II-198a, II-198b	 II-199 II-199a, II-199b	 II-200 II-200a, II-200b
 II-201 II-201a, II-201b	 II-202 II-202a, II-202b	 II-203 II-203a, II-203b	 II-204 II-204a, II-204b



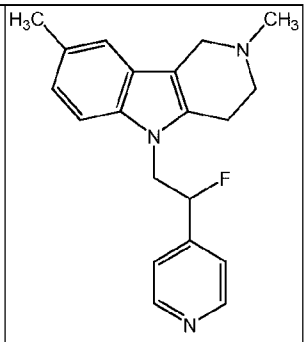
II-205
II-205a, II-205b



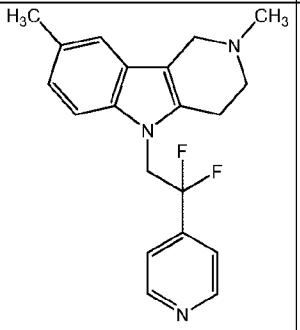
II-206
II-206a, II-206b



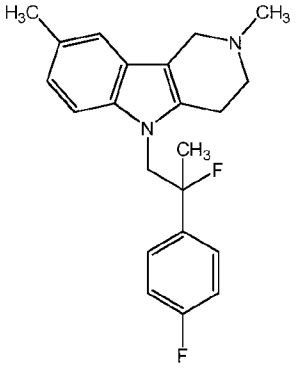
II-207
II-207a, II-207b



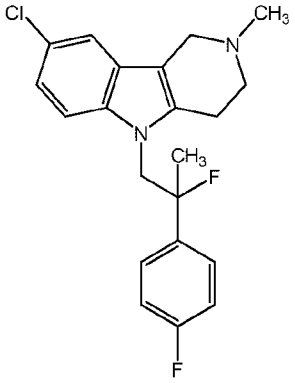
II-208
II-208a, II-208b



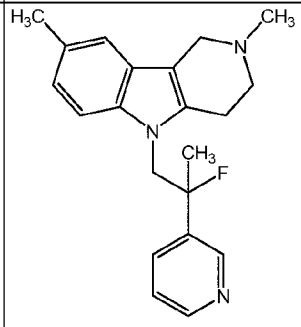
II-209



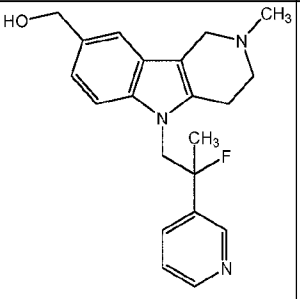
II-210
II-210a, II-210b



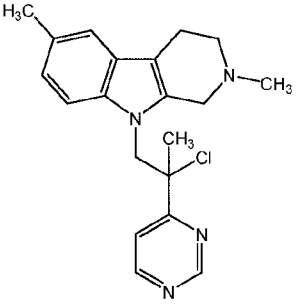
II-211
II-211a, II-211b



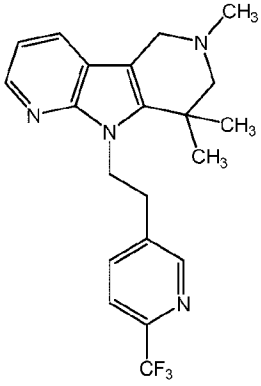
II-212
II-212a, II-212b



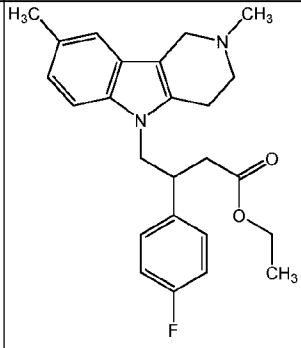
II-213
II-213a, II-213b



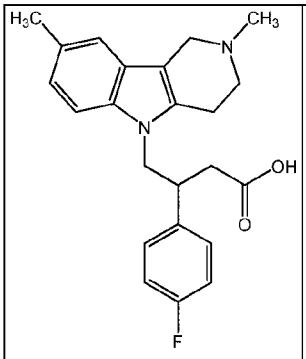
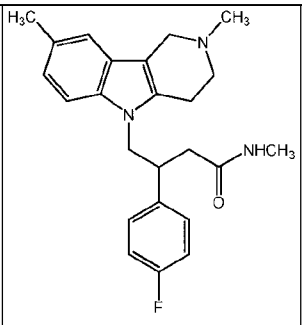
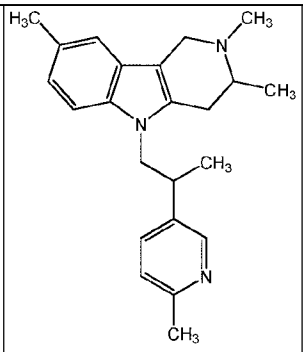
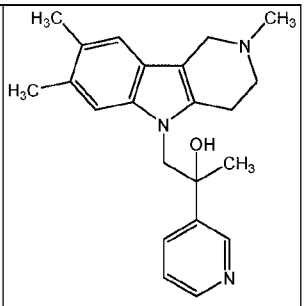
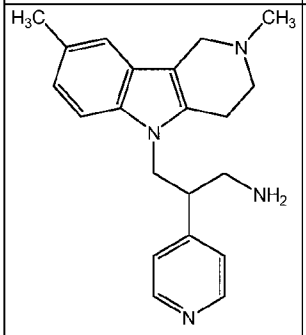
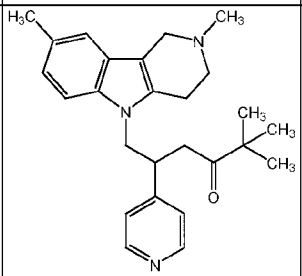
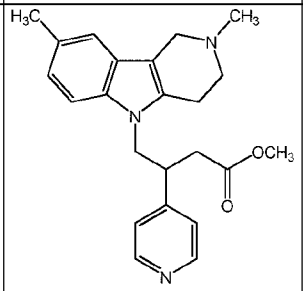
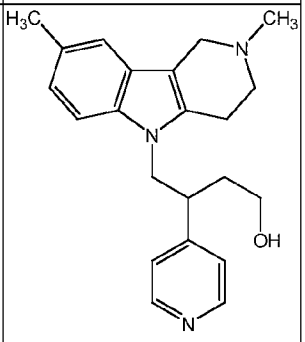
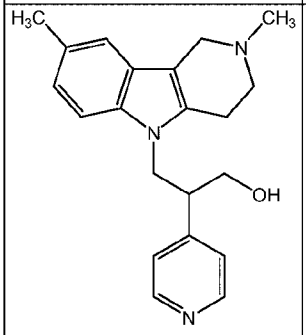
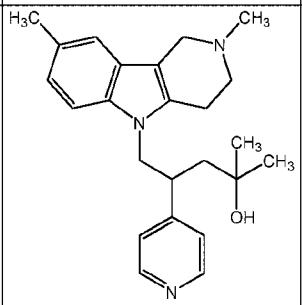
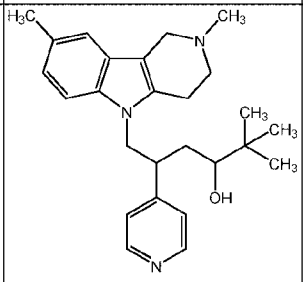
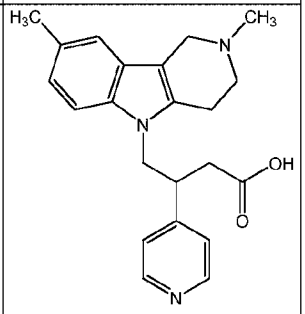
II-214
II-214a, II-214b

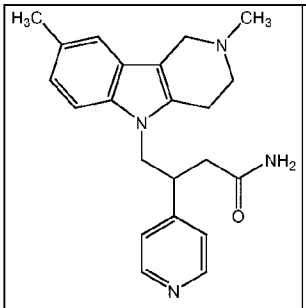
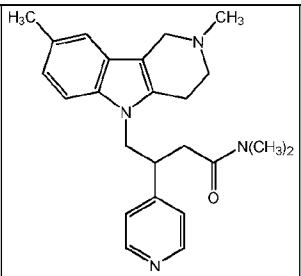
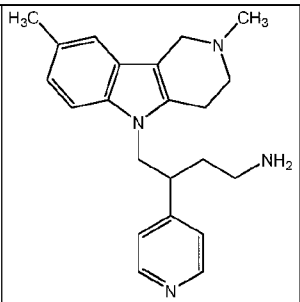
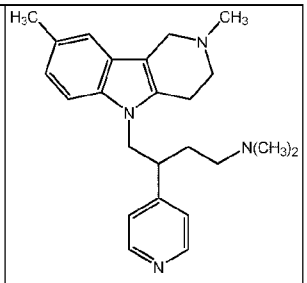
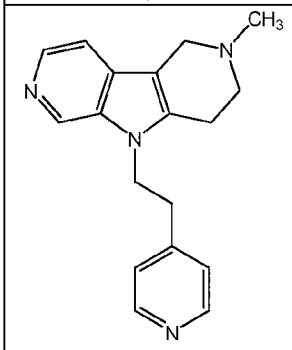
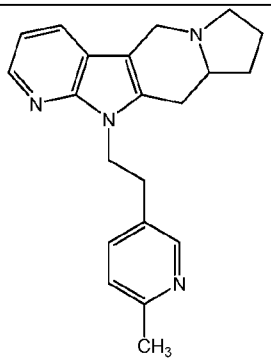
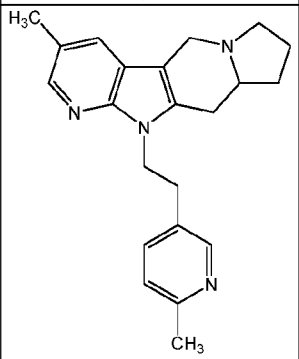
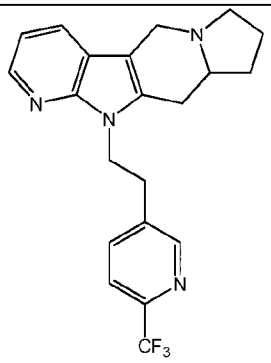
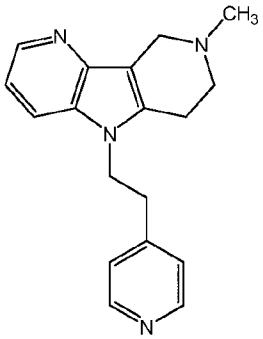
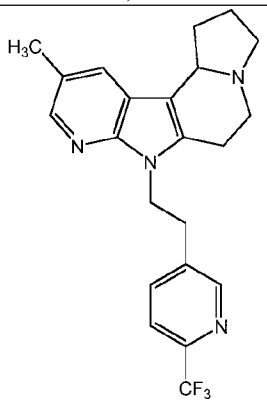
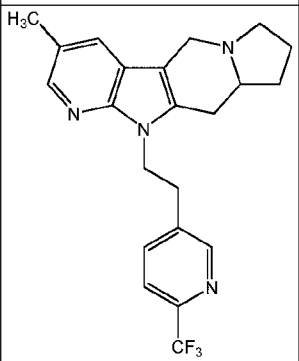
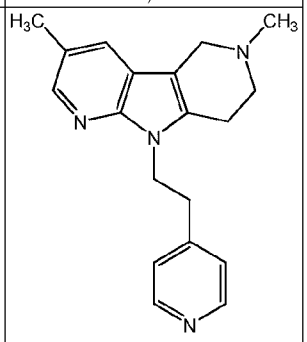


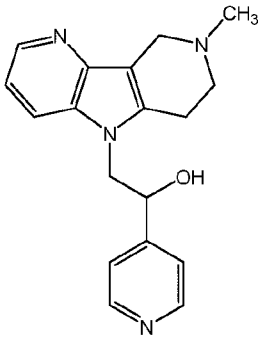
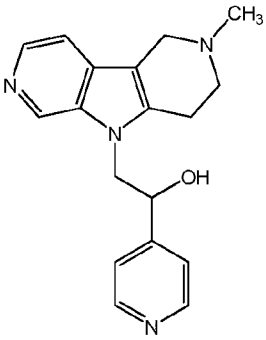
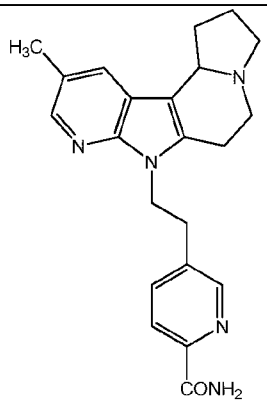
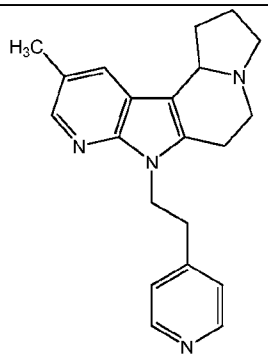
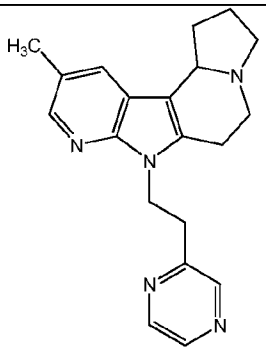
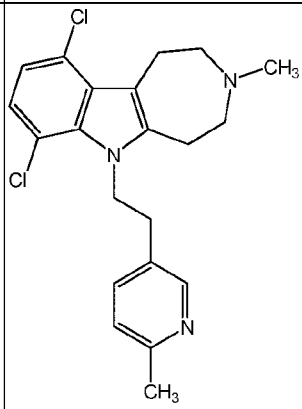
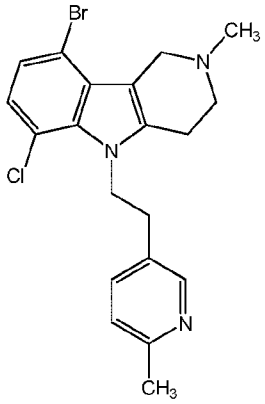
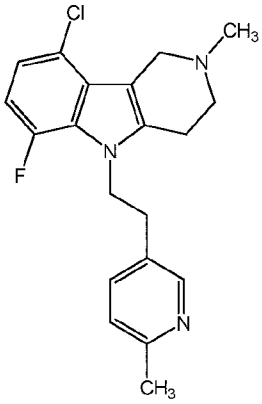
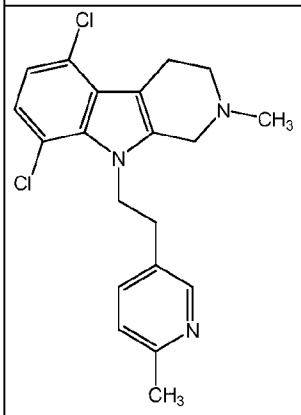
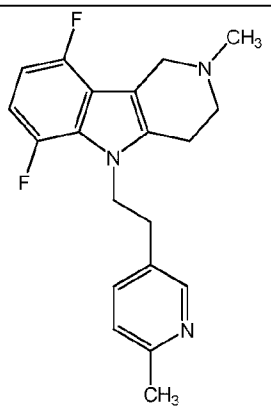
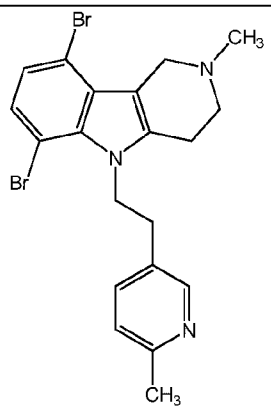
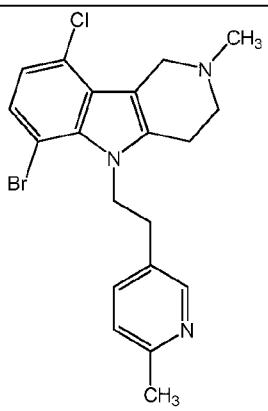
II-215

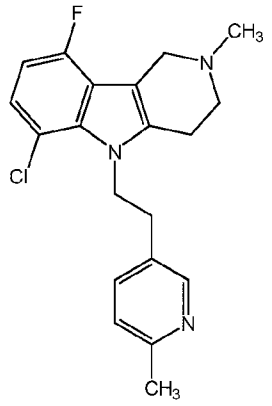
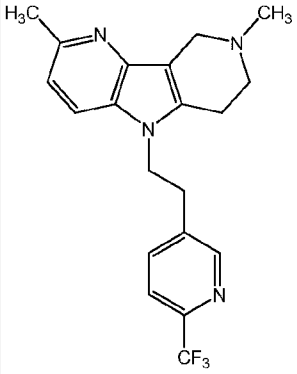
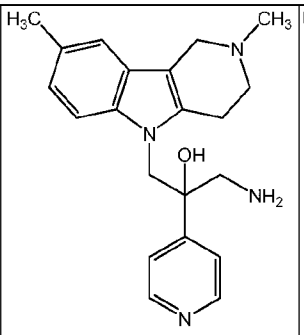
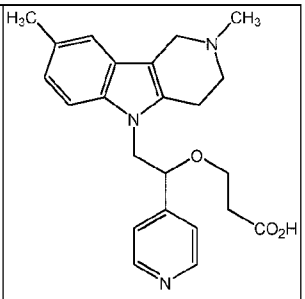
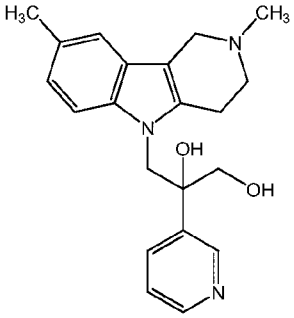
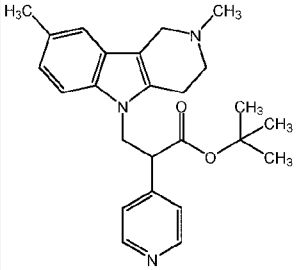
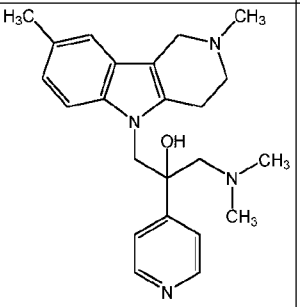
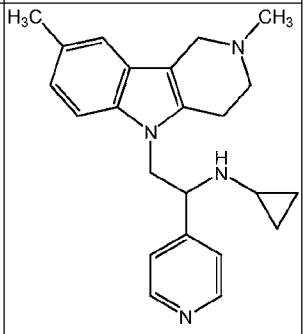
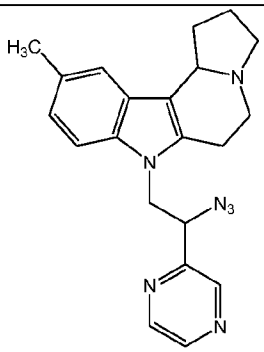
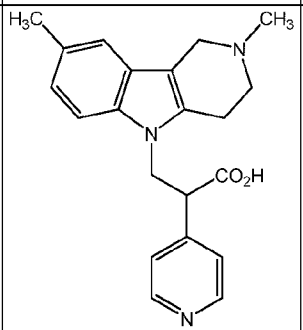
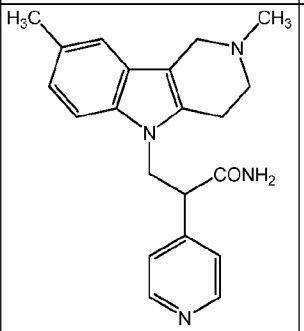
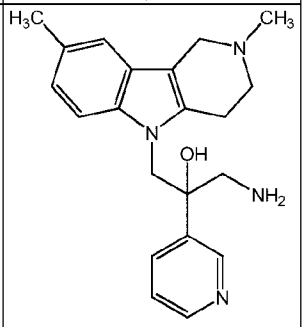


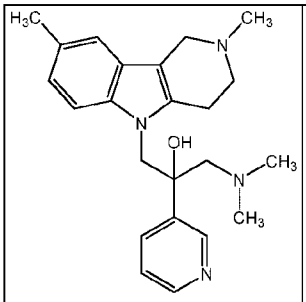
II-216
II-216a, II-216b

 II-217 II-217a, II-217b	 II-218 II-218a, II-218b	 II-219 II-219a, II-219b, II-219c, II-219d	 II-220 II-220a, II-220b
 II-221 II-221a, II-221b	 II-222 II-222a, II-222b	 II-223 II-223a, II-223b	 II-224 II-224a, II-224b
 II-225 II-225a, II-225b	 II-226 II-226a, II-226b	 II-227 II-227a, II-227b, II-227c, II-227d	 II-228 II-228a, II-228b

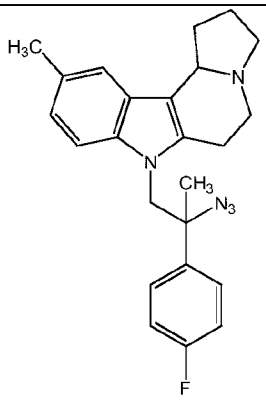
 II-229 II-229a, II-229b	 II-230 II-230a, II-230b	 II-231 II-231a, II-231b	 II-232 II-232a, II-232b
 II-233	 II-234 II-234a, II-234b	 II-235 II-235a, II-235b	 II-236 II-236a, II-236b
 II-237	 II-238 II-238a, II-238b	 II-239 II-239a, II-239b	 II-240

 II-241 II-241a, II-241b	 II-242 II-242a, II-242b	 II-243 II-243a, II-243b	 II-244 II-244a, II-244b
 II-245 II-245a, II-245b	 II-246	 II-247	 II-248
 II-249	 II-250	 II-251	 II-252

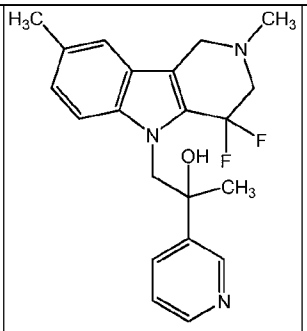
 II-253	 II-254	 II-255 II-255a, II-255b	 II-256 II-256a, II-256b
 II-257 II-257a, II-257b	 II-258 II-258a, II-258b	 II-259 II-259a, II-259b	 II-260 II-260a, II-260b
 II-261 II-261a, II-261b, II-261c, II-261d	 II-262 II-262a, II-262b	 II-263 II-263a, II-263b	 II-264 II-264a, II-264b



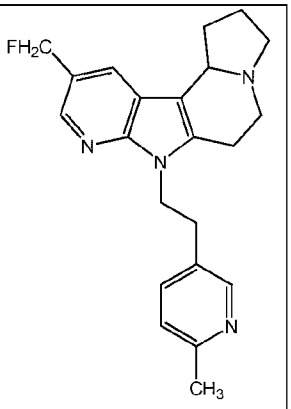
II-265
II-265a, II-265b



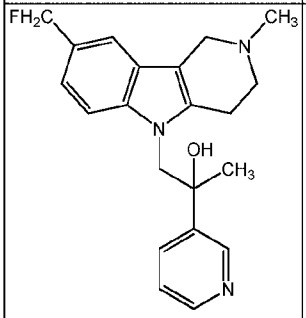
II-266
II-266a, II-266b, II-266c, II-266d



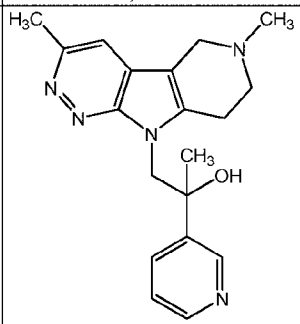
II-267
II-267a, II-267b



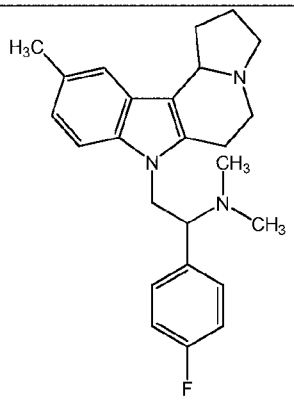
II-268
II-268a, II-268b



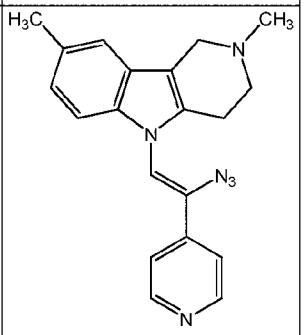
II-269
II-269a, II-269b



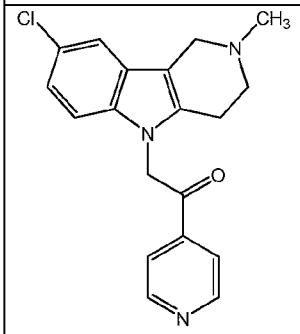
II-270
II-270a, II-270b



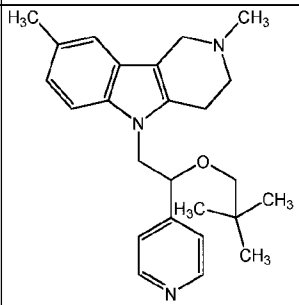
II-271
II-271a, II-271b, II-271c, II-271d



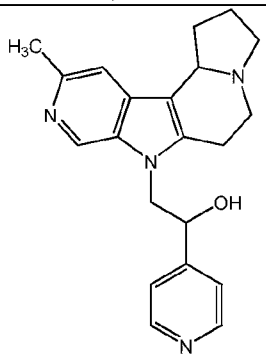
II-272



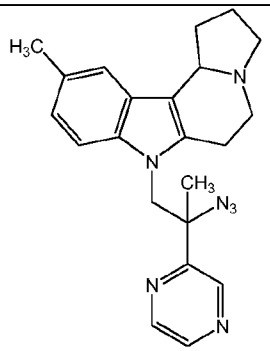
II-273



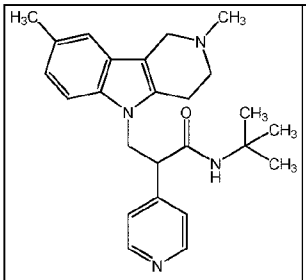
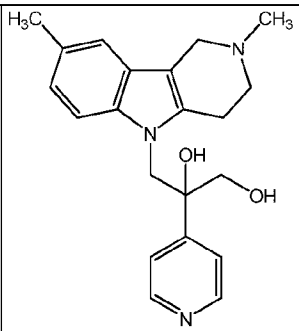
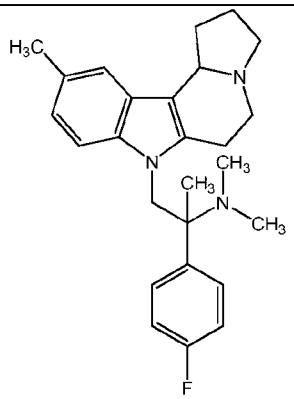
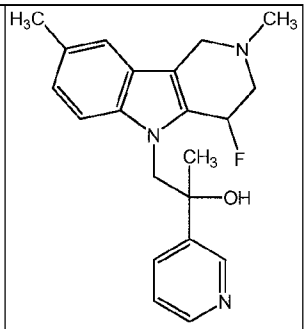
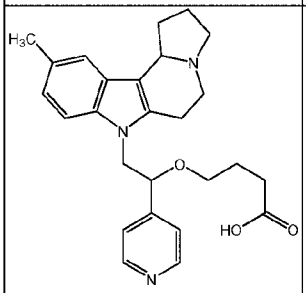
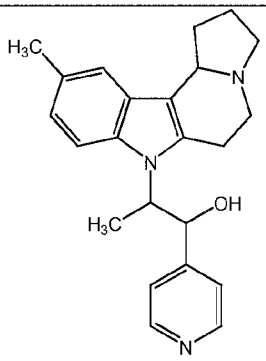
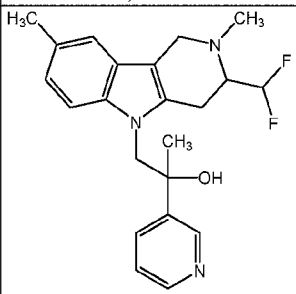
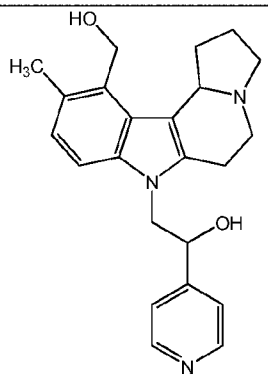
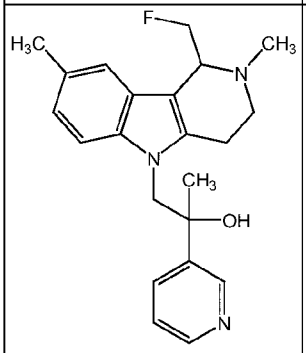
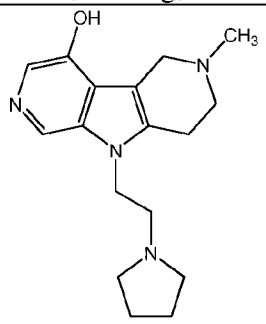
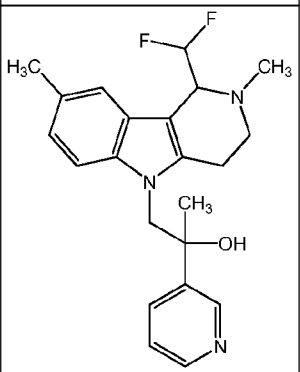
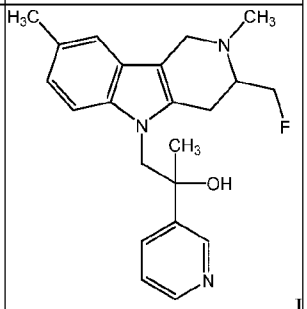
II-274
II-274a, II-274b

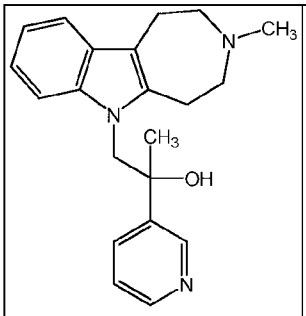
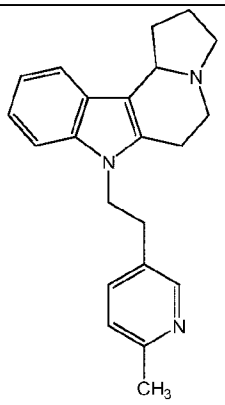
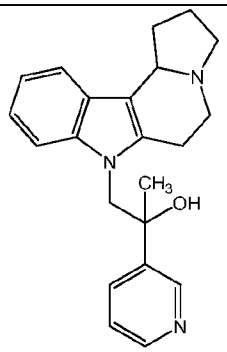
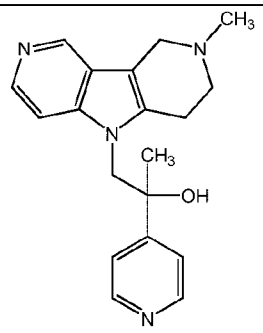
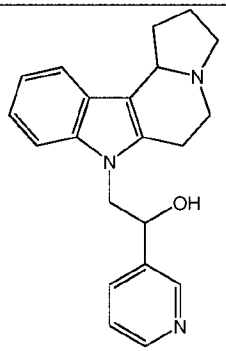
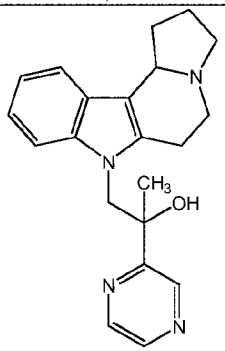
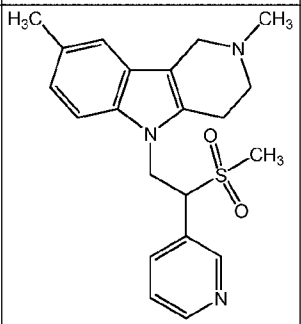
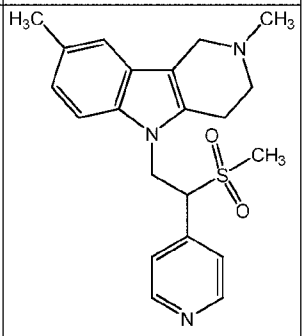
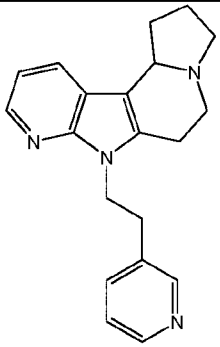
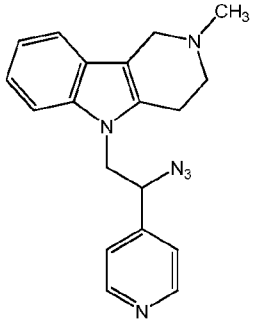
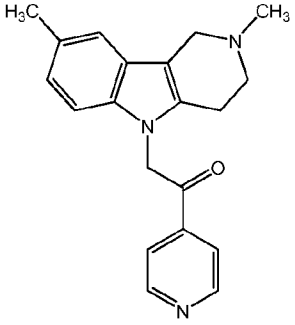


II-275
II-275a, II-275b, II-275c, II-275d

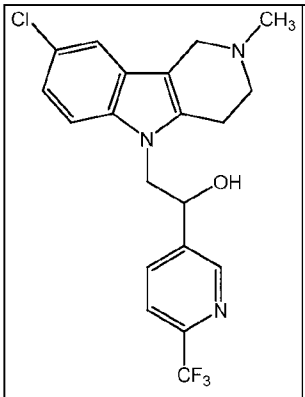


II-276
II-276a, II-276b, II-276c, II-276d

 II-277 II-277a, II-277b	 II-278 II-278a, II-278b	 II-279 II-279a, II-279b, II-279c, II-279d	 II-280 II-280a, II-280b, II-280c, II-280d
 II-281 II-281a, II-281b, II-281c, II-281d	 II-282 II-282a, II-282b, II-282c, II-282d, II-282e, II-282f, II-282g, II-282h	 II-283 II-283a, II-283b, II-283c, II-283d	 II-284 II-284a, II-284b, II-284c, II-284d
 II-285 II-285a, II-285b, II-285c, II-285d	 II-286	 II-287 II-287a, II-287b, II-287c, II-287d	 II-288 II-288a, II-288b, II-288c, II-288d

 II-289 II-289a, II-289b	 II-290 II-290a, II-290b	 II-291 II-291a, II-291b, II-291c, II-291d	 II-292 II-292a, II-292b
 II-293 II-293a, II-293b, II-293c, II-293d	 II-294 II-294a, II-294b, II-294c, II-294d	 II-295 II-295a, II-295b	 II-296 II-296a, II-296b
 II-297 II-297a, II-297b	 II-298 II-298a, II-298b	 II-299	

[0632] Table 3. Representative Compounds of the Invention.



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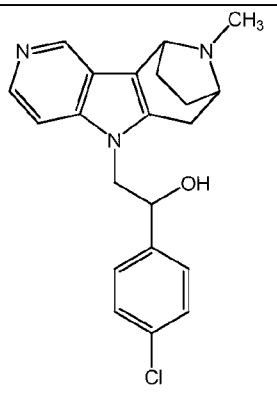
III-1a, III-1b



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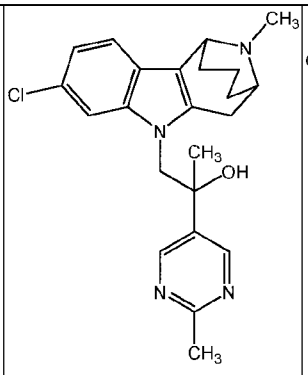
III-2a, III-2b, III-2c, III-2d



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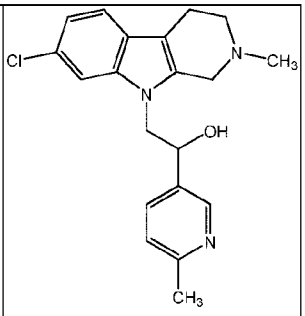
III-3a, III-3b, III-3c, III-3d



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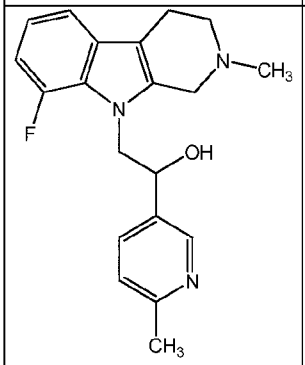
III-4a, III-4b



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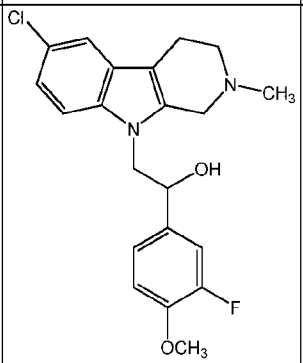
III-5a, III-5b



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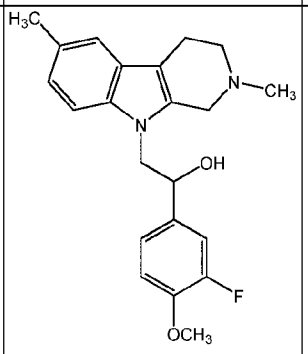
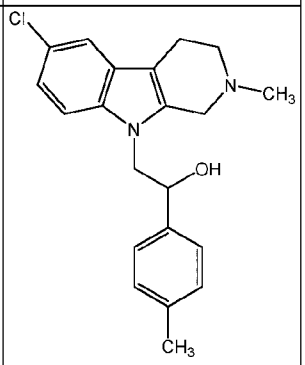
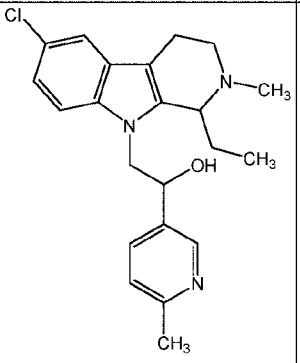
III-6a, III-6b



III-7
III-7a, III-7b



III-8
III-8a, III-8b



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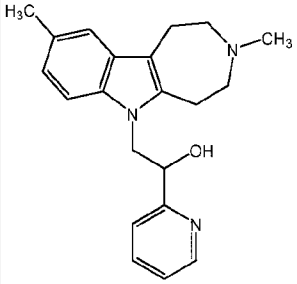

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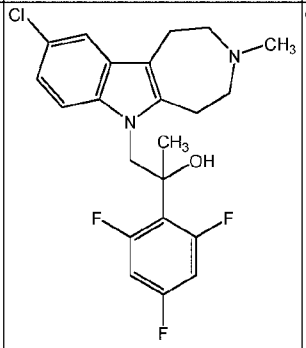
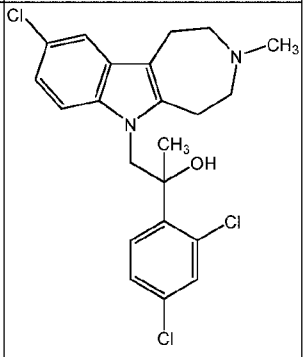
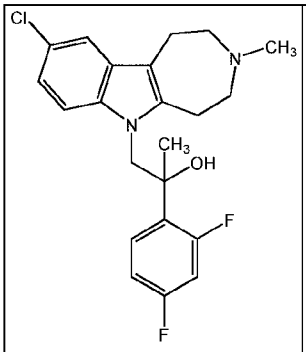
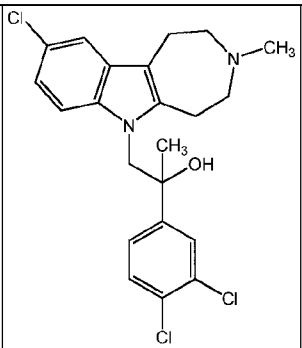
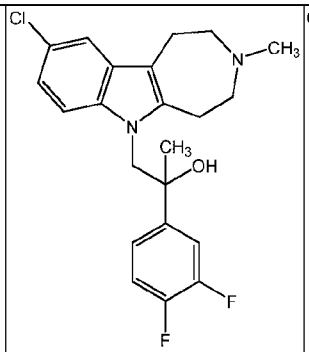
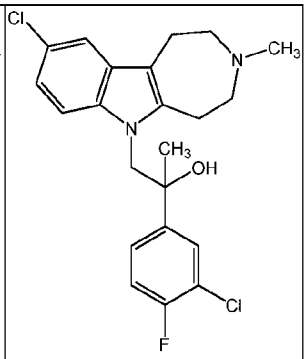
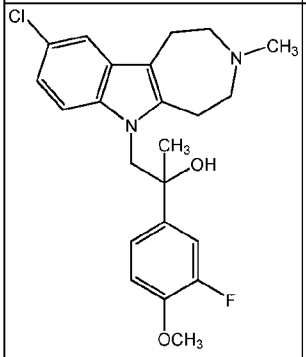
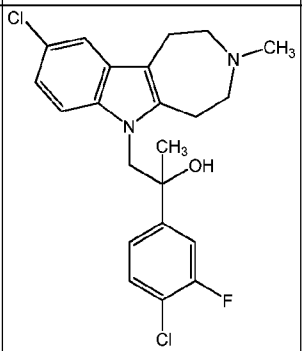
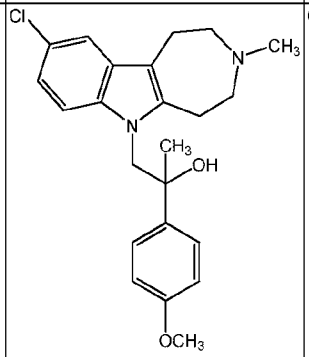
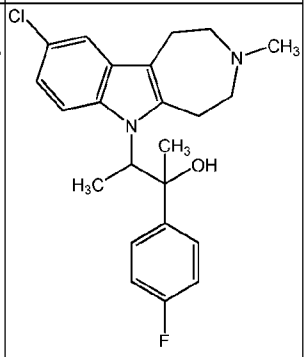
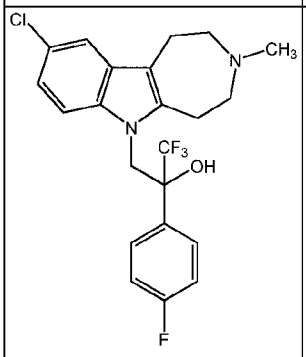
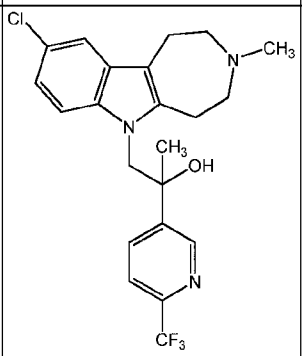
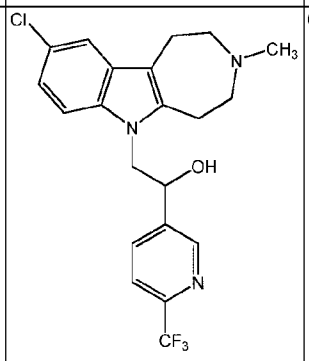
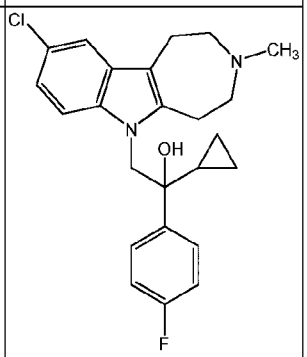
III-10a, III-10b

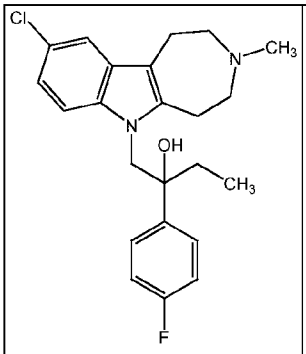
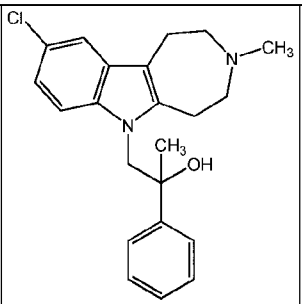
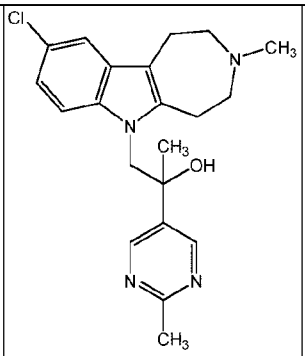
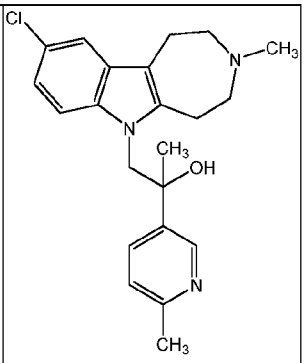
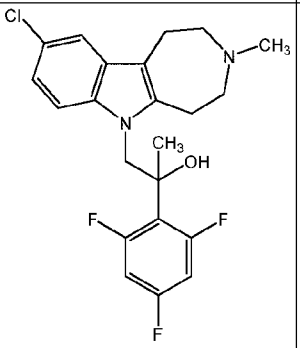
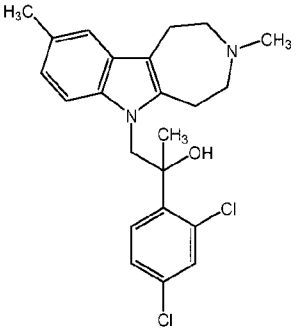
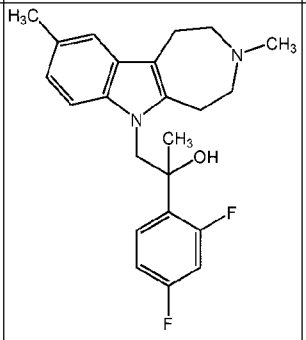
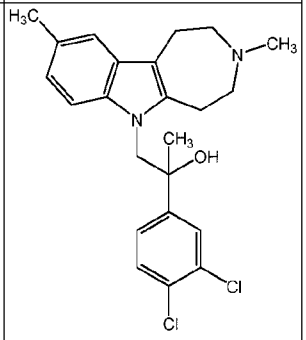
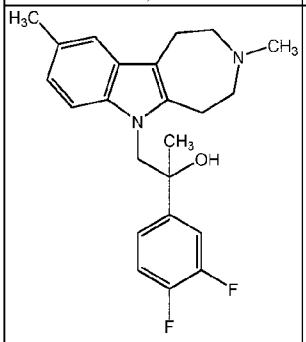
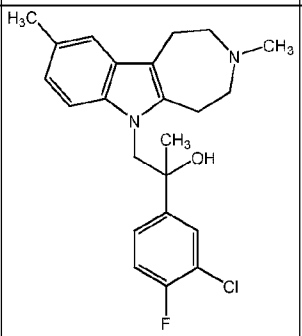
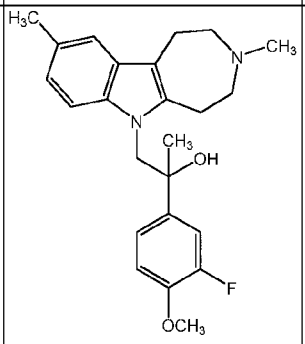
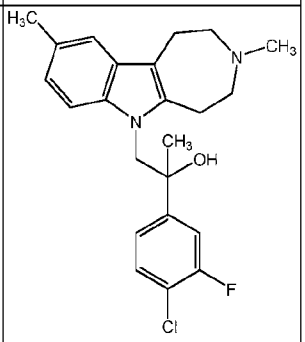


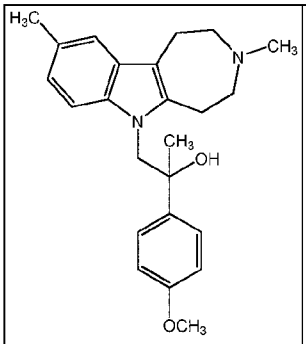
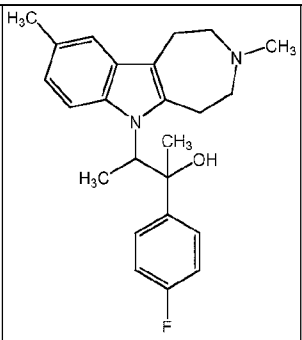
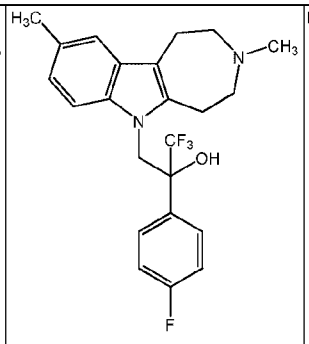
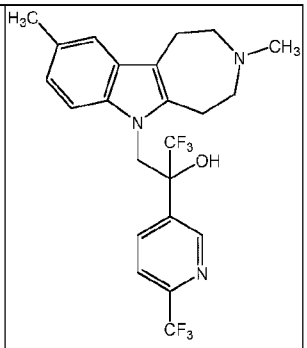
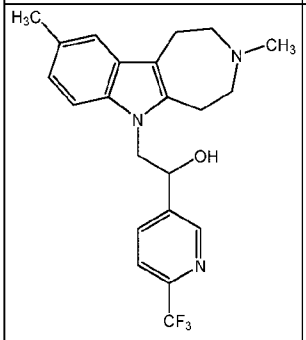
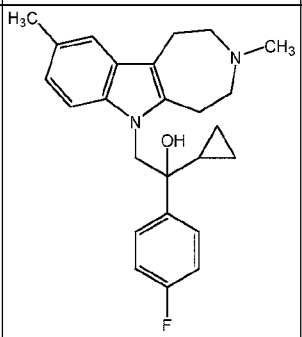
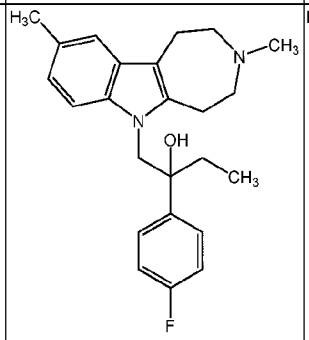
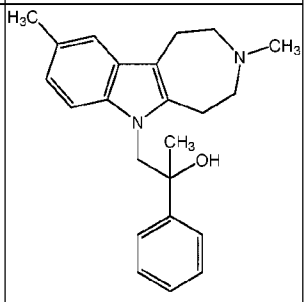
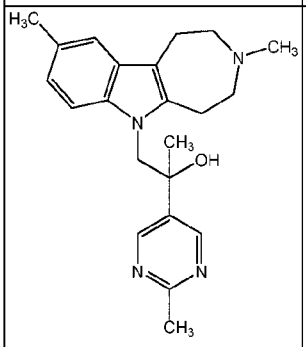
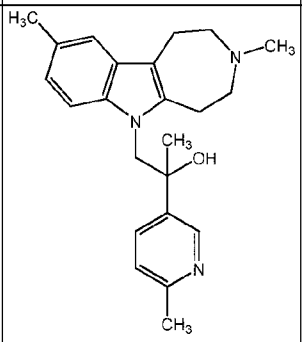
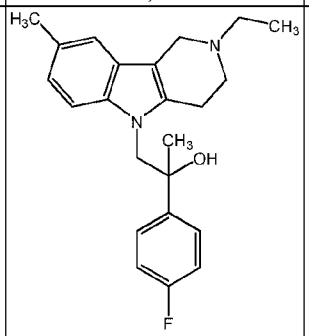
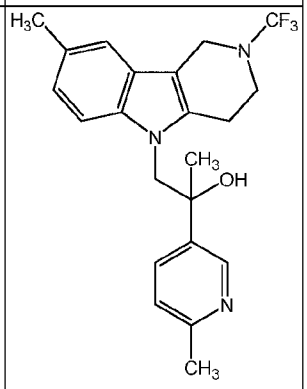
III-11
III-11a, III-11b

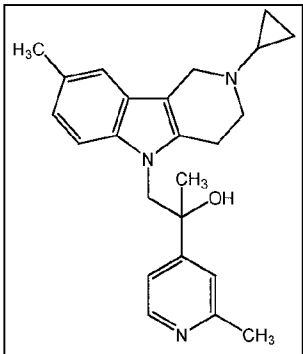
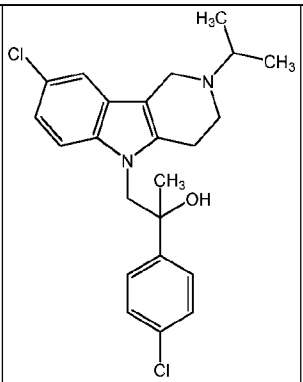
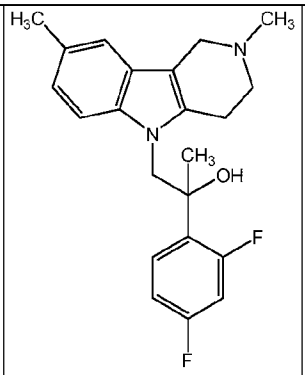
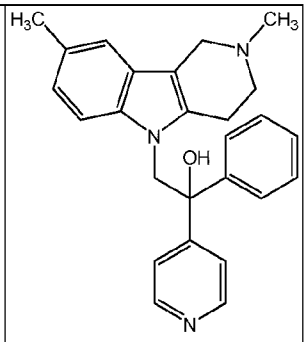
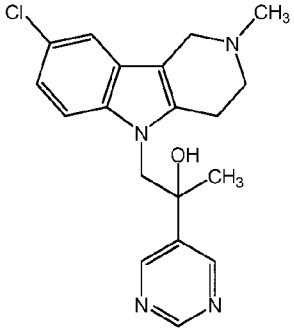
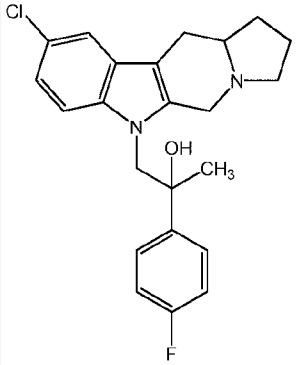
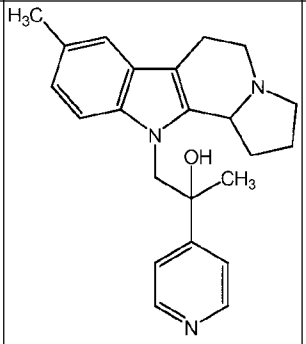
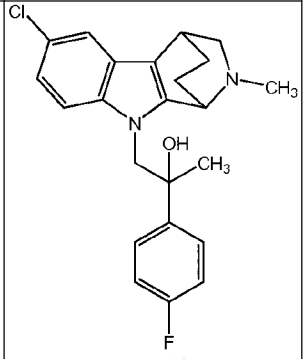
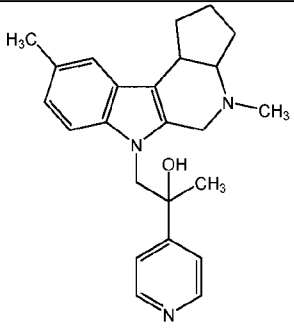
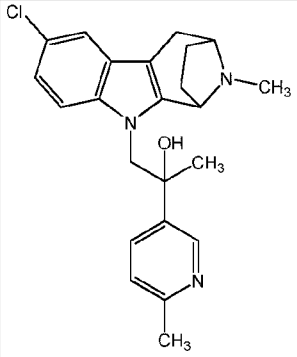
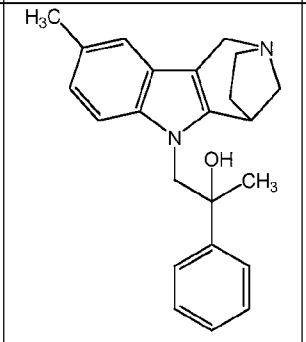
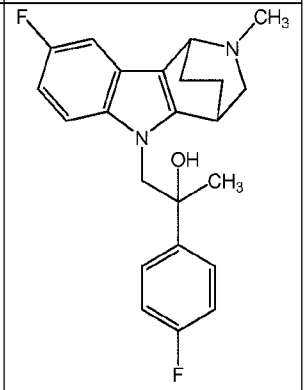


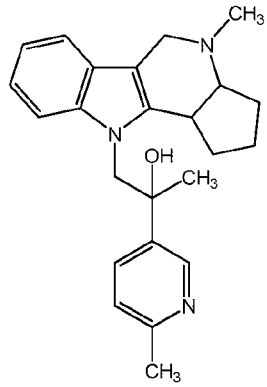
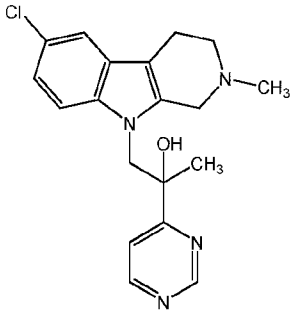
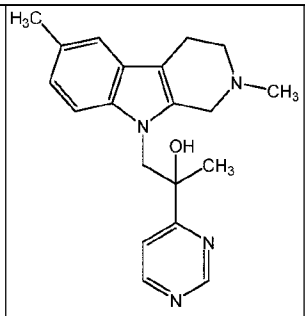
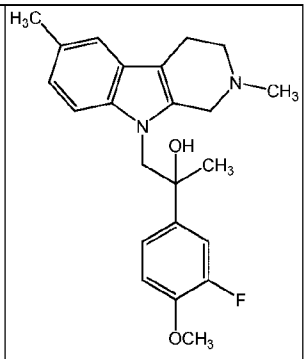
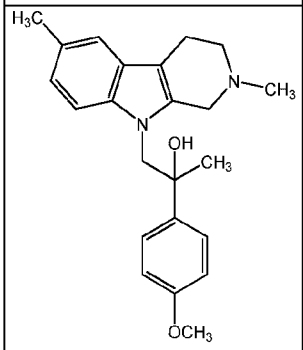
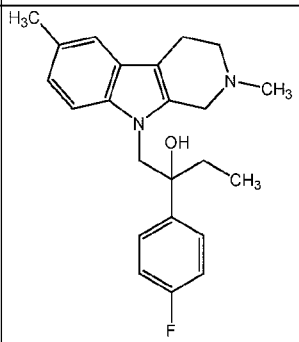
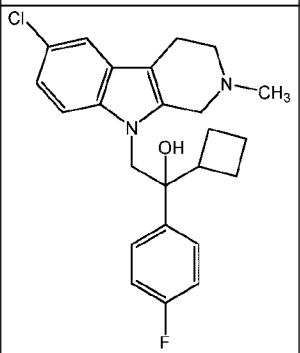
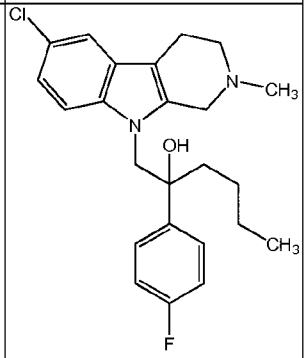
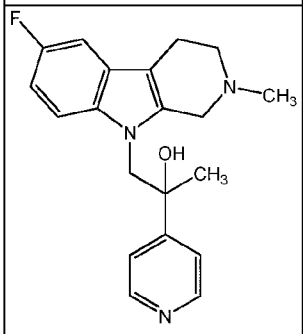
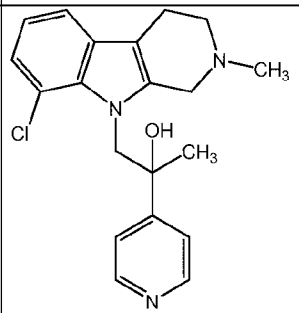
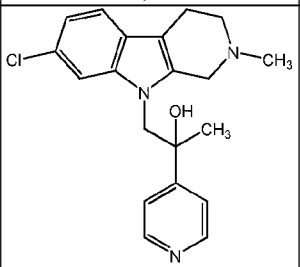
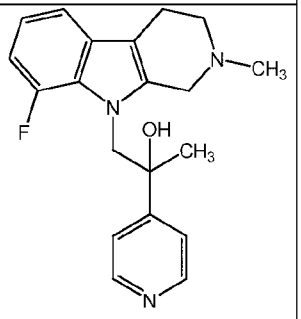
III-12
III-12a, III-12b

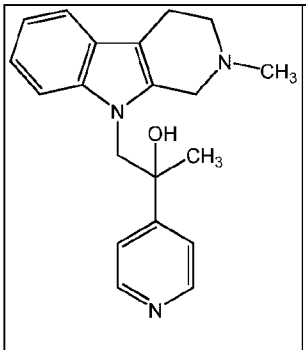
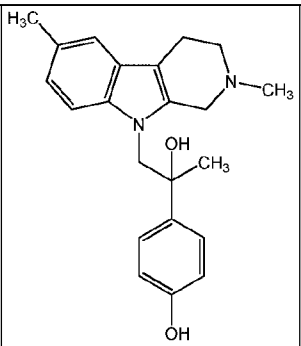
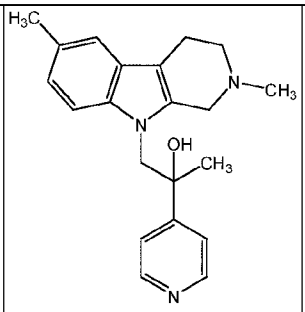
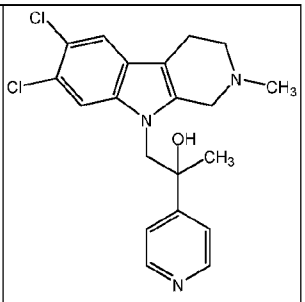
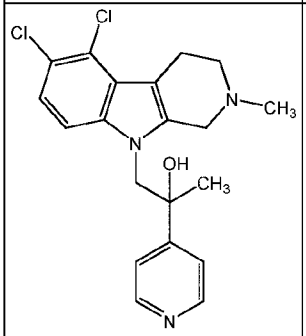
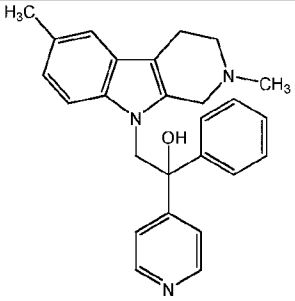
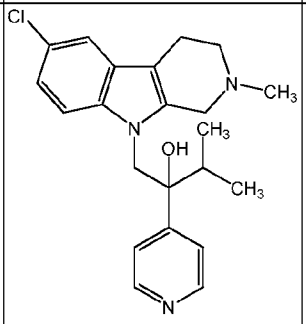
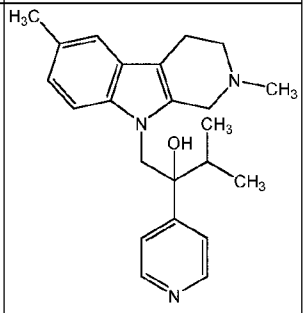
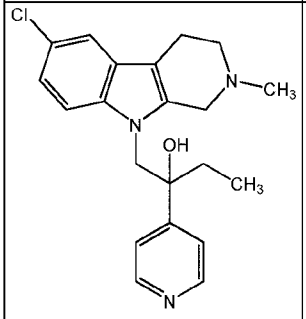
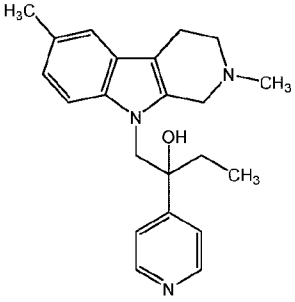
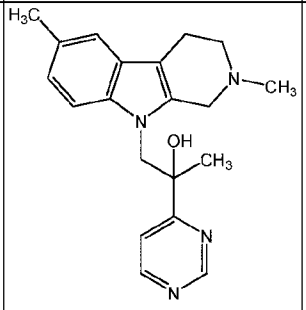
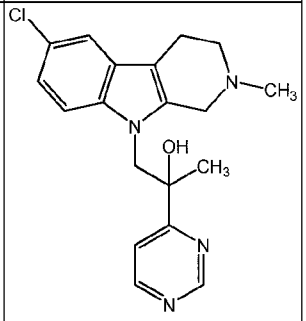
 III-13 III-13a, III-13b	 III-14 III-14a, III-14b	 III-15 III-15a, III-15b	 III-16 III-16a, III-16b
 III-17 III-17a, III-17b	 III-18 III-18a, III-18b	 III-19 III-19a, III-19b	 III-20 III-20a, III-20b, III-20c, III-20d
 III-21 III-21a, III-21b	 III-22 III-22a, III-22b	 III-23 III-23a, III-23b	 III-24 III-24a, III-24b

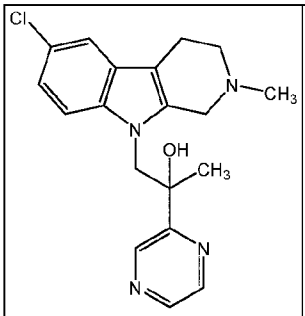
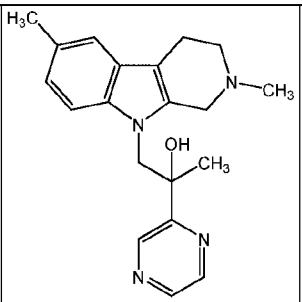
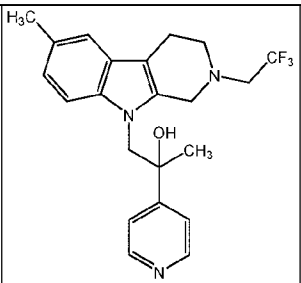
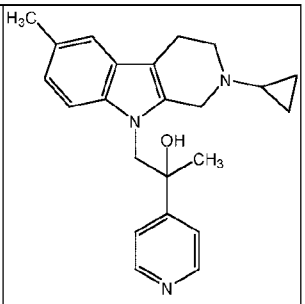
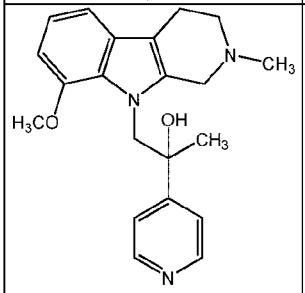
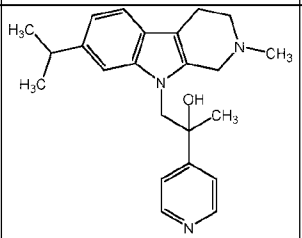
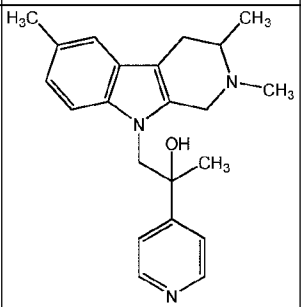
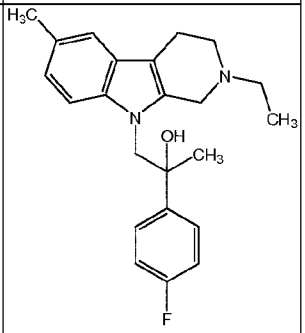
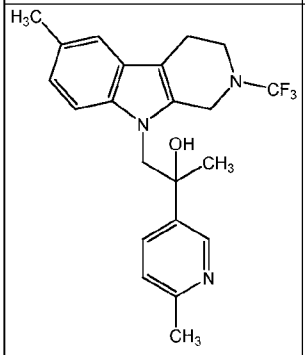
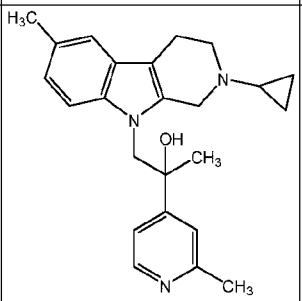
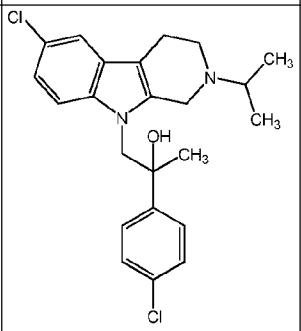
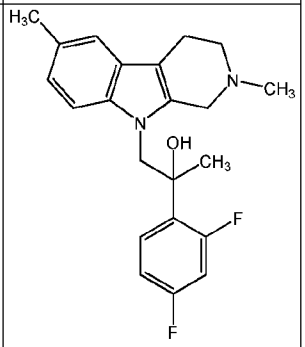
 III-25 III-25a, III-25b	 III-26 III-26a, III-26b	 III-27 III-27a, III-27b	 III-28 III-28a, III-28b
 III-29 III-29a, III-29b	 III-30 III-30a, III-30b	 III-31 III-31a, III-31b	 III-32 III-32a, III-32b
 III-33 III-33a, III-33b	 III-34 III-34a, III-34b	 III-35 III-35a, III-35b	 III-36 III-36a, III-36b

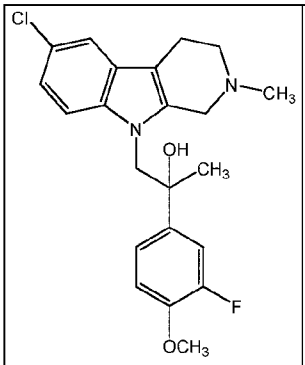
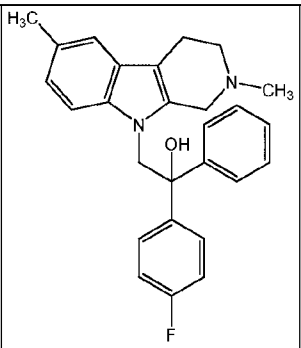
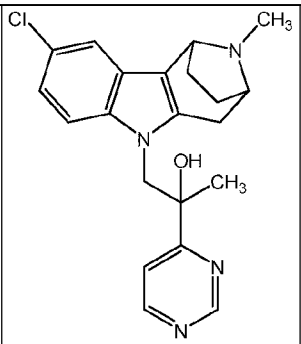
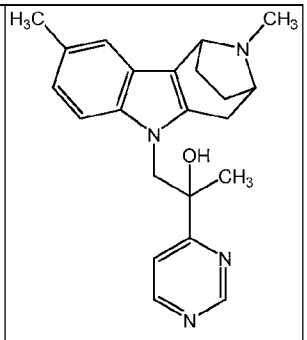
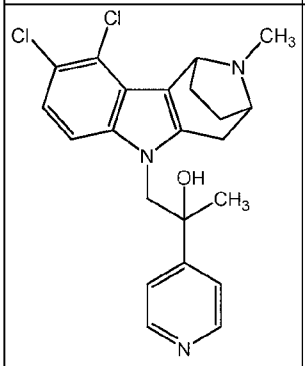
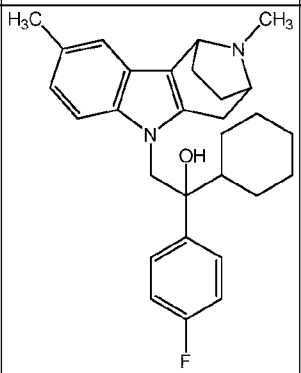
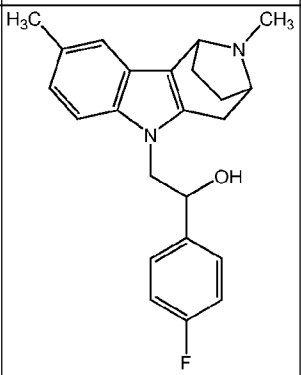
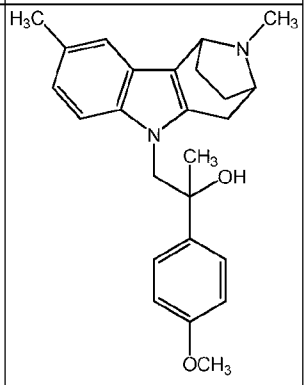
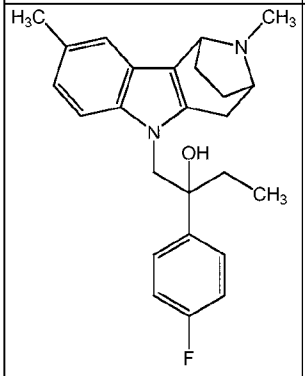
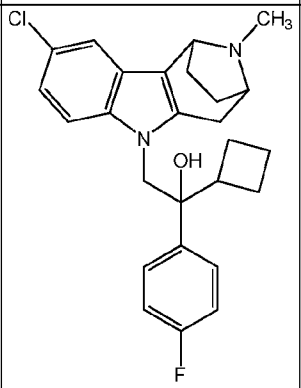
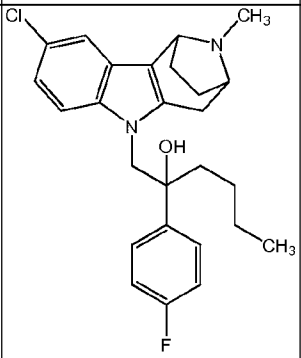
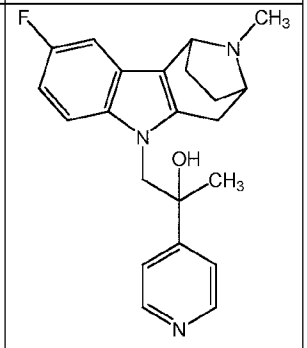
 III-37 III-37a, III-37b	 III-38 III-38a, III-38b, III-38c, III-38d	 III-39 III-39a, III-39b	 III-40 III-40a, III-40b
 III-41 III-41a, III-41b	 III-42 III-42a, III-42b	 III-43 III-43a, III-43b	 III-44 III-44a, III-44b
 III-45 III-45a, III-45b	 III-46 III-46a, III-46b	 III-47 III-47a, III-47b	 III-48 III-48a, III-48b

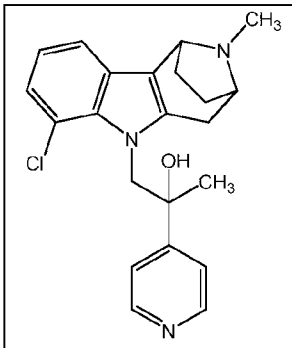
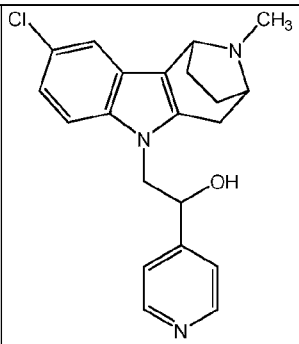
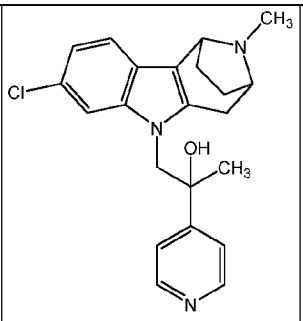
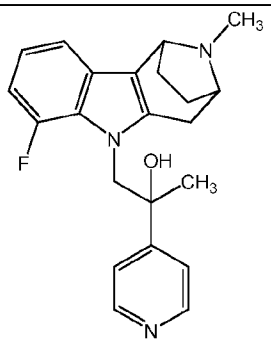
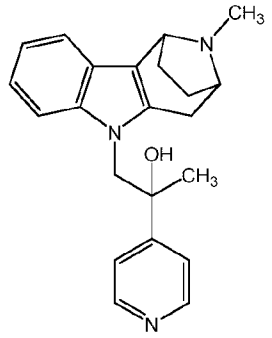
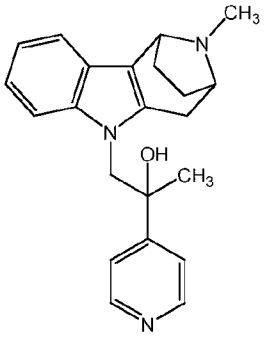
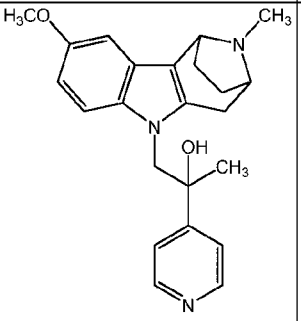
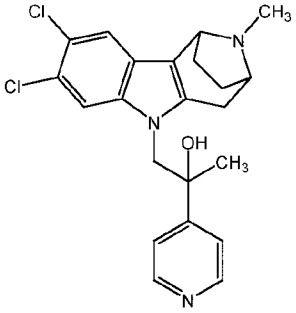
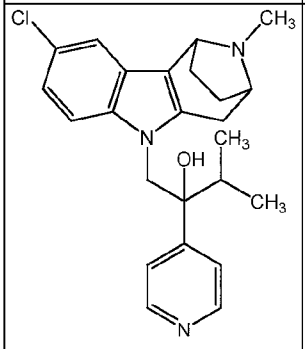
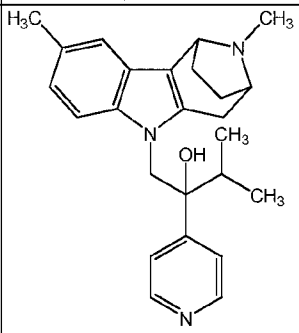
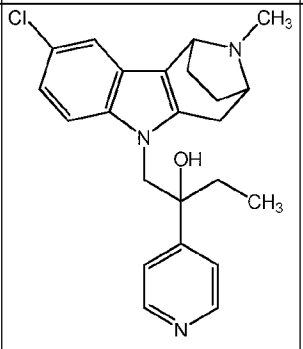
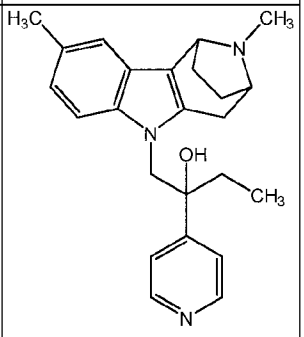
 III-49 III-49a, III-49b	 III-50 III-50a, III-50b	 III-51 III-51a, III-51b	 III-52 III-52a, III-52b
 III-53 III-53a, III-53b	 III-54 III-54a, III-54b, III-54c, III-54d	 III-55 III-55a, III-55b, III-55c, III-55d	 III-56 III-56a, III-56b, III-56c, III-56d
 III-57 III-57a, III-57b, III-57c, III-57d	 III-58 III-58a, III-58b, III-58c, III-58d	 III-59 III-59a, III-59b, III-59c, III-59d	 III-60 III-60a, III-60b, III-60c, III-60d

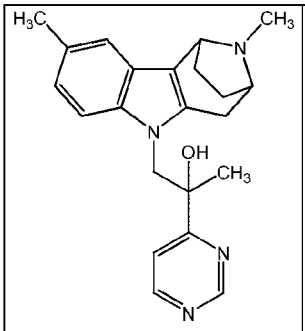
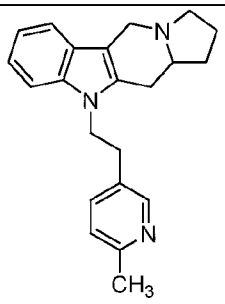
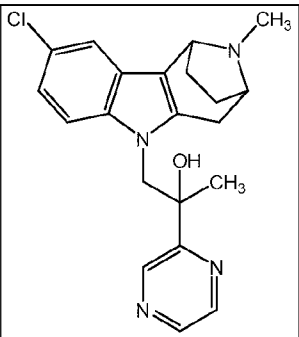
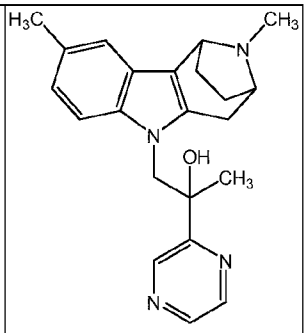
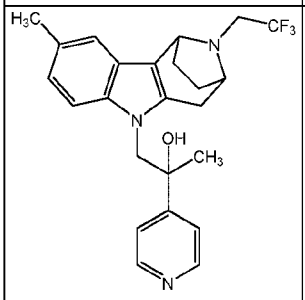
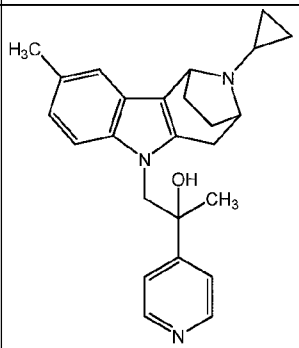
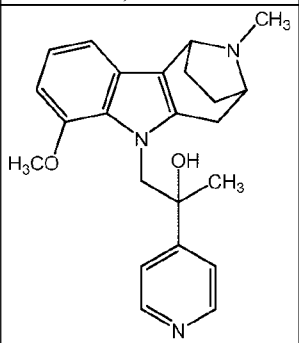
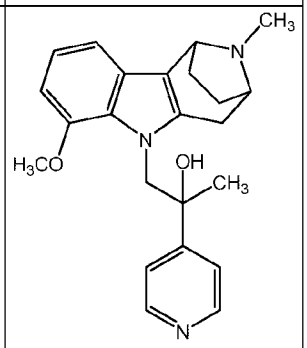
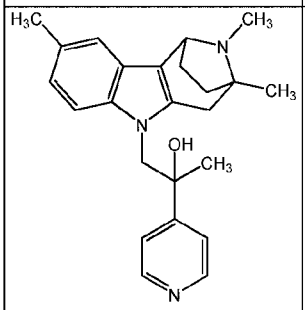
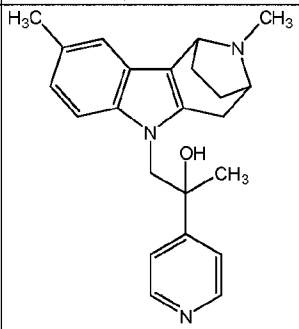
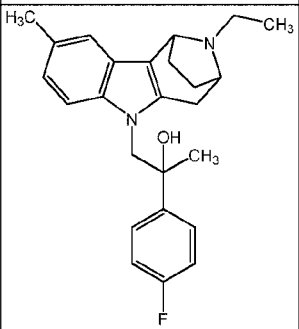
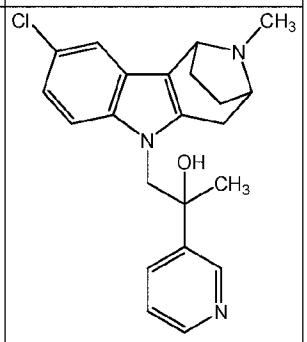
 III-61 III-61a, III-61b, III-61c, III-61d	 III-62 III-62a, III-62b	 III-63 III-63a, III-63b	 III-64 III-64a, III-64b
 III-65 III-65a, III-65b	 III-66 III-66a, III-66b	 III-67 III-67a, III-67b	 III-68 III-68a, III-68b
 III-69 III-69a, III-69b	 III-70 III-70a, III-70b	 III-71 III-71a, III-71b	 III-72 III-72a, III-72b

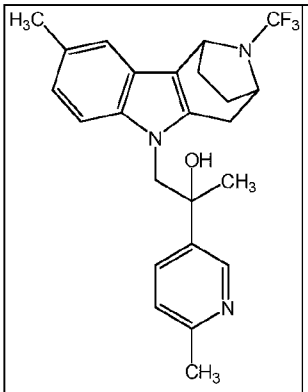
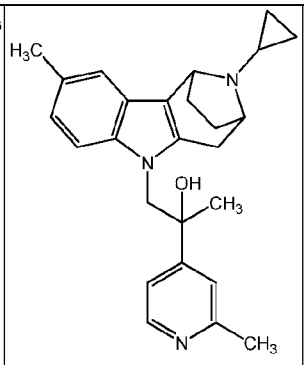
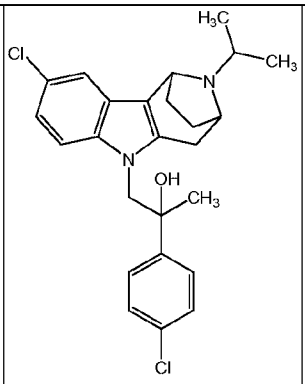
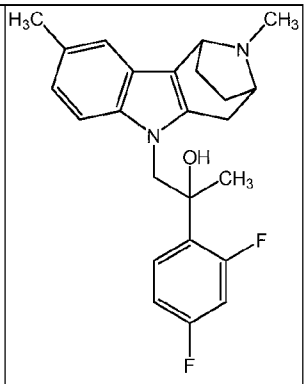
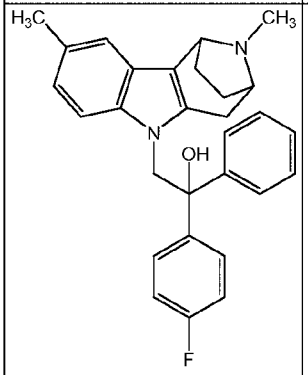
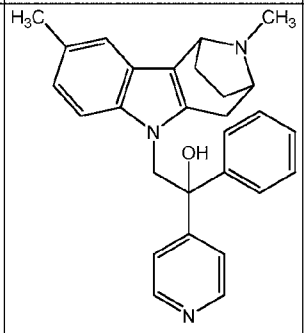
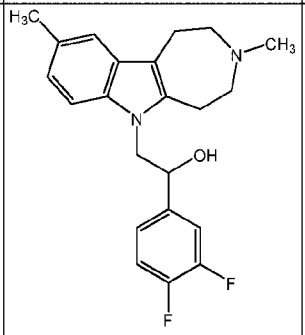
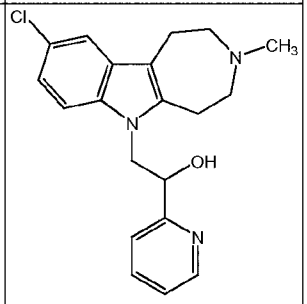
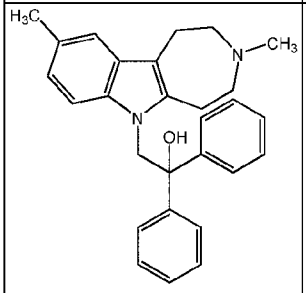
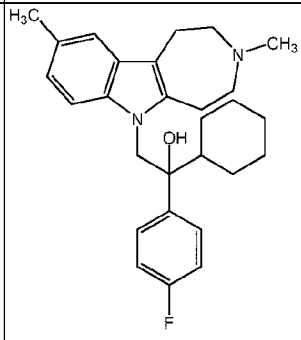
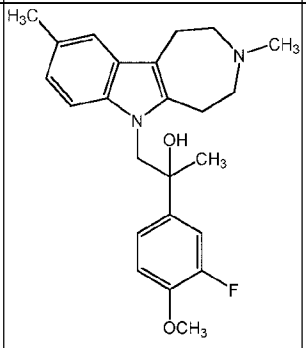
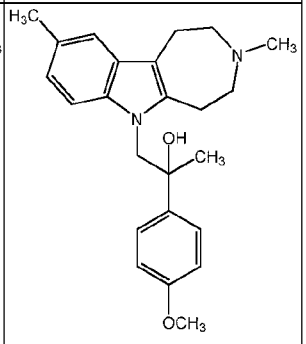
 III-73 III-73a, III-73b	 III-74 III-74a, III-74b	 III-75 III-75a, III-75b	 III-76 III-76a, III-76b
 III-77 III-77a, III-77b	 III-78 III-78a, III-78b	 III-79 III-79a, III-79b	 III-80 III-80a, III-80b
 III-81 III-81a, III-81b	 III-82 III-82a, III-82b	 III-83 III-83a, III-83b	 III-84 III-84a, III-84b

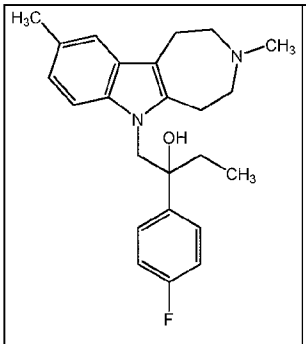
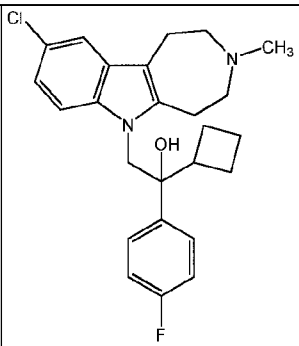
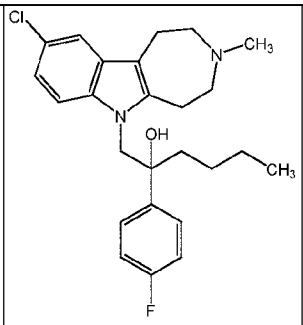
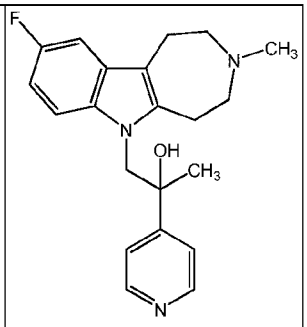
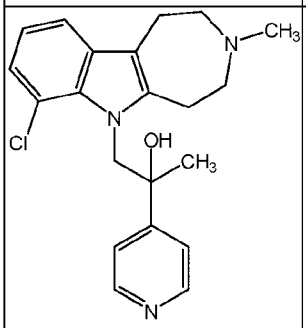
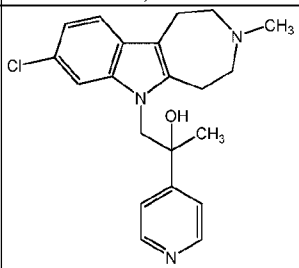
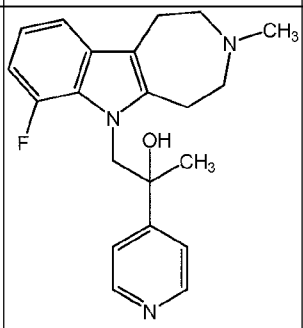
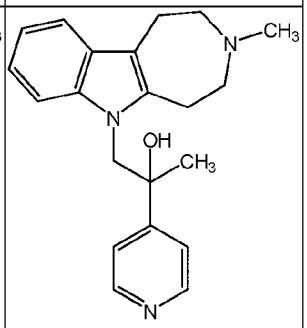
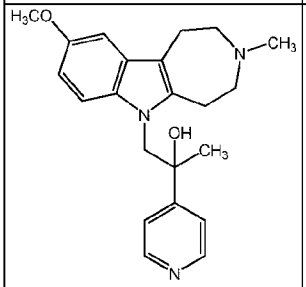
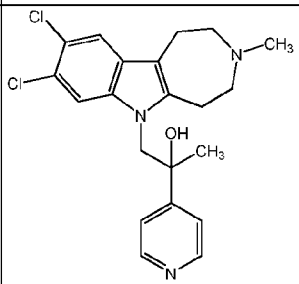
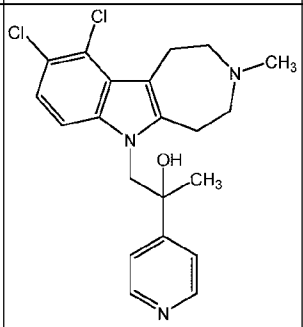
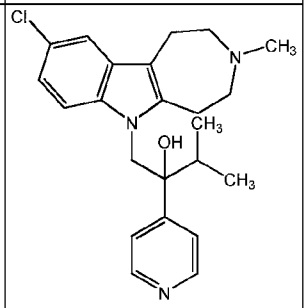
 III-85 III-85a, III-85b	 III-86 III-86a, III-86b	 III-87 III-87a, III-87b	 III-88 III-88a, III-88b
 III-89 III-89a, III-89b	 III-90 III-90a, III-90b	 III-91 III-91a, III-91b, III-91c, III-91d	 III-92 III-92a, III-92b
 III-93 III-93a, III-93b	 III-94 III-94a, III-94b	 III-95 III-95a, III-95b	 III-96 III-96a, III-96b

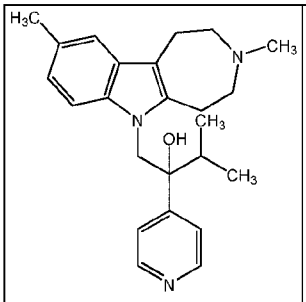
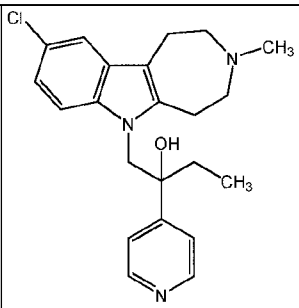
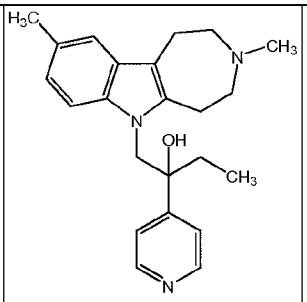
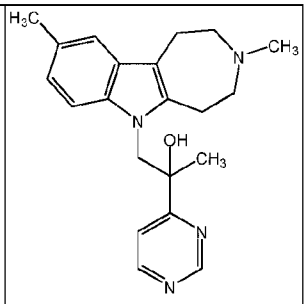
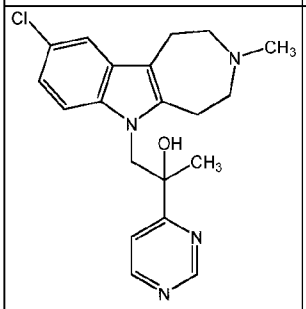
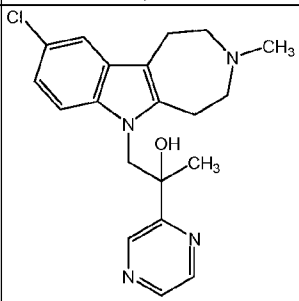
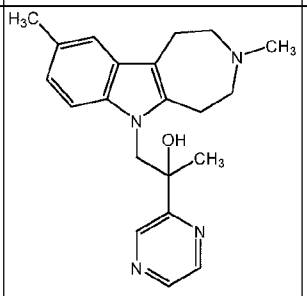
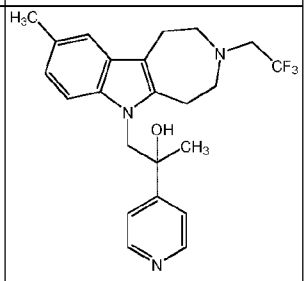
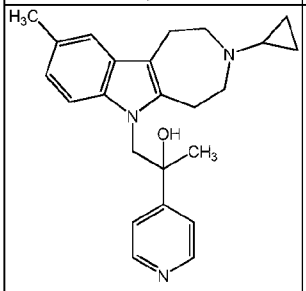
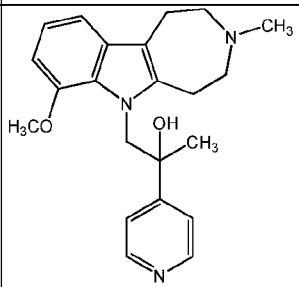
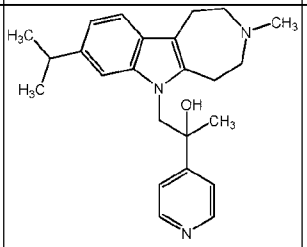
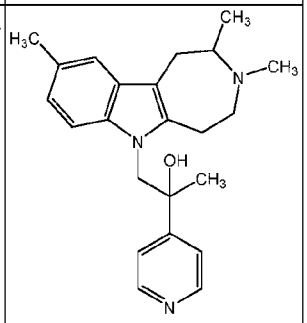
 III-97 III-97a, III-97b	 III-98 III-98a, III-98b	 III-99 III-99a, III-99b, III-99c, III-99d	 III-100 III-100a, III-100b, III-100c, III-100d
 III-101 III-101a, III-101b, III-101c, III-101d	 III-102 III-102a, III-102b, III-102c, III-102d	 III-103 III-103a, III-103b, III-103c, III-103d	 III-104 III-104a, III-104b, III-104c, III-104d
 III-105 III-105a, III-105b, III-105c, III-105d	 III-106 III-106a, III-106b, III-106c, III-106d	 III-107 III-107a, III-107b, III-107c, III-107d	 III-108 III-108a, III-108b, III-108c, III-108d

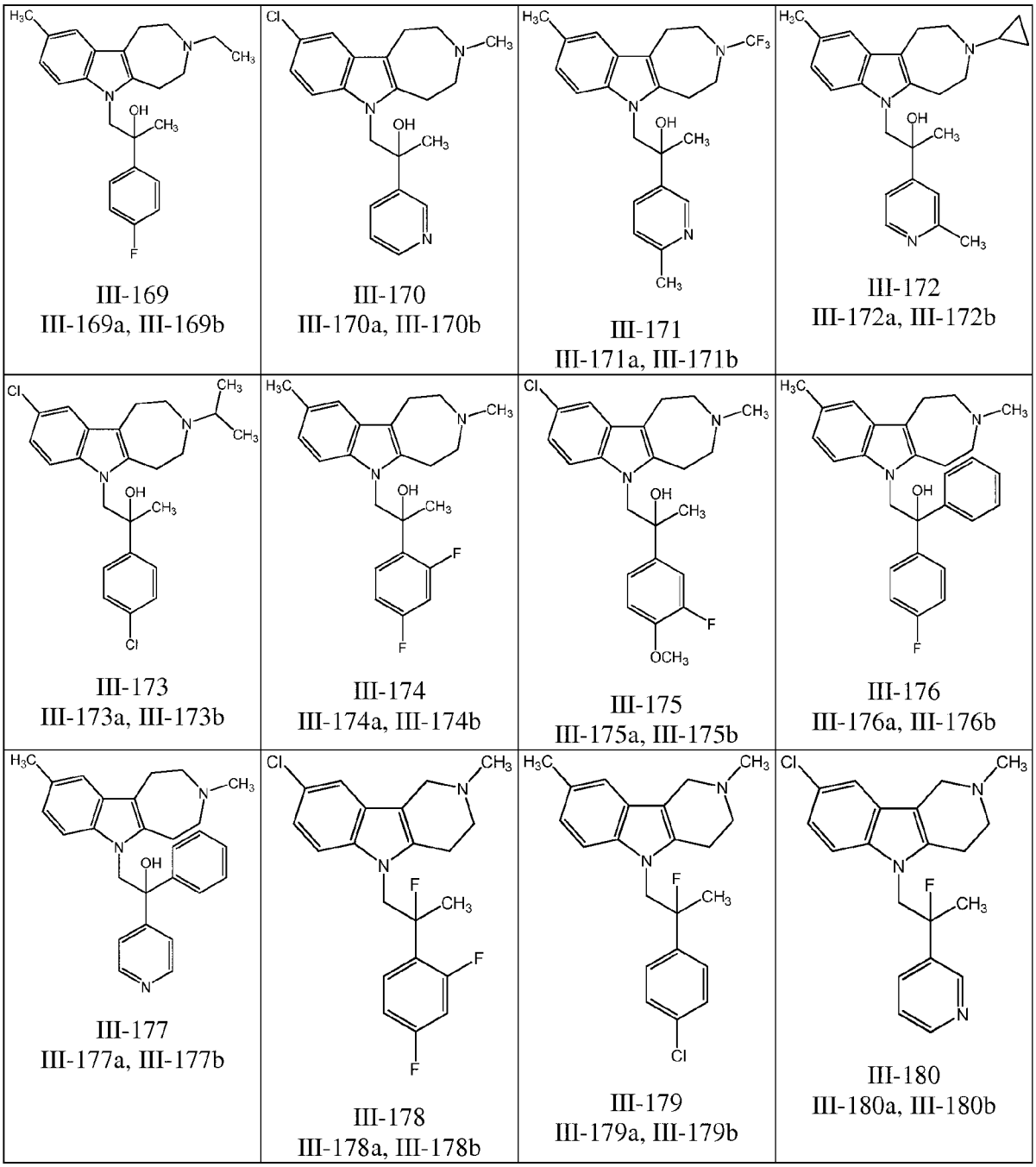
 III-109 III-109a, III-109b, III-109c, III-109d	 III-110 III-110a, III-110b, III-110c, III-110d	 III-111 III-111a, III-111b, III-111c, III-111d	 III-112 III-112a, III-112b, III-112c, III-112d
 III-113 III-113a, III-113b, III-113c, III-113d	 III-114 III-114a, III-114b, III-114c, III-114d	 III-115 III-115a, III-115b, III-115c, III-115d	 III-116 III-116a, III-116b, III-116c, III-116d
 III-117 III-117a, III-117b, III-117c, III-117d	 III-118 III-118a, III-118b, III-118c, III-118d	 III-119 III-119a, III-119b, III-119c, III-119d	 III-120 III-120a, III-120b, III-120c, III-120d

 III-121 III-121a, III-121b, III-121c, III-121d	 III-122 III-122a, III-122b, III-122c, III-122d	 III-123 III-123a, III-123b, III-123c, III-123d	 III-124 III-124a, III-124b, III-124c, III-124d
 III-125 III-125a, III-125b, III-125c, III-125d	 III-126 III-126a, III-126b, III-126c, III-126d	 III-127 III-127a, III-127b, III-127c, III-127d	 III-128 III-128a, III-128b, III-128c, III-128d
 III-129 III-129a, III-129b, III-129c, III-129d	 III-130 III-130a, III-130b, III-130c, III-130d	 III-131 III-131a, III-131b, III-131c, III-131d	 III-132 III-132a, III-132b, III-132c, III-132d

 III-133 III-133a, III-133b, III-133c, III-133d	 III-134 III-134a, III-134b, III-134c, III-134d	 III-135 III-135a, III-135b, III-135c, III-135d	 III-136 III-136a, III-136b, III-136c, III-136d
 III-137 III-137a, III-137b, III-137c, III-137d	 III-138 III-138a, III-138b, III-138c, III-138d	 III-139 III-139a, III-139b	 III-140 III-140a, III-140b
 III-141	 III-142 III-142a, III-142b	 III-143 III-143a, III-143b	 III-144 III-144a, III-144b

 III-145 III-145a, III-145b	 III-146 III-146a, III-146b	 III-147 III-147a, III-147b	 III-148 III-148a, III-148b
 III-149 III-149a, III-149b	 III-150 III-150a, III-150b	 III-151 III-151a, III-151b	 III-152 III-152a, III-152b
 III-153 III-153a, III-153b	 III-154 III-154a, III-154b	 III-155 III-155a, III-155b	 III-156 III-156a, III-156b

 III-157 III-157a, III-157b	 III-158 III-158a, III-158b	 III-159 III-159a, III-159b	 III-160 III-160a, III-160b
 III-161 III-161a, III-161b	 III-162 III-162a, III-162b	 III-163 III-163a, III-163b	 III-164 III-164a, III-164b
 III-165 III-165a, III-165b	 III-166 III-166a, III-166b	 III-167 III-167a, III-167b	 III-168 III-168a, III-168b, III-168c, III-168d



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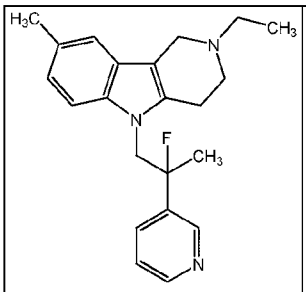

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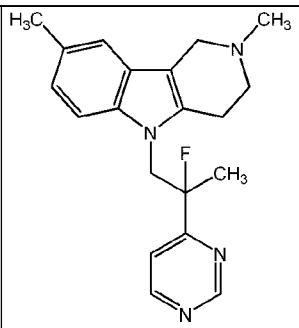

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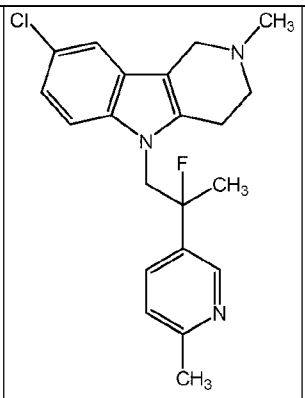

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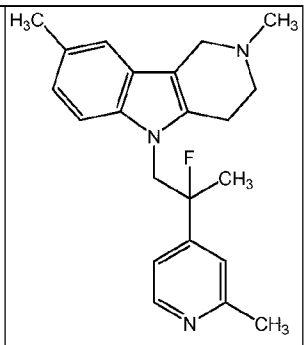

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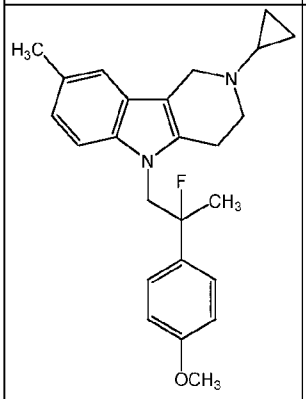

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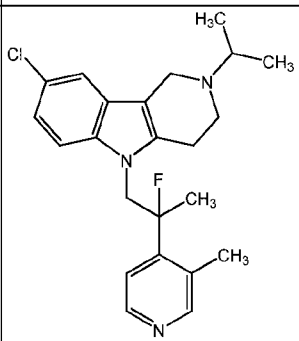

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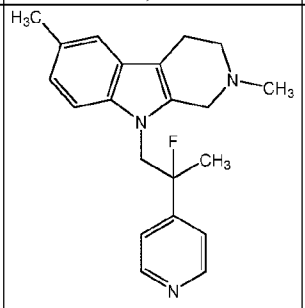

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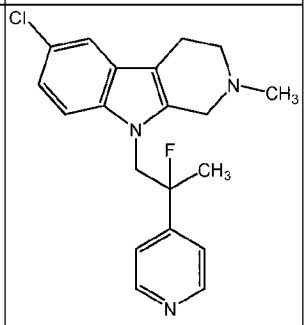

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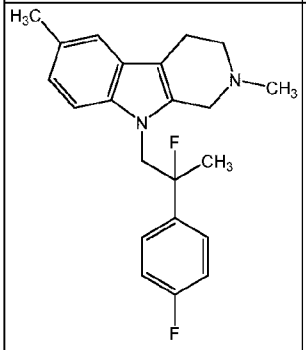

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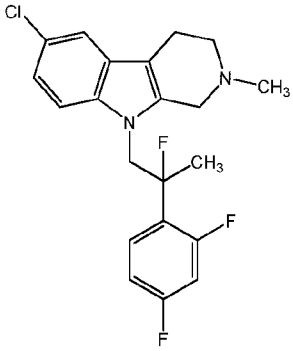

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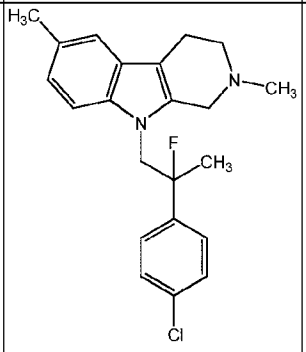

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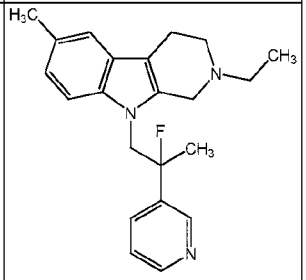

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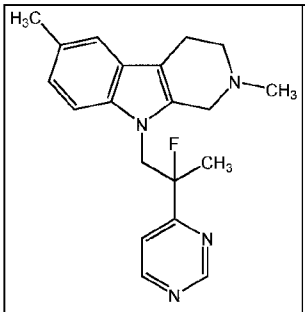
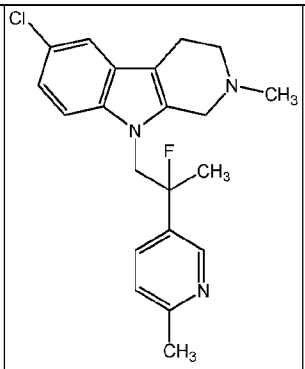
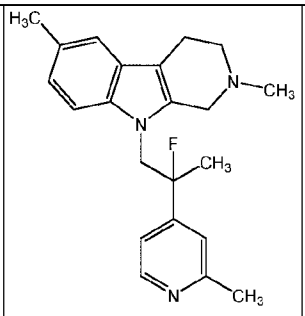
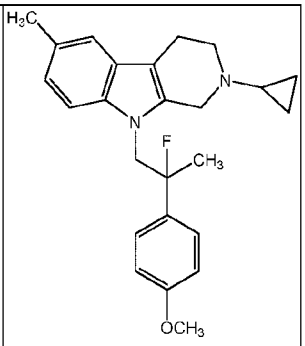
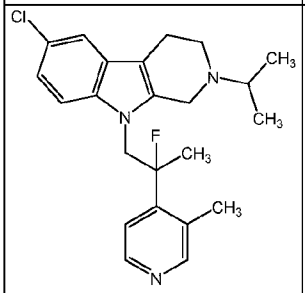
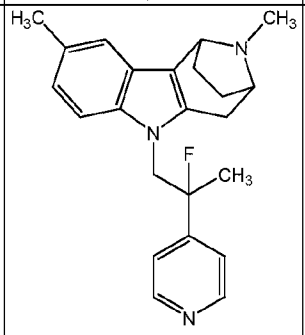
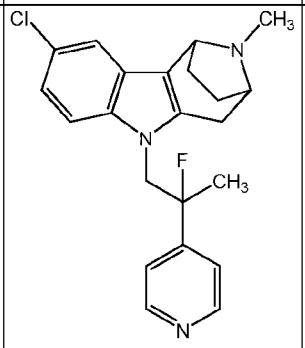
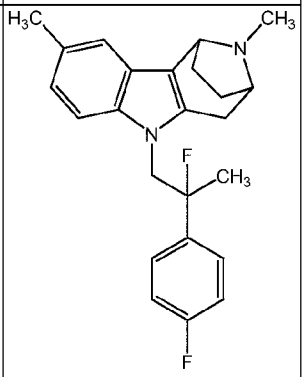
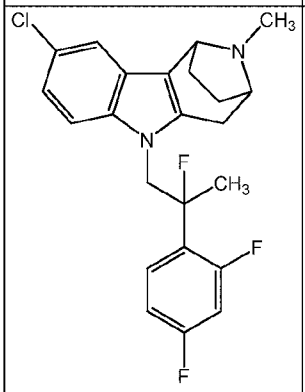
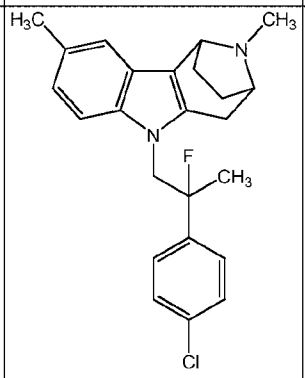
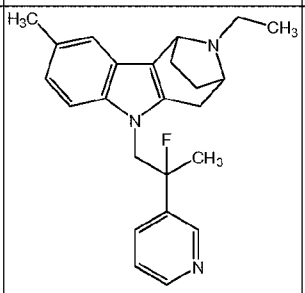
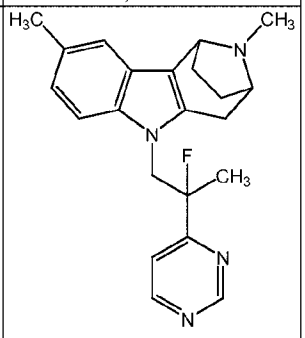
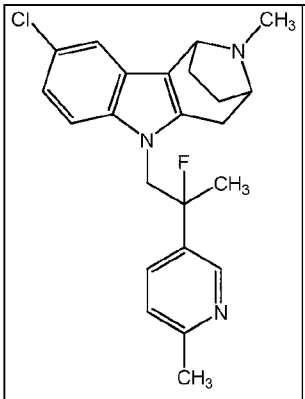
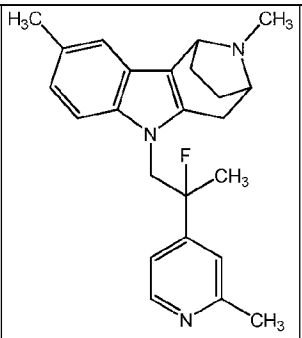
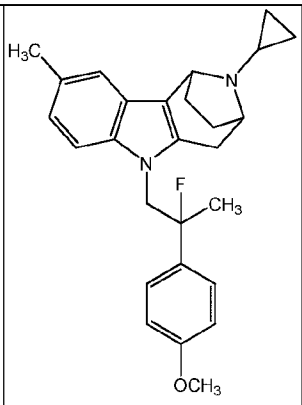
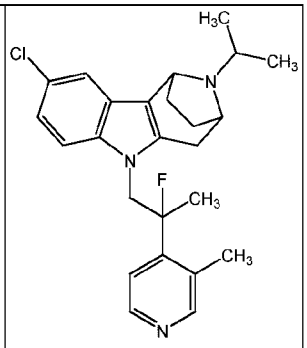
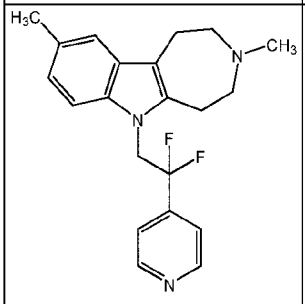
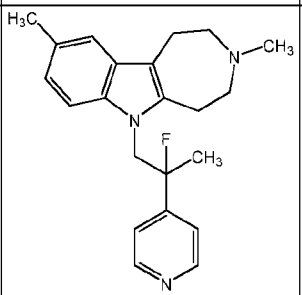
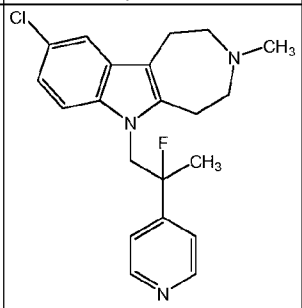
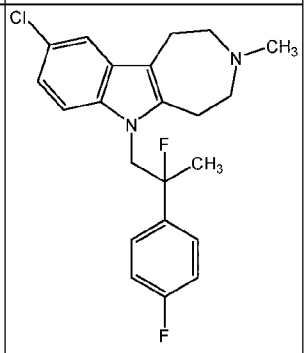
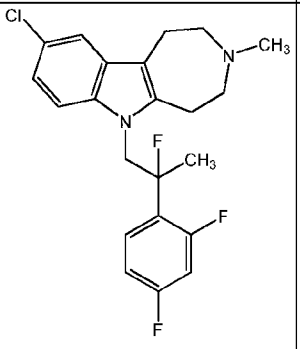
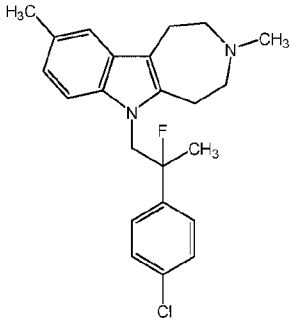
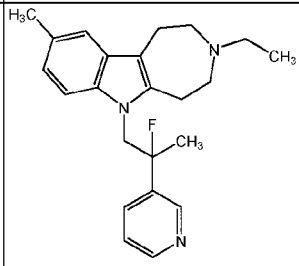
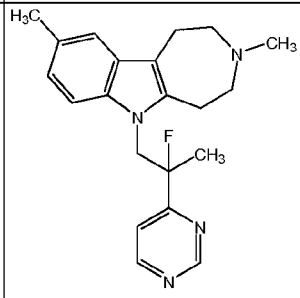
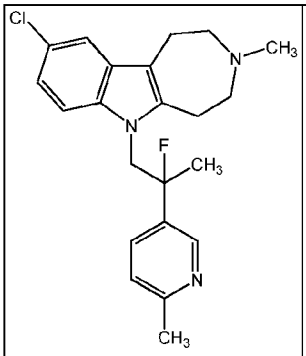
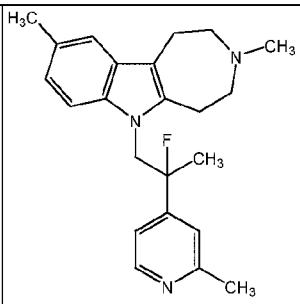
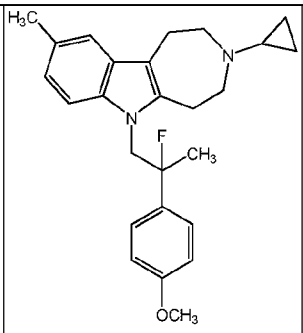
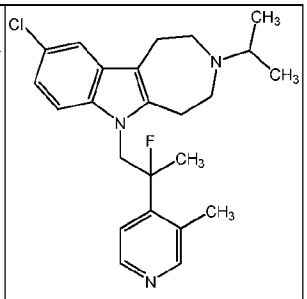
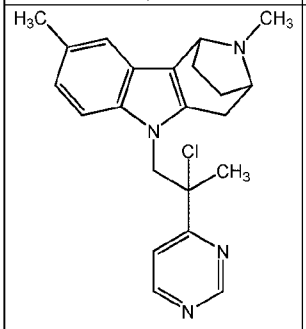
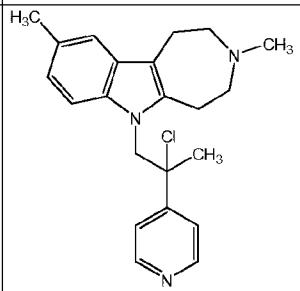
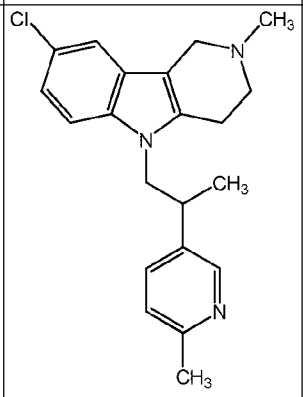
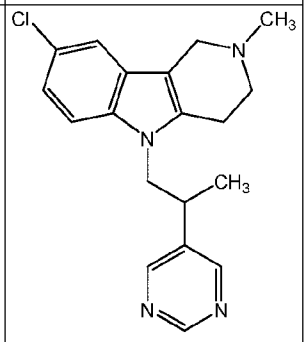
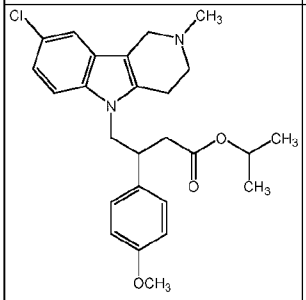
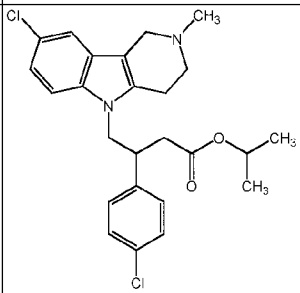
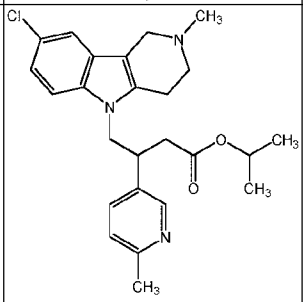
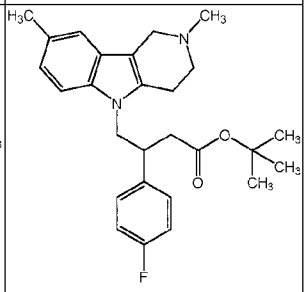
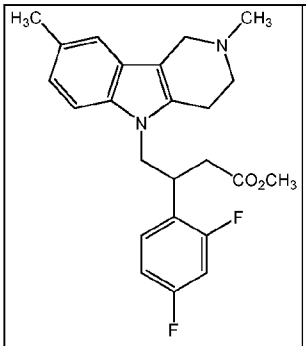
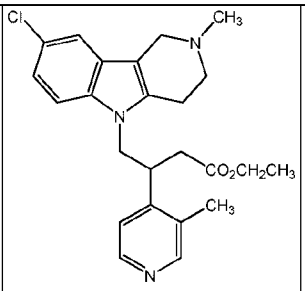
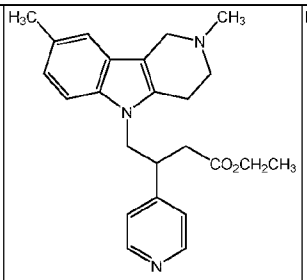
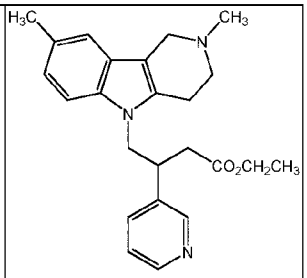
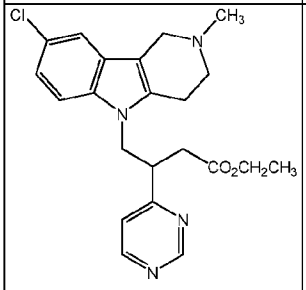
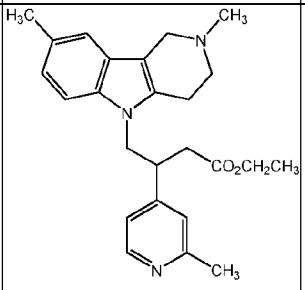
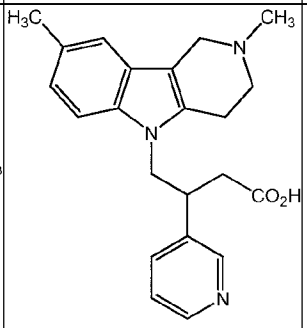
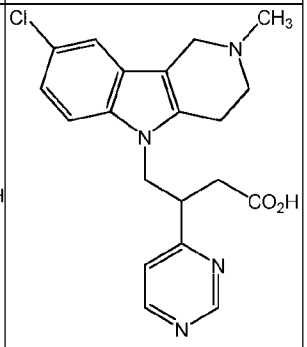
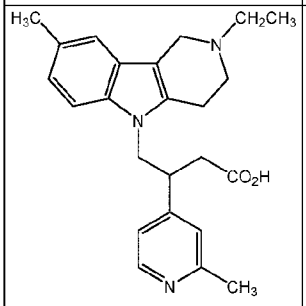
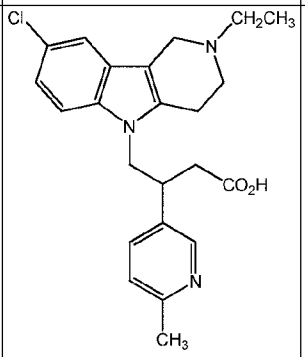
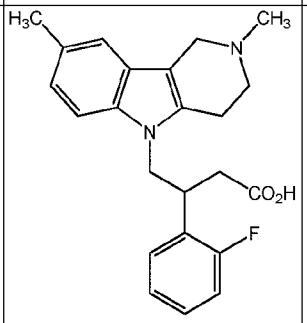
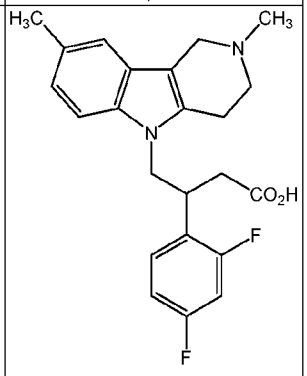
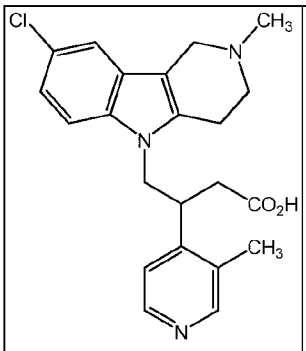
 III-193 III-193a, III-193b	 III-194 III-194a, III-194b	 III-195 III-195a, III-195b	 III-196 III-196a, III-196b
 III-197 III-197a, III-197b	 III-198 III-198a, III-198b, III-198c, III-198d	 III-199 III-199a, III-199b, III-199c, III-199d	 III-200 III-200a, III-200b, III-200c, III-200d
 III-201 III-201a, III-201b, III-201c, III-201d	 III-202 III-202a, III-202b, III-202c, III-202d	 III-203 III-203a, III-203b, III-203c, III-203d	 III-204 III-204a, III-204b, III-204c, III-204d

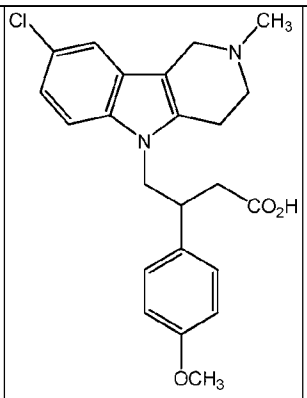
 III-205 III-205a, III-205b, III-205c, III-205d	 III-206 III-206a, III-206b, III-206c, III-206d	 III-207 III-207a, III-207b, III-207c, III-207d	 III-208 III-208a, III-208b, III-208c, III-208d
 III-209	 III-210 III-210a, III-210b	 III-211 III-211a, III-211b	 III-212 III-212a, III-212b
 III-213 III-213a, III-213b	 III-214 III-214a, III-214b	 III-215 III-215a, III-215b	 III-216 III-216a, III-216b

 III-217 III-217a, III-217b	 III-218 III-218a, III-218b	 III-219 III-219a, III-219b	 III-220 III-220a, III-220b
 III-221 III-221a, III-221b, III-221c, III-221d	 III-222 III-222a, III-222b	 III-223 III-223a, III-223b	 III-224 III-224a, III-224b
 III-225 III-225a, III-225b	 III-226 III-226a, III-226b	 III-227 III-227a, III-227b	 III-228 III-228a, III-228b

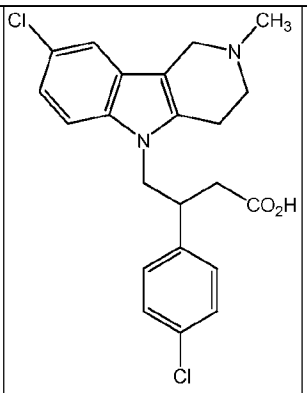
 III-229 III-229a, III-229b	 III-230 III-230a, III-230b	 III-231 III-231a, III-231b	 III-232 III-232a, III-232b
 III-233 III-233a, III-233b	 III-234 III-234a, III-234b	 III-235 III-235a, III-235b	 III-236 III-236a, III-236b
 III-237 III-237a, III-237b	 III-238 III-238a, III-238b	 III-239 III-239a, III-239b	 III-240 III-240a, III-240b



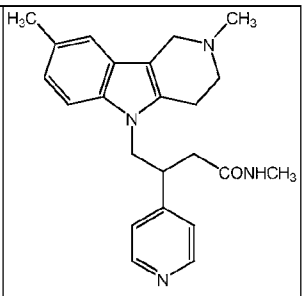
III-241
III-241a, III-241b



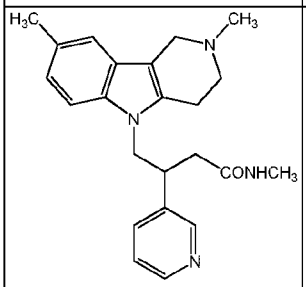
III-242
III-242a, III-242b



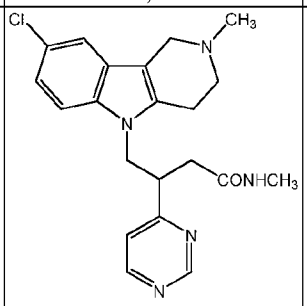
III-243
III-243a, III-243b



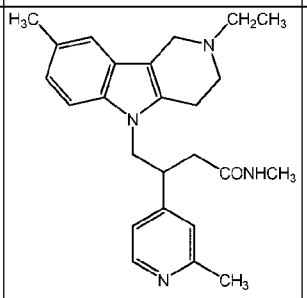
III-244
III-244a, III-244b



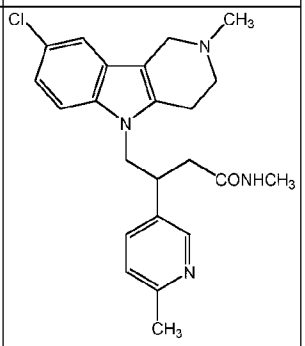
III-245
III-245a, III-245b



III-246
III-246a, III-246b



III-247
III-247a, III-247b



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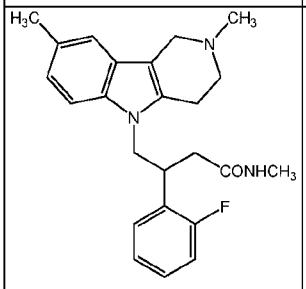
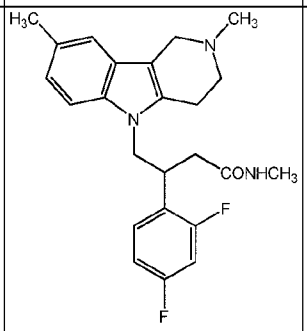
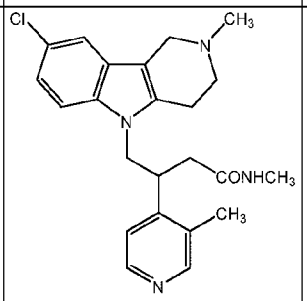
III-248a, III-248b



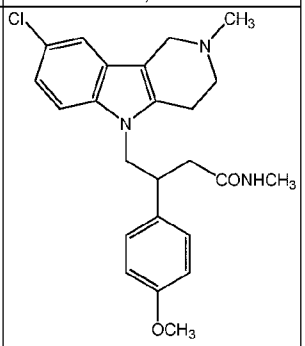
III-249
III-249a, III-249b



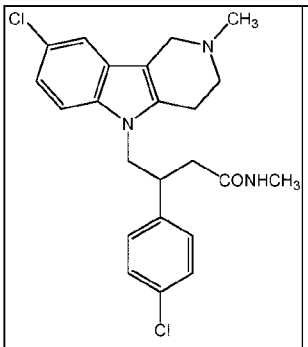
III-250
III-250a, III-250b



III-251
III-251a, III-251b



III-252
III-252a, III-252b



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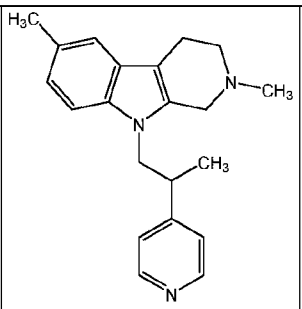
III-253a, III-253b



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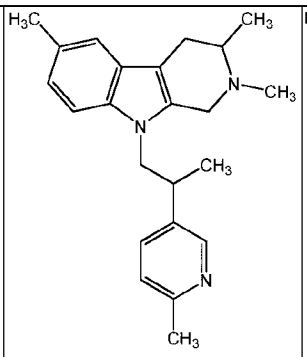
III-254a, III-254b



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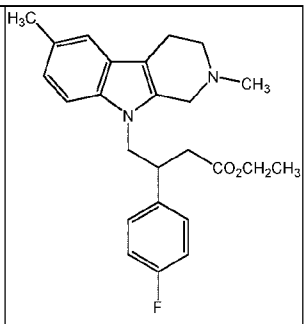
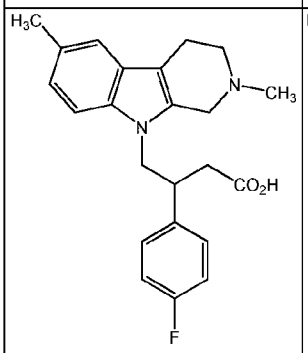
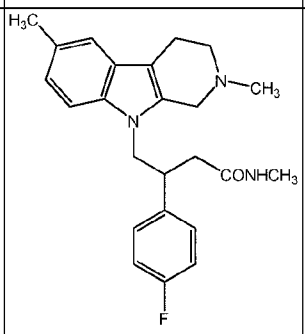
III-255a, III-255b, III-255c, III-255d



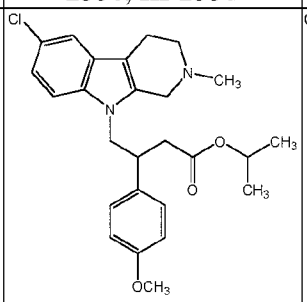
III-256
III-256a, III-256b



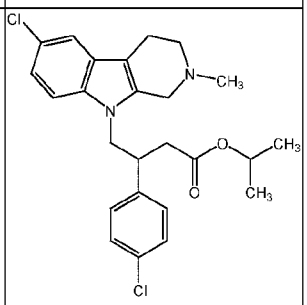
III-257
III-257a, III-257b



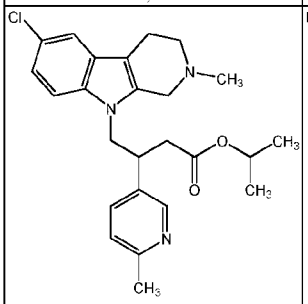
III-258
III-258a, III-258b



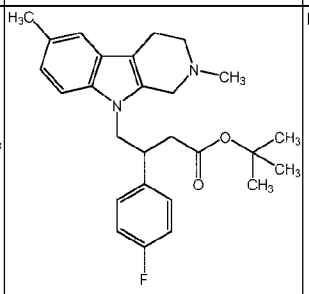
III-259
III-259a, III-259b



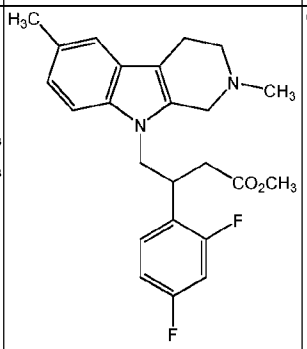
III-260
III-260a, III-260b



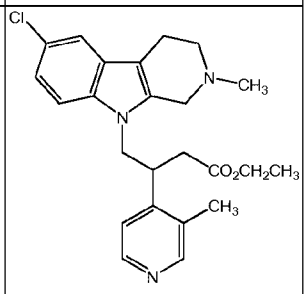
III-261
III-261a, III-261b



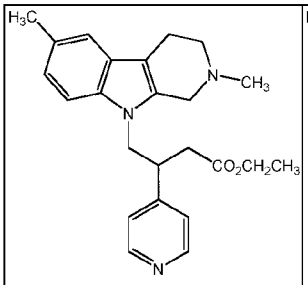
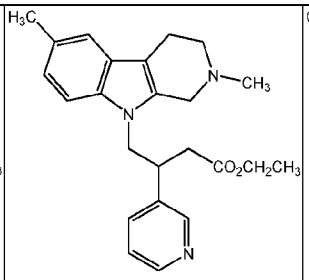
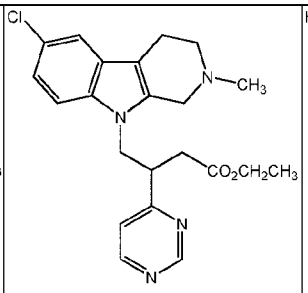
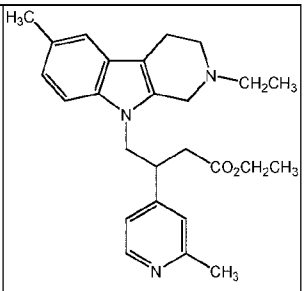
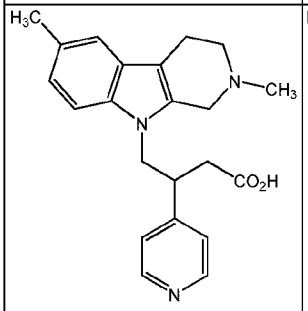
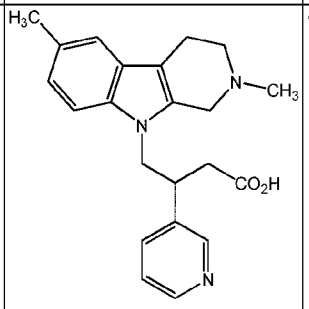
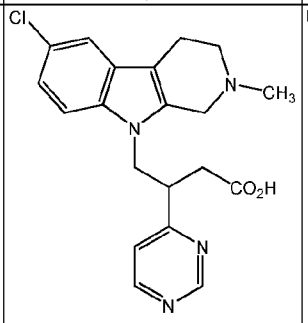
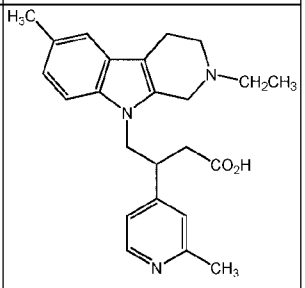
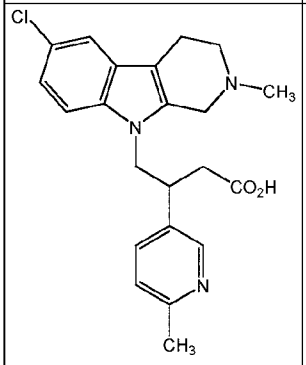
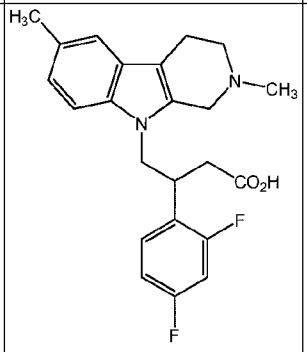
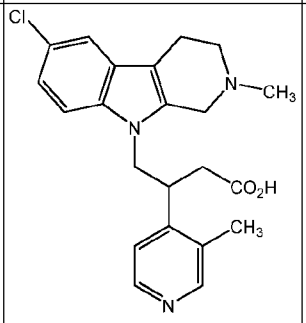
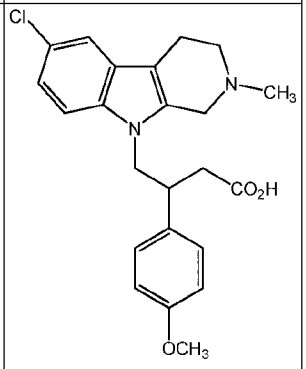
III-262
III-262a, III-262b

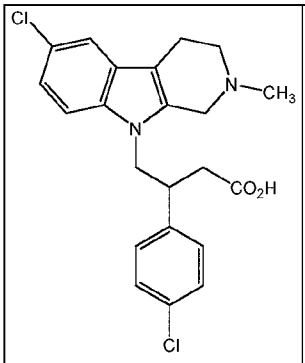
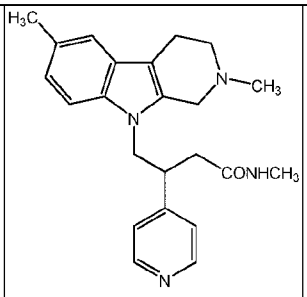
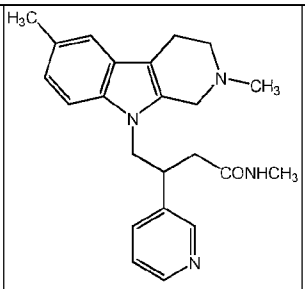
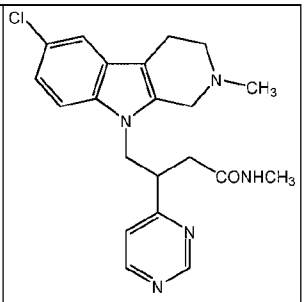
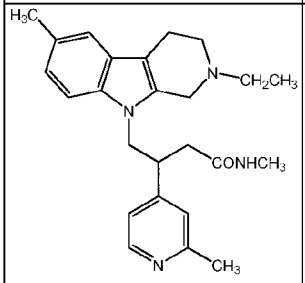
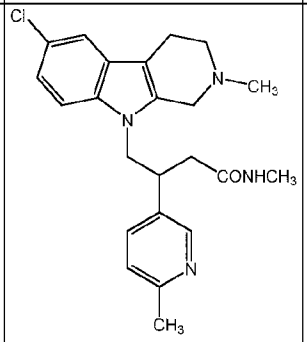
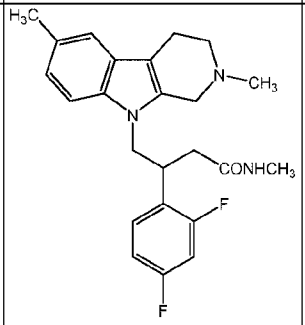
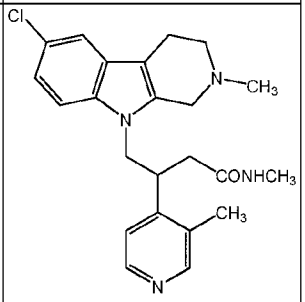
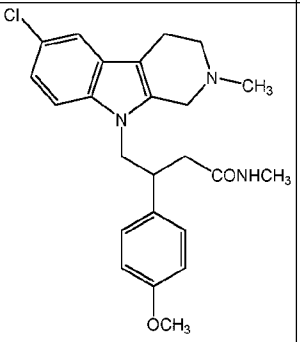
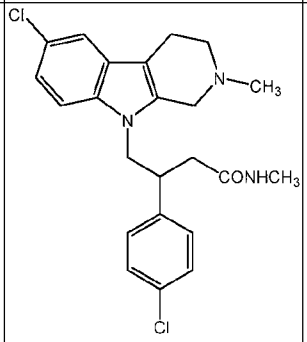
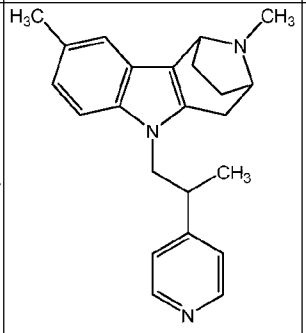
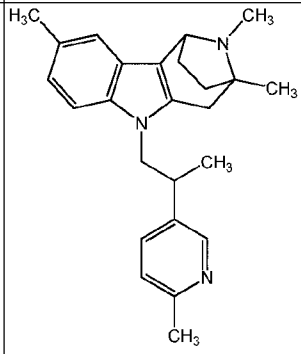


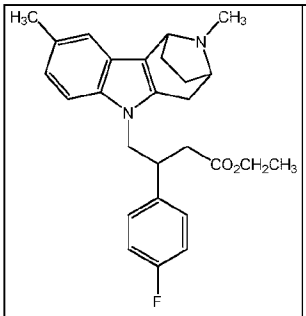
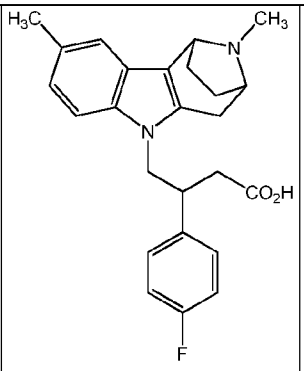
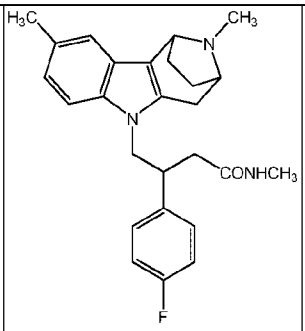
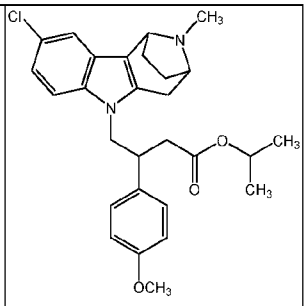
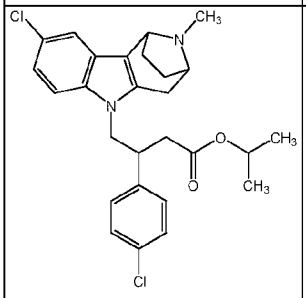
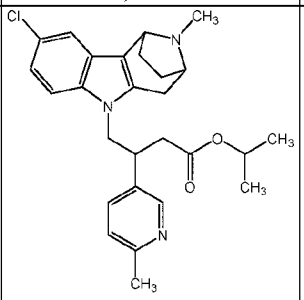
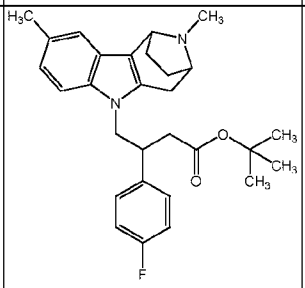
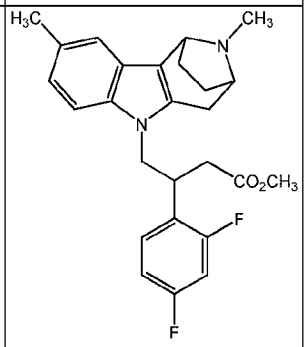
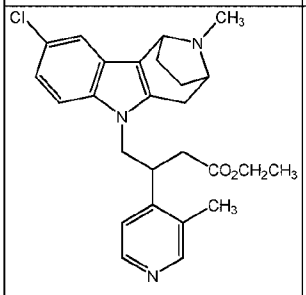
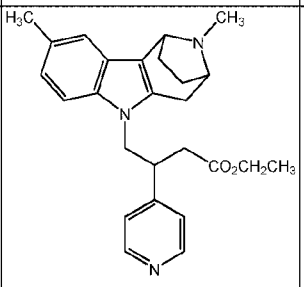
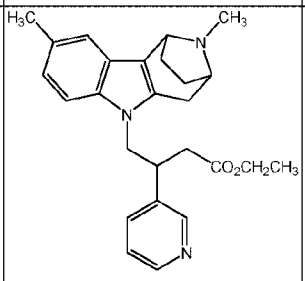
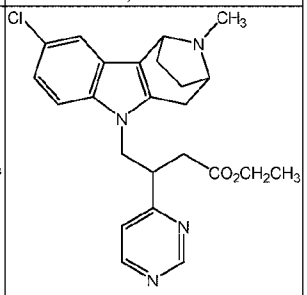
III-263
III-263a, III-263b

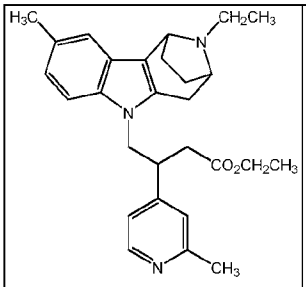
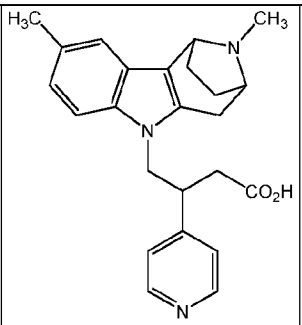
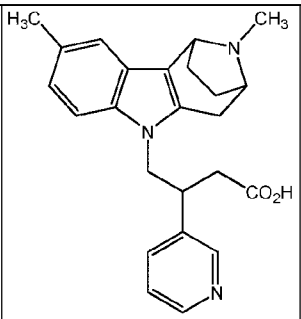
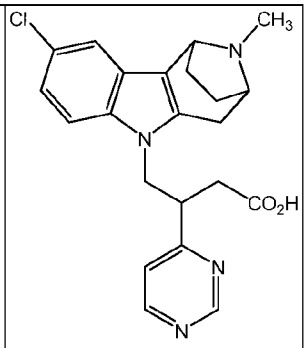
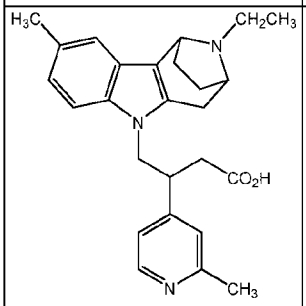
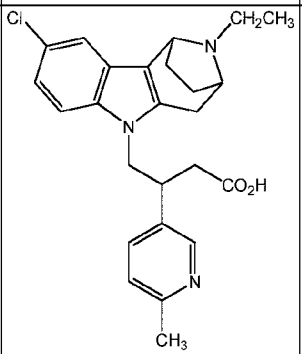
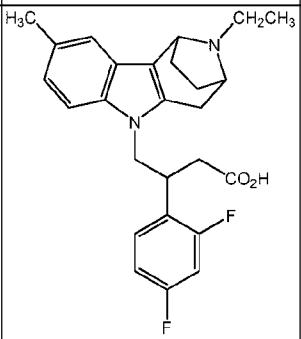
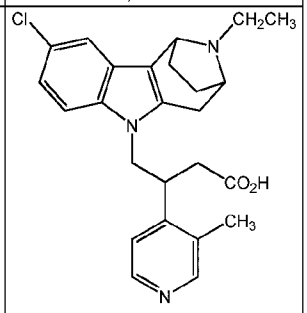
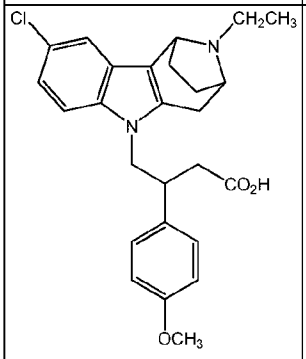
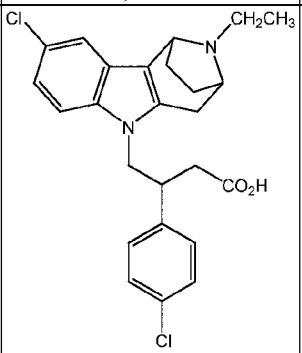
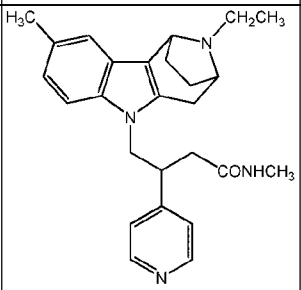
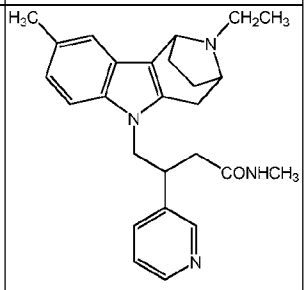


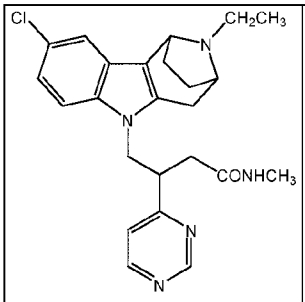
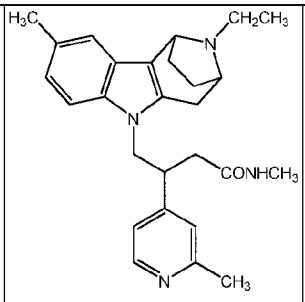
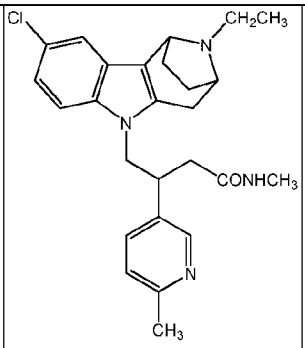
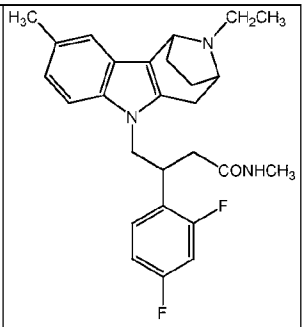
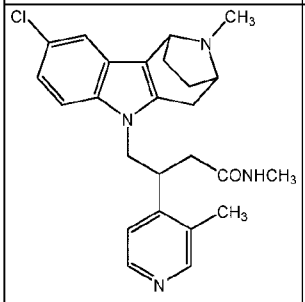
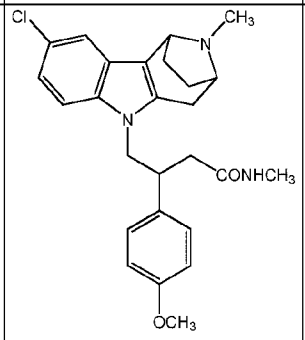
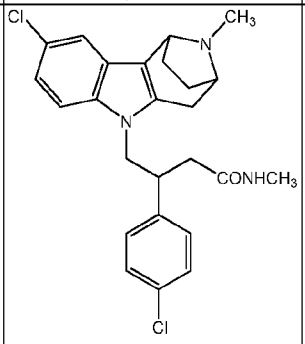
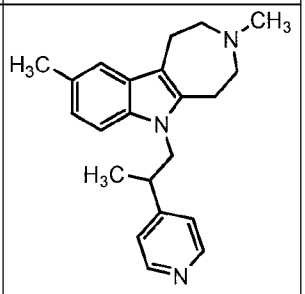
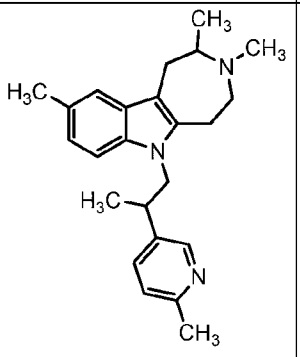
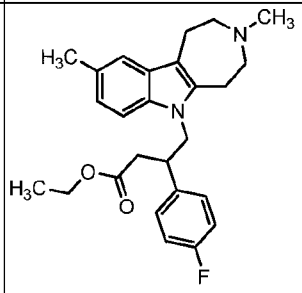
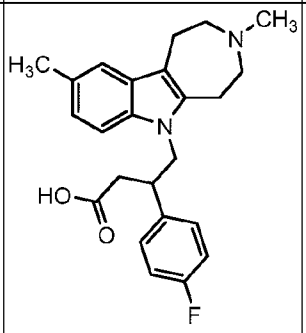
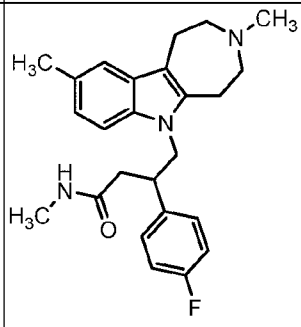
III-264
III-264a, III-264b

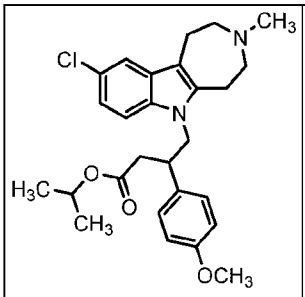
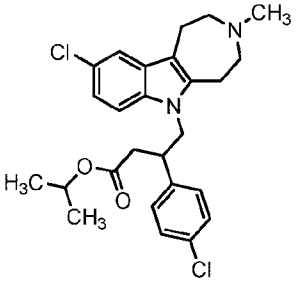
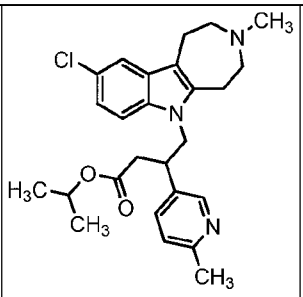
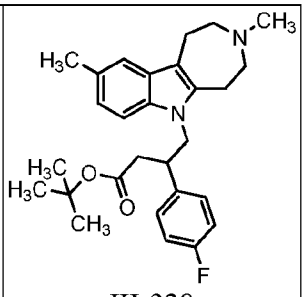
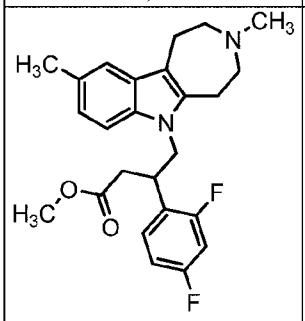
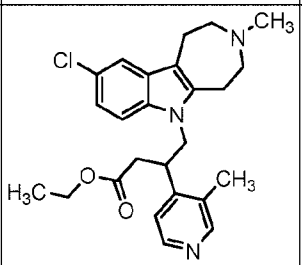
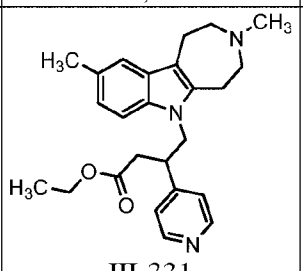
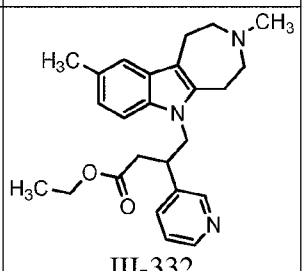
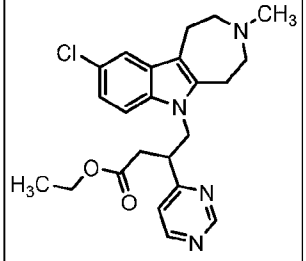
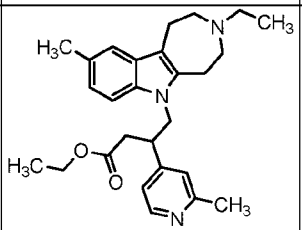
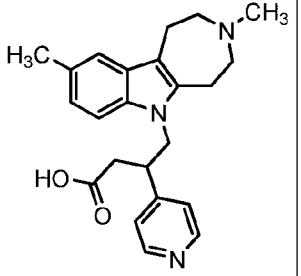
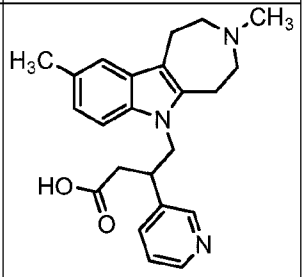
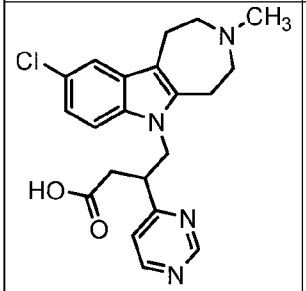
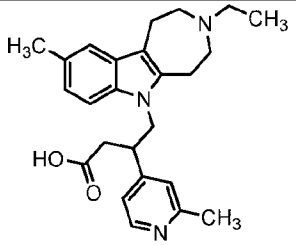
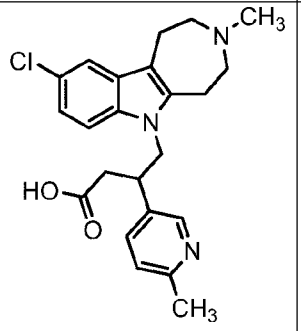
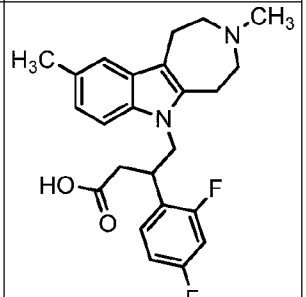
 III-265 III-265a, III-265b	 III-266 III-266a, III-266b	 III-267 III-267a, III-267b	 III-268 III-268a, III-268b
 III-269 III-269a, III-269b	 III-270 III-270a, III-270b	 III-271 III-271a, III-271b	 III-272 III-272a, III-272b
 III-273 III-273a, III-274b	 III-274 III-274a, III-274b	 III-275 III-275a, III-275b	 III-276 III-276a, III-276b

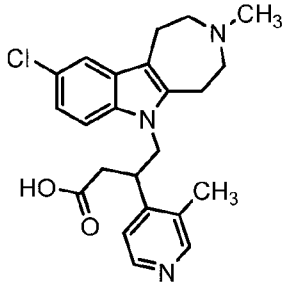
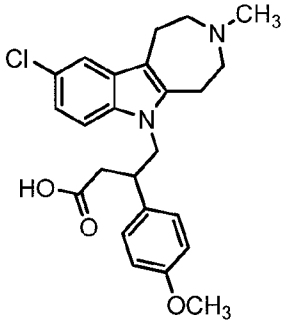
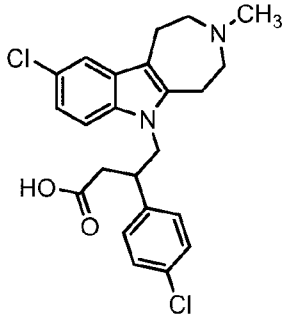
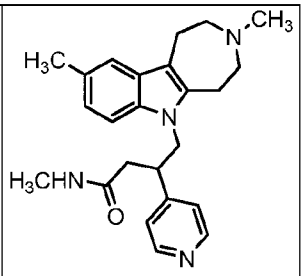
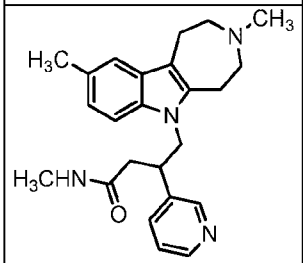
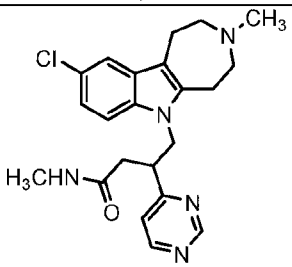
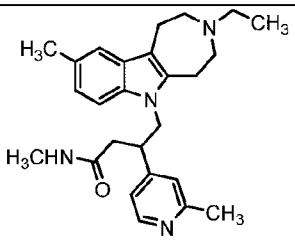
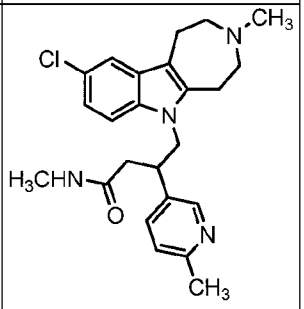
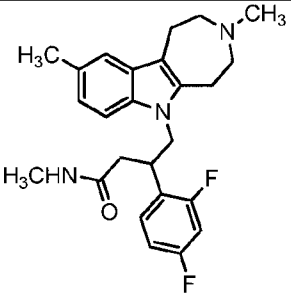
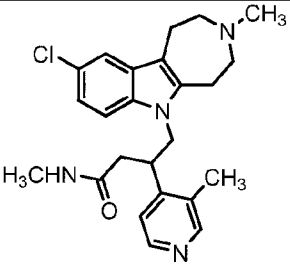
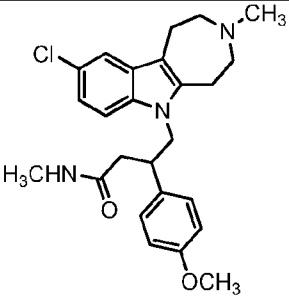
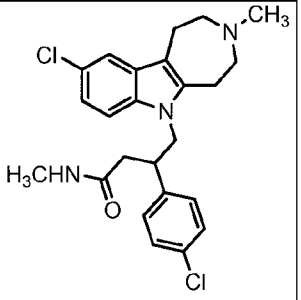
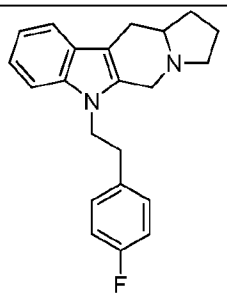
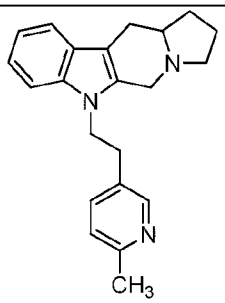
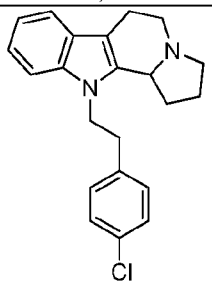
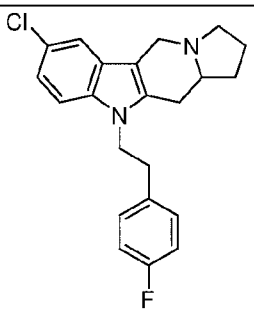
 III-277 III-277a, III-277b	 III-278 III-278a, III-278b	 III-279 III-279a, III-279b	 III-280 III-280a, III-280b
 III-281 III-281a, III-281b	 III-282 III-282a, III-282b	 III-283 III-283a, III-283b	 III-284 III-284a, III-284b
 III-285 III-285a, III-285b	 III-286 III-286a, III-286b	 III-287 III-287a, III-287b, III-287c, III-287d	 III-288 III-288a, III-288b, III-288c, III-288d

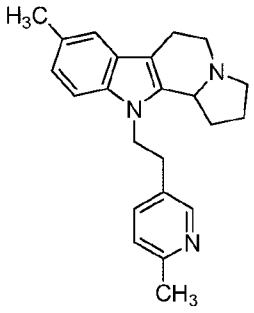
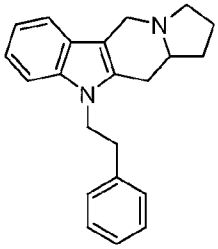
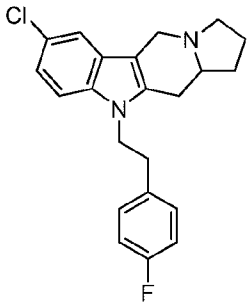
 III-289 III-289a, III-289b, III-289c, III-289d	 III-290 III-290a, III-290b, III-290c, III-290d	 III-291 III-291a, III-291b, III-291c, III-291d	 III-292 III-292a, III-292b, III-292c, III-292d
 III-293 III-293a, III-293b, III-293c, III-293d	 III-294 III-294a, III-294b, III-294c, III-294d	 III-295 III-295a, III-295b, III-295c, III-295d	 III-296 III-296a, III-296b, III-296c, III-296d
 III-297 III-297a, III-297b, III-297c, III-297d	 III-298 III-298a, III-298b, III-298c, III-298d	 III-299 III-299a, III-299b, III-299c, III-299d	 III-300 III-300a, III-300b, III-300c, III-300d

 III-301 III-301a, III-301b, III-301c, III-301d	 III-302 III-302a, III-302b, III-302c, III-302d	 III-303 III-303a, III-303b, III-303c, III-303d	 III-304 III-304a, III-304b, III-304c, III-304d
 III-305 III-305a, III-305b, III-305c, III-305d	 III-306 III-306a, III-306b, III-306c, III-306d	 III-307 III-307a, III-307b, III-307c, III-307d	 III-308 III-308a, III-308b, III-308c, III-308d
 III-309 III-309a, III-309b, III-309c, III-309d	 III-310 III-310a, III-310b, III-310c, III-310d	 III-311 III-311a, III-311b, III-311c, III-311d	 III-312 III-312a, III-312b, III-312c, III-312d

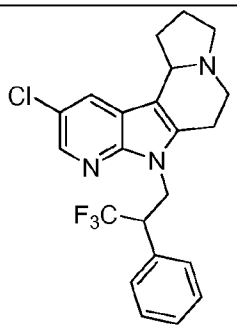
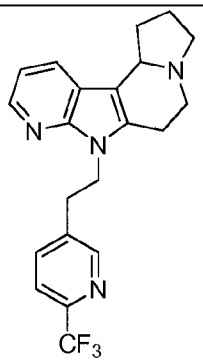
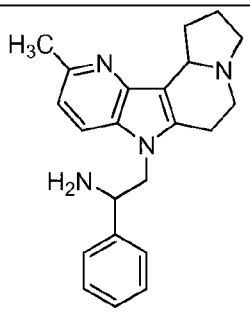
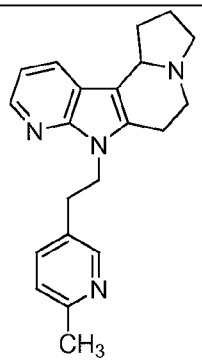
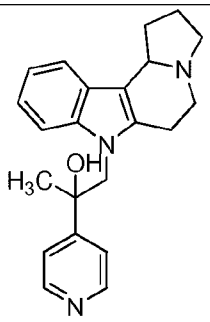
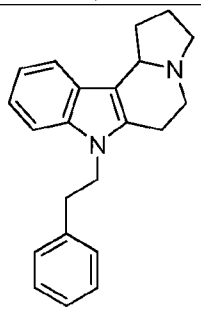
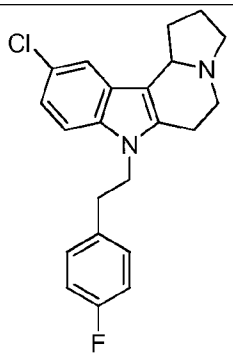
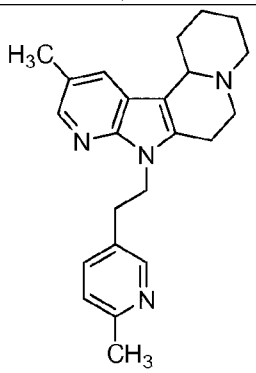
 III-313 III-313a, III-313b, III-313c, III-313d	 III-314 III-314a, III-314b, III-314c, III-314d	 III-315 III-315a, III-315b, III-315c, III-315d	 III-316 III-316a, III-316b, III-316c, III-316d
 III-317 III-317a, III-317b, III-317c, III-317d	 III-318 III-318a, III-318b, III-318c, III-318d	 III-319 III-319a, III-319b, III-319c, III-319d	 III-320 III-320a, III-320b
 III-321 III-321a, III-321b, III-321c, III-321d	 III-322 III-322a, III-322b	 III-323 III-323a, III-323b	 III-324 III-324a, III-324b

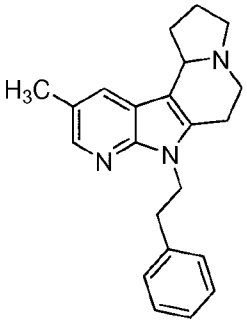
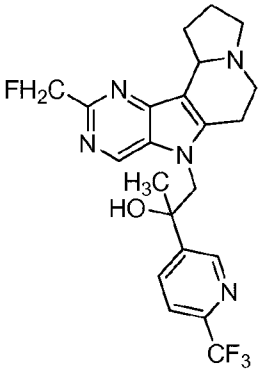
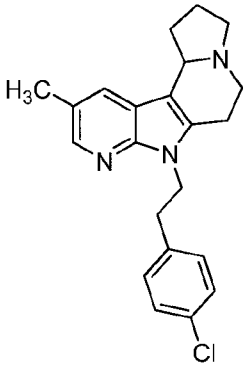
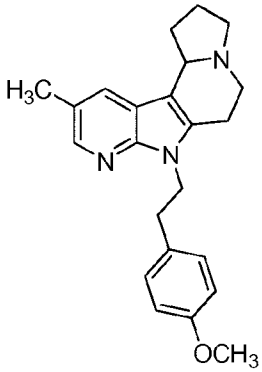
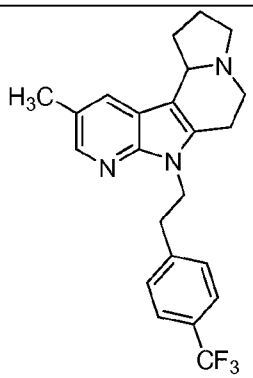
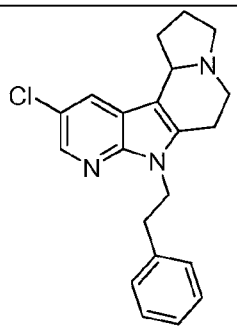
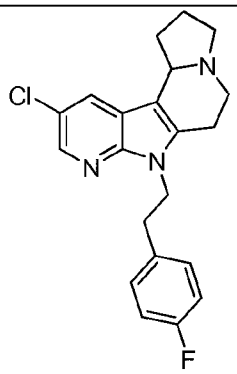
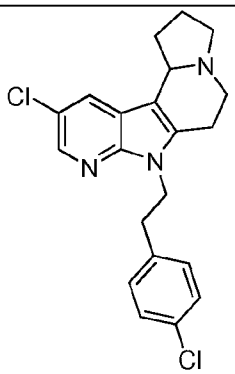
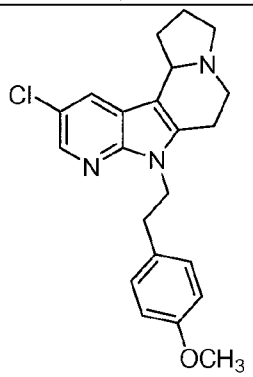
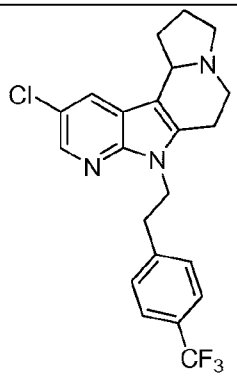
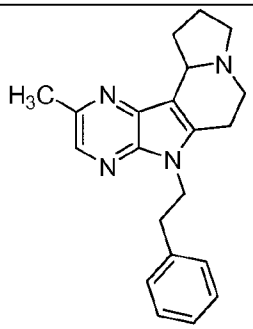
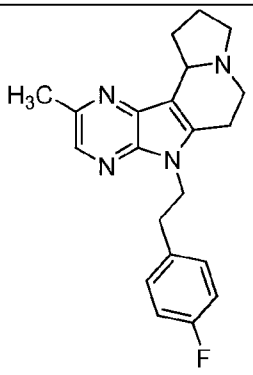
 III-325 III-325a, III-325b	 III-326 III-326a, III-326b	 III-327 III-327a, III-327b	 III-328 III-328a, III-328b
 III-329 III-329a, III-329b	 III-330 III-330a, III-330b	 III-331 III-331a, III-331b	 III-332 III-332a, III-332b
 III-333 III-333a, III-333b	 III-334 III-334a, III-334b	 III-335 III-335a, III-335b	 III-336 III-336a, III-336b
 III-337 III-337a, III-337b	 III-338 III-338a, III-338b	 III-339 III-339a, III-339b	 III-340 III-340a, III-340b

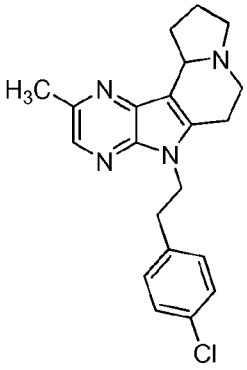
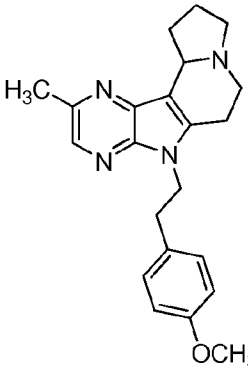
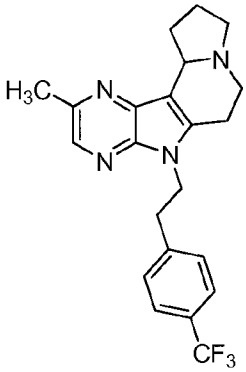
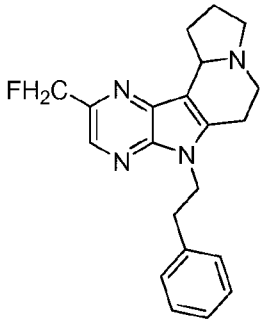
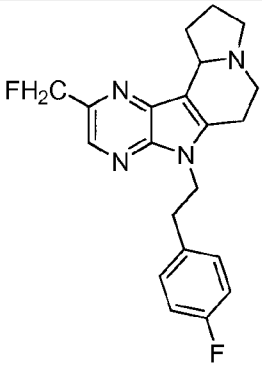
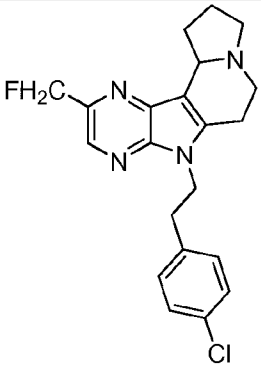
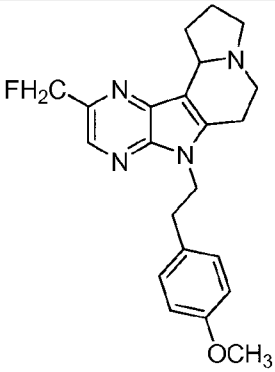
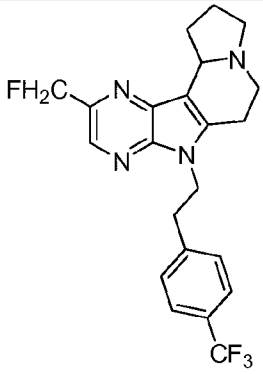
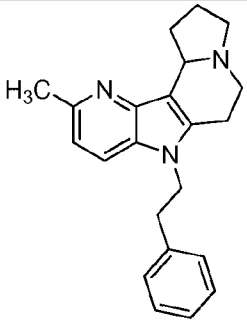
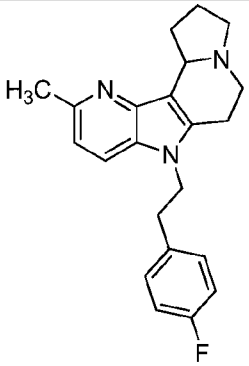
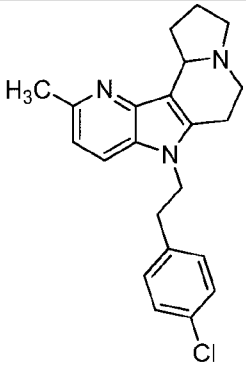
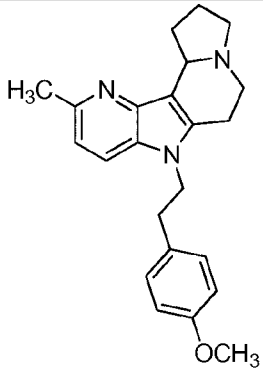
 III-341 III-341a, III-341b	 III-342 III-342a, III-342b	 III-343 III-343a, III-343b	 III-344 III-344a, III-344b
 III-345 III-345a, III-345b	 III-346 III-346a, III-346b	 III-347 III-347a, III-347b	 III-348 III-348a, III-348b
 III-349 III-349a, III-349b	 III-350 III-350a, III-350b	 III-351 III-351a, III-351b	 III-352 III-352a, III-352b
 III-353 III-353a, III-353b	 III-354 III-354a, III-354b	 III-355 III-355a, III-355b	 III-356 III-356a, III-356b

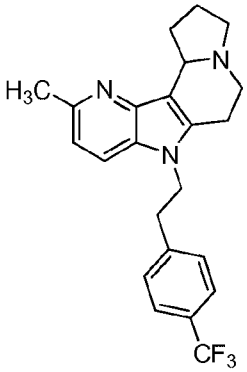
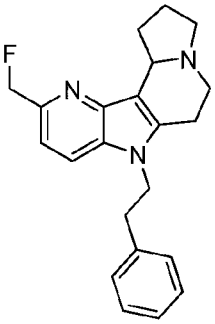
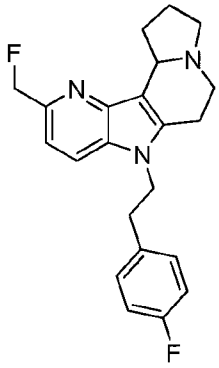
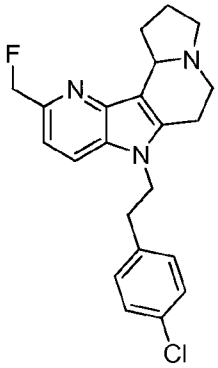
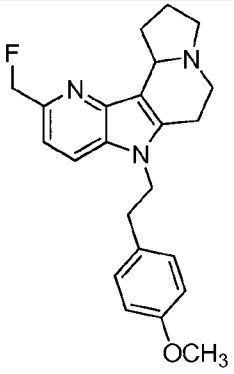
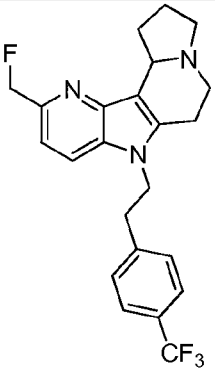
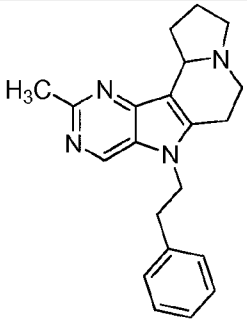
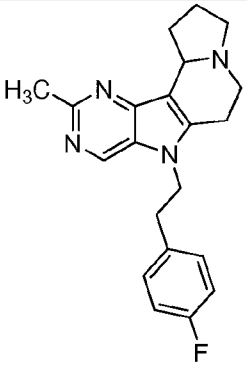
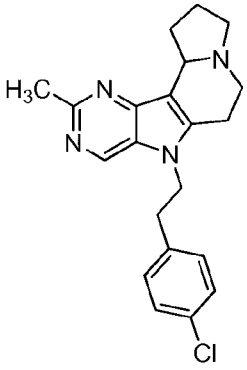
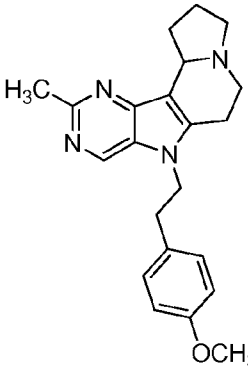
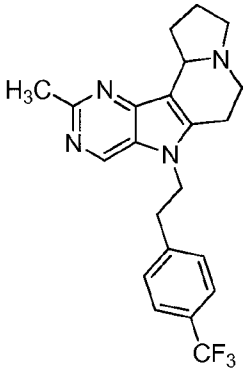
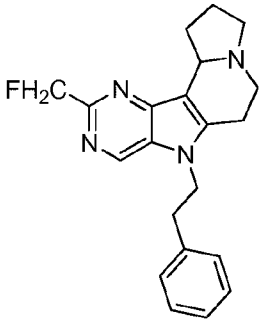
 III-357 III-357a, III-357b	 III-358 III-358a, III-358b	 III-359 III-359a, III-359b	

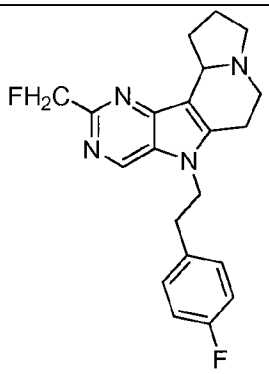
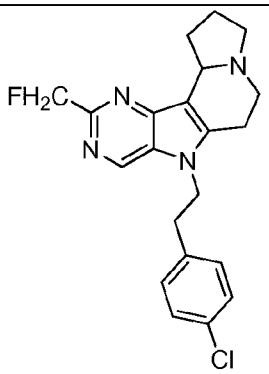
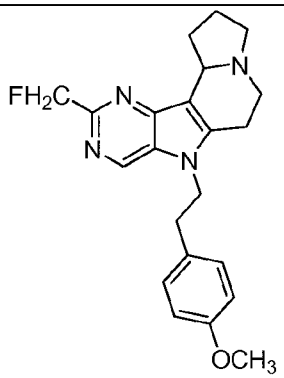
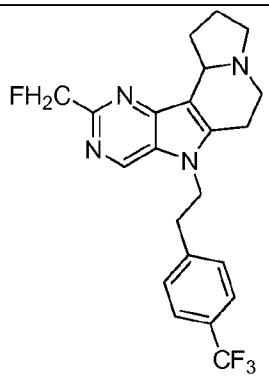
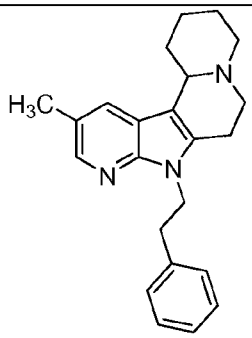
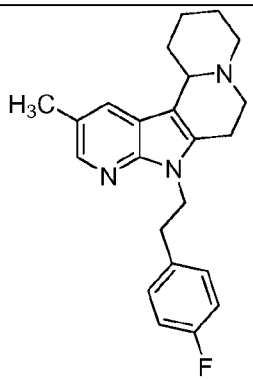
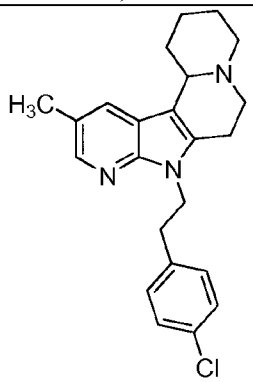
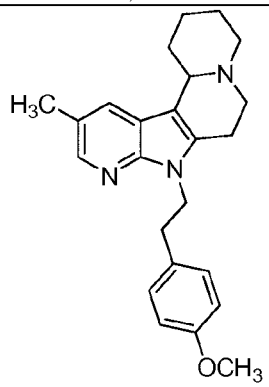
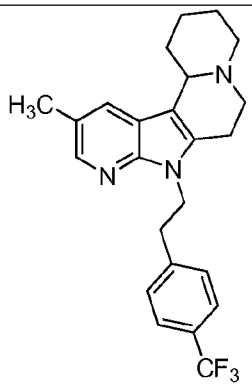
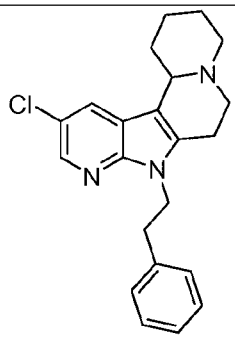
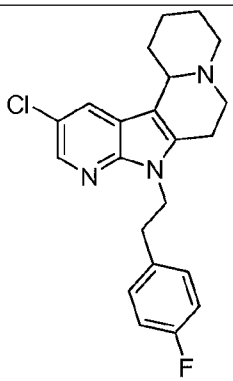
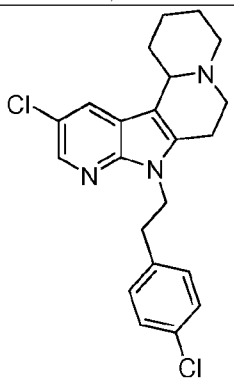
[0633] Table 4. Representative Compounds of the Invention

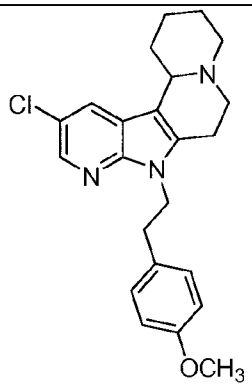
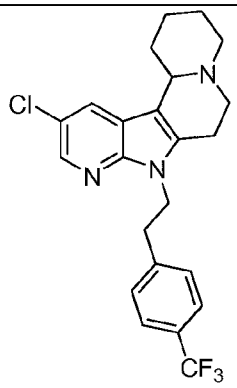
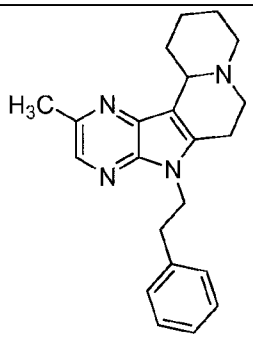
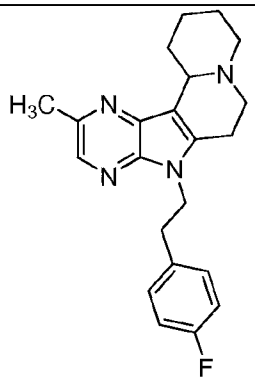
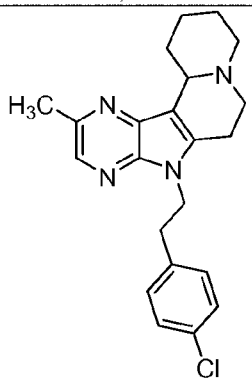
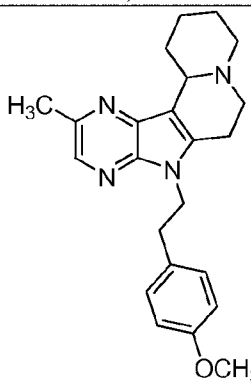
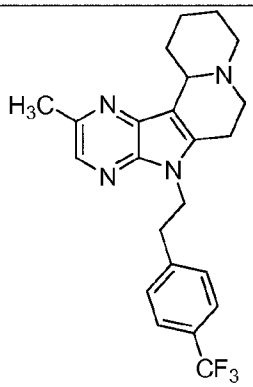
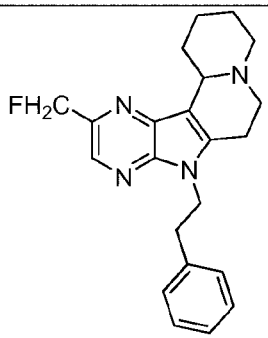
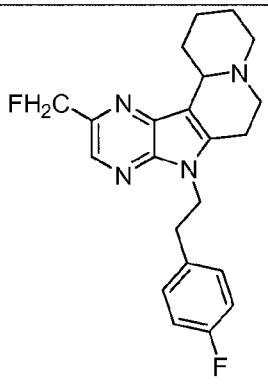
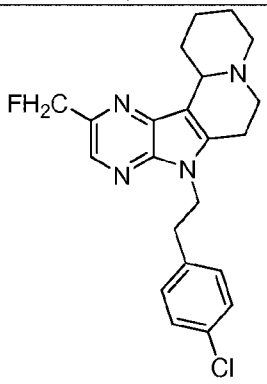
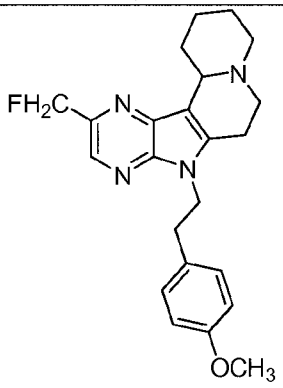
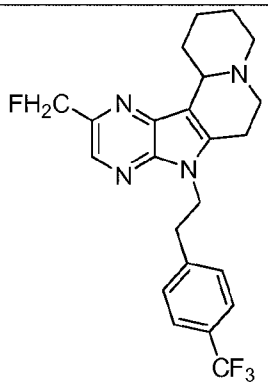
 IV-1 IV-1a, IV-1b	 IV-2 IV-2a, IV-2b	 IV-3 IV-3a, IV-3b, IV-3c, IV-3d	 IV-4 IV-4a, IV-4b
 IV-5 IV-5a, IV-5b, IV-5c, IV-5d	 IV-6 IV-6a, IV-6b	 IV-7 IV-7a, IV-7b	 IV-8 IV-8a, IV-8b

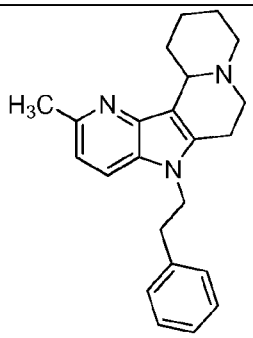
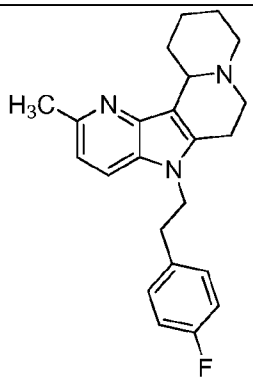
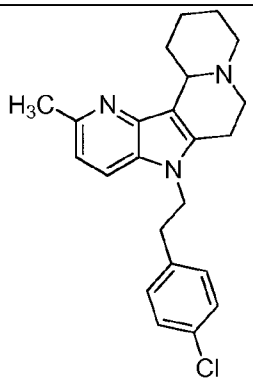
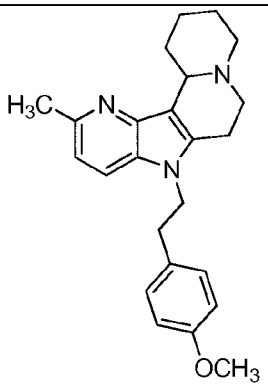
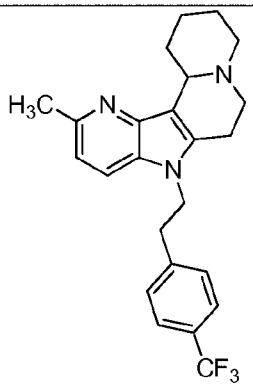
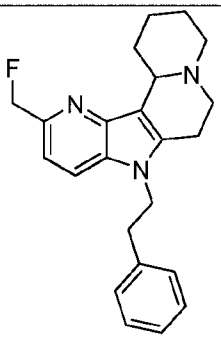
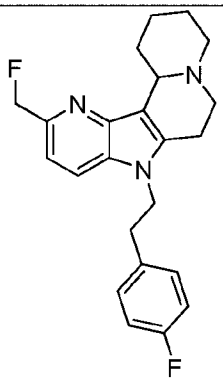
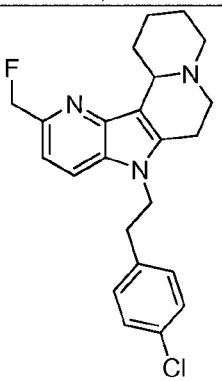
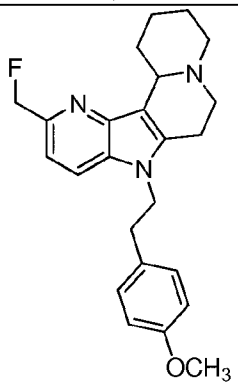
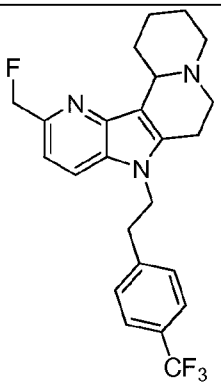
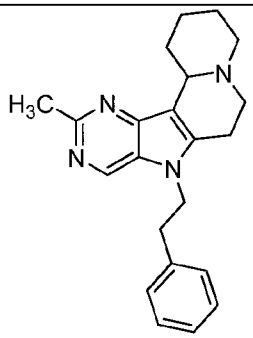
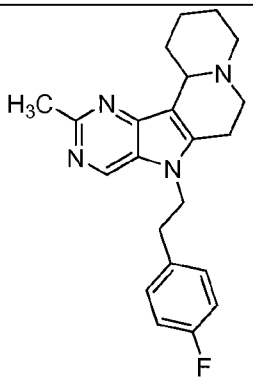
 IV-9 IV-9a, IV-9b	 IV-10 IV-10a, IV-10b, IV-10c, IV-10d	 IV-11 IV-11a, IV-11b	 IV-12 IV-12a, IV-12b
 IV-13 IV-13a, IV-13b	 IV-14 IV-14a, IV-14b	 IV-15 IV-15a, IV-15b	 IV-16 IV-16a, IV-16b
 IV-17 IV-17a, IV-17b	 IV-18 IV-18a, IV-18b	 IV-19 IV-19a, IV-19b	 IV-20 IV-20a, IV-20b

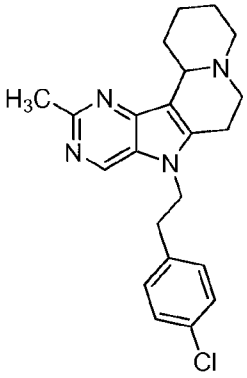
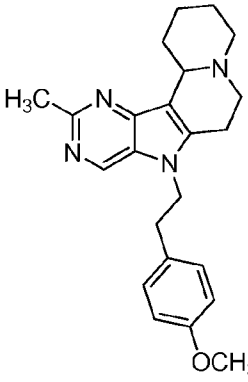
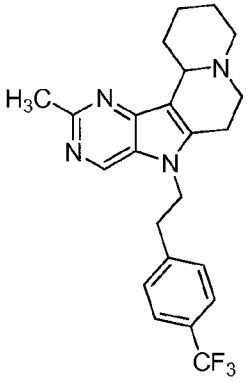
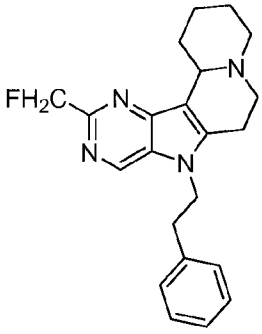
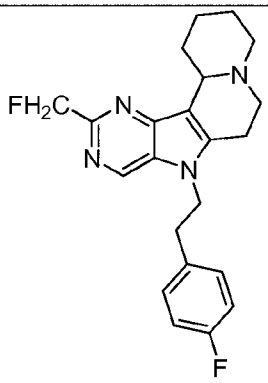
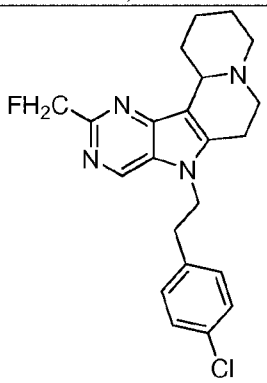
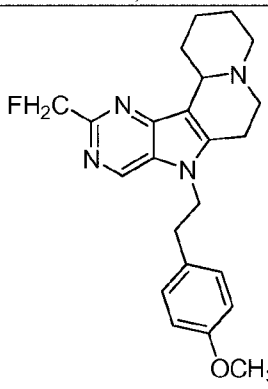
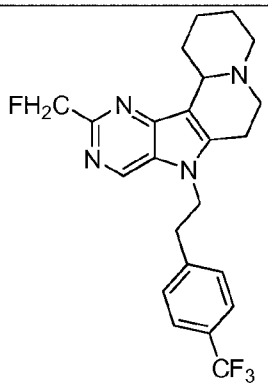
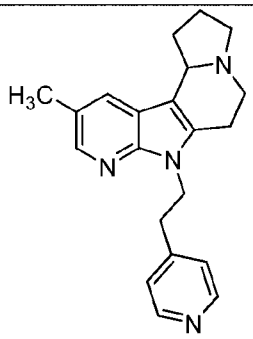
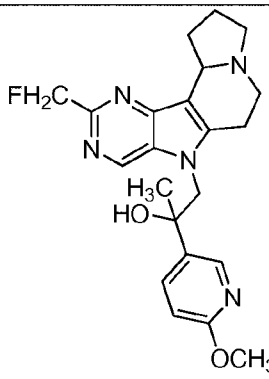
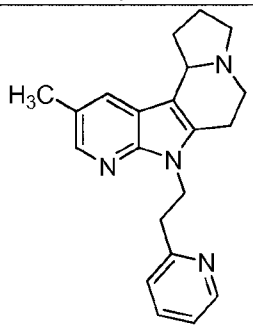
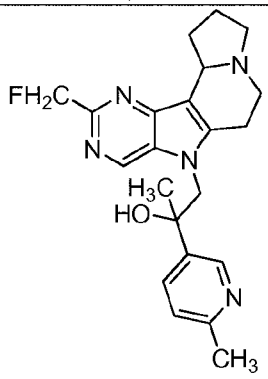
 IV-21 IV-21a, IV-21b	 IV-22 IV-22a, IV-22b	 IV-23 IV-23a, IV-23b	 IV-24 IV-24a, IV-24b
 IV-25 IV-25a, IV-25b	 IV-26 IV-26a, IV-26b	 IV-27 IV-27a, IV-27b	 IV-28 IV-28a, IV-28b
 IV-29 IV-29a, IV-29b	 IV-30 IV-30a, IV-30b	 IV-31 IV-31a, IV-31b	 IV-32 IV-32a, IV-32b

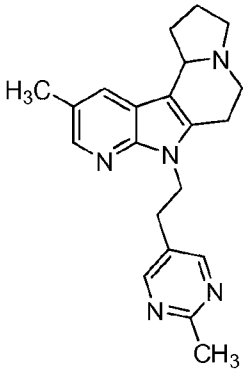
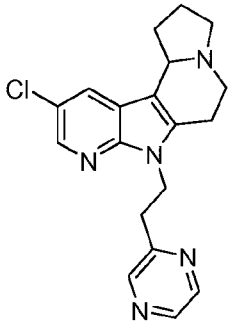
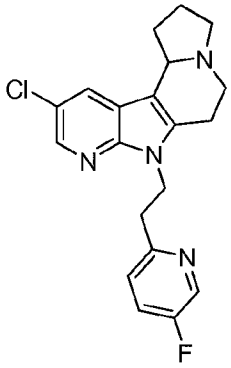
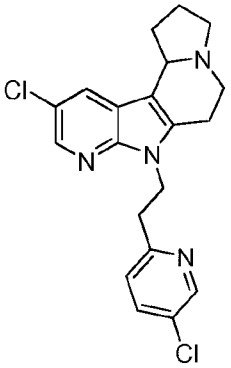
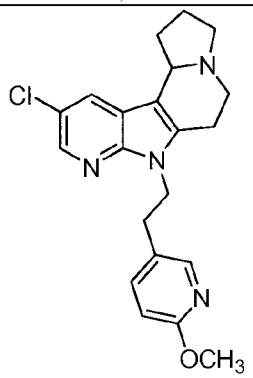
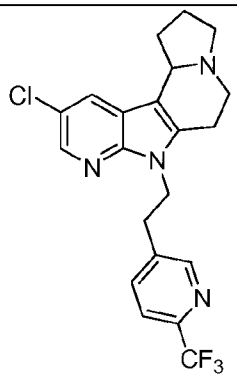
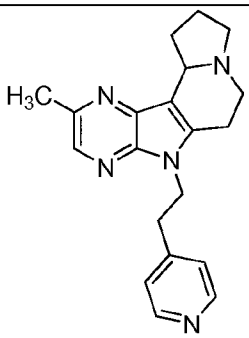
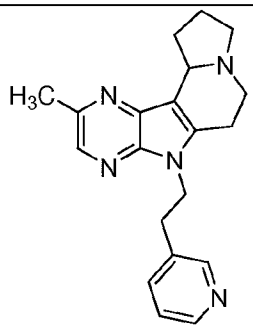
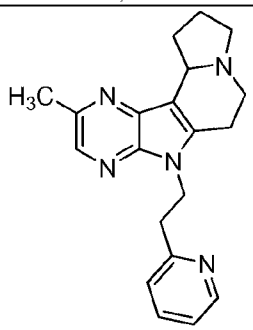
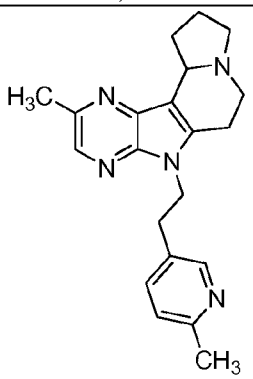
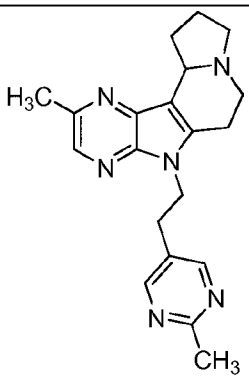
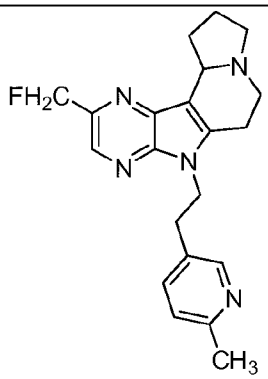
 IV-33 IV-33a, IV-33b	 IV-34 IV-34a, IV-34b	 IV-35 IV35a, IV-35b	 IV-36 IV-36a, IV-36b
 IV-37 IV-37a, IV-37b	 IV-38 IV-38a, IV-38b	 IV-39 IV-39a, IV-39b	 IV-40 IV-40a, IV-40b
 IV-41 IV-41a, IV-41b	 IV-42 IV-42a, IV-42b	 IV-43 IV-43a, IV-43b	 IV-44 IV-44a, IV-44b

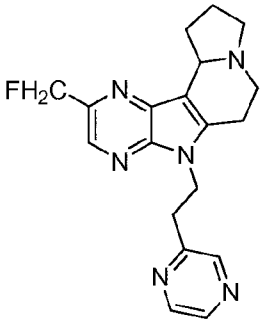
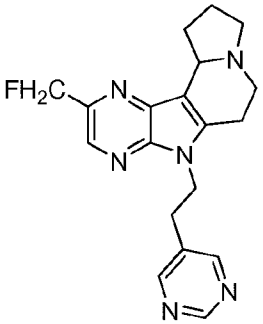
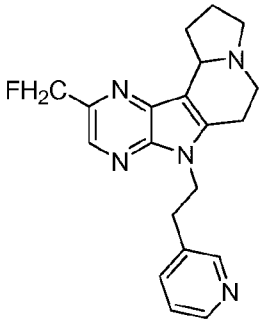
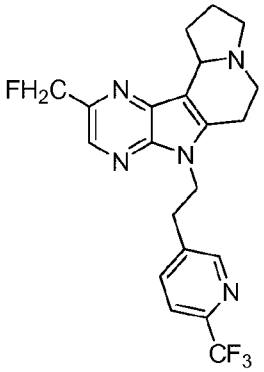
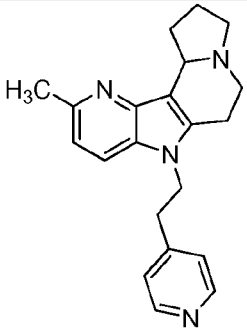
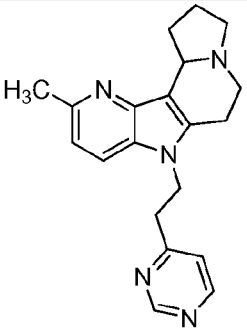
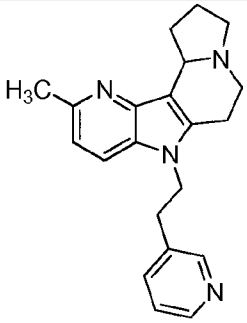
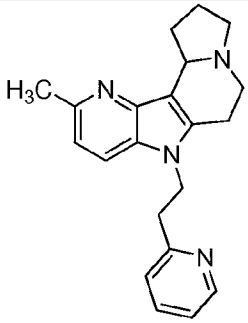
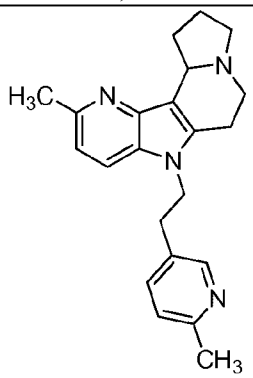
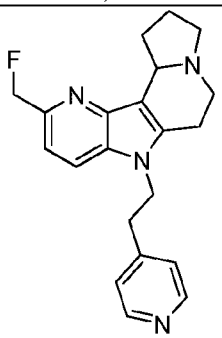
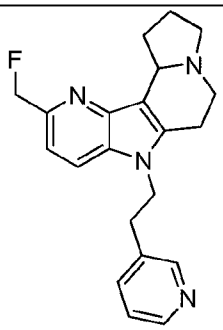
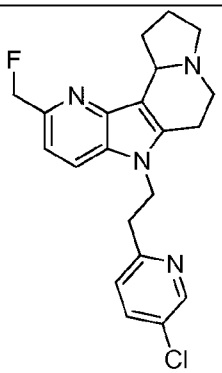
 IV-45 IV-45a, IV-45b	 IV-46 IV-46a, IV-46b	 IV-47 IV-47a, IV-47b	 IV-48 IV-48a, IV-48b
 IV-49 IV-49a, IV-49b	 IV-50 IV-50a, IV-50b	 IV-51 IV-51a, IV-51b	 IV-52 IV-52a, IV-52b
 IV-53 IV-53a, IV-53b	 IV-54 IV-54a, IV-54b	 IV-55 IV-55a, IV-55b	 IV-56 IV-56a, IV-56b

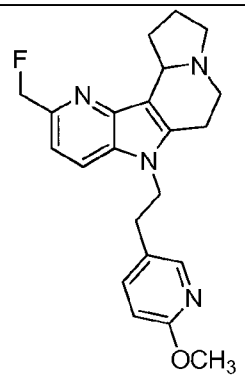
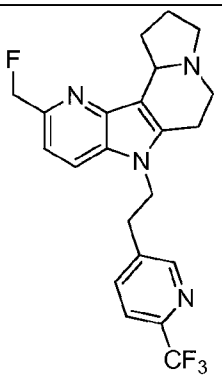
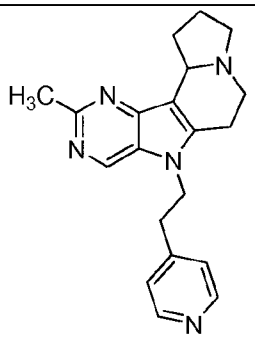
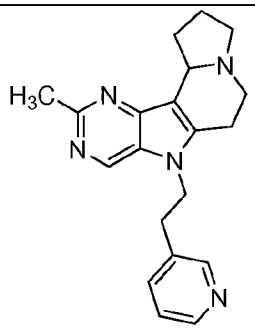
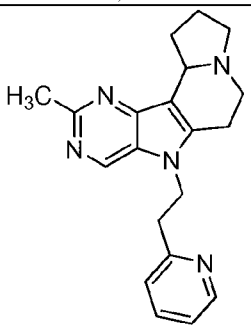
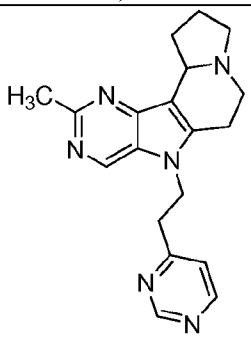
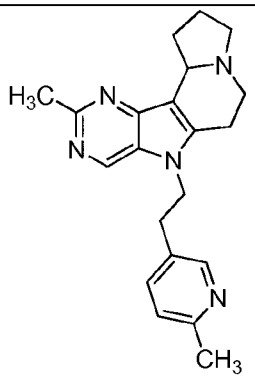
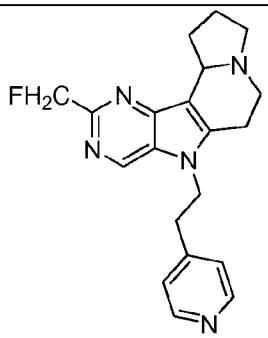
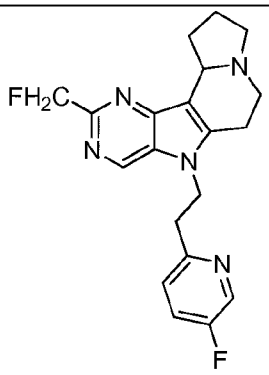
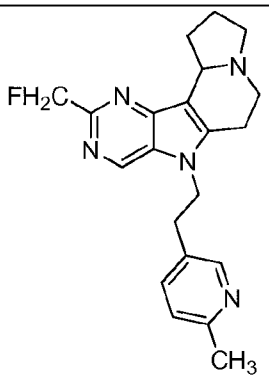
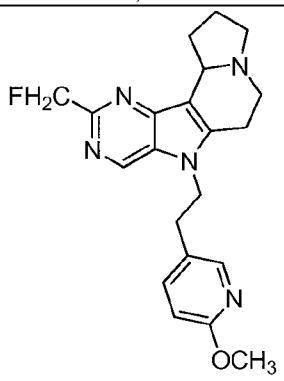
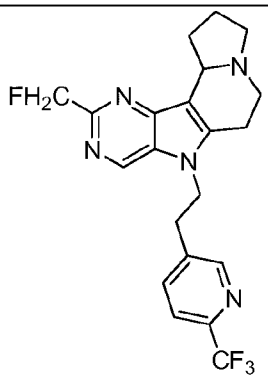
 IV-57 IV-57a, IV-57b	 IV-58 IV-58a, IV-58b	 IV-59 IV-59a, IV-59b	 IV-60 IV-60a, IV-60b
 IV-61 IV-61a, IV-61b	 IV-62 IV-62a, IV-62b	 IV-63 IV-63a, IV-63b	 IV-64 IV-64a, IV-64b
 IV-65 IV-65a, IV-65b	 IV-66 IV-66a, IV-6b	 IV-67 IV-67a, IV-67b	 IV-68 IV-68a, IV-68b

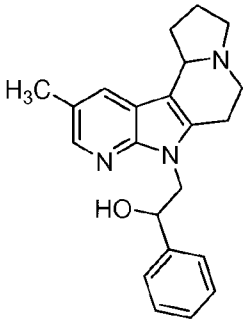
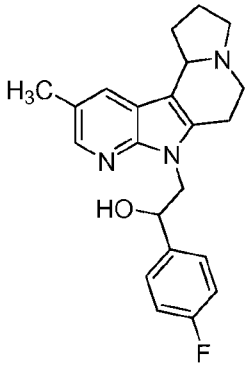
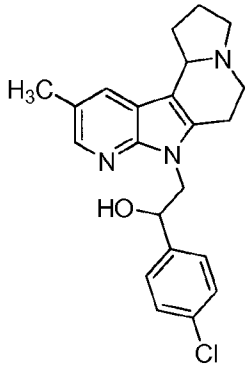
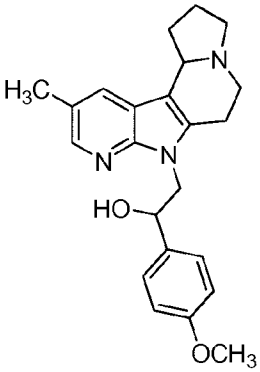
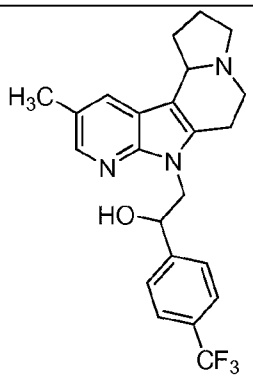
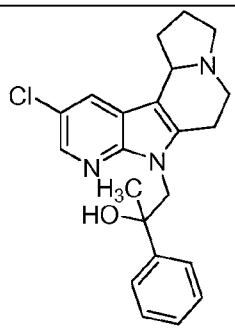
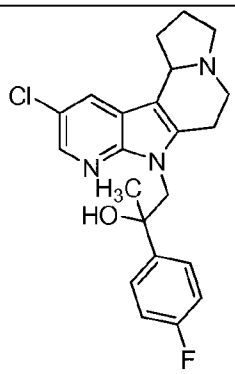
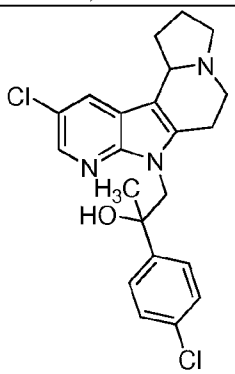
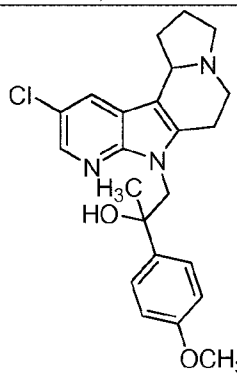
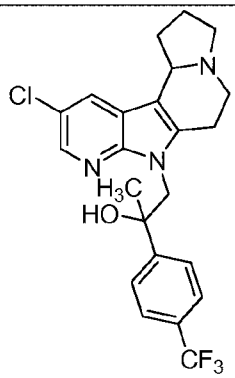
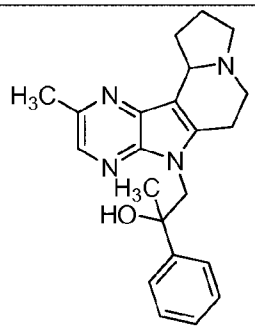
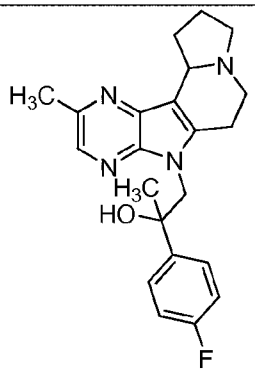
 IV-69 IV-69a, IV-69b	 IV-70 IV-70a, IV-70b	 IV-71 IV-71a, IV-71b	 IV-72 IV-72a, IV-72b
 IV-73 IV-73a, IV-73b	 IV-74 IV-74a, IV-74b	 IV-75 IV-75a, IV-75b	 IV-76 IV-76a, IV-76b
 IV-77 IV-77a, IV-77b	 IV-78 IV-78a, IV-78b	 IV-79 IV-79a, IV-79b	 IV-80 IV-80a, IV-80b

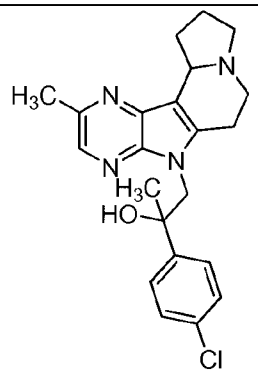
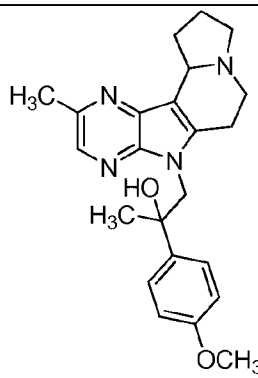
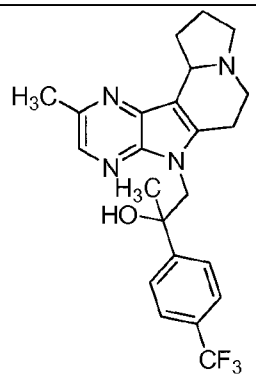
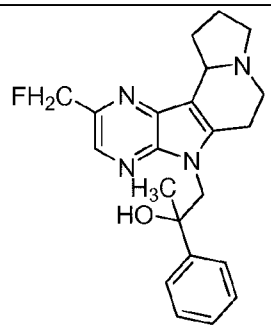
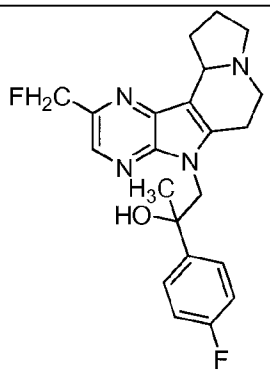
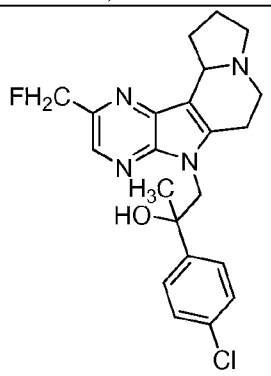
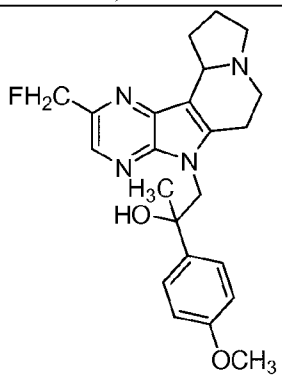
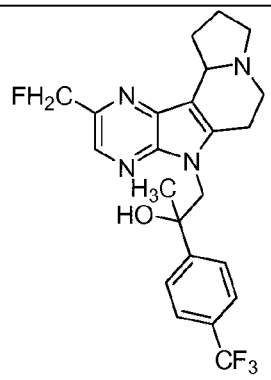
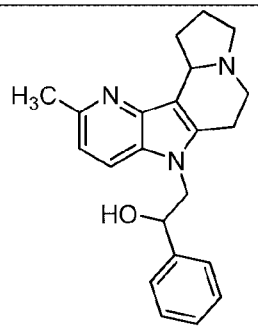
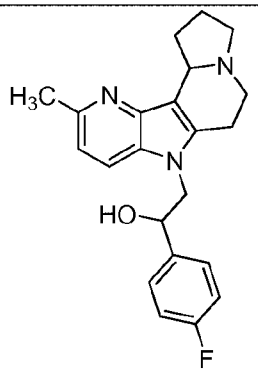
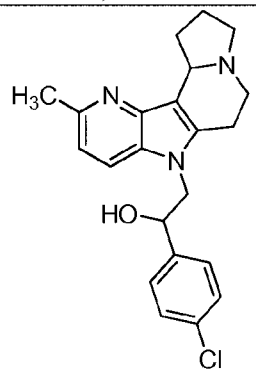
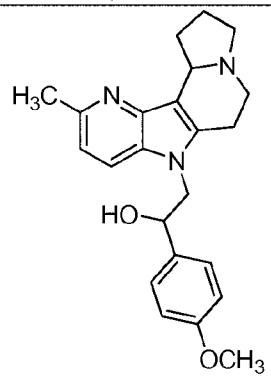
 IV-81 IV-81a, IV-81b	 IV-82 IV-82a, IV-82b	 IV-83 IV-83a, IV-83b	 IV-84 IV-84a, IV-84b
 IV-85 IV-85a, IV-85b	 IV-86 IV-86a, IV-86b	 IV-87 IV-87a, IV-87b	 IV-88 IV-88a, IV-88b
 IV-89 IV-89a, IV-89b	 IV-90 IV-90a, IV-90b, IV-90c, IV-90d	 IV-91 IV-91a, IV-91b	 IV-92 IV-92a, IV-92b, IV-92c, IV-92d

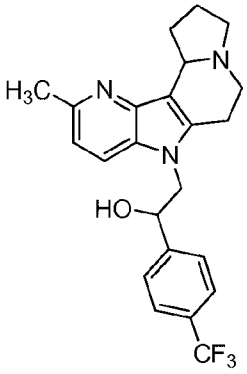
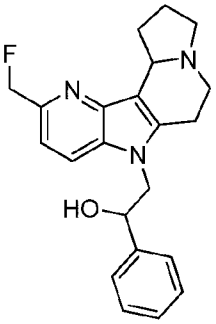
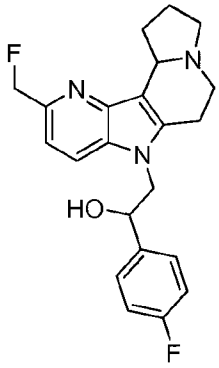
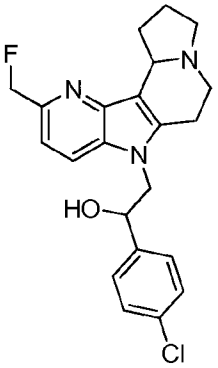
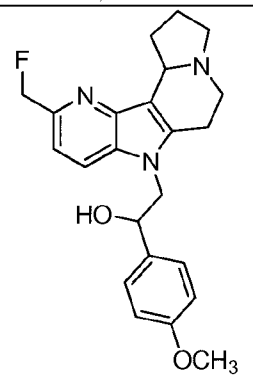
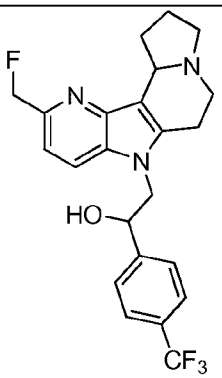
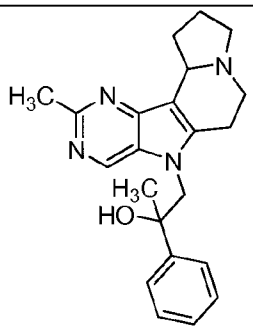
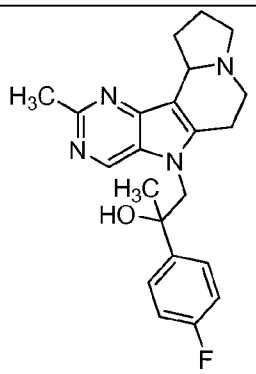
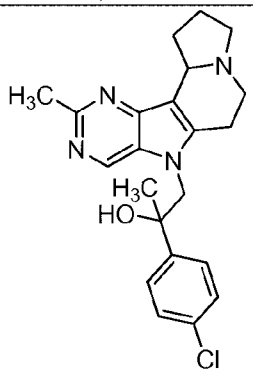
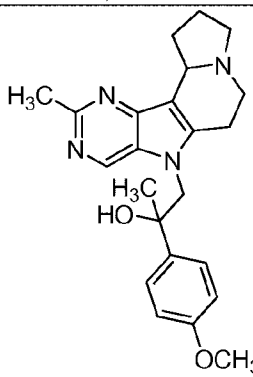
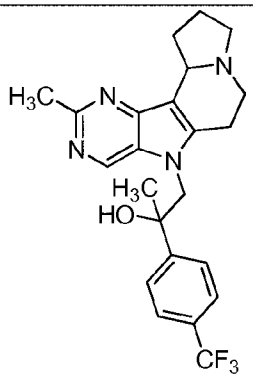
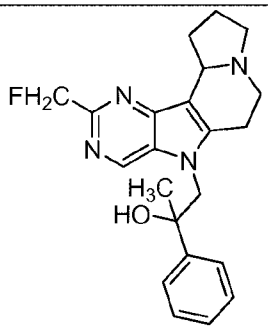
 IV-93 IV-93a, IV-93b	 IV-94 IV-94a, IV-94b	 IV-95 IV-95a, IV-95b	 IV-96 IV-96a, IV-96b
 IV-97 IV-97a, IV-97b	 IV-98 IV-98a, IV-98b	 IV-99 IV-99a, IV-99b	 IV-100 IV-100a, IV-100b
 IV-101 IV-101a, IV-101b	 IV-102 IV-102a, IV-102b	 IV-103 IV-103a, IV-103b	 IV-104 IV-104a, IV-104b

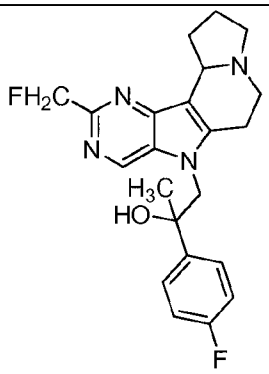
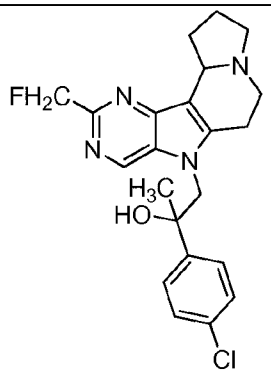
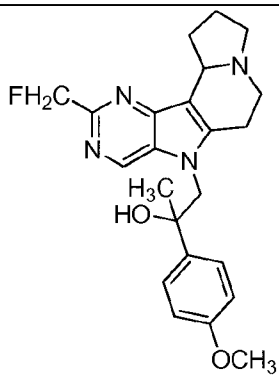
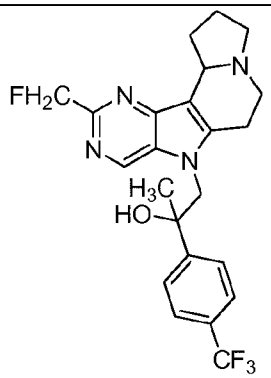
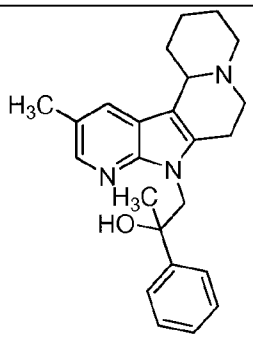
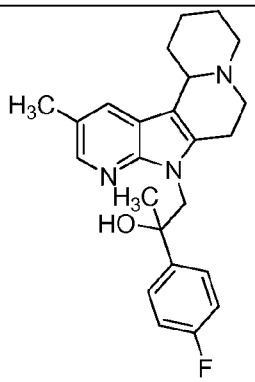
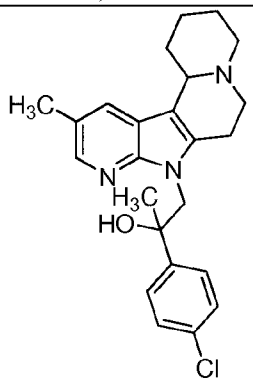
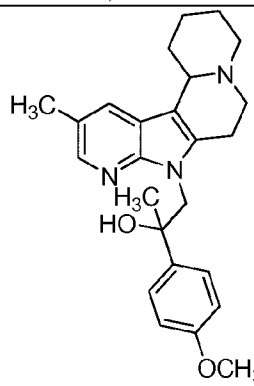
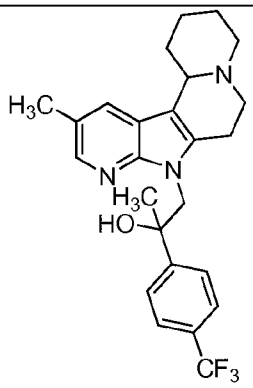
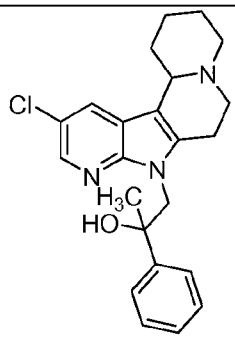
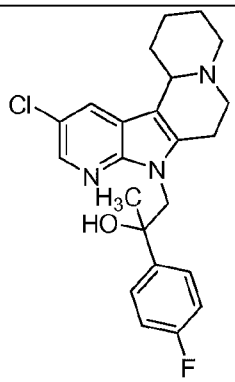
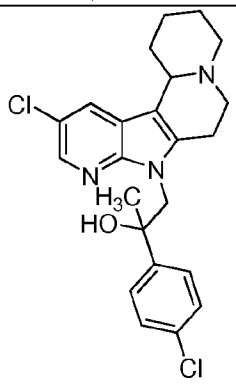
 IV-105 IV-105a, IV-105b	 IV-106 IV-106a, IV-106b	 IV-107 IV-107a, IV-107b	 IV-108 IV-108a, IV-108b
 IV109 IV-109a, IV-109b	 IV-110 IV-110a, IV-110b	 IV-111 IV-111a, IV-111b	 IV-112 IV-112a, IV-112b
 IV-113 IV-113a, IV-113b	 IV-114 IV-114a, IV-114b	 IV-115 IV-115a, IV-115b	 IV-116 IV-116a, IV-116b

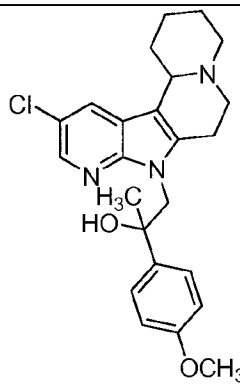
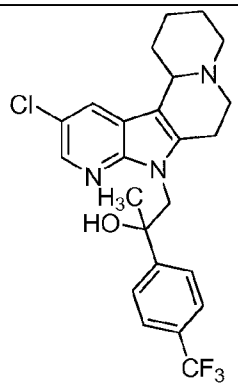
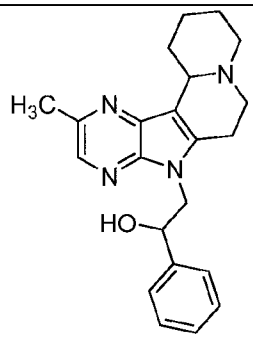
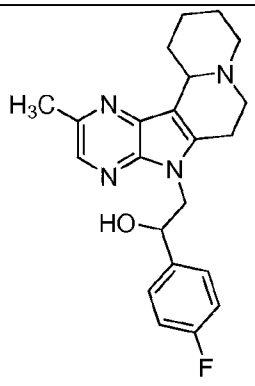
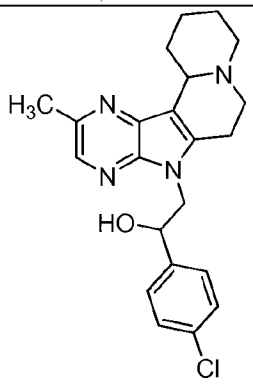
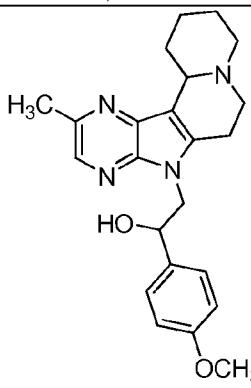
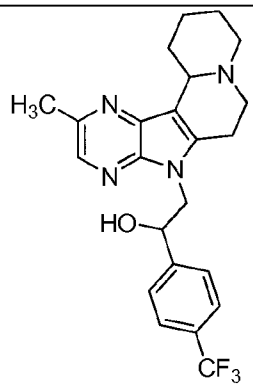
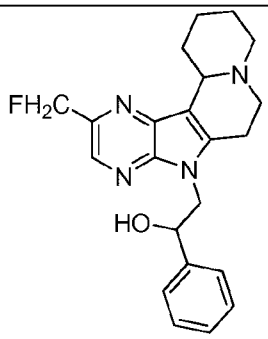
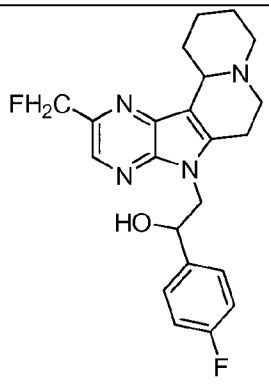
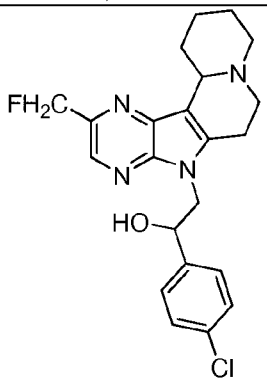
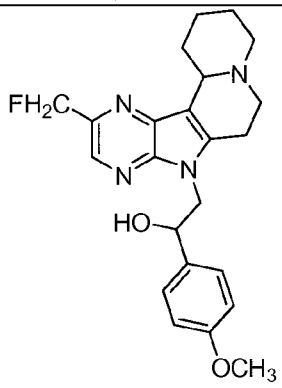
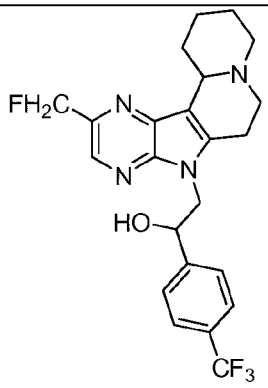
 IV-117 IV-117a, IV-117b	 IV-118 IV-118a, IV-118b	 IV-119 IV-119a, IV-119b	 IV-120 IV-120a, IV-120b
 IV-121 IV-121a, IV-121b	 IV-122 IV-122a, IV-122b	 IV-123 IV-123a, IV-123b	 IV-124 IV-124a, IV-124b
 IV-125 IV-125a, IV-125b	 IV-126 IV-126a, IV-126b	 IV-127 IV-127a, IV-127b	 IV-128 IV-128a, IV-128b

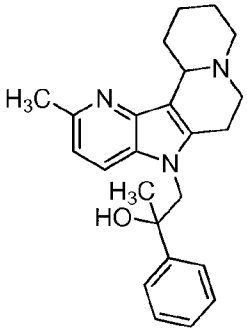
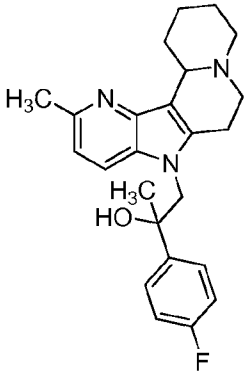
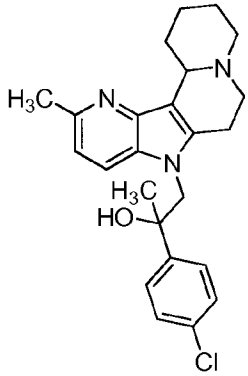
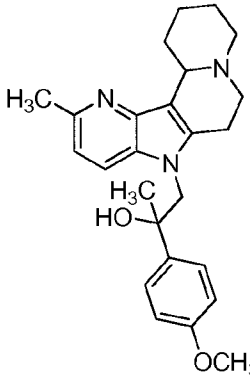
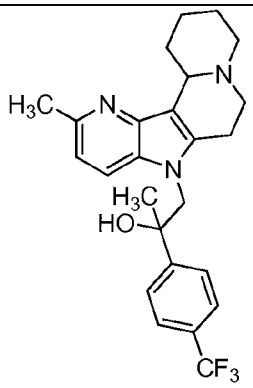
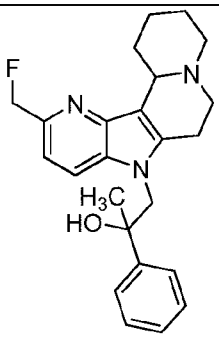
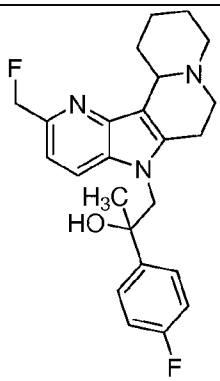
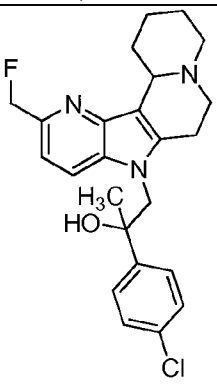
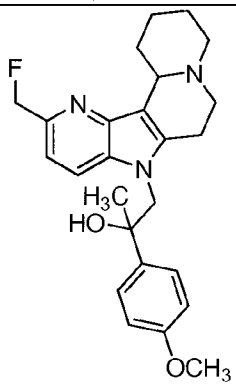
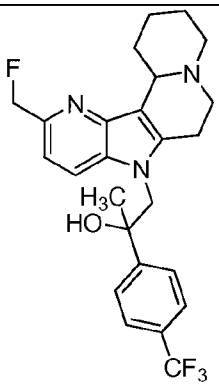
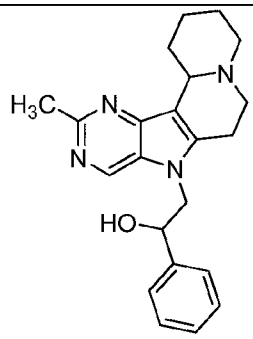
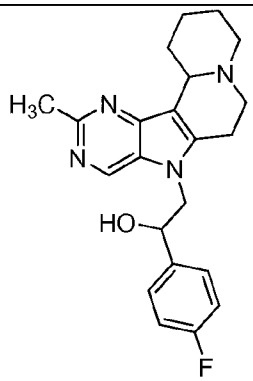
 IV-129 IV-129a, IV-129b, IV-129c, IV-129d	 IV-130 IV-130a, IV-130b, IV-130c, IV-130d	 IV-131 IV-131a, IV-131b, IV-131c, IV-131d	 IV-132 IV-132a, IV-132b, IV-132c, IV-132d
 IV-133 IV-133a, IV-133b, IV-133c, IV-133d	 IV-134 IV-134a, IV-134b, IV-134c, IV-134d	 IV-135 IV-135a, IV-135b, IV-135c, IV-135d	 IV-136 IV-136a, IV-136b, IV-136c, IV-136d
 IV-137 IV-137a, IV-137b, IV-137c, IV-137d	 IV-138 IV-138a, IV-138b, IV-138c, IV-138d	 IV-139 IV-139a, IV-139b, IV-139c, IV-139d	 IV-140 IV-140a, IV-140b, IV-140c, IV-140d

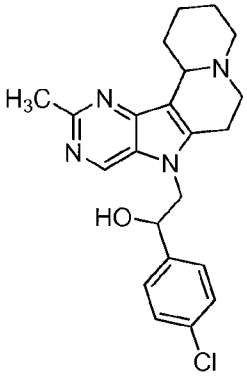
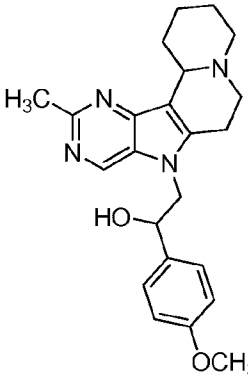
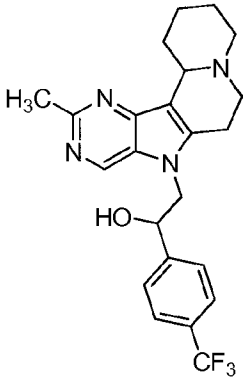
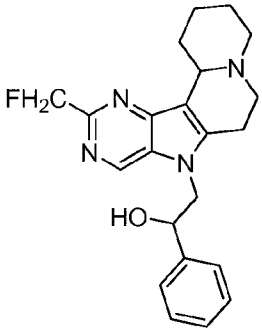
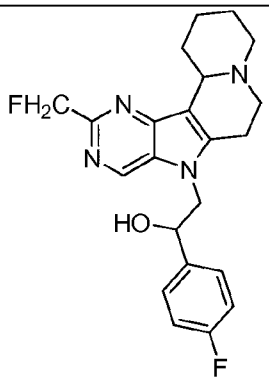
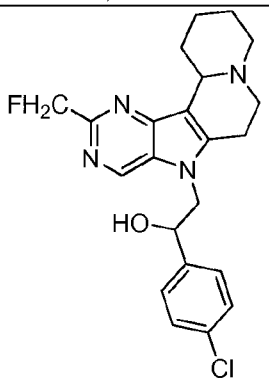
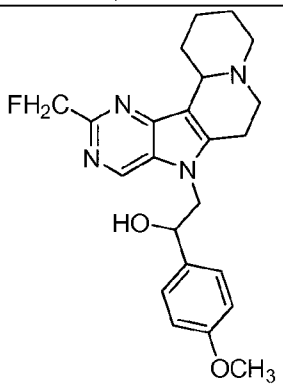
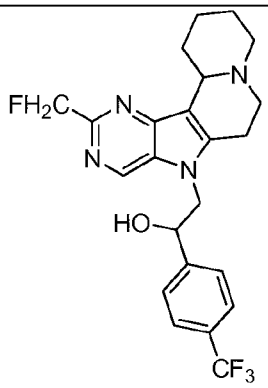
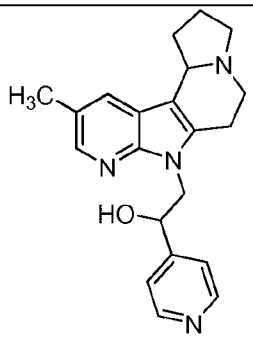
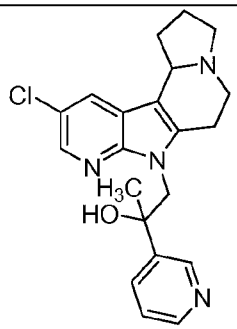
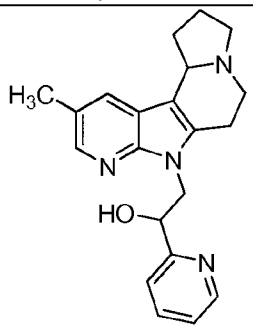
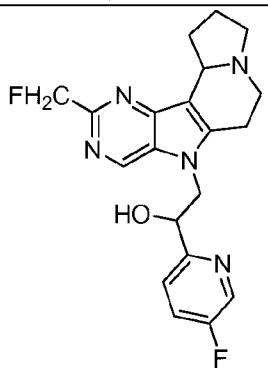
 IV-141 IV-141a, IV-141b, IV-141c, IV-141d	 IV-142 IV-142a, IV-142b, IV-142c, IV-142d	 IV-143 IV-143a, IV-143b, IV-143c, IV-143d	 IV-144 IV-144a, IV-144b, IV-144c, IV-144d
 IV-145 IV-145a, IV-145b, IV-145c, IV-145d	 IV-146 IV-146a, IV-146b, IV-146c, IV-146d	 IV-147 IV-147a, IV-147b, IV-147c, IV-147d	 IV-148 IV-148a, IV-148b, IV-148c, IV-148d
 IV-149 IV-149a, IV-149b, IV-149c, IV-149d	 IV-150 IV-150a, IV-150b, IV-150c, IV-150d	 IV-151 IV-151a, IV-151b, IV-151c, IV-151d	 IV-152 IV-152a, IV-152b, IV-152c, IV-152d

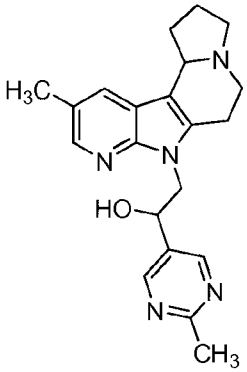
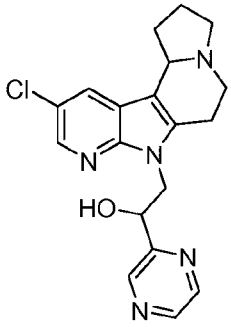
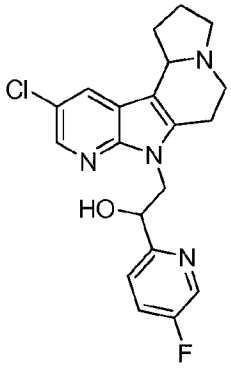
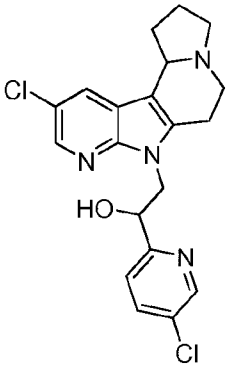
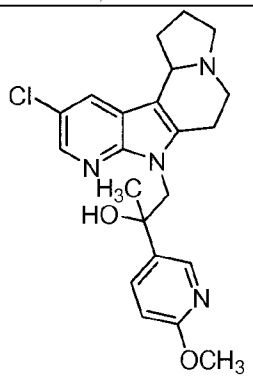
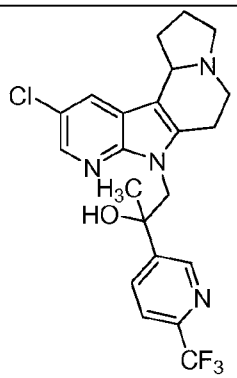
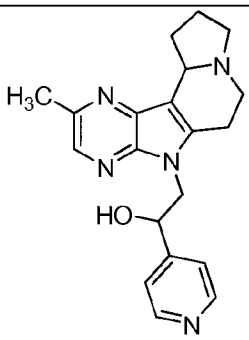
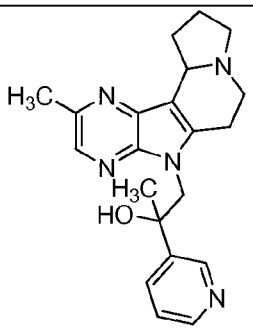
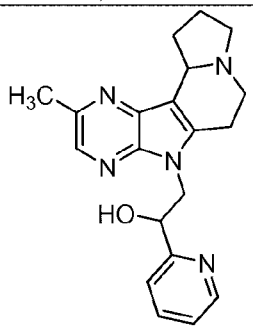
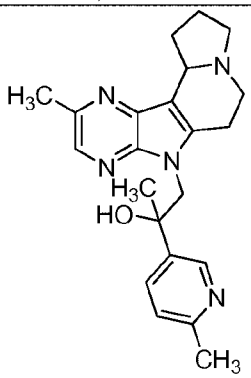
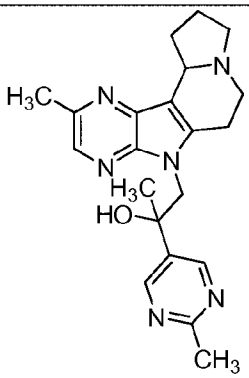
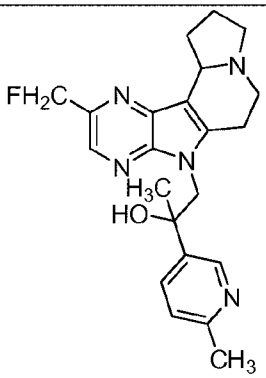
 IV-153 IV-153a, IV-153b, IV-153c, IV-153d	 IV-154 IV-154a, IV-154b, IV-154c, IV-154d	 IV-155 IV-155a, IV-155b, IV-155c, IV-155d	 IV-156 IV-156a, IV-156b, IV-156c, IV-156d
 IV-157 IV-157a, IV-157b, IV-157c, IV-157d	 IV-158 IV-158a, IV-158b, IV-158c, IV-158d	 IV-159 IV-159a, IV-159b, IV-159c, IV-159d	 IV-160 IV-160a, IV-160b, IV-160c, IV-160d
 IV-161 IV-161a, IV-161b, IV-161c, IV-161d	 IV-152 IV-162a, IV-162b, IV-162c, IV-162d	 IV-163 IV-163a, IV-163b, IV-163c, IV-163d	 IV-164 IV-164a, IV-164b, IV-164c, IV-164d

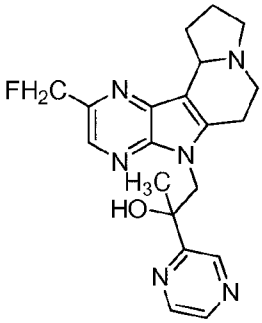
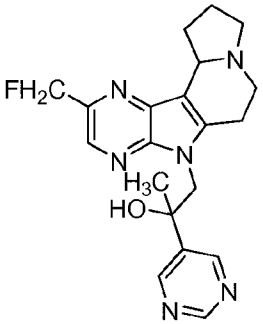
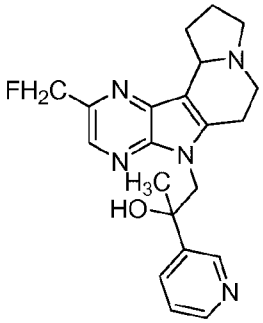
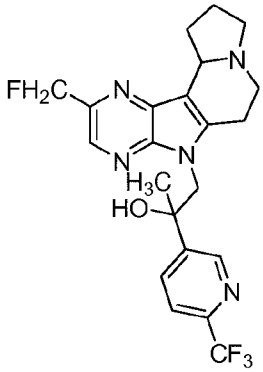
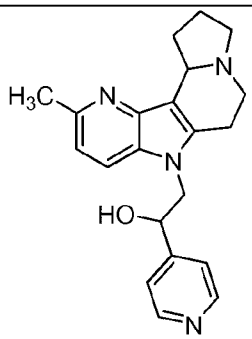
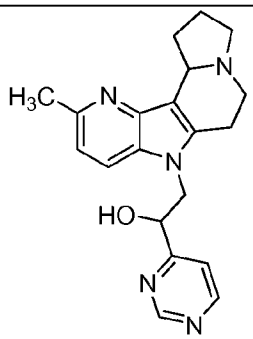
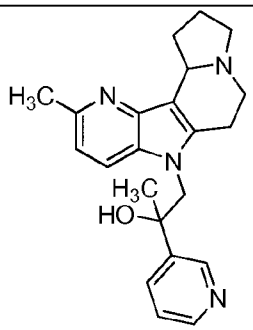
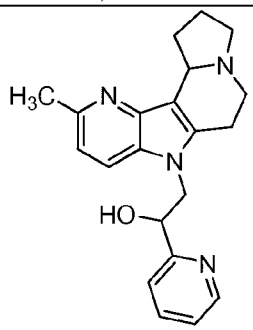
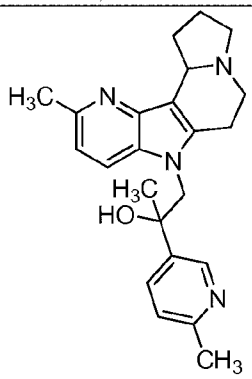
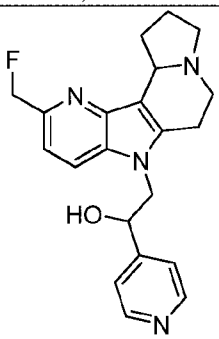
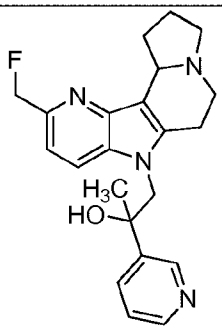
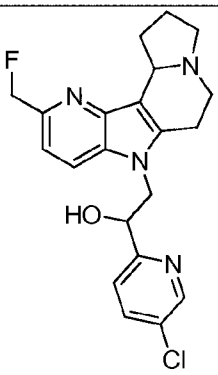
 IV-165 IV-165a, IV-165b, IV-165c, IV-165d	 IV-166 IV-166a, IV-166b, IV-166c, IV-166d	 IV-167 IV-167a, IV-167b, IV-167c, IV-167d	 IV-168 IV-168a, IV-168b, IV-168c, IV-168d
 IV-169 IV-169a, IV-169b, IV-169c, IV-169d	 IV-170 IV-170a, IV-170b, IV-170c, IV-170d	 IV-171 IV-171a, IV-171b, IV-171c, IV-171d	 IV-172 IV-172a, IV-172b, IV-172c, IV-172d
 IV-173 IV-173a, IV-173b, IV-173c, IV-173d	 IV-174 IV-174a, IV-174b, IV-174c, IV-174d	 IV-175 IV-175a, IV-175b, IV-175c, IV-175d	 IV-176 IV-176a, IV-176b, IV-176c, IV-176d

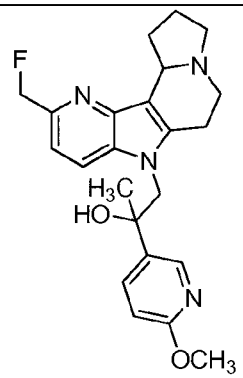
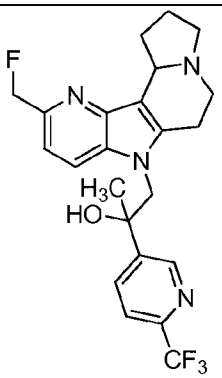
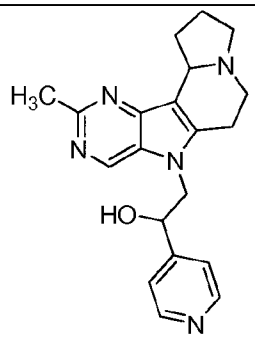
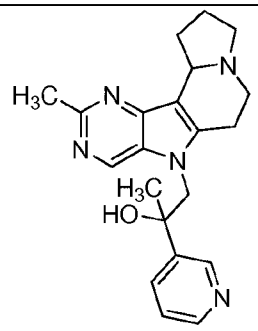
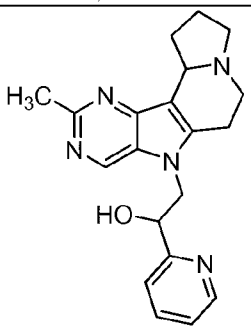
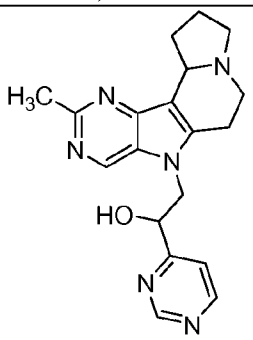
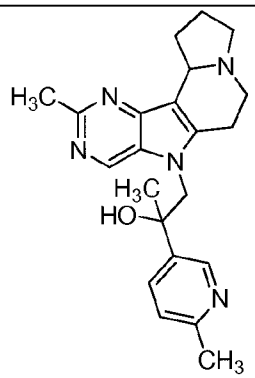
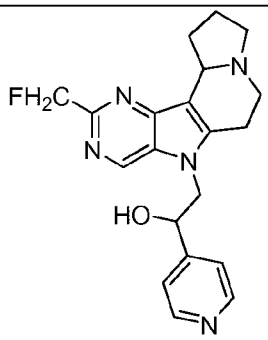
 IV-177 IV-177a, IV-177b, IV-177c, IV-177d	 IV-178 IV-178a, IV-178b, IV-178c, IV-178d	 IV-179 IV-179a, IV-179b, IV-179c, IV-179d	 IV-180 IV-180a, IV-180b, IV-180c, IV-180d
 IV-181 IV-181a, IV-181b, IV-181c, IV-181d	 IV-182 IV-182a, IV-182b, IV-182c, IV-182d	 IV-183 IV-183a, IV-183b, IV-183c, IV-183d	 IV-184 IV-184a, IV-184b, IV-184c, IV-184d
 IV-185 IV-185a, IV-185b, IV-185c, IV-185d	 IV-186 IV-186a, IV-186b, IV-186c, IV-186d	 IV-187 IV-187a, IV-187b, IV-187c, IV-187d	 IV-188 IV-188a, IV-188b, IV-188c, IV-188d

 IV-189 IV-189a, IV-189b, IV-189c, IV-189d	 IV-190 IV-190a, IV-190b, IV-190c, IV-190d	 IV-191 IV-191a, IV-191b, IV-191c, IV-191d	 IV-192 IV-192a, IV-192b, IV-192c, IV-192d
 IV-193 IV-193a, IV-193b, IV-193c, IV-193d	 IV-194 IV-194a, IV-194b, IV-194c, IV-194d	 IV-195 IV-195a, IV-195b, IV-195c, IV-195d	 IV-196 IV-196a, IV-196b, IV-196c, IV-196d
 IV-197 IV-197a, IV-197b, IV-197c, IV-197d	 IV-198 IV-198a, IV-198b, IV-198c, IV-198d	 IV-199 IV-199a, IV-199b, IV-199c, IV-199d	 IV-200 IV-200a, IV-200b, IV-200c, IV-200d

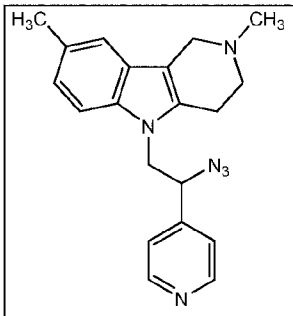
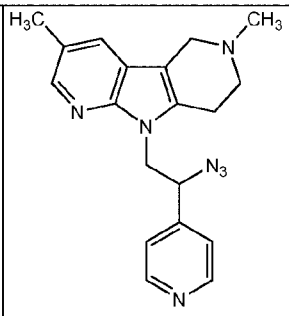
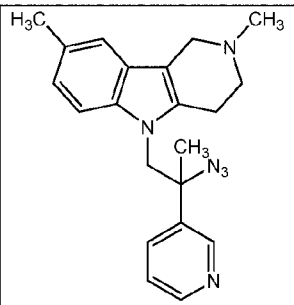
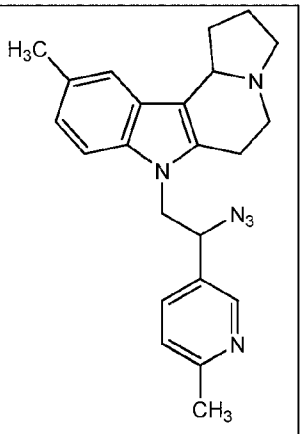
 IV-201 IV-201a, IV-201b, IV-201c, IV-201d	 IV-202 IV-202a, IV-202b, IV-202c, IV-202d	 IV-203 IV-203a, IV-203b, IV-203c, IV-203d	 IV-204 IV-204a, IV-204b, IV-204c, IV-204d
 IV-205 IV-205a, IV-205b, IV-205c, IV-205d	 IV-206 IV-206a, IV-206b, IV-206c, IV-206d	 IV-207 IV-207a, IV-207b, IV-207c, IV-207d	 IV-208 IV-208a, IV-208b, IV-208c, IV-208d
 IV-209 IV-209a, IV-209b, IV-209c, IV-209d	 IV-210 IV-210a, IV-210b, IV-210c, IV-210d	 IV-211 IV-211a, IV-211b, IV-211c, IV-211d	 IV-212 IV-212a, IV-212b, IV-212c, IV-212d

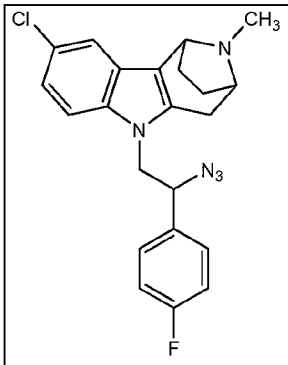
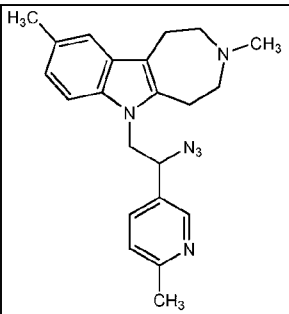
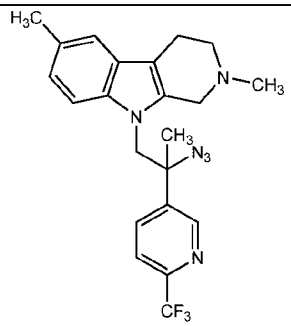
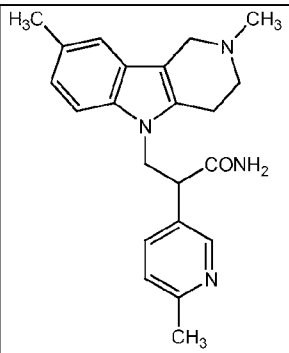
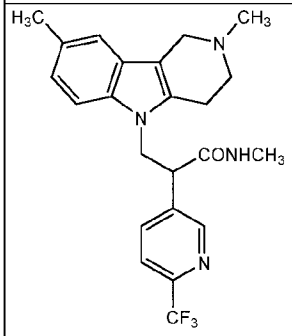
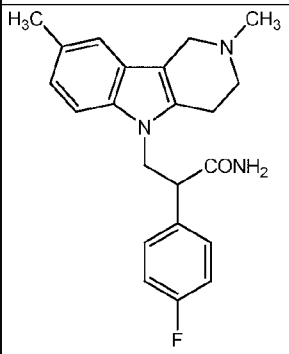
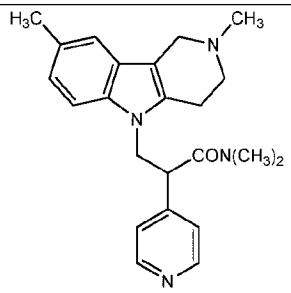
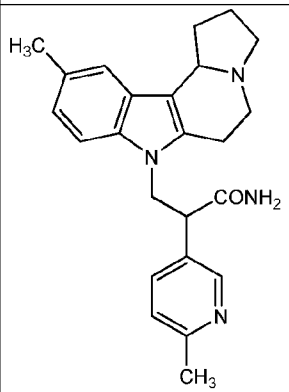
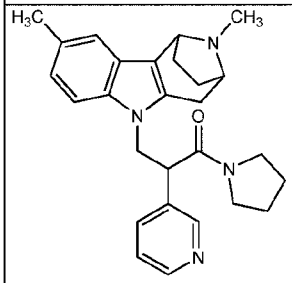
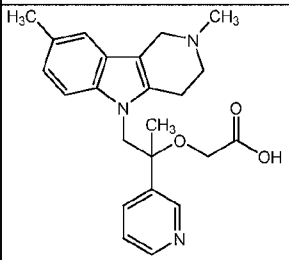
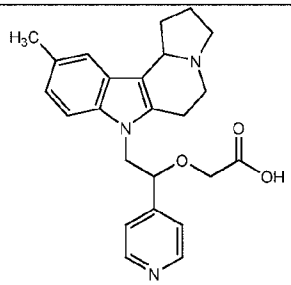
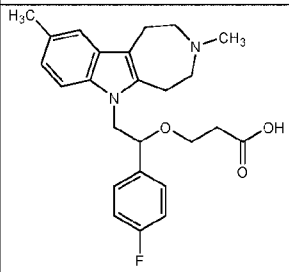
 IV-213 IV-213a, IV-213b, IV-213c, IV-213d	 IV-214 IV-214a, IV-214b, IV-214c, IV-214d	 IV-215 IV-215a, IV-215b, IV-215c, IV-215d	 IV-216 IV-216a, IV-216b, IV-216c, IV-216d
 IV-217 IV-217a, IV-217b, IV-217c, IV-217d	 IV-218 IV-218a, IV-218b, IV-218c, IV-218d	 IV-219 IV-219a, IV-219b, IV-219c, IV-219d	 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

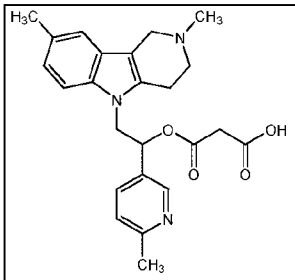
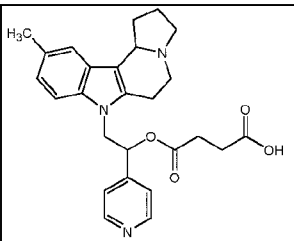
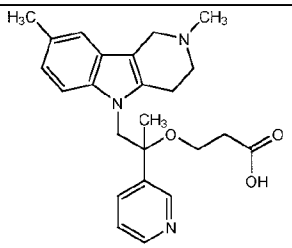
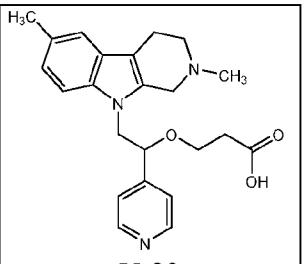
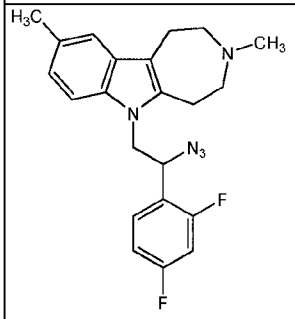
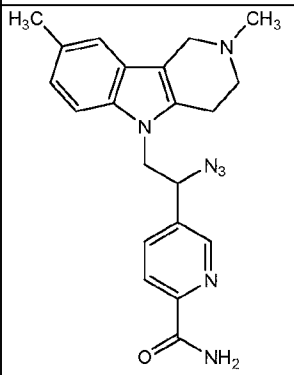
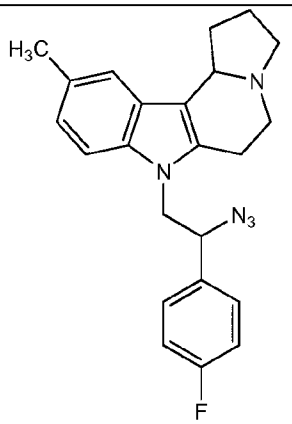
 IV-225 IV-225a, IV-225b, IV-225c, IV-225d	 IV-226 IV-226a, IV-226b, IV-226c, IV-226d	 IV-227 IV-227a, IV-227b, IV-227c, IV-227d	 IV-228 IV-228a, IV-228b, IV-228c, IV-228d
 IV-229 IV-229a, IV-229b, IV-229c, IV-229d	 IV-230 IV-230a, IV-230b, IV-230c, IV-230d	 IV-231 IV-231a, IV-231b, IV-231c, IV-231d	 IV-232 IV-232a, IV-232b, IV-232c, IV-232d
 IV-233 IV-233a, IV-233b, IV-233c, IV-233d	 IV-234 IV-234a, IV-234b, IV-234c, IV-234d	 IV-235 IV-235a, IV-235b, IV-235c, IV-235d	 IV-236 IV-236a, IV-236b, IV-236c, IV-236d

 IV-237 IV-237a, IV-237b, IV-237c, IV-237d	 IV-238 IV-238a, IV-238b, IV-238c, IV-238d	 IV-239 IV-239a, IV-239b, IV-239c, IV-239d	 IV-240 IV-240a, IV-240b, IV-240c, IV-240d
 IV-241 IV-241a, IV-241b, IV-241c, IV-241d	 IV-242 IV-242a, IV-242b, IV-242c, IV-242d	 IV-243 IV-243a, IV-243b, IV-243c, IV-243d	 IV-244 IV-244a, IV-244b, IV-244c, IV-244d

[0634] Table 5. Representative Compounds of the Invention

 V-1 V-1a, V-1b	 V-2 V-2a, V-2b	 V-3 V-3a, V-3b	 V-4 V-4a, V-4b, V-4c,V-4d

 V-5 V-5a, V-5b, V-5c, V-5d	 V-6 V-6a, V-6b	 V-7 V-7a, V-7b	 V-8 V-8a, V-8b
 V-9 V-9a, V-9b	 V-10 V-10a, V-10b	 V-11 V-11a, V-11b	 V-12 V-12a, V-12b, V-12c, V-12d
 V-13 V-13a, V-13b, V-13c, V-13d	 V-14 V-14a, V-14b	 V-15 V-15a, V-15b, V-15c, V-15d	 V-16 V-16a, V-16b

 V-17 V-17a, V-17b	 V-18 V-18a, V-18b, V-18c, V-18d	 V-19 V-19a, V-19b	 V-20 V-20a, V-20b
 V-21 V-21a, V-21b	 V-22 V-22a, V-22b	 V-23 V-23a, V-23b, V-23c, V-23d	

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. Mobile Phase: Hexane:(EtOH:MeOH 80:20) - 93:7. Flow rate: 1 mL/min. Retention Time: Compound No. 138a - 9.939 min. Compound No. 138b - 13.660 min.

[0641] 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:

[0642] 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.

[0643] Analytical Chiral HPLC Data of Compound Nos. II-149a-d.
Column: Chiral Pak AD-H. Column ID: 4.6*250mm, 5μ. Mobile Phase: Hexane (0.2% diethylamine):Isopropanol - 93:7. Flow rate: 1 mL/min. Retention Time: Compound No. II-149a - 15.470 min. Compound No. II-149b - 19.808 min. Compound No. II-149c - 33.280 min. Compound No. II-149d - 39.585 min.

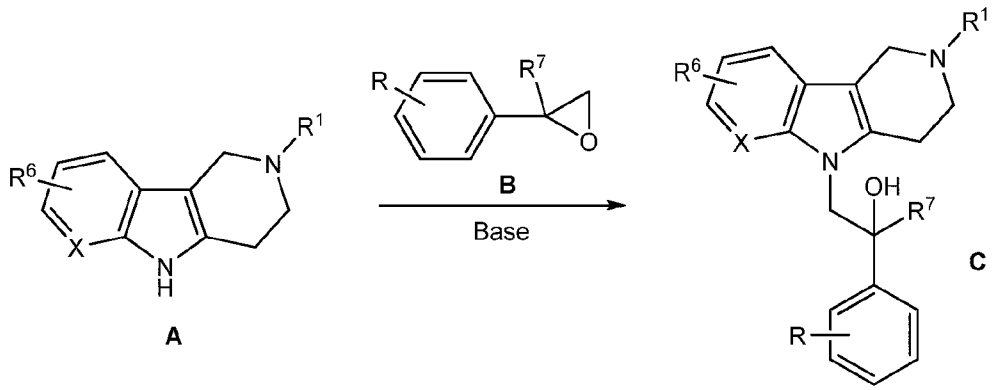
[0644] Chiral Preparative Data of Compound Nos. II-149a-d.
Column: Chiral PAK-AD-H. Column ID: 20*250mm, 5μ. Mobile Phase: Hexane (0.2% diethylamine):Isopropanol - 93:7. Flow rate: 15 mL/min. Solubility: 40 mg/mL in MeOH.

[0645] 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).

[0646] 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



[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, azepino[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.

[0649] All references disclosed herein are incorporated herein by reference in their entireties.

EXAMPLES

Example 1: Preparation of Compound Nos. 1, 1a and 1b

[0650] 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

[0651] 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_3OD, oxalate salt) δ (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

[0652] 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-d6, HCl salt) δ (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

[0653] 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_3OD, HCl salt) δ (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. ^{1}H NMR ($CDCl_3$, 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, 11.81mmol) 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 re-crystallized 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. ^{1}H NMR ($CDCl_3$, 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_3OD, 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-pyridin-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-pyridin-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

[0659] 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, 32.62mmol) and $Pd(PPh_3)_4$ (251mg, 0.217mmol) 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 ($CDCl_3$, 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

[0660] 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 (3x30 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 ($CDCl_3$, 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 N_2 was purged into the reaction mixture. 1,3–Dimethyl barbituric acid (318 mg, 2.04 mmol) and $Pd(PPh_3)_4$ (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 ($CDCl_3$, 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. ^{1}H NMR ($CDCl_3$, freebase) δ (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). ^{1}HNMR (DMSO-d6, TFA salt) δ (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. ^{1}HNMR ($CDCl_3$,

freebase) δ (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

[0666] 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 in to 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) δ (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

[0667] 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 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-carbolin-9-yl)-1-(4-fluoro-phenyl)-ethanol. ^{1}H NMR ($CDCl_3$, Free base) δ (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

[0668] 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 ($CDCl_3$, Free base) 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

[0669] 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. ^{1}H NMR ($CDCl_3$, 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). ^{1}H 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

[0673] 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

[0674] 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_3OD, 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_3OD, Di-TFA salt) δ (ppm): 8.806 (d, 2H), 8.05 (t, 2H), 7.63 (t, 1H), 7.03 (d, 1H), 6.35 (s,

1H), 4.66 (m, 3H), 4.32 (m, 1H), 4.12 (dd, 1H), 3.97 (m, 1H), 3.59 (m, 1H), 3.30 (m, 2H), 3.27 (s, 3H), 3.25 (m,1H) 2.41 (s, 3H), 1.95 (m, 1H), 0.88 (d, 3H), 0.59 (d, 3H).

Example 26: Preparation of Compound Nos. 26, 26a, 26b, 26c and 26d

[0675] 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

[0676] 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

[0677] 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) δ (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) δ (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-d6, 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

[0680] 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_3OD, 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

[0681] A 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-d6, 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) δ (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_3OD, TFA salt) δ (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-ethyloxiran-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}HNMR (DMSO, Oxalate salt) δ (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) δ (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_3OD, Formate salt) δ (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

[0688] 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_3OD, freebase) δ (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

[0689] 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

[0690] 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) δ (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) δ (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) δ (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

[0693] 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

[0694] 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

[0695] 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

[0696] 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

[0697] 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

[0698] 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 (600mg, 15mmol) was added portionwise under nitrogen at 0 °C. 2-Methoxy-5-oxiranyl-pyridine (1.130 g, 7.5mmol) was diluted in DMF (2 mL) 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 (3x40 mL). The combined organic layer was washed with water (4x30 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. ^{1}H NMR ($CDCl_3$, 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 (d, 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

[0699] 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. ^{1}H NMR ($CDCl_3$, 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

[0700] 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. ^{1}H NMR ($CDCl_3$, 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

[0701] 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). ^{1}H NMR ($CDCl_3$, 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

[0702] 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-fluoren-9-yl)-1-pyridin-4-yl-ethanol. ^{1}H NMR ($CDCl_3$, 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

[0703] 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}H NMR (CD_3OD, freebase) δ (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, 4.5mmol) 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 1-(6-chloro-2-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (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 $Pd(PPh_3)_4$ (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}H NMR ($CDCl_3$, freebase) δ (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 N_2. 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: ^{1}H NMR ($CDCl_3$, 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: ^{1}H NMR ($CDCl_3$, 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 18h. 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). ^{1}H 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

[0708] 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 (0.274g, 4.9 mmol) and the reaction mixture was stirred for 10 min at RT. 3-Vinyl pyridine (0.26g, 2.49 mmol) was added and stirring was continued for further 18h 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 (0.040g, 26% yield). ^{1}H 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

[0709] 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. ^{1}H NMR (CD_3OD, 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

[0710] 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 (128mg, 0.74mmol) 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: ^{1}H NMR (CD_3OD, 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_3OD, 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] To a solution of 2-methyl-7-(trifluoromethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 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

[0713] 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. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.19 (m, 2H), 6.98 (d, 1H), 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

[0714] 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. ^{1}H 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

[0715] 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) δ (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) δ (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) δ (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 in to 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 900mg of 1-pyridin-4-yl-2-(2,4,4,8-tetramethyl-1,2,3,4-tetrahydro-pyrido[4, 3-b]indol-5-yl)-ethanol. ^{1}H NMR ($CDCl_3$, 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 b(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

[0719] 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). ^{1}H NMR ($CDCl_3$, 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

[0720] To a solution of carboline (1 g, 4.4mmol) in 10 mL DMF, was added sodium hydride (528 mg, 13.2mmol) 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. ^{1}H NMR ($CDCl_3$, 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. ^{1}H NMR (CD_3OD, 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-indolo[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-Oxiranyl-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. ^{1}H NMR ($CDCl_3$, 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-(oxiran-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_3OD, 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_3OD, 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_3OD, 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_3OD, 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

[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 (5mL) 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. ^{1}H NMR ($CDCl_3$, freebase) δ (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 °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. ^{1}H NMR ($CDCl_3$, freebase) δ (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 (2g, 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 °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 $Pd(PPh_3)_4$ (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. ^{1}H NMR (CD_3OD, 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

[0740] 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 $Pd(PPh_3)_4$ (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. ^{1}H NMR (CD_3OD, 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

[0741] 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 $Pd(PPh_3)_4$ (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. ^{1}H NMR (CD_3OD, 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 $Pd(PPh_3)_4$ (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 (CD_3OD, 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 $Pd(PPh_3)_4$ (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 (CD_3OD, 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 $Pd(PPh_3)_4$ (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 (CD_3OD, 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-enyl)-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 $Pd(PPh_3)_4$ (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 (CD_3OD, 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 $Pd(PPh_3)_4$ (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 (CD_3OD, 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 $Pd(PPh_3)_4$ (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 ($CDCl_3$, 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_3OD, 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.$3H_2O$ (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_3OD, 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_3OD, 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

[0751] 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. ^1H 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

[0752] 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. ^1H NMR (CD_3OD, 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

[0753] 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_3OD, 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 (3x10 mL). The organic layer was washed with water (3x20 mL), followed by brine (25mL), dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, 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 (3x20 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_3OD, 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 $Pd(PPh_3)_4$ (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. ^{1}H NMR (CD_3OD, 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.

[0757] 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. ^{1}H NMR ($CDCl_3$, 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 (s, 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.

[0758] 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. ^{1}H NMR (CD_3OD, 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.

[0759] 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 ($CDCl_3$, 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 ($CDCl_3$, 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 ($CDCl_3$, 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 ($CDCl_3$, 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.

[0760] To an ice-cooled stirred solution of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-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 ($CDCl_3$, 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.

[0761] 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.

[0762] 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.

[0763] 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-triaza-cyclopenta[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) δ (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) δ (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]-benzoicacid 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_3OD, TFA salt) δ (ppm): 7.18 (t, 2H), 7.4 (d, 1H), 7.31 (d, 2H), 7.23 (s , 1H), 7.03 (t, 1H),

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 $Pd(PPh_3)_4$ (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 (3x100 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-pyridin-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 (3x200 mL). The organic layer was washed with water (3x300 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-pyridin-4-yl-ethyl ester (100 mg). ^{1}H NMR (CD_3OD, 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.

[0772] 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-methyloxiran-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 (d, 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.

[0773] 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). ^{1}H NMR ($CDCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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, 2H), 2.6 (m, 1H), 2.46 (s, 3H), 2.41(s, 3H), 2.34 (m, 2H), 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. ^{1}H NMR (CD_3OD, 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.

[0779] 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) δ (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.

[0780] 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): δ (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.

[0781] 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) δ (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.

[0782] 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. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.6 (s, 2H), 7.62 (bs, 2H), 7.23 (s, 1H), 7.0 (d, 1H), 6.98 (d, 1H), 4.9 (m, 1H), 4.8-4.58 (m, 3H), 4.0 (bs, 1H), 3.8 (bs, 1H), 3.6-3.4 (m, 2H), 3.1 (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. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.6 (d, 2H), 7.6 (d, 2H), 7.22 (s, 1H), 7.0 (s, 1H), 6.9 (s, 1H), 4.9 (m, 3H), 4.8 (m, 1H), 4.7 (m, 1H), 3.8-3.6 (m, 2H), 3.2 (m, 2H), 3.18-2.97 (m, 4H), 2.8 (bs, 1H), 2.38 (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. ^{1}H NMR ($CDCl_3$, freebase): δ (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 (119.8mg, 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_3OD, TFA salt) δ (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-amino-2-(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-amino-2-(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) δ (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:H2O (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). ^{1}H NMR (CD_3OD, 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. ^{1}H NMR (CD_3OD, 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)nicotinate 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)nicotinate as starting material. Separation by chiral HPLC provides diastereomers 177a-d.

Example 146: Preparation of Compound Nos. 178 and 178a-b.

[0795] 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.

[0796] 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). ^{1}H NMR (CD_3OD, 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.

[0797] 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.

[0798] 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.

[0799] 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.

[0800] 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. ^{1}H NMR ($CDCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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. ^{1}H NMR ($CDCl_3$, 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 16h (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 ($CDCl_3$, 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}HNMR (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.

[0807] 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. ^{1}HNMR (CD_3OD, 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.

[0808] 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 $Pd(PPh_3)_4$ (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. ^{1}H NMR (CD_3OD, 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.

[0809] 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

extracted with EtOAc (3x15 mL). The combined organic layer was washed with water (2x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (100-200 mesh) eluting with 0-6% MeOH:DCM. The compound was further purified by reverse phase HPLC to obtain 37 mg of product as a freebase. The free base was converted into HCl salt by treatment with ethanolic HCl. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.98 (s, 1H), 8.78 (d, 1H), 8.0 (d, 1H), 7.6 (s, 1H), 7.17 (s, 1H), 6.82 (s, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.82 (m, 1H), 3.61 (m, 1H), 3.18 (m, 5H), 2.90 (s, 3H), 2.51 (s, 3H), 2.38 (s, 3H), 2.01 (s, 3H).

Example 161: Preparation of Compound No. 189.

[0810] 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) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol), potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 3-methylthiophene-2-boronic acid pinacol ester (115 mg, 0.515 mmol) followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material remaining. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated under vacuum and the product isolated by reverse phase HPLC. ^{1}H NMR, (CD_3OD, TFA salt) δ (ppm): 7.32 (m, 2H), 7.13 (m, 2H), 6.97 (d, 1H), 6.79 (s, 1H), 4.67 (d, 1H), 4.40 (d, 1H), 3.83 (m, 1H), 3.58 (m, 1H), 3.14 (m, 5H), 2.40 (s, 6H), 1.87 (s, 3H).

Example 162: Preparation of Compound No. 190.

[0811] To a degassed 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), 5-methylthiophene-2-boronic acid pinacol ester (100 mg, 0.575 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-DME (4 mL) and water (2 mL) was added $Pd(PPh_3)_4$ (17 mg, 0.0147 mmol). The reaction mixture was heated at 90 °C for 45 min. The reaction mixture was concentrated under reduced pressure and the residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-(2-(5-methylthiophen-2-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR, (CD_3OD, TFA salt) δ (ppm): 7.3 (s, 1H), 7.0 (m, 2H), 6.71 (d, 1H), 6.58 (d, 1H), 4.72 (m, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 3.51 (m, 1H), 3.12 (s, 3H), 3.03 (m, 4H), 2.8 (m, 2H), 2.4 (s, 3H), 2.2-2.3 (m, 5H).

Example 163: Preparation of Compound No. 191.

[0812] To a degassed 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), 1-methylindole-5-boronic acid pinacol ester (149 mg, 0.579 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-DME (4 mL) and water (2 mL) was added $Pd(PPh_3)_4$ (17 mg, 0.0147 mmol). The reaction mixture was heated at 90 °C for 45 min. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-(2-(1-methyl-1H-indol-5-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR, (CD_3OD, TFA salt) δ (ppm): 7.21-7.38 (m, 2H), 7.2 (s, 1H), 7.04 (m, 2H), 6.9 (d, 1H), 6.8 (d, 1H), 6.21 (s, 1H), 4.62 (m, 1H), 4.35 (m, 1H), 3.65 (s, 3H), 3.58 (m, 2H), 3.01 (s, 3H), 2.81 (m, 2H), 2.6 (m, 4H), 2.41 (s, 3H), 2.21 (m, 2H).

Example 164: Preparation of Compound Nos. 192 and 192a-d.

[0813] To a solution of ethyl 4-(1-hydroxy-2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)ethyl)picolinate (1 eq) in EtOH is added sodium hydroxide (4 eq, in water) and heated to 65 °C. After conversion of starting material (TLC and LCMS), the EtOH and water are removed under reduced pressure. The crude product is passed through HPLC to yield the title racemic compound. Separation by chiral HPLC provides enantiomers 192a-d.

Example 165: Preparation of Compound Nos. 193 and 193a-b.

[0814] To a degassed solution of 10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (50 mg, 0.22 mmol), potassium phosphate (93 mg , 0.44 mmol), L-proline (2 mg, 0.01 mmol) and Cu(I)iodide (8 mg, 0.04 mmol) in DMF (1 mL) was added 5-(1-bromoprop-1-en-2-yl)-2-methylpyridine (93 mg, 0.44 mmol). The reaction mixture was stirred at 120 °C for 18 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was filtered through Celite and the filtrate was diluted with water (50 mL), extracted with EtOAc (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 10-methyl-7-(2-(6-methylpyridin-3-yl)prop-1-enyl)-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole. ^{1}H NMR, (CD_3OD, formate salt) δ (ppm): 8.65 (s, 1H), 8.0 (d, 1H), 7.4 (d, 1H), 7.35 (s, 1H), 7.15 (d, 1H), 7.08 (d, 2H), 5.0 (t, 1H), 3.6 (m, 3H), 3.4 (m, 1H), 3.09 (q, 2H), 2.85 (m, 1H), 2.6 (s, 3H), 2.42 (s, 3H), 2.2 (m, 3H), 2.0 (s, 3H). Chiral HPLC provided the enantiomers 193a and 193b.

Example 166: Preparation of Compound Nos. 194 and 194a-b.

[0815] To a degassed solution of 10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (50 mg, 0.22 mmol), potassium phosphate (93 mg , 0.44 mmol), L-proline (2 mg, 0.01 mmol) and Cu(I)iodide (8 mg, 0.04 mmol) in DMF (1 mL) was added 1-(1-bromoprop-1-en-2-yl)-4-fluorobenzene (95 mg, 0.44 mmol). The reaction mixture was stirred at 120 °C for 18h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was filtered through Celite. The filtrate was diluted with water (50 mL), extracted with EtOAc (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 7-(2-(4-fluorophenyl)prop-1-enyl)-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole. ^{1}H NMR, (CD_3OD, TFA salt) δ (ppm): 7.65 (t, 2H), 7.35 (s, 1H), 7.19 (t, 2H), 7.1 (m, 2H), 6.95 (s, 1H), 5.1 (t, 1H), 3.79 (m, 1H), 3.62 (m, 2H), 3.41 (m, 1H), 3.1 (m, 2H), 2.75 (m, 1H), 2.41 (s, 3H), 2.28 (m, 3H), 1.95 (s, 3H). Chiral HPLC provided the enantiomers 194a and 194b.

Example 167: Preparation of Compound Nos. 195 and 195a-b.

[0816] This compound is prepared in analogous fashion to Compound Nos. 30 and 30a-b, using 5-(2-methyloxiran-2-yl)oxazole as the oxirane reagent. Separation by chiral HPLC provides enantiomers 195a-b.

Example 168: Preparation of Compound Nos. 196 and 196a-b.

[0817] To a stirred solution of 2,3,4,9-tetrahydro-2,6-dimethyl-1H-pyrido[3,4-b]indole (500 mg, 2.5 mmol) in DMF (2 mL) was added NaH (300 mg, 7.5 mmol). After stirring for 5 min, a solution of 2-methyl-5-(2-methyloxiran-2-yl)pyridine (558 mg, 3.7 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 the title compound. The product was further purified by chiral HPLC separation to give enantiomers 196a and 196b. ^{1}H NMR, ($CDCl_3$, freebase) δ (ppm): 8.6 (s, 1H), 7.6 (d, 1H), 7.27 (s, 1H), 7.1 (d ,1H), 7.05 (d, 1H), 6.9 (d, 1H), 4.1 (d, 1H), 4.0 (d, 1H), 3.62 (d, 1H), 3.43 (d ,1H), 2.8 (m, 4H), 2.59 (s, 3H), 2.5 (s, 3H), 2.4 (s, 3H), 1.6 (s, 3H).

Example 169: Preparation of Compound Nos. 197 and 197a-b.

[0818] To a solution of 9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (100 mg, 0.422 mmol) in DMF (1 mL) was added sodium hydride (53 mg,

1.326 mmol). After stirring for 5 min, a solution of toluene-4-sulfonic acid 2- (6-methyl-pyridin-3-yl) -ethyl ester (386 mg, 1.326 mmol) in DMF (1 mL) was added dropwise at 0 °C and the reaction mixture stirred at RT for 6h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice-cold water and extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (5x20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 9-methyl-6-[2-(6-methyl-pyridin-3-yl)-ethyl]-2,3,4,5,6,10c-hexahydro-1H-3a, 6-diaza-cyclopenta[c]fluorene. ^{1}H NMR, ($CDCl_3$, freebase) δ (ppm): 8.07 (s, 1H), 7.28 (m, 2H), 7.07 (d, 1H), 7.0 (s, 2H), 4.72 (m, 1H), 4.3 (m, 1H), 4.18 (m, 1H), 3.31 (m, 1H), 3.2 (m, 1H), 3.12 (m, 1H), 3.0 (m, 2H), 2.7 (m, 1H), 2.51 (m, 1H), 2.5 (s, 3H), 2.48 (s, 3H), 2.4 (d, 1H), 2.28 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H), 1.8 (m,1H). Chiral HPLC provided enantiomers 197a and 197b.

Example 170: Preparation of Compound Nos. 198 and 198a-d.

[0819] To a solution of 9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (200 mg, 0.88 mmol) in DMF (10 mL) was added sodium hydride (96 mg, 2.6 mmol). After stirring for 5 min, a solution of 2-methyl-5-oxiranyl-pyridine (175 mg, 1.3 mmol) in DMF (1 mL) was added dropwise into the reaction mixture, which was stirred at RT for 5h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice-cold water and extracted with EtOAc (3x25 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 yield 2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-1-(6-methyl-pyridin-3-yl)-ethanol. The product was further purified by chiral HPLC separation to give enantiomers 198a and 198b. Enantiomers 198c and 198d are also obtained by this method. ^{1}H NMR, ($CDCl_3$, freebase) δ (ppm): 8.45 (s, 1H), 7.6 (dd, 1H), 7.22 (m, 2H), 7.1 (t, 1H), 7.05 (t, 1H), 5.08 (q, 1H), 4.8 (dt, 1H), 3.5 (m, 2H), 3.4 (m, 2H), 3.1 (d, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 2.6 (m, 2H), 2.5 (s, 3H), 2.41 (s, 3H), 2.1 (m, 3H).

Example 171: Preparation of Compound Nos. 199 and 199a-b.

[0820] To a degassed solution of 11-methyl-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizine (100 mg, 0.41 mmol), copper(I)iodide, L-proline (9.6 mg, 0.08 mmol) and potassium phosphate (176 mg, 0.83 mmol) in DMF was added dropwise 1-(1-bromoprop-1-en-2-yl)-4-fluorobenzene (107 mg, 53 mmol) and the reaction mixture was stirred at 85 °C

overnight. The DMF was evaporated under reduced pressure, and the residue was diluted with water and the solid filtered. The solid material was purified by silica gel chromatography (100-200 mesh) eluting with 0-5% MeOH-DCM. The product was further purified by reverse phase HPLC followed by chiral HPLC separation to give enantiomers 199a and 199b. ^{1}H NMR, ($CDCl_3$, freebase) δ (ppm): 7.5 (t, 2H), 7.4 (s, 1H), 7.1 (t, 2H), 7.08 (d, 1H), 7.0 (d, 1H), 6.8 (s, 1H), 3.5 (m, 1H), 3.4 (m, 1H), 3.0 (m, 2H), 2.6 (m, 3H), 2.4 (s, 3H), 2.05 (m, 1H), 2.0 (s, 3H), 1.8 (m, 2H),1.5 (m, 3H).

Example 172

[0821] Compound Nos. 200-210, 212-219 and 223 were prepared as described in PCT publication WO2009-055828.

Example 173

[0822] Compound Nos. 211, 225 and 231 were prepared as described in PCT publication WO2009-120720.

Example 174

[0823] Compound Nos. 224 and 239 were prepared as described in PCT publication WO2009-120717.

Example 175

[0824] Compound Nos. 236-237, 243, 250, 252-254, 256-259 and 261-268 were prepared as described in PCT publication WO2010-051501.

Example 176

[0825] Compound Nos. 172, 221-222, 226-230, 232-235, 238, 240-242, 244-249 and 251 were prepared as described in PCT publication WO2010-051503.

Example 177

[0826] Compound Nos. 255 and 260 were prepared as described in PCT publication WO2010-127177.

Example 178: Preparation of Compound Nos. 220 and 220a-b.

[0827] This compound is prepared in analogous fashion to Compound Nos. 30 and 30a-b, using 4-(2-methyloxiran-2-yl)oxazole as the oxirane reagent. Separation by chiral HPLC provides enantiomers 220a-b.

Example 179: Preparation of Compound No. 269.

[0828] To a degassed solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (0.08 g, 0.0004 mol), potassium tert-butoxide (0.112 g, 0.001 mol), (E/Z)-4-(1-bromoprop-1-en-

2-yl)-2-methoxypyridine (0.091g, 0.0004 mol) and 9,9-dimethyl-4,5-bis (diphenylphosphine) xanthene (0.023 g, 0.00004 mol) in toluene (3 mL) was added $Pd_2(dba)_3$ (0.0219 g, 0.000064 mol) and irradiated the reaction mixture at 80 °C for 30 min. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3x20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH-DCM) followed by preparative TLC to yield the title compound. ^{1}H NMR (CD_3OD, Oxalate salt) δ (ppm): 8.19 (d, 1H), 7.27 (s, 1H), 7.24 (m, 2H), 7.05 (m, 2H), 7.0 (s, 1H), 4.58 (s, 3H), 3.93 (s, 3H), 3.65 (m, 2H), 3.17 (m, 4H), 2.41 (s, 3H), 2.01 (s, 3H).

Example 180: Preparation of Compound No. 270.

[0829] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (50 mg, 0.129 mmol), $Pd(PPh_3)_4$ (7.4 mg, 0.0064) in DME (2 mL) were added potassium carbonate (17.8 mg, 0.1287 mmol), water (1 mL) and naphthalene-2-boronic acid (44 mg, 0.258 mmol) and the reaction mixture refluxed for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was dissolved in water (10 mL), extracted into EtOAc (3x25 mL) and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (2.5% MeOH-DCM) to yield the title compound. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.02 (s, 1H), 7.82 (m, 3H), 7.79 (d, 1H), 7.42 (m, 2H), 7.21 (s, 1H), 7.11 (m, 2H), 6.95 (m, 1H), 3.78 (s, 2H), 2.84 (m, 4H), 2.60 (s, 3H), 2.40 (s, 3H), 2.12 (s, 3H).

Example 181: Preparation of Compound No. 271

[0830] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (50 mg, 0.129 mmol) and $Pd(PPh_3)_4$ (7.4 mg, 0.0064) in DME (2 mL) were added potassium carbonate (17.8 mg, 0.1287 mmol), water (1 mL) and naphthalene-2-boronic acid (44 mg, 0.258 mmol), and the reaction mixture refluxed for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was dissolved in water (10 mL), extracted into EtOAc (3x25 mL), washed with brine, and concentrated to afford crude material, which was purified by silica gel column chromatography (2.5% MeOH-DCM) to yield the desired compound. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 7.64 (m, 3H), 7.34 (m, 1H), 7.29 (m, 2H), 7.18 (m, 2H), 6.97 (m, 1H), 6.82 (m, 2H), 3.67 (s, 2H), 2.63 (d, 2H), 2.38-2.47 (m, 8H), 1.84 (s, 3H).

Example 182: Preparation of Compound Nos. 272 and 272a-b.

[0831] A solution of 8-chloro-5-(2-(4-fluorophenyl)allyl)-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (150 mg, 0.423 mmol) and 10% Pd/C (10 mg) in MeOH:acetic acid (9 mL, 10:1) was hydrogenated in a Parr shaker at RT and 50 psi for 18h. The reaction mixture was filtered through a Celite bed and the filtrate concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield the title compound. The product was further purified by reverse phase HPLC followed by chiral HPLC separation to give enantiomers 272a and 272b. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.41-7.43 (m, 2H), 7.2-6.94 (m, 6H), 4.62 (m, 1H), 4.29 (m, 2H), 4.06 (m, 1H), 3.6 (m, 1H), 3.37 (m, 2H), 3.0-2.9 (m, 5H), 1.45 (m, 3H).

Example 183: Preparation of Compound No. 273.

[0832] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (50 mg, 0.128 mmol) and $Pd(PPh_3)_4$ (7.4 mg, 0.0064) in DME (2 mL) were added potassium carbonate (17.8 mg, 0.1287 mmol), water (1 mL) and 1-methyl-1H-pyrazole-5-boronic acid pinacol ester (53.5 mg, 0.2574 mmol) and the reaction mixture refluxed for 2.5h. The reaction mixture was cooled to RT, and concentrated to dryness. The residue was extracted into EtOAc, washed with brine, and concentrated under reduced pressure. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.40 (d, 1H), 7.21 (s, 1H), 7.15 (m, 2H), 6.87 (d, 1H), 6.38 (s, 1H), 4.63 (d, 1H), 4.23 (d, 1H), 3.74 (m, 1H), 3.41 (m, 1H), 3.16 (s, 3H), 3.09 (s, 3H), 2.81 (m, 2H), 2.19 (s, 3H), 2.14 (s, 3H).

Example 184: Preparation of Compound Nos. 274 and 274a-b.

[0833] A solution of 1-(4-allyl-2,4,8-trimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-(4-fluoro-phenyl)-propan-2-ol (300 mg, 0.738 mmol) in 6N HCl (10 mL) was stirred at 80 °C for 2h. The progress of reaction mass was monitored by TLC and LCMS. The reaction mixture was basified with saturated sodium bicarbonate solution and extracted with EtOAc (3x25 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (1% MeOH-DCM) to yield 4-allyl-5-[2-(4-fluoro-phenyl)-propenyl]-2,4,8-trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. The product is further purified by reverse phase HPLC followed by chiral HPLC separation to give enantiomers 274a and 274b. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 7.62 (m, 2H), 7.27 (s, 1H), 7.20 (m, 2H), 7.04 (m, 3H), 6.78-6.82 (m, 1H), 5.18 (d, 2H), 4.78 (d, 1H), 4.37 (d, 1H), 3.58 (m,2H), 3.18 (s, 3H), 2.40 (s, 3H), 2.38 (d, 2H), 1.82 (s, 3H), 1.58 (s, 3H).

Example 185: Preparation of Compound No. 275.

[0834] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) and $Pd(PPh_3)_4$ (15 mg, 0.0128) in DME (4 mL) were added 1-methylpyrazole-4-boronic acid pinacol ester (108 mg, 0.515 mmol), potassium carbonate (3 6 mg, 0.257 mmol) and water (2 mL) and the reaction mixture refluxed for 45 min. The reaction mixture was cooled to RT and the solvent was removed under reduced pressure. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.27 (s, 1H), 7.19 (s, 1H), 7.04 (d, 1H), 6.98 (d, 1H), 6.46 (m, 2H), 4.78 (d, 1H), 4.39 (d, 1H), 3.90 (m, 1H), 3.76 (s, 3H), 3.44 (m, 1H), 3.08 (s, 3H), 2.86 (m, 2H), 2.42 (s, 3H), 2.21 (s, 3H).

Example 186: Preparation of Compound No. 276.

[0835] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128), 2-fluoropyridine-5-boronic acid pinacol ester (115 mg, 0.515 mmol), potassium carbonate (36 mg, 0.257 mmol) and water (2 mL) and the reaction mixture refluxed for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.79 (s, 1H), 7.60 (m, 1H), 7.21 (s, 1H), 7.05 (d, 1H), 6.93 (d, 1H), 6.88 (s, 1H), 6.82 (d, 1H), 4.62 (d, 1H), 4.25 (d, 1H), 3.78 (m, 1H), 3.42 (m, 1H), 3.13 (s, 3H), 2.87 (m, 2H), 2.38 (m, 6H).

Example 187: Preparation of Compound No. 277.

[0836] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128), 5-methylthiophene-2-boronic acid pinacol ester (115 mg, 0.515 mmol), potassium carbonate (36 mg, 0.257 mmol) and water (2 mL) were added followed by nitrogen purging and water (2 mL) and the reaction mixture refluxed for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.25 (s, 1H), 7.13 (d, 1H), 7.0 (d, 1H), 6.82 (d, 1H), 6.60 (d, 1H), 6.43 (s, 1H), 4.76 (d, 1H), 4.40 (d, 1H), 3.67 (m, 1H), 3.43 (m, 1H), 3.13 (s, 3H), 2.81-2.93 (m, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H).

Example 188: Preparation of Compound No. 278.

[0837] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128), 5-methylthiophene-2-boronic acid pinacol ester (115 mg, 0.515 mmol), potassium carbonate (36 mg, 0.257 mmol) and water (2 mL) and the reaction mixture

refluxed for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.27 (s, 1H), 7.09 (m, 3H), 6.98 (s, 1H), 6.79 (s, 1H), 4.78 (d, 1H), 4.40 (d, 1H), 3.87 (m, 1H), 3.61 (m, 1H), 3.0-3.20 (m, 5H), 2.45 (s, 3H), 2.40 (s, 3H), 1.89 (s, 3H).

Example 189: Preparation of Compound No. 279.

[0838] To a degassed solution of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)prop-1-en-2-yl trifluoromethanesulfonate (100 mg, 0.257 mmol) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol), potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 2-(dimethylamino)pyrimidine-5-boronic acid pinacol ester (128 mg, 0.515 mmol). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated and residue purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.98 (s, 2H), 7.22 (s. 1H), 7.08 (d, 1H), 6.99 (d, 1H), 6.80 (s, 1H), 4.65 (d, 1H), 4.31 (d, 1H), 3.80 (m, 1H), 3.51 (m, 1H), 3.01-3.81 (m, 11H), 2.40 (s, 3H), 2.37 (s, 3H).

Example 190: Preparation of Compound No. 280.

[0839] To a solution of (4-(1-bromoprop-1-en-2-yl)phenyl)(methyl)sulfane (132 mg, 0.55 mmol) in DMF (1 mL) were added potassium phosphate (212 mg, 2 mmol), copper(I)iodide (9.5 mg, 0.05 mmol), L-proline (11.5 mg, 0.1 mmol) and 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (110 mg, 0.5 mmol) and the reaction mixture stirred at 85 °C for 16 h. Ice water was added into the reaction mixture and the solid obtained was filtered. The residue was purified by silica gel column chromatography (0-3% MeOH-DCM) to yield the title compound. ^{1}H NMR (CD_3OD, oxalate salt) δ (ppm): 7.58 (m, 3H), 7.37 (d, 2H), 7.21 (s, 2H), 7.0 (s, 1H), 4.60 (s, 2H), 3.76 (s, 2H), 3.16 (m, 5H), 2.57 (s, 3H), 1.97 (s, 3H).

Example 191: Preparation of Compound No. 281.

[0840] To a solution of 1-(1-bromoprop-1-en-2-yl)-4-(methylsulfonyl)benzene (150 mg, 0.55 mmol) in DMF (1 mL) were added potassium phosphate (212 mg, 2 mmol), copper(I)iodide (9.5 mg, 0.05 mmol), L-proline (11.5 mg, 0.1 mmol) and 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (110 mg, 0.5 mmol). The reaction mixture was stirred at 85 °C for 16 h. Ice water was added into the reaction mixture and the solid obtained was filtered. The residue was purified by silica gel column chromatography (0-3% MeOH-DCM) to yield the title compound.

^{1}H NMR (CD_3OD, oxalate salt) δ (ppm): 8.04 (d, 2H), 7.91 (d, 2H), 7.58 (s, 1H), 7.21 (d, 2H), 7.19 (s, 1H), 4.57 (s, 2H), 3.70 (s, 2H), 3.15-3.20 (m, 8H), 2.01 (s, 3H).

Example 192: Preparation of Compound No. 282.

[0841] 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) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol), potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 1H-benzimidazole-5-boronic acid pinacol ester (125 mg, 0.515 mmol). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated and the residue was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 9.37 (s, 1H), 8.02 (s, 1H), 7.90 (m, 2H), 7.37 (s, 1H), 7.16 (m, 3H), 4.76 (bs, 1H), 4.40 (bs, 1H), 3.90 (bs, 1H), 3.60 (bs, 1H), 3.18 (m, 5H), 2.41 (s, 3H), 2.07 (s, 3H).

Example 193: Preparation of Compound No. 283.

[0842] 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) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg), potassium carbonate (36 mg), water (1 mL) and 1-methylindole-5-boronic acid pinacol ester (132 mg). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated and residue was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.80 (d, 1H), 7.42 (d, 1H), 7.39 (d, 1H), 7.31 (s, 1H), 7.20 (s, 1H), 7.18 (d, 1H), 7.10 (d, 1H), 6.91 (s, 1H), 6.43 (d, 1H), 4.73 (d, 1H), 4.38 (d, 1H), 3.81 (s, 4H), 3.60 (m, 1H), 3.17 (m, 5H), 2.42 (s, 3H), 1.98 (s, 3H).

Example 194: Preparation of Compound No. 284.

[0843] 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) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg), potassium carbonate (36 mg), water (1 mL) and 1-methylindole-5-boronic acid pinacol ester (132 mg). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent removed under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated and residue purified by reverse phase HPLC. ^{1}H NMR

(CD_3OD, TFA salt) δ (ppm): 7.31 (d, 2H), 7.20 (s, 1H), 7.05 (m, 3H), 6.80 (d, 1H), 6.76 (s, 1H), 6.21 (d, 1H), 4.51 (d, 1H), 4.20 (d, 1H), 3.70 (s, 3H), 3.52 (m, 2H), 3.19 (m, 2H), 2.80 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H).

Example 195: Preparation of Compound No. 285.

[0844] 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) in DME (4 mL) were added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol), potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 4-methylthiophene-2-boronic acid pinacol ester (115 mg, 0.515 mmol). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated under vacuum and the residue was purified by reverse phase HPLC. ^1H NMR (CD_3OD, TFA salt) δ (ppm): 7.30 (s, 1H), 7.18 (s, 1H), 7.05 (m, 3H), 6.98 (s, 1H), 4.71 (d, 1H), 4.40 (d, 1H), 3.82 (m, 1H), 3.57 (m, 1H), 3.18 (m, 2H), 3.10 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H), 1.87 (s, 3H).

Example 196: Preparation of Compound No. 286.

[0845] 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) in DME (4 mL) were added $P(PPh_3)_4$ (15 mg, 0.0128 mmol), potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and naphthalene-1-boronic acid (88 mg, 0.515 mmol). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated and product isolated by reverse phase HPLC. ^1H NMR (CD_3OD, TFA salt) δ (ppm): 7.92 (d, 1H), 7.78 (d, 1H), 7.67 (m, 1H), 7.29-7.41 (m, 5H), 7.13 (s, 1H), 7.0 (s, 1H), 6.98 (d, 1H), 4.40 (d, 1H), 4.11 (d, 1H), 3.51 (m, 1H), 3.21 (m, 1H), 2.80 (s, 3H), 2.71 (m, 2H), 2.42 (s, 3H), 2.37 (s, 3H).

Example 197: Preparation of Compound No. 287.

[0846] 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, 0.257 mmol) in DME (4 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol) and solution purged with nitrogen for 5 min. Potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 3-methylthiophene-2-boronic acid pinacol ester (115 mg, 0.515 mmol) were added followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture

was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated under reduced pressure and residue purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.21 (d, 1H), 7.19 (s, 1H), 7.12 (d, 1H), 6.96 (d, 1H), 6.82 (s, 1H), 6.61 (d, 1H), 4.60 (d, 1H), 4.23 (d, 1H), 3.68 (m, 1H), 3.40 (m, 1H), 3.0 (s, 3H), 2.80 (m, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 1.58 (s, 3H).

Example 198: Preparation of Compound Nos. 288 and 288a-b.

[0847] A solution of 5-(2-(4-fluorophenyl)prop-1-enyl)-2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole and 5-(2-(4-fluorophenyl)allyl)-2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (1.8 g, 5.38 mmol) and 10% Pd/C (180 mg) in MeOH-acetic acid (50 mL, 10:1) was hydrogenated in a Parr shaker at RT and 60 psi for 18h. The reaction mixture was filtered through a Celite bed and the filtrate concentrated under reduced pressure. The residue was diluted with EtOAc (500 mL) and washed with satd. sodium bicarbonate solution (50 mL) and then brine. The organic layer was dried over anhydrous sodium sulfate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 to 50% EtOAc in hexanes) to yield the title compound. ^{1}HNMR (DMSO, Oxalate salt) δ (ppm):7.38-7.3 (d, 1H), 7.36 (bs, 1H), 7.19 (s, 2H),7.07 (bs, 2H), 6.97-6.95 (d, 1H), 4.53 (m,1H), 4.24-4.12 (m, 3H), 3.86 (m,1H), 3.25 (m, 1H), 3.06 (m, 1H), 2.98 (s, 3H), 2.78 (bs, 1H), 2.62 (bs, 1H), 2.33 (s, 3H), 1.14 (bs, 3H). Separation by chiral HPLC provided enantiomers 288a-b.

Example 199: Preparation of Compound Nos. 289 and 289a-b.

[0848] A solution of 2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)prop-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg) and 10%Pd/C (20 mg) in MeOH (5mL) was hydrogenated in a Parr shaker at RT and 50 psi for 72h. The progress of reaction was monitored by LCMS. The reaction mass was filtered through a Celite bed and the filtrate concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield the title compound. ^{1}HNMR (CD_3OD, TFA salt) δ (ppm): 8.30 (m, 2H), 7.70 (s, 1H), 7.20 (s, 1H), 7.10 (d, 1H), 6.98 (d, 1H), 4.60 (m, 2H), 4.30 (m, 3H), 3.80 (m, 2H), 3.60 (m, 2H), 3.10 (s, 3H), 2.62 (s, 3H), 2.38 (s, 3H), 1.42 (d, 3H). Separation by chiral HPLC provided enantiomers 289a-b.

Example 200: Preparation of Compound No. 290.

[0849] 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, 0.257 mmol) in DME (4 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol) and solution purged with nitrogen for 5 min. Potassium

carbonate (72 mg, 0.515 mmol), water (2 mL) and indazole-4-boronic acid.HCl (102 mg, 0.515 mmol) were added followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated under vacuum and the product isolated by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.57 (s, 1H), 7.40 (d, 1H), 7.31 (m, 2H), 7.12 (s, 1H), 7.05 (d, 1H), 7.0 (s, 2H), 4.51 (d, 1H), 4.17 (d, 1H), 3.58 (m, 1H), 3.21 (m, 1H), 2.81 (s, 3H), 2.60 (m, 2H), 2.41 (s, 3H), 2.38 (s, 3H).

Example 201: Preparation of Compound No. 291.

[0850] 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, 0.257 mmol) in DME (4 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.0128 mmol) and solution purged with nitrogen for 5 min. Potassium carbonate (36 mg, 0.257 mmol), water (2 mL) and 4-methylthiophene-2-boronic acid pinacol ester (115 mg, 0.515 mmol) were added followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc and filtered through a sintered crucible. The filtrate was concentrated under vacuum and the product isolated by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.23 (s, 1H), 7.08 (d, 1H), 7.00 (d, 1H), 6.85 (s, 1H), 6.78 (s, 1H), 6.55 (s, 1H), 4.73 (d, 1H), 4.38 (d, 1H), 3.71 (m, 1H), 3.42 (m, 1H), 3.05 (s, 3H), 2.97 (m, 1H), 2.80 (m, 1H), 2.42 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H).

Example 202: Preparation of Compound No. 292.

[0851] 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) in DME (2 mL) were added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), potassium carbonate (110 mg, 0.77 mmol), water (1 mL) and isoquinoline-4-boronic acid (89 mg, 0.515 mmol). The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3x6 mL) and the combined organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and residue was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 9.8 (s, 1H), 8.78 (s, 1H), 8.6 (d, 1H), 8.46 (d, 1H), 8.38 (dd, 1H), 8.17 (dd,

1H), 7.4 (m, 2H), 7.2 (d, 1H), 7.02 (s, 1H), 4.8 (d, 1H), 4.41 (d, 1H), 3.82 (m, 1H), 3.62 (m, 1H), 3.36 (m, 2H), 3.19 (s, 3H), 2.41 (s, 3H), 2.18 (s, 3H).

Example 203: Preparation of Compound No. 293.

[0852] 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) - water (1 mL) were added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) and thianaphthene-2-boronic acid (91.4 mg, 0.514 mmol) followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3x6 mL) and the combined organic layer dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford crude product which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.78 (d, 1H), 7.52 (d, 1H), 7.5 (s, 1H), 7.32 (s, 1H), 7.2-7.3 (m, 2H), 7.18 (d, 1H), 7.03 (d, 1H), 6.78 (s, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.7 (m, 1H), 3.43 (m, 1H), 3.08 (s, 3H), 2.8 (m, 2H), 2.49 (s, 3H), 2.41 (s, 3H).

Example 204: Preparation of Compound No. 294.

[0853] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (200 mg,1.0 mmol) in NMP (1 mL) were added powdered KOH (392 mg, 7.0 mmol) and 3-vinyl-benzo[b]thiophene (320 mg, 2.0 mmol). The reaction mixture was stirred at 90 °C for 5h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3x20 mL). The combined organic layer was washed with water (5x25 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (3% MeOH-DCM) followed by reverse phase HPLC to yield 5-(2-benzo[b]thiophen-3-yl-ethyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.82 (d, 1H), 7.6 (d, 1H), 7.38 (m, 2H), 7.2 (m, 2H), 7.0 (d, 1H), 6.93 (s, 1H), 4.3 (t, 2H), 3.62 (s, 2H), 3.5 (s, 3H), 3.21 (t, 2H), 2.63 (t, 2H), 2.41 (m, 5H).

Example 205: Preparation of Compound No. 295.

[0854] To a solution of 3-(1-bromoprop-1-en-2-yl)phenyl)(methyl)sulfane (300 mg, 1.2 mmol) in DMF (2 mL) were added potassium phosphate (424 mg, 2 mmol), copper(I)iodide (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol) and 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (220 mg, 1 mmol). The reaction mixture was stirred at 140 °C for 16 h. Ice water was added to the reaction mixture and extracted with EtOAc (3x15 mL). The combined organic layer was washed with water (2x10 mL), dried and concentrated. The residue was

purified by silica gel column chromatography (0-3% MeOH-DCM) followed by reverse phase HPLC to yield the title compound. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.57 (d, 1H), 7.5 (d, 1H), 7.38-7.42 (m, 2H), 7.3 (d, 1H), 7.2 (m, 2H), 6.97 (s, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.82 (m, 1H), 3.6 (m, 1H), 3.1 (m, 5H), 2.5 (s, 3H), 1.98 (s, 3H).

Example 206: Preparation of Compound No. 296.

[0855] To a solution of 1-(1-bromoprop-1-en-2-yl)-3-(methylsulfonyl)benzene (297 mg, 1.1 mmol) in DMF(2 mL) were added potassium phosphate (424 mg, 2 mmol), copper(I)iodide (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol) and 8-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (220 mg, 1 mmol) and purged nitrogen for 2 min and heated at 90 °C for 16 h. Ice water (5 mL) was added and filtered the solid obtained and washed with water (2x10 mL). Product was purified on silica column (100-200 mesh) using 0-3% MeOH:DCM as eluant. The compound was further purified through reverse phase HPLC. Yield: 49.26 mg (freebase). ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.2 (s, 1H), 7.98 (m, 2H), 7.7 (dd, 1H), 7.48 (s, 1H), 7.18 (m, 2H), 7.1 (s, 1H), 4.2 (s, 2H), 3.4 (s, 2H), 3.2 (s, 3H), 3.1 (s, 2H), 2.9 (s, 3H), 1.8 (s, 3H).

Example 207: Preparation of Compound No. 297.

[0856] To a degassed stirred solution of 2,8-dimethyl-5-(6-methyl-pyridin-2-ylethynyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.317 mmol) in MeOH (5 mL) was added Pd/C (35 mg, 35% w/w) and purged the reaction mixture with H_2 gas at RT for 2h. The progress of reaction was monitored by TLC and NMR. Reaction mass was filtered through a Celite bed washed with MeOH (3x5 mL). Filtrate was concentrated under reduced pressure and residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-[2-(6-methyl-pyridin-2-yl)-ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.2 (dd, 1H), 7.63 (d, 1H), 7.57 (d, 1H), 7.21 (d, 1H), 7.02 (d, 1H), 6.96 (d, 1H), 4.7 (d, 1H), 4.58 (t, 2H), 4.37 (d, 1H), 3.82 (m, 1H), 3.57 (m, 1H), 3.4 (t, 2H), 3.2 (m, 2H), 3.18 (s, 3H), 2.61 (s, 3H), 2.4 (s, 3H).

Example 208: Preparation of Compound No. 298.

[0857] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.5 mmol) was in NMP (1mL) were added powdered KOH (196 mg,3.5 mmol) and dimethyl-(3-vinyl-phenyl)-amine (147mg, 1.0 mmol) and the reaction mixture stirred at 100 °C for 16 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (15mL) and extracted with EtOAc (3x25 mL). The combined organic layer was washed with water (5x20 mL), dried over anhydrous sodium sulfate and concentrated. The

residue was purified by silica gel column chromatography (0-3% MeOH-DCM) to yield {3-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethyl]-phenyl}-dimethyl-amine. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.21 (m, 2H), 7.18 (dd, 1H), 7.0 (d, 1H), 6.6 (d, 1H), 6.43 (d, 1H), 6.21 (s, 1H), 4.2 (t, 2H), 3.71 (s, 2H), 2.90 (t, 2H), 2.85 (s, 3H), 2.80 (m, 4H), 2.57 (s, 6H), 2.41 (s, 3H).

Example 209: Preparation of Compound No. 299.

[0858] To a degassed stirred solution of 2,8-dimethyl-5-(5-methyl-pyridin-2-ylethynyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (110 mg, 0.349 mmol) in MeOH (5 mL) was added Pd/C (40 mg, 35% w/w) and purged the reaction mixture with H_2 gas at RT for 2h. The progress of reaction was monitored by TLC and NMR. Reaction mass was filtered through a Celite bed washed with MeOH (3x5 mL). Filtrate was concentrated under reduced pressure and residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-[2-(5-methyl-pyridin-2-yl)-ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.42 (s, 1H), 8.02 (d, 1H), 7.48 (d, 1H), 7.21 (s, 1H), 7.12 (d, 1H), 6.98 (d, 1H), 4.67 (d, 1H), 4.5 (t, 2H), 4.3 (d, 1H), 3.8 (m, 1H), 3.5 (m, 1H), 3.38 (t, 2H), 3.1 (m, 5H), 2.41 (s, 3H), 2.39 (s, 3H).

Example 210: Preparation of Compound No. 300.

[0859] To a degassed stirred 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), 3-pyridinylboronic acid (71 mg, 0.577 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL)-water (2 mL) was added $Pd(PPh_3)_4$ (16 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The reaction mixture concentrated, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-(2-(pyridin-3-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.68 (d, 1H), 8.1 (d, 1H), 7.9 (m, 1H), 7.8 (m, 1H), 7.3 (s, 1H), 6.9-7.1 (m, 2H), 4.7 (m, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 3.58 (m, 1H), 2.8-3.3 (m, 9H), 2.22-2.4 (m, 5H).

Example 211: Preparation of Compound No. 301.

[0860] To a degassed stirred 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), 4-fluorophenylboronic acid (81 mg, 0.578 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL)-water (2 mL) was added $Pd(PPh_3)_4$ (17 mg, 0.0147 mmol). The reaction mixture was stirred at

90 °C for 45 min. The reaction mixture concentrated to dryness, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 5-(2-(4-fluorophenyl)cyclopent-1-enyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.3 (s, 1H), 7.17 (d, 1H), 7.02 (d, 1H), 6.8-6.98 (m, 4H), 4.7 (d, 1H), 4.3 (d, 1H), 3.65 (m, 1H), 3.41 (m, 1H), 2.9-3.18 (m, 7H), 2.52-2.77 (m, 2H), 2.45 (s, 3H), 2.21 (m, 2H).

Example 212: Preparation of Compound No. 302.

[0861] To a degassed stirred 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), 3-methylthiophene-2-boronic acid pinacol ester (129 mg, 0.575 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL)-water (2 mL) was added $Pd(PPh_3)_4$ (16 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was under reduced pressure, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-(2-(3-methylthiophen-2-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.24 (s, 1H), 7.1-7.2 (m, 2H), 7.0 (dd, 1H), 6.6 (s, 1H), 4.6 (m, 1H), 4.4 (m, 1H), 3.64 (m, 1H), 3.2 (m, 1H), 2.8-3.17 (m, 7H), 2.6 (t, 2H), 2.4 (s, 3H), 2.2 (t, 2H), 1.8 (m, 3H).

Example 213: Preparation of Compound No. 303.

[0862] To a degassed stirred 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), 2-(dimethylamino)pyrimidine-5-boronic acid pinacol ester (129 mg, 0.578 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL)-water (2 mL) was added $Pd(PPh_3)_4$ (16 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was removed under reduced pressure, residue diluted with water (20 mL) and extracted with EtOAc (50 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-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)cyclopent-1-enyl)-N,N-dimethylpyrimidin-2-amine. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.8 (d, 2H), 7.3 (s, 1H), 6.98-7.1 (m, 2H), 4.7 (m, 1H), 4.38 (m, 1H), 3.8 (m, 1H), 3.5 (m, 1H), 2.78-3.1 (m, 15H), 2.4 (s, 3H), 2.2 (m, 2H).

Example 214: Preparation of Compound No. 304.

[0863] To a degassed stirred 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), 4-methylthiophene-2-boronic acid pinacol ester (129 mg, 0.578 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL)-water (2 mL) was purged with nitrogen followed by addition of $Pd(PPh_3)_4$ (16 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was removed under reduced pressure, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield 2,8-dimethyl-5-(2-(4-methylthiophen-2-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.3 (s, 1H), 7.0 (m, 3H), 6.78 (s, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.8 (m, 1H), 3.5 (m, 1H), 3.37 (s, 3H), 3.03 (m, 2H), 2.83 (m, 2H), 2.61 (m, 2H), 2.4 (s, 3H), 2.2 (m, 2H), 2.17 (s, 3H).

Example 215: Preparation of Compound No. 305.

[0864] 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), benzo[b]thien-2-ylboronic acid (103 mg, 0.578 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL)-water (2 mL) was purged with nitrogen followed by addition of $Pd(PPh_3)_4$ (16 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was removed under reduced pressure, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield 5-(2-(benzo[b]thiophen-2-yl)cyclopent-1-enyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.2 (d, 1H), 7.5 (d, 1H), 7.38 (s, 1H), 7.2-7.3 (m, 3H), 7.1 (d, 1H), 7.04 (d, 1H), 4.4 (m, 2H), 3.6 (m, 2H), 3.2 (m, 2H), 3.1 (s, 3H), 2.9 (m, 2H), 2.7 (m, 2H), 2.41 (s, 3H), 2.3 m, 2H).

Example 216: Preparation of Compound No. 306.

[0865] 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), naphthalene-1-boronic acid (99 mg, 0.575 mmol) and potassium carbonate (120 mg, 0.87 mmol) in mixture of 1,2-dimethoxyethane (4 mL)-water (2 mL) was purged with nitrogen followed by addition of $Pd(PPh_3)_4$ (16 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was removed under reduced pressure, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by

reverse phase HPLC to yield 2,8-dimethyl-5-(2-(naphthalen-1-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (DMSO, TFA salt) δ (ppm): 8.0 (d, 1H), 7.8 (d, 1H), 7.79 (d, 1H), 7.3-7.5 (m, 5H), 7.1 (s, 1H), 6.9 (d, 1H), 4.21 (m, 2H), 3.4 (m, 2H), 2.77-3.0 (m, 9H), 2.3 (m, 5H).

Example 217: Preparation of Compound No. 307.

[0866] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (150 mg, 0.75 mmol) in NMP (1mL) were added powdered KOH (294 mg, 5.25 mmol) and 2-methyl-5-vinyl-thiophene (186 mg,1.50 mmol), and the reaction mixture stirred at 90 °C for 5h. The reaction mixture was diluted with water (15mL) and extracted with EtOAc (3x20 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 silica gel column chromatography (3% MeOH-DCM) followed by reverse phase HPLC to yield 2,8-dimethyl-5-[2-(5-methyl-thiophen-2-yl)-ethyl]-2,5-dihydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.3 (d, 1H), 7.22 (s, 1H), 7.08 (d, 1H), 6.5 (d, 1H), 6.3 (d, 1H), 4.6 (d, 1H), 4.2-4.4 (m, 3H), 3.7 (m, 2H), 3.2 (m, 3H), 3.03 (s, 3H), 2.7 (m, 1H), 2.38-2.42 (m, 6H).

Example 218: Preparation of Compound No. 308.

[0867] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (250 mg, 1.25 mmol) in NMP (1 mL) were added powdered KOH (490 mg, 8.75 mmol) and 3-methyl-2-vinyl-thiophene (310 mg, 2.25 mmol), and the reaction mixture stirred at 90 °C for 5h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x20 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 yield 2,8-dimethyl-5-[2-(3-methyl-thiophen-2-yl)-ethyl]-2,5-dihydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.25 (d, 1H), 7.22 (s, 1H), 7.1 (d, 1H), 7.02 (d, 1H), 6.7 (d, 1H), 4.41 (s, 2H), 4.3 (t, 2H), 2.42 (bs, 2H), 3.2 (t, 2H), 3.0 (s, 3H), 2.61 (bs, 2H), 2.4 (s, 3H), 1.6 (s, 3H).

Example 219: Preparation of Compound No. 309.

[0868] To a degassed stirred 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), 1-methyl-1H-pyrazole-5-boronic acid pinacol ester (81 mg, 0.576 mmol) and potassium carbonate (120 mg, 0.87 mmol) in 1,2-dimethoxyethane (4 mL) and water (2 mL) was added $Pd(PPh_3)_4$ (17 mg, 0.0147 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was removed under reduced

pressure, residue diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse HPLC to yield 2,8-dimethyl-5-(2-(1-methyl-1H-pyrazol-5-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.32 (s, 1H), 7.18 (s, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 6.01 (s, 1H), 3.6 (s, 2H), 3.2 (s, 3H), 3.0 (m, 4H), 2.7 (m, 4H), 2.52 (s, 3H), 2.4 (s, 3H), 2.2 (m, 2H).

Example 220: Preparation of Compound No. 310.

[0869] To a solution of 1-(1-bromoprop-1-en-2-yl)-3-(methylsulfonyl)benzene (148 mg, 0.55 mmol) in DMF (1 mL) were added potassium phosphate (212 mg, 2 mmol), copper(I)iodide (9.5 mg, 0.05 mmol) and L-proline (11.5 mg, 0.1 mmol). The solution was de-aerated by purging nitrogen followed by addition of 2,3,4,5-tetrahydro-2,6,8-trimethyl-1H-pyrido[4,3-b]indole (114.5 mg, 0.5 mmol). The reaction mixture was again purged with nitrogen for two minutes and then stirred at 85 °C overnight. Ice water was poured into the reaction mixture and the solid obtained was filtered. The crude product was purified by column chromatography using 0-3% MeOH:DCM as eluant. The compound was further purified through reverse phase HPLC to yield the title compound. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.08 (s, 1H), 8.0 (m, 2H), 7.77 (t, 1H), 7.38 (s, 1H), 7.1 (s, 1H), 6.8 (s, 1H), 4.7 (d, 1H), 4.37 (d, 1H), 3.82 (m, 1H), 3.58 (m, 1H), 3.0-3.2 (m, 8H), 2.73 (s, 3H), 2.38 (s, 3H), 1.97 (s, 3H).

Example 221: Preparation of Compound No. 311.

[0870] 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, 0.7 mmol) in DME-water (2:1) were added $Pd(PPh_3)_4$ (20 mg, 0.0130 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (100 mg, 0.392 mmol), followed by nitrogen purging for 5 min. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 9.77 (s, 1H), 8.6 (d, 1H), 8.44-8.58 (m, 3H), 8.4 (d, 1H), 7.57 (s, 1H), 7.37 (s, 1H), 7.2 (d, 1H), 7.17 (d, 1H), 4.71 (d, 1H), 4.4 (d, 1H), 3.9 (m, 1H), 3.6 (m, 1H), 3.2 (m, 5H), 2.42 (s, 3H), 2.2 (s, 3H).

Example 222: Preparation of Compound No. 312.

[0871] To a solution of 4-(1-bromoprop-1-en-2-yl)pyridine (238 mg, 1.2 mmol) in DMF (2 mL) were added potassium phosphate (424 mg, 2 mmol), copper(I)iodide (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol) and 2,3,4,5-tetrahydro-2,6,8-trimethyl-1H-pyrido[4,3-b]indole (214 mg, 1 mmol). The reaction mixture was degassed using nitrogen and stirred overnight at 85 °C. Ice water (5 mL) was added into the reaction mixture and the solid obtained was filtered. The residue was washed with water (2x10 mL) and purified by column chromatography using neutral alumina and 0-1% MeOH:DCM as eluant to yield the desired compound. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.9 (d, 2H), 8.39 (d, 2H), 7.98 (s, 1H), 7.17 (s, 1H), 6.86 (s, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.82 (m, 1H), 3.6 (m, 1H), 3.2 (m, 4H), 3.0 (m, 1H), 2.5 (s, 3H), 2.4 (s, 3H), 2.1 (s, 3H).

Example 223: Preparation of Compound No. 313.

[0872] A mixture of 5-ethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (194 mg, 0.866 mmol, 5-bromo-isoquinoline (150 mg, 0.721 mmol, TBAF.3H_2O (680 mg, 2.15 mmol) and dichlorobis(triphenylphosphine) palladium(II) (25 mg, 0.035 mmol) was stirred at 85 °C for 5 min. The reaction mixture was diluted with water and extracted with EtOAc (3x40 mL). The organic layer was washed with water (5x30 mL), dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography using silica (100:200) and 0.5% MeOH-DCM to yield 5-isoquinolin-5-ylethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 9.3 (s, 1H), 8.62 (d, 1H), 8.17 (d, 1H), 7.93 (dd, 2H), 7.6 (t, 1H), 7.57 (d, 1H), 7.23 (s, 1H), 7.17 (d, 1H), 3.65 (s, 2H), 3.07 (t, 2H), 2.93 (t, 2H), 2.6 (s, 3H), 2.42 (s, 3H).

Example 224: Preparation of Compound Nos. 314 and 314a-b.

[0873] To a solution of 2,3,4,9-tetrahydro-2,6-dimethyl-1-phenyl-1H-pyrido[3,4-b]indole (100 mg, 0.362 mmol) in DMF (2 mL) were added sodium hydride (60 mg, 1.08 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (300 mg, 1.03 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1h. The reaction mixture was cooled to RT and quenched with water. The aqueous layer was extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC. The product is further purified by reverse phase HPLC followed by chiral HPLC separation to give enantiomers 314a and 314b. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.09 (s, 1H), 7.9 (d, 1H), 7.63 (t, 1H), 7.43-7.6 (m, 5H), 7.4 (s, 1H), 7.0 (m, 2H), 6.03 (s, 1H), 4.37 (t,

1H), 4.1 (m, 1H), 3.92 (m, 1H), 3.57-3.65 (m, 2H), 3.18 (t, 1H), 2.9 (bs, 3H), 2.63 (s, 3H), 2.6 (m, 2H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers 314a-b.

Example 225: Preparation of Compound No. 315.

[0874] To a solution of 7-chloro-2-methyl-2,3,4,5- tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.453 mmol) in DMF (2 mL) were added sodium hydride (60 mg, 1.359 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (330 mg, 1.1322 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1h. The reaction mixture was cooled to RT and quenched with water. The aqueous layer was extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), 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_3OD, TFA salt) δ (ppm): 8.21 (s, 1H), 8.1 (d, 1H), 7.7 (d, 1H), 7.38 (d, 1H), 7.1 (s, 1H), 7.0 (d, 1H), 4.7 (d, 1H), 4.42 (t, 2H), 4.5 (d, 1H), 3.82 (m, 1H), 3.57 (m, 1H), 3.1-3.27 (m, 4H), 3.08 (s, 3H), 2.63 (s, 3H).

Example 226: Preparation of Compound No. 316.

[0875] To a solution of 5-isoquinolin-5-ylethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (90 mg, 0.256 mmol) in MeOH (6 mL) were added 10% dry Pd-C (25 mg) and ammonium formate (81 mg, 1.282 mmol). The reaction mixture was refluxed for 2h and filtered through Celite. The filtrate was concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC to yield 20 mg of 5-(2-isoquinolin-5-yl-vinyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 9.7 (s, 1H), 8.57 (d, 1H), 8.5 (d, 1H), 8.3 (d, 1H), 7.65 (t, 1H), 7.59 (d, 1H), 7.4 (d, 1H), 7.22 (d, 1H), 7.2 (s, 1H), 6.7 (m, 2H), 4.63 (d, 1H), 4.3 (d, 1H), 3.7 (m, 1H), 3.47 (m, 1H), 3.08 (s, 3H), 2.9-3.0 (m, 2H), 2.31 (s, 3H).

Example 227: Preparation of Compound No. 317.

[0876] To a solution of 5-isoquinolin-5-ylethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (80 mg, 0.228 mmol) in MeOH (5 mL) were added 10% dry Pd-C (80 mg) and ammonium formate (72 mg, 1.14 mmol). The reaction mixture was refluxed for 4h and filtered through Celite. The filtrate was concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC to yield 20 mg of 2,8-dimethyl-5-[2-(1,2,3,4-tetrahydro-isoquinolin-5-yl)-ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.21 (d, 1H), 7.18 (m, 2H), 7.1 (d, 1H), 7.0 (d, 1H), 6.93 (d,

1H), 4.7 (d, 1H), 4.2-4.4 (m, 5H), 3.7 (m, 1H), 3.2 (m, 3H), 3.08 (t, 2H), 3.02 (s, 3H), 2.83 (m, 1H), 2.6-2.8 (m, 3H), 2.4 (s, 3H).

Example 228: Preparation of Compound No. 318.

[0877] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (250mg,1.255 mmol) in NMP (1mL), was added powdered KOH (490 mg, 8.75 mmol). After stirring for 5 min, 3-methyl-4-vinyl-thiophene (310 mg, 2.50 mmol) was added into the reaction mixture, which was stirred at 85 °C for 16 h. The reaction mixture was diluted with water (15mL) and extracted with EtOAc (3x20 mL). The organic layer was washed with water (6x30 mL), dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography using silica (100:200) and 2% MeOH-DCM, followed by reverse phase HPLC to yield 1.10 mg of 2,8-dimethyl-5-[2-(4-methyl-thiophen-3-yl)-ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.3 (d, 1H), 7.24 (s, 1H), 7.07 (d, 1H), 6.92 (s, 1H), 6.78 (s, 1H), 4.6 (d, 1H), 4.3 (m, 3H), 3.62 (m, 1H), 3.3 (m, 3H), 3.0 (m, 4H), 2.8 (m, 1H), 2.4 (s, 3H), 1.95 (s, 3H).

Example 229: Preparation of Compound No. 319.

[0878] To a solution of 8,9-dichloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (100 mg, 0.392 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 1h. The reaction mixture was cooled to RT and quenched with water. The aqueous layer was extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), 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_3OD, TFA salt) δ (ppm): 8.39 (s, 1H), 8.2 (d, 1H), 7.7 (d, 1H), 7.2 (d, 2H), 5.1 (m, 1H), 4.6 (m, 1H), 4.43 (t, 2H), 3.82 (m, 1H), 3.5 (m, 1H), 3.2-3.3 (m, 4H), 3.1 (m, 3H), 2.7 (s, 3H).

Example 230: Preparation of Compound No. 320.

[0879] To a degassed solution of 2,8-dimethyl-5-quinolin-3-ylethynyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (60 mg, 0.170 mmol) in MeOH (5 mL), were added Pd-C (30 mg, 50% w/w) and ammonium formate (54 mg, 0.857 mmol) under nitrogen. The reaction mixture was stirred at 75 °C for 1h, filtered through a Celite bed and washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure and residue was purified by reverse phase HPLC to yield the desired compound. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.6 (s, 2H), 8.02-

8.18 (m, 3H), 7.82 (t, 1H), 7.2 (s, 1H), 6.98 (d, 1H), 6.77 (d, 1H), 4.68 (d, 1H), 4.56 (t, 2H), 4.3 (d, 1H), 3.8 (m, 1H), 3.45 (m, 1H), 3.4 (t, 2H), 3.21 (m, 1H), 3.1 (m, 4H), 2.3 (s, 3H).

Example 231: Preparation of Compound No. 321.

[0880] A mixture of 5-ethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (260 mg, 1.160 mmol), 3-bromoquinoline (200 mg, 0.961 mmol), TBAF.$3H_2O$ (1.1 g, 3.492 mmol) and dichloro bis(triphenylphosphine) palladium (II) (41 mg, 0.058 mmol) was stirred at 85 °C for 10 min. The reaction mixture was diluted with water and extracted with EtOAc (4x30 mL). The combined organic layer was washed with water (4x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product, which was purified by column chromatography using neutral alumina and 0.5% MeOH-DCM to yield 2,8-dimethyl-5-quinolin-3-ylethynyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 9.0 (s, 1H), 8.25 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 7.7 (t, 1H), 7.6 (t, 1H), 7.5 (d, 1H), 7.2 (s, 1H), 7.1 (d, 1H), 3.62 (s, 2H), 3.0 (t, 2H), 2.7 (t, 2H), 2.6 (s, 3H), 2.42 (s, 3H).

Example 232: Preparation of Compound No. 322.

[0881] To a solution of 7,8-dichloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (100 mg, 0.392 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 1h. The reaction mixture was cooled to RT and quenched with water. The aqueous layer was extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), 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_3OD, TFA salt) δ (ppm): 8.37 (s, 1H), 8.18 (d, 1H), 7.7 (d, 1H), 7.61 (s, 1H), 7.39 (s, 1H), 4.68 (m, 1H), 4.48 (t, 2H), 4.37 (m, 1H), 3.92 (m, 1H), 3.57 (m, 1H), 3.2 (m, 4H), 3.1 (s, 3H), 2.7 (s, 3H).\

Example 233: Preparation of Compound No. 323.

[0882] To a degassed solution of 2,8-dimethyl-5-quinolin-3-ylethynyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (60 mg, 0.170 mmol) in MeOH (5 mL), were added Pd-C (30 mg, 50% w/w) and ammonium formate (54 mg, 0.857 mmol) under nitrogen. The reaction mixture was stirred at 75 °C for 1h, filtered through a Celite bed and washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford crude product, which was purified by reverse phase HPLC to yield the desired compound. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.3

(d, 2H), 8.0 (d, 1H), 7.9 (m, 2H), 7.70 (t, 1H), 7.3 (s, 1H), 7.21 (d, 1H), 6.98 (d, 1H), 6.82 (s, 2H), 4.78 (d, 1H), 4.4 (d, 1H), 3.8 (m, 1H), 3.58 (m, 1H), 3.1 (m, 5H), 2.38 (s, 3H).

Example 234: Preparation of Compound No. 324.

[0883] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (200 mg,1.0 mmol) in DCM (4 mL) were added powdered KOH (392 mg, 7.0 mmol) and phenylamine (111 mg, 1.2 mmol). The reaction mixture was stirred at 85 °C for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with DCM (3x20 mL). The combined organic layer was washed with water (3x30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by silica gel column chromatography (3% MeOH-DCM), followed by reverse phase HPLC to yield (2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-ylmethyl)-phenyl-amine (20 mg). ^{1}H NMR (CD_3OD, freebase) δ (ppm): 7.4 (d, 1H), 7.07 (s, 1H), 7.0 (t, 2H), 6.97 (d, 1H), 6.67 (d, 2H), 6.6 (t, 1H), 5.42 (s, 2H), 3.7 (s, 2H), 3.07 (t, 2H), 2.9 (t, 2H), 2.58 (s, 3H), 2.4 (s, 3H).

Example 235: Preparation of Compound No. 325.

[0884] To a solution of 6,9-dichloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.392 mmol), in DMF (2 mL) were added sodium hydride (60 mg, 1.3 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (285 mg, 0.980 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1h. The reaction mixture was cooled to RT, quenched with water and extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), 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_3OD, TFA salt) δ (ppm): 8.41 (s, 1H), 8.18 (d, 1H), 7.78 (d, 1H), 7.1 (d, 1H), 7.06 (d, 1H), 5.1 (m, 1H), 4.8 (t, 2H), 4.6 (m, 1H), 3.8 (m, 1H), 3.57 (m, 1H), 3.22 (m, 4H), 3.18 (s, 3H), 2.7 (s, 3H).

Example 236: Preparation of Compound No. 326.

[0885] To a stirred solution of 3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propanethioamide (0.287 g, 1.0 mmol) in EtOH.HCl (3 mL) was added 2-bromo-4'-chloroacetophenone (0.349 g, 1.5 mmol). The reaction mixture was stirred at 82 °C for 16 h. Solvent was removed under reduced pressure. The residue was basified with 1N NaOH solution and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to afford crude product, which was purified by column chromatography to yield the desired product. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.8 (d, 2H), 7.4 (d, 2H), 7.3 (s,

1H), 7.2 (m, 2H), 6.98 (d, 1H), 4.46 (t, 2H), 3.6 (s, 2H), 3.4 (t, 2H), 2.1-2.78 (m, 4H), 2.53 (s, 3H), 2.4 (s, 3H).

Example 237: Preparation of Compound No. 327.

[0886] To a de-aerated solution of 6-bromo-2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (85 mg, 0.215 mmol) and potassium carbonate (89 mg, 0.642 mmol) in 1,2-dimethoxyethane-water (2:1) were added 3-methylthiophene-2-boronic acid pinacol ester (96 mg, 0.428 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol). The reaction mixture was stirred at 90 °C for 45 min and concentrated to dryness. The residue 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. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.0 (s, 1H), 7.77 (s, 2H), 7.47 (s, 1H), 7.38 (s, 1H), 7.02 (s, 1H), 6.9 (s, 1H), 4.78 (m, 1H), 4.38 (m, 1H), 4.1 (bs, 1H), 4.0 (m, 1H), 3.9 (bs, 1H), 3.6 (m, 1H), 3.1-3.27 (m, 5H), 2.8 (t, 2H), 2.7 (s, 3H), 2.4 (s, 3H), 1.99 (s, 3H).

Example 238: Preparation of Compound No. 328.

[0887] A mixture of 2-bromo-5-methyl-pyridine (250 mg,1.45 mmol), 5-ethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3- -b]indole (391mg, 1.74 mmol), TBAF.$3H_2O$ (1.374 g,4.36 mmol) and dichloro bistriphenylphosphine palladium(II) (51mg, 0.072 mmol) was stirred at 85 °C for 10 min. The reaction mixture was poured into water and extracted with EtOAc (3x100 mL). The organic layer was washed with water (3x100 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (neutral alumina, eluent- 0.5% MeOH in DCM) to yield 2,8-dimethyl-5-(5-methyl-pyridin-2-ylethynyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.41 (s, 1H), 7.5 (m, 2H), 7.4 (d, 1H), 7.18 (s, 1H), 7.08 (d, 1H), 3.6 (s, 2H), 3.0 (t, 2H), 2.83 (t, 2H), 2.58 (s, 3H), 2.42 (s, 3H), 2.37 (s, 3H).

Example 239: Preparation of Compound No. 329.

[0888] To a degassed solution of 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[4,3-b]indole (276 mg, 0.753 mmol), 5-bromo-2-propylpyridine (100 mg, 0.502) and potassium carbonate (208 mg, 1.507 mmol) in DME (2 mL) and water (1 mL) was added $Pd(PPh_3)_4$ (40.6 mg, 0.035 mmol), followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was cooled to RT and diluted with EtOAc. The aqueous layer

was extracted with EtOAc (3x6 mL) and the combined organic layer dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford crude product, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.8 (s, 1H), 8.36 (d, 1H), 7.62 (d, 1H), 7.3 (s, 1H), 7.2 (s, 1H), 7.16 (d, 1H), 7.05 (d, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.83 (bs, 1H), 3.4 (bs, 1H), 3.18 (m, 2H), 3.1 (s, 3H), 2.9 (t, 2H), 2.4 (s, 3H), 2.0 (s, 3H), 1.8 (m, 2H), 1.0 (t, 3H).

Example 240: Preparation of Compound No. 330.

[0889] A mixture of 4-bromobenzenesulfonamide (200 mg, 0.84 mmol), 5-ethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (391 mg, 1.0 mmol), TBAF.$3H_2O$ (793 mg, 2.5 mmol) and dichloro bis(triphenyl phosphine) palladium (II) (29 mg, 0.042 mmol) was stirred at 85 °C for 10 min. The reaction mixture was poured into water and extracted with EtOAc (3 x 50 mL). The organic layer was washed with water (3 x 100 mL), dried over anhydrous sodium sulfate and concentrated to afford crude material, which was purified by column chromatography using neutral alumina and 5% MeOH-DCM, followed by reverse phase HPLC to yield 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-ylethynyl)-benzenesulfonamide. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 7.92 (d, 2H), 7.7 (d, 2H), 7.58 (d, 1H), 7.38 (s, 1H), 7.23 (d, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.96 (m, 1H), 3.63 (m, 1H), 3.37 (m, 2H), 3.18 (s, 3H), 2.42 (s, 3H).

Example 241: Preparation of Compound No. 331.

[0890] 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[4,3-b]indole (140 mg, 0.382 mmol), 5-bromo-2-(trifluoromethyl)pyridine (87 mg, 0.382)and potassium carbonate (158 mg, 1.147 mmol) in DME (2 mL) and water (1 mL) was added $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), followed by nitrogen purging. The reaction mixture was refluxed for 45 min. At that point, TLC showed no starting material. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 9.0 (s, 1H), 8.27 (d, 1H), 7.88 (d, 1H), 7.37 (s, 1H), 7.25 (s, 1H), 7.18 (d, 1H), 7.1 (d, 1H), 4.7 (d, 1H), 4.4 (d, 1H), 3.82 (bs, 1H), 3.6 (m, 1H), 3.37 (m, 1H), 3.2 (m, 1H), 3.6 (s, 3H), 2.42 (s, 3H), 2.01 (s, 3H).

Example 242: Preparation of Compound No. 332.

[0891] To a de-aerated solution of 2,8-dimethyl-5-naphthalen-2-ylethynyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (50 mg, 0.14 mmol) in MeOH (5 mL), palladium hydroxide (25 mg, 50% w/w) and ammonium formate (45 mg, 0.71 mmol) were added. The reaction mixture was stirred at 80 °C for 1h. The progress of reaction was monitored by TLC and LCMS. The reaction mass was filtered through Celite and washed the residue with MeOH (10 mL). The filtrate was concentrated under reduced pressure to afford crude material, which was purified by reverse phase HPLC to yield 2,8-dimethyl-5-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.26 (d, 1H), 7.22 (d, 1H), 7.02 (d, 1H), 6.9 (d, 1H), 6.63 (d, 1H), 6.58 (s, 1H), 4.6 (d, 1H), 4.4 (m, 1H), 4.2 (t, 2H), 3.62 (m, 1H), 3.02 (m, 1H), 2.9 (m, 4H), 3.0 (s, 3H), 2.7 (bs, 2H), 2.6 (bs, 2H), 2.4 (s, 3H), 1.8 (bs, 4H).

Example 243: Preparation of Compound No. 333.

[0892] A mixture of 4-bromo-benzenesulfonamide (200 mg, 0.84 mmol), 9-ethynyl-2,6-dimethyl-2,3,4,9-tetrahydro-1H-β-carboline (228 mg,1.01 mmol), TBAF.$3H_2O$ (801 mg, 2.54 mmol) and dichloro bis(triphenylphosphine) palladium(II) (30 mg, 0.042 mmol) was stirred at 85 °C for 10 min. The reaction mixture was poured into water and extracted with EtOAc (3x25 mL). The organic layer was washed with water (3x30 mL), dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by reverse phase HPLC to yield 4-(2,6-dimethyl-1,2,3,4-tetrahydro-β-carbolin-9-ylethynyl)-benzenesulfonamide. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.9 (d, 2H), 7.6 (d, 2H), 7.4 (d, 1H), 7.3 (s, 1H), 7.1 (d, 1H), 3.78 (s, 2H), 2.82 (t, 2H), 2.79 (t, 2H), 2.6 (s, 3H), 2.42 (s, 3H).

Example 244: Preparation of Compound No. 334.

[0893] A mixture of 5-bromo-thiophene-2-sulfonic acid amide (200 mg, 0.8 mmol), 5-ethynyl-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (222 mg, 0.9 mmol), TBAF.$3H_2O$ (756 mg, 2.4 mmol) and dichloro bis(triphenyl phosphine) palladium (II) (28 mg, 0.04 mmol) was stirred at 85 °C for 10 min. The reaction mixture was poured into water and extracted with EtOAc (3 x 50 mL). The organic layer was washed with water (3 x 100 mL), dried over anhydrous sodium sulfate and concentrated to afford crude material, which was purified by column chromatography using neutral alumina and 5% MeOH-DCM, followed by reverse phase HPLC to yield 5-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-ylethynyl)-thiophene-2-sulfonic acid amide. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 7.57 (d, 1H), 7.46 (d, 1H), 7.36 (m, 2H), 7.21 (d, 1H), 4.42 (s, 2H), 3.71 (s, 2H), 3.3 (m, 2H), 3.1 (s, 3H), 2.42 (s, 3H).

Example 245: Preparation of Compound No. 335.

[0894] To a degassed solution of 3,6-dimethyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene (201 mg, 1.0 mmol), 1-(2-bromo-1-methyl-vinyl)-4-fluoro-benzene (279 mg, 1.3 mmol), potassium phosphate (530 mg, 2.5 mmol) in DMF (4 mL), L-proline (28 mg, 0.25 mmol) and cuprous iodide (47 mg, 0.25 mmol) were added. The reaction mixture was stirred at 120 °C for 8h. The reaction mixture was cooled to RT, diluted with water (20 mL) and extracted with EtOAc (4x20 mL). The organic layer was washed with water (5x20 mL), dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by silica gel flash chromatography to yield 9-[2-(4-fluoro-phenyl)-propenyl]-3,6-dimethyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.1 (s, 1H), 7.57 (m, 3H), 7.07 (t, 2H), 6.92 (s, 1H), 3.62 (s, 2H), 2.8 (s, 4H), 2.6 (s, 3H), 2.4 (s, 3H), 2.0 (s, 3H).

Example 246: Preparation of Compound Nos. 336 and 336a-b.

[0895] To a solution of 8-aza-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (227 mg, 1.0 mmol) in DMF (5 mL) was added sodium hydride (120 mg, 3.0 mmol). After stirring at RT for 15 min, 4-fluorophenethyl 4-methyl-benzenesulfonate (1.47g, 3 mmol) was added into the reaction mixture, which was stirred at RT for 12 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 (3x100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield the title compound (125 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.18 (s, 1H), 7.53 (s, 1H), 6.82 (m, 4H), 4.86 (m , 1H), 4.44 (m 1H), 4.26 (m,1H) , 3.47 (m, 1H), 3.3 (m, 2H), 3.12 (m, 2H), 2.89 (q, 1H), 2.56 (m, 1H), 2.49 (m, 1H), 244 (s, 3H), 2.29 (m, 1H), 1.8 (m, 1H). Separation by chiral HPLC provides enantiomers 336a-b.

Example 247: Preparation of Compound Nos. 337 and 337a-b.

[0896] This compound can be prepared in analogous fashion to Compound Nos. 30 and 30a-b, using 2-(2-methyloxiran-2-yl)oxazole as the oxirane reagent. Separation by chiral HPLC provides enantiomers 337a-b.

Example 248: Preparation of Compound Nos. 338 and 338a-b.

[0897] To an ice-cooled stirred solution of 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (2.5 g, 7.78 mmol) in DMF (5 mL) was added sodium hydride (373 mg, 15.56 mmol). After stirring for 20 min, heptanoyl chloride (1.9 g, 13.23 mmol) was added into the reaction mixture, which was stirred at 0 °C for 30 min. The progress

of reaction was monitored by LCMS and TLC. The reaction mixture was quenched with ice water (200 mL) and extracted with EtOAc (400 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (6% MeOH-DCM), followed by reverse phase HPLC to yield heptanoic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl ester (20 mg). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.74 (s, 2H), 7.91 (s, 2H), 7.28 (m, 2H), 7.04 (t, 1H), 6.2 (m 1H), 4.7 (d 1H) , 4.59 (m, 2H), 4.3 (m, 1H), 3.5 (t, 1H), 3.34 (m, 1H), 3.31 (m, 2H), 3.12 (s, 3H), 2.4 (s, 3H), 2.3 (m, 2H), 2.1 (m, 1H), 1.35 (m, 2H), 1.22 (m, 2H), 1.15 (m, 3H), 0.86 (t,3H). Separation by chiral HPLC provides enantiomers 338a-b.

Example 249: Preparation of Compound Nos. 339 and 339a-b

[0898] To a solution of 9-chloro-1,2,3,4,5,6-hexahydro-3-methylazepino [4,5-b]indole (1.0 g, 4.27 mmol) in DMF (10 mL) was added potassium tert-butoxide (717.9 mg, 6.41 mmol). After stirring at RT for 15 min, 2-(3,4-difluorophenyl)oxirane (1.33 g, 8.54 mmol) was added into the reaction mixture, which was stirred at RT for 3 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with 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 purified by reverse phase HPLC to yield the title compound, which was resolved by chiral preparative HPLC. ^{1}H NMR (DMSO, TFA salt) δ (ppm): 7.62-7.50 (t, 1H), 7.50-7.30 (t, 3H), 7.25-7.00 (m, 2H), 4.85-4.75 (m, 1H), 4.30-4.20 (t, 2H), 3.80-3.60 (m, 4H), 3.25-3.10 (m, 4H), 2.90 (s, 3H).

Example 250: Preparation of Compound Nos. 340 and 340a-d.

[0899] This compound can be prepared in analogous fashion to Compound Nos. 30 and 30a-b, using 5-(oxiran-2-yl)-1H-1,2,3-triazole as the oxirane reagent. Separation by chiral HPLC provides diastereomers 340a-d.

Example 251: Preparation of Compound Nos. 341 and 341a-d.

[0900] This compound can be prepared in analogous fashion to Compound Nos. 30 and 30a-b, using 5-(oxiran-2-yl)-1H-tetrazole as the oxirane reagent. Separation by chiral HPLC provides diastereomers 341a-d.

Example 252: Preparation of Compound Nos. 342 and 342a-d.

[0901] This compound can be prepared in analogous fashion to Compound Nos. 30 and 30a-b, using 2-(oxiran-2-yl)-1H-imidazole as the oxirane reagent. Separation by chiral HPLC provides diastereomers 342a-d.

Example 253: Preparation of Compound Nos. II-270 and II-270a-b.

[0902] These compounds can be synthesized in an analogous fashion to Compound Nos. 55 and 55a-b, using 3,6-dimethyl-6,7,8,9-tetrahydro-5H-1,2,6,9-tetraaza-fluorene as the carboline portion and 4-(2-methyloxiran-2-yl)pyridine as the epoxide. Separation by chiral HPLC provides enantiomers II-270a-b.

Example 254: Preparation of Compound Nos. II-1 and II-1a-b.

[0903] To a solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethanamine (500 mg, 1. 56 mmol) in DCM (5 mL) was added pyridine (185 mg, 2. 3 mmol). After stirring for 5 min at RT, a solution of acetyl chloride (147. 2 mg, 1. 88 mmol) in DCM (0. 5 mL) was added into the reaction mixture, which was stirred at RT for 16 h. The reaction mixture was diluted with DCM and washed with saturated aq $NaHCO_3$ solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was triturated with ether to yield N-(2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethyl)acetamide (500 mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.42 (d, 2H), 7.25 (s, 1H), 7.15 (d, 1H), 6.92 (d, 2H), 6.9 (d, 1H) , 6.2 (d, 1H), 5.3 (q, 1H), 4.4 (dd, 1H), 4.25 (dd, 1H), 3.58 (dd, 2H), 2.6 (m, 2H), 2.55 (s, 3H), 2.43 (s, 3H), 2.3 (m, 2H), 2.03 (s, 3H). Separation by chiral HPLC provided enantiomers II-1a-b.

Example 255: Preparation of Compound No. II-2.

[0904] Crude 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethyl methanesulfonate was taken in NMP (5 mL), and KOH powder (873 mg, 15. 5 mmol) was added at RT and the mixture stirred at 80 °C for 14 h. The product was detected by LCMS. Water was added to the reaction mixture, which was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was chromatographed on silica gel using 5% MeOH-DCM to afford 400 mg of the title compound. ^{1}H NMR (DMSO, Formate salt) δ (ppm): 8.55-8.50 (d, 2H), 8.05-8.00 (d, 1H), 7.85-7.80 (d, 1H), 7.65-7.55 (d, 2H), 7.25 (s, 1H), 7.15-7.10 (m, 1H), 6.80-6.75 (d, 1H), 3.58 (s, 2H), 3.05 (t, 2H), 2.78 (t, 2H), 2.41 (s, 3H), 2.38 (s, 3H).

Example 256: Preparation of Compound No. II-3.

[0905] To a stirred cooled (-70 °C) solution of 2-methyl-5-[2-(6-methyl-pyridin-3-yl)-propenyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole-8-carboxylic acid methyl ester (100 mg, 0. 26 mmol) in THF (10 mL) was added portionwise LAH (30 mg, 0. 79mmol) and stirring continued at RT for 4 h. The reaction mixture was cooled to -70 °C and quenched with water

(0.1 mL), 15 % NaOH (0.1 mL) and water (0.2 mL). The solid was filtered and the filtrate concentrated to afford crude material, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, Formate salt) δ (ppm): 8.67 (s, 1H), 8.0 (d, 1H), 7.5 (s, 1H), 7.4 (d, 1H), 7.27 (d, 1H), 7.23 (d, 1H), 7.1 (s, 1H), 4.7 (s, 2H), 4.42 (s, 2H), 3.6 (t, 2H), 3.1 (t, 2H), 3.05 (s, 3H), 2.6 (s, 3H), 1.28 (s, 3H).

Example 257: Preparation of Compound Nos. II-4 and II-4a-d.

[0906] 6-(2-Azido-2-pyridin-4-yl-ethyl)-9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (400 mg, 1.07 mmol) was dissolved in ethanol-water (10 mL:1 mL). Zinc dust (280 mg, 4.3 mmol) and ammonium chloride (228 mg, 4.3 mmol) were added and the reaction mixture was heated at 80 °C for 1 h. 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 (2x100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 40 mg of 2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta [c]fluoren-6-yl)-1-pyridin-4-yl-ethylamine as the TFA salt. ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 8.58 (d, 2H), 7.28 (d, 1H), 7.25 (s, 1H), 7.23 (d, 2H), 7.1 (d, 1H), 4.9 (m, 1H), 4.42 (t, 1H), 4.13 (dd, 1H), 3.63 (m, 1H), 3.4 (m, 2H), 3.01 (m, 2H), 2.71 (m, 2H), 2.45 (s, 3H), 2.23 (m, 2H), 2.01 (m, 1H). Chiral HPLC separated the racemate into diastereomers II-4a-d.

Example 258: Preparation of Compound Nos. II-5 and II-5a-d.

[0907] To a solution of 9-aza-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (30 mg, 0.13 mmol) in DMF (5 mL) was added NaH (16 mg, 0.4 mmol, 60% dispersion in mineral oil) at 0 °C and the mixture was stirred for 10 min. 3-(2-Methyl-oxiranyl)-pyridine 36 mg, 0.26 mmol) was added and the reaction mixture was stirred overnight at RT. The reaction was monitored by LCMS. The reaction mixture was quenched with MeOH (1 mL), concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase column chromatography to obtain the pure product (3.3 mg) as the free base. ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 9.1 & 8.91 (s, 1H), 8.8 & 8.7 (s, 1H), 8.6 & 8.5 (d, 1H), 7.6 & 7.8 (d, 1H), 7.18 (s, 2H), 4.4 (dd, 1H), 4.2 (m, 2H), 3.32 (m, 2H), 2.7 (dd, 1H), 2.66 (s, 3H), 1.99 (m, 2H), 1.9 (m, 2H), 1.76 & 1.67 (s, 3H), 1.6 (m, 3H). Chiral HPLC separates the racemate into diastereomers II-5a-d.

Example 259: Preparation of Compound Nos. II-6 and II-6a-d.

[0908] 6-(2-Chloro-2-pyrazin-2-yl-propyl)-9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (500 mg, 1.31 mmol) in 40 % dimethylamine in water (30 mL) was heated at 100 °C for 3 h. The reaction mixture was cooled at RT and extracted with EtOAc (3x50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 62 mg of dimethyl-[1-methyl-2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-1-pyrazin-2-yl-ethyl]-amine. ^{1}H NMR (CD_3OD, TFA salt): δ (ppm): 8.06 (s, 1H), 7.48 (s, 1H), 7.21 (s, 1H), 7.17 (d, 1H),7.00 (d, 1H), 4.98 (t, 1H), 4.28 (d, 2H), 3.6 (m, 3H), 3.39 (m, 2H), 3.2 (m, 1H), 3.15 (s, 6H), 2.8 (m, 1H), 2.7 (m, 1H), 2.39 (s, 3H), 2.17 (m, 3H). Chiral HPLC separated the racemate into diastereomers II-6a-d.

Example 260: Preparation of Compound Nos. II-7 and II-7a-d.

[0909] Methanesulfonic acid 2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c] fluoren-6-yl)-1-pyrazin-2-yl-ethyl ester (300 mg, 0.70 mmol) in 40% dimethylamine in water (20 mL) was heated at 90 °C for 1 h. The reaction mixture was cooled to RT and extracted with DCM (12x50 mL)The combined organic layer was dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 60 mg of dimethyl-[2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-1-pyrazin-2-yl-ethyl]-amine. ^{1}H NMR (CD_3OD, TFA salt): δ (ppm): 8.1 (s, 1H),7.4 (s, 1H), 7.1 (d, 1H), 5.1 (t, 1H), 4.42 (m, 2H), 3.6 (m, 3H), 3.2 (m, 1H), 3.17 (m, 1H), 3.15 (s, 6H), 2.85 (m, 2H), 2.63 (m, 1H), 2.42 (s, 3H), 2.3 (m, 2H), 2.15 (m, 1H). Chiral HPLC separates the racemate into diastereomers II-7a-d.

Example 261: Preparation of Compound Nos. II-8 and II-8a-b.

[0910] Methanesulfonicacid-2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethylester (300 mg, 0.75 mmol) in 70 % ethylamine in water (15 mL) was heated at 100 °C for 18 h. The reaction mixture was cooled to RT and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (2x20 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 55 mg of [2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl]-ethyl-amine. ^{1}H NMR (DMSO, TFA salt): δ (ppm): 8.5 (d, 2H), 7.3 (d, 1H), 7.2 (m, 3H), 6.9 (d, 1H), 4.7 (m, 2H), 4.43 (m, 2H), 4.1 (d, 1H), 3.3 (m, 1H), 3.0 (m, 2H), 2.85 (d, 6H), 2.8 (m, 1H), 2.5 (m, 2H), 2.3 (s, 3H), 1.22 (s, 3H). Chiral HPLC separates the racemate into enantiomers II-8a-b.

Example 262: Preparation of Compound Nos. II-9 and II-9a-b.

[0911] Methanesulfonic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethylester (240 mg, 0.60 mmol) was dissolved in 10 mL of 70 % cyclopentylamine solution in water and heated at 100 °C for 18h. The reaction mixture was cooled to RT and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 11 mg of cyclopentyl-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl]-amine. ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 8.51 (d, 2H), 7.17 (m, 4H), 7.003 (d, 1H), 4.16 (m, 2H), 4.05 (dd, 1H), 3.79 (dd, 2H), 2.9 (m, 1H), 2.83 (m, 2H), 2.55 (s, 3H), 2.44 (s, 3H), 2.39 (m, 1H), 1.99 (s, 2H), 1.7 (m, 2H), 1.5 (m, 2H), 1.4 (m, 1H), 1.9 (m, 2H). Chiral HPLC separates the racemate into enantiomers II-9a-b.

Example 263: Preparation of Compound Nos. II-10 and II-10a-b.

[0912] 2-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethylamine (200 mg, 0.62 mmol) was dissolved in 15 mL DCM, acetone (108 mg, 1.87 mmol), acetic acid (0.5 mL) was added and the reaction mixture was stirred at RT overnight. Sodiumcyanoborohydride (117 mg, 1.87 mmol) was added and stirred at for 1h. The reaction mixture was diluted with DCM (300 mL) and washed with saturated bicarbonate solution (200 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 120 mg of [2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl]-isopropyl-amine as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt): δ (ppm): 8.52 (m, 2H), 7.42 b(s, 2H), 7.30 b(s, 1H), 7.22 (s, 1H), 7.02 (m, 1H), 4.8 (m, 1H), 4.58 (m, 2H), 4.23 (t, 1H), 3.72 (m, 1H), 3.4 (m, 3H), 3.13 (m, 2H), 2.99 (d, 3H), 2.39 (s, 3H), 1.43 (d, 3H), 1.34 (d, 3H). Chiral HPLC separates the racemate into enantiomers II-10a-b.

Example 264: Preparation of Compound Nos. II-11 and II-11a-b.

[0913] To a solution of 5-(2-azido-2-(4-fluorophenyl)ethyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1 g, 2.75 mmol) in ethanol-water (40-5 mL) was added ammonium chloride (590 mg, 11.02 mmol) and zinc dust (716 mg, 11.02 mmol) and heated at 100 °C for 1 h. After complete conversion of starting material (TLC), ethanol was removed under reduced pressure and 50 mL additional water was added and extracted with DCM (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the crude product, which was purified by reverse phase HPLC to obtain 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl) ethanamine (730 mg) as the TFA

salt. ^{1}H NMR (CD_3OD, TFA salt): δ (ppm): 7.27 (m, 1H), 7.21 (m, 3H), 7.10 (m, 3H), 4.60 (m, 3H), 4.50 (m, 1H),4.24 (m, 1H), 3.69 (m, 1H), 3.44 (m, 1H), 3.04 (m, 1H), 2.96 (s, 3H), 2.56 (m, 1H), 2.41 (s, 3H). Chiral HPLC separated the racemate into enantiomers II-11a-b.

Example 265: Preparation of Compound Nos. II-12 and II-12a-b.

[0914] 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)ethyl methane sulfonate (250 mg, 0.6 mmol) in methyl amine (40 % solution in water, 5 mL) was heated at 100 °C for 4 h. The progress of the reaction was monitored by TLC and LCMS. 10 mL of water was added to the reaction mixture and then extracted with EtOAc (2x50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the crude product, which was purified by reverse phase HPLC to obtain 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)-N-methyl ethanamine (30 mg) as the TFA salt. ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 7.32 (t, 2H), 7.24 (m, 1H), 7.21 (s, 1H), 7.01 (m, 3H), 3.91 (m, 2H),3.65 (dd, 2H), 2.80 (m, 3H), 2.62 (m, 1H), 2.54 (s, 3H), 2.45 (s, 3H), 2.14 (s, 3H). Chiral HPLC separated the racemate into enantiomers II-12a-b.

Example 266: Preparation of Compound Nos. II-13 and II-13a-b.

[0915] Methanesulfonicacid2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethylester (300 mg, 0.75 mmol) was dissolved in 70% cyclobutylamine in water (6 mL) and heated at 100 °C for 18 h. The reaction mixture was concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtained 90 mg of cyclobutyl-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl]-amine as the TFA salt. ^{1}H NMR (CD_3OD,TFA salt): δ (ppm): 8.6 (dd, 2H), 7.63 (d, 1H), 7.54 (d, 1H), 7.19 (s, 1H), 7.10 (d, 1H), 6.99 (d, 1H), 4.82 (m, 2H), 4.72 (m, 1H), 4.6 (m, 1H), 4.23 (t, 1H), 3.8 (m, 2H), 3.5 (m, 1H), 3.2 (m, 1H), 3.07 (d, 3H), 2.7 (m, 1H), 2.37 (s, 3H), 2.5 (m, 3H), 2.1 (m, 1H), 1.8 (m, 2H). Chiral HPLC separated the racemate into enantiomers II-13a-b.

Example 267: Preparation of Compound Nos. II-14 and II-14a-b.

[0916] 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl) ethanamine (250 mg, 0.741 mmol), formaldehyde 37- 40 % solution (5 mL) and formic acid (0.25 mL) was heated at 100 °C for 2 h. After the completion of reaction (TLC and LCMS), the reaction mixture was cooled to RT, neutralized by saturated sodium bicarbonate and extracted into DCM (2x50 mL). The combined organic layer was washed with water (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 250 mg of 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(4-fluorophenyl)-N,N-

dimethylethanamine. ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 7.13 (s, 1H), 7.05 (d, 1H),7.02 (t, 2H), 6.88 (m, 3H), 4.56 (dd, 1H), 3.99 (m, 1H), 3.64 (d, 1H) 3.54 (dd, 1H), 3.46 (d, 1H), 2.79 (m, 1H), 2.6 (m, 2H), 2.45 (s, 3H), 2.42 (s, 3H), 2.3 (s, 6H), 1.9 (m, 1H). Chiral HPLC separated the racemate into enantiomers II-14a-b.

Example 268: Preparation of Compound Nos. II-15 and II-15a-b.

[0917] 1-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol (2. 0 g, 5. 97 mmol) was dissolved in DMF (20 ml), sodium hydride (716 mg, 17. 9 mmol) was added and the mixture stirred at RT for 20 min. Acetic anhydride (913 mg, 8. 95 mmol) was added dropwise at the same temperature and stirring continued for 1.5 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured into 250 mL ice water and extracted with EtOAc (3x200 mL), washed with water (3x300 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product that was purified by column chromatography (silica gel: 100-200 mesh, eluent:-6-8% MeOH in DCM) to obtain 110 mg of acetic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-methyl-1-pyridin-3-yl-ethyl ester, which was followed by chiral separation. ^{1}H NMR (CD_3OD, Free base) δ (ppm): 8.38 (d, 1H), 8.15 (s, 1H), 7.45 (d, 1H), 7.22 (t, 1H), 7.1 (s, 1H), 7.0 (s, 1H), 6.8 (d, 1H), 4.43 (d, 1H), 4.2 (d, 1H), 3.7 (d, 1H), 3.5 (d, 1H), 2.8 (m, 2H), 2.53 (m, 1H), 2.5 (s, 3H), 2.4 (s, 3H), 2.2 (m, 1H), 2.07 (d, 6H). Separation by chiral HPLC provided enantiomers II-15a-b.

Example 269: Preparation of Compound Nos. II-16 and II-16a-b.

[0918] 1-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol (5.0 g, 14.9 mmol) was dissolved in DMF (100 mL) and sodium hydride (1.8 g, 45 mmol) was added, and the mixture stirred at RT for 15 min. Pivaloyl chloride (3g, 25 mmol) was added dropwise at the same temperature, and the mixture stirred for 45 min. The reaction was monitored by TLC and LCMS. The reaction mixture was poured into 400 mL ice water to obtain a solid that was filtered. The solid was dissolved in DCM, dried over sodium sulfate and concentrated to obtain the crude product that was purified by column chromatography (silica gel: 100-200 mesh, Eluent:-4-6 % MeOH in DCM) to obtain 1.8 g of 2,2-dimethyl-propionic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-methyl-1-pyridin-3-yl-ethyl ester. The product was further purified by chiral preparative HPLC to give enantiomers II-16a and II-16b. ^{1}H NMR ($CDCl_3$, Free base): δ (ppm): 8.55 (d, 1H), 8.5 (s, 1H), 7.2 (d, 1H), 7.18 (m, 3H), 6.9 (d, 1H), 4.3 (dd, 2H), 3.65 (d, 1H), 3.52 (d, 1H), 2.65 (m, 2H), 2.5 (m, 2H), 2.5 (s, 3H), 2.4 (s, 3H), 2.3 (d,1H), 2.0 (s, 3H), 2.0 (m, 1H), 1.2 (s, 9H).

Example 270: Preparation of Compound Nos. II-17 and II-17a-d.

[0919] To a solution of 11-aza-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (120 mg, 0.52 mmol) in DMF (5 mL) was added NaH (31 mg, 1.06 mmol, 60% dispersion in mineral oil) at 0 °C and the reaction mixture was stirred for 10 min. 3-(2-Methyl-oxiranyl)-pyridine 143 mg, 1.06 mmol) was added and the reaction mixture was stirred at RT overnight. The reaction was monitored with LCMS. The reaction mixture was quenched with MeOH (2 mL), concentrated under reduced pressure to obtain the crude product, which was purified by reverse phase column chromatography to obtain the 30 mg of product as the free base. ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 8.72 & 8.69 (s, 1H), 8.25 (t, 1H), 7.62 & 7.6 (d, 1H), 7.43 (t, 1H), 7.22 & 7.19 (m, 1H), 6.86 (t, 1H), 4.25 (m, 2H),3.2 (m, 1H), 2.99 (m, 1H), 2.85 (t, 2H), 2.7(m, 1H), 2.626 (s, 3H), 2.5 (m, 2H), 2.4 (m, 1H), 2.15 (m, 1H), 1.85 (m, 2H), 1.69 & 1.66 (s, 3H). Chiral HPLC separates the racemate into diastereomers II-17a-d.

Example 271: Preparation of Compound No. II-18.

[0920] To a solution of 2,6,9-trimethyl-2,3,4,5-tetrahydro- 1H-pyrido[4,3-b]indole (100 mg, 0. 466 mmol) in DMF (2 mL) were added sodium hydride (60 mg, 1. 3 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (337.5 mg, 1.16 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1 h. The reaction mixture was cooled to RT, quenched with water and extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.1 (m, 2H), 7.7 (d, 1H), 6.6 (d, 2H), 4.98 (m, 1H), 4.5 (m, 1H), 4.4 (t, 2H), 3.82 (bs, 1H), 3.5 (bs, 1H), 3.2 (t, 2H), 3.1 (m, 5H), 2.65 (s, 3H), 2.5 (s, 3H), 2.31 (s, 3H).

Example 272: Preparation of Compound Nos. II-19 and II-19a-b.

[0921] 1-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol (3.35 g, 10.0 mmol), isonicotinic acid (1.23 g, 10 mmol), DCC (5.0 g, 24.0 mmol) and DMAP (1.2 g, 10 mmol) were suspended in DCM (300 mL) and the resultant mixture was stirred overnight under nitrogen atmosphere. The reaction was monitored by LCMS. The reaction mixture was filtered to remove N,N-dicyclohexyl urea formed during the reaction. The filtrate was washed with water (3x300 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product which was purified by column chromatography (neutral alumina; eluent: 0.5 – 1 % MeOH in DCM) to obtain the product. The

product obtained was triturated with diethyl ether (30 mL) to obtain the pure product (400 mg). ^{1}H NMR ($CDCl_3$, freebase): δ (ppm): 8.71 (d, 2H), 8.58 (s, 1H), 8.56 (d, 1H), 7.64 (d, 2H), 7.32 (d, 1H), 7.21 (s, 1H), 7.18 (d, 2H), 6.97 (d, 1H), 4.45 (dd, 2H), 3.65 (d, 1H), 3.57 (d, 1H), 2.7 (m, 1H), 2.52 (m, 1H), 2.49 (s, 3H), 2.46 (s, 3H), 2.43 (m, 1H), 2.16 (s, 3H), 2.01 (m, 1H). Separation by chiral HPLC provided enantiomers II-19a-b.

Example 273

[0922] Compound Nos. II-21, II-23, II-36, II-56, II-57, II-160, II-188-206, II-233, II-237 and II-254 were synthesized as described in PCT publication WO2009/055828. Compound Nos. II-107 and II-164-165 were synthesized as described in PCT publication WO2009/120720. Compound Nos. II-20, II-48-49, II-52-55, II-156-158 and II-161 were synthesized as described in PCT publication WO2009/120717. Compound Nos. II-47, II-95, II-162-163 and II-166-187 were synthesized as described in PCT publication WO2010/051501. Compound Nos. II-22, II-24-35, II-37-38, II-41-46, II-50-51, II-155 and II-159 were synthesized as described in PCT publication WO2010/051503. Compound No. II-219 was synthesized as described in PCT publication WO2010/127177. Compound Nos. II-207-208, II-216-218 and II-228 were synthesized as described in PCT publication WO2010/019417. Compound No. II-69 was synthesized as described in PCT publication WO2011/038163. Compound Nos. II-79, II-86, II-234-236 and II-238-239 were synthesized as described in PCT publication WO2011/038161. Compound Nos. II-72-74, II-87 and II-214 were synthesized as described in PCT publication WO2011/038162. Compound Nos. II-66 and II-85 were synthesized as described in PCT publication WO2011/038164.

Example 274: Preparation of Compound No. II-39.

[0923] To a solution of 6-bromo-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.359 mmol), in DMF (2 mL) were added sodium hydride (50 mg, 1.07 mmol) and 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (262 mg, 0.899 mmol). The reaction mixture was irradiated in a microwave reactor at 90 °C for 1 h. The reaction mixture was cooled to RT, quenched with water and extracted with EtOAc (3x10 mL). The organic layer was washed with water (2x10 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.36 (s, 1H), 8.17 (d, 1H), 7.7 (d, 1H), 7.21 (s, 1H), 7.18 (s, 1H), 4.8 (m, 1H), 4.62 (t, 2H), 4.3 (m, 1H), 3.82 (m, 1H), 3.5 (m, 1H), 3.2 (m, 3H), 3.1 (m, 4H), 2.7 (s, 3H), 2.38 (s, 3H).

Example 275: Preparation of Compound No. II-40.

[0924] A solution of 2,3,4,5-tetrahydro-2,4,4,8-tetramethyl-1H-pyrido[4,3-b]indole (228 mg, 1 mmol) and KOH (448 mg, 8 mmol) in NMP was heated at 100 °C for 15 min. 2-(Trifluoromethyl)-5-vinylpyridine (381 mg, 2.2 mmol) was added dropwise into the reaction mixture and stirring continued at 45 °C for 30 min. The reaction mixture was diluted with water and extracted with EtOAc (3x25 mL). The organic extract was washed with water (3x25 mL), dried over anhydrous sodium sulfate and evaporated in vacuo to afford crude material, which was purified by silica gel column chromatography using 0-5% MeOH-DCM, followed by reverse phase HPLC to yield desired compound as the TFA salt (41 mg). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.4 (s, 1H), 7.8 (d, 1H), 7.72 (d, 1H), 7.24 (d, 2H), 7.02 (d, 1H), 4.67 (d, 1H), 4.6 (t, 2H), 4.35 (d, 1H), 3.47 (d, 1H), 3.4 (d, 1H), 3.24 (t, 2H), 3.17 (s, 3H), 2.4 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H).

Example 276: Preparation of Compound Nos. II-49 and II-49a-b.

[0925] Sodium hydride (36 mg, 1. 5 mmol) was dissolved in THF. 2,6-Dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (100 mg, 0. 05 mmol) in THF was added dropwise at 0 °C to the NaH solution and the reaction mixture was stirred for 0.5 h. A solution of 2-(2-fluorophenyl) oxirane (103 mg, 0.075 mmol) in THF was added dropwise to the reaction mixture and was stirred at RT for 2h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched with ice-water, the THF was evaporated and the aqueous layer was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate. The crude compound was purified by column chromatography to yield the desired compound (30 mg) which was stirred in ethanolic HCl to yield 2-(2,6-dimethyl-3,4-dihydro-1H-pyrido[3,4-b]indol-9(2H)-yl)-1-(2-fluorophenyl)ethanol hydrochloride salt. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 7.6 (t, 1H), 7.3 (m, 3H), 7.2 (t, 1H), 7.1 (t, 1H), 7.0 (d, 1H), 5.33 (d, 1H), 4.22 (d, 1H), 3.95 (dd, 1H), 3.8 (d, 1H), 3.5 (d, 1H), 2.8 (m, 4H), 2.5 (s, 3H), 2.4 (s, 3H). Separation by chiral HPLC provided enantiomers II-49a-b.

Example 277: Preparation of Compound Nos. II-57 and II-57a-b.

[0926] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1. 35g,6. 65mmol) was taken in DMF (10 mL). NaH (0. 9 g, 19. 5mmol) was added to it portionwise at RT and the mixture stirred for 15 min. 2-Methyl-5-(oxiran-2-yl)pyridine (0. 9 g, 6. 65 mmol) was added to the reaction mixture dropwise at RT. After complete addition, the reaction mixture was stirred at RT for 2 h. The product was detected by LCMS. The reaction mixture was quenched with

MeOH and concentrated to dryness. Water (20 mL) was added and the reaction mixture was extracted in EtOAc (2x100 mL), the extracts dried over anhydrous sodium sulfate and concentrated to obtain a dark brown oil. The crude product was purified by reverse phase chromatography to obtain pure material as a TFA salt (310 mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.45 (s, 1H), 7.52 (d, 1H), 7.2 (s, 1H), 7.19 (d, 1H), 7.12 (d, 1H) , 6.97 (d, 1H), 5.0 (t, 1H), 4.18 (dd, 2H), 3.61 (dd, 2H), 2.9 (m, 1H), 2.82 (m, 2H), 2.65 (m, 1H), 2.50 (s, 3H), 2.48 (s, 3H), 2.41 (s, 3H). Separation by chiral HPLC provided enantiomers II-57a-b.

Example 278: Preparation of Compound Nos. II-58 and II-58a-b.

[0927] 1-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-4-yl-propan-2-ol (350 mg. 1.0 mmol) was dissolved in 10 mL DCM and metachloro perbenzoic acid (216 mg,1.2 mmol) was diluted in DCM and added dropwise at RT. After consumption of starting material by monitoring TLC & LCMS, the reaction mixture was concentrated and purified by reverse phase chromatography to obtain 200 mg of 1-(2,8-dimethyl-2-oxy-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-4-yl-propan-2-ol. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.54 (d, 2H), 7.68 (d, 1H), 7.55 (d, 1H), 7.28 (d, 2H), 7.22 (s, 1H), 7.10 (d, 1H), 6.63 (d, 1H), 4.06 (d, 2H), 3.28 (t, 2H), 2.91 (t, 2H),), 2.46 (s, 3H). Separation by chiral HPLC provides enantiomers II-58a-b.

Example 279: Preparation of Compound No. II-59.

[0928] To a de-aerated solution of 2-allyl-8-methyl-5-[2-(6-methyl-pyridin-3-yl)-propenyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (750 mg, 2.1 mmol) in DCM (7.5 mL) were added 1,3-dimethylbarbutaric acid (984 mg, 6. 302 mmol) and $Pd(PPh_3)_4$ (48 mg, 0. 042 mmol), and the reaction mixture stirred for 1 h at RT. The reaction mixture was concentrated and the residue diluted with 25% saturated potassium carbonate and extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (2x25 mL), dried over anhydrous sodium sulfate and concentrated to afford crude material, which was purified by column chromatography using neutral alumina and 2% MeOH-DCM followed by reverse phase HPLC to yield 8-methyl-5-[2-(6-methyl-pyridin-3-yl)-propenyl]-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (180 mg). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.92 (s, 1H), 8.65 (d, 1H), 7.90 (d, 1H), 7.36 (d, 2H), 7.18 (d, 1H), 7.16 (d, 1H), 4.50 (s, 2H), 3.65 (t, 2H), 3.10 (t, 2H), 2.80 (s, 3H), 2.42 (s, 3H), 2.05 (s, 3H).

Example 280: Preparation of Compound No. II-60 and II-60a-b.

[0929] To a solution of 5-(2-hydroxy-2-pyridin-4-yl-ethyl)-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole-8-carboxylic acid methyl ester (180 mg, 0.493 mmol) in dry THF (12 mL)

was portionwise added LAH (56 mg, 1.479 mmol) under nitrogen atmosphere, and the reaction mixture stirred at RT for 2 h. The reaction mixture was cooled to -78 °C and quenched with ice water (0.6 mL), 10 % NaOH (0.6 mL) and water (1.8 mL), and the solid filtered. The filtrate was concentrated and the residue was purified by reverse phase HPLC to yield 2-(8-hydroxymethyl-2-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.4 (d, 2H), 7.4 (s, 1H), 7.27-7.38 (m, 3H), 7.18 (d, 1H), 5.1 (t, 1H), 4.62 (s, 2H), 4.3 (d, 2H), 4.0 (dd, 2H), 3.2 (m, 1H), 3.1 (m, 2H), 2.73 (m, 1H), 2.7 (s, 3H). Separation by chiral HPLC provides enantiomers II-60a-b.

Example 281: Preparation of Compound No. II-61.

[0930] To a de-aerated solution of 2,4,4,8-tetramethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (228 mg, 1. 00 mmol), potassium phosphate (466 mg, 2. 20 mmol), L-proline (19 mg, 0. 10 mmol) and copper iodide (I) (23 mg, 0. 20 mmol) in DMF (2 mL) was added 5-(1-bromoprop-1-en-2-yl)-2-methylpyridine (424 mg, 2. 00 mmol), and the reaction mixture stirred at 120 °C for 20 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x10 mL). The combined 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_3OD, TFA salt) δ (ppm): 8.97 (s, 1H), 8.66 (d, 1H), 7.9 (d, 1H), 7.42 (s, 1H), 7.37 (s, 1H), 7.1 (q, 2H), 4.7 (m, 1H), 4.37 (m, 1H), 3.5 (m, 2H), 3.2 (s, 3H), 2.8 (s, 3H), 2.42 (s, 3H), 1.97 (s, 3H), 1.5 (bs, 6H).

Example 282: Preparation of Compound Nos. II-62 and II-62a-b.

[0931] To a degassed solution of 1-(2-allyl-8-chloro-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-4-yl-propan-2-ol (300 mg, 0.78 mmol) in DCM (20 mL) were added 1,3-dimethyl barbituric acid (368 mg, 2.3 mmol) and $Pd(PPh_3)_4$ (18 mg, 0.015mmol). After stirring at RT for 30 min, the reaction mixture was diluted with DCM and washed with saturated potassium carbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 1-(8-chloro-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-4-yl-propan-2-ol. ^{1}H NMR (CD_3OD, formate salt) δ (ppm): 8.4 (d, 2H), 7.48 (d, 2H), 7.4 (s, 1H), 7.18 (d, 1H), 6.98 (d, 1H), 4.6 (bs, 1H), 4.4 (s, 2H), 4.3 (m, 2H), 3.6 (m, 2H), 3.4 (m, 2H), 3.1 (m, 2H). Separation by chiral HPLC provides enantiomers II-62a-b.

Example 283: Preparation of Compound Nos. II-63 and II-63a-b.

[0932] To a solution of 2-allyl-2,3,4,5-tetrahydro-8-methyl-1H-pyrido[4,3-b]indole (1000 mg, 4.42 mmol) in DMF (10 mL) was portionwise added sodium hydride (526 mg, 13.26 mmol). After stirring at RT for 5 min., 4-(oxiran-2-yl)pyridine (669 mg, 5.31 mmol) was added dropwise into the reaction mixture, which was stirred at RT for 16 h. Ice water was added into the reaction mixture and the solid mass obtained was filtered, washed with water (2x10 mL), hexane (2x50 mL) and ether to yield 2-(2-allyl-1,2,3,4-tetrahydro-8-methylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethanol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.6 (d, 2H), 7.24 (s, 1H), 7.2 (d, 2H), 7.0 (d, 2H), 5.98 (m, 1H), 5.2 (dd, 2H), 5.0 (m, 1H), 4.1 (m, 2H), 3.6 (dd, 2H), 3.22 (d, 2H), 2.7-2.9 (m, 3H), 2.6 (m, 1H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers II-63a-b.

Example 284: Preparation of Compound Nos. II-64 and II-64a-b.

[0933] To a solution of 2-(8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (100 mg, 0.325 mmol) in acetonitrile (3 mL), potassium carbonate (135 mg, 0.977 mmol) and 2-bromoethanol (61 mg, 0.488 mmol) were added and the reaction mixture stirred at 60 °C for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield 2-[2-(2-hydroxy-ethyl)-8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl]-1-pyridin-4-yl-ethanol. ^{1}H NMR (CD_3OD, formate salt) δ (ppm): 8.41 (d, 2H), 7.38 (d, 2H), 7.2 (m, 2H), 6.99 (d, 1H), 5.03 (t, 1H), 4.4 (bs, 2H), 4.3 (d, 2H), 3.93 (t, 2H), 3.45-3.62 (m, 2H), 3.2 (m, 2H), 2.9 (m, 2H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers II-64a-b.

Example 285: Preparation of Compound Nos. II-65 and II-65a-b.

[0934] To a solution of 2-(8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (200 mg, 0.651 mmol) in acetonitrile (4 mL), potassium carbonate (270 mg, 1.953 mmol) and bromo-acetic acid ethyl ester (163 mg, 0.977 mmol) were added and the reaction mixture was stirred at RT for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to yield [5-(2-hydroxy-2-pyridin-4-yl-ethyl)-8-methyl-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl]-acetic acid ethyl ester (220 mg). To a solution of [5-(2-hydroxy-2-pyridin-4-yl-ethyl)-8-methyl-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl]-acetic acid ethyl ester (120 mg, 0.305 mmol) in

ethanol (2 mL), 1N NaOH (3 mL) was added and the reaction mixture stirred at RT for 1 h. The progress of reaction was monitored by LCMS. The reaction mixture was neutralized with aq HCl. The solvent was removed under reduced pressure and the residue diluted with 90% MeOH in DCM and filtered. The filtrate was concentrated and residue was purified by reverse phase HPLC to yield [5-(2-hydroxy-2-pyridin-4-yl-ethyl)-8-methyl-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl]-acetic acid. ^{1}H NMR (CD_3OD, formate salt) δ (ppm): 8.42 (d, 2H), 7.4 (d, 2H), 7.2 (d, 2H), 6.9 (d, 1H), 5.03 (t, 1H), 4.6 (bs, 1H), 4.57 (bs, 2H), 4.3 (m, 2H), 3.8 (s, 2H), 3.7 (bs, 2H), 3.0 (m, 1H), 2.3 (s, 3H). Separation by chiral HPLC provides enantiomers II-65a-b.

Example 286: Preparation of Compound Nos. II-67 and II-67a-b.

[0935] To a solution of 2-methyl-8-trifluoromethoxy-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 3.70 mmol) in DMF(10 mL) was added sodium hydride (445 mg, 11.12 mmol) under nitrogen at 0 °C. After stirring for 10 min, 4-(oxiran-2-yl)pyridine (806 g, 6.66 mmol) was added dropwise under nitrogen and 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 into ice-cold water and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (5x50 mL) and dried over anhydrous sodium sulfate, concentrated and re-crystallized in diethyl ether to yield 2-(2-methyl-8-trifluoromethoxy-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.58 (d, 2H), 7.17-7.21 (m, 4H), 7.0 (d, 1H), 4.6 (m, 1H), 4.0 (m, 2H), 3.38 (dd, 2H), 2.8 (m, 1H), 2.7 (m, 2H), 2.6 (m, 1H), 2.18 (s, 3H). Separation by chiral HPLC provides enantiomers II-67a-b.

Example 287: Preparation of Compound Nos. II-68 and II-68a-b.

[0936] To a solution of 8-tert-butyl-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 4.1 mmol) in DMF (6 mL) was added sodium hydride (495 mg, 12.3 mmol) under nitrogen at 0 °C and stirred for 10 min. A solution of 4-(oxiran-2-yl)pyridine (898 mg, 7.4 mmol) in DMF (2 mL) was added dropwise into the reaction mixture at RT and stirred for 12 h. The progress of reaction was monitored by TLC and LCMS. The reaction mass 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 re-crystallized with hexane to yield 2-(8-tert-butyl-2-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.7 (d, 2H), 7.3 (s, 1H), 7.2 (d, 1H), 7.19 (d, 2H), 7.17 (d, 1H), 4.7 (t, 1H), 4.0 (d, 2H), 3.5 (dd, 2H), 2.82 (m, 1H), 2.7 (m,

2H), 2.58 (m, 1H), 2.4 (s, 3H), 1.4 (s, 9H). Separation by chiral HPLC provides enantiomers II-68a-b.

Example 288: Preparation of Compound No. II-70.

[0937] A solution of 2-(pyridin-4-yl)-1-(2,4,4,8-tetramethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol (110 mg) in thionyl chloride (2 mL) was stirred at RT for 20 min. The excess thionyl chloride was removed under reduced pressure, and to the residue were added DMF (2 mL) and powdered KOH (140 mg, 0. 303 mmol), followed by stirring at 85 °C for 25 min. The progress of reaction was monitored by LCMS. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3x30 mL). The organic layer was washed with water (2x20 mL), dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.7 (d, 2H), 8.0 (d, 2H), 7.58 (s, 1H), 7.37 (s, 1H), 7.1 (d, 1H), 7.05 (d, 1H), 4.7 (bs, 1H), 4.4 (bs, 1H), 3.5 (d, 2H), 3.18 (s, 3H), 2.42 (s, 3H), 1.97 (s, 3H), 1.57 (bs, 6H).

Example 289: Preparation of Compound Nos. II-71 and II-71a-b.

[0938] To a solution of 9-chloro-2-methyl-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole (1g, 4. 273 mmol) in DMF was added NaH (512 mg,12. 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 (775 mg, 6. 409 mmol) in DMF (1 mL) was added dropwise into the mixture at the same temperature and stirring continued at RT overnight. The progress of reaction was monitored by TLC and LCMS. After completion, ice water was added into the reaction mixture and 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 column chromatography using 10% MeOH/DCM as eluent followed by recrystallization with MeOH and acetonitrile to yield 2-(9-chloro-2-methyl-2,3,4,5-tetrahydroazepino[4,3-b]indol-6(1H)-yl)-1-(pyridin-4-yl)ethanol. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.5 (d, 2H), 7.4 (s, 1H), 7.3 (d, 2H), 7.19 (d, 1H), 7.05 (d, 1H), 4.85 (dd, 1H), 4.18 (m, 2H), 3.8 (d, 1H), 3.65 (d, 1H), 3.0 (m, 2H), 2.8 (m, 1H), 2.69 (m, 1H), 2.42 (s, 3H), 1.85 (m, 2H). Separation by chiral HPLC provides enantiomers II-71a-b.

Example 290: Preparation of Compound Nos. II-75 and II-75a-b.

[0939] To a solution of 3-(3,4-dihydro-8-methyl-1H-pyrido[4,3-b]indol-2(5H)-yl)propan-1-ol (1000 mg, 4.0983 mmol) in DMF (10 mL) was portionwise added sodium hydride (491.8 mg, 12.25 mmol). After stirring at RT for 5 min, 4-(oxiran-2-yl)pyridine (620 mg, 4.92 mmol) was added dropwise into the reaction mixture, which was stirred at RT overnight. Ice water was

added into the reaction mixture and the solid mass filtered, washed with water (2 x10 mL) and hexane (2x50 mL). The residue was purified by reverse phase HPLC to yield 3-(3,4-dihydro-5-(2-hydroxy-2-(pyridin-4-yl)ethyl)-8-methyl-1H-pyrido[4,3-b]indol-2(5H)-yl)propan-1-ol. ^{1}H NMR (CD_3OD, formate salt) δ (ppm): 8.43 (bs, 2H), 7.39 (d, 2H), 7.23 (s, 1H), 7.2 (d, 1H), 7.0 (d, 1H), 5.07 (t, 1H), 4.48 (bs, 2H), 4.23 (m, 2H), 3.7 (t, 2H), 3.6 (bs, 2H), 3.4 (t, 2H), 3.2 (m, 1H), 2.95-3.03 (m, 1H), 2.4 (s, 3H), 2.03 (bs, 2H). Separation by chiral HPLC provides enantiomers II-75a-b.

Example 291: Preparation of Compound No. II-76.

[0940] To a de-aerated 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 (200 mg, 0.515 mmol), 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (225 mg, 1.03 mmol) and K_2CO_3 (215 mg, 1.55 mmol) in DME (2 mL) and water (1 mL) was added $Pd(PPh_3)_4$ (52 mg, 0.045 mmol). The reaction mixture was stirred at 90 °C for 45 min. The solvent was removed under reduced pressure, and the residue was diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and evaporated to afford crude material, which was purified by reverse phase HPLC to yield (E)-2,8-dimethyl-5-(2-(4-methylpyridin-3-yl)prop-1-en-1-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.87 (s, 1H), 8.75 (d, 1H), 8.0 (d, 1H), 7.3 (s, 1H), 7.24 (d, 1H), 7.17 (d, 1H), 6.8 (s, 1H), 4.77 (d, 1H), 4.38 (d, 1H), 3.9 (bs, 1H), 3.4 (bs, 1H), 3.3 (m, 1H), 3.18 (m, 1H), 3.12 (s, 3H), 2.8 (s, 3H), 2.42 (s, 3H), 2.0 (s, 3H).

Example 292: Preparation of Compound No. II-77.

[0941] To a degassed solution of 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[4,3-b]indole (200 mg, 0.546 mmol), 5-bromo-2-ethylpyridine (50 mg, 0.273 mmol) and K_2CO_3 (113 mg, 0.819 mmol) in DME (2 mL) and water (1 mL) was added $Pd(PPh_3)_4$ (22 mg, 0.019 mmol). The reaction mixture was purged with nitrogen and heated to reflux for 45 min. The reaction mixture was cooled to RT, diluted with water and extracted with EtOAc(3x6 mL). The combined organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford crude product which was purified by reverse phase HPLC as a TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.98 (s, 1H), 8.78 (d, 1H), 8.0 (d, 1H), 7.38 (d, 2H), 7.18 (d, 1H), 7.1 (d, 1H), 4.76 (d, 1H), 4.4 (d, 1H), 3.85 (bs, 1H), 3.6 (bs, 1H), 3.2 (m, 2H), 3.18 (s, 3H), 3.1 (s, 2H), 2.64 (s, 3H), 2.05 (s, 3H), 1.5 (t, 3H).

Example 293: Preparation of Compound Nos. II-78 and II-78a-b.

[0942] To a solution of 6-methyl-6,7,8,9-tetrahydro-5H-1,6,9-triaza-fluorene (1.0 g, 0.0053 mole) in DMF (15 mL) were added portionwise NaH (60%, 0.634 g, 0.0159 mole) and 4-(oxiran-2-yl)pyridine (0.807 g, 0.0064 mole). The reaction mixture was stirred at RT overnight. The progress of reaction 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), 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 yield the title compound. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.5 (d, 2H), 8.2 (d, 1H), 7.7 (d, 1H), 7.23 (d, 2H), 7.9 (m, 1H), 5.08 (m, 1H), 4.5 (d, 1H), 4.3 (d, 1H), 3.6 (dd, 2H), 2.9 (m, 1H), 2.8 (m, 1H), 2.7 (m, 1H), 2.6 (m, 1H), 2.5 (s, 3H). Separation by chiral HPLC provides enantiomers II-78a-b.

Example 294: Preparation of Compound Nos. II-80 and II-80a-b.

[0943] A solution 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 (100 mg, 0.27 mmol) in 3N HCl (4 mL) was stirred at 100 °C for 4 h. The reaction mixture was concentrated under reduced pressure and 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-1-methyl-ethyl]-pyridin-2-ol. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 7.58 (d, 1H), 7.2 (s, 1H), 7.1 (s, 1H), 7.0 (d, 1H), 6.8 (d, 1H), 6.4 (d, 1H), 4.6 (bs, 1H), 4.17 (m, 2H), 4.0 (m, 2H), 3.1-3.25 (m, 2H), 2.97 (m, 1H), 2.8 (s, 3H), 2.4 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provides enantiomers II-80a-b.

Example 295: Preparation of Compound Nos. II-81 and II-81a-b.

[0944] To a solution of 5-(2-hydroxy-2-pyridin-4-yl-ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole-8-carboxylic acid ethyl ester (200 mg, 0.547 mmol) in dry THF (10 mL) was added portionwise LAH (63 mg, 1.65 mmol) under nitrogen at RT. After stirring for 2 h, the reaction mixture was quenched with water (0.5 mL), NaOH (1mL). The organic layer was separated and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography to yield 2-(8-hydroxymethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.41 (d, 2H), 7.42 (s, 1H), 7.39 (d, 2H), 7.3 (d, 1H), 7.19 (d, 1H), 5.08 (t, 1H), 4.66 (s, 2H), 4.4 (s, 2H), 4.3 (m, 2H), 3.5 (m, 2H), 3.2 (m, 1H), 2.9 (m, 1H). Separation by chiral HPLC provides enantiomers II-81a-b.

Example 296: Preparation of Compound No. II-82.

[0945] 5-(2-Bromocyclopent-1-enyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.29 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (127 mg, 0.58 mmol) and K_2CO_3 (120 mg, 0.87 mmol) were mixed in 1,2-dimethoxyethane (4 mL) and water (2 mL). The reaction mixture was purged with nitrogen, $Pd(PPh_3)_4$ (17 mg, 0.0147 mmol) was added and the reaction mixture was heated at 90 °C for 45 min. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to yield 26 mg of 2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)cyclopent-1-enyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.0 (d, 1H), 7.8 (dd, 1H), 7.61 (d, 1H), 7.31 (s, 1H), 6.95-7.10 (m, 2H), 4.7 (d, 1H), 4.38 (d, 1H), 3.8 (m, 1H), 3.55 (m, 1H), 2.82-3.2 (m, 9H), 2.61 (s, 3H), 2.4 (s, 3H), 2.3 (m, 2H).

Example 297: Preparation of Compound Nos. II-83 and II-83a-d.

[0946] To a solution of 2-(8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (200 mg, 0.651 mmol) in acetonitrile (4mL), potassium carbonate (270 mg, 1.95 mmol) and 1-bromopropan-2-ol (135 mg, 0.977 mmol) were added and stirred the reaction mixture at 100 °C for 2 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3x20 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 1-[5-(2-hydroxy-2-pyridin-4-yl-ethyl) -8-methyl-1,3,4,5-tetrahydro -pyrido [4,3-b]indol- 2-yl]-propan-2-ol. 1H NMR, ($CDCl_3$, freebase) δ (ppm): 8.58 (s, 2H), 7.36 (m, 2H), 7.2 (m, 2H), 7.02 (d, 1H), 5.1 (s, 1H), 4.3 (m, 1H), 4.1 (m, 2H), 4.0 (m, 2H), 3.56 (m, 1H), 3.37 (m, 1H), 3.1-3.3 (m, 2H), 2.8 (m, 2H), 2.42 (s, 3H), 1.2 (d, 3H). Separation by chiral HPLC provides diastereomers II-83a-d.

Example 298: Preparation of Compound Nos. II-84 and II-84a-b.

[0947] To a solution of 2-(8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethanol (200 mg, 0.651 mmol) in acetonitrile (4 mL), potassium carbonate (270 mg, 1.95 mmol) and 1-chloro-2-methyl-propan-2-ol (105 mg, 0.977 mmol) were added and the reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (Neutral alumina, 1% MeOH-DCM), to yield 1-[5-(2-hydroxy-2-pyridin-4-yl-

ethyl)-8-methyl-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl]-2-methyl-propan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.6 (d, 2H), 7.27 (m, 2H), 7.2 (m, 2H), 7.0 (d, 1H), 5.08 (t, 1H), 4.19 (m, 2H), 3.9 (bs, 2H), 3.0-3.1 (m, 2H), 2.9 (m, 1H), 2.6 (s, 2H), 2.56 (m, 1H), 2.21 (s, 3H), 1.21 (s, 6H). Separation by chiral HPLC provides enantiomers II-84a-b.

Example 299: Preparation of Compound Nos. II-88 and II-88a-b.

[0948] To a solution of 1-(3,4-Bis-allyloxy-phenyl)-2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethanol (500 mg, 1. 15 mmol) in 10 mL MeOH was purged with nitrogen for 10 min. 1,3-Dimethylbarbituric acid (903 mg, 5. 79 mmol) and $Pd(PPh_3)_4$ (80 mg, 0. 069 mmol) were added under nitrogen and the mixture stirred for 30 min at RT. After the complete conversion of starting material (TLC and LCMS), the MeOH was removed under reduced pressure. 100 mL of saturated sodium bicarbonate was added and the mixture was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. The resultant crude product was purified by HPLC to obtain 160 mg of 4-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-hydroxy-ethyl]-benzene-1,2-diol. ^{1}H NMR (CD_3OD, Free base) δ (ppm): 7.3 (d, 1H), 7.2 (s, 1H), 7.05 (dd, 1H), 6.7 (d , 1H), 6.6 (s , 1H), 6.53 (d , 1H), 4.8 (t, 1H), 4.21 (m, 3H), 4.05 (dd, 1H), 3.34 (m, 1H), 3.3 (m, 1H), 2.88 (dt, 1H), 2.81 (s, 3H), 2.5 (dt, 1H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers II-88a-b.

Example 300: Preparation of Compound Nos. II-89 and II-89a-b.

[0949] To a degassed solution of 2-(2-allyl-8-chloro-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-3-yl-ethanol (1.0 g, 2.7 mmol) in DCM were added 1,3-dimethyl barbituric acid (1.27 g, 8.1 mmol) and $Pd(PPh_3)_4$ (63 mg, 0.054 mmol) and the reaction mixture was stirred at RT for 3 h. The solvent was removed under reduced pressure. The residue was dissolved in saturated potassium carbonate solution and extracted with EtOAc (3x50 mL). The combined organic layer was washed with saturated potassium carbonate (6x20 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (neutral alumina, 20% methanol in DCM) followed by reverse phase HPLC to yield 2-(8-chloro-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-3-yl-ethanol. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.4 (d, 1H), 8.37 (s, 1H), 7.8 (d, 1H), 7.4 (d, 1H), 7.39 (m, 1H), 7.2 (d, 1H), 7.02 (d, 1H), 5.1 (t, 1H), 4.33 (d, 2H), 4.3 (s, 2H), 3.38-3.5 (m, 2H), 3.1 (m, 1H), 2.9 (m, 1H). Separation by chiral HPLC provides enantiomers II-89a-b.

Example 301: Preparation of Compound Nos. II-90 and II-90a-b.

[0950] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (300 mg, 1.5 mmol) in DMF (5 mL) was added sodium hydride (180 mg, 4.5 mmol) under nitrogen. After stirring at RT for 10 min, 4-(oxiran-2-yl)quinoline (384 mg, 2.25 mmol) was added dropwise under nitrogen into the reaction mixture, which was stirred at RT for 18 h. The progress of reaction was monitored by TLC, LCMS and NMR. The reaction mixture was poured in ice-cold water and extracted with EtOAc (2x50 mL). The combined organic layer was washed with water (3x50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. Re-crystallization with diethyl ether yielded 2-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(quinolin-4-yl)ethanol (140 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.86 (d, 1H), 8.19 (d, 1H), 7.97 (d, 1H), 7.78 (t, 1H), 7.41 (d, 1H), 7.56 (t, 1H), 7.2 (d, 1H), 6.93-7.01 (m, 2H), 5.57 (t, 1H), 4.2 (dd, 1H), 4.1 (dd, 1H), 3.37 (dd, 2H), 2.83 (m, 1H), 2.71 (bs, 3H), 2.4 (s, 3H), 2.38 (s, 3H). Separation by chiral HPLC provides enantiomers II-90a-b.

Example 302: Preparation of Compound Nos. II-91 and II-91a-b.

[0951] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (525 mg, 2. 6 mmol) in DMF was added sodium hydride (312 mg, 7. 8 mmol) at 0 °C. After stirring the solution for 15 min, a solution of 2-cyclohexyloxirane (500 mg, 3. 9 mmol) was added dropwise into the reaction mixture, which was stirred at RT overnight. The progress of reaction was monitored by TLC, NMR and LCMS. The reaction mixture was quenched with ice-cold water and extracted with EtOAc. The organic layer was thoroughly washed with water, dried over anhydrous sodium sulfate and concentrated. Re-crystallization with ether yielded the desired product (160 mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 7.2 (s, 1H), 7.19 (d, 1H), 6.95 (d, 1H), 4.15 (dd, 1H), 3.92 (dd, 1H), 3.7 (m, 1H), 3.6 (s, 2H), 2.99 (m, 1H), 2.8 (m, 3H), 2.58 (s, 3H), 2.42 (s, 3H), 1.9 (d, 1H), 1.8(m, 2H), 1.7 (d, 2H), 1.52 (m, 1H), 1.22 (m, 5H). Separation by chiral HPLC provides enantiomers II-91a-b.

Example 303: Preparation of Compound No. II-92 and II-92a-b.

[0952] A solution of 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-(6-methoxy-pyridin-3-yl)-ethanol (200 mg, 0.569 mmol) in 3N HCl (8 mL) was stirred at 100 °C for 3 h. The reaction mixture was concentrated under reduced pressure and residue was purified by reverse phase HPLC to yield 5-(2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-hydroxyethyl) pyridin-2(1H)-one. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.5 (m, 1H), 7.23 (s, 1H), 7.2 (s, 1H), 7.19 (d, 1H), 6.5 (s, 1H), 4.62 (d, 1H), 4.19-4.37 (m, 3H), 3.8 (m, 1H), 3.5 (m,

1H), 3.24 (m, 2H), 3.1 (m, 4H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers II-92a-b.

Example 304: Preparation of Compound Nos. II-93 and II-93a-b.

[0953] To a solution of 2-(8-chloro-1,2,3,4-tetrahydropyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethanol (600 mg, 1. 84 mmol) in acetone (20 mL) were added 2-bromoethanol (341 mg, 2. 76 mmol) and K_2CO_3 (761 mg, 5. 52 mmol) and the reaction mixture stirred at 80 °C for 4 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was cooled to RT, filtered and the filtrate concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield the title compound. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.41 (d, 2H), 7.31 (s, 1H), 7.18 (m, 4H), 4.79 (t, 1H), 4.0 (m, 2H) , 3.68 (m, 3H), 3.56 (d, 1H), 2.8 (m, 3H), 2.65 (m, 2H), 2.58 (m, 1H). Separation by chiral HPLC provided enantiomers II-93a-b.

Example 305: Preparation of Compound Nos. II-94 and II-94a-b.

[0954] To a solution of 2-(8-chloro-1,2,3,4-tetrahydropyrido[4,3-b]indol-5-yl)-1-(pyridin-3-yl)ethanol (1.0 g, 3. 05 mmol) in acetone (30 mL) were added 2-bromoethanol (758 mg, 6.12 mmol) and K_2CO_3 (1. 3 g, 9.43 mmol) and the reaction mixture stirred at 80 °C for 4 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was cooled to RT, filtered and the filtrate concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by reverse phase HPLC to yield the title compound. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.39 (d, 1H), 8.2 (s, 1H), 7.6 (d, 1H), 7.27 (s, 1H), 7.2 (m, 2H) , 7.16 (d, 1H), 4.8 (m, 1H), 4.1 (dd, 1H), 4.0 (dd, 1H), 3.7 (m, 2H), 3.6 (d, 1H), 3.5 (d, 1H), 2.85 (m, 3H), 2.8 (m, 1H), 2.63 (m, 2H). Separation by chiral HPLC provided enantiomers II-94a-b.

Example 306: Preparation of Compound Nos. II-95 and II-95a-d.

[0955] Phenyl magnesium bromide (1M solution in THF) (6.24 mL,6.24 mmol) was added dropwise at -70 °C to a stirred solution of 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-propionaldehyde (400 mg, 1.56 mmol) in THF (40 mL), the reaction mixture stirred at RT for 16 h, diluted with EtOAc (75 mL) and water (60 mL). The two layers were separated, the aq. layer extracted with EtOAc (2x75mL), and the combined organic layers dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude (500 mg) was purified by

prep. HPLC to afford 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)1-phenyl-propan-1-ol yielded as the TFA salt(65mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 7.37 (d, 1H), 7.17 (t, 3H), 7.12 (s, 1H), 7.06 (m, 2H), 6.95 (d, 1H), 5.11 (t, 1H), 4.37 (t, 1H), 3.57 (dd, 1H), 3.46 (d, 1H), 2.67 (m, 2H), 2.51 (m, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 1.68 (d, 3H). Separation by chiral HPLC provides diastereomers II-95a-d.

Example 307: Preparation of Compound No. II-96.

[0956] To a solution of 1-(2,8-dimethyl-3,4-dihydro-1h-pyrido[4,3-b]indol-5(2h)-yl)prop-1-en-2-yltrifluoromethanesulfonate (100 mg, 0.257 mmol) in DME (4 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.0128) and the reaction mixture was purged with N_2. 2-Fluoropyridine-5-boronic acid pinacol ester (115 mg, 0.515 mmol), K_2CO_3 (36 mg, 0.257 mmol) and water (2 mL) were added, the reaction mixture was purged with nitrogen and refluxed for 45 min. The reaction mixture was cooled to RT, and the solvent was removed under reduced pressure. The residue was dissolved in water, extracted with EtOAc, washed with brine, and concentrated to afford crude product which was purified by silica gel chromatography followed by reverse phase HPLC to obtain the products as TFA salts. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.42 (s, 1H), 8.21 (m, 1H), 7.28 (s, 1H), 7.02-7.21 (m, 4H), 4.78 (d, 1H), 4.40 (d, 1H), 3.82 (m, 1H), 3.58 (m, 1H), 3.16 (m, 5H), 2.41 (s, 3H), 2.0 (s, 3H).

Example 308: Preparation of Compound Nos. II-97 and II-97a-b.

[0957] To a solution of 2-(1,2,3,4-tetrahydro-8-methylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethanol (200 mg, 0. 652 mmol) and sodium 2-bromoethanesulfonate (164 mg, 0. 78 mmol) in DMF (3 mL) and water (0. 5 mL), were added sodium bicarbonate (164 mg, 1. 95 mmol) and potassium iodide (128 mg, 0. 78 mmol) and the reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was diluted with water and extracted with DCM. The aqueous layer was neutralized with aq HCl and the solid obtained was recrystallized from MeOH to yield 2-(3,4-dihydro-5-(2-hydroxy-2-(pyridin-4-yl)ethyl)-8-methyl-1H-pyrido[4,3-b]indol-2(5H)-yl)ethanesulfonic acid as a white solid (80 mg). ^{1}H NMR (CD_3OD, Free base) δ (ppm): 8.45 (d, 2H), 7.40 (d, 2H), 7.26 (s, 1H), 7.23 (d, 1H), 7.00 (s, 1H), 5.06 (t, 1H), 4.59 (m, 2H), 4.29 (m, 2H), 3.71 (t, 4H), 3.55 (m, 2H), 3.0 (d, 1H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers II-97a-b.

Example 309: Preparation of Compound No. II-98 and II-98a-d.

[0958] 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 stopped) and water was added, 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. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.60 (d, 2H), 7.4 (d, 1H), 7.55 (d, 2H), 7.18 (s, 1H), 6.98 (d, 1H), 5.15 (d, 1H), 4.2 (t, 1H), 3.4 (d, 1H), 3.28 (d, 1H), 2.94 (m, 1H), 2.784 (m, 1H), 2.68 (m, 2H), 2.48(s, 3H), 2.43 (s, 3H), 1.37 (s, 3H). Separation by chiral HPLC provides diastereomers II-98a-d.

Example 310: Preparation of Compound Nos. II-99 and II-99a-b.

[0959] To a solution of 6-aza-2,8-dimethyl carboline (500 mg, 2.5 mmol) in DMF (5 mL) was added NaH (60%, 300 mg, 7.5 mmol). After stirring for 5 min at RT, a solution of 3-(2-methyloxiran-2-yl)pyridine (506.2 mmol, 3.75 mmol) in DMF (1 mL) was added dropwise into the reaction mixture, which was stirred at RT for 12 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 triturated with ether to yield the desired compound (150 mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.7 (s, 1H), 8.41 (d, 1H), 8.02 (s, 1H), 7.8 (d, 1H), 7.5 (s, 1H) , 7.19 (dd, 1H), 4.3 (dd, 2H), 3.6 (d, 1H), 3.5 (d, 1H), 2.8 (m, 2H), 2.65 (m, 1H), 2.55 (s, 3H), 2.49 (m, 1H), 2.4 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provided enantiomers II-99a-b.

Example 311: Preparation of Compound Nos. II-100 and II-100a-b.

[0960] Aza-dimethyl-carboline (100 mg, 0. 497 mmol) was charged in a reaction bottle and N,N-dimethylformamide (2 mL) was added. Sodium hydride (60 % suspension in mineral oil) (60 mg, 1.49 mmol) was added portionwise. The reaction mixture was stirred at RT for 5 min and 2-methyl-5-(oxiran-2-yl)pyridine (300 mg, 2.22 mmol) was added dropwise. The reaction mixture was stirred at RT overnight. The reaction was monitored by LCMS. Ice water (5 mL) was added and the organic layer was extracted with EtOAc (2x15 mL). The combined organic layer was washed with water (3x5mL) and concentrated. The desired product was purified through reverse phase chromatography as a racemate (12.92 mg). ^{1}H NMR ($CDCl_3$, Free base) δ

(ppm): 8.42 (s, 1H), 8.0 (s, 1H), 7.5 (s, 1H), 7.47 (d, 1H), 7.07 (d, 1H) , 5.1 (m, 1H), 4.37 (dd, 1H), 4.26 (dd, 1H), 3.59 (dd, 2H), 2.78 (m, 1H), 2.7 (m, 2H), 2.52 (s, 3H), 2.5 (s, 3H), 2.45 (m, 1H), 2.42 (s, 3H). Separation by chiral HPLC provided enantiomers II-100a-b.

Example 312: Preparation of Compound No. II-101.

[0961] 2,8-Dimethyl-5-(2-pyridin-4-yl-propenyl)-2,3,4,5-tetrahydro-pyrido[4,3-b]indol-1-one (350 mg, 1.057 mmol) was dissolved in dry toluene (6 mL). Methyl magnesium bromide (3M solution in diethyl ether, 1.76 mL, 5.28 mmol) was added and the reaction mixture was heated at 100 °C for 1 h. The reaction mixture was cooled to RT, quenched with ice water and filtered through a Celite bed. The filtrate was extracted with EtOAc (3x70mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography over neutral alumina followed by reverse phase HPLC to obtain 6.5 mg of 1,1,2,8-tetramethyl-5-(2-pyridin-4-yl-propenyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole as a formate salt. ^{1}H NMR (CD_3OD, formate salt) δ (ppm): 8.60 (d, 2H), 7.70 (d, 2H), 7.50 (s, 1H), 7.30 (s, 1H), 7.12 (m, 2H), 3.70 (t, 2H), 3.10 (t, 2H), 3.02 (s, 3H), 2.44 (s, 3H), 2.02 (s, 3H), 1.90 (s, 6H).

Example 313: Preparation of Compound Nos. II-102 and II-102a-b.

[0962] To a solution of methyl carboline ethyl ester (500 mg, 1. 27 mmol) in THF (30 mL) was added LAH (145 mg, 3. 81 mmol) under nitrogen at RT and stirred for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched by adding water (0.5 mL), 1N NaOH (1 mL) and water (0.5 mL). The inorganic material was removed by filtration and the filtrate concentrated under reduced pressure. The residue was triturated with ether to yield the title compound (450 mg). ^{1}H NMR (CD_3OD, Free base) δ (ppm): 8.5 (s, 1H), 8.39 (d, 1H), 7.8 (d, 1H), 7.26 (m, 2H), 7.1 (d, 1H), 7.0 (d, 1H), 4.6 (s,2H), 4.21 (q, 2H), 3.62 (s, 2H), 2.79 (m ,4H), 2.49 (s, 3H), 1.64 (s, 3H). Separation by chiral HPLC provides enantiomers II-102a-b.

Example 314: Preparation of Compound No. II-103.

[0963] To a stirred solution of 6-methyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (200 mg, 1.068 mmol) in NMP (3 mL) was added powdered KOH (419 mg, 7.486 mmol). After stirring for 10 min at RT, 2-(trifluoromethyl)-5-vinylpyridine (370 mg, 2.14 mmol) was added to the reaction mixture and stirring continued for another 3 h. The progress of reaction was monitored by TLC and NMR. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x20 mL). The organic layer was washed with water (5x20 mL), dried

over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by reverse phase HPLC to yield 6-methyl-9-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine as the TFA salt (100 mg). ^{1}H NMR ($CDCl_3$, TFA salt) δ (ppm): 8.4 (s, 1H), 8.2 (s, 1H), 7.7 (d, 1H), 7.5 (d, 1H), 7.4 (d, 1H), 7.0 (s, 1H), 4.4 (s, 2H), 3.6 (s, 2H), 3.2 (s, 2H), 2.78 (s, 2H), 2.6 (s, 2H), 2.5 (s, 3H).

Example 315: Preparation of Compound Nos. II-104 and II-104a-b.

[0964] To a solution of methyl carboline ethyl ester (350 mg, 0. 92 mmol) in THF (5 mL) was added LAH (175 mg, 4. 6 mmol) under nitrogen at RT and stirred for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched by adding water (0.5 mL), 1N NaOH (1 mL) and water (0.5 mL). The inorganic material was removed by filtration, and the filtrate concentrated under reduced pressure. The residue was purified through reverse phase HPLC to yield the title compound. ^{1}H NMR (CD_3OD, Free base) δ (ppm): 8.5 (s, 1H), 8.3 (d, 1H), 7.82 (d, 1H), 7.4 (s ,1H), 7.3 (dd, 1H), 7.0 (m, 2H), 4.6 (s,2H), 4.4 (dd, 2H), 4.41 (d, 1H), 4.2 (d, 1H), 3.5 (m, 2H), 3.21 (m, 1H), 3.0 (m, 1H), 1.64 (s, 3H). Separation by chiral HPLC provides enantiomers II-104a-b.

Example 316: Preparation of Compound Nos. II-105 and II-105a-b.

[0965] 1-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol (500 mg, 1.49 mmol) was dissolved in 10 mL DCM and m-chloro perbenzoic acid (383 mg, 2.24 mmol) was added and the mixture stirred at RT. After consumption of starting material by monitoring TLC and LCMS, the reaction mixture was concentrated and the crude product was purified by reverse phase chromatography, to obtain 110 mg of 1-(2,8-dimethyl-2-oxy-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.7 (s, 1H), 8.25 (d, 1H), 7.8 (d, 1H), 7.4 (bs ,1H), 7.27 (d, 1H), 7.2 (m, 2H), 7.0 (d,1H), 4.79 (d,1H), 4.6 (d, 1H), 4.2 (d ,1H), 4.05 (d, 1H), 3.85 (m, 1H), 3.6 (m, 1H), 3.4 (m, 1H), 2.64 (m, 1H), 2.4 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provides enantiomers II-105a-b.

Example 317: Preparation of Compound Nos. II-106 and II-106a-b.

[0966] 1-(1-(1-Ethoxyethyl)-1H-pyrazol-4-yl)-2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)ethanol (147 mg, 0.3848 mmol) was dissolved in 1,4-dioxane (15 mL) and to it was added 20% aqueous hydrochloride solution (15 mL). The mixture was heated at 55 °C for 1 h. The reaction mixture was neutralized with a saturated solution of sodium bicarbonate and was extracted with EtOAc (3x60 mL). The combined organic layer was washed with water (15 mL) and then brine (2x30 mL). The organic layer was dried over anhydrous sodium sulfate and

concentrated under reduced pressure. The crude product was purified by reverse phase chromatography. Yield: 36.6 mg (TFA salt). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 7.35 (s, 1H), 7.0 (s, 1H), 6.9 (d, 1H), 6.8 (d ,1H), 6.2 (s ,1H), 4.9 (t, 1H), 4.2 (dd, 2H), 3.55 (d,1H), 3.4 (d, 1H), 2.8 (m ,2H), 2.6 (m, 2H), 2.5 (s, 3H), 2.39 (s, 3H). Separation by chiral HPLC provided enantiomers II-106a-b.

Example 318: Preparation of Compound Nos. II-108 and II-108a-b.

[0967] To a solution of dimethyl-aza carboline (400 mg, 1.99 mmol) in DMF (5 mL) was added NaH (239 mg, 5.97 mmol, 60%). After stirring at RT for 10 min, the epoxide (606 mg, 2.98 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 (250 mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.81 (s, 1H), 8.0 (m, 2H), 7.6 (d, 1H), 7.52 (s, 1H), 4.23 (q, 2H), 3.6 (d, 1H), 3.5 (d, 1H), 2.8 (m, 1H), 2.72 (m, 3H), 2.5 (s, 3H), 2.4 (m, 1H), 2.4 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provided enantiomers II-108a-b.

Example 319: Preparation of Compound Nos. II-109 and II-109a-b.

[0968] To a solution of 6-aza-8-chloro-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (400 mg, 1. 8 mmol) in DMF (5 mL) was added NaH (217 mg, 5.42 mmol, 60%). After stirring at RT for 10 min, the epoxide (552 mg, 2.71 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 (340 mg). ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.8 (s, 1H), 8.15 (s, 1H),8.0 (d, 1H), 7.68 (s, 1H), 7.6 (d, 1H), 4.23 (q, 2H), 3.6 (d, 1H), 3.5 (d, 1H), 2.8 (m, 3H), 2.72 (m, 1H), 2.5 (s, 3H), 2.4 (m, 1H), 1.6 (s, 3H). Separation by chiral HPLC provided enantiomers II-109a-b.

Example 320: Preparation of Compound No. II-110.

[0969] To a solution of 3,6-dimethyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (201 mg, 1.0 mmol) in DMF (1 mL) was added a suspension of NaH (128.0 mg, 3.24 mmol) in DMF (1 mL). After stirring for 5 min at RT, a solution of 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (873 mg, 3.0 mmol) in DMF (1 mL) was added dropwise into the

reaction mixture and stirring continued for another 3 h. The progress of reaction was monitored by TLC and NMR. 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 silica gel flash chromatography and 10% MeOH-DCM to yield 3,6-dimethyl-9-(2-(6-methylpyridin-3-yl)ethyl)-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (190 mg). ^{1}H NMR ($CDCl_3$, TFA salt) δ (ppm): 8.2 (s, 1H), 8.04 (s, 1H), 7.43 (s, 1H), 7.18 (d, 1H), 7.0 (d, 1H), 4.3 (t, 2H), 3.6 (s, 2H), 3.0 (t, 2H), 2.7 (t, 2H), 2.5 (s, 8H), 2.4 (s, 3H).

Example 321: Preparation of Compound Nos. II-111 and II-111a-b.

[0970] 5-[2-(3,6-Dimethyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-1-hydroxy-ethyl]-pyridine-2-carbonitrile (600 mg, 1.729 mmol) was dissolved in tert-butanol (12 mL), crushed potassium hydroxide (290 mg, 5.187 mmol) was added, and the mixture heated at 80 °C for 1 h. The reaction was monitored by TLC & LCMS. The reaction mixture was allowed to cool to RT, the solvent was removed under vacuum, and the residue was diluted with water (20 ml) and extracted with EtOAc (2x75 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to obtain the crude product that was purified by reverse phase chromatography to afford 100 mg of 5-[2-(3,6-dimethyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-1-hydroxy-ethyl]-pyridine-2-carboxylic acid amide. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.62 (s, 1H), 8.1 (s, 1H), 8.05 (d, 1H), 7.95 (d ,1H), 7.8 (s ,1H), 5.23 (t, 1H), 4.7 (d, 1H), 4.53 (d, 1H), 4.4 (m, 2H), 3.83 (m, 1H), 3.6 (m, 1H), 3.4 (m, 2H), 3.2 (s, 3H), 2.43 (s, 3H). Separation by chiral HPLC provides enantiomers II-111a-b.

Example 322: Preparation of Compound Nos. II-112 and II-112a-d.

[0971] 2,6-Dimethyl-1-phenyl-2,3,4,9-tetrahydro-1H-β-carboline (300 mg, 1.08 mmol) was dissolved in DMF (4 mL). Sodium hydride (172 mg, 4.32 mmol) was added and the mixture was stirred at RT for 30 min. 3-(2-Methyl-oxiranyl)-pyridine (733 mg, 5.43 mmol) in 1 mL DMF was added dropwise into the reaction mixture, which was stirred for 5 h at RT. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction was quenched with ice and extracted with EtOAc (2x100 mL). The organic layer was washed with water (2x100 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude that was purified by column chromatography (silica gel 100-200 mesh, Eluent: 6% MeOH in DCM) to obtain 120 mg of 1-(2,6-dimethyl-1-phenyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-2-pyridin-3-yl-propan-2-ol (racemate) and followed by chiral separation. ^{1}H NMR (CD_3OD, TFA

salt) δ (ppm): 8.25 (s, 1H), 8.2 (d, 1H), 7.6 (d, 1H), 7.4 (m ,3H), 7.2 (s ,1H), 7.19 (m, 3H), 6.65 (d, 1H), 6.4 (d, 1H), 5.5 (s, 1H), 4.0 (d, 1H), 3.43 (d, 1H), 3.2 (m, 1H), 3.0 (m, 3H), 2.6 (s, 3H), 2.3 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provided diastereomers II-112a-b.

Example 323: Preparation of Compound Nos. II-113 and II-113a-d.

[0972] 2,6-Dimethyl-1-phenyl-2,3,4,9-tetrahydro-1H-β-carboline (300 mg, 1.08 mmol) was dissolved in DMF (3 mL). Sodium hydride (172 mg, 4.32 mmol) was added and the mixture stirred at RT for 30 min. 4-Oxiranyl-pyridine (657 mg, 5.43 mmol) in 1 mL DMF was added dropwise into the reaction mixture, which was stirred at RT for 5 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction was quenched with ice and extracted with EtOAc (2x100 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to obtain the crude product that was purified by column chromatography (eluent: 10% MeOH in DCM) to obtain 220 mg of 2-(2,6-dimethyl-1-phenyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-1-pyridin-4-yl-ethanol (M6792, racemate) and followed by chiral separation. ^{1}H NMR (CD_3OD, Free base) δ (ppm): 8.17 (d, 2H), 7.35 (m, 4H), 7.09 (d, 2H), 7.0 (m, 3H), 6.9 (d, 1H), 4.8 (t, 1H), 4.6 (s, 1H), 4.08 (dd, 1H), 3.45 (dd, 1H), 3.0 (m, 1H), 2.8 (m, 2H), 2.6 (m, 1H), 2.4 (s, 3H), 2.2 (s, 3H). Separation by chiral HPLC provided diastereomers II-113a-b.

Example 324: Preparation of Compound Nos. II-114 and II-114a-b.

[0973] 1-(6-Bromo-pyridin-3-yl)-2-(3,6-dimethyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-ethanol (2 g, 4.9 mmol) was dissolved in DMF (20 mL), and the mixture was purged with nitrogen. Zinc cyanide (1.16 g, 9.9 mmol) and $Pd(PPh_3)_4$ (339 mg, 0. 294 mmol) were added, and the mixture heated at 150 °C for 2 h. The reaction was monitored by LCMS. The reaction mixture was allowed to cool at RT, diluted with EtOAc (250 mL) and filtered. The filtrate was washed with water (3x100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain the crude that was purified by reverse phase chromatography to obtain 100 mg of 5-[2-(3,6-dimethyl-5,6,7,8-tetrahydro-1,6,9-triaza-fluoren-9-yl)-1-hydroxy-ethyl]-pyridine-2-carbonitrile. This was followed by chiral separation. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.62 (s, 1H), 8.03 (s, 1H), 7.73 (d, 1H), 7.6 (d, 1H), 7.5 (s, 1H), 5.25 (d, 1H), 4.45 (d, 1H), 4.3 (dd, 1H), 3.55 (dd, 2H), 2.8 (m, 1H), 2.7 (m, 2H), 2.5 (s, 3H), 2.45 (s, 3H), 2.4 (m, 1H). Separation by chiral HPLC provided enantiomers II-114a-b.

Example 325: Preparation of Compound Nos. II-115 and II-115a-d.

[0974] Compound Nos. II-115 and II-115a-d are prepared in an analogous fashion to Compound Nos. 129 and 129a-d (Example 110), using 2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole as the starting material.

Example 326: Preparation of Compound Nos. II-116 and II-116a-b.

[0975] To a degassed solution of aza-allylcyano alcohol (200 mg, 0.53 mmol) and 1,3-dimethylbarbituric acid (251 mg, 1.61 mmol) in DCM (5 mL) was added $Pd(PPh_3)_4$ (24 mg, 0.020 mmol) at RT and the reaction mixture was stirred at RT for 45 min. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water and the organic layer was separated. The aqueous layer was basified with saturated aq $NaHCO_3$ and extracted with DCM. 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. 1H NMR (CD_3OD, TFA salt) δ (ppm): 8.2 (s, 1H), 8.0 (s, 1H), 7.68 (d, 2H), 7.6 (d ,2H), 5.2 (dd, 1H), 4.5 (dd, 1H), 4.45 (s, 2H), 4.33 (dd, 1H), 3.6 (t, 2H), 3.25 (d, 1H), 3.1 (d, 1H), 2.5 (s, 3H). Separation by chiral HPLC provides enantiomers II-116a-b.

Example 327: Preparation of Compound Nos. II-117 and II-117a-b.

[0976] Compound Nos. II-II7 and II-117a-b are prepared in an analogous fashion to Compound Nos. 5 and 5a-b (Example 5), using 2-fluoro-5-(2-methyloxiran-2-yl)pyridine as the epoxide.

Example 328: Preparation of Compound Nos. II-118 and II-118a-b.

[0977] To an ice-cooled stirred solution of 8-chloro-2-cyclobutyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (1.0 g, 3.84 mmol) in DMF (10 mL) was added sodium hydride (60%, 462 mg, 11.55 mmol). After stirring for 10 min, 3-(2-methyloxiran-2-yl)pyridine (780 mg, 5.77 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 (2x100 mL). The organic layer was washed with water (5x100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was crystallized from ether:hexane (50:50) to yield the title compound (1.0 g). The product was further purified by chiral HPLC to give enantiomers II-118a and II-118b. ^1H NMR (CD_3OD, Di-HCl salt) δ (ppm): 8.7 (m, 3H), 7.79 (d, 1H), 7.43 (d, 1H), 6.9 (m, 2H), 4.7 (d, 1H), 4.4 (dd, 2H), 4.15 (t, 1H), 3.95 (m, 1H), 3.8 (m, 1H), 3.6 (m, 1H), 3.5 (m, 1H), 2.4 (m, 4H), 1.9 (m, 3H), 1.8 (d, 3H).

Example 329: Preparation of Compound No. II-119.

[0978] To a stirred solution of 3,6-dimethyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (201 mg, 1.0 mmol) in NMP (3 mL) was added powdered KOH (392 mg, 7.0 mmol). After stirring for 10 min at RT, 2-(trifluoromethyl)-5-vinylpyridine (346 mg, 2. 0 mmol) was added to the reaction mixture and stirring continued for another 3 h. The progress of reaction was monitored by TLC and NMR. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3x20 mL). The organic layer was washed with water (5x20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude material, which was purified by reverse phase HPLC to yield 3,6-dimethyl-9-(2-(6-(trifluoromethyl)pyridin-3-yl)ethyl)-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (80 mg). ^{1}H NMR ($CDCl_3$, TFA salt) δ (ppm): 8.38 (s, 1H), 8.0 (s, 1H), 7.5 (d, 2H), 7.4 (d, 1H), 4.4 (t, 2H), 3.58 (s, 2H), 3.2 (t, 2H), 2.68 (t, 2H), 2.5 (t, 2H), 2.47 (s, 3H), 2.38 (s, 3H).

Example 330: Preparation of Compound Nos. II-120 and II-120a-d.

[0979] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorine (250 mg, 1.10 mmol) was dissolved in DMF (3 mL), sodium hydride (221 mg, 5.53 mmol) was added and the mixture stirred at RT for 5 min. 2-(4-Fluoro-phenyl)-oxirane (305 mg, 2.21 mmol) in 2 mL DMF was added dropwise into the reaction mixture and was stirred at RT for 16 h. The reaction was monitored by TLC and LCMS. After completion of reaction, the mixture was quenched with ice cold water (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (5x50 mL), dried over sodium sulfate and concentrated to obtain the crude product that was purified by reverse phase HPLC followed by chiral HPLC to obtain 190 mg of 1-(4-fluoro-phenyl)-2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-ethanol. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 7.32 (d, 1H), 7.3 (s, 1H), 7.1 (t, 2H), 7.0 (m, 3H), 5.08 (t, 1H), 4.4 (dd, 1H), 4.19 (dd, 1H), 3.6 (m, 2H), 3.45 (m, 1H), 3.0 (d, 1H), 2.6 (m, 2H), 2.4 (s, 3H), 2.2 (m, 2H), 2.0 (m, 1H). Separation by chiral HPLC provided diastereomers II-120a-b.

Example 331: Preparation of Compound Nos. II-121 and II-121a-d.

[0980] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (150 mg, 0.66 mmol) was dissolved in DMF (2 mL), sodium hydride (79 mg, 1.98 mmol) was added and the mixture was stirred at RT for 5 min. 2-(4-Fluoro-phenyl)-2-methyl-oxirane (201 mg, 1.32 mmol) was added dropwise into the reaction mixture and stirred at RT for 18 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (100 mL) and extracted with EtOAc (2x100 mL). The

combined organic layer was washed with water (2x100 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by column chromatography (neutral alumina) Eluent:-2% MeOH in DCM followed by chiral HPLC to obtain 77 mg of 2-(4-fluoro-phenyl)-1-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-propan-2-ol. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.4 (m, 2H), 7.2 (m, 2H), 7.0 (m, 3H), 5.08 (t, 1H), 4.3 (d, 1H), 4.15 (d, 1H), 3.65 (m, 1H), 3.5 (m, 2H), 3.3 (m, 1H), 2.90 (m, 2H), 2.7 (m, 1H), 2.4 (s, 3H), 2.2 (m, 3H), 1.62 (s, 3H). Separation by chiral HPLC provided diastereomers II-121a-b.

Example 332: Preparation of Compound Nos. II-122 and II-122a-d.

[0981] To a solution of 11-aza-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (200 mg, 0.88 mmol) in DMF (5 mL), NaH (105 mg, 2.6 mmol, 60% dispersion in mineral oil) was added at 0 °C and the reaction mixture was stirred for 10 min. 4-oxiranyl-pyridine (213 mg, 1.76mmol) was added and the reaction mixture was stirred at RT overnight. The reaction was monitored with LCMS. The reaction mixture was quenched with MeOH (2 mL), concentrated under reduced pressure to obtain the product that was purified by reverse phase column chromatography to obtain the 39 mg of product as the free base. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.4 (d, 2H), 7.63 (d, 1H), 7.29 (dd, 2H), 6.95 (t, 1H), 5.0 (t, 1H),4.3 (m, 3H), 3.21 (m, 1H), 2.9 (m, 4H), 2.7 (m, 1H), 2.57 (s, 3H), 2.52 (m, 1H), 1.9 (m, 3H). Separation by chiral HPLC provides diastereomers II-122a-b.

Example 333: Preparation of Compound Nos. II-123 and II-123a-b.

[0982] A mixture of 9-chloro-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole and 7-chloro-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (2.00 g, 8.5 mmol) was dissolved in DMF (15 mL). Sodium hydride (1.708 g, 42.71 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min., 3-(2-methyloxiran-2-yl)pyridine (2.309 g, 17.08 mmol) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (100 mL) and extract with EtOAc (300 mL). The organic layer was washed with water (5x100 mL). The organic layer dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude. The crude product was purified by reverse phase column chromatography to obtain 350 mg of 1-(7-chloro-2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.68 (m, 3H), 7.95 (m, 1H), 7.29 (d, 1H), 6.9 (m, 1H), 4.68 (dd,

1H), 4.38 (m, 2H), 4.32 (dd, 1H), 3.9 (m, 1H), 3.52 (m, 2H), 3.25 (m, 1H), 3.12 (s, 3H), 2.35 (d, 3H), 1.83 (d, 3H). Separation by chiral HPLC provided enantiomers II-123a-b.

Example 334: Preparation of Compound Nos. II-124 and II-124a-b.

[0983] A mixture of 9-chloro-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole and 7-chloro-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (2.00 g, 8.5 mmol) was dissolved in DMF (15 mL). Sodium hydride (1.708 g, 42.71 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min., 3-(2-methyloxiran-2-yl)pyridine (2.309 g, 17.08 mmol) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (100 mL) and extract with EtOAc (300 mL). The organic layer was washed with water (5x100 mL). The organic layer dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude. The crude product was purified by reverse phase column chromatography to obtain 35 mg of 1-(9-chloro-2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.46 (s, 1H), 8.34 (d, 1H), 7.82 (d, 1H), 7.29 (t, 1H), 6.87 (d, 1H), 6.77 (d, 1H), 4.22 (dd, 2H), 3.99 (q, 2H), 2.73 (m, 4H), 2.5 (s, 3H), 2.3 (s, 3H), 1.66 (s, 3H). Separation by chiral HPLC provided enantiomers II-124a-b.

Example 335: Preparation of Compound Nos. II-125 and II-125a-d.

[0984] 8,10-Dimethyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (700 mg, 2.92 mmol) in DMF (20 mL) was stirred at 0 °C for 5 min. NaH (580 mg, 14.60 mmol) was added slowly at 0 °C. After 10 min. stirring, 4-(oxiran-2-yl)pyridine (710 mg, 5.87 mmol) was added and the reaction mixture was stirred at RT for 15 h. The reaction mixture was poured in ice-cold water (150 mL) and extracted with EtOAc (3x200 mL). The combined organic layer was washed with water (6x300 mL), dried over anhydrous sodium sulfate and concentrated to obtain semi-solid residue that was washed with hexane (3x20 mL). The residue was suspended in ether (30 mL) stirred for 1 h. The suspension was filtered to give 200 mg of 2-(8,10-dimethyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-(pyridin-4-yl)ethanol. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.79 (d, 2H), 8.03 (d, 2H), 7.13 (s, 1H), 6.82 (s, 1H), 5.22 (dd, 1H),5.01 (t, 1H), 4.67 (dd, 1H), 4.48 (dd, 1H), 4.79 (m, 1H), 3.64 (t, 2H), 3.4 (m, 3H), 2.9 (m, 1H), 2.73 (s, 3H), 2.37 (s, 3H), 2.22 (m, 3H). Separation by chiral HPLC provided diastereomers II-125a-b.

Example 336: Preparation of Compound Nos. II-126 and II-126a-b.

[0985] 9-Aza-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (160 mg, 0.88 mmol) was dissolved in DMF (8 mL). Sodium hydride (63 mg, 2.64 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min., 3-(2-methyloxiran-2-yl)pyridine (480 mg, 3.55 mmol) in DMF (2 mL) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (4 mL) and solvent was evaporated to obtain the crude product, which was purified by reverse phase column chromatography to obtain 15 mg of product. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.51 (s, 1H), 8.3 (d, 1H), 8.13 (d, 1H), 7.83 (d, 1H), 7.57 (d, 1H),7.31 (t, 1H), 6.99 (t, 1H), 4.33 (dd, 2H), 3.78 (dd, 2H), 3.0 (m, 1H), 2.85 (m, 1H), 2.75 (m, 2H), 2.53 (s, 3H), 1.69 (s, 3H). Separation by chiral HPLC provides enantiomers II-126a-b.

Example 337: Preparation of Compound Nos. II-127 and II-127a-d.

[0986] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (150 mg, 0.66 mmol) was dissolved in DMF (1 mL), sodium hydride (47 mg, 1.98 mmol) was added and the mixture was stirred at RT for 5 min. 3-(2-Methyl-oxiranyl)-pyridine (143 mg, 1.06 mmol) was added dropwise into the reaction mixture and stirred at RT for 2 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (20 mL) and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (2x100 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by column chromatography (silica gel 100-200 mesh, Eluent:-15 % MeOH in DCM) to obtain 80 mg of 1-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c] fluoren-6-yl)-2-pyridin-3-yl-propan-2-ol. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.66 (dd, 2H), 8.56 (s, 1H), 7.92 (t, 1H), 7.20 (s, 1H), 6.77 (t, 2H), 5.04 (t, 1H), 3.75 (dd, 2H),3.72 (m, 2H), 3.6 (m, 1H), 3.44 (m, 2H), 3.22 (d, 1H), 2.75 (m, 1H), 2.73 (s, 3H), 2.16 (m, 3H), 1.8 (s, 3H). Separation by chiral HPLC provided enantiomers II-127a-b.

Example 338: Preparation of Compound Nos. II-128 and II-128a-d.

[0987] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (200 mg, 0.88 mmol) was dissolved in DMF (3 mL), sodium hydride (106 mg, 2.65 mmol) was added and stirred for 15 min. at RT. 2-Methyl-5-(2-methyl-oxiranyl)-pyridine (263 mg, 1.76 mmol) was added dropwise into the reaction mixture and the mixture was stirred at RT for 3 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (20 mL) and extracted with EtOAc (3x30 mL). The combined

organic layer was washed with water (2x60 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 200 mg of 1-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-2-(6-methyl-pyridin-3-yl)-propan-2-ol. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.5 (d, 1H), 8.3 (s, 1H), 7.79 (d, 1H), 7.22 (s, 1H), 6.82 (s, 2H), 5.03 (t, 1H), 4.38 (dd, 2H), 3.8 (m, 1H), 3.66 (m, 2H),3.46 (m, 2H), 3.2 (m, 2H), 2.7 (m, 1H), 2.67 (s, 3H), 2.36 (s, 3H), 2.22 (m, 2H), 1.77 (s, 3H). Separation by chiral HPLC provided enantiomers II-128a-b.

Example 339: Preparation of Compound Nos. II-129 and II-129a-b.

[0988] 7-Aza-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (160 mg, 0.88 mmol) was dissolved in DMF (8 mL). Sodium hydride (63 mg, 2.64 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min., 3-(2-methyloxiran-2-yl)pyridine (480 mg, 3.55 mmol) in DMF (2 mL) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (4 mL) and solvent was evaporated to obtain the crude product, which was purified by reverse phase column chromatography to obtain 3 mg of product as the free base. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.46 (s, 1H), 8.39 (s, 1H), 8.36 (d, 1H), 7.96 (d, 1H), 7.82 (d, 1H),7.37 (d, 1H), 7.31 (t, 1H), 4.4 (dd, 2H),3.71 (dd, 2H), 3.0 (m, 1H), 2.9 (m, 1H), 2.72 (m, 1H), 2.62 (m, 1H), 2.52 (s, 3H), 1.72 (s, 3H). Separation by chiral HPLC provides enantiomers II-129a-b.

Example 340: Preparation of Compound Nos. II-130 and II-130a-d.

[0989] To a stirred solution of 10-chloro-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (1.0 g, 4.06 mmol) in DMF (50 mL) was added sodium hydride (60%, 406 mg, 10.15 mmol). After stirring for 10 min., 3-(2-methyloxiran-2-yl)pyridine (823 mg, 6.09 mmol) was added to 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 (2x100 mL). The organic layer was washed with water (5x100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the residue that was crystallized with ethanol-hexane to yield the 1.2 g of 1-(10-chloro-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-2-(pyridin-3-yl)propan-2-ol. ^{1}H NMR ($CDCl_3$,freebase) δ (ppm): 8.70 (s, 1H), 8.49 (d, 1H), 7.62 (d, 1H), 7.36 (s, 1H), 7.12 (m, 2H), 7.02 (d, 1H), 4.17 (q, 2H), 3.86 (t, 1H), 3.19 (m, 1H), 2.86 (m, 1H), 2.74 (m, 3H), 2.41 (m, 2H), 1.85 (m, 3H), 1.7 (s, 3H). Separation by chiral HPLC provides diastereomers II-130a-d.

Example 341: Preparation of Compound Nos. II-131 and II-131a-d.

[0990] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene (200 mg, 0.88 mmol) was dissolved in DMF (3ml), sodium hydride (106 mg, 2.65 mmol) was added and the mixture was stirred at RT for 15 min. 3-Oxiranyl-pyridine (214 mg, 1.76 mmol) was added dropwise into the reaction mixture and the mixture was stirred at RT for 3 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (20 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (2x60 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 60 mg of 2-(9-Methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-1-pyridin-3-yl-ethanol as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.7 (d, 1H), 8.53 (s, 1H), 8.4 (d, 1H), 7.85 (t, 1H), 7.25 (s, 1H), 7.08 (t, 1H),6.9 (d, 1H), 5.28 (t, 1H), 5.03 (t, 1H), 4.42 (s, 2H), 3.76 (m, 1H), 3.6 (m, 2H), 3.4 (m, 1H), 3.2 (m, 2H),2.7 (m, 1H), 2.38 (s, 3H), 2.2 (m, 3H). Separation by chiral HPLC provides diastereomers II-131a-d.

Example 342: Preparation of Compound Nos. II-132 and II-132a-d.

[0991] 1-(2-Methoxy-pyridin-4-yl)-2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c]fluoren-6-yl)-ethanol (45 mg, 0.119 mmol) and 47% aqueous HBr (4 mL) and heated at 100 °C for 45 min. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was cooled to RT and basified with ammonia and extracted with EtOAc (2x25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated and the crude product was purified by reverse phase chromatography to obtain 20 mg of 4-(2-(2,3,5,6-tetrahydro-10-methyl-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-hydroxyethyl) pyridin-2(1H)-one. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.43 (d, 1H), 7.23 (m, 2H), 7.05 (t, 1H), 6.7 (m, 1H), 6.5 (d, 1H),4.79 (m, 1H), 4.3 (m, 2H), 3.9 (m, 2H), 3.8 (m, 1H), 3.6 (m, 1H), 3.4 (m, 2H), 3.1 (m, 1H), 2.6 (m, 1H), 2.4 (s, 3H), 2.3 (m, 2H), 1.9 (m, 1H). Separation by chiral HPLC provided enantiomers II-132a-b.

Example 343: Preparation of Compound No. II-133.

[0992] To a stirred solution of 6,8,8-trimethyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (75 mg, 0. 348 mmol) in DMF (1.5 mL) was added sodium hydride (42 mg, 1.0465 mmol). After stirring for 10 min at RT, a solution of 2-(6-methylpyridin-3-yl)ethyl trifluoromethanesulfonate (304 mg, 1. 046 mmol) in DMF (1. 5 mL) was added to the reaction mixture and stirring continued at RT for 16 h. The progress of reaction was monitored by TLC

and LCMS. The reaction mixture was 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 to afford crude mass, which was purified by reverse phase HPLC. ^{1}H NMR ($CDCl_3$, TFA salt) δ (ppm): 8.42 (s, 1H), 8.31 (d, 1H), 7.7 (d, 1H), 7.57 (d, 1H), 7.1 (d, 1H), 7.0 (t, 1H), 4.5 (t, 2H), 3.63 (s, 2H), 3.2 (t, 2H), 2.57 (s, 8H), 1.42 (s, 6H).

Example 344: Preparation of Compound Nos. II-134 and II-134a-b.

[0993] To a solution of 1,2,3,4,5,6-hexahydro-3,9-dimethylazepino[4,5-b]indole (3 g, 14.01 mmol) in DMF (40 mL), NaH (2.8 g, 70 mmol, 60% dispersion in mineral oil) was added slowly at 0 °C. The solution was stirred at 0 °C for 10 min. 4-(2-Methyloxiran-2-yl)pyridine (3.8 g, 2.8 mmol) was added and the reaction mixture was stirred at RT for 15 h. The reaction mixture was poured into ice-cold water (300 mL) and extracted with EtOAc (2x200 mL). The organic layer was washed with water (5x200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure gave an oily residue that was purified by column chromatography using silica gel (100-200 mesh) and 10 MeOH-DCM as eluting system followed by chiral preparative HPLC to afford the 300 mg of pure product. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.59 (d, 2H), 7.38 (d, 2H), 7.25 (s, 1H), 7.18 (d, 1H), 6.96 (d, 1H), 4.23 (dd, 2H), 2.89 (m, 2H), 2.75 (m, 4H), 2.6 (m, 2H), 2.43 (s, 3H), 2.42 (s, 3H),1.58 (s, 3H). Separation by chiral HPLC provided enantiomers II-134a-b.

Example 345: Preparation of Compound Nos. II-135 and II-135a-b.

[0994] 3,9-Dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (1 g, 4.6 mmol) in DMF (10 mL) was stirred at RT for 5 min. NaH (60 %, 933 mg, 23.33 mmol) was added and the reaction mixture was stirred at RT for 10 min. 3-(2-methyloxiran-2-yl)pyridine (1.26 g, 9.34 mmol) was added to the reaction mixture and the mixture was stirred at RT for 16 h. The reaction mixture was poured into ice-water and extracted with EtOAc (200 mL).The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the crude product, which was purified by column chromatography using silica gel:100-200 mesh and 10 % MeOH/ DCM/ 1 mL NH4OH to obtain 600 mg of 1-(3,9-dimethyl-2,3,4,5-tetrahydroazepino[4,5-b]indol-6(1H)-yl)-2-(pyridin-3-yl)propan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.74 (s, 1H), 8.54 (d, 1H), 7.71 (d, 1H), 7.26 (s, 1H), 7.27 (m, 1H),7.19 (d, 1H), 6.96 (d, 1H), 4.26 (dd, 2H), 2.91 (m, 2H), 2.9 (m, 4H), 2.74 (m, 2H), 2.44 (s, 6H), 1.63 (s, 3H). Separation by chiral HPLC provided enantiomers II-135a-b.

Example 346: Preparation of Compound Nos. II-136 and II-136a-b.

[0995] A mixture of 5-(1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxypropan-2-yl)picolinonitrile (300 mg, 0.833 mmol), crushed KOH (140 mg, 2.499 mmol) in 12 mL tert-butanol was heated at 80 °C for 2 h. The reaction was monitored by TLC. The reaction mixture was allowed to cool at RT, diluted with brine (30 mL) and extracted with ethyl acetate (2x100 mL). The combined organic layer was washed with water (3x100 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by Preparative HPLC followed by chiral HPLC to obtain 5-(1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-hydroxypropan-2-yl)pyridine-2-carboxamide. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.49 (s, 1H), 8.04 (d, 1H), 7.86 (d, 1H), 7.66 (s, 1H), 7.01 (s, 1H), 6.85 (s, 1H), 6.78 bs (NH), 5.48 s (OH),4.16 (dd, 2H), 3.44 (q, 2H), 2.9 (m, 2H), 2.7 (m, 2H), 2.45 (s, 3H), 2.35 (s, 3H), 2.35 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provided enantiomers II-136a-b.

Example 347: Preparation of Compound Nos. II-137 and II-137a-b.

[0996] These compounds were synthesized in an analogous fashion to Compound Nos. 55 and 55a-b, using 3,6-dimethyl-6,7,8,9-tetrahydro-5H-1,2,6,9-tetraaza-fluorene as the carboline portion. Separation by chiral HPLC provides enantiomers II-137a-b.

Example 348: Preparation of Compound Nos. II-138 and II-138a-d.

[0997] A solution of benzyl protected fused carboline compound (70 mg, 0.16 mmol) in HPLC grade MeOH (70 mL) was subjected to hydrogenation in H-Cube. The solvent was removed under reduced pressure to afford an oily residue that was purified by preparative HPLC to give 3 mg of desired compound. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.67 (s, 2H), 7.28 (m, 3H), 7.04 (d, 1H), 5.21 (m, 1H), 5.04 (t, 1H), 4.39 (m, 2H), 3.67 (m, 3H), 3.25 (m, 2H), 3.03 (m, 1H), 2.68 (m, 1H), 2.41 (s, 3H), 2.19 (m, 3H). Separation by chiral HPLC provides diastereomers II-138a-d.

Example 349: Preparation of Compound Nos. II-139 and II-139a-d.

[0998] A suspension of 2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-(1-trityl-1H-imidazol-2-yl)ethanol (0.4 g, 0.69 mmol) in MeOH (10 mL), 1N HCl (1 mL) was added and the reaction mixture was stirred at RT for 2 h. The reaction mixture concentrated under vacuum to obtain the crude product that was basified with satd. sodium bicarbonate solution and extracted with EtOAc (50 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated under vacuum to obtain the crude product, which was purified by reverse HPLC to obtain 11.30 mg 1-(1H-imidazol-2-yl)-2-(10-methyl-2,3,5,6-tetrahydro-1H-

indolizino[7,8-b]indol-7(11cH)-yl)ethanol. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.44 (s, 2H), 7.27 (s, 1H), 7.13 (d, 1H), 6.99 (d, 1H), 5.37 (t, 1H), 5.1 (m, 1H),4.56 (dd, 1H), 4.46 (dd, 1H), 3.67 (m, 3H), 3.42 (m, 1H), 3.24 (m, 2H), 2.7 (m, 1H), 2.4 (s, 3H),2.2 (m, 3H).

Example 350: Preparation of Compound Nos. II-140 and II-140a-d.

[0999] To a stirred solution of compound 2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-(1-trityl-1H-imidazol-5-yl)ethanol (400 mg, 0.69 mmol) in MeOH (10 mL), 1N HCl (1 mL) at 0 °C was added. The reaction mixture was stirred at RT for 2 h. The reaction mixture concentrated under vacuum to obtain the crude product that was basified with sat sodium bicarbonate solution and extracted with EtOAc (50 mL). The organic layer dried on anhydrous sodium sulfate, and concentrated under vacuum to obtain the crude product that was purified by reverse phase HPLC to obtain 1-(1H-imidazol-5-yl)-2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)ethanol (12 mg) as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.79 (s, 1H), 7.4 (s, 1H), 7.27 (s, 1H), 7.2 (dd, 1H), 7.01 (d, 1H), 5.18 (t, 1H), 5.04 (m, 1H), 4.39 (m, 2H), 3.67 (m, 3H), 3.42 (m, 2H), 3.2 (m, 1H), 2.7 (m, 1H), 2.4 (s, 3H), 2.2 (m, 3H). Separation by chiral HPLC provides diastereomers II-140a-d.

Example 351: Preparation of Compound Nos. II-141 and II-141-a-b.

[1000] To a solution of 2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (90 mg, 0.466 mmol) in DMF (2 mL), sodium hydride (60%, 33 mg, 1.44 mmol) was added. After stirring for 10 min., methyl 5-(2-methyloxiran-2-yl)nicotinate (1.09 g, 12.4 mmol) was added to 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 (2x100 mL). The aqueous layer was lyophilized and purified by reverse phase HPLC purification to obtain the 10 mg of 5-(1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-hydroxypropan-2-yl)pyridine-3-carboxylic acid. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.9 (d, 1H), 8.7 (d, 1H), 8.57 (d, 1H), 7.11 (s, 1H), 6.74 (d, 2H), 4.67 (dd, 1H),4.33 (m, 2H), 4.29 (dd, 1H), 3.9 (t, 1H), 3.6 (m, 2H), 3.2 (m, 1H), 3.11 (s, 3H), 2.3 (s, 3H), 1.79 (d, 3H). Separation by chiral HPLC provides enantiomers II-141a-b.

Example 352: Preparation of Compound Nos. II-142 and II-142a-b.

[1001] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (40 mg, 0.200 mmol) was dissolved in 1ml DMF. Sodium hydride (24 mg, 0.600 mmol) was added at 0 °C and the reaction mixture was stirred at RT for 10 min. 5-(2-methyloxiran-2-yl)oxazole (35 mg, 0.280 mmol) in DMF (1 mL) was added dropwise over 10 min. and the reaction mixture was stirred at

RT for 12 h. The reaction was monitored by TLC and LCMS. Ice cold water was added to the reaction mixture and then extracted with EtOAc (3x20 mL). The combined organic layer was washed with water (4x10 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain the 20 mg of 1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-(oxazol-5-yl)propan-2-ol as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.09 (s, 1H), 7.18 (s, 1H), 6.97 (d, 1H), 6.92 (d, 1H), 6.8 (s, 1H), 4.7 (m, 1H), 4.35 (m, 3H), 3.9 (m, 1H), 3.56 (m, 1H), 3.25 (m, 2H), 3.09 (s, 3H), 2.37 (s, 3H), 1.58 (s, 3H). Separation by chiral HPLC provides enantiomers II-142a-b.

Example 353: Preparation of Compound Nos. II-143 and II-143a-b.

[1002] 2-(2-Chloropyridin-3-yl)-1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol (100 mg, 0.277 mmol) and crushed potassium hydroxide (106 mg, 1.89mmol) in 3 mL tert. butanol were heated at 90 °C for 4 h. The reaction mixture was monitored by TLC and LCMS. The reaction mixture was cooled at RT, diluted with 100 mL brine solution and extracted with EtOAc (3x100 mL). The combined organic layer was washed with brine (3x100 mL),dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to get the 35 mg of 3-(1-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-2-hydroxypropan-2-yl)pyridin-2(1H)-one as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 7.79 (d, 1H), 7.35 (m, 2H), 7.17 (s, 1H), 6.93 (d, 1H), 6.34 (t, 1H), 4.61 (d, 2H), 4.3 (d, 2H), 3.9 (m, 1H), 3.8 (m, 1H), 3.36 (m, 2H), 3.1 (s, 3H), 2.37 (s, 3H), 1.51 (s, 3H). Separation by chiral HPLC provides enantiomers II-143a-b.

Example 354: Preparation of Compound No. II-144.

[1003] To a solution of 6-methyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (200 mg, 1.068 mmol) in DMF (1 mL) was added a suspension of NaH (128.0 mg, 3.24 mmol) in DMF (1 mL). After stirring for 5 min. at RT, a solution of 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (932 mg, 3.204 mmol) in DMF (1 mL) was added dropwise into the reaction mixture and stirring continued for another 3 h. The progress of reaction was monitored by TLC and NMR. 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 silica gel flash chromatography eluting with 10% MeOH-DCM to yield 6-methyl-9-(2-(6-methylpyridin-3-yl)ethyl)-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (90 mg) as a free base. The free base was converted into tri-HCl salt by treatment with ethanolic HCl. ^{1}H

NMR (CD_3OD, Tri-HCl salt) δ (ppm): 8.76 (s, 1H), 8.40 (m, 3H), 7.80 (d, 1H), 7.50 (t, 1H), 4.90-4.70 (m, 3H), 4.42 (m, 1H), 3.95 (m, 1H), 3.66 (m, 1H), 3.42-3.30 (m, 4H), 3.15 (s, 3H), 2.76 (s, 3H).

Example 355: Preparation of Compound Nos. II-145 and II-145a-b.

[1004] 2,8,9-Trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (400 mg, 1.86 mmol) 4 mL DMF, cooled to 0 °C and sodium hydride (224 mg,5.60 mmol) was added portionwise at the same temperature. 3-(2-methyloxiran-2-yl)pyridine (504 mg, 3.73 mmol) in DMF (1 mL) was added to the reaction mixture and allowed to stir at RT for 12 h. After complete consumption of starting material, the reaction mixture was poured in to ice water and extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (3x50 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was crystallized with ether and hexane to obtain 400 mg of 2-(pyridin-3-yl)-1-(2,8,9-trimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol. ^{1}H NMR (DMSO, freebase) δ (ppm): 8.59 (s, 1H), 8.42 (d, 1H), 7.73 (d, 1H), 7.31 (t, 1H), 7.1 (d, 1H), 6.73 (d, 1H), 4.11 (dd, 2H), 3.74 (s, 2H), 3.4 (m, 2H), 2.6 (m, 2H), 2.37 (s, 6H), 2.22 (s, 3H), 1.5 (s, 3H). Separation by chiral HPLC provides enantiomers II-145a-b.

Example 356: Preparation of Compound Nos. II-146 and II-146a-d.

[1005] 2,3,8-Trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (214 mg, 1 mmol) was dissolved in DMF (3 mL) and NaH (80 mg, 3.33 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. The solution of 3-(2-methyloxiran-2-yl)pyridine (270 mg,2 mmol) in DMF (2 mL) was added dropwise at 0 °C and the reaction mixture was stirred at 0 °C for 10 min and at RT for 16 h. Completion of reaction was monitored by LCMS. The reaction mixture was poured onto crushed ice slowly and extracted with EtOAc (3x30 mL). The organic layer was washed with water (7x40 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the crude product that was purified by reverse HPLC to give 23 mg of 2-(pyridin-3-yl)-1-(2,3,8-trimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.73 (s, 1H), 8.47 (d, 1H), 7.2 (d, 1H), 7.11 (s, 1H), 7.04 (d, 2H), 6.90 (d, 1H), 4.15 (dd, 2H), 3.78 (dd, 1H), 3.6 (dd, 1H), 2.9 (m, 2H), 2.7 (dd, 1H), 2.43 (s, 3H), 2.4 (s, 3H), 1.6 (s, 3H), 1.14 (d, 3H). Separation by chiral HPLC provided diastereomers II-146a-d.

Example 357: Preparation of Compound Nos. II-147 and II-147a-d.

[1006] To a solution of 8-chloro-2,3-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.13 mmol) in 4 mL of DMF was added sodium hydride (256 mg, 6.40 mmol) at 0 °C., and stirred for 10 min. 3-(2-methyloxiran-2-yl)pyridine (432 mg, 3.20 mmol) was added and the mixture was stirred at RT for 12 h. The reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice cold water and extracted with EtOAc (2x50 mL). The combined organic layer was washed with water (5x25 mL), dried over anhydrous sodium sulfate, concentrated to obtain the crude product, which was crystallized in n-hexane to obtain 350 mg of 1-(8-chloro-2,3-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.72 (s, 1H), 8.47 (d, 1H), 7.52 (d, 1H), 7.23 (s, 1H), 6.94 (m, 3H),4.10 (dd, 2H), 3.65 (m, 1H), 3.40 (m, 1H), 2.86 (m, 2H), 2.38 (s, 3H), 2.36 (m, 1H),1.62 (s, 3H), 1.07 (d, 3H). Separation by chiral HPLC provided diastereomers II-147a-b.

Example 358: Preparation of Compound Nos. II-148 and II-148a-b.

[1007] To a solution of 2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (700 mg, 3.5 mmol) in 3 mL of DMF was added sodium hydride at 0 °C and stirred for 10 min. 4-Chloro-3-(2-methyloxiran-2-yl)pyridine (888 mg, 5.25 mmol) in 2 mL of DMF was added and allowed to stir at RT for 12 h. The reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was poured into ice cold water and extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (5x50 mL), Dried over anhydrous sodium sulfate, concentrated under reduced pressure and crystallized in diethyl ether to get the desired compound (700 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 9.1 (s, 1H), 8.43 (d, 1H), 7.38 (d, 1H), 7.29 (d, 1H), 7.25 (d, 1H), 6.97 (d, 1H),4.7 (d, 1H), 4.23 (d, 1H), 3.63 (m, 2H), 2.8 (m, 2H), 2.75 (m, 2H), 2.51 (s, 3H), 2.41 (s, 3H), 1.71 (s, 3H). Separation by chiral HPLC provided enantiomers II-148a-b.

Example 359: Preparation of Compound Nos. II-149 and II-149a-d.

[1008] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6,7-triaza-cyclopenta[c]fluorene (700 mg, 3.0 mmol) was dissolved in DMF (7 mL) and sodium hydride (360 mg, 9.0 mmol) was added portionwise at 0 °C and stirred for 10 min. 2-(4-Fluoro-phenyl)-2-methyl-oxirane (720 mg, 4.8 mmol) in 3 mL DMF was added dropwise into the reaction mixture and the mixture was stirred at RT for 18 h. The reaction mixture was quenched with ice cooled water and extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (4x75 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by

passing through a column of silica gel (100-200 mesh), using the eluent 5% MeOH in DCM to obtain 520 mg of 2-(4-fluoro-phenyl)-1-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6,7-triaza cyclopenta[c]fluoren-6-yl)-propan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.02 (s, 1H), 7.54 (s, 1H), 7.43 s (OH), 7.37 (t, 2H), 6.93 (t, 2H), 4.37 (d, 1H), 4.22 (d, 1H), 4.04 (t, 1H), 3.23 (dd, 1H), 2.9 (m, 1H), 2.7 (m, 2H), 2.5 (m, 2H), 2.42 (s, 3H), 2.3 (m, 1H), 1.84 (m, 3H), 1.6 (s, 3H). Separation by chiral HPLC provided diastereomers II-149a-d.

Example 360: Preparation of Compound Nos. II-150 and II-150a-d.

[1009] 2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethanol (350 mg, 1 mmol), formaldehyde (37%, 0.89 g, 10 mmol) and formic acid (922 mg, 20 mmol) was stirred at 100 °C for 12 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was washed with saturated sodium bicarbonate and extracted with DCM (2x25 mL). The combined organic layer was washed with water (5x25 mL) dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the crude product, which was subjected to preparative HPLC to obtain 25 mg of 2-(9-(hydroxymethyl)-2,8-dimethyl-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): 8.56 (d, 2H), 7.29 (d, 2H), 7.12 (d, 1H), 6.98 (d, 1H), 4.9 (dd, 1H), 4.79 (q, 2H), 4.13 (m, 2H), 3.78 (d, 1H), 3.72 (d, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 2.67 (m, 2H), 2.49 (s, 3H), 2.32 (s, 3H). Separation by chiral HPLC provided diastereomers II-150a-d.

Example 361: Preparation of Compound Nos. II-151 and II-151a-d.

[1010] 2,8-Dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-4-ol (500 mg, 2.314 mmol) in DMF (5.0 mL) was cooled to 0 °C. NaH (0.462 mg, 11.57 mmol) was added portionwise and stirred for 5 min. 3-(2-Methyl-oxiranyl)-pyridine (620 mg, 4.629 mmol) was added dropwise and the reaction mixture was stirred at RT for 4 h. The reaction was quenched with ice water and extracted with EtOAc (3x50 mL). The combined organic layer was washed with water (2x25 mL), dried over anhydrous sodium sulfate and concentrated to get 900 mg crude that was purified by reverse phase HPLC to obtain the product. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.57 (m, 2H), 8.48 (m, 1H), 7.85 (m, 1H), 7.21 (s, 1H), 6.78 (d, 1H),6.64 (m, 1H), 5.72 (m, 1H), 4.66 (t, 2H), 4.45 (d, 1H), 4.30 (d, 1H), 3.78 (m, 2H), 3.16 (s, 3H), 2.31 (s, 3H), 1.87 (s, 3H). Separation by chiral HPLC provided diastereomers II-151a-b.

Example 362: Preparation of Compound Nos. II-152 and II-152a-d.

[1011] 1,2,8-Trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (500 mg, 2.3 mmol) in DMF (2.5 mL) was stirred at 0 °C for 5 min. NaH (279 mg, 6.97 mmol) was added slowly at 0

°C. After 10 min. stirring, 3-(2-methyloxiran-2-yl)pyridine (630 mg, 4.6 mmol) in DMF (2.5 mL) was added and the reaction mixture was stirred at RT for 18 h. The reaction mixture was poured in ice-cold water (50 mL) and extracted with EtOAc (2x50 mL). The combined organic layer was washed with water (6x50 mL), dried over anhydrous sodium sulfate and concentrated to obtain semi-solid residue that was washed with hexane (3x20 mL) to obtain 350 mg of product that was submitted to chiral reverse phase column chromatography. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.74 (s, 1H), 8.49 (d, 1H), 7.60 (d, 1H), 7.20 (s, 1H), 7.07 (m, 2H),6.90 (d, 1H), 4.16 (dd, 2H), 3.72 (m, 1H), 2.97 (m, 1H), 2.69 (m, 2H), 2.47 (s, 3H), 2.44 (m, 1H),2.42 (s, 3H), 1.66 (s, 3H), 1.42 (d, 3H). Separation by chiral HPLC provided diastereomers II-152a-d.

Example 363: Preparation of Compound Nos. II-153 and II-153a-b.

[1012] 1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol (1 g, 2.99 mmol) in formaldehyde (37%, 5.69 mL, 59.6 mmol) and formic acid (2.25 mL, 59.6 mmol) was stirred at 100 °C for 24 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to obtain the crude product, which was subjected to preparative HPLC to obtain pure compound (100 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.7 (s, 1H), 8.5 (d, 1H), 7.8 (d, 1H), 7.23 (m, 1H), 7.15 (d, 1H), 6.94 (d, 1H), 4.80 (q, 2H), 4.19 (dd, 2H), 4.17 (m, 2H), 3.0 (m, 4H), 2.6 (s, 3H), 2.47 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provides enantiomers II-153a-b.

Example 364: Preparation of Compound Nos. II-154 and II-154a-b.

[1013] 1-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol (1 g, 2.99 mmol) in formaldehyde (37%, 5.69 mL, 59.6 mmol) and formic acid (2.25 mL, 59.6 mmol) was stirred at 100 °C for 24 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated under vacuum to obtain the crude product, which was subjected to preparative HPLC to obtain pure compound (100 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.7 (s, 1H), 8.42 (d, 1H), 7.6 (d, 1H), 7.1 (s, 1H), 6.9 b(s, 2H), 4.7 (s, 2H), 4.1 (q, 2H), 3.9 (s, 2H), 2.9 (m, 3H), 2.8 (m, 1H), 2.6 (s, 3H), 2.39 (s, 3H), 1.6 (s, 3H). Separation by chiral HPLC provides enantiomers II-154a-b.

Example 365: Preparation of Compound No. II-209.

[1014] 2-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethanone (0.1 g, 0.313 mmol) in 6 mL of DCM was cooled to 0 °C, DAST (0.062 mL, 0.47 mmol) was added dropwise and the mixture stirred at RT for 2 h. The reaction was monitored by LCMS. After completion of the reaction, DCM (10 mL) was added, and the reaction was

quenched with satd. $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by preparative HPLC to afford 40 mg of the desired compound as the TFA salt. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.61 (d, 2H), 7.15-7.2 (m, 3H), 6.83-6.95 (m, 2H), 4.5 (t, 2H), 3.6 (s, 2H), 2.78-2.63 (m, 2H), 2.6-2.45 (m, 5H), 2.4 (s, 3H).

Example 366: Preparation of Compound No. II-210 and II-210a-b.

[1015] To an ice-cooled stirred solution of 1-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido(4,3-b)indol-5-yl)-2-(4-flurophenyl)-propan-2-ol (500 mg, 1.418 mmol) in DCM (50mL) was added diethylaminosulfur trifluoride (DAST) (0.374 mL, 2.85mmol) and the reaction mixture was stirred at RT for 1 h. The DCM layer was diluted and washed with aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and evaporated. The residue was purified by reverse phase HPLC. ^{1}H NMR (DMSO, oxalate salt) δ (ppm): 7.45 (m, 2H), 7.30 (d, 1H), 7.18 (m, 3H), 6.90 (d, 1H), 4.50 (m, 2H), 4.30 (s, 2H), 3.40 (m, 2H), 3.05 (m, 1H), 2.85 (s, 3H), 2.78 (m, 1H), 2.38 (s, 3H), 1.65 (d, 3H). Separation by chiral HPLC provides enantiomers II-210a-b.

Example 367: Preparation of Compound No. II-211 and II-211a-b.

[1016] To an ice-cooled stirred solution of 1-(8-chloro-1,2,3,4-tetrahydro-2-methylpyrido[4,3-b]indol-5-yl)-2-(4-fluorophenyl)propan-2-ol (500 mg, 1.3 mmol) in DCM (50 mL) was dropwise added DAST (443 mg, 2.6 mmol) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (50 mL), washed with saturated sodium bicarbonate solution (3x30 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified with reverse phase HPLC to yield 8-chloro-5-(2-fluoro-2-(4-fluorophenyl)propyl)-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole. ^{1}H-NMR (DMSO-d6, oxalate salt) δ (ppm): 7.50 (s, 1H), 7.40 (m, 3H), 7.18 (t, 2H), 7.05 (d, 1H), 4.60 (m, 2H), 4.25 (m, 2H), 3.05 (m, 2H), 2.85 (s, 3H), 2.70 (m, 2H), 1.65 (d, 3H). Separation by chiral HPLC provides enantiomers II-211a-b.

Example 368: Preparation of Compound Nos. II-212 and II-212a-b.

[1017] 1-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol (500 mg, 1.492 mmol) was dissolved in 20 mL DCM, cooled to 0 °C and diethylaminosulfur trifluoride (720 mg, 4.477 mmol) in DCM (5 mL) was added dropwise at the same temperature and stirred for 1 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with saturated bicarbonate and extracted

with DCM. The organic layer was washed with bicarbonate and brine solution, dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 60 mg of 5-(2-Fluoro-2-pyridin-3-yl-propyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.61 (s, 1H), 8.56 (d, 1H), 7.55 (d, 1H), 7.23 (d, 1H), 7.16 (s, 1H),7.05 (d, 1H), 6.93 (d, 1H), 4.3 (m, 2H), 3.8 (dd, 2H), 2.96 (m, 1H), 2.9 (m, 1H), 2.7 (m, 1H), 2.6 (m, 1H), 2.58 (s, 3H), 2.41 (s, 3H), 1.75 (d, 3H). Separation by chiral HPLC provided enantiomers II-212a-b.

Example 369: Preparation of Compound Nos. II-213 and II-213a-b.

[1018] 1-(8-Hydroxymethyl-2-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridin-3-yl-propan-2-ol (700 mg, 1.99 mmol) was dissolved in 70 mL DCM and cooled to 0 °C. Diethylaminosulfur trifluoride (800 mg, 4.9 mmol) in DCM (5 mL) was added dropwise at the same temperature and stirred for 45 min. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with saturated bicarbonate and extracted with DCM. The organic layer was washed with water and brine solution, dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 14 mg of [5-(2-fluoro-2-pyridin-3-yl-propyl)-2-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl]-methanol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.6 (s, 1H), 8.57 (d, 1H), 7.6 (d, 1H), 7.35 (s, 1H), 7.2 (m, 1H), 7.125 (m, 2H), 4.72 (s, 2H), 4.3 (m, 2H), 3.6 (q, 2H), 2.8 (m, 1H), 2.7 (dd, 2H), 2.6 (m, 1H), 2.52 (s, 3H), 1.75 (d, 3H). Separation by chiral HPLC provides enantiomers II-213a-b.

Example 370: Preparation of Compound No. II-215.

[1019] To a stirred solution of 6,8,8-trimethyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (75 mg, 0.348 mmol) in DMF (1.5 mL) was added potassium hydroxide (156 mg, 2.784 mmol). After stirring for 10 min at RT, a solution of 2-(trifluoromethyl)-5-vinylpyridine (181 mg, 1.046 mmol) in DMF (1.5 mL) was added to the reaction mixture and stirring continued at RT for 24 h and then at 80 °C for 48 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was diluted with water and extracted with EtOAc (3x30 mL). The organic layer was washed with water (2x20 mL), dried over anhydrous sodium sulfate and concentrated to afford crude product, which was purified by reverse phase HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.48 (s, 1H), 8.3 (d, 1H), 7.97 (d, 1H), 7.9 (d, 1H), 7.7 (d, 1H), 7.2 (t, 1H), 4.6 (m, 3H), 4.3 (m, 1H), 3.5 (d, 2H), 3.38 (bs, 2H), 3.2 (s, 3H), 1.6 (s, 6H).

Example 371: Preparation of Compound Nos. II-220 and II-220a-b.

[1020] 2,7,8-Trimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (400 mg, 1.86 mmol) was dissolved in DMF (4 mL), cooled to 0 °C and sodium hydride (224 mg, 5.60 mmol) was added portionwise at the same temperature. 3-(2-methyloxiran-2-yl)pyridine (504 mg, 3.73 mmol) in DMF (1 mL) was added to the reaction mixture and allowed to stir at RT for 12 h. After complete consumption of starting material, the reaction mixture was poured in to ice water and extracted with EtOAc (3x100 mL). The combined organic layer was washed with water (3x50 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was crystallized with ether and hexane to obtain 400 mg 2-(pyridin-3-yl)-1-(2,7,8-trimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)propan-2-ol. ^{1}H NMR (DMSO, freebase) δ (ppm): 8.60 (s, 1H), 8.4 (d, 1H), 7.7 (d, 1H), 7.28 (t, 1H), 7.06 (s, 1H), 7.01 (s, 1H), 4.11 (dd, 2H), 3.41 (m, 2H), 2.53 (m, 2H), 2.44 (m, 2H), 2.35 (s, 3H), 2.22 (s, 6H), 1.5 (s, 3H). Separation by chiral HPLC provides enantiomers II-220a-b.

Example 372: Preparation of Compound Nos. II-221 and II-221a-b.

[1021] To a solution of 3-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b] indol-5-yl)-2-pyridine-4-yl-propionitrile (50 mg, 0.1515 mmol) in anhydrous THF (4 mL) was added $LiAlH_4$ (17 mg, 0.4545 mmol) at 0 °C under nitrogen atmosphere. After the addition, the reaction mixture was stirred at RT for 1 h. The progress of the reaction was monitored by LCMS. After completion of reaction, 0.5 mL of water was added dropwise and then 0.5 mL of NaOH solution to quench the excess $LiAlH_4$. The reaction mixture was evaporated and the crude product purified by preparative HPLC. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.36 (d, 2H), 7.35 (m, 1H), 7.22 (s, 1H), 6.99 (d, 1H), 6.72 b(s, 2H), 4.23 (m, 1H), 3.71 (dd, 1H), 3.59 (m, 3H), 3.15 (dd, 1H), 3.07 (dd, 1H), 2.77 (m, 2H), 2.47 (s, 3H), 2.45 (s, 3H), 2.1 (m, 3H). Separation by chiral HPLC provides enantiomers II-221a-b.

Example 373: Preparation of Compound Nos. II-222 and II-222a-b.

[1022] 4-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyricacidmethylester (1.5g, 3.9mmol) was dissolved in THF (50 mL) and cooled to -78 °C, tert-butyl lithium (16 % in pentane) (6 mL, 15.13mmol) was added dropwise under nitrogen. The reaction mixture was stirred at -78 °C for 90 min. After complete consumption of starting material, the reaction mixture was quenched with ammonium chloride solution and the reaction mixture was allowed to come to RT and extracted with EtOAc (3x100 mL), The combined organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 1.7g of crude 6-(2,8-dimethyl-1,2,3,4-tetra hydro -pyrido[4,3-b]indol-5-yl)-2,2-dimethyl-5-pyridin-4-yl-hexan-

3-one. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.41 (d, 2H), 7.31 (d, 1H), 7.19 (s, 1H), 7.1 (d, 1H), 6.93 (d, 2H),4.25 (dd, 1H), 3.9 (t, 2H), 3.8 (m, 1H), 3.67 (dd, 1H), 2.87 (m, 3H), 2.71 (m, 2H), 2.51 (s, 3H), 2.42 (s, 3H), 2.1 (m, 1H), 1.21 s (9H). Separation by chiral HPLC provides enantiomers II-222a-b.

Example 374: Preparation of Compound Nos. II-223 and II-223a-b.

[1023] 4-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-but-3-enoicacid methyl ester (100 mg, 0.266 mmol) was dissolved in MeOH (10 mL) and 10 % dry Pd/C (50 mg) was added and hydrogen gas was purged in to the reaction mixture at RT for 12 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was filtered through Celite. The filtrate was concentrated to obtain the crude product, which was recrystallized in ether - hexane to obtained 50 mg of 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyric acid methyl ester. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.47 (d, 2H), 7.18 (s, 1H), 7.16 (d, 1H), 6.98 (d, 3H), 4.22 (dd, 1H), 4.05 (dd, 1H), 3.7 (m, 2H), 3.57 (s, 3H), 3.5 (dd, 1H), 2.74 (m, 3H), 2.71 (m, 2H), 2.49 (s, 3H), 2.43 (s, 3H), 2.2 (m, 1H). Separation by chiral HPLC provides enantiomers II-223a-b.

Example 375: Preparation of Compound Nos. II-224 and II-224a-b.

[1024] A solution of 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyric acid methyl ester (300 mg, 0.795 mmol) in THF (5 mL) was added dropwise to a solution of $LiAlH_4$ (93 mg,2.37 mmol) in THF (10 mL). The reaction mixture was stirred at RT for 30 min. After consumption of starting material, the reaction mixture was cooled to -78 °C. 0.2 mL of water and 0.2 mL of 15% NaOH solution was added and the reaction mixture was allowed to come to RT and diluted with THF and filtered. The filtrate was concentrated and the crude product was purified by passing through a column of silica gel (100-200 mesh) by using eluent 2% MeOH in DCM to obtain 69 mg of 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butan-1-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.48 (d, 2H), 7.18 (s, 1H), 7.1 (d, 1H), 7.01 (d, 2H), 6.97 (d, 1H), 4.2 (dd, 1H), 4.15 (dd, 1H), 3.64 (d, 1H), 3.56 (m, 2H), 3.4 (m, 2H), 2.7 (m, 3H), 2.4 (m, 1H), 2.5 (s, 3H), 2.43 (s, 3H), 1.94 (m, 2H). Separation by chiral HPLC provided enantiomers II-224a-b.

Example 376: Preparation of Compound Nos. II-225 and II-225a-b.

[1025] To a compound 3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propanoic acid (250 mg, 0.7 mmol) in THF was added $LiAlH_4$ (81.6 mg, 2.1 mmol) and the resultant reaction mixture was stirred at RT for 1 h. The progress of the reaction

was monitored by TLC and LCMS. The reaction was quenched by NaOH (0.5 mL), water (3 mL) at 0 °C and extracted with DCM (3x25 mL). The combined organic layer was dried on anhydrous sodium sulfate and concentrated under vacuum to obtain the crude product, which was subjected to reverse phase HPLC to obtain pure compound (30 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.41 (d, 2H), 7.28 b(s, 1H), 7.2 (s, 1H), 7.1 (d, 1H), 6.78 (d, 2H), 4.4 bs (OH), 4.3 (m, 1H), 4.0 (m, 1H), 3.62 (d, 1H), 3.42 (m, 3H), 3.1 (dd, 1H), 2.7 (m, 3H), 2.46 (m, 1H), 2.43 (s, 6H). Separation by chiral HPLC provides enantiomers II-225a-b.

Example 377: Preparation of Compound Nos. II-226 and II-226a-b.

[1026] 4-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyricacid methyl ester (400 mg, 1.06 mmol) was dissolved in THF (20 mL) and methyl magnesium chloride (3 M in THF) (2 mL, 6.3mmol) was added dropwise under nitrogen. The reaction mixture was stirred at 60 °C for 1 h. After consumption of starting material, the reaction mixture was quenched with ammonium chloride solution and the reaction mixture was extracted with EtOAc (3x100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 400 mg crude of 5-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-methyl-4-pyridin-4-yl-pentan-2-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.43 (d, 2H), 7.16 (s, 1H), 7.14 (d, 1H), 6.99 (d, 3H), 4.3 (dd, 1H),3.98 (d, 1H), 3.9 (dd, 1H), 3.8 (d, 1H), 3.5 (m, 1H), 3.15 (dd, 1H), 2.84 (m, 3H), 2.59 (s, 3H), 2.42 (s, 3H), 2.3 (dd, 1H), 1.85 (dd, 1H), 1.15 (s, 3H), 1.02 (s, 3H). Separation by chiral HPLC provides enantiomers II-226a-b.

Example 378: Preparation of Compound Nos. II-227 and II-227a-d.

[1027] 6-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2,2-dimethyl-5-pyridin-4-yl-hexan-3-one (400 mg, 0.99 mmol) was dissolved in MeOH (30 mL). Sodium borohydride (263 mg, 6.9 mmol) was added under nitrogen. The reaction mixture was heated at 60 °C for 8 h. After consumption of starting material, the reaction mixture was concentrated and 2N HCl was added (pH-acidic) and extracted with DCM (2x200 mL) for removing impurities. The aqueous layer was basified with saturated bicarbonate and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 350 mg of 6-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2,2-dimethyl-5-pyridin-4-yl-hexan-3-ol. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.44 (d, 2H), 7.15 (s, 1H), 7.0 (d, 1H), 6.94 (d, 1H), 6.92 (d, 2H),4.25 (dd, 1H), 4.0 (dd, 1H), 3.64 (d, 1H), 3.51 (m, 2H), 2.88 (dd, 1H), 2.73 (t, 1H), 2.58 (m, 1H), 2.48 (s, 3H), 2.42 (s, 3H), 2.2 (m, 1H), 2.02 (t, 1H), 1.71 (t, 2H), 0.837 s (9H). Separation by chiral HPLC provided diastereomers II-227a-b.

Example 379: Preparation of Compound Nos. II-229 and II-229a-b.

[1028] 4-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyric acid (175 mg, 0.482 mmol) was dissolved in DCM (5 mL), ammonium chloride (51 mg, 0.964 mmol), PYBOP (300 mg, 0.578 mmol) and triethylamine (0.69 mL, 4.82 mmol) were added and the reaction mixture was stirred at RT for 4 h. The reaction progress was monitored by LC-MS. After completion of the reaction, the reaction mixture was concentrated and the crude product was purified by reverse phase chromatography to obtain 45 mg of 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyramide as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.6 (d, 2H), 7.8 (d, 2H), 7.25 (s, 1H), 7.15 (d, 1H), 6.9 (d, 1H), 4.63 (t, 1H), 4.5 (m, 1H), 4.4 (m, 1H), 4.3 (dd, 1H), 4.0 (m, 1H), 3.85 (m, 1H), 3.6 (m, 1H), 3.2 (m, 1H), 3.1 (s, 3H), 3.0 (m, 1H), 2.9 (m, 2H), 2.4 (d, 3H). Separation by chiral HPLC provides enantiomers II-229a-b.

Example 380: Preparation of Compound Nos. II-230 and II-230a-b.

[1029] 4-(2,8-Dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyric acid (130 mg, 0.358 mmol) was dissolved in DCM (5 mL), dimethyl amine hydrochloride (57 mg, 0.716 mmol), PYBOP (223 mg, 0.429 mmol) and triethylamine (0.51 mL, 3.58 mmol) were added and the reaction mixture was stirred at RT for 4 h. The reaction progress was monitored by LC-MS. After completion of the reaction, the reaction mixture was concentrated and the crude product was purified by reverse phase chromatography to obtain 77 mg of 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-N,N-dimethyl-3-pyridin-4-yl-butyramide as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.56 (d, 2H), 7.28 (d, 2H), 7.19 (s, 1H), 7.17 (d, 1H), 6.94 (d, 1H), 4.63 (dd, 1H), 4.54 (dd, 1H), 4.39 (d, 1H), 4.37 (t, 1H), 4.0 (m, 1H), 3.8 (m, 1H), 3.6 (m, 1H), 3.45 (m, 1H), 3.3 (m, 1H), 3.1 (s, 6H), 3.0 (d, 3H), 2.9 (m, 2H), 2.8 (d, 3H). Separation by chiral HPLC provides enantiomers II-230a-b.

Example 381: Preparation of Compound Nos. II-231 and II-231a-b.

[1030] Methanesulfonic acid4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyl ester (200 mg, 0.468 mmol) in 10 mL of aqueous ammonia was heated at 100 °C for 1 h. The progress of reaction was monitored by TLC. After consumption of starting material, the reaction mixture was dried and the crude product was purified by reverse phase chromatography to obtain 33 mg of 4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butylamine as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.5 (d, 2H), 7.5 (m, 2H), 7.25 (d, 1H), 7.24 (s, 1H), 7.05 (t, 1H), 4.6 (d, 1H), 4.5 (d, 1H), 4.3 (m, 1H), 4.23 (t,

1H), 3.8 (m, 1H), 3.5 (m, 1H), 3.08 (d, 3H), 2.8 (m, 2H), 2.7 (m, 2H), 2.4 (s, 3H), 2.25 (m, 1H), 2.2 (m, 1H). Separation by chiral HPLC provides enantiomers II-231a-b.

Example 382: Preparation of Compound Nos. II-232 and II-232a-b.

[1031] Methanesulfonic acid-4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyl ester (200 mg, 0.468 mmol) in 10 mL of 40 % aqueous dimethyl amine was heated at 100 °C for 1 h. The progress of reaction was monitored by TLC. After consumption of starting material, the reaction mixture was dried and the crude product was purified by reverse phase chromatography to obtain 170 mg of [4-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-3-pyridin-4-yl-butyl]-dimethyl-amine as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.57 b(s, 2H), 7.65 (dd, 2H), 7.23 (d, 1H), 7.21 (s, 1H), 6.99 (d, 1H),4.62 (m, 1H), 4.48 (m, 1H), 4.42 (m, 1H), 4.26 (t, 1H), 3.81 (m, 1H), 3.55 (m, 2H), 3.35 (m, 1H), 3.1 (m, 1H), 3.0 (s, 3H), 2.9 (m, 2H), 2.83 (s, 6H), 2.4 (m, 1H), 2.38 (s, 3H),2.29 (m, 1H). Separation by chiral HPLC provides enantiomers II-232a-b.

Example 383: Preparation of Compound No. II-240.

[1032] Aza-methylcarboline (50 mg, 0.248 mmol), 4-vinylpyridine (49.6 mg, 0.472 mmol), tetrabutylammoniumbromide (79.8 mg, 0.248 mmol) were charged in 50% solution of sodium hydroxide (2 mL), and the reaction mixture was heated at 95 °C for 1.5 h. The reaction mixture was monitored with TLC and LCMS. The reaction mixture was extracted with EtOAc (2x25 mL). The combined organic layer was washed with water (2x20 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated and purified through reverse phase chromatography. Yield: 19.20 mg. ^{1}H NMR (CD_3OD, Free base) δ (ppm): 8.38 (d, 2H), 8.0 (s, 1H), 7.63 (s, 1H), 7.1 (d ,2H), 4.4 (t, 2H), 3.8 (s, 2H), 3.15 (t, 2H), 3.0 (t, 2H), 2.75 (t, 2H), 2.61 (s ,3H), 2.4 (s, 3H).

Example 384: Preparation of Compound Nos. II-241 and II-241a-b.

[1033] Aza-carboline (100 mg, 0.53 mmol) was dissolved in DMF (8 mL). Sodium hydride (38 mg, 1.59 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min. 4-(oxiran-2-yl)pyridine (254 mg, 2.12 mmol) in DMF (2 mL) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (4 mL) and solvent was evaporated to obtain the crude product, which was purified by reverse phase column chromatography to obtain 10 mg of product. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.41 (d, 2H), 8.19 (d, 1H), 7.73 (s, 1H), 7.36 (d, 2H), 7.06 (m, 1H),5.04 (t, 1H), 4.6 (m,

1H), 4.33 (m, 2H), 3.76 (dd, 2H), 2.9 (m, 4H), 2.5 (s, 3H). Separation by chiral HPLC provides enantiomers II-241a-b.

Example 385: Preparation of Compound No. II-242 and II-242a-b.

[1034] Aza-carboline (300 mg, 1.60 mmol) was dissolved in DMF (8 mL). Sodium hydride (153 mg, 6.4 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min., 4-(oxiran-2-yl)pyridine (769 mg, 6.41 mmol) in DMF (2 mL) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (4 mL) and solvent was evaporated to obtain the crude product, which was purified by reverse phase column chromatography to obtain 8 mg of product. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.5 (s, 1H), 8.43 (d, 2H), 8.01 (d, 1H), 7.4 (d, 1H), 7.38 (d, 2H),5.07 (t, 1H), 4.4 (m, 2H), 3.68 (s, 2H), 3.3 (s, 2H), 2.85 (m, 4H), 2.45 (s, 3H). Separation by chiral HPLC provides enantiomers II-242a-b.

Example 386: Preparation of Compound Nos. II-243 and II-243a-b.

[1035] 5-[2-(9-Methyl-1,2,3,4,5,10c-hexahydro-3a,6,7-triaza-cyclopenta[c]fluoren-6-yl)-ethyl]-pyridine-2-carboxylic acid (400 mg, 1.063 mmol) was dissolved in 15 mL DCM and cooled at 0 °C. Oxalyl chloride (669 mg, 5.315 mmol) and catalytic amount of DMF was added and the reaction mixture was stirred at RT for 1 h. The reaction was monitored by LCMS. The reaction mixture was concentrated and aqueous ammonia was added at 0 °C. The reaction mixture was warmed to RT and stirred for 1 h. The reaction mixture was concentrated to obtain the crude product that was purified by reverse phase chromatography to obtain 2.5 mg of 5-[2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6,7-triaza-cyclopenta[c]fluoren-6-yl)-ethyl]-pyridine-2-carboxylic acid amide as the TFA salt. ^{1}H NMR TFA:-CD_3OD : 8.2 (s, 2H), 7.95 (d, 1H), 7.8 (s, 1H), 7.6 (d ,1H), 5.0 (t ,1H), 4.6 (m, 2H), 3.62 (m, 1H), 3.5 (m, 2H), 3.3 (m, 3H), 2.8 (d, 1H), 2.63 (m, 2H), 2.4 (s, 3H), 2.2 (m, 2H), 2.1 (m, 1H). Separation by chiral HPLC provides enantiomers II-243a-b.

Example 387: Preparation of Compound Nos. II-244 and II-244a-b.

[1036] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a, 6, 7-triaza-cyclopenta[c]fluorene (250 mg, 1.10 mmol), 4-vinyl-pyridine (347 mg, 3.30 mmol), tetrabutyl ammonium bromide (355 mg, 1.10 mmol) were charged in a screw cap bottle and a 60 % solution of sodium hydroxide (5 mL) was added and heated to 100 °C for 12 h. The reaction was monitored by TLC and LCMS. The reaction mixture was diluted with 25 mL of water and extracted with EtOAc (2x50 mL). The

combined organic extracts were washed with water (25 mL), dried over anhydrous sodium sulfate and concentrated. The resultant crude product was purified by reverse phase chromatography to obtain 85 mg of 9-methyl-6- (2-pyridin-4-yl-ethyl) -2,3,4,5,6,10c-hexahydro-1H-3a,6,7-triaza-cyclopenta[c]fluorene as the formate salt (the product was a racemate which was purified by chiral prep HPLC to obtain product II-244a & product II-244b as the freebase). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.45 (d, 2H), 8.17 (s, 1H), 7.56 (s, 1H), 6.91 (d, 2H), 4.5 (m, 1H),4.42 (t, 1H), 4.35 (m, 1H), 3.26 (m, 2H), 3.16 (m, 5H), 2.81 (m, 1H), 2.45 (m, 1H), 2.41 (s, 3H), 2.1 (m, 2H), 1.9 (m, 1H). Separation by chiral HPLC provided enantiomers II-244a-b.

Example 388: Preparation of Compound Nos. II-245 and II-245a-b.

[1037] A suspension of azabicyclic carboline (0.2 g, 0.8 mmol), vinylpyrazine (0.375 g, 3.5 mmol), and tetrabutylammoniumbromide (0.855 g, 2.6 mmol) in 50 % NaOH solution (2 mL) was heated at 100 °C for overnight. The reaction mixture diluted with EtOAc (50 mL), organic layer washed with water (20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum to obtain the crude product that was purified by reverse phase HPLC to obtain 2.4 mg of desired compound. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.48 (s, 1H), 8.39 (s, 1H), 8.1 (s, 1H), 8.06 (s, 1H), 7.7 (s, 1H),5.1 (m, 1H), 4.64 (t, 2H), 3.7 (m, 4H), 3.03 (t, 2H), 2.7 (m, 2H), 2.45 (s, 3H), 2.15 (m, 4H). Separation by chiral HPLC provides enantiomers II-245a-b.

Example 389: Preparation of Compound No. II-246.

[1038] To a solution of 7,10-dichloro-1,2,3,4,5,6-hexahydro-3-methylazepino[4,5-b]indole (200 mg, 0.746 mmol) in DMF (2 mL), sodium hydride (90 mg, 2.25 mmol) was added. After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl) ethyl 4-methylbenzenesulfonate (543 mg, 1.86 mmol) was added to the reaction mixture and the reaction mixture was stirred at the same temperature for 40 min. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to obtain the residue that was purified by reverse phase HPLC to obtain 7,10-dichloro-1,2,3,4,5,6-hexahydro-3-methyl-6-(2-(6-methylpyridin-3-yl)ethyl)azepino [4,5-b]indole. ^{1}H NMR TFA:-CD_3OD : 8.4 (s, 1H),8.1 (d, 1H), 7.75 (d, 1H), 7.0 (q, 2H), 4.8 (m, 1H), 4.0 (m, 1H), 3.8 (m, 2H), 3.4 (m, 3H), 3.3 (m, 2H),3.2 (t, 3H),3.0 (s, 3H), 2.7 (s, 3H).

Example 390: Preparation of Compound No. II-247.

[1039] To a solution of 9-bromo-6-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (500 mg, 1.67 mmol) in DMF (5 mL), sodium hydride (200 mg, 5.0 mmol) was added. After

stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl) ethyl 4-methylbenzenesulfonate (1.2 g, 4.2 mmol) was added to the reaction mixture and stirred at the same temperature for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase HPLC to obtain the 9-bromo-6-chloro-2,3,4,5-tetrahydro-2-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.39 (s, 1H), 8.12 (d, 1H), 7.66 (d, 1H), 7.26 (d, 1H), 7.1 (d, 1H),4.67 (m, 4H), 3.7 (m, 2H), 3.27 (t, 2H), 3.18 (m, 2H), 3.15 (s, 3H), 2.69 (s, 3H).

Example 391: Preparation of Compound No. II-248.

[1040] To a solution of 9-chloro-6-fluoro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (500 mg, 2.1 mmol) in DMF (5 mL), sodium hydride (252 mg, 6.3 mmol) was added. After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (1.5 g, 5.25 mmol) was added to the reaction mixture and stirred at the same temperature for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase HPLC to obtain the 9-chloro-6-fluoro-2,3,4,5-tetrahydro-2-methyl-5-(2-(6-methylpyridin-3-yl)ethyl)-1H-pyrido[4,3-b]indole. ^{1}H NMR (CD_3OD, TFA) δ (ppm): 8.37 (s, 1H), 8.12 (d, 1H), 7.73 (d, 1H), 7.02 (dd, 1H), 6.86 (t, 1H), 5.1 (m, 1H), 4.57 (t, 2H), 4.56 (m, 1H), 3.85 (m, 1H), 3.6 (m, 1H), 3.27 (m, 3H), 3.2 m (2,H), 3.1 (s, 3H), 2.69 (s, 3H).

Example 392: Preparation of Compound No. II-249.

[1041] To a solution of 5,8-dichloro-2,3,4,9-tetrahydro-2-methyl-1H-pyrido[3,4-b]indole (200 mg, 0.78 mmol) in DMF (2 mL), sodium hydride (94 mg, 2.36 mmol) was added. After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (572 mg, 1.96 mmol) was added to the reaction mixture and stirred at the same temperature for 40 min. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to get the residue that was purified by reverse phase HPLC to obtain the 5,8-dichloro-2,3,4,9-tetrahydro-2-methyl-9-(2-(6-methylpyridin-3-yl)ethyl)-1H-pyrido[3,4-b]indole. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.43 (s, 1H), 8.18 (d, 1H), 7.74

(d, 1H), 7.09 (d, 1H), 7.04 (d, 1H), 4.79 (t, 2H),4.65 b(s, 1H), 3.62 b(s, 1H), 3.5 (m, 2H), 3.35 (m, 2H), 3.25 (t, 2H), 3.16 (s, 3H), 2.75 (s, 3H).

Example 393: Preparation of Compound No. II-250.

[1042] To a solution of 6,9-difluoro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (550 mg, 2.42 mmol) in DMF (3.5 mL) was added sodium hydride (300 mg, 7.4 mmol). After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (1.8 g, 6.1 mmol) was added to the reaction mixture, which was stirred at the same temperature for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with 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 (540 mg, TFA salt). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.35 (s, 1H), 8.13 (d, 1H), 7.73 (d, 1H), 6.7 (m, 2H), 4.8 (m, 1H), 4.57 (t, 2H),4.5 (m, 1H), 3.9 (m, 1H), 3.6 (m, 1H), 3.35 (m, 2H), 3.19 (m, 2H), 3.13 (s, 3H), 2.69 (s, 3H).

Example 394: Preparation of Compound No. II-251.

[1043] To a solution of 6,9-dibromo-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (800 mg, 2.32 mmol) in DMF (5 mL) was added sodium hydride (0.279 g, 6.9 mmol). After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (1.7 g, 5.8 mmol) was added to the reaction mixture, which was stirred at the same temperature for 1 h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was quenched with 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 (460 mg, TFA salt). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.46 (s, 1H), 8.18 (d, 1H), 7.72 (d, 1H), 7.28 (d, 1H), 7.18 (d, 1H), 5.2 (m, 2H),4.6 (m, 2H), 3.9 (m, 1H), 3.6 (m, 1H), 3.2 (m, 4H), 3.15 (s, 3H), 2.71 (s, 3H).

Example 395: Preparation of Compound No. II-252.

[1044] To a solution of 6-bromo-9-chloro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (500 mg, 1.67 mmol) in DMF (4 mL) was added sodium hydride (120 mg, 5.0 mmol). After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (1.2 g, 4.19 mmol) was added to the reaction mixture, which was stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with 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 (279 mg, TFA salt). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.43 (s, 1H), 8.14 (d, 1H), 7.7 (d, 1H), 7.35 (d, 1H), 7.03 (d, 1H),5.0 (m, 2H), 4.6 (m, 2H), 3.8 (m, 1H), 3.6 (m, 1H), 3.27 (t, 2H), 3.22 (t, 2H), 3.14 (s, 3H), 2.7 (s, 3H).

Example 396: Preparation of Compound No. II-253.

[1045] To a solution of 6-chloro-9-fluoro-2,3,4,5-tetrahydro-2-methyl-1H-pyrido[4,3-b]indole (500 mg, 2.1 mmol) in DMF (5 mL) was added sodium hydride (252 mg, 6.3 mmol). After stirring at 60 °C for 30 min., 2-(6-methylpyridin-3-yl)ethyl 4-methylbenzenesulfonate (1.5 g, 5.25 mmol) was added to the reaction mixture, which was stirred at the same temperature for 1 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with 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 (463 mg, TFA salt). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.42 (s, 1H), 8.15 (d, 1H), 7.7 (d, 1H), 7.1 (dd, 1H), 6.8 (t, 1H),4.8 (m, 2H), 4.5 (m, 2H), 3.8 (m, 1H), 3.6 (m, 1H), 3.3 (t, 2H), 3.2 (t, 2H), 3.1 (s, 3H), 2.7 (s, 3H).

Example 397: Preparation of Compound Nos. II-255 and II-255a-b.

[1046] 3-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-hydroxy-2-(pyridin-4-yl)propanenitrile.diHCl salt (500 mg,1.19 mmol) was dissolved in 500 mL Ethanol. The solution was passed through H-Cube as condition 70 mbar at 70 °C (Ra/Ni as catalyst). The product formation observed by LCMS. The solvent was concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography to obtain 1-amino-3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propan-2-ol (31 mg) as the TFA salt. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.61 (d, 2H), 7.42 (d, 2H), 7.23 (d, 1H), 7.18 (s, 1H), 6.95 (d, 1H), 4.17 (dd, 2H), 3.68 (q, 2H), 3.2 (d, 1H), 3.1 (m, 1H), 2.76 (m, 3H), 2.63 (m, 1H), 2.55 (s, 3H), 2.43 (s, 3H). Separation by chiral HPLC provided enantiomers II-255a-b.

Example 398: Preparation of Compound Nos. II-256 and II-256a-b.

[1047] A solution of alcohol (2 g, 6.2 mmol) in THF (150 mL) was cooled at -78 °C, NaH (0.3 g, 12.4 mmol, 60% dispersion in mineral oil) was added and the reaction mixture was stirred at the same temperature for 30 min. Methyl acrylate (2.1 g, 31.1 mmol) was added slowly and the reaction mixture was stirred at -78 °C for 1 h and at RT for further 2 h. The reaction mixture was quenched with water (60 mL) and extracted with EtOAc (2x60 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Sodium sulfate. Removal of solvent

under reduced pressure gave crude product that was purified by column chromatography using neutral alumina and 1-2% MeOH-DCM system as eluent to give 0.8 g pure desired ester. To a solution of ester (0.2 g, 0.49 mmol) in MeOH (5 mL) was added 1 N LiOH (1 mL) at RT and the reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated to dryness under reduce pressure to give crude product which was purified by reverse phase preparative HPLC to give 108 mg pure product. ^{1}H NMR (CD_3OD, TFA) δ (ppm): 8.66 (d, 2H), 7.8 (d, 2H), 7.23 (s, 1H), 7.1 (d, 1H), 7.0 & 6.9 (d, 1H), 4.8 (m, 1H), 4.7 (m, 1H), 4.4 (m, 3H), 3.85 (m, 1H), 3.6 (m, 2H), 3.45 (m, 1H), 3.24 (m, 4H), 3.12 (s, 3H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers II-256a-b.

Example 399: Preparation of Compound Nos. II-257 and II-257a-b.

[1048] A mixture of 2,8-dimethyl-5-((2-(pyridin-3-yl)oxiran-2-yl)methyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.3 mmol) in 20% aq. TFA (2 mL) was stirred at RT overnight. The reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with EtOAc (2x30 mL) to remove the impurities. The aqueous layer was lyophilized to obtain the crude product that was purified by reverse phase HPLC to obtain 5 mg of 3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propane-1,2-diol as the TFA salt. ^{1}H NMR (CD_3OD, TFA) δ (ppm): 8.75 (s, 1H), 8.6 (m, 2H), 7.83 (m, 1H), 7.25 (s, 1H), 6.9 (d, 1H), 6.8 (d, 1H), 4.62 (d, 1H), 4.45 (dd, 2H), 4.3 (t, 1H), 4.05 (t, 1H), 3.8 (m, 2H), 3.5 (m, 3H), 3.1 (s, 3H), 2.3 (s, 3H). Separation by chiral HPLC provides enantiomers II-257a-b.

Example 400: Preparation of Compound Nos. II-258 and II-258a-b.

[1049] 3-(2,8-Dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propanoic acid (20 mg, 0.057 mmol) was charged in pyridine (0.5 mL) under nitrogen. DMAP (9.73 mg, 0.08 mmol) and $(Boc)_2O$ (14 mg, 0.069 mmol) were added into it. The reaction mixture was stirred at 60 °C for 30 min and allowed to come to RT. Tert-butanol (84.81 mg, 1.146 mmol) was added dropwise and the reaction mixture was stirred at RT for 1 h. 1M citric acid (5 mL) was added and reaction mixture was then washed with DCM (5 mL). The organic layer was concentrated and the crude product was purified by reverse phase HPLC to obtain tert-butyl 3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propanoate (15.4 mg, TFA salt). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.49 (d, 2H), 7.53 (d, 2H), 7.3 (t, 1H), 7.24 (s, 1H), 7.05 (m, 1H) , 5.5 (m, 1H), 4.6 (t, 1H), 4.24 (t, 1H), 3.8 (m, 3H),

3.3 (m, 2H), 3.13 (d, 2H), 2.89 (m, 1H), 2.77 (m, 1H), 2.4 (s, 3H), 1.39 s (9H). Separation by chiral HPLC provides enantiomers II-258a-b.

Example 401: Preparation of Compound Nos. II-259 and II-259a-b.

[1050] 2,8-Dimethyl-5-((2-(pyridin-4-yl)oxiran-2-yl)methyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.3 mmol) was added to 2M dimethyl amine solution in THF (5 mL) and the reaction mixture was allowed to stir at 60 °C overnight. The progress of reaction was monitored by LCMS. The solvent was removed under reduced pressure to obtain a crude oily product that was purified by reverse phase HPLC to afford 5 mg of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-(dimethylamino)-2-(pyridin-4-yl)propan-2-ol as the TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.58 (d, 2H), 7.81 (m, 2H), 7.18 (d, 1H), 7.05 (m, 1H), 6.91 (m, 1H) , 4.63 (m, 1H), 4.51 (s, 2H), 4.27 (d, 1H), 4.18 (m, 2H), 3.58 (m, 2H), 3.48 (m, 1H), 3.1 (s, 6H), 2.89 (m, 1H), 2.8 (s, 3H), 2.35 (s, 3H). Separation by chiral HPLC provides enantiomers II-259a-b.

Example 402: Preparation of Compound Nos. II-260 and II-260a-b.

[1051] Methanesulfonic acid 2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethylester (1.0 g, 3.5 mmol) was dissolved in 70% cyclopropylamine in water (50 mL) and heated at 90 °C for 18 h. The reaction mixture was concentrated to obtain the crude product that was purified by reverse phase chromatography to obtain 300 mg of cyclopropyl-[2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-1-pyridin-4-yl-ethyl]-amine. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.52 (d, 2H), 7.18 (s, 1H), 7.14 (d, 1H), 7.13 (d, 2H), 6.99 (d, 1H) , 4.22 (m, 2H), 3.98 (dd, 1H), 3.76 (d, 1H), 3.70 (d, 1H), 2.85 (m, 1H), 2.74 (m, 2H), 2.55 (s, 3H), 2.44 (s, 3H), 2.36 (m, 2H), 0.33 (m, 2H), 0.23 (m, 2H). Separation by chiral HPLC provided enantiomers II-260a-b.

Example 403: Preparation of Compound Nos. II-261 and II-261a-d.

[1052] Methanesulfonicacid2-(9-methyl-1,2,3,4,5,10c-hexahydro-3a,6-diaza-cyclopenta[c] fluoren-6-yl)-1-pyrazin-2-yl-ethyl ester (280 mg, 0.65 mmol) was dissolved in 3 mL DMF, sodium azide (64 mg, 0.98 mmol) was added and heated at 90 °C for 1 h. The reaction mixture was monitored by LCMS. After consumption of starting material, the reaction mixture was cooled to RT, diluted with water (3 mL) and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 60 mg of 6-(2-azido-2-pyrazin-2-yl-ethyl)-9-methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6-diaza-cyclopenta[c]fluorene. ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.65 (d, 1H), 8.60 (s, 1H), 8.50 (s, 1H), 7.8 (d, 1H), 7.22 (d, 1H),7.09 (t, 1H),

5.1 (m, 1H), 4.8 (m, 1H), 4.6 (dd, 1H), 4.3 (m, 1H), 3.45 (m, 3H), 2.97 (m, 2H), 2.84 (m, 2H), 2.6 (m, 1H), 2.45 (d, 3H), 2.2 (m, 1H), 1.9 m (1`H). Separation by chiral HPLC provided enantiomers II-261a-b.

Example 404: Preparation of Compound Nos. II-262 and II-262a-b.

[1053] 3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propanenitrile (80 mg, 0.24 mmol) in conc. HCl (2 mL) was heated at 80 °C for 1 h. The reaction mixture was concentrated to obtain a residue that was purified by reverse phase chromatography to obtain 5.3 mg of 3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-4-yl)propanoic acid as the free base. ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.1 (d, 2H), 7.3 (d, 1H), 7.13 (s, 1H), 6.98 (d, 1H), 6.8 (d, 2H), 4.09 (s, 2H), 3.6 (dd, 1H), 3.4 (m, 3H), 2.9 (m, 2H), 2.8 (s, 3H), 2.39 (s, 3H), 2.32 (m, 1H). Chiral HPLC provides enantiomers II-262a and II-262b.

Example 405: Preparation of Compound Nos. II-263 and II-263a-b.

[1054] To a solution of tert-butanol (4 mL) containing crushed KOH (20.36 mg, 0.363 mmol) was added 3-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-2-pyridine-4-yl-propionitrile (40 mg, 0.121 mmol) and the resultant reaction mixture was stirred at 80 °C for 90 min. The progress of the reaction was monitored by TLC and LCMS. After completion of the reaction, the tert-butanol was evaporated under vacuum and resultant reaction mixture was purified by preparative HPLC to obtain the desired compound (15 mg). ^{1}H NMR ($CDCl_3$, freebase): 8.32 (d, 2H), 7.25 (d, 2H), 7.15 (d, 1H), 7.01 (d, 1H),6.63 (d, 1H), 4.8 (d, 1H), 3.77 (m, 2H), 3.39 (t, 2H), 2.8 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.3 (m, 1H). Chiral HPLC provides enantiomers II-263a and II-263b.

Example 406: Preparation of Compound Nos. II-264 and II-264a-b.

[1055] 2,8-Dimethyl-5-((2-(pyridin-3-yl)oxiran-2-yl)methyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (100 mg, 0.3 mmol) was dissolved in MeOH (2 mL) and aq. ammonia (2 mL) and the reaction mixture was allowed to stir at RT for 24 h. The progress of reaction was monitored by LCMS. The volatiles were removed under reduced pressure to obtain a crude oily product that was purified by reverse phase HPLC to afford 7 mg of 1-amino-3-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol as TFA salt. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.65 (m, 2H), 8.43 (dd, 1H), 7.75 (m, 1H), 7.18 (d, 1H), 6.88 (m, 2H) , 4.67 (d, 1H), 4.55 (m, 2H), 4.29 (t, 1H), 3.90 (m, 2H), 3.69 (m, 1H), 3.5 (m, 2H), 3.1 (m, 1H), 3.11 (s, 3H), 2.34 (s, 3H). Separation by chiral HPLC provides enantiomers II-264a-b.

Example 407: Preparation of Compound Nos. II-265 and II-265a-b.

[1056] 2,8-Dimethyl-5-((2-(pyridin-3-yl)oxiran-2-yl)methyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (200 mg, 0.6 mmol) was added to 2M dimethylamine solution in THF (5 mL) and the reaction mixture was allowed to stir at 40 °C overnight. The progress of reaction was monitored by LCMS. The solvent was removed under reduced pressure to obtain a crude oily product that was purified by reverse phase HPLC to afford 50 mg of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-3-(dimethylamino)-2-(pyridin-3-yl)propan-2-ol as the TFA salt. ^{1}H NMR ($CDCl_3$, Free base) δ (ppm): 8.74 (s, 1H), 8.50 (d, 1H), 7.79 (d, 1H), 7.25 (dd, 1H), 7.16 (s, 1H) , 7.1 (d, 1H), 6.97 (d, 1H), 4.08 (m, 2H), 3.83 (dd, 2H), 2.98 (m, 4H), 2.74 (d, 2H), 2.70 (s, 3H), 2.42 (s, 3H), 1.98 (s, 6H). Separation by chiral HPLC provided enantiomers II-265a-b.

Example 408.

[1057] Compounds III-1, III-53 and III-223-224 were synthesized as described in PCT publication WO2009/055828. Compounds III-2-3 were synthesized as described in PCT publication WO2009/120720. Compounds III-4-9 were synthesized as described in PCT publication WO2009/120717. Compounds III-10-46, III-209-220 and III-320-352 were synthesized as described in PCT publication WO2010/051503. Compounds III-47-51 were synthesized as described in PCT publication WO2010/127177. Compounds III-52 and III-225-253 were synthesized as described in PCT publication WO2010/019417. Compounds III-54-58, III-353-355 and III-357 were synthesized as described in PCT publication WO2011/038163. Compounds III-59-61, III-356 and III-358-361 were synthesized as described in PCT publication WO2011/038161. Compounds III-62-98, III-187-197 and III-256-258 were synthesized as described in PCT publication WO2011/038162. Compounds III-99-138, III-198-208, III-221 and III-289-319 were synthesized as described in PCT publication WO2011/038164.

Example 409.

[1058] Compounds IV-2, IV-4-7 and IV-10 were synthesized as described in PCT publication WO2011/038161. Compounds IV-1, IV-3, IV-9, IV-11-92, IV-94-208 and IV-211-244 can be synthesized using similar conditions to those described in both Examples 410-412 below, and in PCT publication WO2011/038161.

Example 410: Preparation of Compound Nos. IV-8 and IV-8a-b.

[1059] To a solution of 10-methyl-1,2,3,4,5,6,7,11c-octahydro-4a,7,8-triaza-benzo[c]fluorene (150 mg, 0.622 mmol) in DMF (2 mL) were added sodium hydride (75 mg, 1.86 mmol) and a

solution of toluene-4-sulfonic acid 2-(6-methyl-pyridin-3-yl)-ethyl ester (544 mg, 1.86 mmol) in DMF (2 mL) at 0 °C. The reaction mixture was stirred at RT for 1h. The progress of reaction was monitored by TLC and LCMS. The reaction mixture was poured into ice-cold water and extracted with EtOAc (2x50 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 chromatography to yield compound 8 (140 mg). This product was further purified by chiral preparative HPLC to give compounds 8a and 8b. Compound 8a: ^{1}HNMR ($CDCl_3$, freebase) δ (ppm): 8.21 (s, 1H), 8.07 (s, 1H), 7.6 (s, 1H), 7.21 (d, 1H), 7.0 (d, 1H), 4.3 (m, 2H), 3.28 (d, 1H), 3.08 (m, 1H), 3.0 (m, 4H), 2.54 (m, 1H), 2.54 (s, 3H), 2.5 (m, 1H), 2.4 (m, 1H), 2.4 (s, 3H), 2.3 (d, 1H), 1.9 (m, 1H), 1.72 (m, 2H), 1.5 (q, 2H). Compound 8b: ^{1}HNMR ($CDCl_3$, freebase) δ (ppm): 8.21 (s, 1H), 8.07 (s, 1H), 7.6 (s, 1H), 7.21 (d, 1H), 7.0 (d, 1H), 4.3 (m, 2H), 3.28 (d, 1H), 3.08 (m, 1H), 3.0 (m, 4H), 2.54 (m, 1H), 2.54 (s, 3H), 2.5 (m, 1H), 2.4 (m, 1H), 2.4 (s, 3H), 2.3 (d, 1H), 1.9 (m, 1H), 1.72 (m, 2H), 1.5 (q, 2H).

Example 411: Preparation of Compound Nos. IV-209 and IV-209a-d.

[1060] 9-Methyl-2,3,4,5,6,10c-hexahydro-1H-3a,6,7-triaza-cyclopenta[c]fluorene (600 mg, 2.643 mmol) was dissolved in DMF (18 mL), and cooled to 0 °C. Potassium tert-butoxide (444 mg, 3.964 mmol) was added and stirred for 5 min. 4-Oxiranyl-pyridine (639 mg, 5.286 mmol) in DMF (3 mL) was added dropwise into the reaction mixture and the mixture was stirred at RT for 12 h. The reaction was monitored by TLC and LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (100 mL) and extracted with EtOAc (2x100 mL). The combined organic layer was washed with water (4x70 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product, which was purified by reverse phase chromatography to obtain 400 mg of 2-(9-Methyl-1,2,3,4,5,10c-hexahydro-3a,6,7-triaza-cyclopenta[c]fluoren-6-yl)-1-pyridin-4-yl-ethanol. ^{1}H NMR (CD_3OD, HCl salt) δ (ppm): 8.8 (d, 2H), 8.2 (d, 2H), 8.1 (s, 1H), 7.9 (s, 1H), 5.38 (m, 1H),5.09 (t, 1H), 4.68 (dd, 2H), 4.4 (m, 1H), 3.75 (m, 4H), 3.43 (m, 2H), 2.7 (m, 2H), 2.46 (s, 3H), 2.2 (m, 3H). Separation by chiral HPLC provided diastereomers IV-209a-d.

Example 412: Preparation of Compound Nos. IV-210 and IV-210a-d.

[1061] Chloroaza carboline (500 mg, 2.02 mmol) was dissolved in DMF (8 mL), sodium hydride (404 mg, 10.12 mmol) was added at 0 - 10°C and stirred at the same temperature for 15 min. 3-(2-Methyloxiran-2-yl)pyridine (546 g, 4.04 mmol) was added dropwise into the reaction mixture and the mixture was stirred at RT for 16 h. The reaction was monitored by TLC and

LCMS. After consumption of starting material, the reaction mixture was quenched with ice cold water (100 mL) and extract with EtOAc (200 mL). The organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the crude product, which was purified by crystallization using Diethyl ether to obtain 200 mg of product. ^{1}H NMR (CD_3OD, HCl salt): 8.8 (s, 1H), 8.6 (d, 2H), 7.88 (s, 2H), 7.84 (d, 1H), 4.99 (m, 2H), 4.4 (d, 1H), 3.78 (m, 2H),3.4 (m, 2H), 3.4 (m, 2H), 2.7(m, 1H), 2.2 (m, 3H), 1.83 (s, 3H). Separation by chiral HPLC provided diastereomers IV-210a-d.

Example 413.

[1062] Compound Nos. V-4 to V-13, V-16 to V-17 and V-19 to V-20 can be synthesized using similar conditions to those described in Examples 414-422 below.

Example 414: Preparation of Compound Nos. V-1 and V-1a-b.

[1063] To a solution of 2-(1,2,3,4-tetrahydro-2,8-dimethylpyrido[4,3-b]indol-5-yl)-1-(pyridin-4-yl)ethyl methanesulfonate (900 mg, 2.18 mmol) in DMF (10 mL) was added sodium azide (212.5 mg, 3.2 mmol) and the reaction mixture was stirred at 100 °C for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 5-(2-azido-2-(pyridin-4-yl)ethyl)-2,3,4,5-tetrahydro-2,8-dimethyl-1H-pyrido[4,3-b]indole (650 mg). The resulting racemate was purified and resolved by chiral preparative HPLC. ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.8 (d, 2H), 8.0 (d, 2H), 7.31 (d, 1H), 7.3 (s ,1H), 7.04 (d, 1H), 5.45 (m, 1H), 4.7 (d, 1H), 4.59 (t, 1H), 4.4 (m, 2H), 3.9 (d, 1H), 3.6 (m, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 3.1 (s, 3H), 2.4 (s, 3H).

Example 415: Preparation of Compound Nos. V-2 and V-2a-b.

[1064] To a solution of 2-(2,8-dimethyl-6-aza-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-1-(pyridin-4-yl)ethyl methanesulfonate (300 mg, 0.724 mmol) in DMF (4 mL) was added sodium azide (70.65 mg, 1.08 mmol) and the reaction mixture was stirred at 100 °C for 1 h. The progress of reaction was monitored by NMR. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was thoroughly washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 9-(2-azido-2-(pyridin-4-yl)ethyl)-3,6-dimethyl-6,7,8,9-tetrahydro-5H-pyrrolo[2,3-b:4,5-c']dipyridine (160 mg). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 8.6 (d, 2H), 8.07 (s, 1H), 7.55 (s, 1H), 7.27 (d ,2H), 5.23 (m 1H), 4.37 (dd,1H) , 4.19 (m, 1H), 3.62 (dd, 2H), 2.88 (m, 2H), 2.82 m, 2H), 2.56 (s, 3H), 2.42 (s, 3H). Separation by chiral HPLC provided enantiomers V-2a-b.

Example 416: Preparation of Compound Nos. V-3 and V-3a-b.

[1065] 5-(2-Chloro-2-(pyridin-3-yl)propyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (crude) (700 mg) was dissolved in DMF (4 mL). Sodium azide (975 mg, 15 mmol) was added and reaction mixture was stirred at 80 °C for 1h. The reaction mixture was diluted with water, basified with aqueous $NaHCO_3$ solution and was extracted with EtOAc (200 mL). The organic layer was washed with water (6x50 mL), dried over anhydrous sodium sulfate and evaporated in vacuo to obtain the crude product that was purified by reverse phase HPLC to obtain 1 mg of 5-(2-azido-2-(pyridin-3-yl)propyl)-2,8-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole as the TFA salt. ^1H NMR (CD_3OD, TFA salt) δ (ppm): 8.56 (m, 2H), 8.11 (dd, 1H), 7.6 (t, 1H), 7.2 (s ,1H), 6.85 (m, 2H), 4.67 (d, 1H) , 4.47 (d, 1H), 4.39 (s, 2H), 3.84 (m, 1H), 3.48 (m, 1H), 3.34 (m, 1H) , 3.12 (s, 3H), 3.12 (m, 1H), 2.36 (s, 3H), 2.03 (s, 3H). Separation by chiral HPLC provides enantiomers V-3a-b.

Example 417: Preparation of Compound Nos. V-14 and V-14a-b.

[1066] To a solution of 1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-ol (200 mg, 0.597 mmol) in DMF (5 mL) was added potassium carbonate (412 mg, 2.98 mmol). After stirring for 5 min at RT, ethyl bromoacetate (200 mg, 1.19 mmol) was added into the reaction mixture, which was stirred at RT for 2 h. The progress of reaction was monitored by LCMS. The reaction was quenched with water and extracted with EtOAc. The aqueous layer was concentrated and residue was purified by reverse HPLC to yield 2-((1-(2,8-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-2-(pyridin-3-yl)propan-2-yl)oxy)acetic acid (80 mg). The resulting racemate was purified and resolved by chiral preparative HPLC. ^1H NMR (CD_3OD, freebase) δ (ppm): 8.5 (d, 1H), 8.36 (s, 1H), 7.8 (dd, 1H), 7.31 (m ,1H), 7.19 (s, 1H), 7.1 (d, 1H) , 6.88 (d, 1H), 4.86 (m, 1H), 4.58 (s, 1H) , 4.32 (d, 1H), 4.25 (m, 2H), 3.94 (m, 2H), 3.8 (m, 1H), 3.35 (s, 3H), 3.2 (m ,1H), 3.0 (m, 1H), 2.36 (s,3H), 1.69 (s, 3H).

Example 418: Preparation of Compound Nos. V-15 and V-15a-d.

[1067] Ethyl 2-(2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-(pyridin-4-yl)ethoxy)acetate (170 mg, 0.392 mmol) in 2N LiOH solution (5 mL) was stirred at RT for 3 h. The desired product was detected by LCMS. The reaction mixture was concentrated and the crude product was purified by reverse phase chromatography to yield 2-(2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-(pyridin-4-yl)ethoxy)acetic acid (13 mg). ^1H NMR (CD_3OD, freebase) δ (ppm): 8.45 (d, 2H), 7.42 (d, 2H), 7.22 (s, 1H), 7.2 (d ,1H),

7.0 (d, 1H), 5.09 (m, 2H) , 4.6 (s, 1H), 4.45 (dd, 1H), 4.29 (m, 2H), 4.19 (m, 1H) , 3.96 (m, 2H), 3.81 (d, 1H), 3.7 (t, 1H), 3.2 (d, 1H), 3.1 (m, 1H), 3.82 (m ,1H), 2.4 (s, 3H), 2.34 (m,1H), 2.09 (m, 1H). Separation by chiral HPLC provides diastereomers V-15a-d.

Example 419: Preparation of Compound Nos. V-18 and V-18a-d.

[1068] 2-(10-Methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)- yl)-1-(pyridin-4-yl)ethanol (350 mg, 1 mmol), succinic acid (118 mg, 1 mmol) and dimethylaminopyridine (122 mg, 1 mmol) in DCM (20 mL) were stirred at RT. Dicyclohexylcarbodiimide (206 mg, 1.6 mmol) in DCM (20 mL) was added dropwise and the reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated to obtain the crude product that was purified by reverse phase HPLC to yield 4-(2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)-1-(pyridin-4-yl)ethoxy)-4-oxobutanoic acid (96 mg). ^{1}H NMR (CD_3OD, freebase) δ (ppm): 8.46 (d, 2H), 7.33 (d, 2H), 7.27 (d, 1H), 7.23 (s, 1H), 7.01 (d, 1H), 6.07 (t, 1H), 4.8 (t, 2H), 4.5 (m, 2H), 3.55 (m, 2H), 3.45 (m, 1H), 3.0 (q, 2H), 2.7 (m, 1H), 2.54 (m, 2H), 2.39 (s, 3H), 2.37 (m, 1H), 2.1 (m, 4H). Separation by chiral HPLC provided diastereomers V-18a-d.

Example 420: Preparation of Compound Nos. V-21 and V-21a-b.

[1069] To a solution of the mesylate compound (2 g, 4.46 mmol) in DMF (25 mL) was added sodium azide (435 mg, 6.69 mmol) and reaction mixture was stirred at 100 °C for 1 h. The progress of reaction was monitored by NMR. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2x150 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield 6-(2-azido-2-(2,4-difluorophenyl)ethyl)-3,9-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (1.6 g). ^{1}H NMR ($CDCl_3$, freebase) δ (ppm): 7.4 (q, 1H), 7.2 (s, 1H), 7.18 (d, 1H),7.01 (d, 1H), 6.99 (d, 1H), 6.92 (d, 1H), 5.13 (dd, 1H), 4.26 (dd, 1H), 4.2 (dd, 1H), 2.9 (d, 1H), 2.93 (m, 2H), 2.8 (m, 1H), 2.83 m (4,H), 2.5 (s, 3H), 2.46 (s, 3H). Separation by chiral HPLC provides enantiomers V-21a-b.

Example 421: Preparation of Compound Nos. V-22 and V-22a-b.

[1070] Methanesulfonic acid-1-(6-carbamoyl-pyridin-3-yl)-2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethyl ester (300 mg, 0.678 mmol) was dissolved in 5 mL DMF, and sodium azide (88 mg, 1.357 mmol) was added, and the mixture heated at 100 °C for 1 h. The reaction mixture was monitored by LCMS. After completion of reaction, the reaction mixture was cooled to RT and diluted with water (15 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was washed with water (4x40 mL), dried over anhydrous sodium

sulfate and concentrated to obtain the crude product that was purified by reverse phase chromatography to yield 5-[1-azido-2-(2,8-dimethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-ethyl]-pyridine-2-carboxylic acid amide (135 mg). ^{1}H NMR (CD_3OD, TFA salt) δ (ppm): 8.6 (dd, 1H), 8.1 (t, 1H), 7.9 (t, 1H), 7.33 (dd, 1H), 7.26 (s, 1H), 7.06 (t, 1H), 5.3 (t, 1H), 4.7 (dd, 1H), 4.42 (dd, 1H), 4.4 (dd, 2H), 4.3 (m, 1H), 3.8 (m, 1H),3.6 (m, 1H), 3.34 (dd, 1H), 3.1 (d, 3H), 2.4 (s, 3H). Separation by chiral HPLC provides enantiomers V-22a-b.

Example 422: Preparation of Compound Nos. V-23 and V-23a-d.

[1071] A solution of 1-(4-fluorophenyl)-2-(10-methyl-2,3,5,6-tetrahydro-1H-indolizino[7,8-b]indol-7(11cH)-yl)ethyl methanesulfonate (400 mg, 0.9 mmol) and sodium azide (88 mg, 1.3 mmol) in dimethylformamide (10 mL) was stirred at RT for 18 h. The reaction mixture was diluted with ice cooled water (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with water (5x50 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product that was purified by reverse phase HPLC to yield 7-(2-azido-2-(4-fluorophenyl)ethyl)-10-methyl-2,3,5,6,7,11c-hexahydro-1H-indolizino[7,8-b]indole (25 mg). ^{1}H NMR (CD_3OD, freebase) δ (ppm): 7.32 (m, 3H), 7.26 (s, 1H), 7.13 (m, 2H), 7.09 (d, 1H), 5.09 (t, 1H), 4.8 (m, 1H), 4.32 (m, 2H), 3.44 (m, 2H), 3.3 (m, 1H), 3.1 (m, 1H), 3.0 (d, 1H), 2.8 (m, 1H), 2.6 (m, 1H), 2.4 (s, 3H), 2.18 (m, 2H), 2.0 (m, 1H). Separation by chiral HPLC provides diastereomers V-23a-d.

Example 423.

[1072] Compounds II-266 to II--269 and II-271 to II-299 can be synthesized in an analogous fashion to other compounds described herein and by reference to the PCT publications listed in the General Methods above.

Example B1: Determination of the ability of compounds of the invention to bind an adrenergic receptor.

Adrenergic α_{2B}

[1073] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{2B} receptor expressed in Chinese hamster ovary (CHO) K1 cells (Uhlen, S. et al, Eur. J. Pharmacol. 343(1):93, 1998) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 12.5 mM MgCl2, 1 mM EDTA, 0.2% BSA) was used. Compounds of the invention were incubated with 2.5 nM [3H]Rauwolscine for 60 min at 25 °C. Non-specific binding was estimated in the presence of 10 μM Prazosin. Receptor proteins were filtered and

washed, the filters were then counted to determine [3H]Rauwolscine specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Compounds of the invention were tested in this biochemical assay and percent inhibition of specific binding was determined. Biochemical assay results are presented as the percent inhibition of specific binding in Table B1.

Adrenergic α_{2A}

[1074] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{2A} receptor expressed in insect Sf9 cells (Uhlen, S. et al, J. Pharmacol. Exp. Ther. 271:1558, 1994) in a modified Tris-HCl buffer (50 mM Tris-HCl, pH 7.4, 12.5 mM $MgCl_2$, 2 mM EDTA) was used. Compounds of invention were incubated with 1 nM [^{3}H]MK-912 for 60 min at 25 °C. MK912 is (2S-trans)-1,3,4,5',6,6',7,12b-octahydro-1',3'-dimethyl-spiro[2H-benzofuro[2,3-a]quinolizine-2,4'(1'H)-pyrimidin]-2'(3'H)-one hydrochloride. Non-specific binding was estimated in the presence of 10 μM WB-4101 (2-(2,6-Dimethoxyphenoxyethyl)aminomethyl-1,4-benzodioxane hydrochloride). Receptor proteins were filtered and washed, the filters were then counted to determine [^{3}H]MK-912 specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Compounds of the invention were tested in this biochemical assay and percent inhibition of specific binding was determined. Biochemical assay results are presented as the percent inhibition of specific binding in Table B1.

Adrenergic α_{1B}

[1075] To evaluate in radioligand binding assays the activity of compounds of the invention, rat adrenergic α_{1B} receptor obtained from Wistar Rat liver (Garcia-S'ainz, J. et al, Biochem. Biophys. Res. Commun. 186:760, 1992; Michel, A. et al, Br. J. Pharmacol. 98:883, 1989) in a modified Tris-HCl buffer (50 mM Tris-HCl buffer, pH 7.4, 0.5 mM EDTA) was used. Compounds of the invention were incubated with 0.25 nM [^{3}H]Prazosin for 60 min at 25 °C. Non-specific binding was estimated in the presence of 10 μM phentolamine. Receptor proteins were filtered and washed, the filters were then counted to determine [^{3}H]Prazosin specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Compounds of the invention were tested in this biochemical assay and percent inhibition of specific binding

was determined. Biochemical assay results are presented as the percent inhibition of specific binding in Table B1.

Adrenergic α_{1D}

[1076] To evaluate in radioligand binding assays the activity of compounds of the invention, human recombinant adrenergic α_{1D} receptor expressed in human embryonic kidney (HEK-293) cells (Kenny, B. et al, Br. J. Pharmacol. 115(6):981, 1995) in a 50 mM Tris-HCl buffer, pH 7.4, was used. Compounds were incubated with 0.6 nM [3H]Prazosin for 60 min at 25 °C. Non-specific binding was estimated in the presence of 10 μM phentolamine. Receptor proteins were filtered and washed, the filters were then counted to determine [3H]Prazosin specifically bound. Compounds were screened at 1 μM or lower, using 1% DMSO as vehicle. Biochemical assay results are presented as the percent inhibition of specific binding in Table B1.

Table B1: Percentage inhibition of ligand binding to aminergic G protein-coupled receptors by compounds of the invention:

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
1	32	16	6	74	-	-	-	-
2	27,28	13	4,19	95	-	-	-	75
3	51,54	12	12,37	100,103	24	-	4	99
3a	12,44	-	16	62	18	-	-	26,30
3b	50,55, 57,61	18	21,22, 23,25	-	27,32, 34	-	1	100,101, 102,112
4	51,60	12	12,41	101	-	-	-	106
4a	52,57	-	19,24	104	25	-	5	99,103
4b	58	-	7	-	-	-	-	46
5	14,21	4	13	96	-	-	-	100
5a	18	-	0	57	-	-	-	29,38
5b	23,30, 33	1	18,21, 22	82,100, 107	10,11, 15	-	4,6,15	81,86, 90,100
6	8	-	2	-	-	-	-	62
7	35	-	16	-	-	-	-	59
7a	28	-	1	-	-	-	-	59
7b	37	-	25	-	-	-	-	74
8	58	-	23	-	-	-	-	61
8a	39	-	15	-	-	-	-	22
8b	61,63	-	8,12	78	24	-	-	49
9	5	-	-4	-	-	-	-	36
9a	11	-	4	-	-	-	-	23

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
9b	10	-	10	-	-	-	-	50
10a	30	-	8	-	-	-	-	34
10b	28	-	15	-	-	-	-	91
11a	16	-	-6	-	-	-	-	28
11b	18	-	13	-	-	-	-	64
12a	23	-	3	-	-	-	-	24
12b	8	-	3	-	-	-	-	21
13	83	-	18	-	-	-	-	92
13a	75	-	-2	-	-	-	-	37
13b	91	-	-2,21	-	68	-	-	100,102
14a	43,44	-	8,26	-	17	-	-	97,98
14b	25	-	-6	-	-	-	-	14
15	93	-	19	-	-	-	-	93
15a	81	-	6	-	-	-	-	65
15b	89,93	-	21,24	-	73	-	-	103
16a	47	-	9	-	-	-	-	33
16b	16	-	2	-	-	-	-	2
17	18	-	19	-	-	-	-	37
17a	13	-	19	-	-	-	-	32
17b	16	-	9	-	-	-	-	20
18a	55	-	50	-	-	-	-	54
18b	87	-	32	-	-	-	-	61
19a	75	-	21	-	-	-	-	75
19b	62	-	9	-	-	-	-	27
20a	67	-	29	-	-	-	-	28
20b	94	-	28	-	-	-	-	36
21a	5	-	-1	-	-	-	-	-2
21b	-2	-	-3	-	-	-	-	1
22a	19	-	16	-	-	-	-	22
22b	9	-	0	-	-	-	-	30
23a	-20	-	4	-	-	-	-	6
23b	4	-	1	-	-	-	-	-3
24a	8	-	8	-	-	-	-	63
24b	8	-	15	-	-	-	-	29
25a	4	-	15	-	-	-	-	54
25b	12	-	18	-	-	-	-	75
26a	52,61	-	23,33	-	32	-	14	101,107
26b	15	-	12	100	-	-	-	75,88
26c	1	-	19	-	-	-	-	1,7
26d	-2	-	0	-	-	-	-	6,11

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
27a	59,64	-	2,11	94	34	-	-	76,83
27b	6,16	-	0,18	48	-	-	-	30,36
28a	41	-	28	-	-	-	-	96
28b	20	-	24	-	-	-	-	37
29	24	1	10	100	-	-	-	-
29a	32,38	-	35,39	-	19	-	16	98,100
29b	14	-	10	-	-	-	-	46
30	86	49	63	91	-	-	-	-
30a	57	-	19	-	-	-	-	79
30b	89,91	-	74,75	-	68	-	42	100,102
31a	25,28	-	19,27	-	16	-	11	93,97
31b	3	-	14	-	-	-	-	36
32	12	7	28	86	-	-	-	-
33a	-2	23	26	-3	-	-	-	-
33b	0	14	-7	2	-	-	-	-
34	30	2	28	38	-	-	-	-
34a	11	19	29	20	-	-	-	-
34b	-2	13	3	1	-	-	-	-
35a	9	6	20	62	-	-	-	-
35b	5	-13	12	47	-	-	-	-
36a	14	-	8	-	-	-	-	33
36b	11	-	0	-	-	-	-	-1
37a	-5	-	18	-	-	-	-	2
37b	-10	-	-20	-	-	-	-	-3
37c	2	-	6	-	-	-	-	0
37d	2	-	8	-	-	-	-	-3
38	20	-	-1	-	-	-	-	56
38a	11	-	14	-	-	-	-	35
38b	20	-	-1	-	-	-	-	17
39	25	-	1	-	-	-	-	89
39a	38,33	-	13,15	92	9	-	5	86
39b	24	-	1	-	-	-	-	28
40a	2	-	7	-	-	-	-	27
40b	-2	-	13	-	-	-	-	29
41	57	-	24	-	-	-	-	45
41a	43	-	-9	-	-	-	-	14
41b	50	-	8	-	-	-	-	50
42a	15	-	3	-	-	-	-	29
42b	19	-	12	-	-	-	-	34
43	21	-	-1	-	-	-	-	24

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
43a	33	-	9	-	-	-	-	51
43b	46	-	13	-	-	-	-	27
44	-3	-	-1	-	-	-	-	56
44a	12	-	11	-	-	-	-	33
44b	18	-	1	-	-	-	-	75
45a	23	-	-4	-	-	-	-	54
45b	24	-	16	-	-	-	-	96
47a	58	-	10	-	-	-	-	40
47b	70	-	41	-	-	-	-	119
47c	6	-	4	-	-	-	-	53
47d	5	-	-3	-	-	-	-	30
48a	16	-	12	-	-	-	-	58
48b	14	-	17	-	-	-	-	86
49a	4	-	1	-	-	-	-	18
49b	5	-	6	-	-	-	-	19
51	43	-	20	-	-	-	-	82
51a	8	-	11	-	-	-	-	21
51b	36	-	26	-	-	-	-	90
52a	9	-	5	-	-	-	-	21
52b	73	-	29	-	-	-	-	93
53a	12	-	10	-	-	-	-	37
53b	14	-	12	-	-	-	-	85
54a	39	-	30	-	-	-	-	105
54b	71	-	66	-	-	-	-	106
55	37	-	13	-	-	-	-	63
55a	28	-	11	-	-	-	-	14
55b	57	-	7	-	-	-	-	67
56a	1	-	11	-	-	-	-	20
56b	6	-	17	-	-	-	-	28
57a	3	-	22	-	-	-	-	16
57b	9	-	24	-	-	-	-	84
58	21	-	-1	-	-	-	-	26
58a	7	-	9	-	-	-	-	5
58b	24	-	0	-	-	-	-	39
59a	11	-	18	-	-	-	-	15
59b	7	-	12	-	-	-	-	31
60	65	35	26	93	-	-	-	66
61	60	37	30	85,94	28	14	-	65,80
62	16	-	1	-	-	-	-	76
63a	10	-	16	-	-	-	-	83

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
63b	-5	-	3	-	-	-	-	41
64	25	-	12	-	-	-	-	62
65	-13	-	-3	-	-	-	-	64
66	48	-	15	-	-	-	-	69
67	12	-	-7	-	-	-	-	17
68	2	-	1	-	-	-	-	4
69a	4	-	11	-	-	-	-	10
69b	8	-	7	-	-	-	-	19
70	8	-	10	-	-	-	-	26
71	11	-	11	-	-	-	-	9
72	6	-	-2	-	-	-	-	12
73	17	-	15	-	-	-	-	61
74	81	57	6	104	-	-	-	-
74a	91,96	61	22,27	101	81	42	-	93
74b	28	-	14	-	-	-	-	27
75a	61	-	11	-	-	-	-	77
75b	16	-	5	-	-	-	-	43
75c	59	-	-2	-	-	-	-	11
75d	26	-	49	-	-	-	-	102
76a	78	-	21	-	-	-	-	92
76b	71	-	18	-	-	-	-	34
76c	33	-	5	-	-	-	-	35
76d	51	-	40	-	-	-	-	91
77	5,6	10	-1,22	91	-	-	-	84
78	11,12	22	-7,18	87	-	-	-	67
79	34	-	19	-	-	-	-	77
80	49	-	12	-	-	-	-	81
81	25	-	26	-	-	-	-	96
82	16	-	5	-	-	-	-	79
83	9,15	13	21,29	78	-	-	-	63
84	69	36	27	84	-	-	-	-
85	26	17	12	60	-3	-	-	40
86	62	62	27	77	-	-	-	-
87	5	24	14	66	-	-	-	-
88	10	36	2	90	-	-	-	-
89	79	68	23	57,79	-	-	-	25
90	57	20	22	91	-	-	-	-
90a	74	-	71	-	-	-	-	97
90b	81	-	82	-	-	-	-	97
91	52,53,	25,30,	5	82,83,	25,28,	7,11,	6	53,56

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
	58	32		87	32	21		
92	77	46	30	77	-	-	-	-
93	25	6	21	87	-	-	-	-
93a	37	-	25,36	-	13	-	14	63,102
93b	1	-	-5	-	-	-	-	26
94	40	10	11	66	-	-	-	-
95	52	29	9	105	-	-	-	-
96	25	3	29	71	-	-	-	-
97	3	-7	-12	88	-	-	-	-
98	81,83	31,35	26,32	96,103	-	-	-	-
99	69	34	29	85	-	-	-	-
100	73	47	20	72	-	-	-	-
101	61,79	45,48	14,15	63,76	-	-	-	-
102	40	21	21	77	-	-	-	-
103	49	20	19	80	-	-	-	-
105	57	36	14	68	-	-	-	-
106	65	45	6	79	-	-	-	-
107	56	63	10	85	-	-	-	-
108	42	21	20	88	-	-	-	-
109	13	21	25	69	-	-	-	-
110	5	35	27	62	-	-	-	-
111	56	77	0	65	-	-	-	-
112	44	40	26	79	-	-	-	-
113	12	3	29	87	-	-	-	-
114	15	15	21	58,71	-	-	-	42
115	19	24	21	94	-	-	-	-
116	23	26	22	75	-	-	-	-
117	59	-	18	68	-	-	-	-
118	35	7	19	60	-	-	-	-
119	14	-6	14	60	-	-	-	-
120	21,22	14,26	45,48	55,70	4	3	25	39
121	6	44	16	88	-	-	-	-
122	51	84	13	96	-	-	-	-
124	19	12	-2	63	-	-	-	-
125	-3	1	-4	68	-	-	-	-
126	30	46	12	82	-	-	-	-
127a	26	-	9	74	-	-	-	43
127b	13	-	4	-	-	-	-	1
128a	37,45	-	31,34	104	14		9	97,100
128b	45	-	22	-	-	-	-	54

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
129a	73	-	46	-	-	-	-	86
129b	69	-	55	-	-	-	-	89
129c	94,96	-	29,35	-	86	-	14	100
129d	94,99	-	90,96	-	93	-	87	97,104
130a	66,68	-	82,89	107	32	-	56	100,104
130b	8,11	-	31,44	93	2	-	13	89,92
131a	24	-	10	-	-	-	-	30
131b	36	-	11	90	-	-	-	53,63
132	28	-	19	-	-	-	-	91
133a	57	-	13	-	-	-	-	52
133b	40,42	-	34,39	94	16		27	87,88
134a	27	-	4	-	-	-	-	42
134b	93,95	-	23,29	-	78	-	-	102,103
135a	60	-	4	-	-	-	-	42
135b	30	-	22	-	-	-	-	68
136a	54	-	16	-	-	-	-	34
136b	90	-	21	-	-	-	-	69
137a	94	-	19	-	-	-	-	104
137b	23	-	6	-	-	-	-	30
138a	61	-	-8	-	-	-	-	63
138b	22	-	4	-	-	-	-	25
139	72	-	-2	87	46	-	-	59,83
139a	17	-	16	-	-	-	-	88,101
139b	11	-	6	-	-	-	-	59
140	37	-	-2	-	-	-	-	49
140a	59	-	11	-	-	-	-	76
140b	18	-	3					52
141	23	-	5	-	-	-	-	76
141a	25	-	-5	-				70
141b	28	-	19	-				79,86
142a	68	-	19	95	-	-	-	71
142b	83	-	63	-	-	-	-	99
143a	43	-	19	-	-	-	-	77
143b	17	-	0	-	-	-	-	49
144a	57	-	1	-	-	-	-	40
144b	53,60,66	-	3,4	100,102	28,36	-	-	83,85,87
145	49	-	6	-	-	-	-	61
146a	41	-	-1	-	-	-	-	37
146b	11	-	21	-	-	-	-	63
147	7	-	19	-	-	-	-	91,102

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
147a	33	-	3	-	-	-	-	72
147b	82	-	36	-	-	-	-	93
148a	23	-	-5	-	-	-	-	52
148b	71,74	-	37	106	35	-	-	105
148c	6	-	-1	-	-	-	-	16
148d	19	-	-11	-	-	-	-	11
149a	12	-	-4	-	-	-	-	16
149b	16	-	19	-	-	-	-	32
150a	16	-	16	100	-	-	-	88,96
150b	7	-	5	-	-	-	-	9
151a	11	-	15	-	-	-	-	93
151b	9	-	8	-	-	-	-	37
152a	20	-	17	-	-	-	-	20
152b	7	-	10	-	-	-	-	19
153	17	-	6	-	-	-	-	17
154	86	-	15	-	-	-	-	58
154a	39	-	4	-	-	-	-	31
154b	95	-	5	95	80	-	-	80,83
155	15	-	14	-	-	-	-	36
155a	9	-	-1	-	-	-	-	10
155b	1	-	5	-	-	-	-	5
156	21	-	1	-	-	-	-	6
157	57	-	6	-	-	-	-	43
158	8	-	-1	-	-	-	-	43
159a	-2	-	10	-	-	-	-	37
159b	53	-	-12	-	-	-	-	52
160a	35	-	-12	-	-	-	-	43
160b	65	-	5	-	-	-	-	41
168	23	-	16	-	-	-	-	32
169	2	-	15	-	-	-	-	20
172a	54	-	18	-	-	-	-	65
172b	92	-	46	-	-	-	-	93
173a	5	-	15	82	-	-	-	61,68
173b	8	-	-2	-	-	-	-	28
174a	13	-	22	86	-	-	-	62,71
174b	11	-	6	-	-	-	-	15
175a	11	-	11	90	-	-	-	69,73
175b	4	-	7	-	-	-	-	4
176a	79	-	32	105	52	-	-	93,98,100
176b	41	-	12	-	-	-	-	67

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
179	6	-	6	-	-	-	-	8
180	87	74	95	99	70	-	-	91
181	30	32	89	92	-4	-	-	70
182	29	16	69	91	13	-	-	83
183	71	36	93	80	50	-	-	68
183a	77	-	56	-	-	-	-	82
183b	93	-	93,97	-	-	-	84	98
184	-	-	93	-	60	24	-	95
185	86	58	62	94,97	63	47	37	73,77
186	53,55	51,55	54,72	100,101	24	31	53	94,97
187	71	83	63,84	84,98	-	-	41	78
188	60	48	66,90	105	-	-	35	-
189	31,55	16	81,86	104,107	26	-	71	96
190	14,15	31	70,89	84,99	9	-	49	88
191	10,20	43	89,98	89,99	2	-	85	84
193	93	88	77	103	-	-	-	-
193a	89	-	85	-	-	-	-	98
193b	91	-	83	-	-	-	-	104
194a	100	-	98	-	-	-	-	106
194b	100	-	94	-	-	-	-	103
196a	54.6	-	58,71	-	30	-	37	93,103
196b	37	-	19	-	-	-	-	-2
197a	82	-	31	-	-	-	-	81
197b	96	-	56,77	-	89	-	50	101,105
198a	24	-	10	-	-	-	-	47
198b	84	-	44	-	-	-	-	103
199a	82	-	96	-	-	-	-	94
199b	88	-	61	-	-	-	-	27
200	83	69	92	-	63	-	81	-
201	50	18	67	36	22	-	-	16
202	52	52	92	22	29	-	-	7
203	71	47	88	41	37	-	-	23
203a	76	-	71	-	-	-	-	36
203b	47	-	31	-	-	-	-	24
204	-	-	87	107	-	-	-	-
205	-	-	69	70	-	-	-	-
206	-	-	86	102	46	42	-	-
207	-	-	90	106	49	39	-	-
208	-	-	101	97	60	41	-	-
209	-	-	80	84	-	-	-	-

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
210	-	-	88	63	-	-	-	-
211	-	-	88	108	63	44	-	-
212	-	-	66	64	-	-	-	-
213	-	-	98	68,97	53	53	-	26
214	18	-	58,64	80	-	-	37	48
215	-	-	97	102	-	-	-	-
216	65	-	76,98	103,106	34,47	38	58	98
217	62	-	74	102	-	-	-	-
218	-	-	-	-	79	60	85	110
219	-	-	-	-	-	3	69	-
221	65	16	56	80	-	-	-	-
222	95	101	96	104	-	-	-	-
223	21	-	69	-	-	-	-	47
224	70	26	52	69	-	-	-	-
225	27	12	75	80	-	-	-	-
226	88	48	85	83	-	-	-	-
227	21	-2	66	98	-	-	-	-
228	64	19	77	42	-	-	-	-
229	17	8	53	90	-	-	-	-
230	94	58	87	93	-	-	-	-
231	48	26	65	87	-	-	-	-
232	87	43	87	102	-	-	-	-
233	73	28	80	103	-	-	-	-
235	48	11	80	96	-	-	-	-
236	94	85	99	98	-	-	-	-
237	80	52	98	99	-	-	-	-
238	67	25	94	98	-	-	-	-
239	19	-11	52	30	-	-	-	-
240	74,75	44,47	82,87	83,97	-	-	-	-
241	81,82	47,49	75,78	91,93	-	-	-	-
242	53	37	50	98	-	-	-	-
243	58	45	90,98	105	-	-	73	-
244	78	42	76	99	-	-	-	-
245	69	35	65	96	-	-	-	-
246	82	68	86	101	-	-	-	-
247	95	81	96	89	-	-	-	-
248	76	31	90	95	-	-	-	-
249	95	82	98	98	-	-	-	-
250	37	22	62	105	-	-	-	-
251	89	53	85	101	-	-	-	-

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
252	36	13	66	52	-	-	-	-
253	54,55	18,24	44,64	64,86	-	-	-	-
254a	75	36	58	85	-	-	-	-
254b	63	22	57	79	-	-	-	-
255	55	43	63	96	-	-	-	-
256	47	23	55	58	-	-	-	-
257	51	24	84	100	-	-	-	-
258	93	74	94	99	-	-	-	-
259	71	53	82	98	-	-	-	-
260	45	26	54	92	-	-	-	-
261	50	30	84	84	-	-	-	-
262	52	35	87	74	-	-	-	-
263	1	6	61	54	-	-	-	-
264	79	46	81	82	-	-	-	-
265	50	30	67	70	-	-	-	-
266	63	72	62	92	-	-	-	-
267	7	26	63	85	-	-	-	-
268	57	39	90	94	-	-	-	-
269	36	44	61	83	-	-	-	-
270	50	66	96	76	-	-	-	-
271	65	83	97	71	-	-	-	-
272a	27	12	33	-10	-	-	-	-
272b	30	36	68	72	-	-	-	-
273	88	71	67	89	-	-	-	-
274	28	25	68	27	-	-	-	-
275	75	61	51	94	-	-	-	-
276	86	81	71	101	-	-	-	-
277	71	84	98	97	-	-	-	-
278	62	44	93	98	-	-	-	-
279	79	93	90	92	-	-	-	-
280	76	65	97	98	-	-	-	-
281	67	47	72	90	-	-	-	-
282	33	30	75	101	-	-	-	-
283	63	46	90	89	-	-	-	-
284	83	81	97	76	-	-	-	-
285	63	71	98	97	-	-	-	-
286	26	19	80	60	-	-	-	-
287	81	69	99	98	-	-	-	-
288a	89	88	98	104	-	-	-	-
288b	39	17	67	84	-	-	-	-

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
289a	51	57	60	90	-	-	-	-
289b	12	-2	53	54	-	-	-	-
290	90	79	80	96	-	-	-	-
291	88	85	102	105	-	-	-	-
292	13	23	58	104	-	-	-	-
293	73	82	96	93	-	-	-	-
294	76	39	94	41	-	-	-	-
295	15	7	69	79	-	-	-	-
296	20	33	60	70	-	-	-	-
297	69	36	50	46	-	-	-	-
298	60	17	54	51	-	-	-	-
299	78	47	52	54	-	-	-	-
300	14	29	67	86	-	-	-	-
301	29	36	87	84	-	-	-	-
302	23	17	81	35	-	-	-	-
303	16	51	62	71	-	-	-	-
304	15	27	79	81	-	-	-	-
305	20	41	93	79	-	-	-	-
306	18	12	78	14	-	-	-	-
307	93	81	93	98	-	-	-	-
308	79	56	86	97	-	-	-	-
309	23	40	57	37	-	-	-	-
310	63	47	69	87	-	-	-	-
311	87	79	91	97	-	-	-	-
312	71	50	56	93	-	-	-	-
313	92	53	73	73	-	-	-	-
314	92	71	91	50	-	-	-	-
315	4	3	59	48	-	-	-	-
316	93	81	90	45	-	-	-	-
317	89	71	61	7	-	-	-	-
318	94	60	95	103	-	-	-	-
319	13	8	63	4	-	-	-	-
320	61	56	66	18	-	-	-	-
321	94	66	59	90	-	-	-	-
322	59	22	58	49	-	-	-	-
323	85	69	92	95	-	-	-	-
324	63	31	67	99	-	-	-	-
325	-1	1	81,84	-6	-	-	53	-
326	33	35	51	93	-	-	-	-
327	-5	4	58	-4	-	-	-	-

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
328	95	80	76	93	-	-	-	-
329	68	78	60	104	-	-	-	-
330	98	72	58	99	-	-	-	-
331	53	70	53	99	-	-	-	-
332	41	51	94	86	-	-	-	-
333	65	16	52	88	-	-	-	-
334	91	72	55	82	-	-	-	-
335	82	73	60	99	-	-	-	-
336	98	-	66	-	-	-	-	104
338	16	-	60	-	-	-	-	102
339a	13	-	37	-	-	-	-	86
339b	10	-	64	-	-	-	-	87
II-1a	6	-	15	-	-	-	-	14
II-1b	-7	-	1	-	-	-	-	32
II-2	74	-	49	-	-	-	-	96
II-4a	72	-	35	-	-	-	-	79
II-4b	98	-	57	-	-	-	-	100
II-5	2	-	9	-	-	-	-	4
II-6a	66	-	45	-	-	-	-	85
II-6b	91	-	81	-	-	-	-	102
II-7	95	-	52	-	-	-	-	100
II-8	6	-	9	-	-	-	-	70
II-9	30	-	7	-	-	-	-	78
II-10	7	-	10	-	-	-	-	47
II-11	63	-	25	-	-	-	-	70
II-11a	9	-	22	-	-	-	-	53
II-11b	76	-	43	-	-	-	-	89
II-12	18	-	11	-	-	-	-	65
II-12a	26	-	25	-	-	-	-	89
II-12b	11	-	15	-	-	-	-	65
II-13	9	-	9	-	-	-	-	73
II-14a	30	-	34	-	-	-	-	88
II-14b	8	-	17	-	-	-	-	33
II-15a	61	-	7	-	-	-	-	47
II-15b	5	-	18	-	-	-	-	40
II-16a	20	-	11	-	-	-	-	39
II-16b	32,46	-	32	88	16	-	-	65,73
II-17	8	-	4	-	-	-	-	7
II-18	-7	-9	14	-15		-	-	-
II-19	8	-	8	-	-	-	-	21

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
II-39	16	13	27	-14	-	-	-	-
II-40		-	-	36	-	-	-	-
II-48	27	8	26	0	-	-	-	-
II-49a	47	-	34	-	-	-	-	43
II-49b	69	-	18	-	-	-	-	50
II-56	54	11	31	78	-	-	-	-
II-57a	20	-	22	-	-	-	-	38
II-57b	31	-	31	-	-	-	-	45
II-58	16	-	16	-	-	-	-	58
II-60	11	-	9	-	-	-	-	54
II-61	-	-	-	47	-	-	-	-
II-62	14	-	5	-	-	-	-	37
II-63	55	-	39	-	-	-	-	90
II-64	23	-	-3	-	-	-	-	54
II-65	10	-	12	-	-	-	-	25
II-66	27	-	0	-	-	-	-	46
II-67	7	-	-11	-	-	-	-	43
II-68	12	-	5	-	-	-	-	17
II-69	45	-	11	-	-	-	-	14
II-70	-	-	-	34	-	-	-	-
II-71	3	-	-3	-	-	-	-	11
II-72	30	-	25	-	-	-	-	47
II-73	34	-	28	-	-	-	-	33
II-74	11	-	10	-	-	-	-	18
II-75	8	-	15	-	-	-	-	35
II-76	-	-	-	103	-	-	-	-
II-77	54	66	43	108	-	-	-	-
II-78	-11	-	1	-	-	-	-	-9
II-79	7	-	0	-	-	-	-	59
II-80	4	-	3	-	-	-	-	9
II-81	-1	-	15	-	-	-	-	-9
II-82	13	23	45	48,53	-	-	-	35
II-83	12	-	2	-	-	-	-	24
II-84	2	-	11	-	-	-	-	-11
II-85	-7	-	15	-	-	-	-	-2
II-86	44	-	27	-	-	-	-	35
II-87	11	-	1	-	-	-	-	24
II-88	68	-	-2	-	-	-	-	48
II-89	13	-	-5	-	-	-	-	35
II-90	62	-	19	-	-	-	-	55

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
II-91	16	-	-2	-	-	-	-	25
II-92	13	-	0	-	-	-	-	25
II-93a	6	-	7	-	-	-	-	24
II-93b	18	-	4	-	-	-	-	56
II-94a	10	-	0	-	-	-	-	8
II-94b	7	-	-5	-	-	-	-	24
II-95a	32	-	16	-	-	-	-	53
II-95b	-1	-	-1	-	-	-	-	12
II-96	39	31	49	95	-	-	-	-
II-97	-4	-	4	-	-	-	-	24
II-98a	33	-	12	-	-	-	-	10
II-98b	10	-	19	-	-	-	-	5
II-99a	12	-	24	-	-	-	-	49
II-99b	5	-	16	-	-	-	-	7
II-100a	10	-	7	-	-	-	-	12
II-100b	24	-	4	-	-	-	-	1
II-102	2	-	10	-	-	-	-	49
II-103	1	8	-5	35	-	-	-	-
II-104	3	-	10	-	-	-	-	21
II-105	5	-	7,18	27	-	-	-	5,30
II-106a	25	-	18	-	-	-	-	20
II-106b	31	-	8	-	-	-	-	36
II-108a	13	-	-2	-	-	-	-	27
II-108b	-2	-	-6	-	-	-	-	11
II-109a	27	-	2	-	-	-	-	41
II-109b	5	-	-10	-	-	-	-	2
II-110	25,36	17	1,2	47	-	-	-	11
II-111	42	-	3	-	-	-	-	35
II-112a	5	-	10	-	-	-	-	36
II-112b	10	-	3	-	-	-	-	31
II-113a	9	-	-3	-	-	-	-	39
II-113b	5	-	19	-	-	-	-	38
II-114a	45	-	12	-	-	-	-	40
II-114b	7	-	-5	-	-	-	-	40
II-116	4	-	3	-	-	-	-	43
II-118a	18	-	3	-	-	-	-	27
II-118b	11	-	5	-	-	-	-	-3
II-119	23	53	-4	27	-	-	-	-
II-120a	99	-	65	-	-	-	-	101
II-120b	100	-	98	-	-	-	-	98

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
II-121a	97,98	-	91,92	-	90	-	65	103,104
II-121b	93,96	-	80,85	-	77	-	54	100,103
II-122	-2	-	-10	-	-	-	-	47
II-123a	41	-	16	-	-	-	-	62
II-123b	61	-	75	-	-	-	-	93
II-124a	-2	-	23	-	-	-	-	26
II-124b	10	-	7	-	-	-	-	18
II-125a	92	-	62	-	-	-	-	100
II-125b	97,102	-	97,98	-	89	-	89	103,106
II-125c	42	-	9	-	-	-	-	67
II-125d	64	-	71	-	-	-	-	88
II-126	-4	-	4	-	-	-	-	4
II-127a	83	-	79	-	-	-	-	105
II-127b	65	-	54	-	-	-	-	104
II-128a	61	-	34	-	-	-	-	97
II-128b	84,86	-	74,77	-	56		50	102,106
II-129	2	-	12	-	-	-	-	1
II-130	43	-	41	-	-	-	-	97
II-130a	92	-	86	-	-	-	-	103
II-130b	3	-	15	-	-	-	-	33
II-131	90	-	85	-	-	-	-	103
II-132a	33	-	8	-	-	-	-	40
II-132b	68	-	22	-	-	-	-	70
II-133	-	-	-	-5	-	-	-	-
II-134a	86	-	19	-	-	-	-	89
II-134b	65	-	6	-	-	-	-	79
II-135a	48	-	-3	-	-	-	-	34
II-135b	60,70	-	40	105	26	-	-	103,105
II-136a	60	-	7	-	-	-	-	36
II-136b	31	-	5	-	-	-	-	32
II-138	57	-	9	-	-	-	-	77
II-139	34	-	7	-	-	-	-	72
II-140	53	-	3	-	-	-	-	72
II-141	7	-	-2	-	-	-	-	22
II-142	5	-	-4	-	-	-	-	23
II-143	13	-	-3	-	-	-	-	22
II-146a	23	-	47	-	-	-	-	102
II-146b	13	-	5	-	-	-	-	43
II-146c	17	-	8	-	-	-	-	42
II-146d	13	-	3	-	-	-	-	16

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
II-147a	32	-	57	-	-	-	-	102
II-147b	20	-	15	-	-	-	-	66
II-147c	7	-	3	-	-	-	-	38
II-147d	10	-	4	-	-	-	-	13
II-148	21	-	27	-	-	-	-	93
II-149a	90	-	53	-	-	-	-	104
II-149b	59	-	27	-	-	-	-	96
II-149c	49	-	5	-	-	-	-	41
II-149d	41	-	7	-	-	-	-	44
II-150	14	-	5	-	-	-	-	30
II-151a	11	-	1	-	-	-	-	27
II-151b	13	-	11	-	-	-	-	78
II-152a	19	-	9	-	-	-	-	93
II-152b	2	-	6	-	-	-	-	61
II-152c	6	-	1	-	-	-	-	14
II-152d	5	-	8	-	-	-	-	9
II-153	2	-	2	-	-	-	-	7
II-154	2	-	11	-	-	-	-	73
II-160	7,14	15	17,37	35	-	-	-	39
II-161	7	2	7	13	-	-	-	-
II-163	66	28	41	86	-	-	-	-
II-164	12	0	15	40	-	-	-	-
II-171	95	55	96	94	-	-	-	-
II-187	54	-	10	-	-	-	-	27
II-212	29	-	19	-	-	-	-	73
II-213	-3	-	12	-	-	-	-	11
II-215	-	-	-	-5	-	-	-	-
II-221	-1	-	10	-	-	-	-	0
II-222	19	-	26	-	-	-	-	99
II-223	9	-	8	-	-	-	-	88
II-224	13	-	22	-	-	-	-	68
II-225	9	-	-1	-	-	-	-	8
II-226	15	-	4	-	-	-	-	40
II-227a	25	-	15	-	-	-	-	86
II-227b	8	-	6	-	-	-	-	18
II-227c	20	-	24	-	-	-	-	94
II-227d	12	-	6	-	-	-	-	26
II-228	-2	-	3	-	-	-	-	10
II-229	3	-	6	-	-	-	-	12
II-230	-2	-	1	-	-	-	-	22

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
II-231	11	-	9	-	-	-	-	-2
II-232	3	-	3	-	-	-	-	28
II-234	-8	-1	7	33	-	-	-	-
II-235	58	28	3	45	-	-	-	-
II-236	-	-	-	-4	-	-	-	-
II-238	-	-	-	98	-	-	-	-
II-239	-	-	-	17	-	-	-	-
II-240	57	-	7	-	-	-	-	53
II-241	5	-	-1	-	-	-	-	-1
II-242	4	-	2	-	-	-	-	3
II-243	91,93	-	19	82	79	-	-	58,61
II-244a	95	-	22	-	-	-	-	102
II-244b	12	-	2	-	-	-	-	16
II-245	27	-	7	-	-	-	-	44
II-246	-2	-	47	-	-	-	-	5
II-247	3	-	83	-	-	-	-	19
II-248	4	-	88	-	-	-	-	5
II-249	6	-	74	-	-	-	-	4
II-250	-5	-	57	-	-	-	-	6
II-251	-7	-	81	-	-	-	-	-4
II-252	-1	-	91	-	-	-	-	1
II-253	9	-	54	-	-	-	-	16
II-261	71	-	70	-	-	-	-	103
II-262	3	-	10	-	-	-	-	11
II-263	2	-	10	-	-	-	-	10
IV-2	-	-	-	50	-	-	-	-
IV-4	2	15	-3	56	-	-	-	-
IV-8a	49	-	7	-	-	-	-	4
IV-8b	5	-	22	-	-	-	-	3
IV-93a	7	-	18	-	-	-	-	52
IV-93b	65	-	-1	-	-	-	-	44
IV-209a	89	-	6	-	-	-	-	72
IV-209b	11	-	10	-	-	-	-	13
IV-209c	98	-	59	-	-	-	-	102
IV-209d	54	-	8	-	-	-	-	79
IV-210a	70,75	-	37	-	43	-	-	101,103
IV-210b	10	-	8	-	-	-	-	29
IV-210c	-4	-	1	-	-	-	-	10
IV-210d	19	-	13	-	-	-	-	87
V-1	15	-	35	-	-	-	-	102

Compound No.	Adrenergic (0.1 μM)*				Adrenergic (0.03 μM)*			
	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{1B}	α_{1D}	α_{2A}	α_{2B}
V-1a	20	-	36	-	-	-	-	88
V-1b	57	-	29	-	-	-	-	102
V-2	49	-	2	-	-	-	-	61
V-3	22	-	40	-	-	-	-	71
V-14a	0	-	18	-	-	-	-	7
V-14b	2	-	3	-	-	-	-	0
V-15	4	-	7	-	-	-	-	20
V-18a	78	-	13	-	-	-	-	57
V-18b	95	-	57	-	-	-	-	98
V-21a	68	-	62	-	-	-	-	98
V-21b	34	-	43	-	-	-	-	93
V-22	28	-	18	-	-	-	-	90
V-23	94	-	109	-	-	-	-	105

* Where shown, some compounds were tested in repeat assays, each datapoint is shown.

Table B2: Ki values of compounds of the invention:

Compound No.	α_{2B} (nM)	α_{2A} (nM)	α_{1B} (nM)	α_{1D} (nM)
3	0.64	0.26	-	-
3a	27.41	-	-	-
3b	0.26, 0.28, 0.46	139, 166, 222	51	258
4a	0.64	176	-	-
5a	35	-	-	-
5b	0.95, 1.06, 4.53	152, 192, 195	184	-
8b	11.65	2104	-	-
13b	0.62	199	-	-
14a	1.92	123	-	-
15b	0.64	112	-	-
26a	0.56	113	-	-
26b	3.06		-	-
27a	4.32	1101	-	-
27b	43.43	3713	-	-
29a	1.09	77.23	-	-
30b	1.13	14.25	-	-
31a	1.58	167	-	-
39a	2.50	1659	-	-
74a	1.42	234	4.72	-
60	5.84	-	-	-
61	5.89	-	-	-
89	32	-	-	-
91	9.84, 10.68, 11.97	-	-	-
93a	1.14	90.50	-	-
114	17.38	-	-	-

Compound No.	α_{2B} (nM)	α_{2A} (nM)	α_{1B} (nM)	α_{1D} (nM)
120	20.52	65.83	-	-
127a	15.14	-	-	-
128a	0.97	98.62	-	-
129c	0.77	88.55	-	-
129d	0.35	1.87	-	-
130a	1.66	6.91	-	-
130b	2.52	72.60	-	-
131b	7.95	-	-	-
133b	2.42	59.45	-	-
134b	0.43	102	-	-
139a	2.36	-	-	-
139	8.12	390	-	-
141b	3.44	-	-	-
144b	1.70, 2.36	-	-	-
148b	0.43	-	-	-
147	1.49	-	-	-
150a	1.57	-	-	-
154b	3.33	-	-	-
173a	8.77	-	-	-
174a	7.91	-	-	-
175a	4.42	-	-	-
176a	0.53	-	-	-
183b	-	2.72	-	-
184	-	184	-	-
185	3.80	20.97	-	-
186	0.52	11.04	-	-
187	4.43	17.89	-	-
189	0.86	2.86	-	-
190	2.26	12.83	-	-
191	3.23	2.10	-	-
196a	1.83	16.80	-	-
197b	0.78	11.90	-	-
200	-	1.63, 3.21	-	-
204	-	2.48	-	-
206	-	1.12, 6.79	-	-
207	-	1.16	-	-
213	26.30	-	-	-
214	12.91	22.67	-	-
216	0.95	9.59	-	-
243	-	3.86	-	-
325	206	9.88	-	-
II-16b	5.58	-	-	-
II-82	26.76	-	-	-
II-105	152	-	-	-

Compound No.	α_{2B} (nM)	α_{2A} (nM)	α_{1B} (nM)	α_{1D} (nM)
II-121a	-	4.52	-	-
II-121b	0.22	9.18	-	-
II-125b	0.16	1.21	-	-
II-128b	0.49	13.07	-	-
II-135b	0.53	-	-	-
II-243	9.44	-	-	-
IV-210a	0.33	-	-	-
V-1	0.51	-	-	-

Example B2. Functional activity on recombinant adrenergic α_{1B}, adrenergic α_{2A}, adrenergic α_{2B} and adrenergic α_{1D} receptors using Aequorin and GTPγS functional assays

[1077] To study the functional activity of compounds of the invention on the human recombinant adrenergic α_{2B}, adrenergic α_{2A}, adrenergic α_{1B} or adrenergic α_{1D} with Aequorin functional assays and on the human recombinant adrenergic α_{2B} receptor with GTPγS assay, CHO-K1 cell lines expressing adrenergic α_{2B}, adrenergic α_{2A}, adrenergic α_{1B} or adrenergic α_{1D} recombinant receptor, mitochondrial apoaequorin and Gα16 were used for the Aequorin assay. CHO-K1 cell line expressing the recombinant α_{2B} receptor was amplified to prepare membranes used for the GTPγS assay.

[1078] The following reference agonists were used as both the reference ligand in agonist mode and as the agonist that needs to be inhibited in antagonist mode.

Assay	α_{1B} (aeq)	α_{1D} (aeq)	α_{2A} (aeq)	α_{2B} (aeq)	α_{2B} (GTPgS)
Agonist ligand	Cirazoline	Cirazoline	UK 14304	Oxymetazoline	Guanfacine

[1079] **Aequorin Assay Procedure:** Aequorin adrenergic α_{1B} (FAST-008A) (Figure 5), adrenergic α_{2A} (FAST-006A) (Figure 3) or adrenergic α_{2B} (FAST-007A) (Figures 1, 2, 3, 6) cells were grown 18h prior to the test in media without antibiotics. They were then detached by gentle flushing with PBS-EDTA (5 mM EDTA), recovered by centrifugation and re-suspended in "assay buffer" (DMEM/HAM's F12 with HEPES + 0.1% BSA protease free). Cells were incubated at RT for at least 4h with Coelenterazine h (Molecular Probes). Dose response curves with reference compounds were performed before testing the compounds of the invention. The α_{1B} reference agonist and antagonist were cirazoline and qinazoline, respectively. The α_{2A}

reference agonist and antagonist were UK14,304 and rauwolscine, respectively. The α_{2B} reference agonist and antagonist were oxymetazoline and rauwolscine, respectively.

[1080] For agonist testing, 50 µL of cell suspension were injected on 50µL of test compound or reference agonist plated in a 96-well plate. The resulting emission of light was recorded using the Hamamatsu Functional Drug Screening System 6000 (FDSS 6000). For antagonist testing, following an incubation of 15 min. after the first injection, 100 µL of reference agonist at a concentration corresponding to its EC_{80} was injected on the 100 µL of the mixture of cell suspension and test compound. The resulting emission of light was recorded using the same luminometer as for agonist testing. To standardize the emission of recorded light (determination of the "100% signal") across plates and across different experiments, some of the wells contained 100 µM digitonin or a saturating concentration of ATP (20 µM). Plates also contained the reference agonist at a concentration equivalent to the EC_{80} obtained during the test validation.

[1081] Agonist activity of test compound was expressed as a percentage of the activity of the reference agonist at its EC_{100} concentration. Antagonist activity of test compound was expressed as a percentage of the inhibition of reference agonist activity at its EC_{80} concentration.

[1082] Compounds were tested for agonist & antagonist activity at the human adrenergic α_{1B} (FAST-008A), adrenergic α_{2A} (FAST-006A) or adrenergic α_{2B} (FAST-007A) at the following nanomolar concentrations, in duplicate: Agonist (nM): 0.3, 1, 3, 10, 30, 100, 300, 1000, 3000, 10000; Antagonist (nM): 0.15, 0.5, 1.5, 5, 15, 50, 150, 500, 1500, 5000.

[1083] **GTPγS Assay Procedure:** The procedure was carried out with the following: assay buffer [20mM HEPES pH 7.4; 100mM NaCl, 10 µg/mL saponin, 1mM $MgCl_2$]; membranes [Recombinant CHO-K1-adrenergic α_{2B} membrane extracts thawed on ice and diluted in assay buffer to give 10 µg /well and kept on ice]; GDP [diluted in assay buffer to give 3 µM final concentration]; beads [PVT-WGA (Amersham, RPNQ0001), diluted in assay buffer at 0.5mg/well]; GTPγ^{35}S [(PerkinElmer NEG030X), diluted in assay buffer to give 0.1 nM final concentration]; ligand [Guanfacine (Tocris, 1030) as reference agonist and Rauwolscine (Tocris, 891) as reference antagonist, diluted in assay buffer]. Membranes were mixed with GDP (volume:volume) and incubated for at least 15 min. on ice. In parallel, GTPγ[^{35}S] was mixed with the beads (volume:volume) just before starting the reaction.

[1084] For agonist testing, the following reagents were successively added in the wells of an Optiplate (Perkin Elmer): 50 μL of test or reference ligand, 20 μL of the membranes:GDP mix, 10 μL of assay buffer and 20 μL of the GTPγ[^{35}S]:beads mix. For antagonist testing, the following reagents were successively added in the wells of an Optiplate (Perkin Elmer): 50 μL of test or reference ligand, 20 μL of the membranes:GDP mix, and then after an incubation of 15 min. at RT, 10 μL of reference ligand at historical EC_{80} concentration and 20 μL of the GTPγ[^{35}S]:beads mix.

[1085] The plates were covered with a top seal, mixed on an orbital shaker for 2 min, and then incubated for 1h at RT. Then the plates were centrifuged for 10 min. at 2000 rpm, incubated at RT 4h and counted for 1 min/well with a Perkin Elmer TopCount reader.

[1086] Compounds were tested for antagonist activity at the human adrenergic α_{2B} receptor (FAST-007G) (Figure 4) at the following nanomolar concentrations, in duplicate: Agonist and antagonist (nM): 0.3, 1, 3, 10, 30, 100, 300, 1000, 3000, 10000.

Inverse Agonist Activity

[1087] SPA 35S-GTPgS and Radioligand Binding experiments were conducted with Euroscreen membrane preparations. Compound was tested for inverse agonist activity at the human Adrenergic a2A receptor using GTPg35S binding functional assay (FAST-006G) in dose-response and in duplicates. As shown in the Figure. 28, Compound 129d showed inverse agonist activity to adrenergic α_{2A} receptor.

Example B3 Cell culture and cell viability assay

[1088] SH-SY5Y cells cultured in DMEM/F12 media supplemented with 10% FBS were seeded in 96-well microplates at 150,000 cells/cm^2. After 24 h, cells were depleted from FBS and kept in culture for 24 h before the experiment. Cells were then treated with 4-Br-A23187 (2 μM), hydrogen peroxide (300 μM) or the mitochondrial toxin rotenone (25 μM) in the presence of vehicle or Compound of the Invention for 24 h. Cell death was determined by measurements of LDH release according to the Cytotoxicity Detection KitPlus (Roche, Mannheim, Germany). Cell viability was determined by measuring the capacity of cells to metabolize MTS tetrazolium (MTS) according to the Cytotoxicity Detection KitPlus (Roche, Mannheim, Germany) and MTS reduction is assessed by the CellTiter 96® AQueous One Solution Cell Proliferation assay (Promega Corporation, Madison, WI, USA). Compounds were screened at 10 nM, using DMSO

as vehicle. Assay results for the experiments with hydrogen peroxide are presented as the LDH release (cell death) of untreated cells (control), hydrogen peroxide -treated cells (vehicle), and co-incubation of hydrogen peroxide with Compounds of the Invention treated cells normalized to the vehicle (Figure 17A). This assay assesses the ability of the test compounds to protect against cell death that is mediated by mitochondrial dysfunction. In the assay, the calcium ionophore 4-Br-A23187 is used to challenge the cells, causing calcium levels to rise in mitochondria, which leads to depolarization and cell death. Test compounds are assessed for their ability to prevent cell death in response to challenge with 4-Br-A23187.

Table B3: Relative Cell Death protection of compounds of the invention

Compound No.	Relative cell death protection	SE	p value
Control	43.78	2.72	<0.0001
Vehicle	100	0	-
Dimebon (DMB)	91.15	2.07	0.0128
3b	86.70	1.55	0.0033
39a	82.94	2.11	0.0013
4a	81.64	2.06	0.0009
5b	73.73	2.55	0.0005

[1089] Assay results for the experiments with Br-A23187 are presented as the MTS reduction capacity (cell viability) of untreated cells (control), 4-Br-A23187-treated cells (vehicle), and co-incubation of Br-A23187 with Compounds of the Invention treated cells and using p-trifluoromethoxyphenylhydrazone (FCCP) at 10 μM for 30 min as a control (Figure 17B)

Table B4: Relative cell viability protection of compounds of the invention

Compound No.	Relative cell viability protection	SE	p value
Control	0.3945	0.04025	--
Vehicle	0.23688	0.00966	0.0034
Dimebon (DMB)	0.35375	0.02209	ns.
39[a]	0.36	0.00668	ns.
4[a]	0.34625	0.01367	ns.
5b	0.37475	0.01533	ns.
3b	0.36725	0.0224	ns.
FCCP	0.1035	2.89E-04	<0.0001

Example B4.Cell culture and Cell Viability Assay

[1090] Cell Culture. SH-SY5Y cells stably transfected with a doxycyline-inducible wild-type α-synuclein (α-syn) gene along with control SH-SY5Y cells over-expressing the β-galactosidase (β-gal) gene (a gift from L. Stefanis, Division of Basic Neurosciences, Biomedical Research Foundation of the Academy of Athens, Athens, Greece) are cultured as described by Vekrellis et

al.(Vekrellis K, Xilouri M, Emmanouilidou E, Stefanis L. (2009). Inducible over-expression of α-syn in human neuronal cells leads to caspase-dependent non-apoptotic death. J Neurochem *109*, 1348-1362). In accordance with this method, cells are cultured and maintained in RPMI 1640, 10% fetal bovine serum supplemented with 250 μg/mL G418 and 50 μg/mL Hygromycin B. Expression of α-syn is switched off in stock cultures with doxycycline (2 μg/mL). For experimental procedures, cells are plated at (4-8x10^4 cells/cm^2) and differentiated in absence of doxycycline and in the presence of 20 μM all-trans retinoic acid (RA) (Sigma, St Louis, MO, USA).

[1091] Viability Assay: Cells are cultured in 96-well plates. After 24 h, cells are treated with RA and Compounds of Invention at 0.1 and 10 nM in the absence of doxycyline. Culture medium with RA and drugs is fully replaced after 7 days. Cell viability is measured by the release of lactate dehydrogenase (LDH) from necrotic cells into the culture medium and by measuring the capacity of cells to metabolize MTS tetrazolium (MTS) after 14 days in culture. LDH leakage is assessed according to the Cytotoxicity Detection KitPlus (Roche, Mannheim, Germany) and MTS reduction is assessed by the CellTiter 96® AQueous One Solution Cell Proliferation assay (Promega Corporation, Madison, WI, USA).

[1092] Assay results for the experiments with α-syn over-expression are presented as the MTS reduction capacity (cell viability) of control cells (+ dox), cells over-expressing α-syn (- dox), and cells over-expressing α-syn incubated with Compounds of the Invention at 0.1 nM (Figure 18A) or 10 nM (Figure 18B).

Table B5: Relative cell viability protection of compounds of the invention at 0.1nM (Fig 17A)

Compound No.	Relative cell viability protection	SE	p value
+dox (control)	100	2.32	
-dox	61.46	2.42	
Dimebon (DMB)	70.53	1.74	0.0125
3b	70.84	1.25	0.0007
39a	72.53	3.07	0.0177
4a	73.39	2.41	0.0058
5b	76.52	3.24	0.0039

Table B6: Relative cell viability protection of compounds of the invention at 10nM (Fig 17B)

Compound No.	Relative cell viability protection	SE	p value
+dox (control)	100	2.32	

-dox	61.46	2.42	
DMB	85.70	3.10	<0.0001
Cpd3b	78.32	2.54	0.0007
Cpd39a	80.85	3.48	0.001
Cpd4a	77.46	2.28	0.0007
Cpd5b	85.29	3.92	0.0004

[1093] Immunoblotting of α-synuclein and α-synuclein Aggregates: Cells stably expressing α-synuclein are cultured in 6-well plates at a density of 4 x 10^4 cells/cm^2 cells per well. Cells are differentiated and treated with Compound of the Invention at 10 nM in absence of dox after 24 h of plating. Drug treatments are repeated after 7 days in freshly prepared medium containing RA. After 14 days, cells are washed twice with cold PBS and lysed in lysis buffer containing 1% Triton X-100, 20 mM HEPES, 150 mM NaCl, 10% glycerol, 1 mM EGTA, 1.5 mM $MgCl_2$, 1mM PMSF pH 7.4, and 1X protease inhibitor mixture (Roche, Mannheim, Germany). Lysates are homogenized and subjected to four successive freeze-thaw cycles to disrupt membranes. Triton soluble fractions and triton insoluble pellets are obtained by ultracentrifugation at 100,000 x g for 30 min at 4 °C. The concentration of protein in each fraction is determined by BCA assay (Thermo Scientific). Samples from total, soluble and triton insoluble fractions, are boiled in 1X sample buffer (20 mM Tris, 1% glycerol, 180 mM β-mercaptoethanol, 0.003% bromophenol blue, and 2% SDS, pH 6.8), loaded on 12% SDS-PAGE gels, and transferred to polyvinylidene difluoride (PVDF) membranes (0.2 μM-pore immobilon Biorad). Membranes are blocked in 1X TBS-Tween (20 mM Tris, pH 7.4, 150 mM NaCl, and 0.2% Tween 20) containing 5% milk for 1 h and incubated overnight at 4 °C with the following primary antibodies in blocking solution at the indicated dilutions: monoclonal anti-α-synuclein α-syn-1 (1:1000; BD Transduction Laboratories). (Perrin, R.J., Payton, J.E., Barnett, D.H., Wraight, C.L., Woods, W.S., Ye, L., and George, J.M. (2003). Epitope mapping and specificity of the anti-α-_synuclein monoclonal antibody Syn-1 in mouse brain and cultured cell lines. Neurosci Lett *349*, 133-135), and monoclonal vimentin (1:1000; BD PharMingen). Primary antibodies are detected with secondary anti-mouse antibodies conjugated to HRP (1:5000).

[1094] Isolation of RNA and RT-quantitative PCR (RT-qPCR): SH-SY5Y cells stably over-expressing α-syn are treated with Compound of the Invention (10 nM). Total RNA from these cells as well as control cells not treated with Compound is extracted using the E.Z.N.A RNA extraction Kit (OMEGAbiotek, Norcross, GA). 1 μg of RNA is reverse transcribed to cDNA using the M-Mulv reverse transcriptase enzyme (Promega Corporation, Madison, WI, USA).

RT-qPCR of cDNA templates is carried out using TAQMAN probes for human α-synuclein (Hs00240906_M1) and TAQMAN masterMix (Applied Biosystems) and a Mx3005P real-time PCR system (Agilent Technologies Inc., Santa Clara, CA). Levels of alpha-tubulin mRNA are used to normalize the amounts of total RNA between samples. Fold changes are calculated as described by (Pfaffl, M.W. (2001). A new mathematical model for relative quantification in real-time RT-PCR. Nucleic Acids Res *29*, e45).

Example B5. α_{2B} Pharmacology: Studies in Spontaneously Hypertensive Rat (SHR) Model of Hypertension:

[1095] Male spontaneously hypertensive rats (SHR), approximately 3 months of age and weighting approximately 250 grams were utilized. Free access to standard lab chow for rats and reverse osmosis (RO) water was granted. All aspects of this work, including housing, experimentation and disposal of animals were performed in general accordance with the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, D. C., 1996).

[1096] The animals were anaesthetized with sodium pentobarbital (50 mg/kg IP). The left carotid artery when compound dosed orally (PO) or subcutaneously (SC); and both left carotid and femoral artery when compound dosed intravenous (i.v.) were cannulated with a polyethylene catheter (38 cm in length; PE60, Portex, Ltd.) connected with a polyurethane tubing (12 cm in length; PU-40, Cat. # BB520-40, Scientific Commodities, Inc.), which was tunneled under the skin and exited through the nape of the neck. The arterial cannula was connected to a pressure transducer through a swivel system, allowing free roaming during continuous recording of mean arterial pressure and heart rate. The animals were housed individually with food and water freely available during recovery. On the following day, the arterial cannula was connected via a Statham (P 23 x L) pressure transducer to a NEC/San-Ei amplifier and data acquisition and analysis system (Power Lab 8/SP) for direct mean arterial pressure and heart rate measurements.

[1097] The test compounds, dissolved in sterile saline, were administered subcutaneously (SC) or orally (PO), or by intravenous (i.v.) bolus administration in two minutes or the escalating doses of compound administration in every 30 minutes, with each dose and its strength delivered over 2 minutes as shown in the respective figures; the internal standard phentolamine was given by oral gavage. The control group received vehicle alone. Immediately before (-10 min and -5

min) and at 15 min, 30 min, 1 hr, 1.5 hr, 2 hr, 2.5 hr, 3 hr, 3.5 hr, and 4 hr post-dosing, systolic pressure blood pressure values were recorded.

[1098] Certain compounds of the invention, when they were administered SC route or PO, remarkably lowered systolic blood pressure from 15 minutes through 2.5 hours and the effect was still evident throughout the 4 hour study period (See Figure 7). In addition, compound 3 was associated with a dose-dependent reduction in systolic blood pressure throughout the 4 hour study period (Figure 8). As illustrated, compound 3b (Figure 9) and compound 13b (Figure 10) lowered systolic blood pressure in SHR rats. Compound 41a, a mixed inhibitor of α_{2B} and α_{1B} markedly lowered blood pressure in SHR rats (Figure 10). When Compound 144b was tested i.v. bolus in 2 minutes, a marked reduction in systolic blood pressure was found (Figure 19). Compound 27a, Compound 176a and Compound 26a were tested escalating doses (1, 3, 10 and 30 mg/kg/iv for every 30 minutes), their systolic blood pressure lowering effects were robust (Figure 20, Figure 21, and Figure 22 respectively). Compound 27a had a neutral effect on heart rate when systolic blood pressure falls suggesting a peripheral effect (data not shown).

Example B6. α_{2B} Pharmacology: Studies in healthy dogs and dexmedetomidine (DEX) induced beagle dog model of hypertension.

[1099] These studies were conducted in both acute and chronic modes.

[1100] Four adult beagle dogs of both sex and weighted around 10 kg were chosen for the acute studies after a preliminary qualitative electrocardiogram/ECG, clinical pathology and physical examination. Upon arrival at the laboratory, the dogs were weighed and acclimated for a period of one week. Lab Diet certified canine diet # 5007, PMI Nutrition International Inc was made available ad libitum to all dogs except during fasting periods. The dogs were surgically implanted with a pressure transducer equipped telemetry transmitter under sodium pentobarbitone anesthesia. The transmitter assembly was secured internally, the fluid-filled catheter was placed into an appropriate artery.

[1101] In the acute studies, the test compounds 3b and 5b at different doses (dosing sequences provided in Table B7 for compound 3b and Table B8 for compound 5b) was administered by oral gavage, 30 minutes prior to intravenous dexmedetomidine (5 μg/kg) challenge. Dexmedetomidine administration was enabled by prior placement of a peripheral intravenous line. The same four dogs were received all four treatments in the order noted in the table below, with at least a 3-day washout period between treatments.

Table B7: Acute dosing sequence for Compound 3b

Compound 3b – 30 minute Pretreatment (mg/kg, p.o.)	Dexmedetomidine Challenge (µg/kg, i.v.)	Number of Dogs
18	0	4
18	5	4
6	5	4
2	5	4

Table B8: Acute dosing sequence for Compound 5b

Compound 5b – 30 minute Pretreatment (mg/kg, p.o.)	Dexmedetomidine Challenge (µg/kg, i.v.)	Number of Dogs
0	5	4
2	5	4
6	5	4
18	5	4
2	0	4
6	0	4
18	0	4

[1102] In another acute study with compound 41a, the test agent was administered a dose of 6 mg/kg by oral gavage to 4 healthy dogs; and the blood pressure monitored for a period of 4 hours.

[1103] For the chronic study mode (see Table B9), the test compound 3b at 3 doses was administered by oral gavage once on day 1 and then twice/day on days 2 to 14, and finally once on day 15. The dexmedetomidine was administered on day -4 to check its effectiveness in inducing blood pressure, and once following the morning dose of compound 3b or vehicle on days 2, 7 and 14. Blood pressure and heart rate data were collected 1h prior & 4h post-morning dose on days 1, 2, 7, 14 and 15 to allow the appropriate data comparisons. Blood aliquots were saved at 4h post-morning dose for exposure determination.

Table B9: Chronic dosing sequence and study design for Compound 3b

Compound 3b – 30 minute Pretreatment (mg/kg, p.o.) with b.i.d. regimen for 14 days			Dexmedetomidine Challenge (µg/kg, i.v.)			Number of Dogs
0			5			6
6			5			6
18			5			6
	Day					
	-4	1	2	7	14	15

Compound dosed on	-	am	am/pm	from day 2 am/pm	to day 14 am/pm	am
DEX*	am	-	am	am	am	-

* DEX administered 30 min following am dose of compound 3b.

[1104] In both acute and chronic studies, dogs were weighed before dosing. Cardiovascular evaluations at each dose of test compound were collected with animals gently restrained in a sling. Dogs were placed in the sling at least 1 hour prior to dose administration, and after at least 30 minutes of stable baseline data collection. The dogs were monitored continuously for 3-4 hours subsequent to test compound administration and summarized in 5-minute bins. The systolic blood pressure was collected. Data was reported as mean ± SEM or mean as presented in the Figures.

[1105] In acute studies, oral administration of compound 3b dose-dependently reduced systolic blood pressure in both healthy and dexmedetomidine induced dogs that were tested in the acute mode. Data on dexmedetomidine induced dogs is presented in Figure 11. Compound 5b as well dose-dependently reduced systolic blood pressure (Figure 12) in both healthy and dexmedetomidine induced (Figure 13) dogs tested. Compound 41a, mixed inhibitor of α_{2B} and α_{1B} caused a robust and long lasting reduction in systolic blood pressure (Figure 14) in all the 4 healthy dogs, with a slight decrease or neutral effect but not with an expected raise on heart rate, *i.e.*, blocking compensatory tachycardia when blood pressure falls suggests a peripheral mode of action. Compound 41a effects on several cardiovascular parameters and body temperature are also comparable with that of the same class (A1B) of marketed drug prazosin.

[1106] In chronic studies, oral administration of compound 3b dose dependently reduced systolic blood pressure on day 1 and 15 in healthy dogs; and dexmedetomidine induced dogs on day , 2, 7 and 14 of the 15-day study. Data on systolic blood pressure on day 1 in healthy dogs and dexmedetomidine induced dogs on day 2 are shown in the Figure 15 and Figure 16, respectively.

[1107] Adrenergic receptors α_{2B} and α_{2A} mixed inhibitor's pharmacology – Studies in Spontaneously Hypertensive Rat (SHR) Model of Hypertension: Similar to dosing regimen for selective antagonists of adrenergic receptor α_{2B}, the mixed inhibitors (e.g., Compound 129d) was dosed orally (PO) or intravenous (i.v bolus or escalating doses) to SHR rats. When compound 129d was tested oral or iv bolus or i.v. escalating does, its effects on systolic blood

pressure is robust (see Figure 23, Figure 24 and Figure 25) with tachycardia; and it is a perfect example that 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 metabolic syndrome.

Example B7. Peripheral and central effects of Compound 3d on blood pressure in conscious rabbits

[1108] **Methods:** Four adult New Zealand White rabbits of both sexes were chosen for these studies. The experiments were conducted in accordance with the Australian code of Practice for the Care and use of Animals for Scientific Purposes and approval was sought from the Animal Experimental Committee of Alfred Hospital, Baker IDI, Melbourne, Australia. The conscious rabbits were implanted with an intravenous catheter in marginal ear vein or by centrally by intracisternal catheter interfaced to a pressure transducer connected to a suitable recorder. To unveil peripheral effects of Compound 3b, two sets of acute studies were conducted in rabbits. In the first set of studies, Compound 3b was dosed to rabbit intravenously for a dose-response study with cumulative doses starting 0 (Ringer's Lock solution as a vehicle), 0.1, 0.3, 1, 3.2 and 10 mg/kg where each dose was tested on a separate day. A single intravenous bolus dose at 3 mg/kg was given and a time-course study was conducted in the second set of studies. Systolic, diastolic, mean and diastolic blood pressures were recorded in both the studies. Data collections were made for 3 hours in the second set of studies. Heart rate (HR) was derived electronically using an algorithm to determine HR from pulse interval. In a separate set of studies, Clonidine (positive control) was tested where all experimental procedures including dose-regimen were identical to that of the studies with Compound 3d.

[1109] **Results:** The mean arterial pressure responses to Compound 3d are dose-dependent in the dose-response study with cumulative doses (Figure 26, first panel). Compound 3b caused a maximum arterial blood drop of -11. 6 mmHg at a dose of 10 mg/kg. This effect is similar to the effect on diastolic blood pressure and greater than on systolic blood pressure (Figure 26, second and third panels). The dose that produced 80% of the maximum drop in blood pressure is 3 mg/kg. The reduction in blood pressure is associated with tachycardia (Figure 26, fourth panel). Clonidine produced a maximum drop of arterial blood pressure of -6 mmHg before the blood pressure reversed back (Figure 26, first panel) . In a single bolus dose at 3 mg/kg time-course study, Compound 3b produced relatively -6 mmHg drop in arterial blood pressure and it is stable

from 90 to 180 minutes and no indication of reversal of the effect (Figure 27, first panel). Identical effects were seen with systolic and diastolic blood pressures (Figure 27, second and third panels). These findings suggest that Compound 3b dose-dependently lowers blood pressure, most prominently mean arterial blood pressure, and these effects are stable for a period for 3 hours when it is administered intravenously.

[1110] In addition to studying the effect of Compound 3b on blood pressure and heart rate when the compound is administered intravenously, the blood pressure and heart rate effect of Compound 3b will also be measured following infusion of the compound directly into the brain with the cannula delivering the compound placed directly into the 4th ventrical of the brain. Several doses will be tested for cardiovascular effects following direct brain infusion. Comparison of the blood pressure effects following intravenous and ventricular infusion will determine whether the compound exerts its cardiovascular actions by the brain.

[1111] The long duration of blood pressure effect of Compound 3b suggests a reduction in blood volume that might result from diueresis and/or the movement of fluid from the vascular space to the extravascular space. This will be studied further by measuring the effect of Compound 3b as well as other α_{2B} antagonists on hematocrit as agents that reduce blood volume should increase hematocrit. Characterization of the effect of α_{2B} antagonists on renal function will also be studied 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 Sandra L. Burke, Roger G. Evans and Geoffrey A. Head. Journal of Hypertens 29:945–952 (2011).

Example B8. Human clinical studies

[1112] The compound is studied in a clinical trial of hypertensive patients who have not reached their blood pressure goals on current therapy. The target patient population are patients with refractory hypertension that have not reached their blood pressure goals despite use of at least 3 different blood pressure agents. The study compares the active compound against a matched placebo compound with the primary objective of comparing mean blood pressure change from baseline to the end of the study between the active compound and placebo.

[1113] All references throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

[1114] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.

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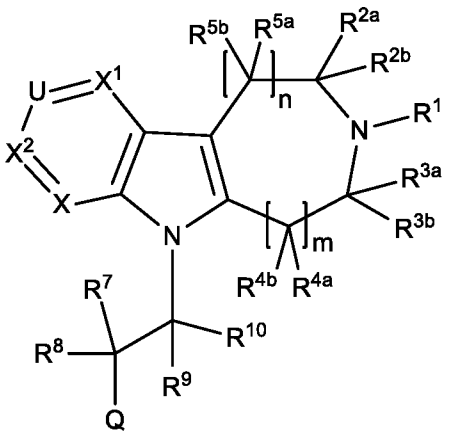
CLAIMS

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):



(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_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;

each R^{1a} is independently 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; 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}, 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; 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 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.

2. The method of claim 1, wherein:

(i) the individual has high blood pressure;

(ii) the method reduces systolic blood pressure of the individual;

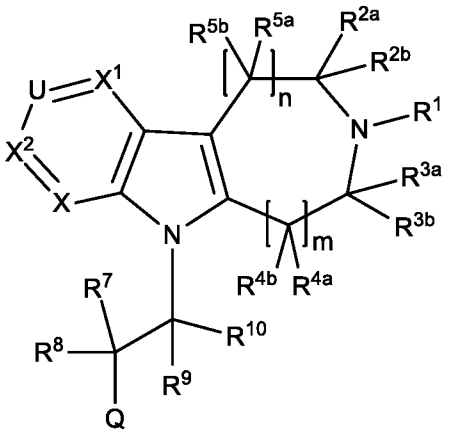
(iii) the method reduces diastolic blood pressure of the individual;

(iv) the method reduces (a) mean arterial blood pressure, or (b) pulse pressure, of the individual;

(v) the method does not substantially increase heart rate of the individual; and/or

(vi) the individual has one or more risk factors for developing high blood pressure.

3. 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):



(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_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;

each R^{1a} is independently 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; 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}, 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; 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 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.

4. The method of claim 3, wherein:

(i) the method results in increase in renal blood flow;

(ii) the method results in decrease in sodium reabsorption;

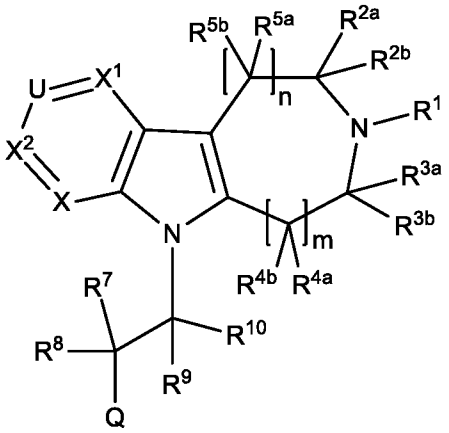
(iii) the method results in increase in urine sodium content and/or increase in urine volume;

(iv) the method results in any one or more of: (a) reducing edema, (b) reducing elevated blood urea nitrogen to creatinine (BUN/Cr) ratio, and (c) decreasing creatinine levels; and/or

(v) the individual has or is at risk of developing acute or chronic congestive heart failure, acute decompensated congestive heart failure, acute or chonic renal failure, or acute or chronic renal failure due to renal insufficiency.

5. 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):



(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_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;

each R^{1a} is independently 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; 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}, 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; 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 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.

6. The method of claim 5, wherein the disease or condition is hypertension.

7. The method of claim 5, wherein the disease or condition is:

(i) treatment-resistant hypertension;

(ii) hypertensive emergency; and/or

(iii) a cardiac or renal disease or condition.

8. The method of any one of claims 1-7, wherein:

(i) 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;

(ii) 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; or

(iii) each X^1, X^2, X and U is independently CR^6.

9. The method of any one of claims 1-8, wherein Q is:

unsubstituted aryl;

unsubstituted heteroaryl;

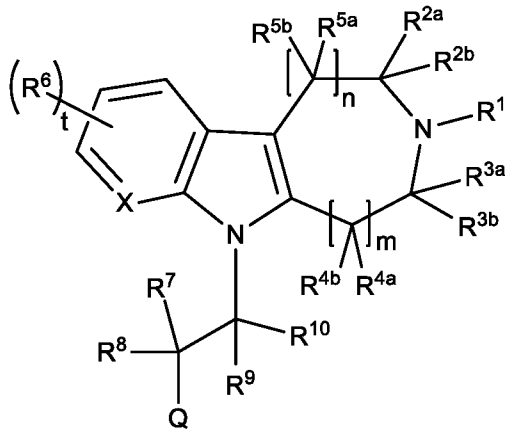
aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl, $N(R^{16})(R^{17})$, $-C(O)OR^{18}$, SR^{18}, $S(O)R^{18}$ and SO_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, aminoacyl, $N(R^{16})(R^{17})$, $-C(O)OR^{18}$, 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.

10. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (A-III):



(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 ($-CH_2CH_2CH_2-$) 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 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; 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 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.

11. The method of claim 10, wherein at least one of the following applies:

(i) X is CR^{6a}, wherein each R^{6a} is independently H, halo or C_1-C_5 alkyl;

(ii) R^{6a} is H;

(iii) each R^6 is independently H, halo or C_1-C_5 alkyl;

(iv) X is N;

(v) R^1 is H or C_1-C_5 alkyl;

(vi) each R^{2a} and R^{3a} is H;

(vii) R^7 is H or C_1-C_5 alkyl;

(viii) R^8 is H, hydroxyl, $N(R^{11})R^{12}$ or -$OC(O)C_1$-C_5 alkyl;

(ix) R^8 is hydroxyl;

(x) 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;

(xi) R^7 is H, and R^8 is H, hydroxyl, $N(R^{11})R^{12}$ or -$OC(O)C_1$-C_5 alkyl;

(xii) 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;

(xiii) R^7 is H or C_1-C_5 alkyl, and R^8 is H or hydroxyl;

(xiv) R^7 is H or C_1-C_5 alkyl, and R^8 is hydroxyl;

(xv) R^7 is H, and R^8 is hydroxyl;

(xvi) R^7 is methyl, and R^8 is hydroxyl;

(xvii) R^7 is H, and R^8 is NH_2;

(xviii) R^7 is H, and R^8 is -$OC(O)C_1$-C_5 alkyl;

(xix) R^9 is H or C_1-C_5 alkyl;

(xx) R^{10} is H or C_1-C_5 alkyl;

(xxi) R^9 and R^{10} is H;

(xxii) one of R^9 and R^{10} is H and the other is C_1-C_5 alkyl; and

(xxiii) 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 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;

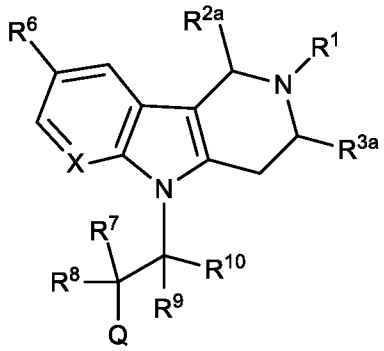
pyrazinyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and $-C(O)NR^{16}R^{17}$, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl;

phenyl 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;

imidazolyl 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; or

triazolyl 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.

12. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (A-IIIA):



(A-IIIA)

,

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^{2a} or R^{3a} to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 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, 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.

13. The method of claim 12, wherein at least one of the following applies:

(i) X is CH;

(ii) X is N;

(iii) R^1 is H or CH_3;

(iv) R^{2a} is H or is taken together with R^1 to form a propylene ($-CH_2CH_2CH_2-$) moiety;

(v) R^{3a} is H;

(vi) each R^6 and R^{6a} is independently H, halo or C_1-C_5 alkyl;

(vii) R^7 is H or CH_3;

(viii) R^8 is hydroxyl; and

(ix) 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;

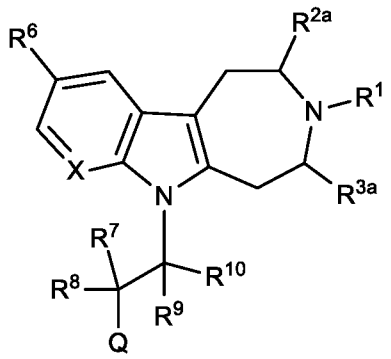
pyrimidyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3;

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.

14. The method of claim 12, wherein X is N.

15. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (A-IIID):



(A-IIID) ,

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^{2a} or R^{3a} to form a propylene (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 (-$CH_2CH_2CH_2$-) moiety or a butylene (-$CH_2CH_2CH_2CH_2$-) 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 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, 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.

16. The method of claim 15, wherein at least one of the following applies:

(i) X is CH;

(ii) R^1 is H or CH_3;

(iii) each R^6 and R^{6a} is independently H, halo or C_1-C_5 alkyl;

(iv) R^7 is H or CH_3;

(v) R^8 is hydroxyl; and

(vi) Q is:

unsubstituted pyridyl;

unsubstituted pyrimidyl;

unsubstituted pyrazinyl;

unsubstituted phenyl;

unsubstituted imidazolyl;

unsubstituted triazolyl;

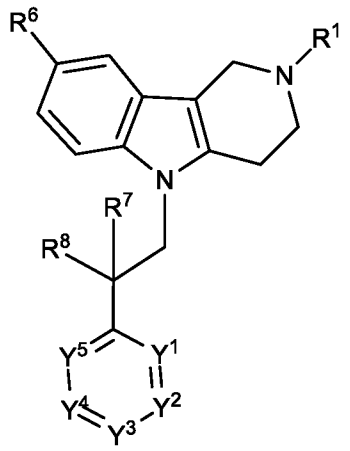
pyridyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3;

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.

17. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (A-IIIE-2):



(A-IIIE-2)

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;

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.

18. The method of claim 17, wherein at least one of the following applies:

(i) 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;

(ii) 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;

(iii) each R^4 is independently H, halo, CH_3, CF_3, or OCH_3;

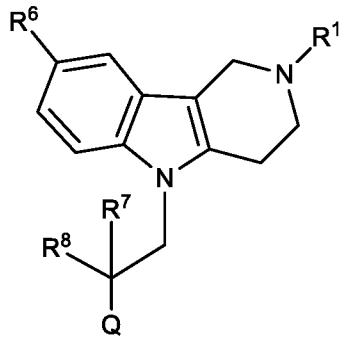
(iv) R^1 is H or CH_3;

(v) R^6 is CH_3 or chloro;

(vi) R^7 is H or CH_3; and

(vii) R^8 is hydroxyl.

19. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (A-IIIE-6):



(A-IIIE-6)

,

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;

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;

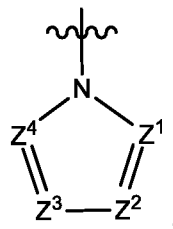
R^8 is H, halo, hydroxyl, $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, -OC(O)$N(R^{14})R^{15}$, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a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

Q is



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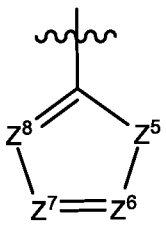

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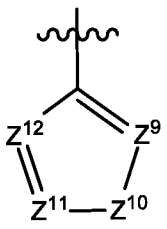


,

wherein

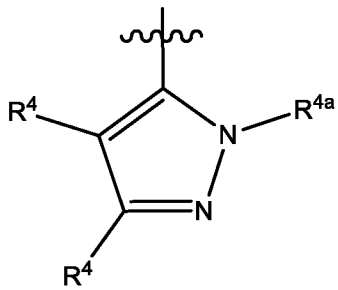
each Z^1, Z^2, Z^3 and Z^4 is independently N or CR^4 such that no more than two of Z^1, Z^2, Z^3 and Z^4 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3;

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^4 is H, halo, CH_3, CF_3, or OCH_3.

20. The method of claim 19, wherein at least one of the following applies:

(i) Q is selected from the group consisting of: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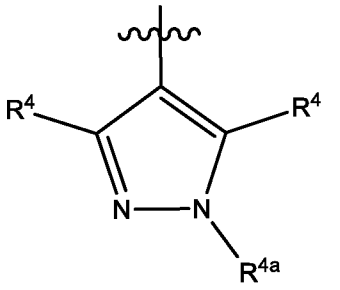
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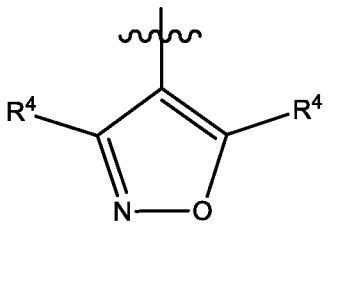
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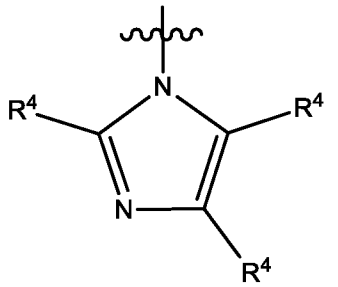
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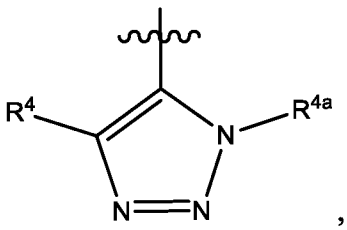
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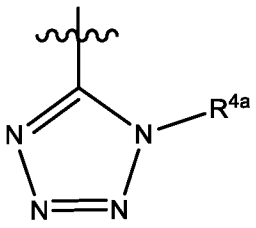
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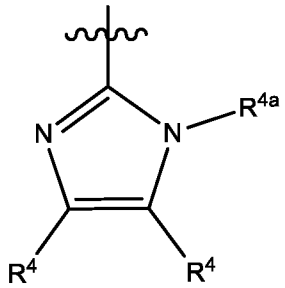
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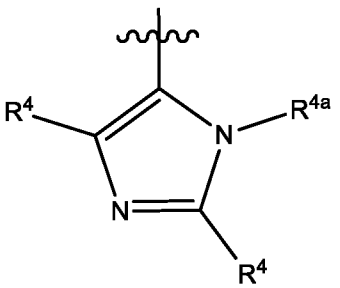
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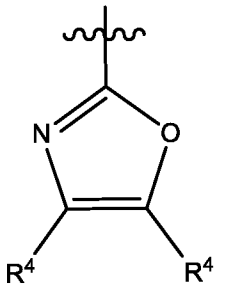
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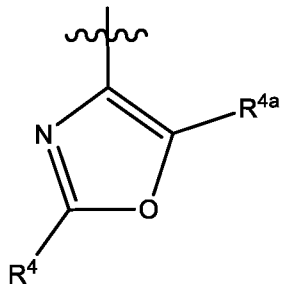
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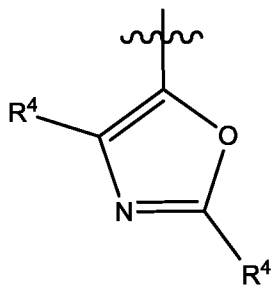
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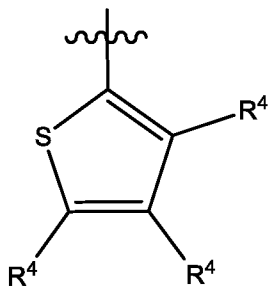
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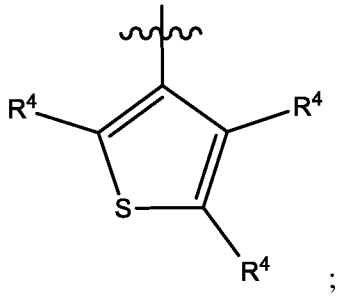

;

(ii) R^1 is H or CH_3;

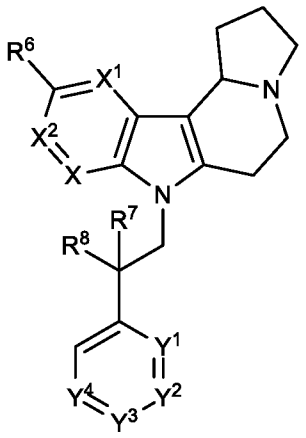
(iii) R^6 is CH_3 or chloro;

(iv) R^7 is H or CH_3;

(v) R^8 is hydroxyl; and

(vi) R^8 is hydroxyl.

21. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (C-IA):



(C-IA)

,

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

R^6 is H; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substitutents independently selected from halogen atoms and 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; or -$OC(O)C_1$-C_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-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; 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.

22. The method of claim 21, wherein at least one of the following applies:

(i) each of X^1, X^2 and X is CH;

(ii) R^6 is CH_3 or chloro;

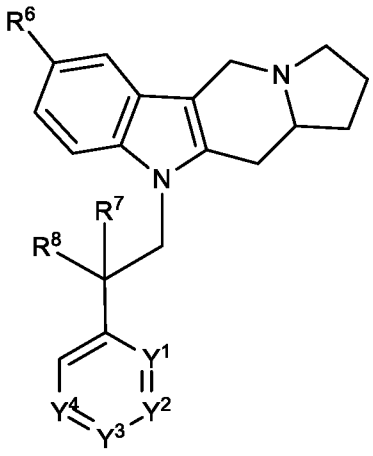
(iii) R^7 and R^8 are H;

(iv) 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;

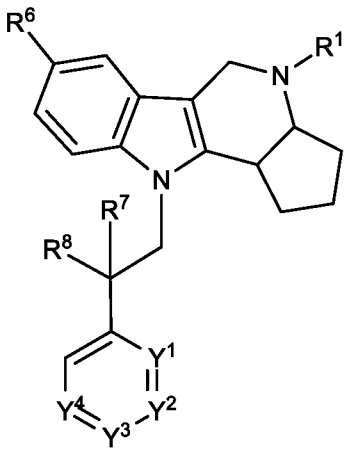
(v) each of Y^1, Y^3 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^2 is N; and

(vi) 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.

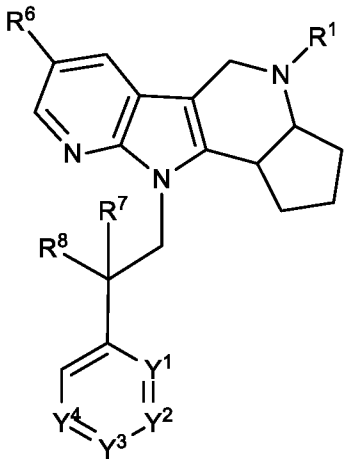
23. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (D-IIA-1), (E-IIA-1), (E-IIA-2), (F-IIA-1), (F-IIA-2), (G-IIA-1), or (G-IIA-2):



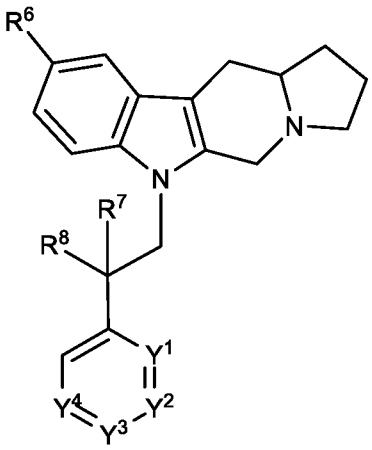
(D-IIA-1),



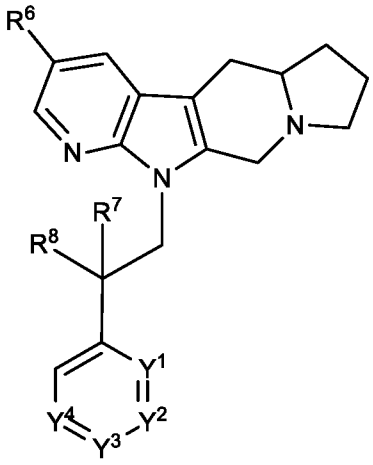
(E-IIA-1),



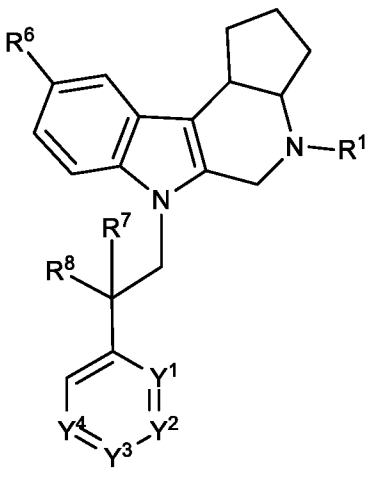
(E-IIA-2),



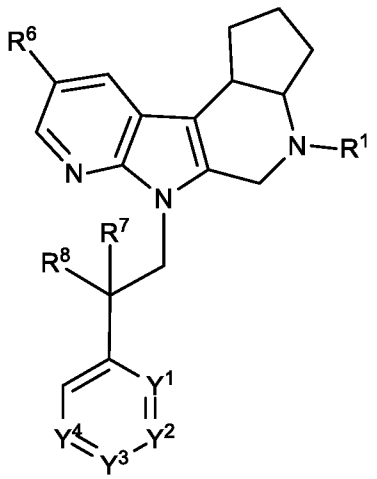
(F-IIA-1),



(F-IIA-2),



(G-IIA-1),



or (G-IIA-2) ,

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

R^6 is H; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halogen atoms and hydroxyl; C_3-C_8 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halogen atoms and 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; or $-OC(O)C_1$-C_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-C_5 alkyl; 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 R^4 is H, halo, CH_3, CF_3, or OCH_3.

24. The method of claim 23, wherein at least one of the following applies:

(i) R^6 is unsubstituted C_1-C_5 alkyl or halo;

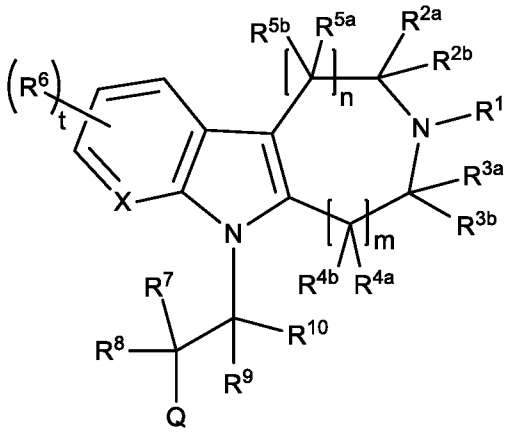
(ii) R^7 and R^8 are H;

(iii) 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;

(iv) 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; and

(v) 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.

25. The method of any one of claims 1-7, wherein the compound of formula (I) is a compound of formula (B-I):



(B-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 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 (-$CH_2CH_2CH_2$-) 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 (-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 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 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 1-3 substituents 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;

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 1-3 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.

26. The method of claim 25, wherein at least one of the following applies:

(i) X is CR^{6a}, wherein each R^{6a} is independently H, halo or C_1-C_5 alkyl;

(ii) each R^6 is independently H, halo or C_1-C_5 alkyl;

(iii) X is N;

(iv) R^1 is H or C_1-C_5 alkyl;

(v) each R^{2a} and R^{3a} is H;

(vi) R^7 is H or optionally substituted C_1-C_5 alkyl;

(vii) R^8 is azido;

(viii) R^9 is H or C_1-C_5 alkyl;

(ix) R^{10} is H or C_1-C_5 alkyl; and

(x) 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.

27. The method of any one of claims 1-7, wherein the compound is:

(i) selected from Table I, Table II, Table III, Table IV or Table V; or a salt, solvate or N-oxide thereof;

(ii) 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;

(iii) 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, 144b, 148, 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; or

(iv) 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, 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, 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, 127, 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, 193, 193a, 193b, 194a, 194b, 196, 196a, 196b, 197, 197a, 197b, 198, 198a, 198b, 198c, 198d, 199a, 199b, 203a, 203b, 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, II-9, II-10, II-11, II-11a, II-11b, II-12, II-12a, II-12b, II-13, II-13a, II-13b, II-14a, II-14b, II-15a, II-15b, II-16a, II-16b, II-17, II-18, II-19, II-39, II-40, II-49a, II-49b, II-57a, II-57b, II-58, II-59, II-60, II-61, II-62, II-63, II-64, II-65, II-67, II-68, II-70, II-71, II-75, II-76, II-77, II-78, II-80, II-81, II-82, II-83, II-84, II-88, II-89, II-90, II-91, II-92, II-93a, II-93b, II-94a, II-94b, II-95a, II-95b, II-96, II-97, II-98a, II-98b, II-99a, II-99b, II-100a, II-100b, II-101, II-102, II-103, II-104, II-105, II-106a, II-106b, II-108a, II-108b, II-109a, II-109b, II-110, II-111, II-112a, II-112b, II-113a, II-113b, II-114a, II-114b, II-115a, II-115b, II-115c, II-115d, II-116, II-117, II-118a, II-118b, II-119, II-120a, II-120b, II-121a, II-121b, II-122, II-123a, II-123b, II-124a, II-124b, II-125a, II-125b, II-125c, II-125d, II-126, II-127a, II-127b, II-128a, II-128b, II-129, II-130, II-130a, II-130b, II-131, II-132a, II-132b, II-133, II-134a, II-134b, II-135a, II-135b, II-136a, II-136b, II-137, II-138, II-139, II-140, II-141, II-142, II-143, II-144, II-145, II-146a, II-146b, II-146c, II-146d, II-147a, II-147b, II-147c, II-147d, II-148, II-148a, II-148b, II-149a, II-149b, II-149c, II-149d, II-150, II-151a,

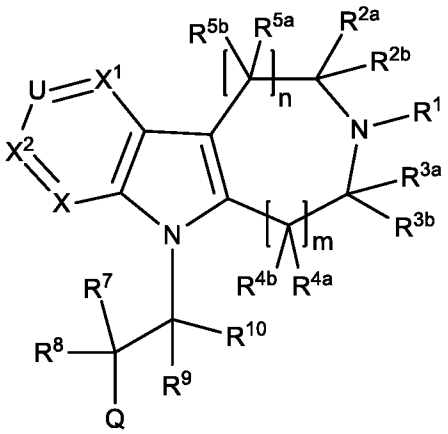
II-151b, II-152a, II-152b, II-152c, II-152d, II-153, II-154, II-209, II-210, II-211, II-212, II-212a, II-212b, II-213, II-215, II-220, II-221, II-222, II-223, II-224, II-224a, II-224b, II-225, II-226, II-227a, II-227b, II-227c, II-227d, II-229, II-230, II-231, II-232, II-240, II-241, II-242, II-243, II-244a, II-244b, II-245, II-246, II-247, II-248, II-249, II-250, II-251, II-252, II-253, II-255a, II-255b, II-256, II-257, II-258, II-259, II-260a, II-260b, II-261, II-261a, II-261b, II-262, II-263, II-264, II-265a, II-265b, II-266, II-267, II-268, II-269, II-270, II-271, II-272, II-273, II-274, II-275, II-276, II-277, II-278, II-279, II-280, II-281, II-282a, II-282b, II-282c, II-282d, II-283, II-284, II-285, II-286, II-287, II-288, II-289, II-290a, II-290b, II-291a, II-291b, II-291c, II-291d, II-292, II-293a, II-293b, II-293c, II-293d, II-294a, II-294b, II-294c, II-294d, II-295, II-296a, II-296b, II-297, II-298, II-299, IV-8, IV-8a, IV-8b, IV-93a, IV-93b, IV-209a, IV-209b, IV-209c, IV-209d, IV-210a, IV-210b, IV-210c, IV-210d, V-1, V-1a, V-1b, V-2, V-2a, V-2b, V-3, V-3a, V-3b, V-14, V-14a, V-14b, V-15, V-15a, V-15b, V-15c, V-15d, V-18, V-18a, V-18b, V-18c, V-18d, V-21, V-21a, V-21b, V-22, V-22a, V-22b, V-23, V-23a and V-23b; or a salt, solvate or N-oxide thereof.

28. The method of any one of claims 1-27, wherein the compound is an adrenergic receptor α_{2B} antagonist, and optionally:

(i) an adrenergic receptor α_{1B} antagonist; and/or

(ii) an adrenergic receptor α_{1D} antagonist.

29. A kit comprising (i) a compound of formula (I)



(I)

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;

each R^{1a} is independently 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; 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}, 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; 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 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

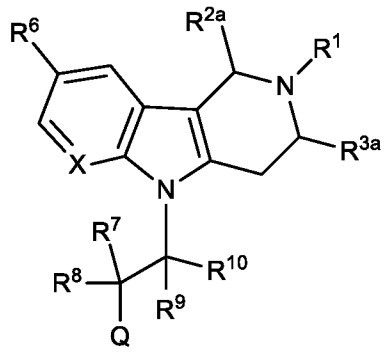
Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl,

or a pharmaceutically acceptable salt thereof,

and

(ii) instructions for use, when used according to the method of any one of claims 1 to 7.

30. A kit comprising (i) a compound of formula (A-IIIA):



(A-IIIA)

,

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^{2a} or R^{3a} to form a propylene ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 ($-CH_2CH_2CH_2-$) moiety or a butylene ($-CH_2CH_2CH_2CH_2-$) 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 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, 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,

or a pharmaceutically acceptable salt thereof,

and

(ii) instructions for use, when used according to the method of any one of claims 12 to 14.

31. A compound selected from the group consisting of Compound Nos. 6, 9 to 12, 14, 16 to 21, 23 to 28, 39, 40, 42, 44 to 59, 63 to 72, 77 to 82, 104, 108 to 116, 118 to 131, 133 to 142, 144 to 171, 173 to 179, 187 to 192, 195 to 198, 220, 269 to 271, 273 to 287, 290 to 306,

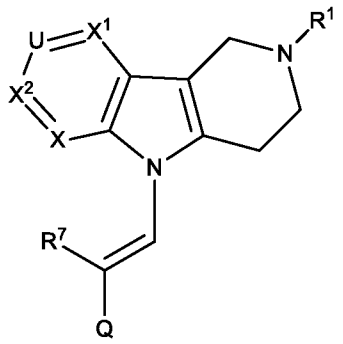
308 to 319, 321 to 338, 340 to 343, II-1 II-19, II-39 to II-40, II-58 to II-65, II-67 to II-68, II-70 to II-71, II-75 to II-77, II-80 to II-84, II-88 to II-94, II-96 to II-106, II-108 to II-118, II-120 to II-154, II-188 to II-206, II-212 to II-213, II-215, II-220-II-227, II-229 to II-232, II-240 to II-253, II-255 to II-272, II-274 to II-298, IV-1, IV-3, IV-8 to IV-244, and V-1 to V-23, or a salt thereof.

32. A pharmaceutical composition comprising a compound of claim 31, or a salt thereof, and a pharmaceutically acceptable carrier.

33. A kit comprising (i) a compound of claim 31 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.

34. The kit of claim 33, 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.

35. A compound of formula (H-IC):



(H-IC)

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

X is N;

each X^1, X^2, 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.

36. The compound of claim 35, or a salt, solvate or N-oxide thereof, wherein Q is optionally substituted pyridyl.

37. The compound of claim 35, wherein the compound is Compound No. 78, or a salt thereof.

38. The compound of claim 35, wherein the compound is Compound No. 124, or a salt thereof.

39. The compound of claim 35, wherein the compound is Compound No. 335, or a salt thereof.

40. A pharmaceutical composition comprising a compound of any one of claims 37 to 39, or a salt thereof, and a pharmaceutically acceptable carrier.

41. A composition of substantially pure Compound No. 3b, or a salt thereof.

42. The composition of claim 41, wherein the composition contains no more than 15% of Compound No. 3a, or a salt thereof.

43. The composition of claim 41, wherein the composition contains no more than 5% of Compound No. 3a, or a salt thereof.

44. The composition of claim 41, wherein the composition contains no more than 3% of Compound No. 3a, or a salt thereof.

45. The composition of claim 41, wherein the composition contains no more than 1% of Compound No. 3a, or a salt thereof.

46. A pharmaceutical composition comprising a compositon of any one of claims 41 to 45, or a salt thereof, and a pharmaceutically acceptable carrier.

47. A composition of substantially pure Compound No. 5b, or a salt thereof.

48. The composition of claim 47, wherein the composition contains no more than 15% of Compound No. 5a, or a salt thereof.

49. The composition of claim 47, wherein the composition contains no more than 5% of Compound No. 5a, or a salt thereof.

50. The composition of claim 47, wherein the composition contains no more than 3% of Compound No. 5a, or a salt thereof.

51. The composition of claim 47, wherein the composition contains no more than 1% of Compound No. 5a, or a salt thereof.

52. A pharmaceutical composition comprising a compositon of any one of claims 47 to 51, or a salt thereof, and a pharmaceutically acceptable carrier.

Figure 1

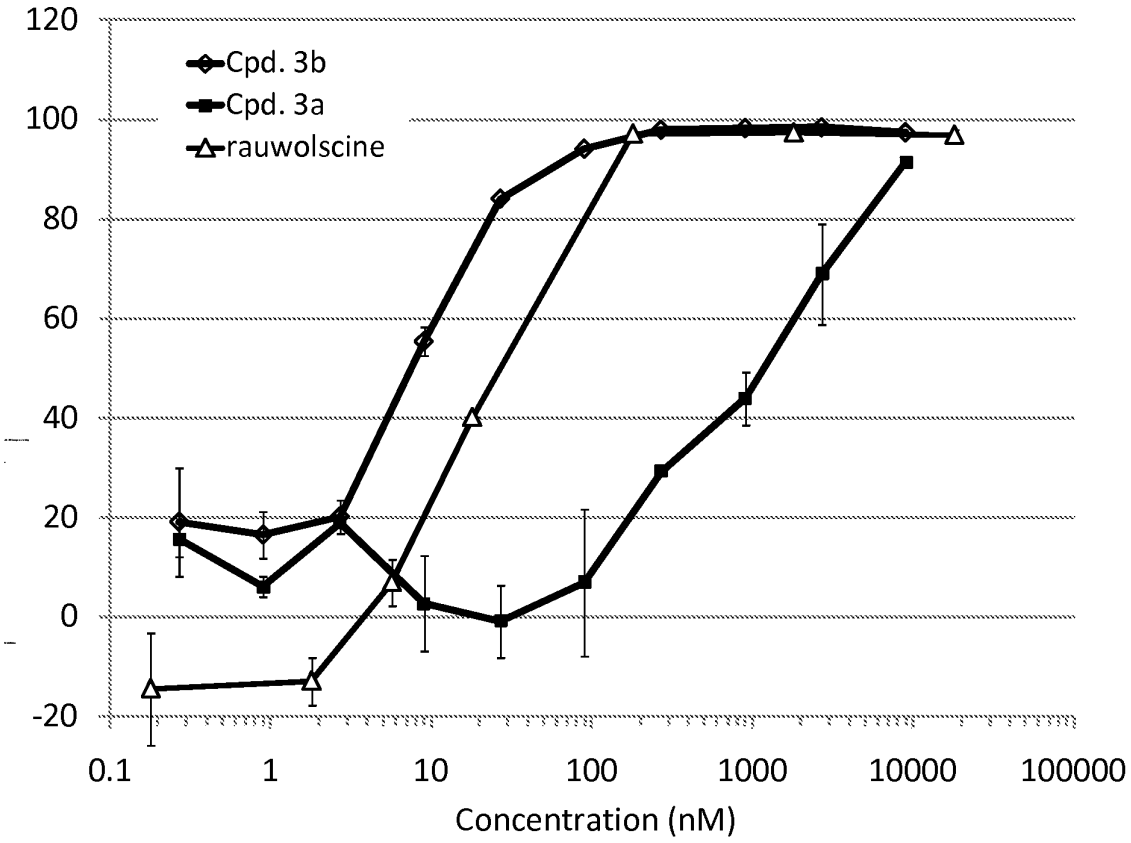

120
100
80
60
40
20
0
-20
Cpd. 3b
Cpd. 3a
rauwolscine
0.1
1
10
100
1000
10000
100000
Concentration (nM)

Figure 2

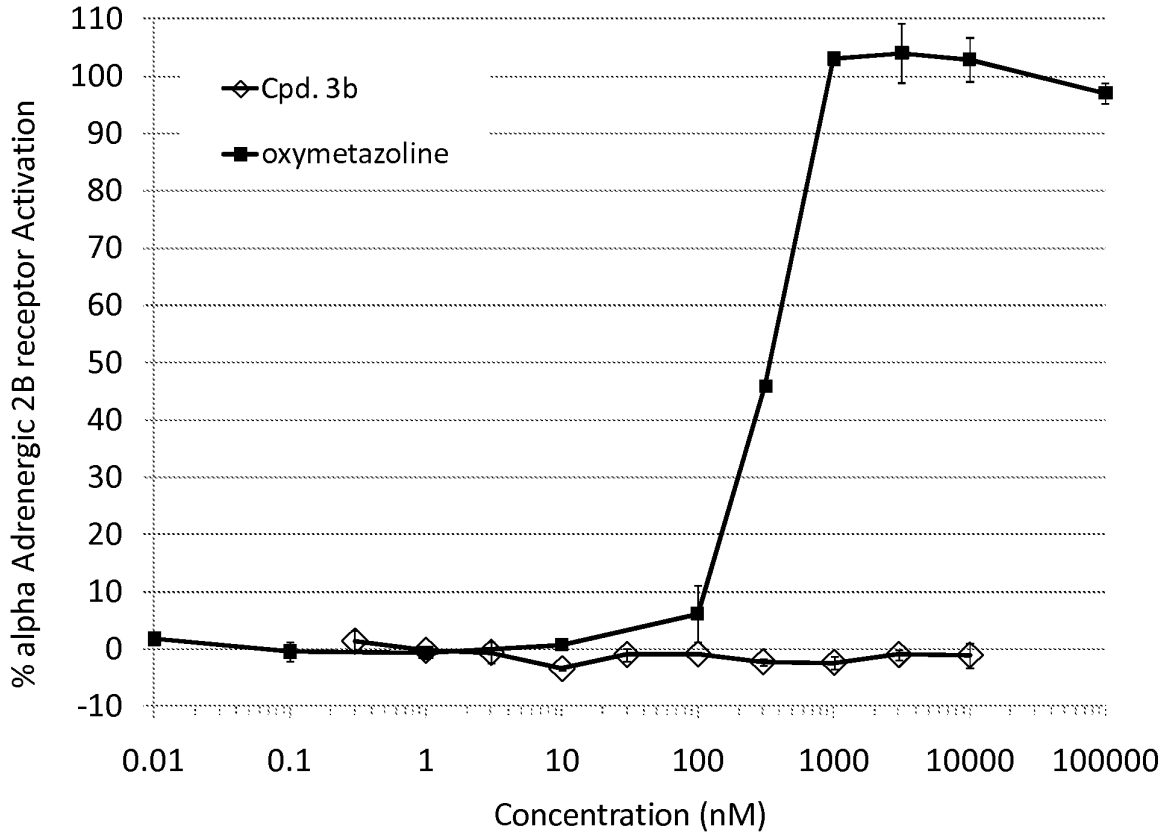

110
100
90
80
70
60
50
40
30
20
10
0
-10
% alpha Adrenergic 2B receptor Activation
Cpd. 3b
oxymetazoline
0.01
0.1
1
10
100
1000
10000
100000
Concentration (nM)

Figure 3

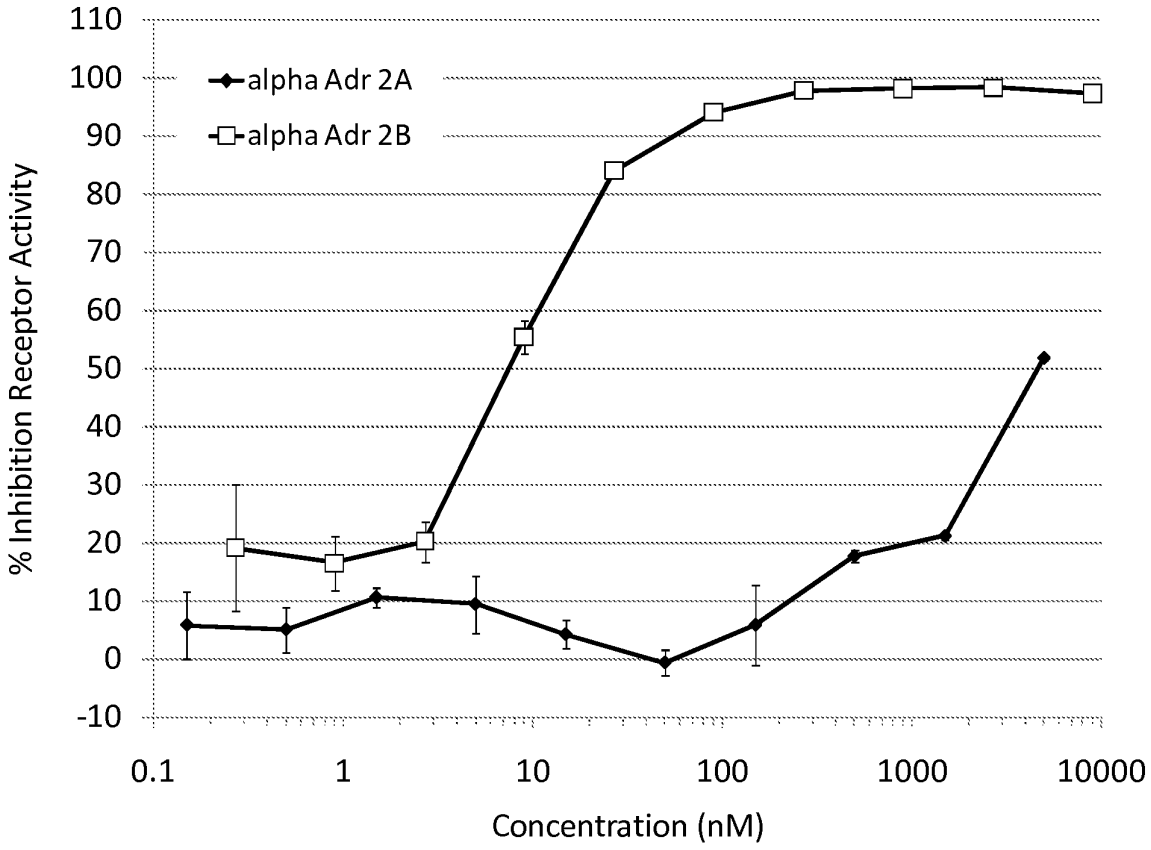

110
100
90
80
70
60
50
40
30
20
10
0
-10
% Inhibition Receptor Activity
alpha Adr 2A
alpha Adr 2B
0.1
1
10
100
1000
10000
Concentration (nM)

Figure 4

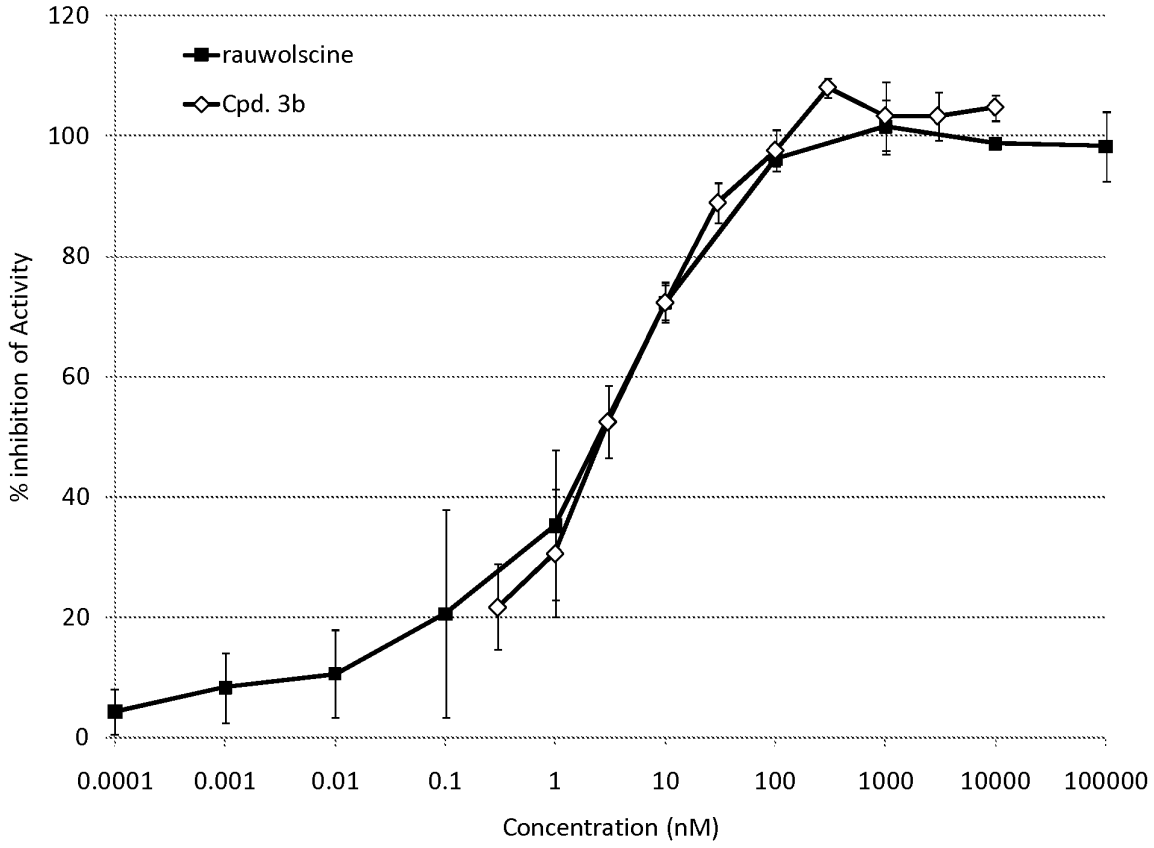

120
100
80
60
40
20
0
% inhibition of Activity
rauwolscine
Cpd. 3b
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
100000
Concentration (nM)

Figure 5

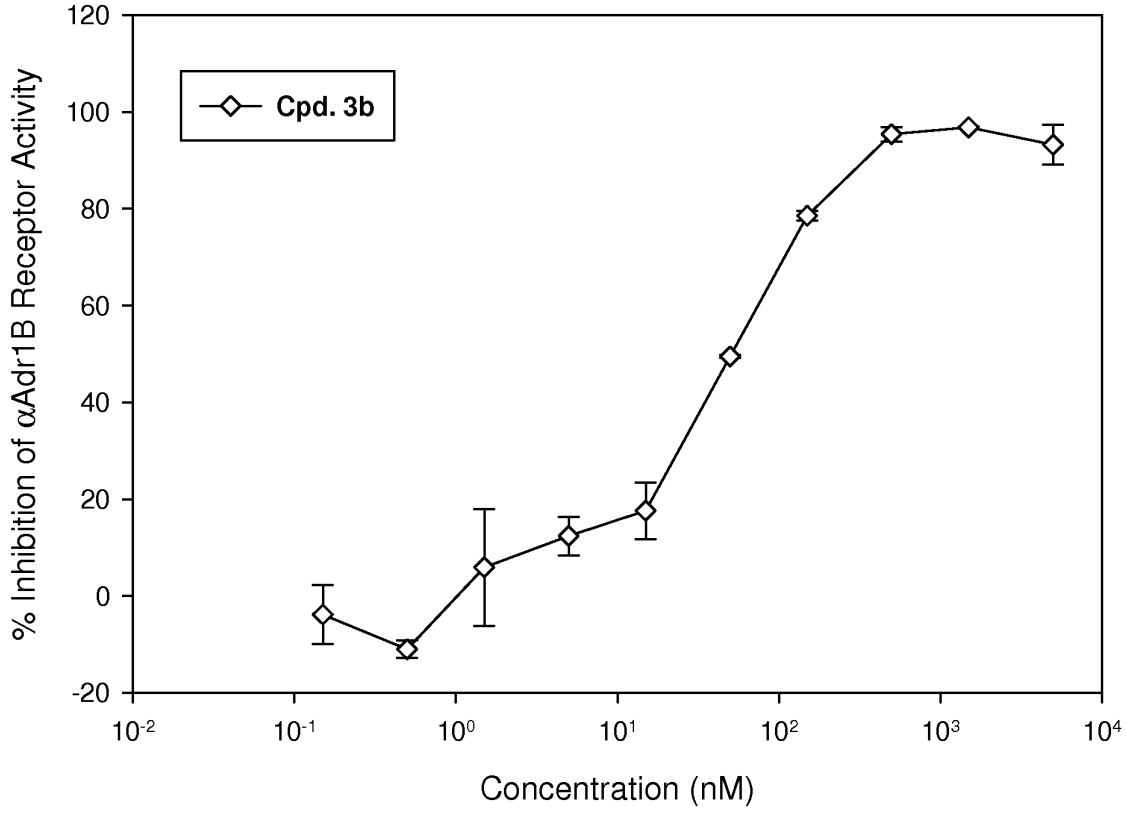

120
100
80
60
40
20
0
-20
% Inhibition of αAdr1B Receptor Activity
Cpd. 3b
10-2
10-1
100
101
102
103
104
Concentration (nM)

Figure 6

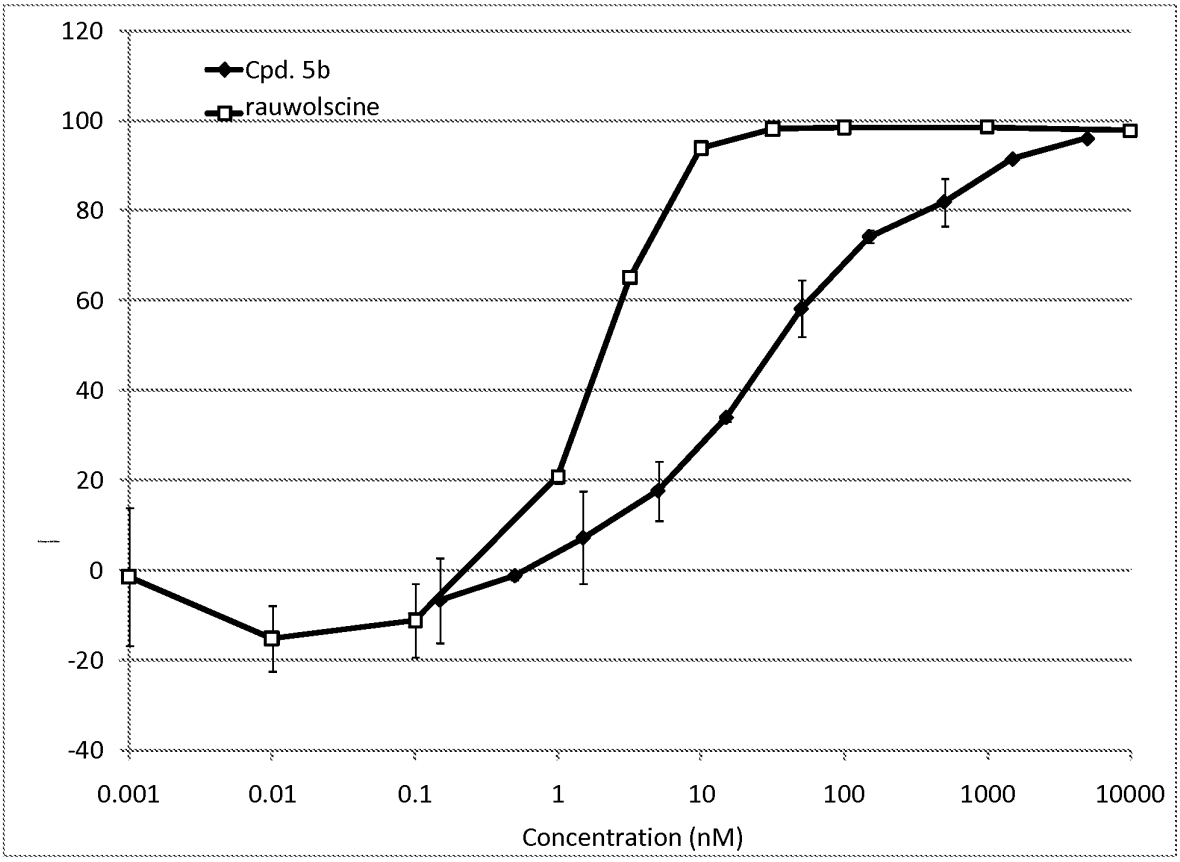

120
100
80
60
40
20
0
-20
-40
Cpd. 5b
rauwolscine
0.001
0.01
0.1
1
10
100
1000
10000
Concentration (nM)

Figure 7

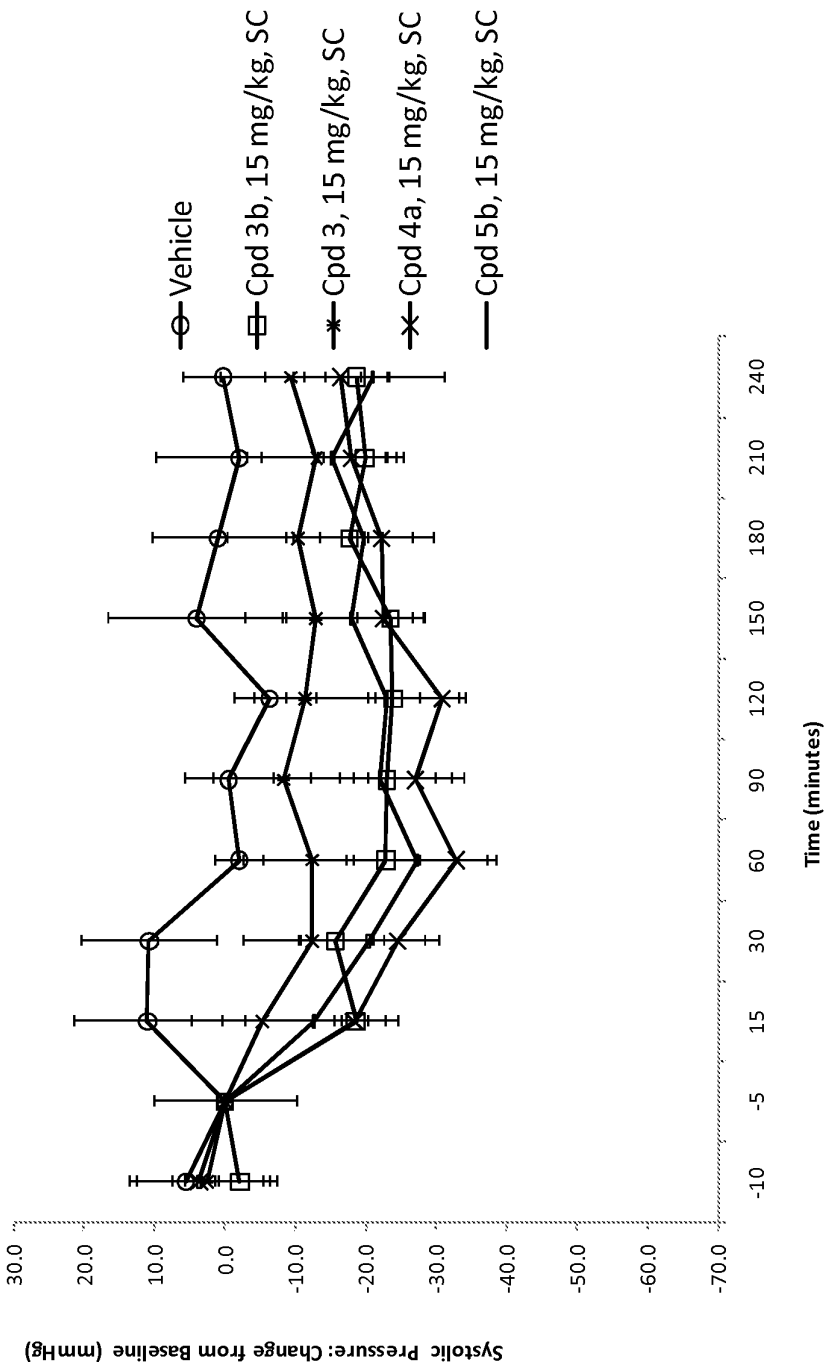

Vehicle
Cpd 3b, 15 mg/kg, SC
Cpd 3, 15 mg/kg, SC
Cpd 4a, 15 mg/kg, SC
Cpd 5b, 15 mg/kg, SC
30.0
20.0
10.0
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-10
-5
15
30
60
90
120
150
180
210
240
Time (minutes)
Systolic Pressure: Change from Baseline (mmHg)

Figure 8

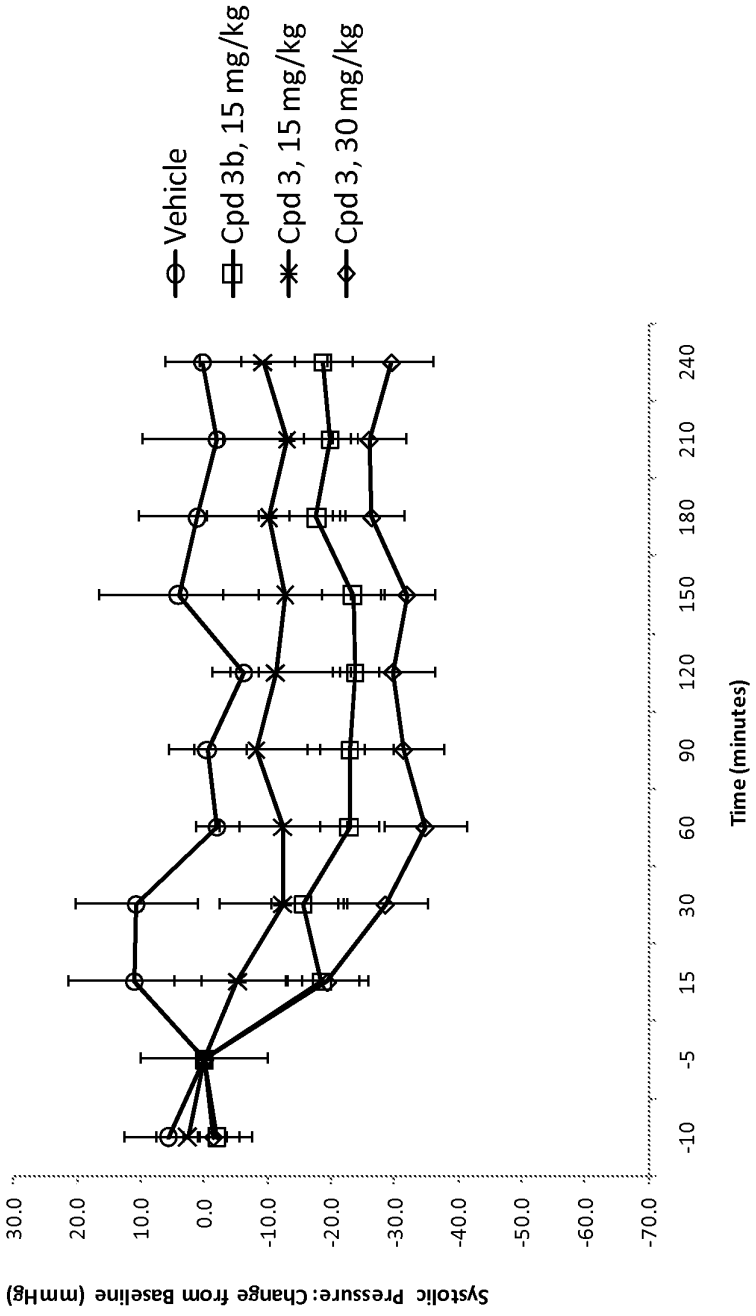

Vehicle
Cpd 3b, 15 mg/kg
Cpd 3, 15 mg/kg
Cpd 3, 30 mg/kg
30.0
20.0
10.0
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-10
-5
15
30
60
90
120
150
180
210
240
Time (minutes)
Systolic Pressure: Change from Baseline (mmHg)

Figure 9

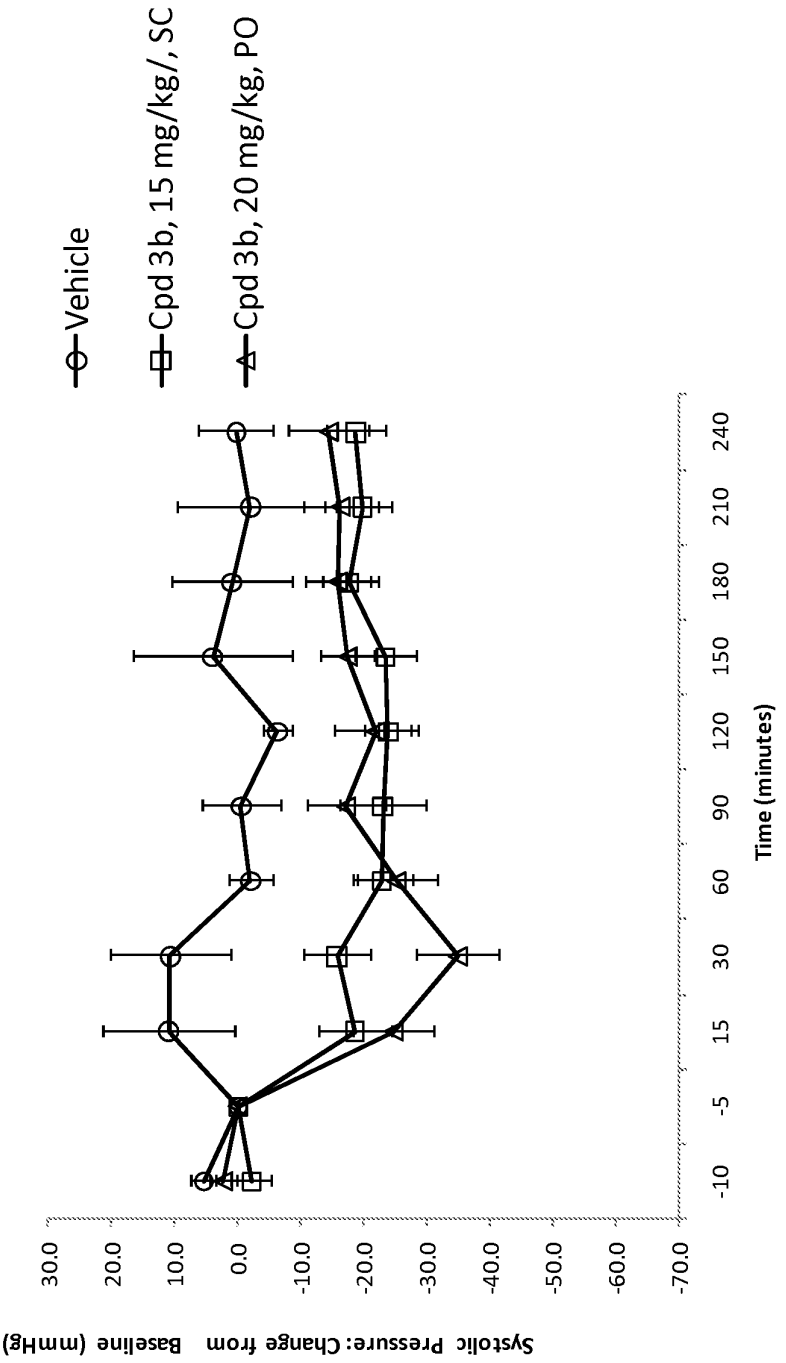

Vehicle
Cpd 3b, 15 mg/kg/, SC
Cpd 3b, 20 mg/kg, PO
30.0
20.0
10.0
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-10
-5
15
30
60
90
120
150
180
210
240
Time (minutes)
Systolic Pressure: Change from Baseline (mmHg)

Figure 10

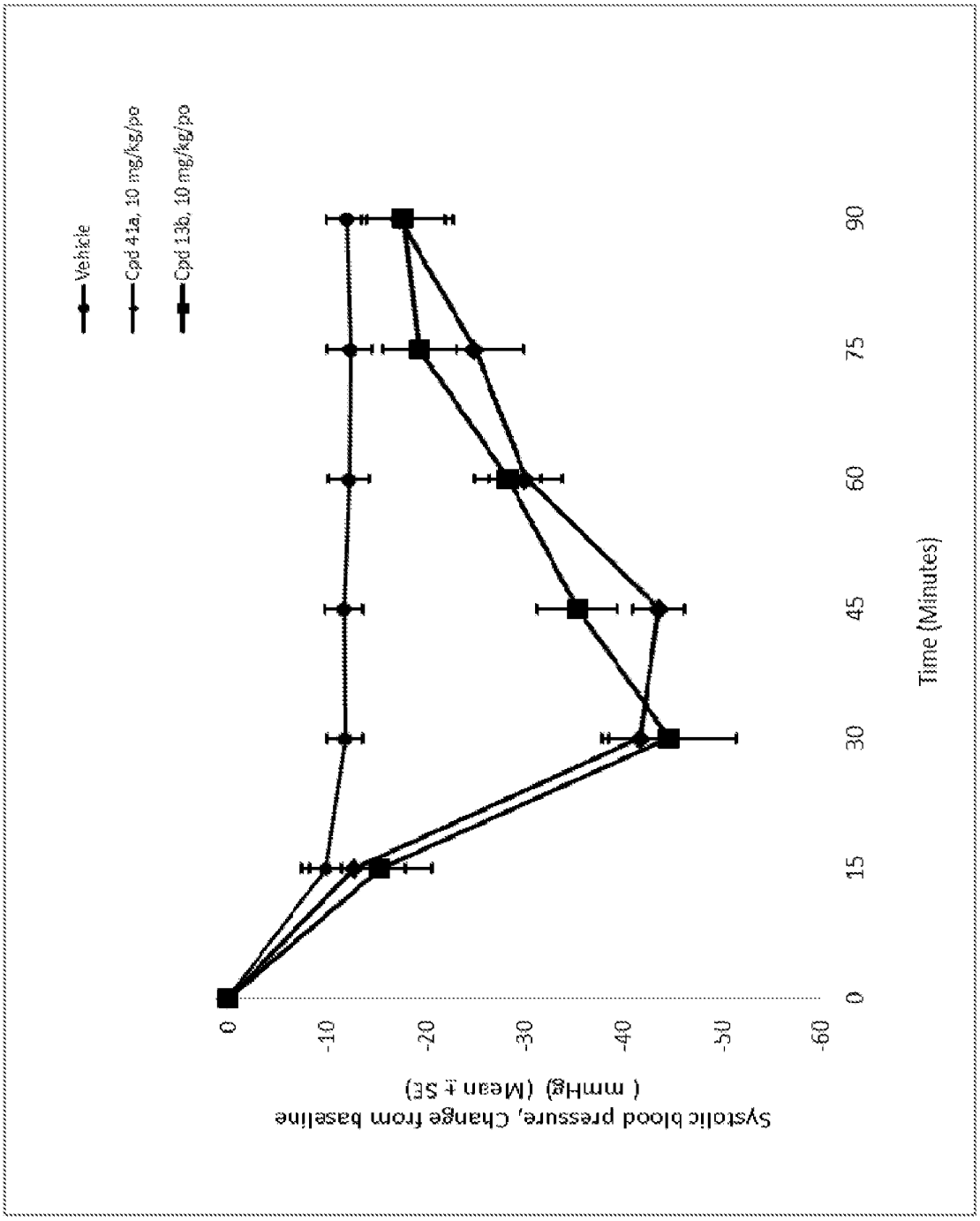

Vehicle
Cpd 41a, 10 mg/kg/po
Cpd 13b, 10 mg/kg/po
Systolic blood pressure, Change from baseline
(mmHg) (Mean ± SE)
0
-10
-20
-30
-40
-50
-60
0
15
30
45
60
75
90
Time (Minutes)

Figure 11

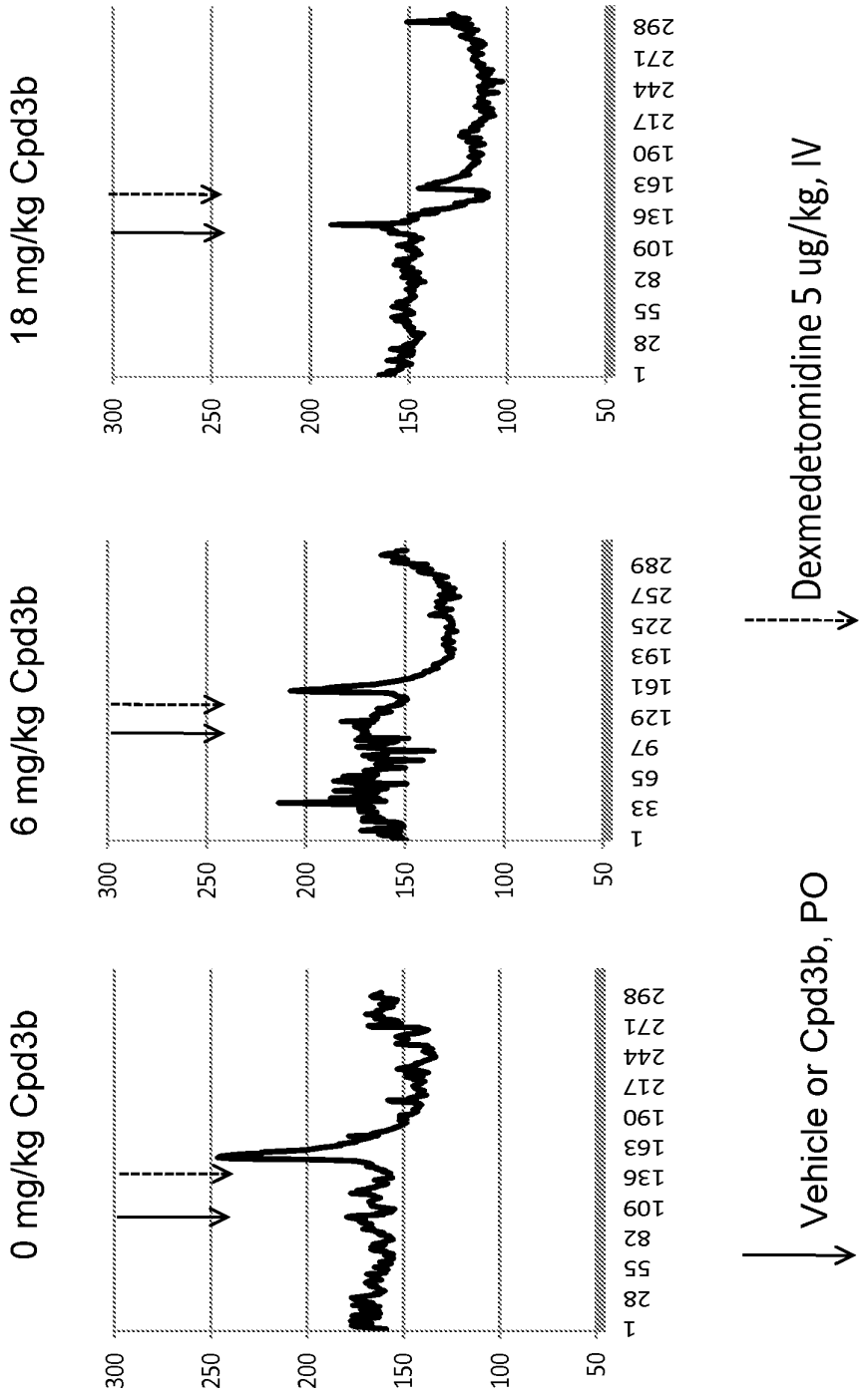

0 mg/kg Cpd3b
6 mg/kg Cpd3b
18 mg/kg Cpd3b
300
250
200
150
100
50
1
28
55
82
109
136
163
190
217
244
271
298
289
257
225
193
161
129
97
65
33
Vehicle or Cpd3b, PO
Dexmedetomidine 5 ug/kg, IV

Figure 12

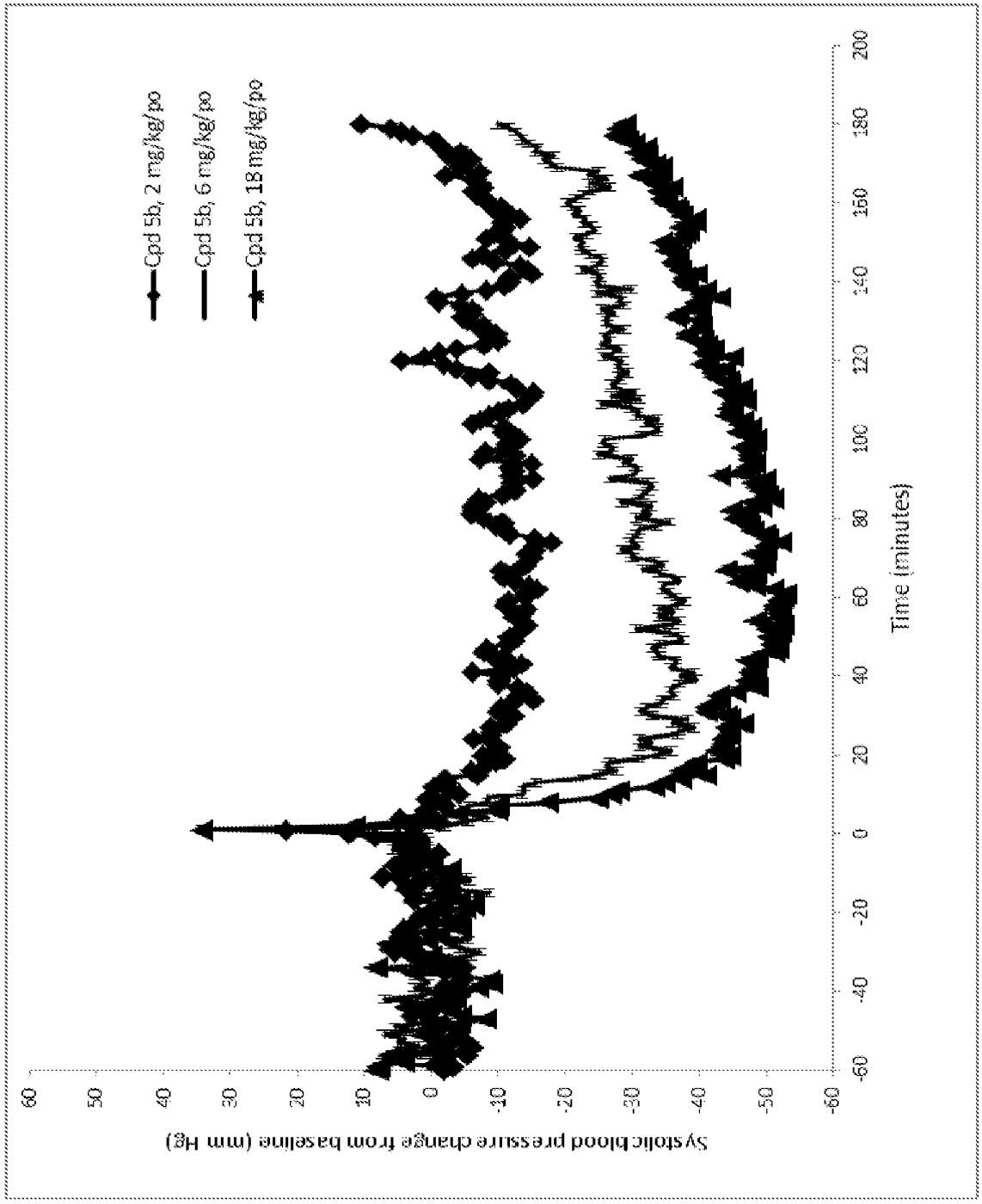

Cpd 5b, 2 mg/kg/po
Cpd 5b, 6 mg/kg/po
Cpd 5b, 18 mg/kg/po
Systolic blood pressure change from baseline (mm Hg)
Time (minutes)
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-60
-40
-20
0
20
40
60
80
100
120
140
160
180
200

Figure 13

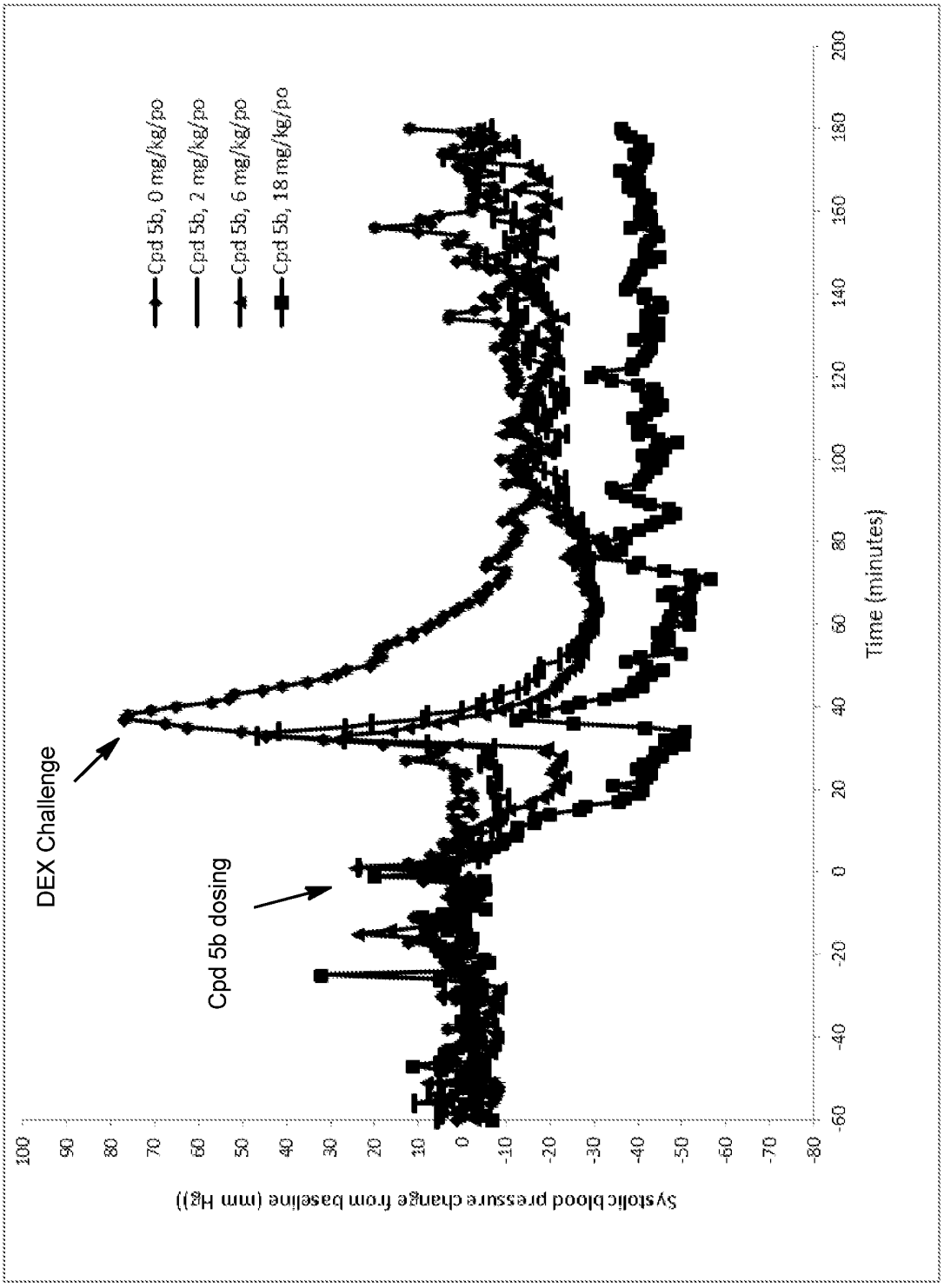

Cpd 5b, 0 mg/kg/po
Cpd 5b, 2 mg/kg/po
Cpd 5b, 6 mg/kg/po
Cpd 5b, 18 mg/kg/po
DEX Challenge
Cpd 5b dosing
Systolic blood pressure change from baseline (mm Hg))
Time (minutes)
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-60
-40
-20
0
20
40
60
80
100
120
140
160
180
200

Figure 14

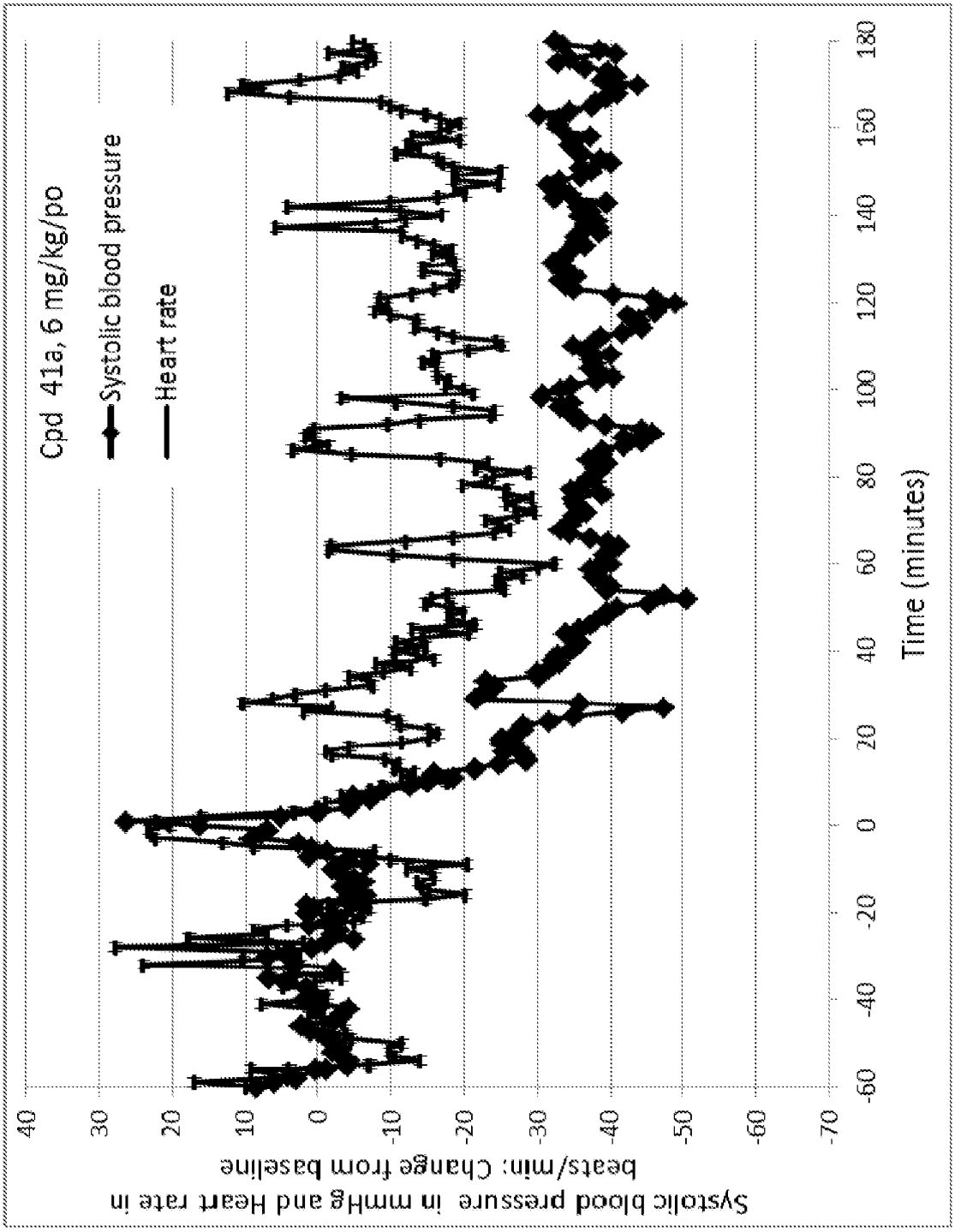

Cpd 41a, 6 mg/kg/po
Systolic blood pressure
Heart rate
Systolic blood pressure in mmHg and Heart rate in beats/min: Change from baseline
Time (minutes)
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-60
-40
-20
0
20
40
60
80
100
120
140
160
180

Figure 15

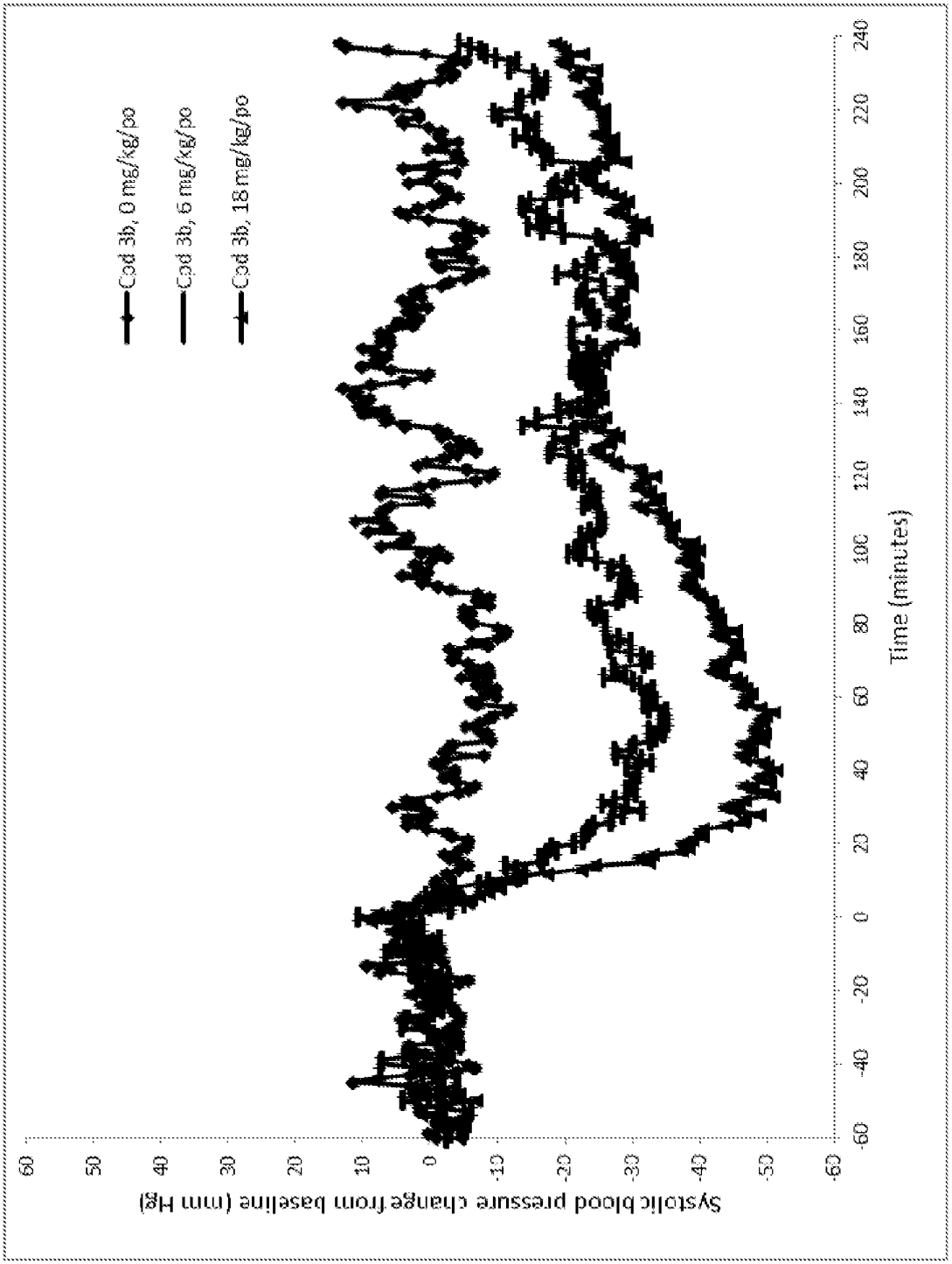

Cpd 3b, 0 mg/kg/po
Cpd 3b, 6 mg/kg/po
Cpd 3b, 18 mg/kg/po
Systolic blood pressure change from baseline (mm Hg)
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-60
-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240
Time (minutes)

Figure 16:

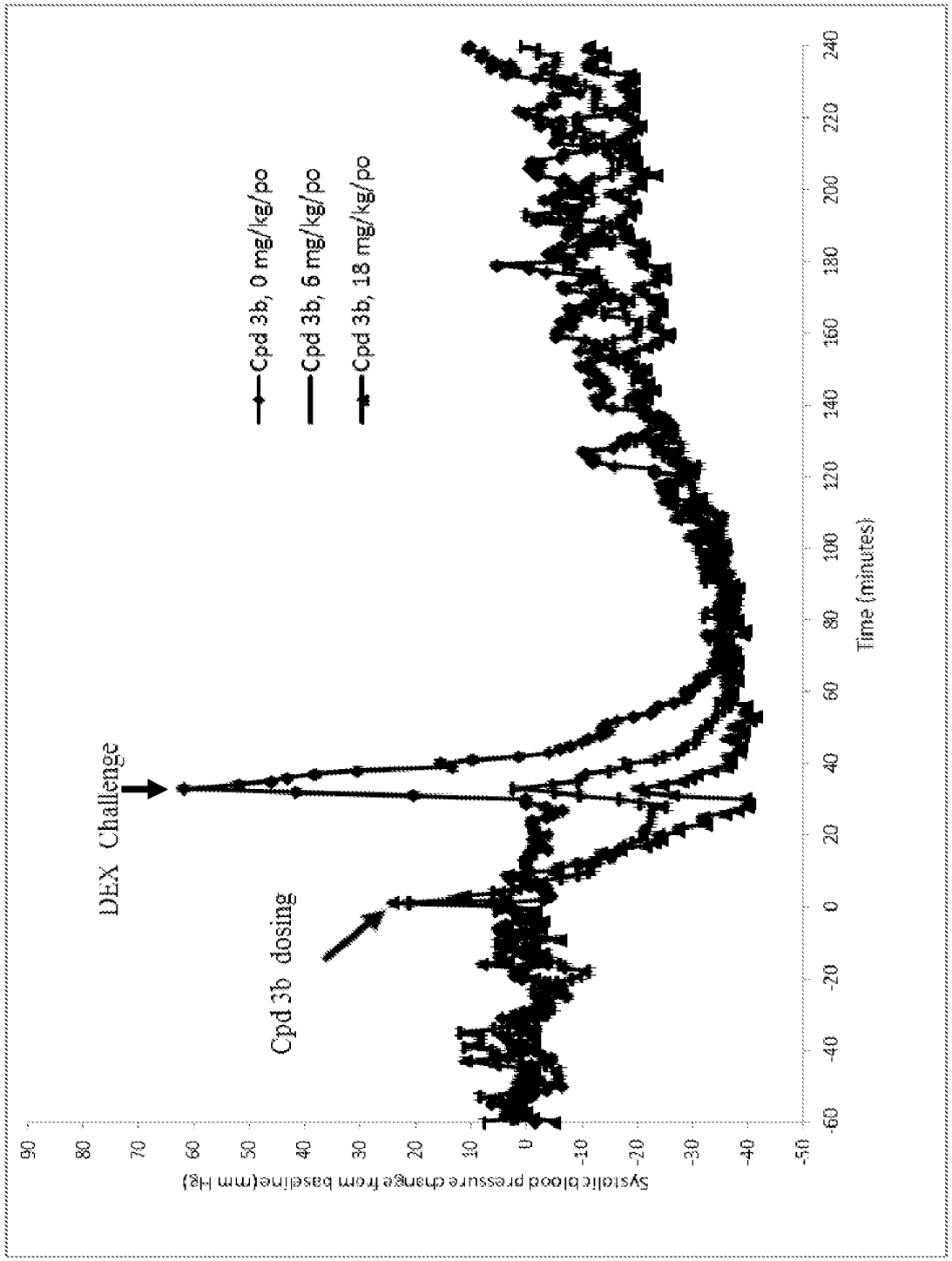

Cpd 3b, 0 mg/kg/po
Cpd 3b, 6 mg/kg/po
Cpd 3b, 18 mg/kg/po
DEX Challenge
Cpd 3b dosing
Systolic blood pressure change from baseline(mm Hg)
Time (minutes)
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-40
-20
0
20
40
60
80
100
120
140
160
180
200
220
240

Figure 17A

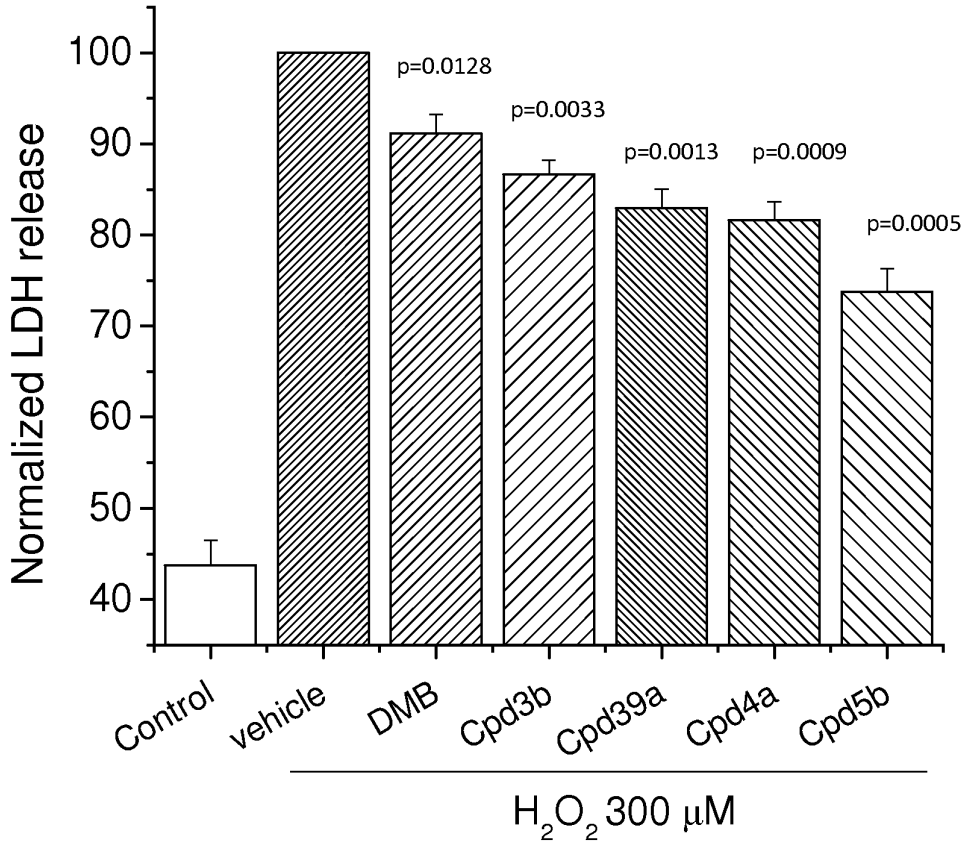

Normalized LDH release
100
90
80
70
60
50
40
p=0.0128
p=0.0033
p=0.0013
p=0.0009
p=0.0005
Control
vehicle
DMB
Cpd3b
Cpd39a
Cpd4a
Cpd5b
H2O2 300 μM

Figure 17B

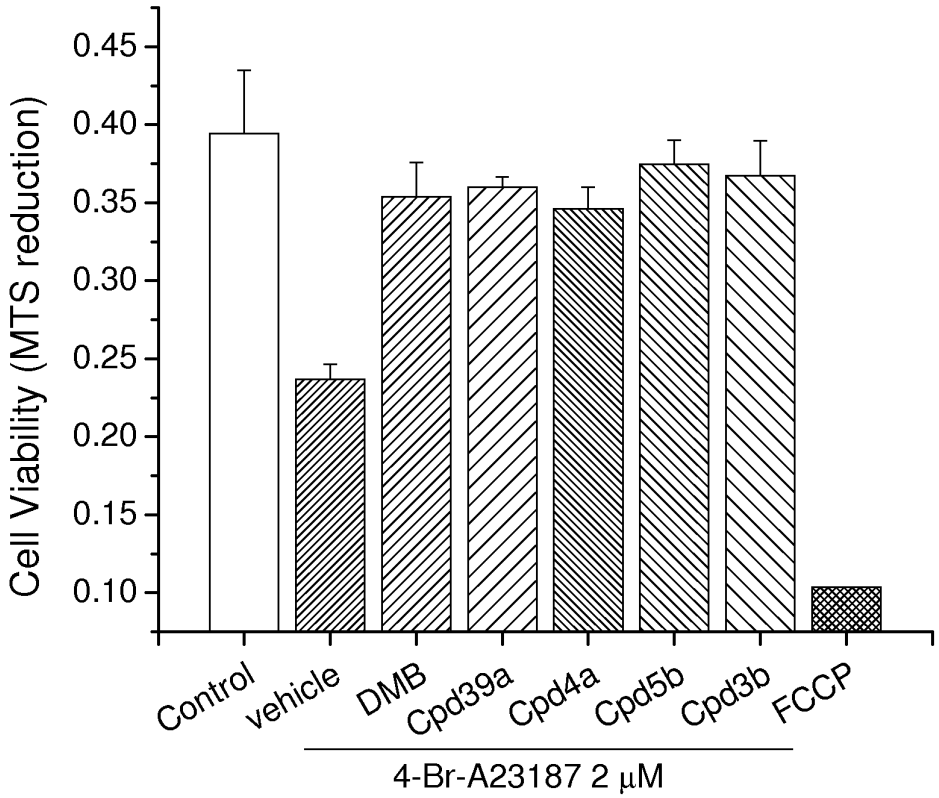
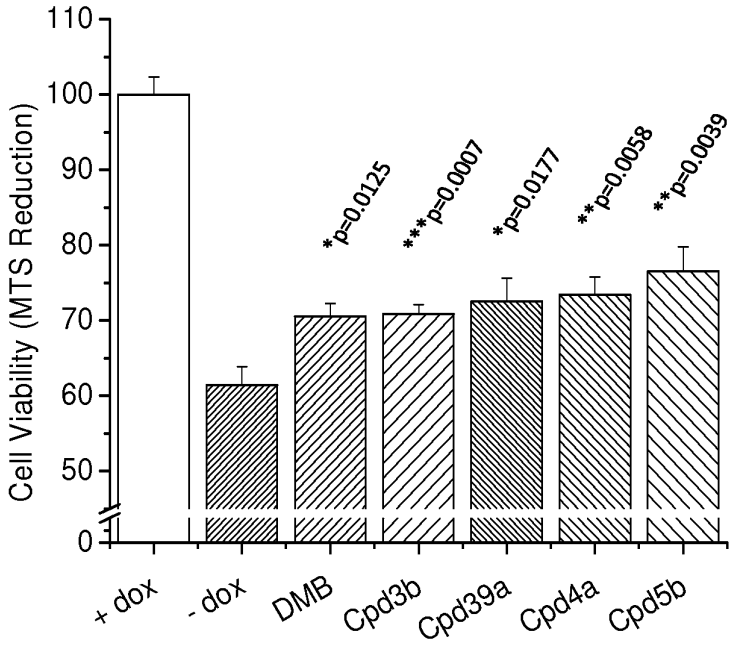
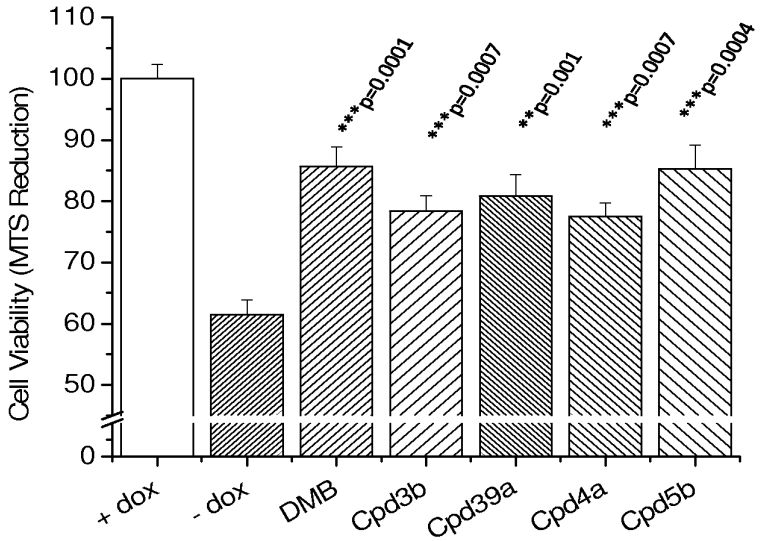

Cell Viability (MTS reduction)
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
Control
vehicle
DMB
Cpd39a
Cpd4a
Cpd5b
Cpd3b
FCCP
4-Br-A23187 2 μM

Figure 18A



0.1 nM

Figure 18B



10 nM

Figure 19

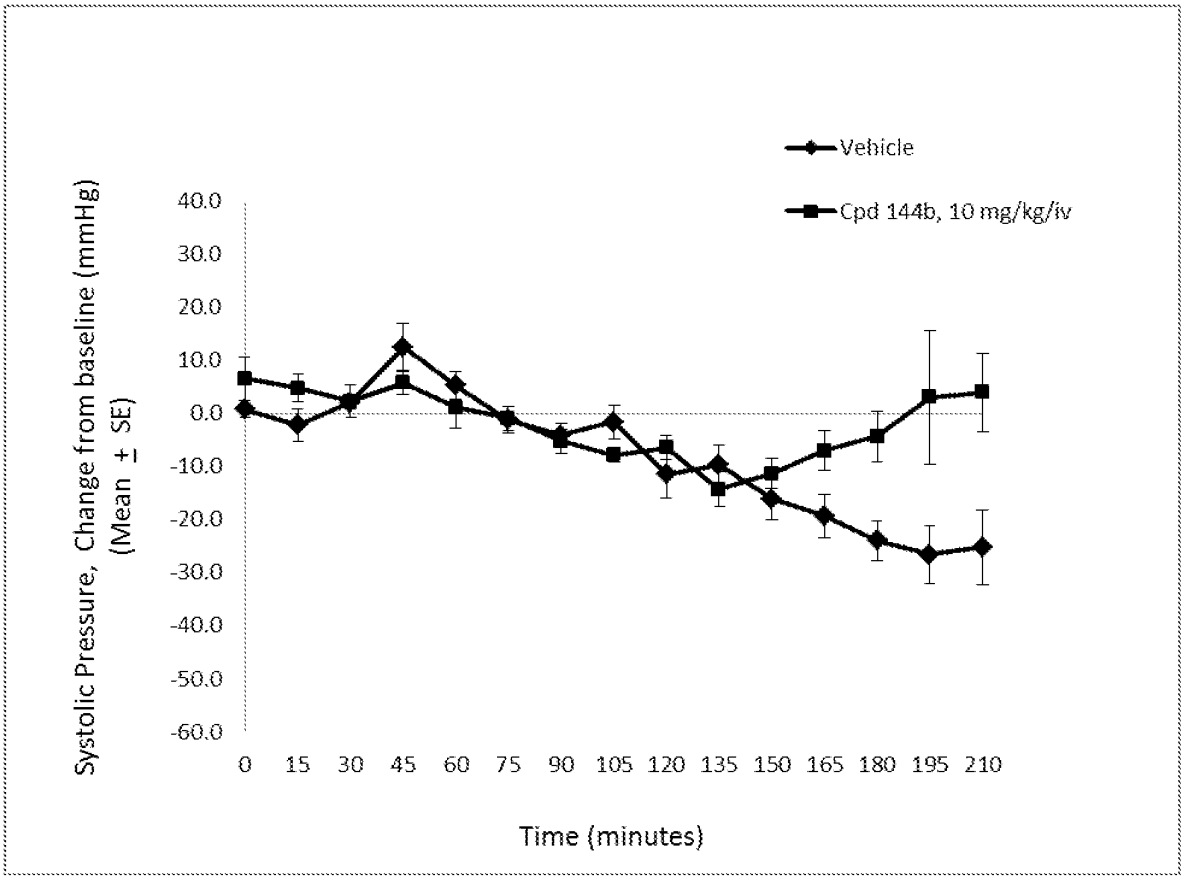

Vehicle
Cpd 144b, 10 mg/kg/iv
Systolic Pressure, Change from baseline (mmHg)
(Mean ± SE)
40.0
30.0
20.0
10.0
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210
Time (minutes)

Figure 20

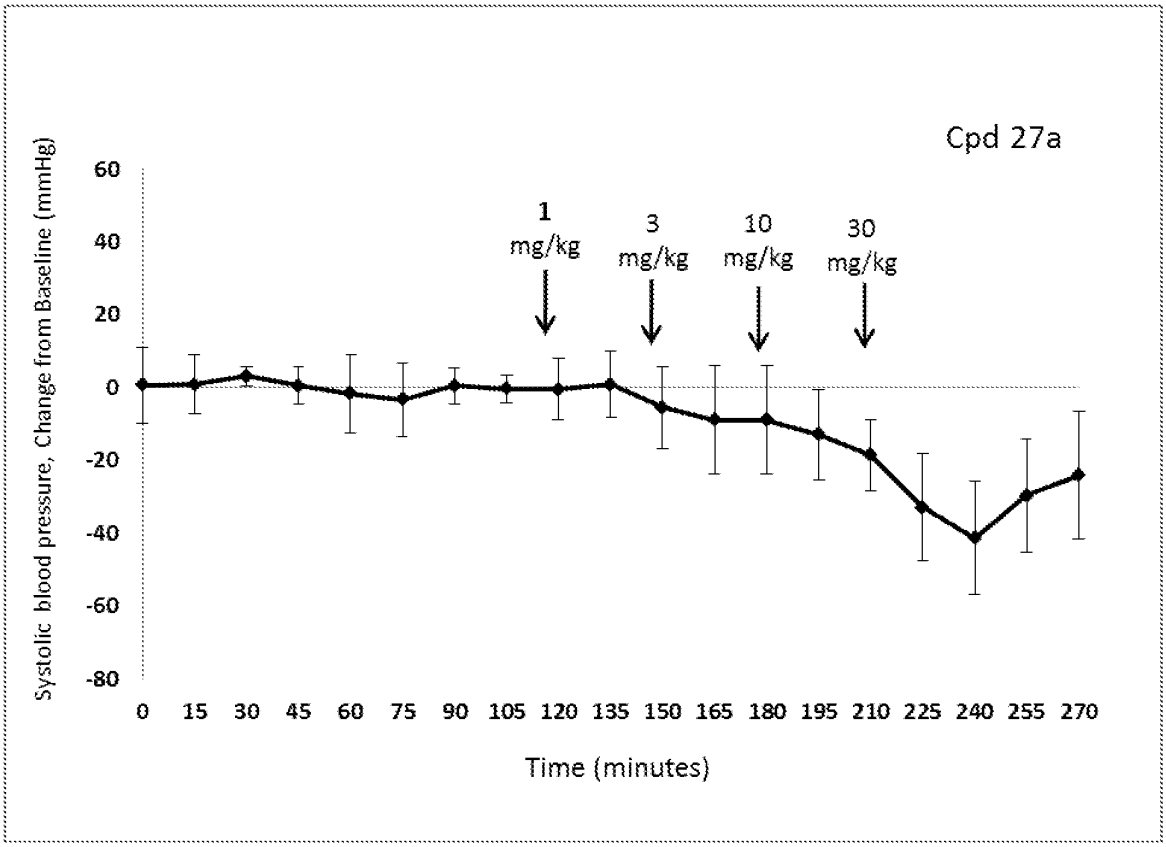

Cpd 27a
Systolic blood pressure, Change from Baseline (mmHg)
60
40
20
0
-20
-40
-60
-80
1 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240 255 270
Time (minutes)

Figure 21

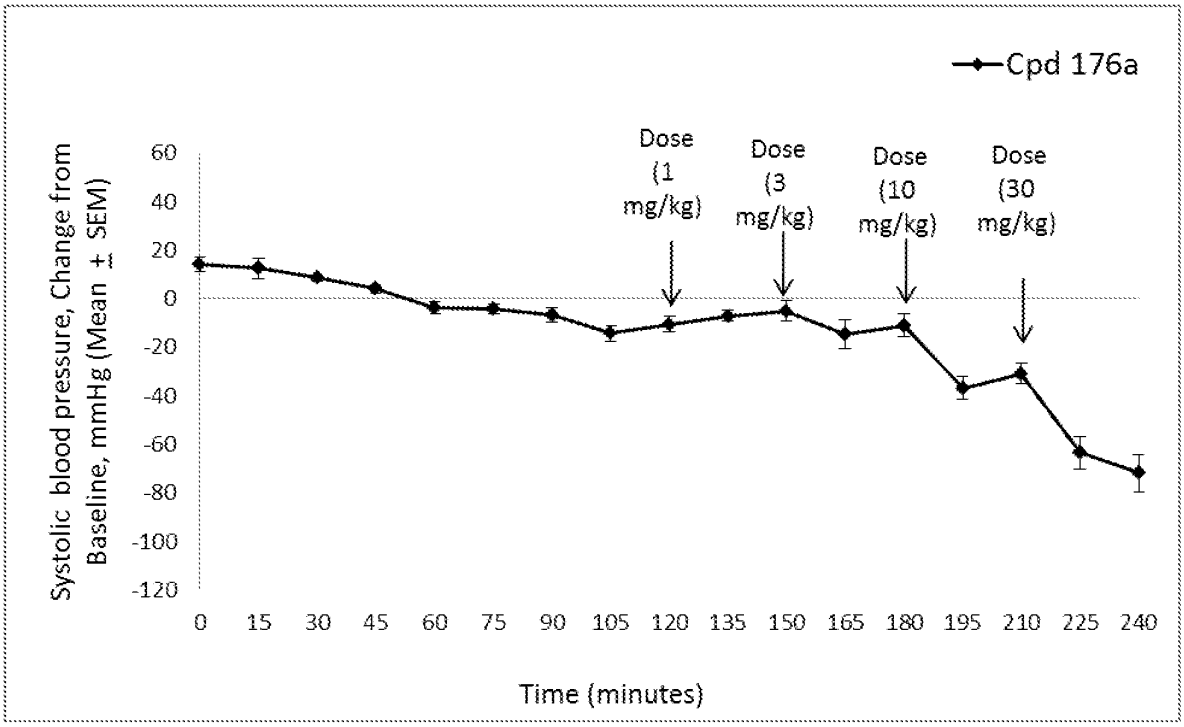

Cpd 176a
Dose (1 mg/kg)
Dose (3 mg/kg)
Dose (10 mg/kg)
Dose (30 mg/kg)
Systolic blood pressure, Change from Baseline, mmHg (Mean ± SEM)
60
40
20
0
-20
-40
-60
-80
-100
-120
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240
Time (minutes)

Figure 22

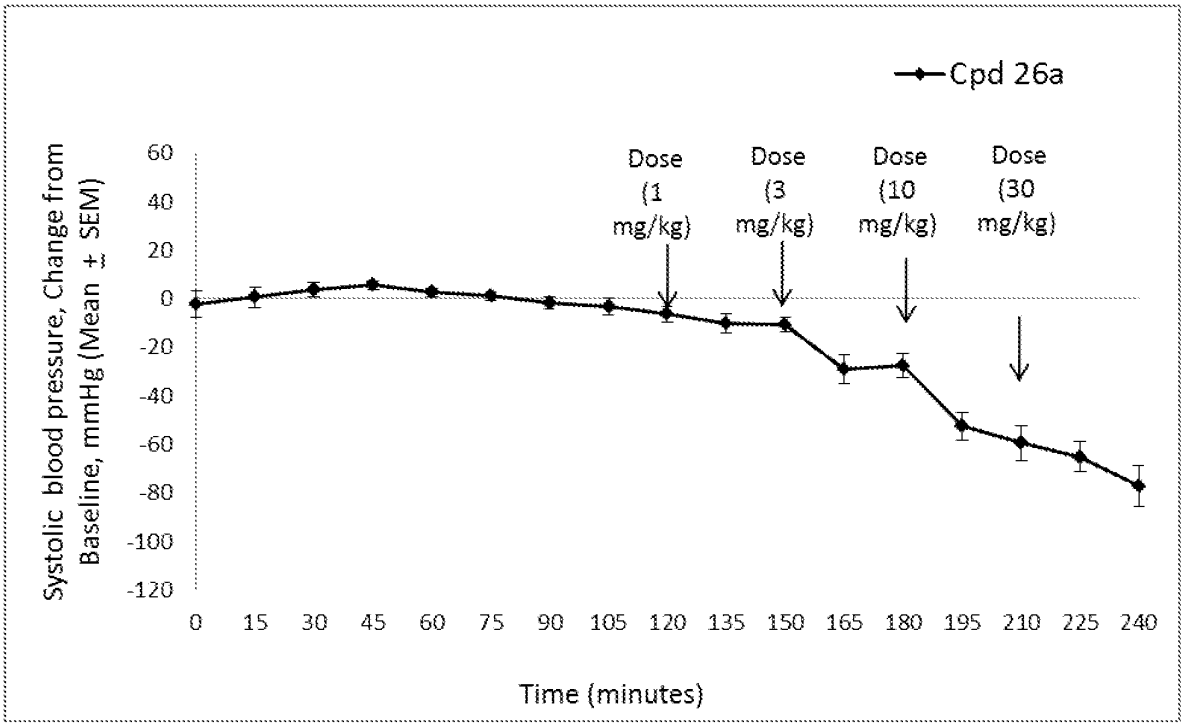

Cpd 26a
Systolic blood pressure, Change from Baseline, mmHg (Mean ± SEM)
60
40
20
0
-20
-40
-60
-80
-100
-120
Dose (1 mg/kg)
Dose (3 mg/kg)
Dose (10 mg/kg)
Dose (30 mg/kg)
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240
Time (minutes)

Figure 23

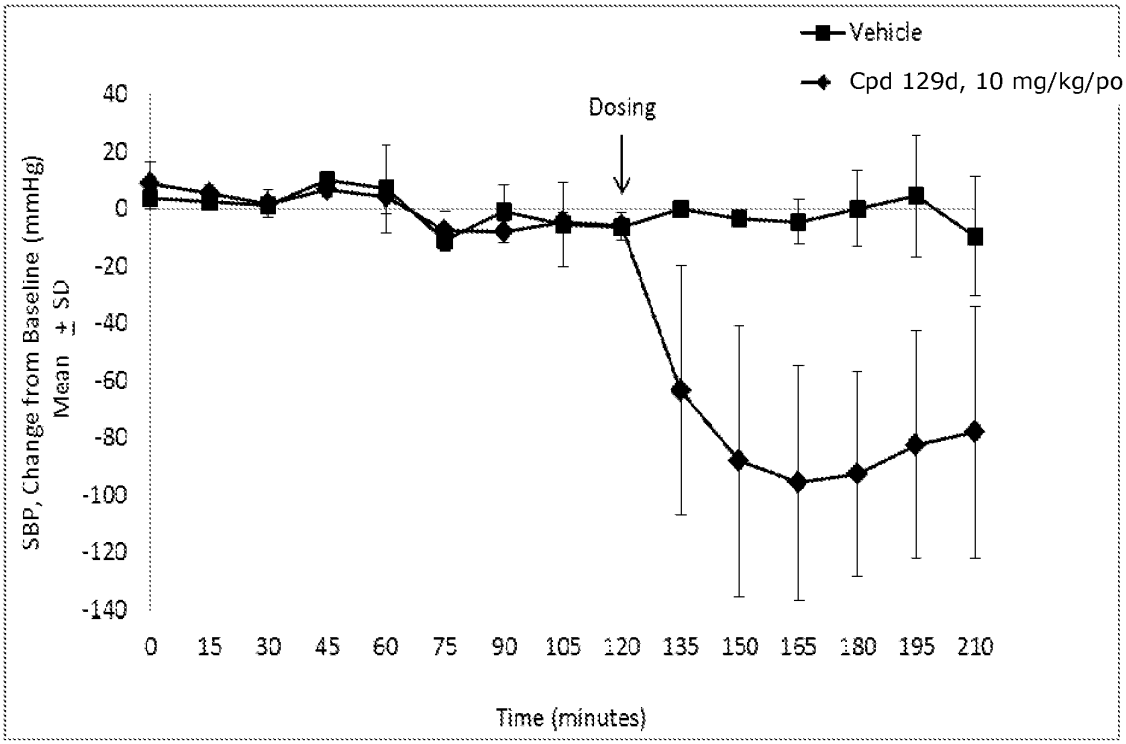

Vehicle
Cpd 129d, 10 mg/kg/po
Dosing
SBP, Change from Baseline (mmHg)
Mean ± SD
40
20
0
-20
-40
-60
-80
-100
-120
-140
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
Time (minutes)

Figure 24

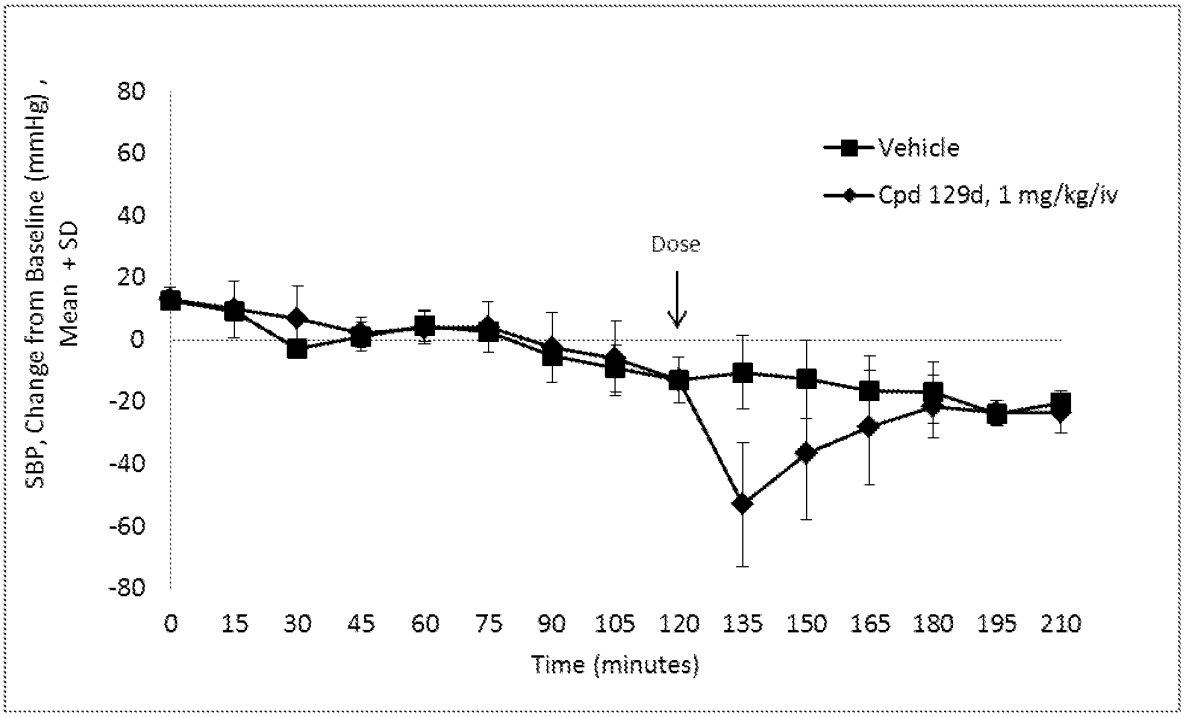

SBP, Change from Baseline (mmHg) , Mean + SD
80
60
40
20
0
-20
-40
-60
-80
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
Time (minutes)
Dose
Vehicle
Cpd 129d, 1 mg/kg/iv

Figure 25

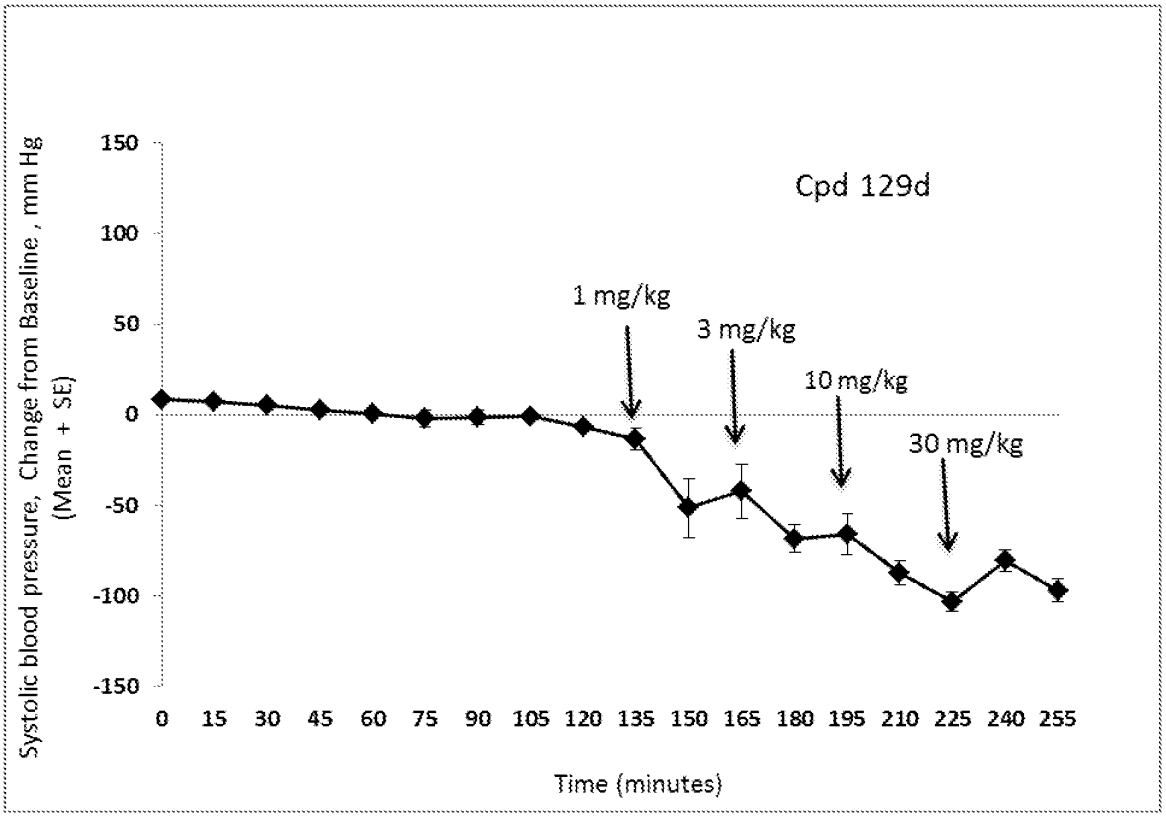

Cpd 129d
1 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
Systolic blood pressure, Change from Baseline , mm Hg (Mean + SE)
150
100
50
0
-50
-100
-150
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240 255
Time (minutes)

Figure 26

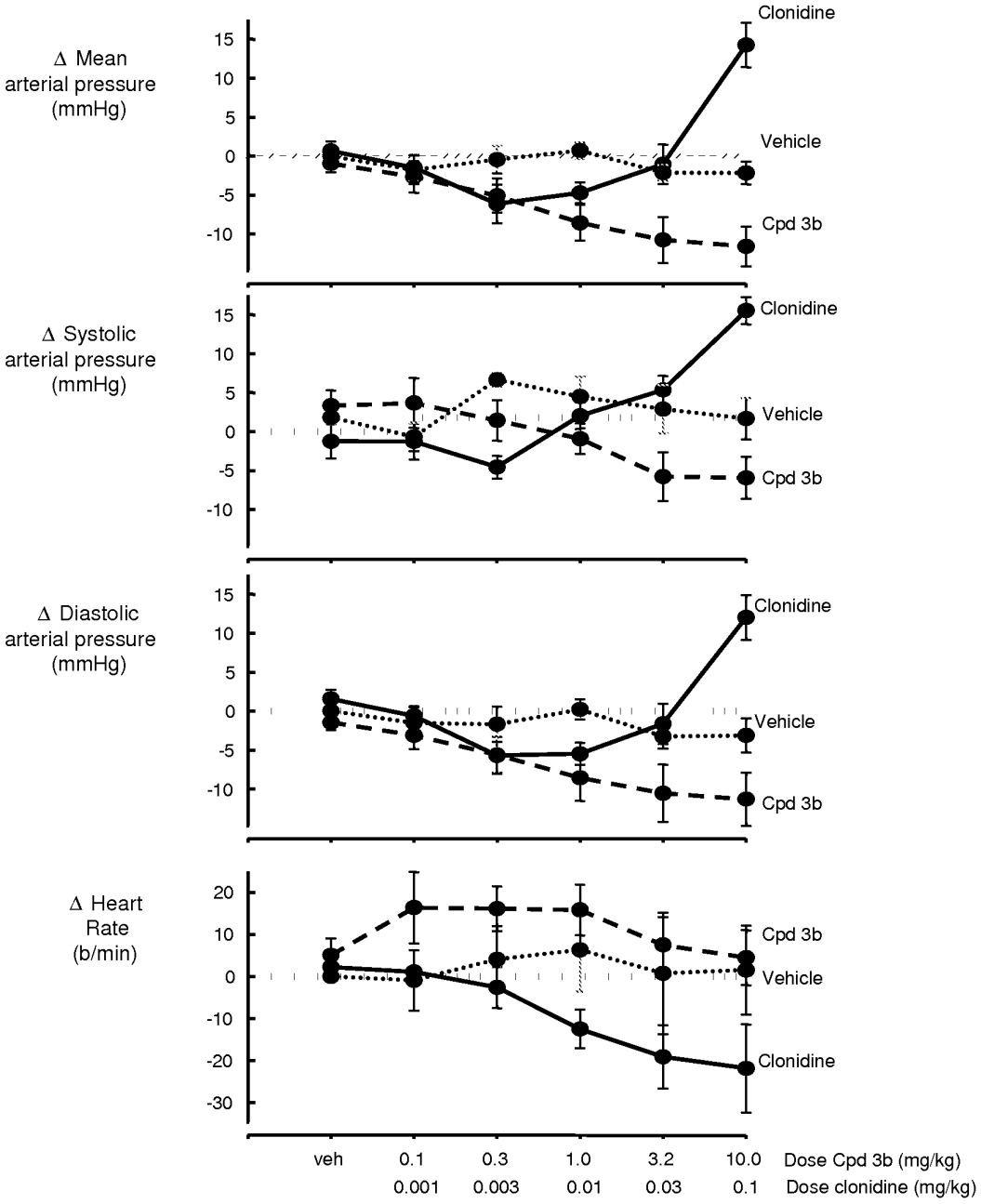

Δ Mean arterial pressure (mmHg)
15
10
5
0
-5
-10
Clonidine
Vehicle
Cpd 3b
Δ Systolic arterial pressure (mmHg)
15
10
5
0
-5
-10
Clonidine
Vehicle
Cpd 3b
Δ Diastolic arterial pressure (mmHg)
15
10
5
0
-5
-10
Clonidine
Vehicle
Cpd 3b
Δ Heart Rate (b/min)
20
10
0
-10
-20
-30
Cpd 3b
Vehicle
Clonidine
veh
0.1
0.3
1.0
3.2
10.0
Dose Cpd 3b (mg/kg)
0.001
0.003
0.01
0.03
0.1
Dose clonidine (mg/kg)

Figure 27

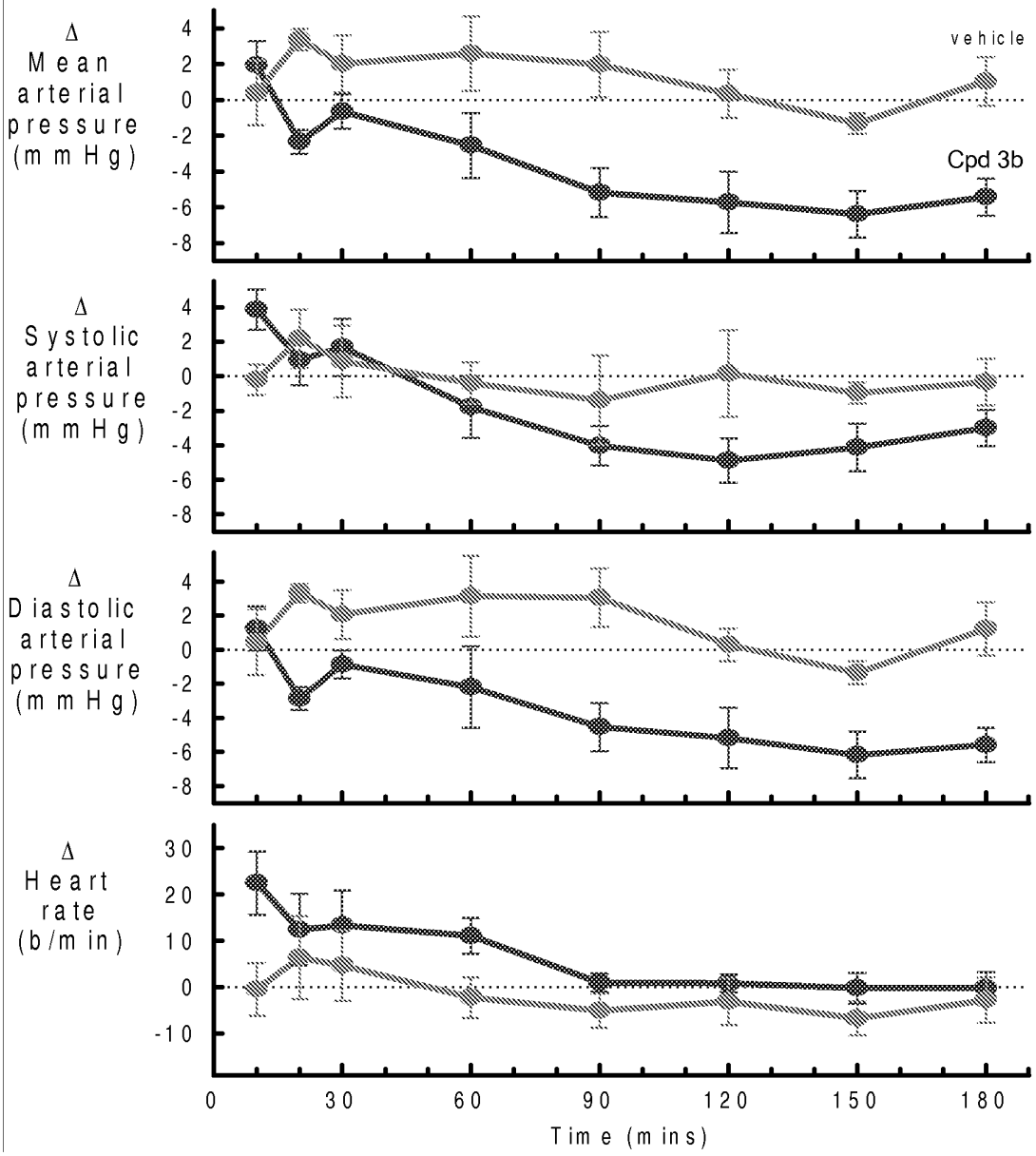
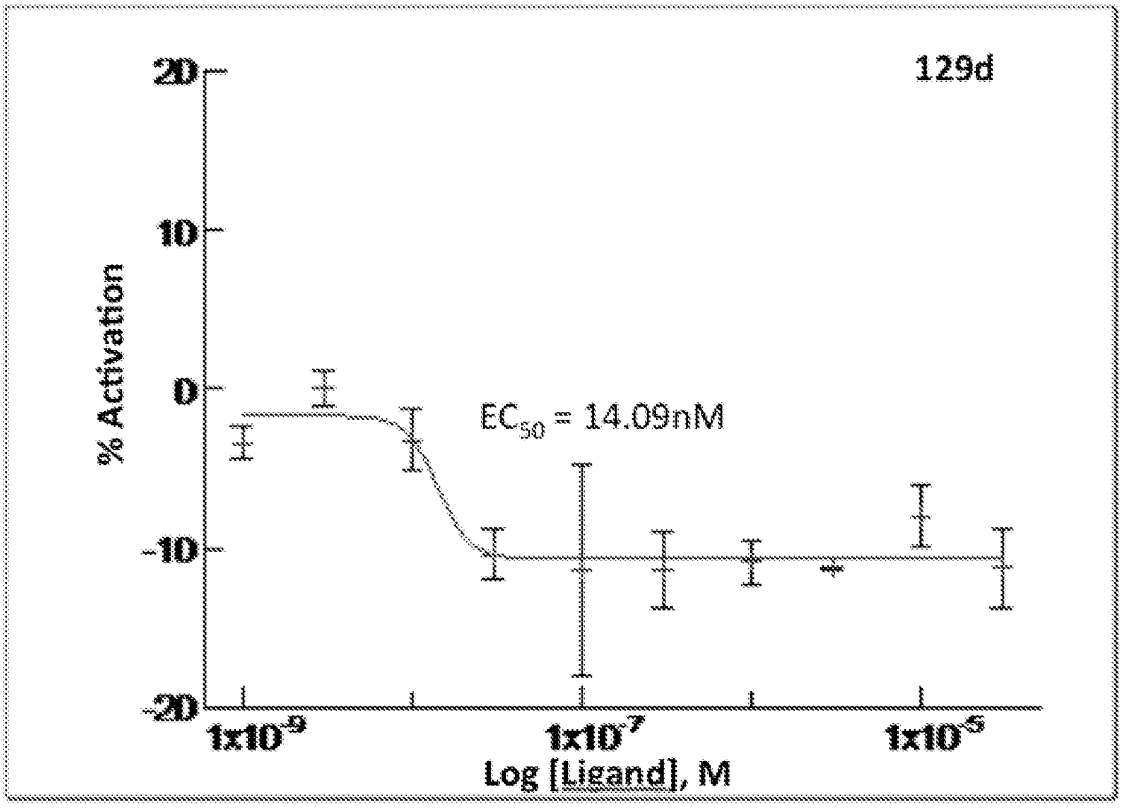

Δ Mean arterial pressure (mmHg)
Δ Systolic arterial pressure (mmHg)
Δ Diastolic arterial pressure (mmHg)
Δ Heart rate (b/min)
vehicle
Cpd 3b
4
2
0
-2
-4
-6
-8
30
20
10
0
-10
0
30
60
90
120
150
180
Time (mins)

Figure 28


129d
20
10
0
-10
-20
% Activation
EC50 = 14.09nM
1x10-9
1x10-7
1x10-5
Log [Ligand], M