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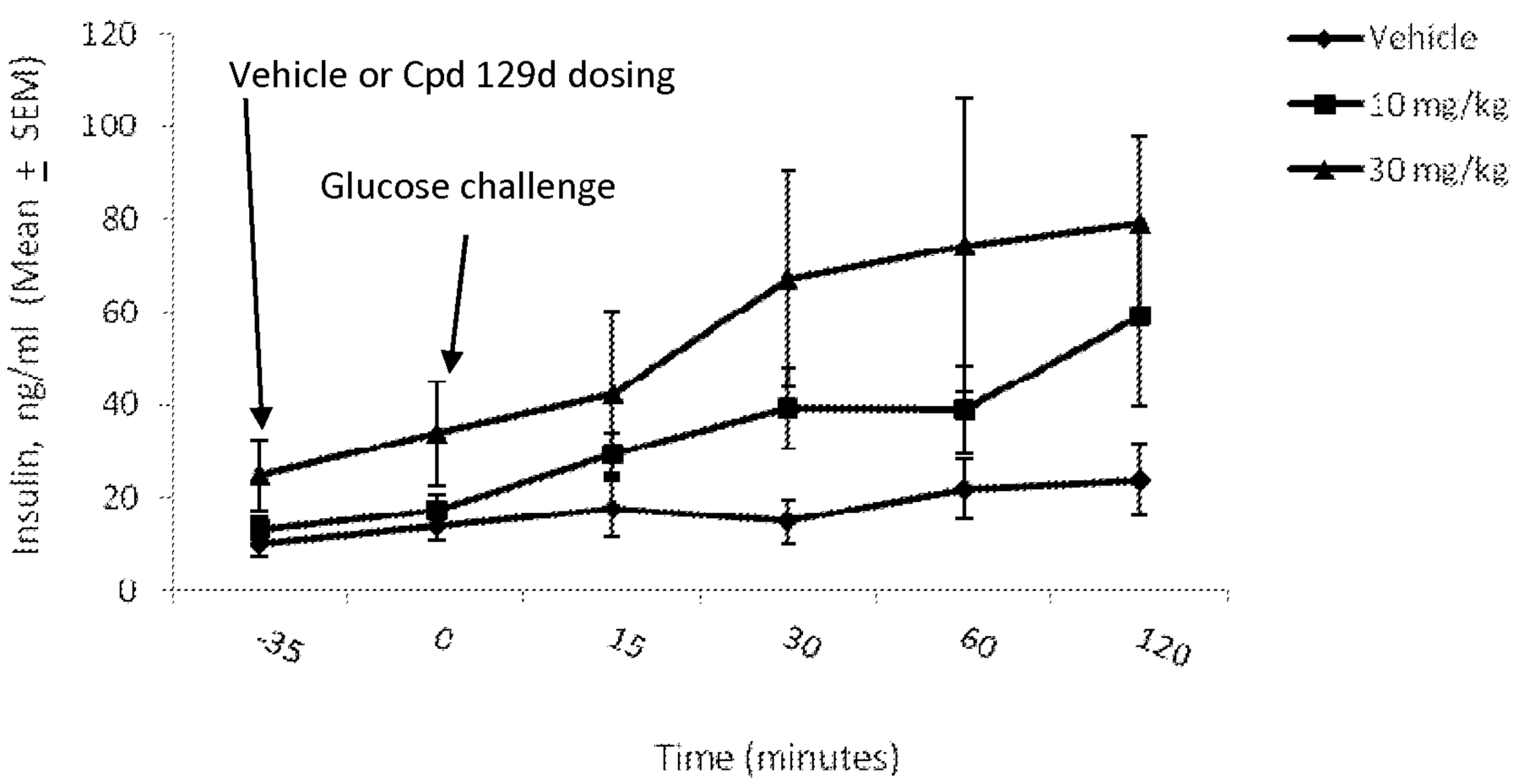
(54) Titre : COMPOSES ET METHODES DE TRAITEMENT DU DIABETE
(54) Title: COMPOUNDS AND METHODS OF TREATING DIABETES

Figure 18



(57) Abrégé/Abstract:
Hydrogenated pyrido[4,3-b]indoles, pyrido [3, 4-b]indoles and azepino[4,5-b]indoles are described. The compounds may bind to and are antagonists of the adrenergic receptor α_{2A}. The compounds may also bind to and are an antagonist of the adrenergic receptor α_{2B}; or the compounds are not antagonists of the adrenergic receptor α_{2B} and the compounds are administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. The compounds may find use in therapy, e.g., to regulate blood glucose level, increase insulin secretion and treat diseases or conditions that are, or are expected to be, responsive to an increase in insulin production. Use of the compounds to treat type 2 diabetes is particularly described.

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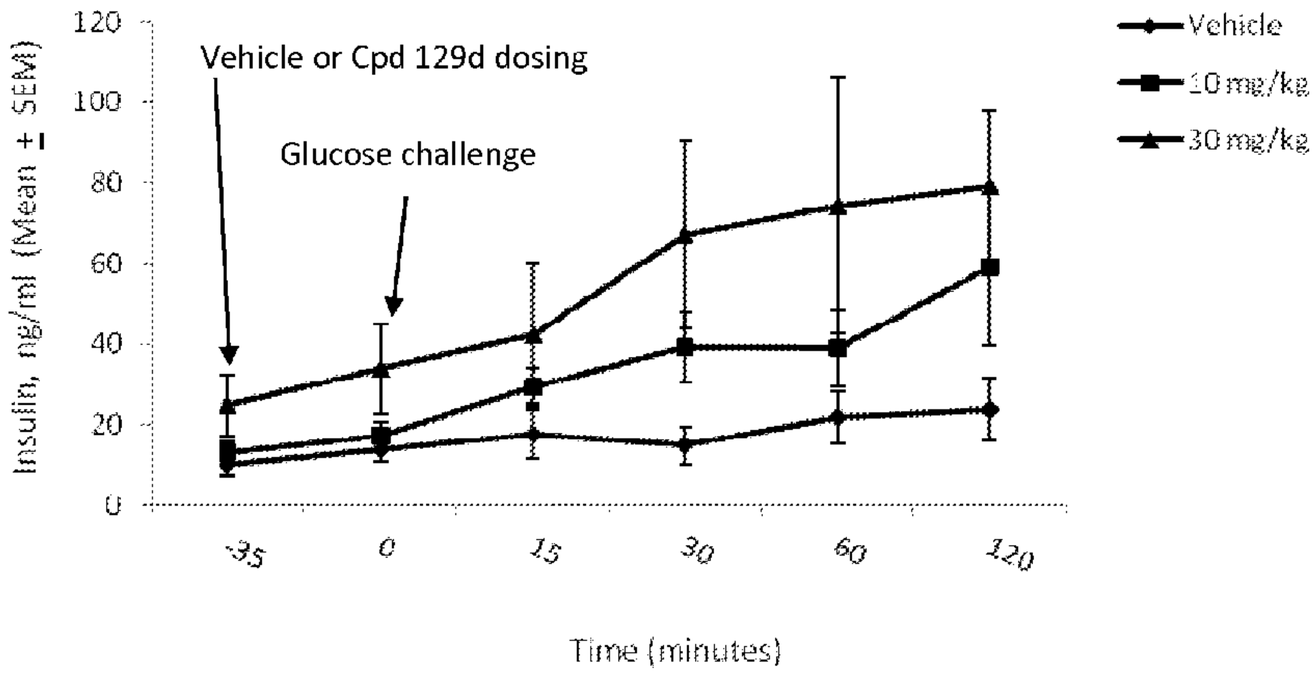
(54) Title: COMPOUNDS AND METHODS OF TREATING DIABETES

Figure 18



(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 antagonists of the adrenergic receptor α_{2A}. The compounds may also bind to and are an antagonist of the adrenergic receptor α_{2B}; or the compounds are not antagonists of the adrenergic receptor α_{2B} and the compounds are administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. The compounds may find use in therapy, *e.g.*, to regulate blood glucose level, increase insulin secretion and treat diseases or conditions that are, or are expected to be, responsive to an increase in insulin production. Use of the compounds to treat type 2 diabetes is particularly described.

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

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COMPOUNDS AND METHODS OF TREATING DIABETES

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. 61/469,664 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] Type 2 diabetes is a serious and prevalent disease. This form of diabetes may involve insulin resistance and impaired insulin release. Approximately 25.8 million people in the United States alone suffer from diabetes, whereby type 2 diabetes accounts for about 90-95% of all diagnosed diabetes cases. From 1980 to 2008 the number of Americans with diabetes has more than tripled. Diabetes is also increasingly prevalent elsewhere, such as in certain Asian countries whose populations have experienced a dramatic increase in the disease. For example, in India and China, where rapid lifestyle and economic changes have led to a more sedentary lifestyle and poorer diet among the overall population, diabetes is becoming a major health concern. In addition, more than a third of adults at least 20 years old have pre-diabetes, which is a significant risk factor for developing type 2 diabetes. Other diseases and indications, such as glucose intolerance and metabolic syndrome may also be associated with impaired insulin release.

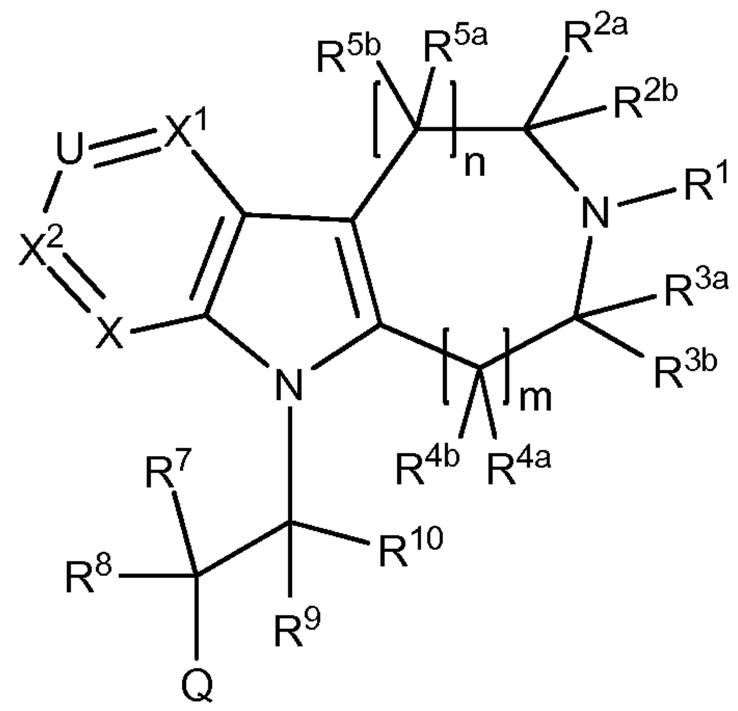
[0003] There remains a need for new and improved therapies that enhance insulin secretion and/or promote insulin release into the blood stream in individuals who have a reduced or impaired ability to secrete insulin and/or release insulin into the blood stream.

BRIEF SUMMARY OF THE INVENTION

[0004] 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 therapy, *e.g.*, to regulate blood glucose level, increase insulin secretion and treat diseases or conditions that are, or are expected to be, responsive to an increase in insulin production. In one aspect, compounds provided herein are α_{2A} antagonists that may find use in therapy, *e.g.*, to increase insulin secretion and treat diseases or conditions that are, or are expected to be, responsive to an increase in insulin production. Use of the compounds to treat type 2 diabetes is particularly described.

[0005] In one aspect, the present invention discloses methods of regulating blood glucose levels 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; 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.

[0006] In one embodiment, the method reduces blood glucose level in the individual. In another embodiment, the method reduces blood glucose level in the individual for a period of more than 0.5 hours following administration. In another embodiment, the method stabilizes blood glucose level in the individual at a desired level.

[0007] In another aspect, the present invention provides methods of (i) increasing insulin secretion, and/or (ii) promoting insulin release into the blood stream, in an individual in need thereof comprising administering to the individual an effective amount of a compound of the formula (I), or a salt, solvate or N-oxide thereof. In one embodiment, the method increases

insulin secretion.In another embodiment, the method promotes insulin release into the blood stream.

[0008] In one embodiment, the individual has a disease or condition that involves impaired insulin secretion. In another embodiment, the individual has one or more risk factors for developing a disease or condition that involves impaired insulin secretion. In another embodiment, the administration results in decrease of blood pressure in the individual.

[0009] In one aspect, a method is provided for one or more of the following: reducing blood glucose levels, increasing insulin secretion, and promoting insulin release in the blood stream.

[0010] In another aspect, the invention presents methods of treating a disease or condition that is responsive to an increase in insulin secretion, comprising administering to an individual in need thereof an effective amount of a compound of the formula (I), or a salt, solvate or N-oxide thereof.

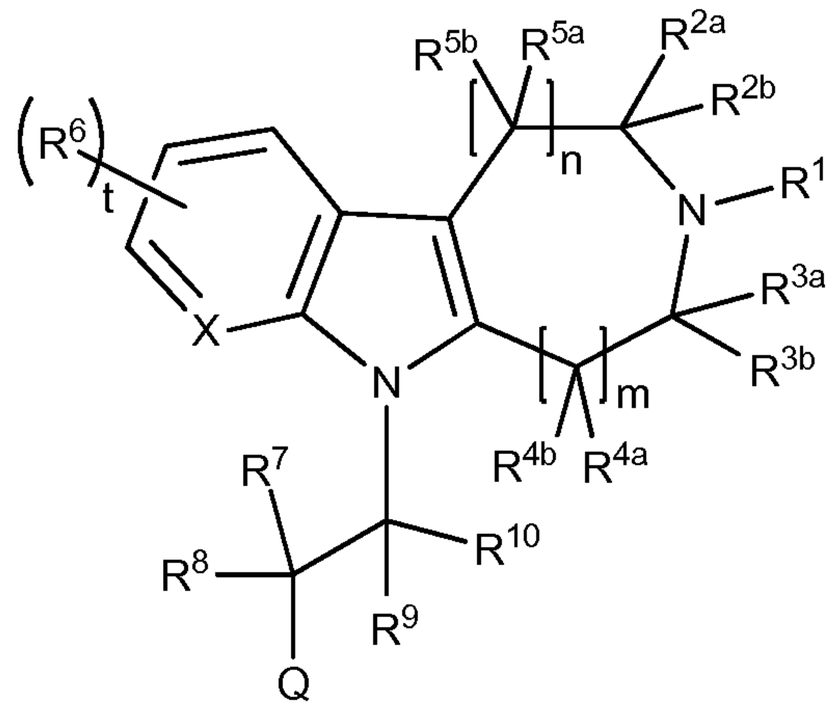
[0011] In a further aspect, the present invention provides methods of delaying the onset of a disease or condition that is responsive to an increase in insulin secretion, comprising administering to an individual in need thereof an effective amount of a compound of the formula (I), or a salt, solvate or N-oxide thereof.

[0012] In one embodiment, with respect to the method, the disease or condition is type 2 diabetes. In another embodiment, the disease or condition is glucose intolerance. In another embodiment, the disease or condition is metabolic syndrome.

[0013] In oner embodiment, with respect to the above method, the individual is not responsive to standard treatment of type 2 diabetes.

[0014] In another embodiment, with respect to the method, the method further comprising administering to the individual in need thereof one or more anti-diabetic agents. In one embodiment, the anti-diabetic agents is an insulin sensitizer.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] In another embodiment, with respect to the methods of the invention, the compound binds to and is an antagonist of the adrenergic receptor α_{2A} and, wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) the compound is not an antagonist of the adrenergic receptor α_{2B} and the compound is administered in conjunction with a second agent that reduces blood pressure in the individual. In one embodiment, the compound binds to and is an antagonist of the adrenergic receptor α_{2B}. In another embodiment, the compound binds to and is an antagonist of the adrenergic receptor α_{1B}. In another embodiment, the compound is not an antagonist of the adrenergic receptor α_{2B} and the compound is administered in conjunction with a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist, a beta blocker, a calcium channel blocker, or any combination thereof.

[0019] Also 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 methods of described herein. Further 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 herein.

[0020] 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 regulating (reducing and/or stabilizing) blood glucose, increasing insulin secretion, and/or promoting insulin release in the blood stream. 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 an increase in insulin secretion, such as type 2 diabetes, glucose intolerance and metabolic syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Figure 1 illustrates the effects of Compound No. 129d on blood glucose levels in clonidine induced hyperglycemic SHR.OB rats. The term "Compound" may be defined as "Cpd" in the Figures.

[0022] Figure 2 illustrates the effects of Compound No. 129d on blood glucose levels in clonidine induced hyperglycemic Wistar rats.

[0023] Figure 3 illustrates the effects of Compound No. 129d on blood glucose levels in norepinephrine induced hyperglycemic SHR.OB rats.

[0024] Figure 4 illustrates the effects of Compound No. 129d on blood glucose levels in norepinephrine induced hyperglycemic Wistar rats.

[0025] Figure 5 illustrates the effects of Compound No. 129d on blood glucose levels in normoglycemic SHR.OB rats.

[0026] Figure 6 illustrates the effect of Compound No. 129d on insulin levels (competition with clonidine) [With 0% as the insulin secreted at low glucose (LG) and 100% the insulin secreted at high glucose (HG)].

[0027] Figure 7 illustrates the effect of Compound No. 129d on insulin levels (competition with norepinephrine) [With 0 % as the insulin secreted at low glucose (LG) and 100% the insulin secreted at high glucose (HG)].

[0028] Figure 8 illustrates the effect of Compound No. 129d with Nateglinide / Meglitinide induced insulin release in pancreatic beta cell model.

[0029] Figure 9 illustrates the effect of Compound No. 129d on blood glucose levels in norepinephrine induced hyperglycemic SHR.OB rats.

[0030] Figure 10 illustrates the effect of Compound No. 129d on serum insulin levels in norepinephrine induced hyperglycemic SHR.OB rats.

[0031] Figure 11 illustrates the effect of Compound No. 129d on blood glucose levels in norepinephrine induced hyperglycemic Wistar rats.

[0032] Figure 12 illustrates the effect of Compound No. 129d on serum insulin levels in norepinephrine induced hyperglycemic Wistar rats.

[0033] Figure 13 illustrates the effect of Compound No. 129d on blood glucose levels in norepinephrine induced hyperglycemic ob/ob mice.

[0034] Figure 14 illustrates the effect of Compound No. 129d on serum insulin levels in norepinephrine induced hyperglycemic ob/ob mice.

[0035] Figure 15 illustrates the effect of Compound No. 129d on blood glucose levels in spontaneously hyperglycemic ob/ob mice (No NE challenge).

[0036] Figure 16 illustrates the effect of Compound No. 129d on serum insulin levels in spontaneously hyperglycemic ob/ob mice (No NE challenge).

[0037] Figure 17 illustrates the effect of Compound No. 129d on blood glucose levels in glucose challenged hyperglycemic (OGTT) SHR.OB rats.

[0038] Figure 18 illustrates the effect of Compound No. 129d on serum insulin levels in glucose challenged hyperglycemic (OGTT) SHR.OB rats.

[0039] Figure 19 illustrates the effect of Compound No. 129d (oral) on systolic blood pressure in SHR rats.

[0040] Figure 20 illustrates the effect of Compound No. 129d (i.v., bolus) on systolic blood pressure in SHR rats.

[0041] Figure 21 illustrates the effect of Compound No. 129d (i.v., escalating doses) on systolic blood pressure in SHR rats.

[0042] Figure 22 illustrates Compound No. 129d in a human adrenergic a2A receptor inverse agonist activity (using GTPg35S binding functional) assay.

[0043] Figure 23 illustrates the synergistic effect of Compound No. 129d with glibenclamide in rat pancreatic islets.

[0044] Figure 24 illustrates the synergistic effect of Compound No. 129d with glimepiride in rat pancreatic islets.

[0045] Figure 25 illustrates that Compound No. 129d blocks pERK1/2 norepinephrine mediated effects in rat pancreatic islets.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0046] Unless clearly indicated otherwise, the terms "a," "an," and the like, refer to one or more.

[0047] 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.

[0048] 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".

[0049] 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.

[0050] 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).

[0051] As used herein, "treatment" or "treating" is an approach for obtaining a beneficial or desired result, including clinical results.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] "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.

[0057] 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.

[0058] 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.

[0059] "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.

[0060] "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.

[0061] "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.

[0062] "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.

[0063] "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.

[0064] "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.

[0065] "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.

[0066] "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.

[0067] "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.

[0068] "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.

[0069] "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.

[0070] "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.

[0071] "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.

[0072] "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.

[0073] "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.

[0074] "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").

[0075] "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.

[0076] "Unsubstituted amino" refers to the group -NH_2.

[0077] "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.

[0078] "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.

[0079] "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.

[0080] "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.

[0081] "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.

[0082] "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.

[0083] "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.

[0084] "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.

[0085] "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).

[0086] "Carbonyl" refers to the group C=O.

[0087] "Cyano" refers to the group -CN.

[0088] "Oxo" refers to the moiety =O.

[0089] "Nitro" refers to the group -NO_2.

[0090] "Thioalkyl" refers to the groups -S-alkyl.

[0091] "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.

[0092] "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.

[0093] "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.

[0094] "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.

[0095] 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.

Receptor Binding Profile

[0096] In some embodiments, compounds provided herein bind to and are antagonists of the adrenergic receptor α_{2A}. In one variation, compounds provided herein bind to and are antagonists of the adrenergic receptor α_{2A} and either (a) also bind to and are antagonists of the adrenergic receptor α_{2B} or (b) are not antagonists of the adrenergic receptor α_{2B} but are administered in the methods detailed herein in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. By exhibiting the dual properties of binding to and being an antagonist of both the adrenergic receptor α_{2A} and the adrenergic receptor α_{2B}, compounds provided herein may exert the beneficial effect of increasing insulin secretion and/or promoting insulin release in an individual while reducing or eliminating the side effect of an increase in blood pressure that may be associated with antagonizing the adrenergic receptor α_{2A}. Alternatively, compounds provided herein that bind to and are antagonists of the adrenergic receptor α_{2A}, but which do not bind to and are not antagonists of the adrenergic receptor α_{2B}, may be used in therapy in conjunction with a second agent that reduces, or is expected to reduce,

blood pressure in an individual, thereby allowing the adrenergic receptor α_{2A} antagonist to exert its therapeutic effects while reducing or eliminating the side effect of an increase in blood pressure that may be associated with antagonizing the adrenergic receptor α_{2A}. Thus, it is understood that a second compound that reduces, or is expected to reduce, blood pressure in an individual includes a second compound that reduces or prevents an increase in an individual's blood pressure associated with antagonizing the adrenergic receptor α_{2A}. It is further understood that any of the compounds provided herein may be administed in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. For example, such a combination therapy may be utilized in an individual who has high blood pressure or has a propensity toward high blood pressure that is not associated with being administered a compound that antagonizes the adrenergic receptor α_{2A}. Compounds that exhibit the dual properties of binding to and being an antagonist of both the adrenergic receptor α_{2A} and the adrenergic receptor α_{2B} may also be administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual.

[0097] Compounds that antagonize the adrenergic receptor α_{2A} and the adrenergic receptor α_{2B} may lower blood glucose and reduce blood pressure and be of therapeutic utility in individuals with high glucose and high blood pressure, for example individuals who have metabolic syndrome. Compounds that antagonize the adrenergic receptor α_{2A} and the adrenergic receptor α_{2B} may also block the adrenergic receptor α_{1B} and have utility in individuals with high blood glucose and high blood pressure.

[0098] The compounds provided herein may in some embodiments also bind to and be antagonists of the adrenergic receptor α_{1B}, which activity may also help reduce or eliminate an increase in blood pressure in an individual in response to a compound that is an adrenergic receptor α_{2A} antagonist. Thus, in one variation, compounds that bind to and are antagonists of the adrenergic receptor α_{2A} are provided, wherein the compounds also bind to and are antagonists of the adrenergic receptors α_{2B} and α_{1B}. In another variation, compounds that bind to and are antagonists of the adrenergic receptor α_{2A} are provided, wherein the compounds also bind to and are antagonists of the adrenergic receptor α_{1B} but which are not antagonists of the adrenergic receptor α_{2B}. Such compounds, when are administered in the methods detailed herein, may be administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual.

[0099] The compounds provided herein may in some embodiments also bind to and be antagonists of the adrenergic receptor α_{1D}, which activity may also help reduce or eliminate an increase in blood pressure in an individual in response to a compound that is an adrenergic receptor α_{2A} antagonist. Thus, in one variation, compounds that bind to and are antagonists of the adrenergic receptor α_{2A} are provided, wherein the compounds also bind to and are antagonists of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another variation, compounds that bind to and are antagonists of the adrenergic receptor α_{2A} are provided, wherein the compounds also bind to and are antagonists of the adrenergic receptor α_{1B} and α_{1D} but which are not antagonists of the adrenergic receptor α_{2B}. In another variation, compounds that bind to and are antagonists of the adrenergic receptor α_{2A} are provided, wherein the compounds also bind to and are antagonists of the adrenergic receptor α_{2B} and α_{1D} but which are not antagonists of the adrenergic receptor α_{1B}. In another variation, compounds that bind to and are antagonists of the adrenergic receptor α_{2A} are provided, wherein the compounds also bind to and are antagonists of the adrenergic receptors α_{1D}, but which are not antagonists of the adrenergic receptor α_{2B} or α_{1B}. Such compounds, when administered in the methods detailed herein, may be administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual.

[0100] The second agent that reduces, or is expected to reduce, blood pressure in an individual may be a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist, a beta blocker, a calcium channel blocker, or any combination thereof. In one variation, the second agent that reduces, or is expected to reduce, blood pressure in an individual is a compound that binds to and is an antagonist of the adrenergic receptor α_{2B} but which is not an antagonist of the adrenergic receptor α_{2A}. In one variation, the second agent is a single compound. However, it is understood that the second agent in one embodiment may be two or more compounds, such as a second agent that comprises a first compound that is a diuretic and a second compound that is an ACE-inhibitor.

[0101] In one variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A}. In one variation, a compound provided herein exhibits greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% or between about 50% and about 90% or between about 60% and about 90% or between about 70% and about 90% or between about 80% and about 100% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist

activity to adrenergic receptor α_{2A}. In one variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2A}. In one variation, a compound provided herein exhibits greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% or between about 50% and about 90% or between about 60% and about 90% or between about 70% and about 90% or between about 80% and about 100% inhibition of α_{2A} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2A}.

[0102] In another variation, a compound as provided herein (i) binds to and is an antagonist of adrenergic receptor α_{2A} and (ii) exhibits greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1μM and antagonist activity to adrenergic receptor α_{2B}. In one such variation, a compound as provided herein exhibits (i) greater than or equal to about 50% inhibition of α_{2A} ligand binding at 0.1μM and antagonist activity to adrenergic receptor α_{2A} and (ii) greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1μM and antagonist activity to adrenergic receptor α_{2B}. When the compound exhibits greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1μM and antagonist activity to adrenergic receptor α_{2B}, in some embodiments, it exhibits greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% or between about 50% and about 90% or between about 60% and about 90% or between about 70% and about 90% or between about 80% and about 100% inhibition of α_{2B} ligand binding at 0.1μM and antagonist activity to adrenergic receptor α_{2B}. In another variation, a compound as provided herein exhibits (i) greater than or equal to about 50% inhibition of α_{2A} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2A} and (ii) greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}. In another variation, a compound as provided herein exhibits (i) greater than or equal to about 50% inhibition of α_{2A} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2A} and (ii) greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B}. In another variation, a compound as provided herein exhibits (i) greater than or equal to about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A} and (ii) greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}. When the compound exhibits greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{2B}, in some embodiments, it exhibits greater than or equal to about any one of 50%,

55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% or between about 50% and about 90% or between about 60% and about 90% or 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}. It is understood and clearly conveyed herein that an adrenergic receptor α_{2A} antagonist can exhibit any of the adrenergic receptor α_{2A} binding profiles described herein in combination with any of the adrenergic receptor α_{2B} binding profiles described herein, as if each and every combination were listed separately.

[0103] The adrenergic receptor α_{2A} antagonists may also be used in conjunction with other agents that antagonize the adrenergic receptor α_{2B}. Administration in conjunction with another compound includes administration in the same or different composition, either sequentially, simultaneously, or continuously.

[0104] In one variation, compounds provided herein that bind to and are antagonists of the adrenergic receptor α_{2A} will also bind to and antagonize the adrenergic receptor α_{1B}. In another variation, compounds provided herein that bind to and are antagonists of the adrenergic receptor α_{2A} and either (a) also bind to and are antagonists of the adrenergic receptor α_{2B} or (b) are administered in the methods detailed herein in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual, will also bind to and antagonize the adrenergic receptor α_{1B}. In some embodiments, compounds provided herein may exhibit greater than or equal to about 50% inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}. In some embodiments, compounds provided herein may exhibit greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 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}. In some embodiments, compounds provided herein may exhibit greater than or equal to about 50% inhibition of α_{1B} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1B}. In some embodiments, compounds provided herein may exhibit greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 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}. For example, in one variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1μM and antagonist activity to adrenergic

receptor α_{2A} and greater than or equal to about 50% inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}. In another variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A}, greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B} and greater than or equal to about 50% inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}. In one variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A}, greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B} and greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 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 an adrenergic receptor α_{2A} antagonist can exhibit any of the adrenergic receptor α_{2A} binding profiles described herein in combination with any of the adrenergic receptor α_{2B} binding profiles described herein, and/or any of the adrenergic receptor α_{1B} binding profiles described herein as if each and every combination were listed separately.

[0105] The adrenergic receptor α_{2A} 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.

[0106] In one variation, compounds provided herein that bind to and are antagonists of the adrenergic receptor α_{2A} will also bind to and antagonize the adrenergic receptor α_{1D}. In another variation, compounds provided herein that bind to and are antagonists of the adrenergic receptor α_{2A} and either (a) also bind to and are antagonists of the adrenergic receptor α_{2B} or (b) are administered in the methods detailed herein in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual, will also bind to and antagonize the adrenergic receptor α_{1D}. In another variation, compounds provided herein that bind to and are antagonists of the adrenergic receptor α_{2A} and either (a) also bind to and are antagonists of the adrenergic receptor α_{2B} or (b) are administered in the methods detailed herein in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual, and

bind to and are antagonists of the adrenergic receptor α_{1B} will also bind to and antagonize the adrenergic receptor α_{1D}. In some embodiments, compounds provided herein may exhibit greater than or equal to about 50% inhibition of α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1D}. In some embodiments, compounds provided herein may exhibit greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 90%, or between about 80% and about 100% inhibition of α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1D}. In some embodiments, compounds provided herein may exhibit greater than or equal to about 50% inhibition of α_{1D} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1D}. In some embodiments, compounds provided herein may exhibit greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 90%, or between about 80% and about 100% inhibition of α_{1D} ligand binding at 0.03 μM and antagonist activity to adrenergic receptor α_{1D}. For example, in one variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1μM and antagonist activity to adrenergic receptor α_{2A} and greater than or equal to about 50% inhibition of α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1D}. In another variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A}, greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B} and greater than or equal to about 50% inhibition of α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1D}. In another variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A}, greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B}, greater than or equal to about 50% inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B}, and greater than or equal to about 50% inhibition of α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1D}. In one variation, a compound provided herein exhibits equal to or greater than about 50% inhibition of α_{2A} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2A}, greater than or equal to about 50% inhibition of α_{2B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{2B}, greater than or equal to about 50%

inhibition of α_{1B} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1B} and greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%, or between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 90%, or between about 80% and about 100% inhibition of α_{1D} ligand binding at 0.1 μM and antagonist activity to adrenergic receptor α_{1D}. It is understood and clearly conveyed herein that an adrenergic receptor α_{2A} antagonist can exhibit any of the adrenergic receptor α_{2A} binding profiles described herein in combination with any of the adrenergic receptor α_{2B} binding profiles described herein, and/or any of the adrenergic receptor α_{1B} binding profiles described herein and/or any of the adrenergic receptor α_{1D} binding profiles described herein as if each and every combination were listed separately.

[0107] The adrenergic receptor α_{2A} 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.

[0108] 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

[0109] Antagonist activity to the adrenergic receptor $\alpha_{2A,}$ α_{2B}, α_{1B} and α_{1D} may be assessed by methods known in the art, such as standard $\alpha_{2A,}$ α_{2B}, α_{1B} and α_{1D} receptor cell membrane-based or intact cell-based activity assays. For example, the Aequorin-based assay may be used to assess antagonist activity to the adrenergic receptor $\alpha_{2A,}$ α_{2B}, α_{1B} or α_{1D} and the cell membrane-based GTPγS binding assay may be used to assess antagonist activity to the adrenergic receptor α_{2B}.

[0110] In one variation, adrenergic receptor α_{2A} antagonists as provided herein 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 UK14304 (for Aequorin assay) in an adrenergic receptor α_{2A} antagonist assay.

[0111] In another variation, a compound provided herein binds to and is an antagonist of the adrenergic receptor α_{2A}, wherein the compound is also an antagonist of the adrenergic receptor α_{2B} and exhibits an IC_{50} value that is 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) in an adrenergic receptor α_{2B} antagonist assay. In some embodiments, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) an IC_{50} value in an α_{2A} 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 UK14304 (for Aequorin assay), and (ii) an IC_{50} value in an α_{2B} antagonist assay that is 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). In another variation, a compound provided herein binds to and is an antagonist of the adrenergic receptor α_{2A}, wherein the compound is also an antagonist of the adrenergic receptor α_{1B} and exhibits an IC_{50} value that is 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 cirazoline (for Aequorin assay) in an adrenergic receptor α_{1B} antagonist assay. In some embodiments, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) 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 UK14304 (for Aequorin assay) in an adrenergic receptor α_{2A} antagonist assay, and (ii) an IC_{50} value 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 an adrenergic receptor α_{1B} antagonist assay. In yet another variation, a compound provided herein binds to and is an antagonist of the adrenergic receptor α_{2A}, wherein the compound is also an antagonist of the adrenergic receptor α_{1D} and exhibits an IC_{50} value that is 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 cirazoline (for Aequorin assay) in an adrenergic receptor α_{1D} antagonist assay. In some embodiments, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) 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 UK14304 (for Aequorin assay) in an adrenergic receptor α_{2A} antagonist assay, and (ii) an IC_{50} value 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 an adrenergic receptor α_{1D} antagonist assay.

[0112] In yet another embodiment, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) an IC_{50} value in an α_{2A} 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 UK14304 (for Aequorin assay); (ii) an IC_{50} value in an α_{2B} antagonist assay that is 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 (iii) an IC_{50} value equal 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 cirazoline) in an adrenergic receptor α_{1B} antagonist assay. In another embodiment, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) an IC_{50} value in an α_{2A} 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 UK14304 (for Aequorin assay); (ii) an IC_{50} value in an α_{2B} antagonist assay that is 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 (iii) an IC_{50} value equal 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 cirazoline) in an adrenergic receptor α_{1D} antagonist assay. In another embodiment, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) an IC_{50} value in an α_{2A} 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 UK14304 (for Aequorin assay); (ii) an IC_{50} value equal 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 cirazoline) in an adrenergic receptor α_{1B} antagonist assay; and (iii) an IC_{50} value equal 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 cirazoline) in an adrenergic receptor α_{1D} antagonist assay.

[0113] In yet another embodiment, adrenergic receptor α_{2A} antagonists as provided herein exhibit: (i) an IC_{50} value in an α_{2A} 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 UK14304 (for Aequorin assay); (ii) an IC_{50} value in an α_{2B} antagonist assay that is 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); (iii) an IC_{50} value equal 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 cirazoline) in an adrenergic receptor α_{1B} antagonist assay; and (iv) an IC_{50} value equal 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 cirazoline) in an adrenergic receptor α_{1D} antagonist assay.

[0114] In one variation, adrenergic receptor α_{2A} antagonists as provided herein 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 UK14304 (for Aequorin assay) in an adrenergic receptor α_{2A} antagonist assay. In one variation, adrenergic receptor α_{2A} antagonists as provided herein exhibit an IC_{50} value equal to or less than about 10 nM at a given concentration of agonist (*e.g.* concentration corresponding to EC_{80} of UK14304 (for Aequorin assay) in an adrenergic receptor α_{2A} antagonist assay. In one variation, adrenergic receptor α_{2A} antagonists as provided herein exhibit an 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. In one variation, adrenergic receptor α_{2A} antagonists as provided herein exhibit an IC_{50} value equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of UK14304 between about 0.4 and about 40 nM in an adrenergic receptor α_{2A} (Aequorin) antagonist assay. In one variation, adrenergic receptor α_{2A} antagonists as provided herein exhibit an IC_{50} value equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of about 4.57 nM UK14304 in an adrenergic receptor α_{2A} (Aequorin) antagonist assay.

[0115] In one variation adrenergic receptor α_{2A} antagonists as provided herein 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 some embodiments, adrenergic receptor α_{2A} antagonists as provided herein exhibit an IC_{50} value equal to or less than about 10 nM at a given concentration of agonist (*e.g.* concentration corresponding to EC_{80} of oxymetazoline (for Aequorin assay) or guanfacine (for GTPγS assay) in an α_{2B} antagonist assay. In some embodiments, a compound described herein 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 some embodiments, a compound described herein exhibits an IC_{50} value in an α_{2B} antagonist (Aequorin) assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of oxymetazoline between about 50 nM to about 5000 nM. In some embodiments, a compound described herein exhibits an IC_{50} value in an α_{2B} antagonist (Aequorin) 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 some embodiments, a compound described herein exhibits an IC_{50} value in an α_{2B} antagonist (GTPγS) assay equal to or less than about any one of 100 nM, 30 nM or 10 nM at a concentration of guanfacine between about 50 nM to about 5000 nM. In some embodiments, a compound described herein 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 is a particular variation, is 504 nM guanfacine.

[0116] In one variation, a compound described herein exhibits 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 given concentration of agonist (*e.g.* concentration corresponding to EC_{80} of cirazoline) in an adrenergic receptor α_{1B} antagonist assay. In some embodiments, a compound described herein exhibits an IC_{50} value in an α_{1B} antagonist assay equal to 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 some embodiments, a compound described herein exhibits 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 corresponding to its EC_{80} concentration as obtained by assay protocols described herein. In some embodiments, a compound described herein exhibits an IC_{50} value in an α_{1B} antagonist (Aequorin) 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 some embodiments, a compound described herein exhibits an IC_{50} value in an α_{1B} antagonist (Aequorin) 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.

[0117] In one variation, a compound described herein exhibits 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 given concentration of agonist (*e.g.* concentration corresponding to EC_{80} of cirazoline) in an adrenergic receptor α_{1D} antagonist assay. In some embodiments, a compound described herein

exhibits an IC_{50} value in an α_{1D} antagonist assay equal to 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 some embodiments, a compound described herein exhibits 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 corresponding to its EC_{80} concentration as obtained by assay protocols described herein. In some embodiments, a compound described herein exhibits 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 some embodiments, a compound described herein exhibits 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.

[0118] In some embodiments, compounds provided herein exhibit inverse agonist activity for the adrenergic receptor α_{2A}. In some embodiments, the compound binds to and is an inverse agonist of the adrenergic receptor α_{2A} and binds to and is antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In one variation, the compound binds to and is an inverse agonist of the adrenergic receptor α_{2A} and binds to and is antagonist of any one of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another variation, the compound binds to and is an inverse agonist of the adrenergic receptor α_{2A} and binds to and is antagonist of any two of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In yet another variation, the compound binds to and is an inverse agonist of the adrenergic receptor α_{2A} and binds to and is antagonist of adrenergic receptors α_{2B}, α_{1B} and α_{1D}. Inverse agonist activity to the adrenergic receptor α_{2A} may be assessed by methods known in the art, such as those described in Wade, S.M. et al., *Mol. Pharmacol.* 59:532–542 (2001).

[0119] It is understood and clearly conveyed herein that any of the binding profiles detailed herein can be combined with any of the antagonist profiles detailed herein, as if each and every combination were listed separately. For example, in one variation, a compound provided herein exhibits (i) greater than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 80%, 85%, 90%, 95%, or between about 50% and 90%, between about 60% and about 90%, between about 70% and about 90%, or about 80% and about 100% inhibition of α_{2A} ligand binding at 0.1μM to adrenergic receptor α_{2A} and 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 UK14304 (for Aequorin assay) in an adrenergic receptor α_{2A} antagonist assay; and (ii) greater

than or equal to about any one of 50%, 55%, 60%, 65%, 70%, 80%, 85%, 90%, 95%, or between about 50% and 90%, between about 60% and about 90%, between about 70% and about 90%, or about 80% and about 100% inhibition of α_{2B} ligand binding at 0.1μM to adrenergic receptor α_{2B} and 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.

Medical Use

[0120] Without being bound by theory, it is believed that compounds that bind to and are antagonists of the adrenergic receptor α_{2A} affect an increase in insulin secretion and/or promote insulin release into the blood stream in an individual, which aids in glucose uptake. However, such compounds may also increase an individual's blood pressure. When the adrenergic receptor α_{2A} antagonists as provided herein also bind to and are antagonists of the adrenergic receptor α_{2B} and/or the adrenergic receptor α_{1B}, and/or the adrenergic receptor α_{1D}, it is believed that the increases in an individual's blood pressure due to antagonizing the adrenergic receptor α_{2A} may be reduced or eliminated. If an adrenergic receptor α_{2A} antagonist as provided herein is not also an antagonist of the adrenergic receptor α_{2B} and/or the adrenergic receptor α_{1B} and/or the adrenergic receptor α_{1D}, then the increase in an individual's blood pressure as a result of the adrenergic receptor α_{2A} antagonist may be reduced or eliminated by administering the compound in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual.

[0121] Compounds provided herein, such as the adrenergic receptor α_{2A} antagonists provided herein, are expected to find use in therapy, particularly in indications in which an increase in an individual's insulin secretion and/or an increase in insulin release into the blood stream would be, or would be expected to be, beneficial. Thus, individuals who have a disease or condition that involves reduced or impaired insulin secretion and/or release may benefit from the compounds detailed herein, or pharmaceutically acceptable salts thereof. Such indications include, but are not limited to type 2 diabetes, glucose intolerance and metabolic syndrome. An individual who has a disease or condition that involves reduced or impaired insulin secretion and/or release may experience one or more beneficial or desirable results upon administration of an adrenergic receptor α_{2A} antagonist provided herein, or pharmaceutically acceptable salt thereof. In one aspect, the beneficial or desirable result is a reduction in the individual's blood

glucose level for a period of time (*e.g.*, about any one of 6, 12, 24 or 48 hours or more) following administration of the compound or pharmaceutically acceptable salt thereof. In another aspect, the beneficial or desirable result is an increase in glucose metabolism for a period of time (*e.g.*, about any one of 6, 12, 24 or 48 hours or more) following administration of the compound or pharmaceutically acceptable salt thereof.

[0122] Compounds that are inverse agonists of the adrenergic receptor α_{2A} may stimulate islet cell release of insulin even in the absence of sympathetic stimulation of the adrenergic receptor α_{2A} with epinephrine and/or norepinephrine. Inverse agonists of the adrenergic receptor α_{2A} provided herein are thus expected to find use in therapy, particularly in indications in which stimulation of islet cell release of insulin would be, or would be expected to be, beneficial. Individuals who have a disease or condition responsive to inhibition of the adrenergic receptor α_{2A} may benefit from the compounds detailed herein, or pharmaceutically acceptable salts thereof. Such indications include, but are not limited to type 2 diabetes, metabolic syndrome, and glucose intolerence.

[0123] 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.

[0124] The adrenergic receptor α_{2A} antagonists provided herein may also be administered in combination with an insulin sensitizer, and as such find use in therapy for treating indications in which increasing in an individual's insulin secretion and/or insulin release into the blood stream would be, or would be expected to be, beneficial, provided that the therapy also promotes insulin responsiveness to glucose. In one aspect, where the adrenergic receptor α_{2A} antagonists provided herein may be administered in combination with another anti-diabetic drug, such as an insulin sensitizer, the beneficial or desirable result of which is a reduction in the individual's blood glucose levels for a period of time (*e.g.*, about any one of 6, 12, 24 or 48 hours or more) following administration of the compound or pharmaceutically acceptable salt thereof. In a particular variation, such a therapy may include an adrenergic receptor α_{2A} antagonist provided herein and a second agent that reduces, or is expected to reduce, blood pressure and an insulin sensitizer. In a further variation, such a therapy may include an adrenergic receptor α_{2A} antagonist provided herein and a second agent that (i) is an agent that reduces, or is expected to reduce, blood pressure; (ii) is an agent that is an insulin sensitizer or (iii) is an agent that induces no or reduced (in number and/or severity) hypoglycemic episodes.

Methods

[0125] Methods of using the compounds detailed herein, or pharmaceutical salts thereof, to increase an individual's ability to secrete insulin and/or to release insulin into the blood stream are provided. In any of the methods detailed herein, the method may comprise the step of administering an adrenergic receptor α_{2A}antagonist, or pharmaceutically acceptable salt thereof, to an individual in need thereof. In one aspect, the adrenergic receptor α_{2A} antagonists of the methods also bind to and are antagonists of one or more of the adrenergic receptors α_{2B}, α_{1B} and $\alpha_{1D.}$ In one variation, a method of increasing insulin secretion and/or release into the blood stream in an individual in need thereof is provided, wherein the method comprises administering to an individual in need thereof a compound that binds to and is an antagonists of the adrenergic receptor α_{2A}. In another variation, a method of increasing insulin secretion and/or release into the blood stream in an individual in need thereof is provided, wherein the method comprises administering to an individual in need thereof a compound that binds to and is an antagonists of the adrenergic receptor α_{2A}, wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in the individual. In some variations, methods

of using the compounds detailed herein to increase an individual's ability to secrete insulin and/or release insulin into the blood stream while reducing or eliminating an increase in the individual's blood pressure due to antagonizing the adrenergic receptor α_{2A} are thus provided. Methods of using the compounds detailed herein to promote an individual's ability to metabolize glucose while reducing or eliminating an increase in the individual's blood pressure due to antagonizing the adrenergic receptor α_{2A} are also provided. It is understood that in methods of promoting an individual's ability to metabolize glucose, the method in one variation may employ administration of both an adrenergic receptor α_{2A} antagonist and an insulin sensitizer. The compounds or pharmaceutical salts thereof may also find use in treating a disease or condition that is, or is expected to be, responsive to an increase in an individual's ability to secrete insulin and/or release of insulin into the blood stream. Individuals to be treated in such methods in one variation have a reduced or impaired ability to secrete insulin and/or release insulin into the blood stream. 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 reduced or impaired ability to secrete insulin and/or release insulin into the blood stream, 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 reduced or impaired ability to secrete insulin and/or release insulin into the blood stream. 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 reduced or impaired ability to metabolize glucose, comprising administering an adrenergic receptor α_{2A} antagonist as provided herein, or a pharmaceutical salt thereof, to an individual who is at risk of developing a disease or condition associated with reduced or impaired ability to metabolize glucose. The individual may be an adult, child or teen who has or is at risk of developing type 2 diabetes, glucose intolerance or metabolic syndrome.

[0126] Non-limiting examples of a second agent that lowers blood pressure includes diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 receptor antagonists, beta blockers, calcium channel blockers, or any combination thereof.

[0127] Also provided herein are methods of using an adrenergic receptor α_{2A} antagonist, or a pharmaceutically acceptable salt thereof, in combination with one or more of other anti-diabetic agents, such as insulin sensitizers and secretagogue agents. Non-limiting examples of anti-diabetic agents includes insulin therapies (e.g., insulin glargine and insulin lispro), secretagogue agents that increase insulin secretion and/or release (e.g., sulfonylureas such as glimepiride,

glipizide and glyburide; meglitinides such as repaglinide and nateglinide), agents that increase insulin sensitivity (e.g., thiazolidinediones, such as pioglitazone and rosiglitazone), agents that decrease glucose absorption (e.g., alpha-glucosidase inhibitors such as miglitol and acarbose); and agents that reduce gluconeogenesis (biguanide such as metformin); amylinomimetics such as pramlintide, and agents that sequester bile acids.

[0128] Further provided herein are methods of using an adrenergic receptor α_{2A} antagonist, or a pharmaceutically acceptable salt thereof, in combination with an insulin sensitizer to promote insulin responsiveness and increase an individual's ability to secrete insulin and/or to release insulin into the blood stream. In one aspect, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In one variation, a method of promoting insulin responsiveness and increasing insulin secretion and/or release into the blood stream in an individual in need thereof is provided, wherein the method comprises administering to an individual in need thereof an insulin sensitizer and an adrenergic receptor α_{2A} antagonist. In another variation, a method of promoting insulin responsiveness and increasing insulin secretion and/or release into the blood stream in an individual in need thereof is provided, wherein the method comprises administering to an individual in need thereof an insulin sensitizer and a compound that binds to and is an antagonists of the adrenergic receptor α_{2A}, wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in the individual. In a particular variation, a method of promoting insulin responsiveness and increasing insulin secretion and/or release into the blood stream in an individual in need thereof is provided, wherein the method comprises administering to an individual in need thereof an insulin sensitizer and an adrenergic receptor α_{2A} antagonist that also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In some embodiments, the method comprises administering any of the compounds detailed herein in combination with an insulin sensitizer.

[0129] In one aspect, a method of treating type 2 diabetes is provided, where the method comprises administering to an individual in need thereof a compound detailed herein, such as an adrenergic receptor α_{2A} antagonist detailed herein. In one aspect, the compound binds to and is an adrenergic receptor α_{2A} antagonist. In some embodiments, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another aspect, a method of treating type 2 diabetes is provided, where the method

comprises administering to an individual in need thereof a compound as provided herein, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2A} and wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. Individuals to be treated in such methods in one variation have type 2 diabetes. The compounds as provided herein may also be used in a method of delaying the onset and/or development of type 2 diabetes, comprising administering an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, to an individual who has one or more risk factors associated with developing type 2 diabetes. In one variation, the compounds as provided herein are used in a method of delaying the onset and/or development of type 2 diabetes; and inducing extra-pancreatic effects such as reducing hepatic glucose production via glycogenolysis or gluconegogenesis or both, comprising administering an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, to an individual such as an individual who has one or more risk factors associated with developing type 2 diabetes. In one variation, compounds provided herein may (i) have an extra-pancreatic effect and/or (ii) prevent or lower hepatic glucose production.

[0130] Risk factors may include gender, race, ethnicity, age, family history, weight and/or lifestyle. For example, certain races and ethnicities (*e.g.*, Blacks, Hispanics, Native Americans and Asians (which as used herein includes individuals of the continent of Asia, such as Indians and Chinese) and individuals of such descent) are more likely to develop type 2 diabetes. Being overweight (*e.g.*, having a body mass index > 25) is also a risk factor for type 2 diabetes, with higher amount of fatty tissue also correlating with higher resistance of cells to insulin. Inactivity, which can lead to weight gain, is also a risk factor for type 2 diabetes (physical activity helps not only to control an individual's weight, but also utilizes glucose as energy and makes cells more sensitive to insulin). Family history is often a risk factor for many diseases, including type 2 diabetes, where the risk of developing type 2 diabetes increases if a parent or sibling has type 2 diabetes. The risk of developing type 2 diabetes also increases with age, especially after age 45, which may also correlate with a tendency to exercise less, lose muscle mass and gain weight with age. However, as obesity rates rise in children and young adults, type 2 diabetes is increasing common in these individuals and children and young adults who are overweight and/or sedentary are also at risk of developing type 2 diabetes. Being pre-diabetic, in which an individual's blood sugar level is higher than normal, but not high enough to be

classified as type 2 diabetes, if left untreated, often progresses to type 2 diabetes. Other risk factors associated with type 2 diabetes include: a woman who has had gestational diabetes, gave birth to a baby weighing more than 9 pounds or has a history of polycystic ovary disease (PCOS); an individual who has metabolic syndrome; an individual who has hypertension; an individual who has a high-density lipoprotein (HDL) value under 35 mg/dL (milligrams per deciliter) and/or a triglyceride level over 250 mg/dL; and an individual with a history of vascular disease, such as stroke. Individuals who have more than one risk factor are particularly susceptible to developing type 2 diabetes.

[0131] In one aspect, a method of treating glucose intolerance is provided, where the method comprises administering to an individual in need thereof an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof. In one aspect, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another aspect, a method of treating glucose intolerance is provided, where the method comprises administering to an individual in need thereof a compound as provided herein, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2A} and wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in the individual. The compounds as provided herein may also be used in a method of delaying the onset and/or development of glucose intolerance, comprising administering a compound as provided herein to an individual who has one or more risk factors associated with developing glucose intolerance. A method of reducing blood glucose levels in an individual in need thereof is also provided, the method comprising administering an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, to the individual. A method of enhancing glucose metabolism in an individual in need thereof is also provided, the method comprising administering an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, to the individual.

[0132] Further provided are methods of using the compounds detailed herein, or pharmaceutical salts thereof, to regulate blood glucose levels in an individual, for example, an individual experiencing hyperglycemia and/or undesirable fluctuation in blood glucose levels. In some embodiments, provided is a method of regulating blood glucose levels in an individual in need thereof, where the method comprises administering to an individual in need thereof an adrenergic receptor α_{2A} antagonist. In some embodiments, administration of an adrenergic

receptor α_{2A} antagonist reduces the blood glucose levels in an individual (e.g., a hyperglycemic individual). In some embodiments, administration of an adrenergic receptor α_{2A} antagonist stabilizes the blood glucose levels in an individual (e.g., an individual experiencing undesirable fluctuations in blood glucose levels). In some embodiments, administration of an adrenergic receptor α_{2A} antagonist reduces and stabilizes the blood glucose levels in an individual. In one aspect, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another aspect, provided is a method of regulating (e.g., reducing and/or stabilizing) blood glucose levels in an individual in need thereof, where the method comprises administering to an individual in need thereof a compound as provided herein, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2A} and wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. In some embodiments, the adrenergic receptor α_{2A} antagonist described herein may also be an inverse agonist of the adrenergic receptor α_{2A}.

[0133] In some embodiments, provided is a method of reducing blood glucose level in an individual in need thereof, comprises administering to an individual in need thereof an adrenergic receptor α_{2A} antagonist, wherein the blood glucose level is reduced to a desirable level. The adrenergic receptor α_{2A} antagonist may be administered alone or in combination with other agents such as an agent that reduces blood pressure in the individual. In some embodiments, the blood glucose level is reduced by about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, or about 70%, provided that the reduction in glucose level does not result in hypoglycemia. In some embodiments, the blood glucose level is reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, or at least about 60%, provided that the reduction in glucose level does not result in hypoglycemia. In some embodiments, the blood glucose level is reduced by less than about 10%, between about 10% and about 30%, between about 30% and about 50%, between about 10% and about 50%, between about 50% and about 70%, between about 30% and about 70%, between about 20% and about 40%, between about 40% and about 60%, or between about 20% and about 60%, provided that the reduction in glucose level does not result in hypoglycemia. The reduction of blood glucose level occurs over a period of time after administration of the adrenergic receptor α_{2A} antagonist. In some embodiments, the reduction of blood glucose occurs within about 15 minutes after administration of the the compound or pharmaceutically acceptable salt thereof. In

some embodiments, the reduction of blood glucose occurs within about 30 minutes, within about 1 hour, or within about 2 hours after administration of the adrenergic receptor α_{2A} antagonist. In some embodiments, the reduction of blood glucose occurs at about 15 minutes or more, at about 30 minutes or more, at about 1 hour or more, or at about 2 hours or more after administration of the adrenergic receptor α_{2A} antagonist. In some embodiments, the method results in a reduction in the individual's blood glucose level by any of the amount described herein for a period of time (e.g., about any one of 0.5, 1, 2, 3, 6, 12, 24 or 48 hours or more) following administration of the compound or pharmaceutically acceptable salt thereof. In some embodiments, the method results in a reduction in the individual's blood glucose level by any of the amount described herein for a period of about 1 hour, about 2 hours, about 3 hours, about 6 hours, about 12 hours, or about 24 hours or more following administration of the compound or pharmaceutically acceptable salt thereof.

[0134] The blood glucose levels in an individual can be measured by methods known in the art, such as by a calorimetric method or by using a device (e.g., a glucose meter). A blood glucose level in the range of about 80 to 120 mg/dL pre-meal and about 100 to 140 mg/dL post-meal is considered desirable in healthy human beings. A blood glucose level at above the desirable level is considered hyperglycemic, such as that in diabetic patients. The blood glucose level in a mildly diabetic human is about 100 to 200 mg/dL. The blood glucose level in a moderately diabetic human is about 200 to 350 mg/dL. The blood glucose level in a severely diabetic human is above 400 mg/dL. A blood glucose level at below the desirable level is considered hypoglycemic, e.g., at below 60 to 80 mg/dL. The blood glucose levels may be measured at a single time point. However, a more accurate measurement requires an average over multiple time points or an area under the curve (AUC) over a period of time (e.g., 2 to 3 hours). The blood glucose level over a past period of about 2~3 months may be established by measuring the glycosylated hemoglobin (HbA1c) level in the blood. HbA1c is a useful way to monitor a patient's overall response to diabetes treatment over time. The HbA1c in a healthy human being is about 5%. It is desirable for a diabetic patient to keep the HbA1c level below about 7%. Provided is a method of reducing blood glucose level in an individual having an Hb1Ac level of above about 7%, comprises administering to the individual an adrenergic receptor α_{2A} antagonist, wherein the Hb1Ac level is reduced to below about 7% following administration of the compound or pharmaceutically acceptable salt thereof. In some

embodiments, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}.

[0135] In one aspect, a method of treating metabolic syndrome is provided, where the method comprises administering to an individual in need thereof a compound detailed herein, such as an adrenergic receptor α_{2A} antagonist detailed herein. In one aspect, the compound binds to and is an adrenergic receptor α_{2A} antagonist. In some embodiments, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another aspect, a method of treating metabolic syndrome is provided, where the method comprises administering to an individual in need thereof a compound as provided herein, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2A}, and wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. The compounds as provided herein may also be used in a method of delaying the onset and/or development of metabolic syndrome, comprising administering a compound as provided herein to an individual who has one or more risk factors associated with developing metabolic syndrome. In a particular variation of the methods relating to metabolic syndrome, the adrenergic receptor α_{2A} antagonist is administered to an individual in conjunction with an insulin sensitizer.

[0136] As is understood by those of skill in the art, metabolic syndrome is a cluster of conditions, which may include increased blood pressure, excess body fat around the waist, abnormal cholesterol levels and elevated insulin levels due to insulin resistance whereby cells have a diminished ability to respond to insulin and the pancreas compensates by secreting more insulin leading to high insulin levels in blood. According to the American Heart Association and the National Heart, Lung, and Blood Institute, metabolic syndrome is present if an individual has three or more of the following signs: blood pressure equal to or higher than 130/85 mm Hg; fasting blood sugar (glucose) equal to or higher than 100 mg/dL; large waist circumference, which for men is 40 inches or more and for women is 35 inches or more; low HDL cholesterol, which for men is under 40 mg/dL and for women is under 50 mg/dL; and triglycerides equal to or higher than 150 mg/dL.

[0137] Treatment of metabolic syndrome requires a careful and well-balanced approach to account for both treatment of elevated insulin levels and high blood pressure. Thus, it is desirable in the context of treating metabolic syndrome that a compound that is an antagonist of

the adrenergic receptor α_{2A} is also an antagonist of the adrenergic receptor α_{2B} and/or α_{1B} and/or α_{1D} to reduce blood pressure. Alternatively, an adrenergic receptor α_{2A} antagonist that does not also antagonize the adrenergic receptor α_{2B} and/or α_{1B} may be administered in conjunction with a second agent that reduces, or is expected to reduce blood pressure in an individual. In one aspect, provided is a method of regulating (e.g., reducing and/or stabilizing) blood glucose levels and reducing the blood pressure in an individual in need thereof (e.g., an individual experiencing metabolic syndrome, or an individual with hypertension who is also suffering from obesity and/or type 2 diabetes), where the method comprises administering to an individual in need thereof an adrenergic receptor α_{2A} antagonist. In one aspect, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In another aspect, provided a method of regulating (e.g., reducing and/or stabilizing) blood glucose levels and reducing the blood pressure in an individual in need thereof, where the method comprises administering to an individual in need thereof a compound as provided herein, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2A}, and wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) is administered in conjunction with a second agent that reduces, or is expected to reduce, blood pressure in an individual. In some embodiments, the compound is an antagonist and an inverse agonist of the adrenergic receptor α_{2A}.

[0138] Risk factors associated with developing metabolic syndrome include: more than one parent or sibling who has type 2 diabetes, individuals with high blood pressure and/or cardiovascular disease; individuals who are obese or overweight (*e.g.*, individual's having a body mass index above 25); individuals who have more fat around their waist than around their hips (an apple shape); age greater than 40 years (although it is understood that children and young adults, particularly those who are overweight and/or sedentary, may also be at risk for developing metabolic syndrome); a woman who had gestational diabetes when pregnant or who has a history of polycystic ovary syndrome (PCOS); individuals who are pre-diabetic and individuals of Latino, Black, Asian or Native American ethnicity.

[0139] Further provided herein are methods of determining if an individual suffering from glucose intolerance (*e.g.*, an individual testing negative in a glucose tolerance test) has (i) reduced or impaired insulin secretion or (ii) has reduced or impaired responsiveness to insulin, the method comprising administering a compound provided herein to the individual and testing the individual in a glucose tolerance test, wherein an increase in insulin levels after glucose

challenge (the glucose tolerance test) indicates that the individual has reduced or impaired insulin secretion; or wherein insufficient increases in insulin levels indicates that the individual has reduced or impaired responsiveness to insulin.

[0140] Provided herein are methods of assessing whether an individual is likely to be responsive to a compound that promotes an increase in insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof), administered either alone or in conjunction with an insulin sensitizer. In one aspect of such a method, an individual who has failed a glucose tolerance test (*e.g.*, an individual whose glucose levels do not return to normal levels following glucose challenge and/or whose insulin levels are not sufficiently elevated in response to administration of glucose, as measured by methods and as assessed by standards known in the art), is administered glucose following administration of an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, and their insulin levels are then assessed. In one embodiment of such methods, the adrenergic receptor α_{2A} antagonist is administered to the individual about any one of 5, 10, 15, 30 and 60 minutes or more or between about 5 and about 15 or between about 5 and about 30 or between about 5 and about 60 or between about 15 and about 30 or between about 15 and about 60 or between about 30 and about 60 minutes prior to administration of glucose. If such an individual, after administration of glucose and an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, exhibits an increase in insulin levels, the individual may be an individual who is responsive to a compound that promotes an increase in insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof). If such an individual exhibits an increase in insulin levels, but the individual's glucose levels do not decrease, then the individual may be an individual who is responsive to a compound that can increase insulin secretion and/or release (including but not limited to an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof), used in conjunction with an insulin sensitizer. Sufficient levels of insulin increase and/or glucose decrease are known by those of skill in the art. Thus, a method of assessing whether an individual suffering from glucose intolerance (*e.g.*, an individual who has failed (*e.g.*, within the last 6 months, 3 months, 1 month, 2 weeks or 1 week) a glucose tolerance test administered in the absence of an adrenergic receptor α_{2A} antagonist) is more likely to be responsive or less likely to be responsive to a therapy that can increase insulin secretion and/or release (including but not limited to an adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof), is provided, the method comprising administering an

adrenergic receptor α_{2A} antagonist, or pharmaceutically acceptable salt thereof, to the individual and testing the individual in a glucose tolerance test, wherein an increase in insulin levels after glucose challenge (the glucose tolerance test) indicates that the individual is more likely to be responsive to said therapy, and wherein a reduced or insignificant or no increase in insulin levels indicates that the individual is less likely to be responsive to said therapy.

[0141] Also provided herein are methods of selecting an individual suffering from glucose intolerance (*e.g.*, an individual who has failed a glucose tolerance test) for a therapy comprising a compound which increases insulin secretion and/or release (*e.g.* an adrenergic receptor α_{2A} antagonist) based on the levels of insulin and/or glucose of the individual following a glucose tolerance test in which the individual is administered an adrenergic receptor α_{2A} antagonist prior to glucose challenge, wherein an increase in insulin levels after glucose challenge and/or failure of the individual's glucose levels to return to normal selects the individual for said therapy. Thus, a method of selecting an individual for therapy comprising a compound that increases insulin secretion and/or release is provided (*e.g.*, an adrenergic receptor α_{2A} antagonist), the method comprising the steps of (i) administering an adrenergic receptor α_{2A} antagonist to an individual who has failed (*e.g.*, within the last 6 months, 3 months, 1 month, 2 weeks or 1 week) a glucose tolerance test administered in the absence of an adrenergic receptor α_{2A} antagonist; (2) administering a glucose tolerance test in which glucose is administered after the administration of the adrenergic receptor α_{2A} antagonist; and (3) correlating the results of the glucose tolerance test administered in conjunction with the administration of the adrenergic receptor α_{2A} antagonist to the individual (*e.g.*, where glucose is administered about any one of 5, 15, 30, 60 or more minutes following administration of the adrenergic receptor α_{2A} antagonist) with whether the individual is more or less likely to be responsive to an adrenergic receptor α_{2A} antagonist, either alone, or in conjunction with an insulin sensitizer; and (4) selecting an individual who is more likely to be responsive to a compound that increases insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist for adrenergic receptor α_{2A} antagonist therapy). An individual so selected may then be administered a compound that increases insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist for adrenergic receptor α_{2A} antagonist therapy). In one aspect, the individual is selected for therapy if their insulin levels increase in response to the glucose tolerance test administered in conjunction with the administration of the adrenergic receptor α_{2A} antagonist. If such an individual also exhibits a normal reduction in glucose levels, the individual may be selected for monotherapy with a compound that increases insulin secretion

and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist). However, if such an individual does not exhibit a normal reduction in glucose levels, the individual may be selected for therapy with a compound that increases insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist) in conjunction with an insulin sensitizer. Individuals so selected may then be administered a compound that increases insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist), either alone or in conjunction with an insulin sensitizer. Methods of monitoring the treatment of an individual for glucose intolerance are also provided.

[0142] Also provided herein are methods of treating an individual suffering from a disease or condition which is, or is expected to be, responsive to an increase in insulin secretion and/or release, the method comprising (i) determining insulin levels of an individual in a glucose tolerance test after administration of an adrenergic receptor α_{2A} antagonist and (ii) administering a compound that increases insulin secretion and/or release (*e.g.*, an adrenergic receptor α_{2A} antagonist) to an individual having an increase in insulin levels after the glucose tolerance test. In one aspect of such a method, the individual has failed (*e.g.*, recently failed) a glucose tolerance test administered in the absence of an adrenergic receptor α_{2A} antagonist and the individual's insulin levels increase in response to a glucose tolerance test which employed administration of glucose and an adrenergic receptor α_{2A} antagonist.

[0143] In any of the methods employing a glucose tolerance test in conjunction with an adrenergic receptor α_{2A} antagonist, in one variation, if the individual's insulin does not increase in response to a glucose challenge in conjunction with an adrenergic receptor α_{2A} antagonist, the individual may have type 2 diabetes with a defect in insulin secretion. Therefore, also provided are methods of identifying individuals who may have type 2 diabetes with a defect in insulin secretion.

[0144] Some genetic polymorphisms of the adrenergic receptor α_{2A} gene associate with high blood glucose and can be used to screen for patients who respond to an adrenergic receptor α_{2A} antagonist with an increase in insulin secretion and a decrease in blood glucose. For example the DNA polymorphism Rs553668 located in the 3′ UTR region of adrenergic receptor α_{2A} associates with overexpression of the adrenergic receptor α_{2A}, reduced insulin secretion, and increased type 2 diabetes risk (Rosengren et al., *Science* 327:217 (2010) and Talmud et al., *Diabetologia* 54:1710 (2011)). Human pancreatic islets from Rs553668 allele carriers exhibited reduced granule docking and secreted less insulin in response to glucose. Individuals with elevated blood glucose would be screened for the polymorphism. Individuals heterozygous or

homozygous for this polymorphism would be anticipated to respond to treatment with an adrenergic receptor α_{2A} antagonist. Other DNA polymorphisms may also be used to identify individuals with elevated blood sugar that would respond to an adrenergic receptor α_{2A} antagonist; for example Rs7911129, Rs1971596, Rs602618, and Rs2203616. Thus provided herein is a method of selecting an individual for therapy comprising a compound that (i) increases insulin secretion and/or release, and/or (ii) regulates blood glucose (*e.g.*, an adrenergic receptor α_{2A} antagonist), the method comprising screening the individual for polymorphisms of the adrenergic receptor α_{2A} gene associate with high blood glucose, such as one or more of the DNA polymorphisms Rs553668, Rs7911129, Rs1971596, Rs602618 and Rs2203616.

[0145] Also provided is a method of regulating (e.g., reducing and/or stabilizing) blood glucose levels in an individual, the method comprises the steps of (i) screening the individual for genetic polymorphisms of the adrenergic receptor α_{2A} gene associate with high blood glucose; and (ii) administering to the individual carrying one or more genetic polymorphisms of the adrenergic receptor α_{2A} gene associated with high blood glucose an adrenergic receptor α_{2A} antagonist. In one variation, provided is a method of increasing insulin seretion and/or release into the blood stream in an individual, the method comprises the steps of (i) screening the individual for genetic polymorphisms of the adrenergic receptor α_{2A} gene associate with high blood glucose; and (ii) administering to the individual carrying one or more genetic polymorphisms of the adrenergic receptor α_{2A} gene associated with high blood glucose an adrenergic receptor α_{2A} antagonist. Further provided are methods of treating type 2 diabetes, glucose intolerance and/or metabolic syndrome, where the method comprises administering to an individual in need thereof an adrenergic receptor α_{2A} antagonist, wherein the individual carries one or more genetic polymorphisms of the adrenergic receptor α_{2A} gene associated with high blood glucose, such as one or more of the DNA polymorphisms Rs553668, Rs7911129, Rs1971596, Rs602618 and Rs2203616. In some embodiments, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of one or more of the adrenergic receptors α_{2B}, α_{1B} and α_{1D}. In some embodiments, the adrenergic receptor α_{2A} antagonist also binds to and is an antagonist of the adrenergic receptors α_{2B}. In some embodiments, the method of regulating blood glucose levels, increasing insulin seretion and/or release into the blood stream, or treating type 2 diabetes, glucose intolerance and/or metabolic syndrome, further comprises administering to the individual a second agent that reduces, or is expected to reduce, blood pressure in an individual.

[0146] Compounds described herein showing adrenergic receptors α_{2A} and adrenergic receptor α_{2B} antagonist activity may find particular use in patients with fatty liver or/and obesity or/and hypertension with type-2 diabetes associated with glucose intolerance; and super-added with polymorphisms in the adrenergic receptor α_{2A} gene.

Cell viability and mitochondrial health

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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.

[0151] 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.

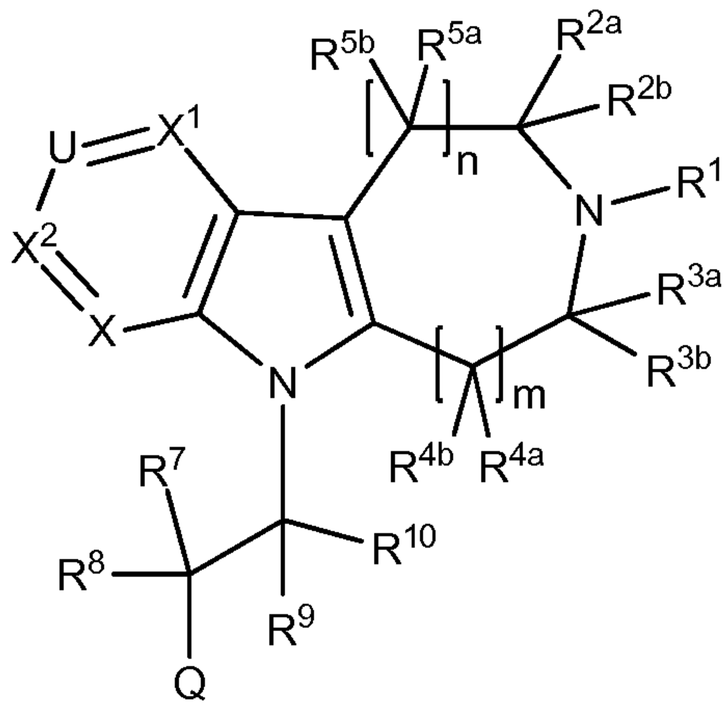
[0152] It is understood and clearly conveyed that the binding and activity profiles detailed herein (*e.g.*, in the disclosure above) in one variation apply to the formulae provided herein (*e.g.*, the formulae for use in the methods). In one aspect, selective adrenergic receptor α_{2B} antagonists are 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

[0153] 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.

[0154] 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;

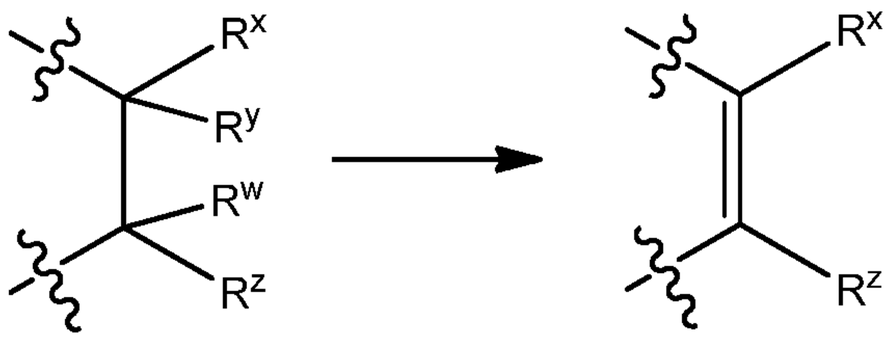
R^{13} is H or optionally substituted C_1-C_5 alkyl;

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.

[0155] 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.



[0156] 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.

[0157] 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 $CH_2CH{=}CH_2$.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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.

[0162] 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

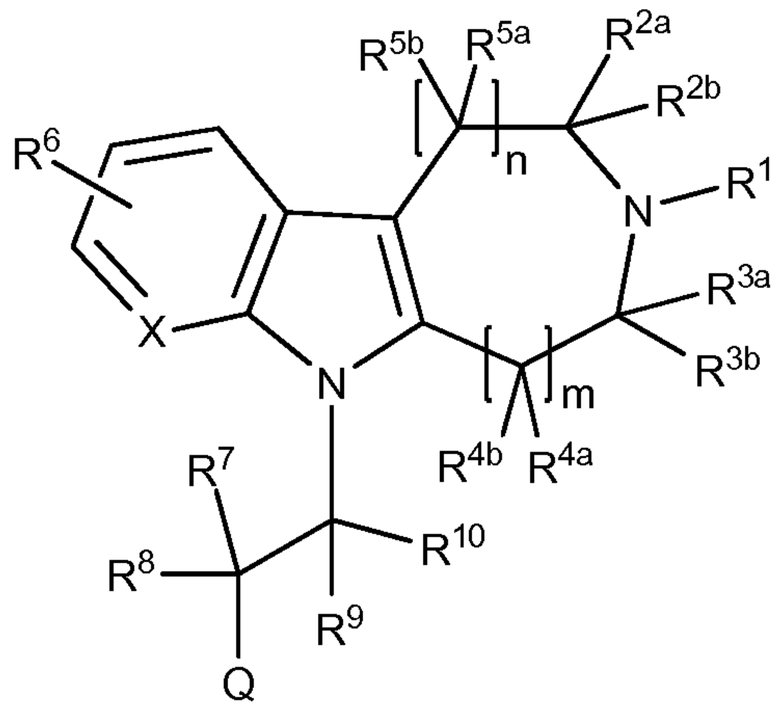
Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl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

[0163] 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.

[0164] 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.

[0165] 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.

[0166] 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;

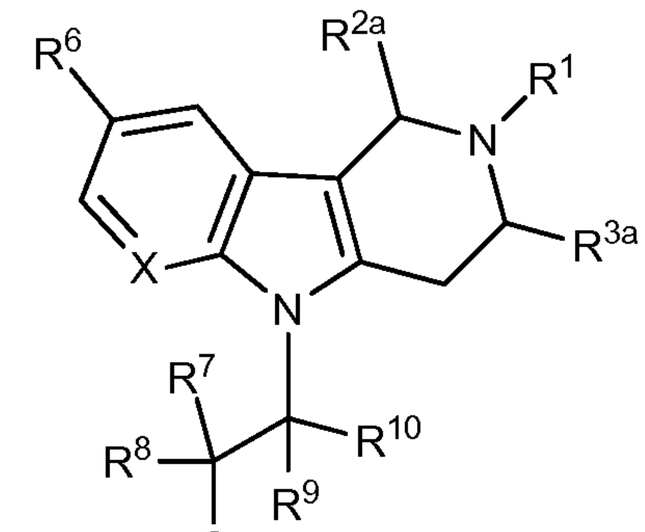
or R^{10} and R^8 are taken together to form a bond;

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;

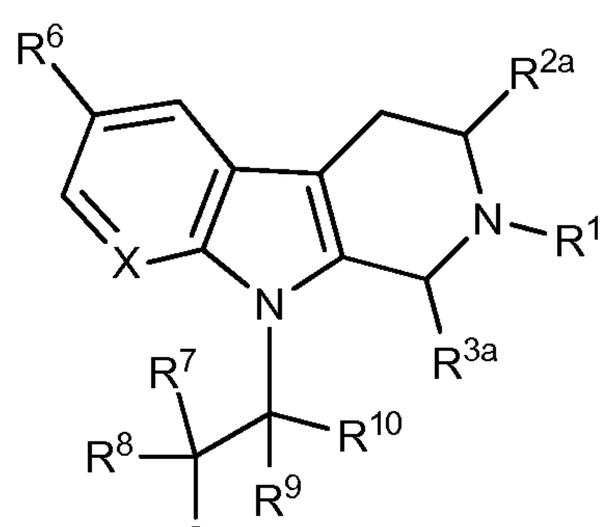
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl; and

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.

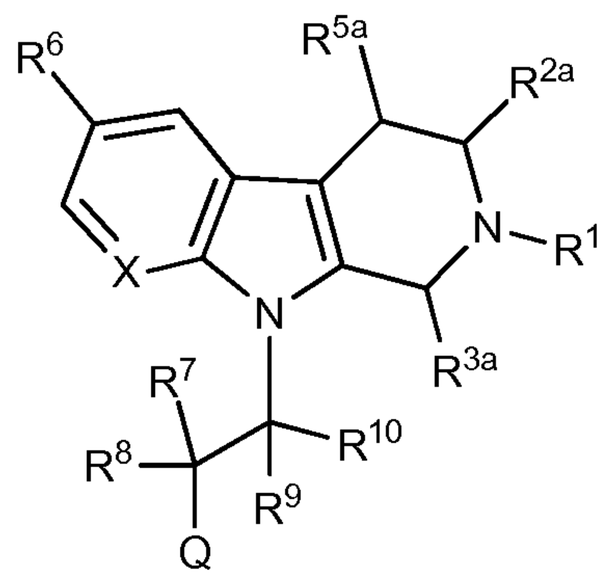
[0167] In another embodiment, the compound is of the formula (A-IIA), (A-IIB), (A-IIC) or (A-IID):



(A-IIA)

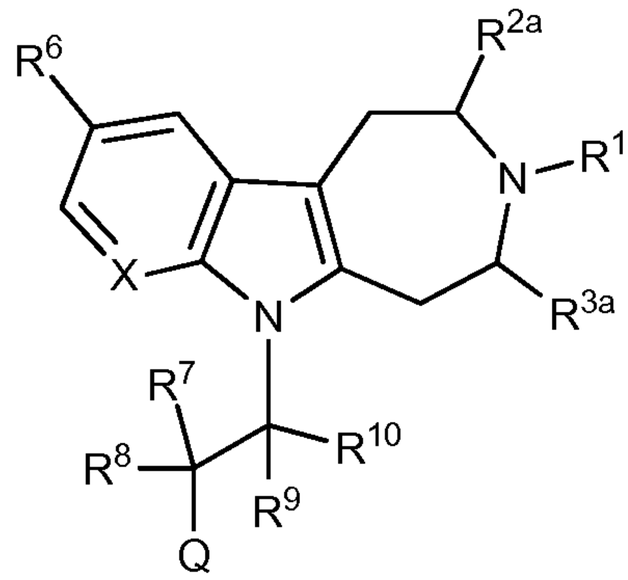


(A-IIB)



(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;

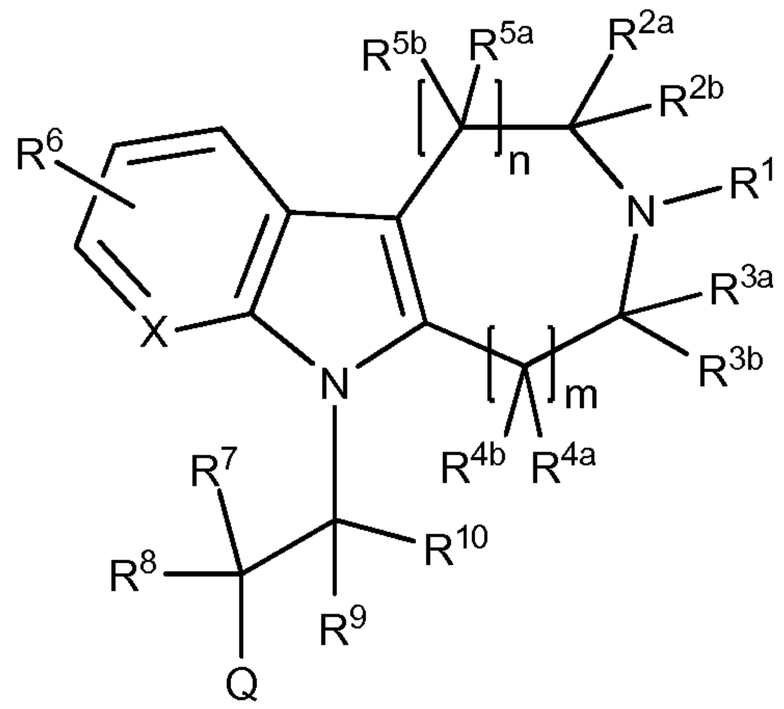
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl; and

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.

[0168] 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.

[0169] 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.

[0170] 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;

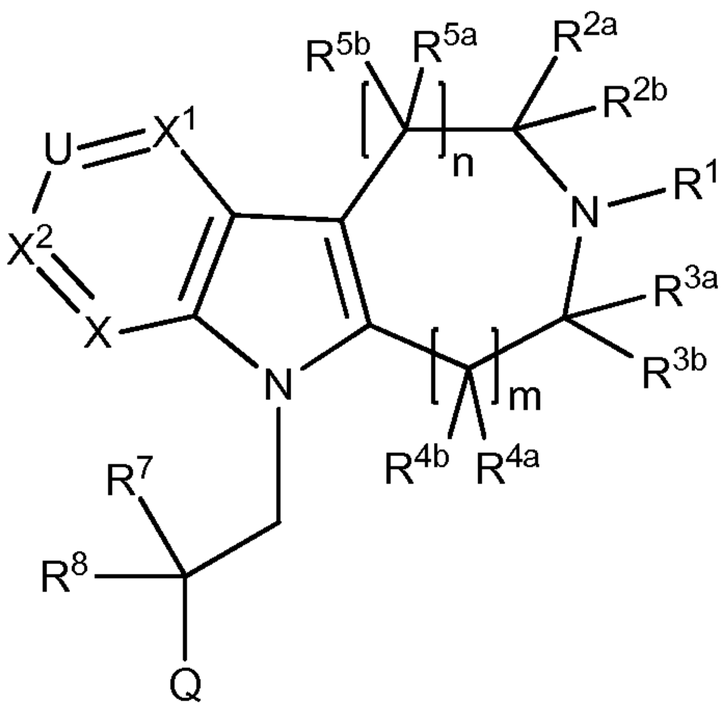
each R^7, R^9 and R^{10} is independently H or optionally substituted C_1-C_5 alkyl;

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;

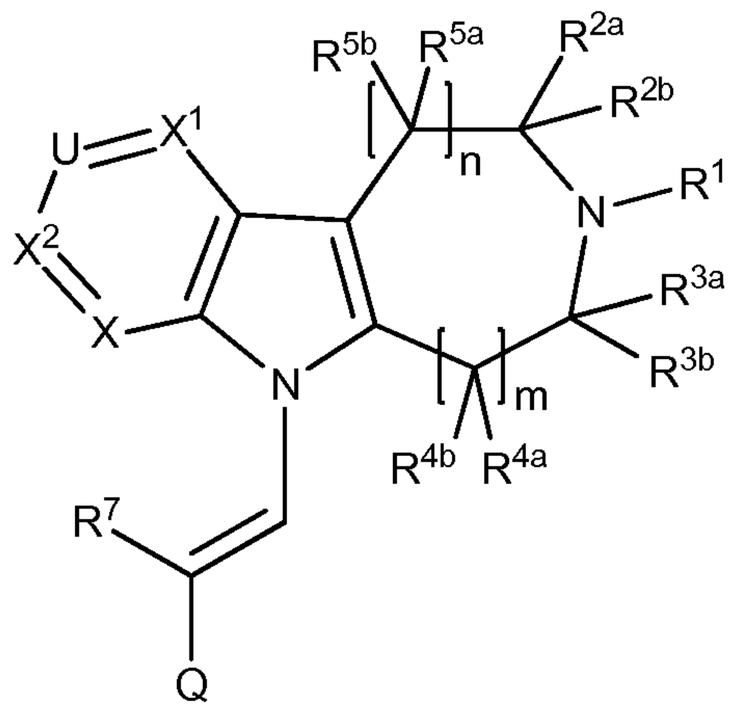
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl; and

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.

[0171] In one aspect, the present invention provides compounds according to formula (A-IB), (A-IC) or (A-ID):

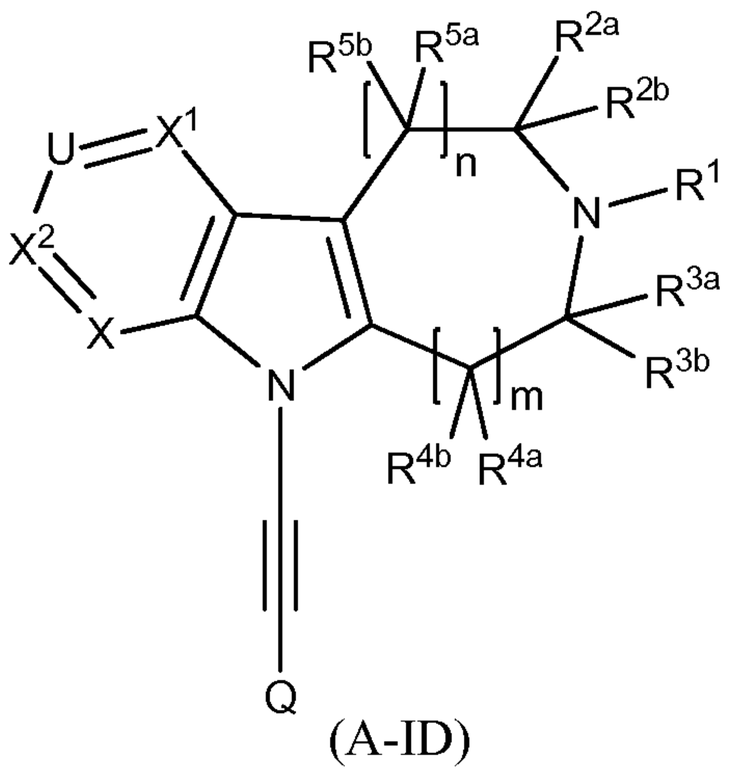


(A-IB)



(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.

[0172] 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.

[0173] 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

[0174] 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.

[0175] 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.

[0176] 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.

[0177] 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.

[0178] 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.

[0179] 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.

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

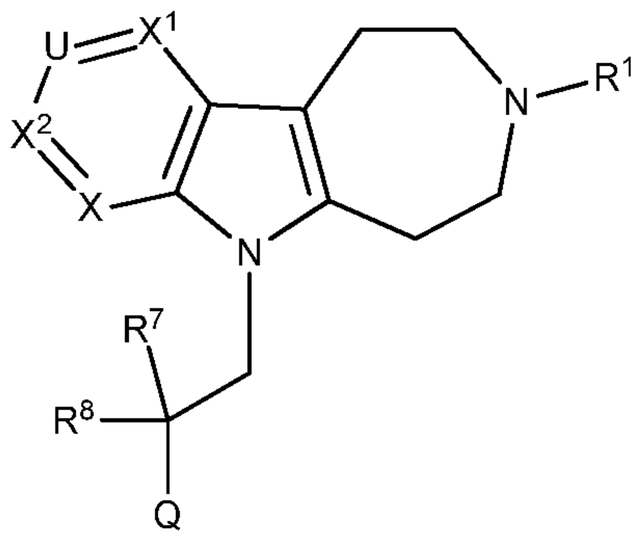
[0189] In certain embodiments, with respect to the compounds of formula (A-IB), (A-IC), or (A-ID), R^{2a} together with R^{4a} form a propylene or ethylene moiety.

[0190] 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.

[0191] 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.

[0192] 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.

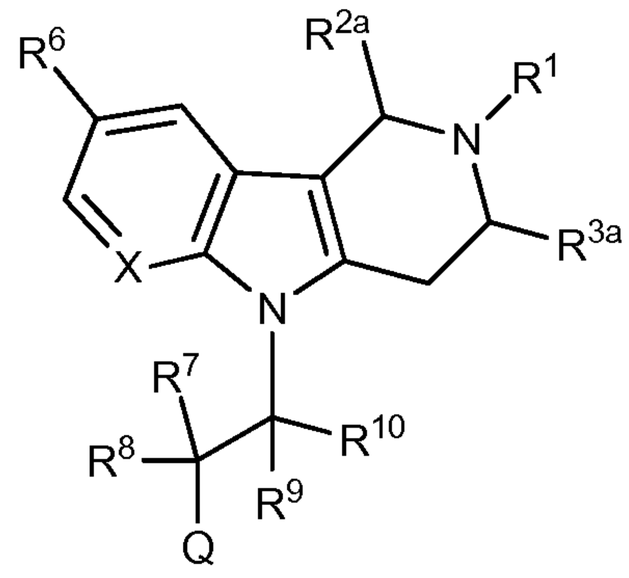
[0193] In one embodiment, the present invention provides compounds according to formula (A-IE):



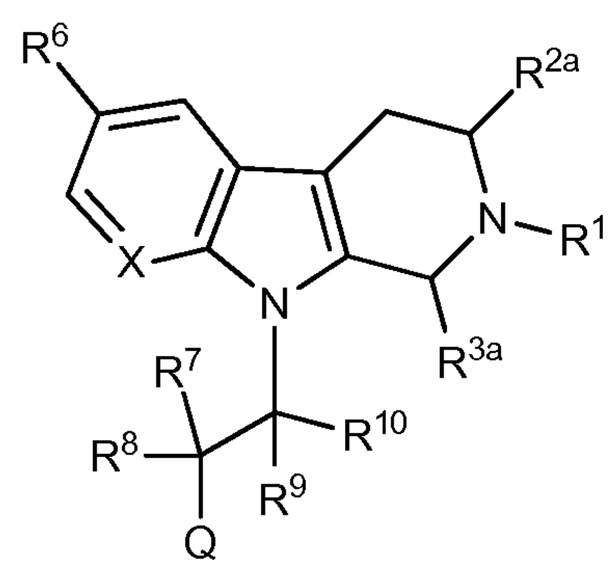
(A-IE)

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

[0194] 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.

[0195] In one variation, each R^6 and R^{6a} is independently H, CH_3 or Cl.

[0196] 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 $-OC(O)CH(NH_2)-CH_3-CH(CH_3)_2$.

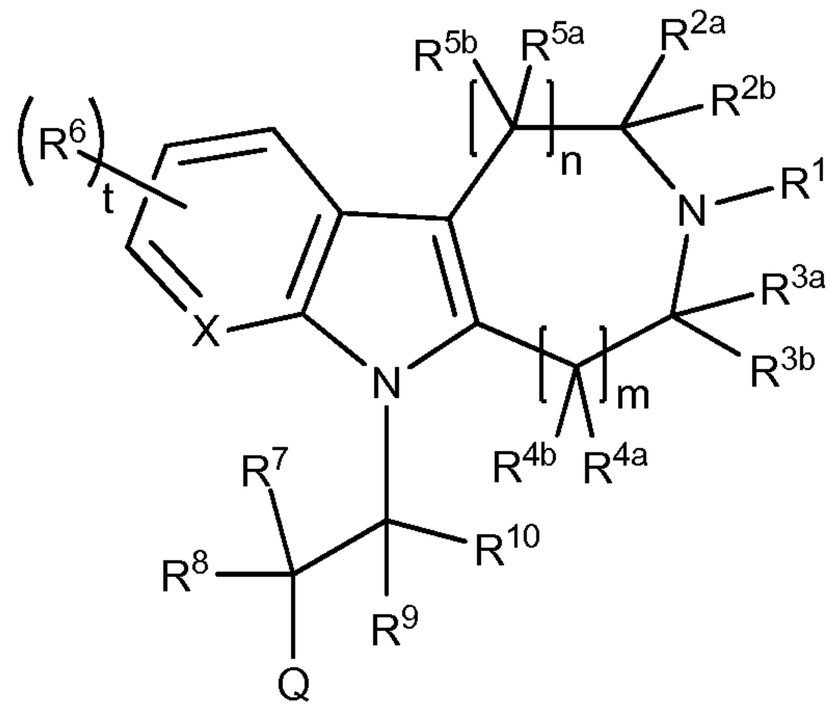
[0197] In one variation, R^{10} and R^8 are taken together to form a bond.

[0198] 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.

[0199] 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.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] 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.

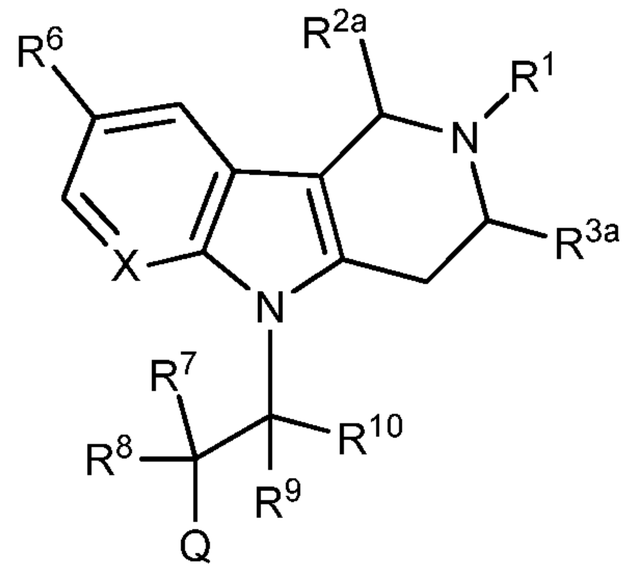
[0209] In some variations, n is 0 and m is 1; R^1 is taken together with R^{2a} to form a propylene (-$CH_2CH_2CH_2$-) moiety; X is CR^{6a}, wherein R^{6a} is H, halo or C_1-C_5 alkyl; each R^6 is independently H, halo or C_1-C_5 alkyl; R^7 is H or C_1-C_5 alkyl; R^8 is H, hydroxyl, $N(R^{11})R^{12}$ 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.

[0210] In some variations, the compound is Compound No. 325, 129d, 130a, II-121b, II-123b, II-127a, II-128b, II-130a, II-131, and II-6b.

[0211] In some variations, n is 0 and m is 1; each of R^{2b}, R^{3b}, R^{4a} and R^{4b} is H; t is 1. In certain variations, X is CH. In other variations, X is N. In yet other variations, wherein 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 yet other 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. 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. 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. In some variations, the compound is Compound No. 325, 129d, 130a, II-121b, II-127a, II-128b, II-130a, II-131, and II-6b.

[0212] 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.

[0213] 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.

[0214] 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.

[0215] 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.

[0216] 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,

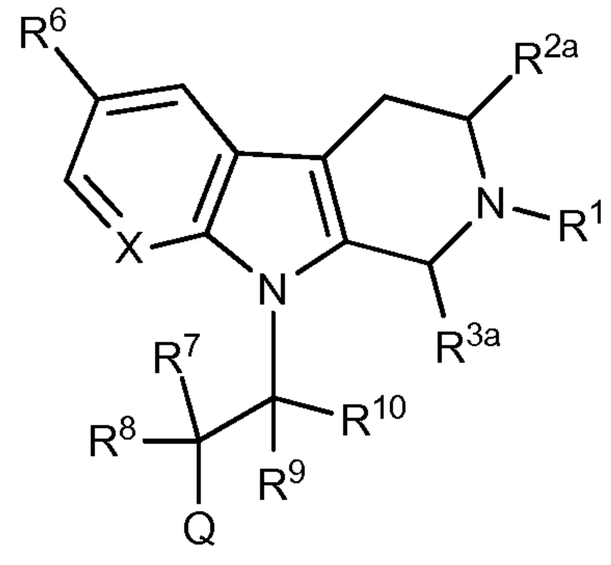
Q is pyridyl substituted a methyl (*e.g.*, 6-methyl-3-pyridyl and 3-methyl-4-pyridyl). In some of these variations, phenyl substituted with a halo group (*e.g.*, fluorophenyl). In some of these variations, Q is 4-fluorophenyl. In some of these variations, Q is phenyl substituted with $-C(O)NR^{16}R^{17}$ where each R^{16} and R^{17} is H. In some of these variations, Q is 4-carbamoylphenyl.

[0217] 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.

[0218] 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.

[0219] In another embodiment, the compound of formula (A-III) has the formula (A-IIIB):



(A-IIIB)

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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 – 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

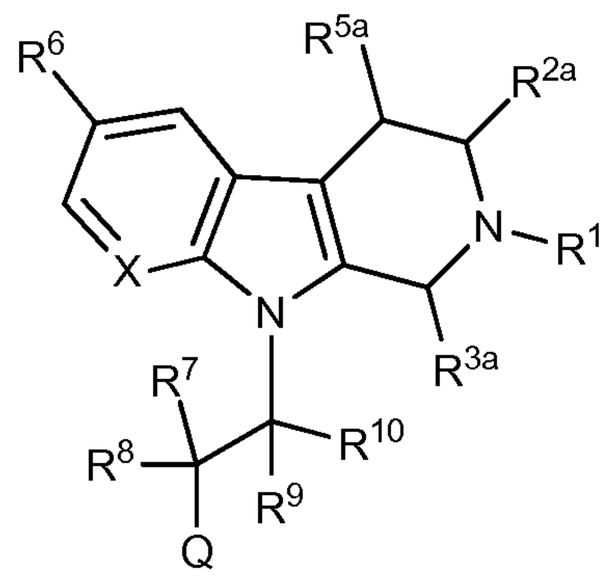
Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl,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

[0220] 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.

[0221] 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.

[0222] 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

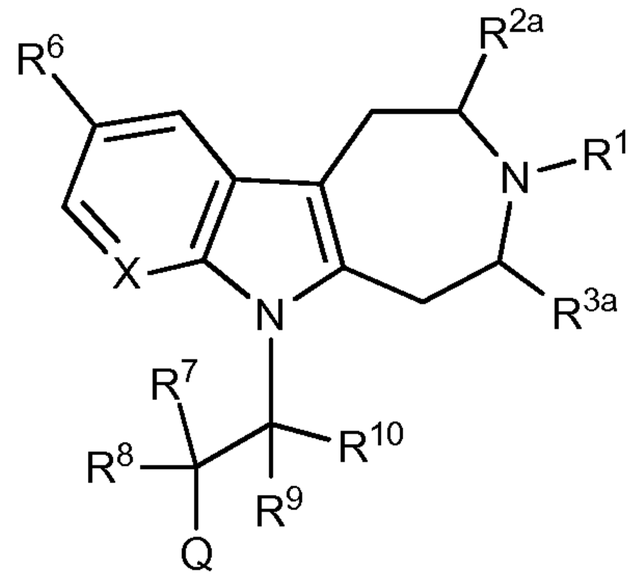
Q is unsubstituted aryl; unsubstituted heteroaryl; aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl,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

[0223] 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.

[0224] 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.

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



(A-IIID)

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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;

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.

[0226] 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

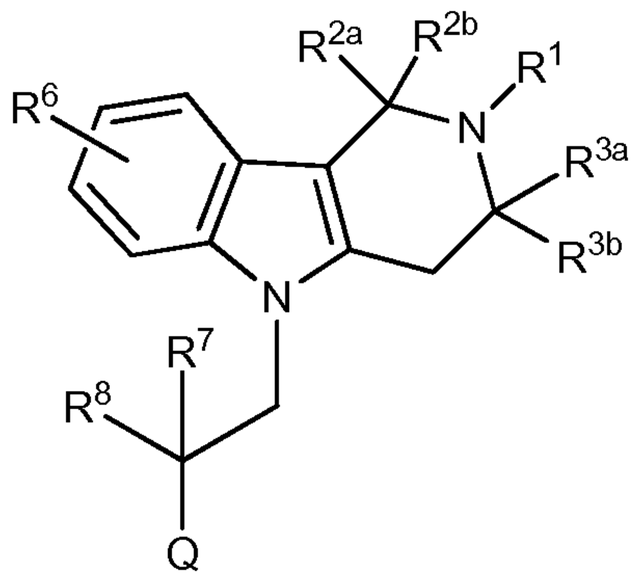
substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3; pyrazinyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3; or phenyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3.

[0227] 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.

[0228] 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.

[0229] 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.

[0230] 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,

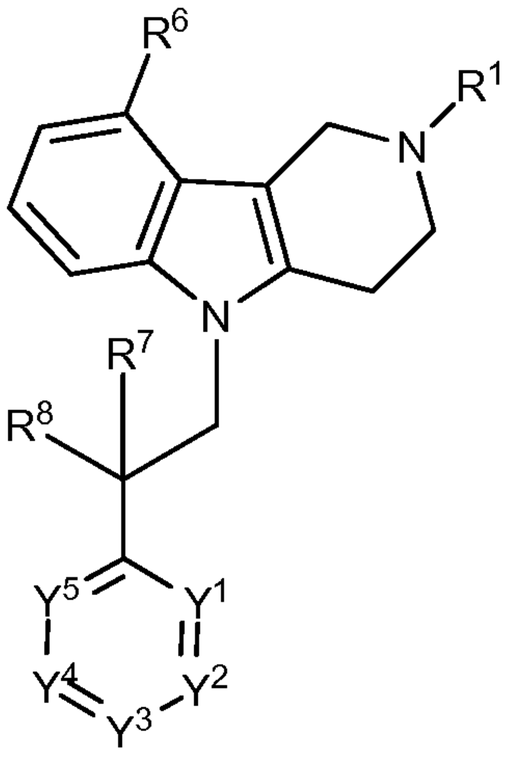
cyano, carboxyl, aminoacyl and acylamino; or heteroaryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl,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

[0231] 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.

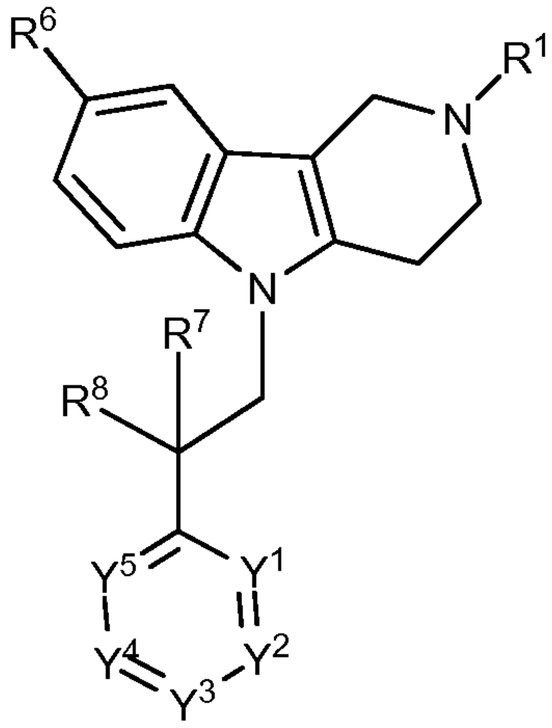
[0232] In some variations of the compound of formula (A-IIIE), R^6 is halo, C_1-C_5 alkyl, or perhaloalkyl. In certain variations, R^6 is methyl or isopropyl. In other variations of the compound of formula (A-IIIE), each R^{2a}, R^{2b}, R^{3a} and R^{3b} is H. In yet other variations of the compound 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.

[0233] 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.

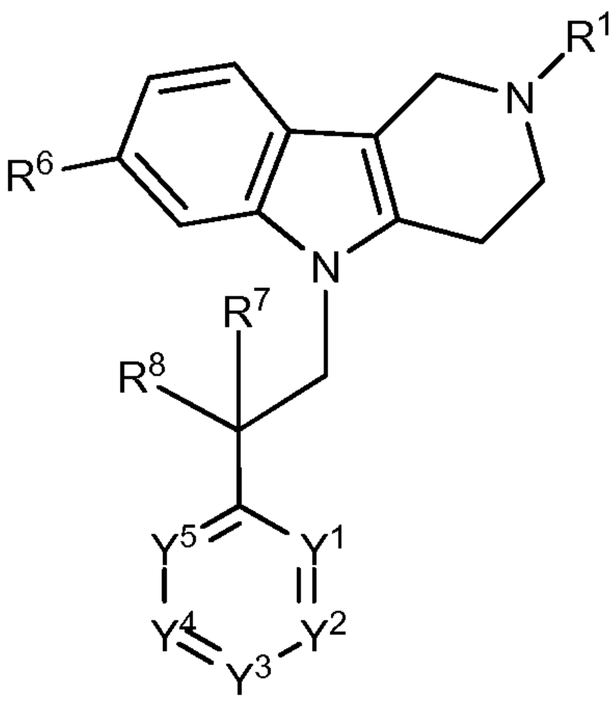
[0234] In another embodiment, the compound is of the formula (A-IIIE-1), (A-IIIE-2), (A-IIIE-3) or (A-IIIE-4):



(A-IIIE-1),

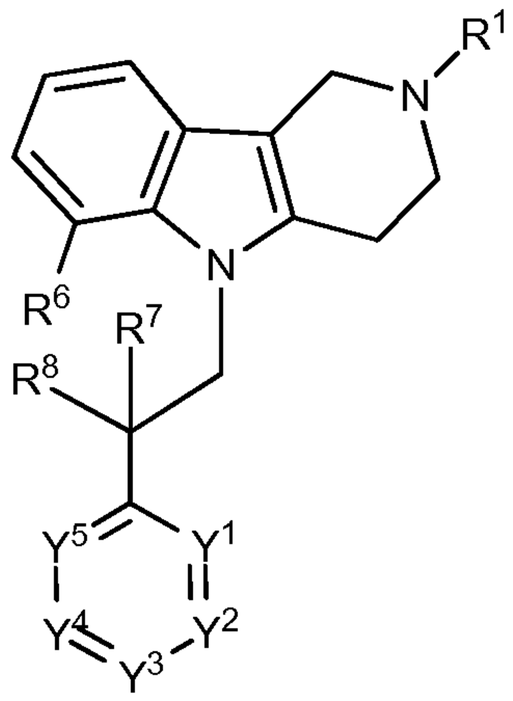


(A-IIIE-2),



(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.

[0235] 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.

[0236] 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.

[0237] In certain embodiments, with respect to the compounds of formula (A-IIIE-1), the compound is Compound No. 214.

[0238] 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.

[0239] 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.

[0240] 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.

[0241] 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.

[0242] 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.

[0243] 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.

[0244] 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.

[0245] 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.

[0246] 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.

[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^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. 30, 52, 66, 67, 139, 142, 183, or 203.

[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, Y^4 and Y^5 is CR^4, and the compound is Compound No. II-88 or II-192.

[0249] 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.

[0250] 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.

[0251] 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.

[0252] 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.

[0253] 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.

[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^2, Y^3, Y^4 and Y^5 is CR^4, and the compound is Compound No. 90, 98, or 254.

[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^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.

[0256] 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.

[0257] 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.

[0258] 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.

[0259] 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.

[0260] 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.

[0261] 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.

[0262] 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.

[0263] 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.

[0264] 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.

[0265] 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.

[0266] 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.

[0267] 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.

[0268] 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.

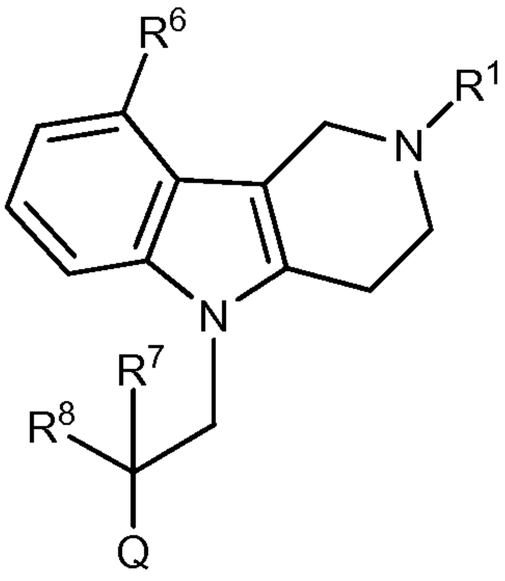
[0269] In some embodiments, the compound is of formula (A-IIIE-3), when each R^7 and R^8 is H; R^1 is methyl; R^6 is chloro; each Y^1, Y^2, Y^4 and Y^5 is CR^4, and Y^3 is CH, CF, or CCl; then at least one of Y^1, Y^2, Y^4 and Y^5 is other than CH.

[0270] 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.

[0271] 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.

[0272] 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.

[0273] 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)

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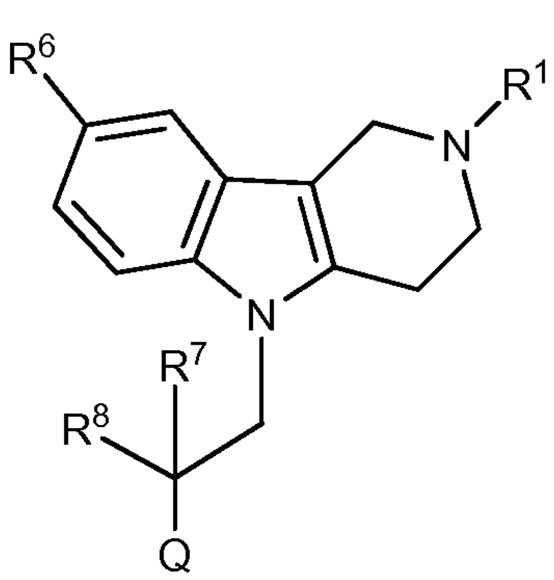

(A-IIIE-6)

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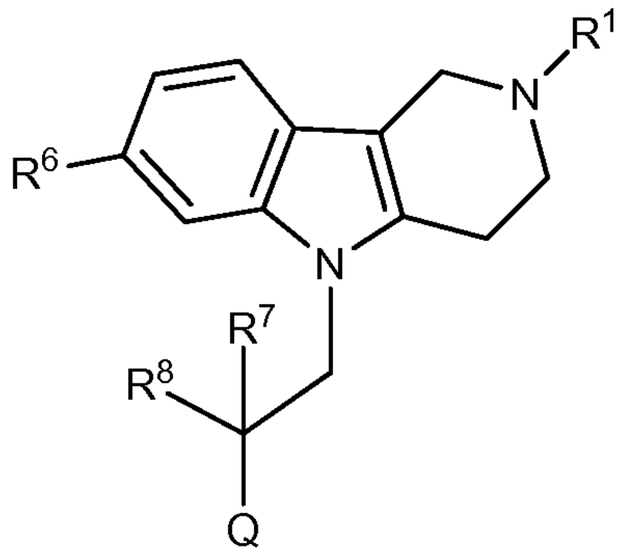
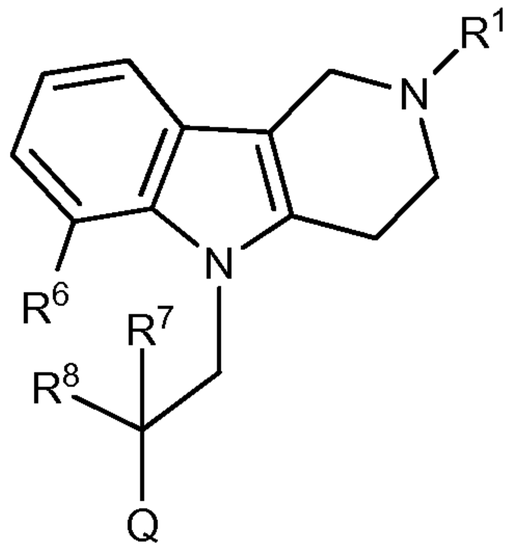


(A-IIIE-7)



(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;

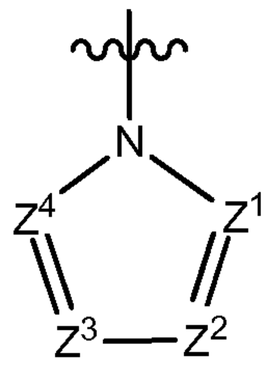
R^8 is H, halo, hydroxyl, $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, -OC(O)$N(R^{14})R^{15}$, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a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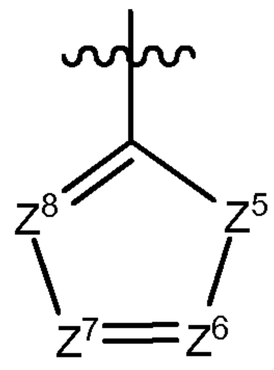
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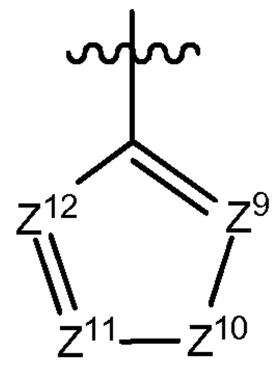
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wherein

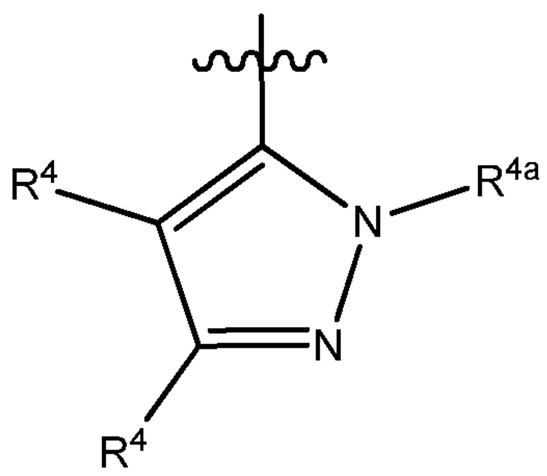
each Z^1, Z^2, Z^3 and Z^4 is independently N or CR^4 such that no more than two of Z^1, Z^2, Z^3 and Z^4 are N, wherein R^4 is H, halo, CH_3, CF_3, or OCH_3;

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.

[0274] 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.

[0275] In some variations, Q is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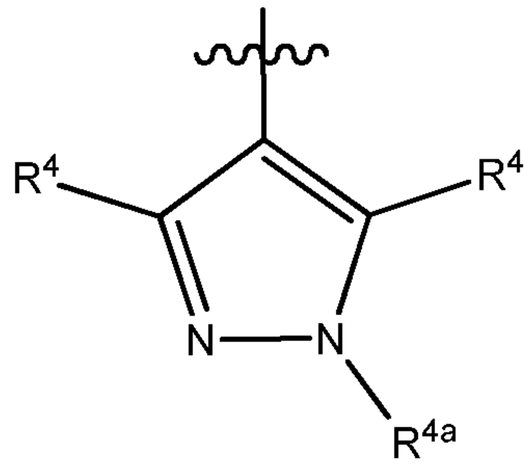
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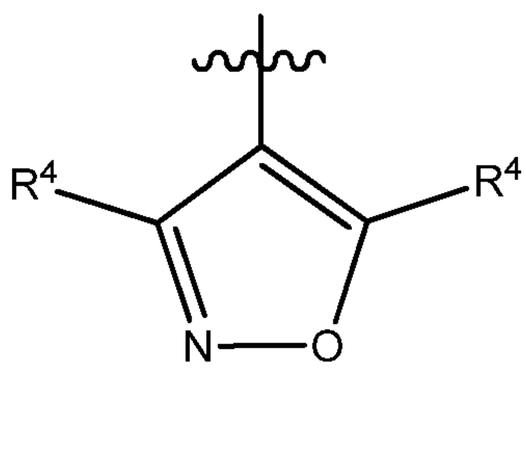
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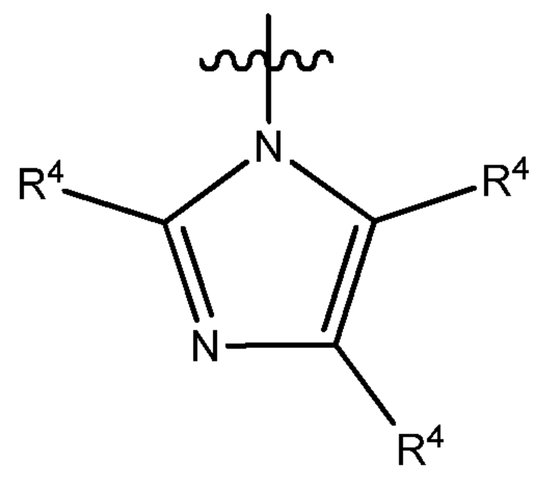
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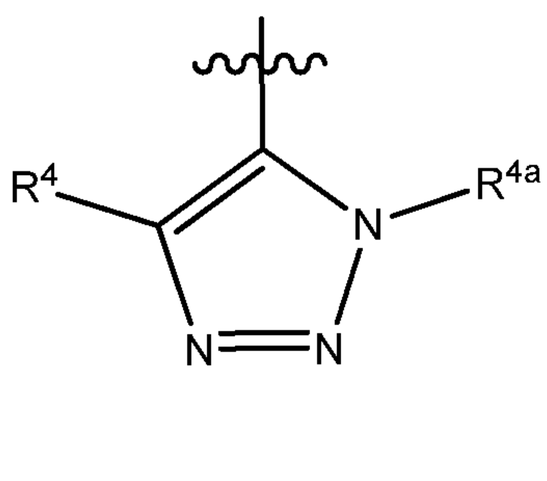
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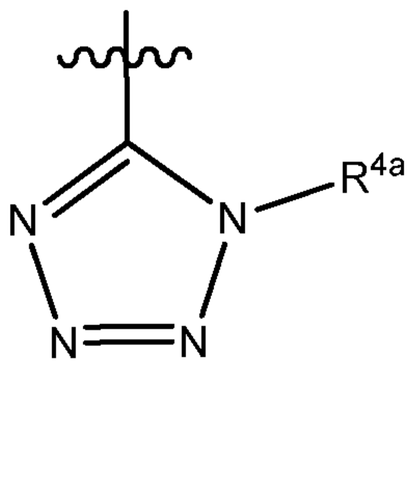
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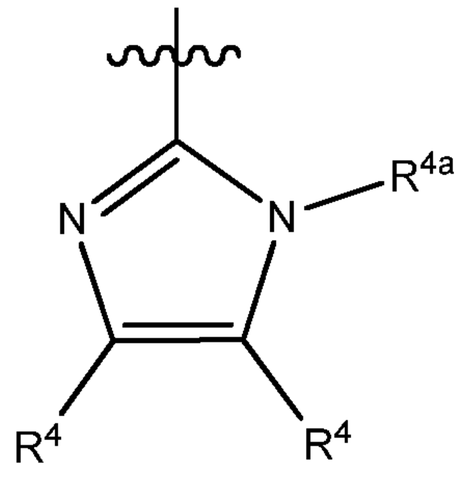
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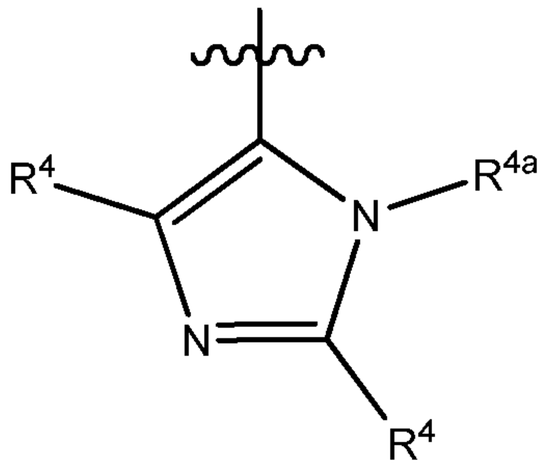
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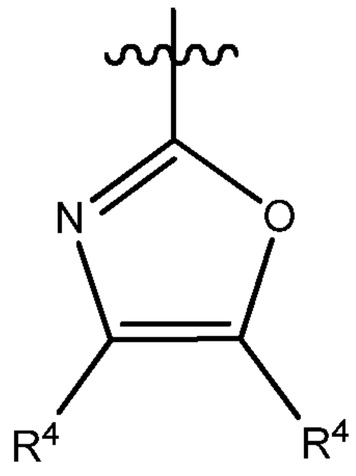
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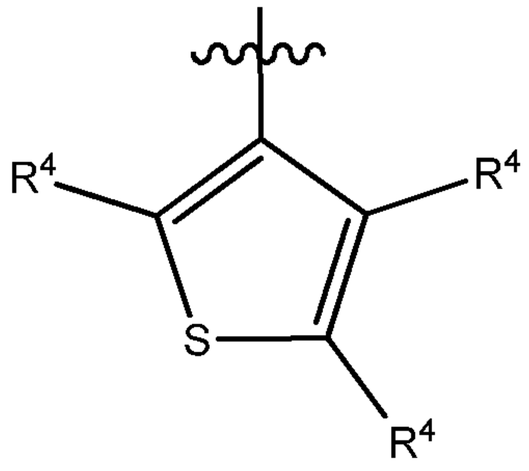


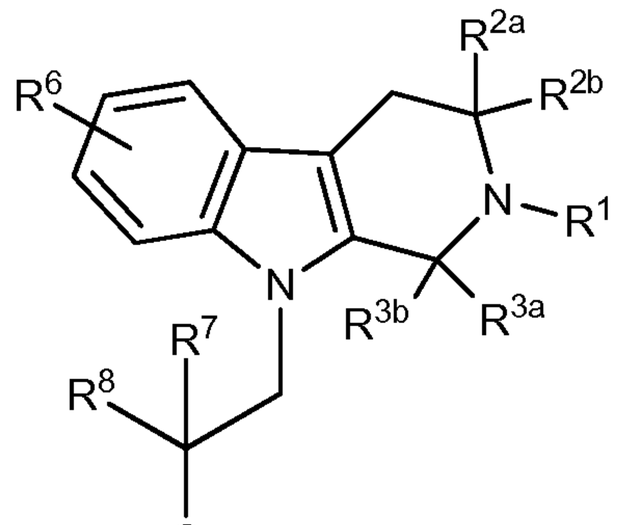
. In some variations, R^4 is H, halo, CH_3, CF_3, or OCH_3.

[0276] 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.

[0277] 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.

[0278] 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.

[0279] 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;

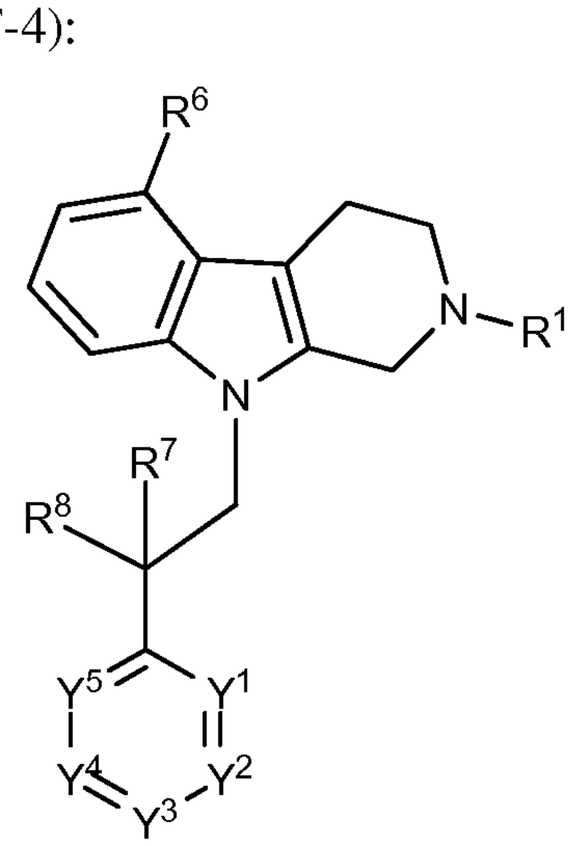
each R^{11} and R^{12} is independently H or optionally substituted C_1-C_5 alkyl, or R^{11} and R^{12} are taken together to form C_3-C_5 alkylene;

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

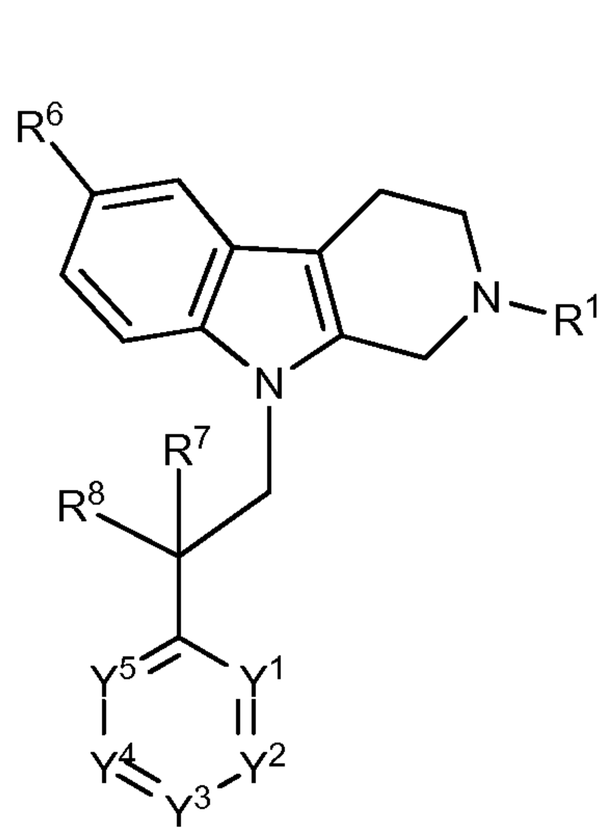
each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene; and

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.

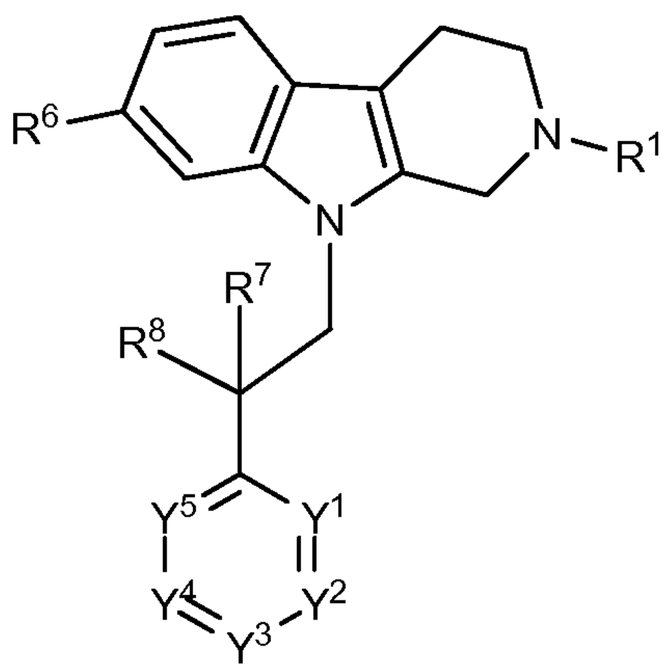
[0280] In another embodiment, the compound is of the formula (A-IIIF-1), (A-IIIF-2), (A-IIIF-3) or (A-IIIF-4):



(A-IIIF-1),

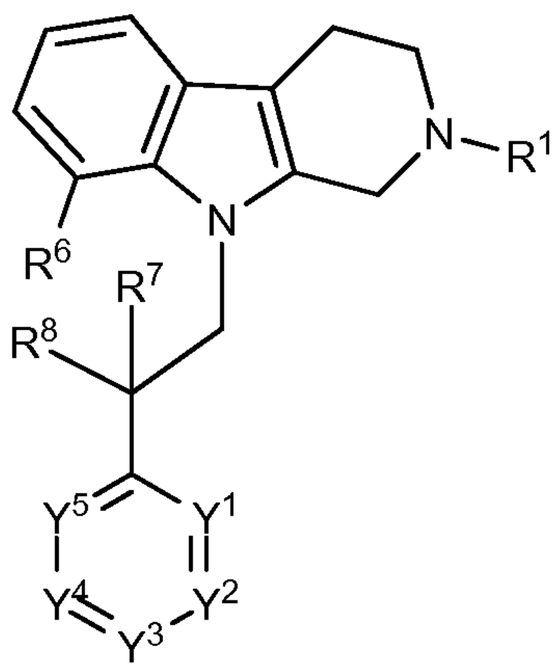


(A-IIIF-2),



(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.

[0281] 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.

[0282] 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.

[0283] 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.

[0284] 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.

[0285] In some embodiments, the compound is of formula (A-IIIF-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.

[0286] 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.

[0287] 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.

[0288] 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.

[0289] 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.

[0290] 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.

[0291] 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.

[0292] 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.

[0293] 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.

[0294] 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.

[0295] 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.

[0296] 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.

[0297] 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.

[0298] 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.

[0299] 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.

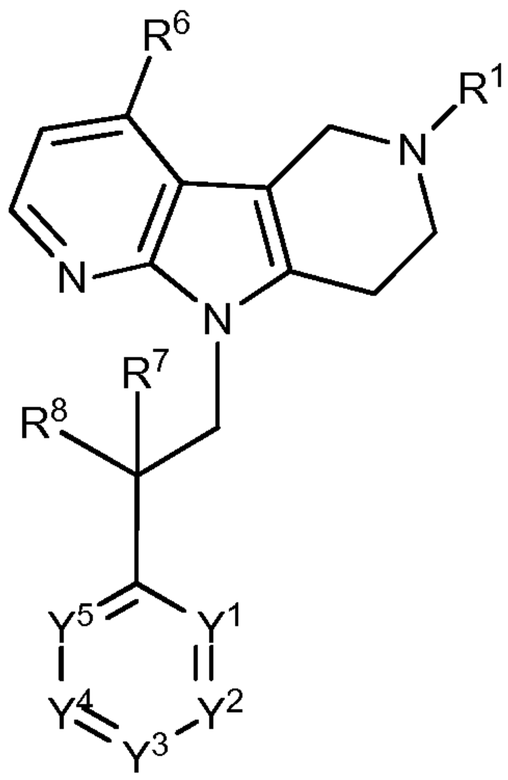
[0300] In some embodiments, the compound is of formula (A-IIIF-3), when R^7 is H or methyl; R^8 is OH; R^6 is chloro or iso-propyl; Y^2 or Y^3 is N; then R^1 is other than methyl.

[0301] 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.

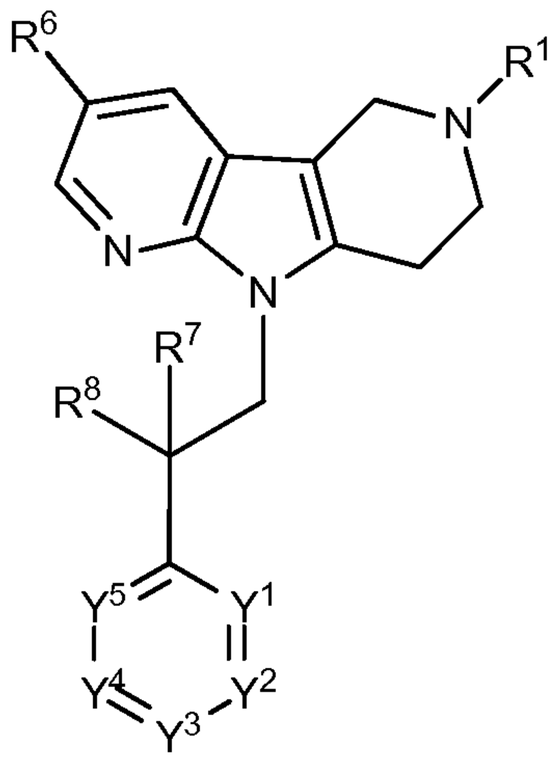
[0302] In some embodiments, the compound is of formula (A-IIIF-4), when R^7 is H or methyl, R^8 is OH, R^1 is methyl, R^6 is Cl, F, or methoxy; then Y^3 is other than N.

[0303] 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.

[0304] In another embodiment, the compound is of the formula (A-IIIG-1), (A-IIIG-2) or (A-IIIG-3):

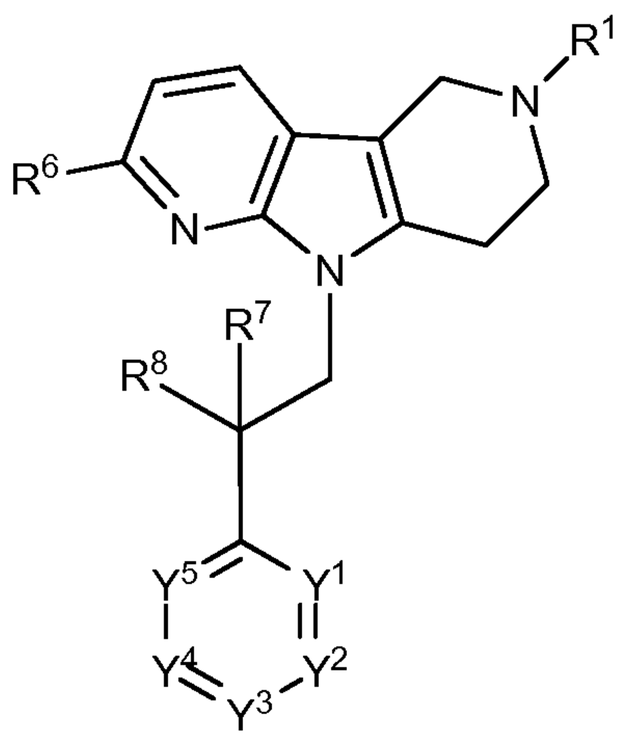


(A-IIIG-1)



(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.

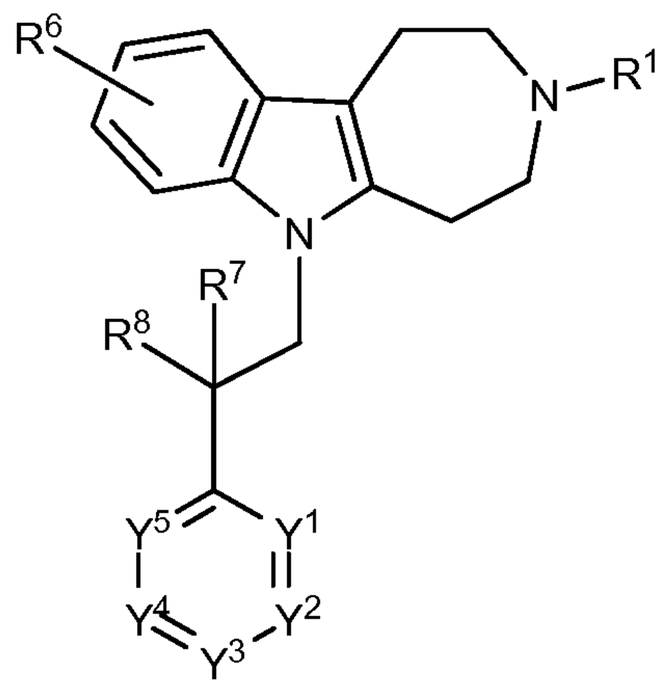
[0305] In some embodiments, the compound is of the formula (A-IIIG-2). In some variations, R^1 is H or CH_3. In other variations, R^7 is H or CH_3. In yet other variations, R^8 is hydroxyl or NH_2. In yet other variations, each R^7 and R^8 is H. In yet other variations, one of Y^1, Y^2, Y^3, Y^4 and 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.

[0306] 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.

[0307] 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.

[0308] 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.

[0309] 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.

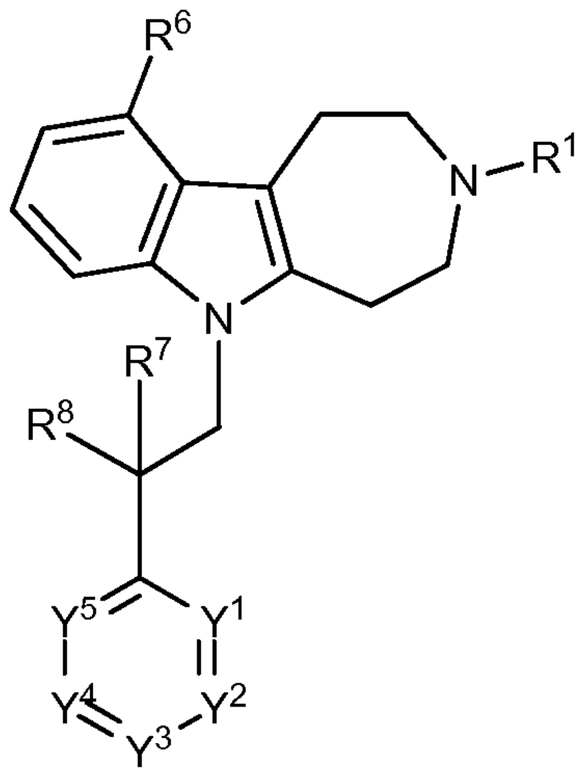
[0310] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. 13, 15, 92, 154, 172, 221, or 339.

[0311] 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.

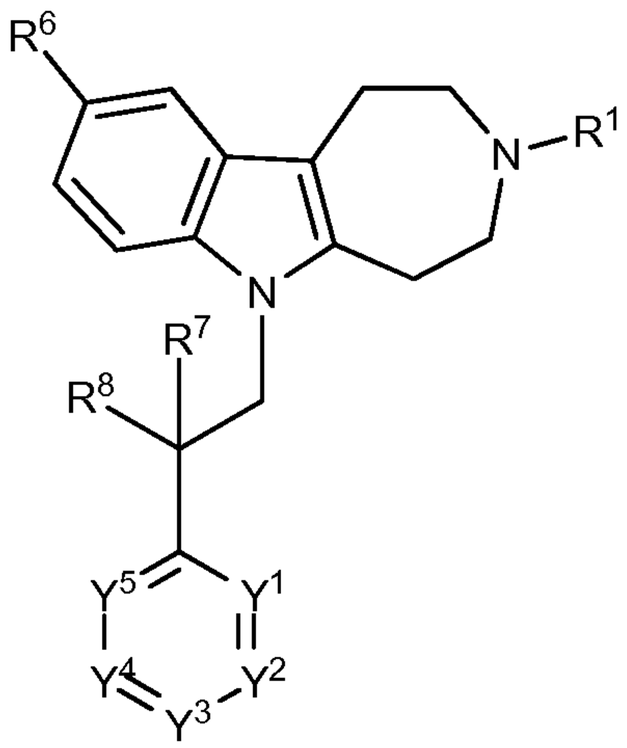
[0312] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. III-9-46, III-209 to III-220, III-320 to III-351, or III-352.

[0313] In certain embodiments, with respect to the compounds of formula (A-IIIH), the compound is Compound No. V-21.

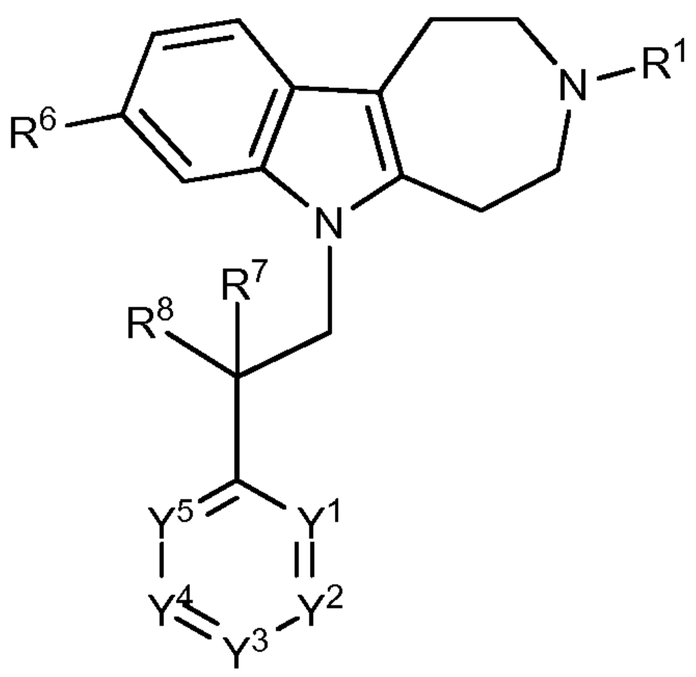
[0314] In another embodiment, the compound is of the formula (A-IIIH-1), (A-IIIH-2), (A-IIIH-3) or (A-IIIH-4):



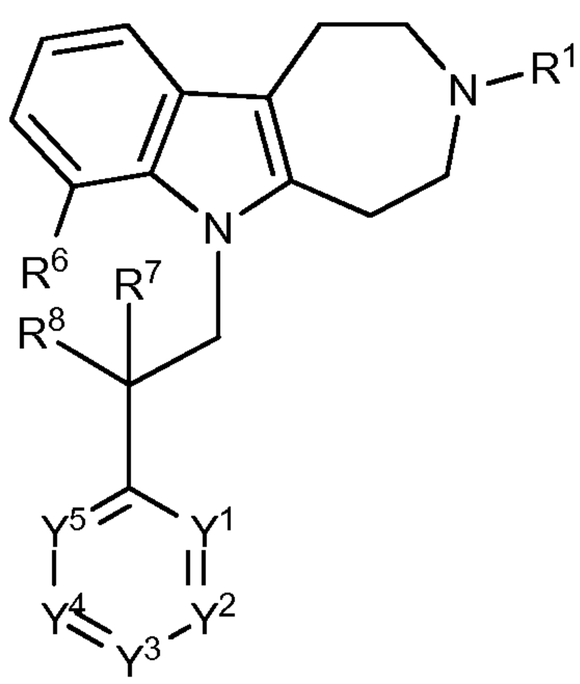
(A-IIIH-1),



(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.

[0315] 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.

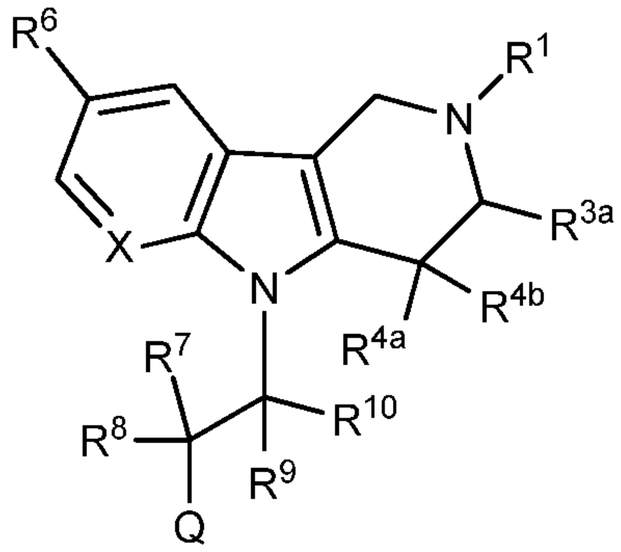
[0316] In certain embodiments, with respect to the compounds of formula (A-IIIH-2), R^6 is methyl or chloro, R^7 is H or methyl, R^8 is H or OH, Y^1 or Y^2 is independently C-H, C-F, C-Cl, or C-methoxy, and Y^3 is other than CH, CF, CCl, or C-OCH_3.

[0317] 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.

[0318] 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.

[0319] 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.

[0320] In one aspect, provided is a compoud of formula (A-IIIA'):



(A-IIIA')

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

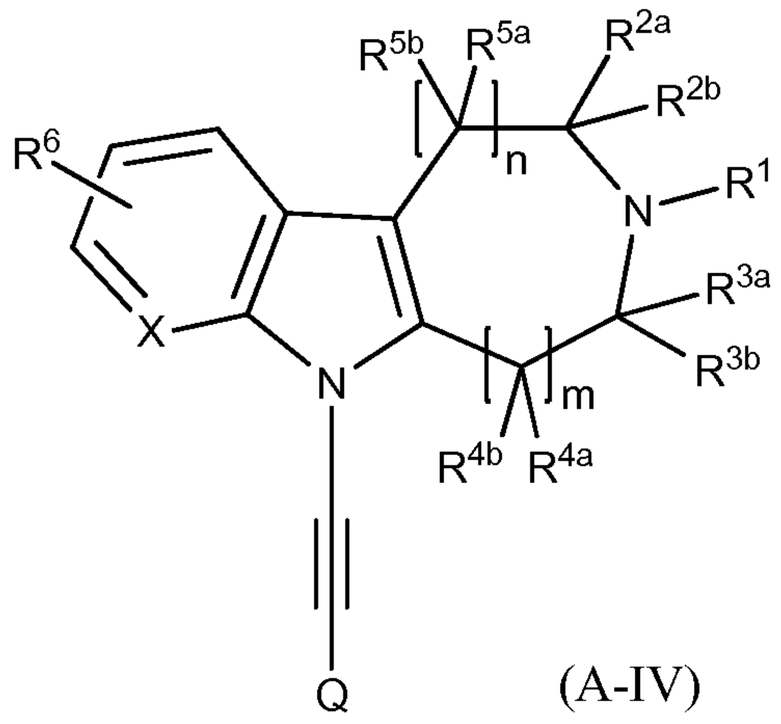
X, R^1, R^{3a}, R^6, R^7, R^8, R^9, R^{10} and Q are as defined for formula (A-IIIA),

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;

[0321] 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.

[0322] 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.

[0323] 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};

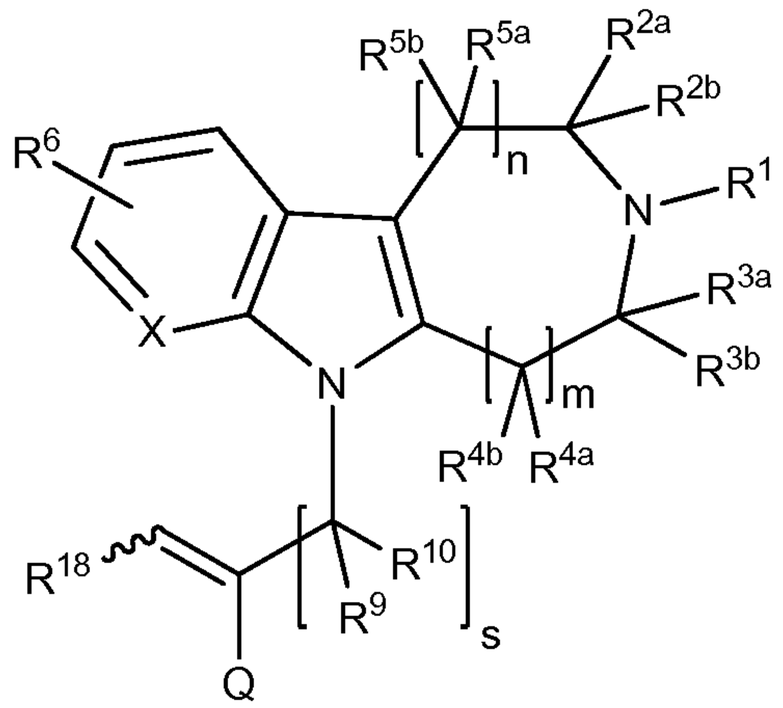
each R^6 and R^{6a} is independently H, hydroxyl, halogen, C_1-C_5 alkyl optionally substituted with 1 to 3 halogen atoms, optionally substituted C_1-C_5 alkoxy or optionally substituted $-C(O)C_1$-C_5 alkyl;

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.

[0324] 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.

[0325] 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.

[0326] 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;

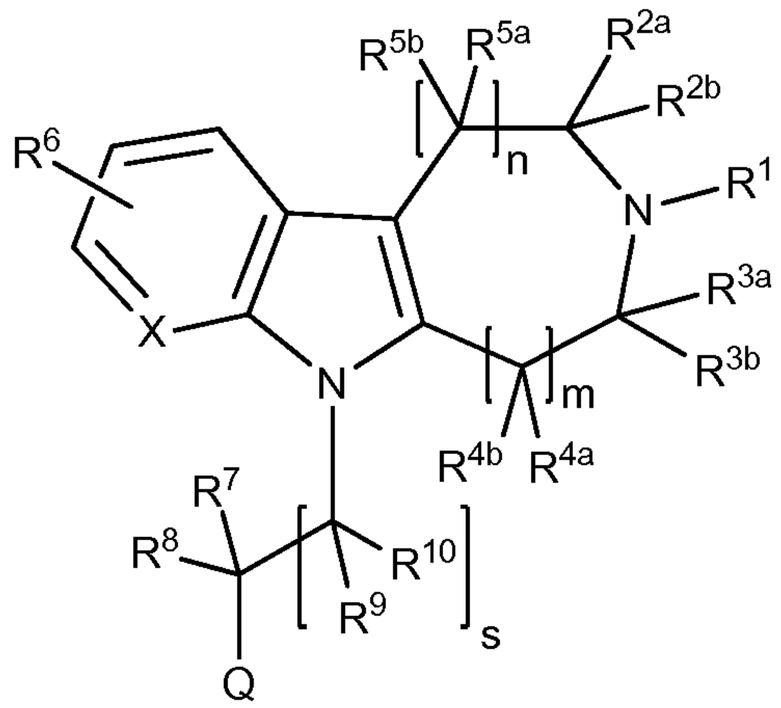
R^{18} is H or optionally substituted C_1-C_5 alkyl, and ∿∿∿ indicates the presence of either an (*E*) or (*Z*) double bond configuration;

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.

[0327] In certain embodiments, with respect to the compounds of formula (A-V), the compound is Compound No. 116, 121, or 132.

[0328] 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.

[0329] 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;

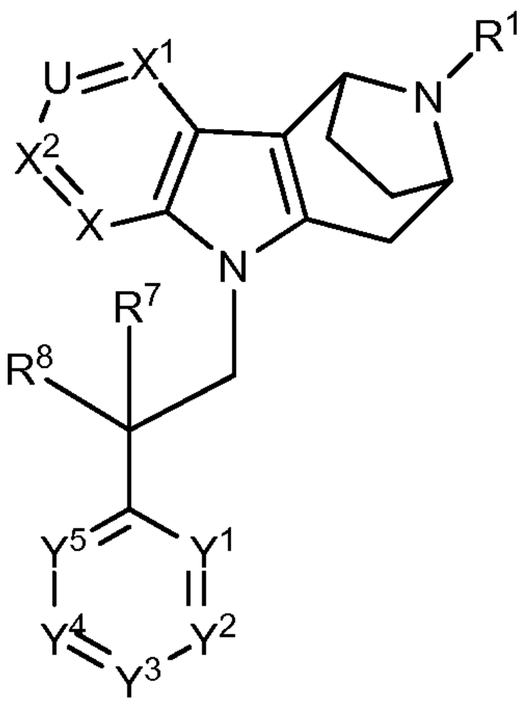
R^8 is H, halo, hydroxyl, $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, $-OC(O)N(R^{14})R^{15}$, or $-OC(O)C_1$-C_5 alkyl optionally substituted with amino;

s is 0 or 1;

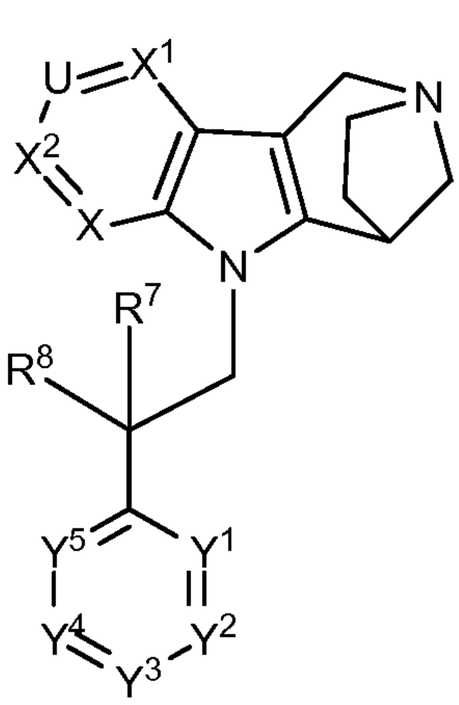
each R^9 and R^{10}, where present, is independently H or optionally substituted C_1-C_5 alkyl; and

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

[0330] In another embodiment, the compound is of formula (A-VIIA), (A-VIIB), (A-VIIC), (A-VIID), (A-VIIE) or (A-VIIF):



(A-VIIA),



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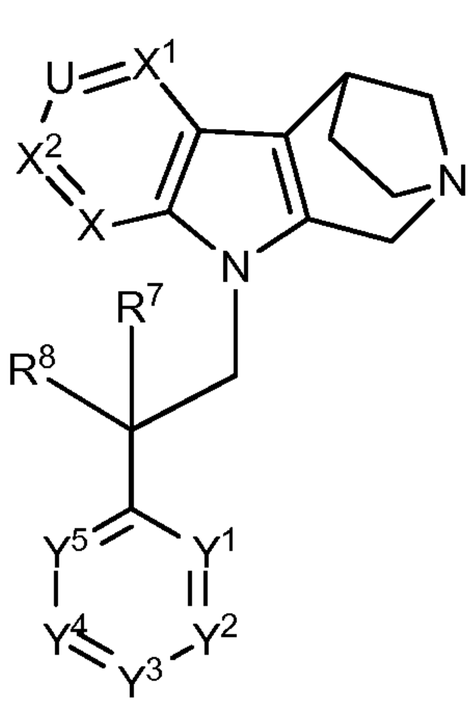
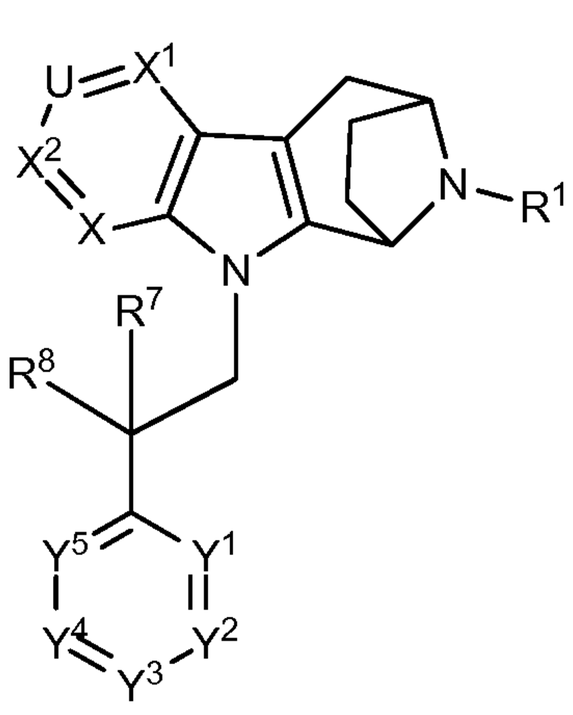


(A-VIIC),



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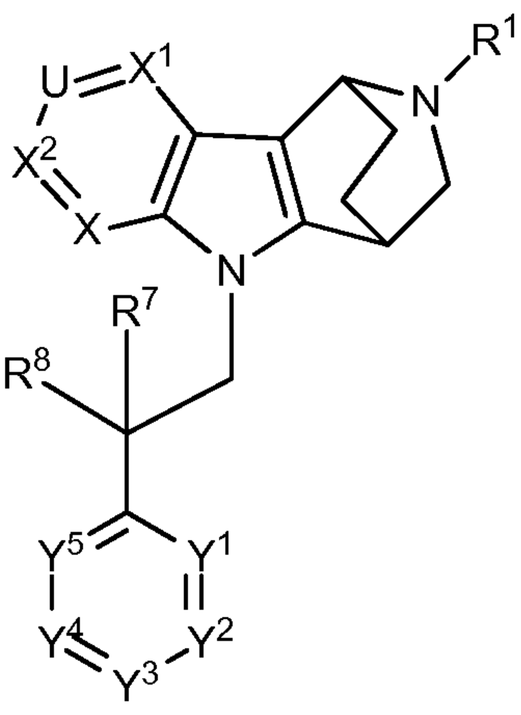
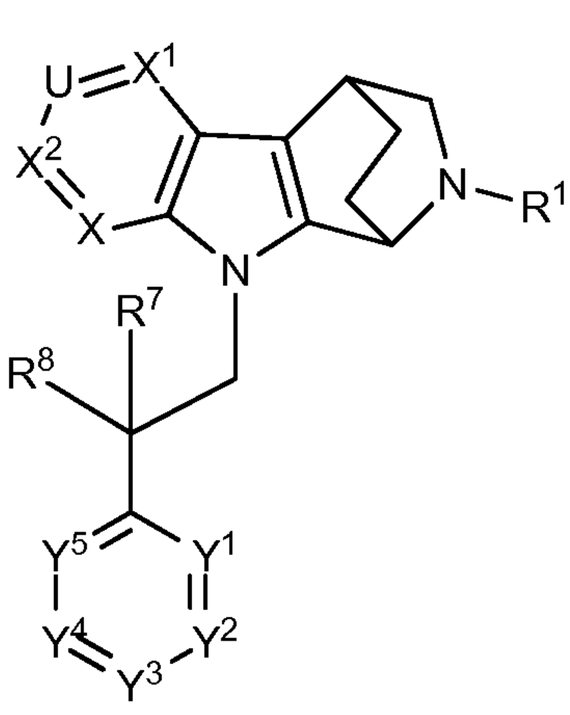


(A-VIIE),

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.

[0331] 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.

[0332] 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.

[0333] 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.

[0334] 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.

[0335] 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.

[0336] 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.

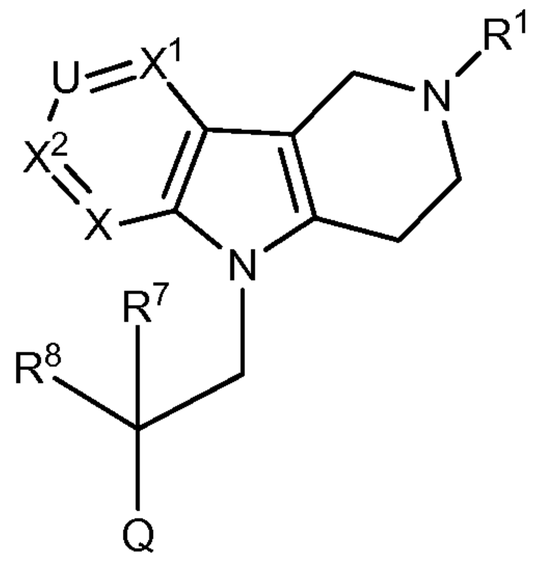
[0337] In certain embodiments, with respect to the compounds of formula (A-VIIC), each X^1, X^2, X and U is independently CR^6, R^8 is OH, each Y^1, Y^2, Y^4 and Y^5 is independently CR^4, Y^3 is N, and the compound is Compound No. 36, 38, or II-69.

[0338] 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.

[0339] 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.

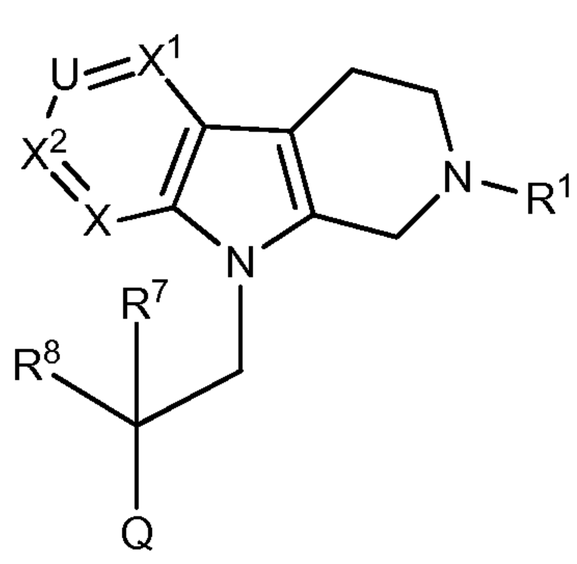
[0340] In certain embodiments, with respect to the compounds of formula (A-VIIE), each X^1, X^2, X and U is independently CR^6, R^8 is OH, and the compound is Compound No. III-56.

[0341] 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.

[0342] 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.

[0343] 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.

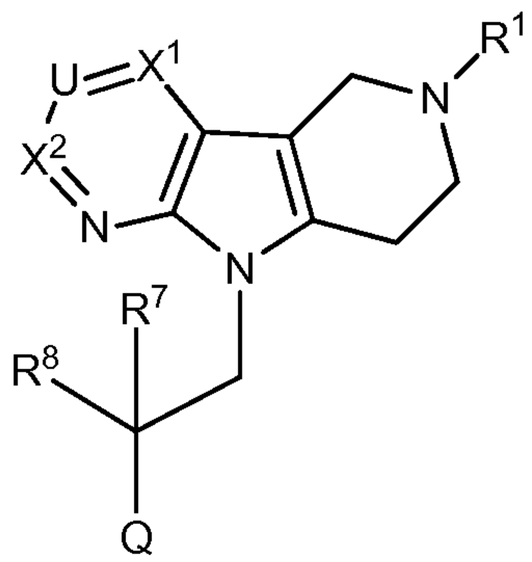
[0344] In some variations of the compounds of formula (A-VIIIA), U is N, each X^1, X^2 and X is CR^6, wherein each R^6 is H; R^1 is methyl; R^7 is H or methyl; R^8 is H, OH or methyl; and Q is other than unsubstituted phenyl, phenyl substituted with chloro, unsubstituted pyridyl, or pyridyl substituted with methyl or CF_3.

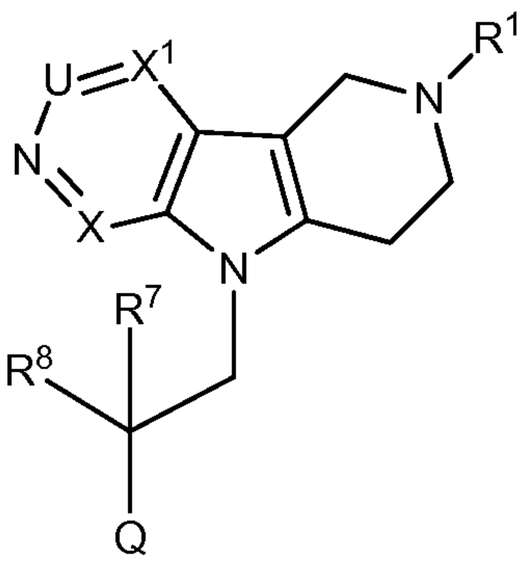
[0345] In some variations of the compounds of formula (A-VIIIA), X^2 is N, each X^2 and X is CR^6, wherein each R^6 is H; U is CR^6, wherein R^6 is H or methyl; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl, unsubstituted pyridyl, or pyridyl substituted with CF_3.

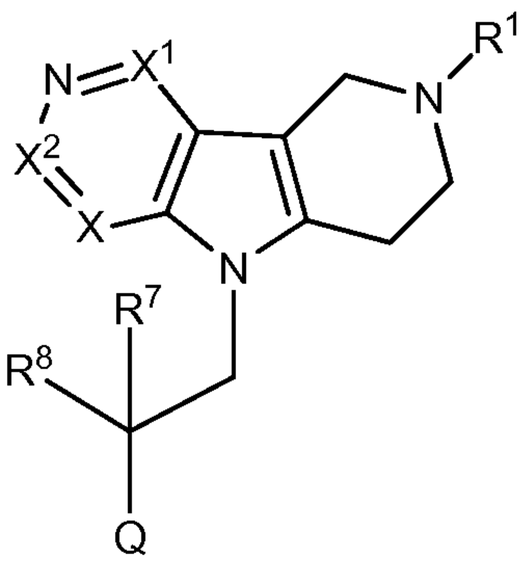
[0346] In some variations of the compounds of formula (A-VIIIA), X is N, each X^1, U and X^2 is CR^6, wherein each R^6 is H; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl.

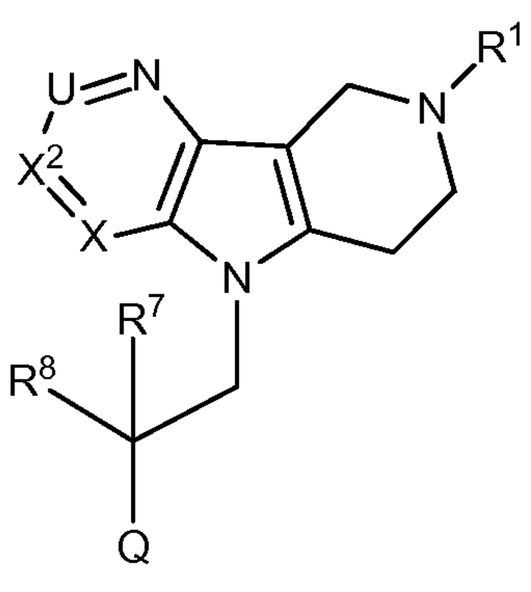
[0347] In some variations of the compounds of formula (A-VIIIA), each X and U is N, each X^1 and X^2 is CR^6, wherein each R^6 is H; R^1 is methyl; each of R^7 and R^8 is H; and Q is other than unsubstituted phenyl.

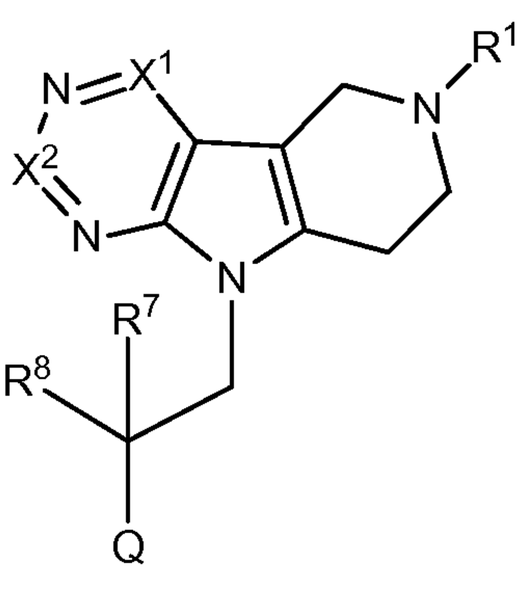
[0348] In some variations of the compounds of formula (A-VIIIA), the compound is according to formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7):

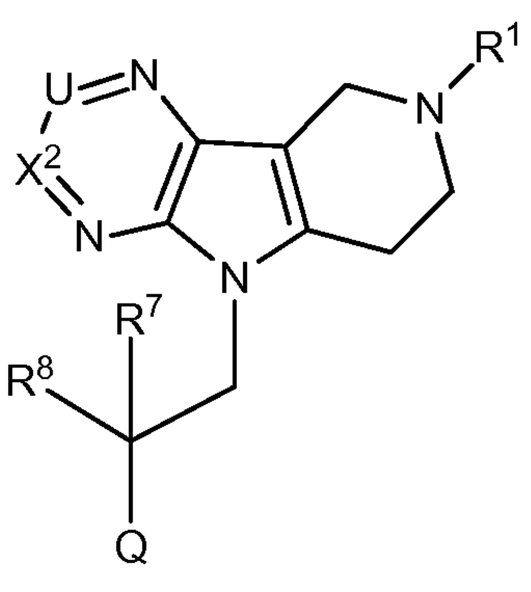


(A-VIIIA-1), 

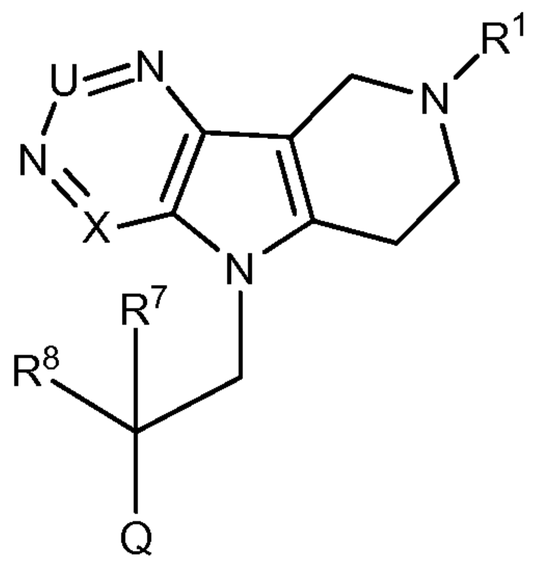
(A-VIIIA-2), 

(A-VIIIA-3), 

(A-VIIIA-4), 

(A-VIIIA-5), 

(A-VIIIA-6), or



(A-VIIIA-7)

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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.

[0349] 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.

[0350] 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.

[0351] 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.

[0352] 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.

[0353] 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.

[0354] 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.

[0355] 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.

[0356] 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.

[0357] 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.

[0358] 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.

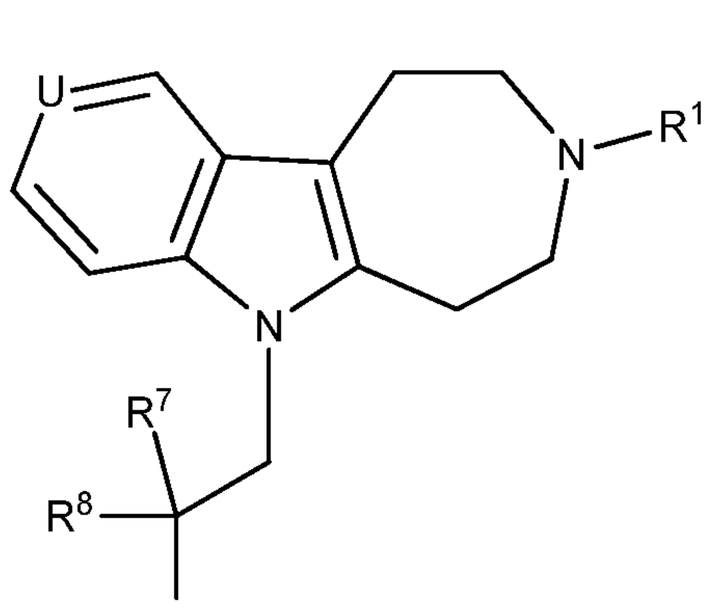
[0359] In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is phenyl substituted with methyl, ethyl, fluoro, chloro, methoxy, or CF_3.

[0360] 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.

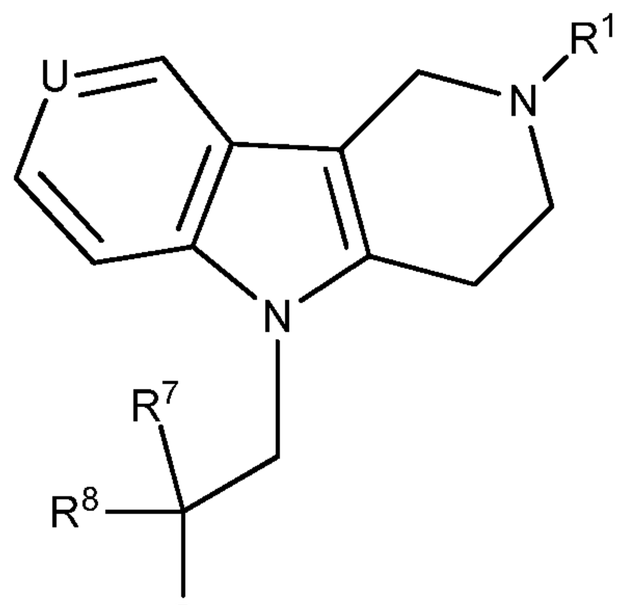
[0361] In another embodiment, with respect to the compounds of formula (A-VIIIA-1), (A-VIIIA-2), (A-VIIIA-3), (A-VIIIA-4), (A-VIIIA-5), (A-VIIIA-6), or (A-VIIIA-7), Q is pyridyl substituted with C_1-C_5 alkyl, halo, halo or C_1-C_5 alkyl.

[0362] 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.

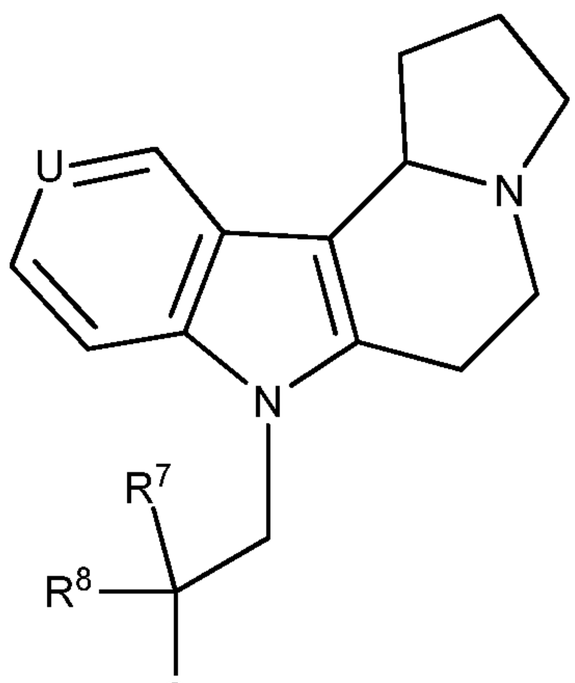
[0363] In one embodiment, provided are compounds of formula (A-IXA), (A-IXB), (A-IXC) or (A-IXD):



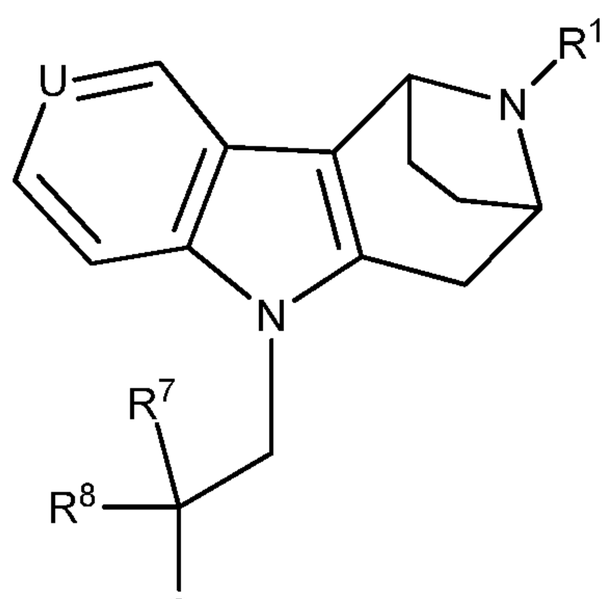
(A-IXA),



(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).

[0364] 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.

[0365] 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.

[0366] 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.

[0367] 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.

[0368] 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.

[0369] 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.

[0370] In certain embodiments, R^7 is C_1-C_5 alkyl, substituted with 1-3 halo.

[0371] 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.

[0372] 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.

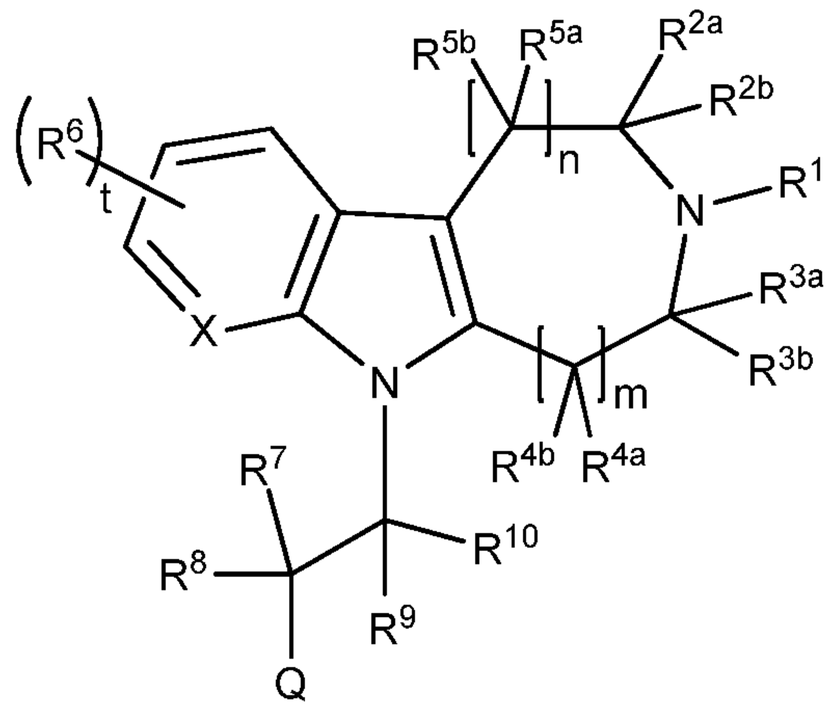
[0373] In one particular embodiment, R^8 is -C(O)N(R^{14})R^{15}; and each R^{14} and R^{15} is independently H or methyl, R^1 is methyl, U is CR^6, and R^6 is methyl; and Q is other than cyclobutyl.

[0374] 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.

[0375] 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.

[0376] 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.

[0377] 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

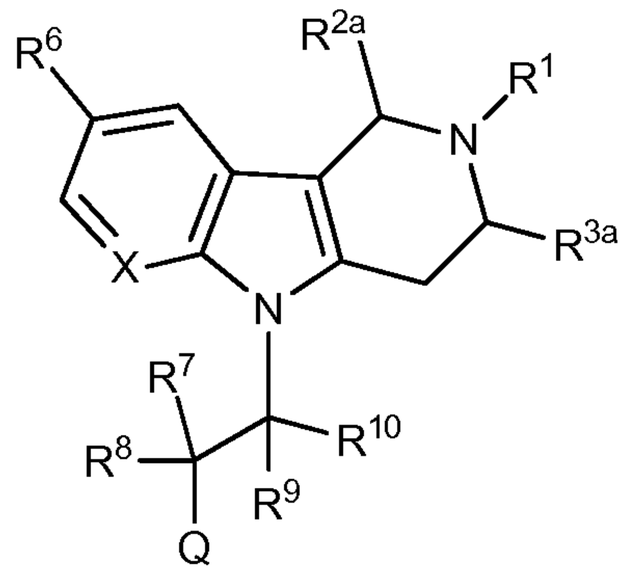
Q is cycloalkyl, aryl or heteroaryl optionally substituted with 1-3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl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

[0378] 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.

[0379] 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.

[0380] 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.

[0381] 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.

[0382] 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.

[0383] 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.

[0384] 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.

[0385] 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.

[0386] 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.

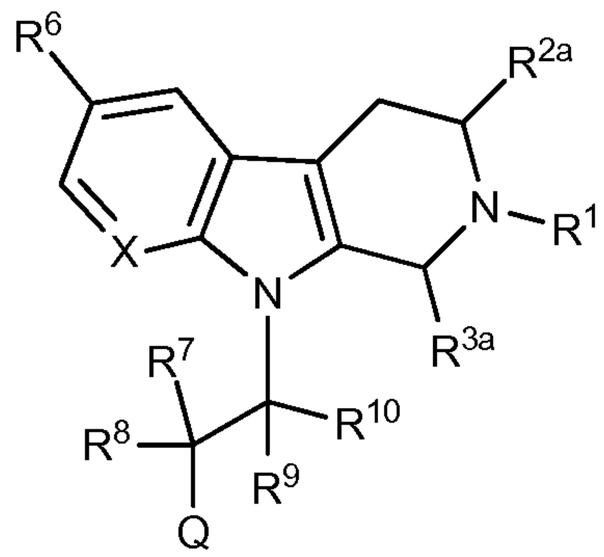
[0387] In certain embodiments, with respect to the compounds of formula (B-IA), X is CR^6, R^8 is azido, and the compound is Compound No. II-261, II-266, II-276, II-298, V-1, V-3, V-22, or V23.

[0388] 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.

[0389] 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.

[0390] 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.

[0391] 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;

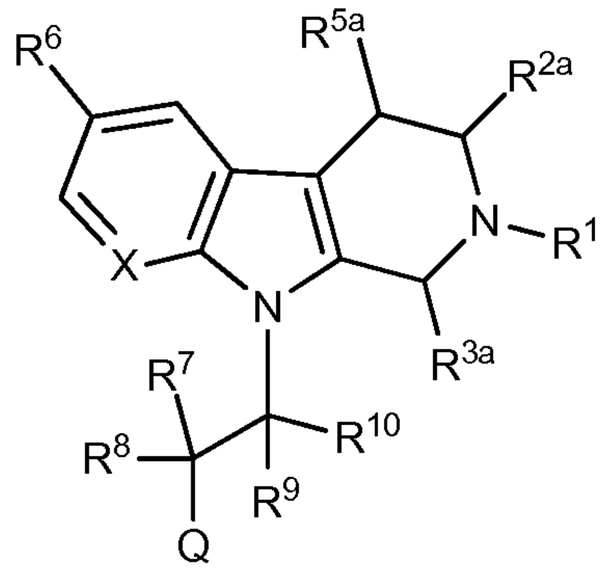
each R^9 and R^{10} is independently H or optionally substituted C_1-C_5 alkyl; and

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.

[0392] 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.

[0393] 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.

[0394] 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;

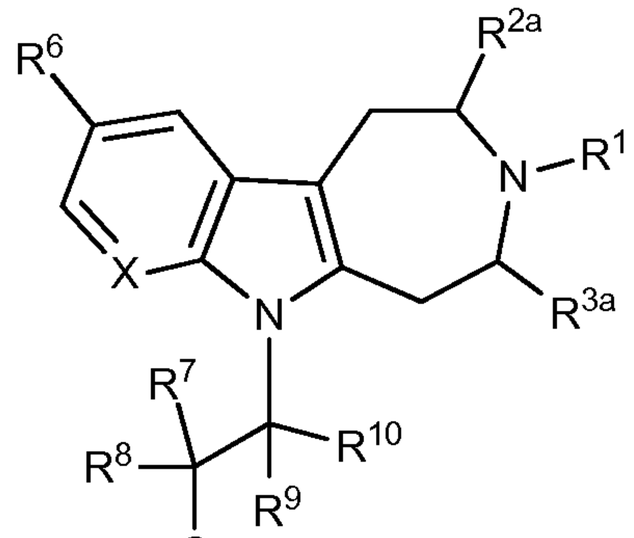
R^8 is azido, acylamino, carboxyl, carbonylalkoxy, –OC(O)C_1-C_5 alkyl substituted with carboxyl or –OC_1-C_5 alkyl optionally substituted with carboxyl;

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.

[0395] 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.

[0396] 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.

[0397] 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.

[0398] 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.

[0399] 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.

[0400] 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.

[0401] 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.

[0402] 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.

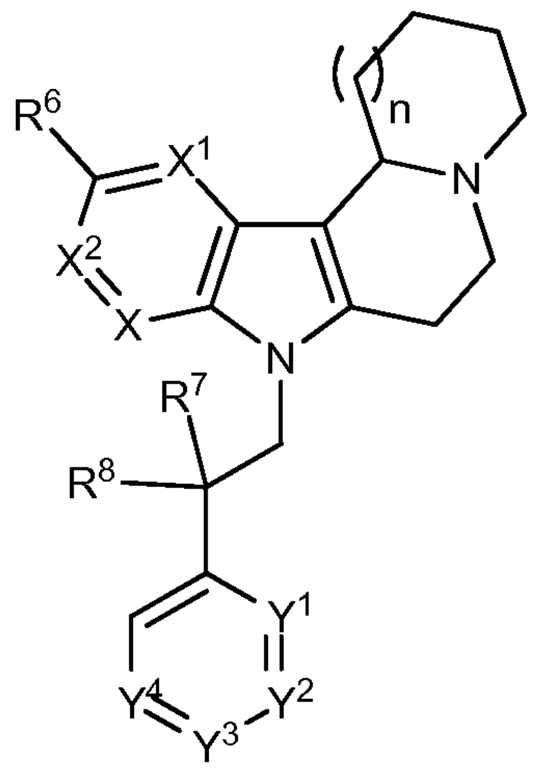
[0403] In certain embodiments of the compounds any formula detailed herein, where applicable, such as compounds of the formulae (B-I), (B-IA), (B-IB), (B-IC) and (B-ID), R^8 is azido. In another variation, R^8 is carboxyl. In another variation, R^8 is carbonylalkoxy. In another variation, R^8 is $–OC(O)C_1$-C_5 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.

[0404] 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.

[0405] In certain embodiments, with respect to the compounds of formula (B-ID), the compound is Compound No. V-21.

[0406] 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.

[0407] 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.

[0408] 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.

[0409] In another variation of formula (C-I), R^6 is halo, CH_3, CH_2F, CHF_2, CF_3 or CD_3.

[0410] 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.

[0411] 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}.

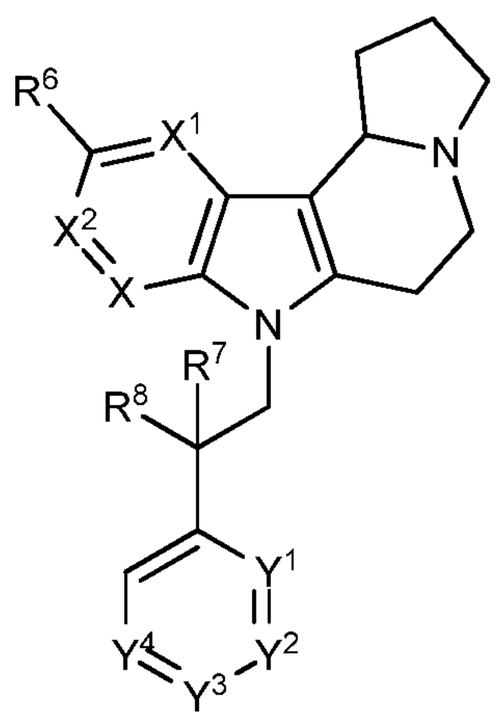
[0412] In another variation of formula (C-I), at least one of Y^1, Y^2, Y^3 and Y^4 is N. In another variation, Y^1 and Y^3 are each N. In another variation, Y^2 and Y^4 are each N. In another variation, Y^1 and Y^4 are each N.

[0413] 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.

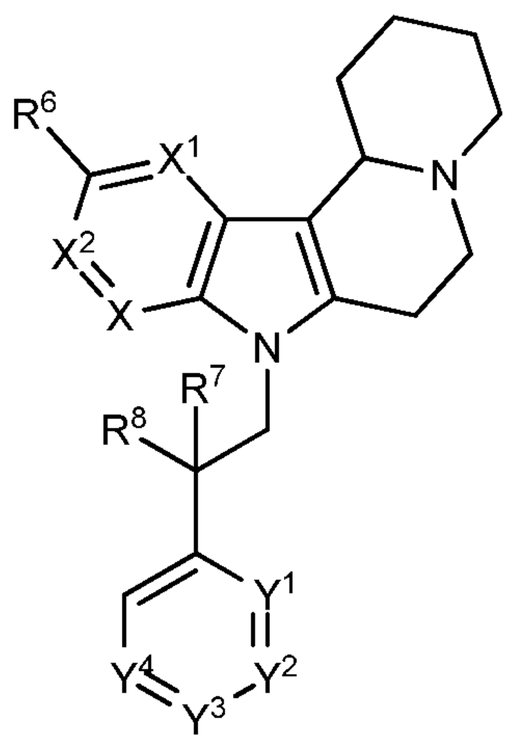
[0414] In another variation of formula (C-I), R^6 is F, Cl, Br, CD_3 or CH_2F; X^1, X^2 and X are each N or CH; Y^2 and Y^3 are each N or CR^4, wherein R^4 is CH_3 or CF_3; R^8 is H or hydroxyl; and n is 0 or 1. In another variation, of formula (C-I), R^6 is F, Cl, Br, CD_3 or CH_2F; R^7 is H, CH_3, 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.

[0415] 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.

[0416] 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.

[0417] 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.

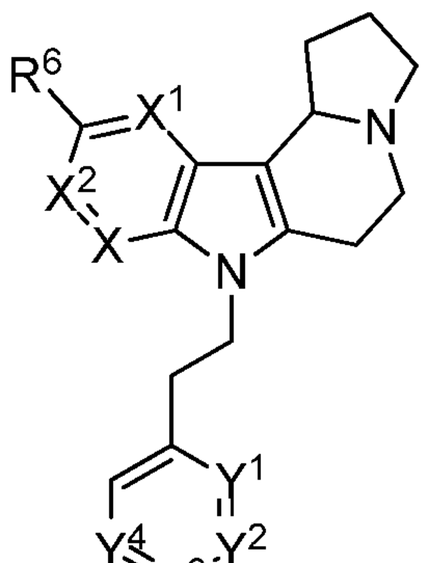
[0418] In certain embodiments, with respect to the compounds of formula (C-IA), X^2 is N, and the compound is Compound No. II-5 or II-275.

[0419] 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.

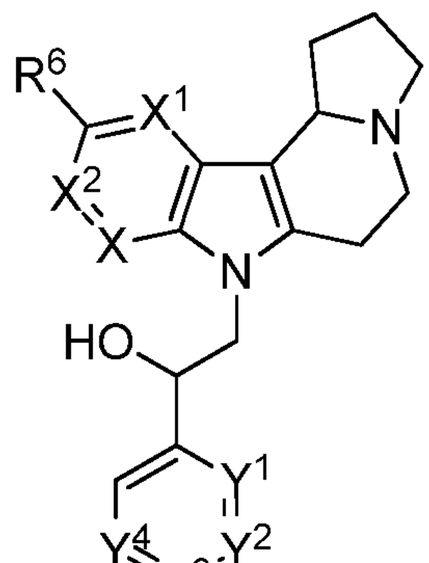
[0420] In certain embodiments, with respect to the compounds of formula (C-IB), X^1 is N, and the compound is Compound No. IV-69 to IV-78, IV-189 to IV-197, or IV-198.

[0421] 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.

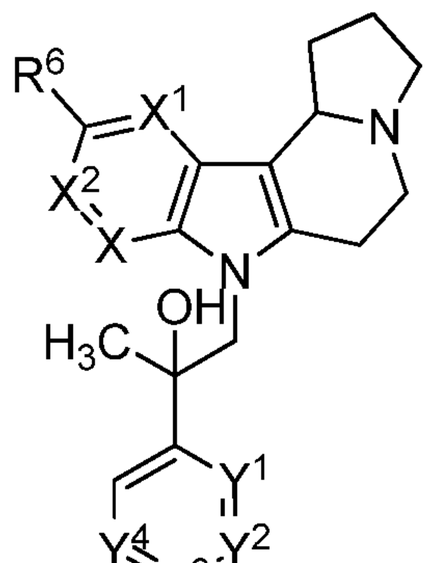
[0422] In specific variations, compounds of formula (C-IA) have the structure:



(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).

[0423] 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.

[0424] 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.

[0425] 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.

[0426] 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.

[0427] 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.

[0428] 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).

[0429] 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.

[0430] 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).

[0431] 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.

[0432] 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.

[0433] 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.

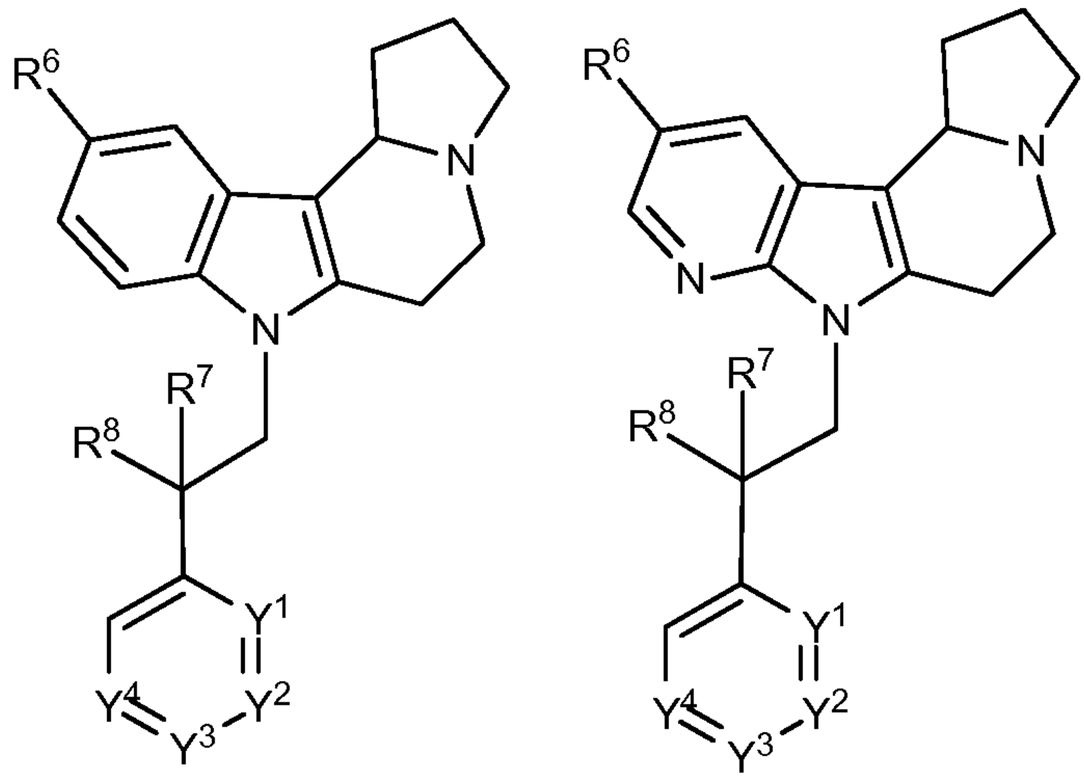
[0434] In certain embodiments, with respect to the compounds of formula (C-IA-3), X is N, and the compound is Compound No. II-149.

[0435] 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.

[0436] 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.

[0437] 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.

[0438] 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).

[0439] In one variation, R^7 and R^8 are both H.

[0440] 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.

[0441] 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.

[0442] 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.

[0443] 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.

[0444] 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.

[0445] 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.

[0446] 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.

[0447] 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.

[0448] 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.

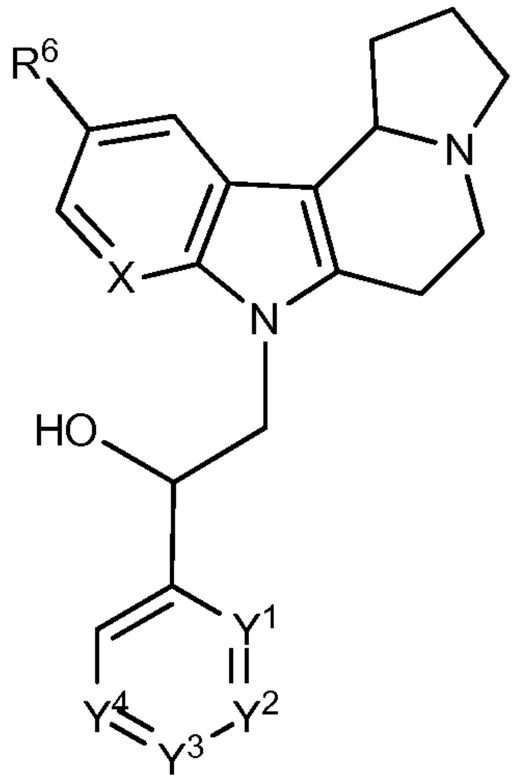
[0449] In certain embodiments, with respect to the compounds of formula (C-IA-5), each Y^1, Y^2, Y^3 and Y^4 is independently CR^4; and the compound is Compound No. IV-1, IV-9, IV-11 to IV-18, IV-129, IV-130 to IV-137, or IV-138.

[0450] 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.

[0451] 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.

[0452] 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.

[0453] In other variations, compounds of formula (C-IA) have the structure:



(C-IA-6)

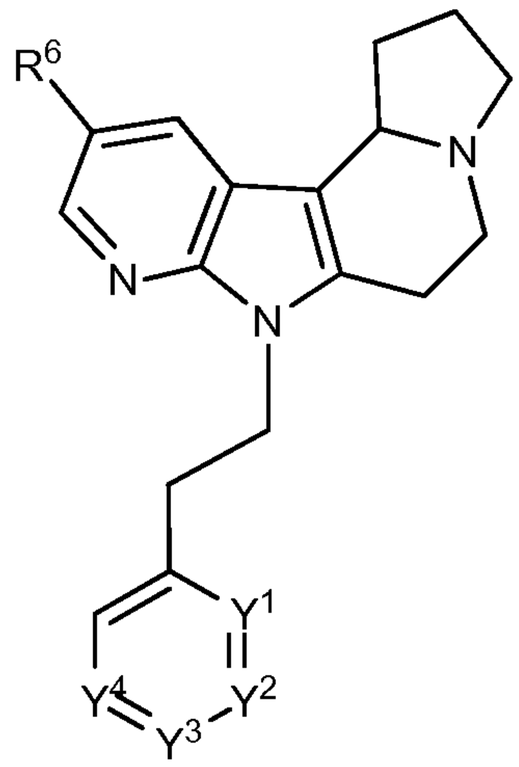
or a salt or solvate thereof, wherein X is C or N; and R^6, Y^1, Y^2, Y^3 and Y^4 are defined as for formula (C-I).

[0454] In certain embodiments, with respect to the compounds of formula (C-IA-6), the compound is Compound No. 129, 168, or 198.

[0455] 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.

[0456] 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.

[0457] 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).

[0458] In certain embodiments, with respect to the compounds of formula (C-IA-7); the compound is Compound No. 74, 134, 137, or 336.

[0459] 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.

[0460] 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.

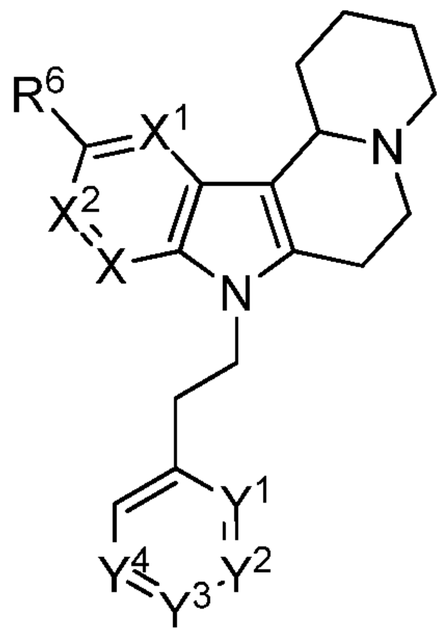
[0461] In one variation of formula (C-IA-1) one or more of the following apply: (i) R^6 is other than Cl when each X^1, X^2, X, Y^1, Y^2 and Y^4 is CH and Y^3 is CF; (ii) R^6 is other than H when each X^1, X^2, X, Y^1, Y^2 and Y^4 is CH and Y^3 is CF; (iii) R^6 is other than H when each X^1, X^2, Y^1 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.

[0462] 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.

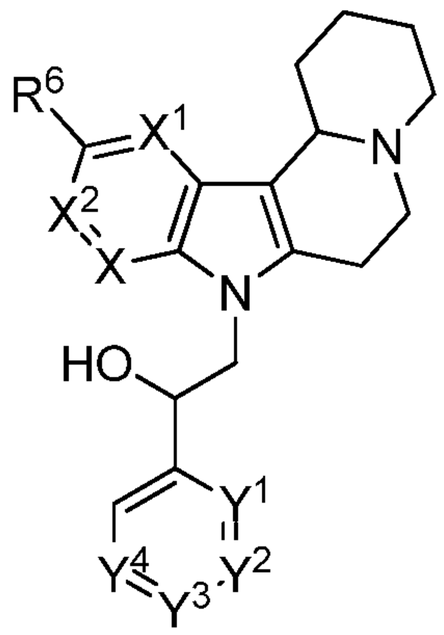
[0463] In one variation of formula (C-IA-3), R^6 is other than H when each X^1, X^2, X, Y^1, Y^2 and Y^4 is CH and Y^3 is N.

[0464] 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.

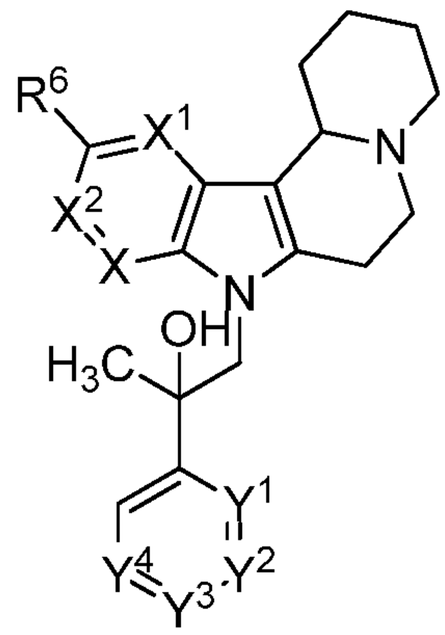
[0465] In specific variations, compounds of formula (C-IB) have the structure:



(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).

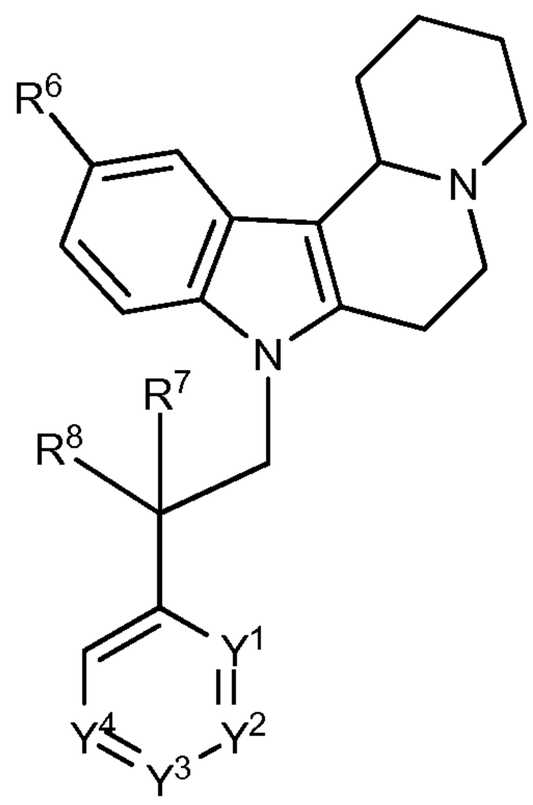
[0466] In certain embodiments, with respect to the compounds of formula (C-IB-1); the compound is Compound No. IV-8, IV-49 to IV-87, or IV-88.

[0467] In certain embodiments, with respect to the compounds of formula (C-IB-2); the compound is Compound No. 47.

[0468] 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.

[0469] 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.

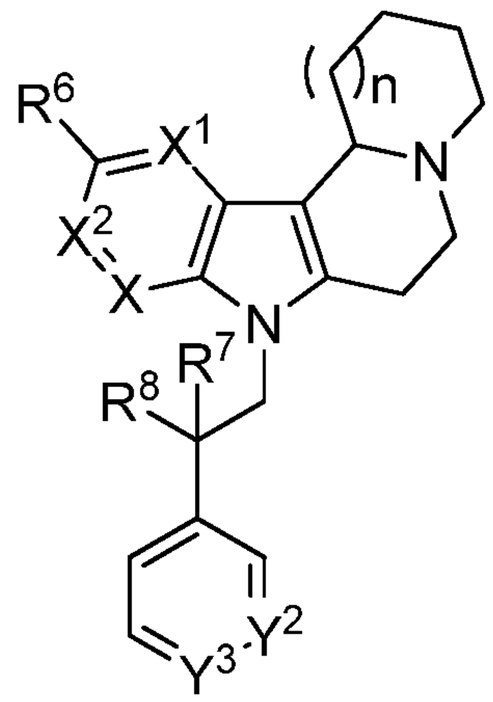
[0470] In one embodiment, the compound is of formula (C-IC-1):



(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).

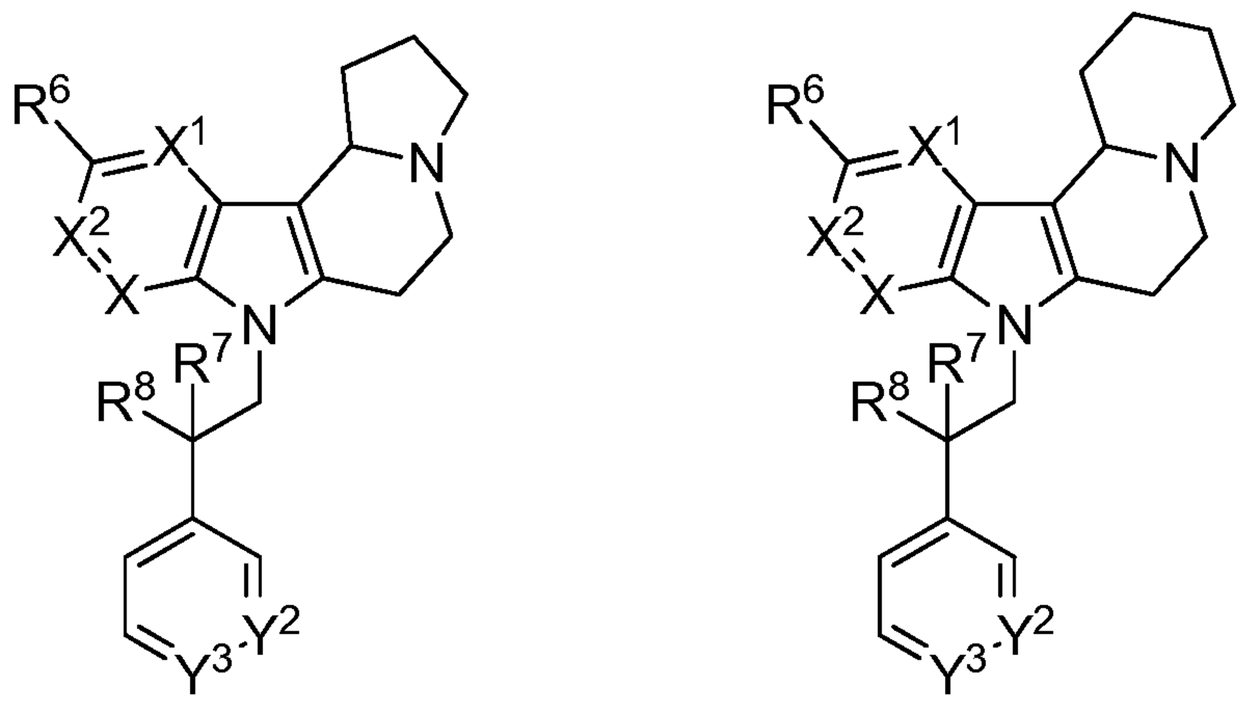
[0471] In one embodiment, the compound is of formula (C-II):



(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.

[0472] In one embodiment, the compound is of formula (C-IIA) or (C-IIB):



(C-IIA) (C-IIB)

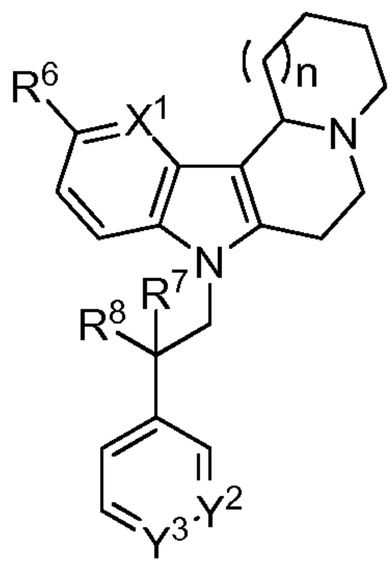
wherein R^6, R^7, R^8, X^1, X^2, X, Y^2, and Y^3 are as described for formula (C-I). In one variation of formula (C-IIA), one or more of the following apply (i) R^6 is other than Cl when n is 0, each R^7 and R^8 is H, each X^1, X^2, X, Y^2 is CH and Y^3 is CF; (ii) R^6 is other than H when n is 0 and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

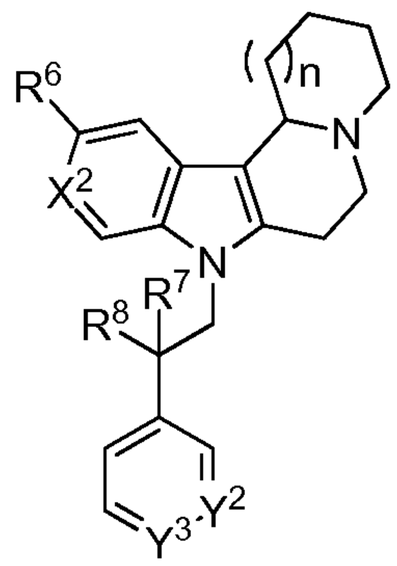
Table A: Representative Compounds of formula (C-IIA)

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

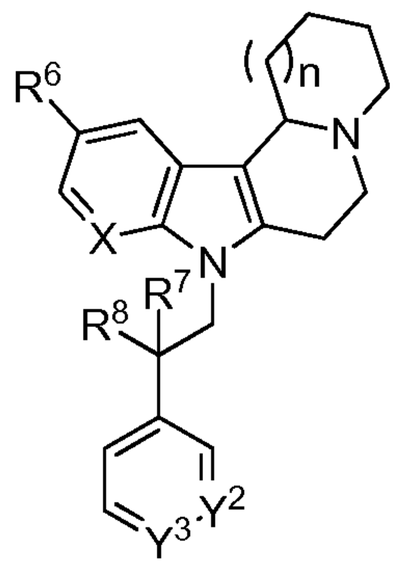
[0473] In one embodiment, the compound is of formulae (C-IIIA)-(C-IIIF):



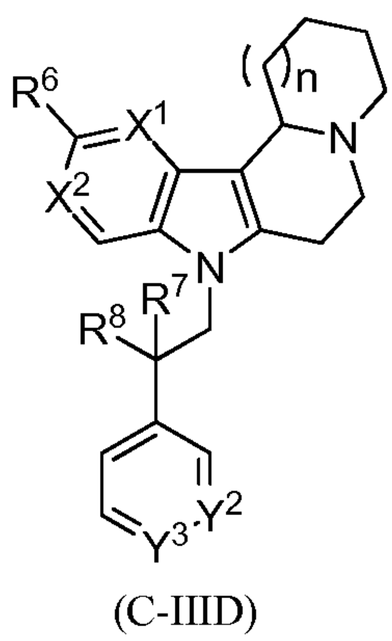
(C-IIIA)



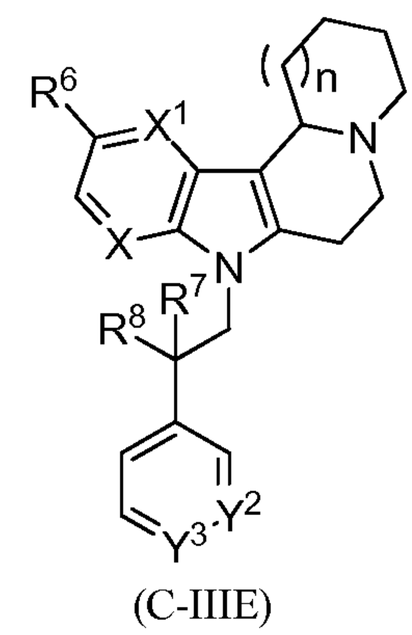
(C-IIIB)



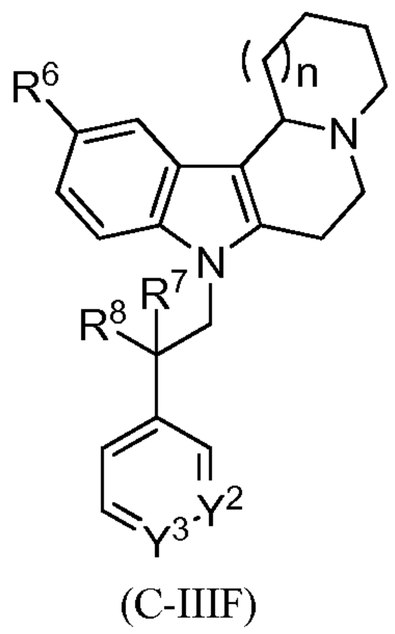
C-(IIIC)



(C-IIID)



(C-IIIE)

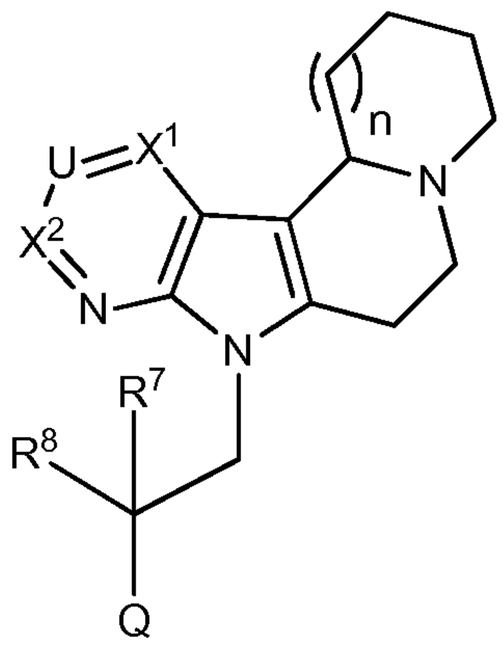


(C-IIIF)

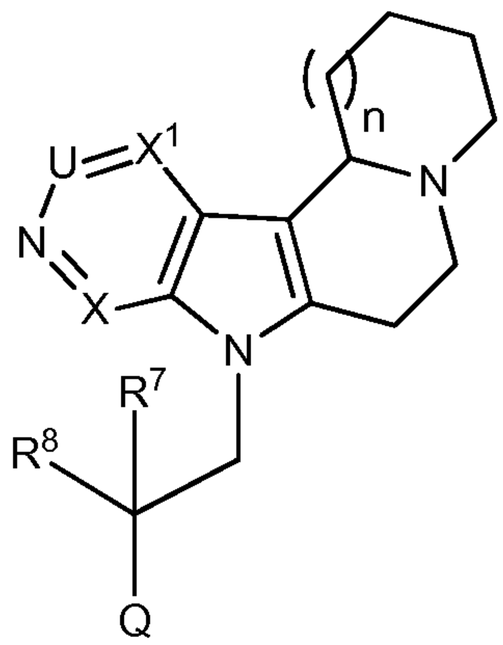
wherein R^6, R^7, R^8, X^1, X^2, X, Y^2, Y^3 and n are as described for formula (C-I). In one variation, the compound is of formula (C-IIIA), (C-IIIB), (C-IIIC), (C-IIID), (CIII-E) or (C-IIIF), wherein n is 0. In one variation compound is of formulae (C-IIIA), (C-IIIB), (C-IIIC), (C-IIID), (CIII-E) or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

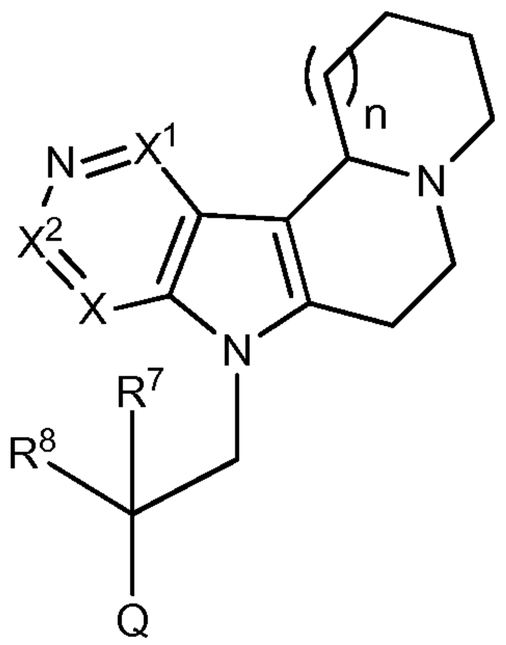
[0474] In another embodiment the compound is according to formula (C-IVA), (C-IVB), (C-IVC), (C-IVD), (C-IVE), (C-IVF) or (C-IVG):



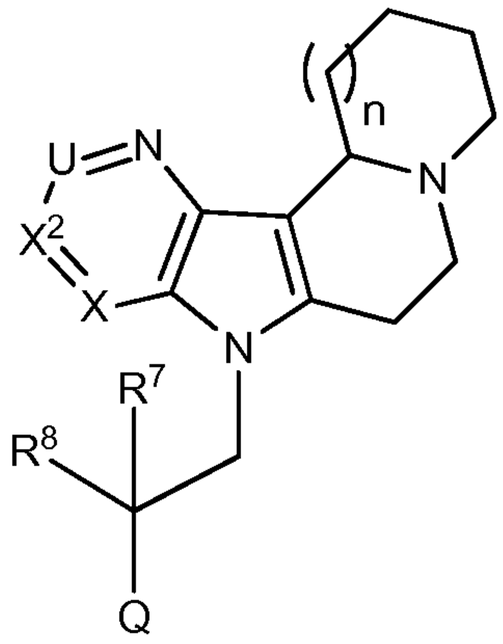
(C-IVA),



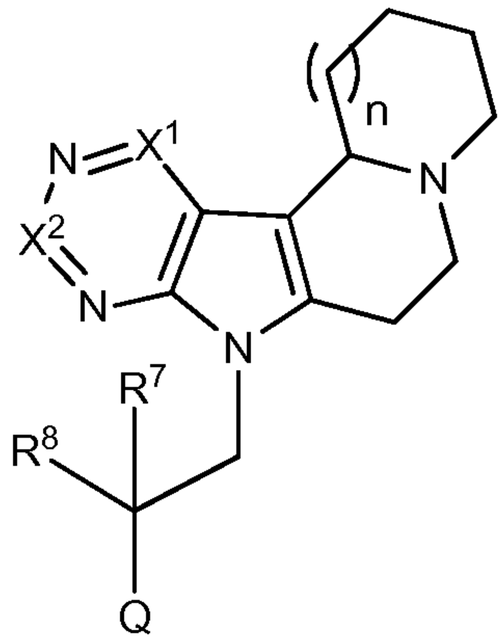
(C-IVB),



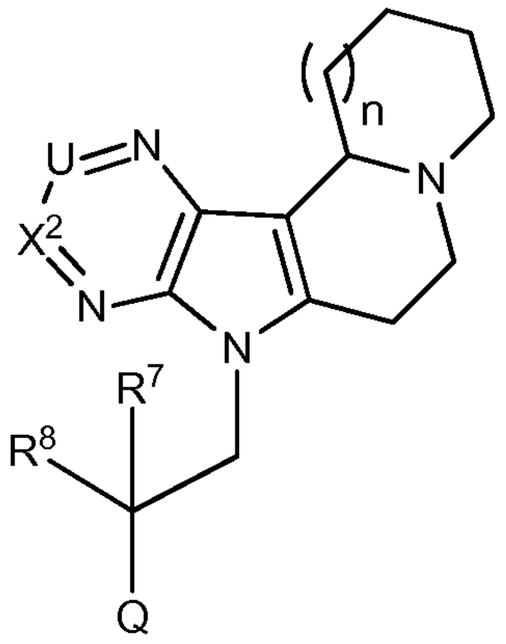
(C-IVC),



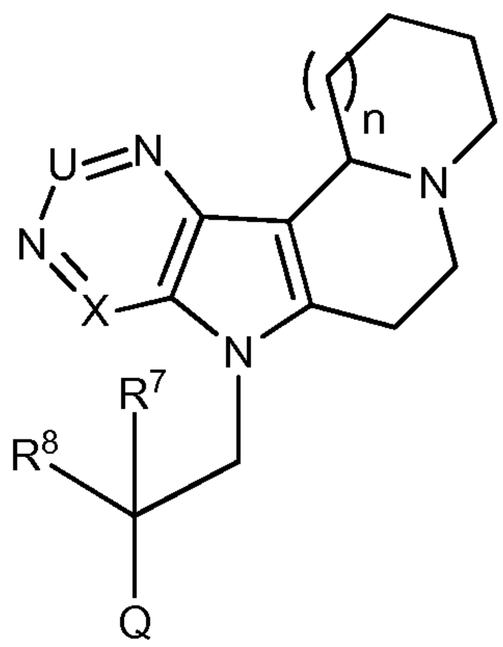
(C-IVD),



(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.

[0475] 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.

[0476] 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.

[0477] 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.

[0478] 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.

[0479] 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.

[0480] 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.

[0481] 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.

[0482] 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.

[0483] 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.

[0484] 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.

[0485] 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.

[0486] 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.

[0487] 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.

[0488] 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.

[0489] 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.

[0490] 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.

[0491] 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.

[0492] 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.

[0493] 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.

[0494] 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.

[0495] 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.

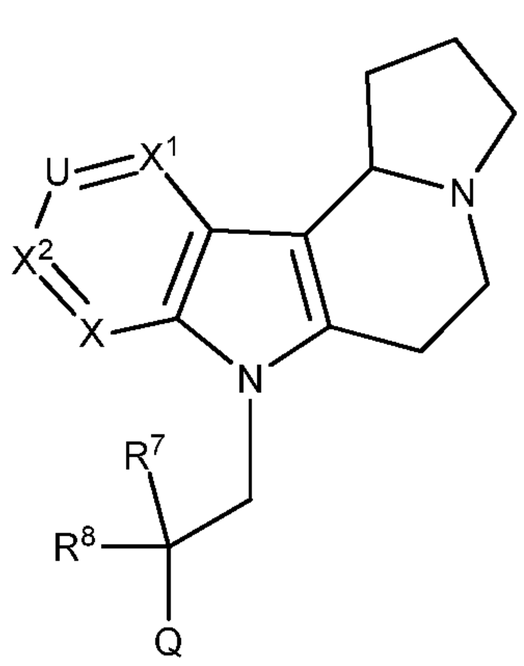
[0496] In certain embodiments, with respect to the compounds of formula (C-IVD), n is 0, and the compound is Compound IV-3, IV-29 to IV-38, IV-109 to IV-118, IV-149 to IV-158, IV-229 to IV-237, or IV-238.

[0497] 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.

[0498] 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.

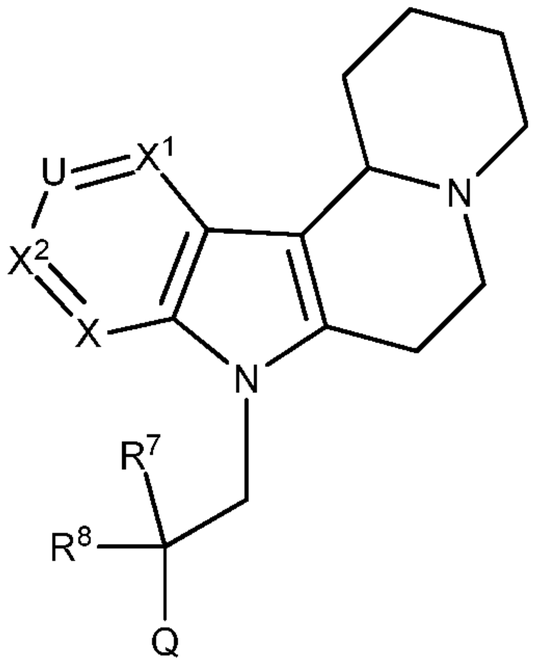
[0499] In certain embodiments, with respect to the compounds of formula (C-IVG), the compound is Compound No. IV-10, IV-39 to IV-48, IV-79 to IV-88, IV-90, IV-92, IV-119 to IV-128, IV-159 to IV-168, IV-199 to VI-208, IV-212, IV-239 to IV-243, or IV-244.

[0500] 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;

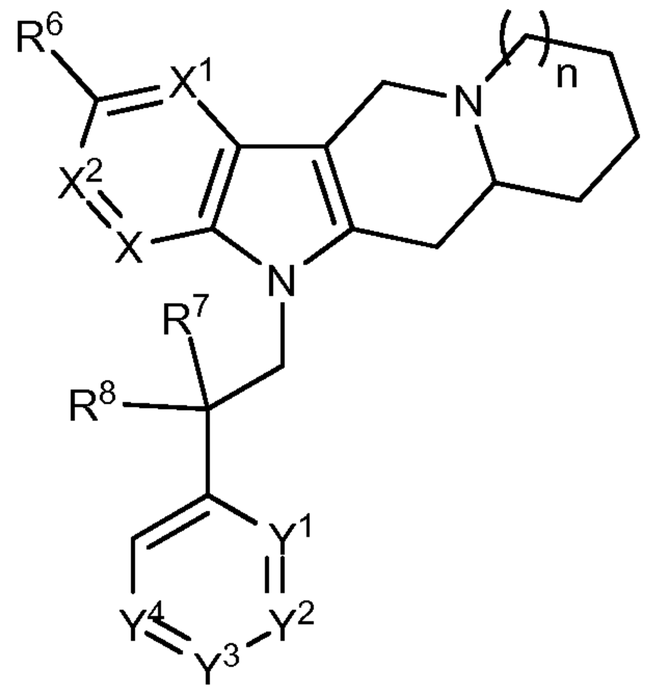
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl, or is taken together with R^8 and the carbon atom to which they are attached to form a dioxolane ring or a carbonyl moiety;

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.

[0501] 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};

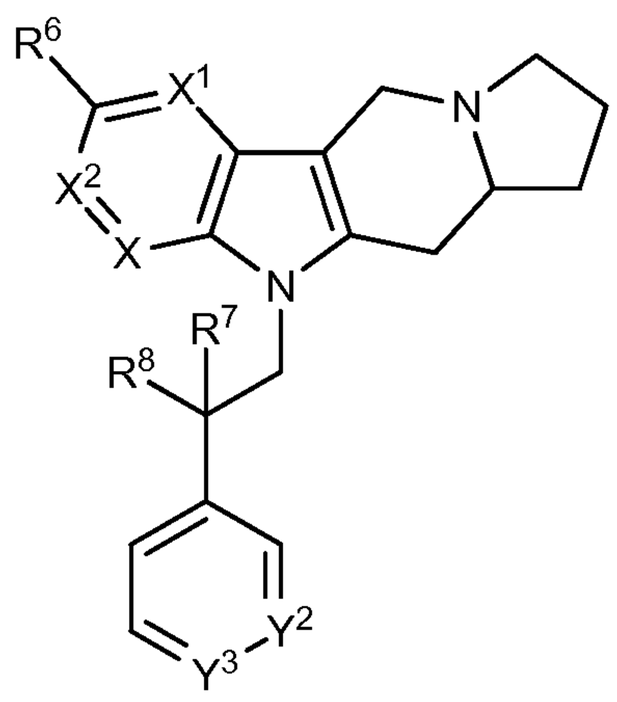
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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

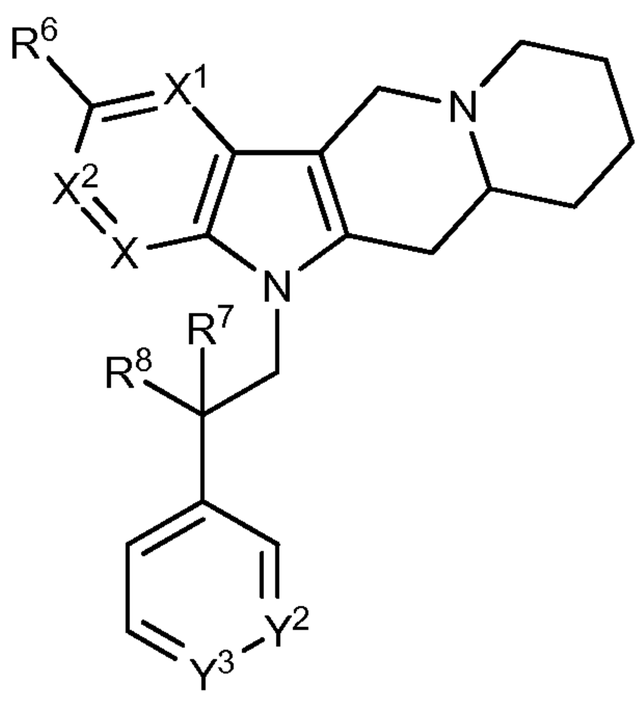
n is 0 or 1.

[0502] In one variation, the compound is of formula (D-IIA) or (D-IIB):



(D-IIA)

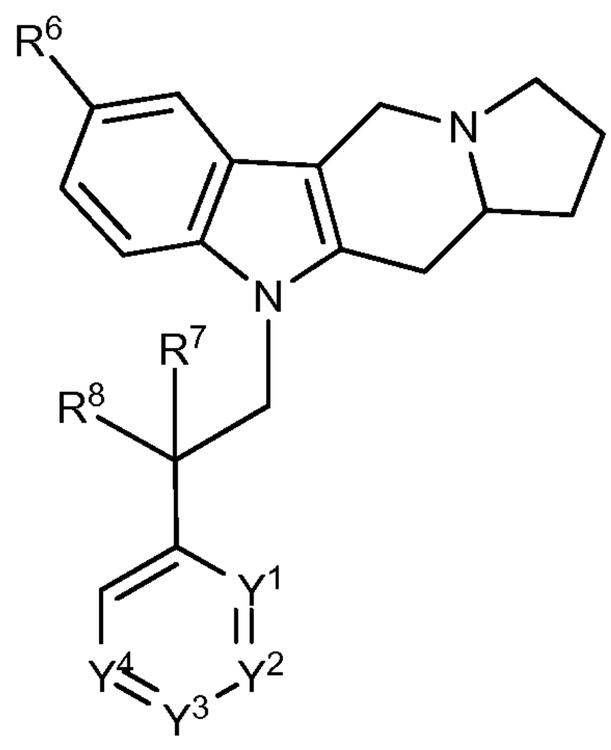
or



(D-IIB)

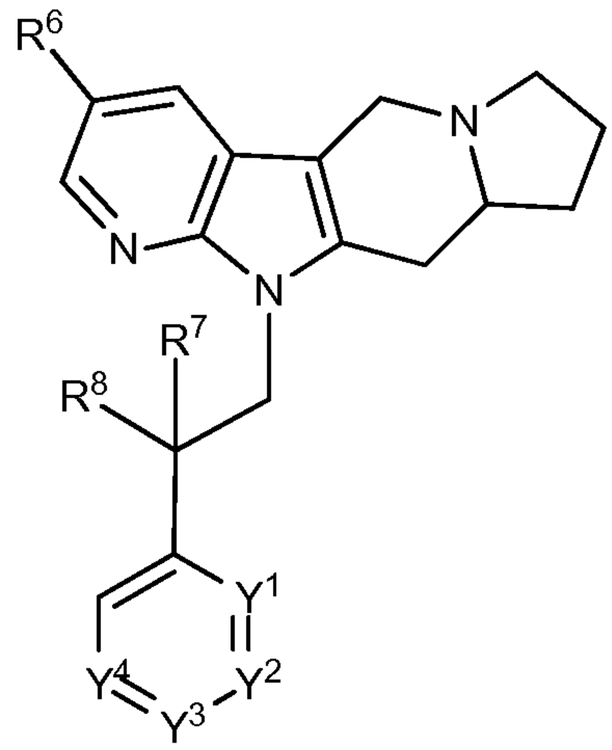
or a salt or solvate thereof, wherein R^6, X^1, X^2, X, Y^2 and Y^3 are defined as for formula (D-I).

[0503] In other variations, compounds of formula (D-IIA) have the structure:



(D-IIA-1)

or



(D-IIA-2)

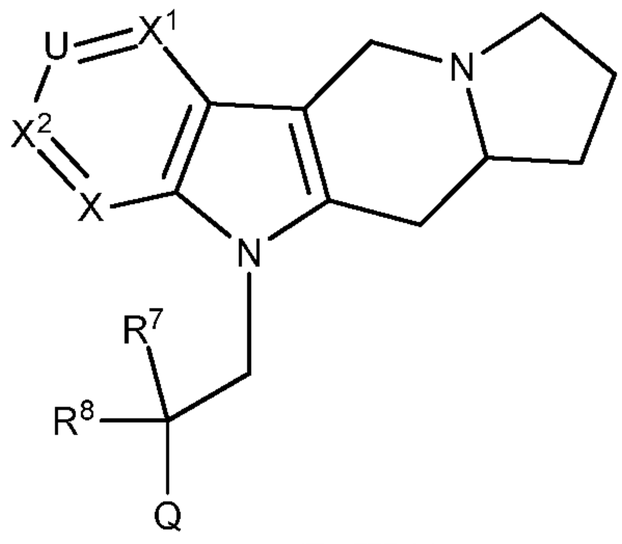
or a salt or solvate thereof, wherein R^6, R^7, R^8, Y^1,Y^2, Y^3 and Y^4 are defined as for formula (D-I).

[0504] In certain embodiments, with respect to the compounds of formula (D-IIB), the compound is Compound No. 75.

[0505] 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.

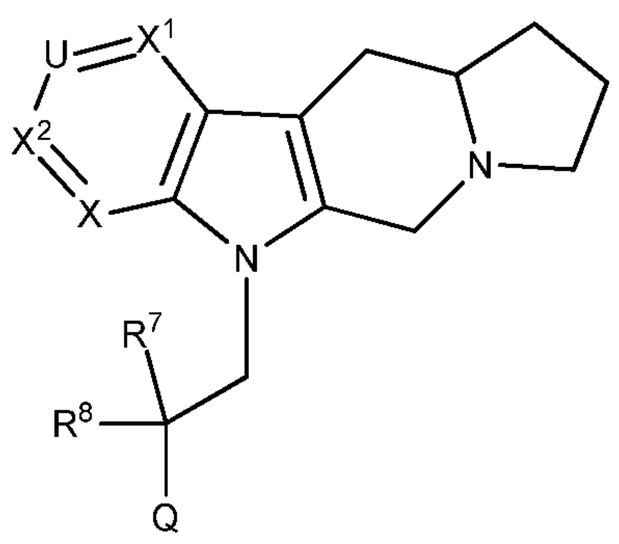
[0506] In certain embodiments, with respect to the compounds of formula (D-IIA-2), the compound is Compound No. 37, II-86, II-234, II-235, II-236, or II-239.

[0507] 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

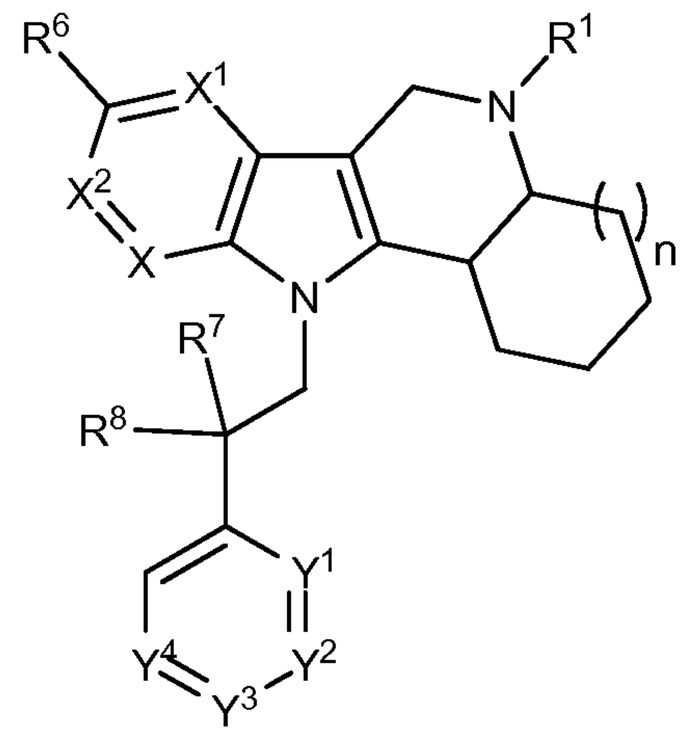
each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

[0508] 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..

[0509] 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.

[0510] In certain embodiments, with respect to the compounds of formula (D-IIIB), the compound is Compound No. III-54, III-353, or III-354.

[0511] 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};

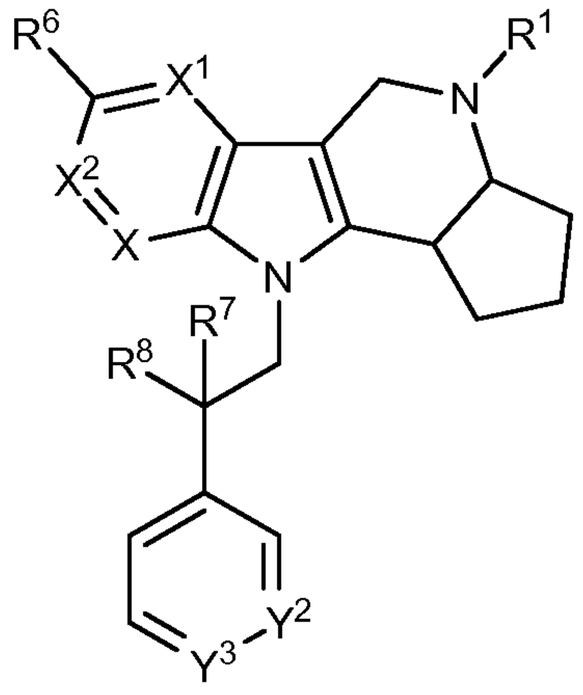
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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

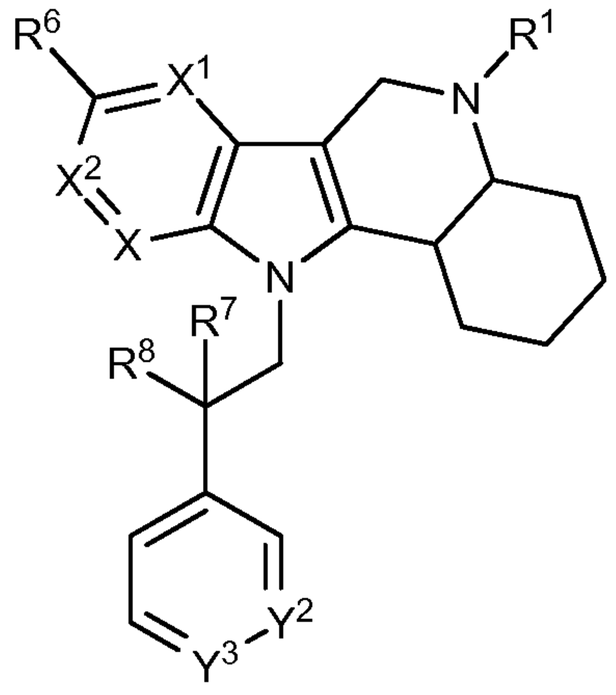
n is 0 or 1.

[0512] In one variation, the compound is of formula (E-IIA) or (E-IIB):



(E-IIA)

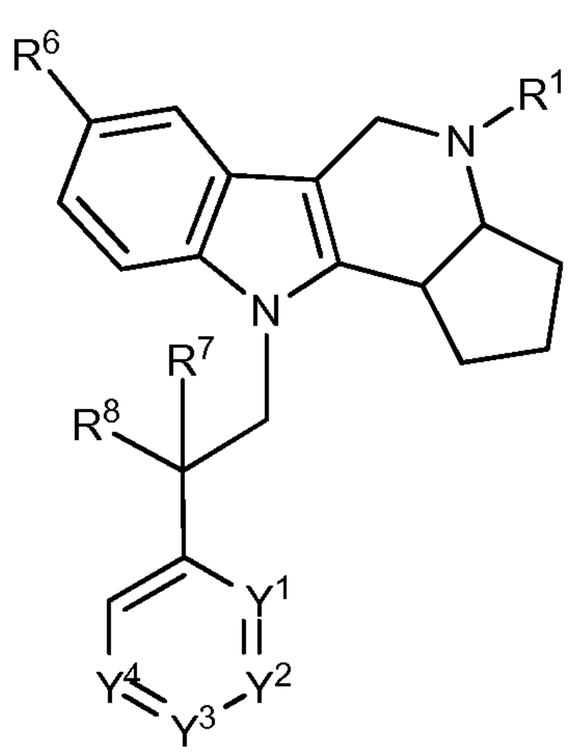
or



(E-IIB)

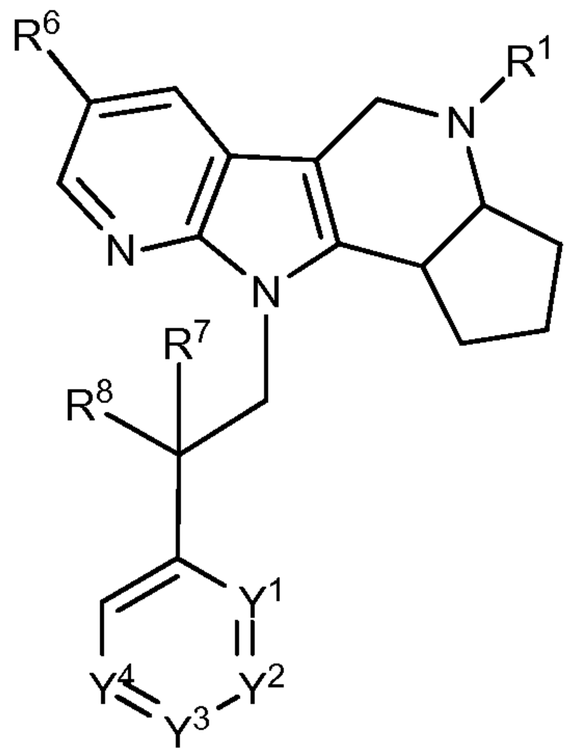
or a salt or solvate thereof, wherein R^1, R^6, X^1, X^2, X, Y^2 and Y^3 are defined as for formula (E-I).

[0513] In other variations, compounds of formula (E-IIA) have the structure:



(E-IIA-1)

or

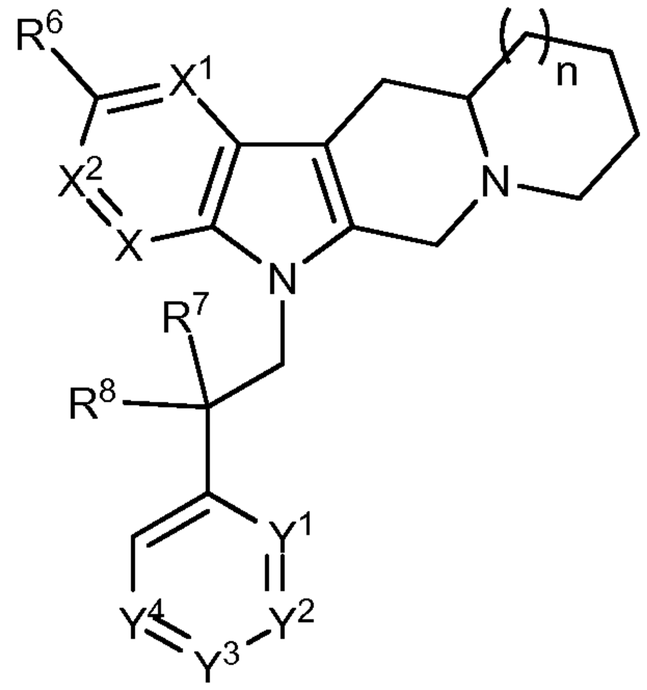


(E-IIA-2)

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).

[0514] In certain embodiments, with respect to the compounds of formula (E-IIA), the compound is Compound No. III-61.

[0515] 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};

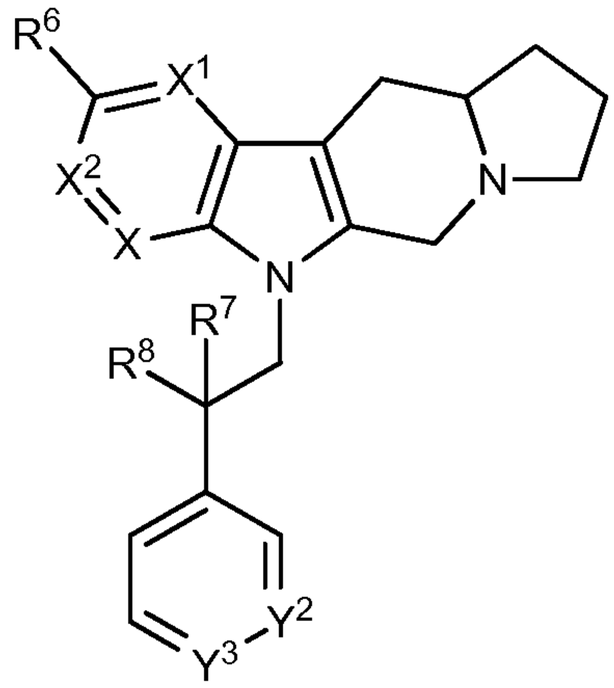
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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

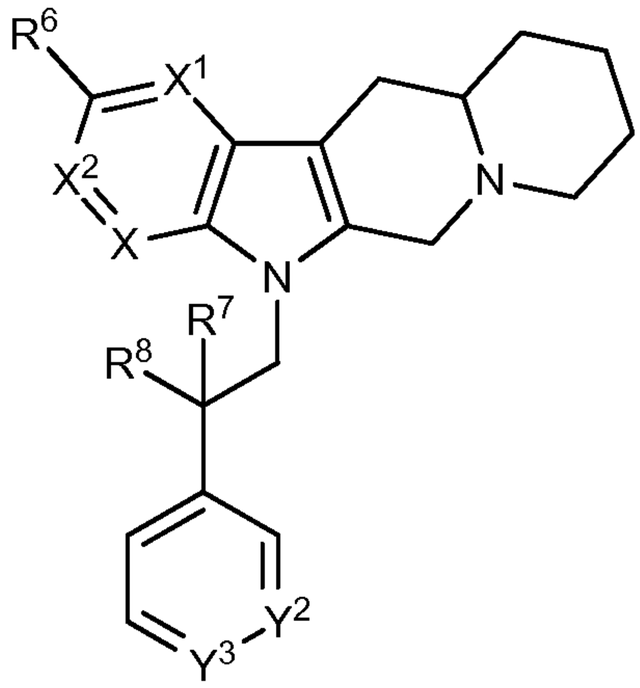
n is 0 or 1.

[0516] In one variation, the compound is of formula (F-IIA) or (F-IIB):



(F-IIA)

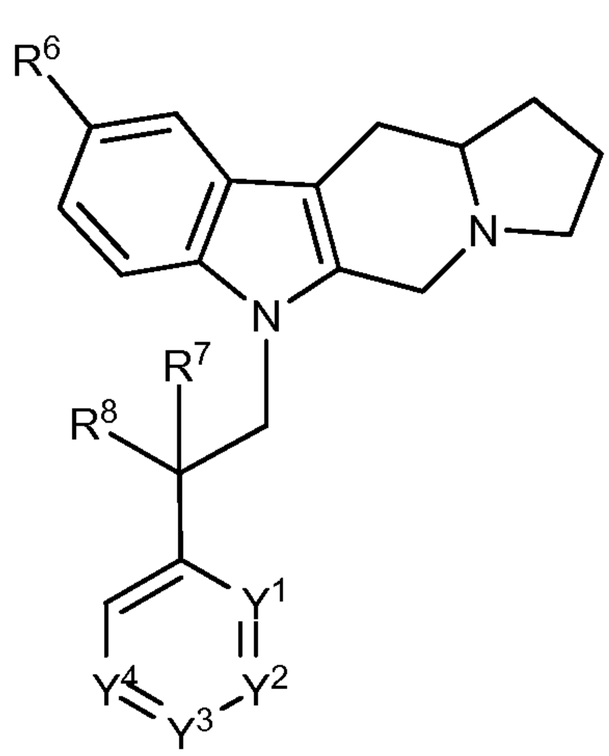
or



(F-IIB)

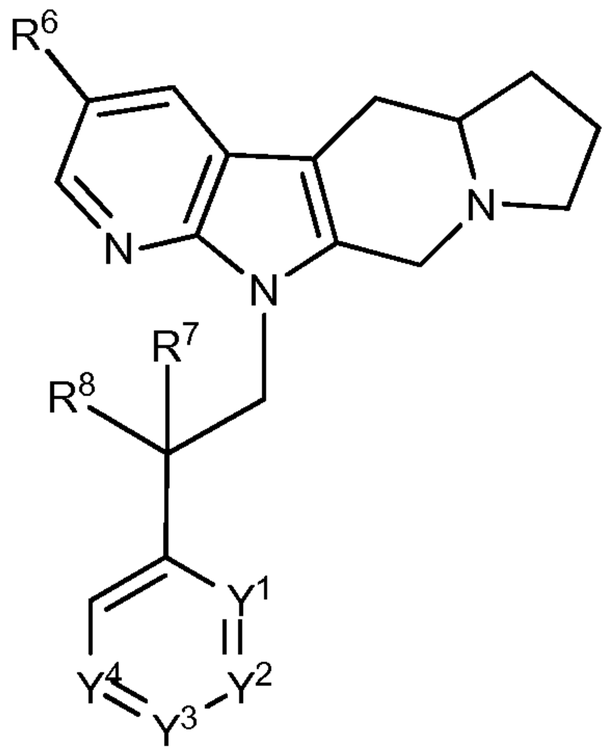
or a salt or solvate thereof, wherein R^6, X^1, X^2, X, Y^2 and Y^3 are defined as for formula (F-I).

[0517] In other variations, compounds of formula (F-IIA) have the structure:



(F-IIA-1)

or

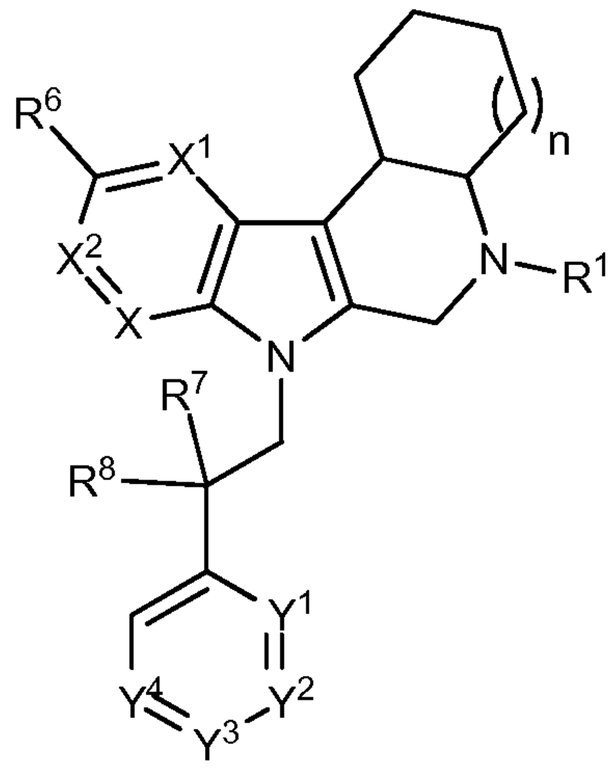


(F-IIA-2)

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).

[0518] In certain embodiments, with respect to the compounds of formula (F-IIA), the compound is Compound No. III-54, III-353, or III-354.

[0519] 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};

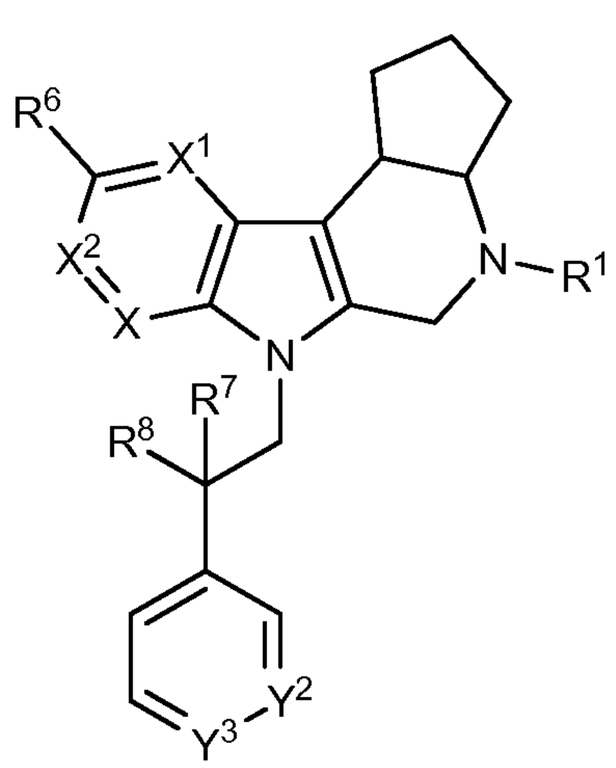
each R^{11}, R^{12} and R^{13} is independently H or optionally substituted C_1-C_5 alkyl;

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

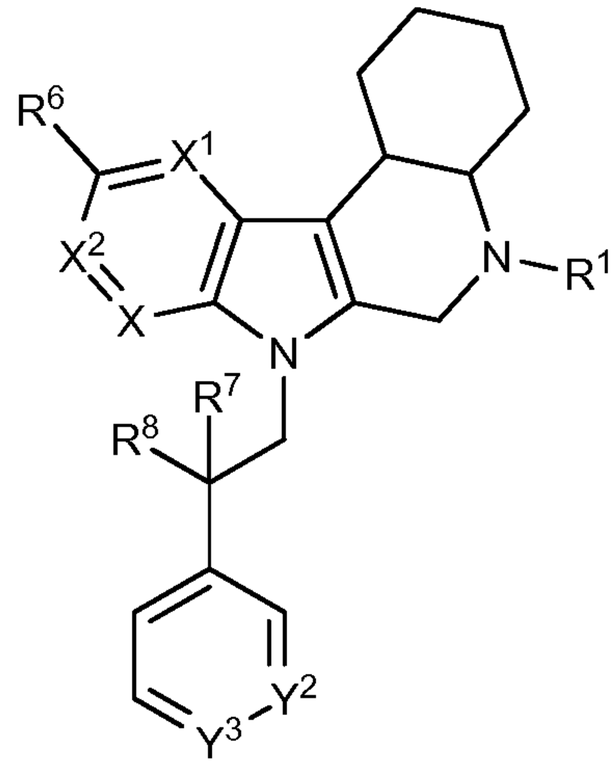
n is 0 or 1.

[0520] In one variation, the compound is of formula (G-IIA) or (G-IIB):



(G-IIA)

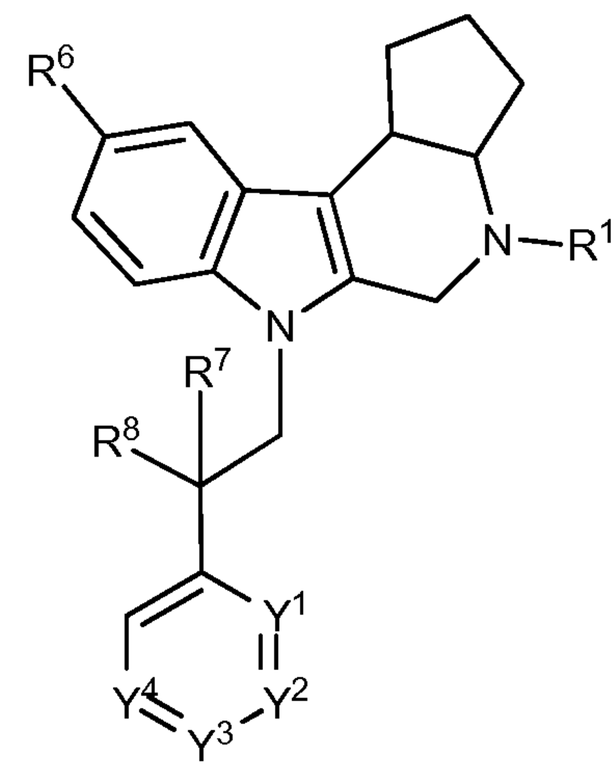
or



(G-IIB)

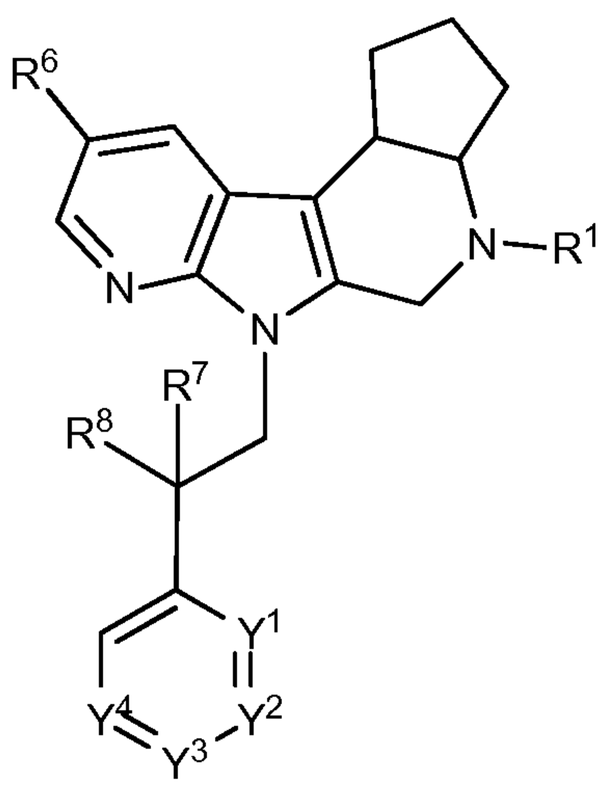
or a salt or solvate thereof, wherein R^1, R^6, X^1, X^2, X, Y^2 and Y^3 are defined as for formula (G-I).

[0521] In other variations, compounds of formula (G-IIA) have the structure:



(G-IIA-1)

or

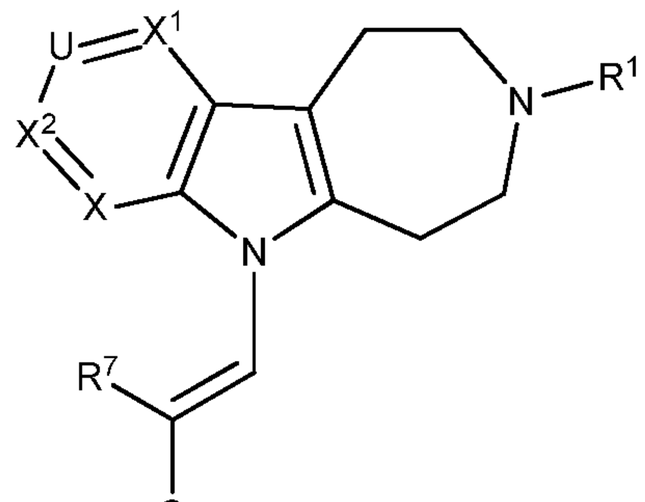


(G-IIA-2)

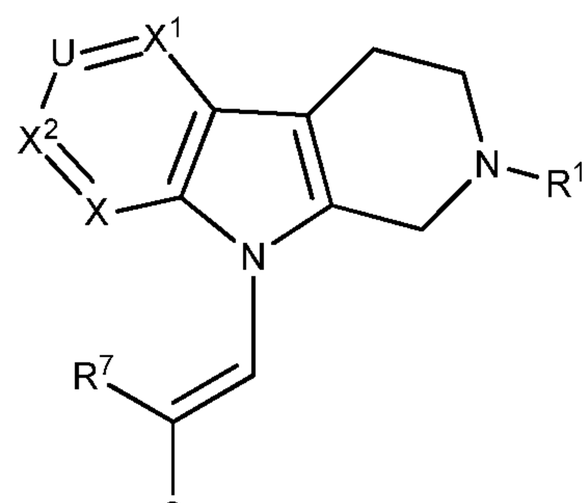
or a salt or solvate thereof, wherein R^6, R^7, R^8 , Y^1, Y^2, Y^3 and Y^4 are defined as for formula (G-I).

[0522] 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.

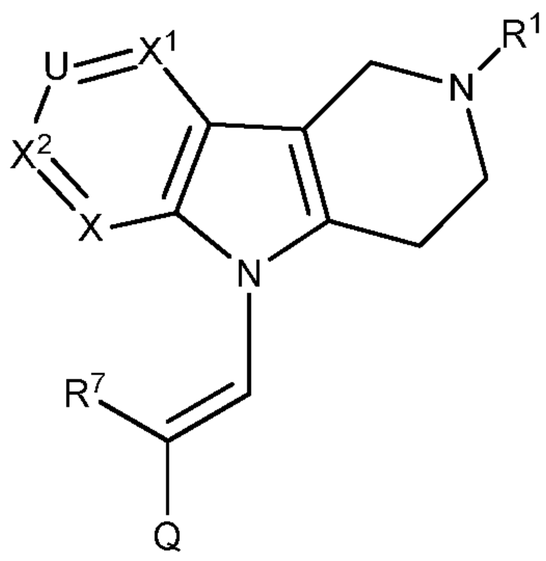
[0523] In one embodiment, compounds of formula (H-IA), (H-IB), (H-IC) or (H-ID) are provided:



(H-IA)

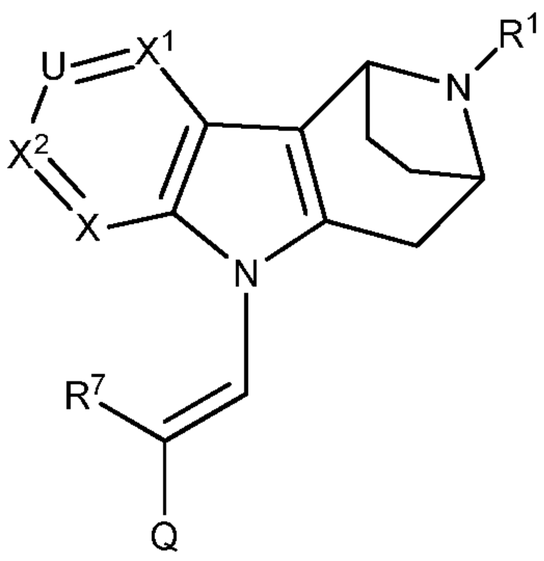


(H-IB)



(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;

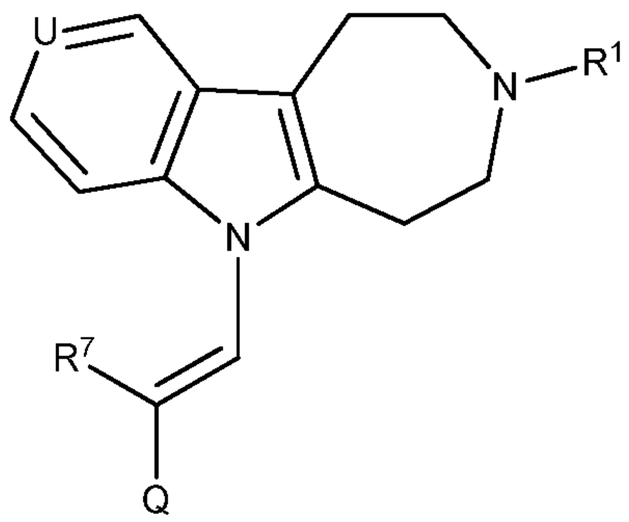
R^7 is H, halo, optionally substituted C_1-C_5 alkyl, or optionally substituted aryl;

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

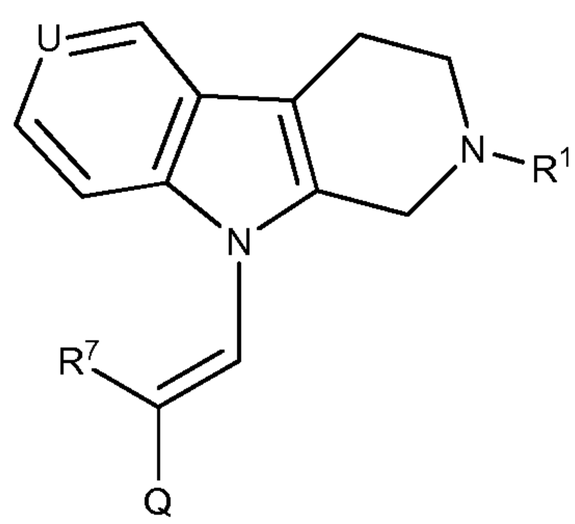
each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl.

[0524] 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.

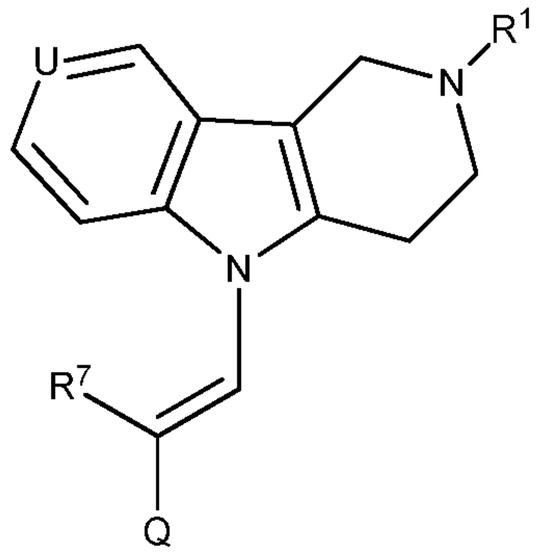
[0525] In one embodiment, compounds of formula (H-IA-1), (H-IB-1), (H-IC-1) or (H-ID-1) are provided:



(H-IA-1)

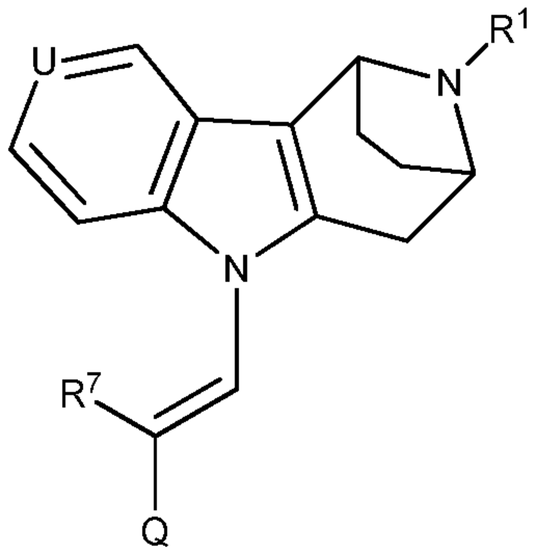


(H-IB-1)



(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.

[0526] 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.

[0527] 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.

[0528] 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.

[0529] 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.

[0530] In certain embodiments, with respect to the compounds of formula (H-IB-1), the compound is Compound No. 224 or 239.

[0531] 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.

[0532] 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.

[0533] 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.

[0534] 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.

[0535] 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.

[0536] 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.

[0537] 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.

[0538] 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.

[0539] 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.

[0540] In certain embodiments, with respect to the compounds of formula (H-IIB-1), the compound is Compound No. 333.

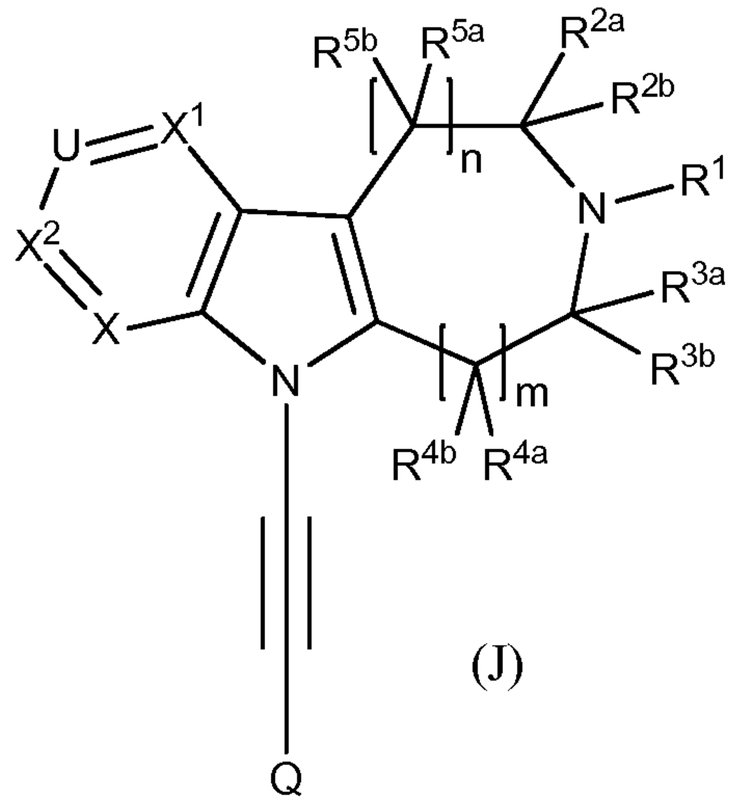
[0541] In certain embodiments, with respect to the compounds of formula (H-IIC-1), the compound is Compound No. 242, 256, 264, 313, 321, 328, 330, or 334.

[0542] In certain embodiments, with respect to the compounds of formula (H-IID-1), the compound is Compound No. 95.

[0543] 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.

[0544] 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.

[0545] 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;

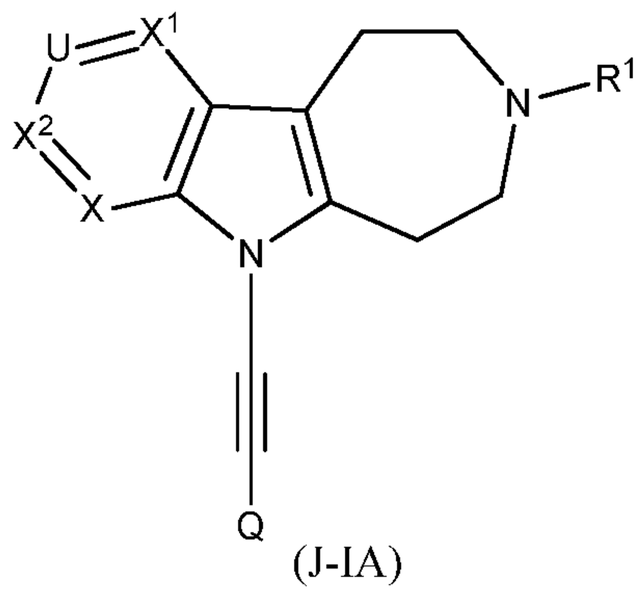
each n and m is 1, or n is 0 and m is 1, or n is 1 and m is 0;

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

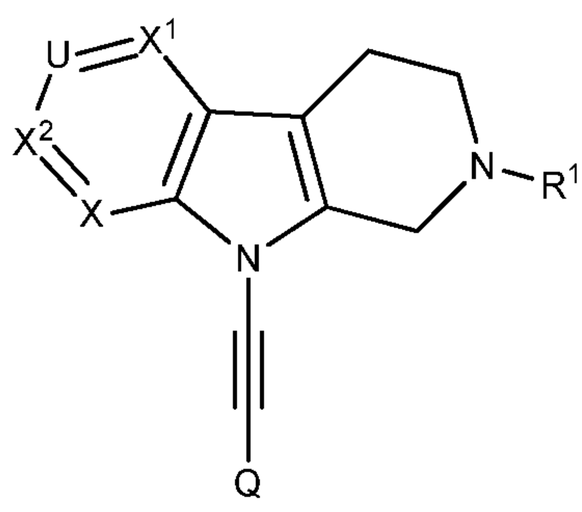
each R^6 is independently H; hydroxyl; halo; C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, carboxyl and perhaloalkyl; C_2-C_5 alkenyl; optionally substituted C_1-C_5 alkoxy; or optionally substituted –$C(O)C_1$-C_5 alkyl;

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

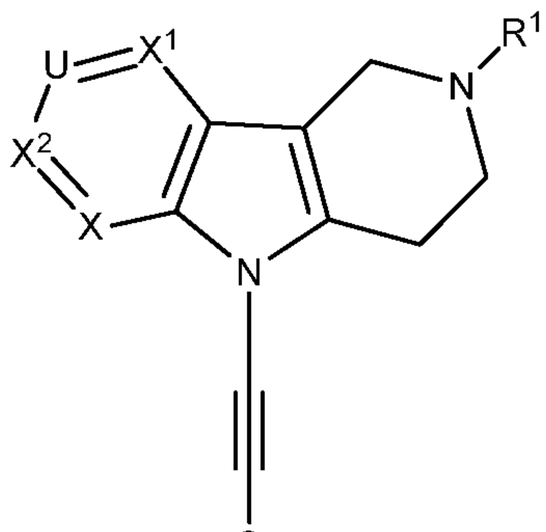
[0546] In one embodiment, compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID):



(J-IA),

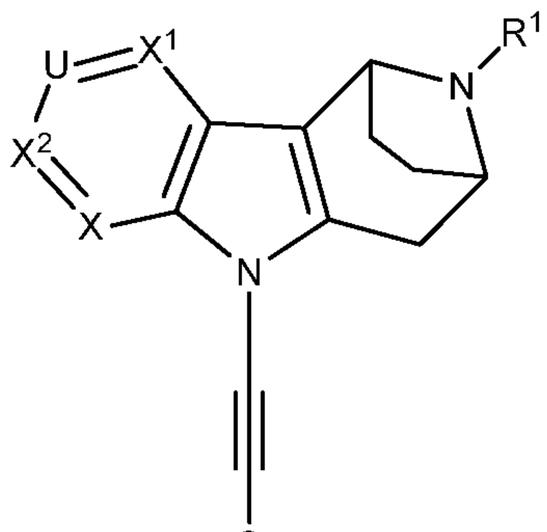


(J-IB),



(J-IC)

or



(J-ID)

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

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

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

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

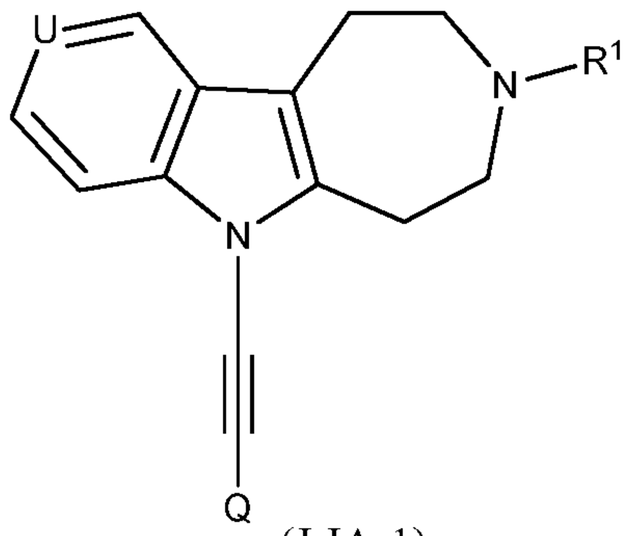
Q is aryl or heteroaryl optionally substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, -NHC(O)CH_3 and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

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

[0547] 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.

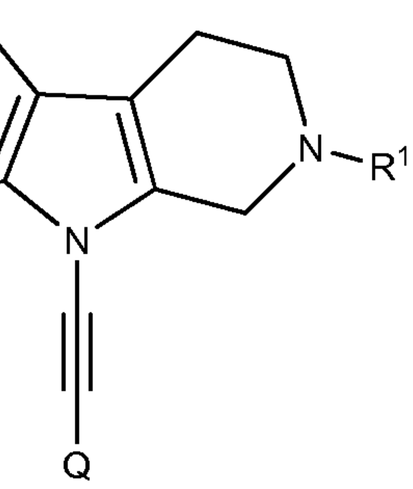
[0548] In certain embodiments, with respect to the compounds of formula (J-IA), (J-IB), (J-IC) or (J-ID), X is CR^6, wherein R^6 is fluoro; and R^1 is other than methyl.

[0549] 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)

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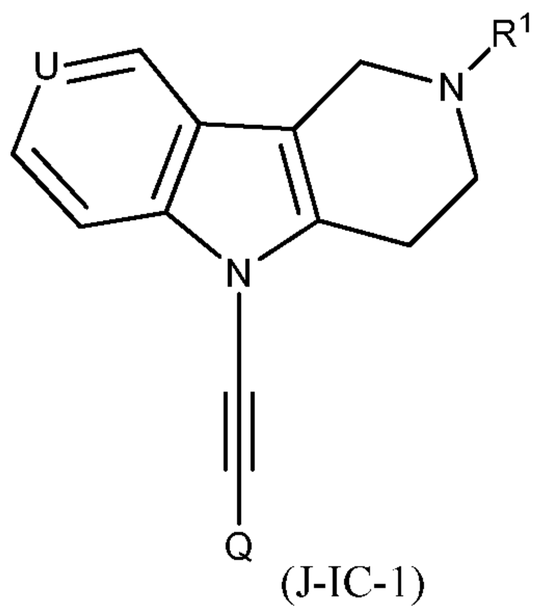
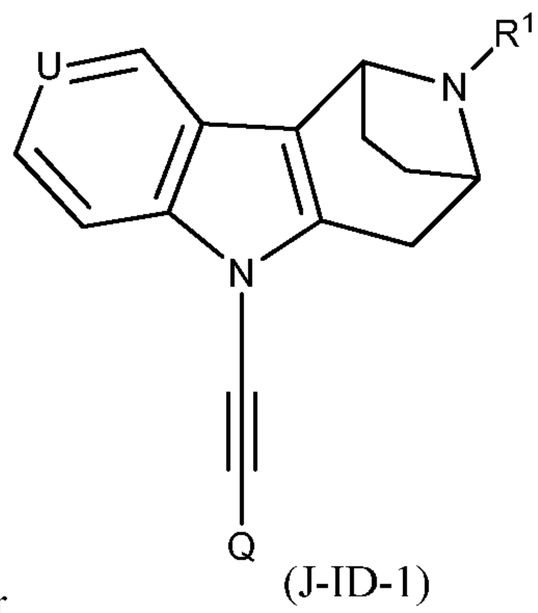


(J-IC-1)

or



(J-ID-1)

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

U is N or CR^6;

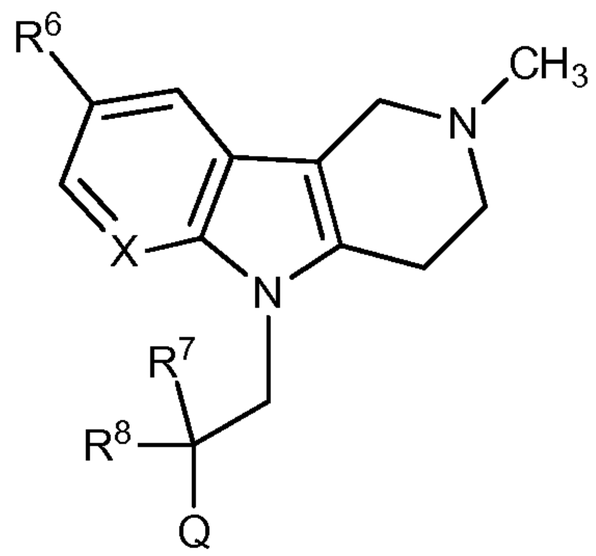
R^1 is H, C_1-C_5 alkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C_3-C_8 cycloalkyl optionally substituted with 1 to 3 substituents independently selected from halo, hydroxyl, carboxyl and perhaloalkyl, C_2-C_5 alkenyl optionally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

[0550] In another embodiment, the compound is of the formula (K-IA), (K-IB), (K-IC) or (K-ID):



(K-IA)

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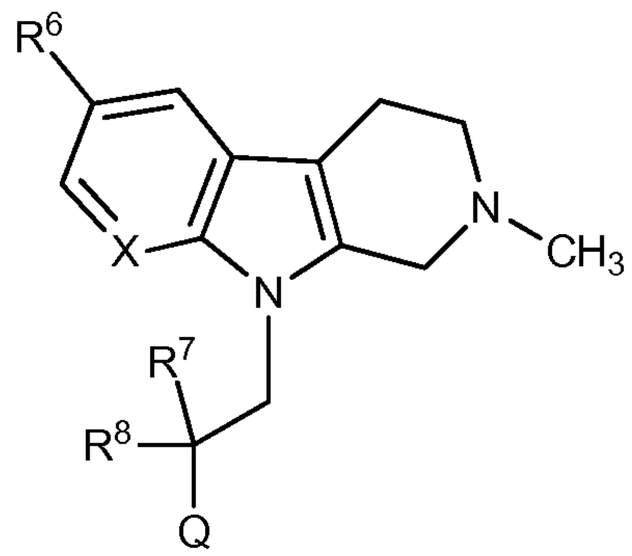

(K-IB)

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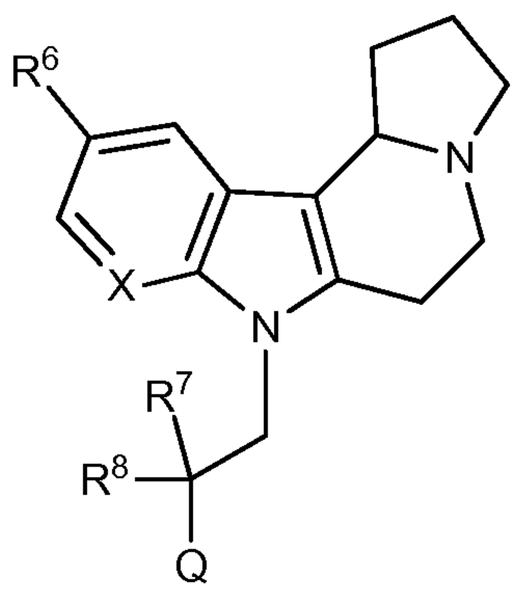
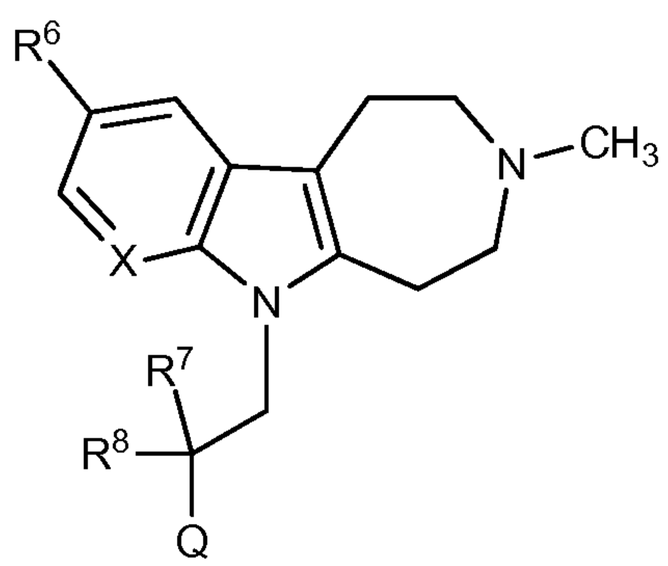


(K-IC)

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.

[0551] 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 No. 3, 4, 13, 39, 41, 129, or 144 (Table I); or II-132, II-138, II-139, or II-140 (Table II).

[0552] 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 No. 5, 14, 26, 29, 31, 148, 173, 174, or 176 (Table I); or II-148 (Table II).

[0553] 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 No. 27, 150, 151, or 154 (Table I); or II-4, II-7, II-13, or II-260 (Table II).

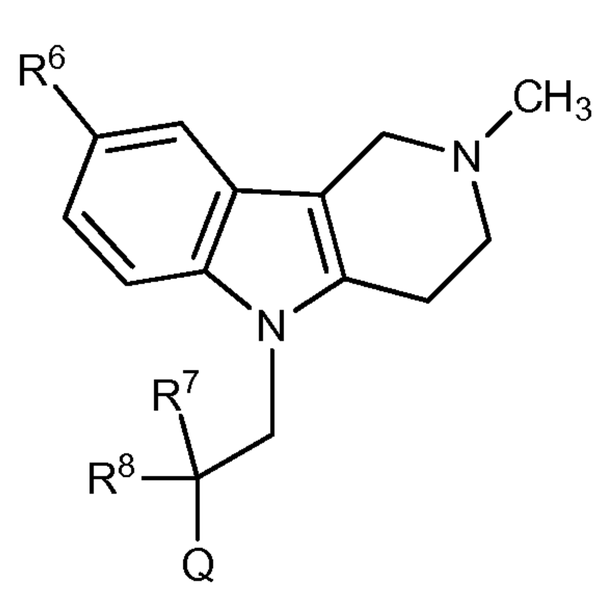
[0554] In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); each R^7 and R^8 is H. In one embodiment, the compound is Compound 74, 134, or II-244 (Table I and II).

[0555] 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).

[0556] 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 No. 141.

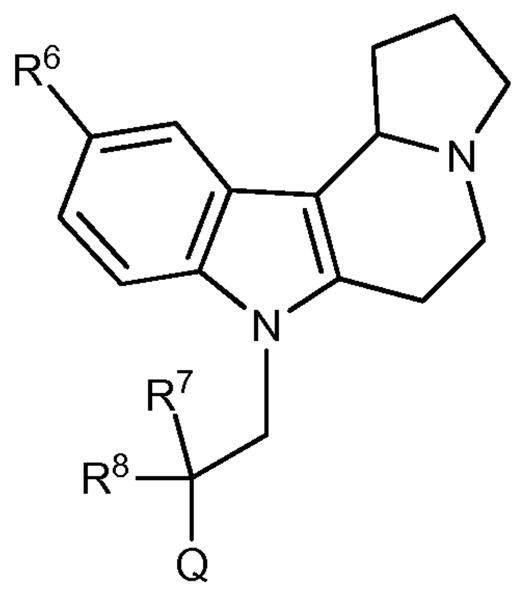
[0557] In certain embodiments, with respect to the compounds of formula (K-IA), (K-IB), (K-IC) or (K-ID); R^7 is 3,3-dimethyl-2-hydroxybutyl. In one embodiment, the compound is Compound II-227 (Table II).

[0558] 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.

[0559] 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 No. 129 (Table I); or II-131 (Table II).

[0560] 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).

[0561] In certain embodiments, with respect to the compounds of formula (K-IE), or (K-IF); $N(CH_3)_2$. In one embodiment, the compound is Compound II-6 (Table II).

[0562] In one embodiment, the compound is Compound II-123 (Table II).

[0563] In one embodiment, the compound is Compound No. 325 (Table I).

[0564] 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.

[0565] 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.

[0566] 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.

[0567] 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 $-OC(O)N(CH_3)_2$.

[0568] 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.

[0569] 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.

[0570] 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.

[0571] In certain embodiments, with respect to the compounds of formula (A-IIIE-6), and Q is triazolyl, or imidazolyl.

[0572] 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.

[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^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.

[0574] 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.

[0575] 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.

[0576] 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.

[0577] 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.

[0578] 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.

[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), (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.

[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 (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.

[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), Q is phenyl substituted with methyl, ethyl, F, Cl, OCH_3, or CF_3.

[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), Q is optionally substituted pyridyl, or optionally substituted pyrimidinyl.

[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), (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.

[0584] 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.

[0585] 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.

[0586] 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.

[0587] 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.

[0588] 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.

[0589] 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.

[0590] 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.

[0591] 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.

[0592] 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.

[0593] 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.

[0594] 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.

[0595] In another embodiment, the invention relates to Compound No. 129d and uses thereof.

[0596] In one embodiment, the invention relates to Compound Nos. 325, 129d, 130a, II-121b, II-123b, II-127a, II-128b, II-130a, II-131, and II-6b, and uses thereof.

[0597] In one embodiment, the invention relates to Compound Nos. 18, 18a, 18b, 30a, 30b, 54, 54a, 54b, 90a, 90b, 129, 129a, 129b, 129c, 129d, 130, 130a, 130b, 142, 142a, 142b, 168, 168a, 168b, 168c, 168d, 169, 169a, 169b, 179, 179a, 179b, 183a, 183b, 187, 188, 189, 190, 191, 193, 193a, 193b, 194a, 194b, 196a, 196b, 197, 197a, 197b, 198, 198a, 198b, 199a, 199b, 203a, 203b, 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, 338, 338a, 338b, 339, 339a, 339b.

[0598] 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.

[0599] 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, 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.

[0600] 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, 180

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.

[0601] 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.

[0602] In another embodiment, the invention relates to one or more of the Compounds described in Table 3, and uses thereof.

[0603] In another embodiment, the invention relates to one or more of the Compounds described in Table 4, and uses thereof.

[0604] In another embodiment, the invention relates to one or more of the Compounds described in Table 5, and uses thereof.

[0605] 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 increase insulin secretion and treat diseases or conditions that are, or are expected to be, responsive to an increase in insulin production, or to treat type 2 diabetes.

[0606] The embodiments and variations described herein are suitable for compounds of any formulae detailed herein, where applicable.

[0607] 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.

[0608] 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.

[0609] 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.

[0610] 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.

[0611] 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.

[0612] 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.

[0613] 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 indication for which enhancing insulin secretion and/or promoting insulin release is expected to be or is beneficial.

[0614] 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.

[0615] In one aspect, an adrenergic receptor α_{2A} antagonist as provided herein exhibits the ability to cross the blood-brain barrier. In another aspect, an adrenergic receptor α_{2A} antagonist as provided herein is not able to cross the blood-brain barrier. In one aspect, an adrenergic receptor α_{2A} antagonist as provided herein exerts its therapeutic effect in the brain only. In one aspect, an adrenergic receptor α_{2A} antagonist as provided herein exerts its therapeutic effect in the periphery only. In one aspect, an adrenergic receptor α_{2A} antagonist as provided herein exerts its therapeutic effect both in the brain and peripherally. In some embodiments, the adrenergic receptor α_{2A} antagonist also exhibits adrenergic receptor α_{2A} inverse agonist activity.

[0616] Blood brain barrier permeability can be measured in rodents or dog by administering the compound orally or intravenously, recovering a blood and brain tissue sample at different time points and comparing how much compound is in each sample. Blood fraction is typically processed to plasma for determination of compound content. Brain exposure can be described from the ratio of brain to plasma levels of drug. In one variation, a compound that poorly crosses the blood brain barrier has a brain to plasma ratio of compound of about 0.1 or less. In another

variation, the compound has a brain to plasma ratio of about 0.2 or less, about 0.3 or less, about 0.4 or less, about 0.5 or less, about 0.8 or less, or about 1.0 or less.

[0617] Preferably, the compounds provided herein are orally bioavailable. However, the compounds may also be formulated for parenteral (*e.g.*, intravenous) administration. In some settings, parenteral administration may be desired.

[0618] 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 pharmaceutically 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.*, increasing insulin secretion of an individual or treating or delaying the onset and/or development of type 2 diabetes, glucose intolerance or metabolic syndrome.

[0619] 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.

[0620] 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.

[0621] 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.

[0622] 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.

[0623] 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.

[0624] 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.

[0625] 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.

[0626] 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 diabetes type 2 and/or a disease or condition which is responsive, or expected to be responsive, to an increase in insulin secretion.

[0627] 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.

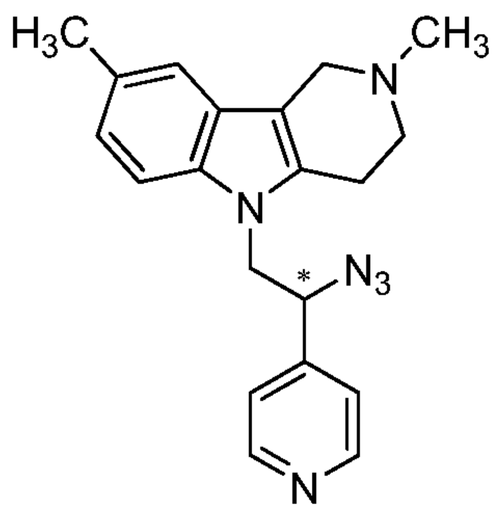
[0628] The kits may be in unit dosage forms, bulk packages (*e.g.*, multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as disclosed herein and/or a second pharmaceutically active compound useful for a disease detailed herein (e.g., type 2 diabetes) 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).

[0629] 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.

[0630] 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 diabetes type 2 and/or a disease or condition which is responsive, or expected to be responsive, to an increase in insulin secretion 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., type 2 diabetes).

[0631] 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.

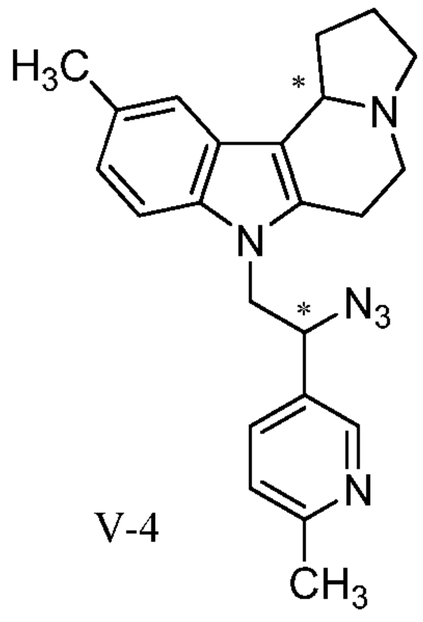


V-1

⟹ Enantiomers V-1a and V-1b

* = chiral center

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.



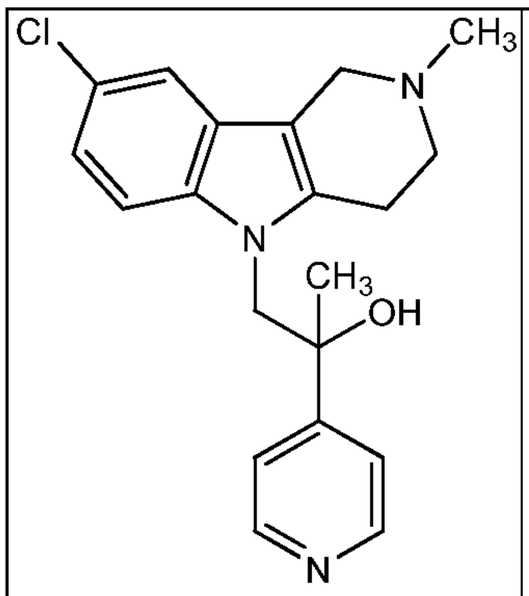
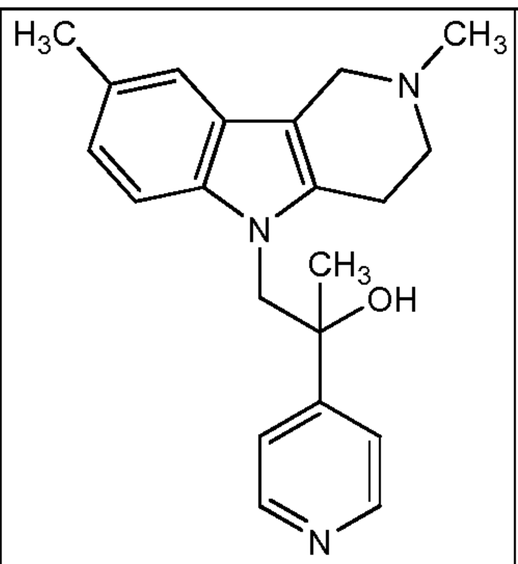
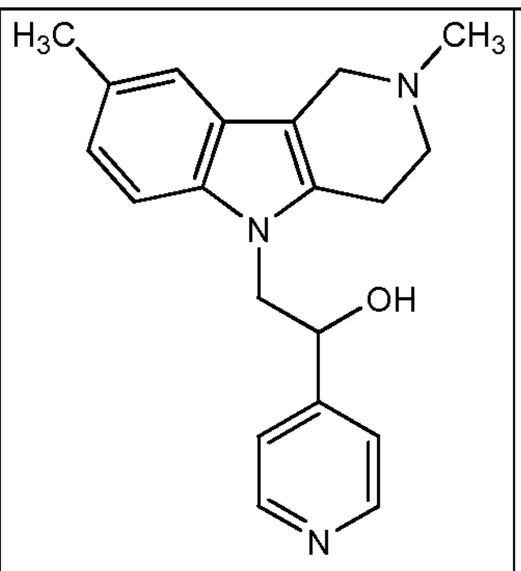
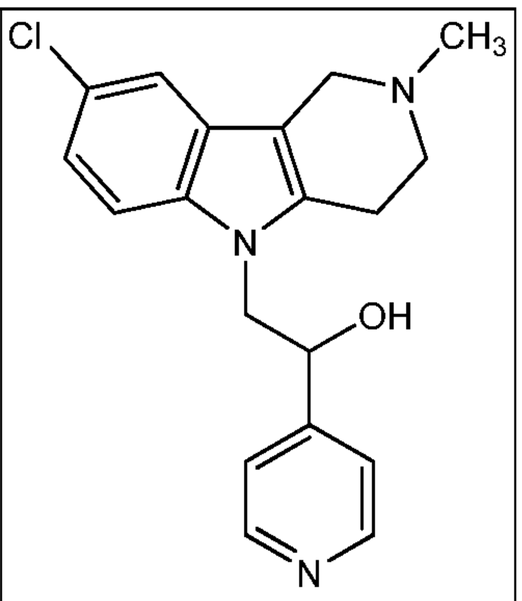
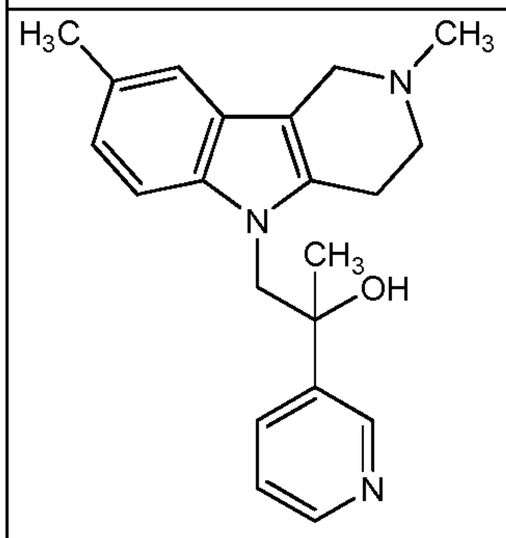
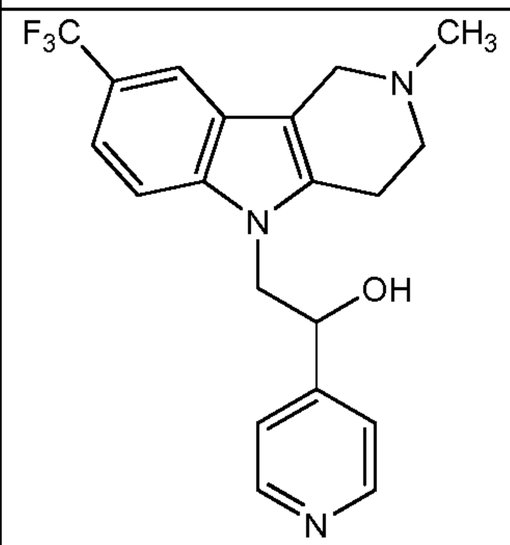
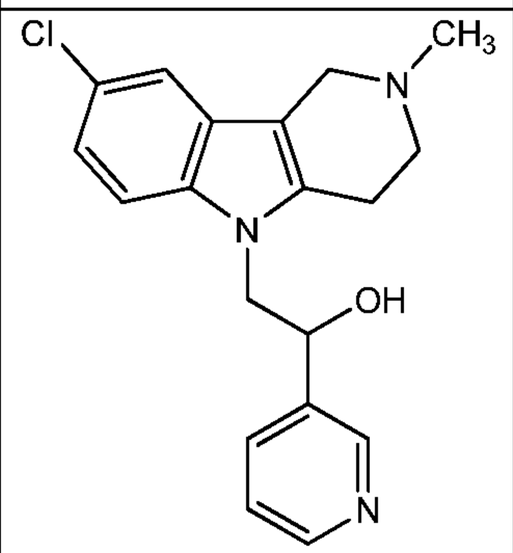
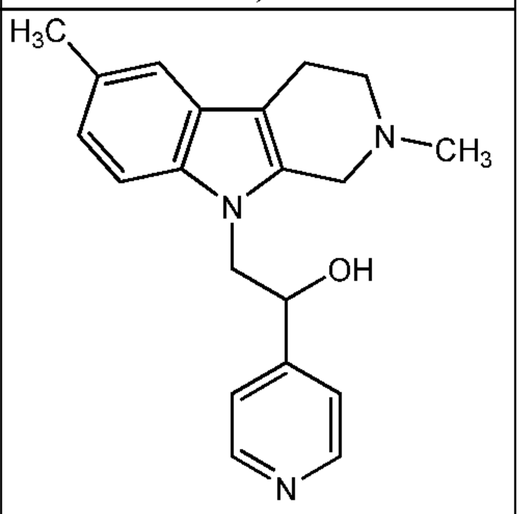
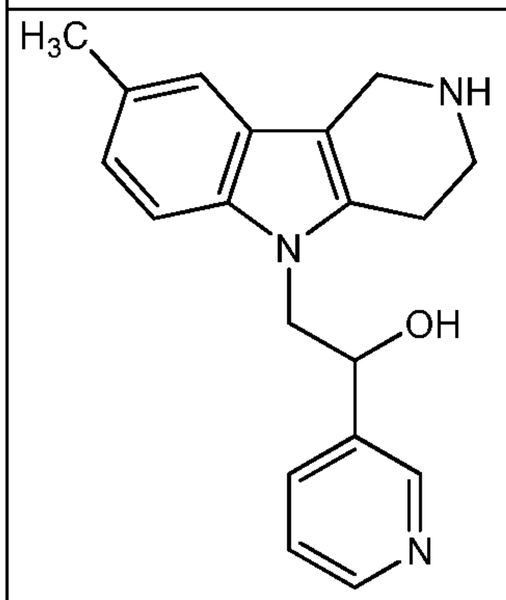
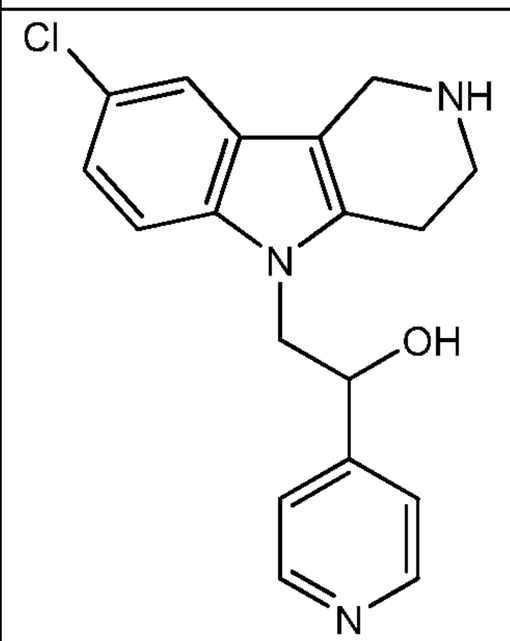
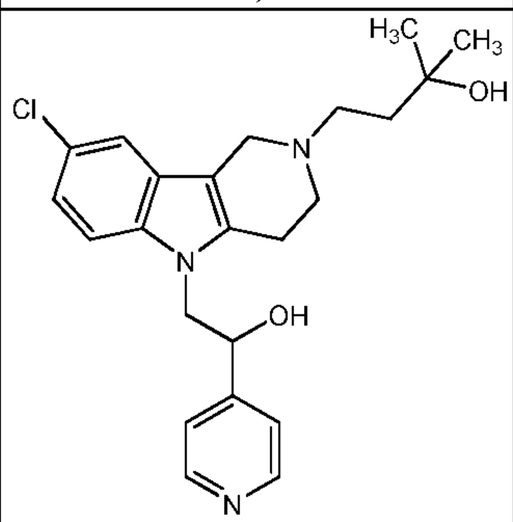
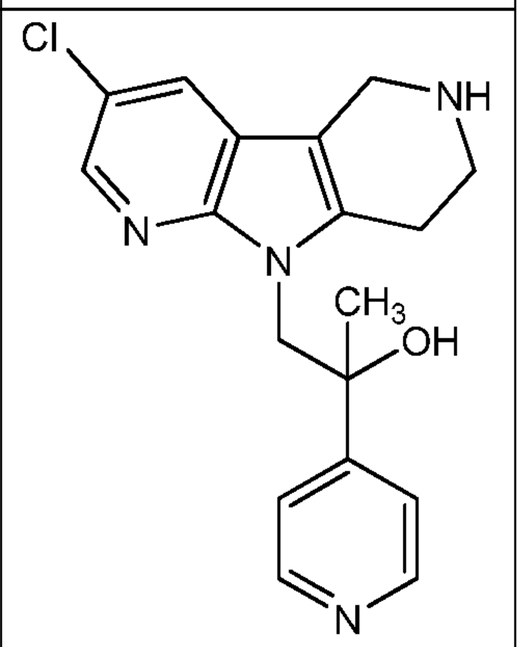
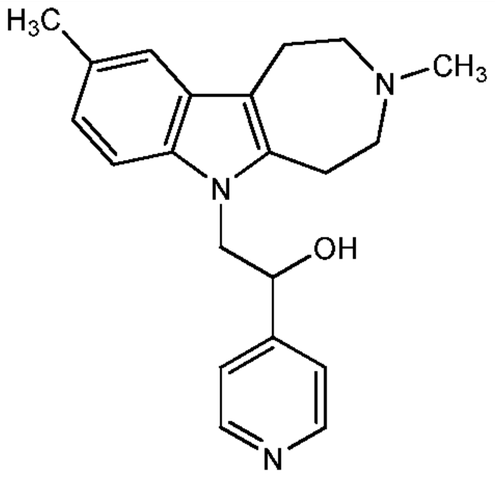
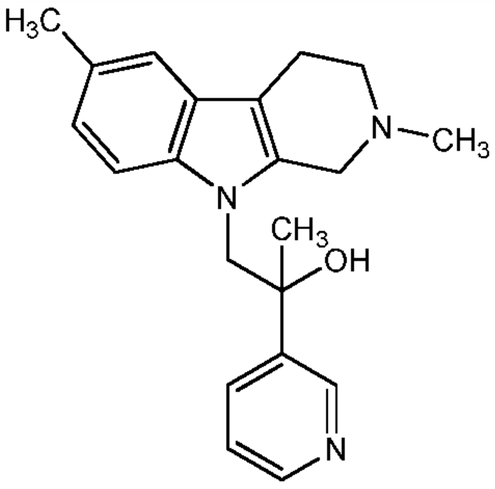
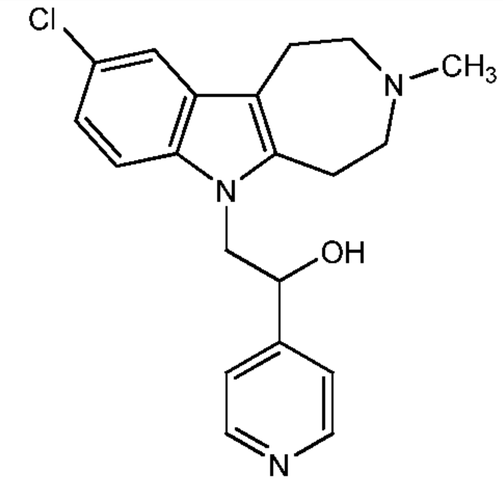
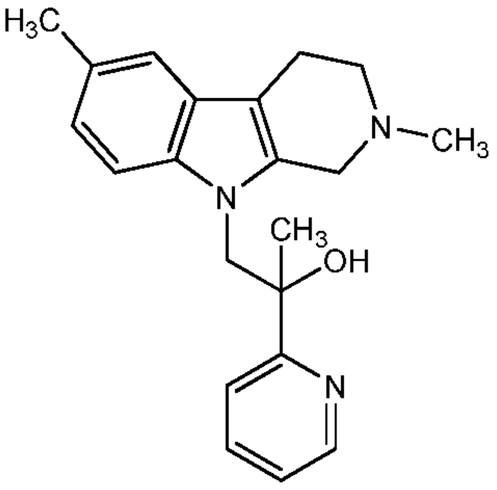
V-4

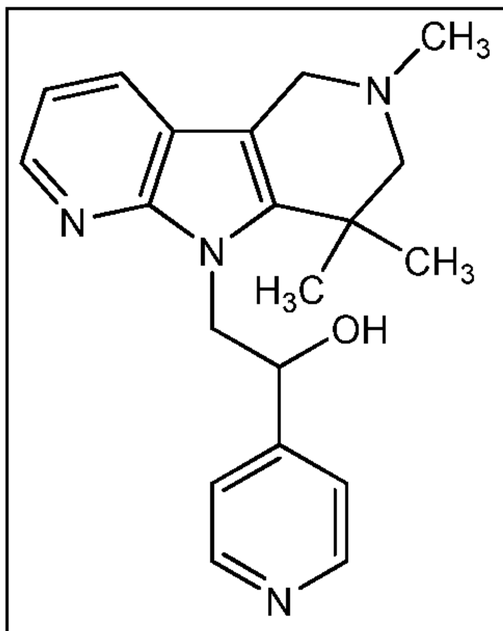
⟹ Diastereomers V-4a, V-4b, V-4c and V-4d

* = chiral center

[0632] Representative compounds of the invention are shown in Tables 1-5.

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



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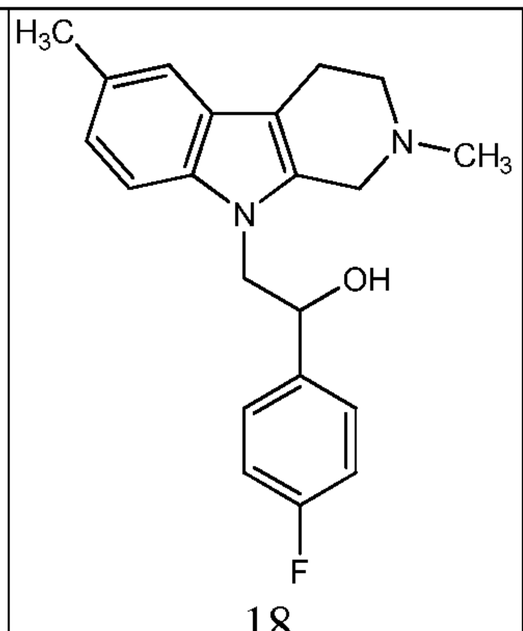

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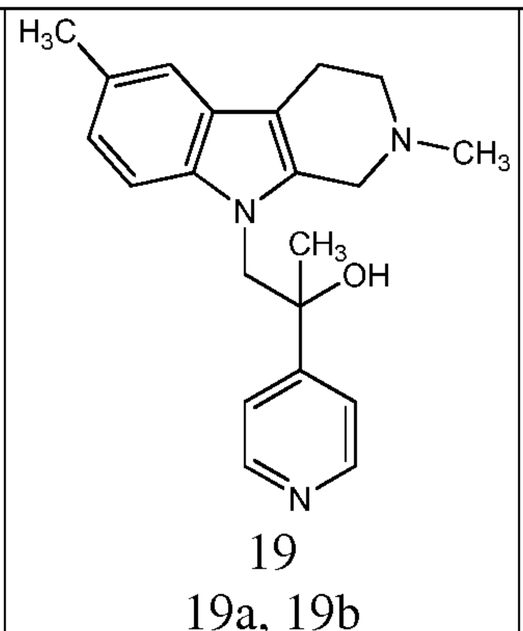

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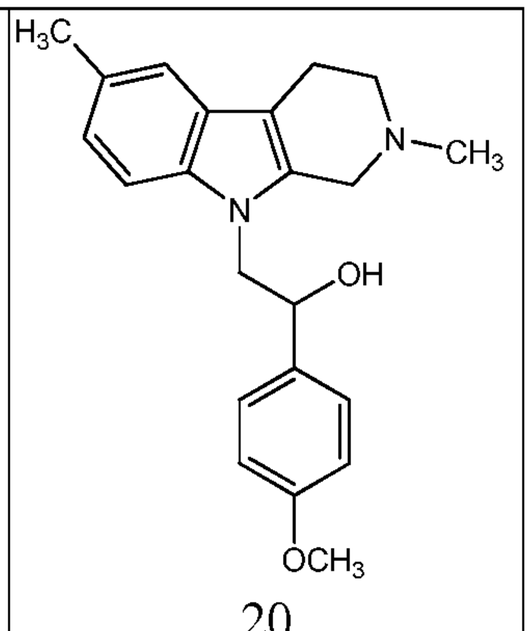

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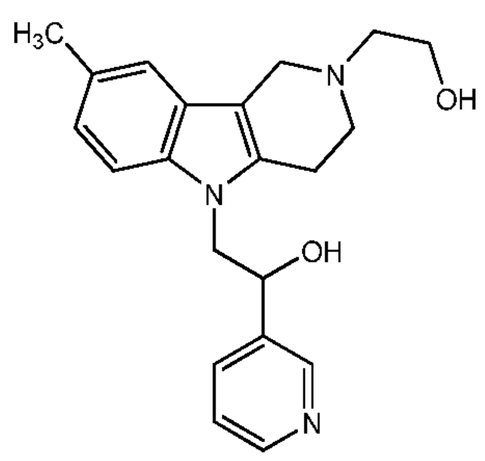

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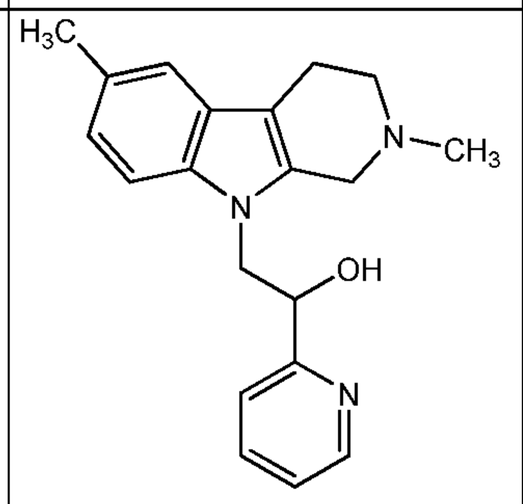

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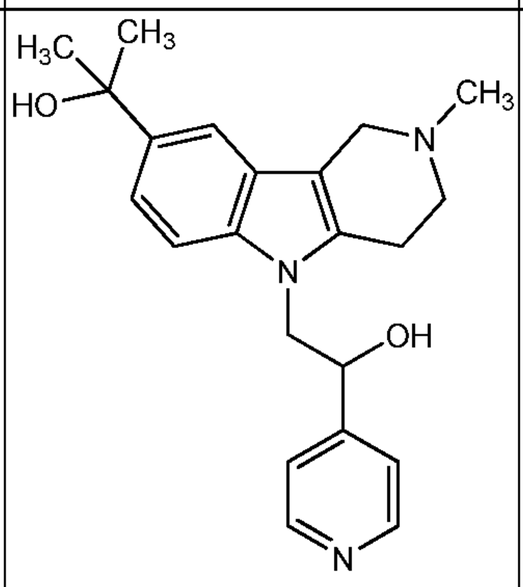

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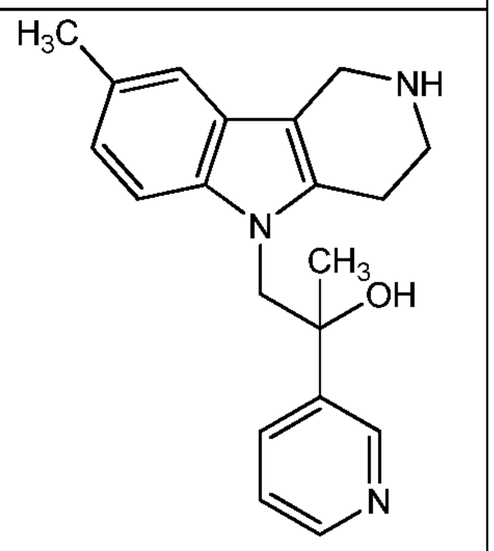

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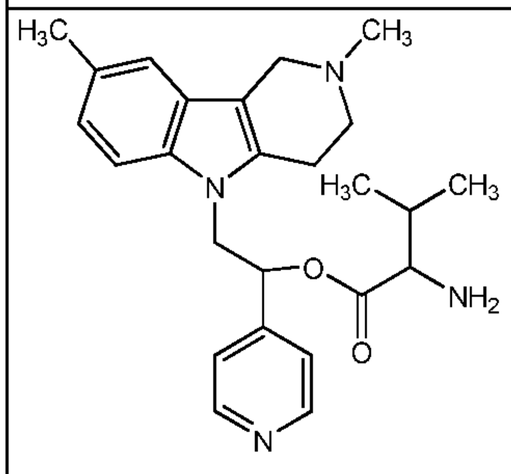

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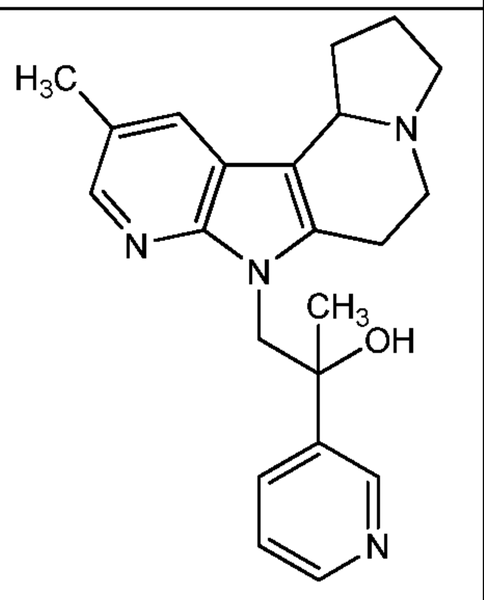

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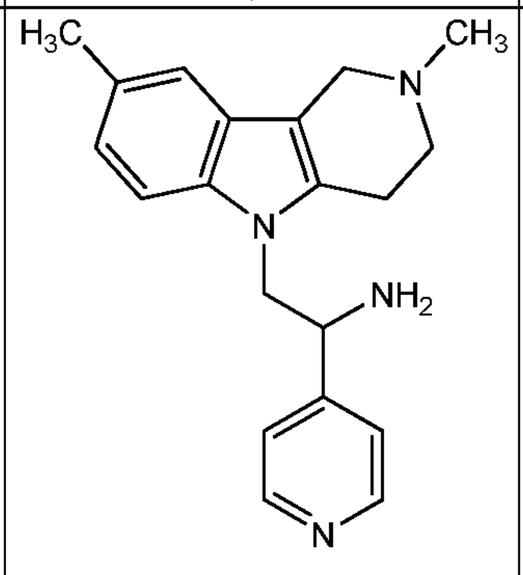

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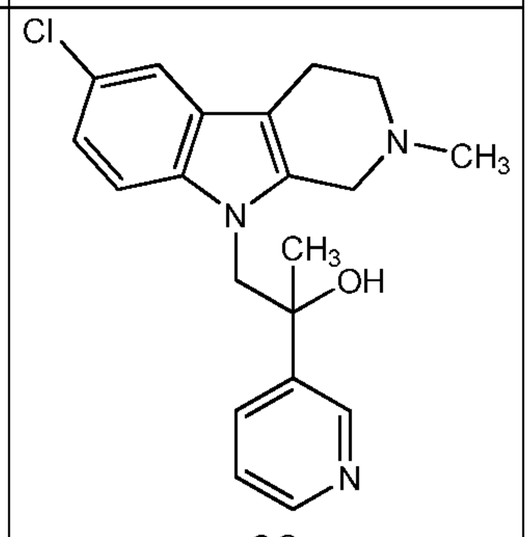

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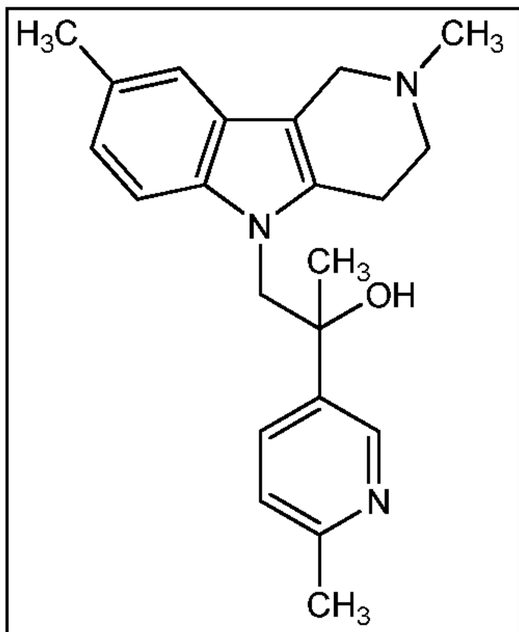

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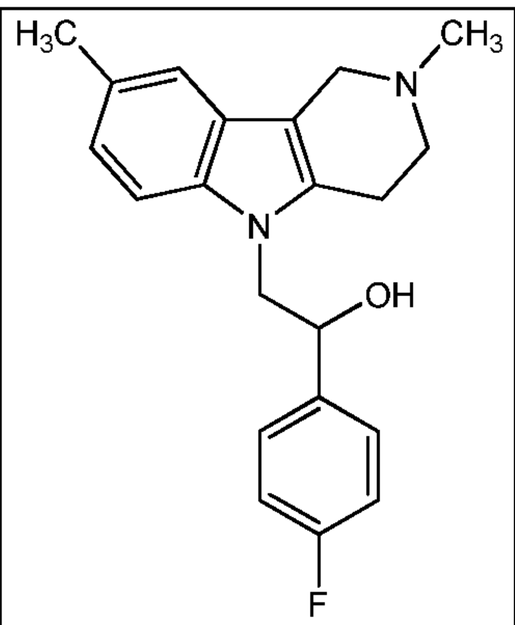

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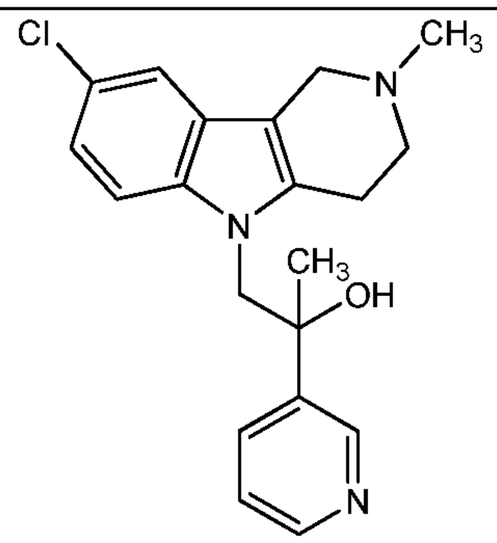

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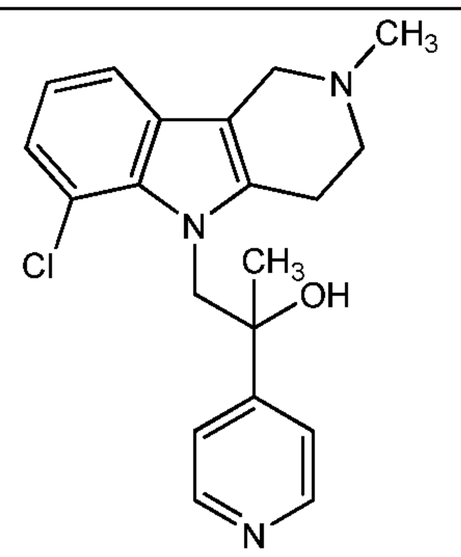

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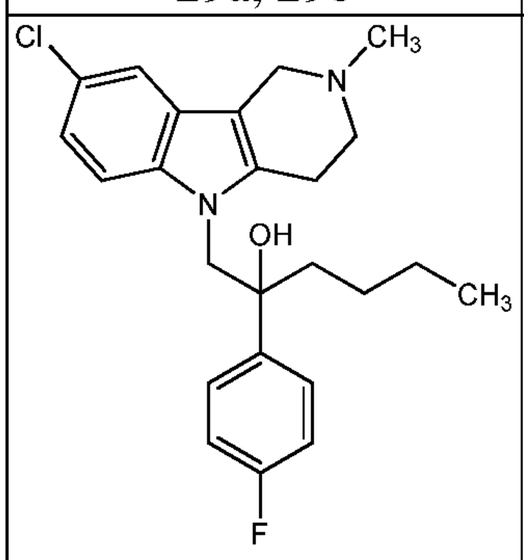

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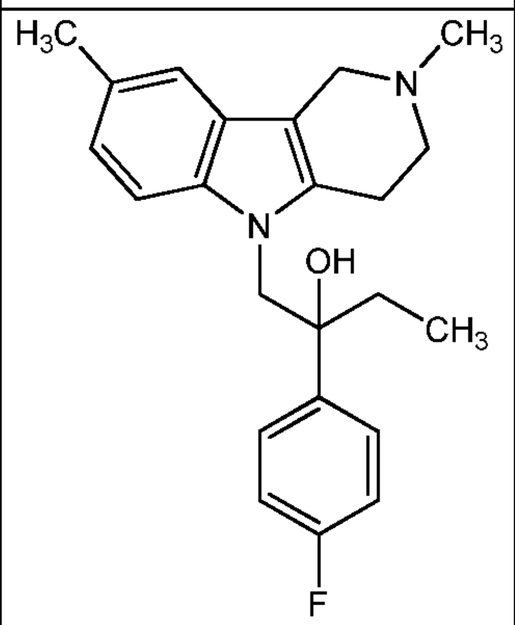

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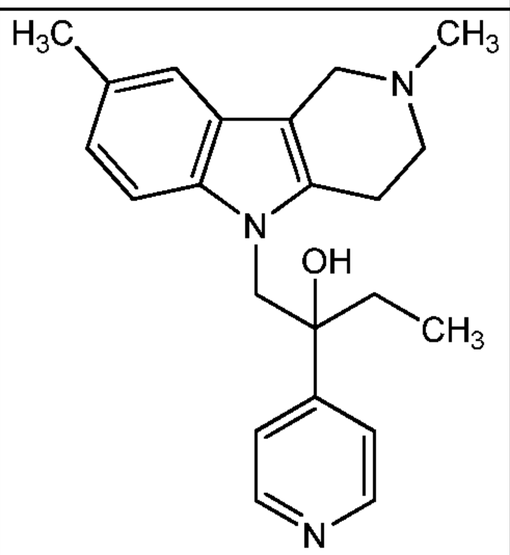

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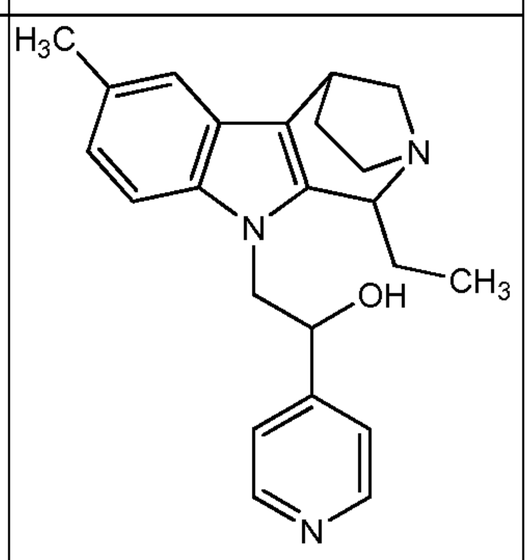

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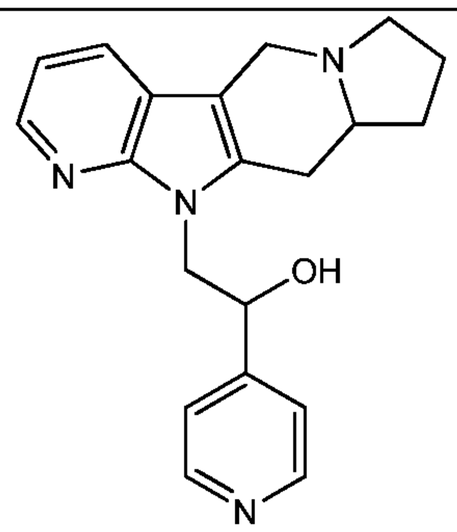

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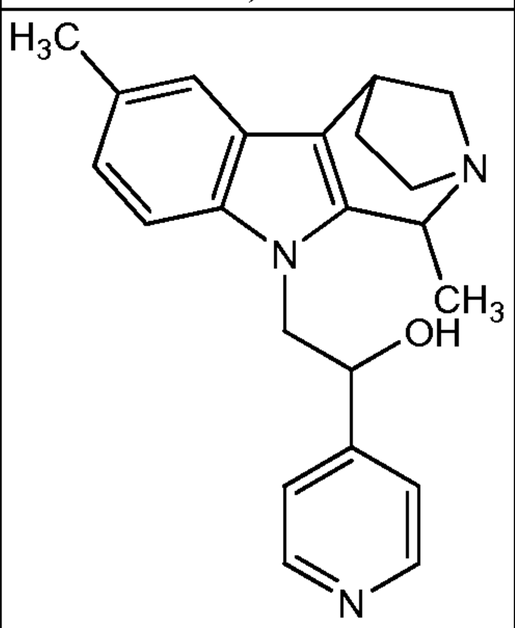

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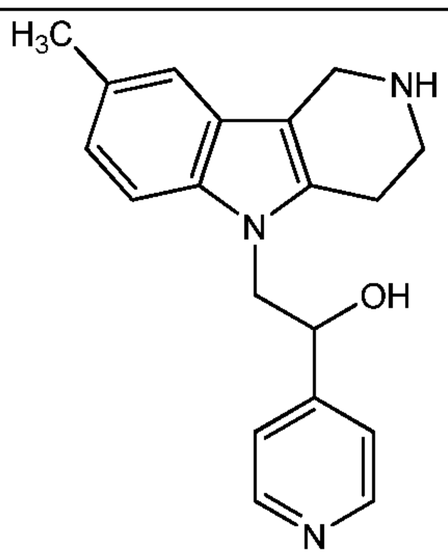

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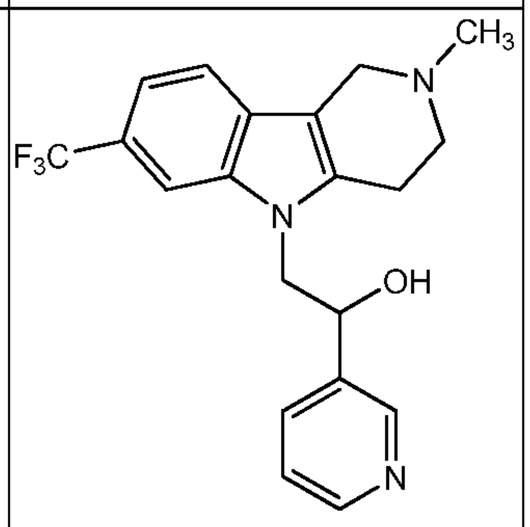

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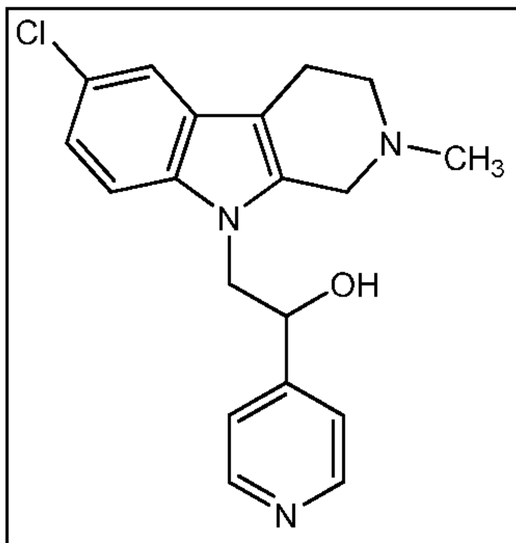

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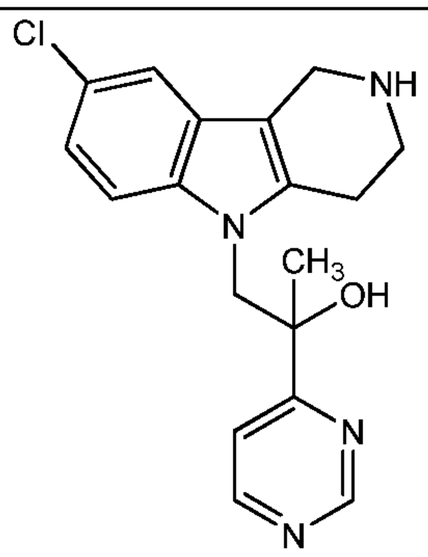

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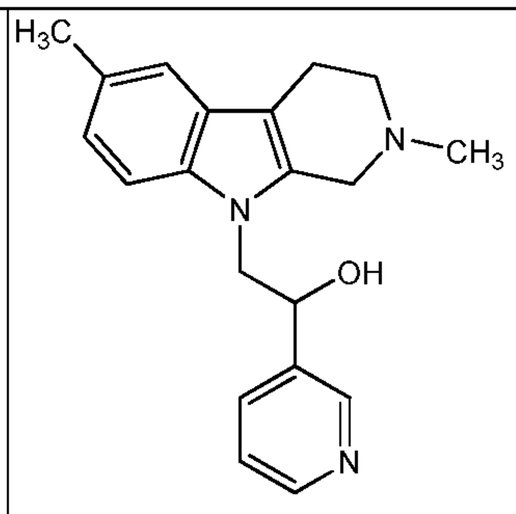

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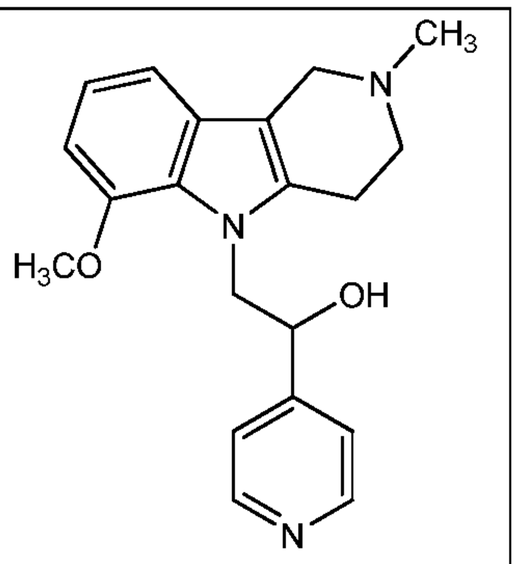

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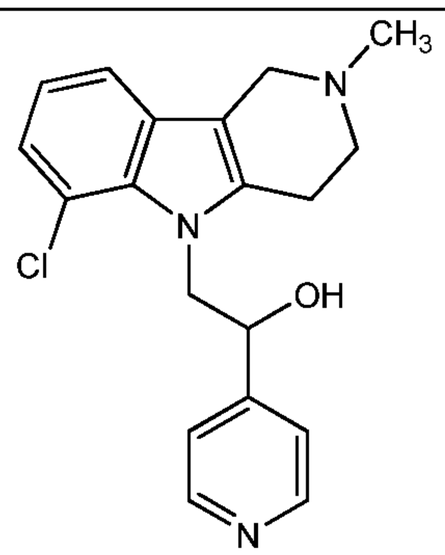

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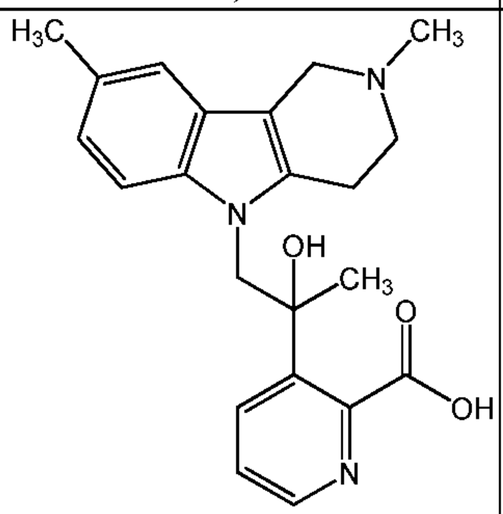

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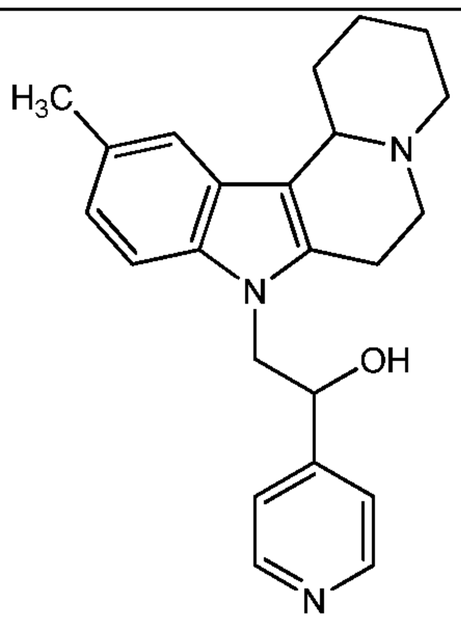

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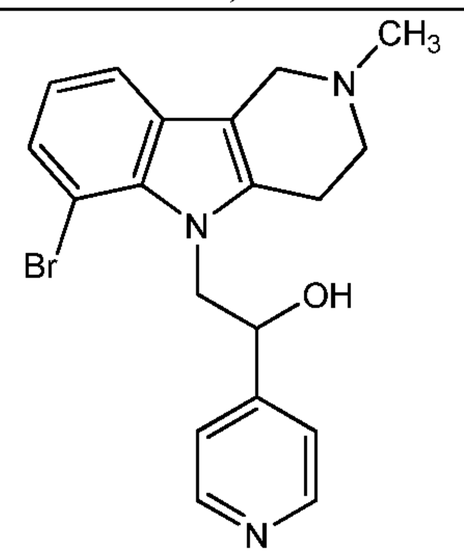

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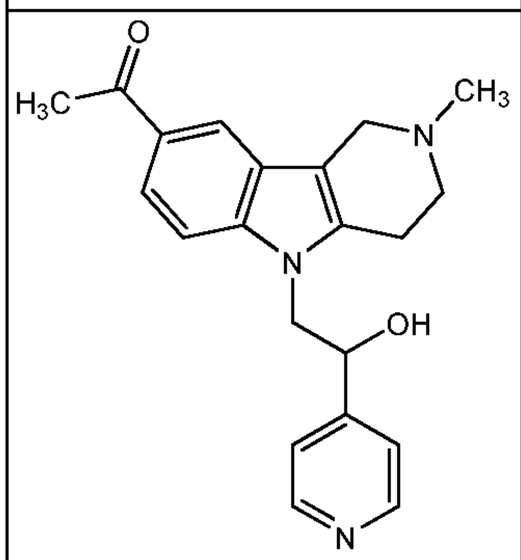

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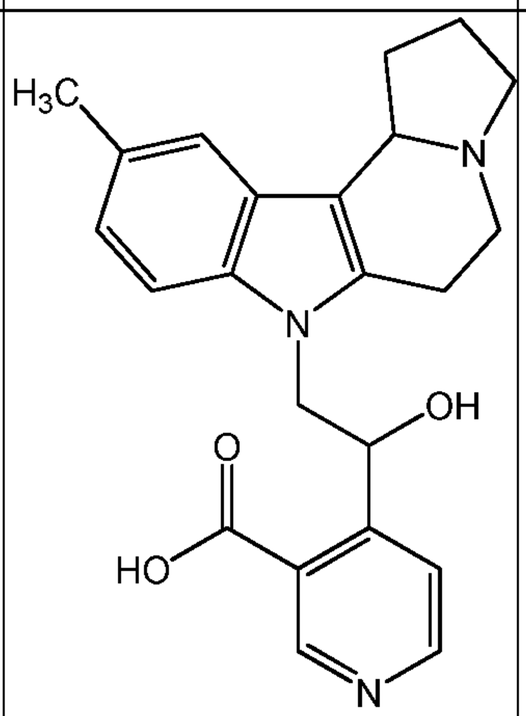

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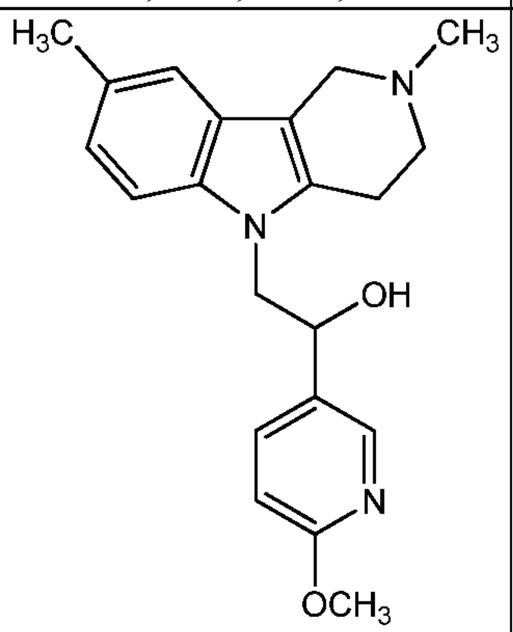

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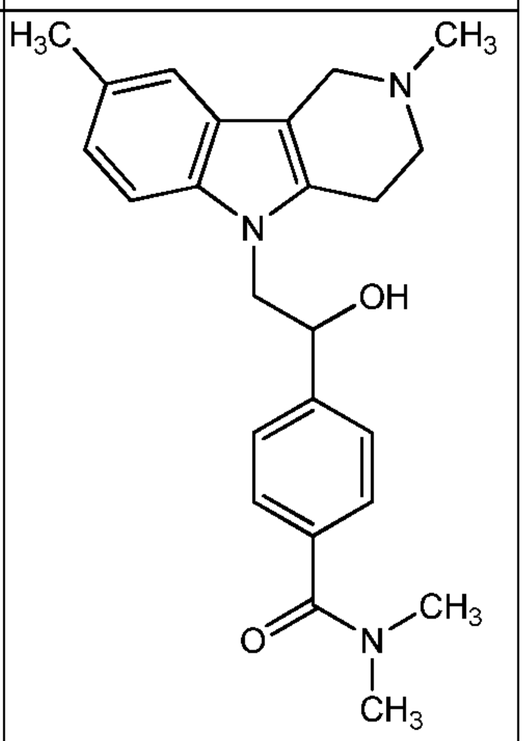

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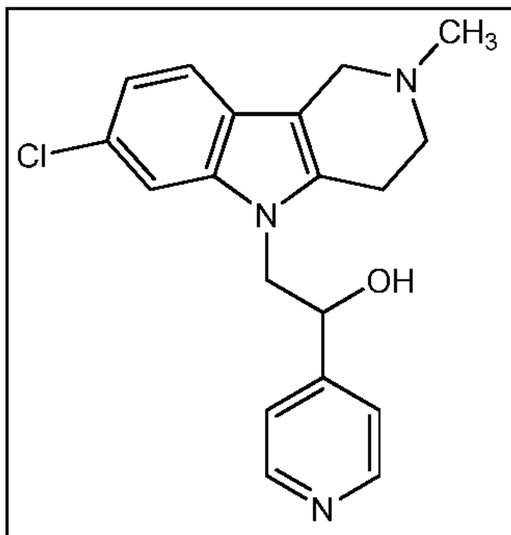

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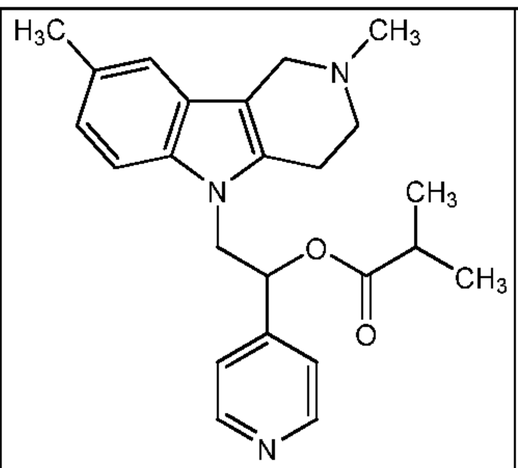

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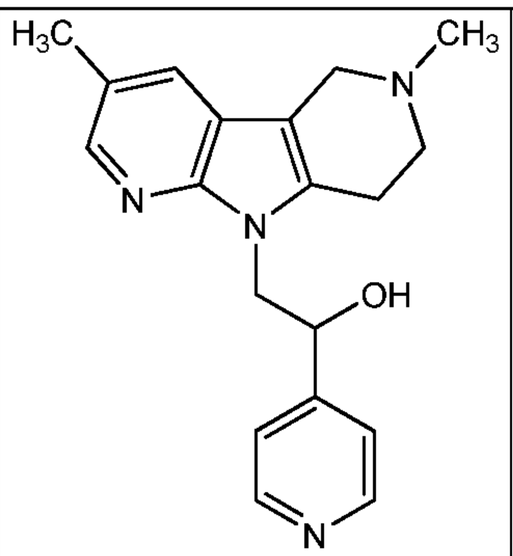

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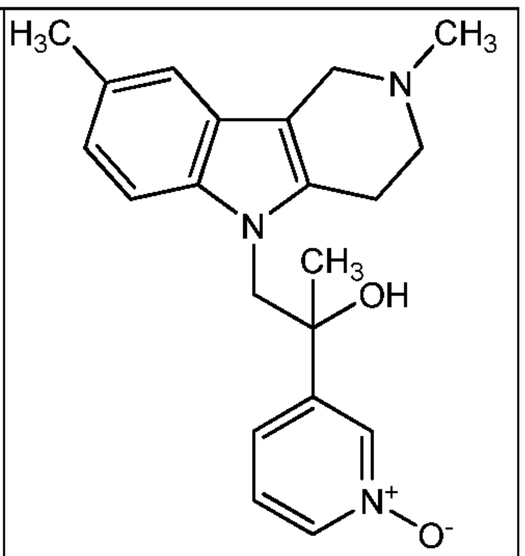

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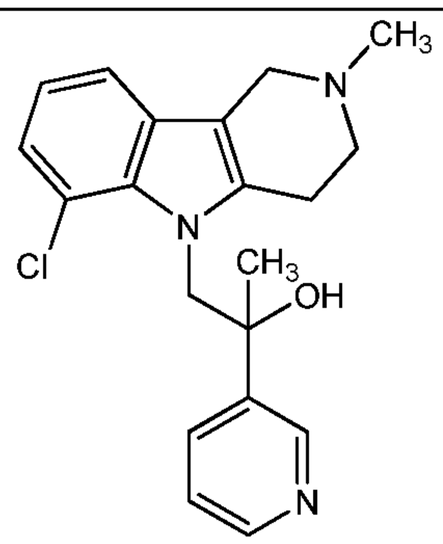

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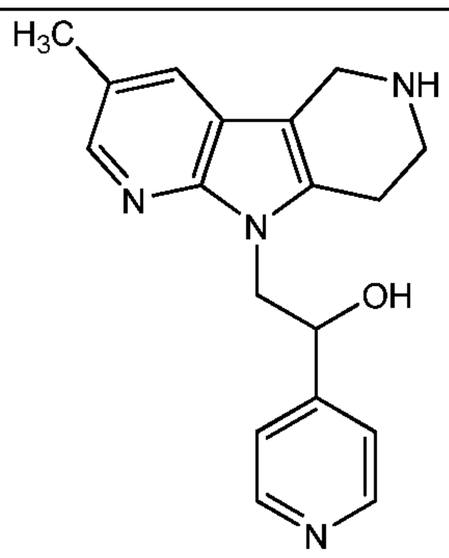

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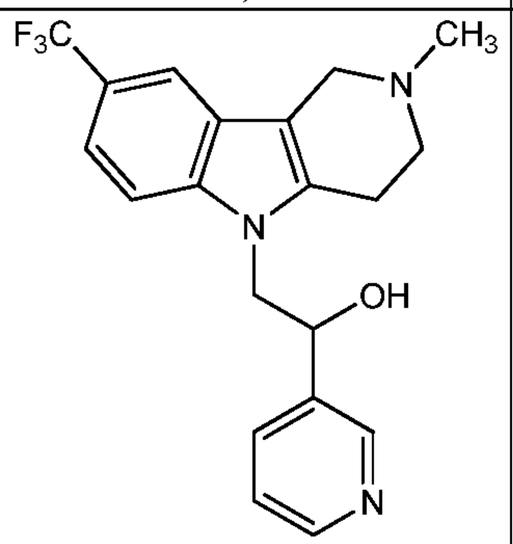

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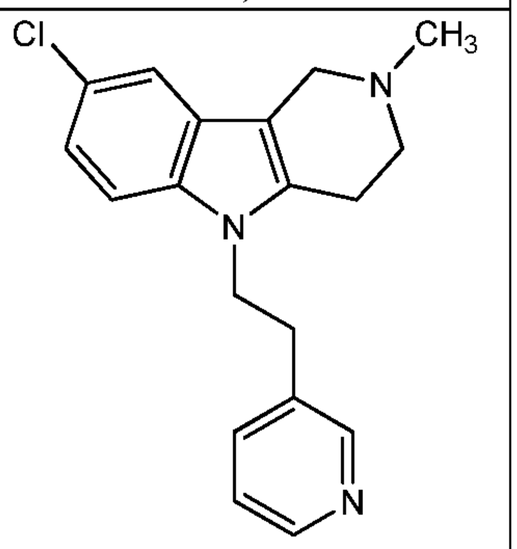

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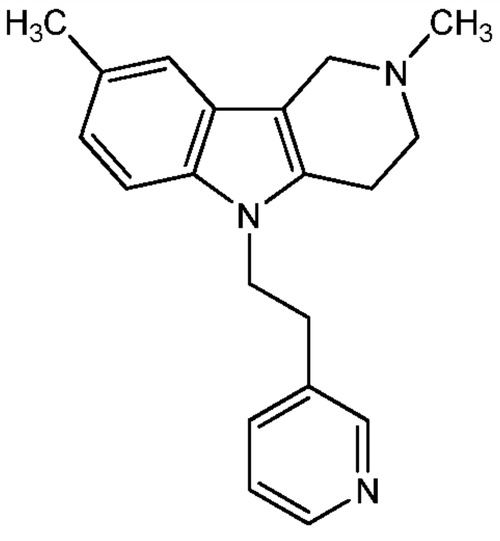

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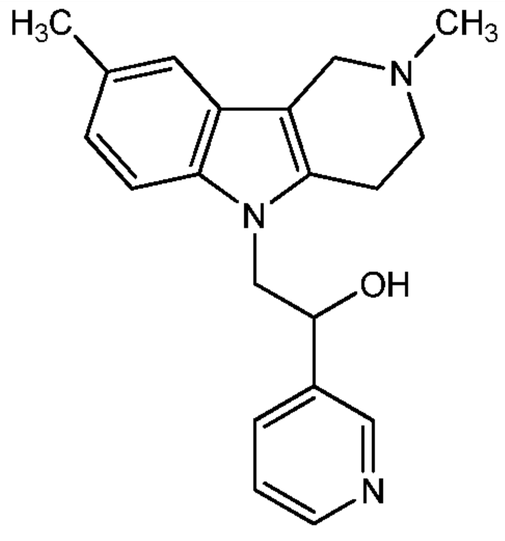

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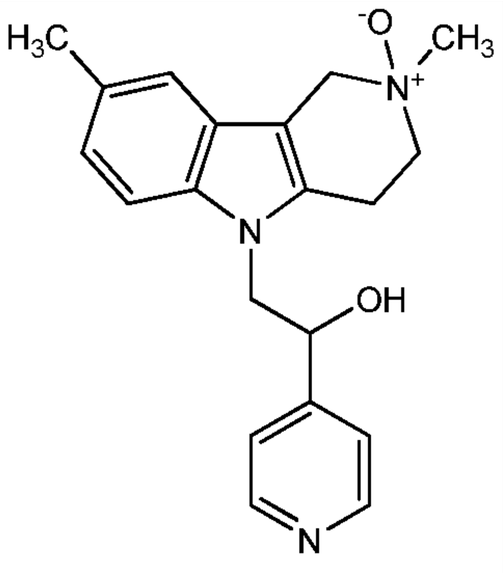

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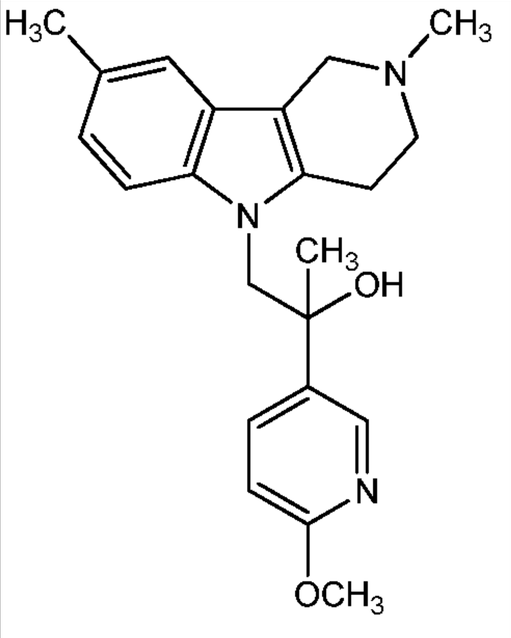

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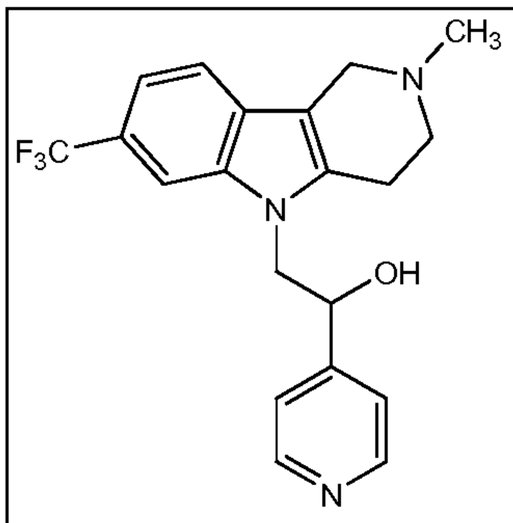

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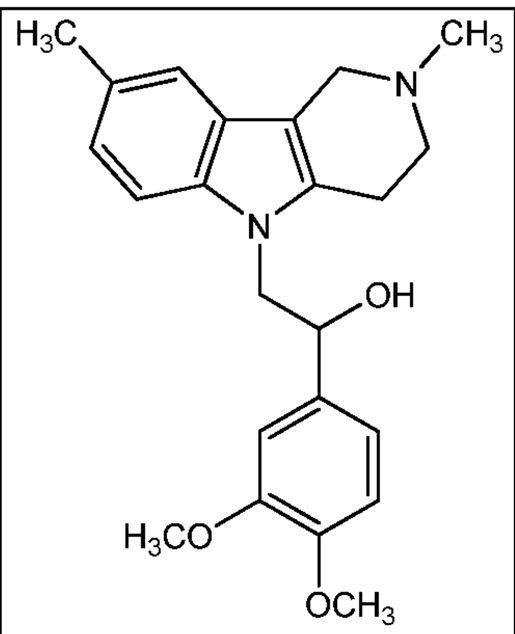

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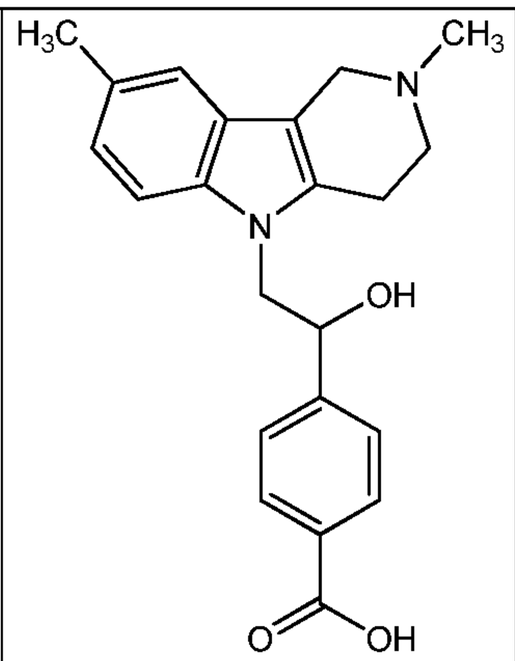

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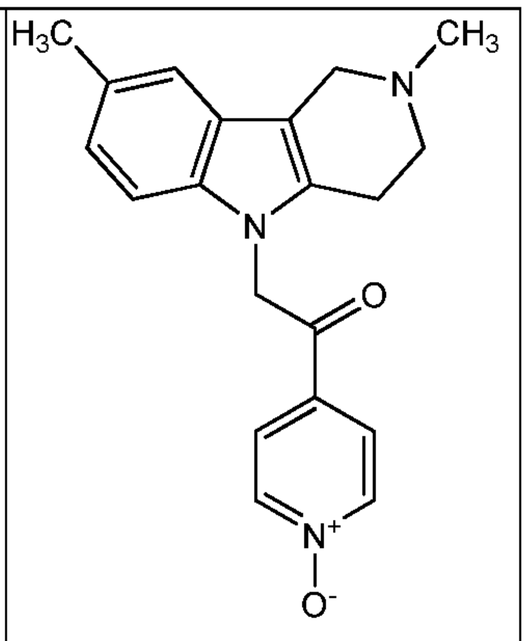

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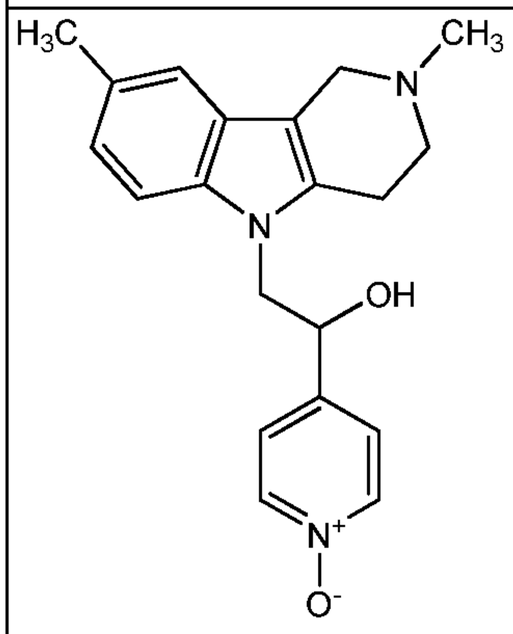

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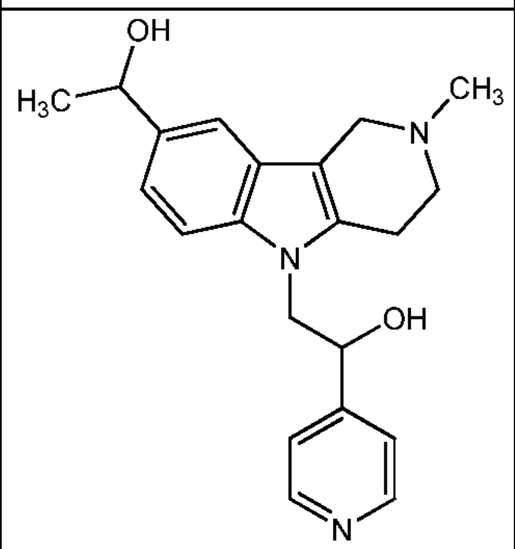

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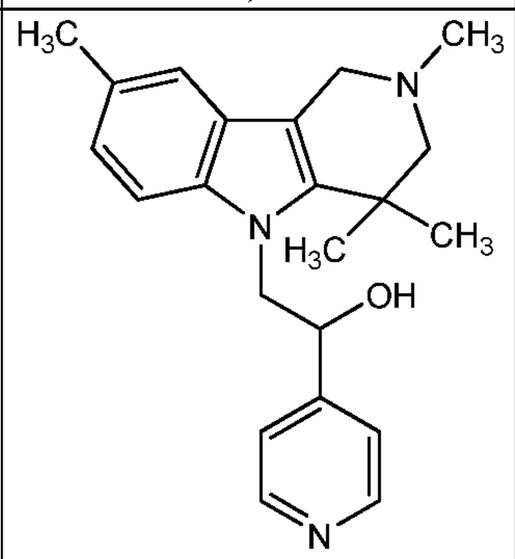

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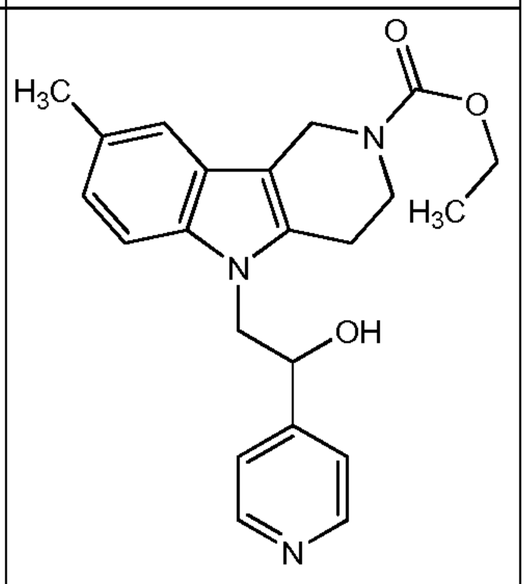

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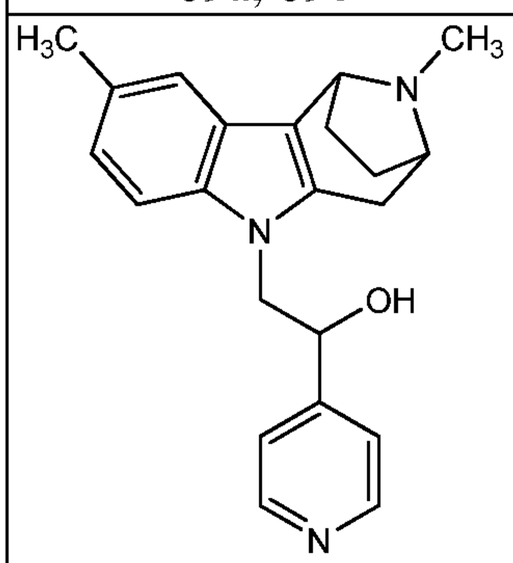

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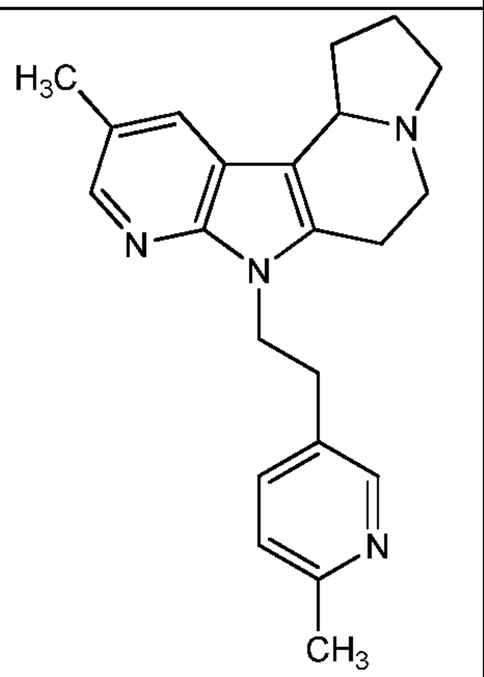

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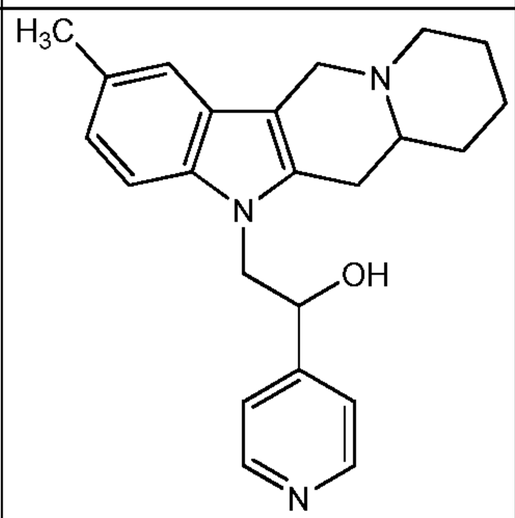

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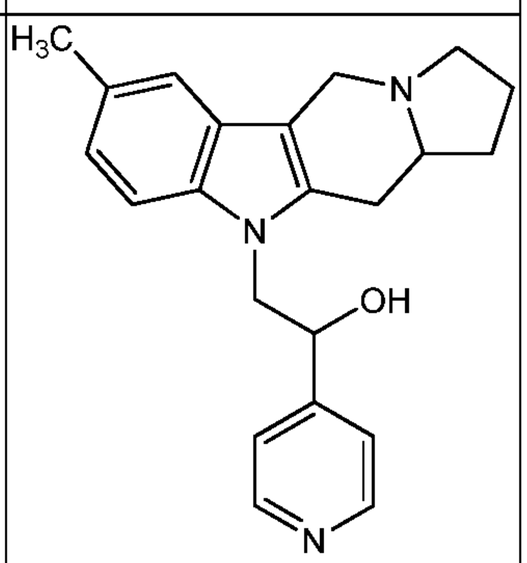

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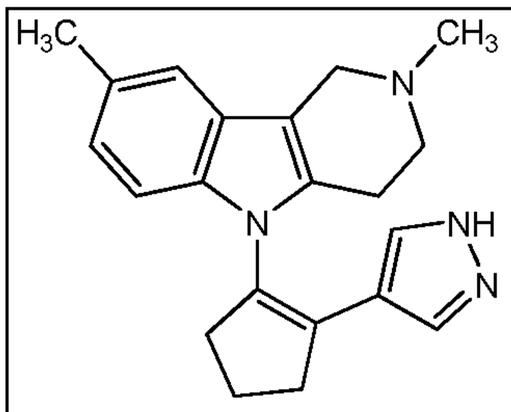

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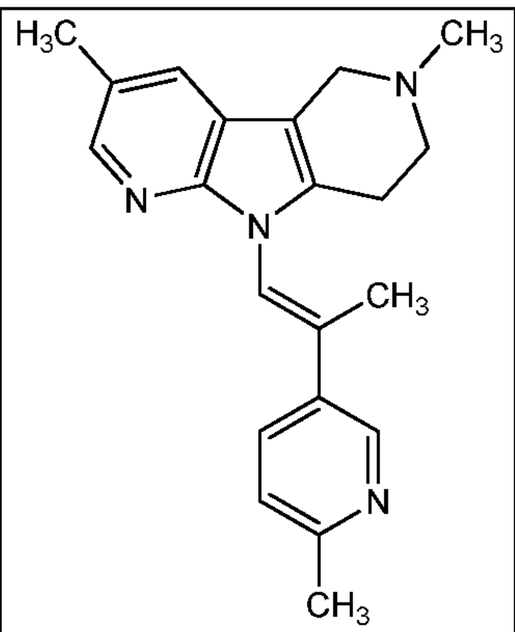

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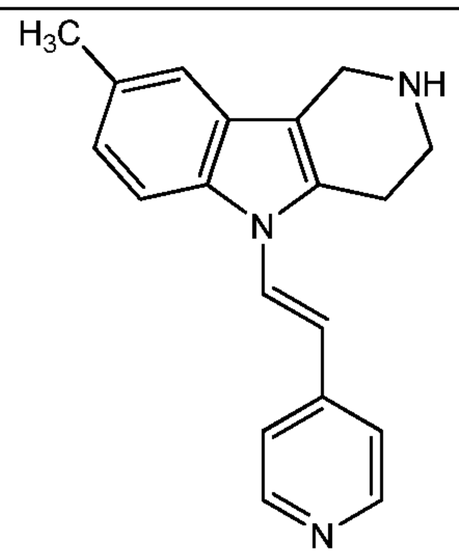

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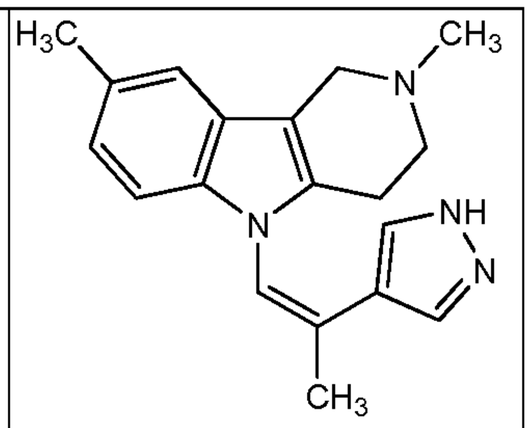

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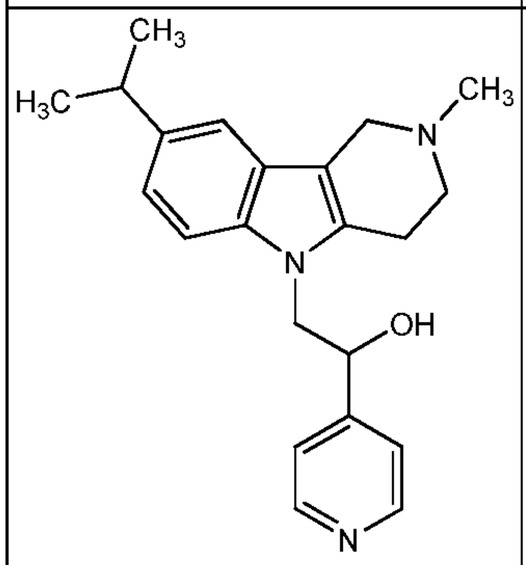

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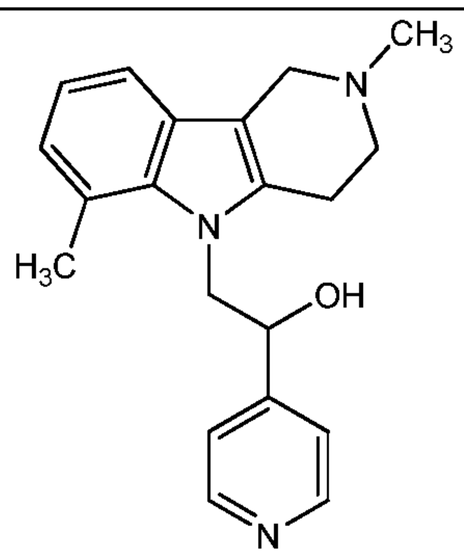

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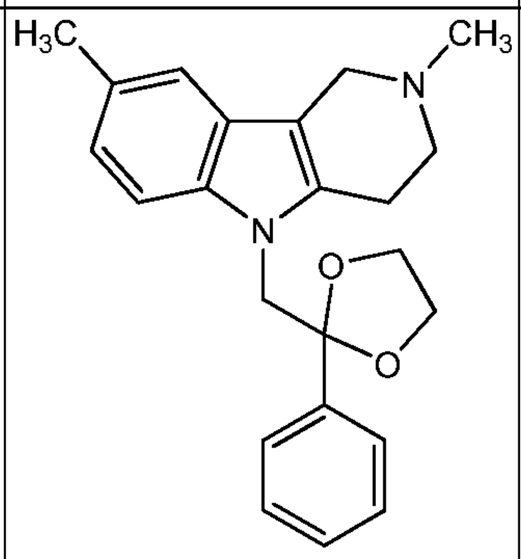

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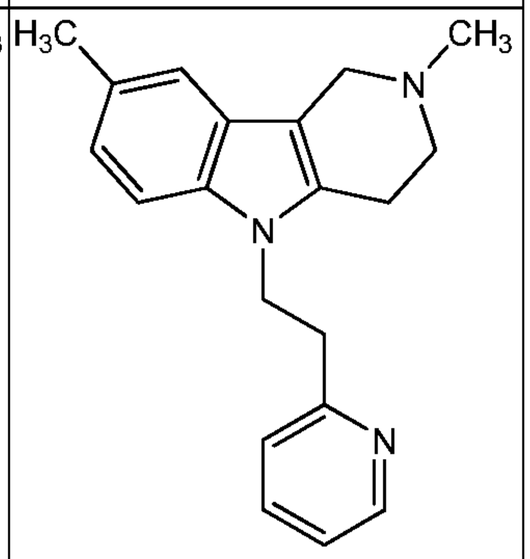

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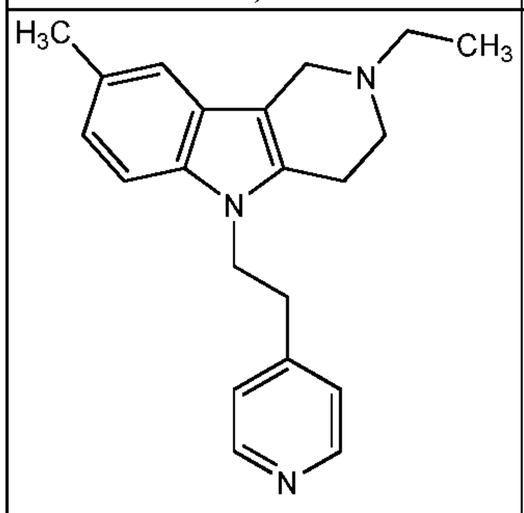

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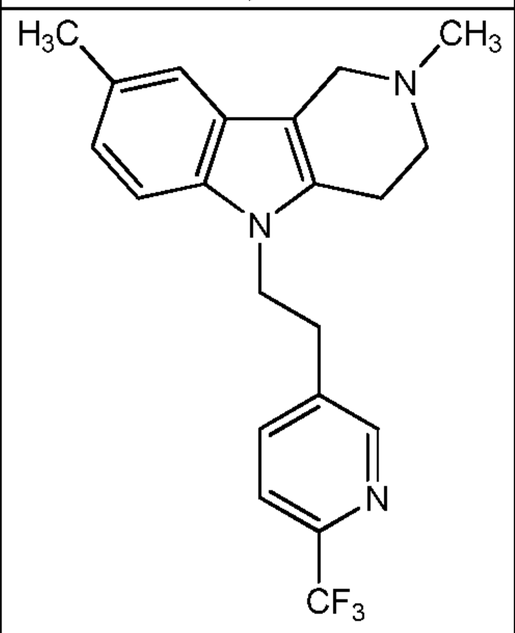

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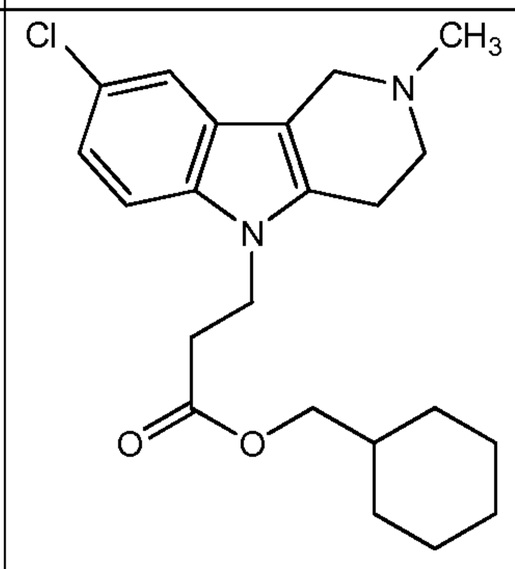

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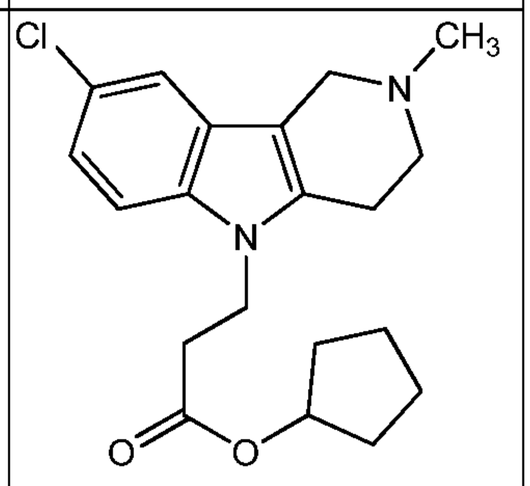

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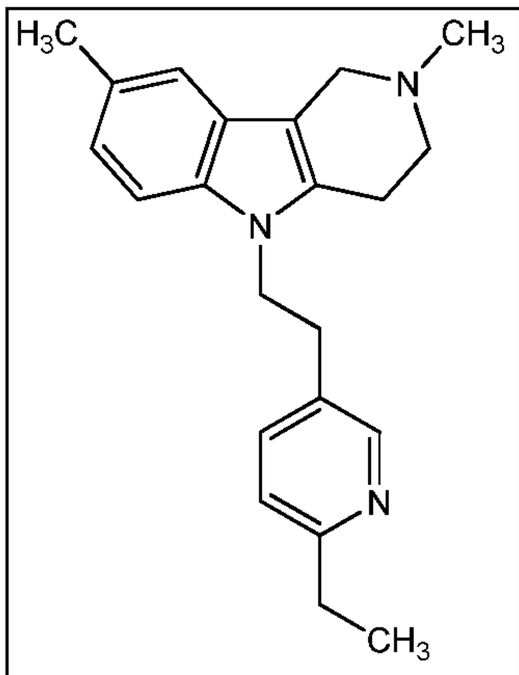

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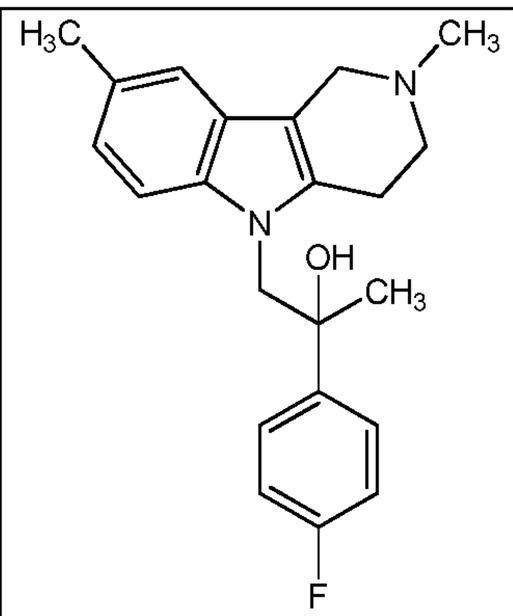

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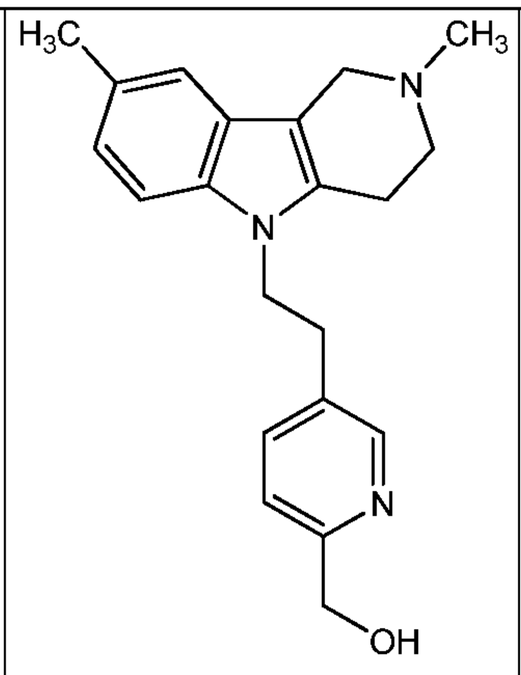

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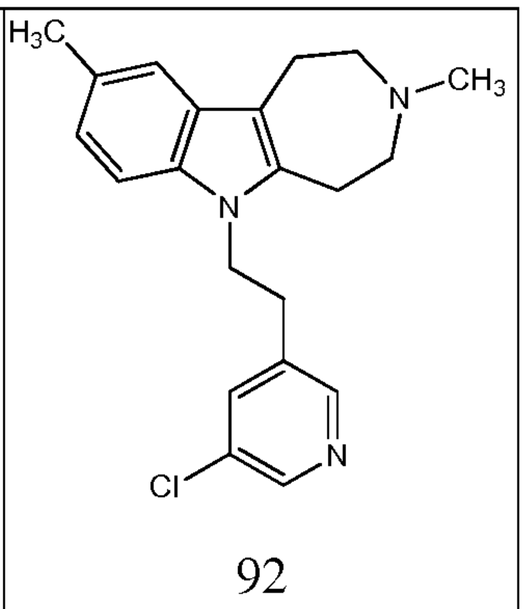

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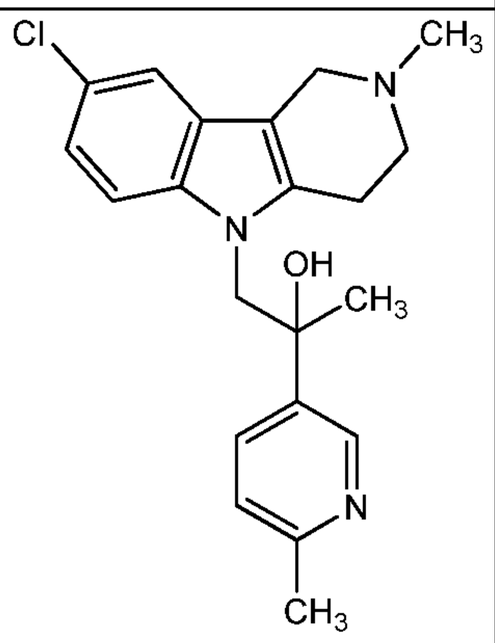

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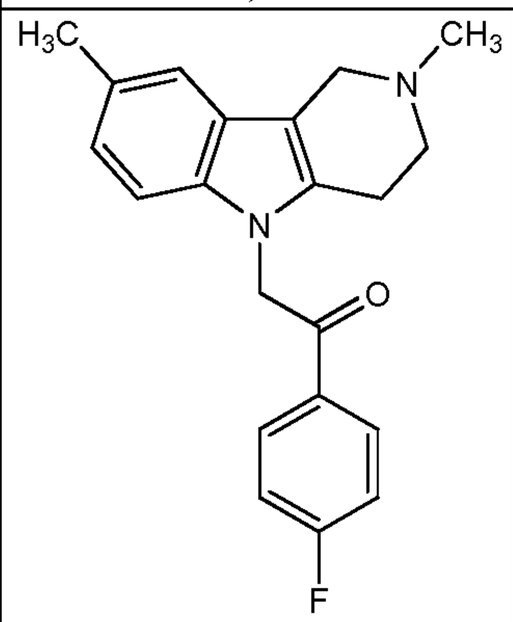

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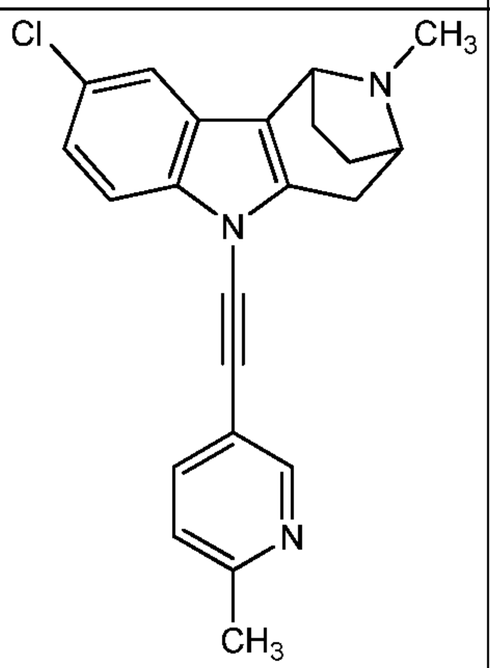

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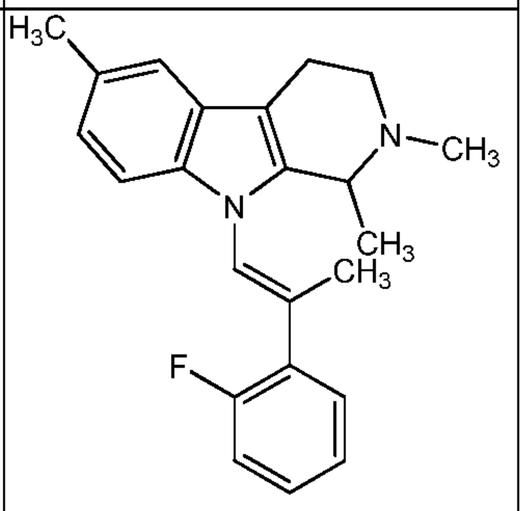

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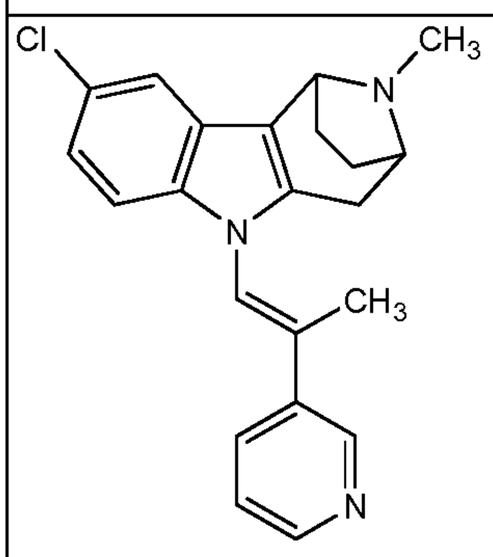

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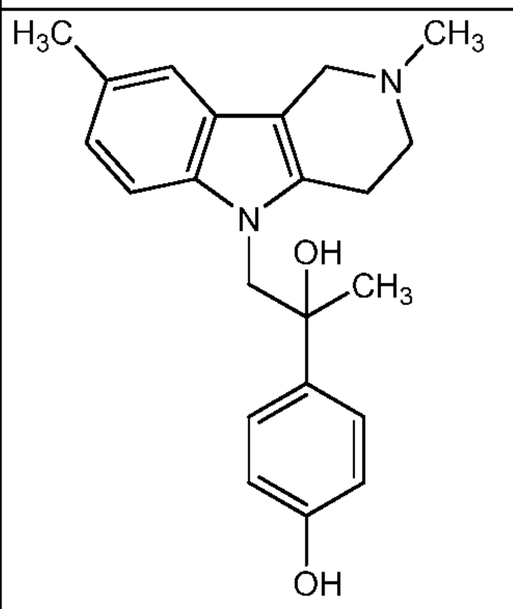

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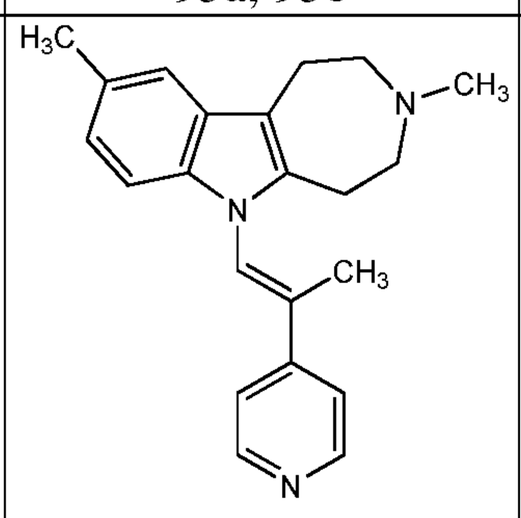

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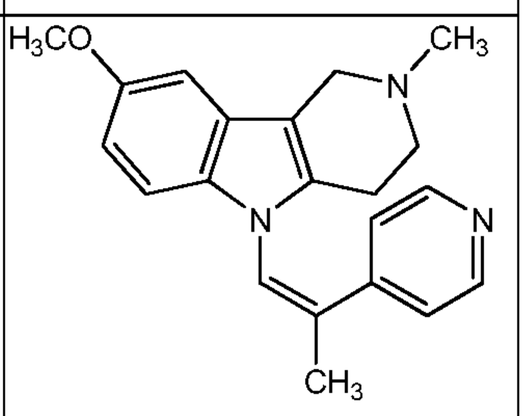

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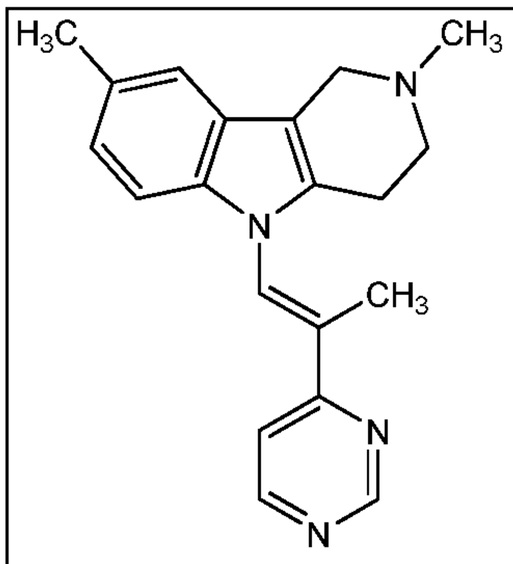
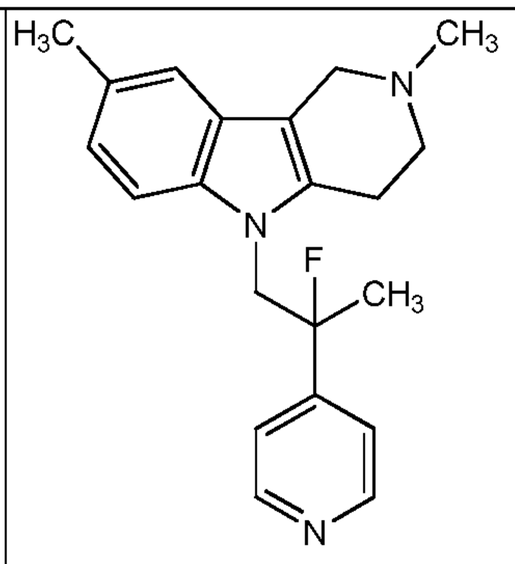
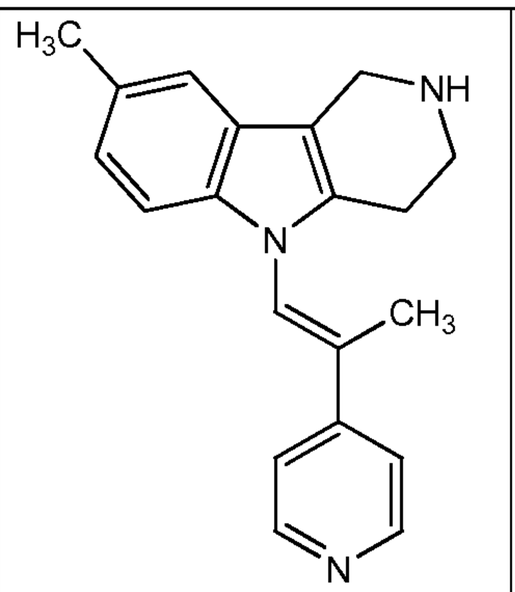
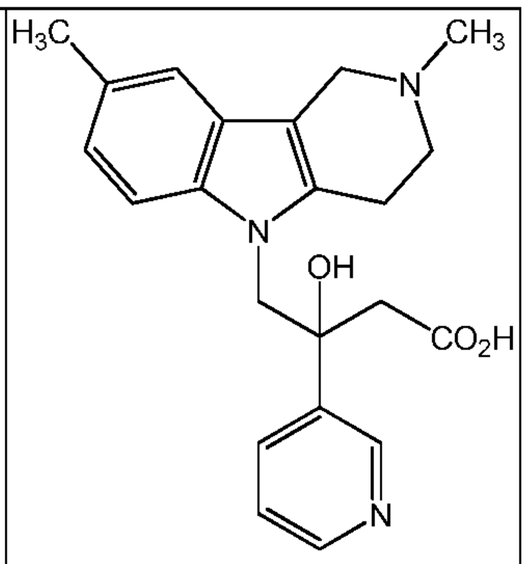
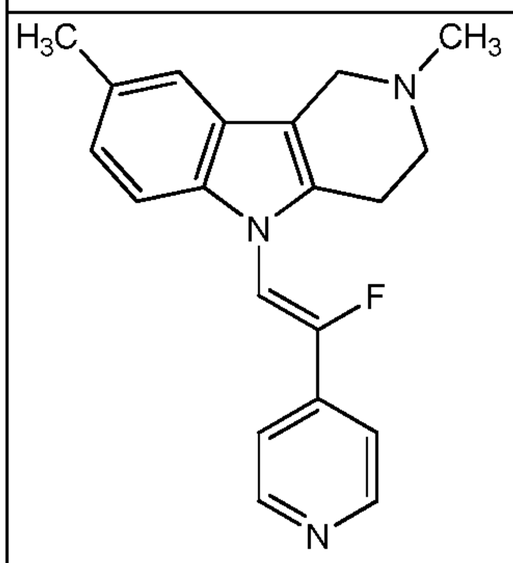
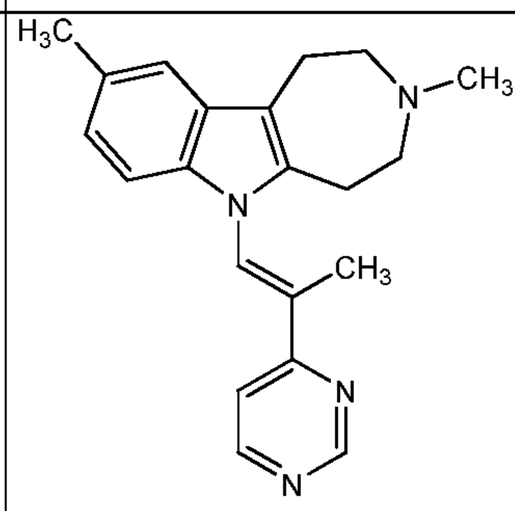
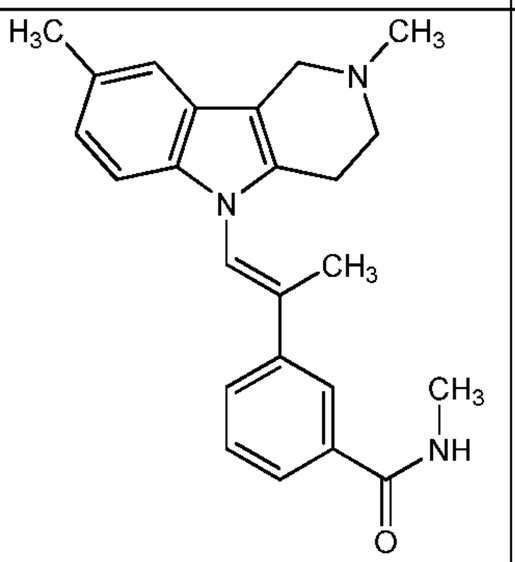
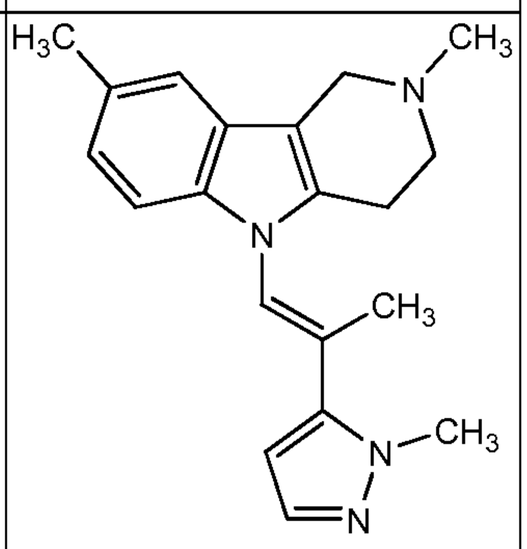
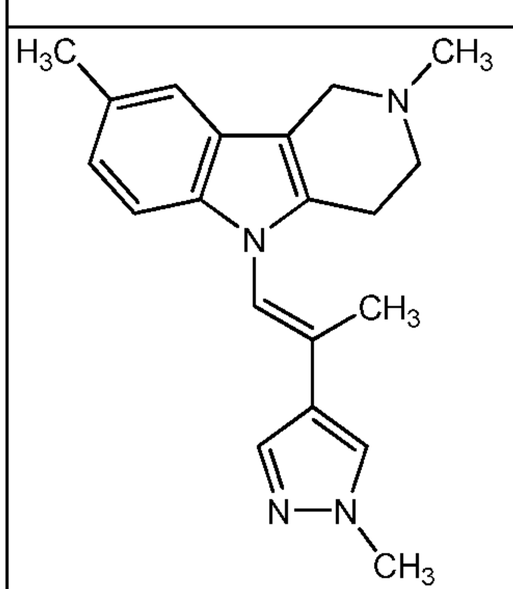
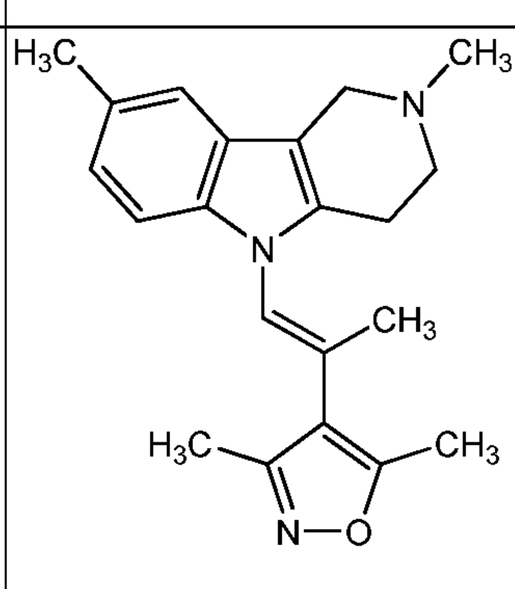
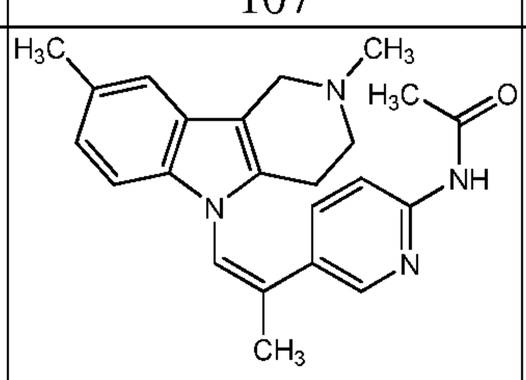
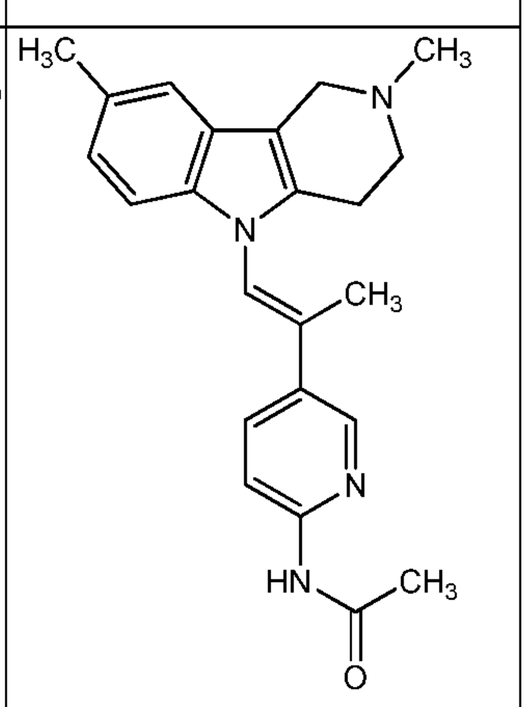
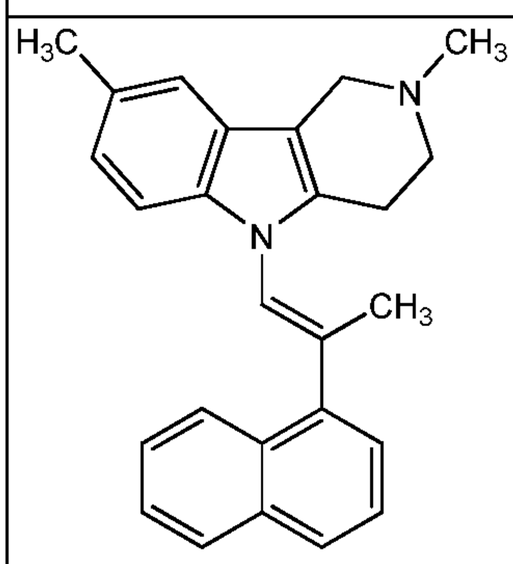
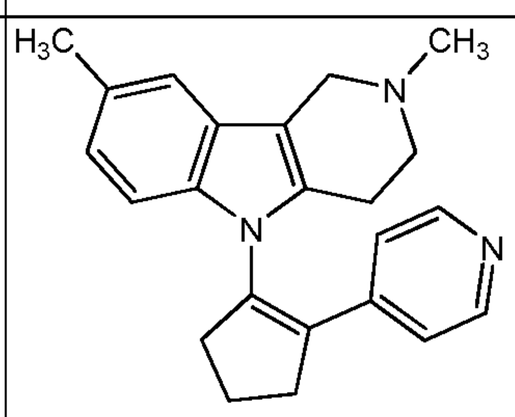
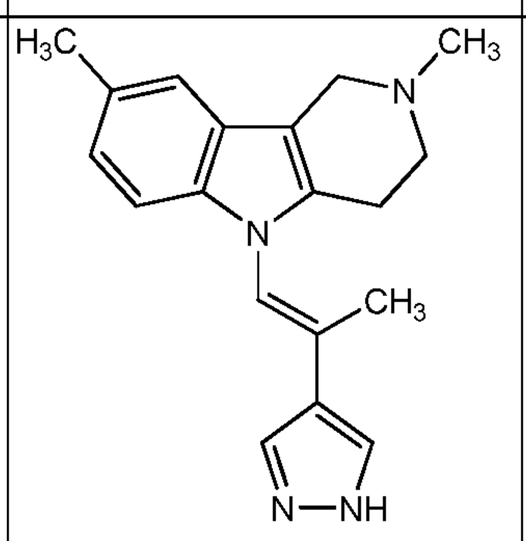
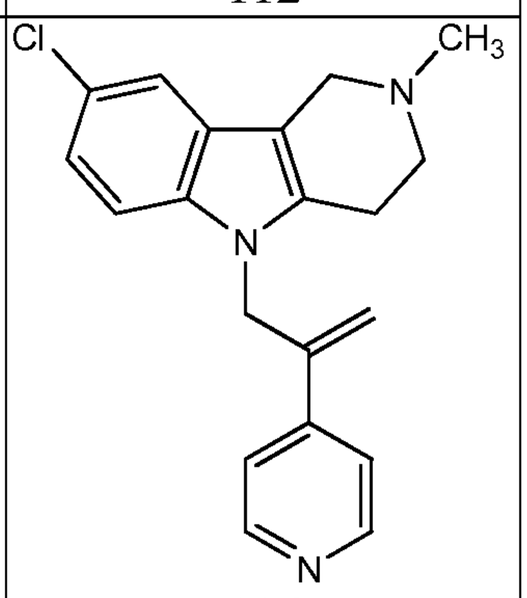
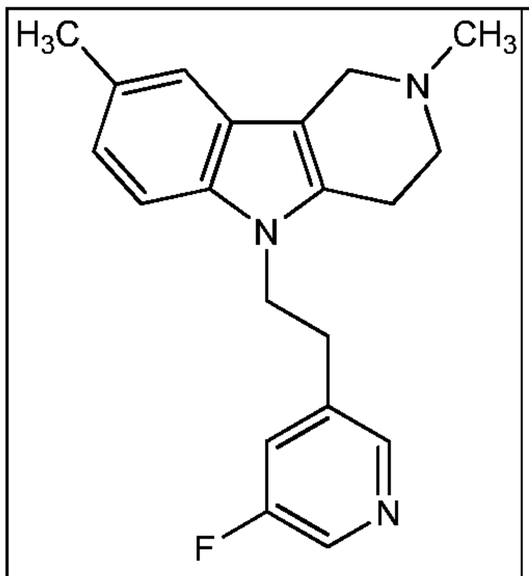
 101	 102 102a, 102b	 103	 104 104a, 104b
 105	 106	 107	 108
 109	 110	 111	 112
 113	 114	 115	 116



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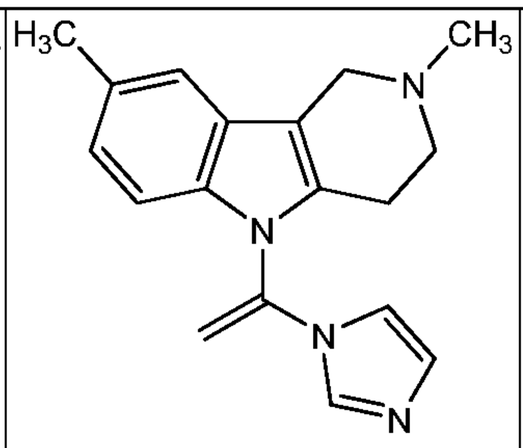

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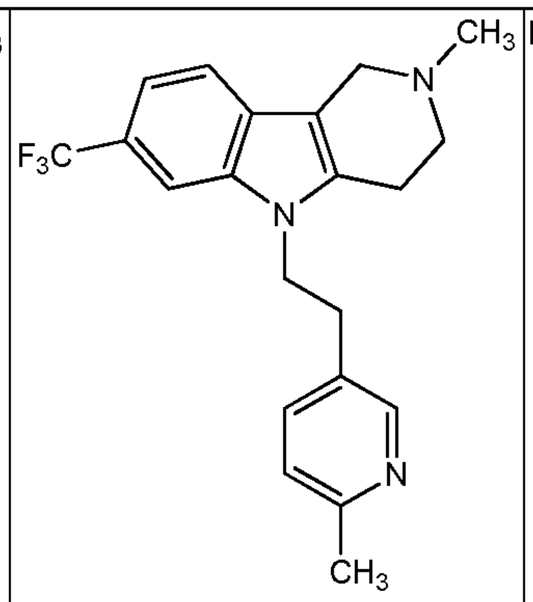

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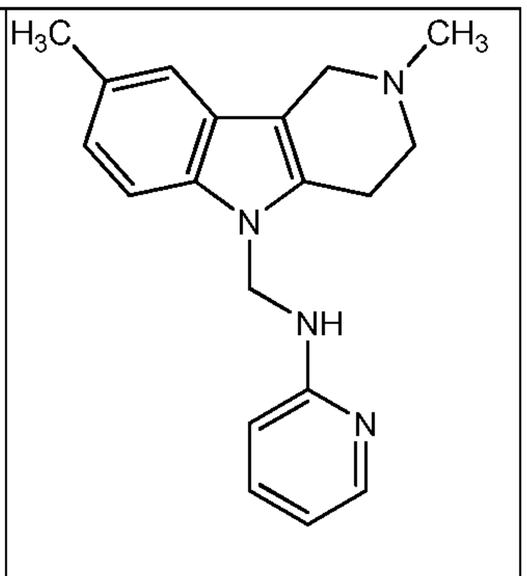

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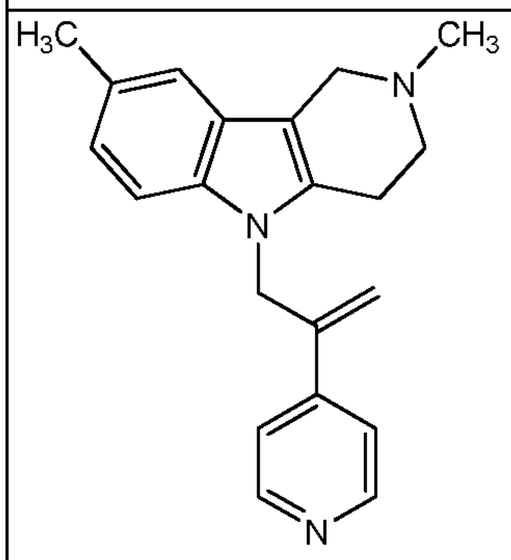

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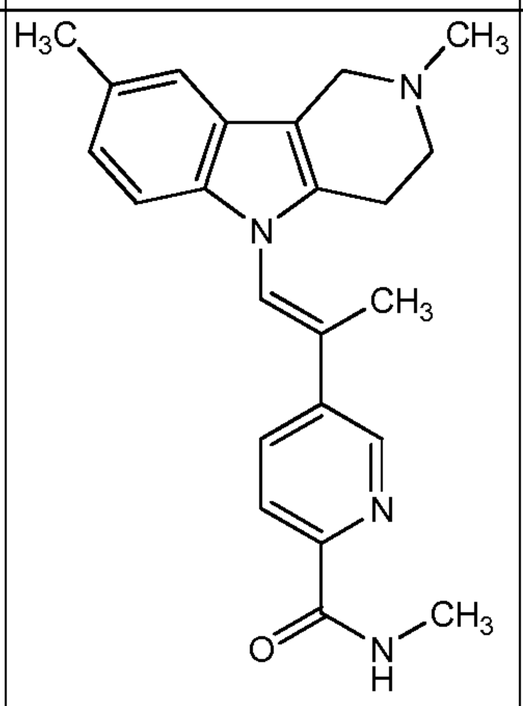

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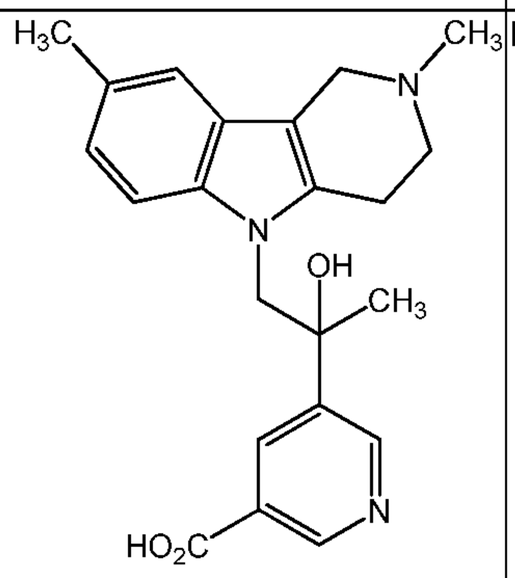

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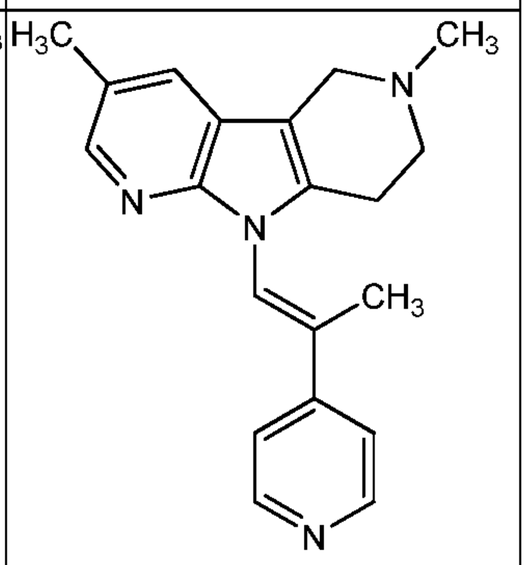

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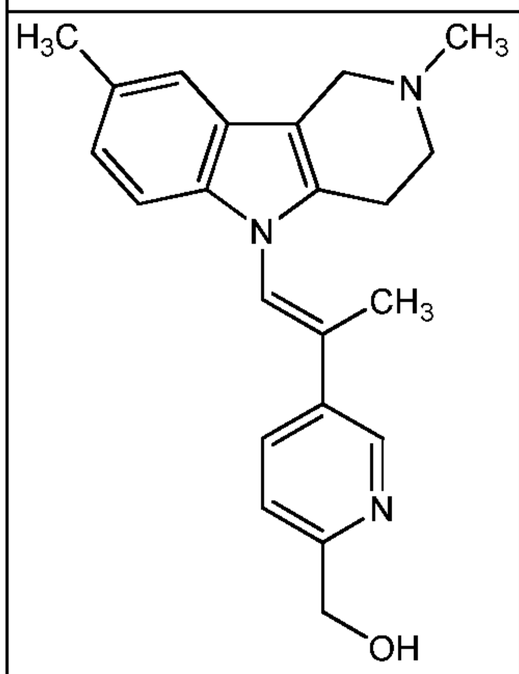

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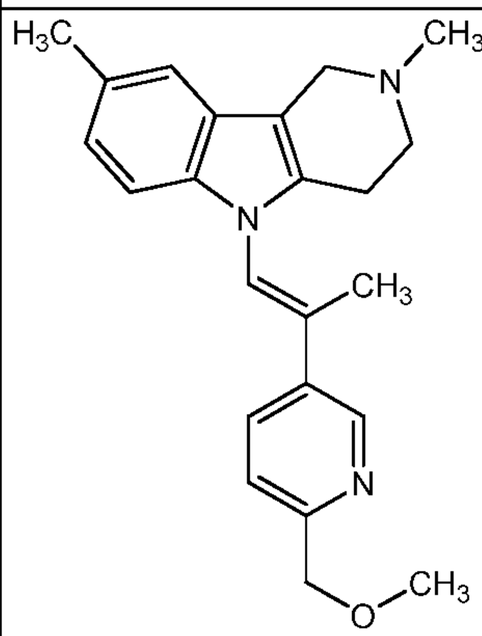

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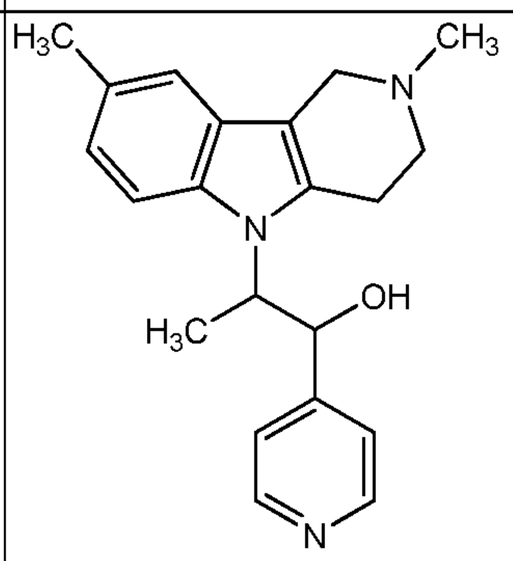

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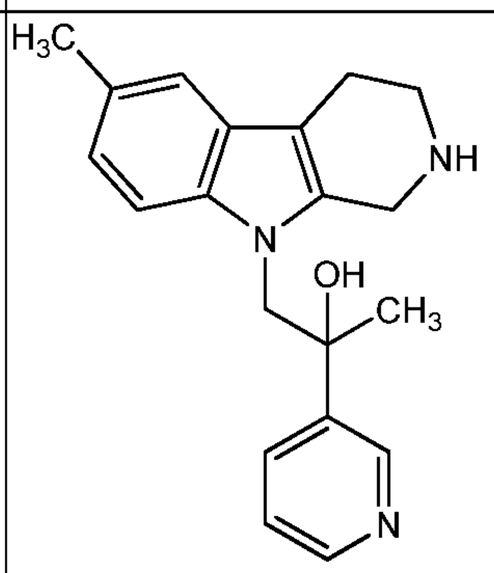

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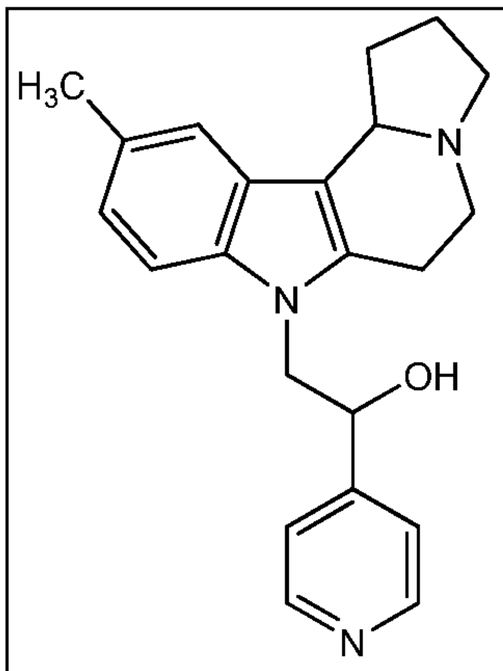
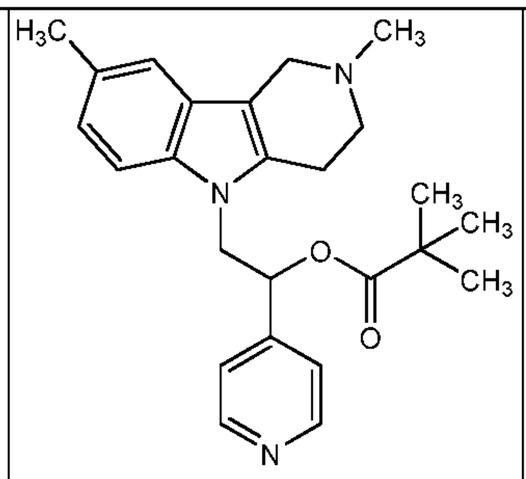
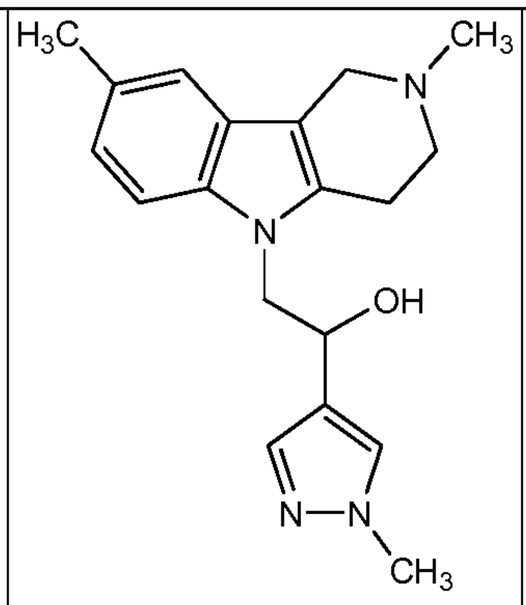
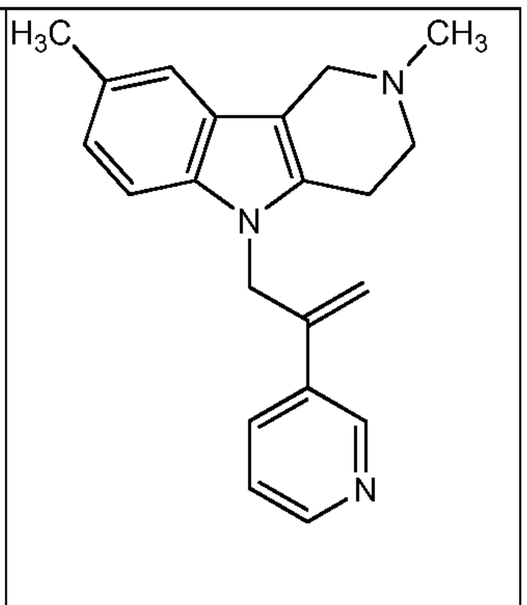
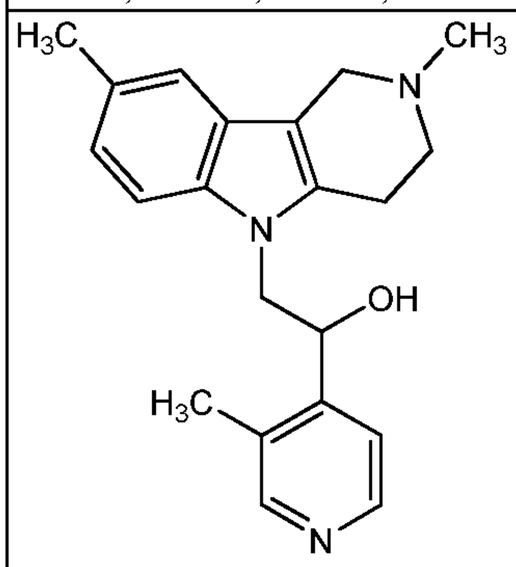
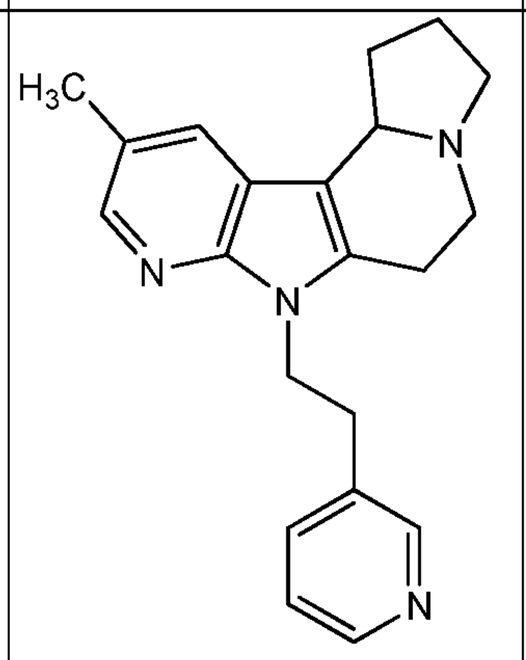
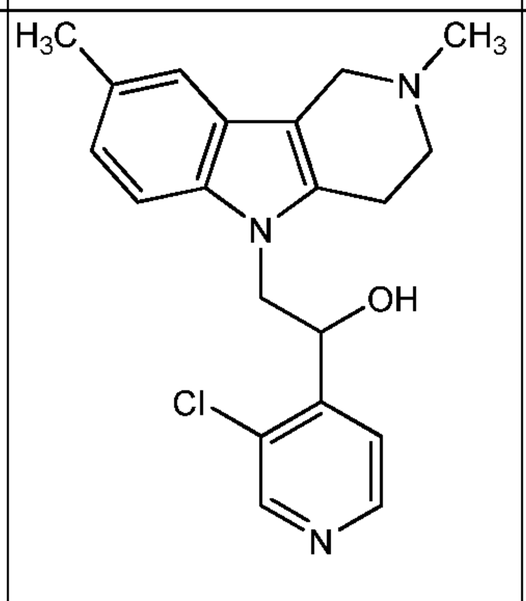
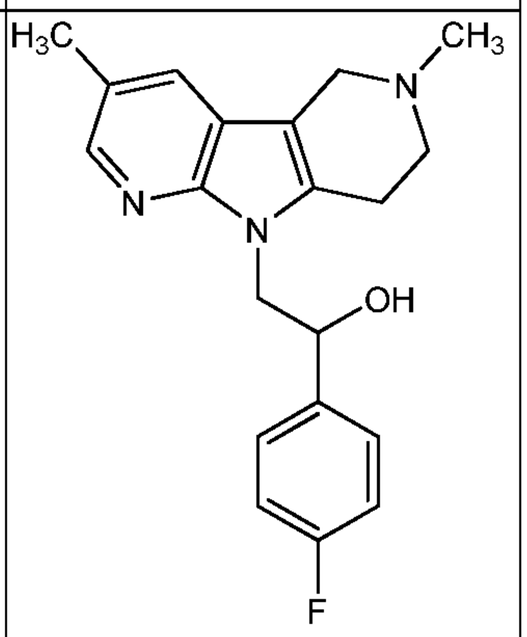
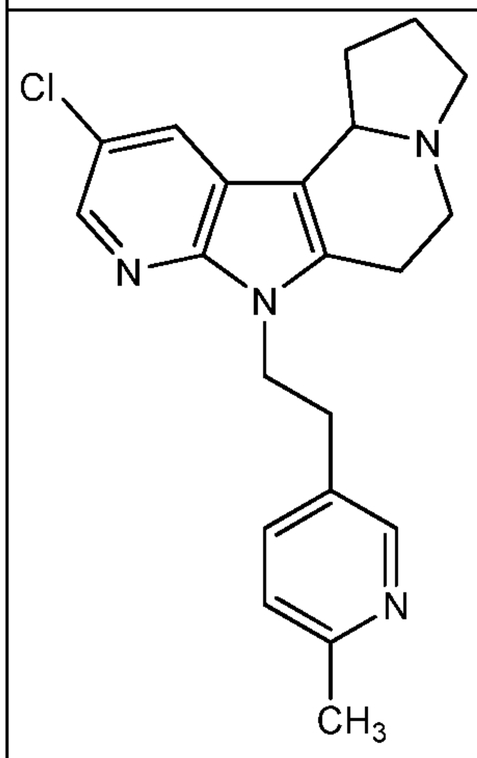
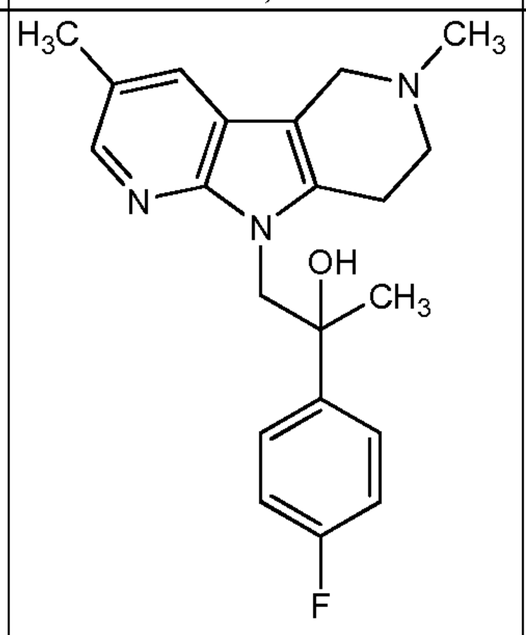
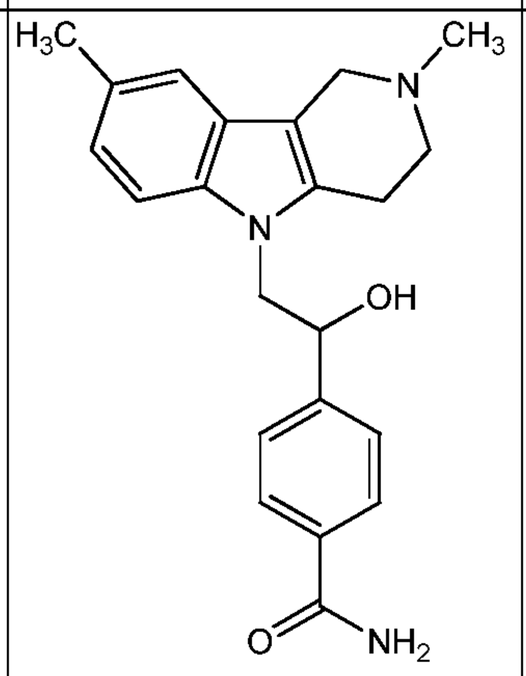
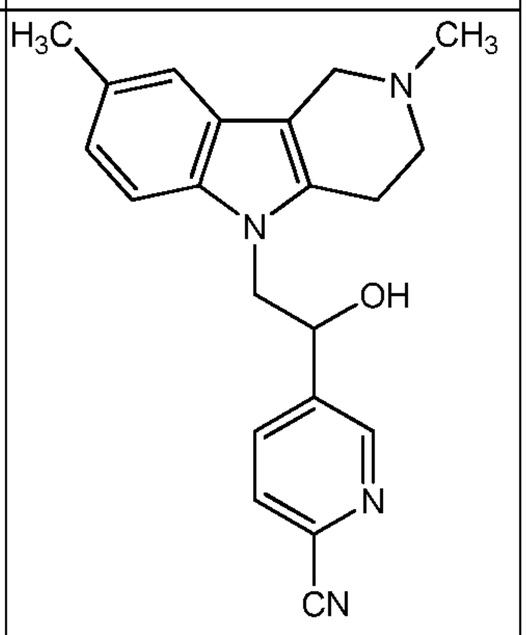
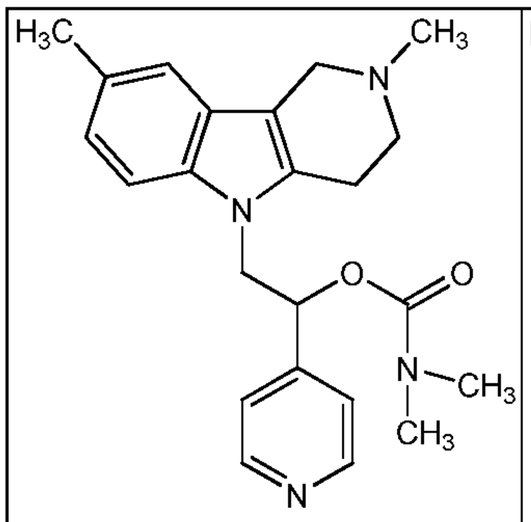
 129 129a, 129b, 129c, 129d	 130 130a, 130b	 131 131a, 131b	 132
 133 133a, 133b	 134 134a, 134b	 135 135a, 135b	 136 136a, 136b
 137 137a, 137b	 138 138a, 138b	 139 139a, 139b	 140 140a, 140b



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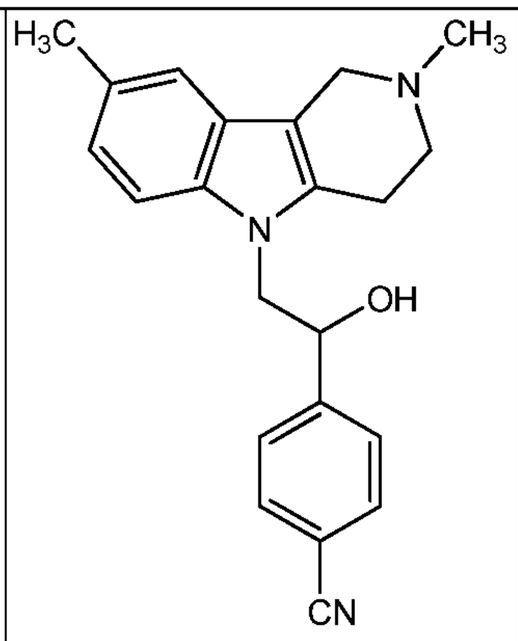

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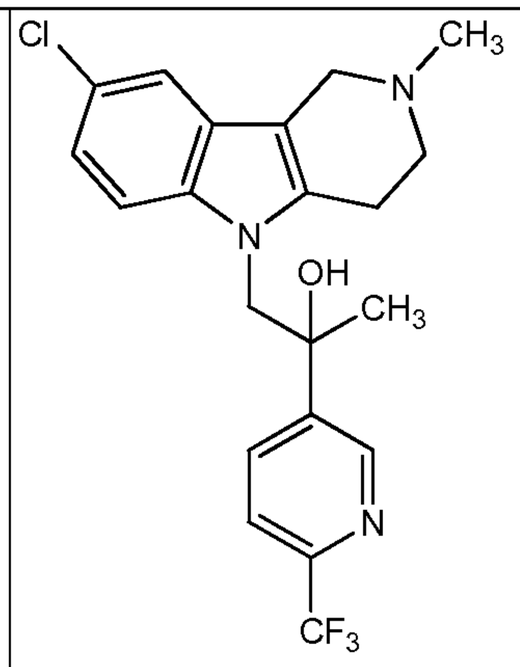

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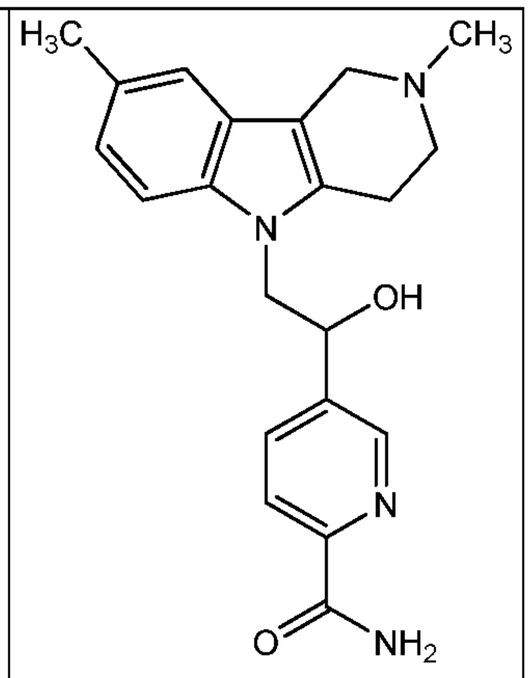

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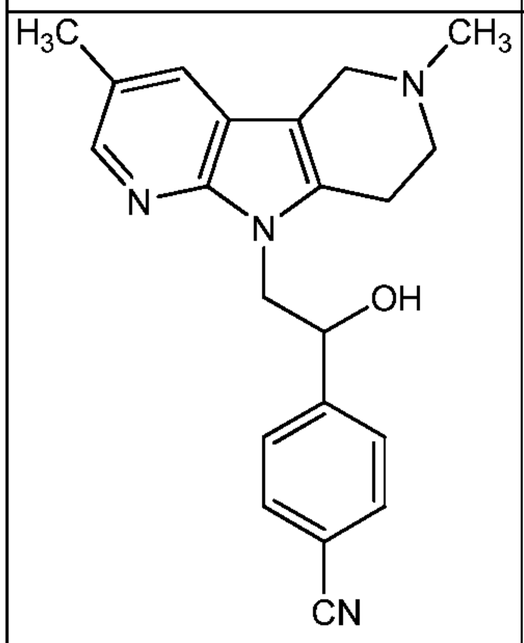

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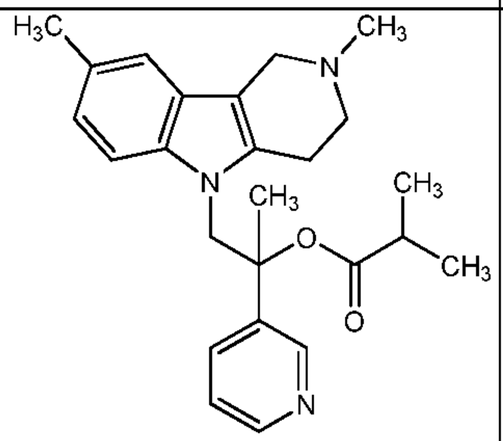

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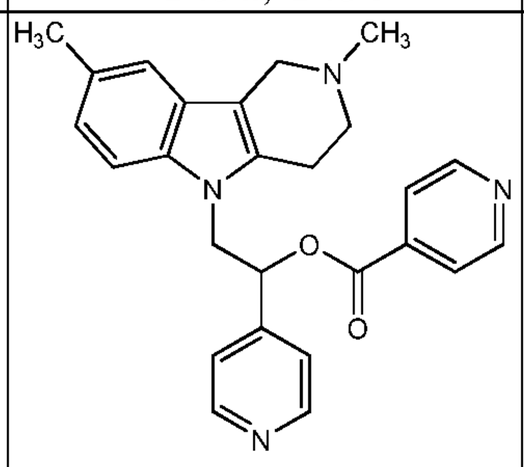

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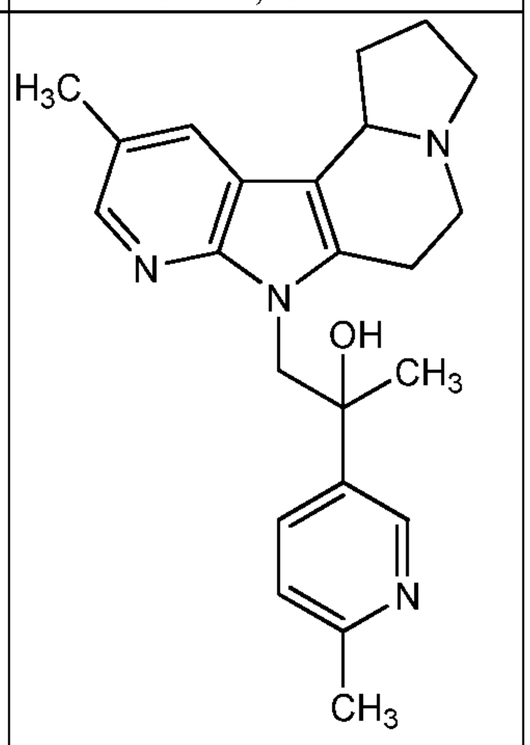

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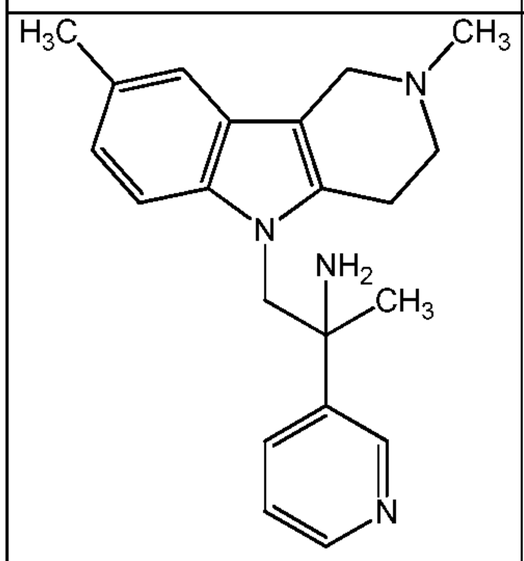

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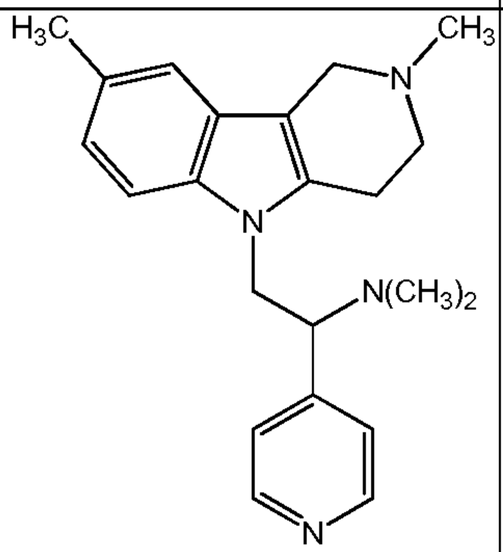

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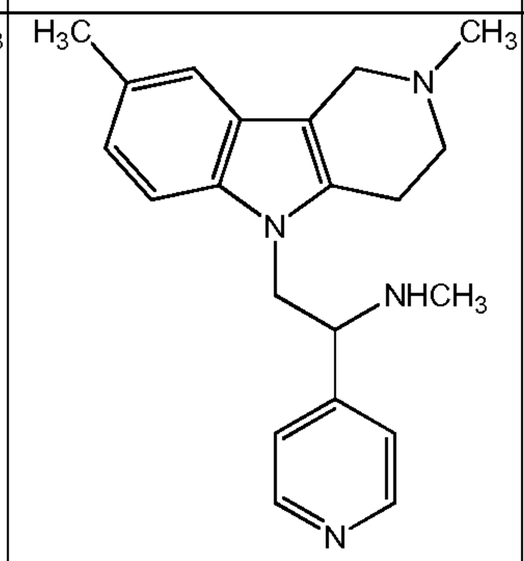

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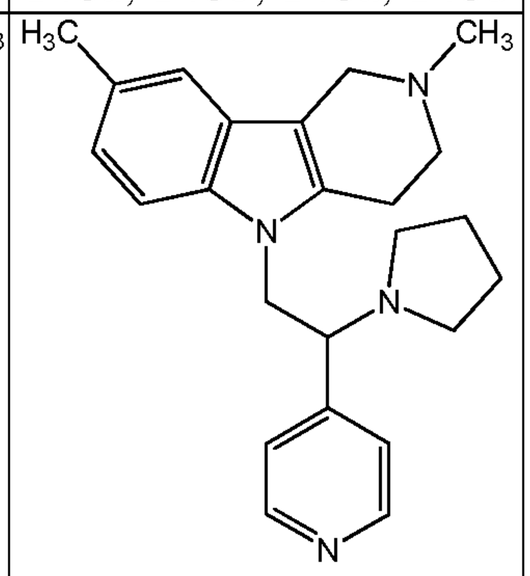

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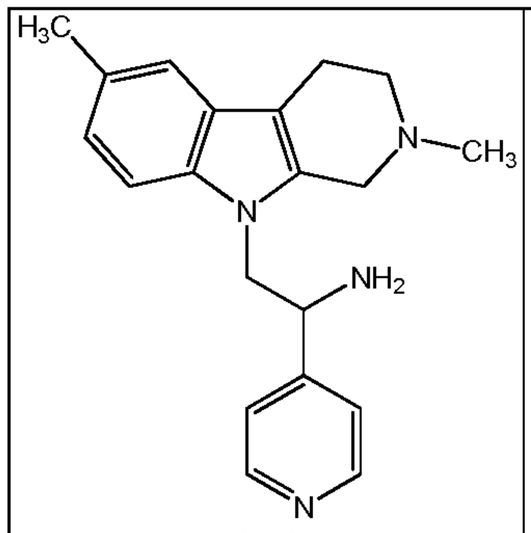
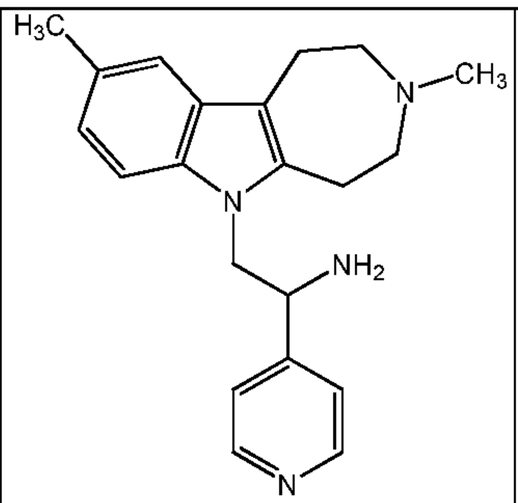
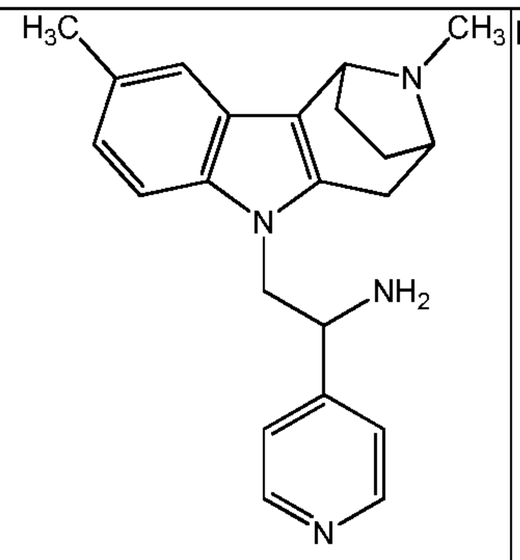
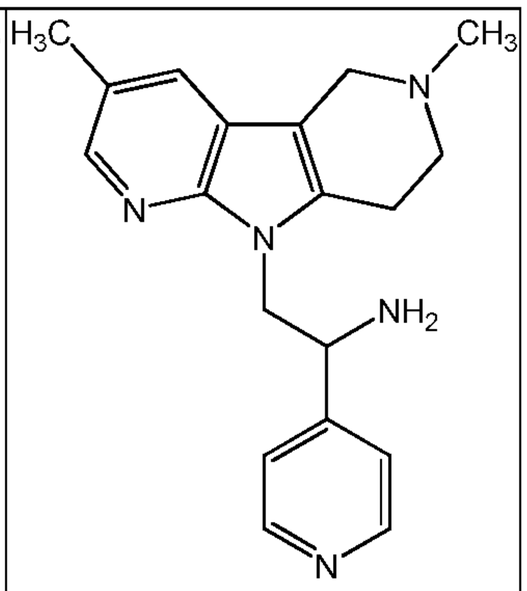
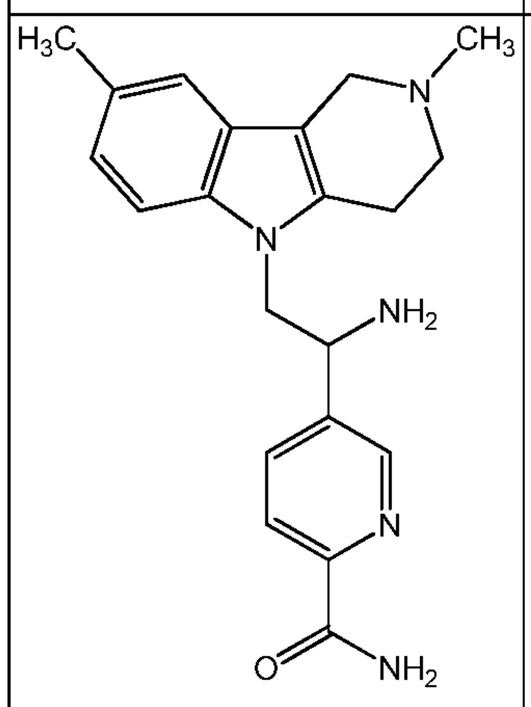
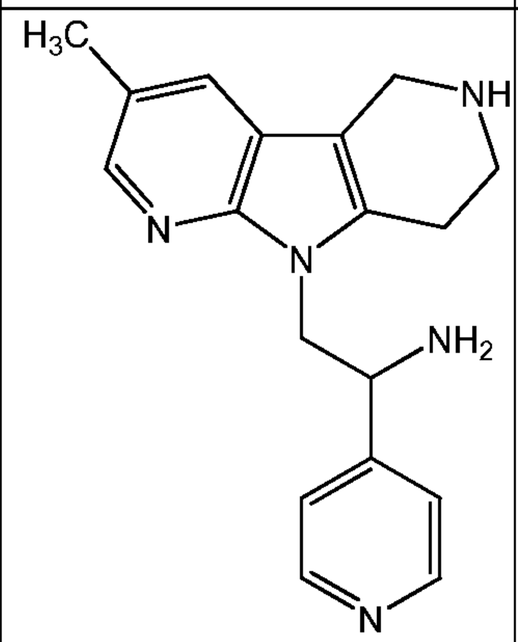
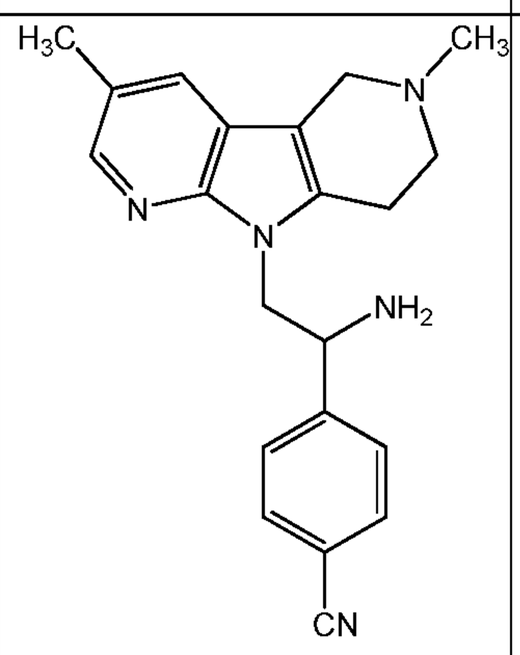
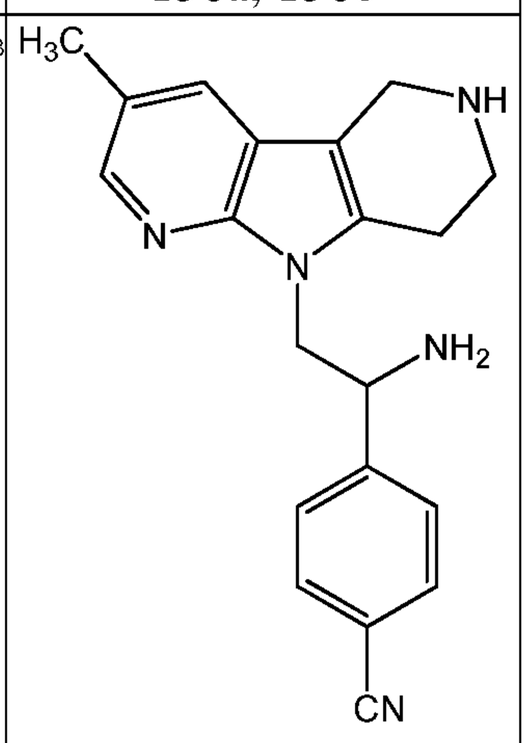
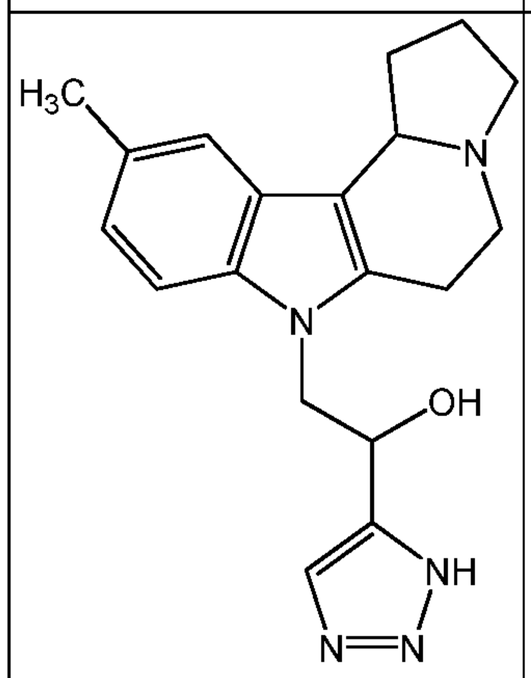
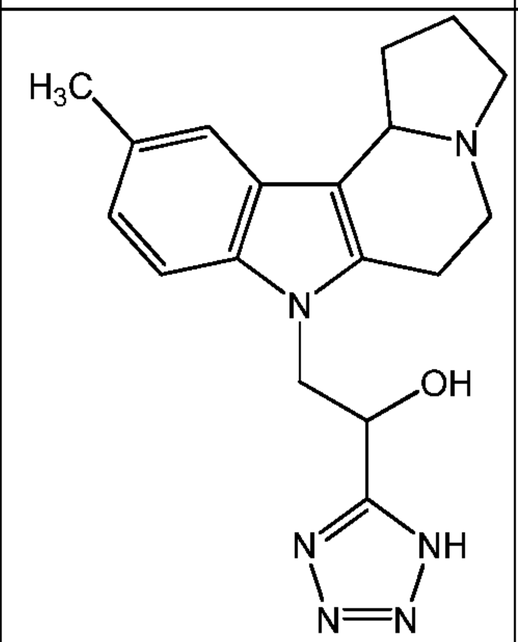
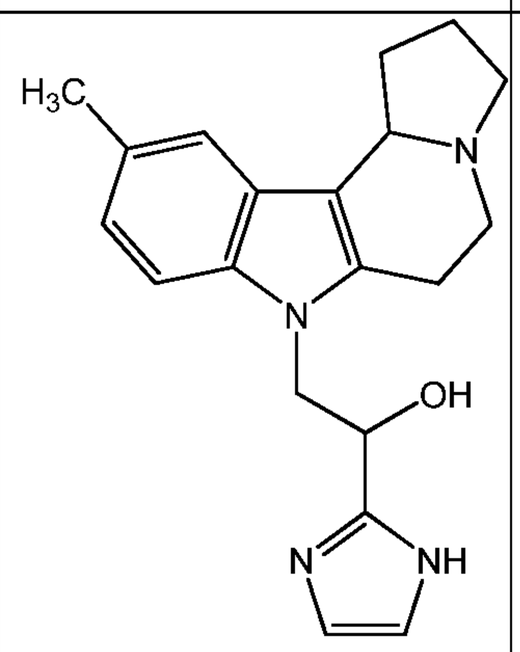
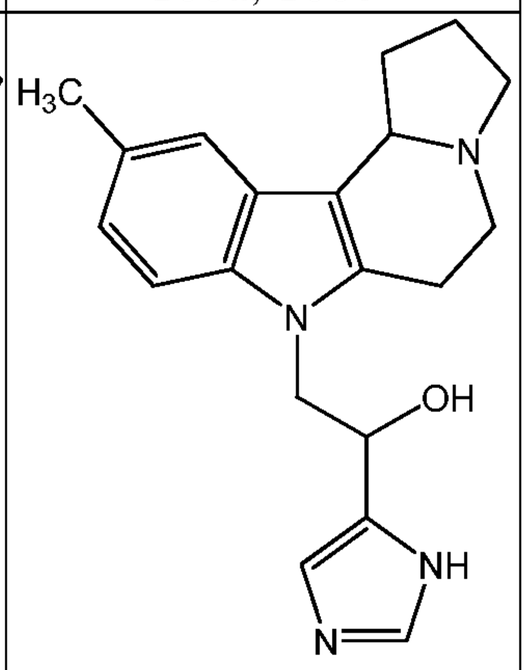
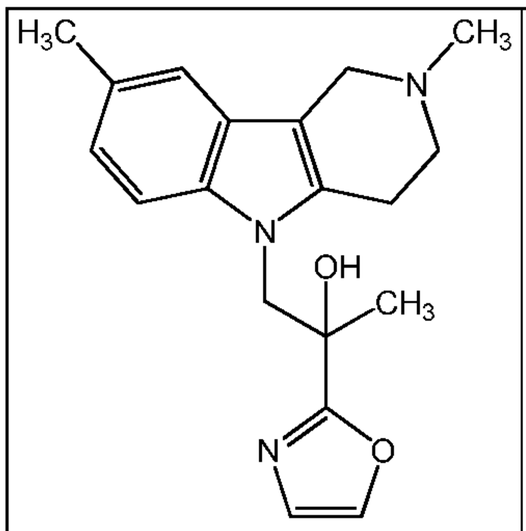
 153 153a, 153b	 154 154a, 154b	 155 155a, 155b, 155c, 155d	 156 156a, 156b
 157 157a, 157b	 158 158a, 158b	 159 159a, 159b	 160 160a, 160b
 161 161a, 161b, 161c, 161d	 162 162a, 162b, 162c, 162d	 163 163a, 163b, 163c, 163d	 164 164a, 164b, 164c, 164d



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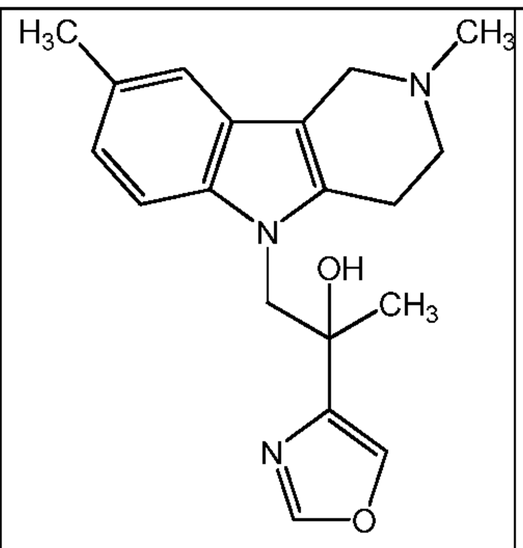

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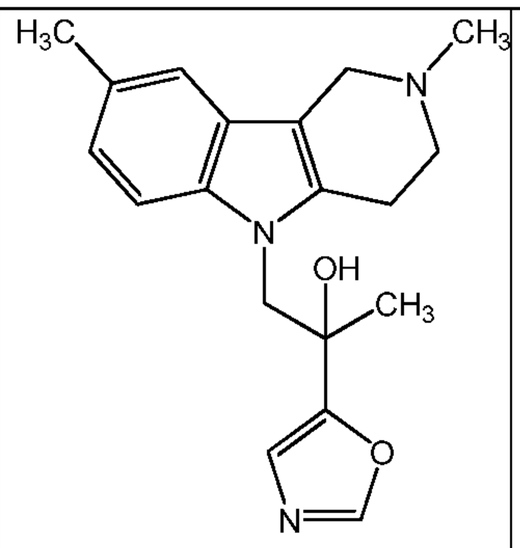

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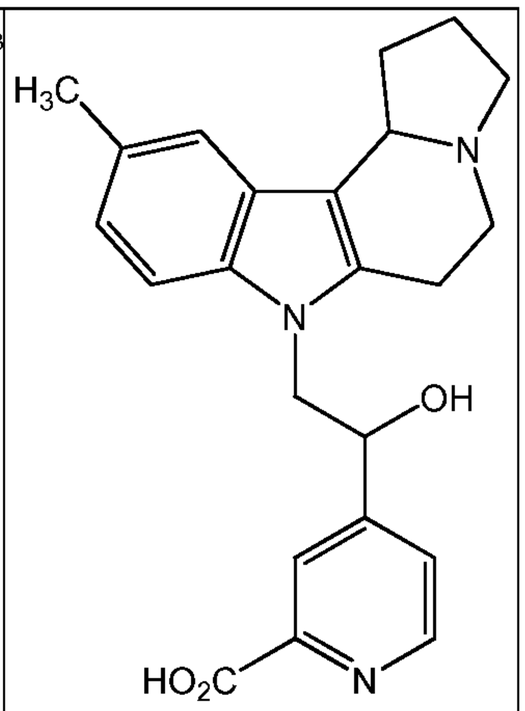

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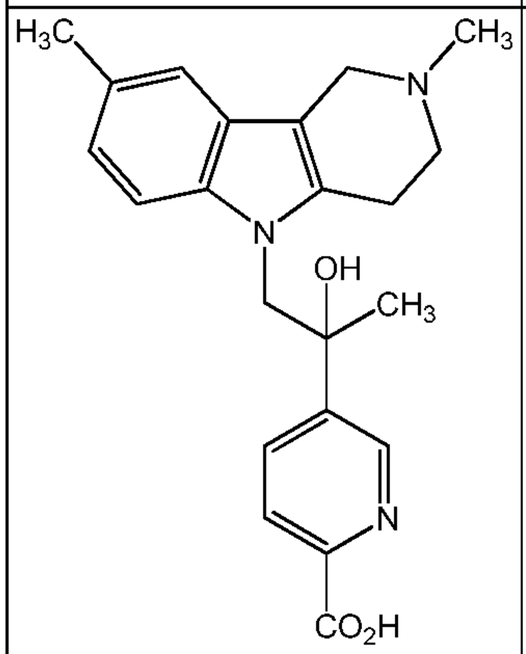

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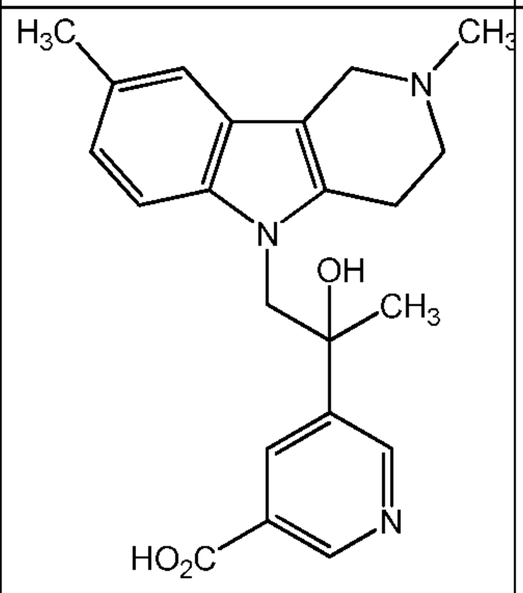

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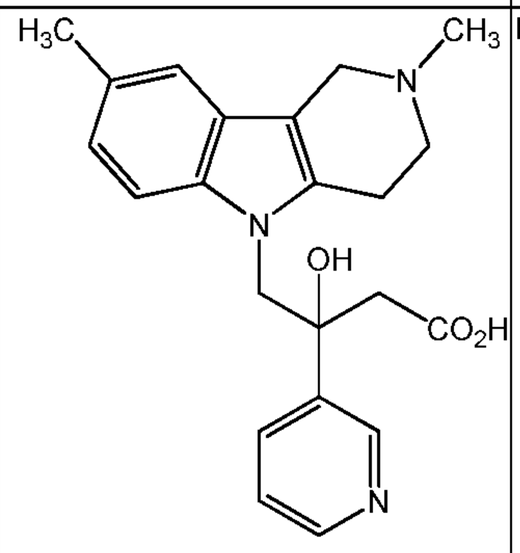

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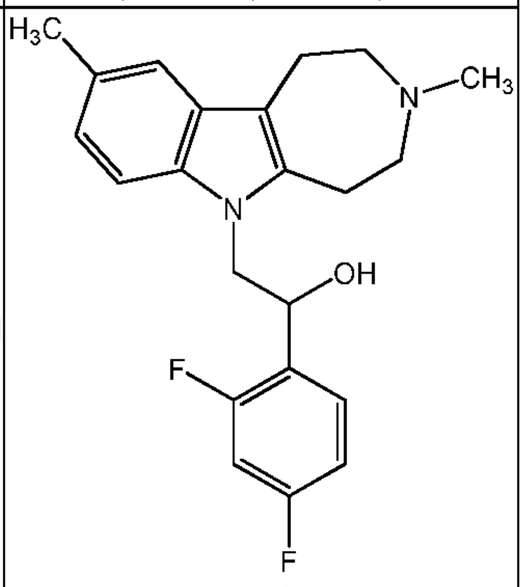

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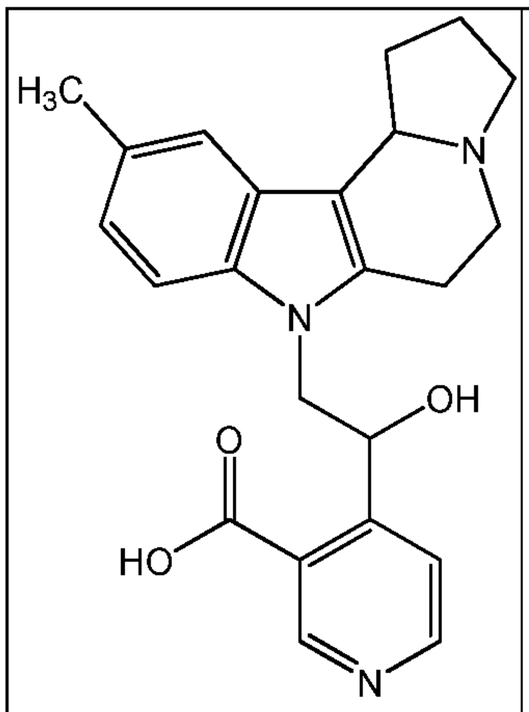
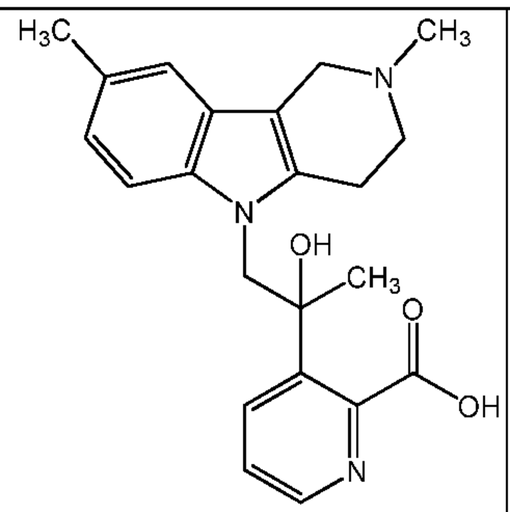
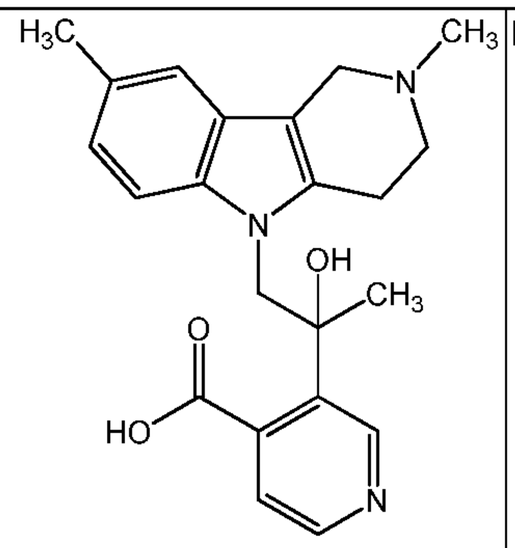
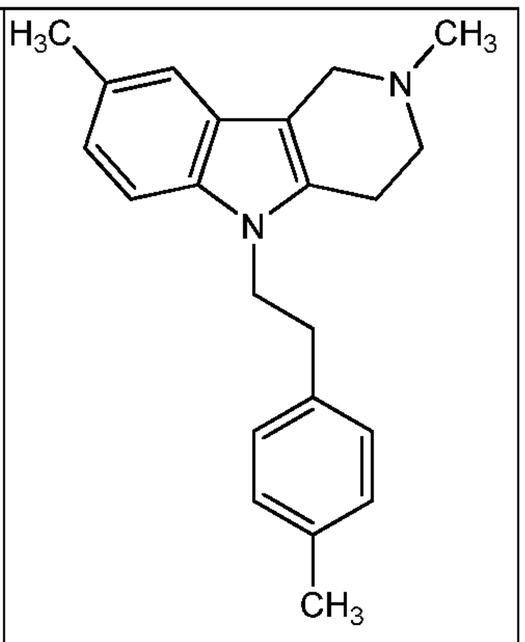
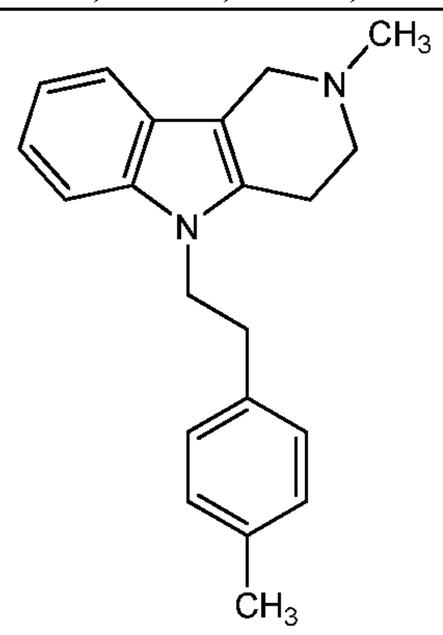
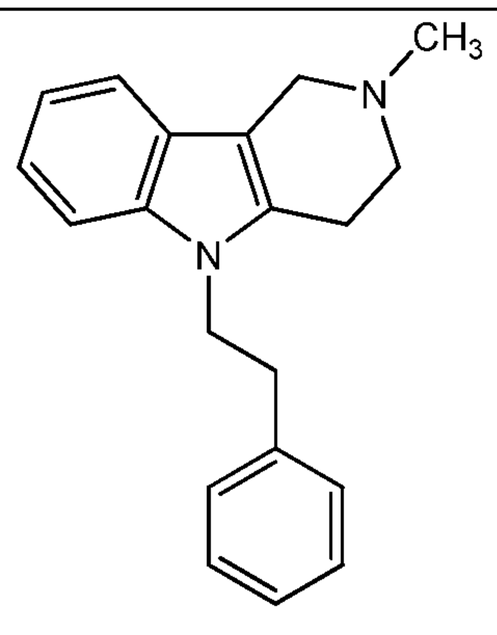
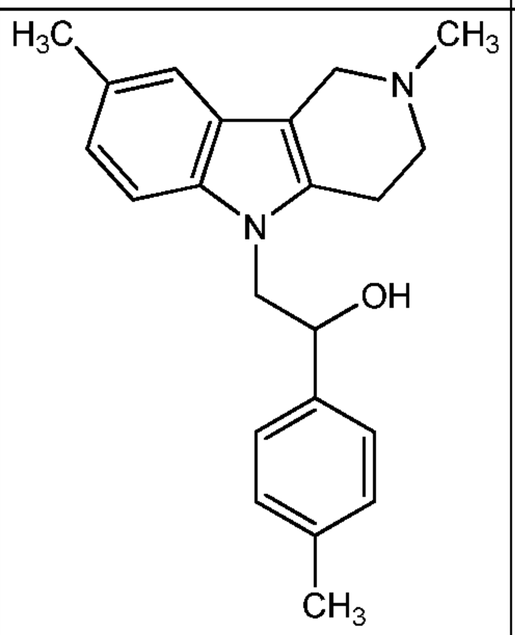
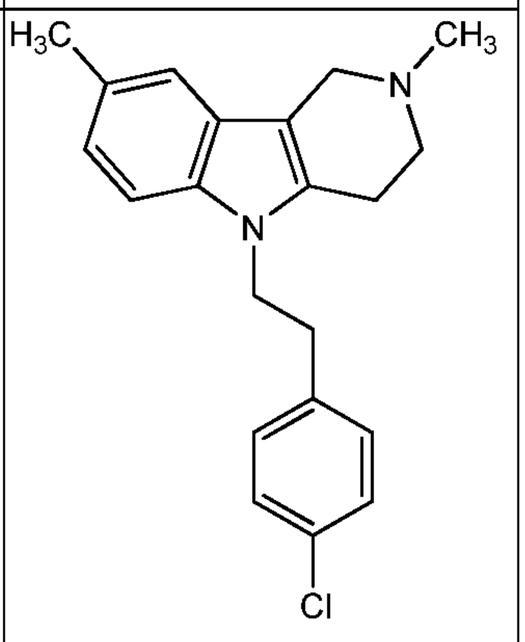
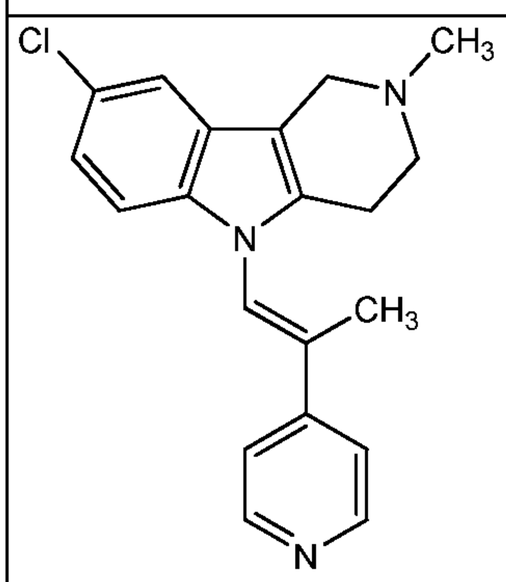
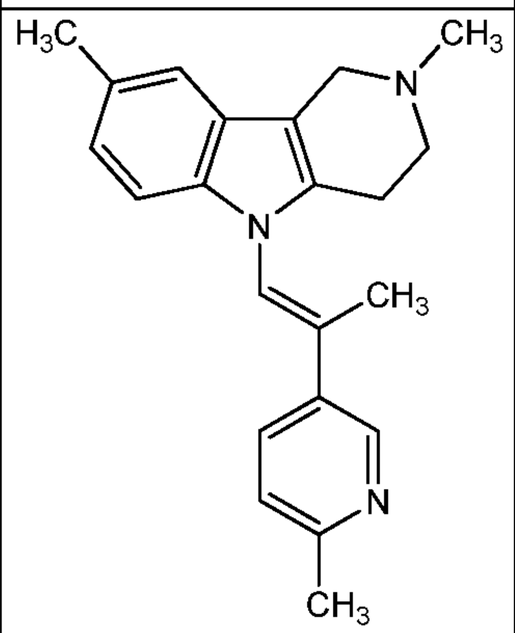
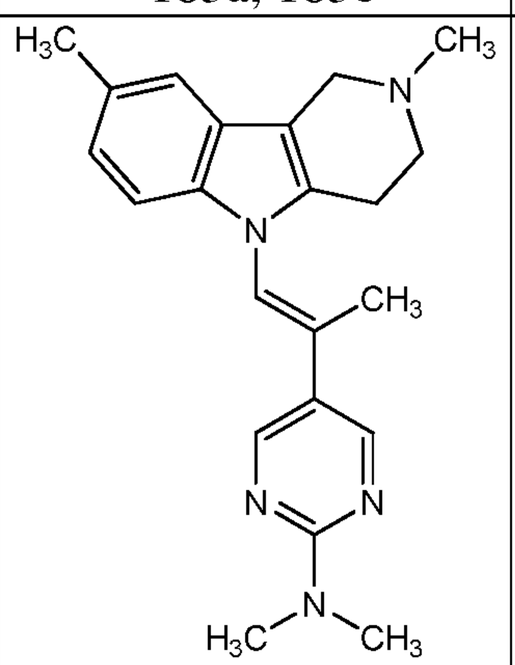
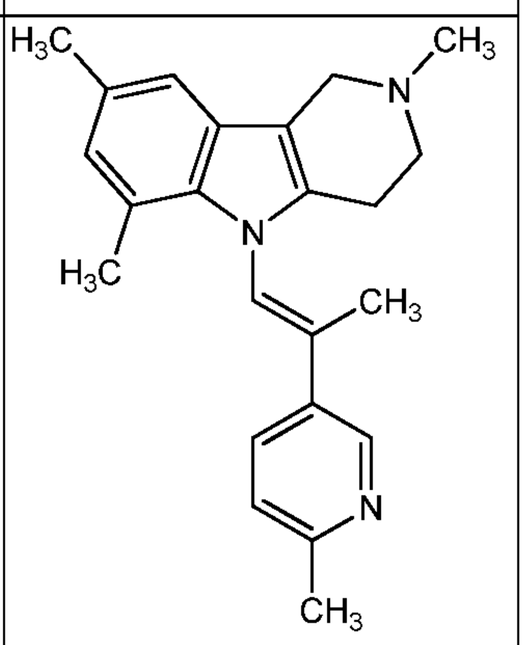
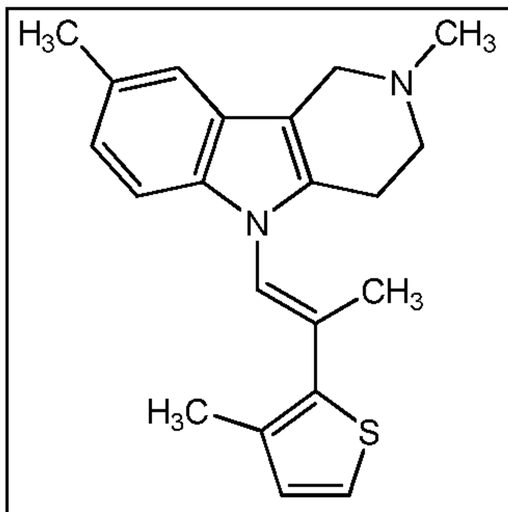
 177 177a, 177b, 177c, 177d	 178 178a, 178b	 179 179a, 179b	 180
 181	 182	 183 183a, 183b	 184
 185	 186	 187	 188



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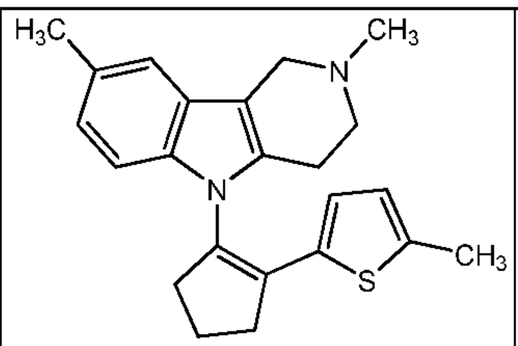

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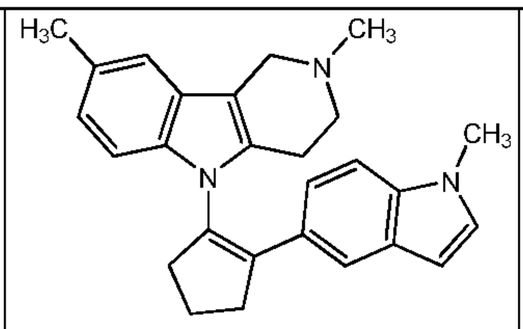

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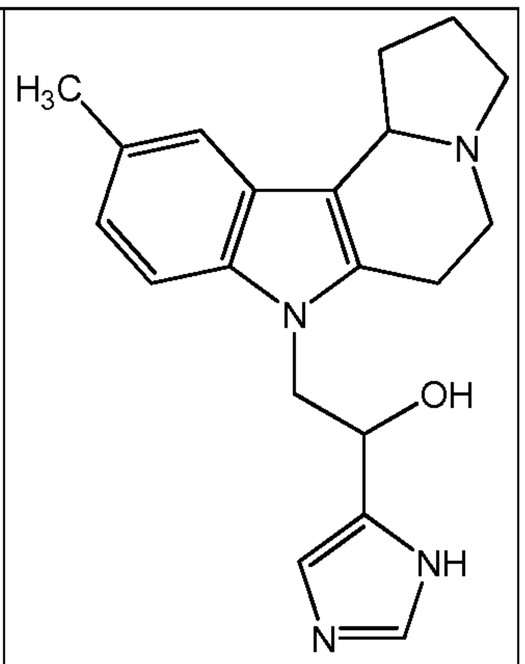

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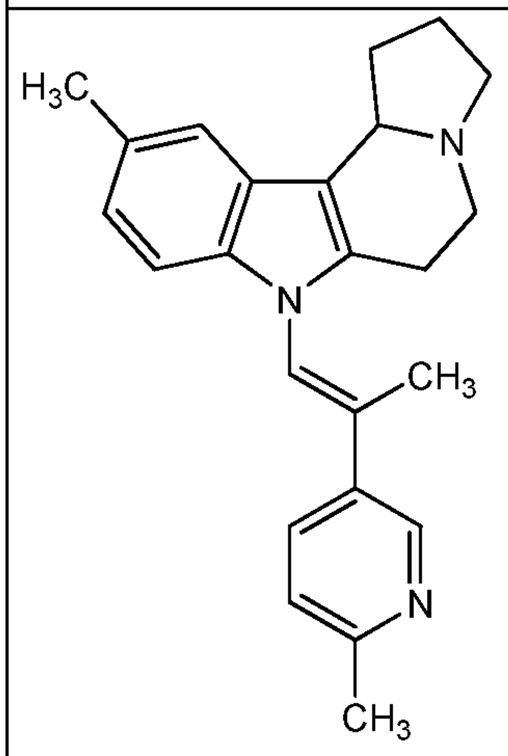

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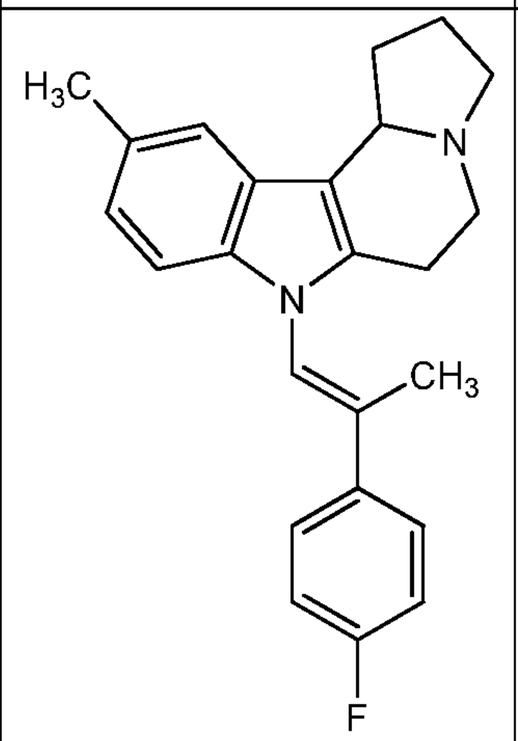

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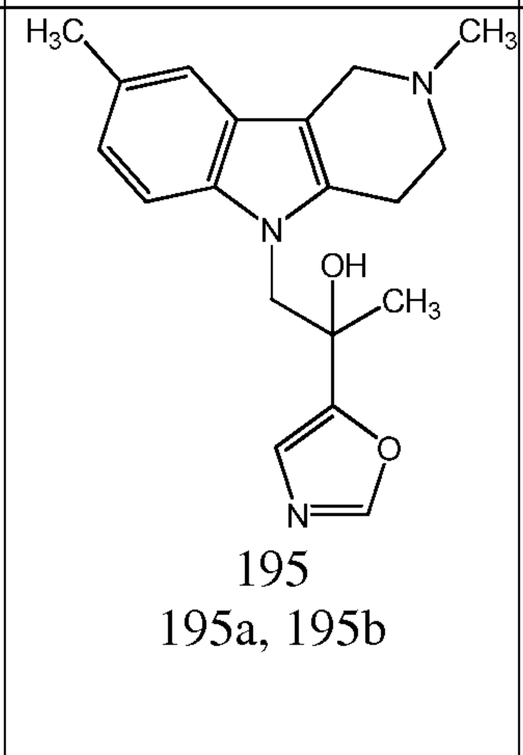

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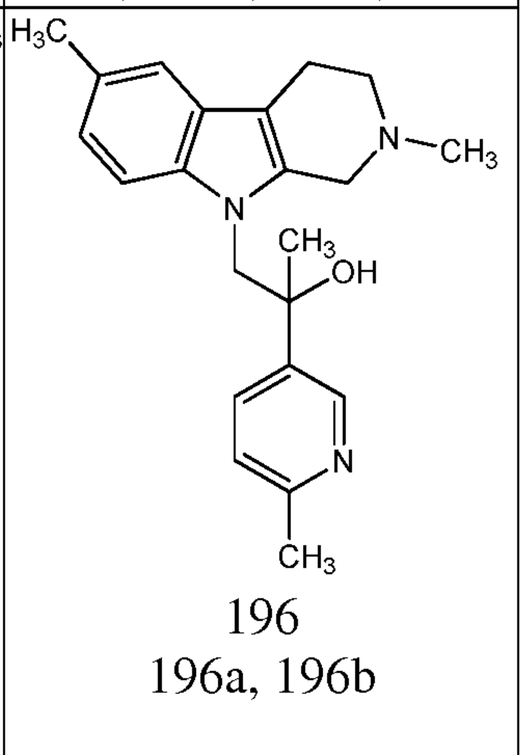

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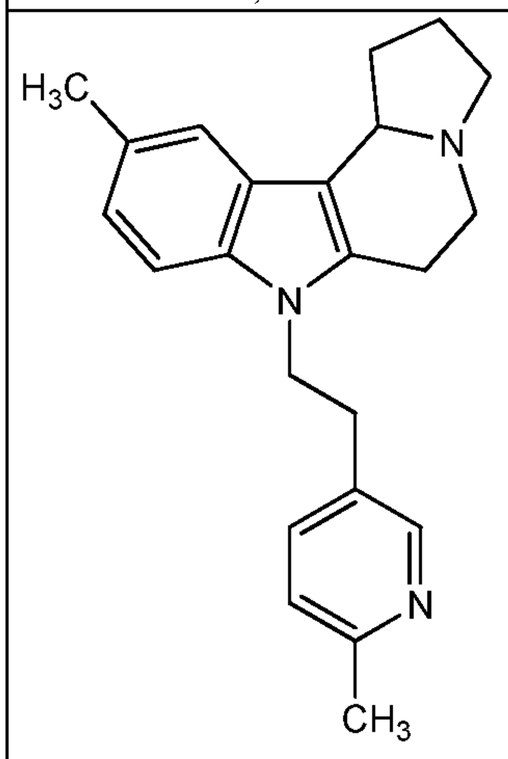

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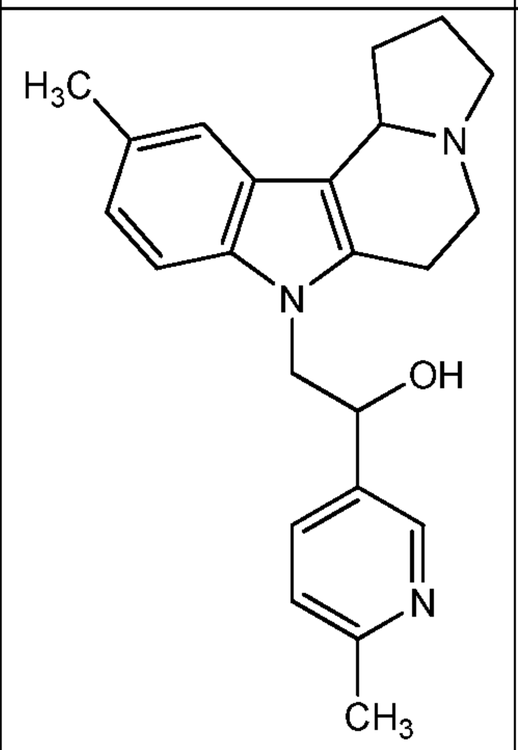

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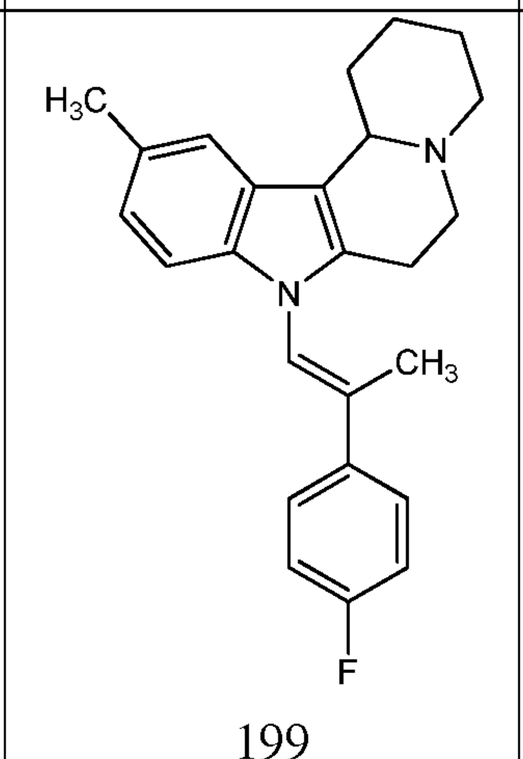

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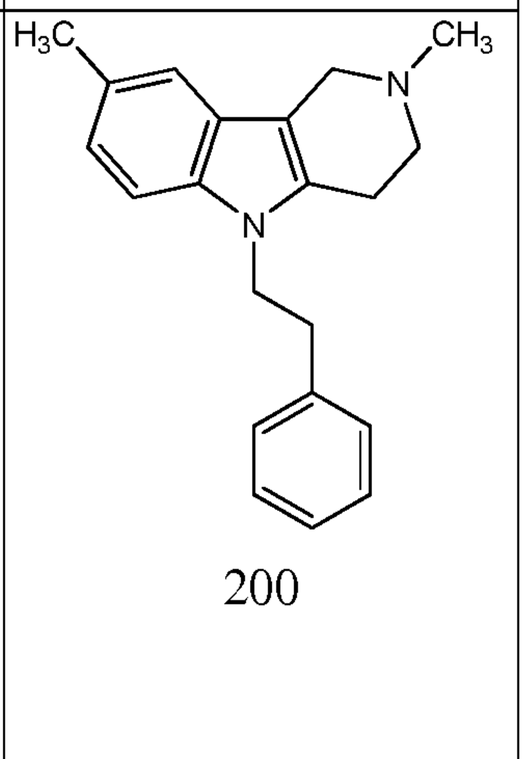

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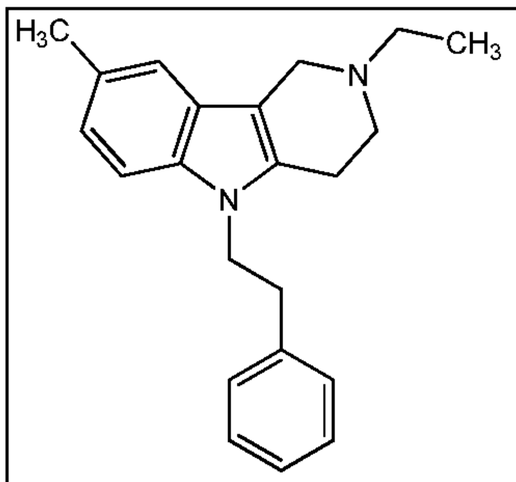

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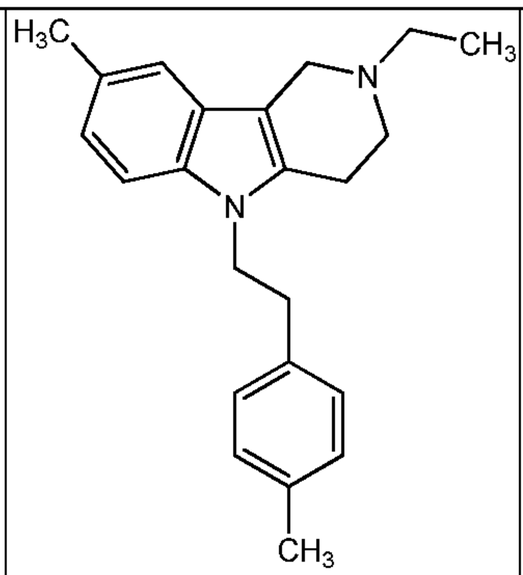

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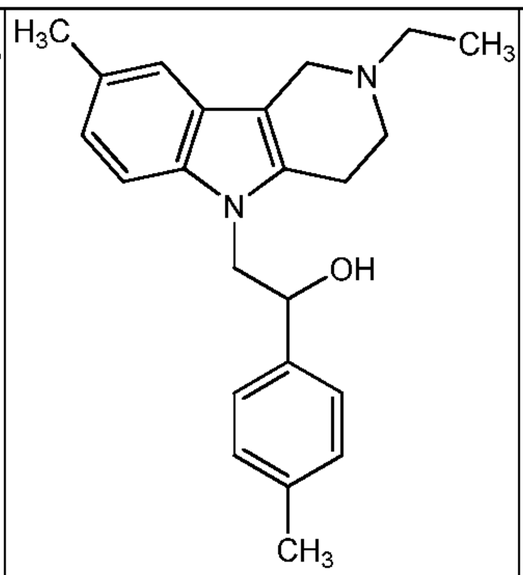

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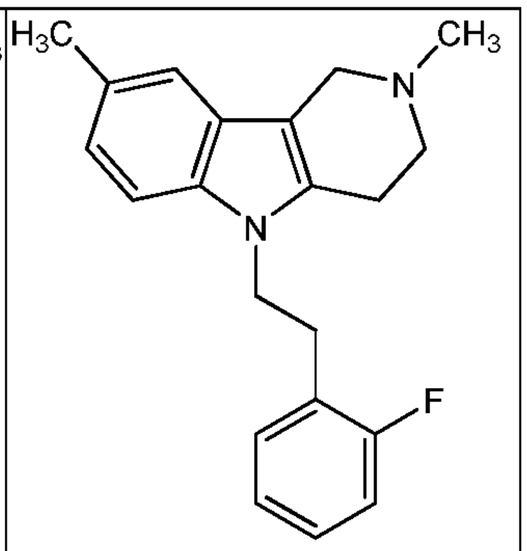

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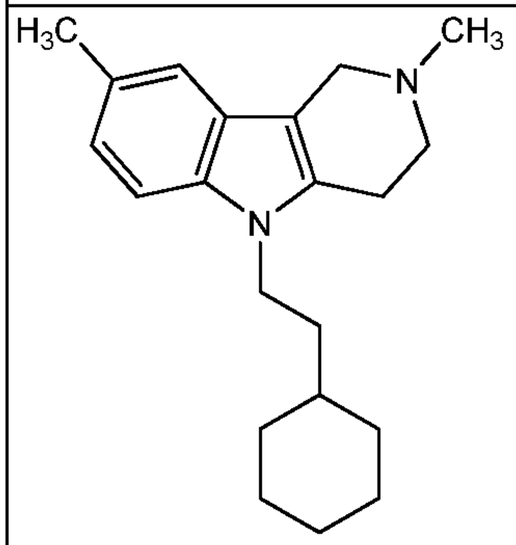

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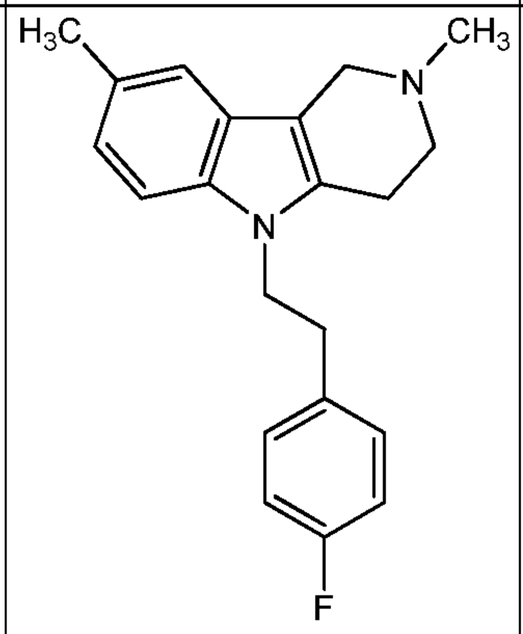

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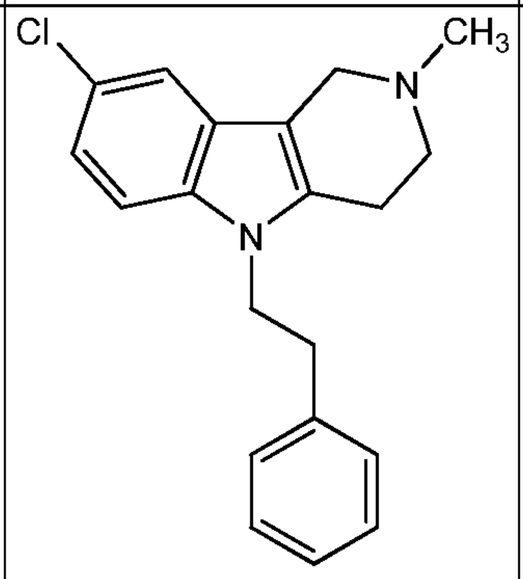

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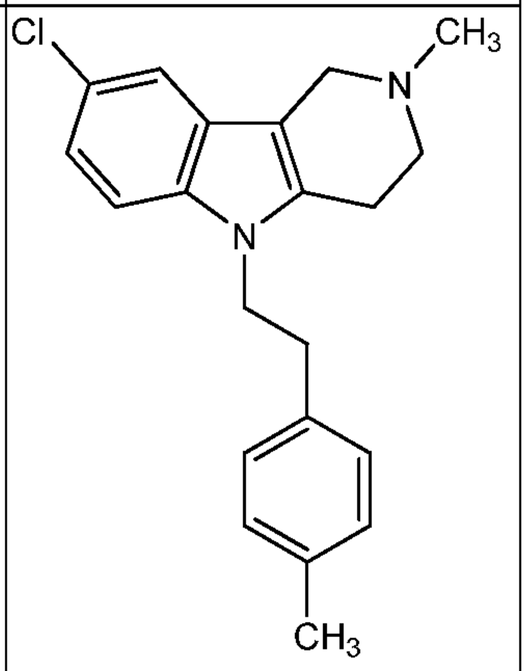

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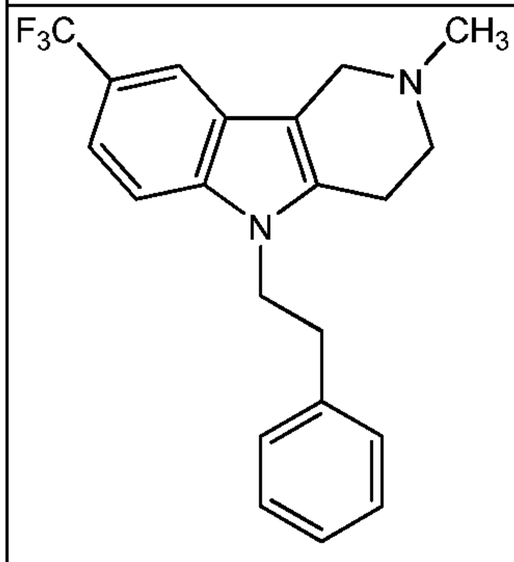

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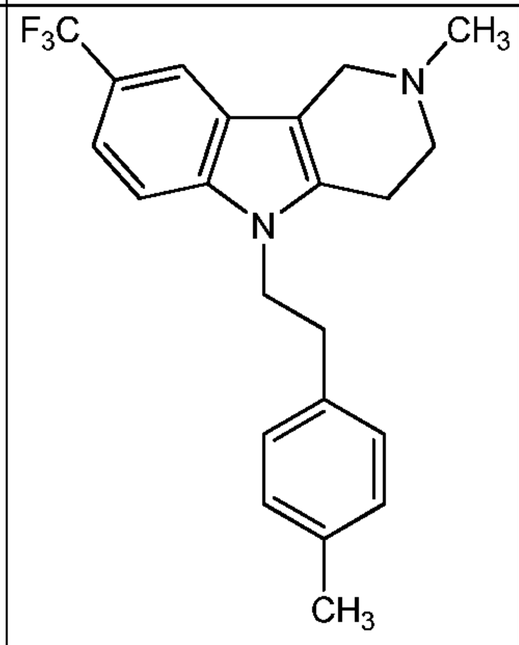

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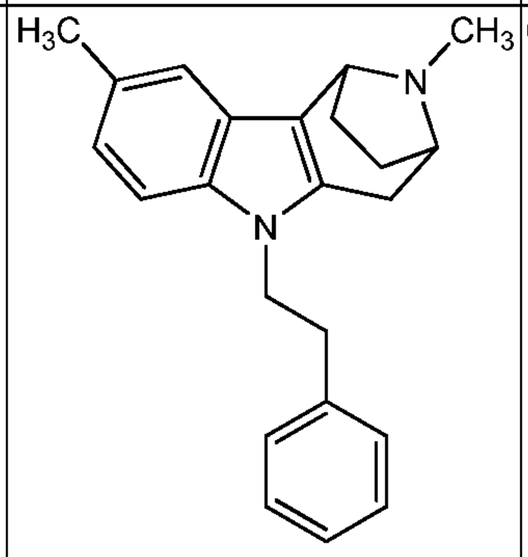

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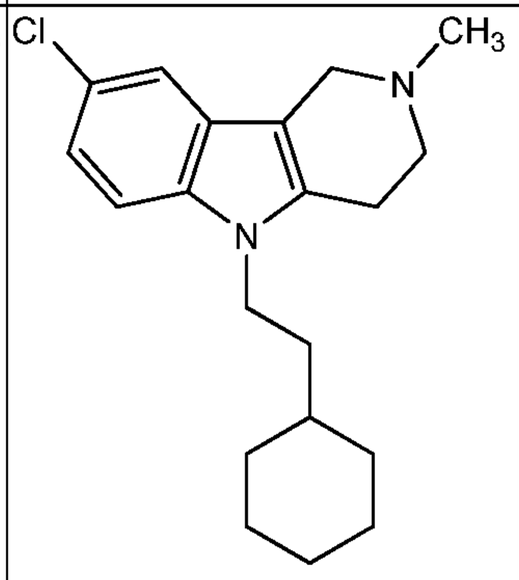

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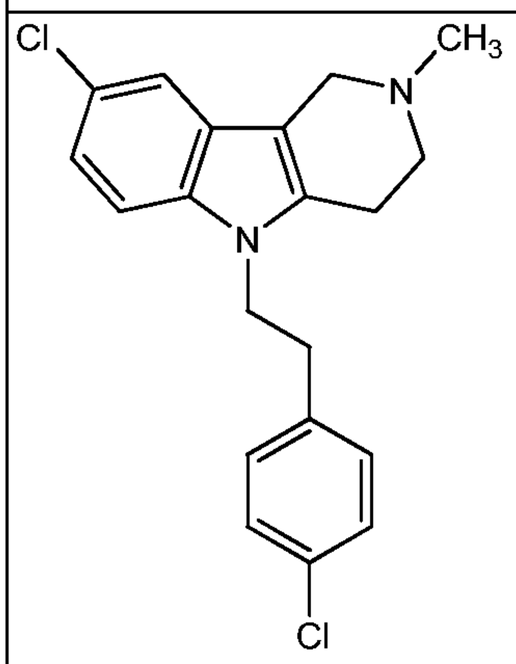

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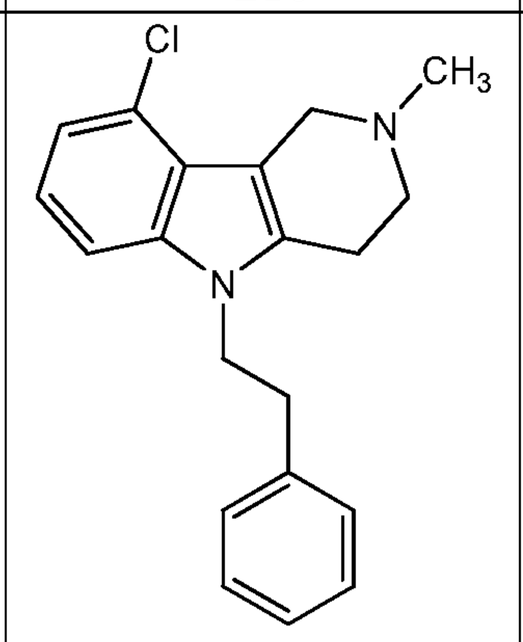

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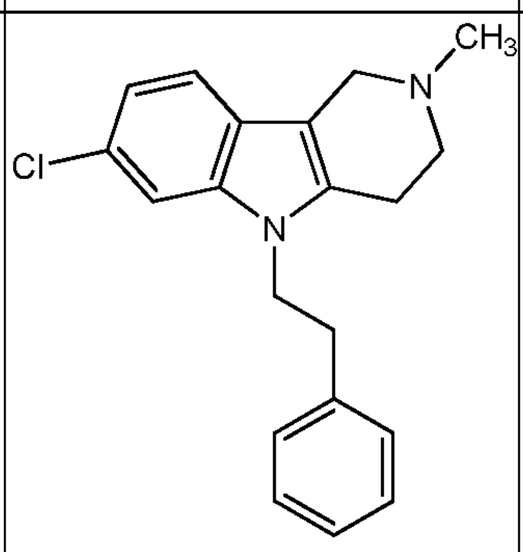

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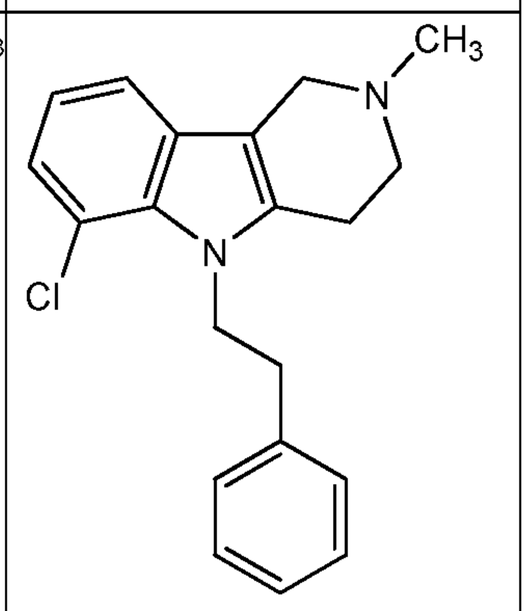

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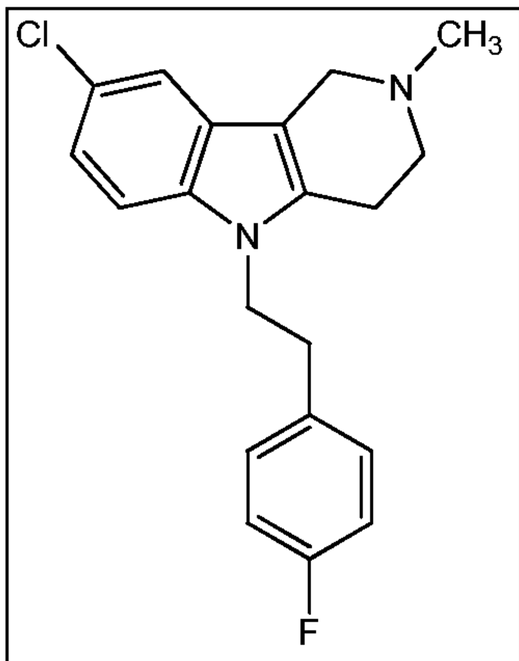

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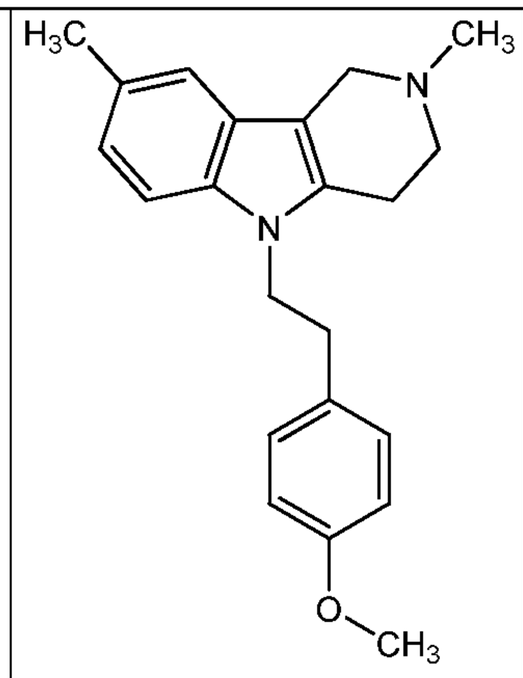

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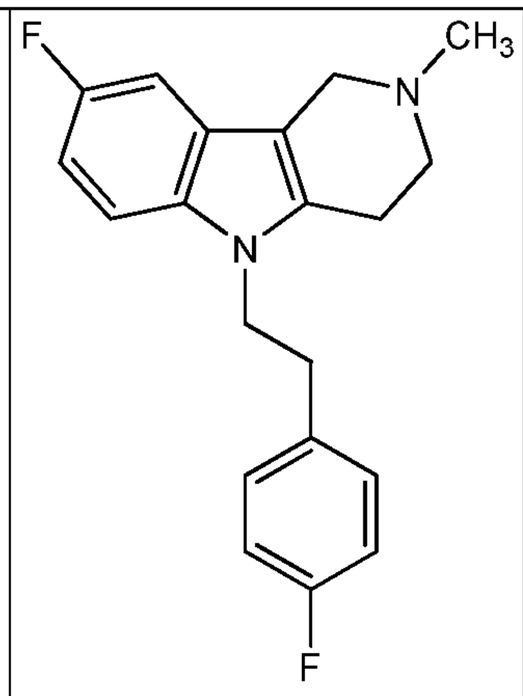

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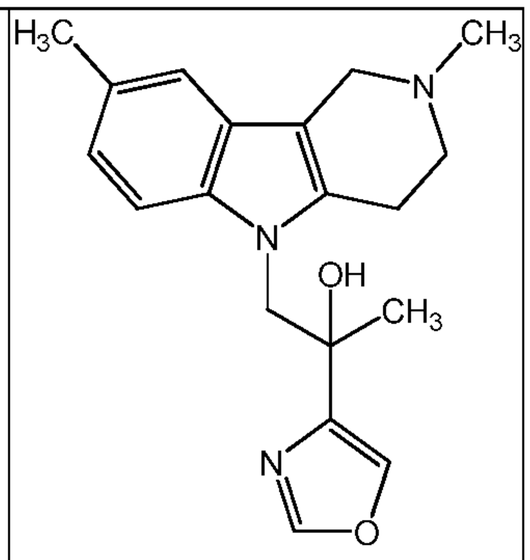

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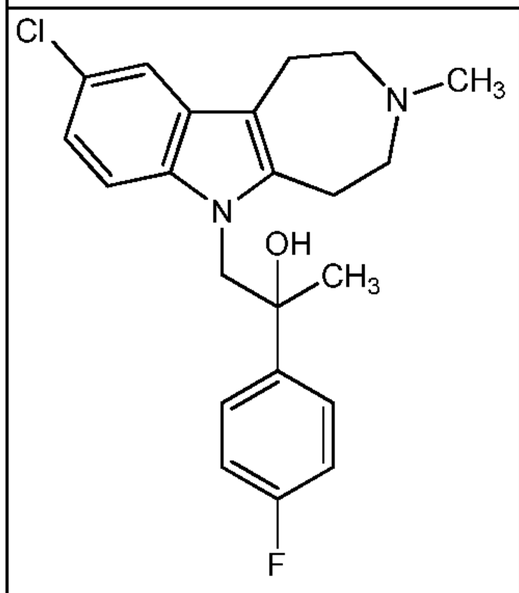

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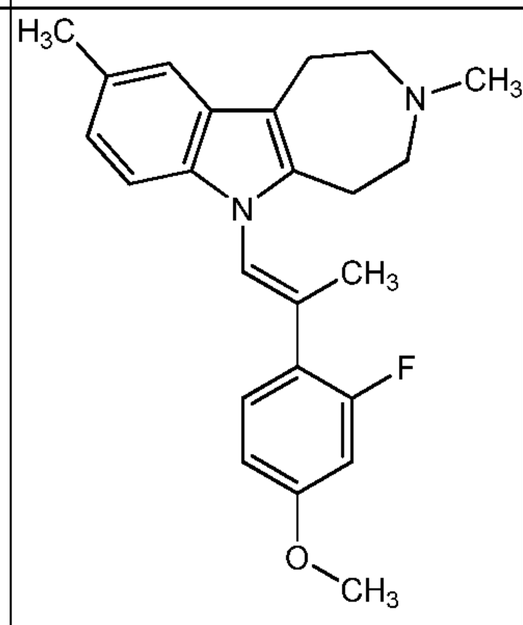

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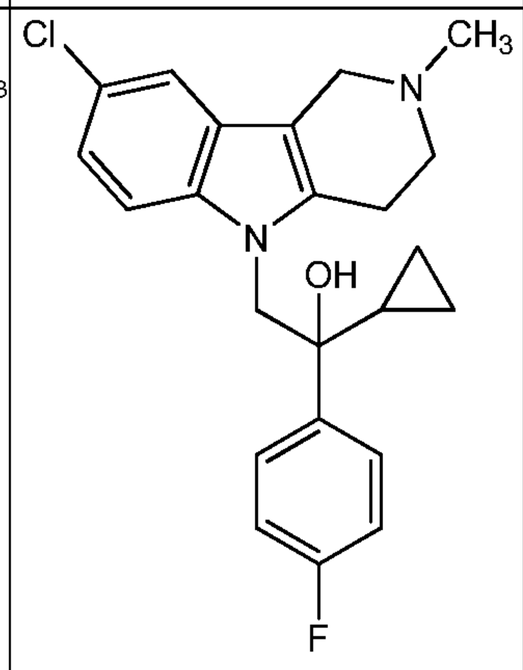

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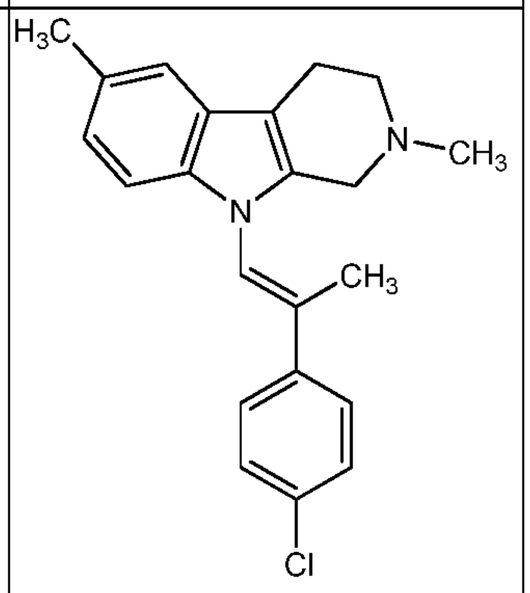

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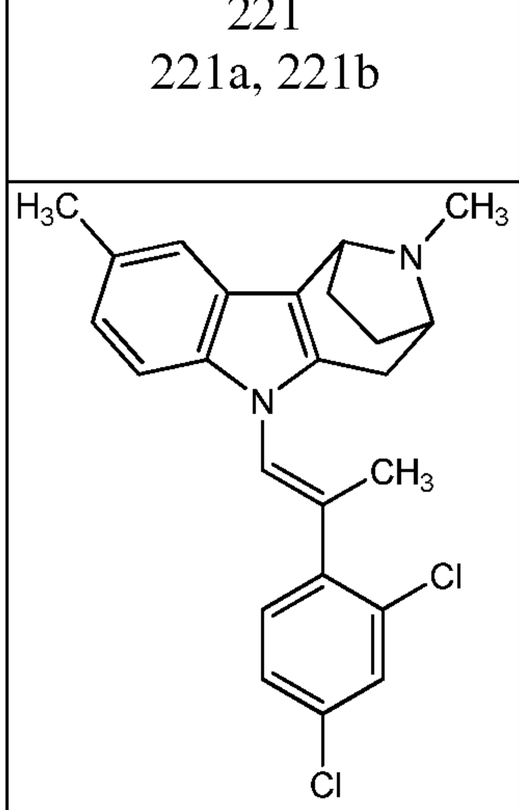

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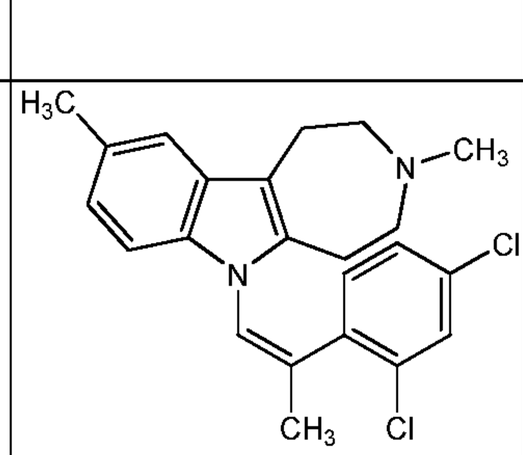

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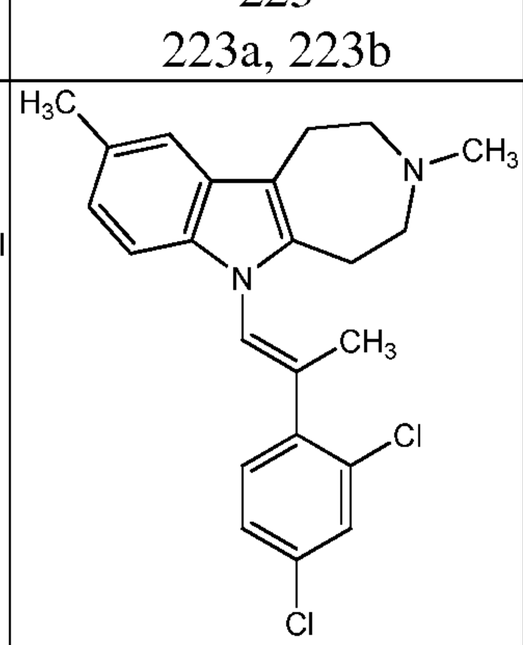

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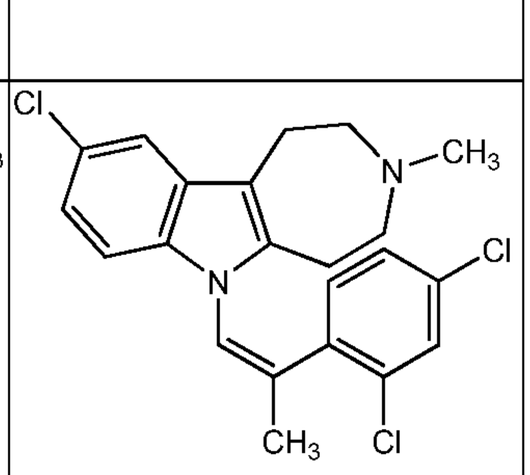

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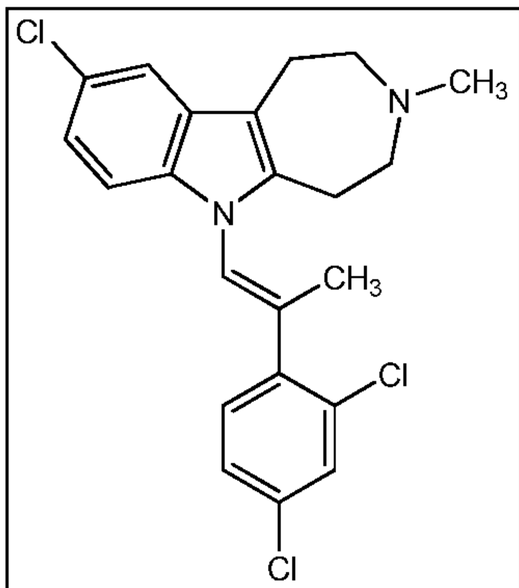
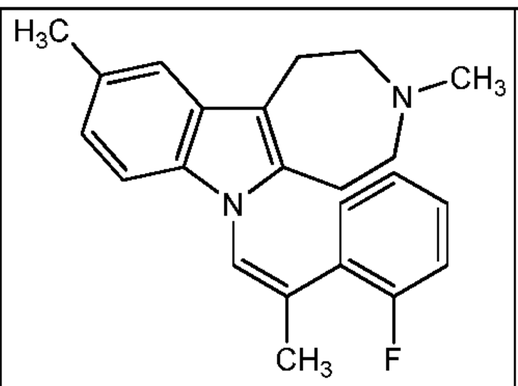
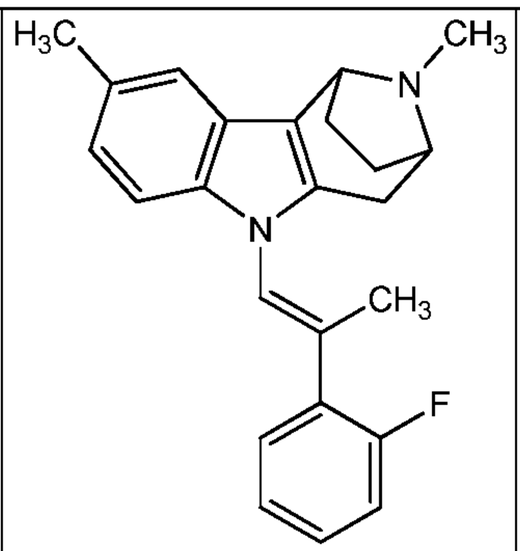
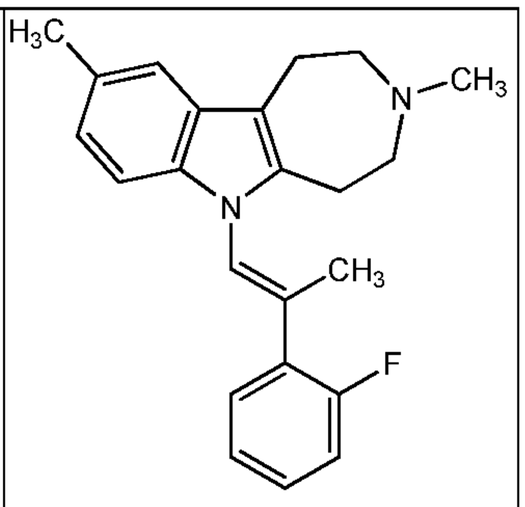
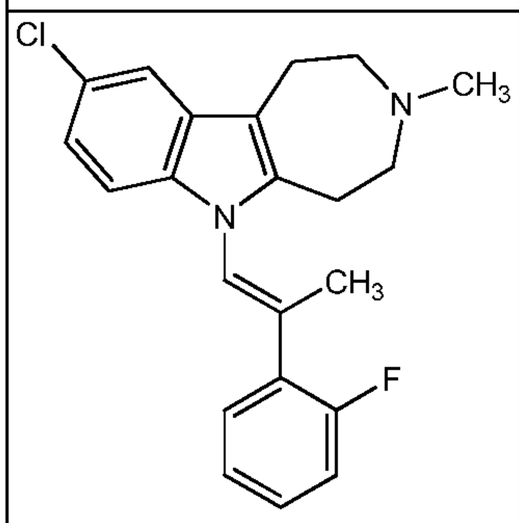
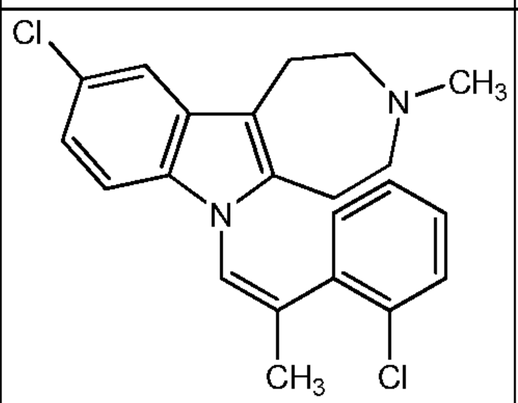
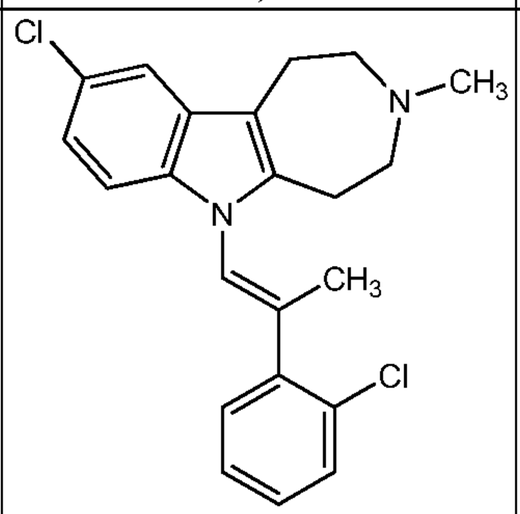
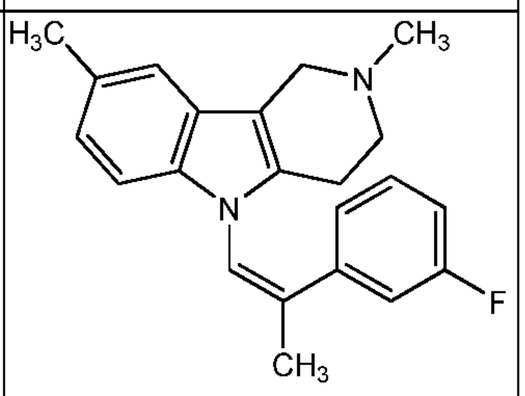
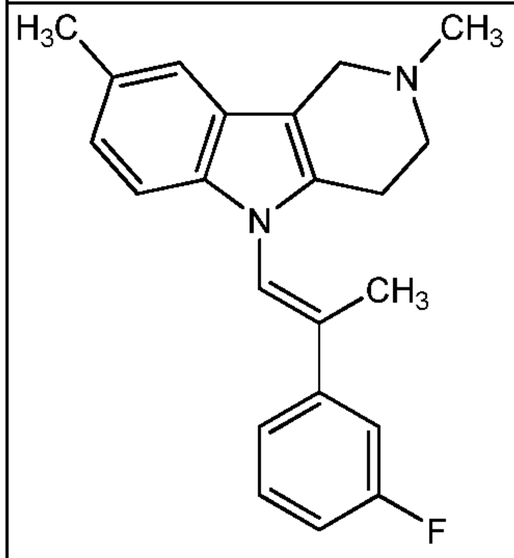
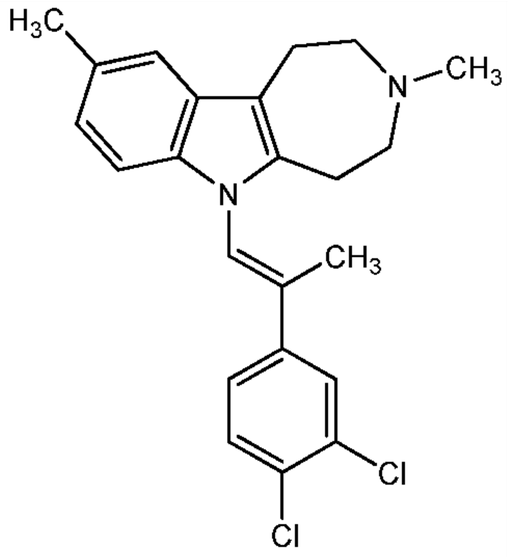
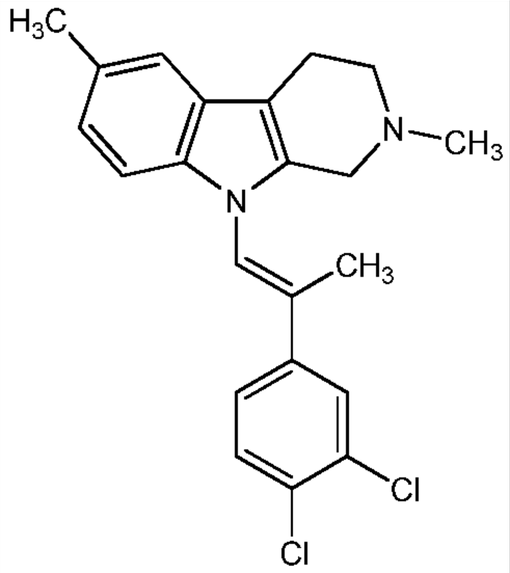
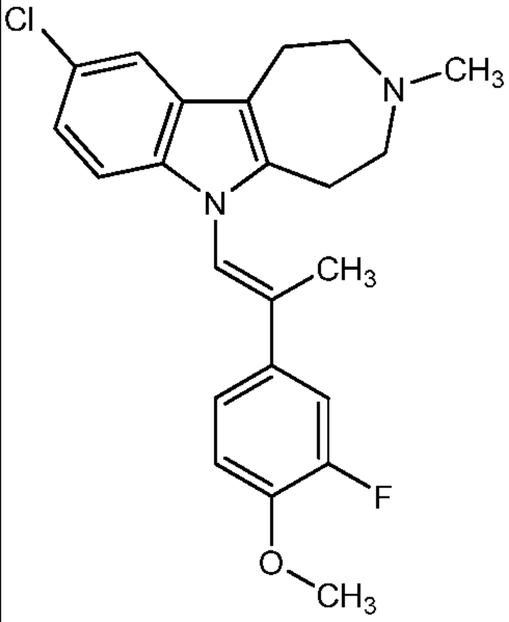
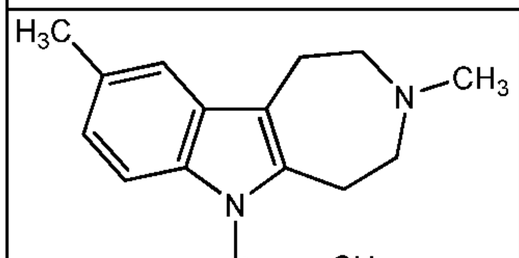
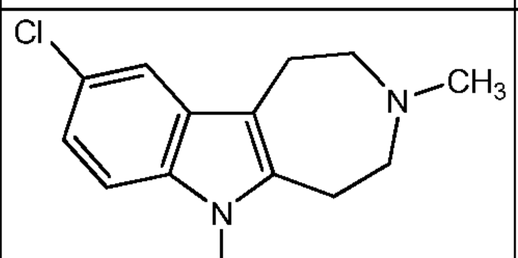
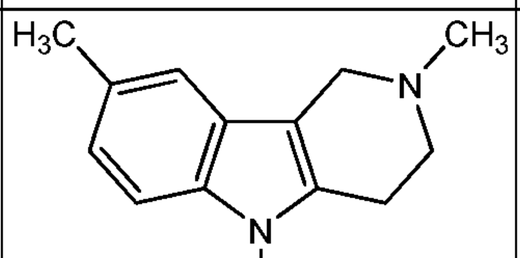
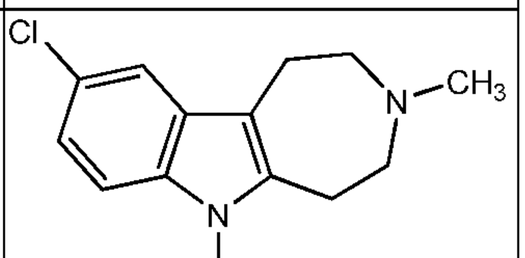
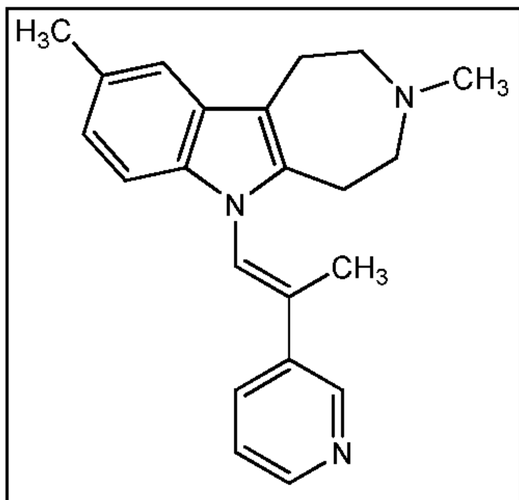
 229	 230	 231 231a, 231b	 232
 233	 234	 235	 236
 237	 238	 239	 240
 241	 242	 243	 244



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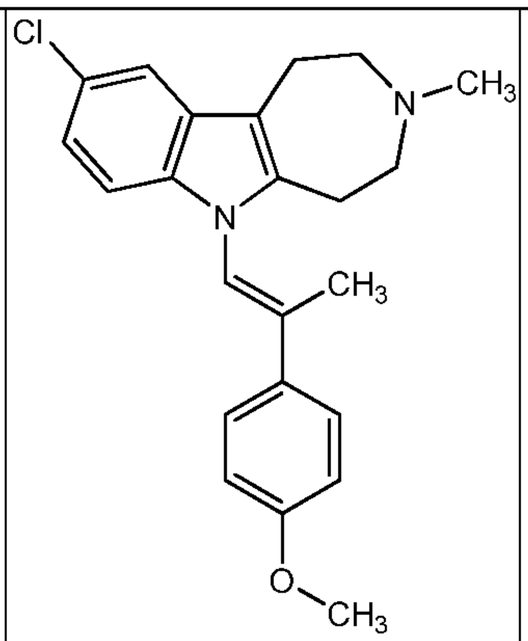

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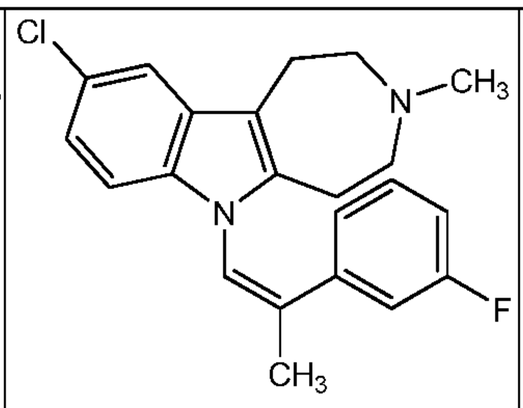

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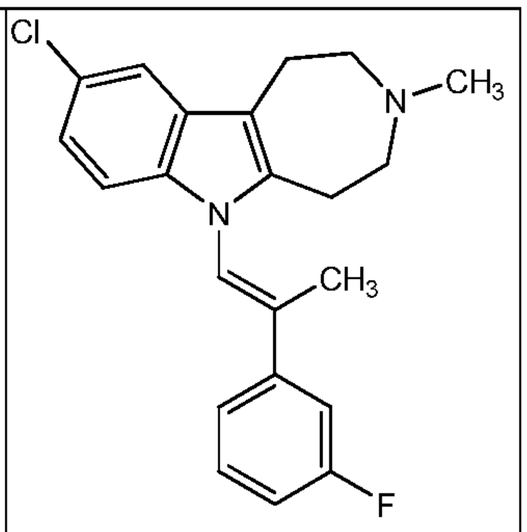

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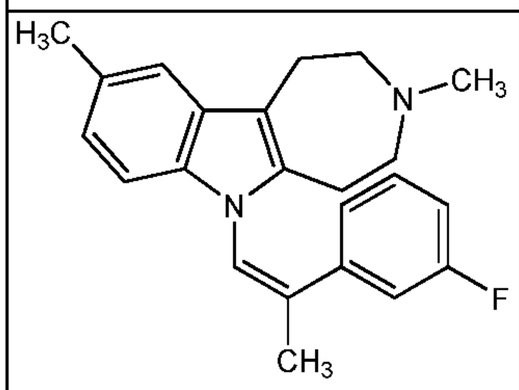

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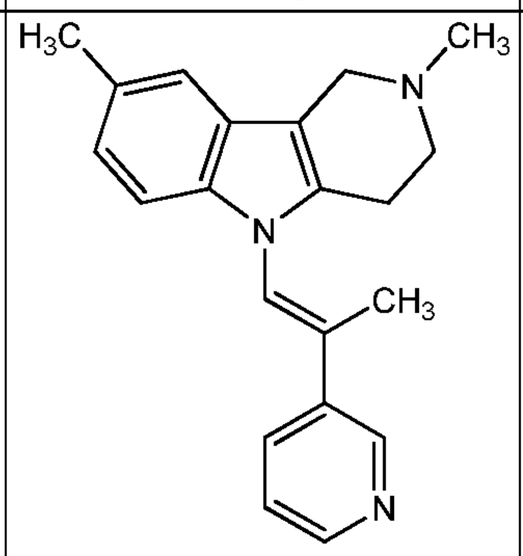

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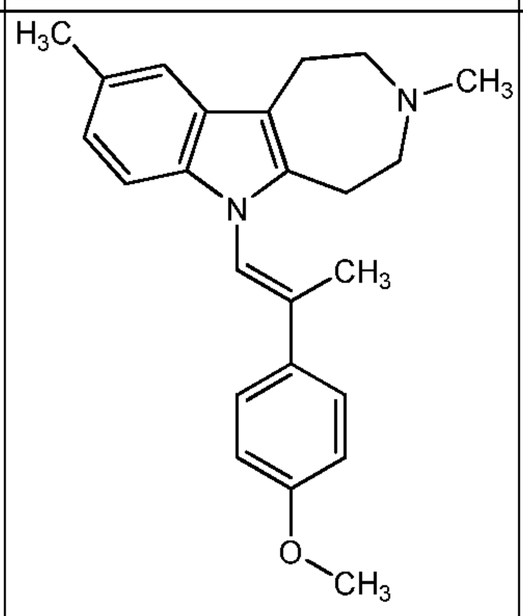

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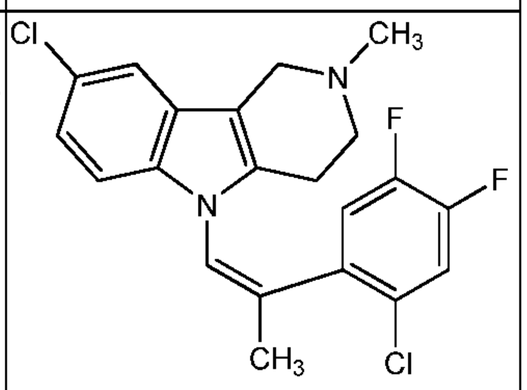

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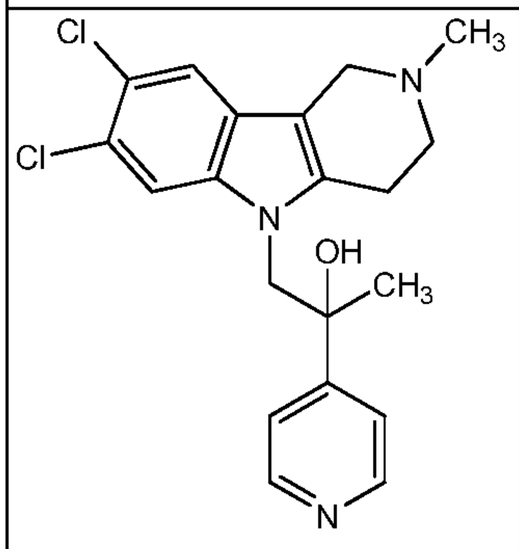

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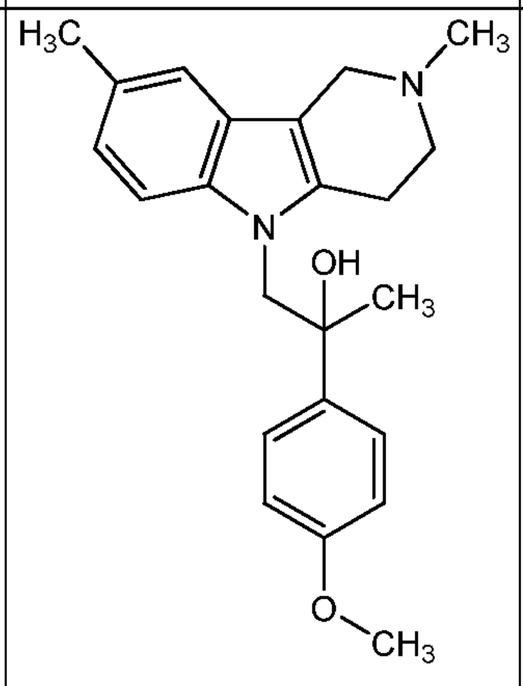

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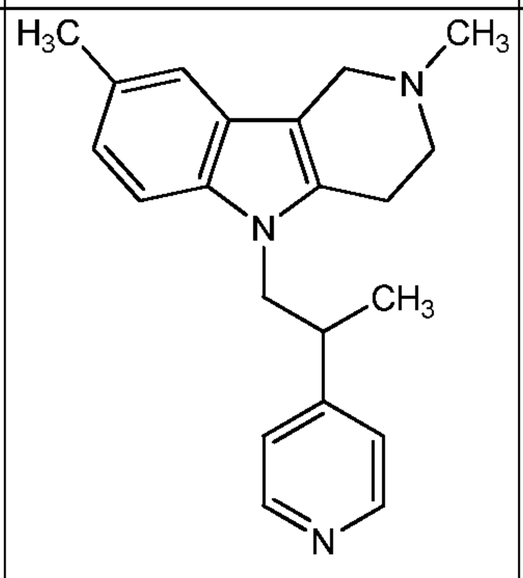

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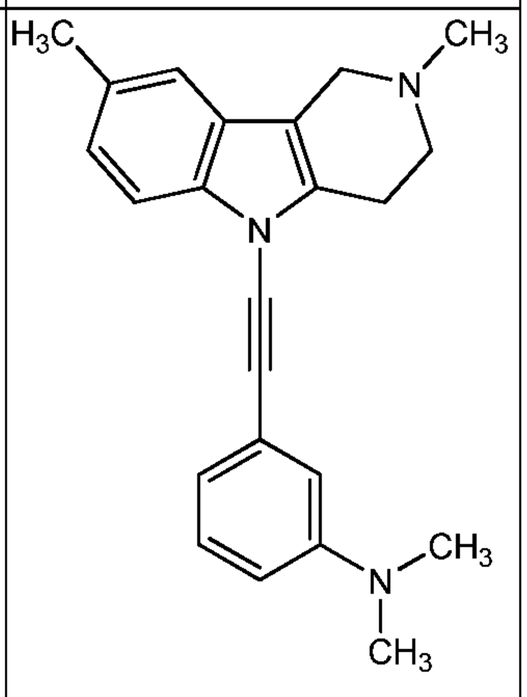

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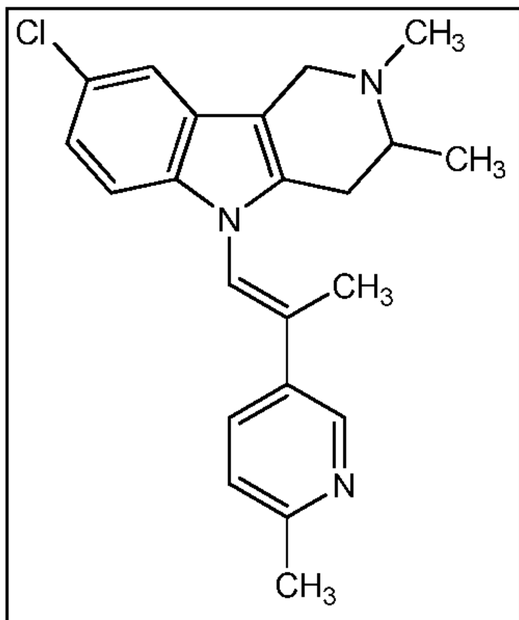

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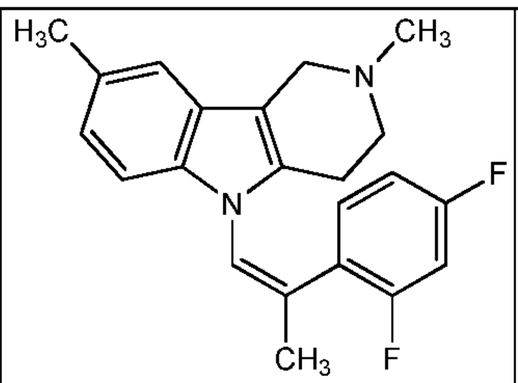

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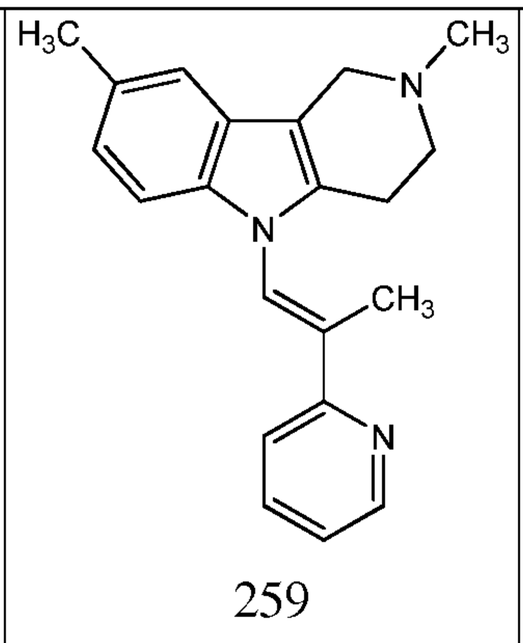

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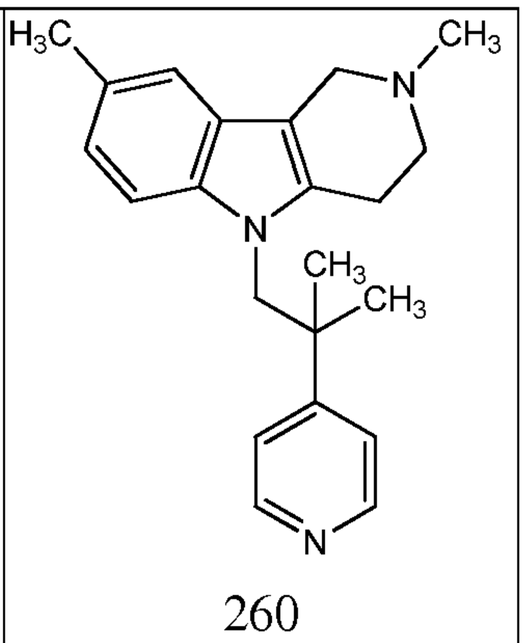

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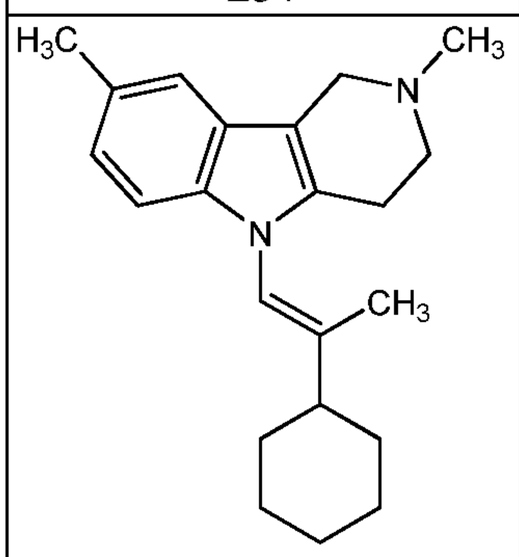

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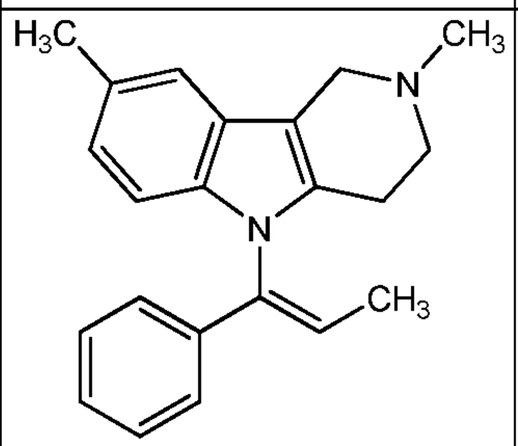

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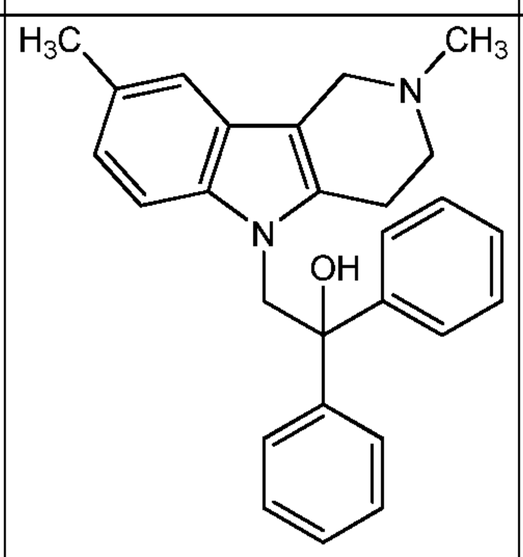

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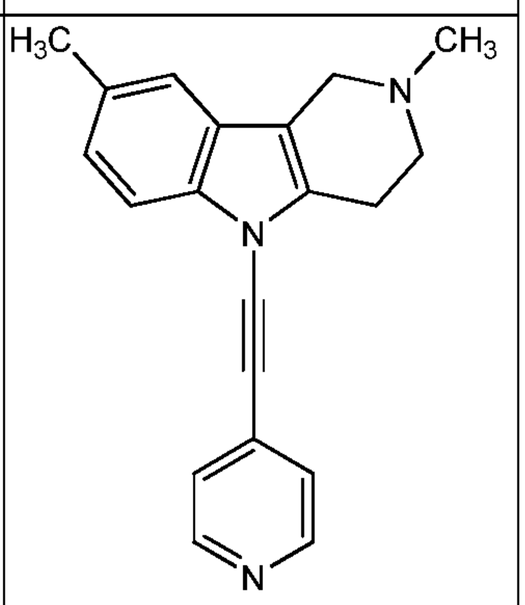

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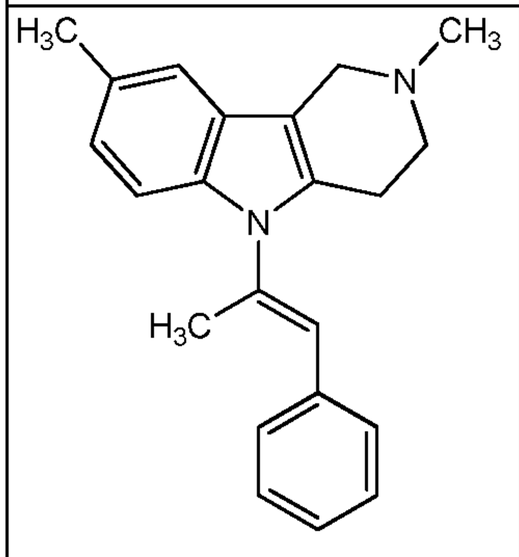

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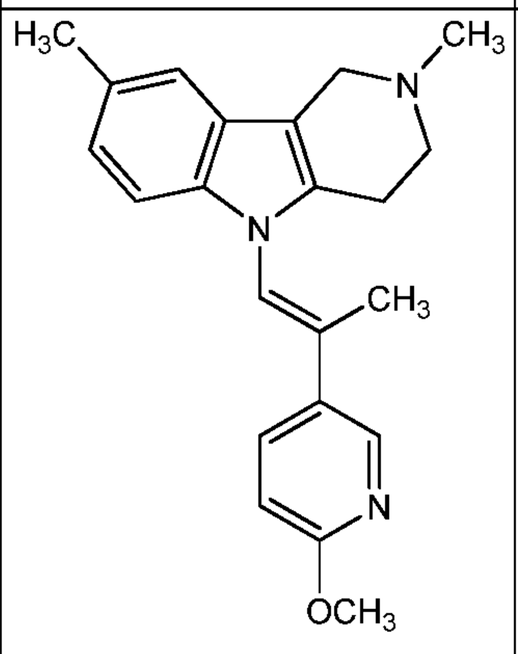

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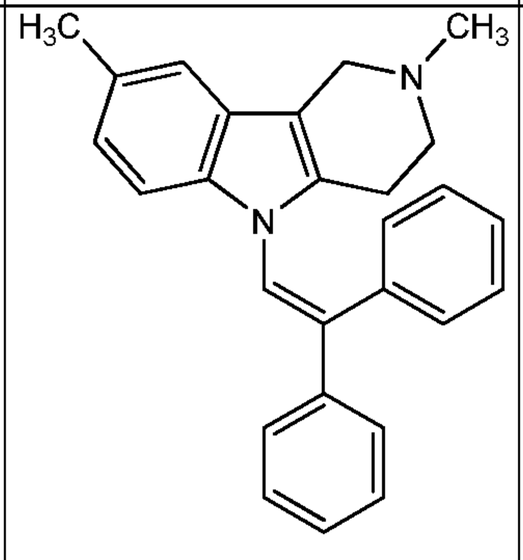

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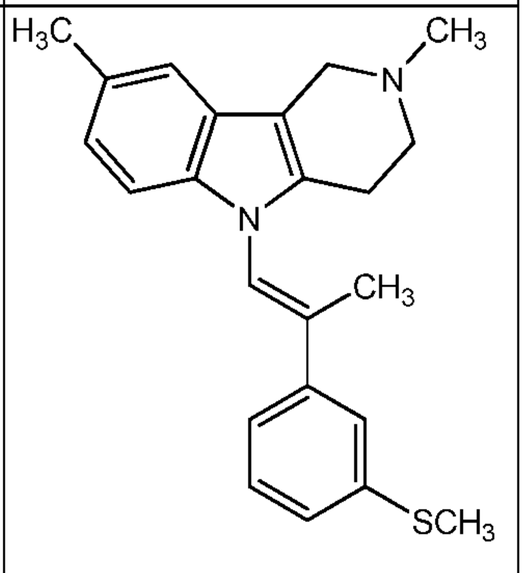

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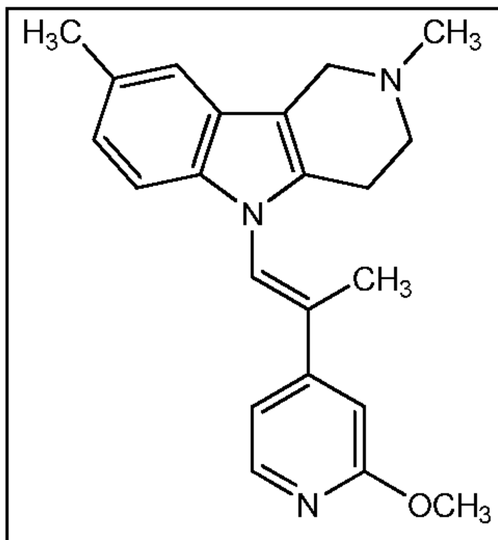

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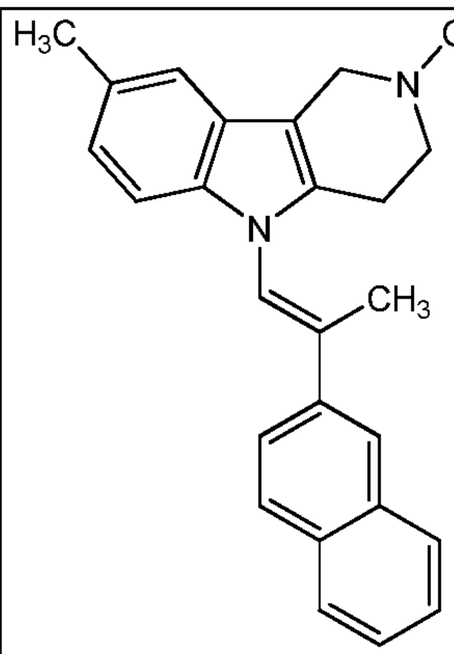

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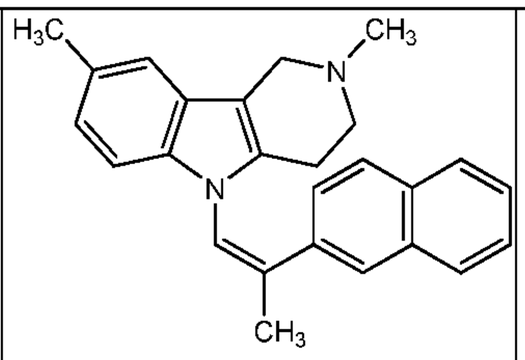

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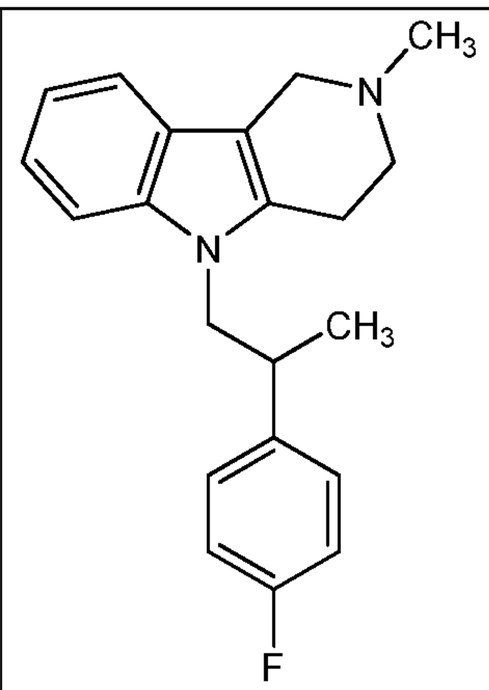

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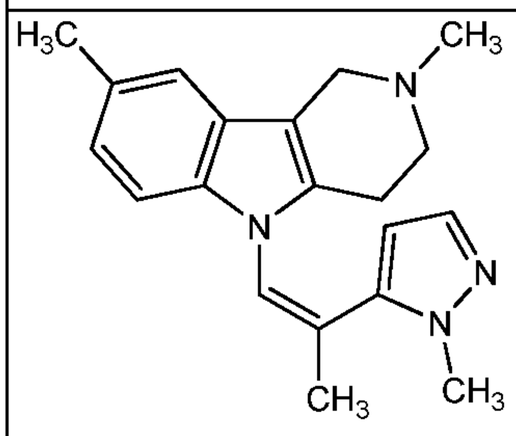

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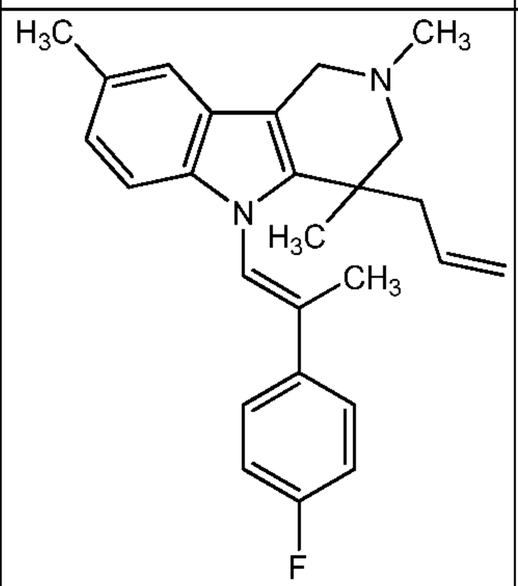

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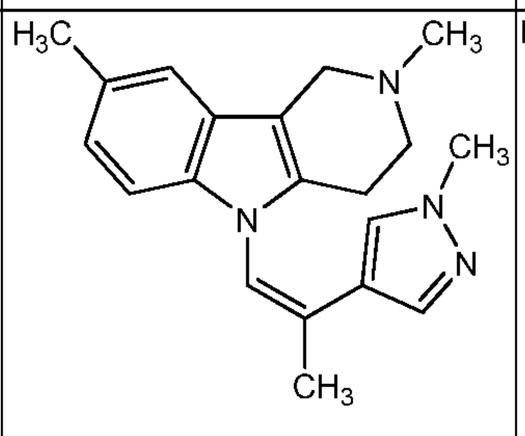

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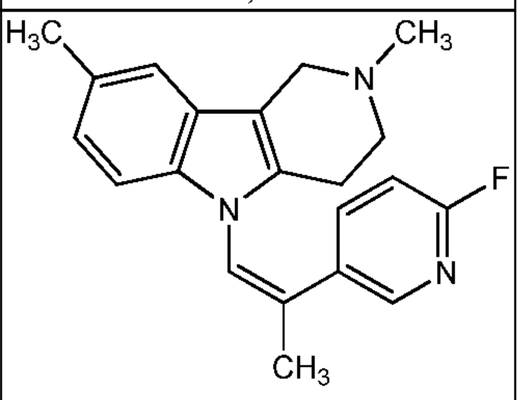

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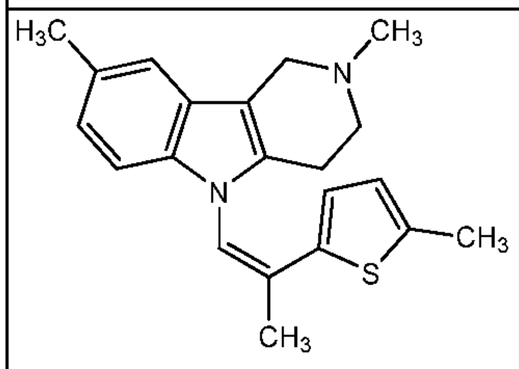

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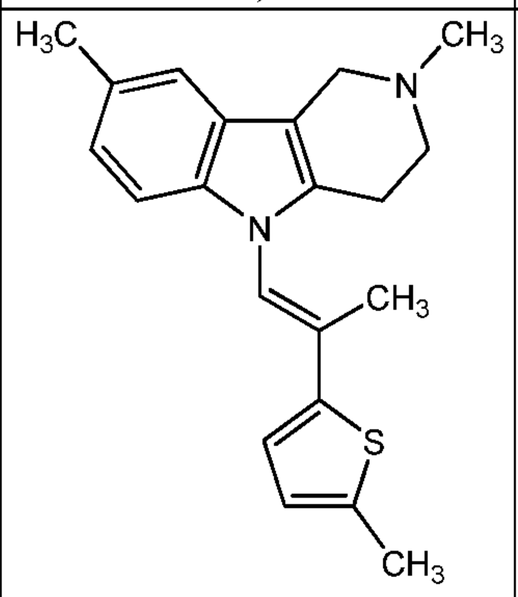

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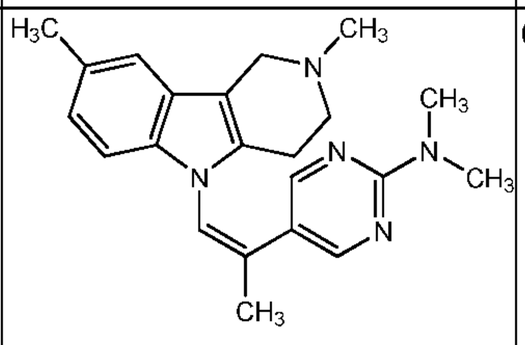

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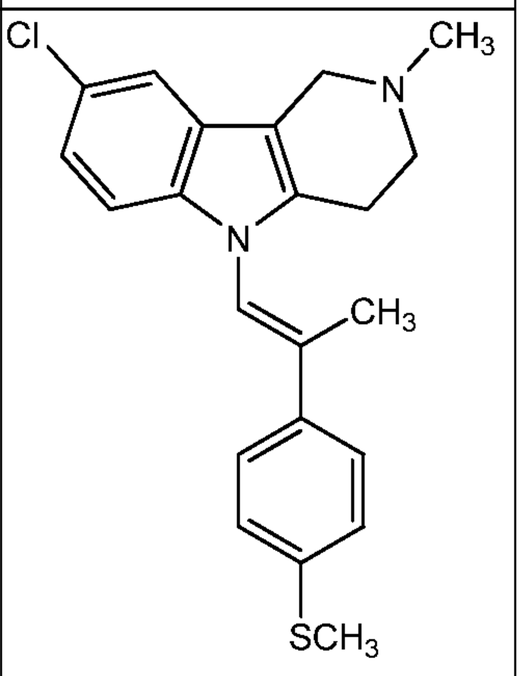

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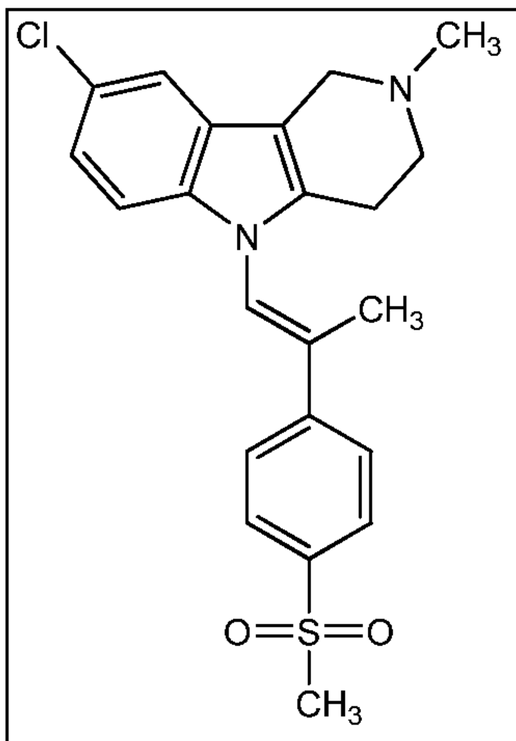

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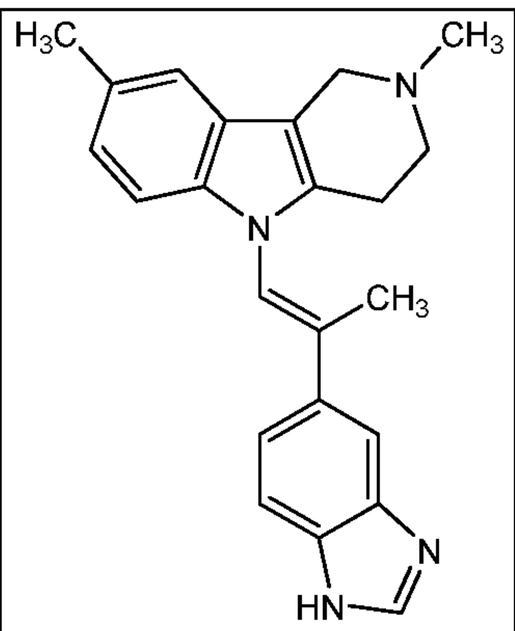

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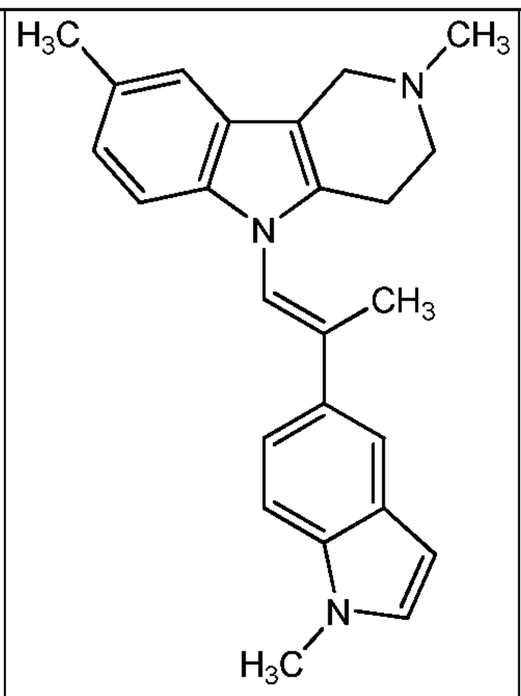

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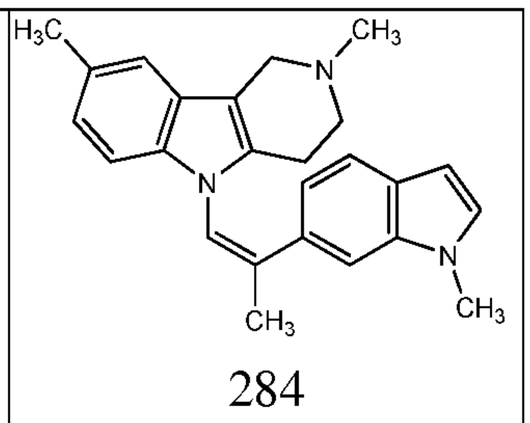

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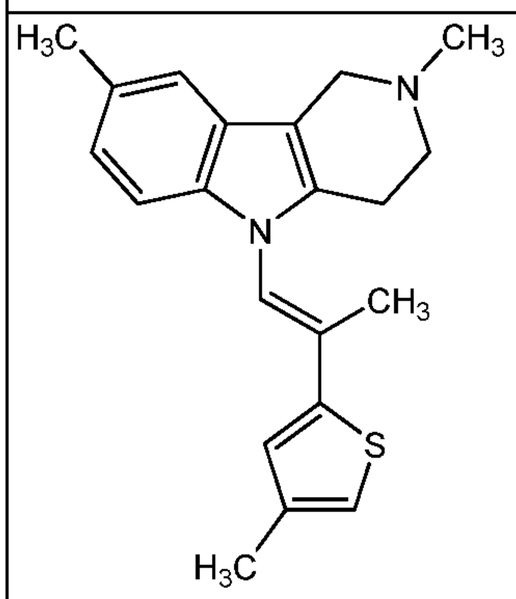

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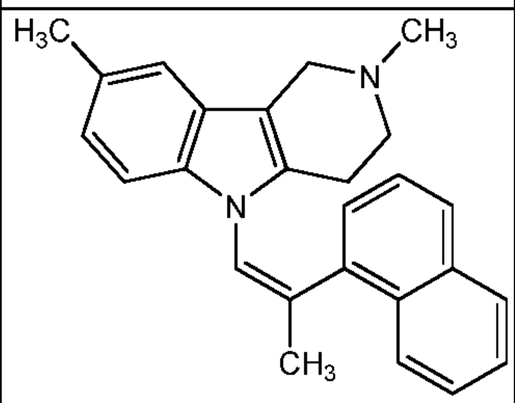

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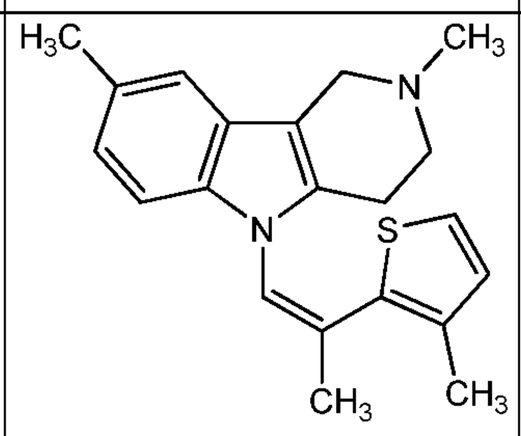

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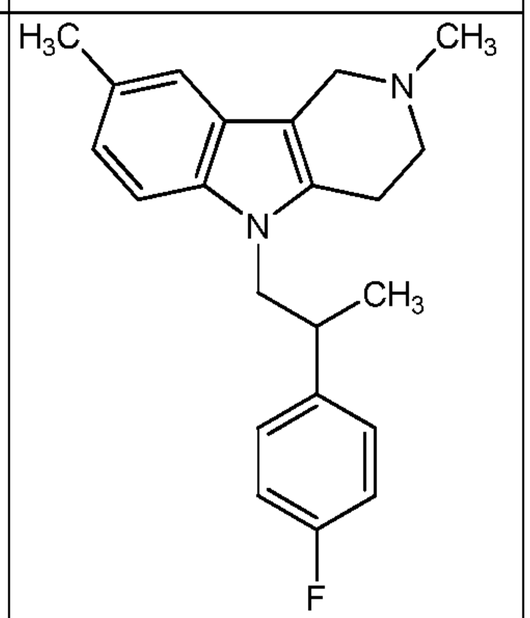

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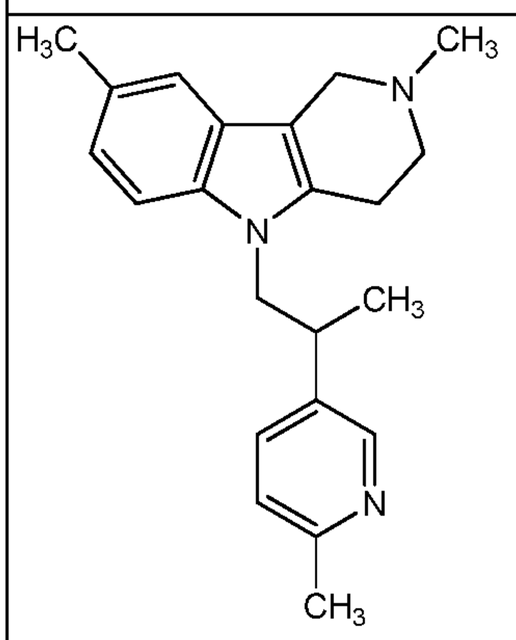

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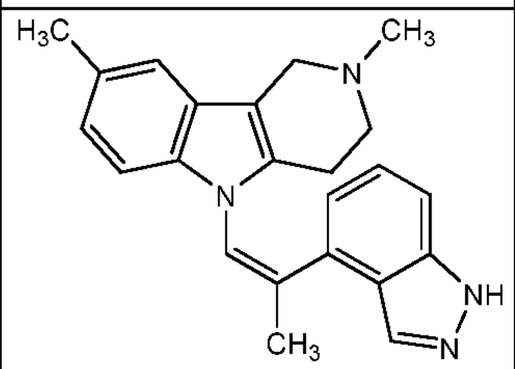

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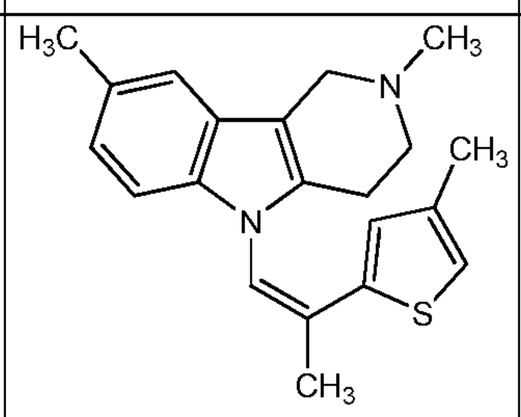

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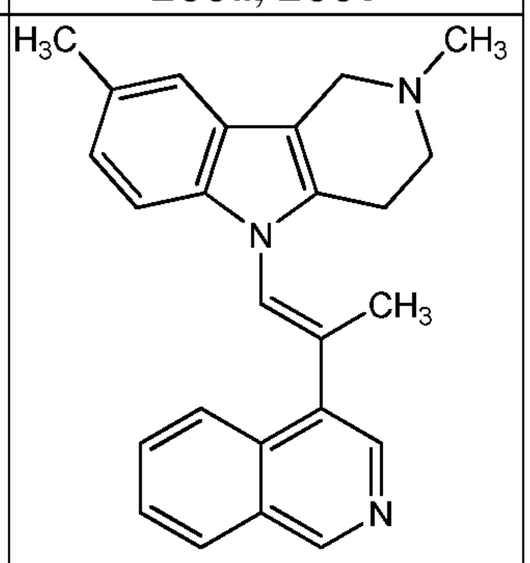

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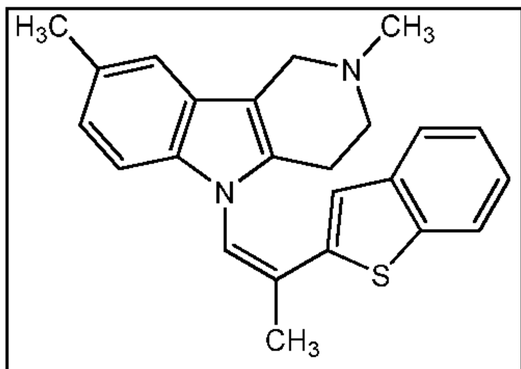

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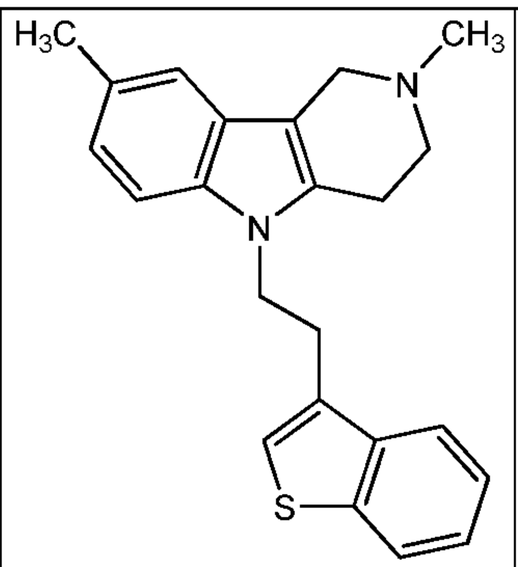

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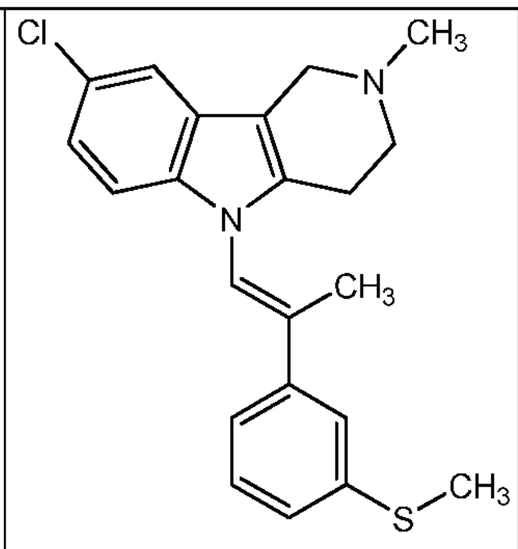

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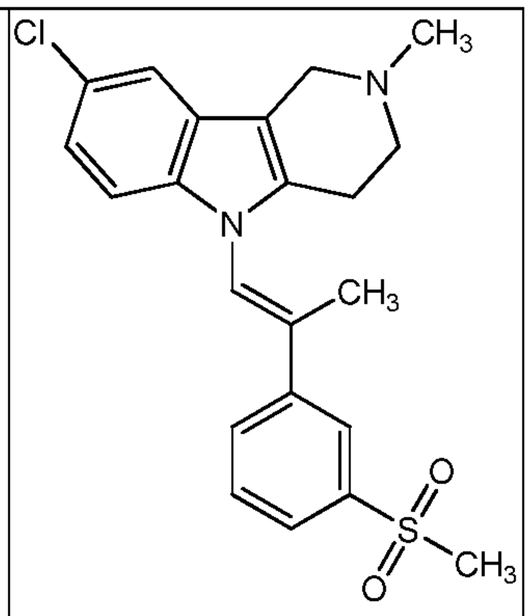

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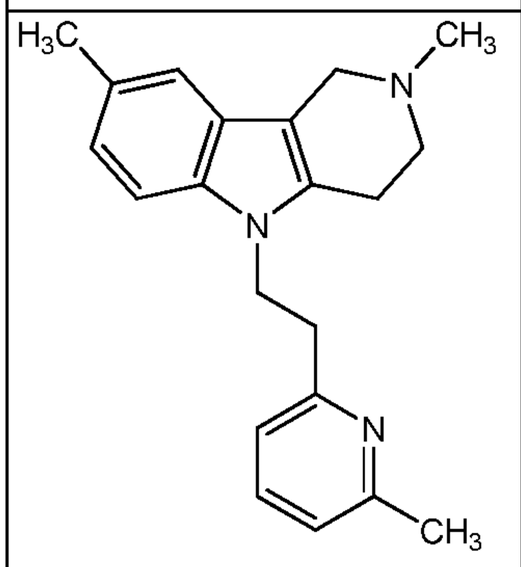

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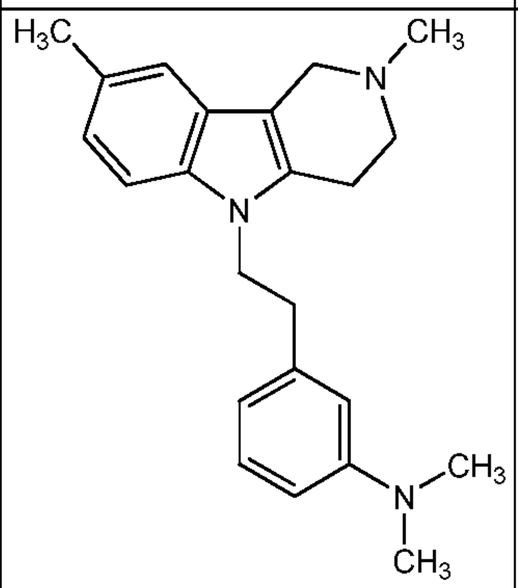

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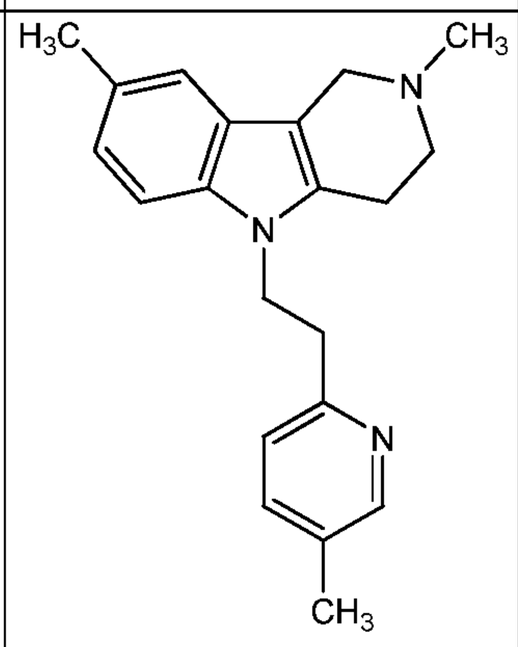

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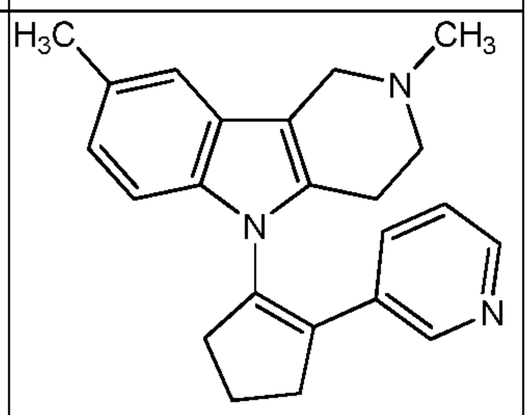

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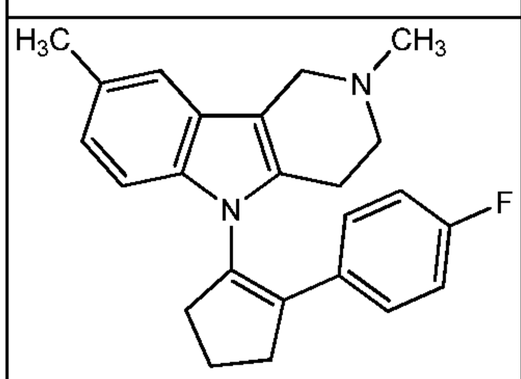

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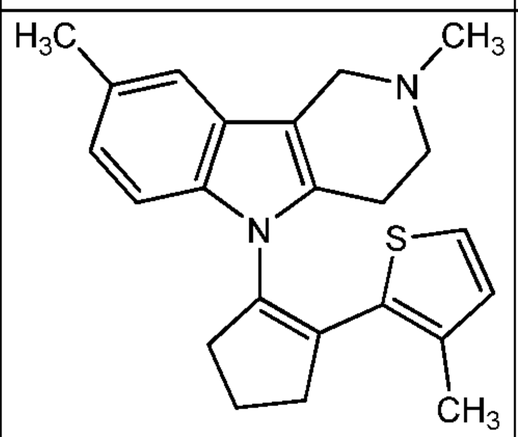

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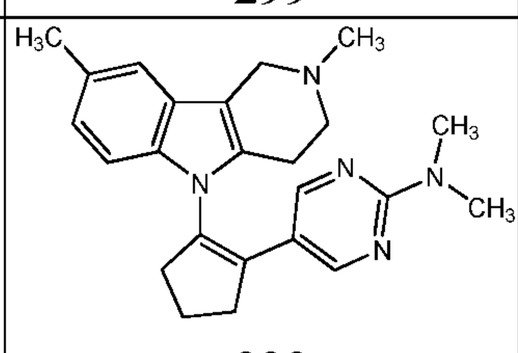

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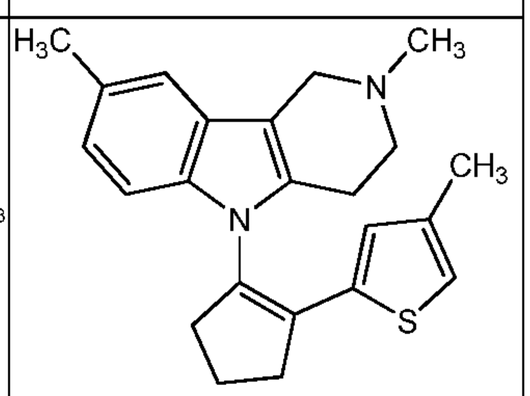

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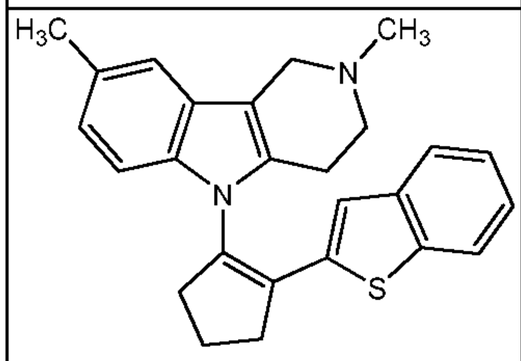

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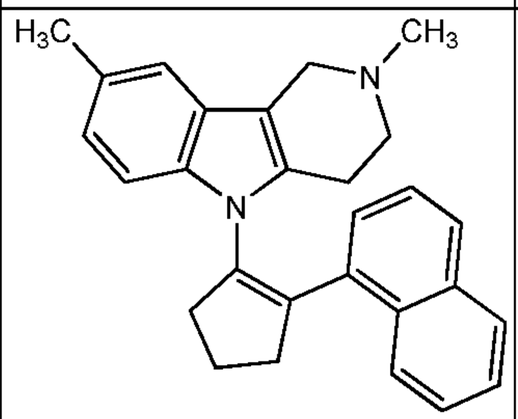

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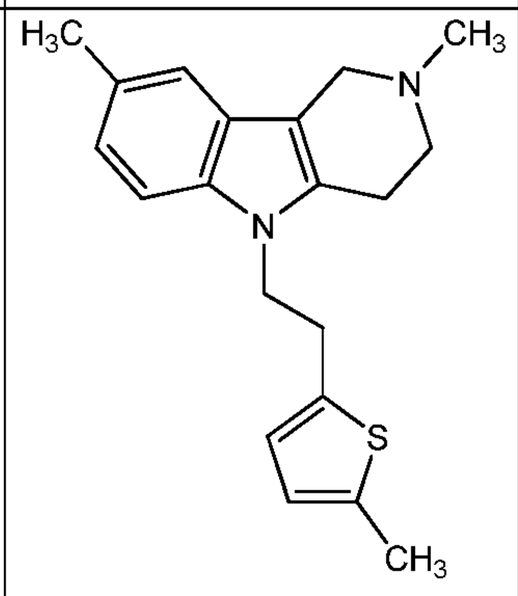

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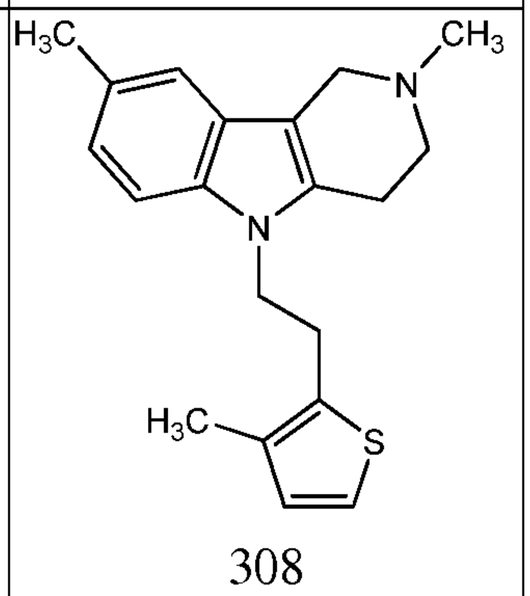

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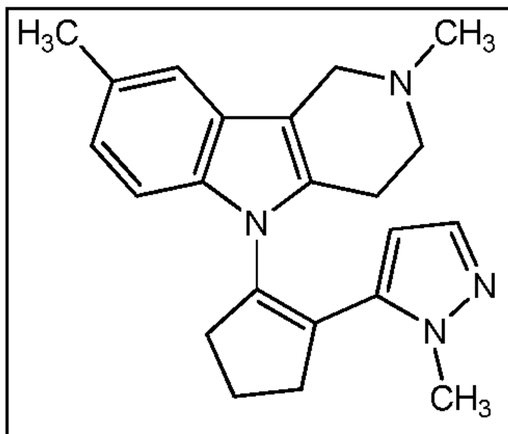

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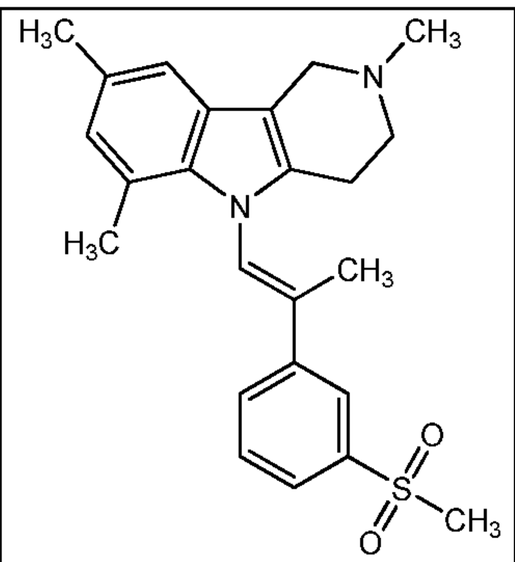

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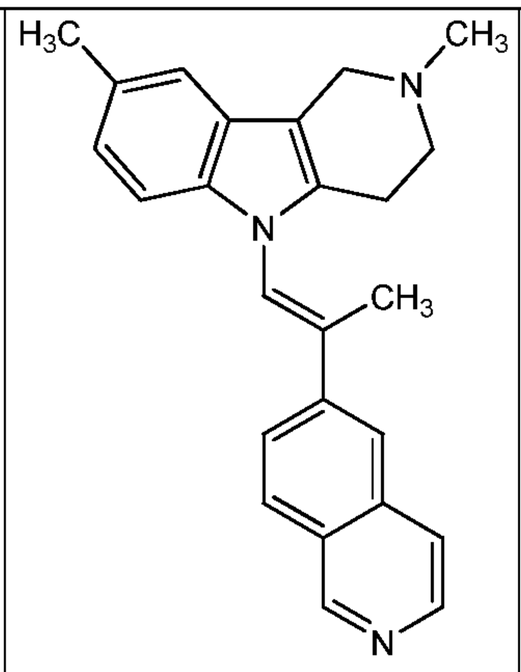

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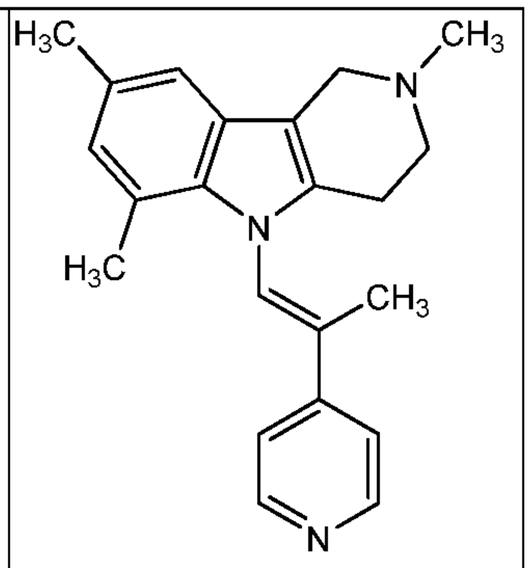

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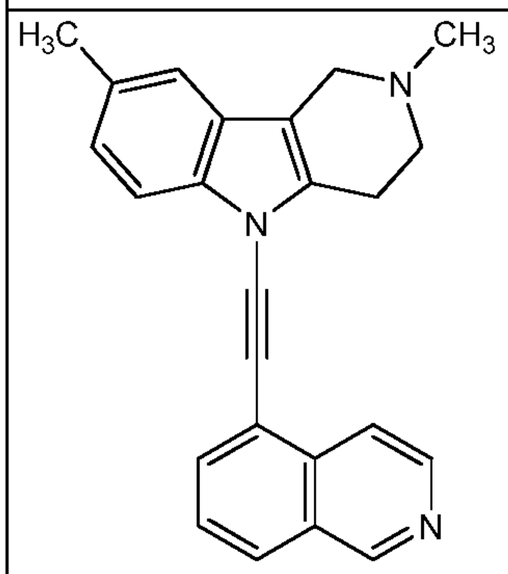

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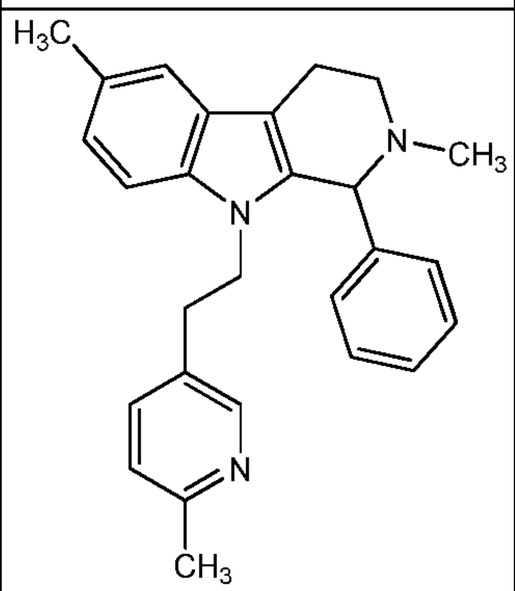

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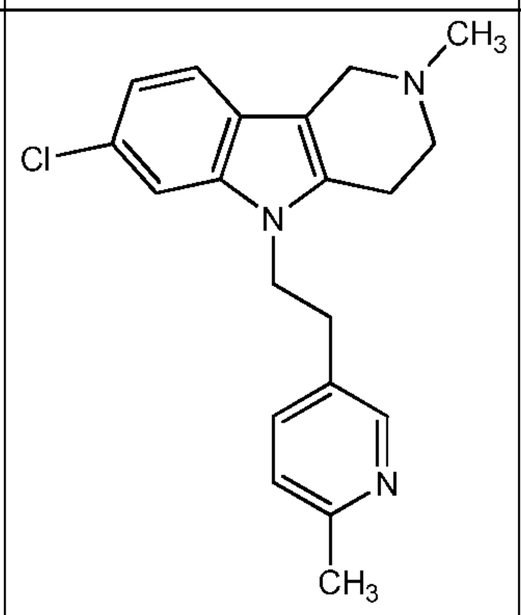

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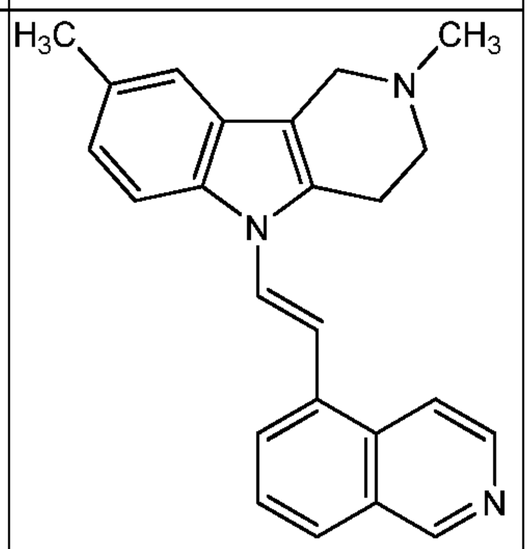

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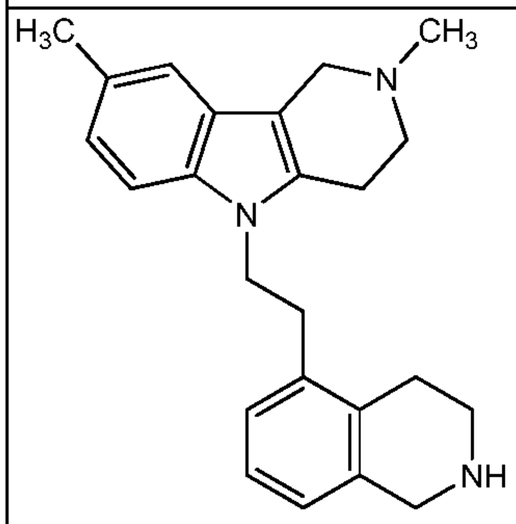

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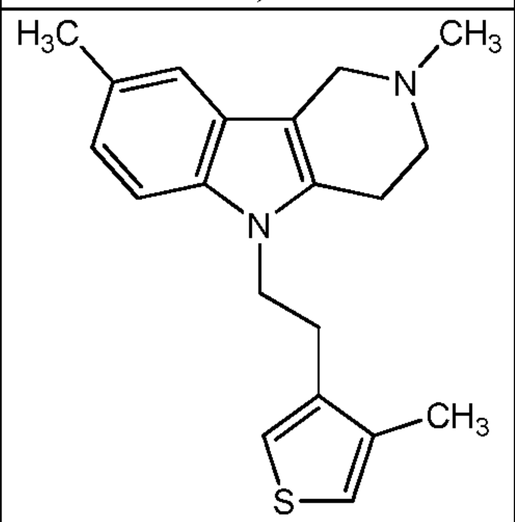

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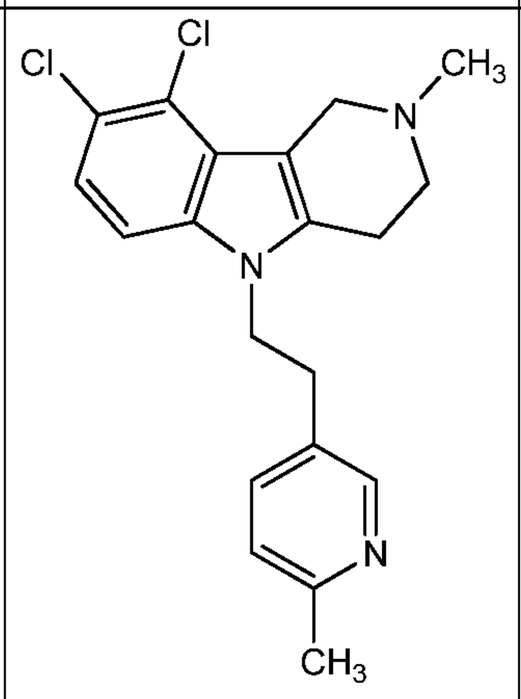

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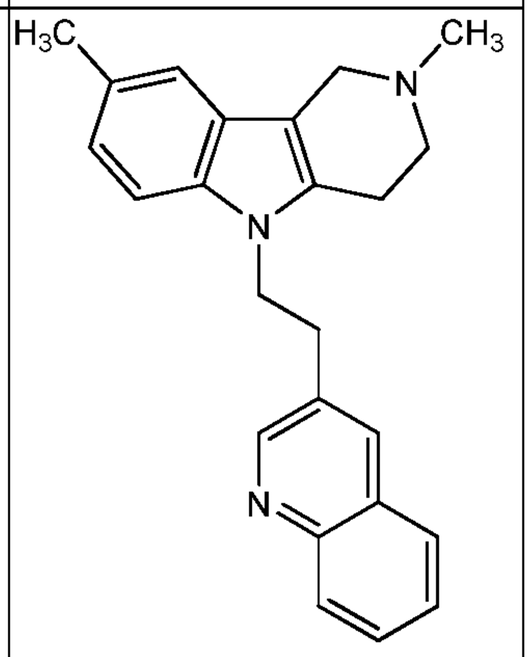

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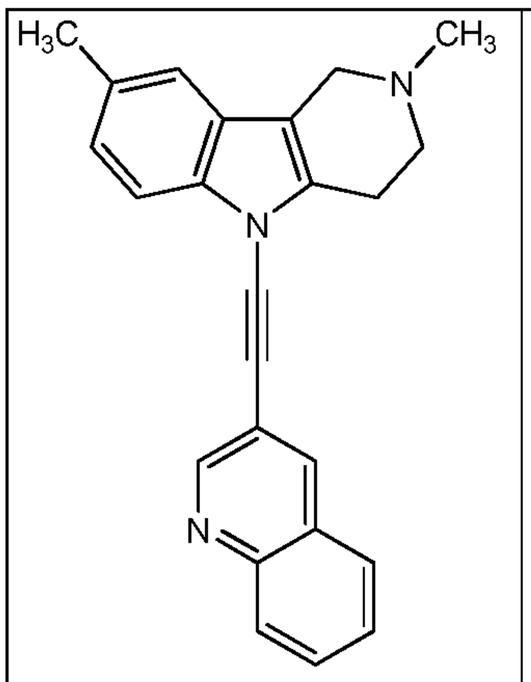

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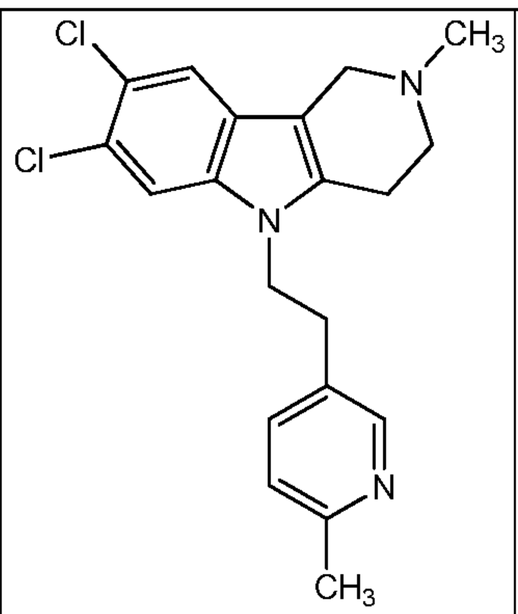

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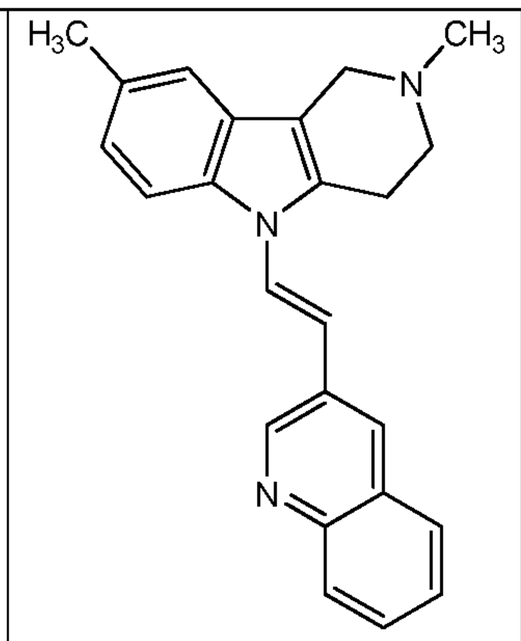

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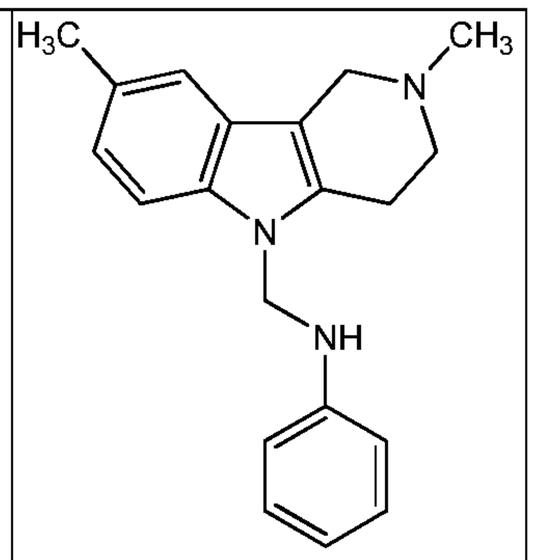

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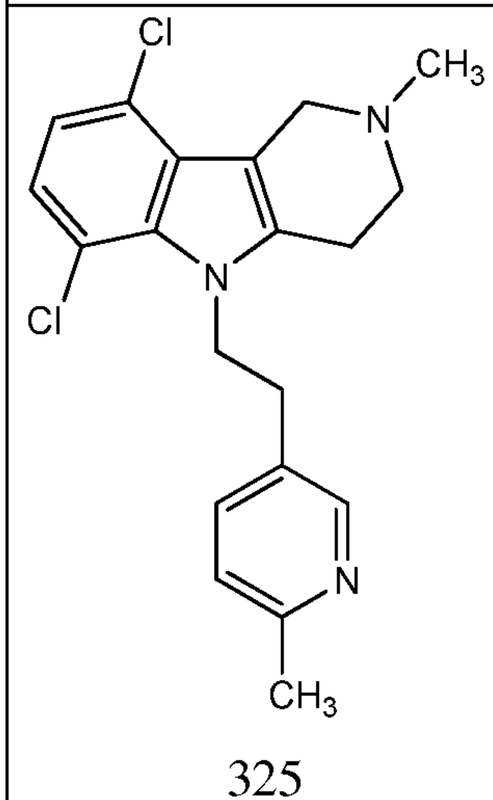

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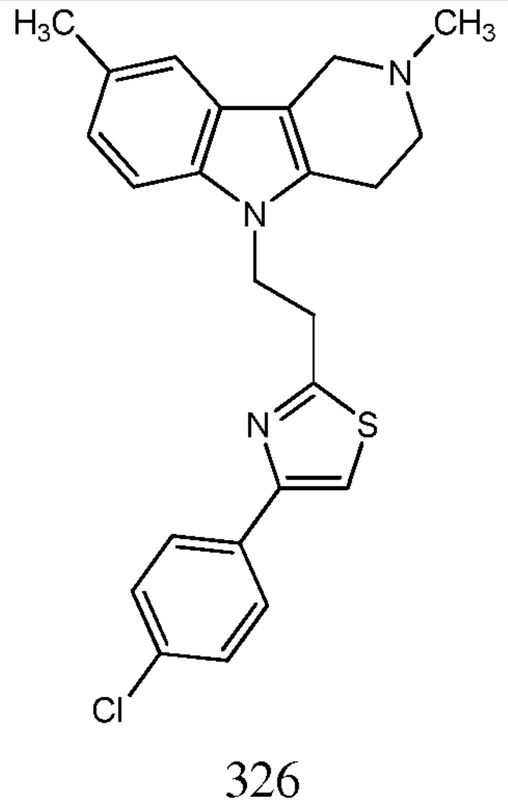

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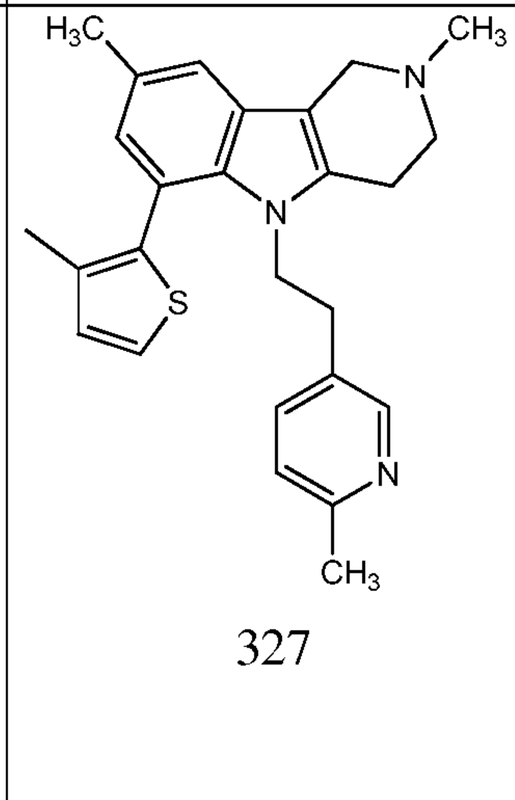

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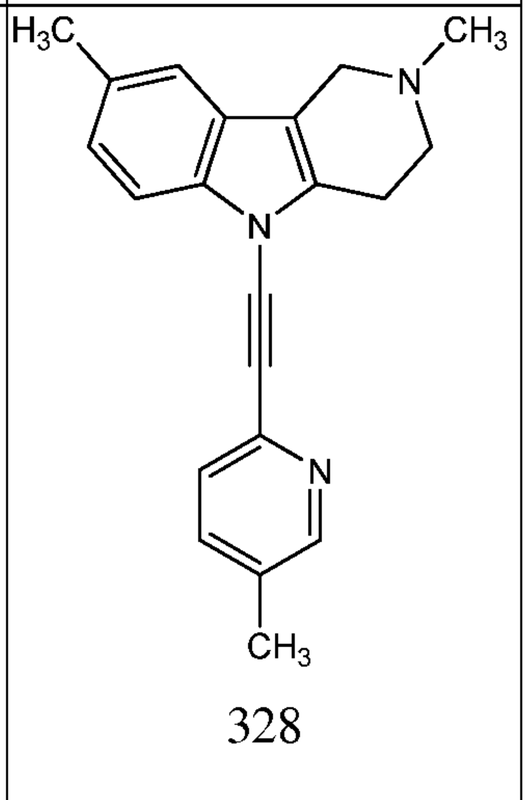

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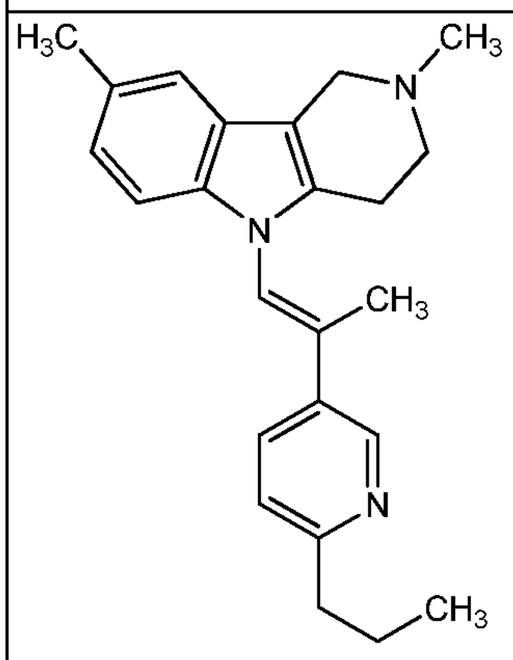

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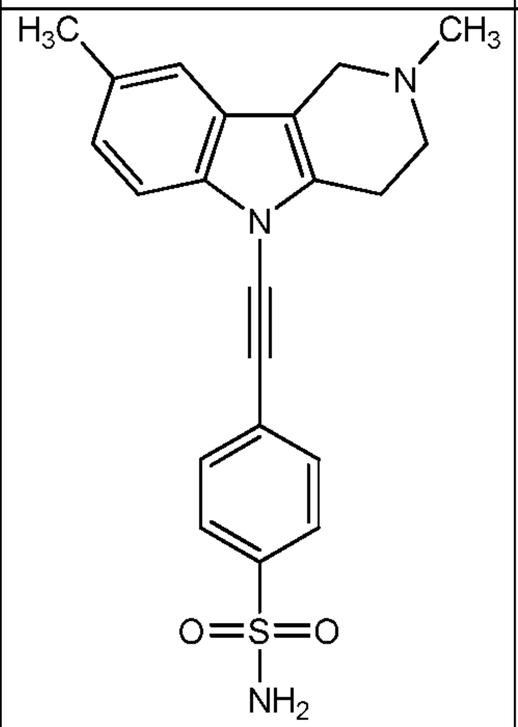

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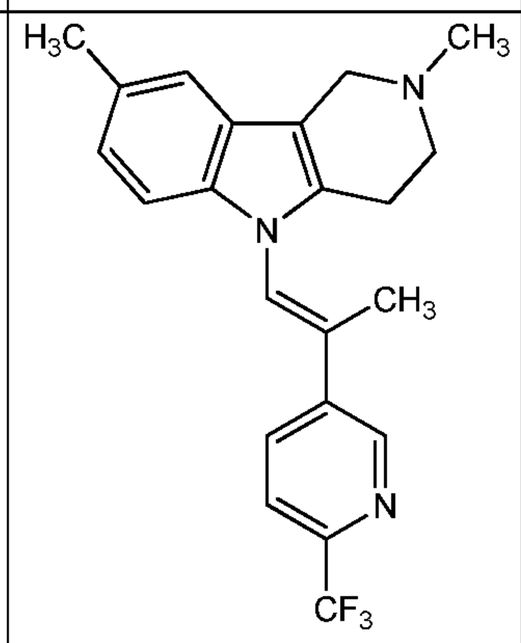

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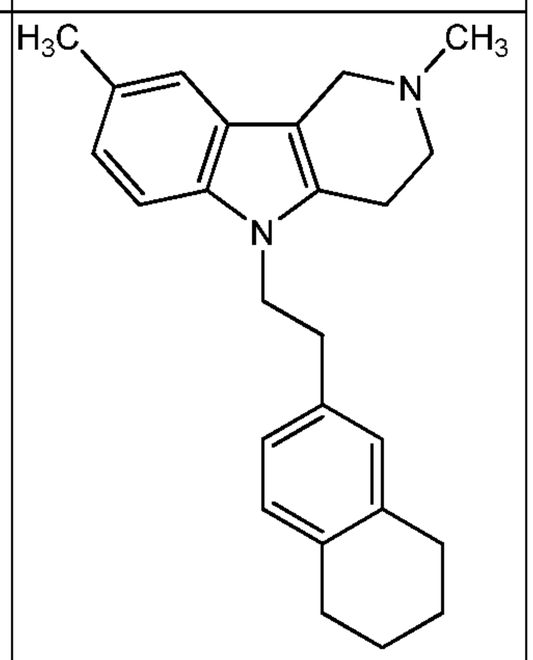

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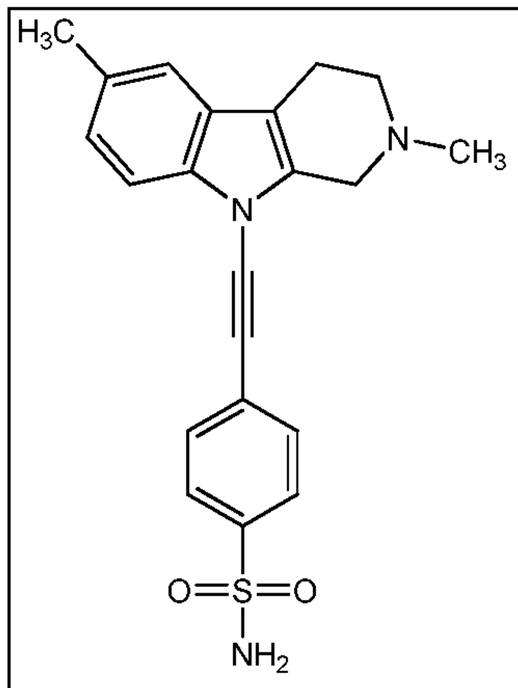
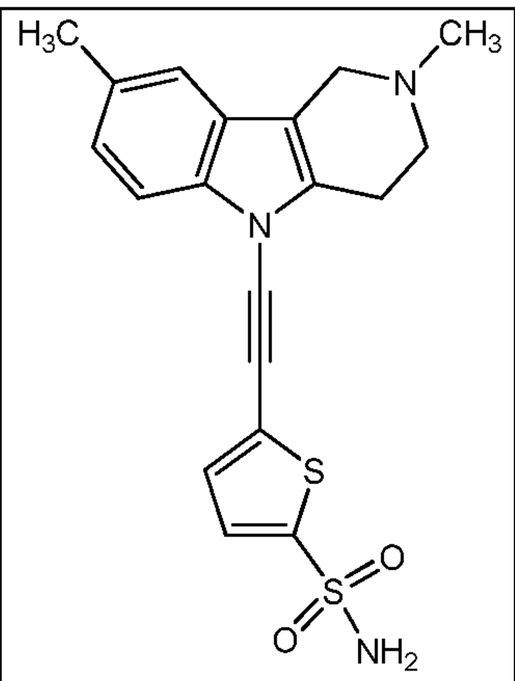
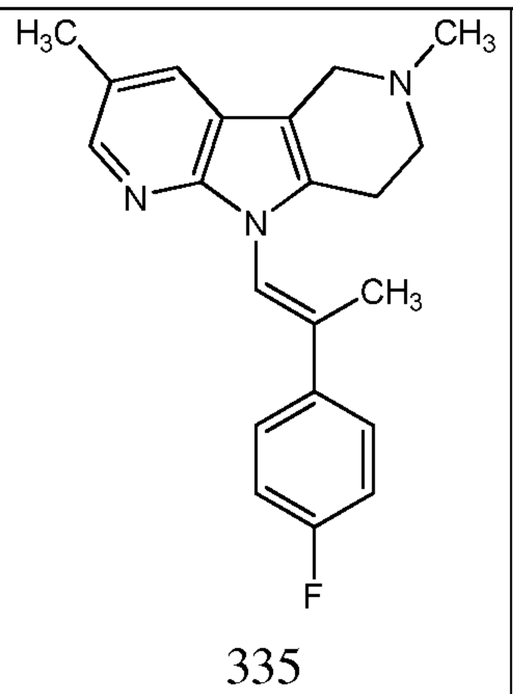
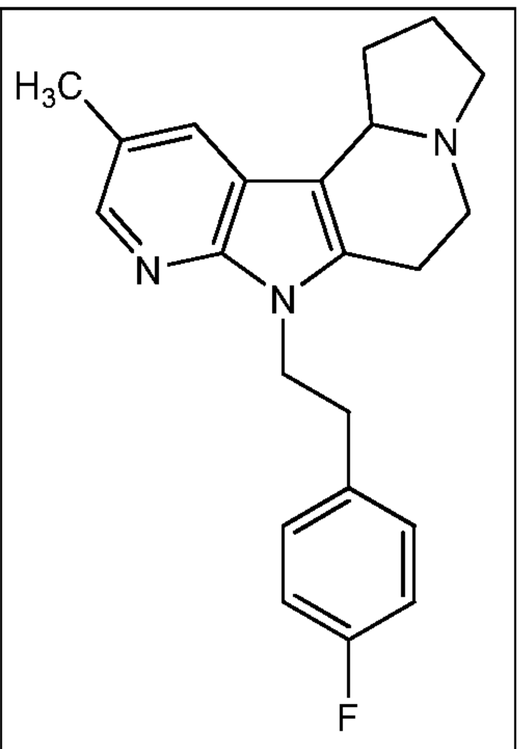
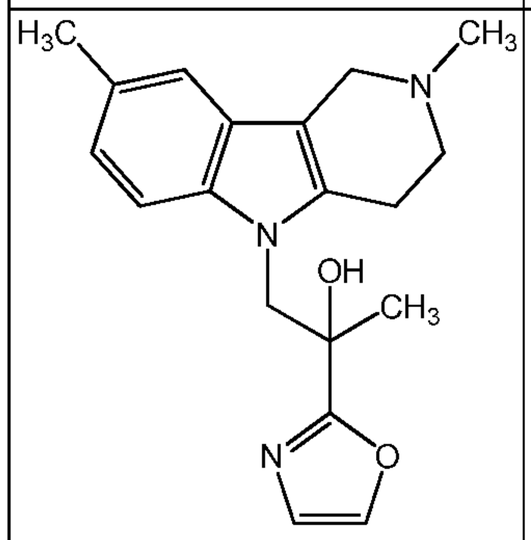
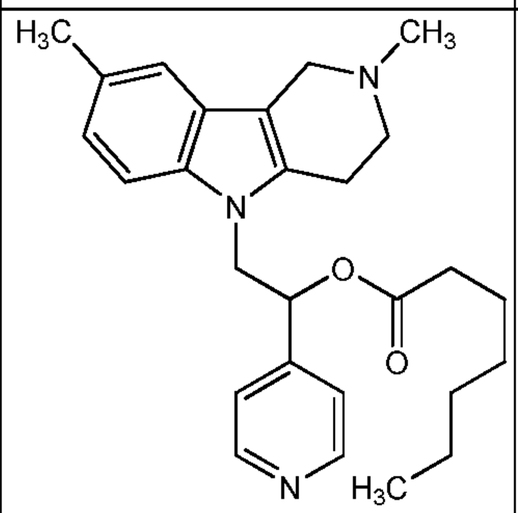
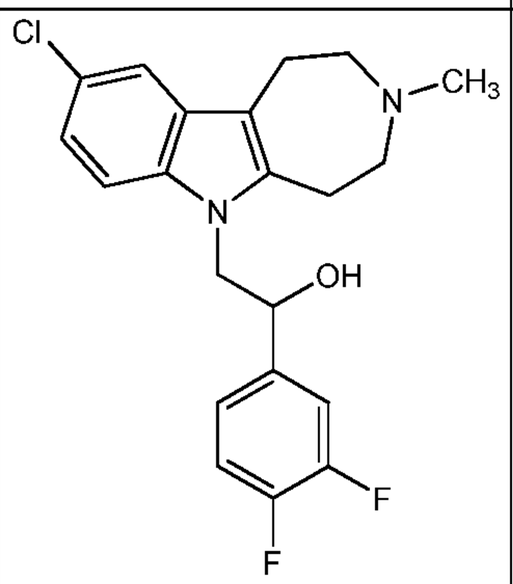
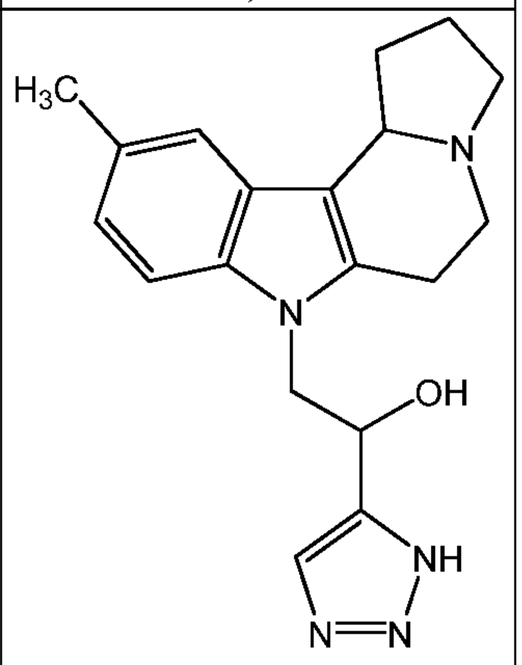
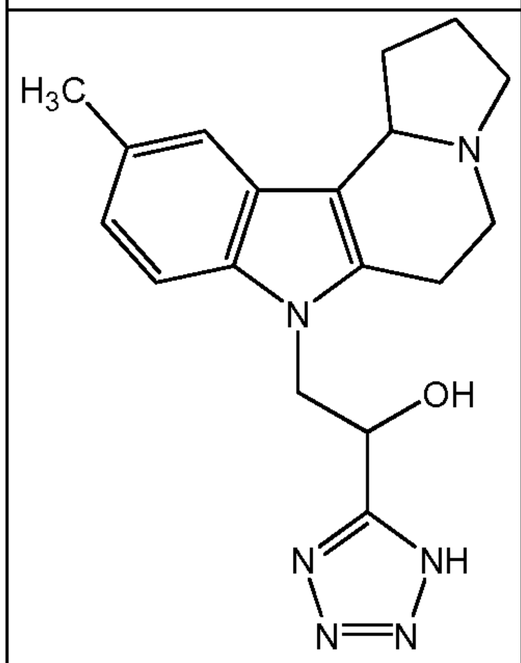
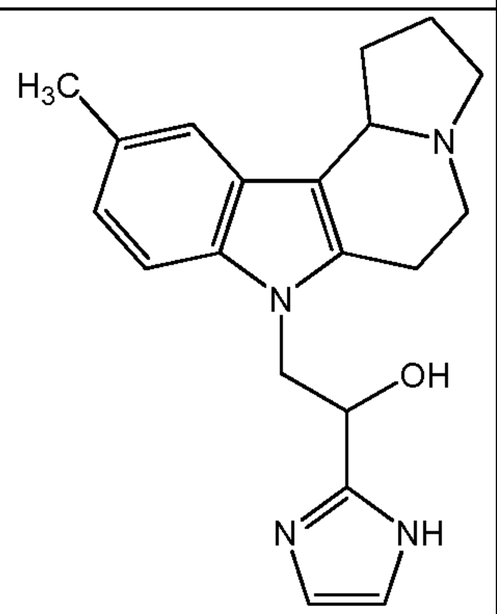
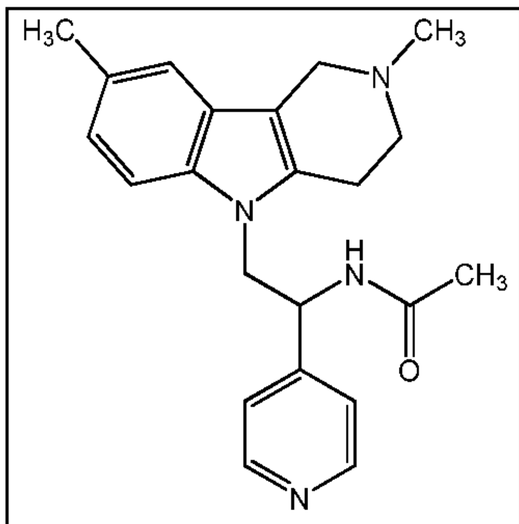
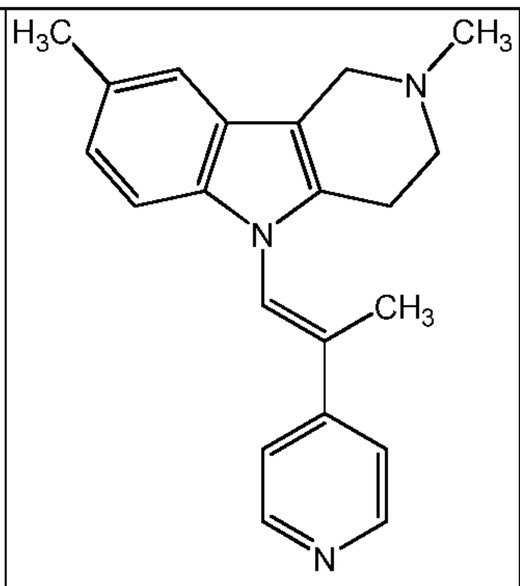
 333	 334	 335	 336 336a, 336b
 337 337a, 337b	 338 338a, 338b	 339 339a, 339b	 340 340a, 340b, 340c, 340d
 341 341a, 341b, 341c, 341d	 342 342a, 342b, 342c, 342d		

[0633] Table 2. Representative Compounds of the Invention



II-1
II-1a, II-1b



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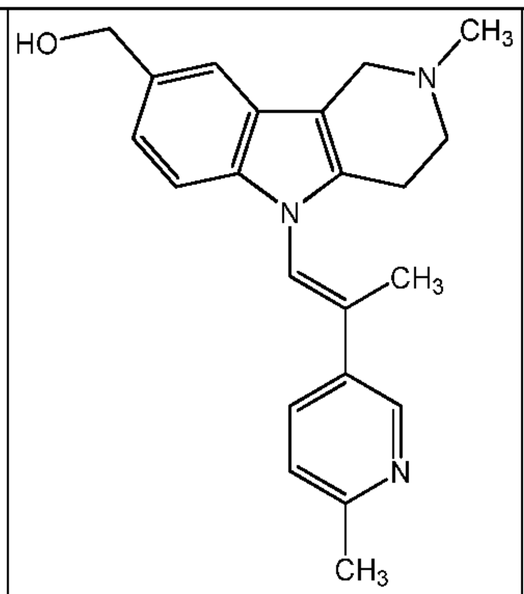

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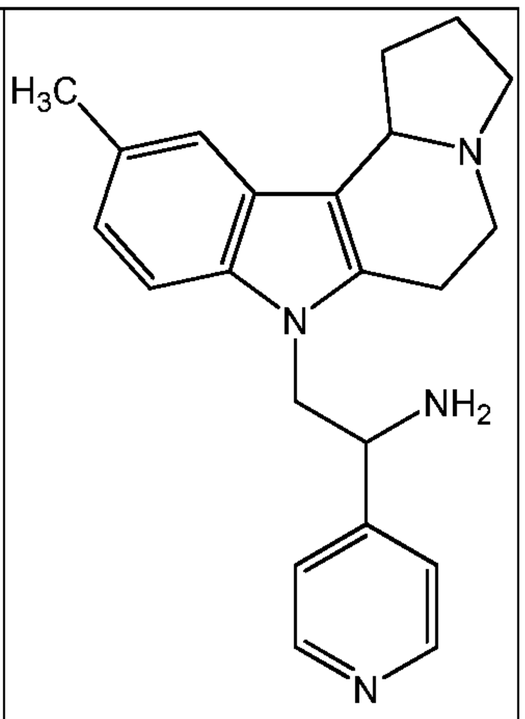

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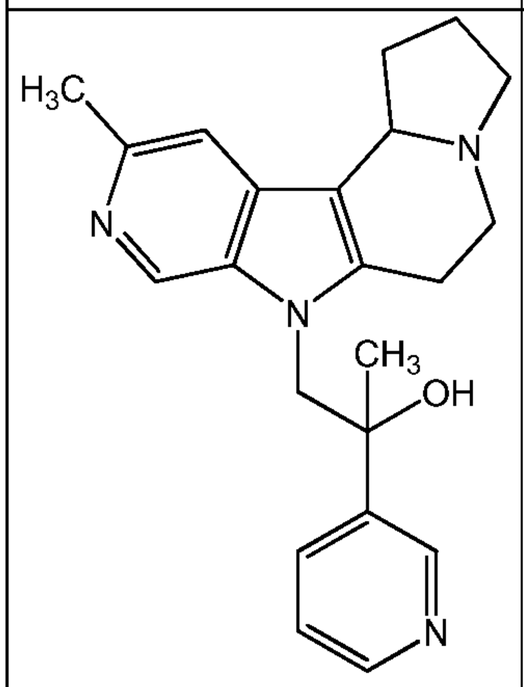
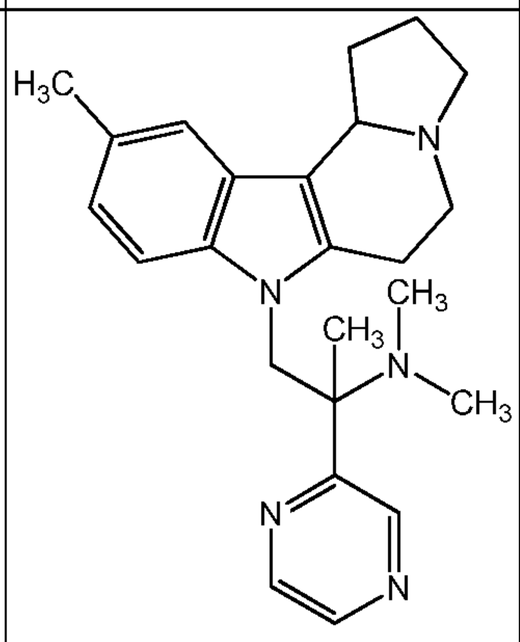
II-4a, II-4b, II-4c, II-4d



II-5
II-5a, II-5 II-5c, II-5d



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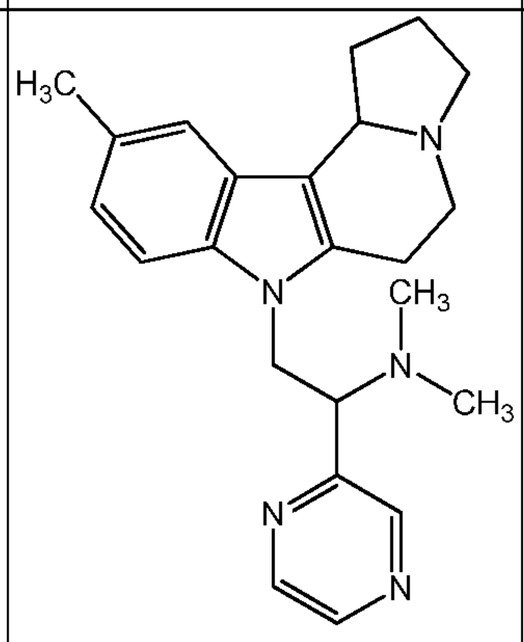
II-6a, II-6b, II-6c, II-6d



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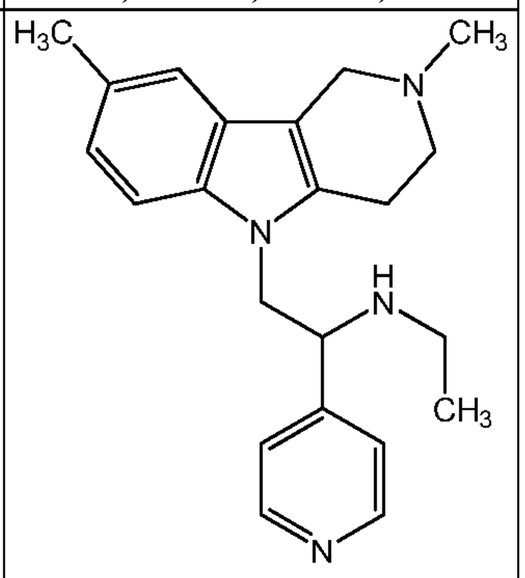

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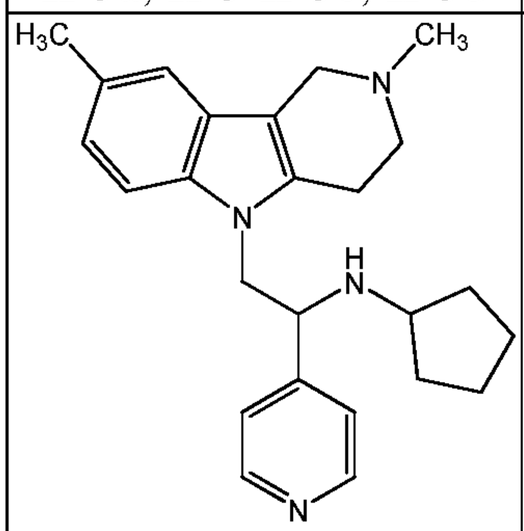

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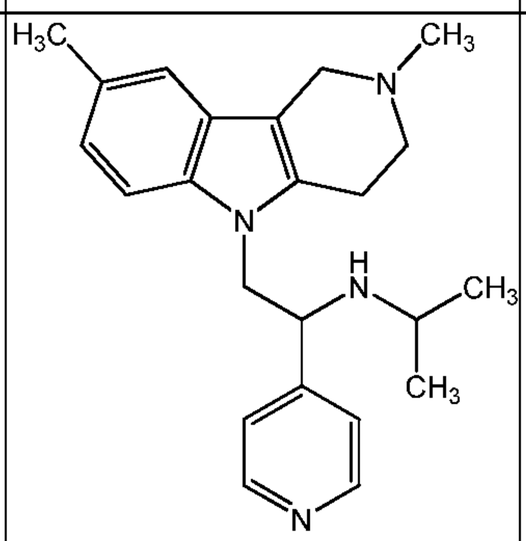

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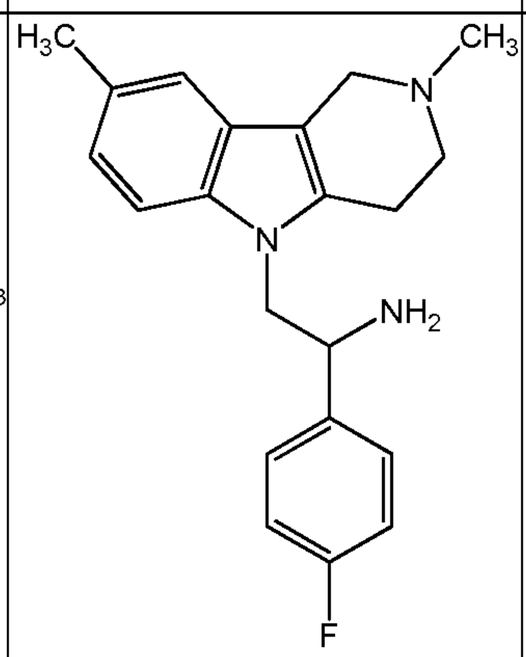

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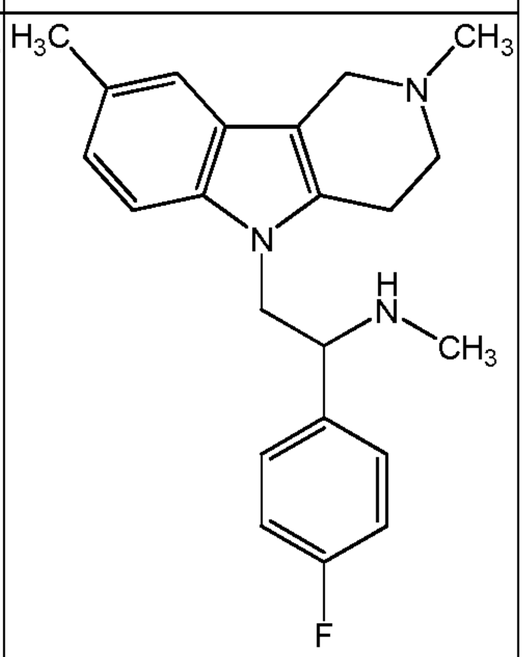

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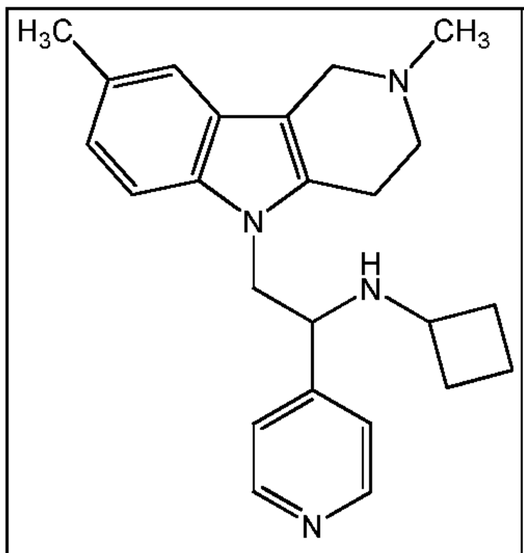
<td> 
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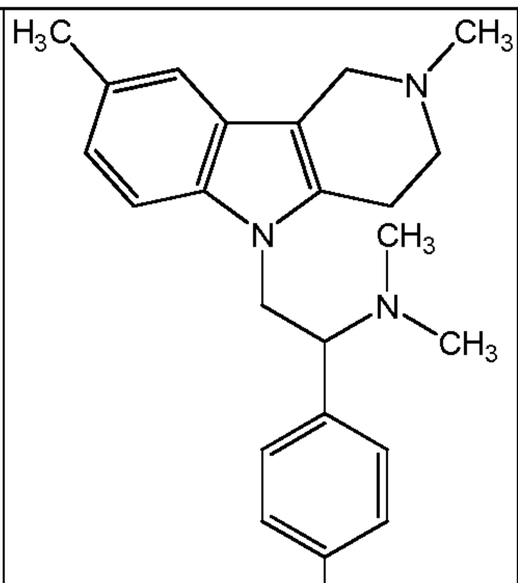
<td> 
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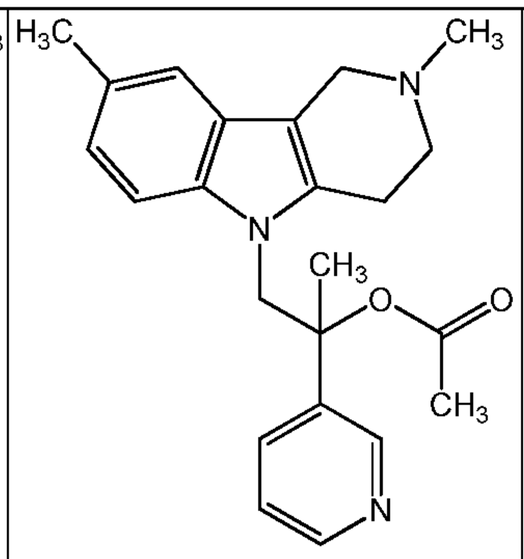
<td> 
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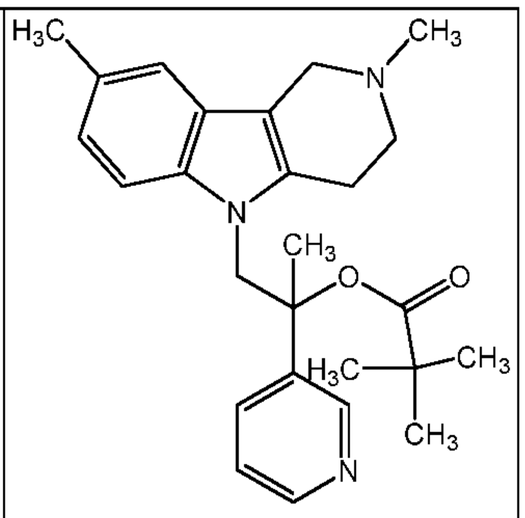
<td> 
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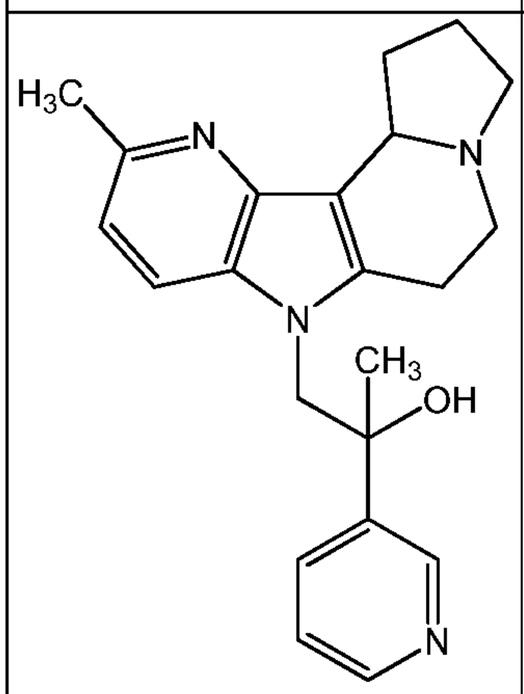
<td> 
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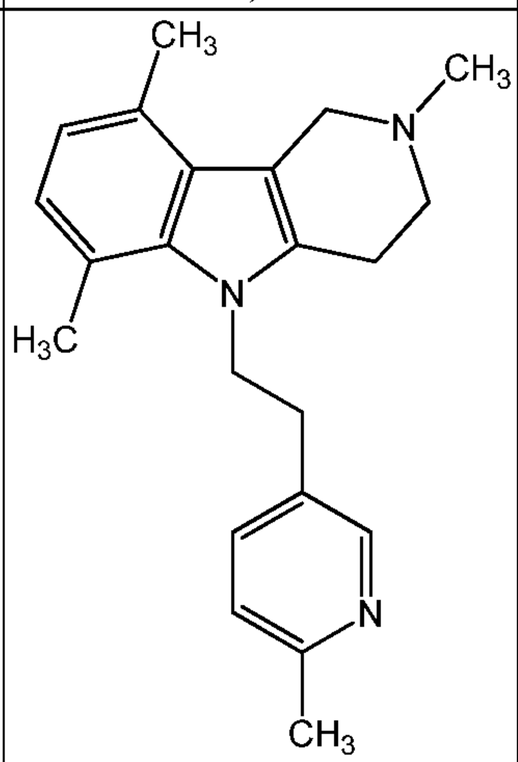
<td> 
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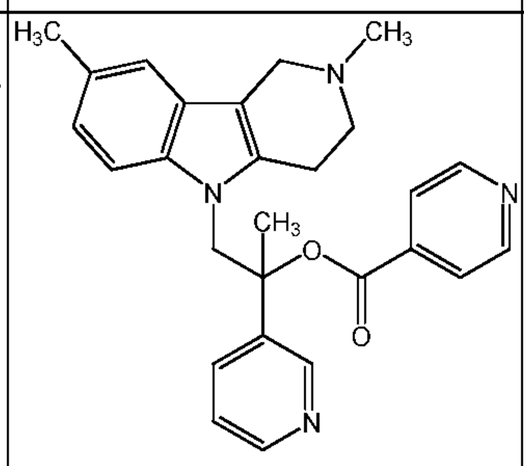
<td> 
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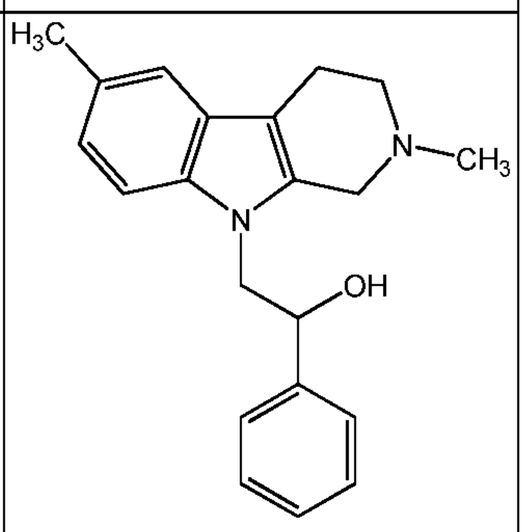
<td> 
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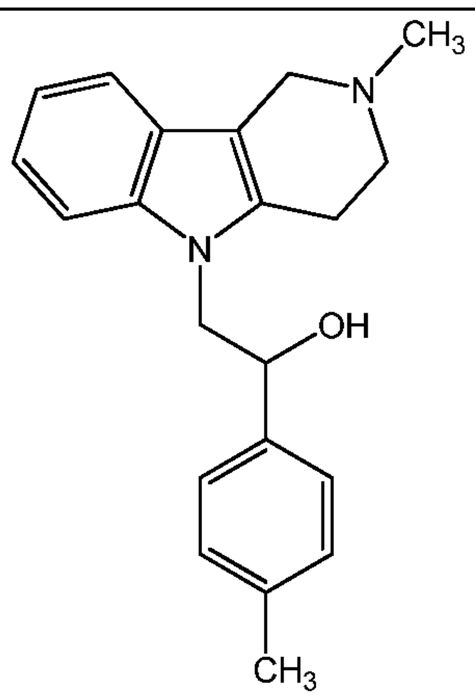
<td> 
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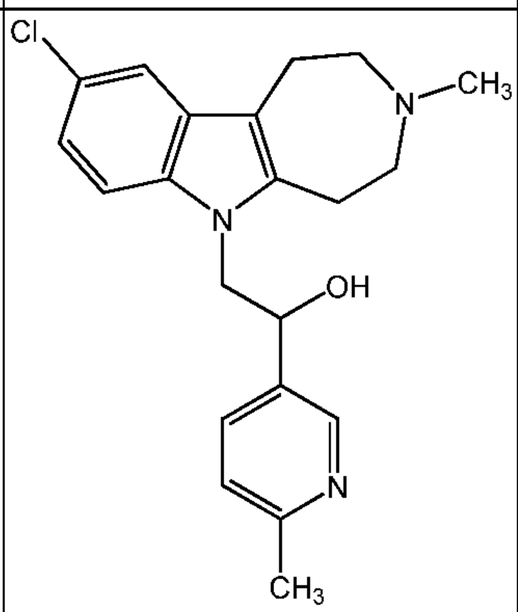
<td> 
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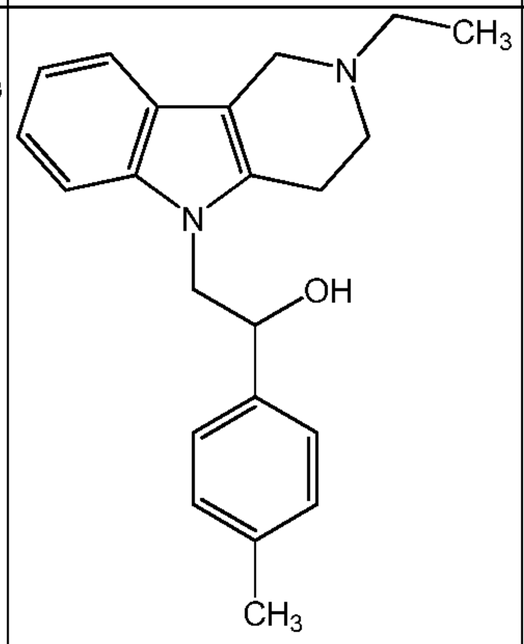
<td> 
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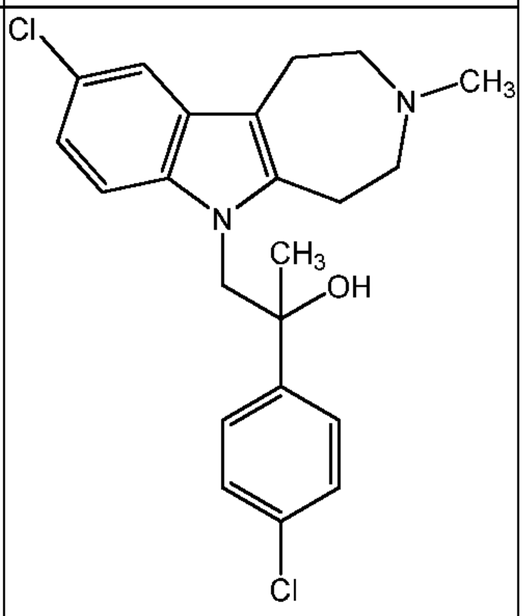
<td> 
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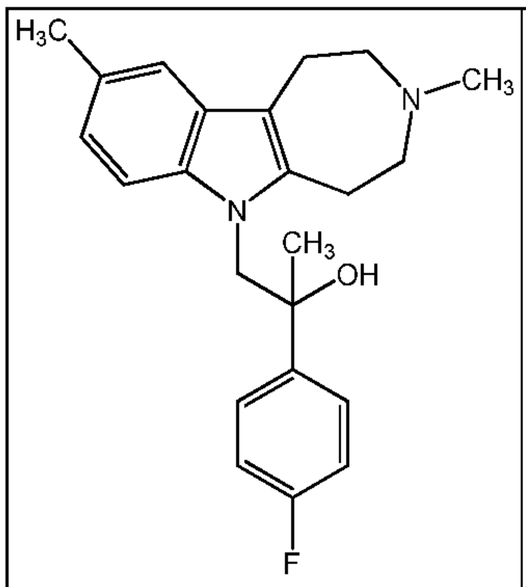

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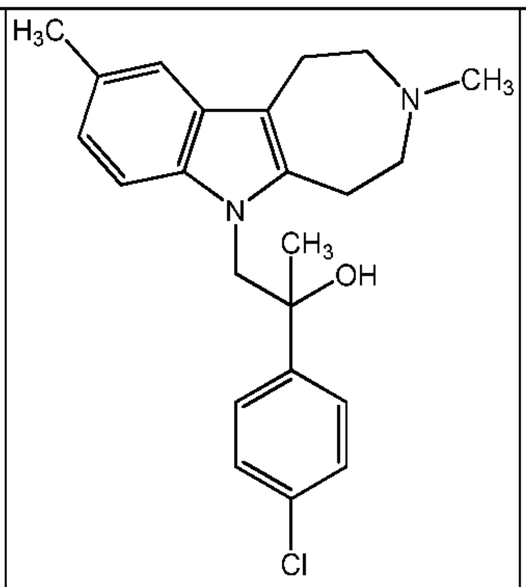

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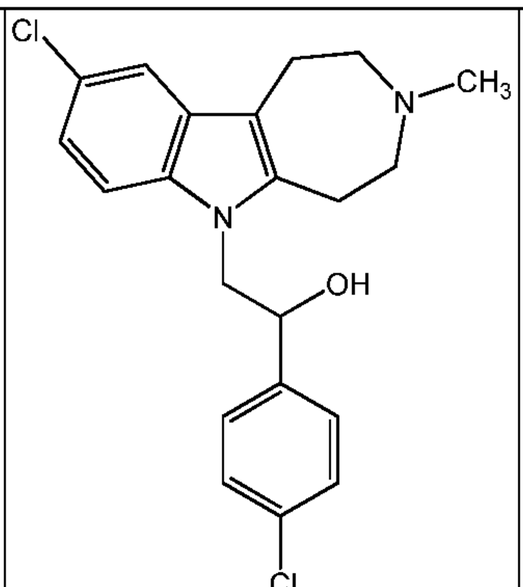

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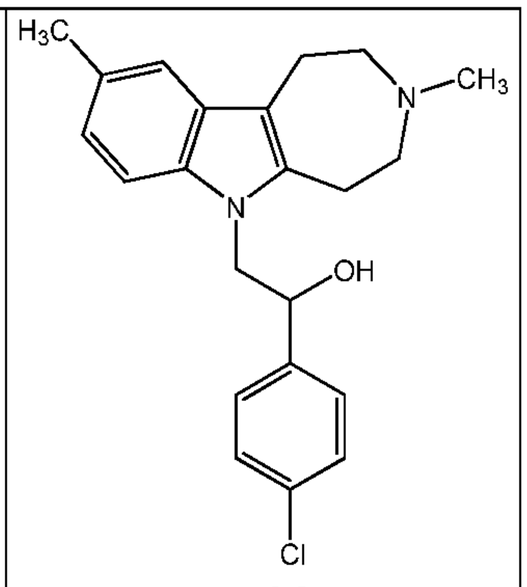

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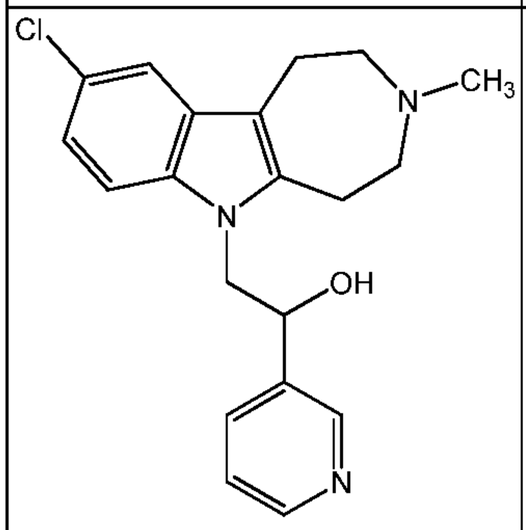

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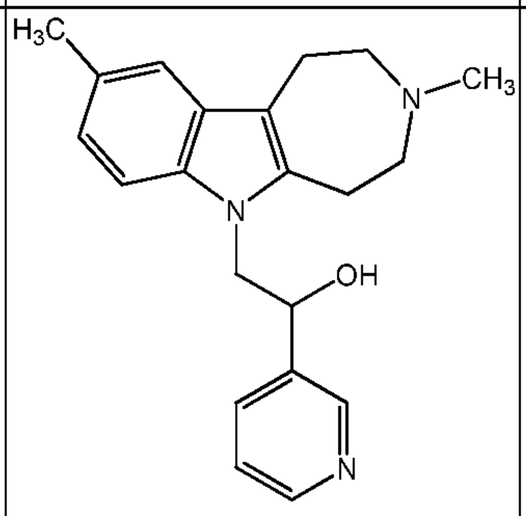

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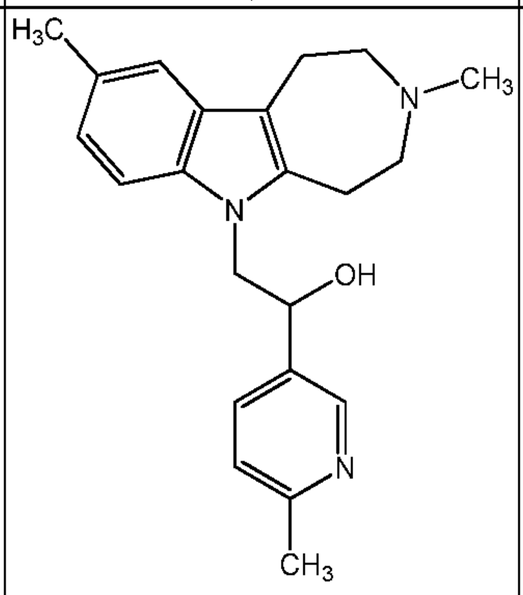

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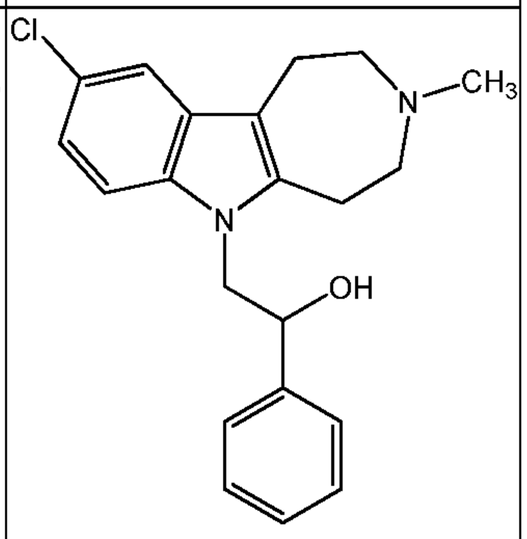

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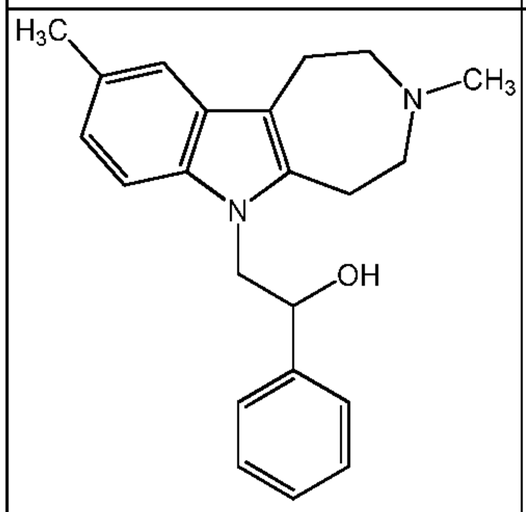

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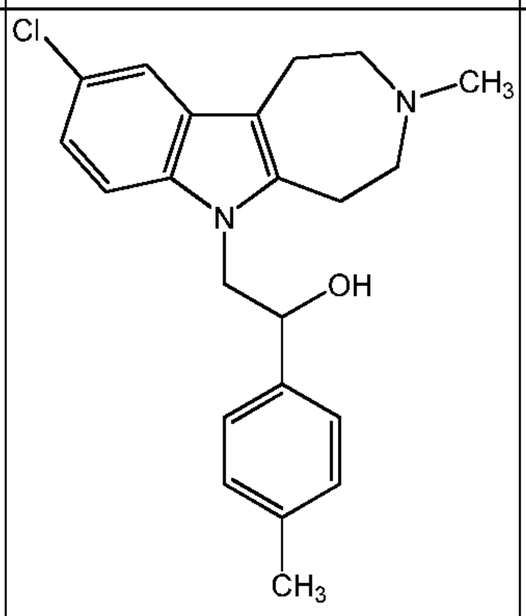

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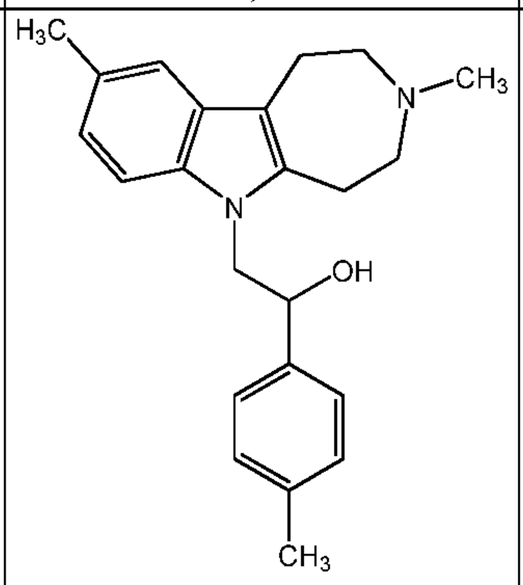

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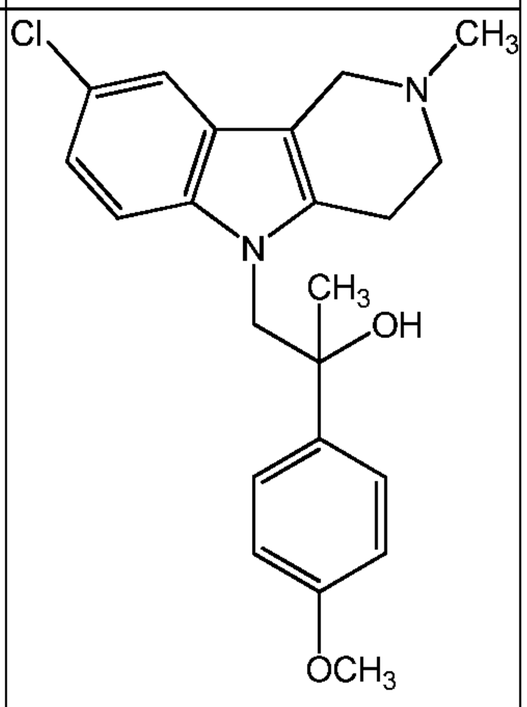

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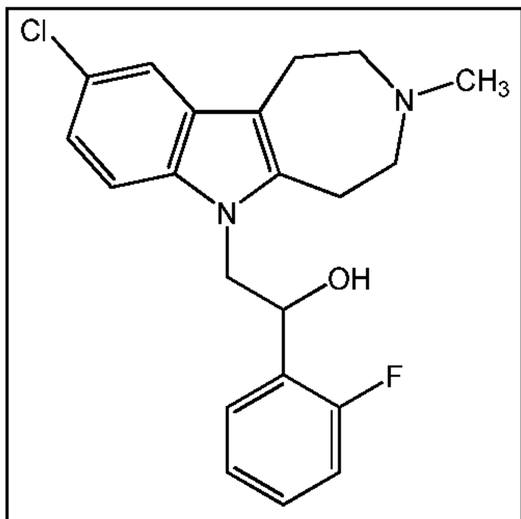

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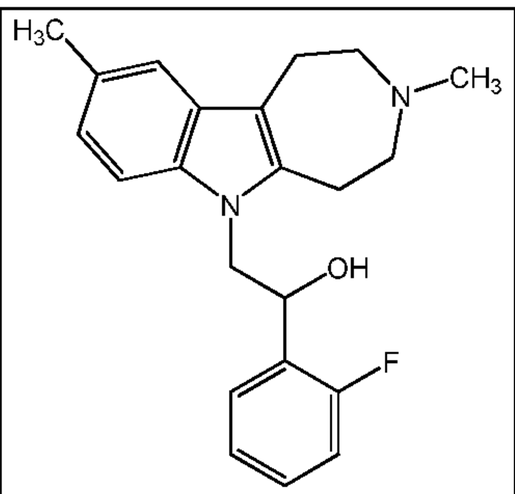

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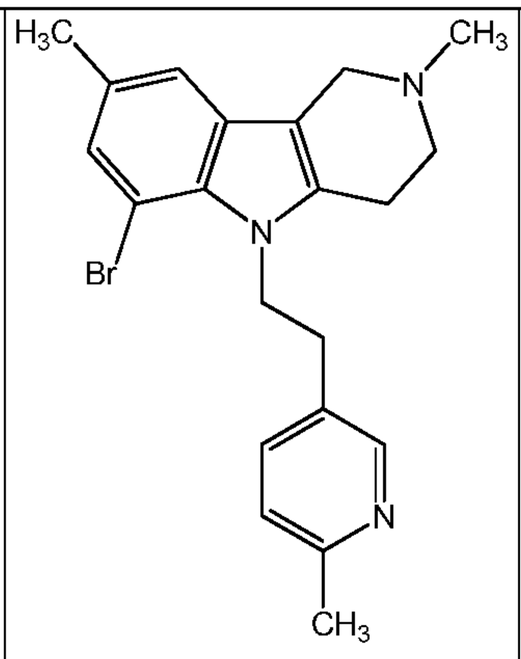

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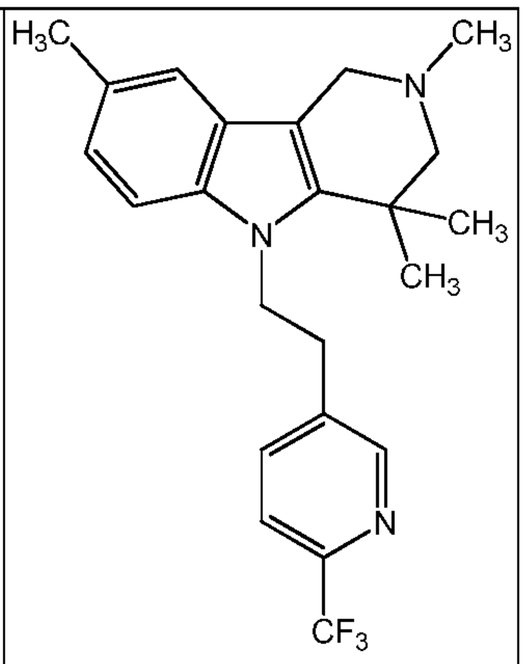

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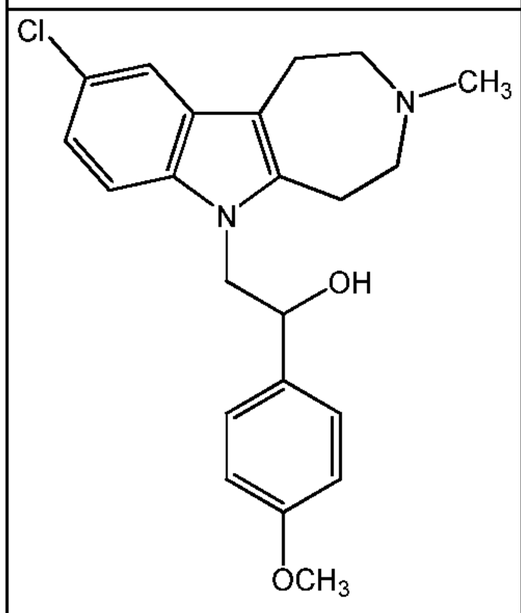

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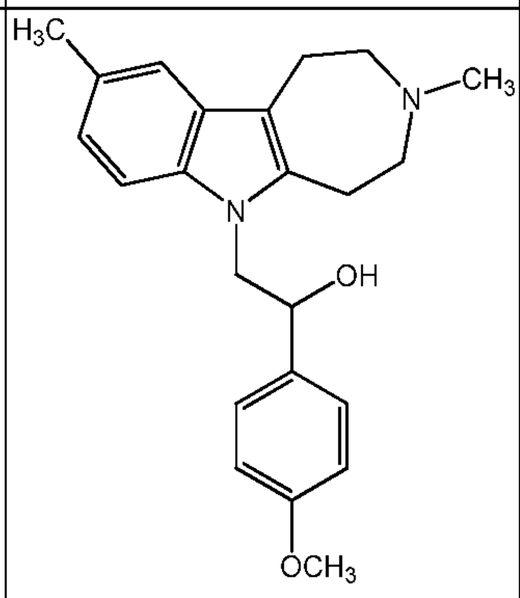

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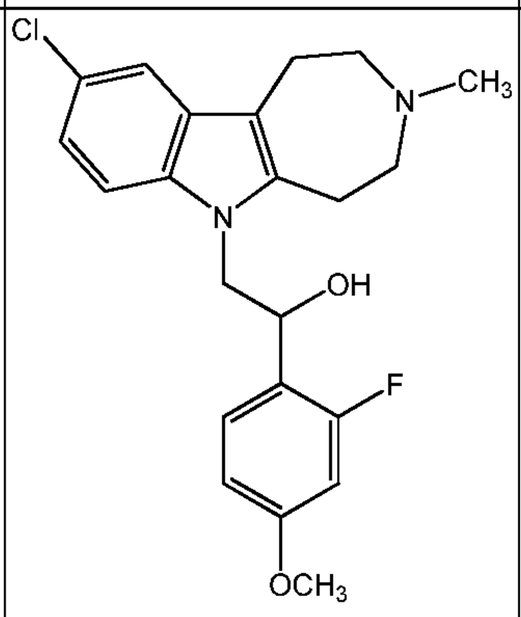

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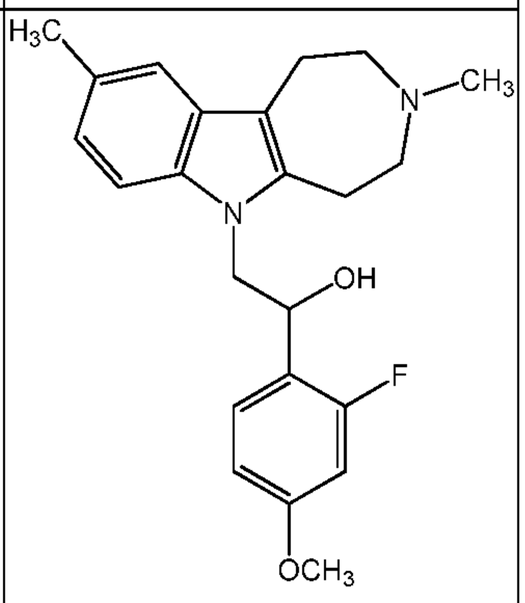

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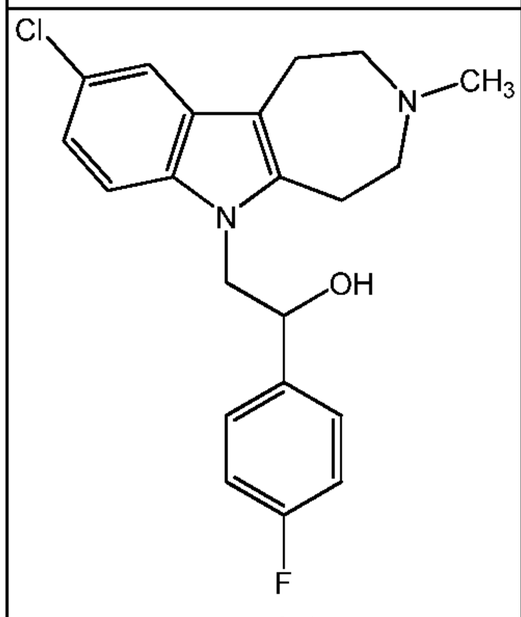

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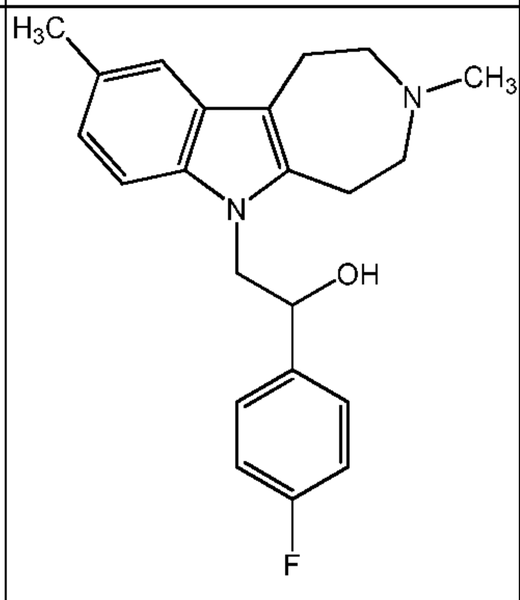

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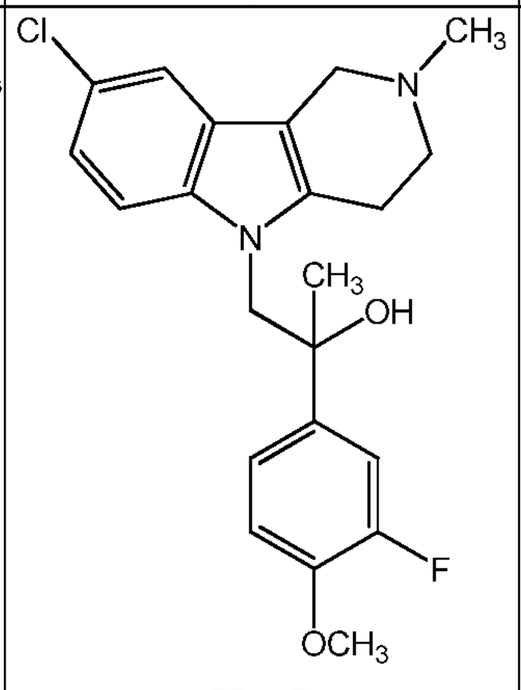

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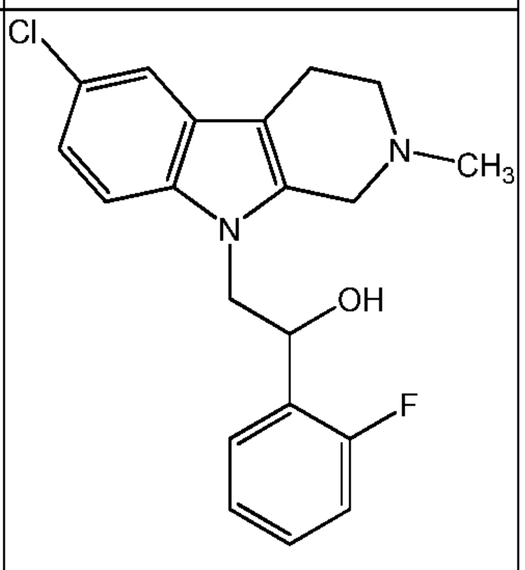

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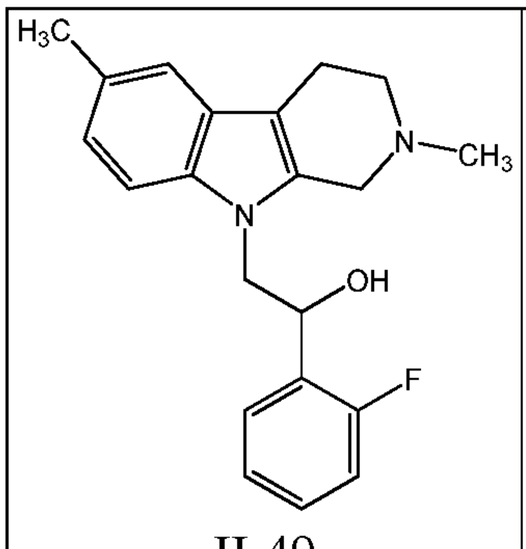

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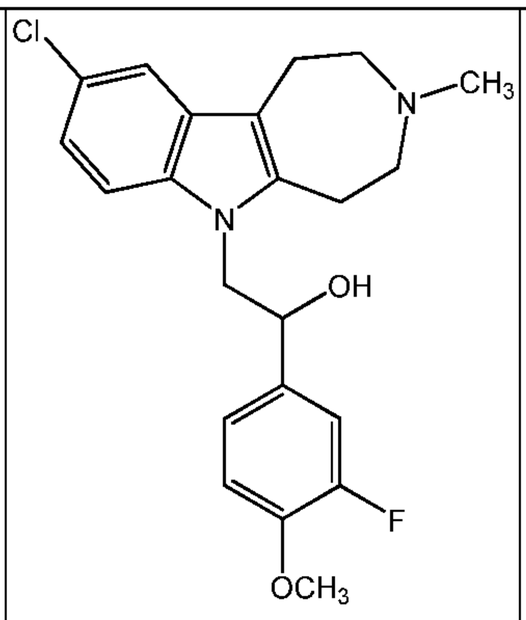

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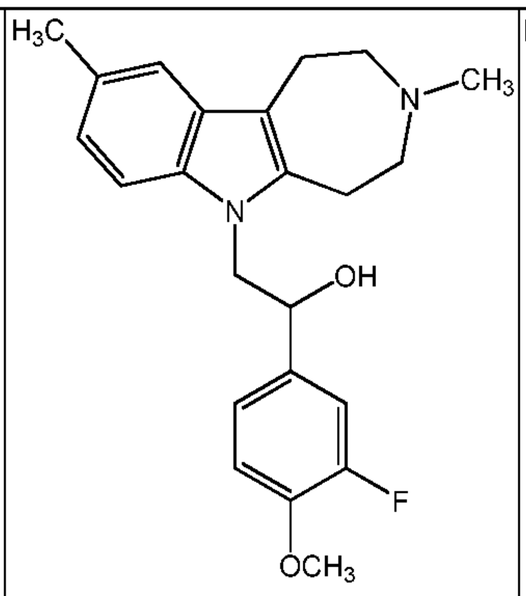

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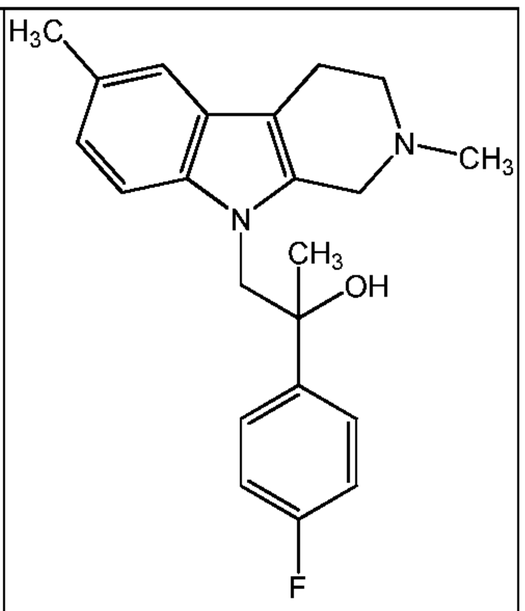

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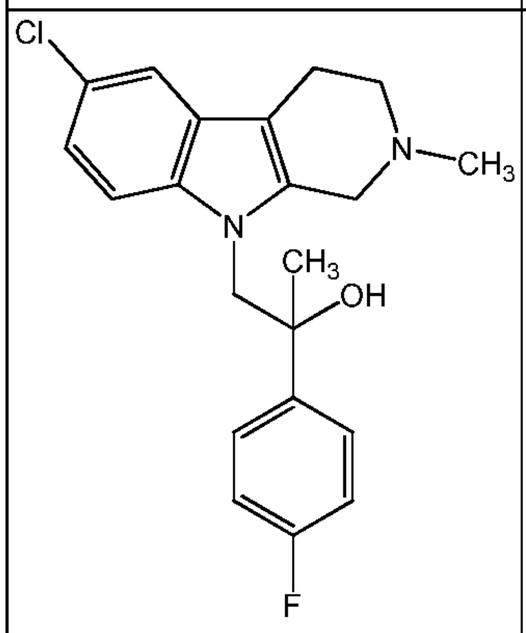

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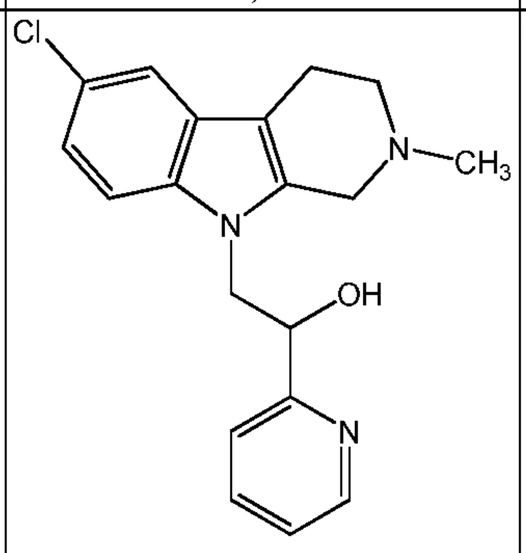

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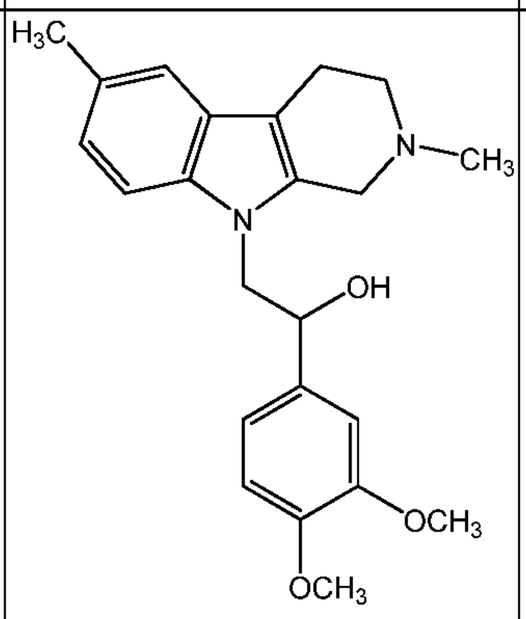

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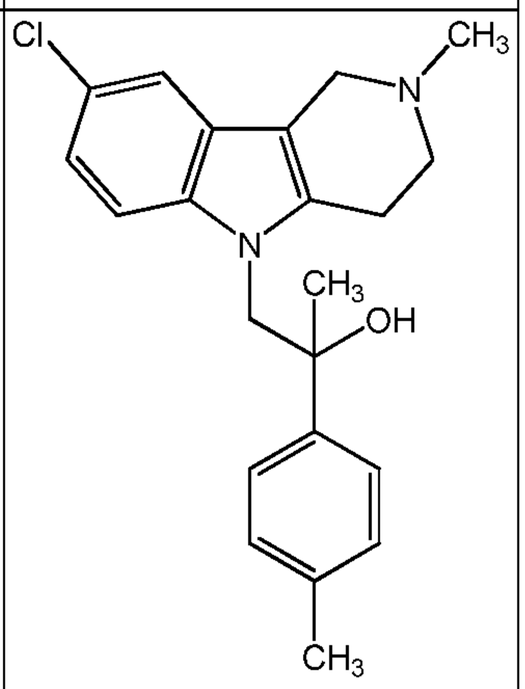

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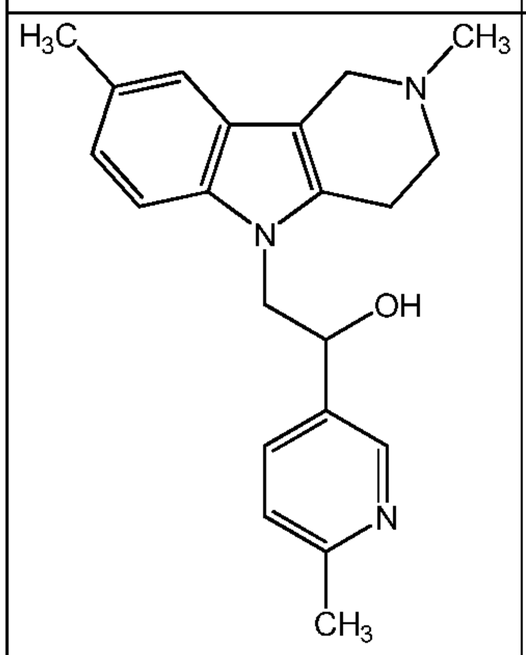

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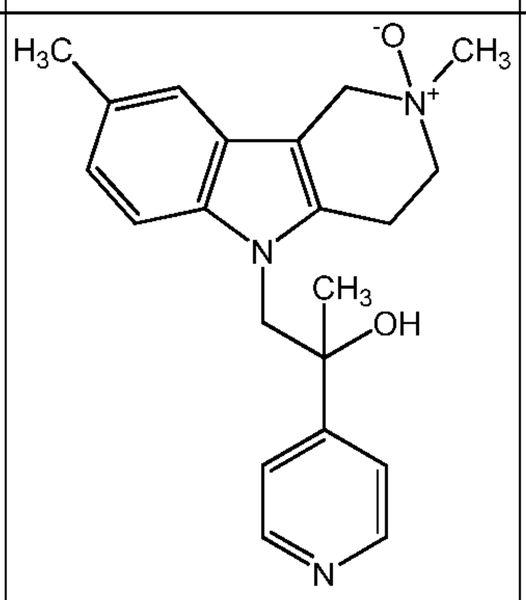

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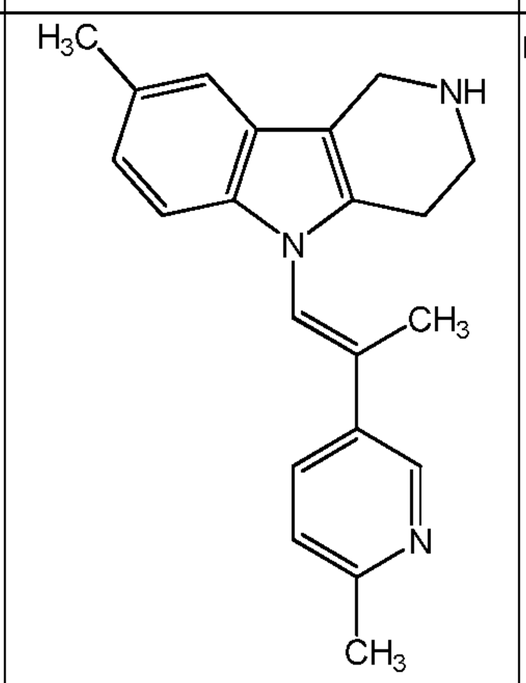

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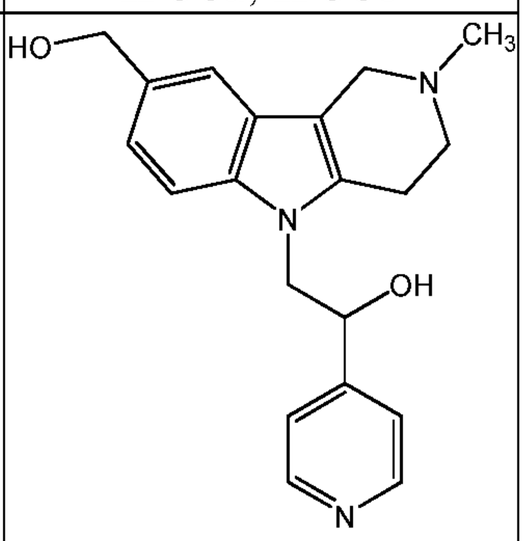

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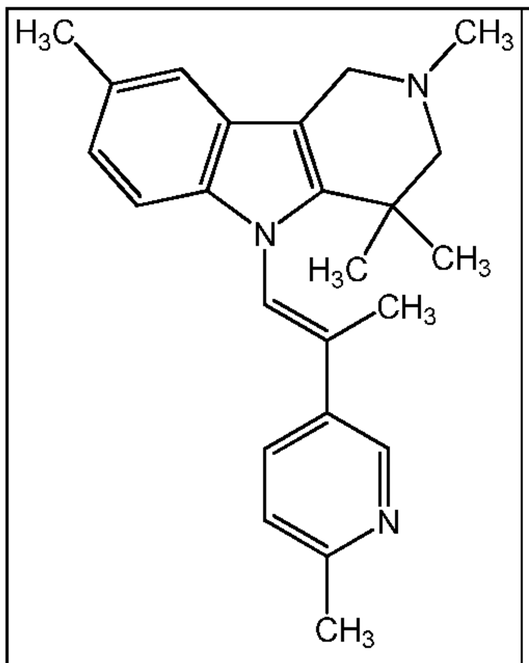

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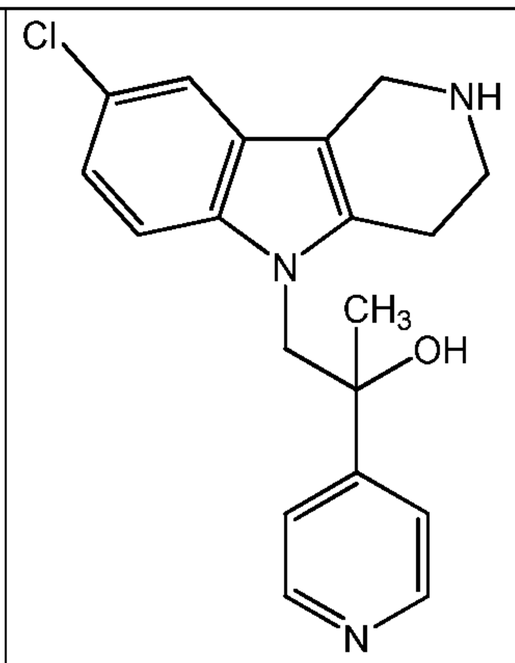

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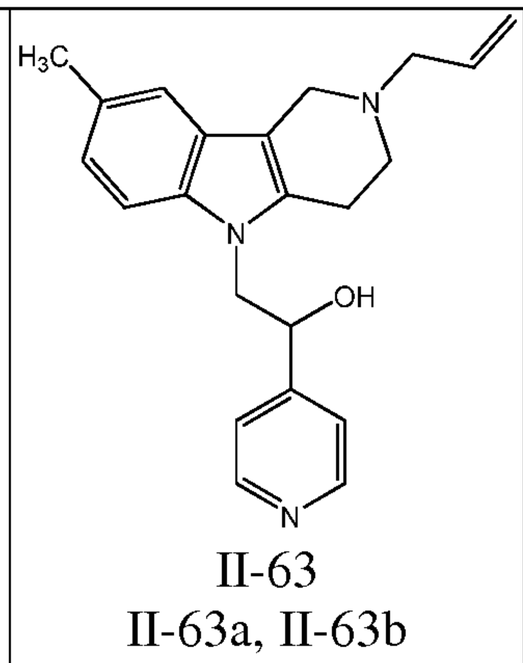

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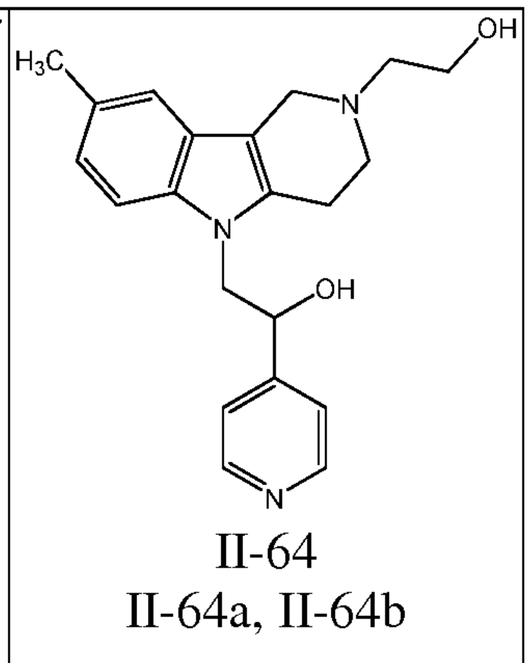

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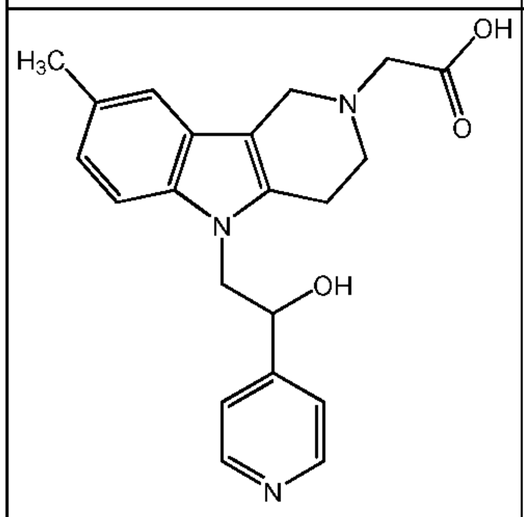

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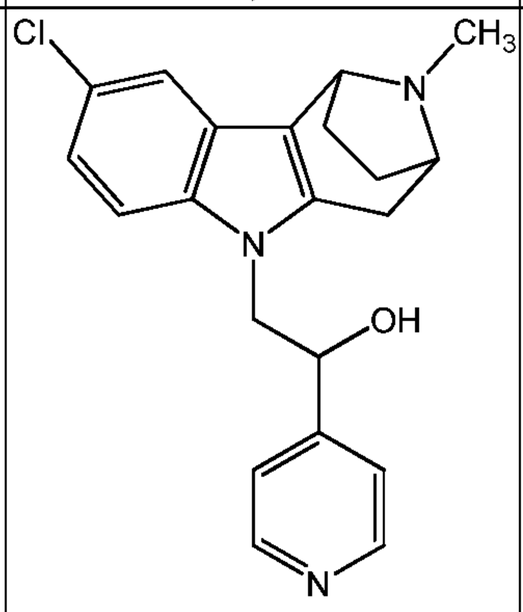

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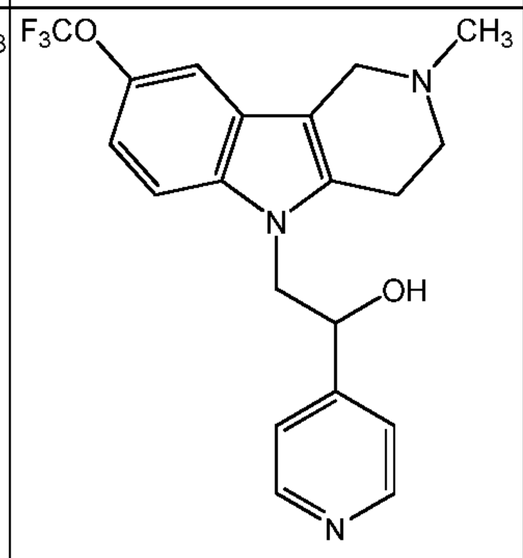

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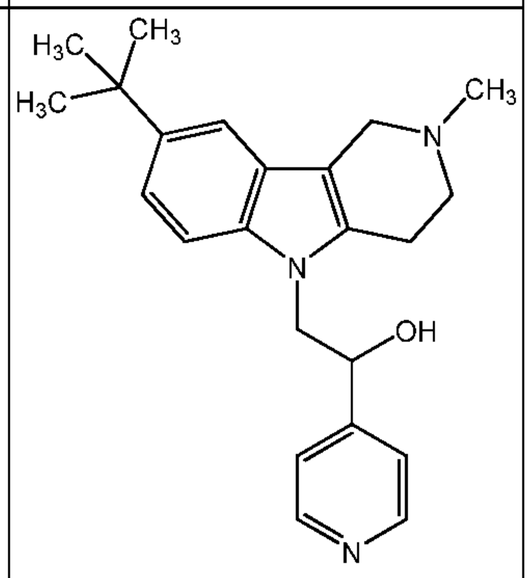

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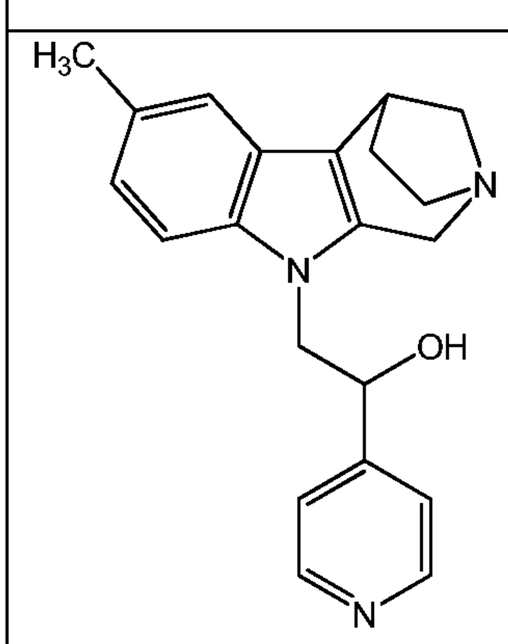

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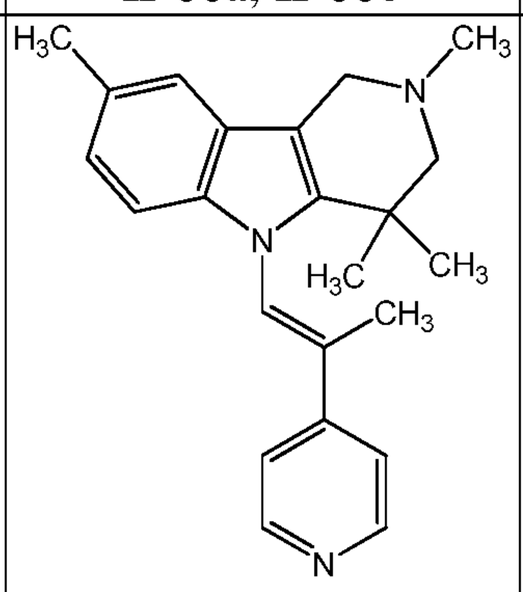

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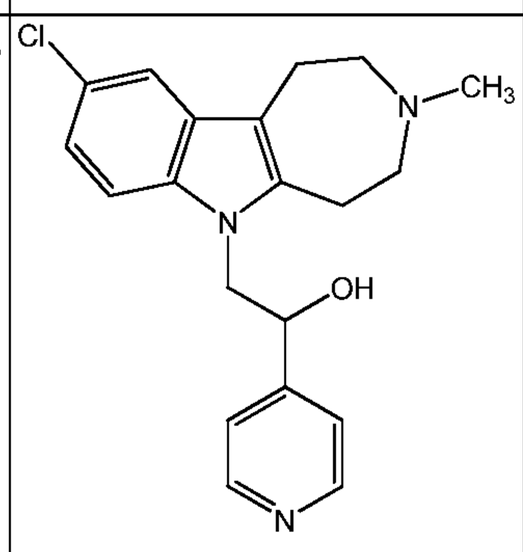

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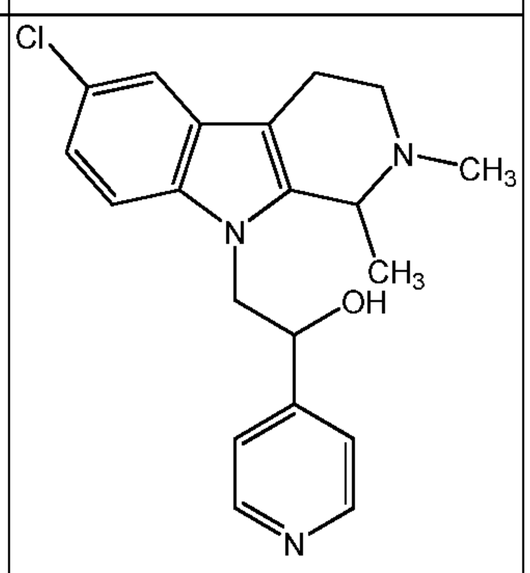

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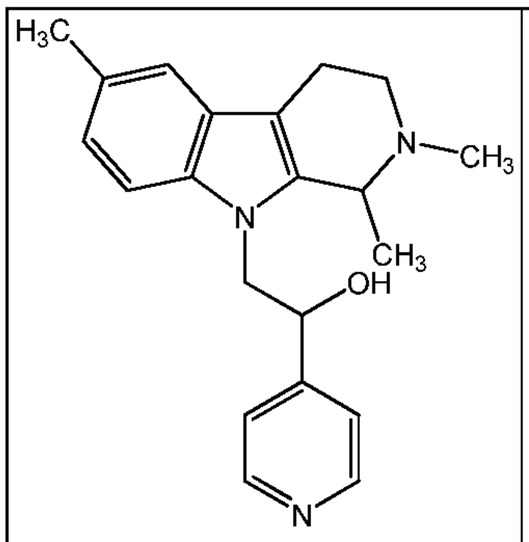

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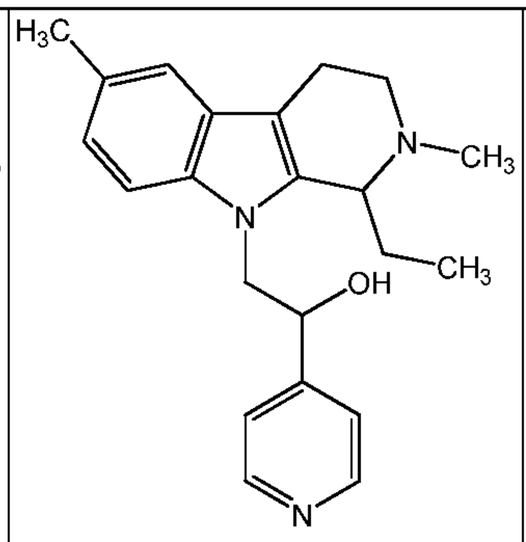

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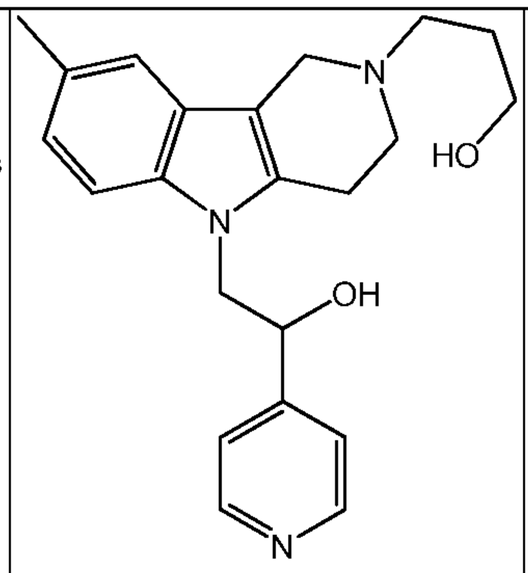

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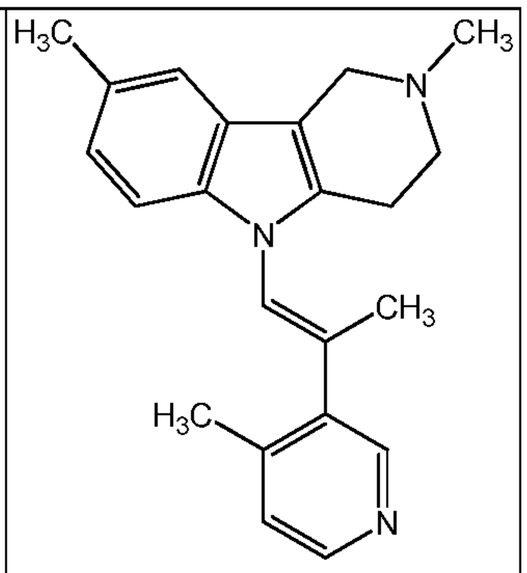

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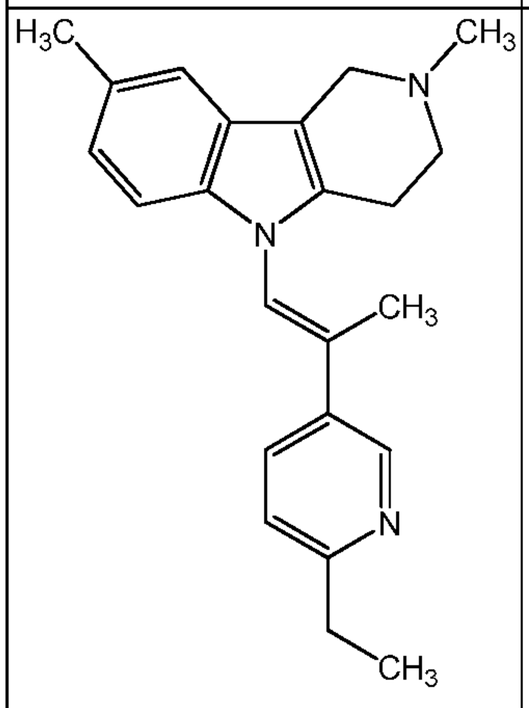

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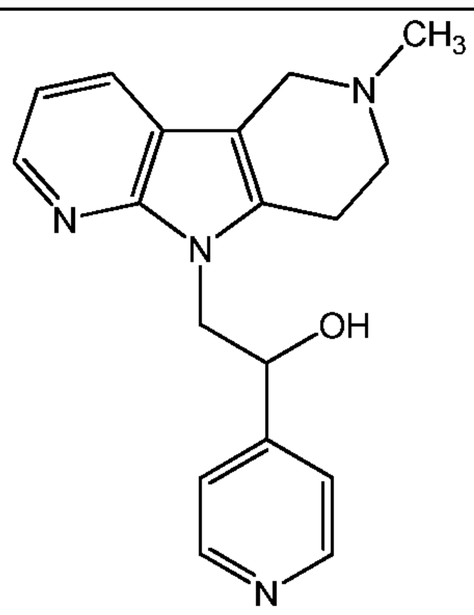

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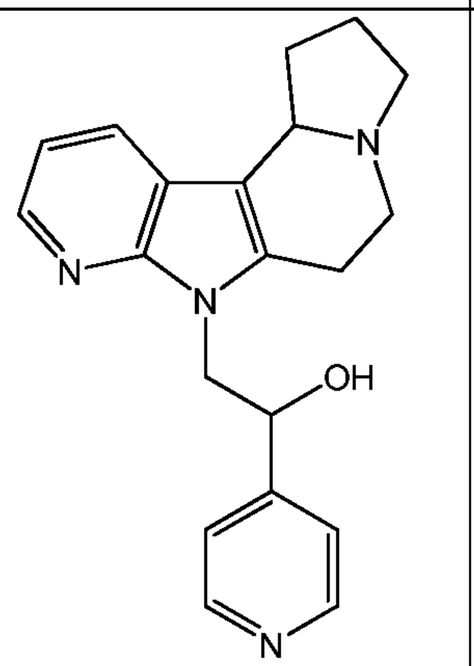

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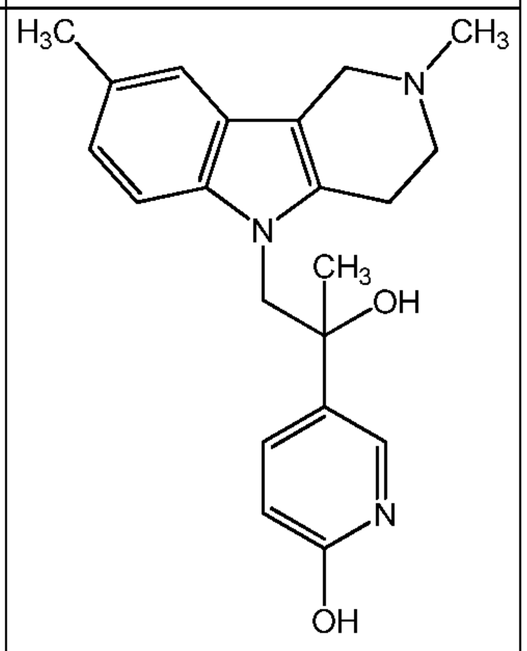

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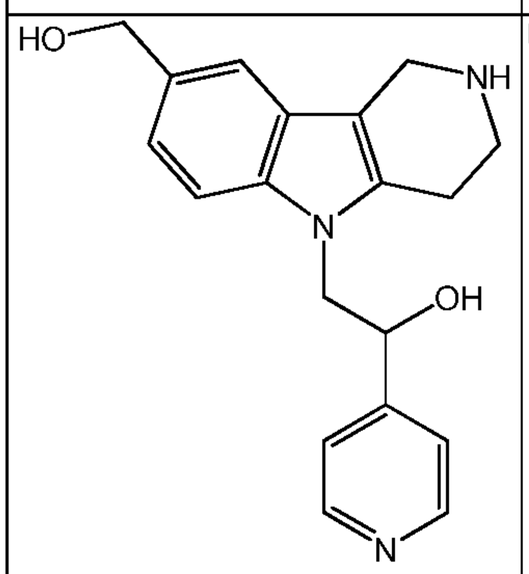

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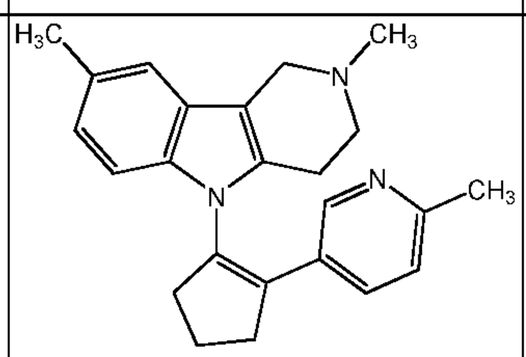

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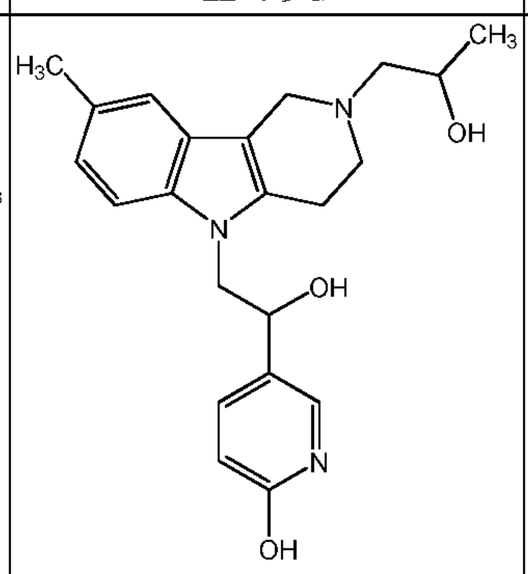

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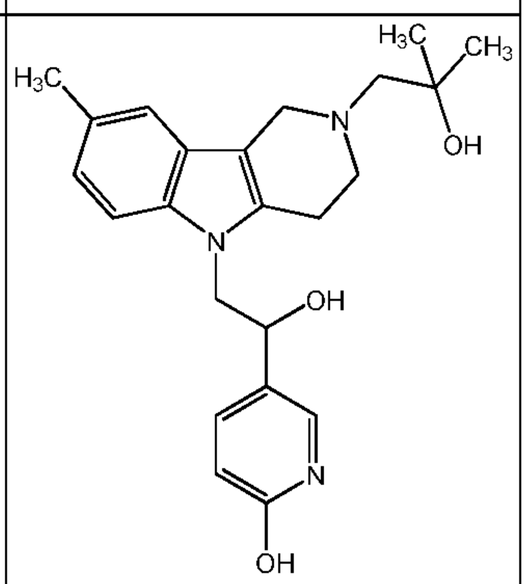

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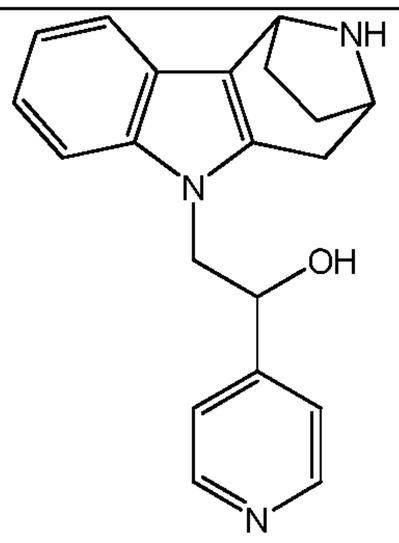
<td> 
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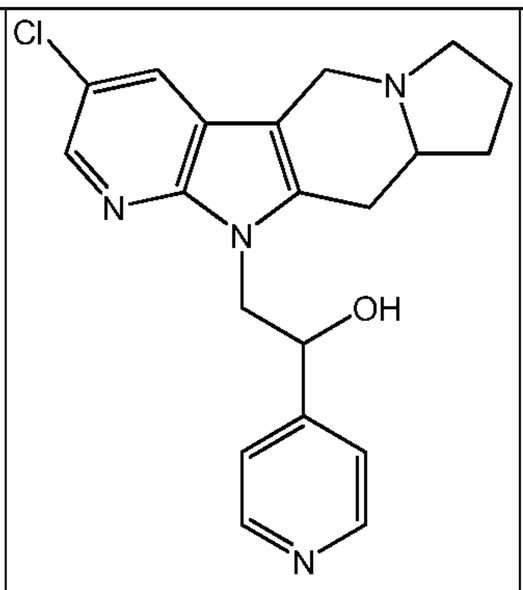
<td> 
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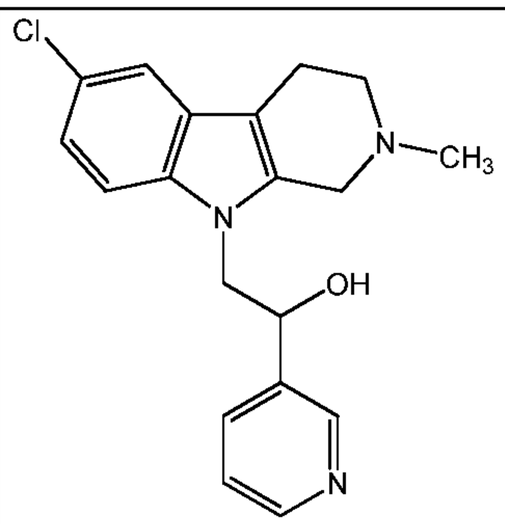
<td> 
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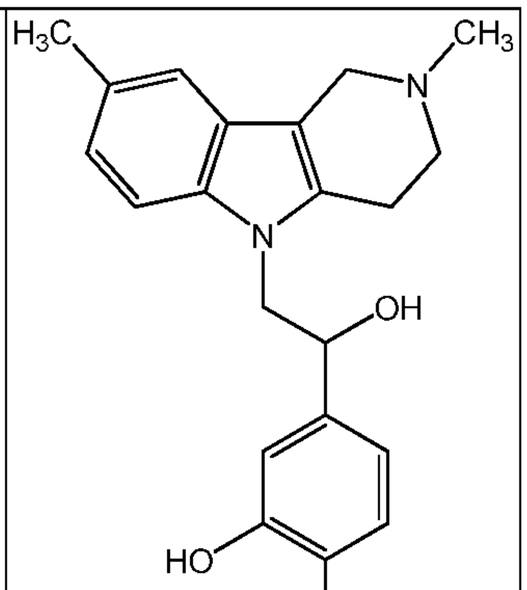
<td> 
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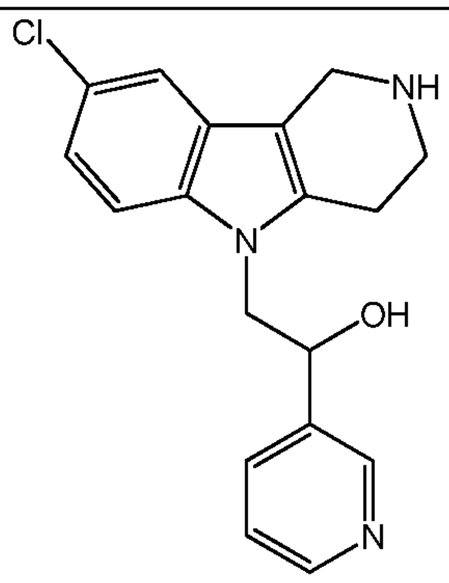
<td> 
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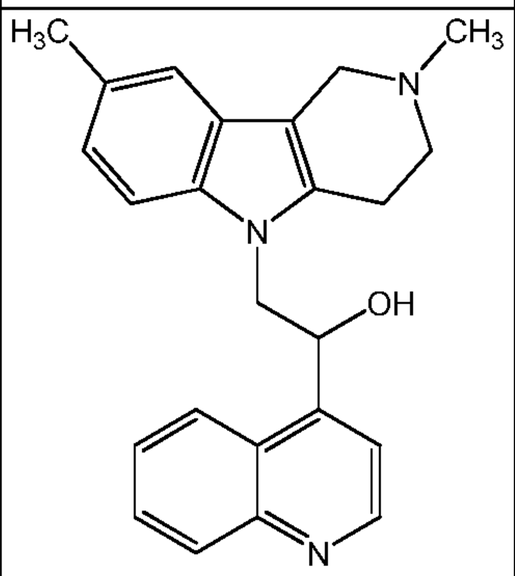
<td> 
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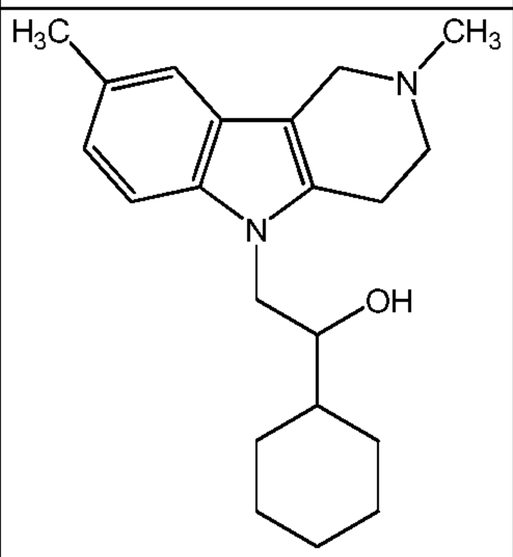
<td> 
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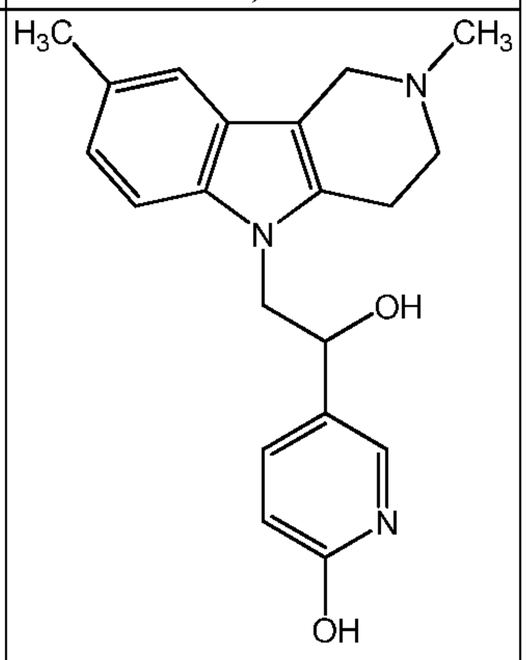
<td> 
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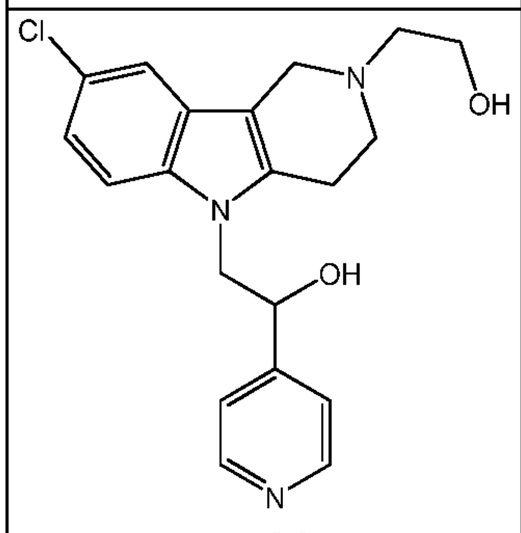
<td> 
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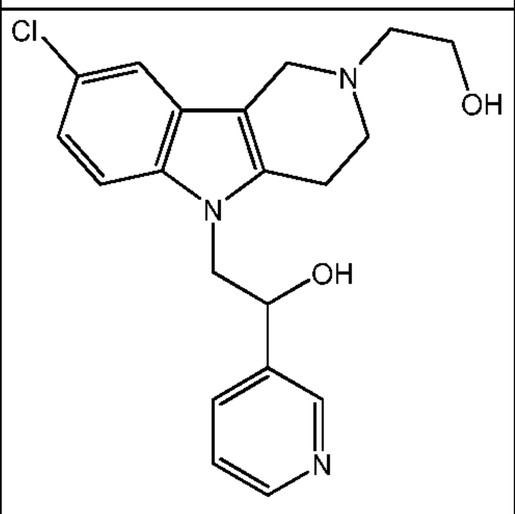
<td> 
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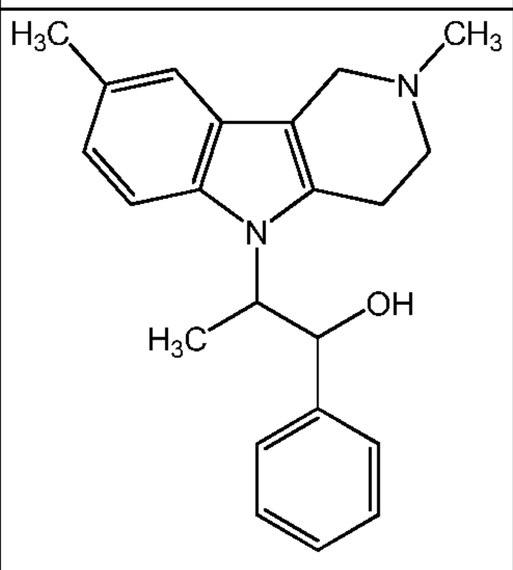
<td> 
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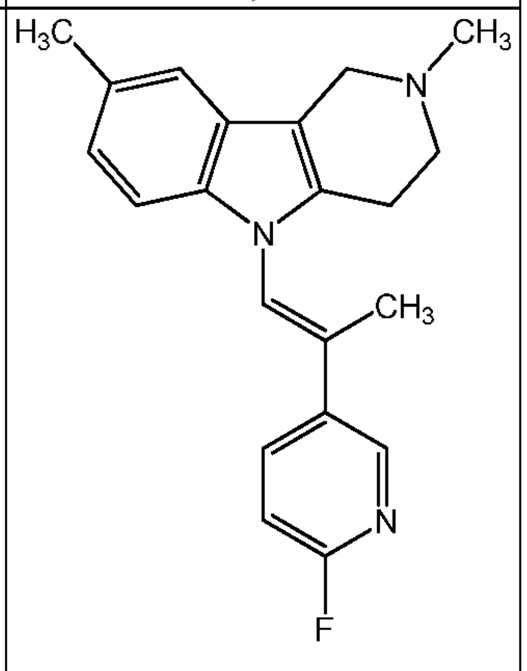
<td> 
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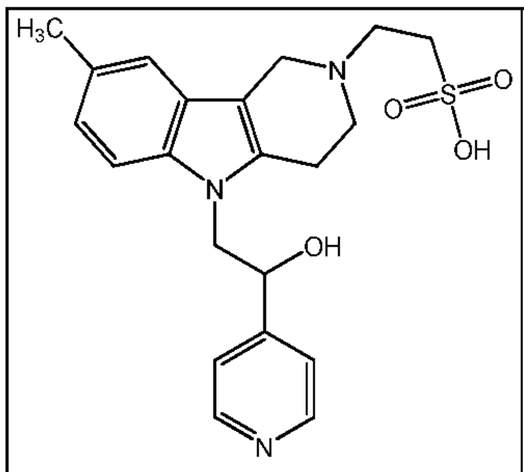

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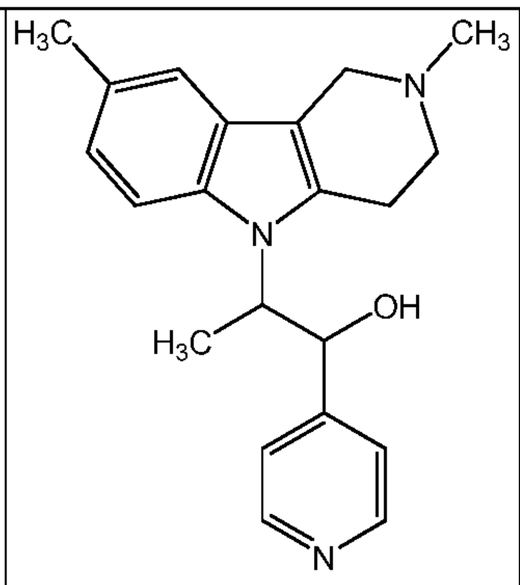

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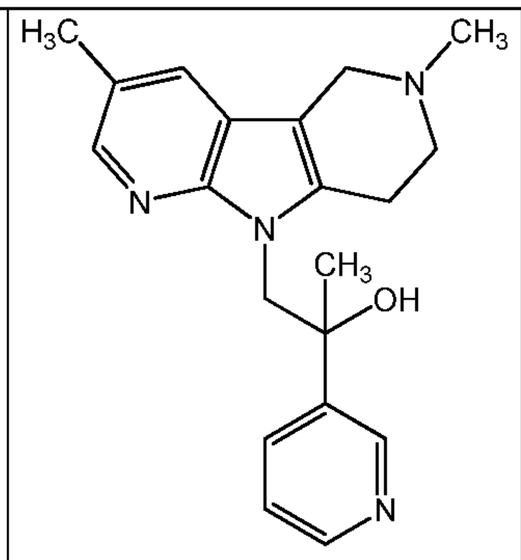

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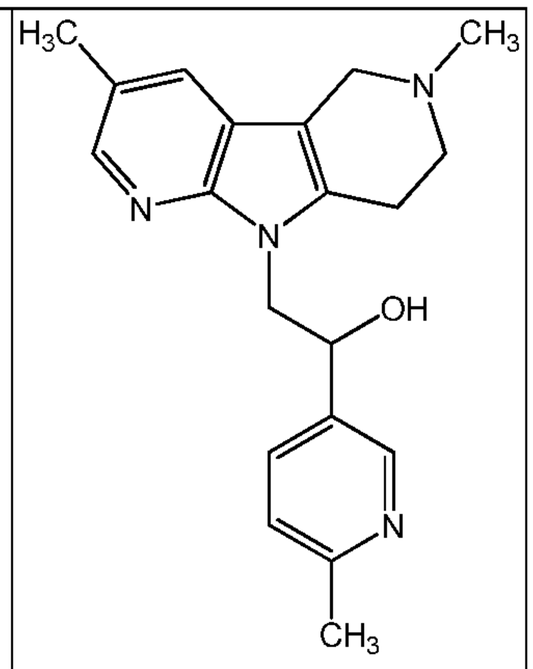

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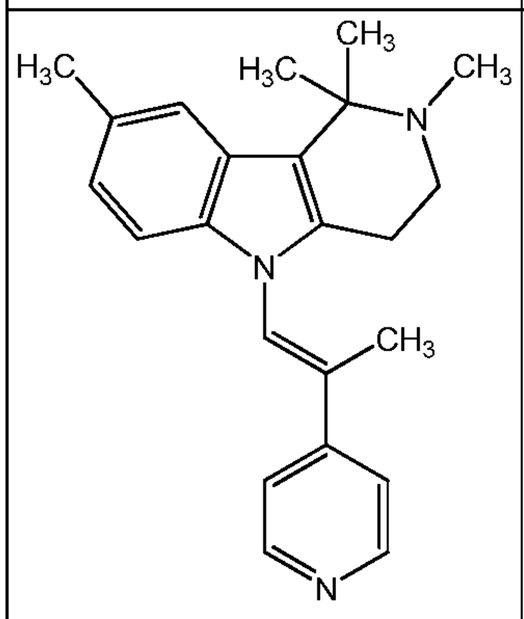

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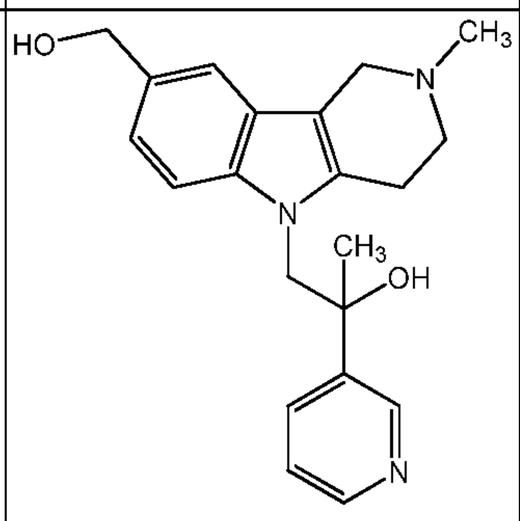

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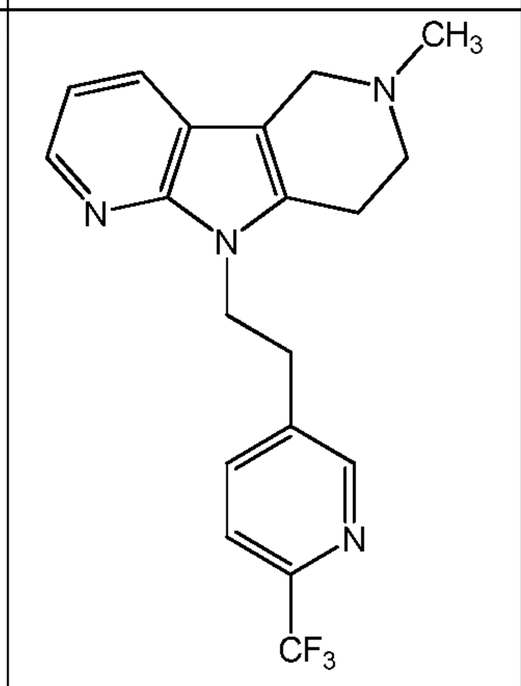

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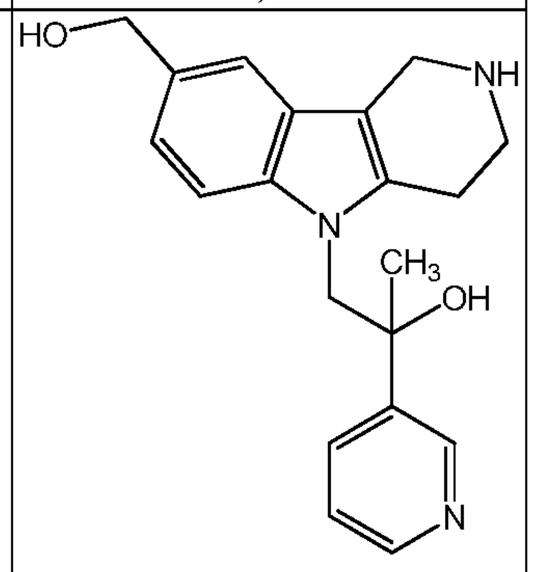

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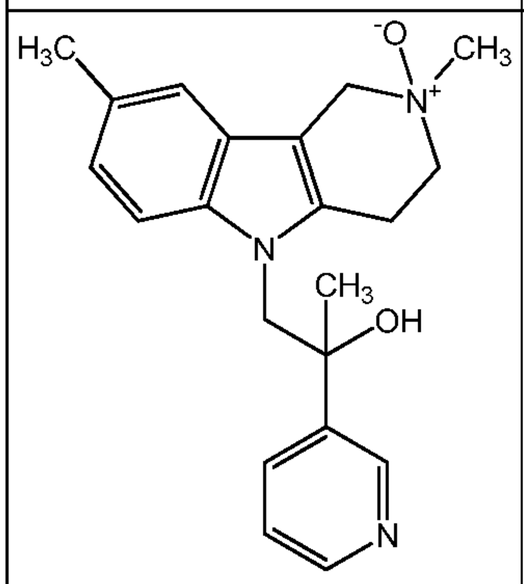

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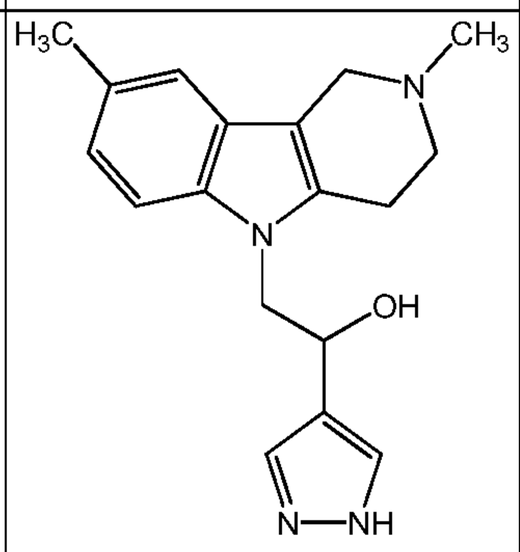

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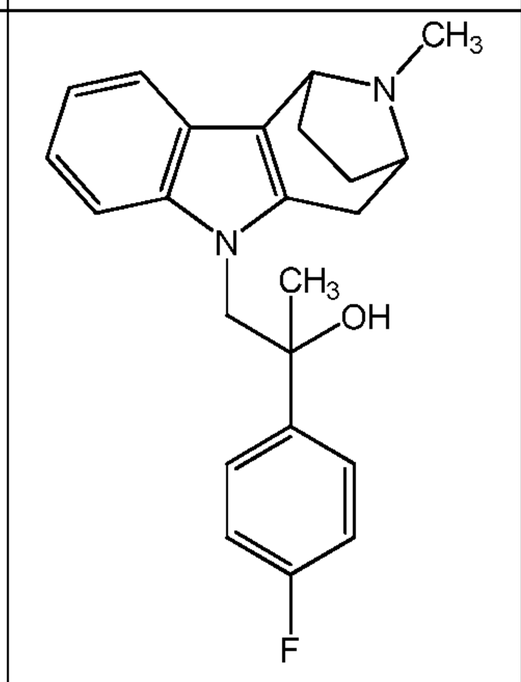

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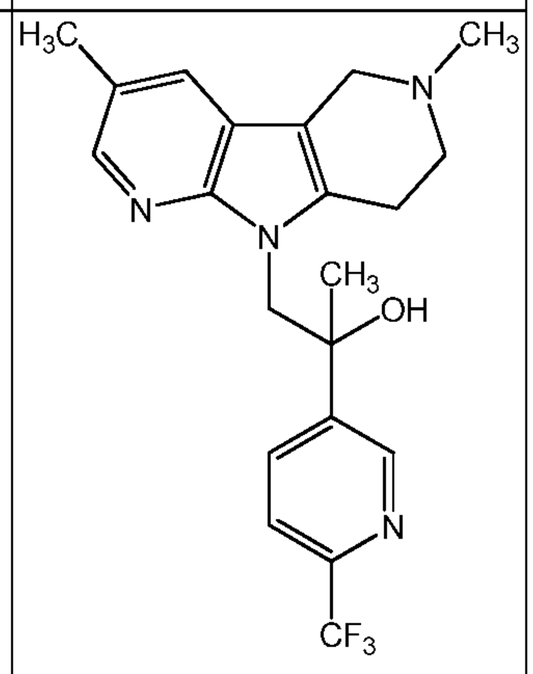

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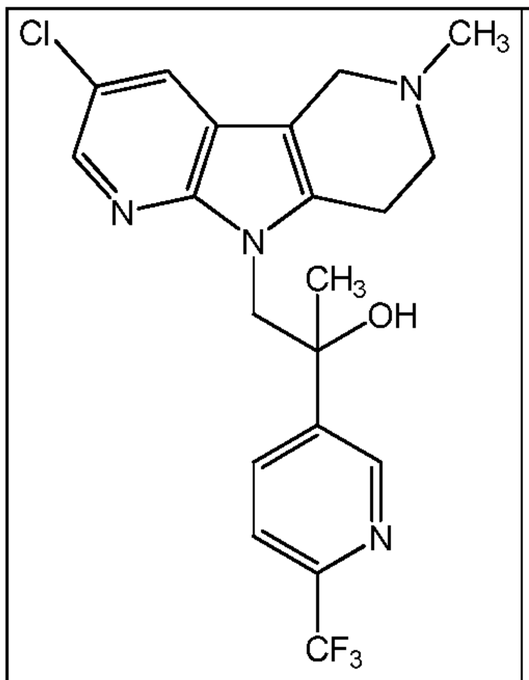

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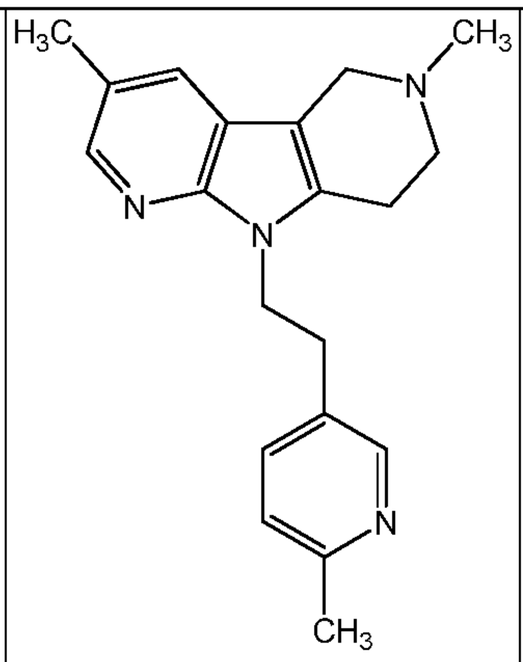

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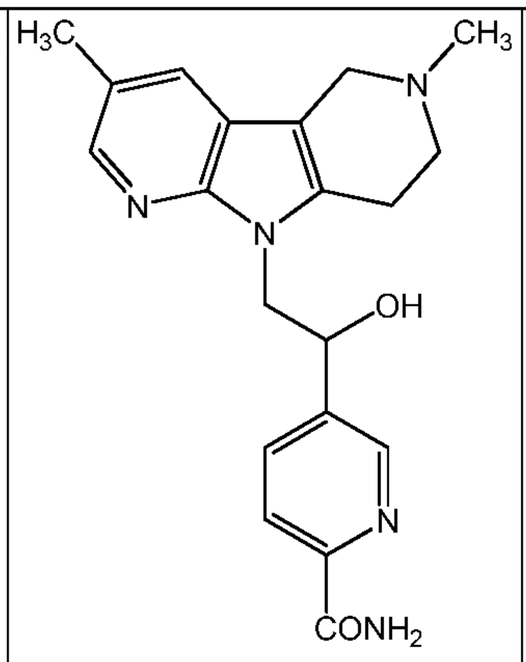

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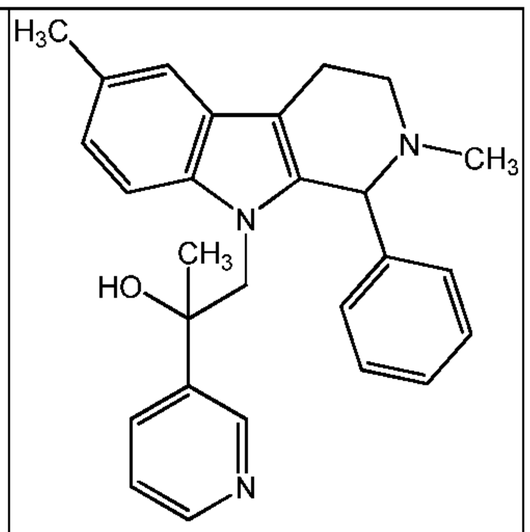

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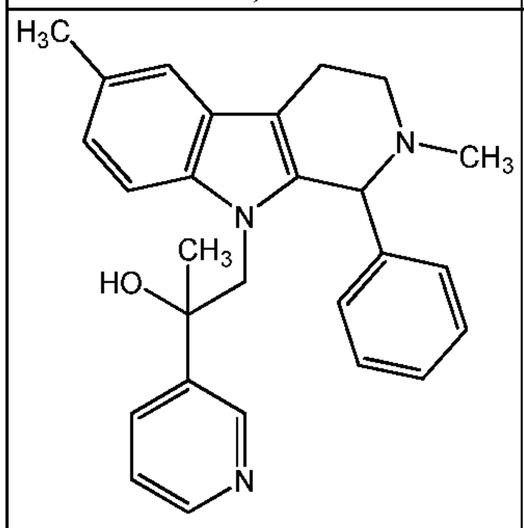

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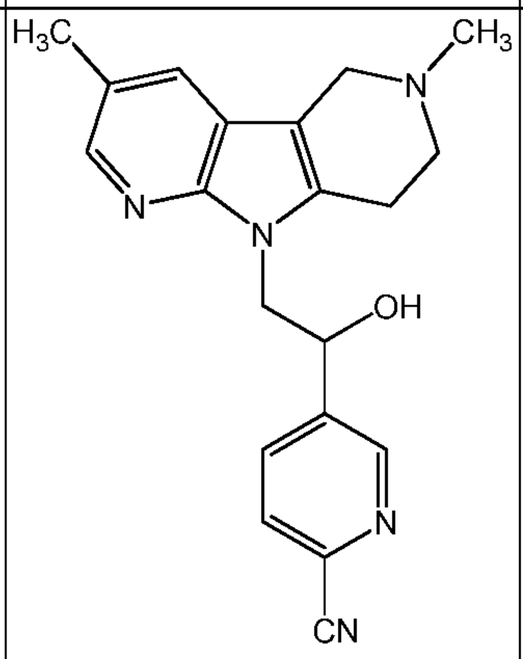

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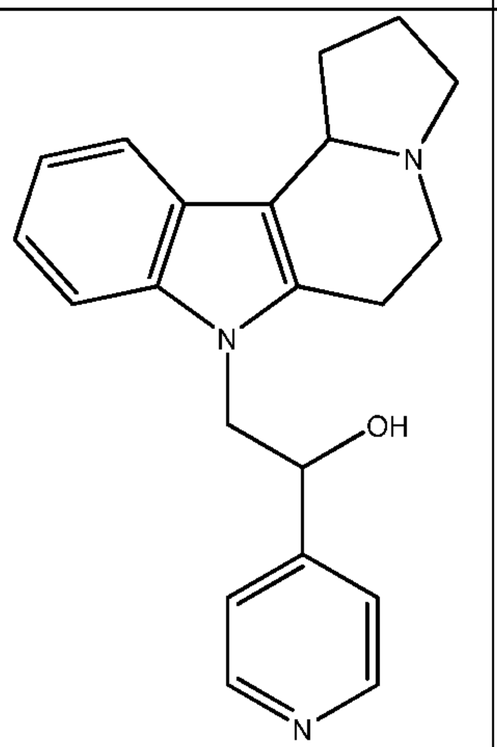

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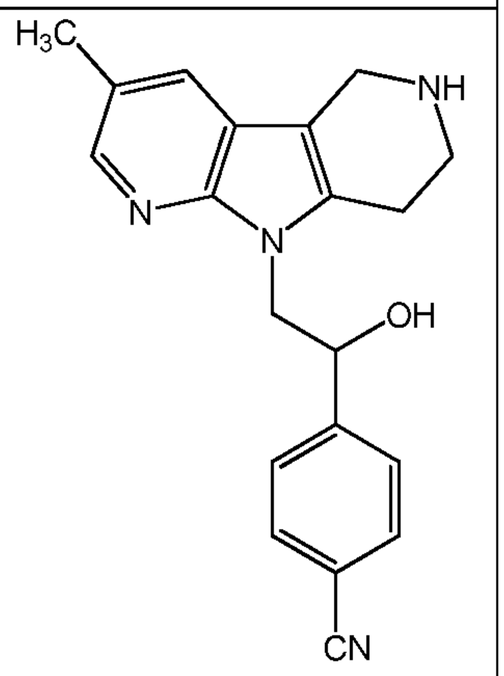

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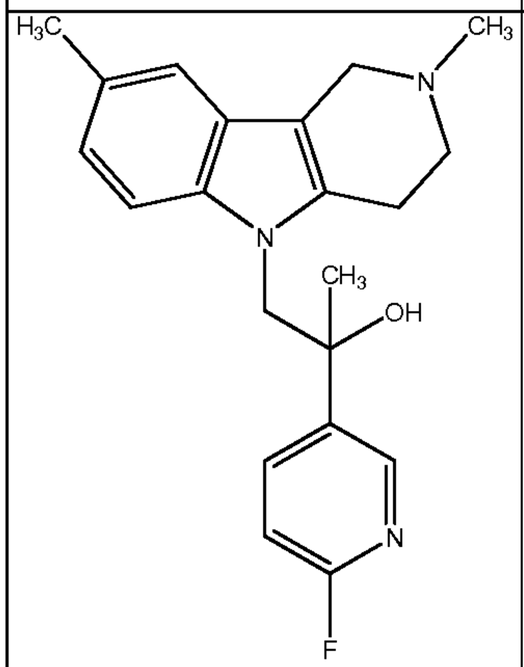

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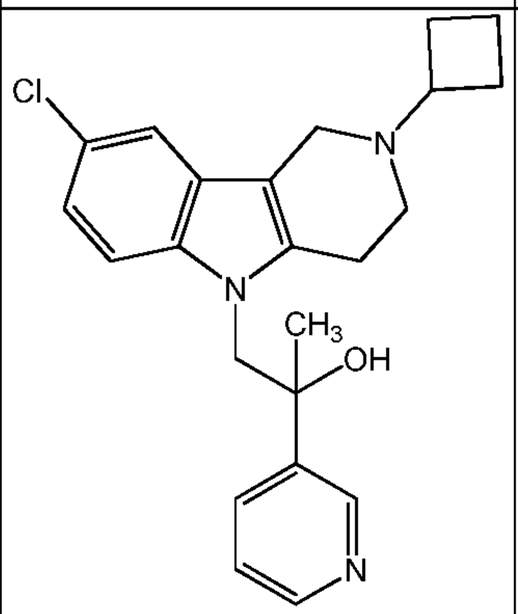
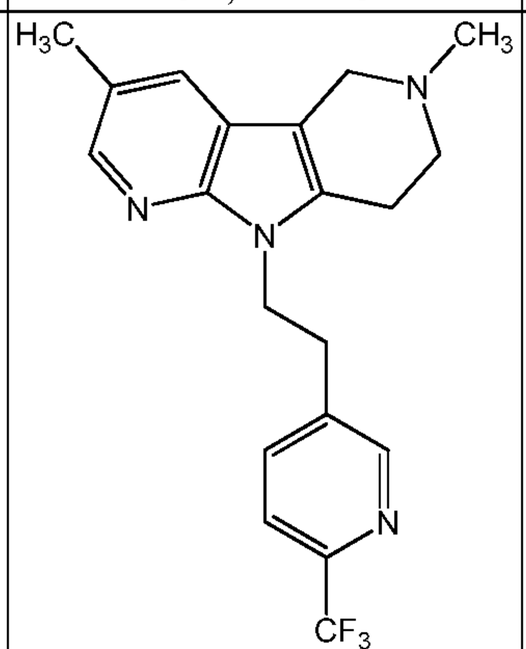
II-117a, II-117b



II-118
II-118a, II-118b



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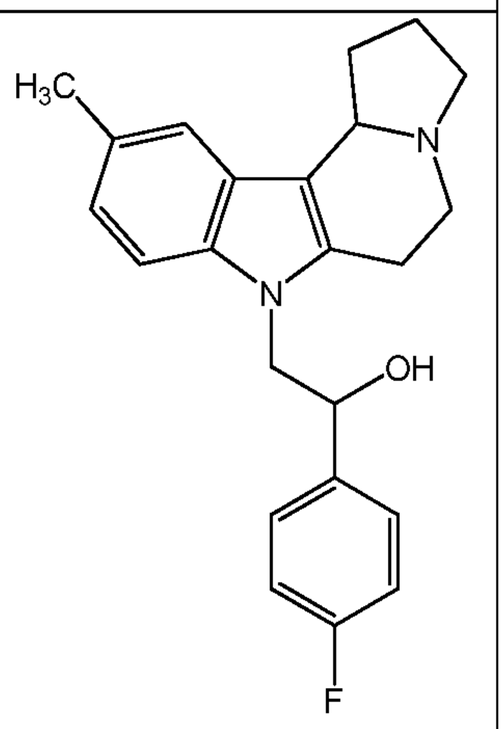

II-120
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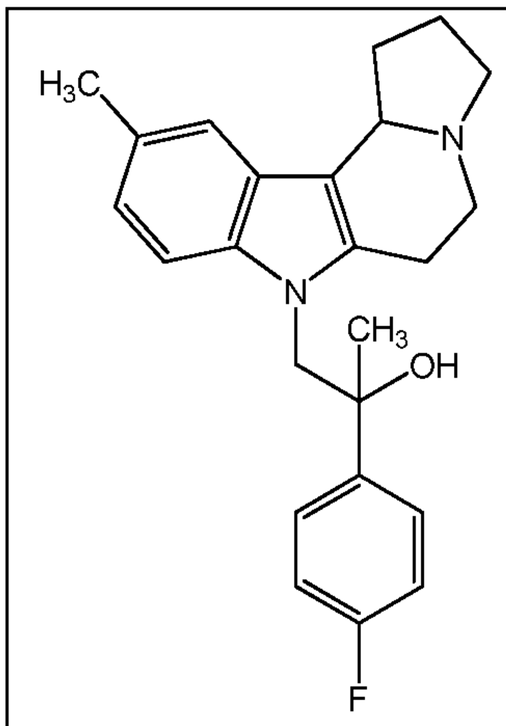
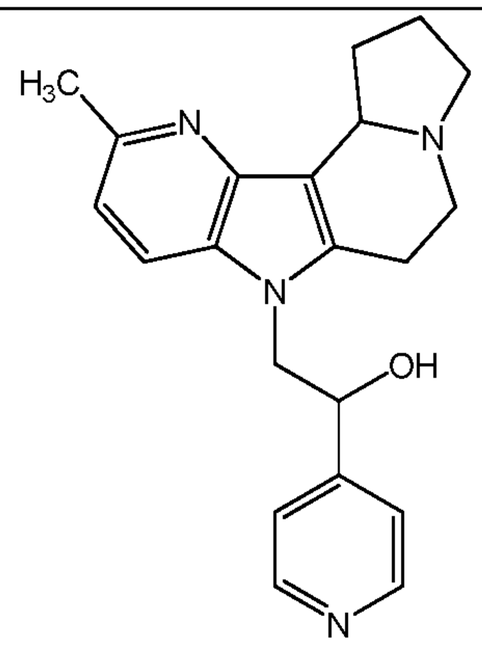
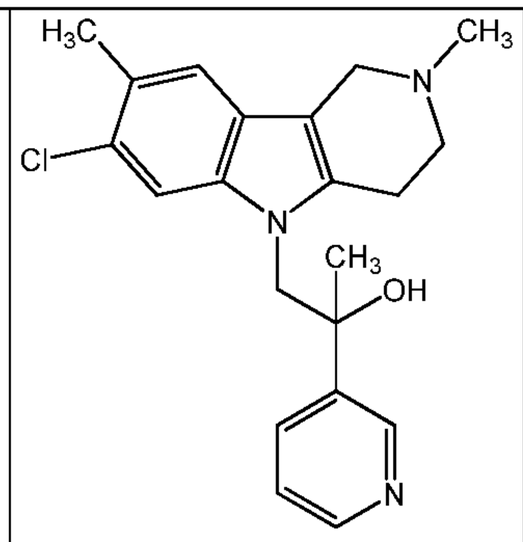
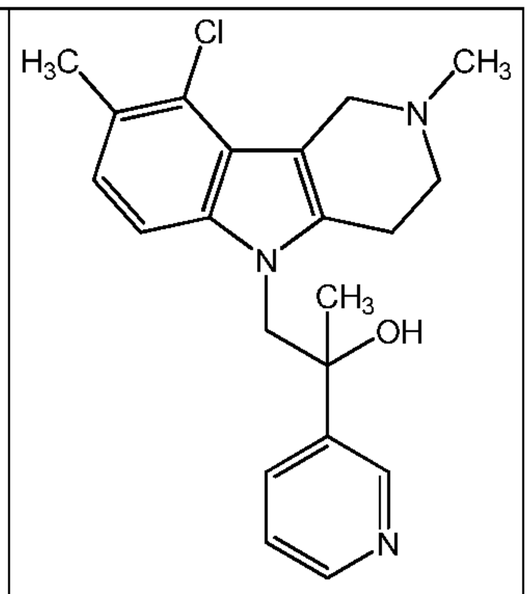
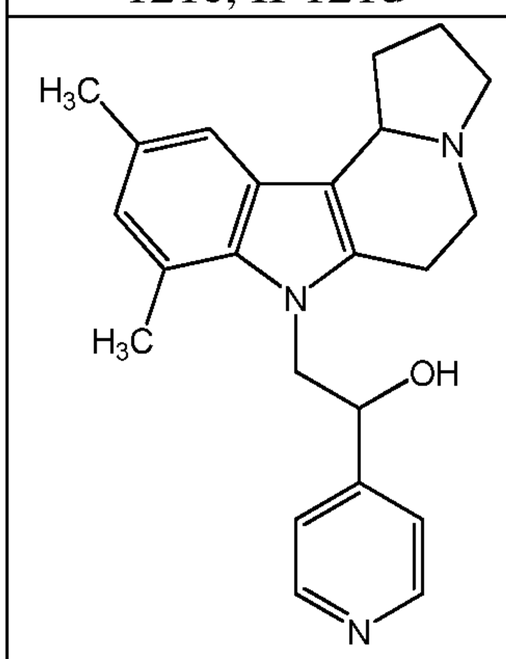
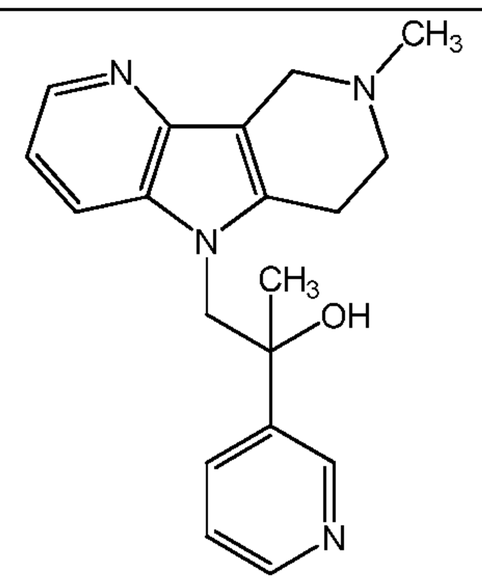
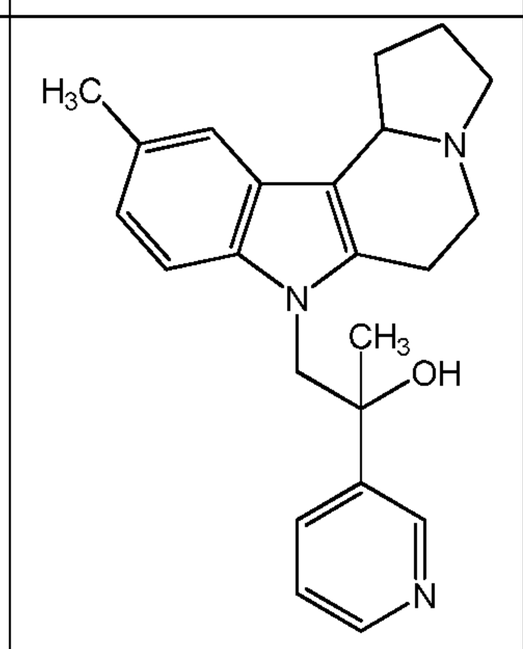
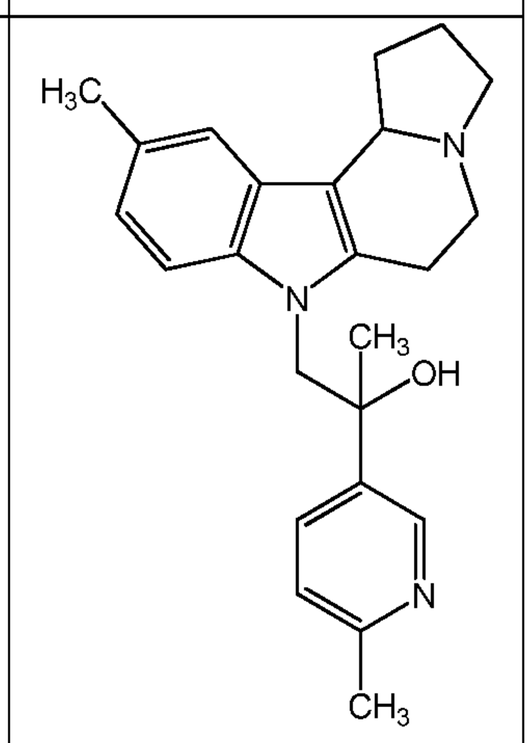
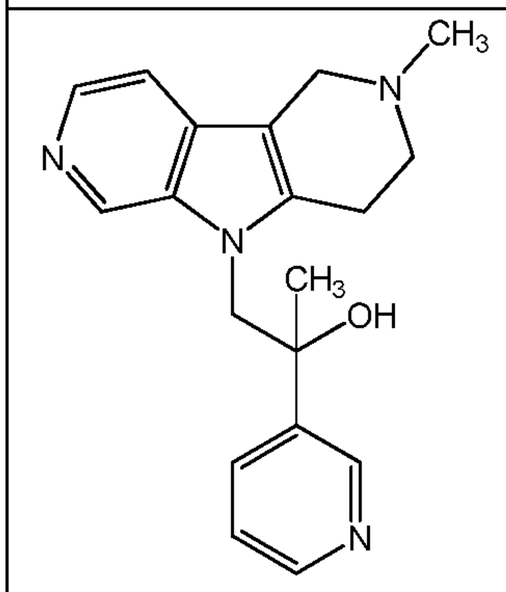
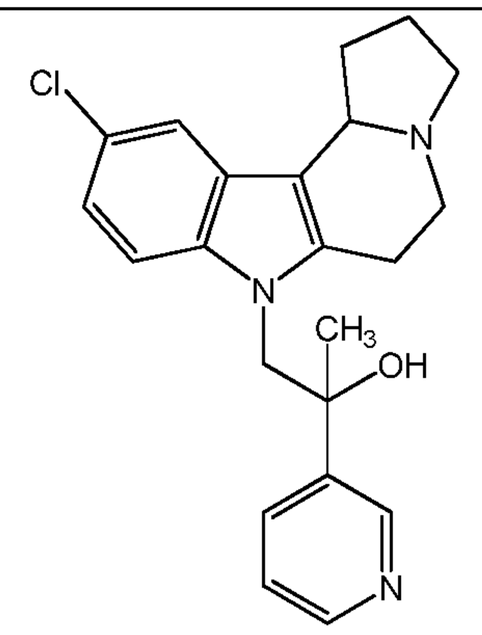
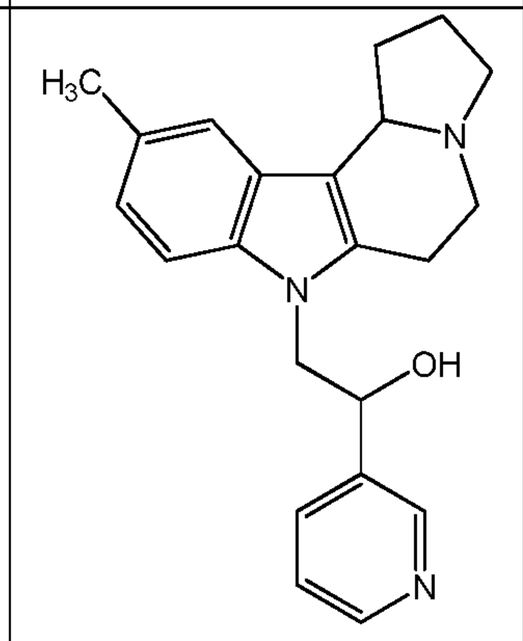
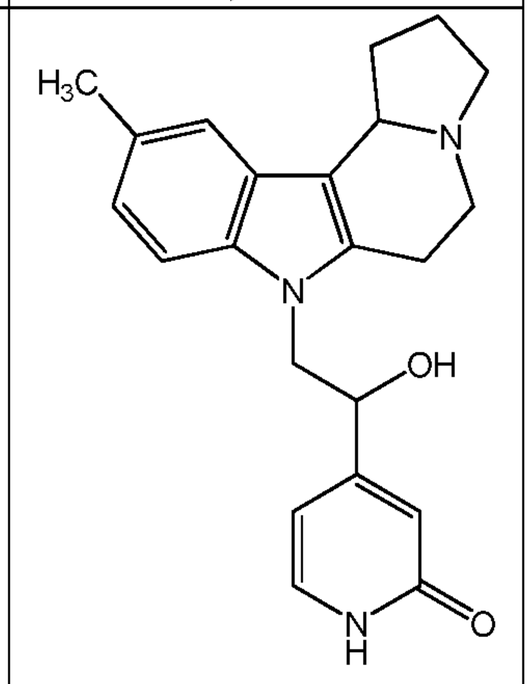
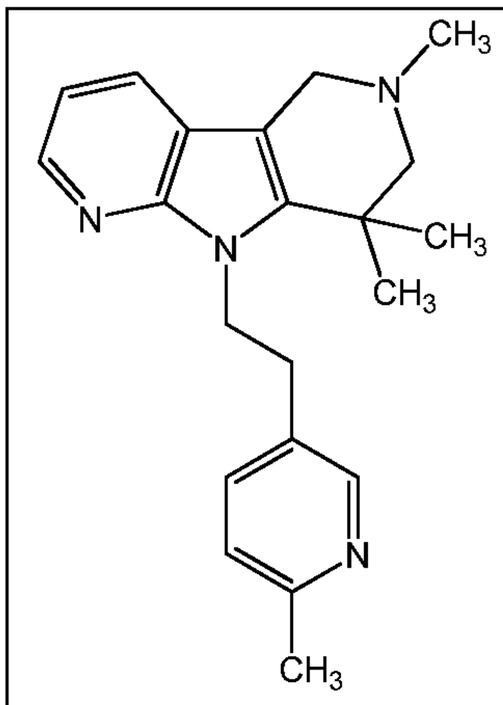
 II-121 II-121a, II-121b, II-121c, II-121d	 II-122 II-122a, II-122b, II-122c, II-122d	 II-123 II-123a, II-123b	 II-124 II-124a, II-124b
 II-125 II-125a, II-125b, II-125c, II-125d	 II-126 II-126a, II-126b	 II-127 II-127a, II-127b, II-127c, II-127d	 II-128 II-128a, II-128b, II-128c, II-128d
 II-129 II-129a, 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



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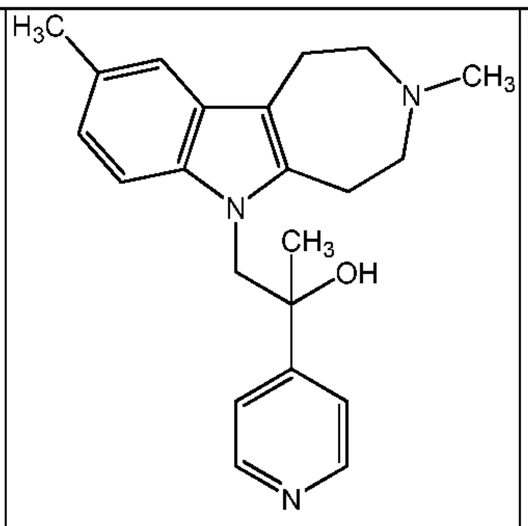

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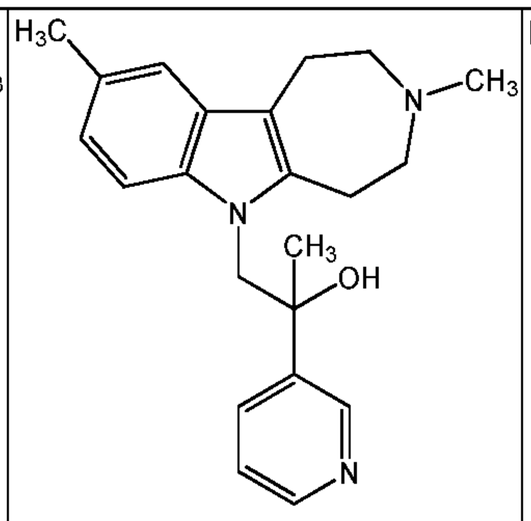
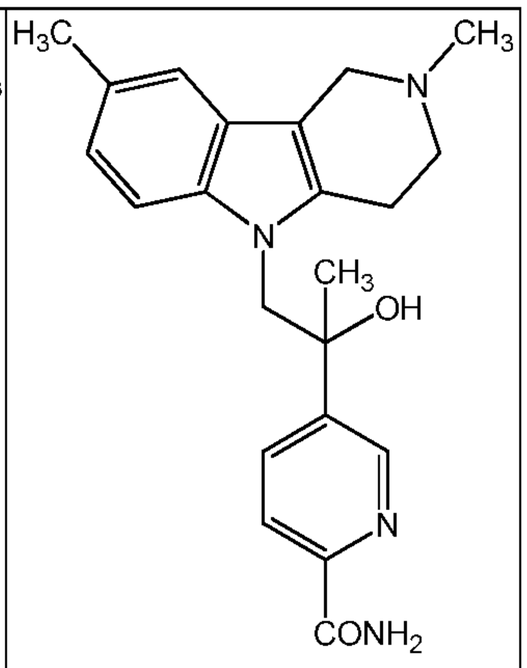
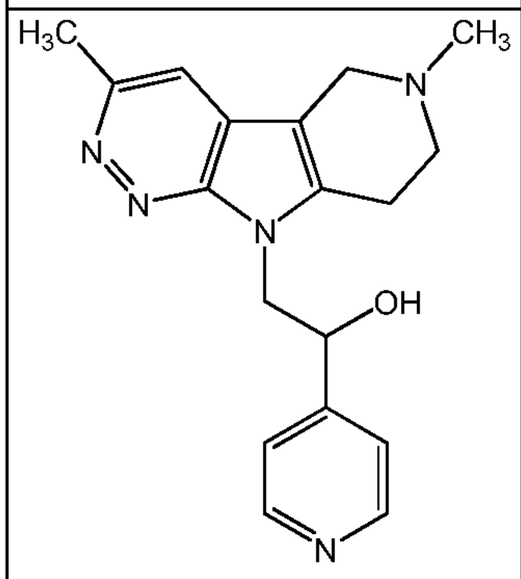
II-134a, II-134b



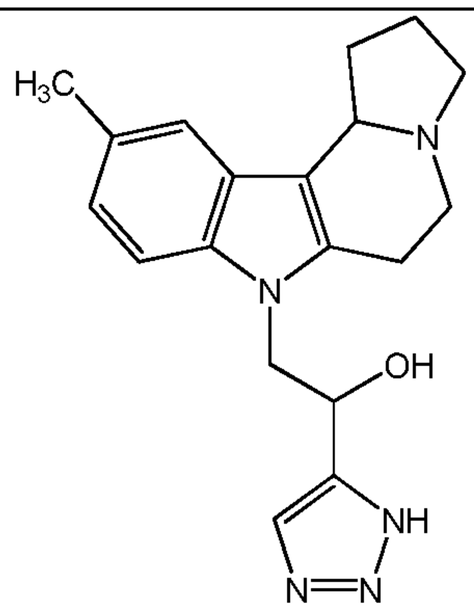
II-135
II-135a, II-135b



II-136
II-136a, II-136b



II-137
II-137a, II-137b



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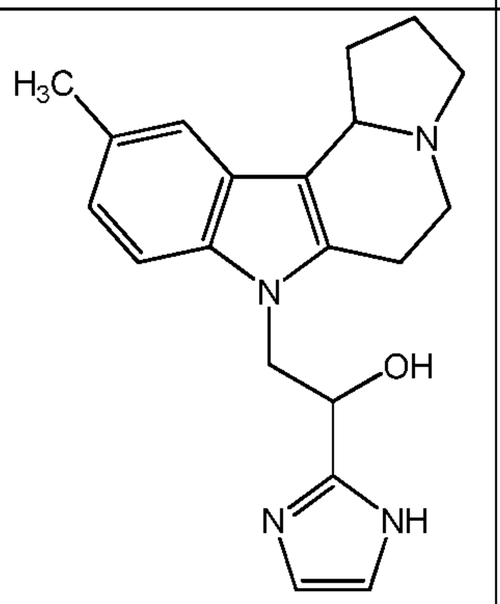
II-138a, II-138b, II-138c, II-138d



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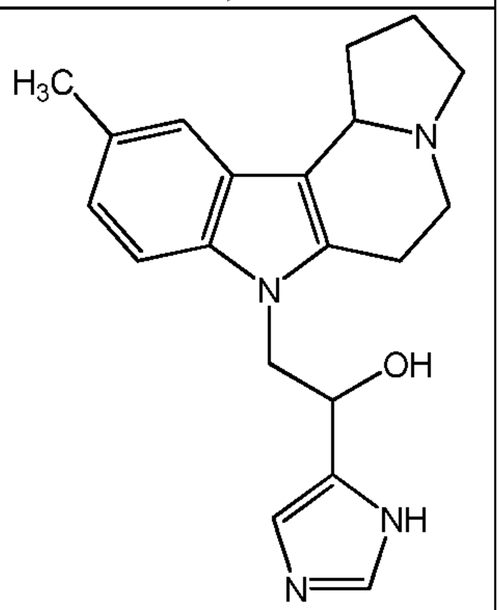

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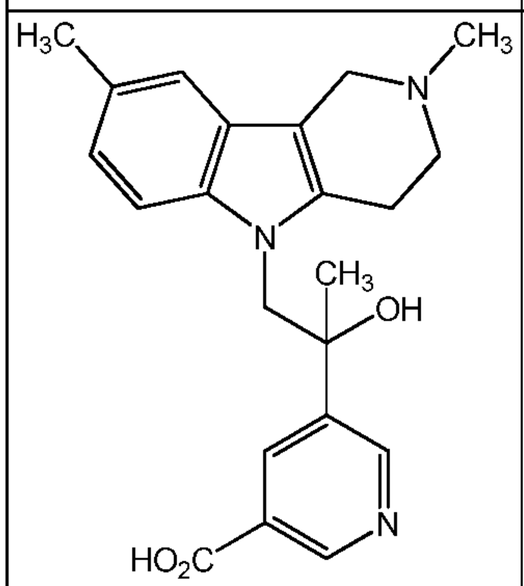

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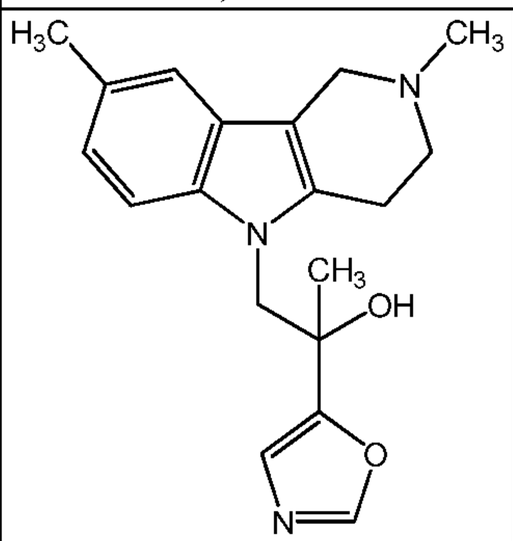
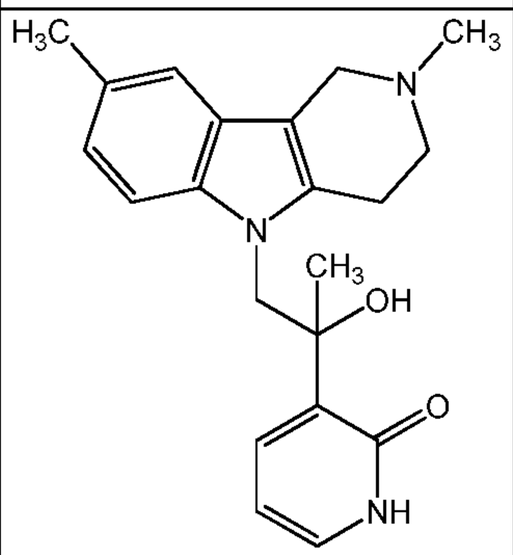
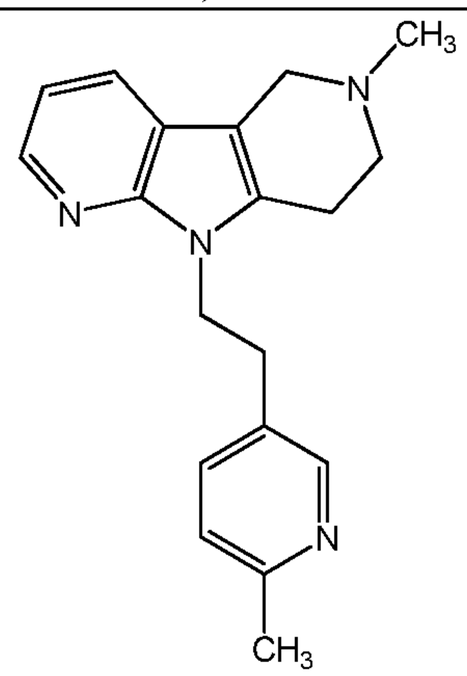
II-141a, II-141b



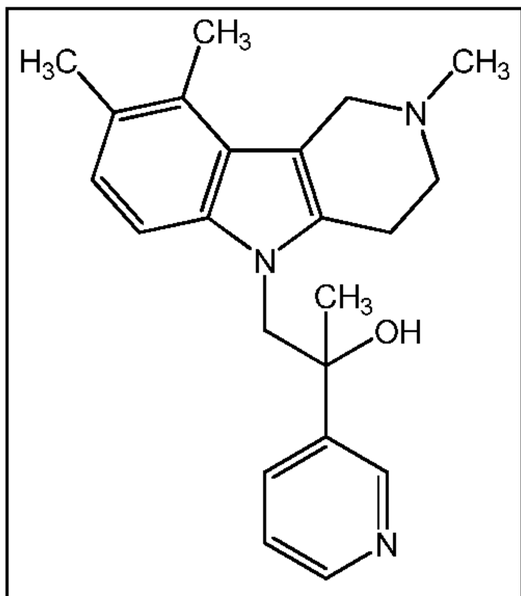
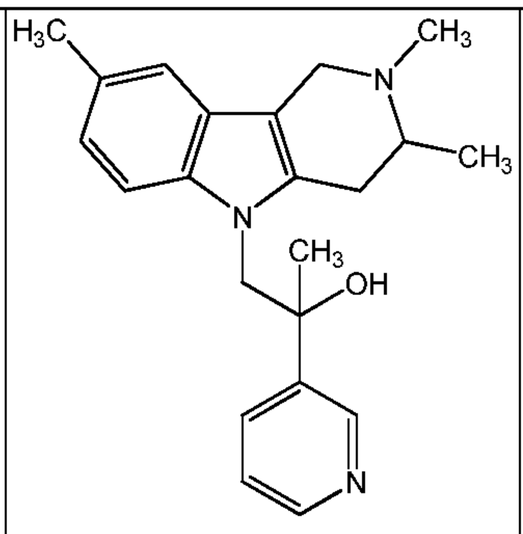
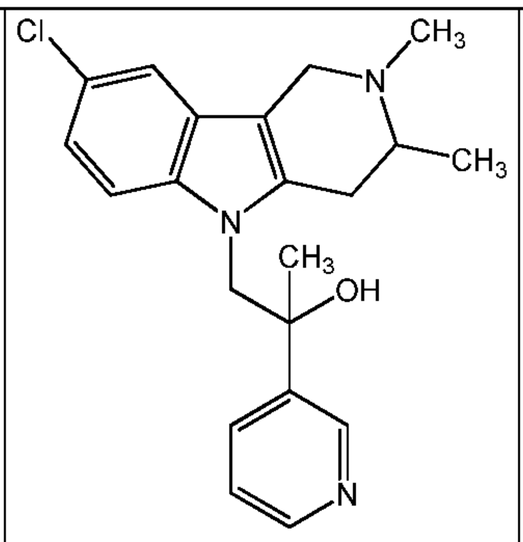
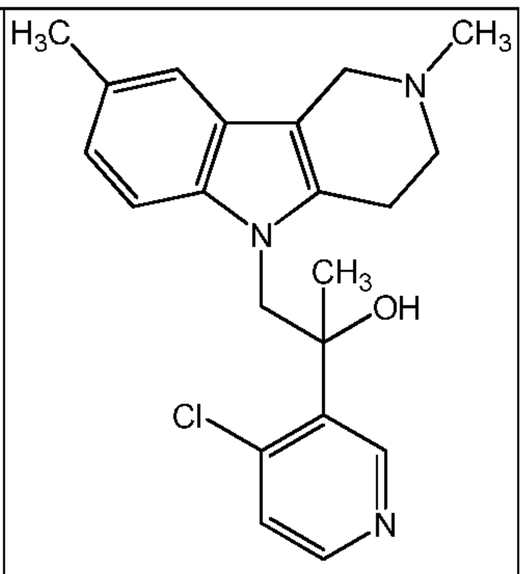
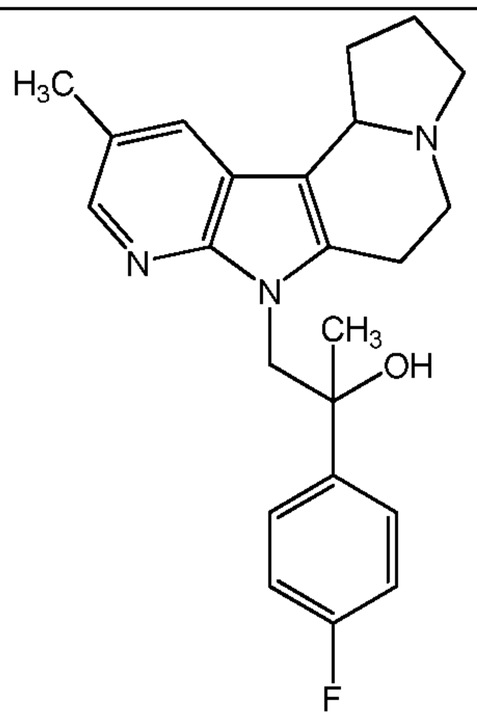
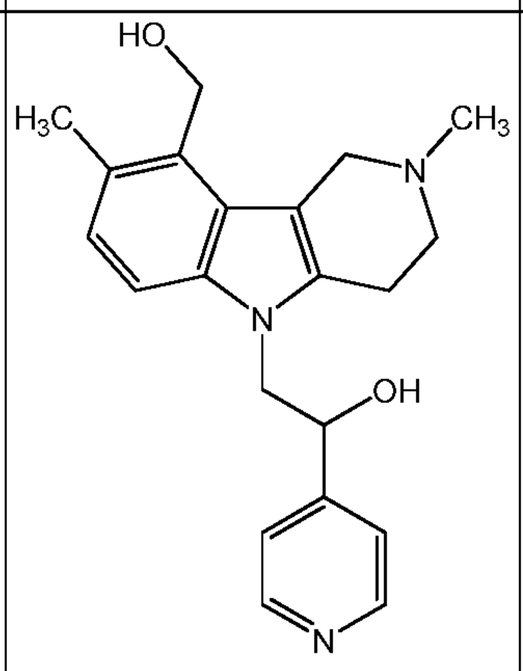
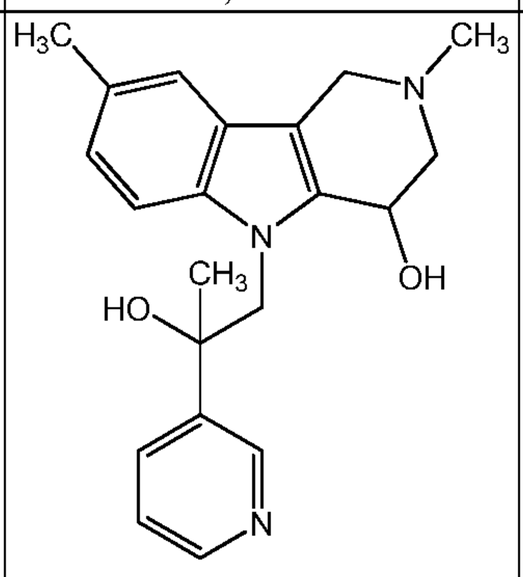
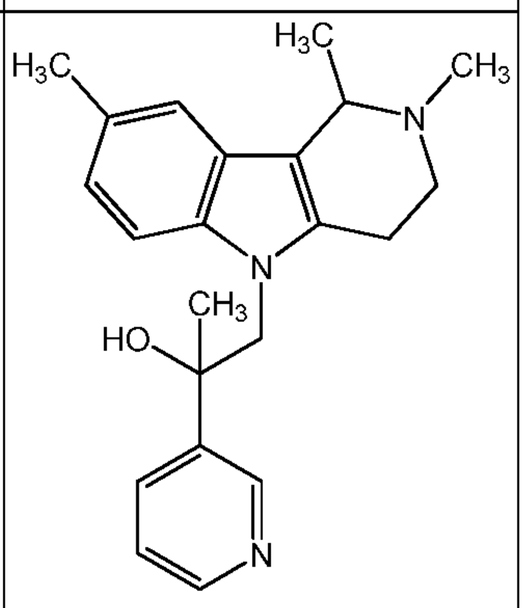
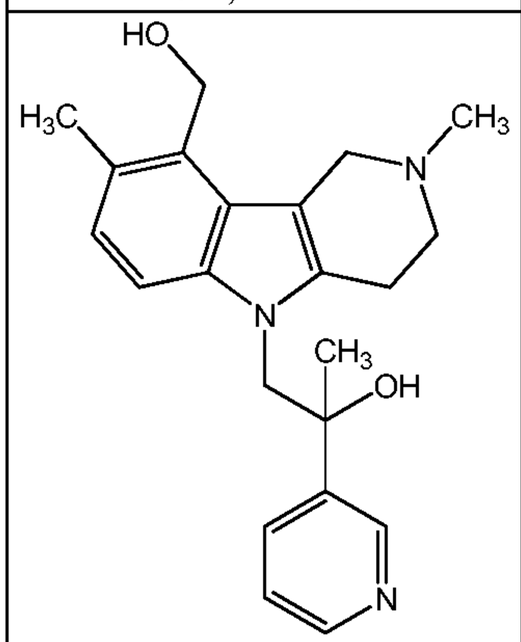
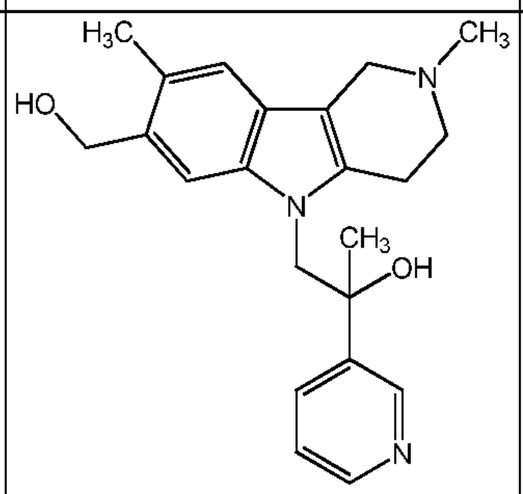
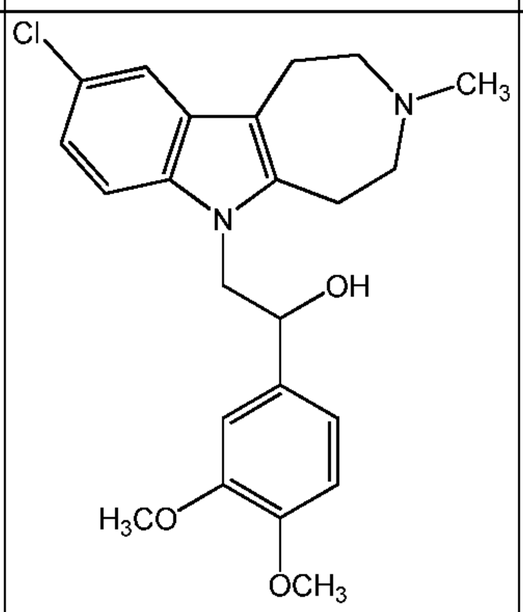
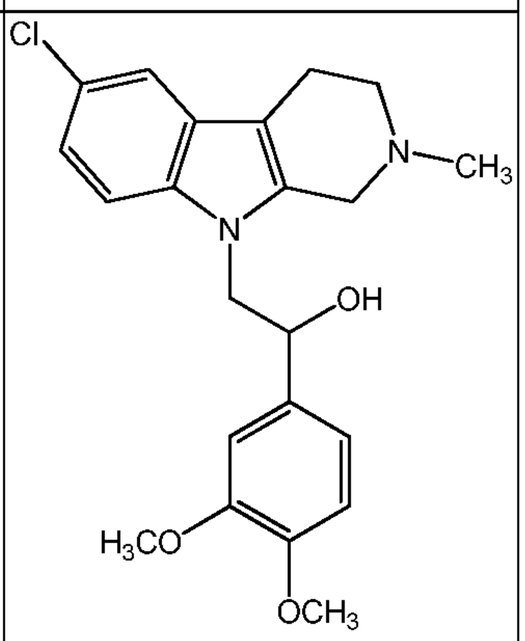
II-142
II-142a, II-142b

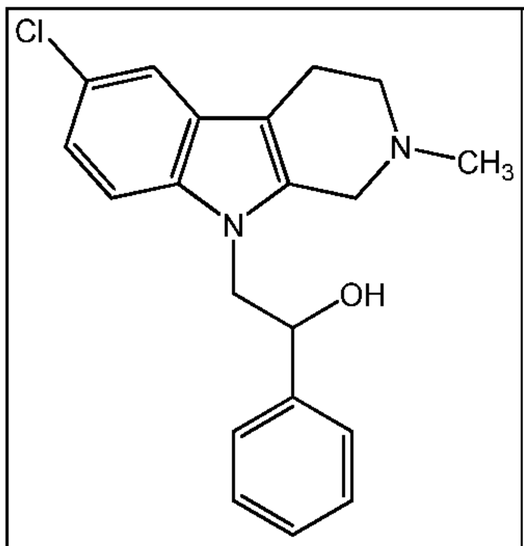
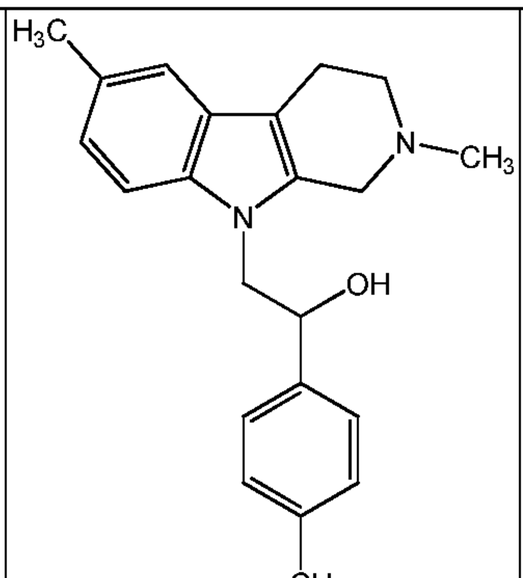
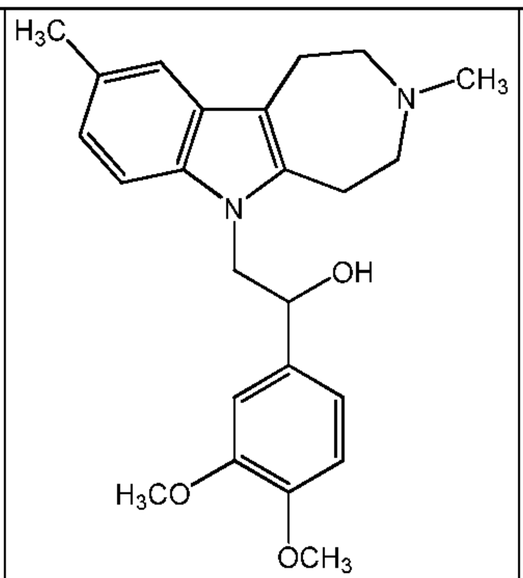
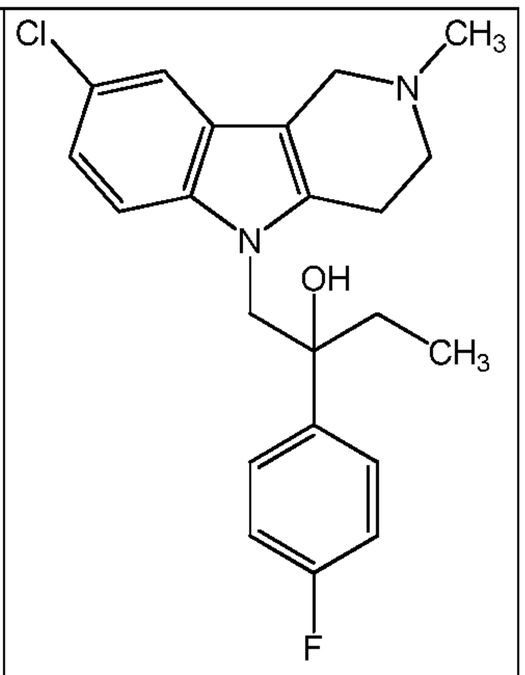
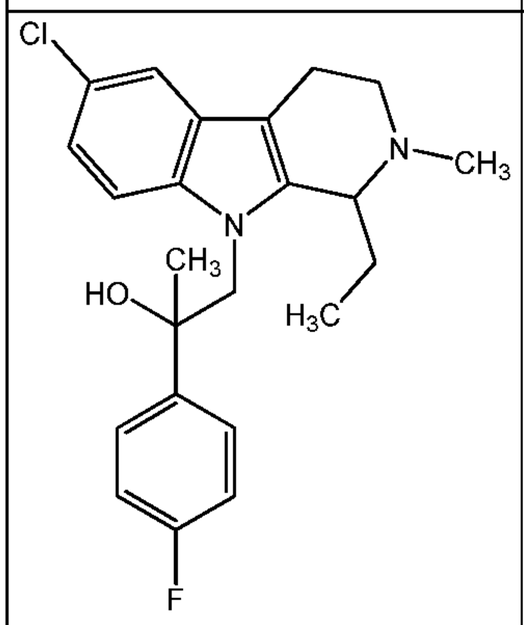
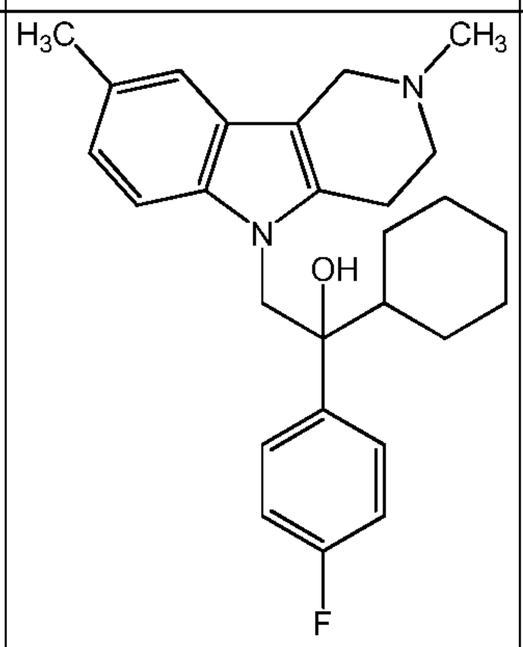
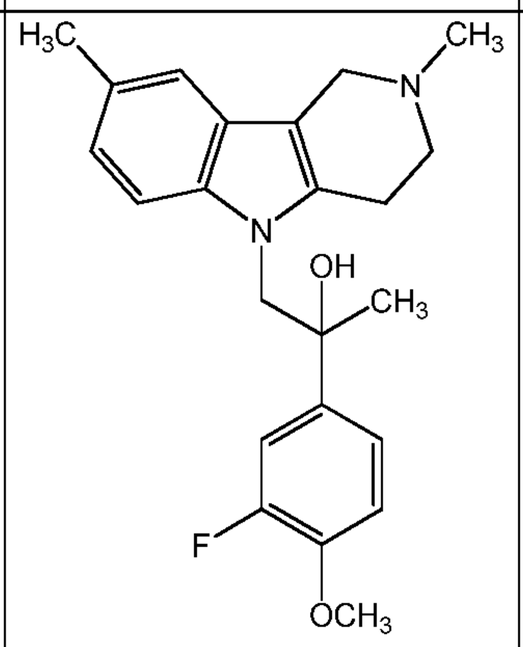
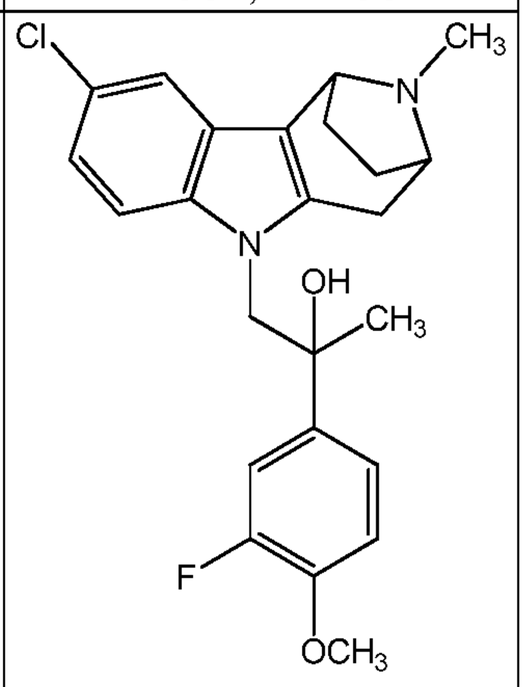
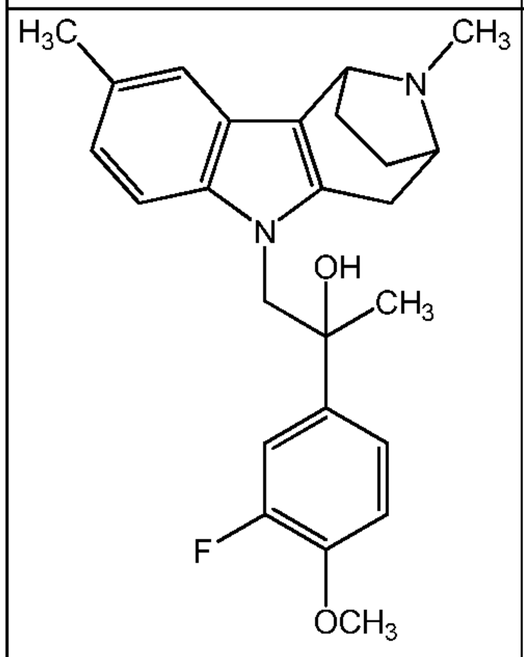
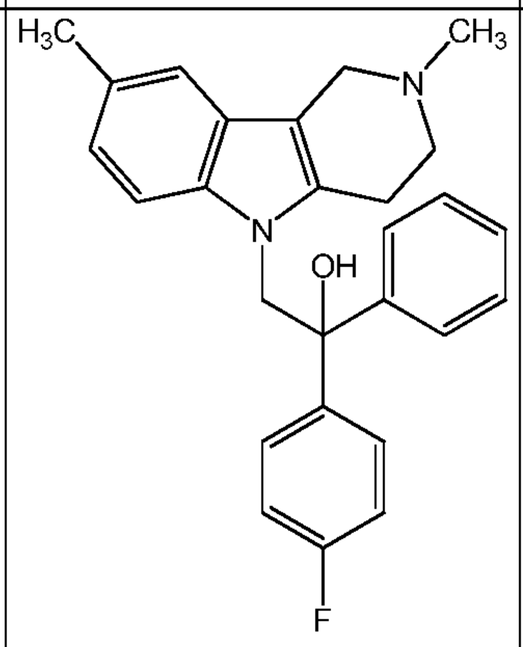
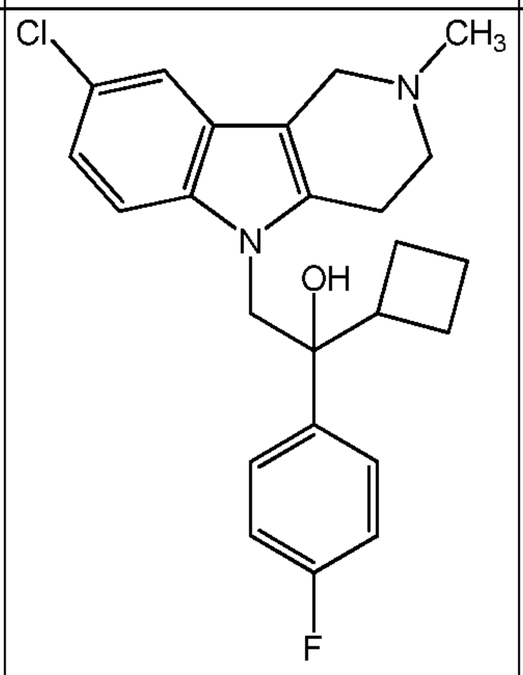
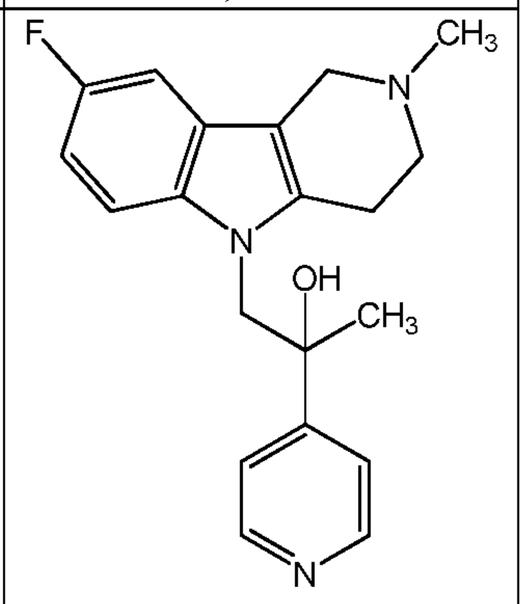


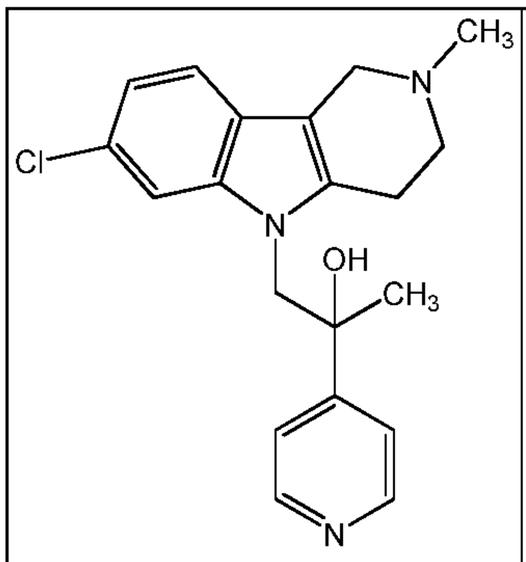
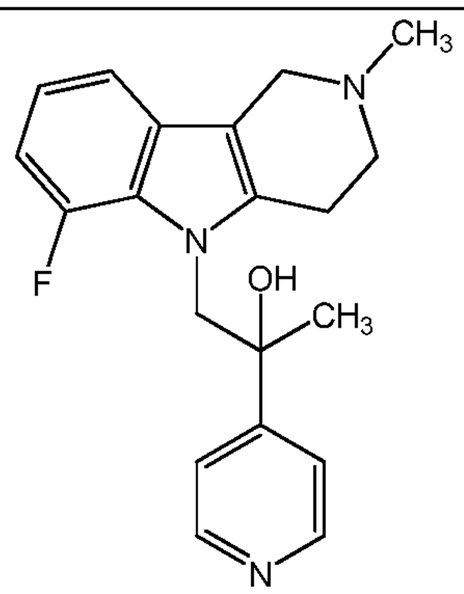
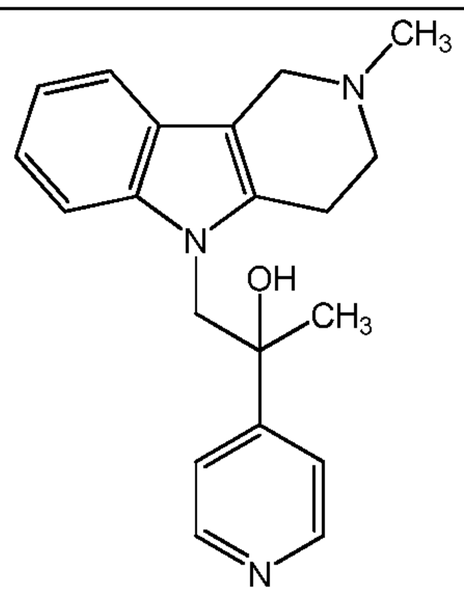
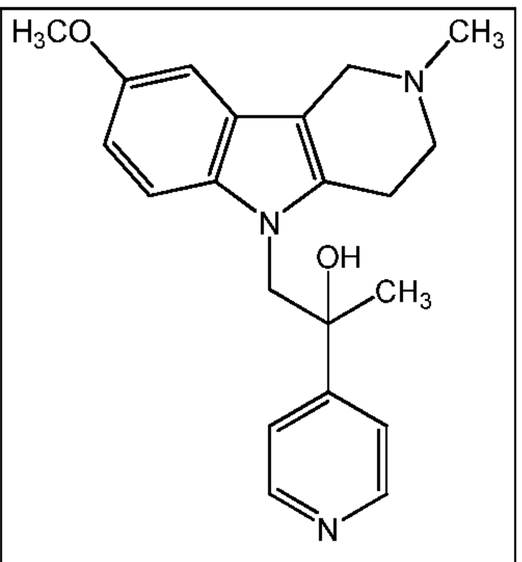
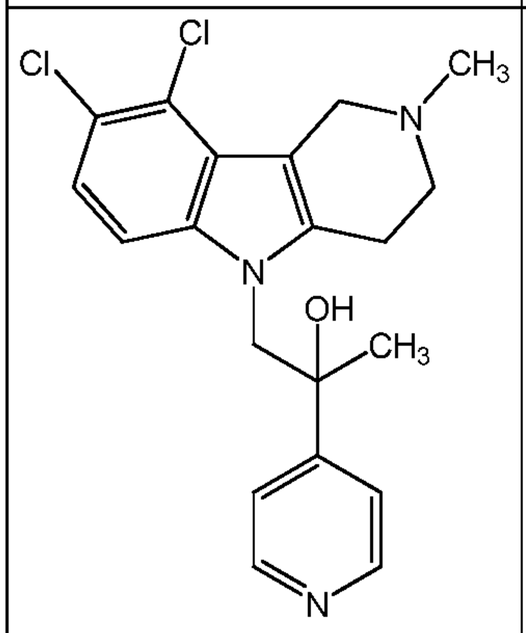
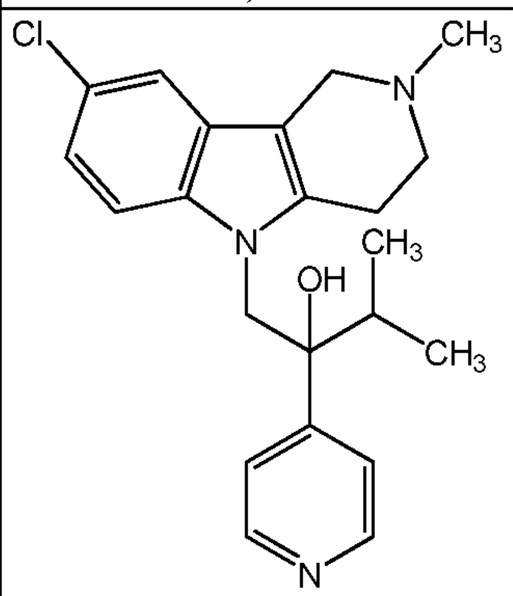
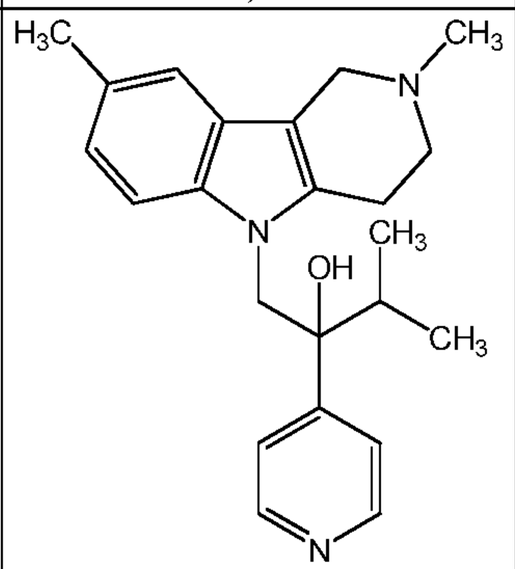
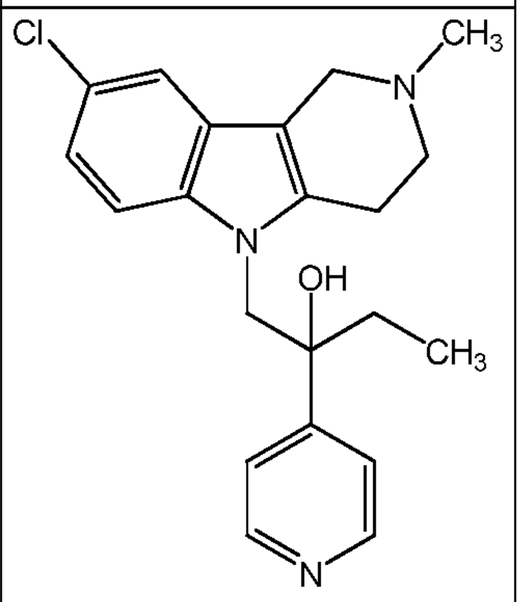
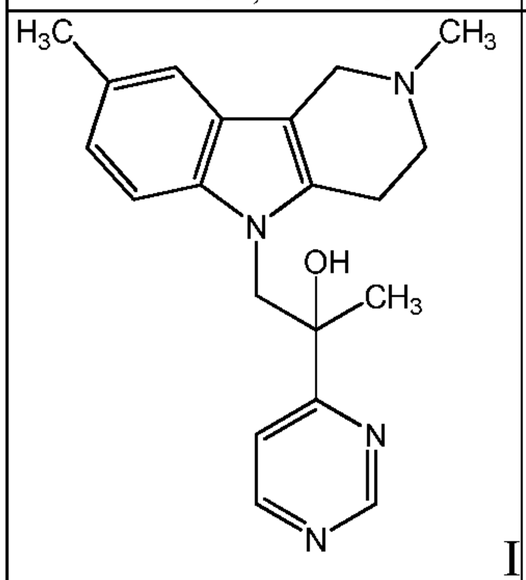
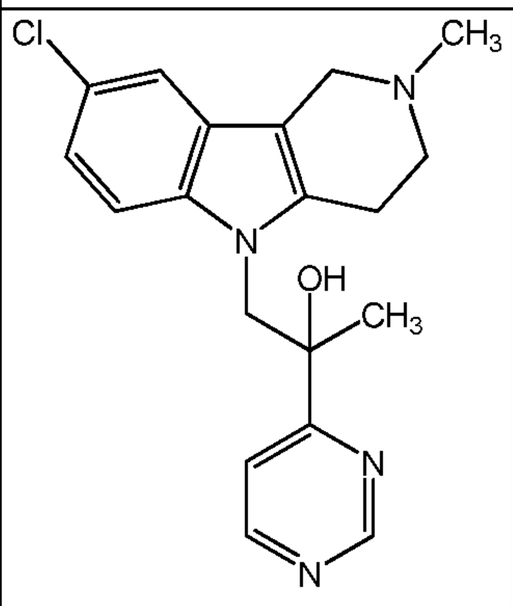
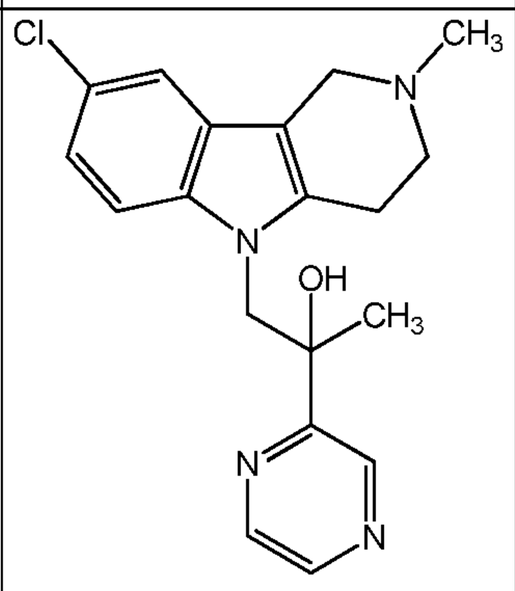
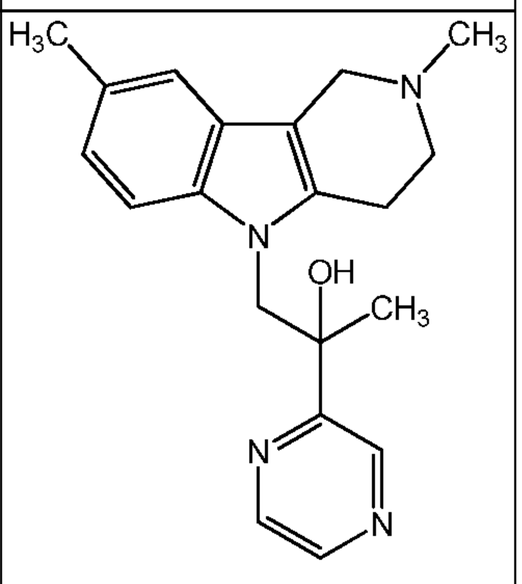
II-143
II-143a, II-143b

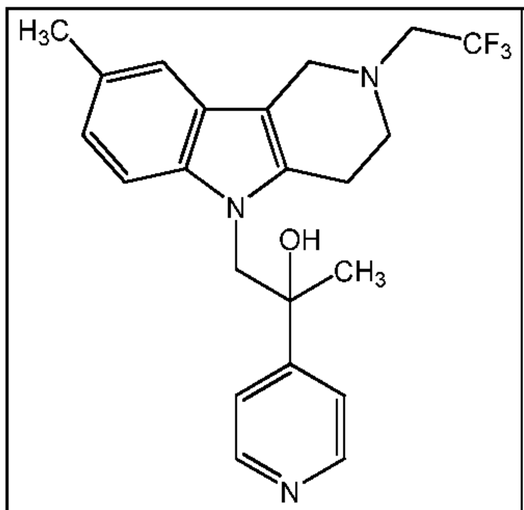


II-144

 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



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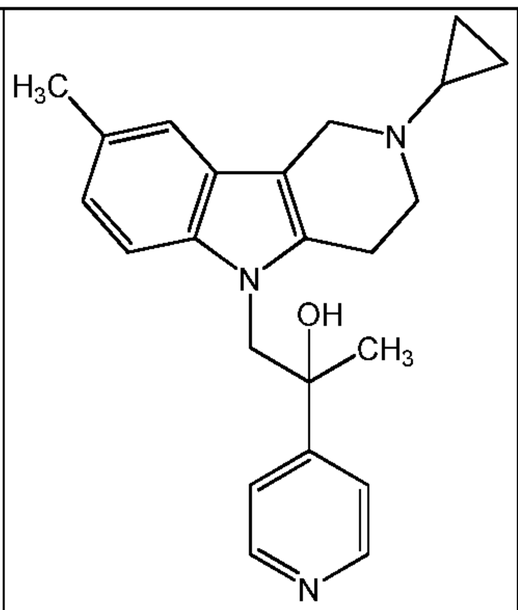
II-181a, II-181b



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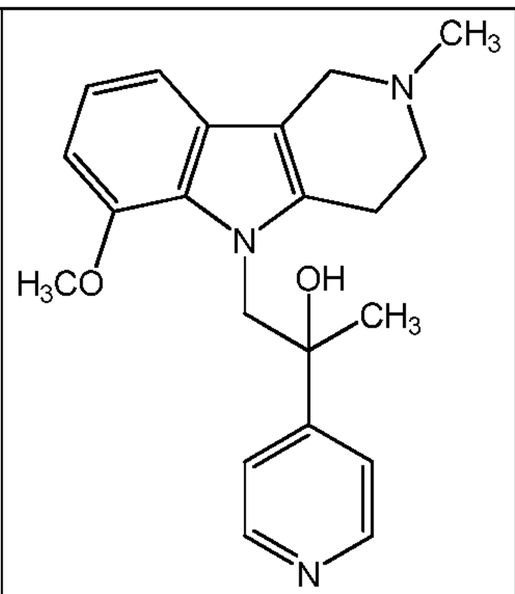
II-182a, II-182b



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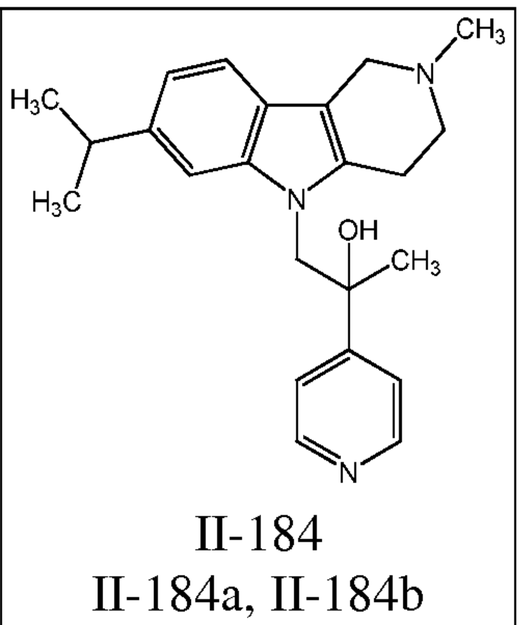
II-183a, II-183b



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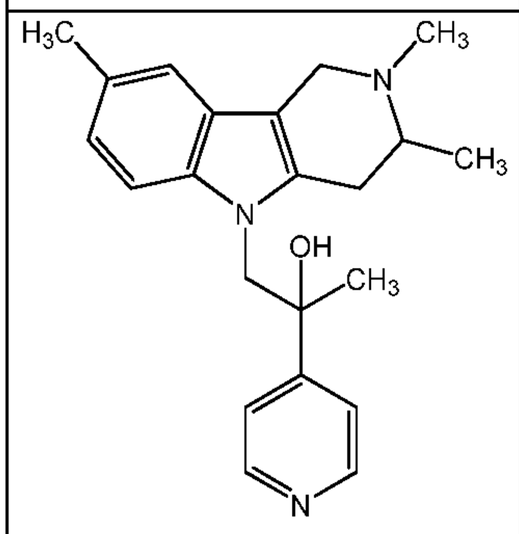
II-184a, II-184b



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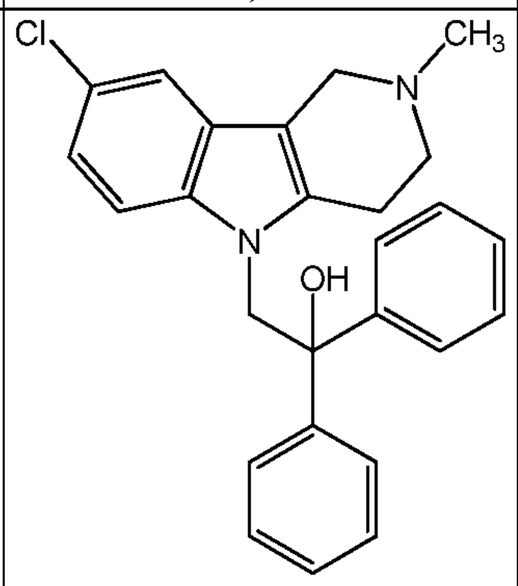
II-185a, II-185b, II-185c, II-185d



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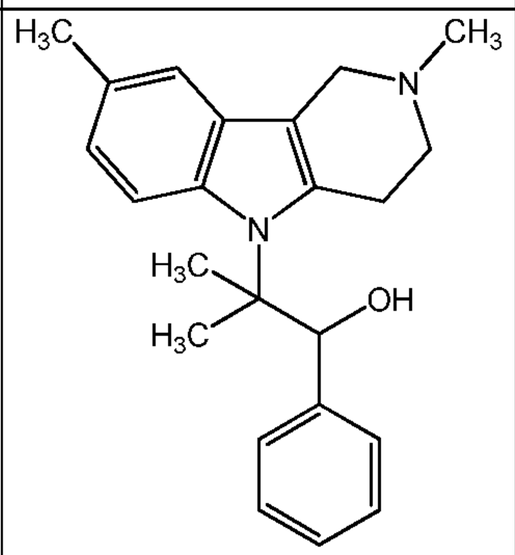

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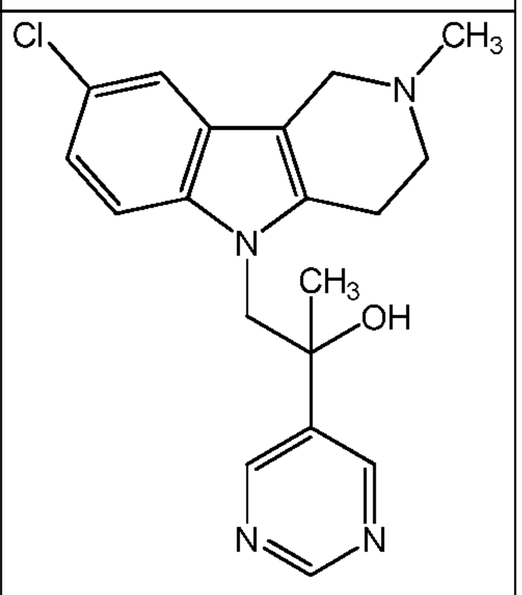
II-187a, II-187b



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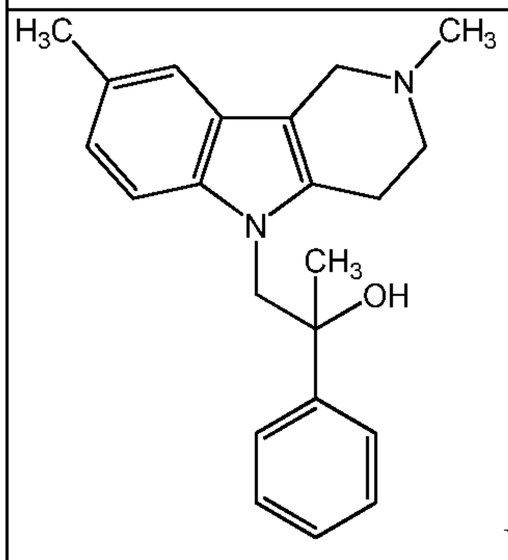
II-188a, II-188b



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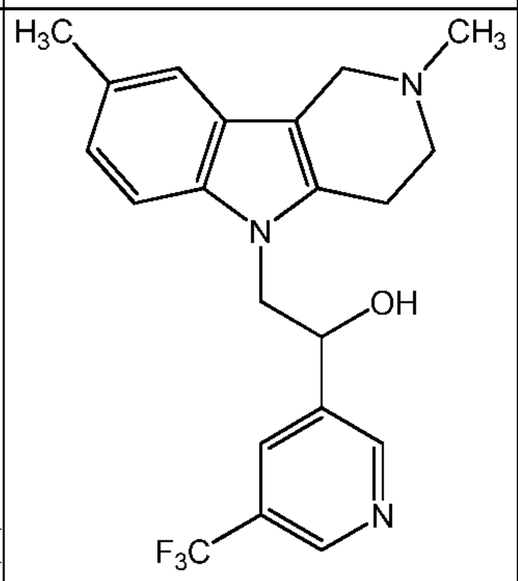
II-189a, II-189b



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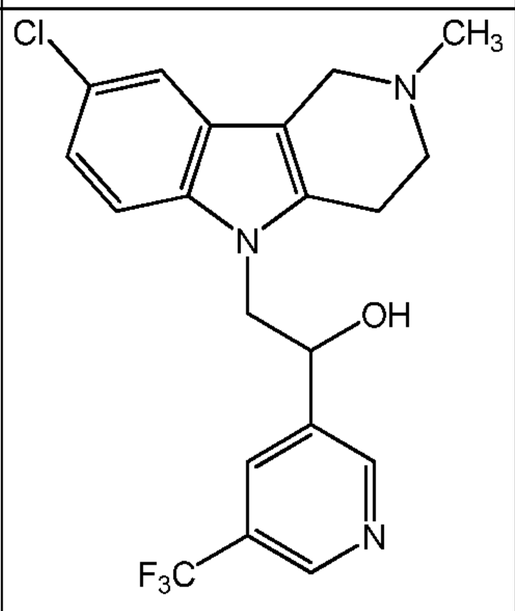
II-190a, II-190b



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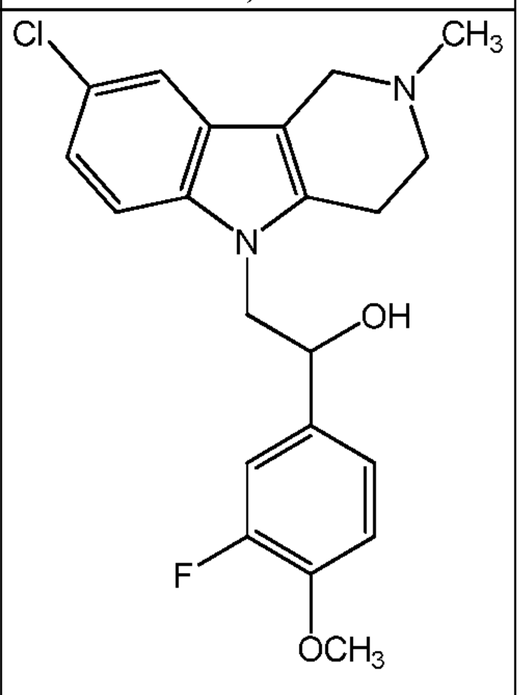
II-191a, II-191b



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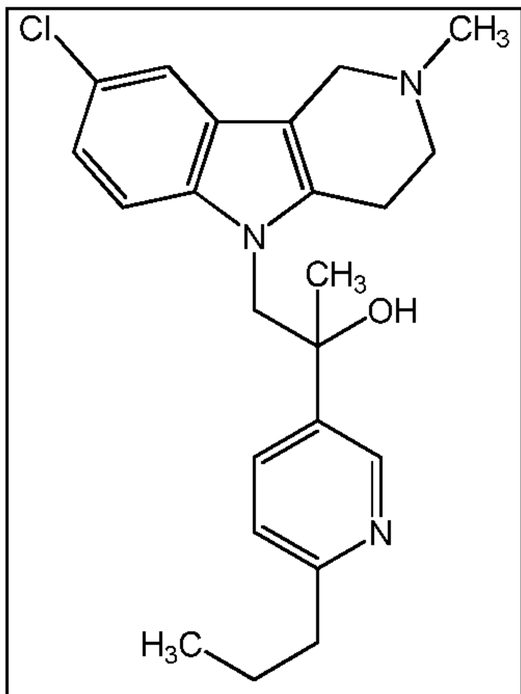
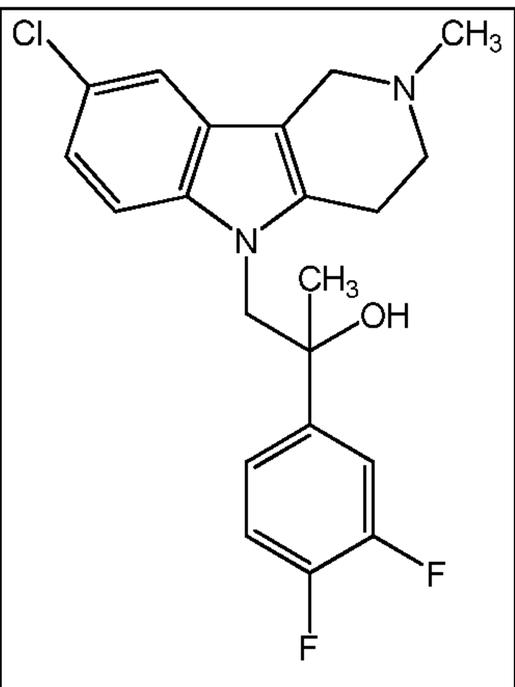
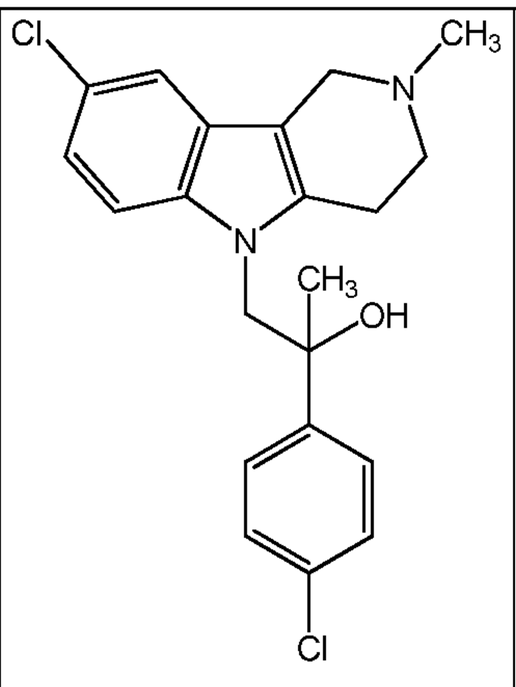
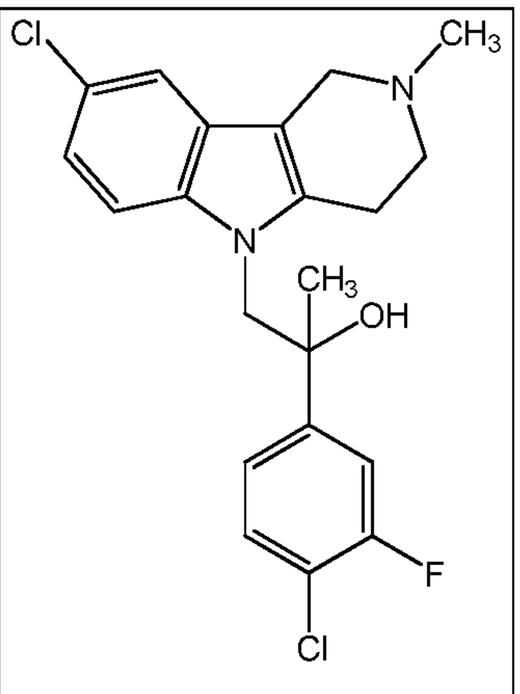
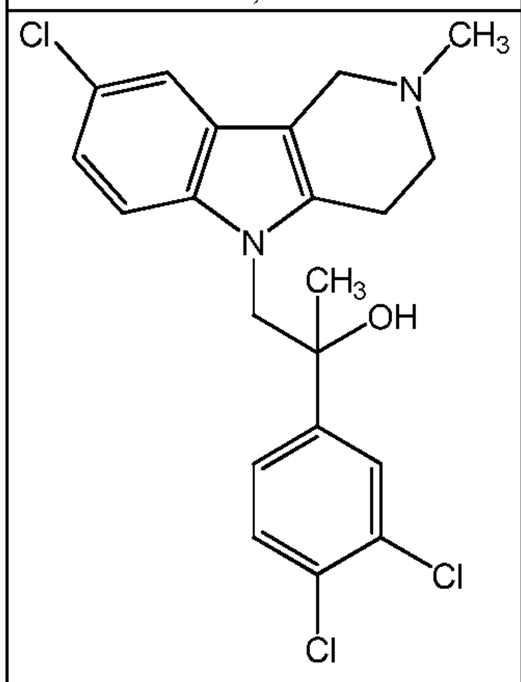
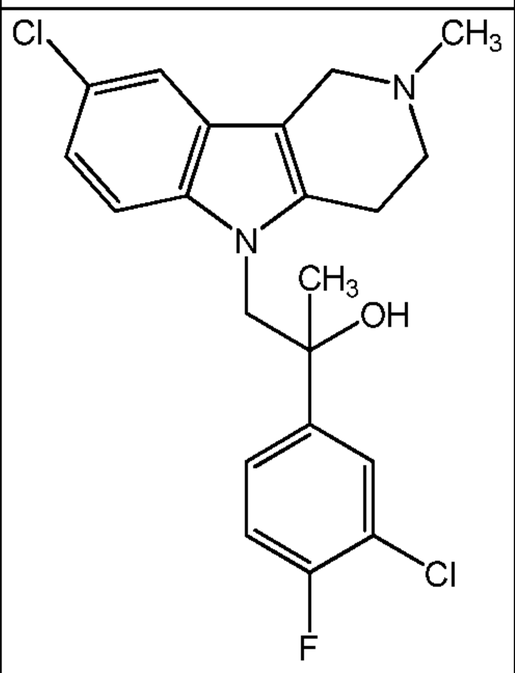
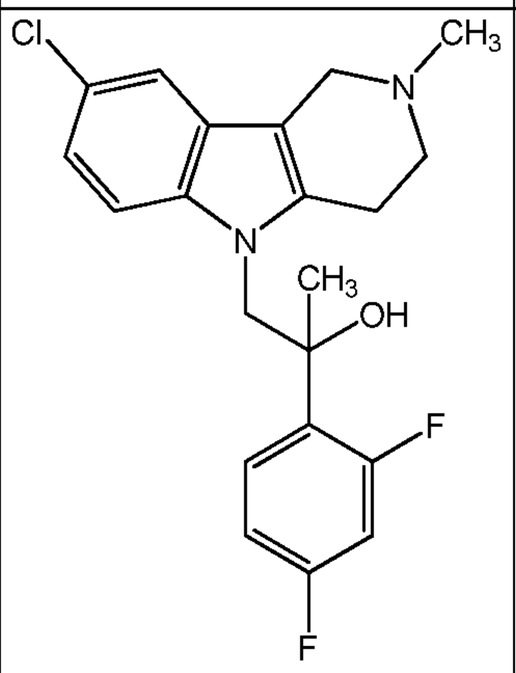
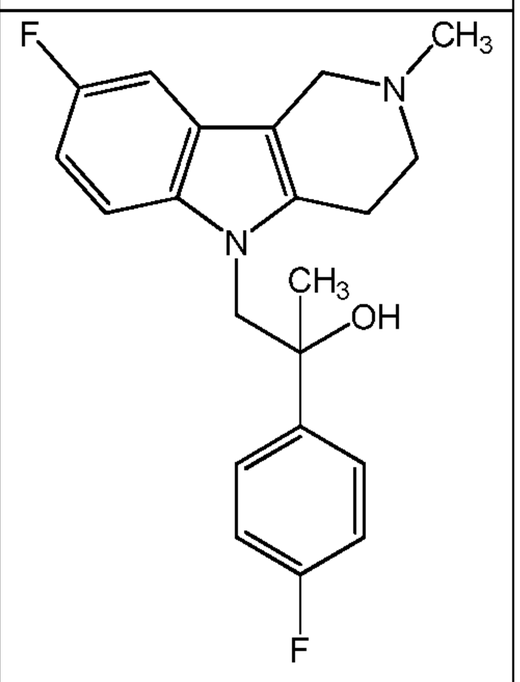
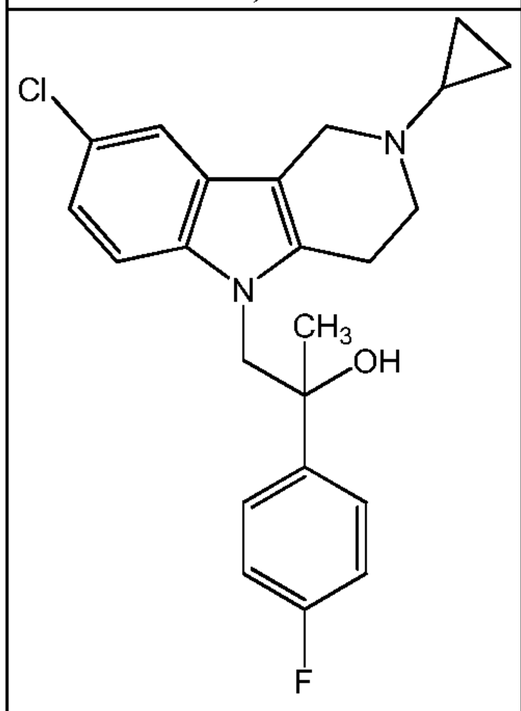
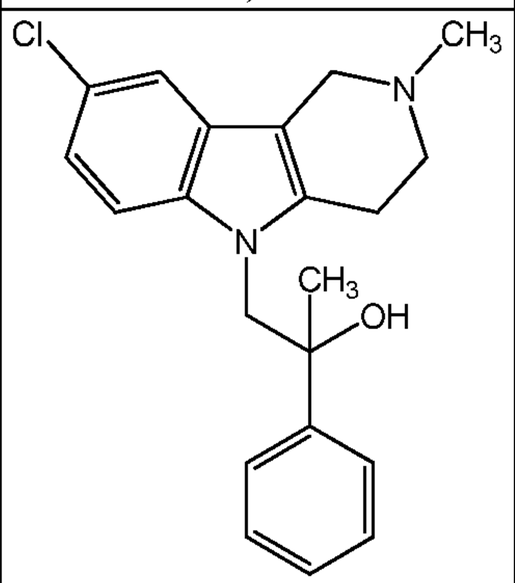
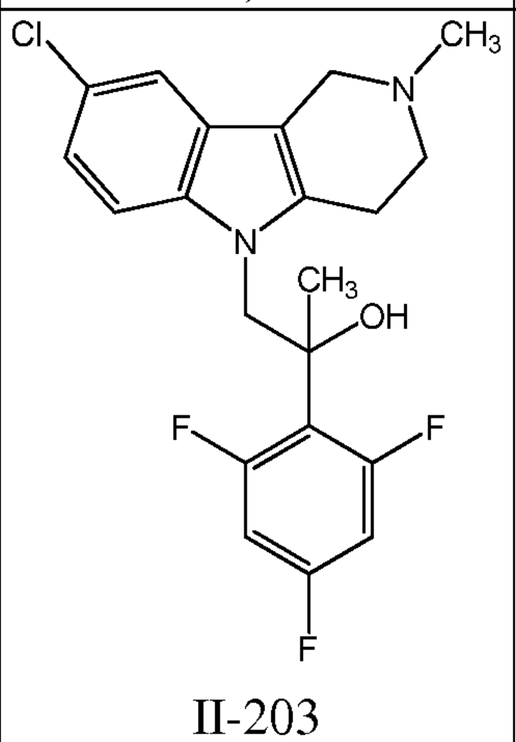
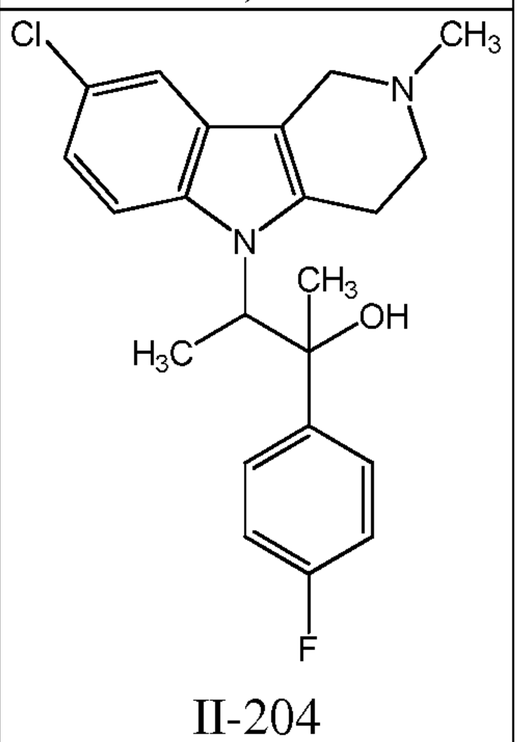
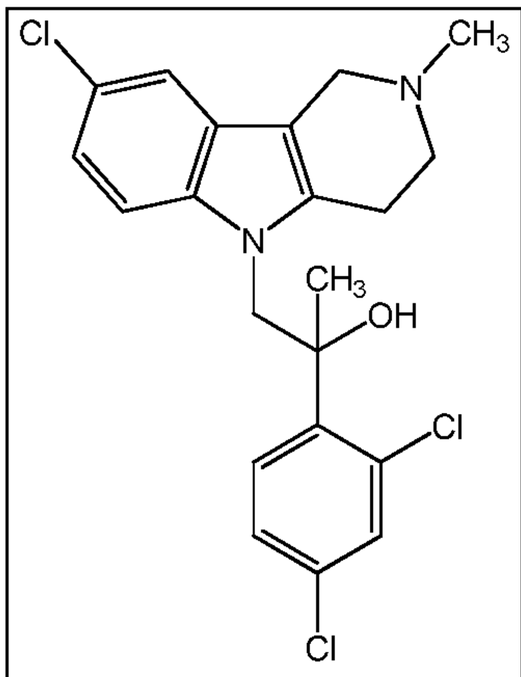
II-192a, II-192b

 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



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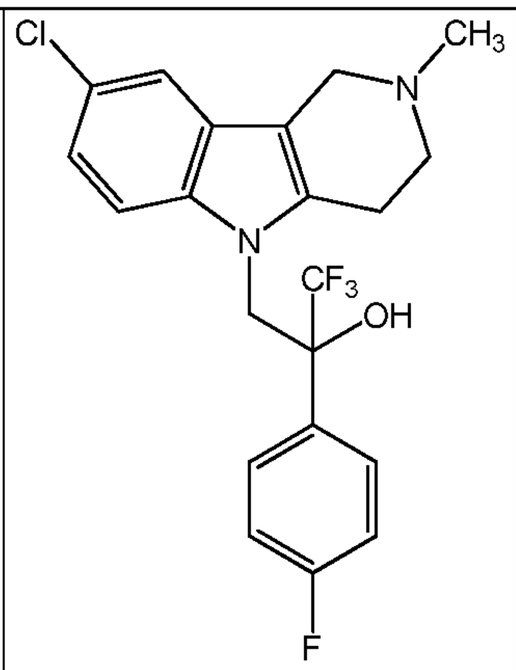
II-205a, II-205b



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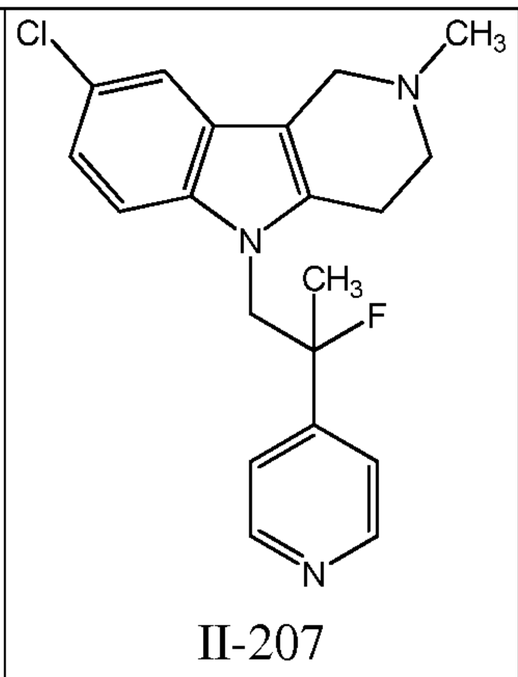
II-206a, II-206b



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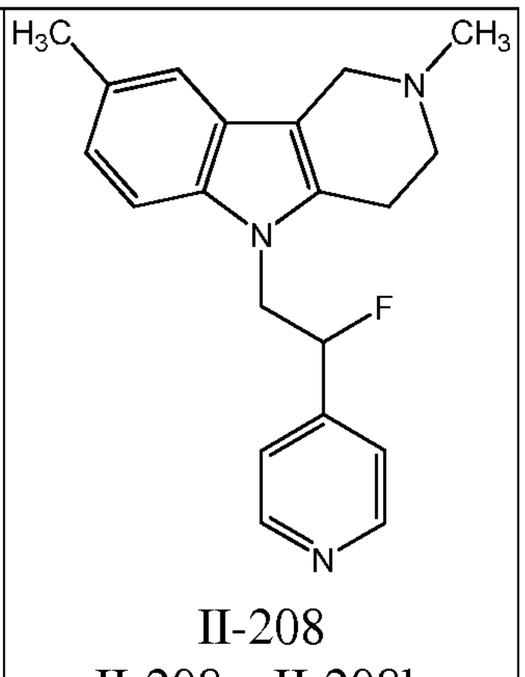
II-207a, II-207b



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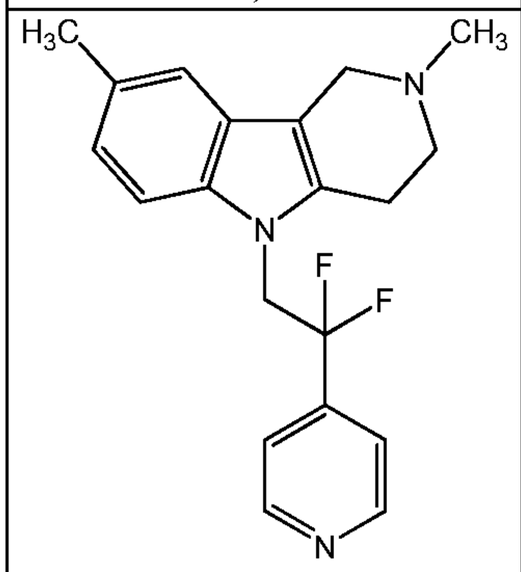
II-208a, II-208b



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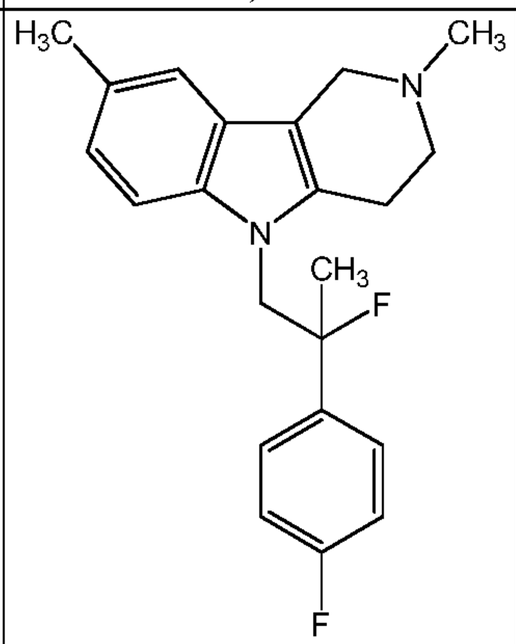

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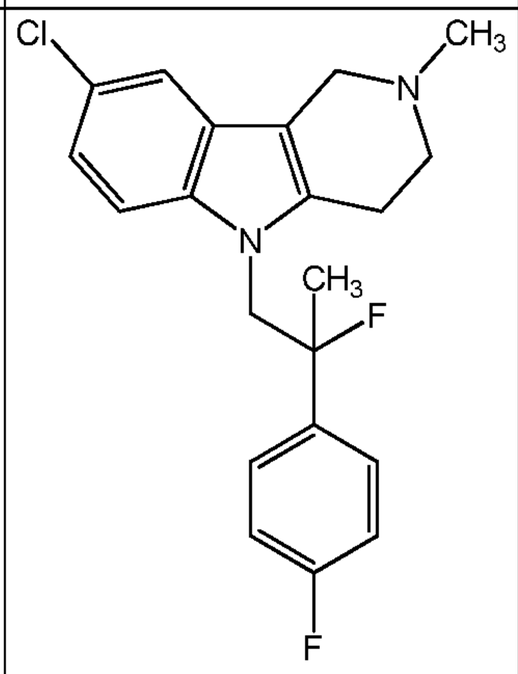
II-210a, II-210b



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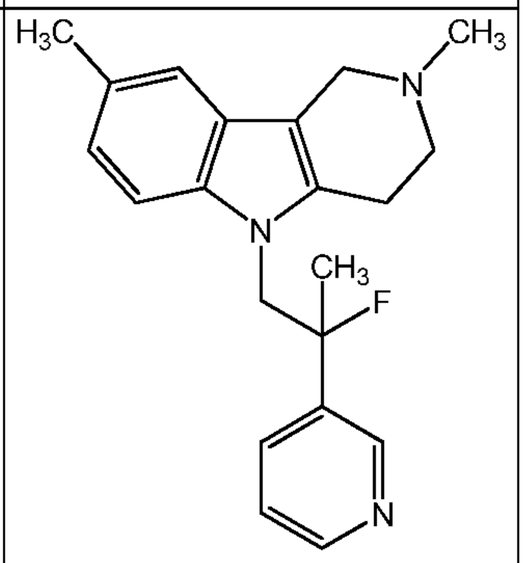
II-211a, II-211b



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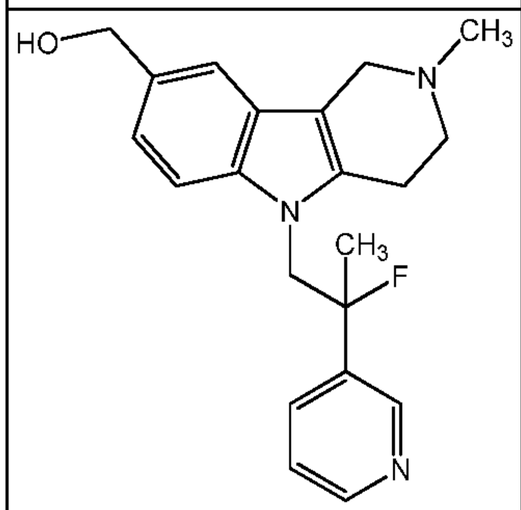
II-212a, II-212b



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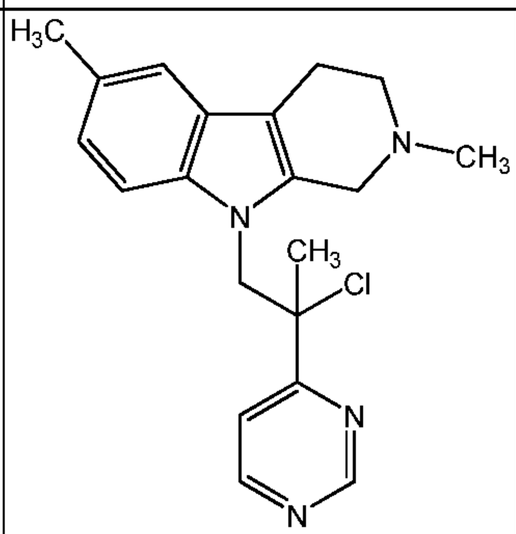
II-213a, II-213b



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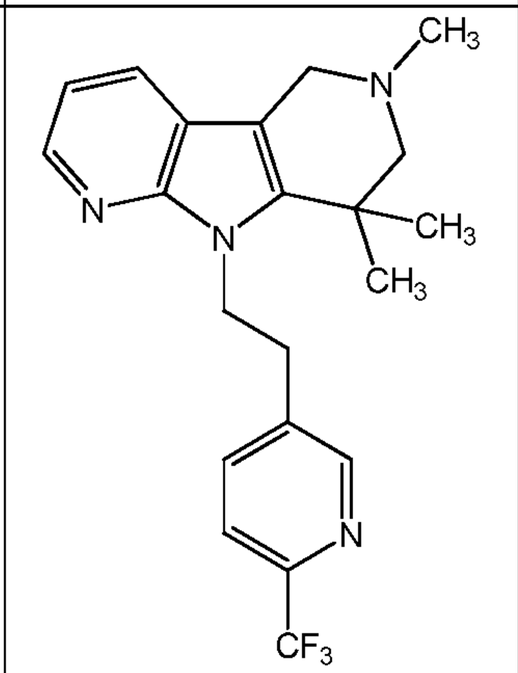
II-214a, II-214b



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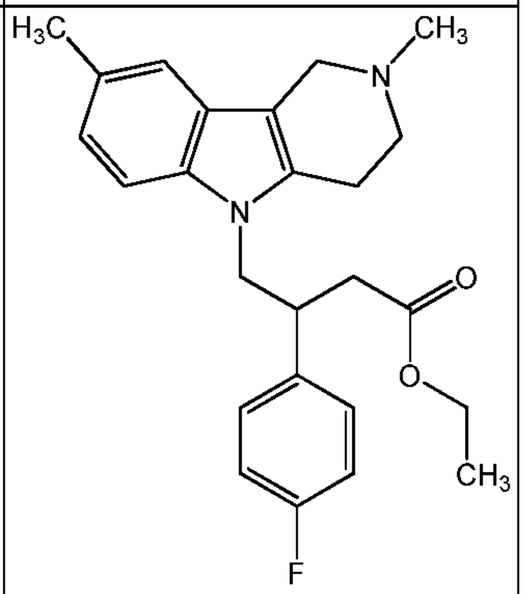

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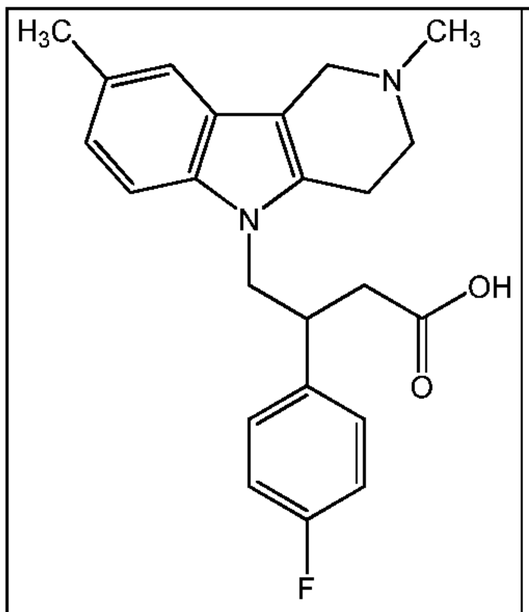
II-216a, II-216b



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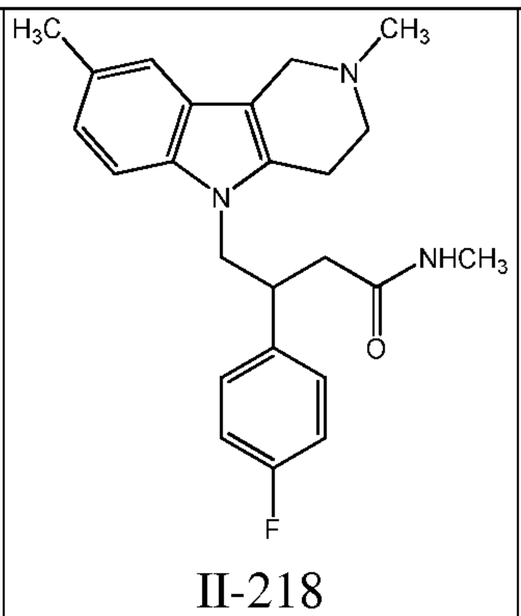
II-217a, II-217b



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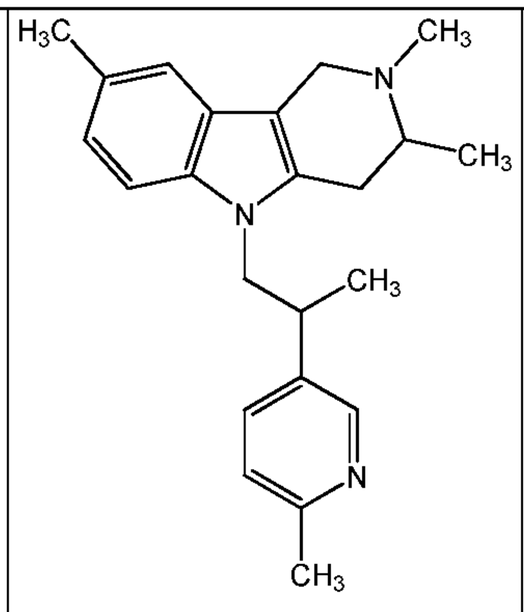
II-218a, II-218b



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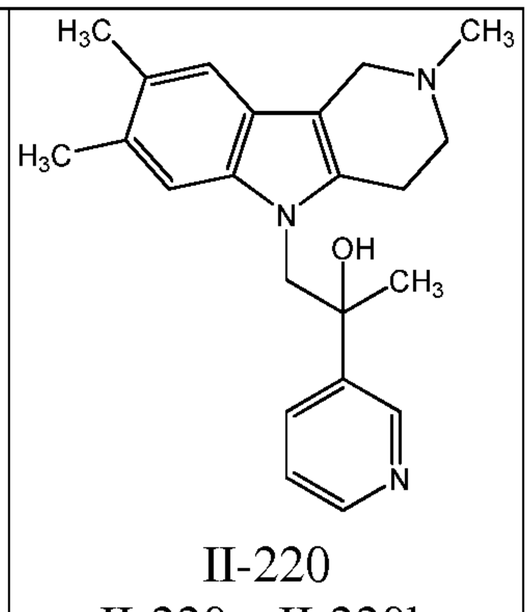
II-219a, II-219b, II-219c, II-219d



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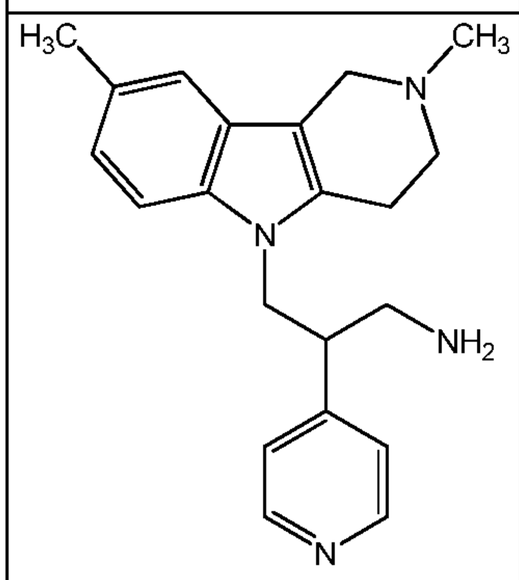
II-220a, II-220b



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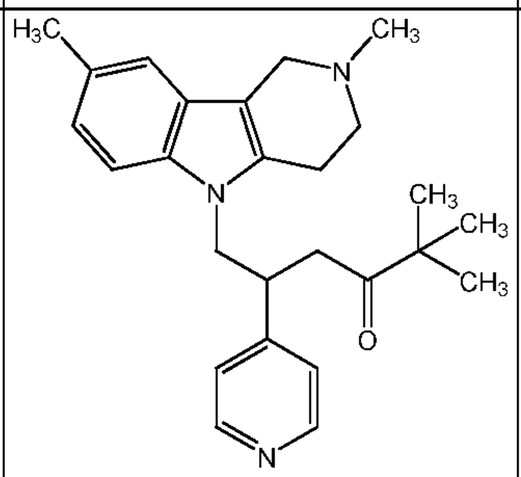

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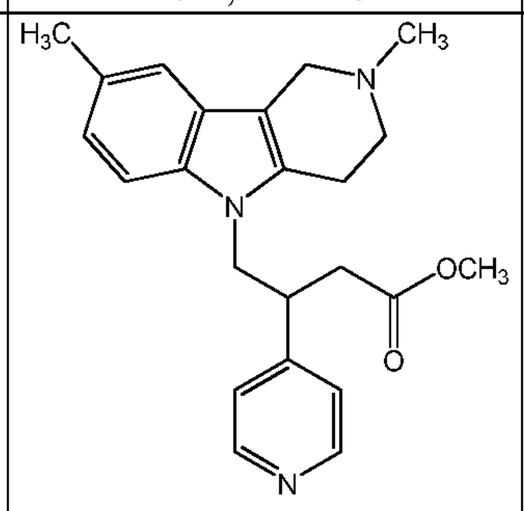

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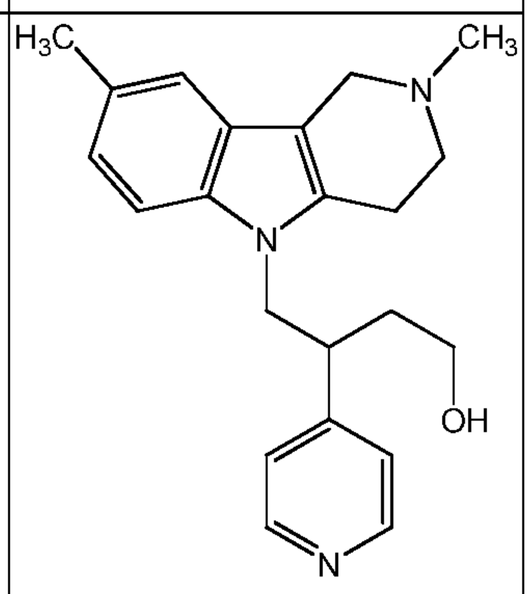

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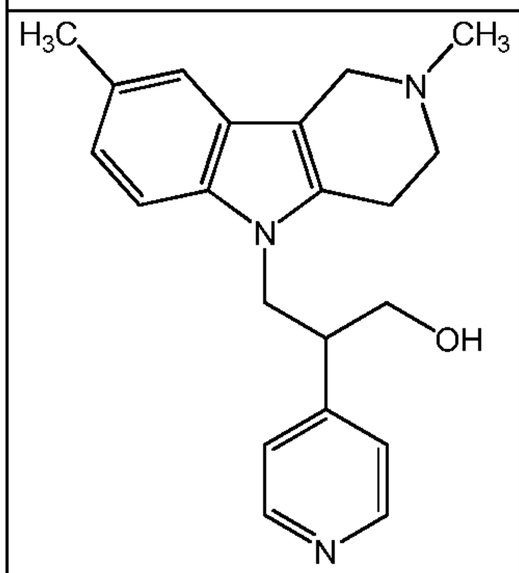

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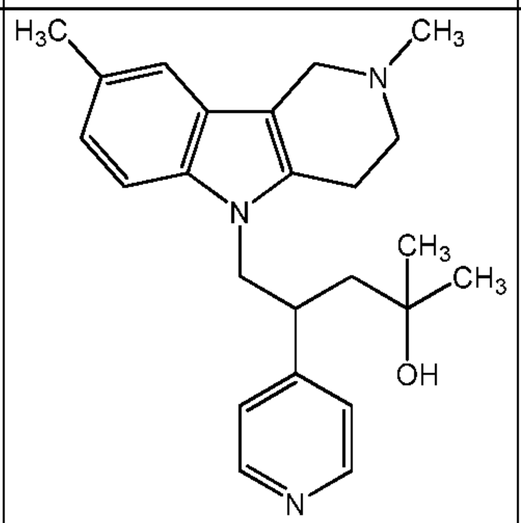

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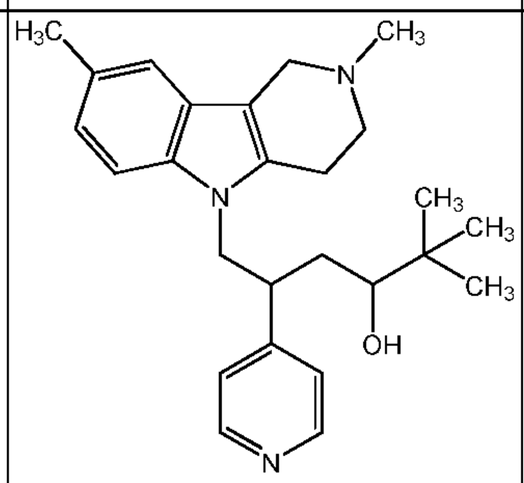

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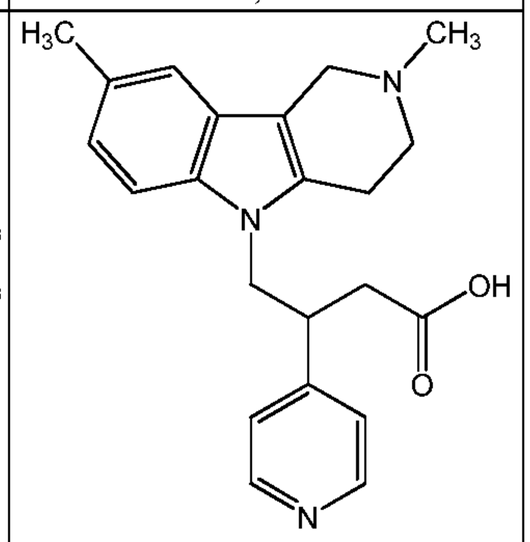

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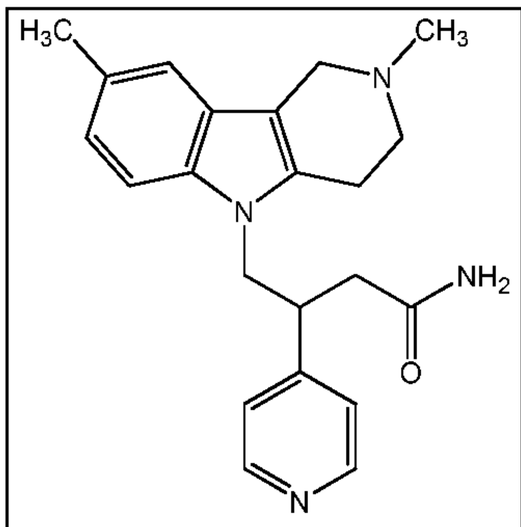

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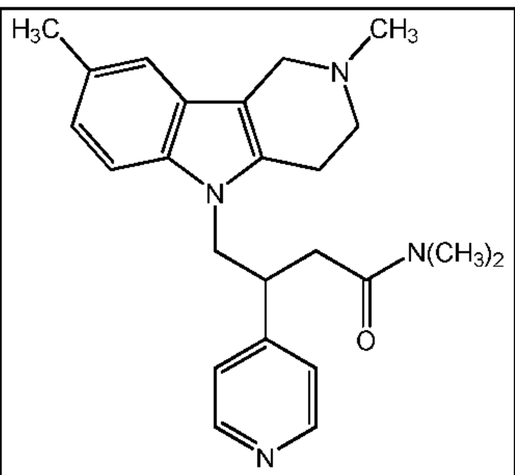

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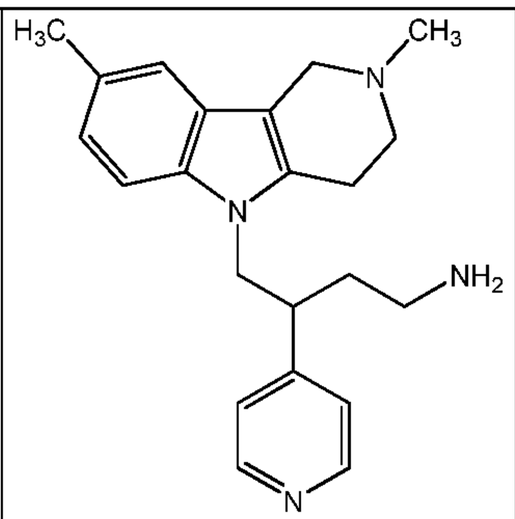

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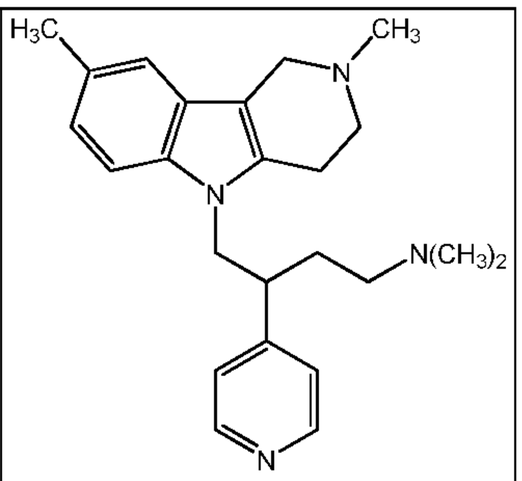

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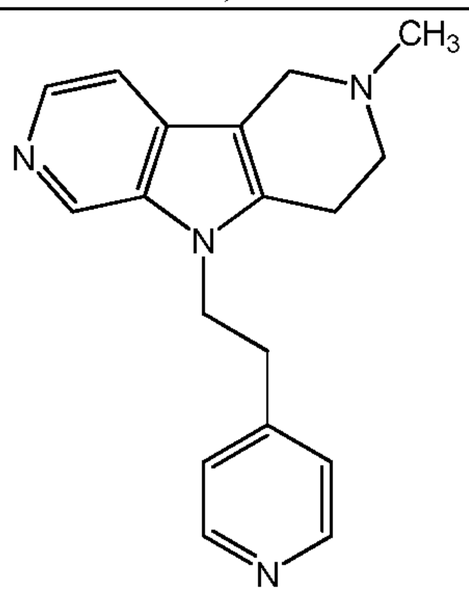

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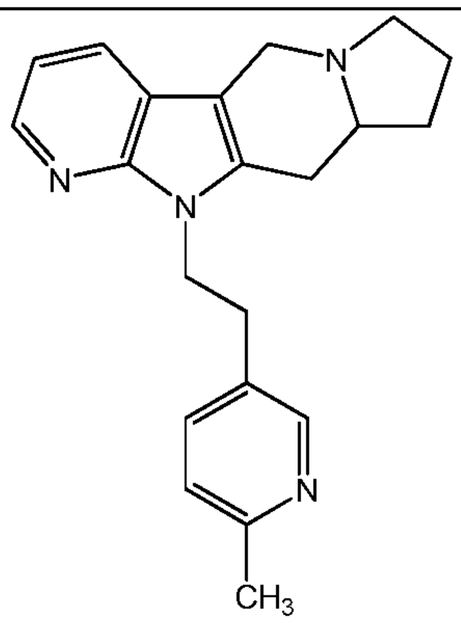

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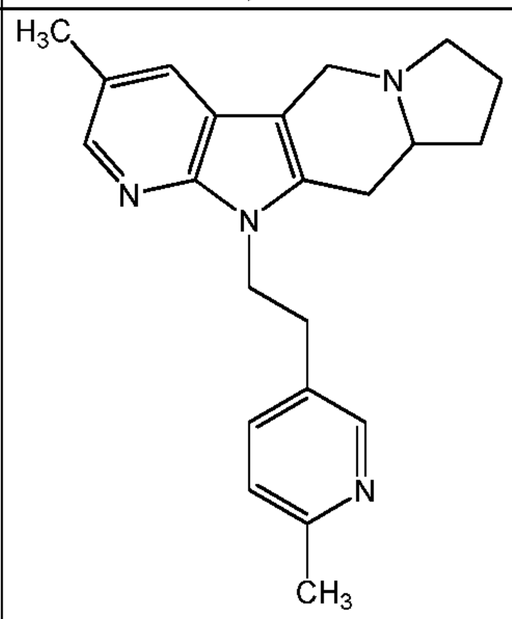

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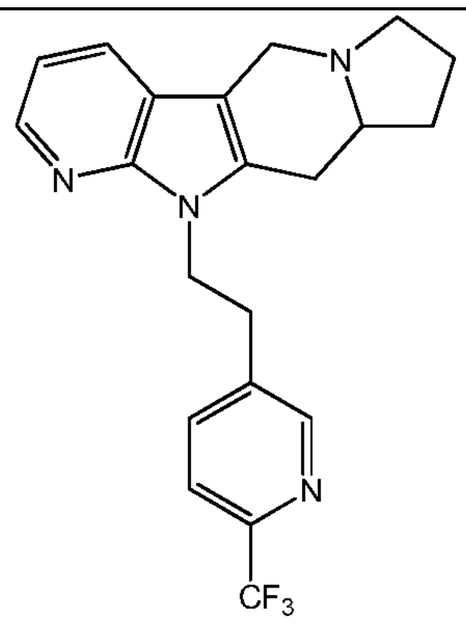

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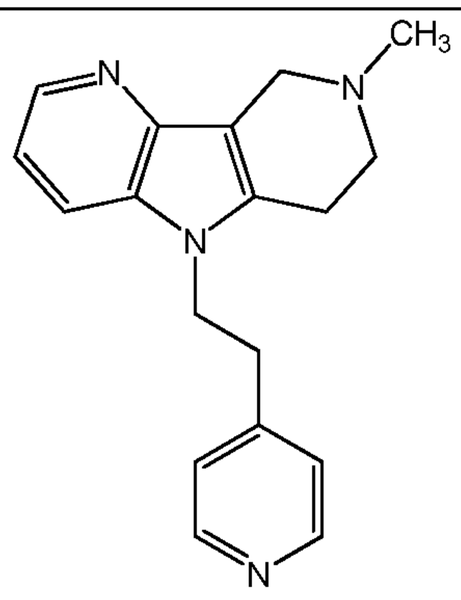
II-236a, II-236b



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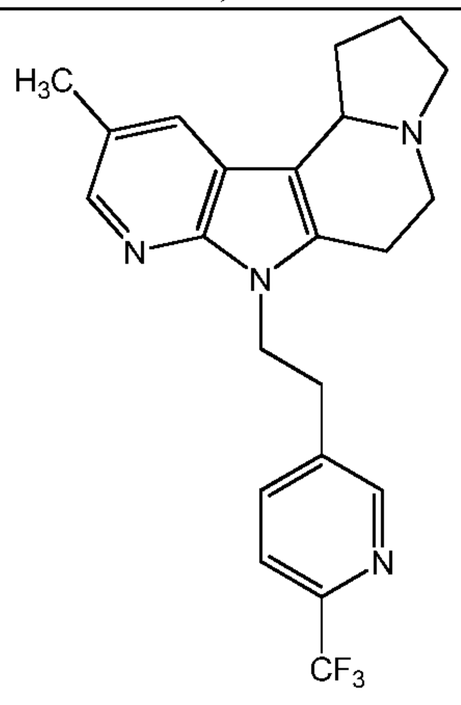

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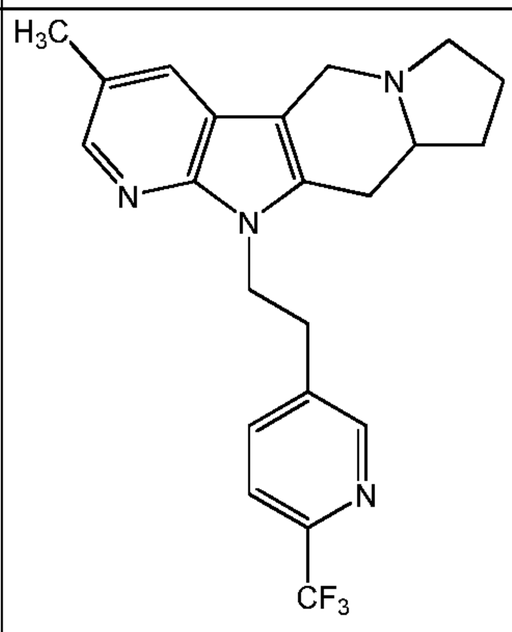
II-238a, II-238b



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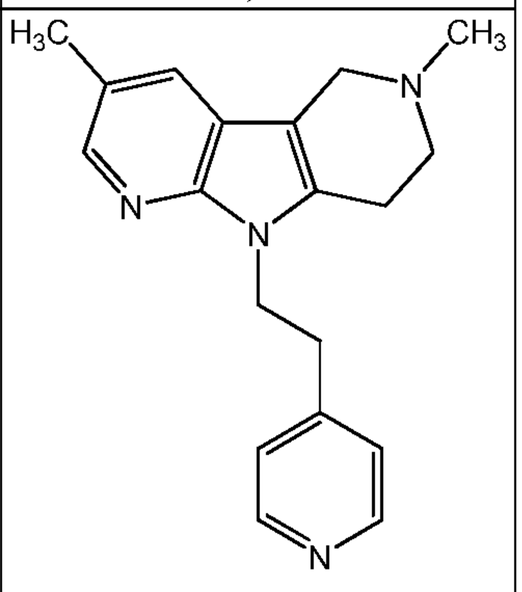
II-239a, II-239b



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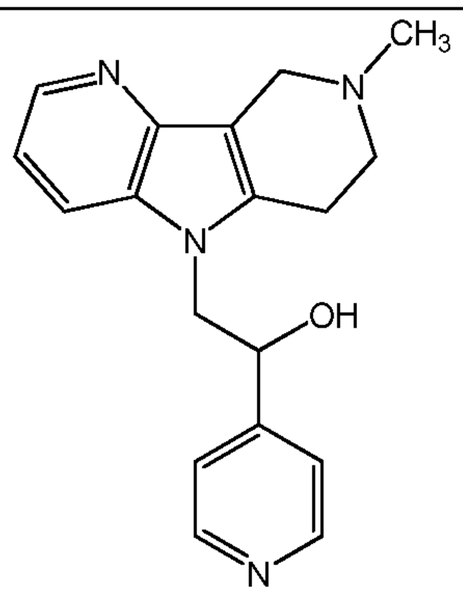

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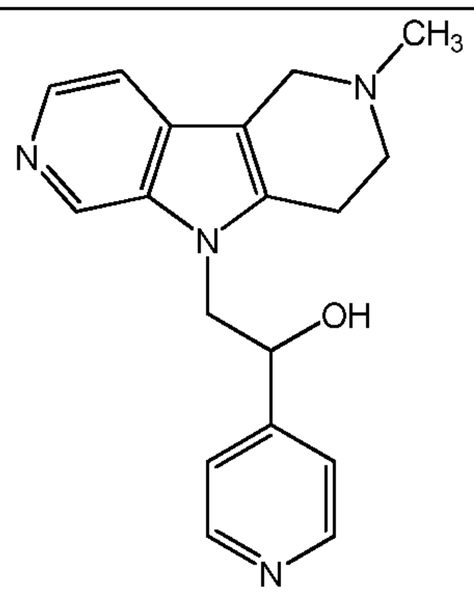

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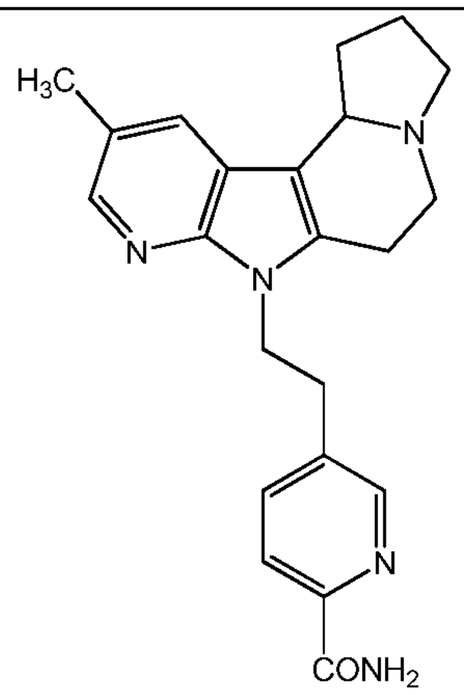

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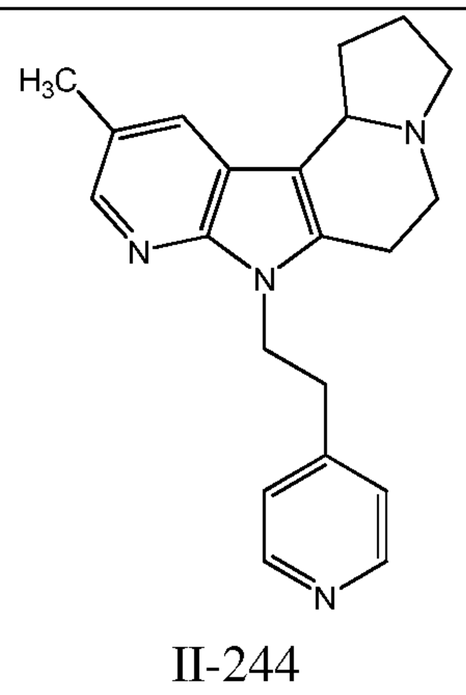

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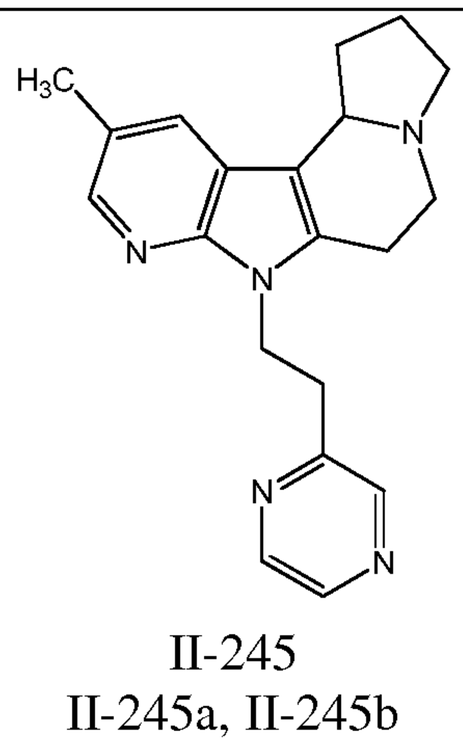

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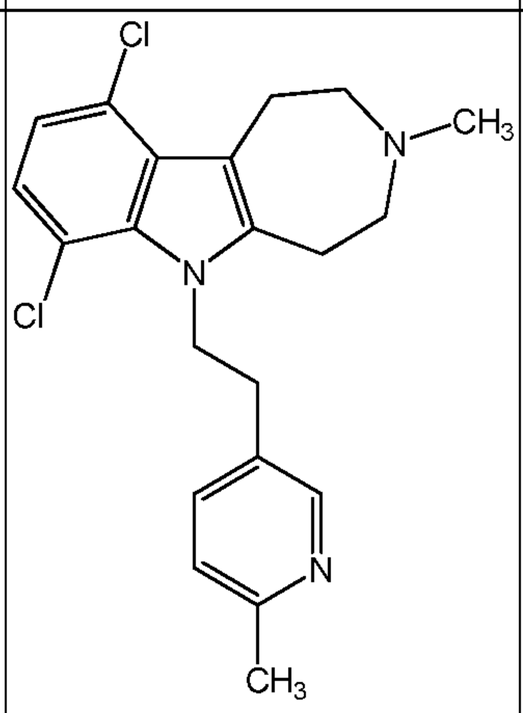

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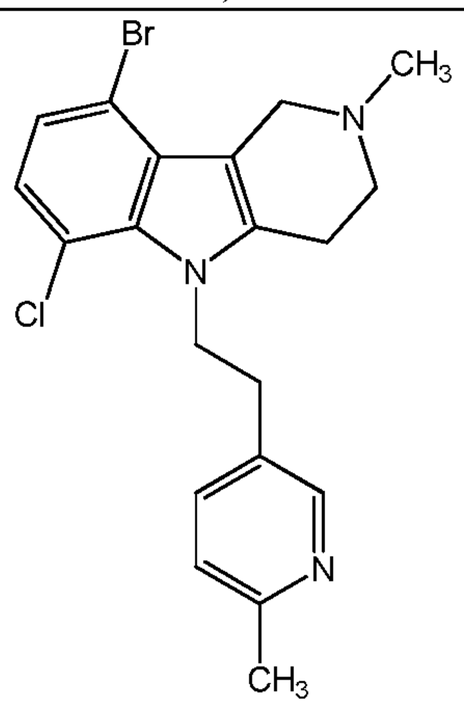

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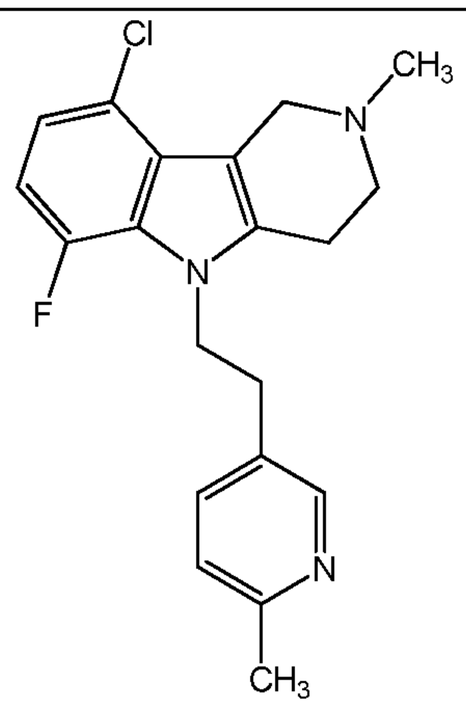

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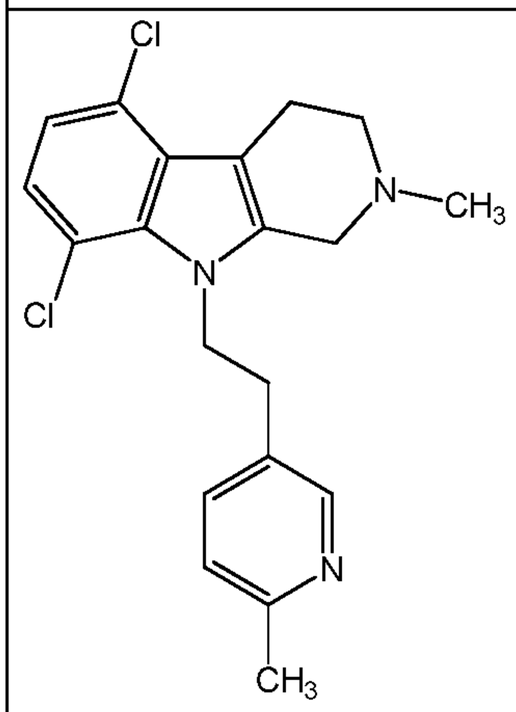

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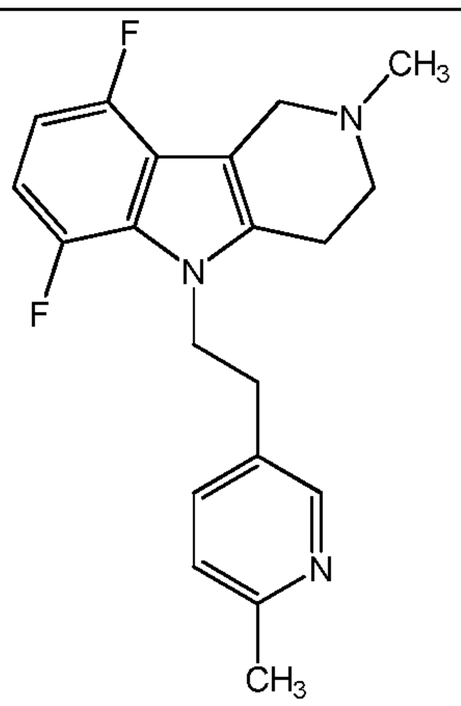

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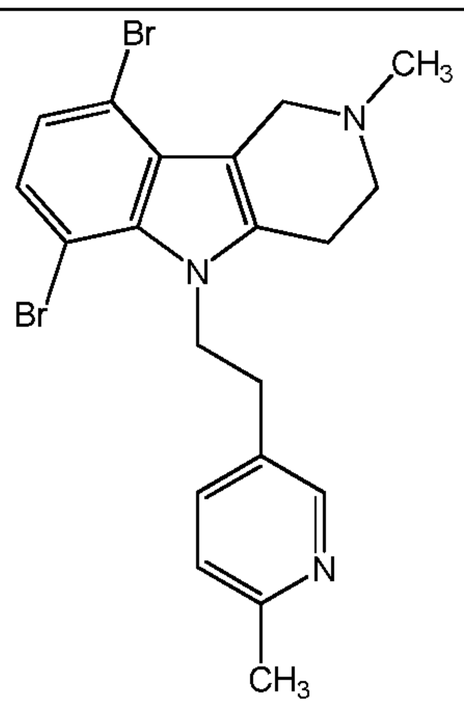

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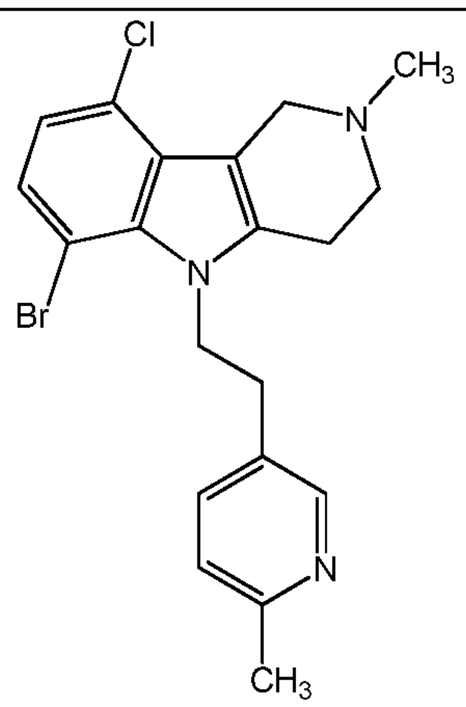

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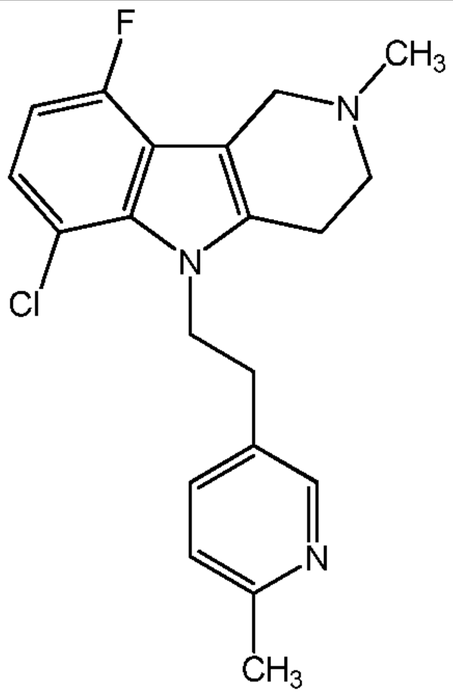

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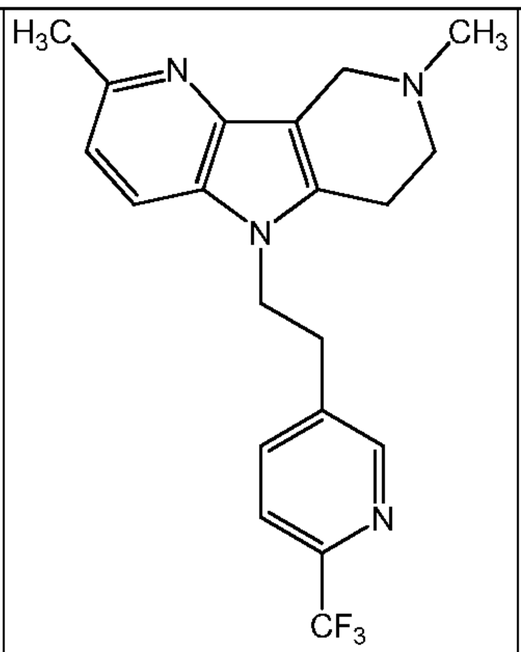

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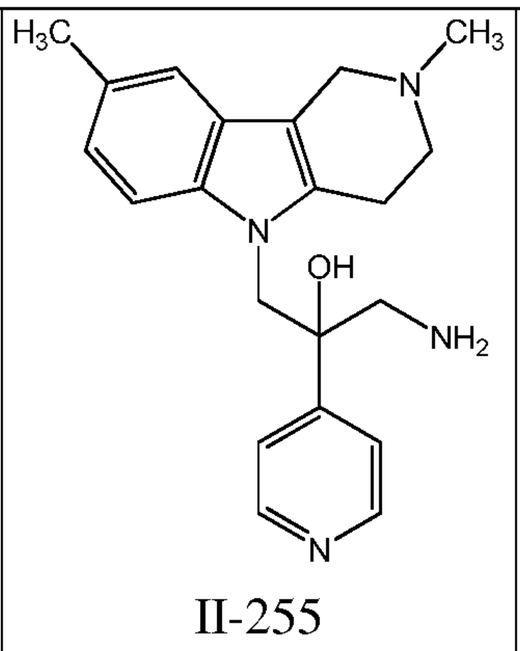

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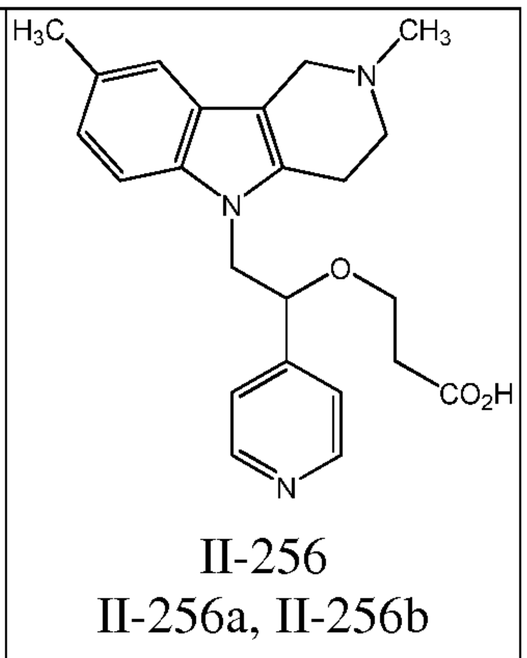

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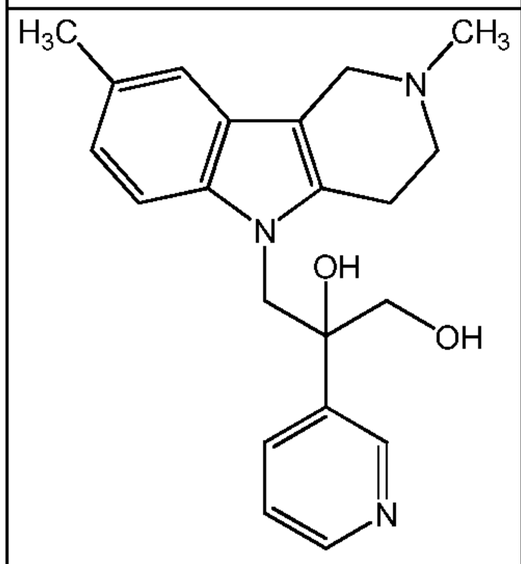

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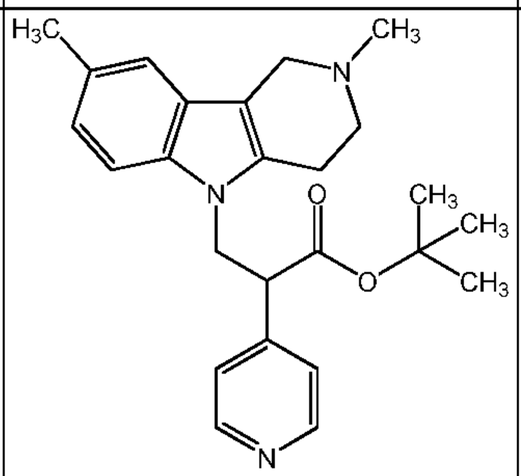

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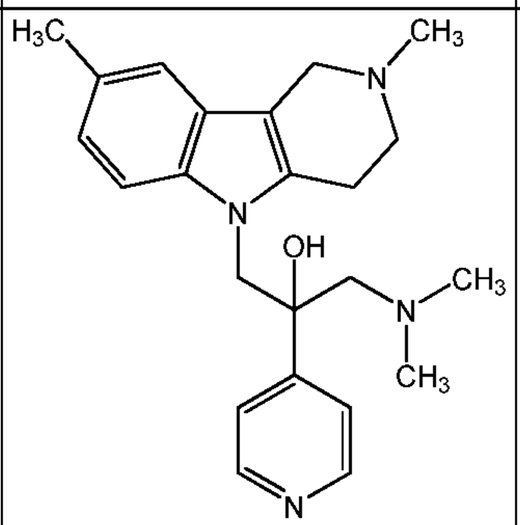
II-258a, II-258b



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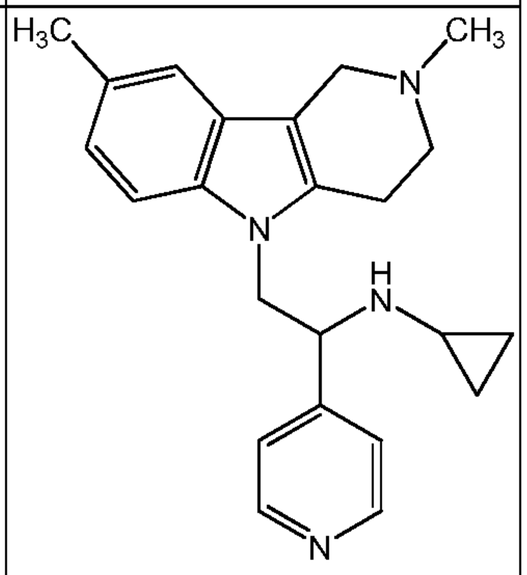

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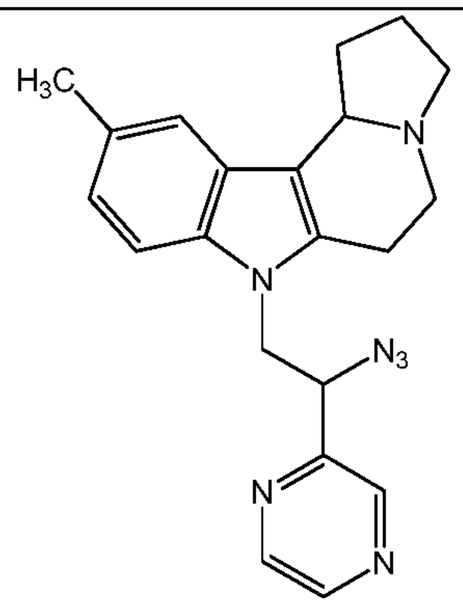
II-260a, II-260b



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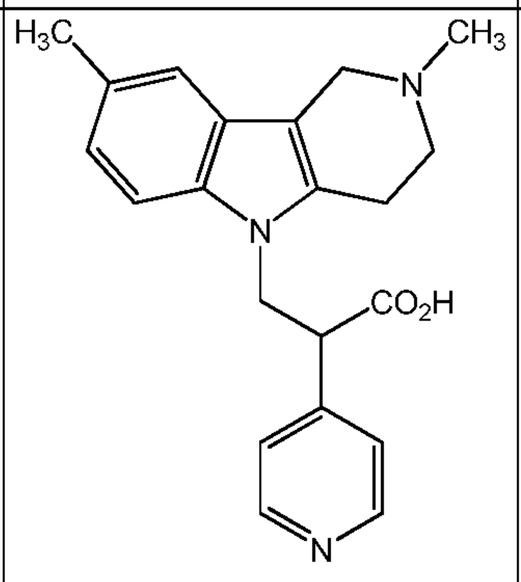

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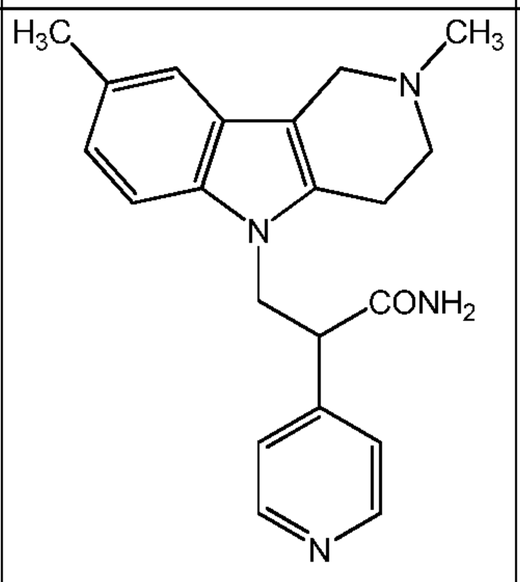
II-262a, II-262b



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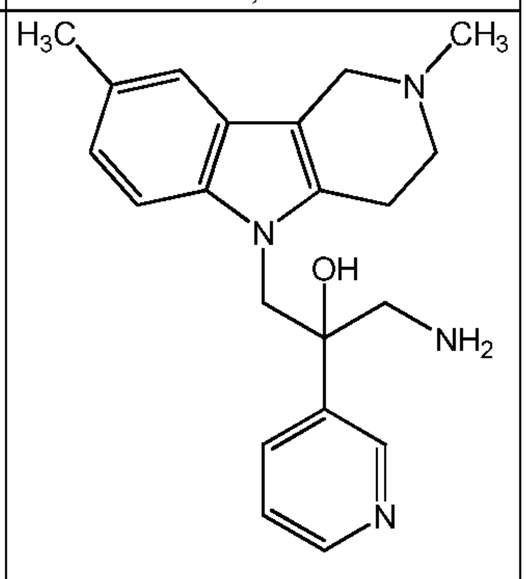
II-263a, II-263b



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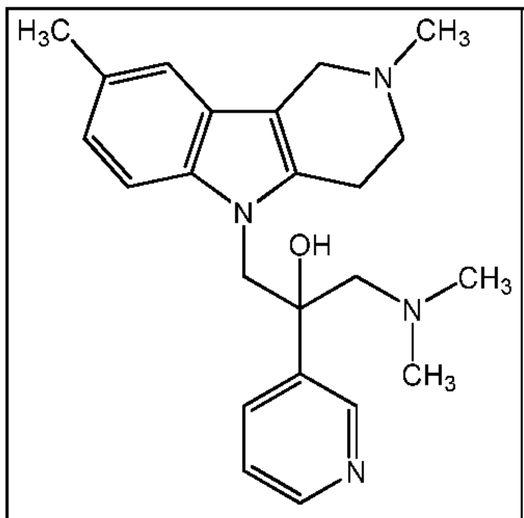
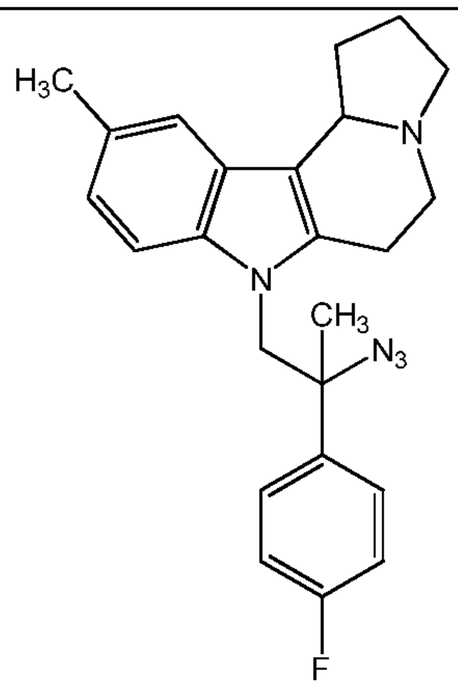
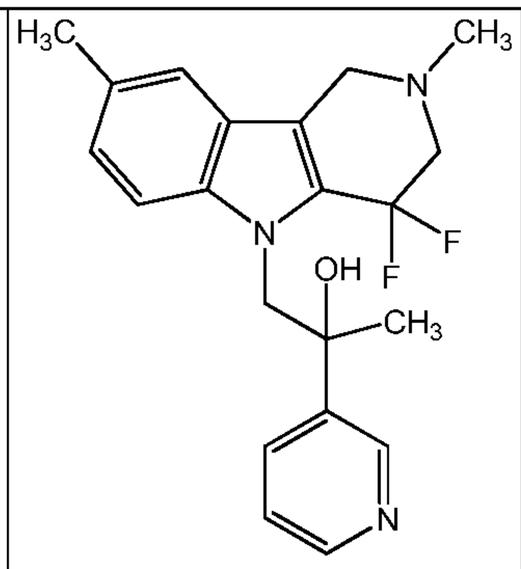
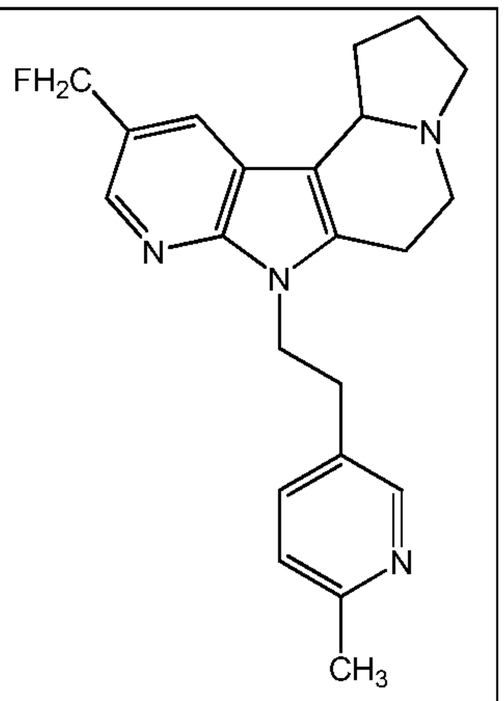
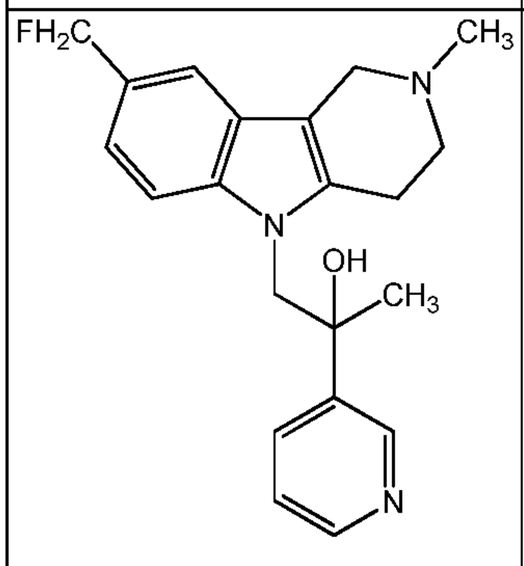
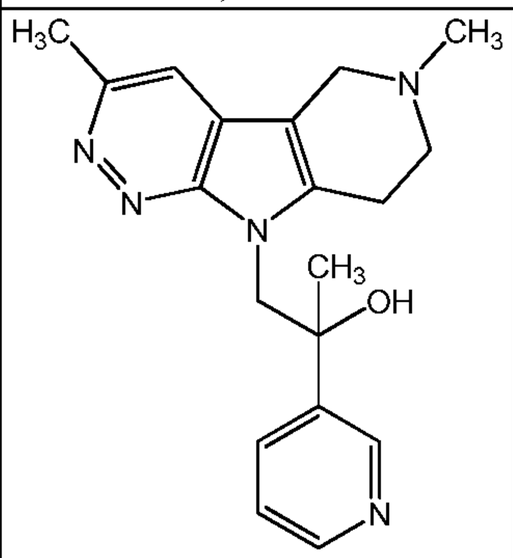
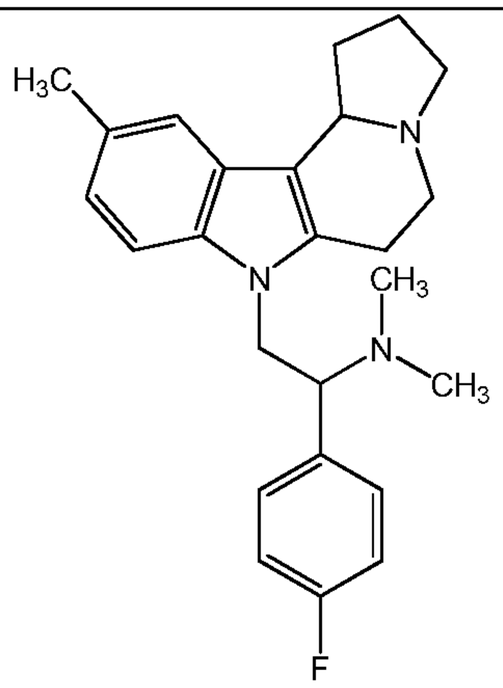
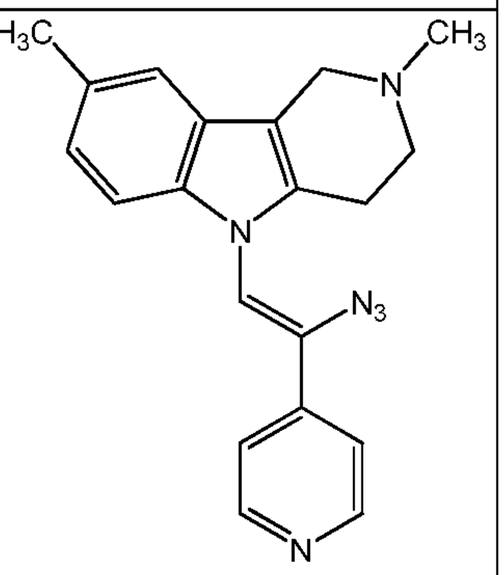
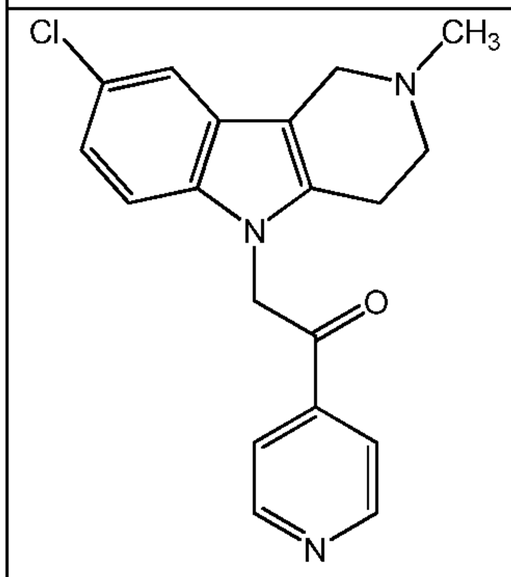
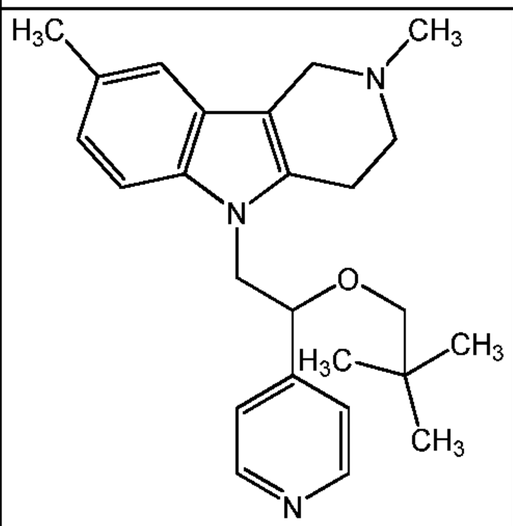
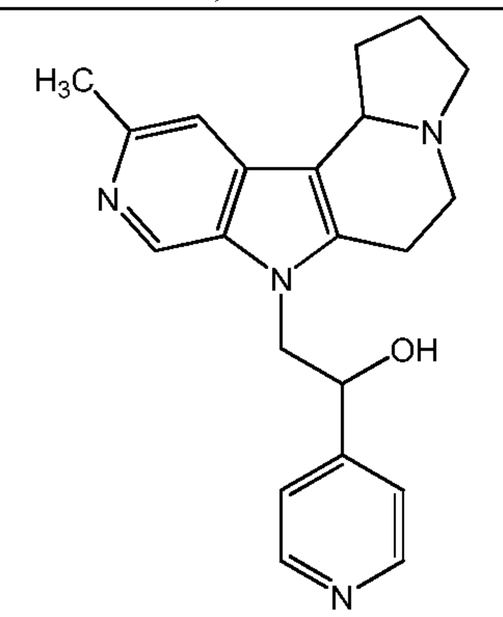
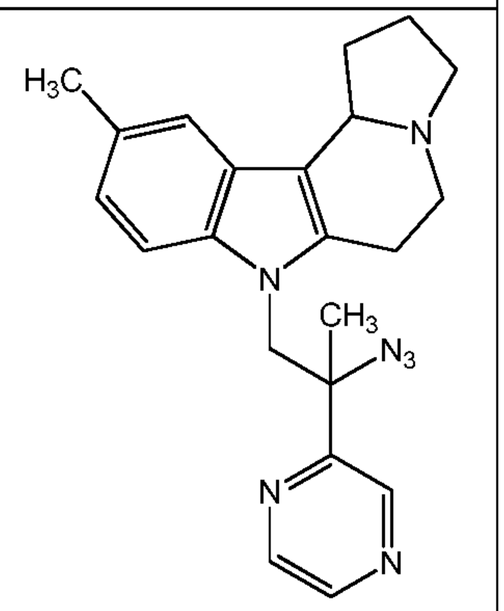
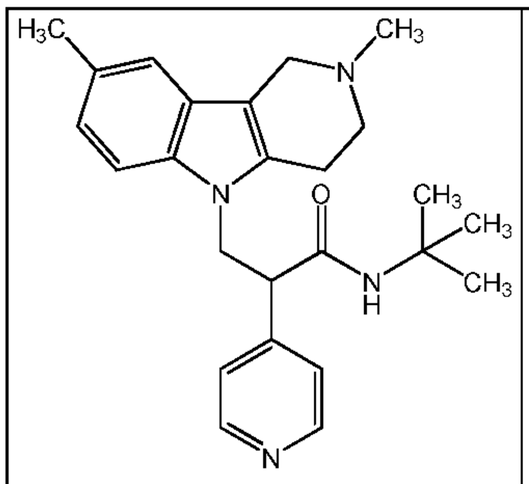
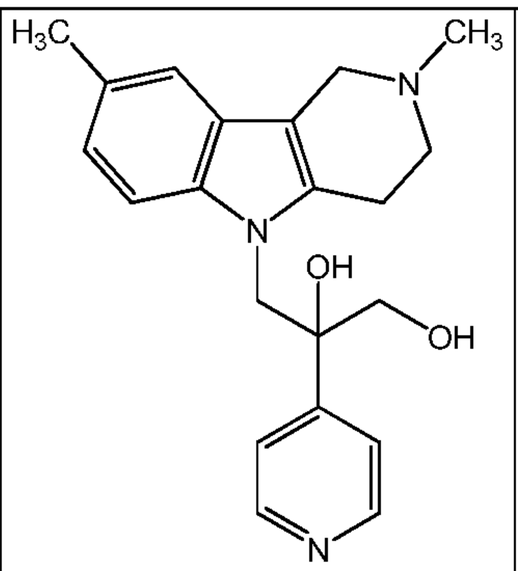
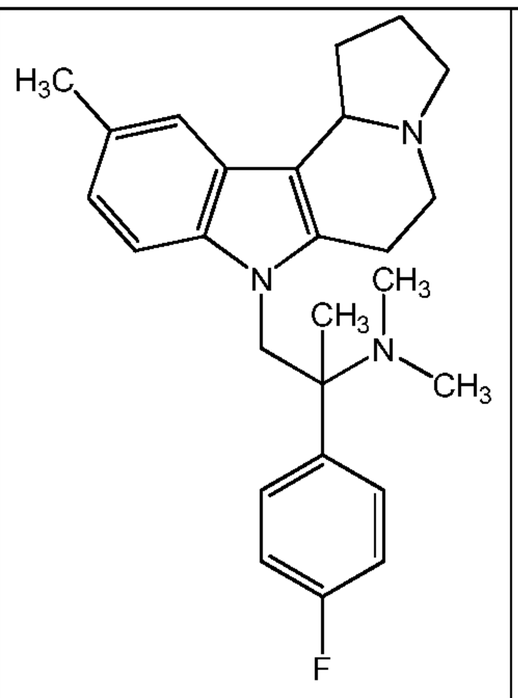
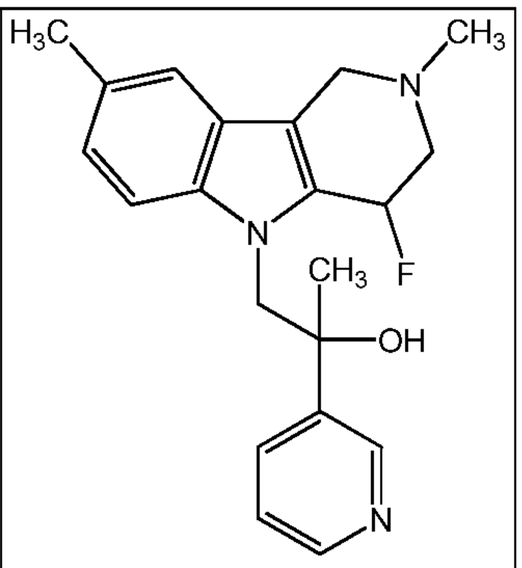
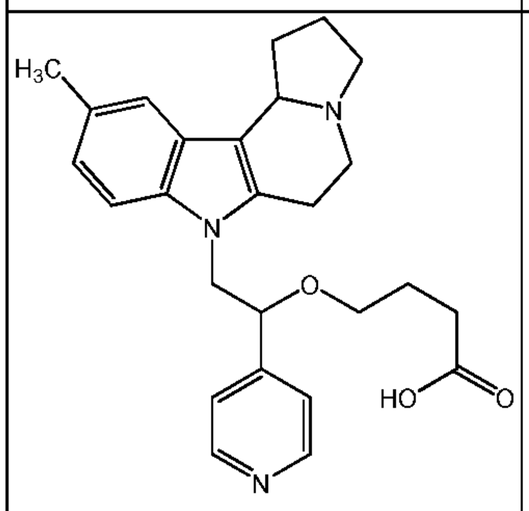
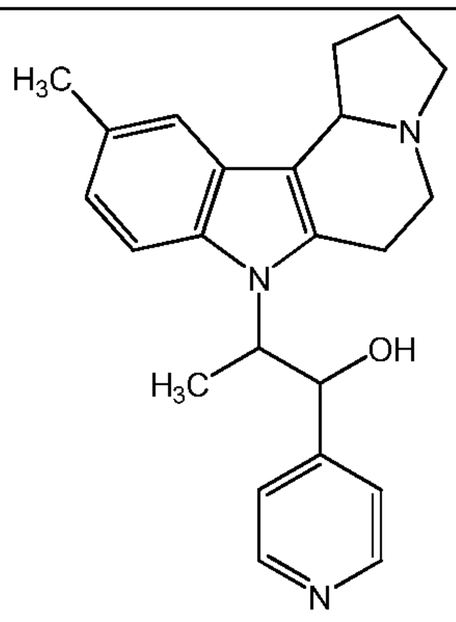
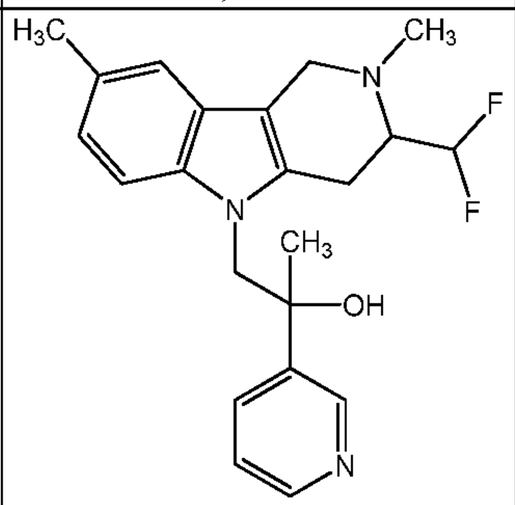
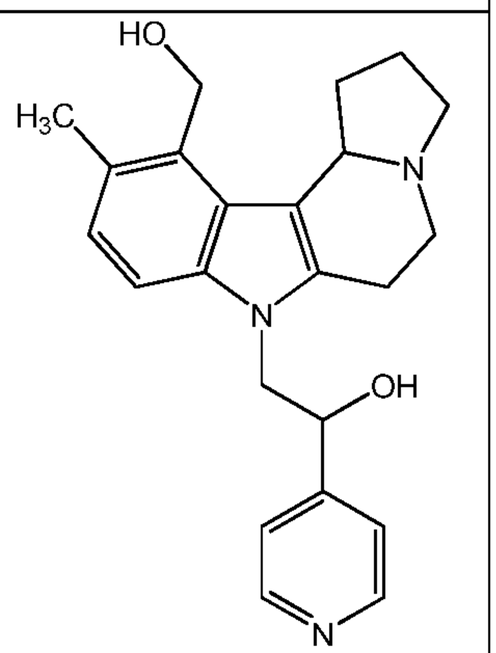
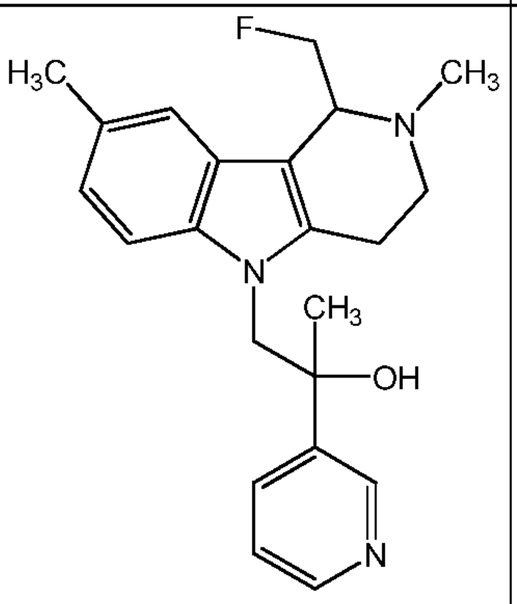
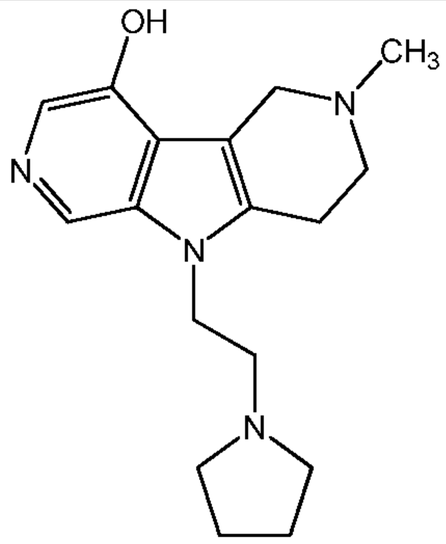
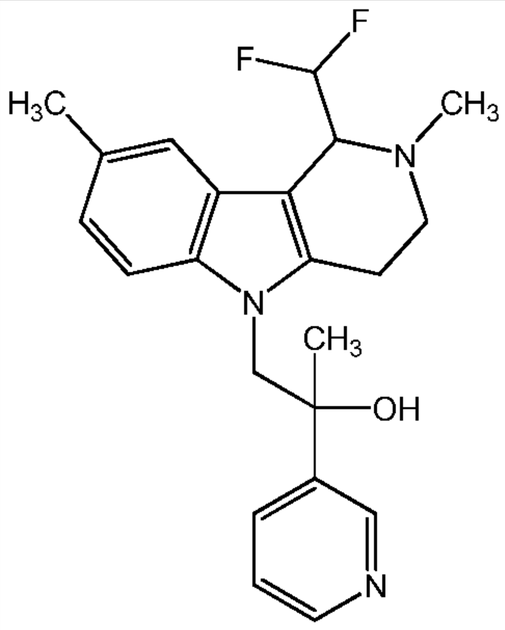
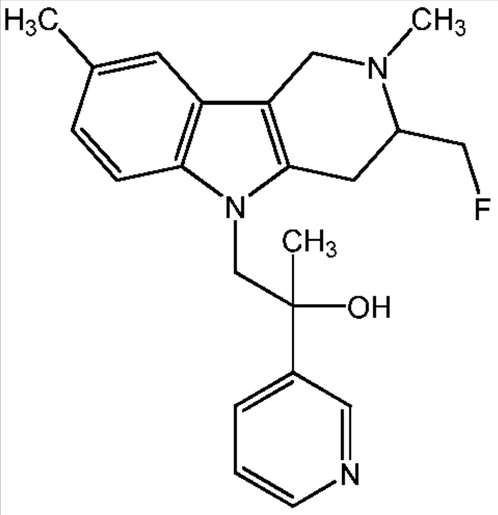
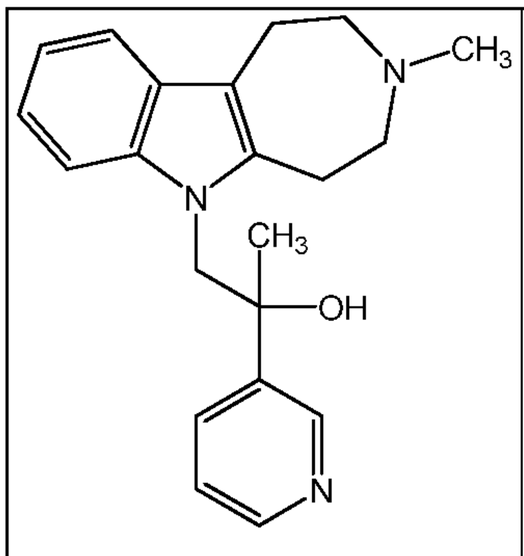
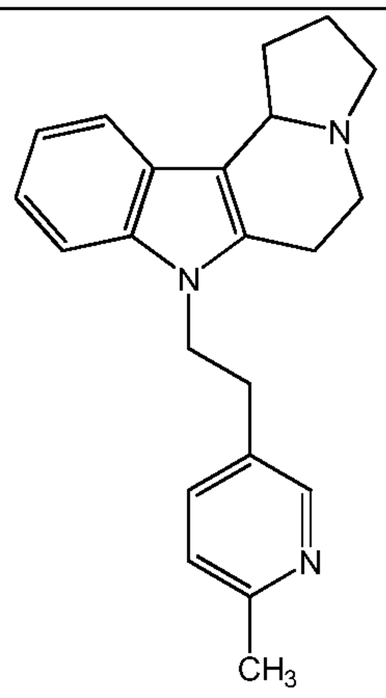
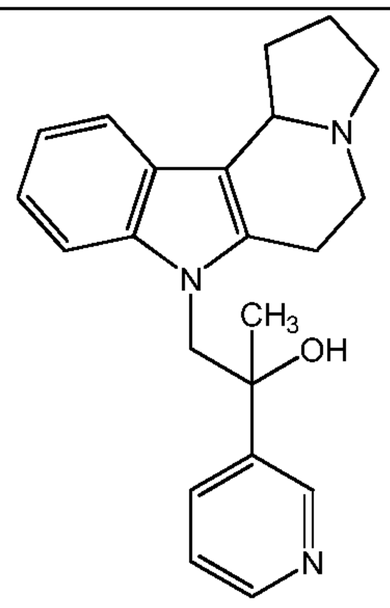
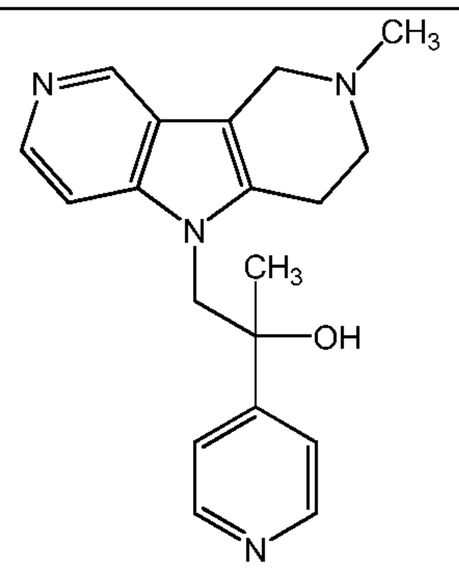
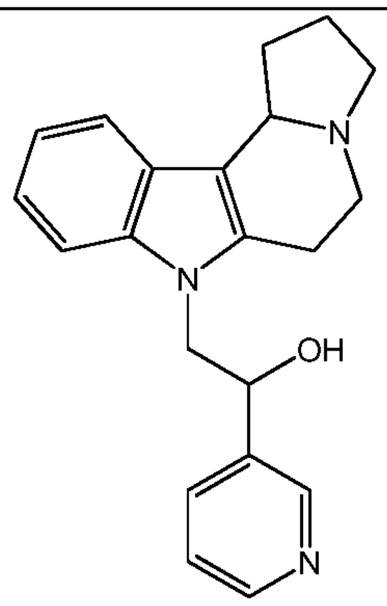
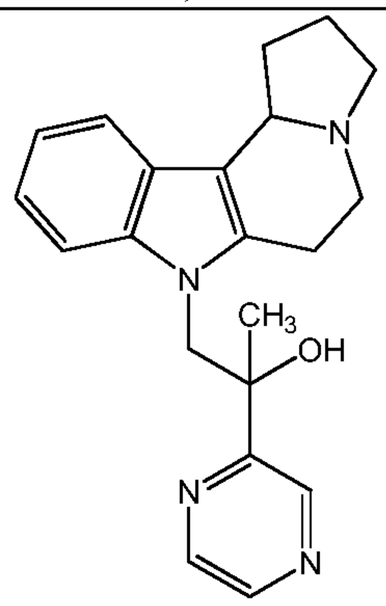
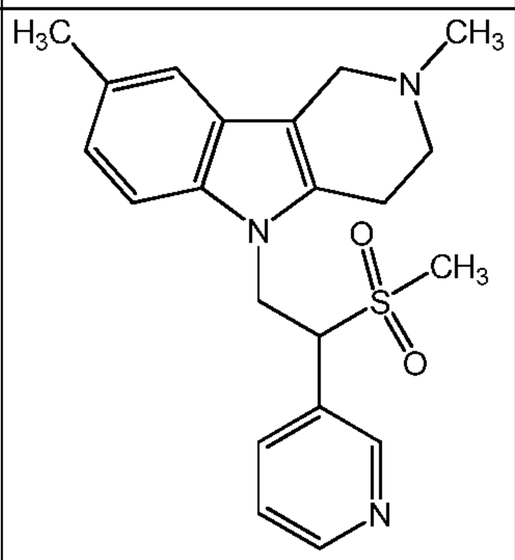
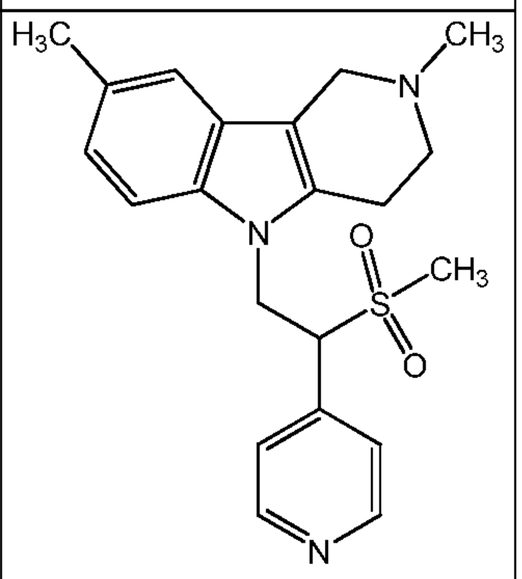
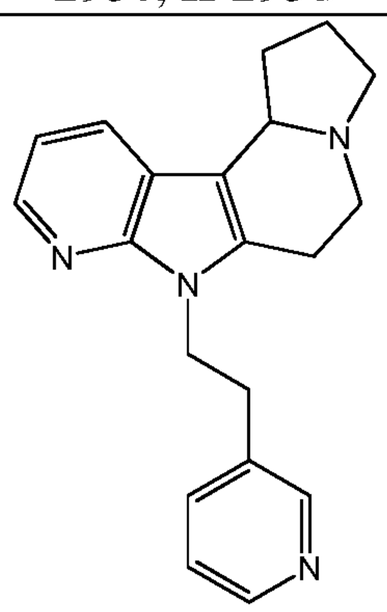
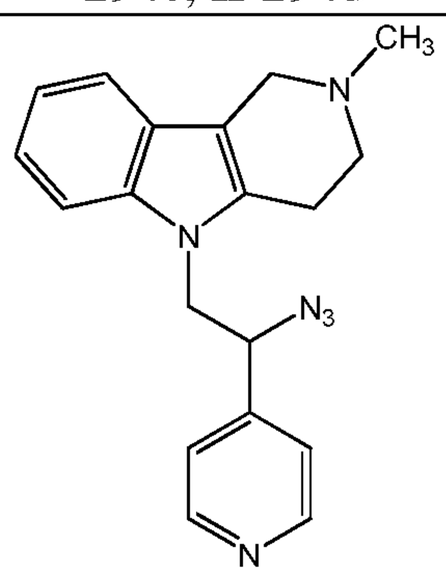
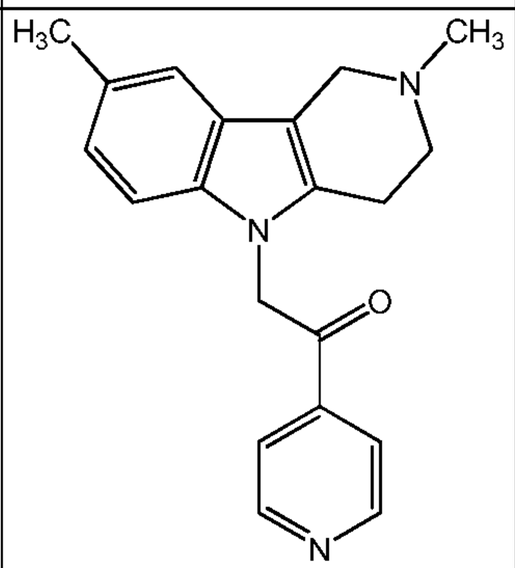
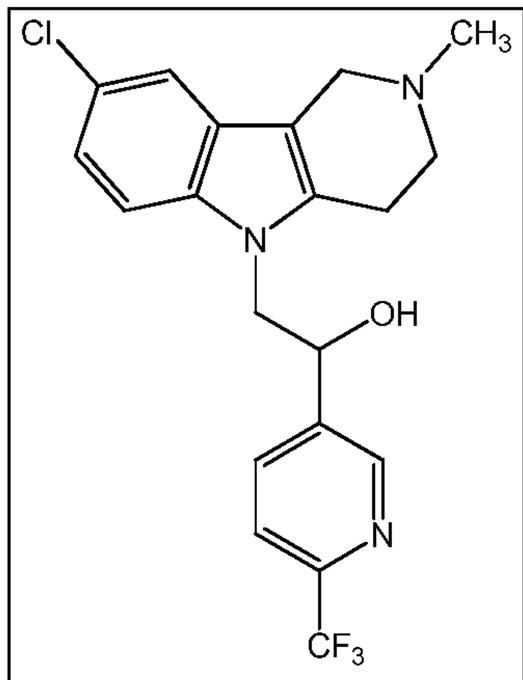
II-264a, II-264b

 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

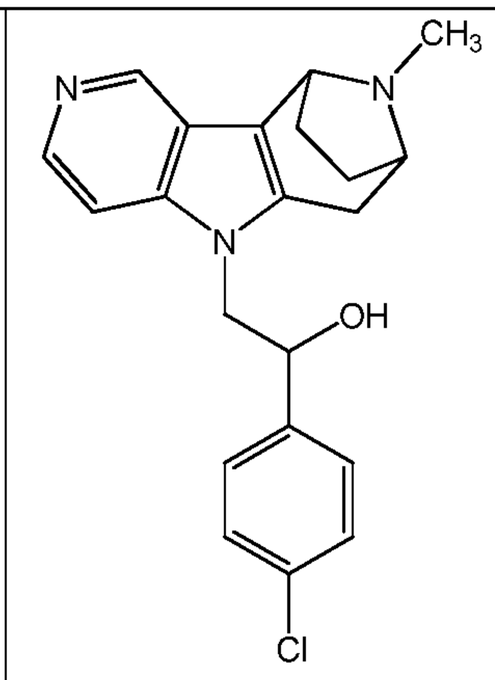
 II-277 II-277a, II-277b	 II-278 II-278a, II-278b	 II-279 II-279a, II-279b, II-279c, II-279d	 II-280 II-280a, II-280b, II-280c, II-280d
 II-281 II-281a, II-281b, II-281c, II-281d	 II-282 II-282a, II-282b, II-282c, II-282d, II-282e, II-282f, II-282g, II-282h	 II-283 II-283a, II-283b, II-283c, II-283d	 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	

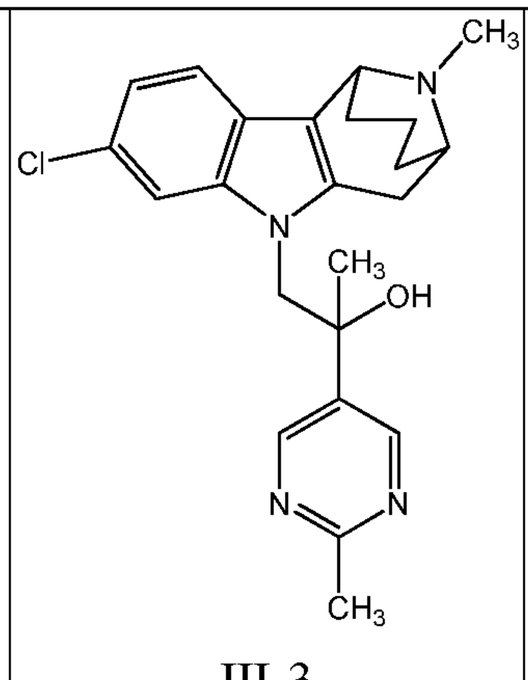
[0634] Table 3. Representative Compounds of the Invention.



III-1
III-1a, III-1b



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



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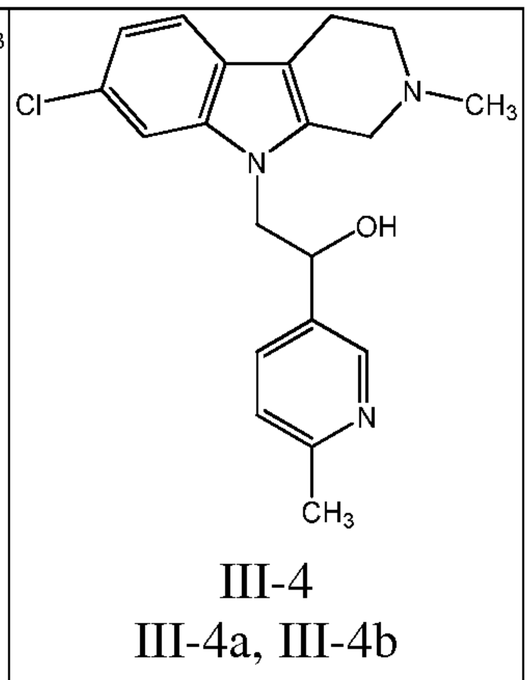
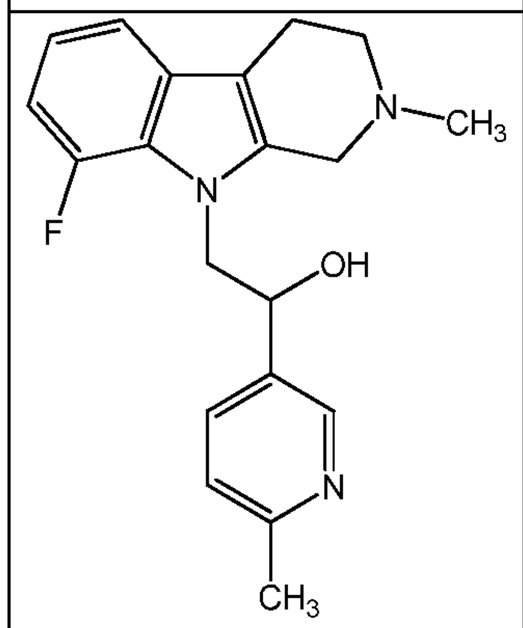
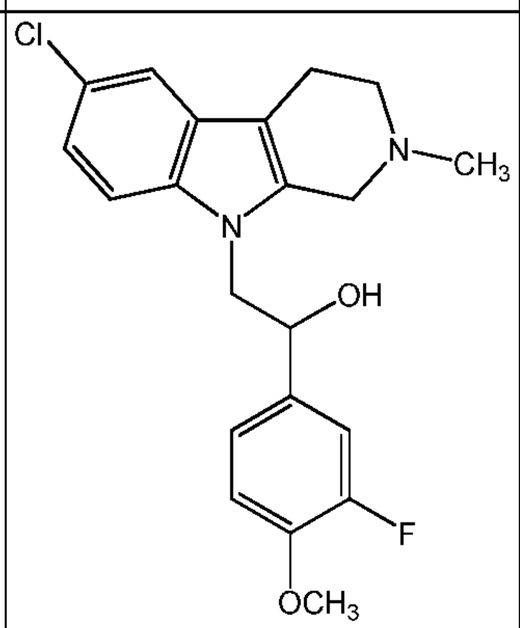
III-3a, III-3b, III-3c, III-3d



III-4
III-4a, III-4b



III-5
III-5a, III-5b



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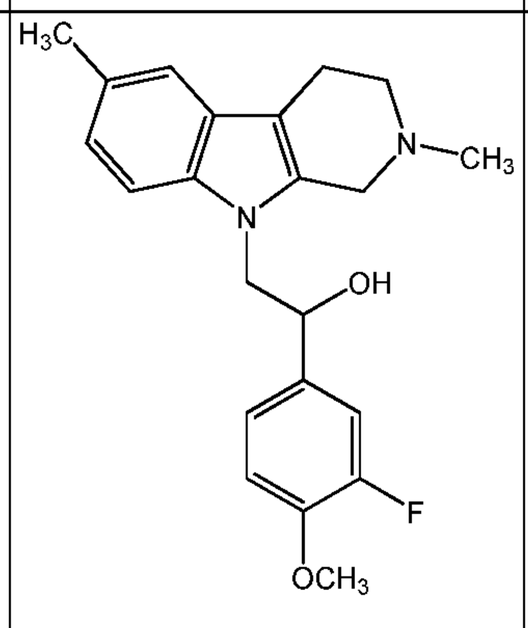
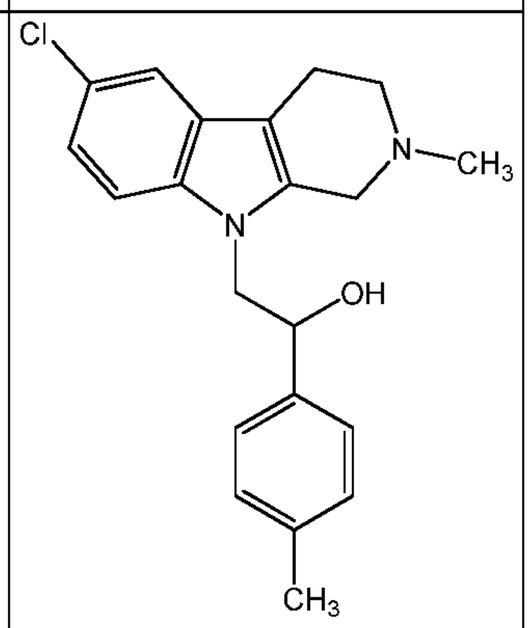
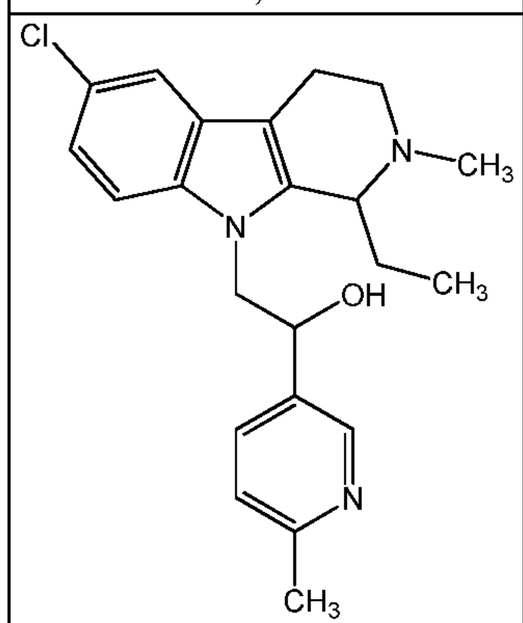
III-6a, III-6b



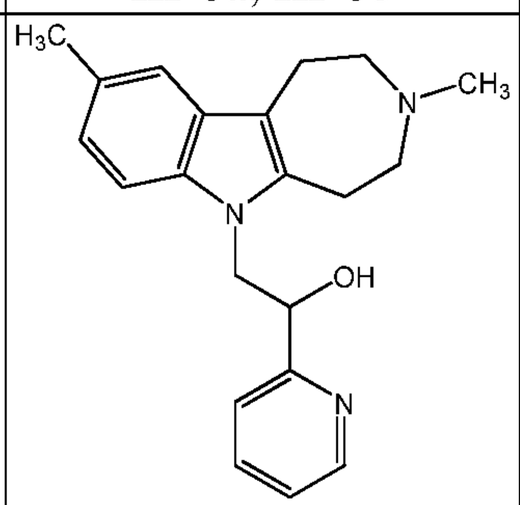
III-7
III-7a, III-7b



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



III-9
III-9a, III-9b, III-9c, III-9d



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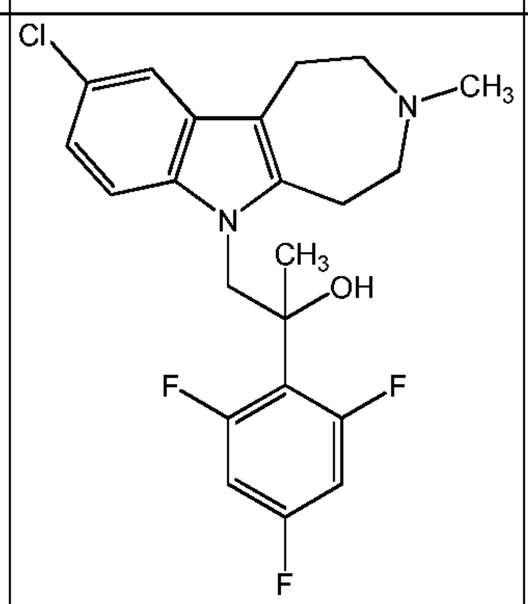
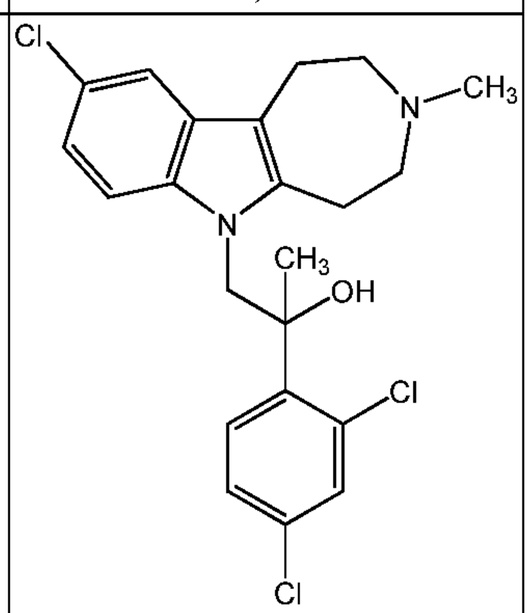
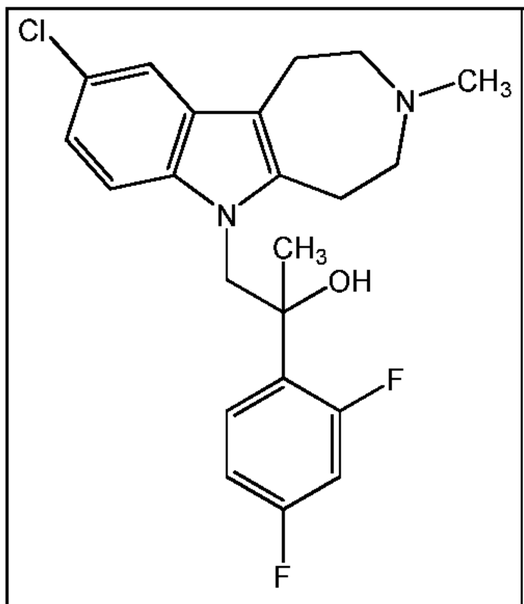
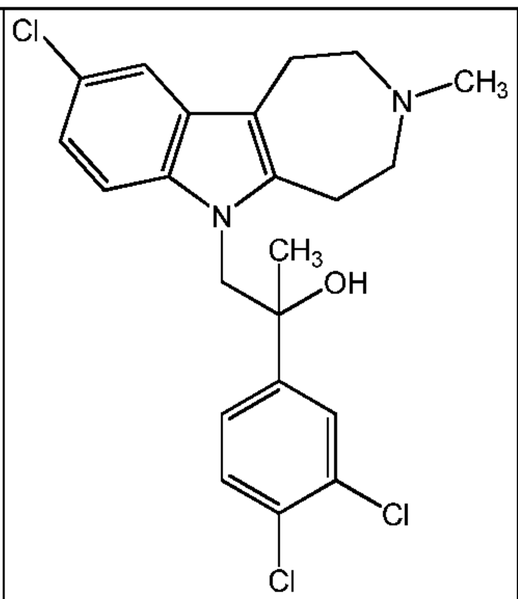
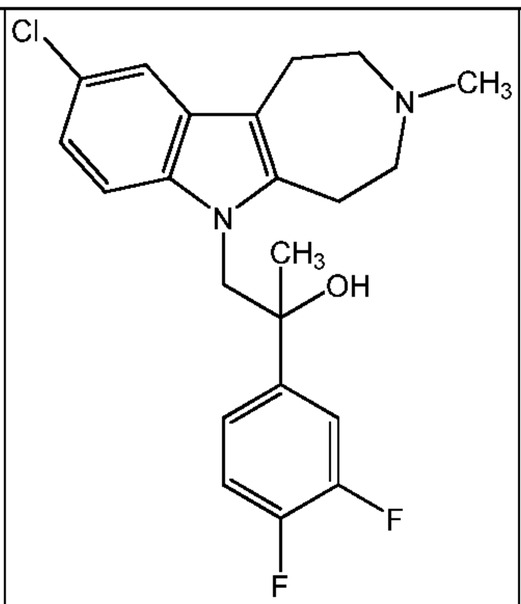
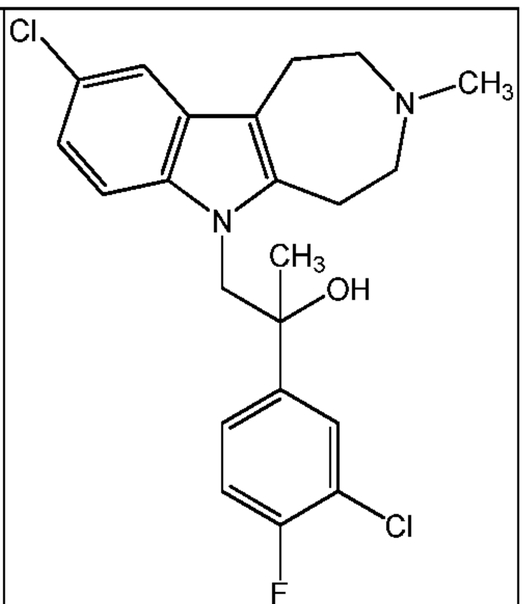
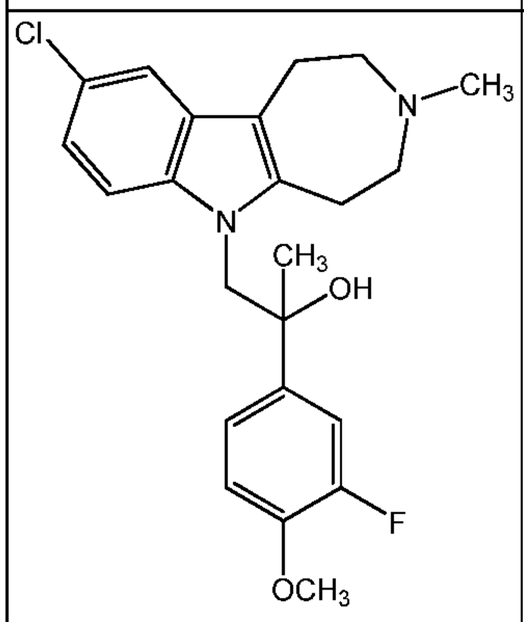
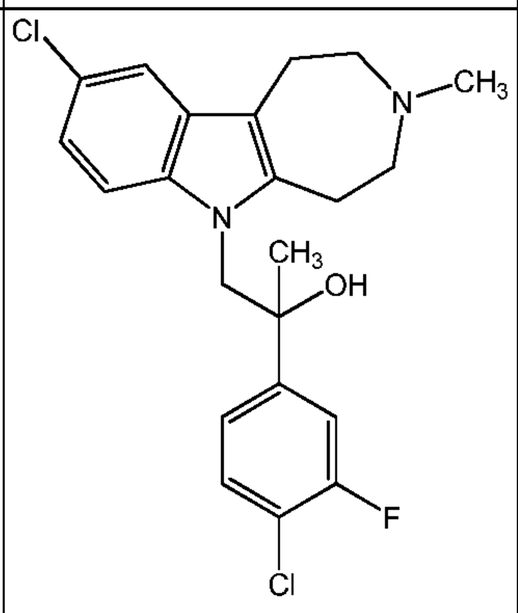
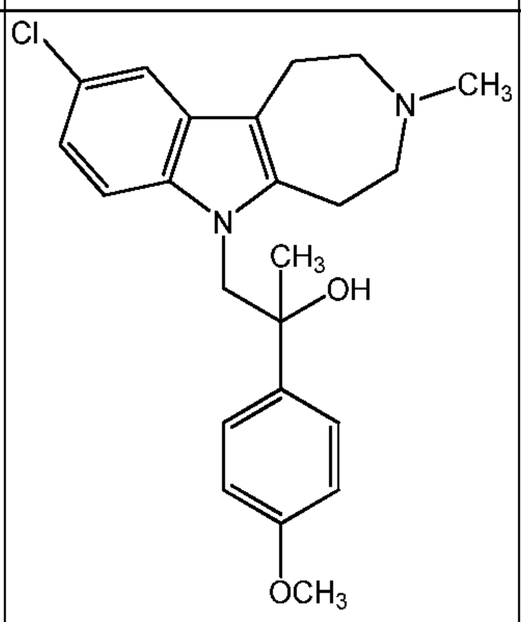
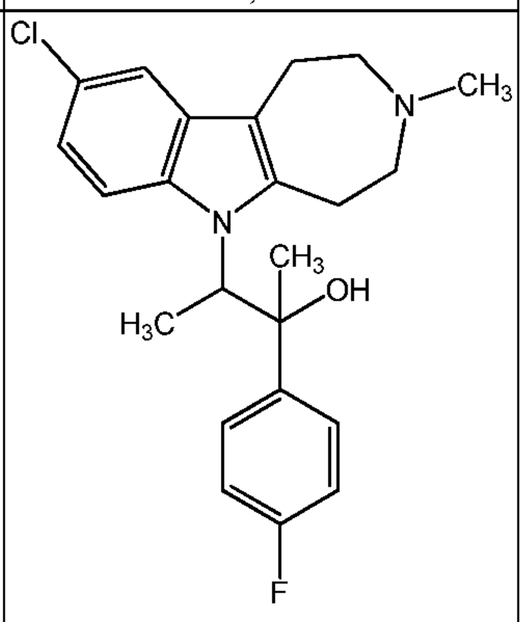
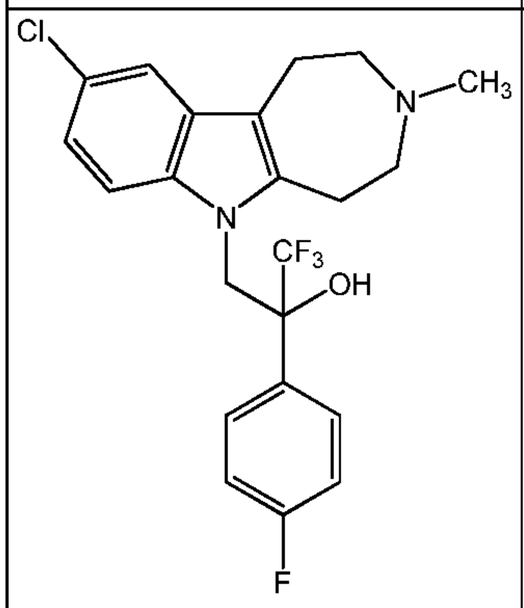
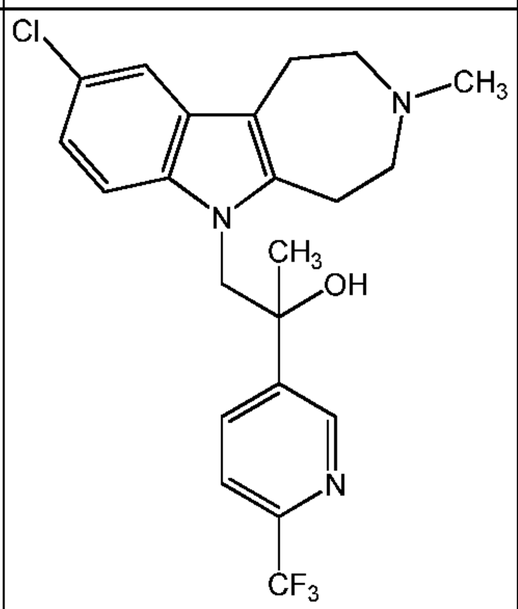
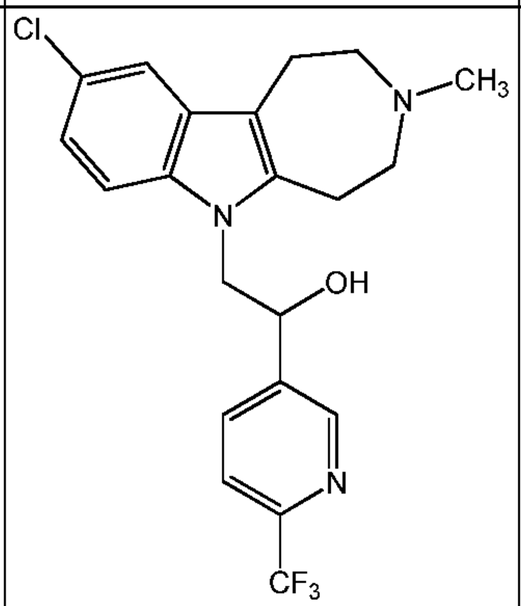
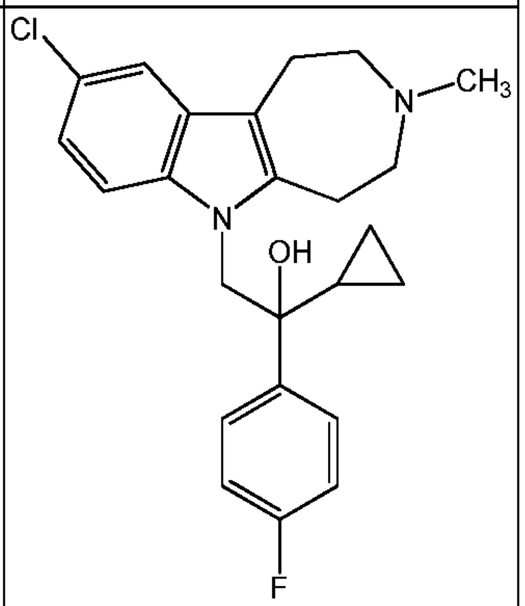
III-10a, III-10b

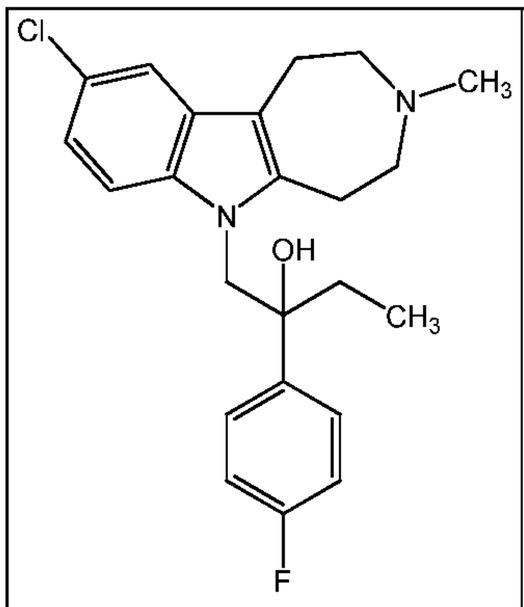
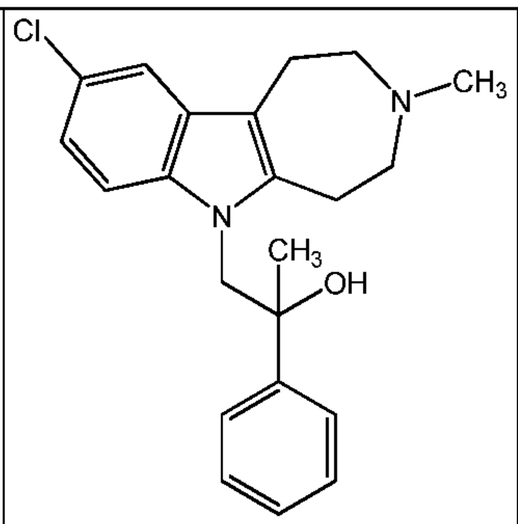
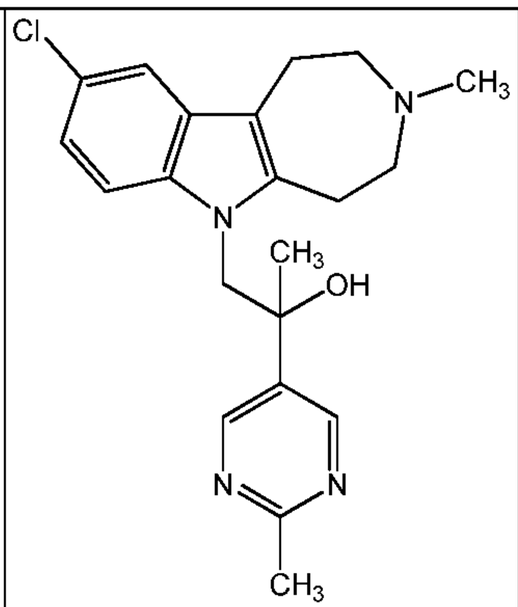
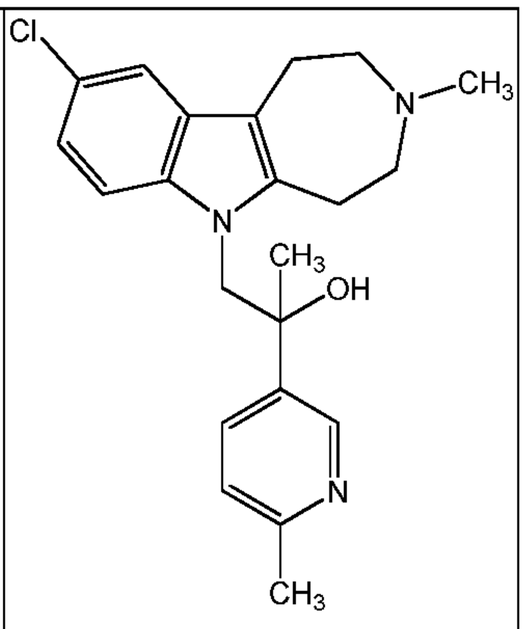
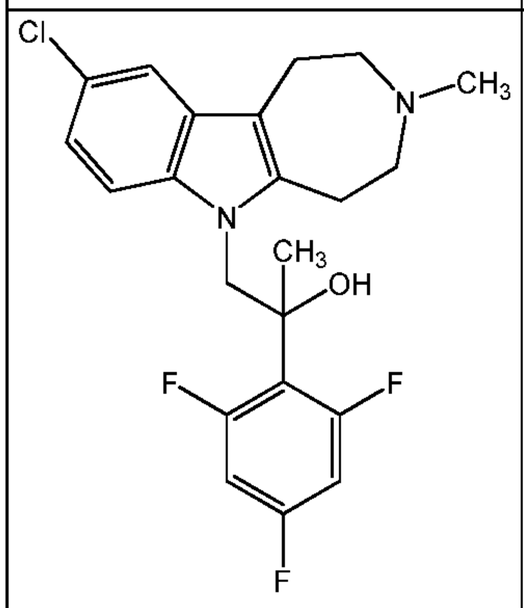
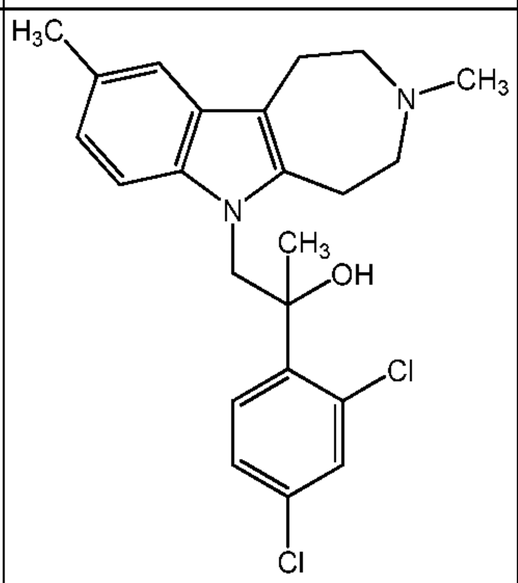
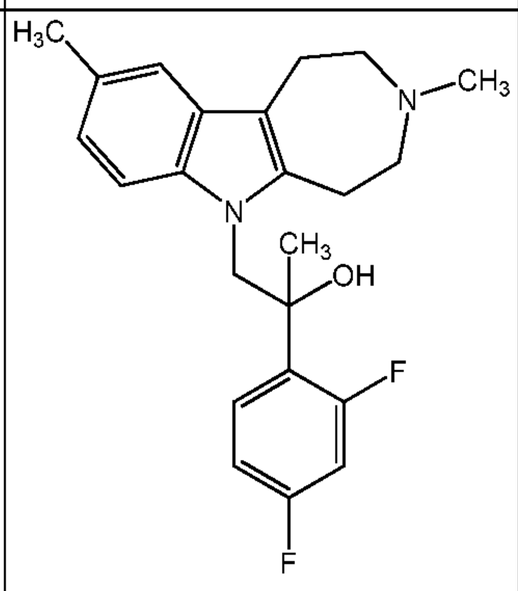
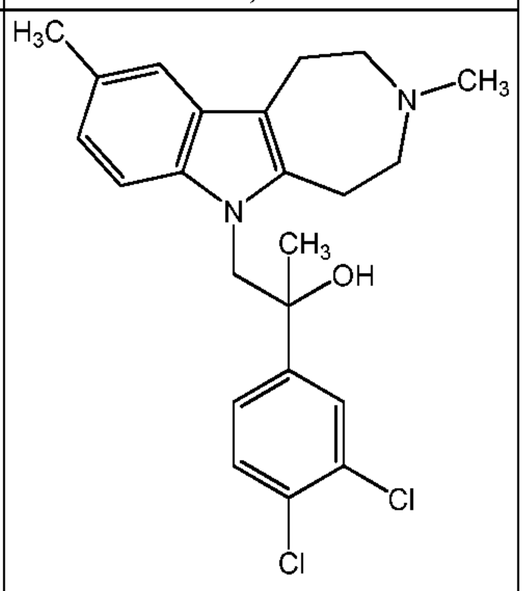
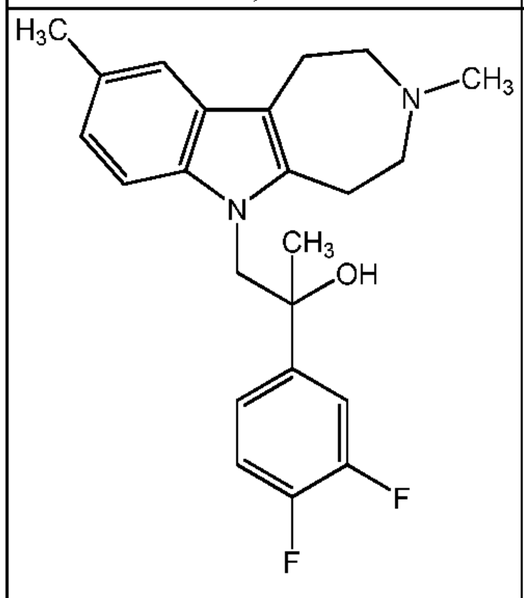
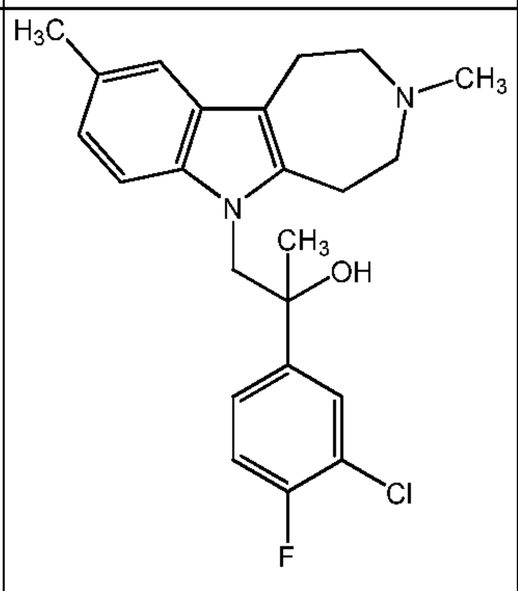
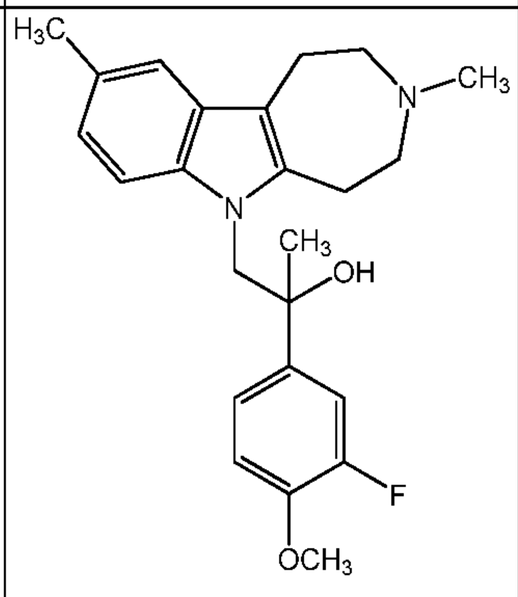
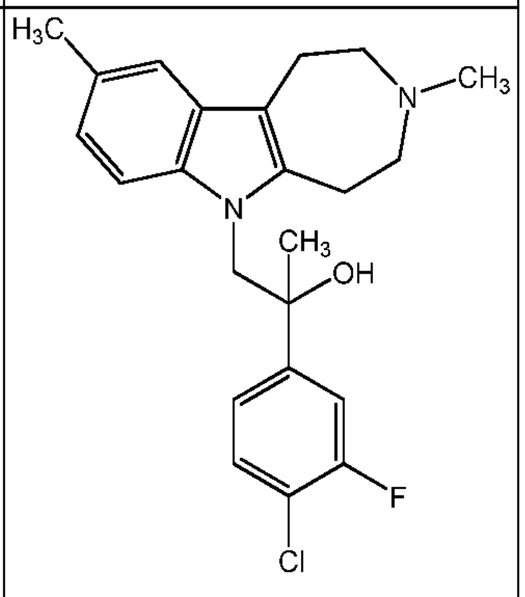


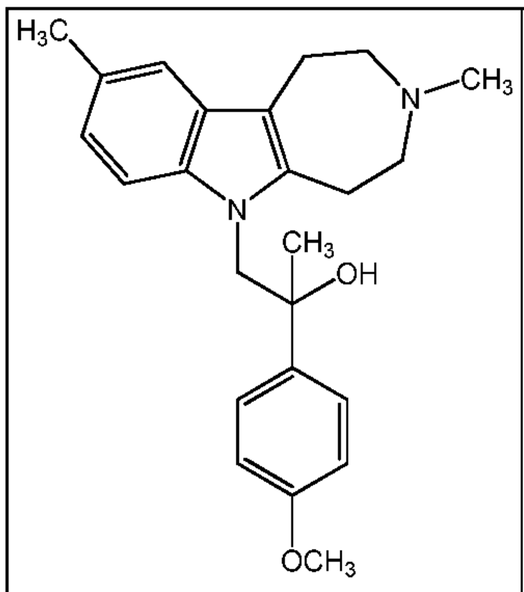
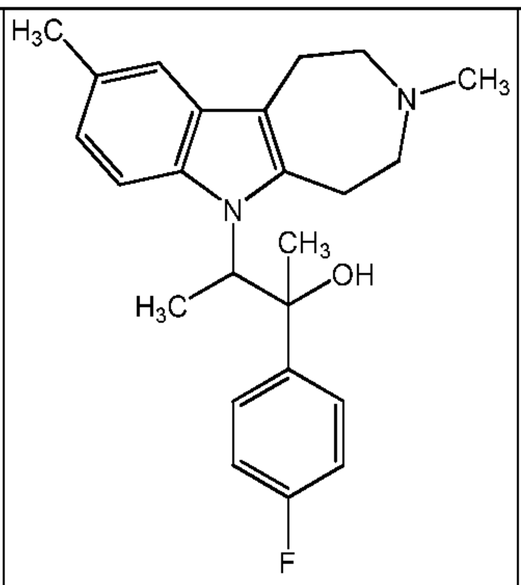
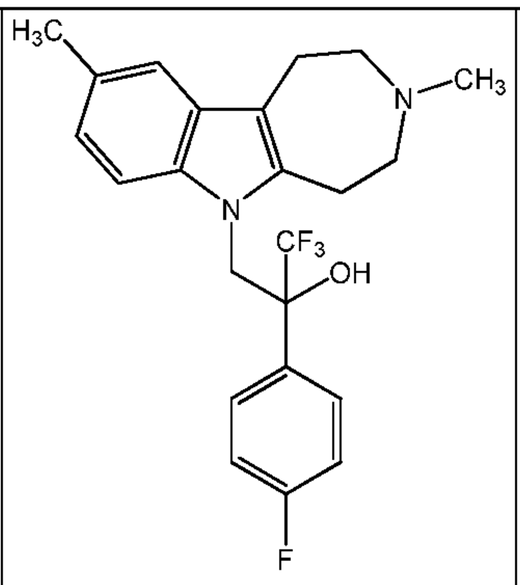
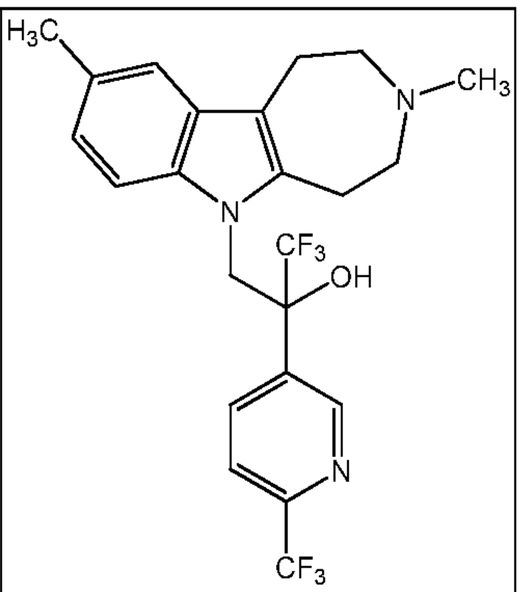
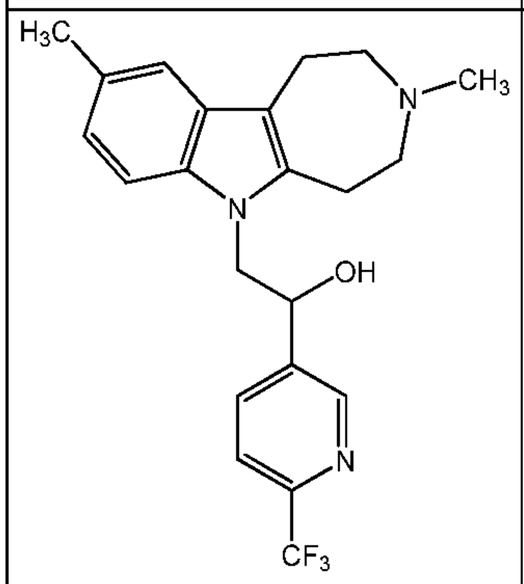
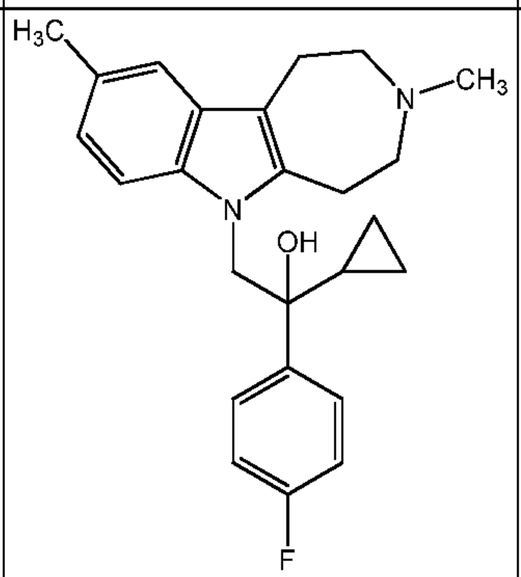
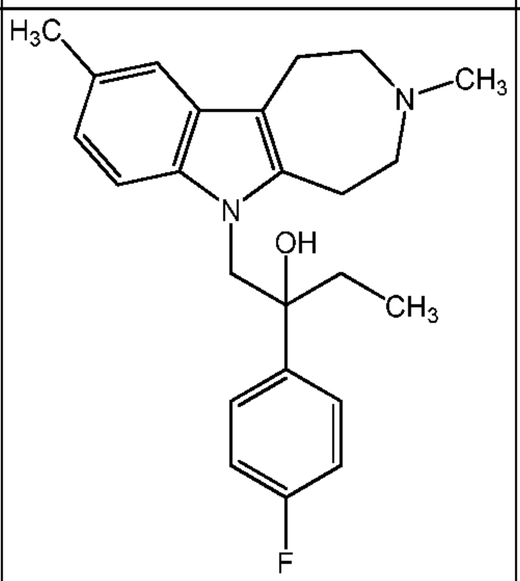
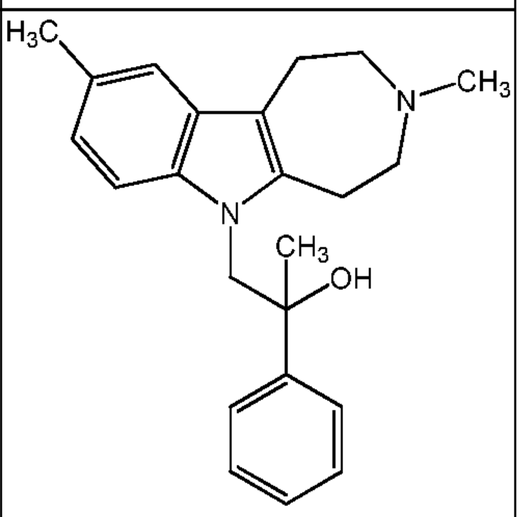
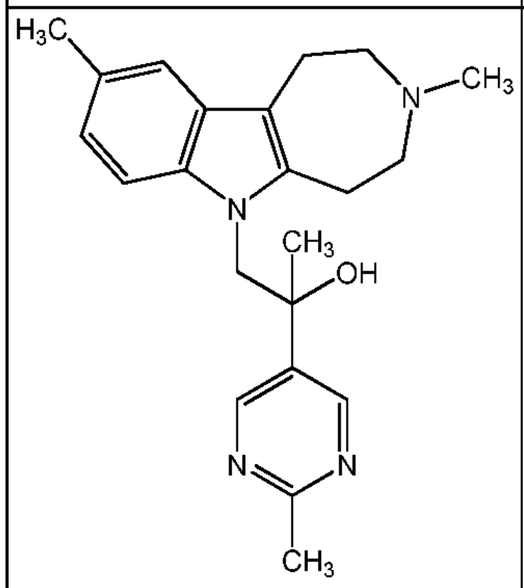
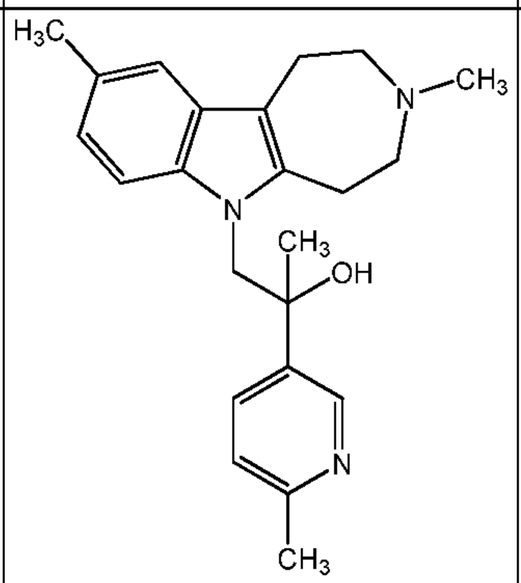
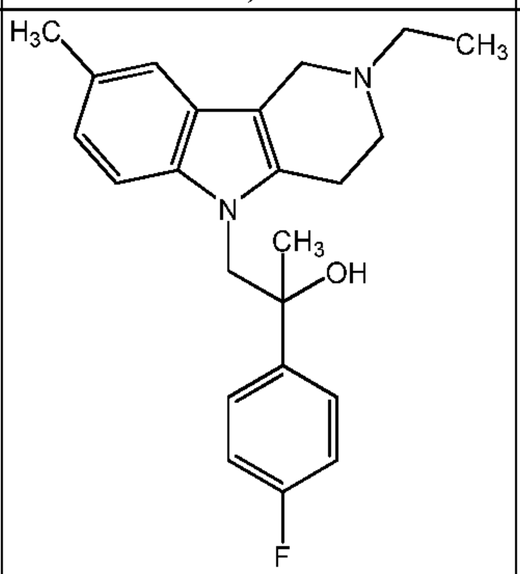
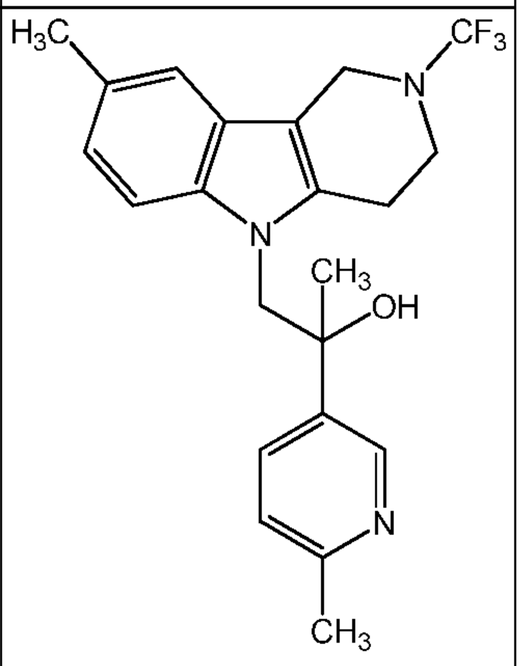
III-11
III-11a, III-11b

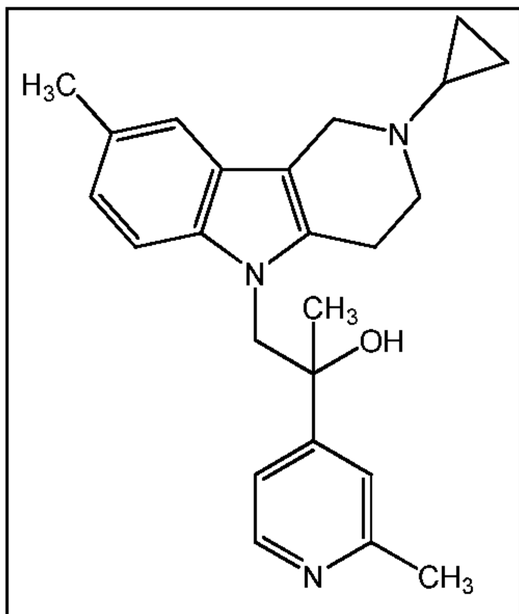
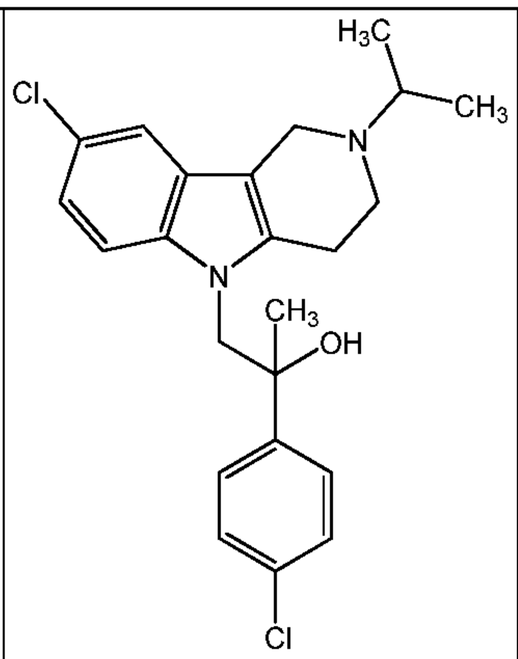
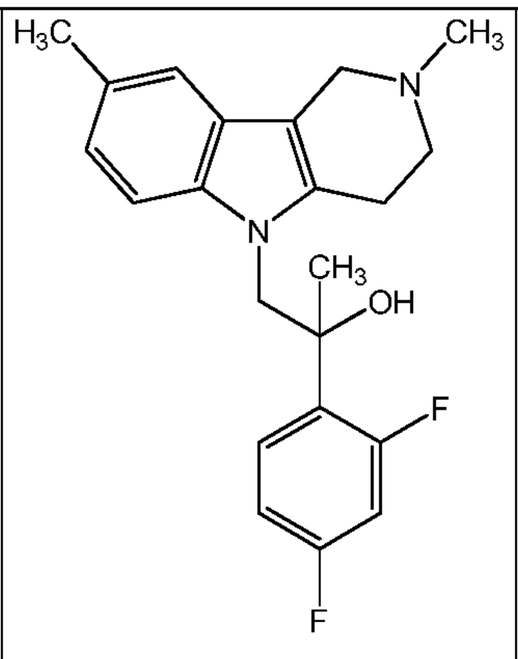
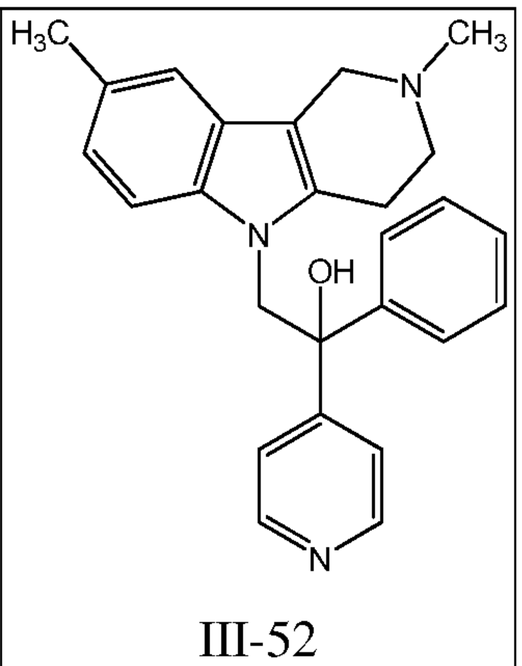
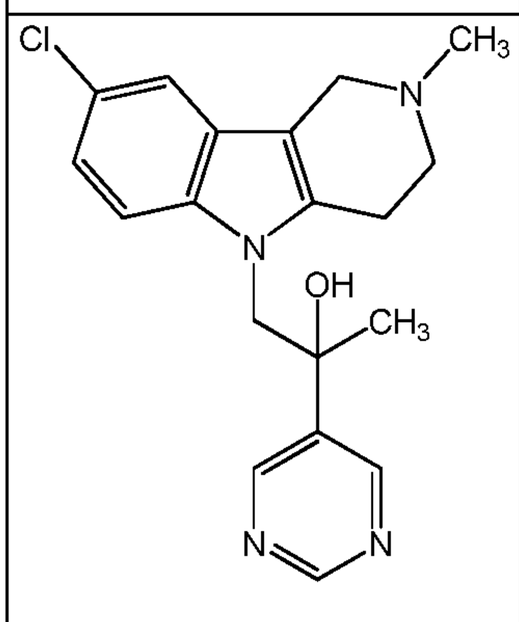
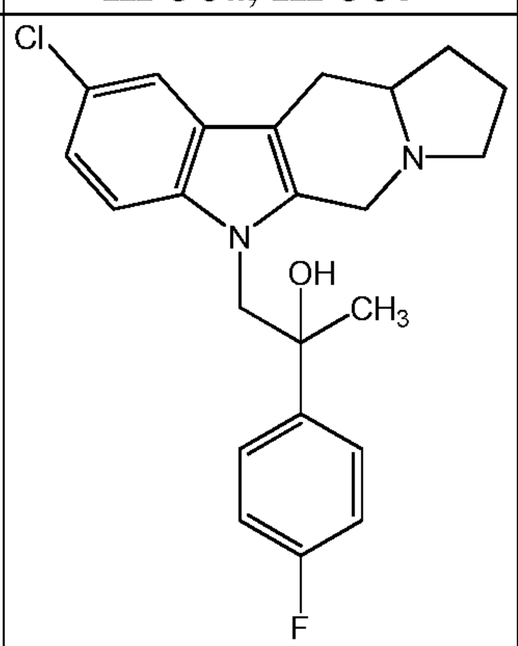
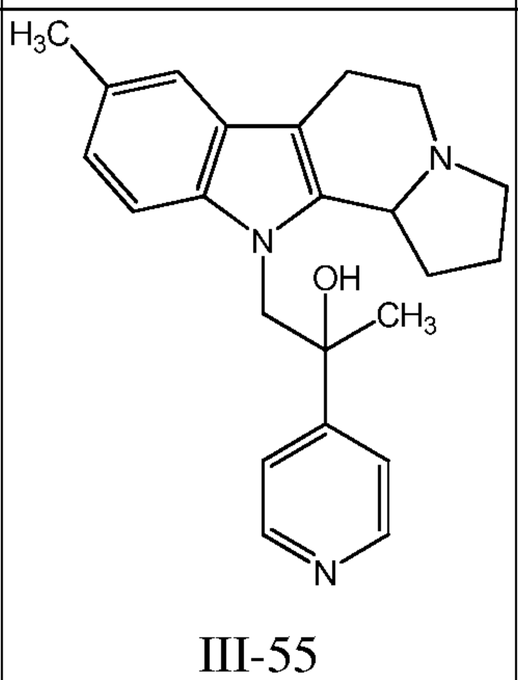
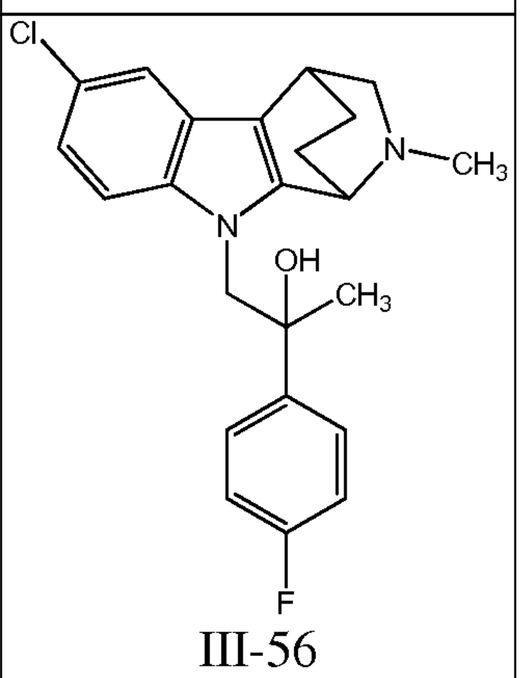
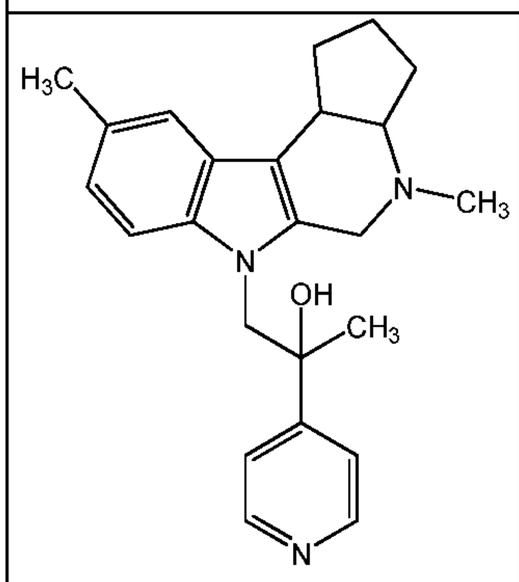
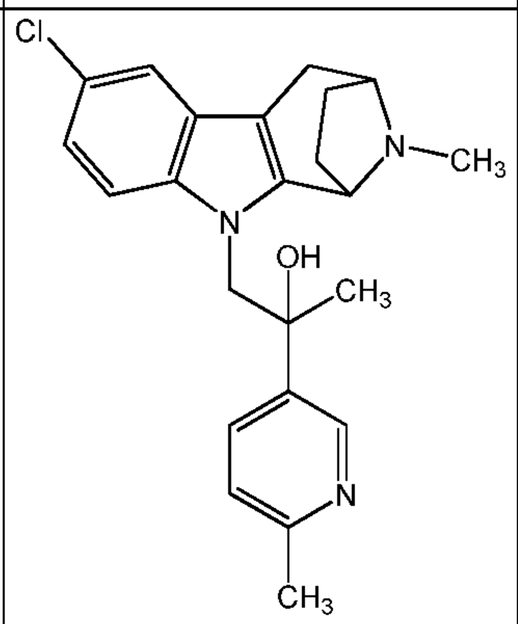
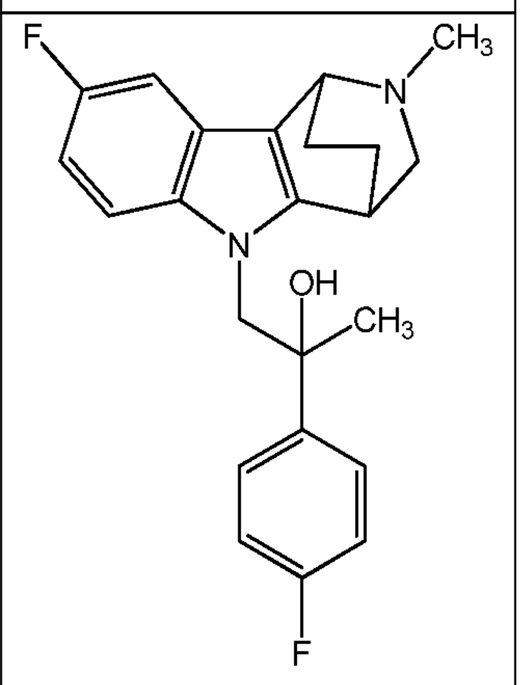


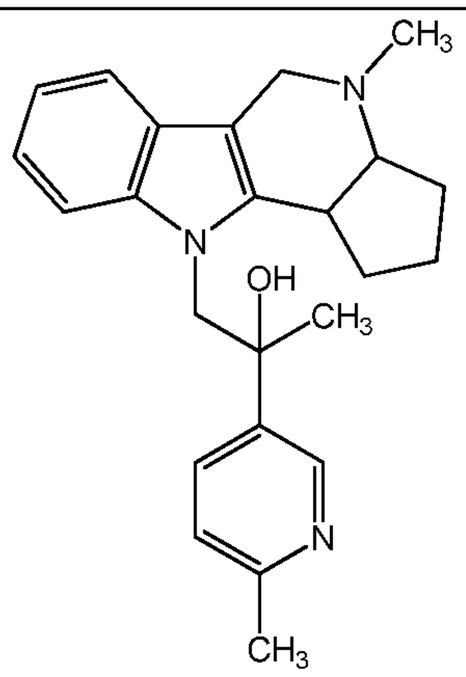
III-12
III-12a, III-12b

 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

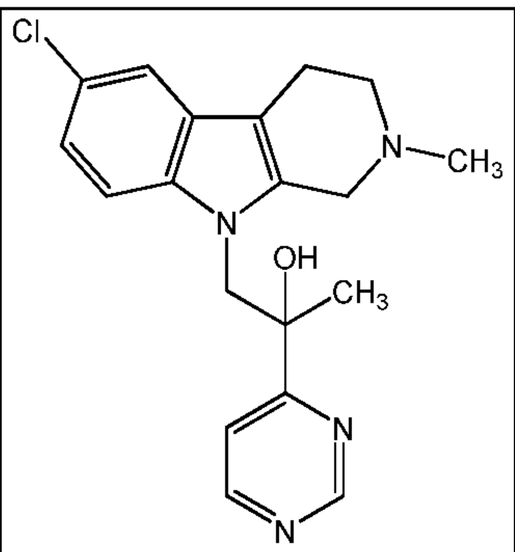
 III-25 III-25a, III-25b	 III-26 III-26a, III-26b	 III-27 III-27a, III-27b	 III-28 III-28a, III-28b
 III-29 III-29a, III-29b	 III-30 III-30a, III-30b	 III-31 III-31a, III-31b	 III-32 III-32a, III-32b
 III-33 III-33a, III-33b	 III-34 III-34a, III-34b	 III-35 III-35a, III-35b	 III-36 III-36a, III-36b

 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

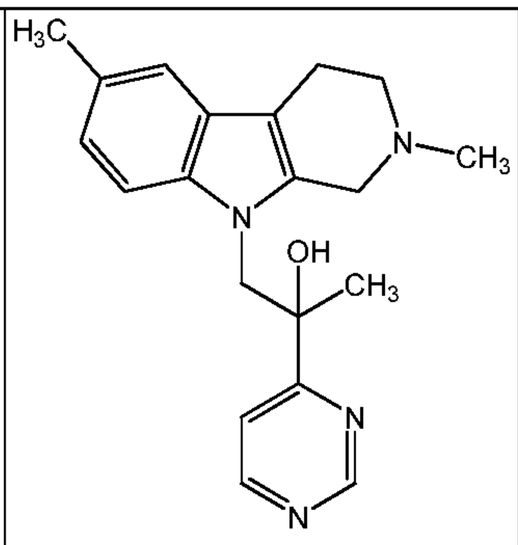
 III-49 III-49a, III-49b	 III-50 III-50a, III-50b	 III-51 III-51a, III-51b	 III-52 III-52a, III-52b
 III-53 III-53a, III-53b	 III-54 III-54a, III-54b, III-54c, III-54d	 III-55 III-55a, III-55b, III-55c, III-55d	 III-56 III-56a, III-56b, III-56c, III-56d
 III-57 III-57a, III-57b, III-57c, III-57d	 III-58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



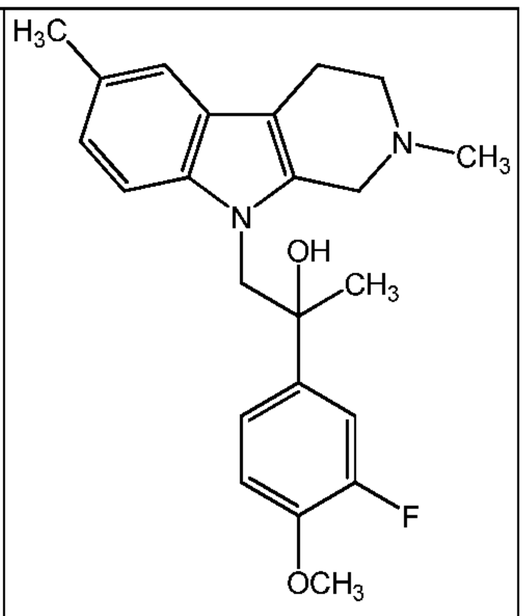
III-61
III-61a, III-61b, III-61c, III-61d



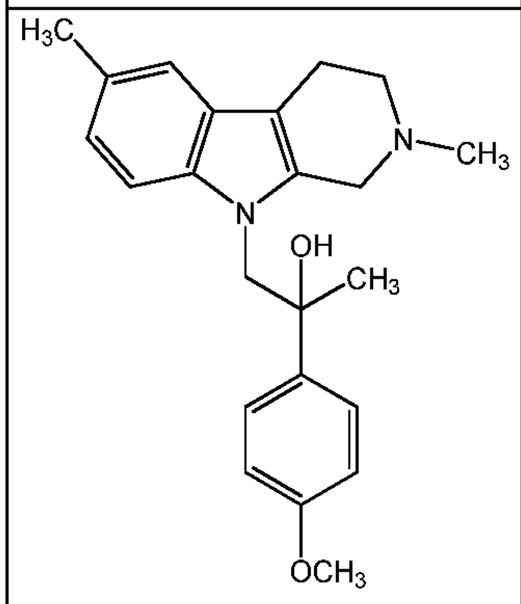
III-62
III-62a, III-62b



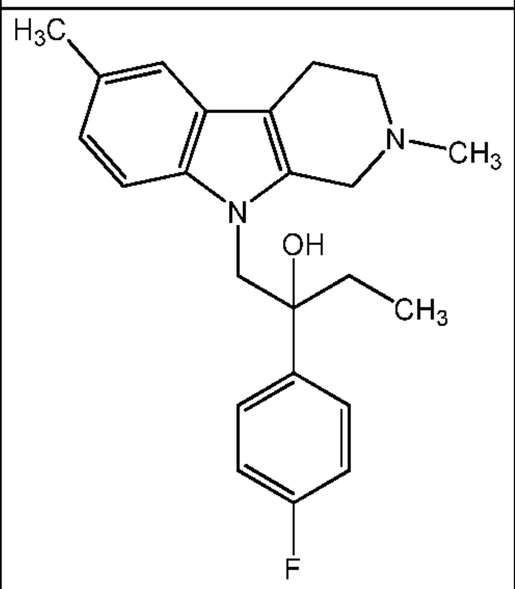
III-63
III-63a, III-63b



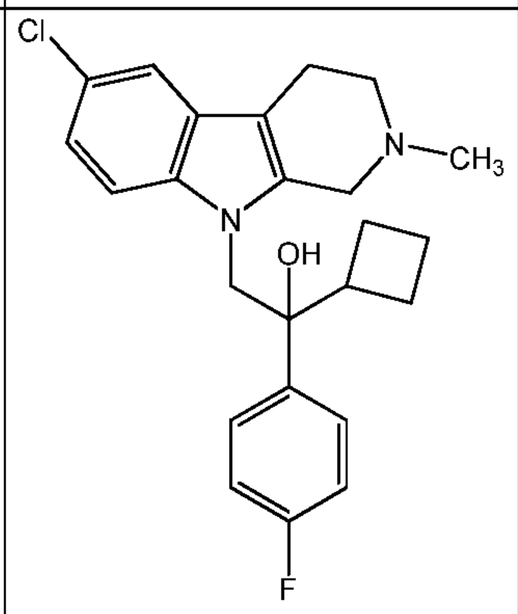
III-64
III-64a, III-64b



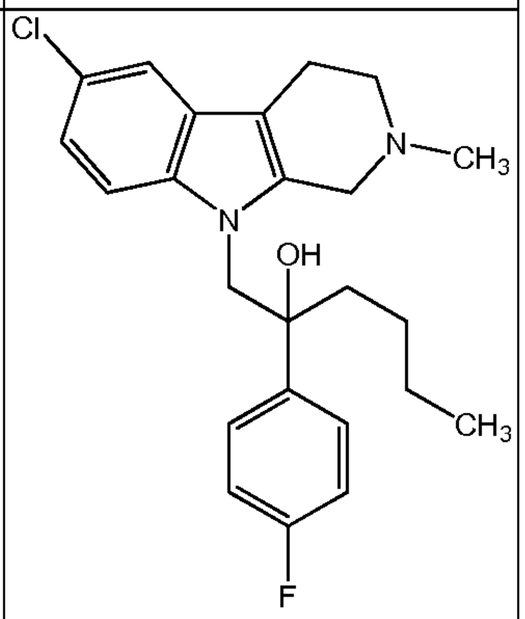
III-65
III-65a, III-65b



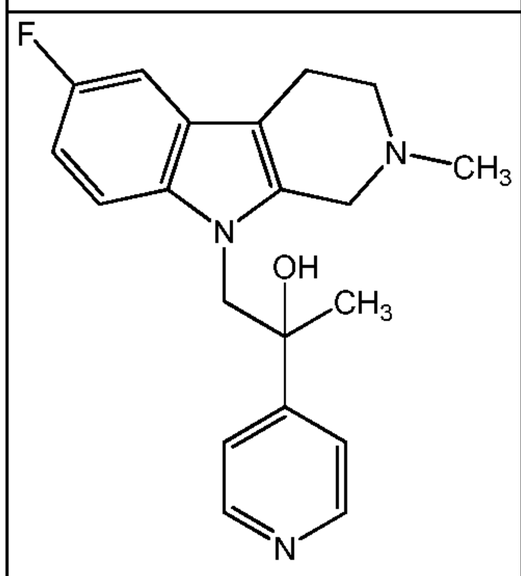
III-66
III-66a, III-66b



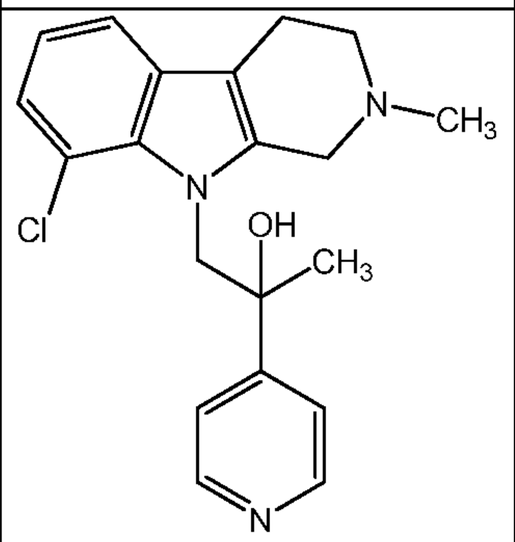
III-67
III-67a, III-67b



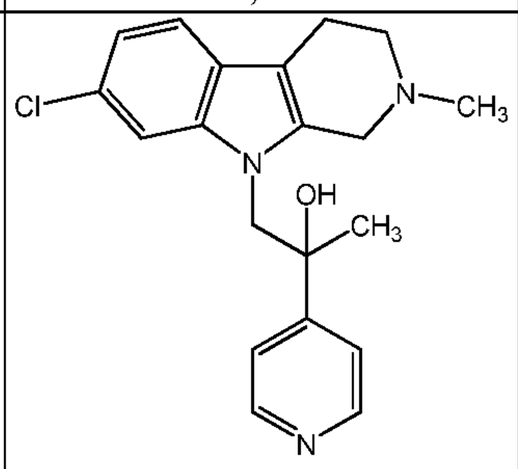
III-68
III-68a, III-68b



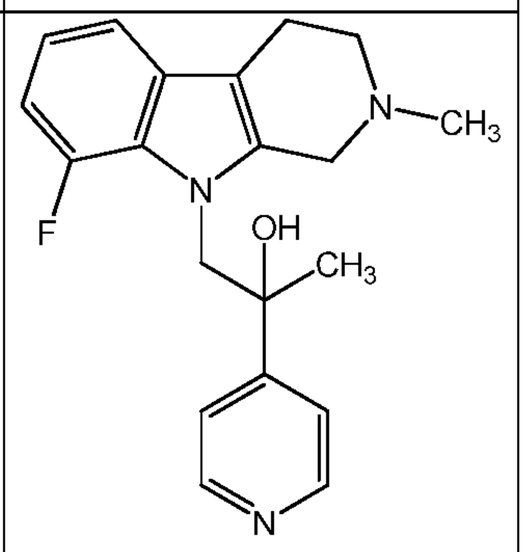
III-69
III-69a, III-69b



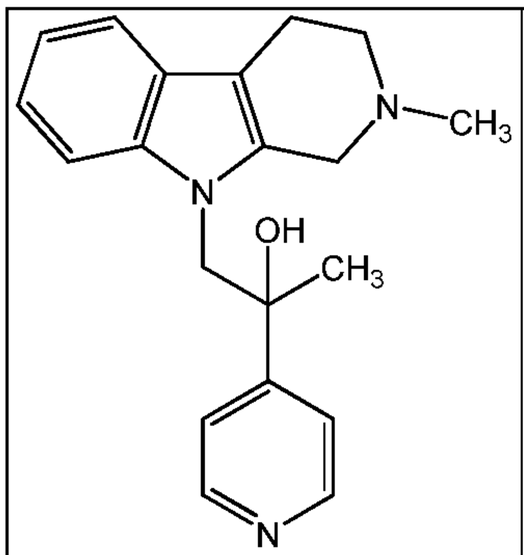
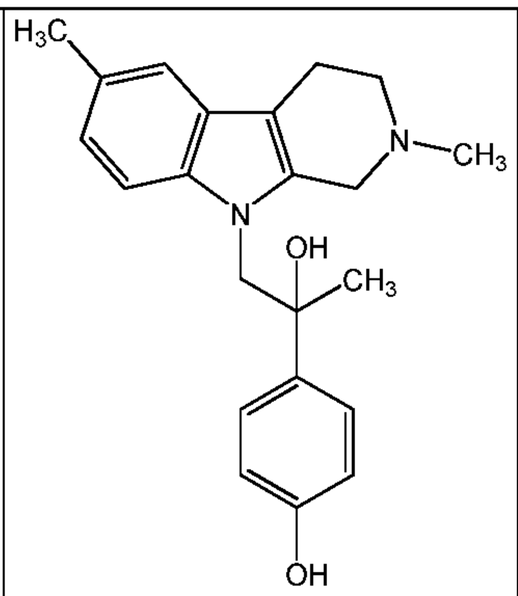
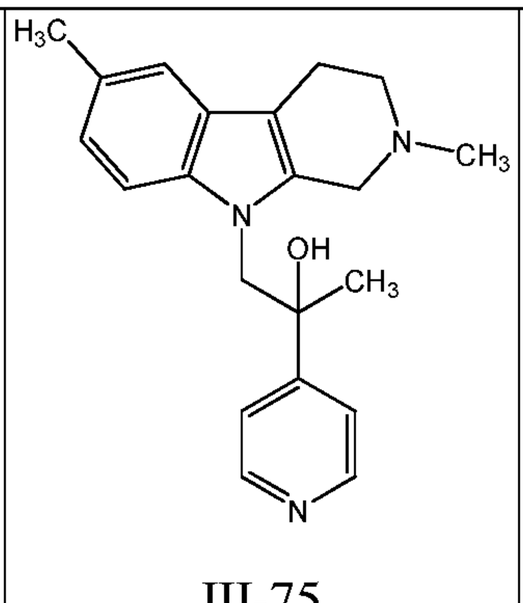
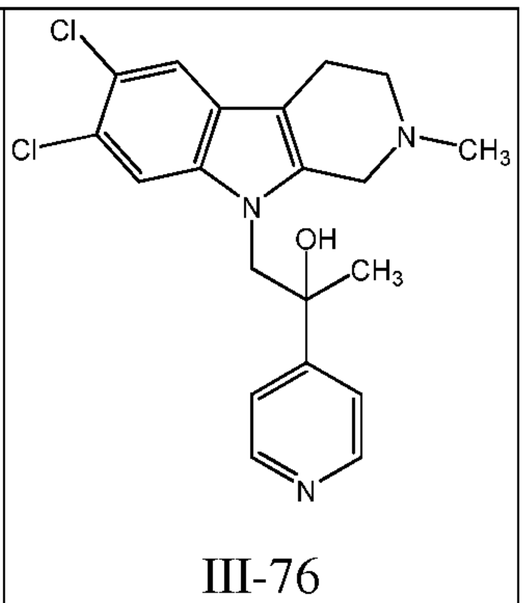
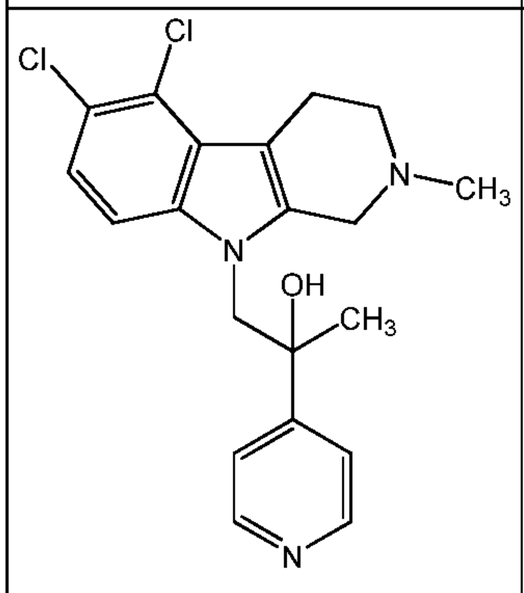
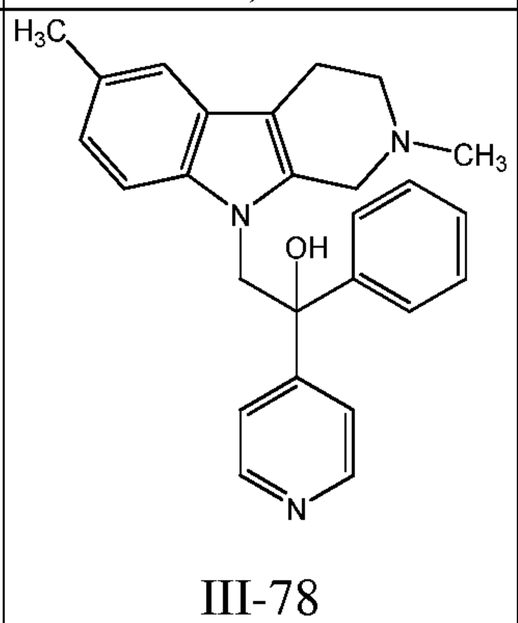
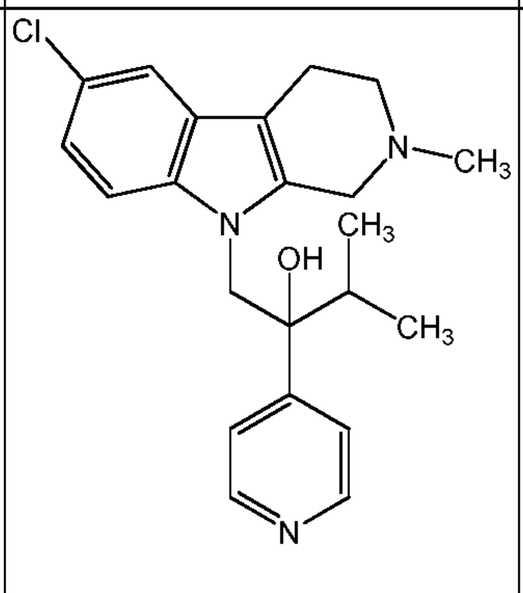
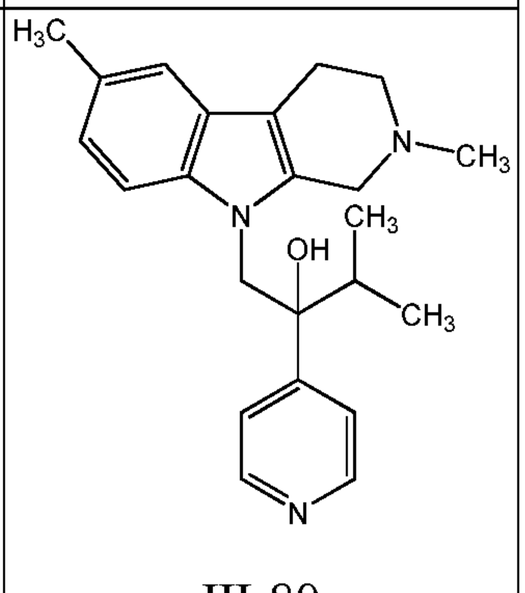
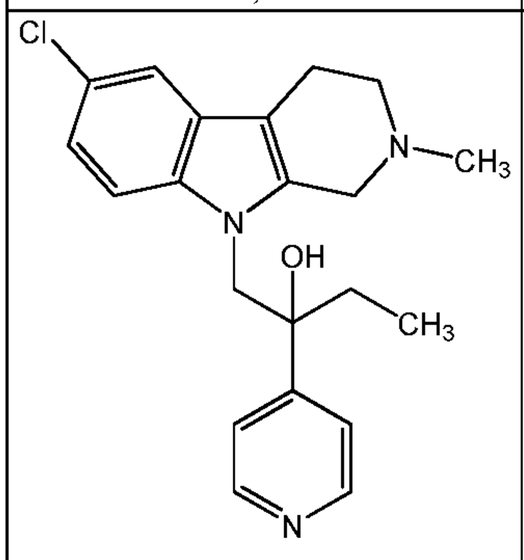
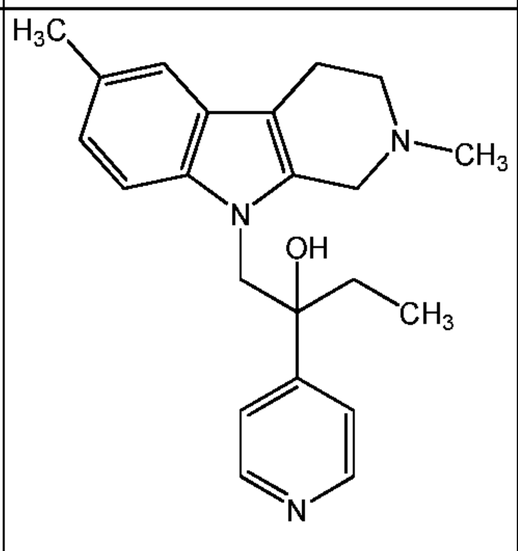
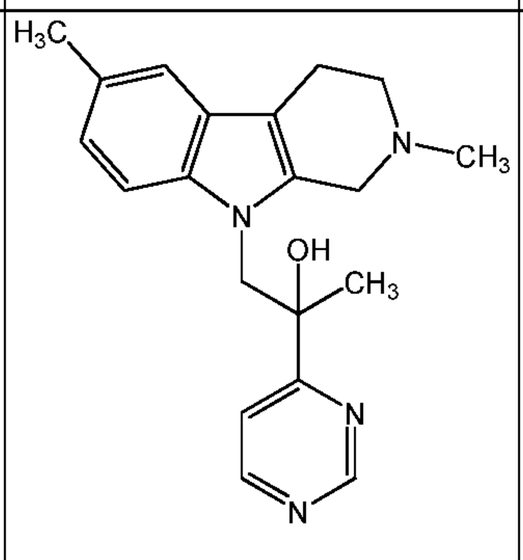
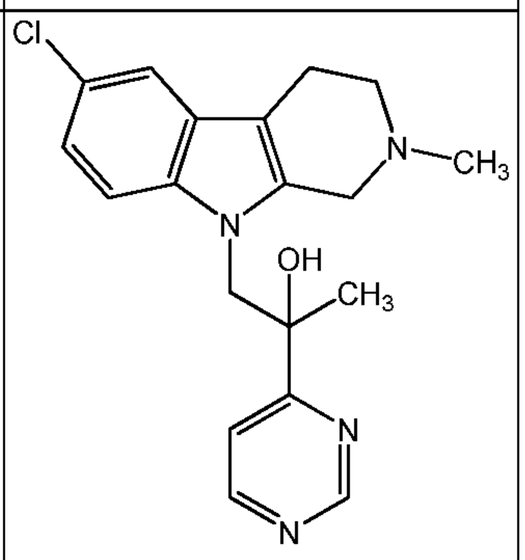
III-70
III-70a, III-70b

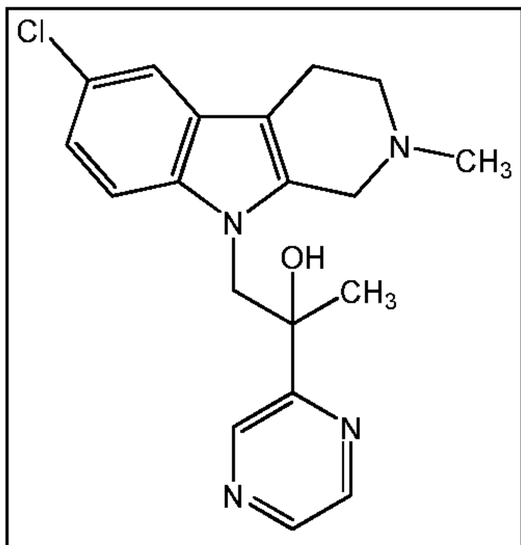


III-71
III-71a, III-71b

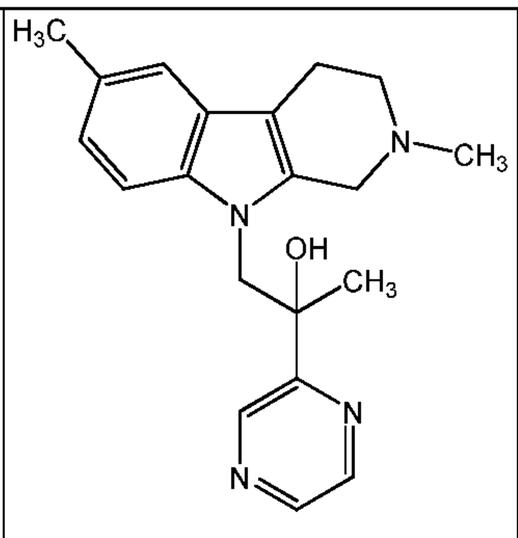


III-72
III-72a, III-72b

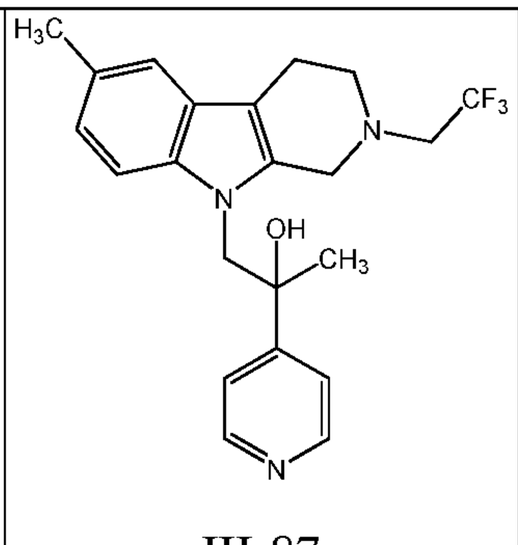
 III-73 III-73a, III-73b	 III-74 III-74a, III-74b	 III-75 III-75a, III-75b	 III-76 III-76a, III-76b
 III-77 III-77a, III-77b	 III-78 III-78a, III-78b	 III-79 III-79a, III-79b	 III-80 III-80a, III-80b
 III-81 III-81a, III-81b	 III-82 III-82a, III-82b	 III-83 III-83a, III-83b	 III-84 III-84a, III-84b



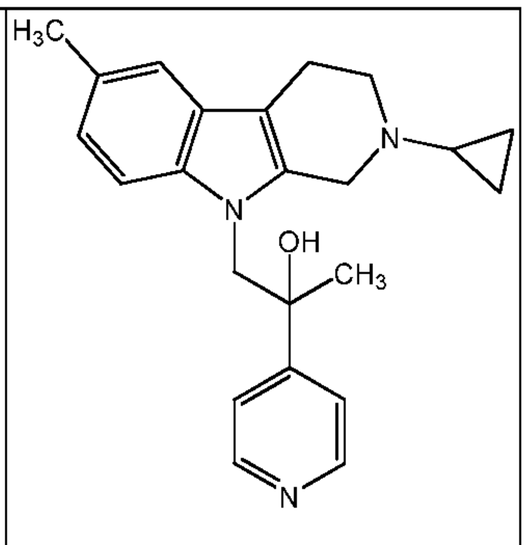
III-85
III-85a, III-85b



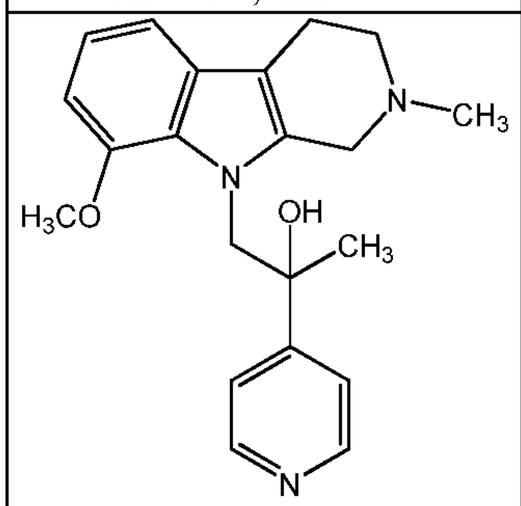
III-86
III-86a, III-86b



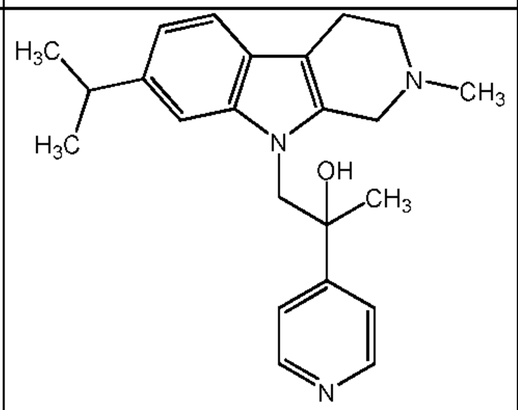
III-87
III-87a, III-87b



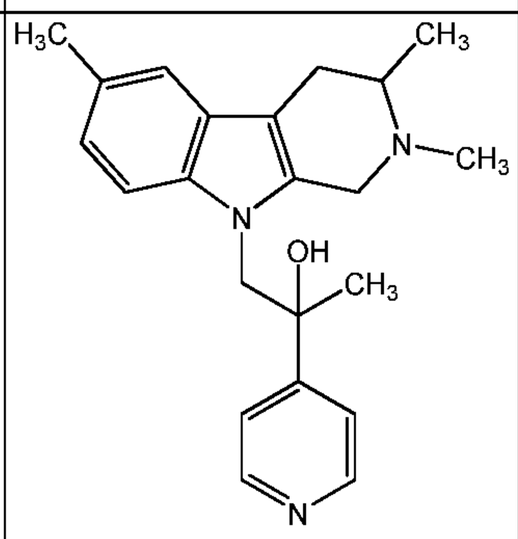
III-88
III-88a, III-88b



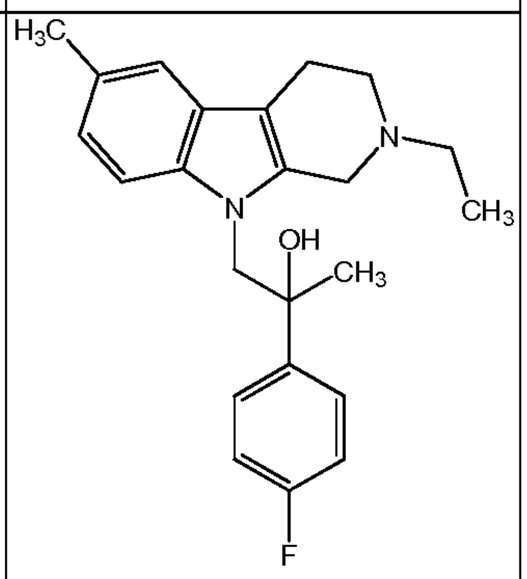
III-89
III-89a, III-89b



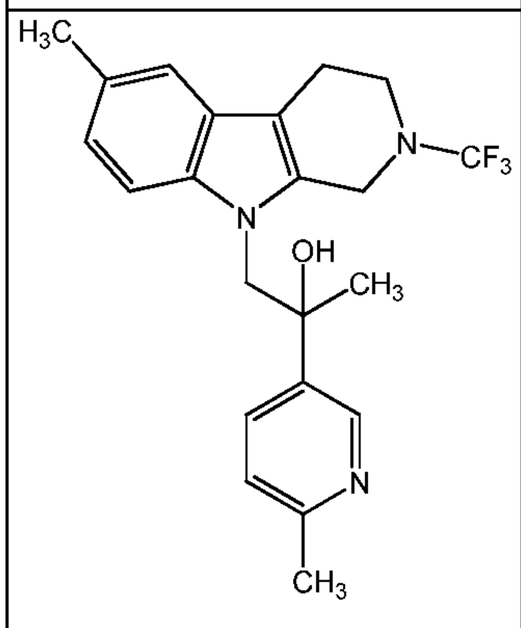
III-90
III-90a, III-90b



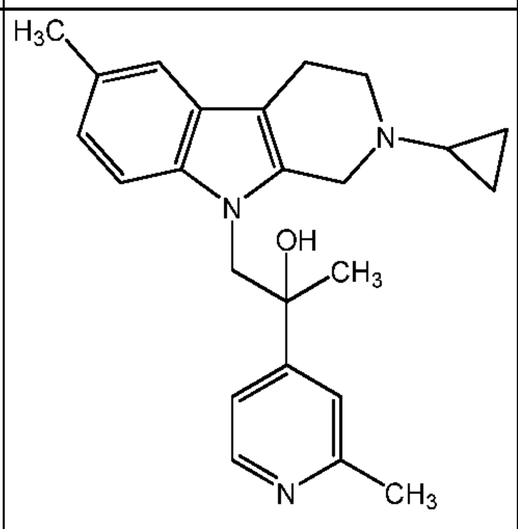
III-91
III-91a, III-91b, III-91c,
III-91d



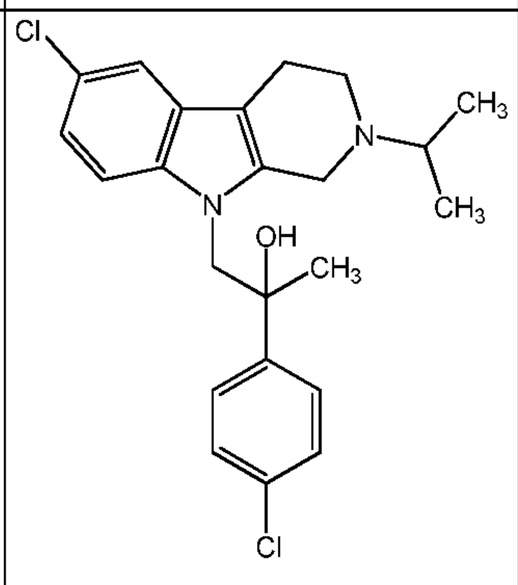
III-92
III-92a, III-92b



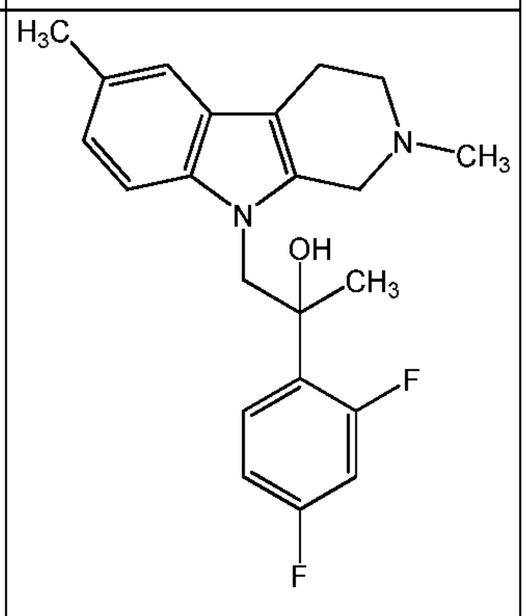
III-93
III-93a, III-93b



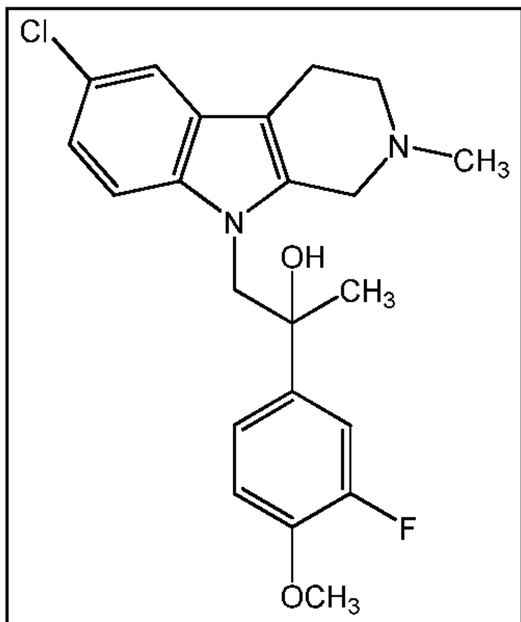
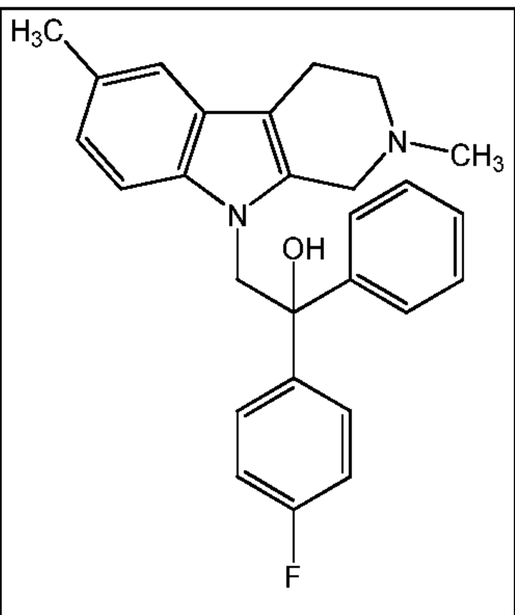
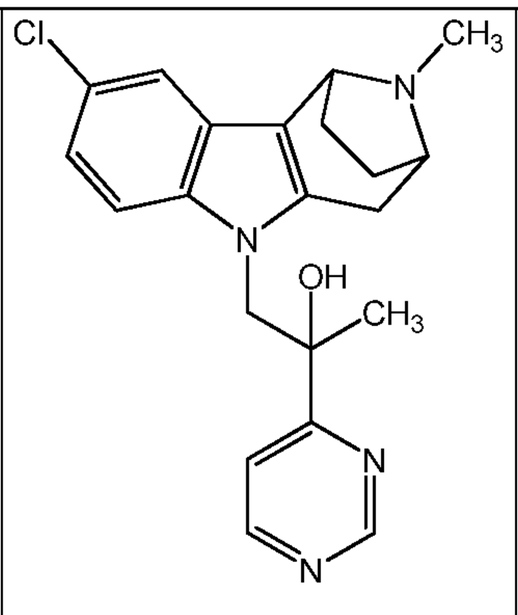
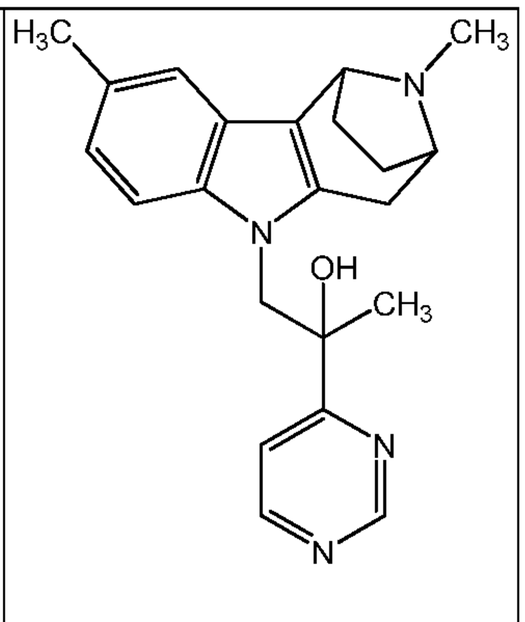
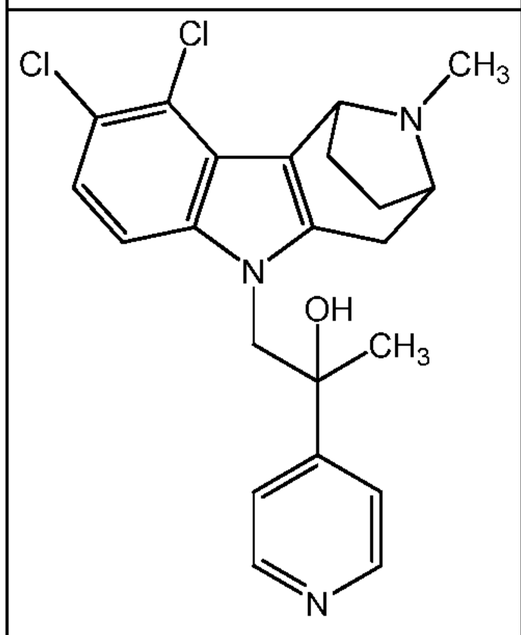
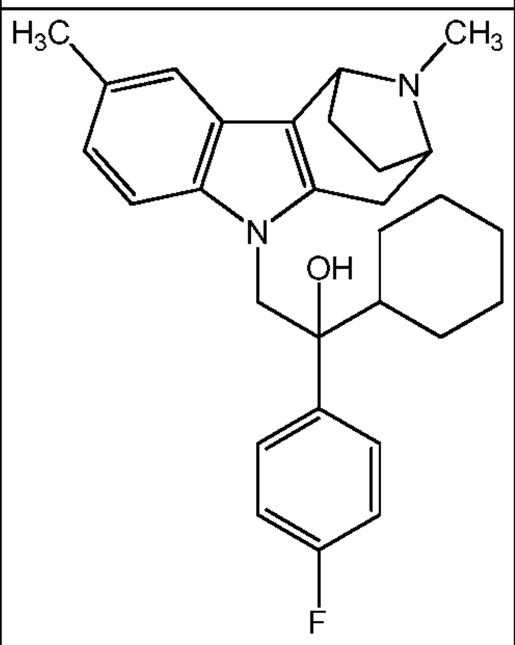
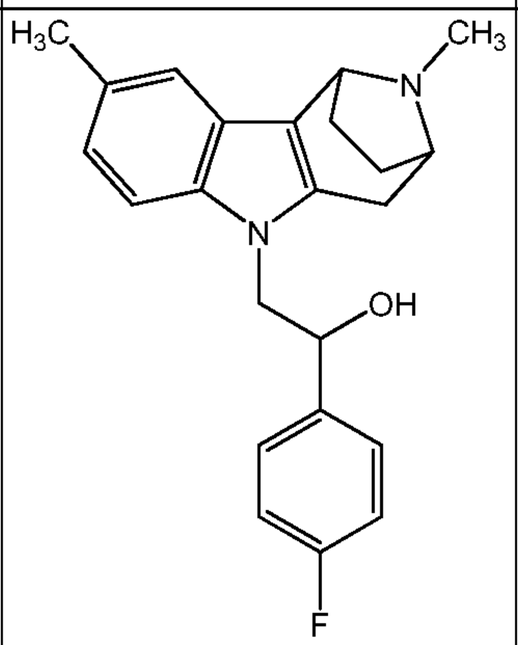
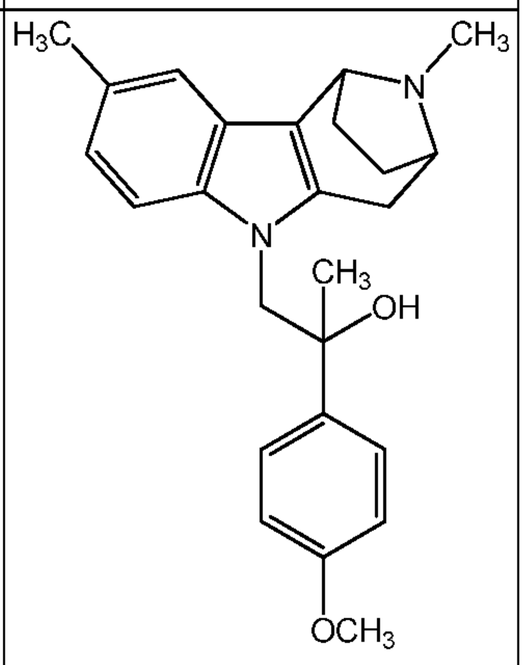
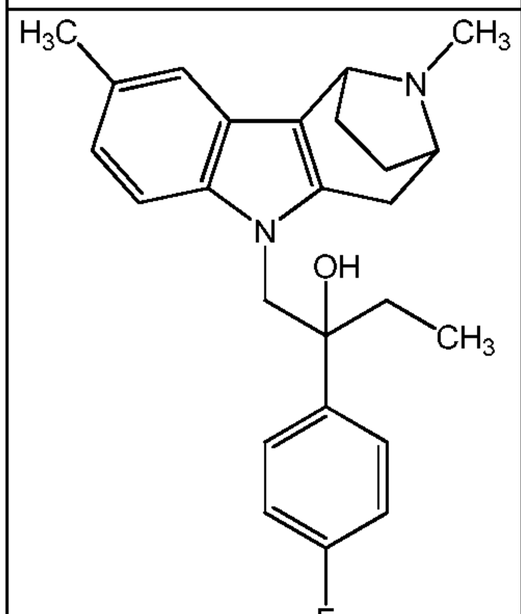
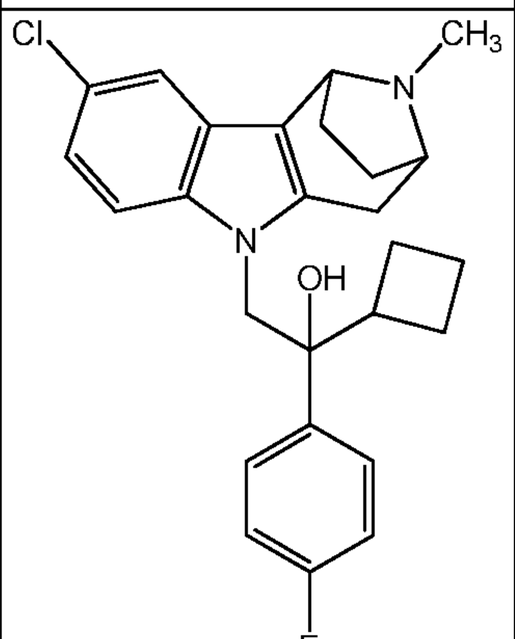
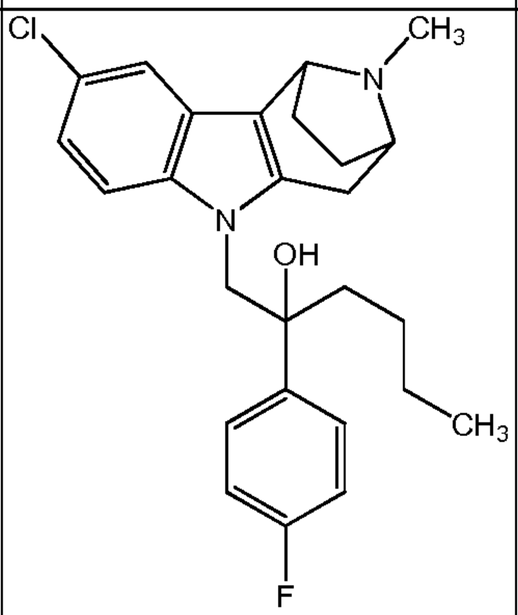
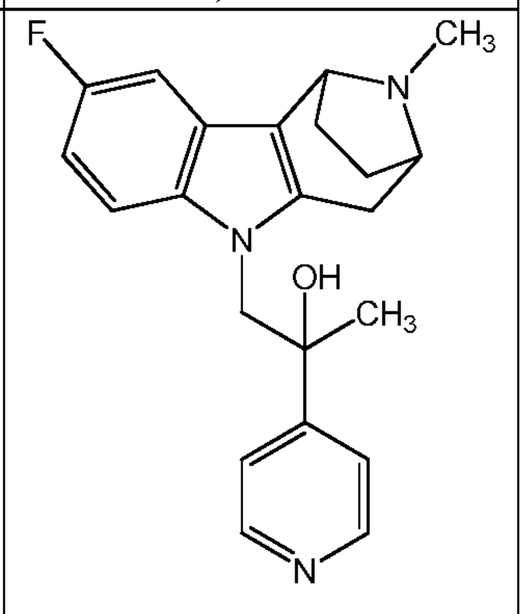
III-94
III-94a, III-94b

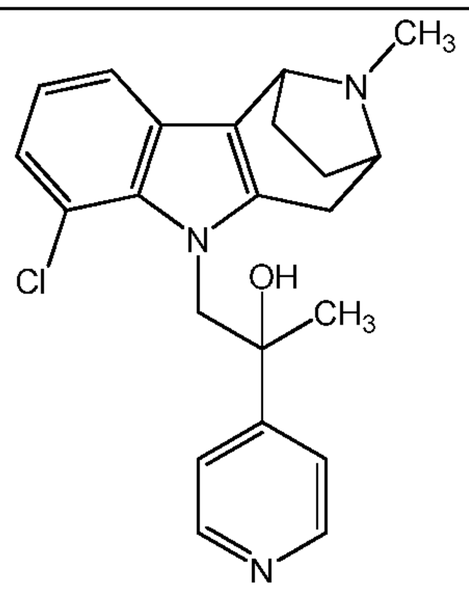
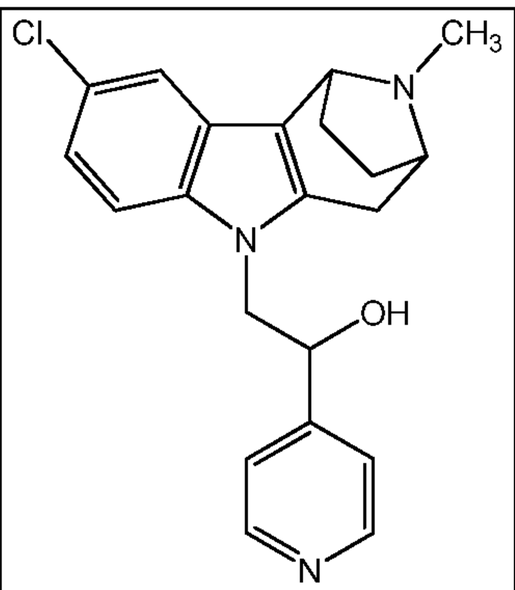
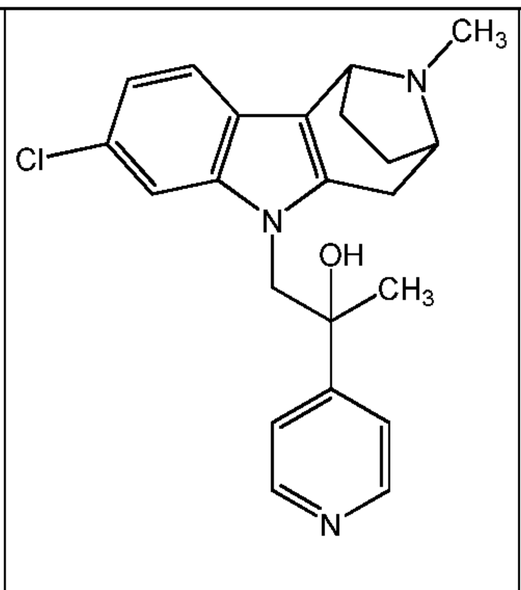
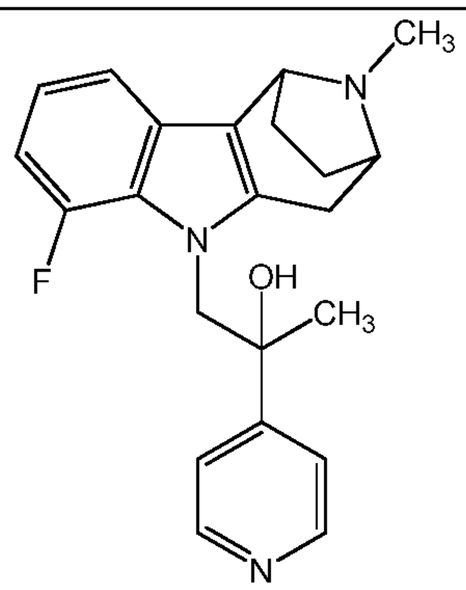
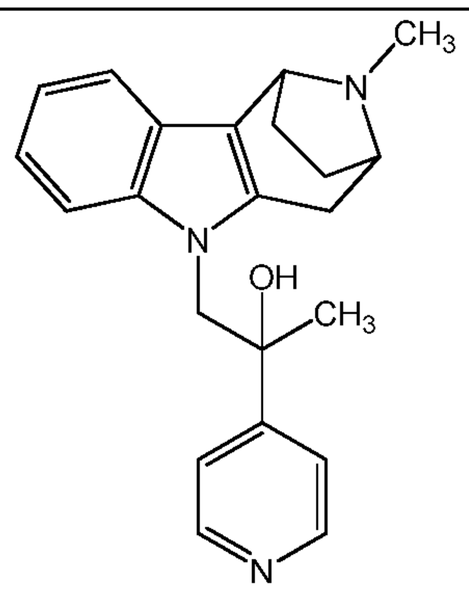
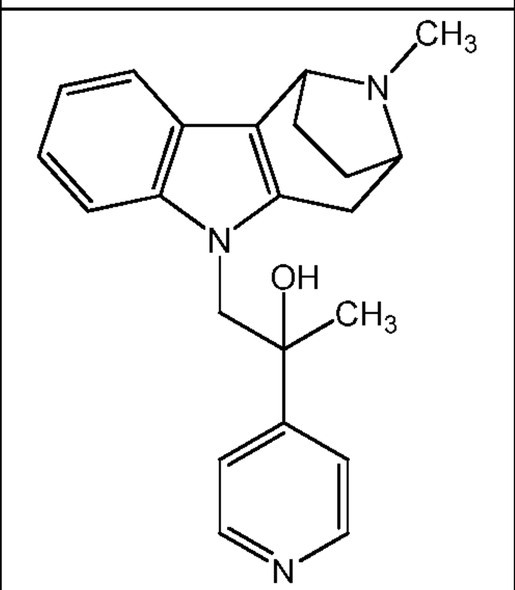
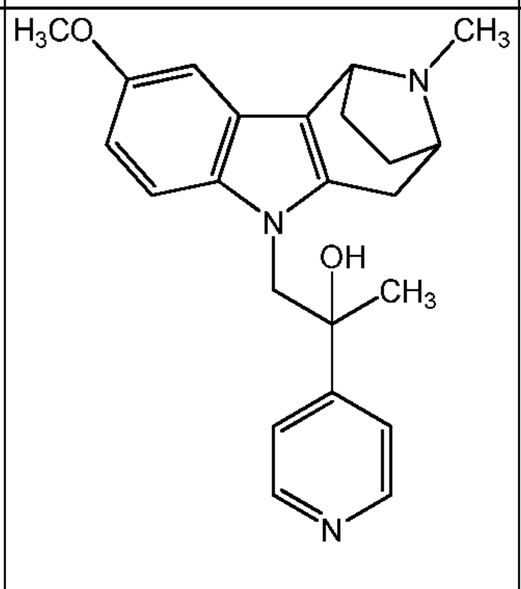
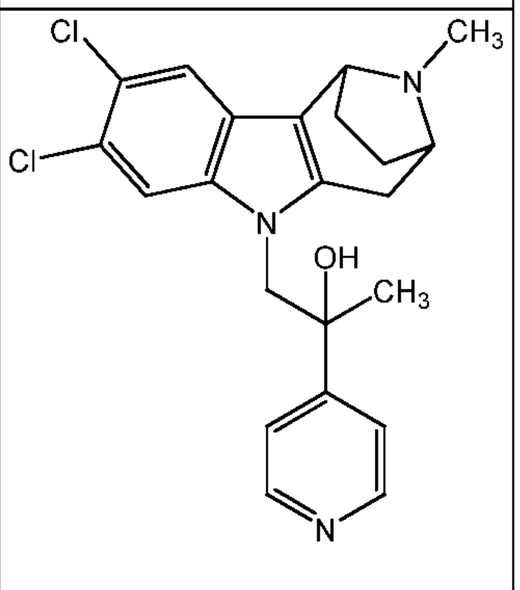
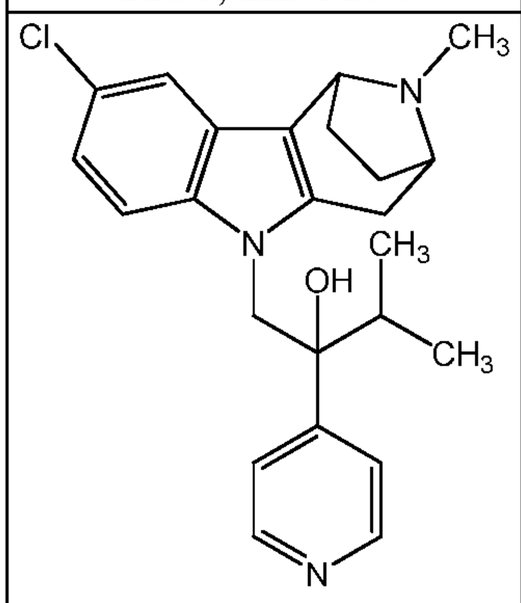
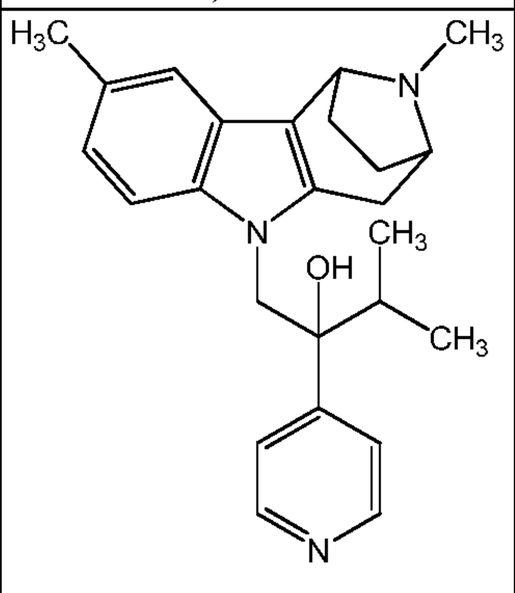
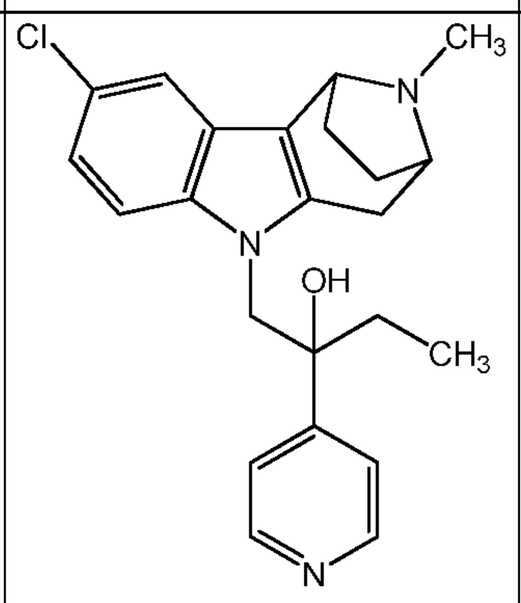
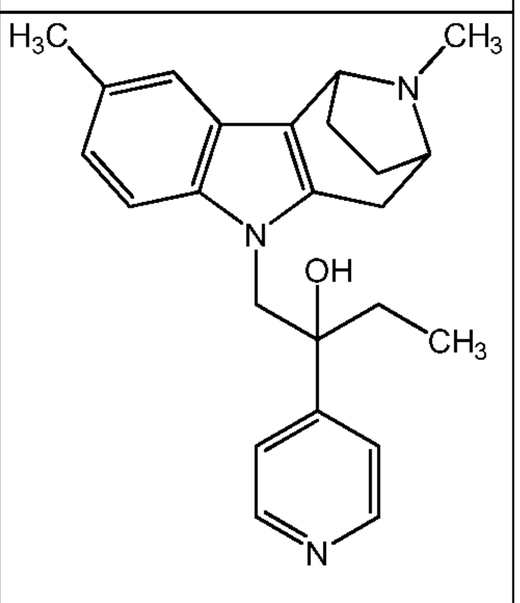


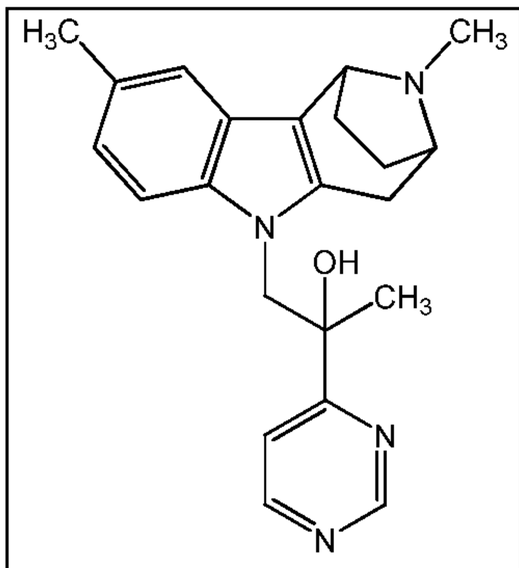
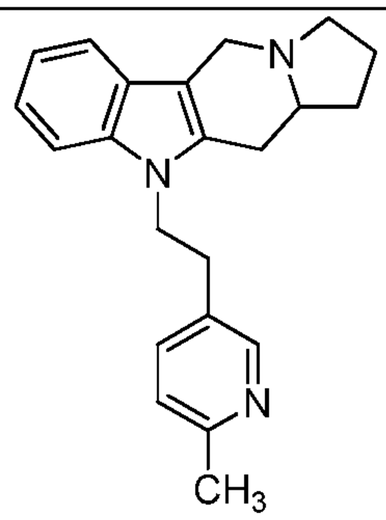
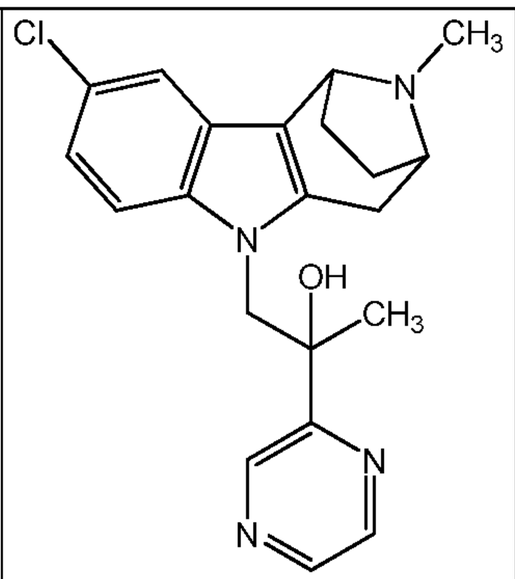
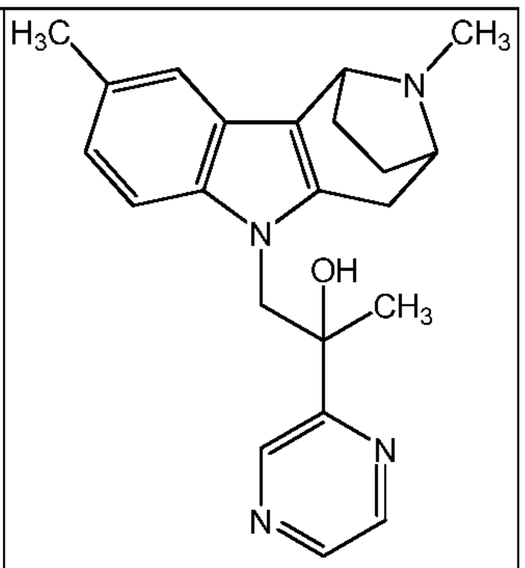
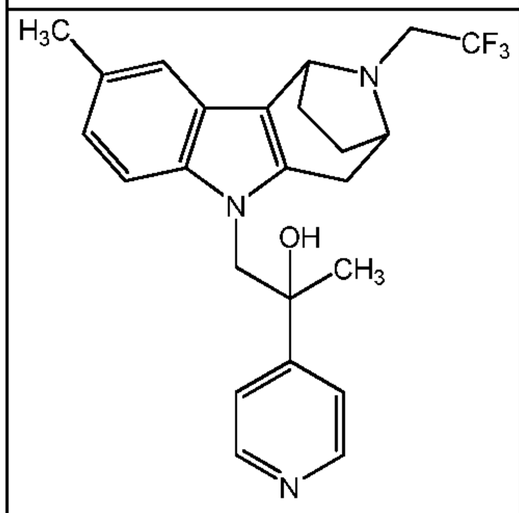
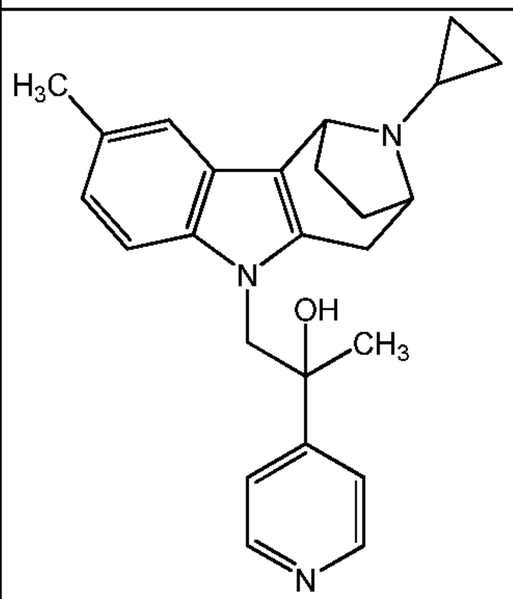
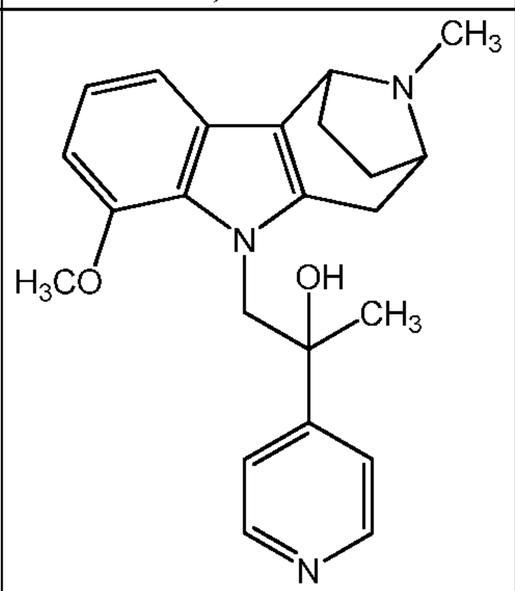
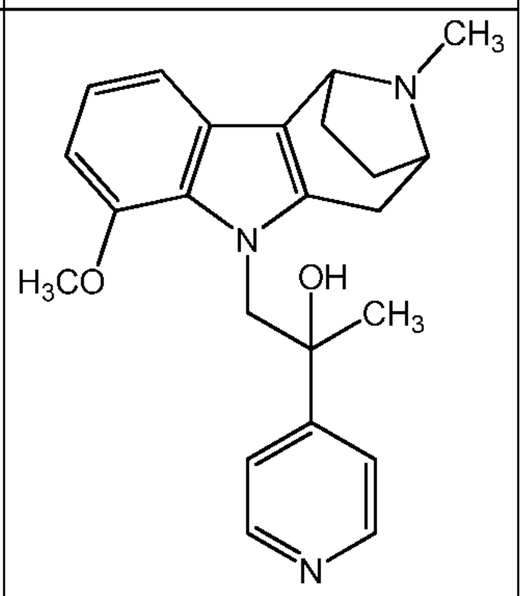
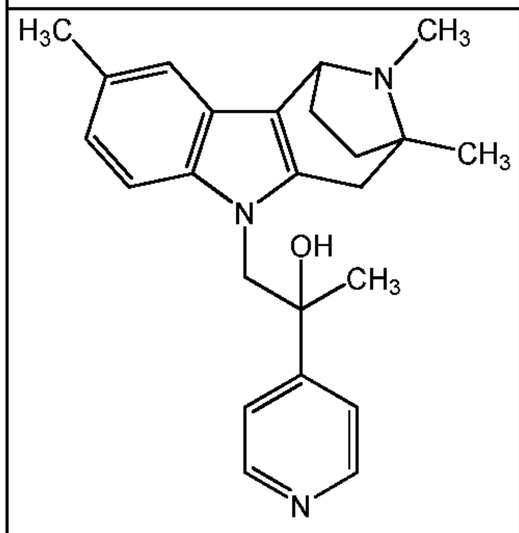
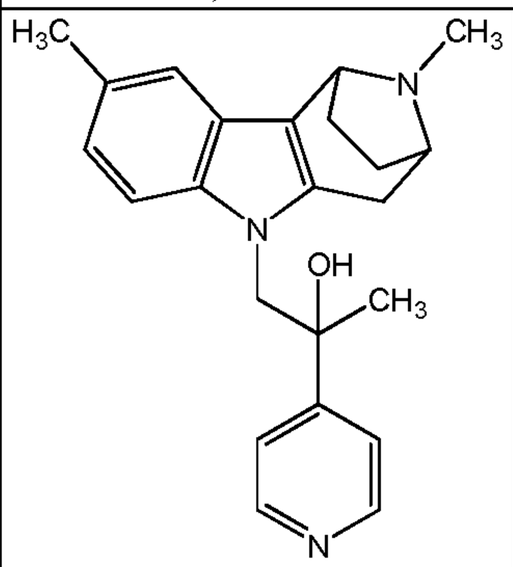
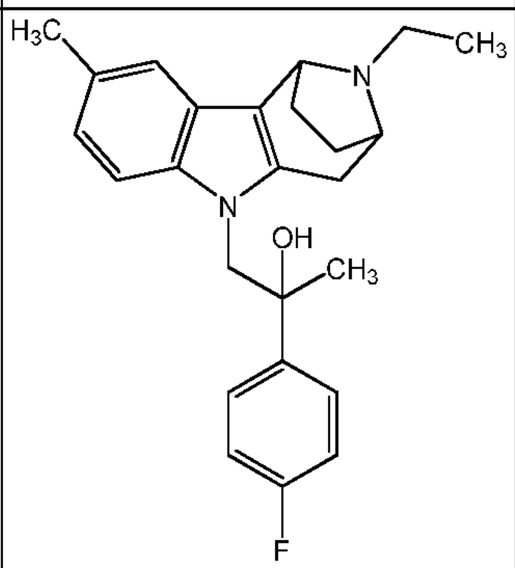
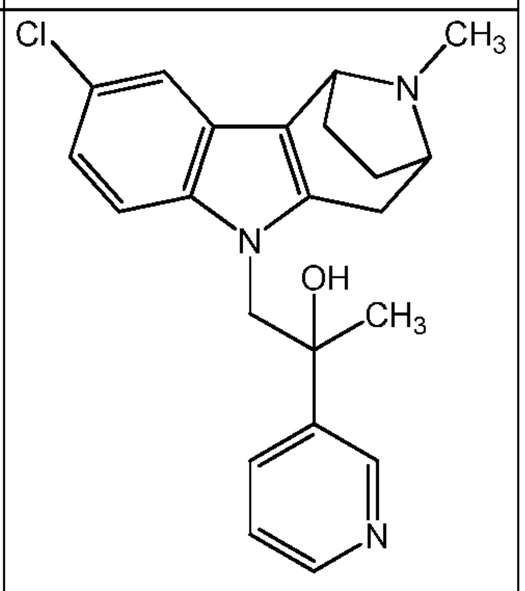
III-95
III-95a, III-95b

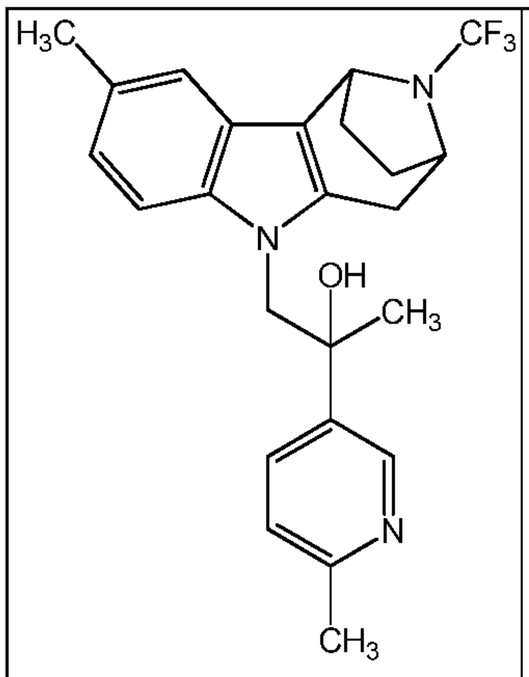
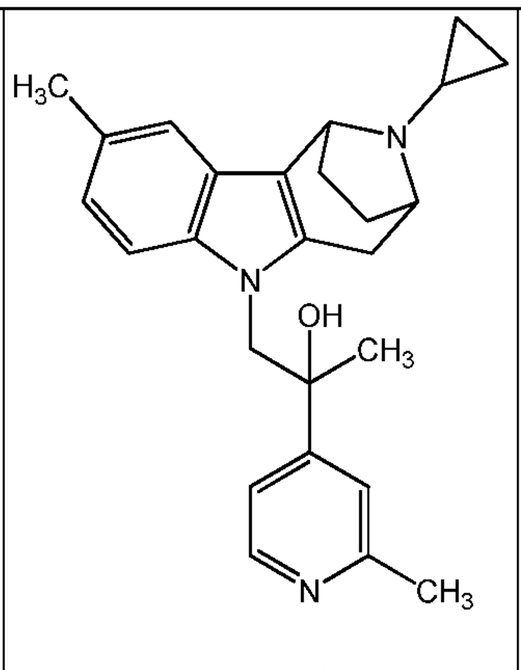
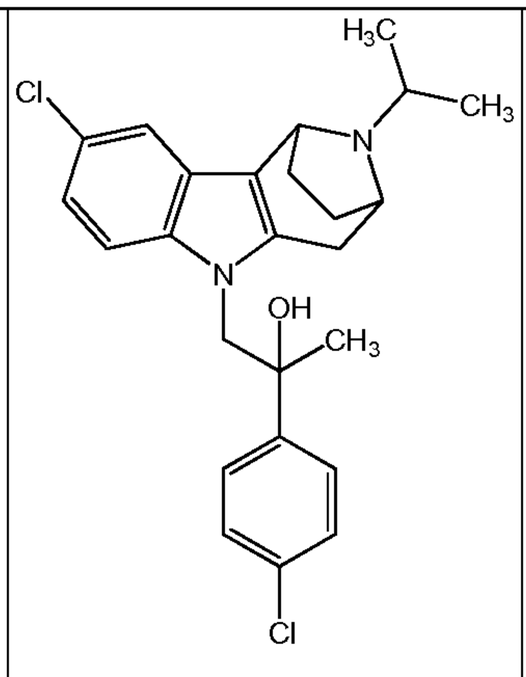
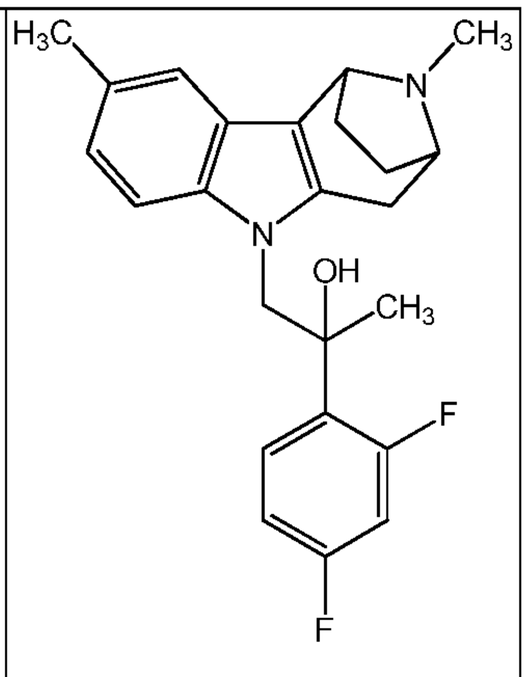
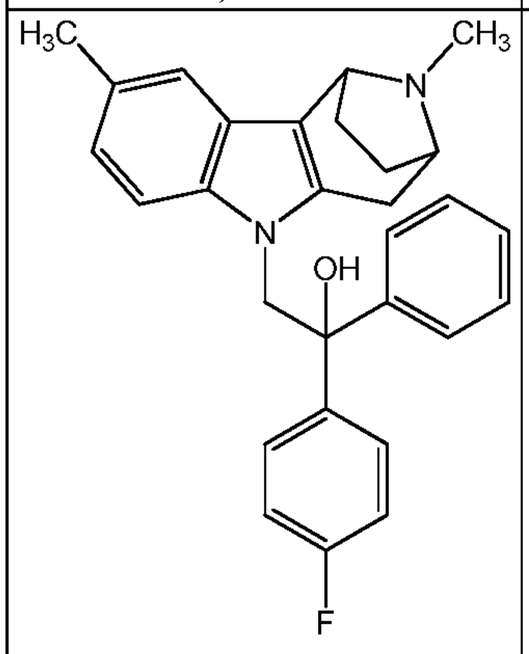
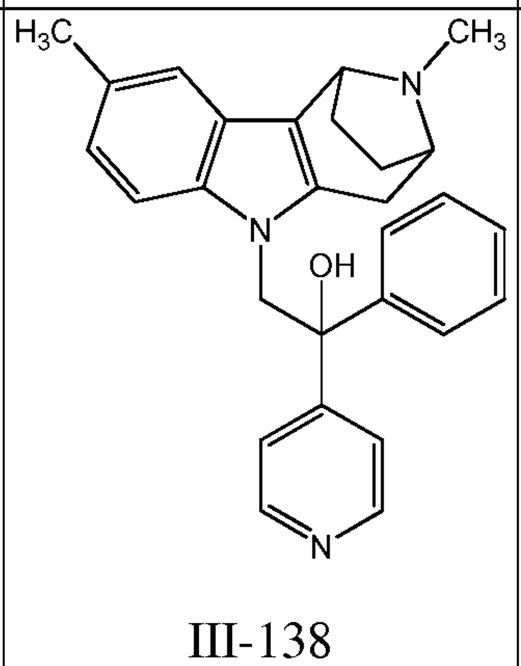
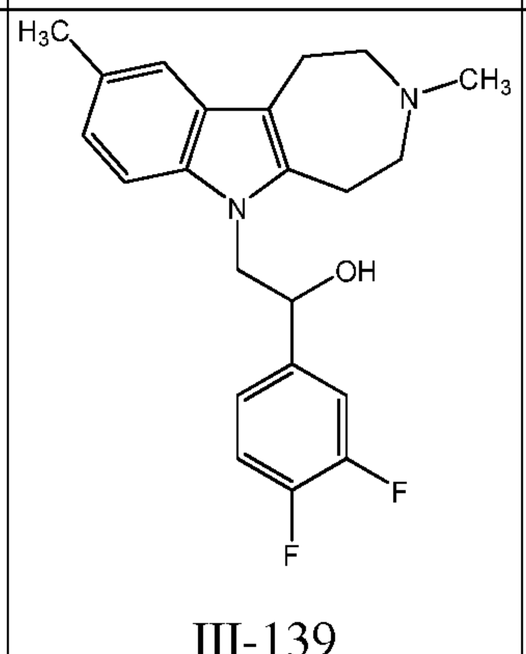
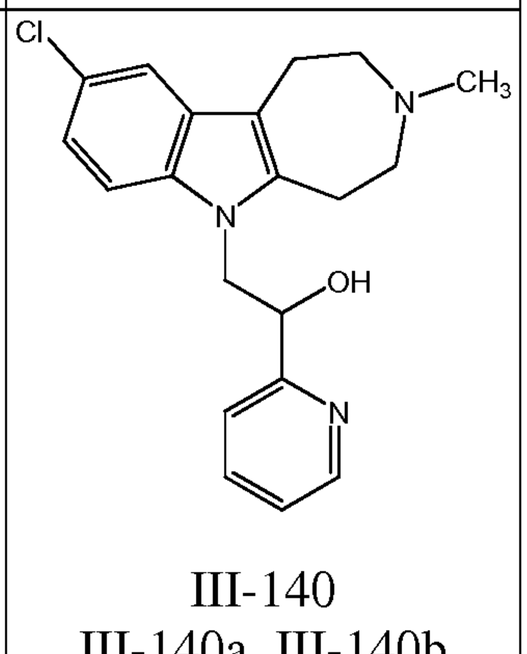
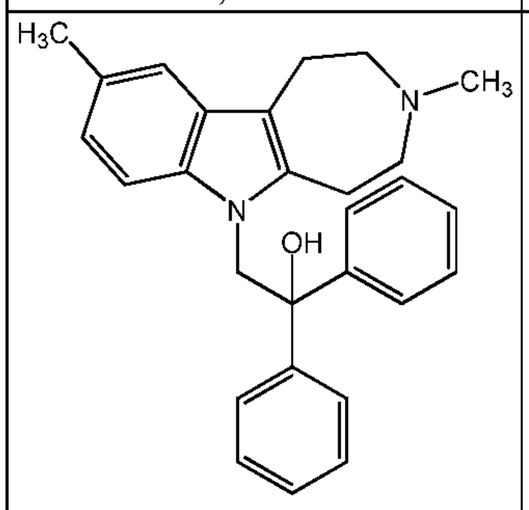
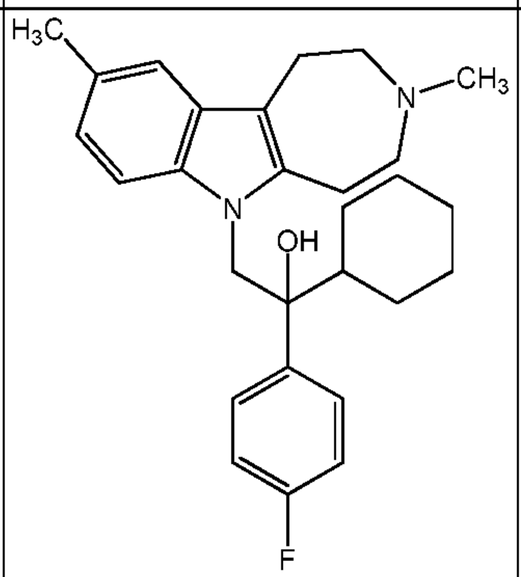
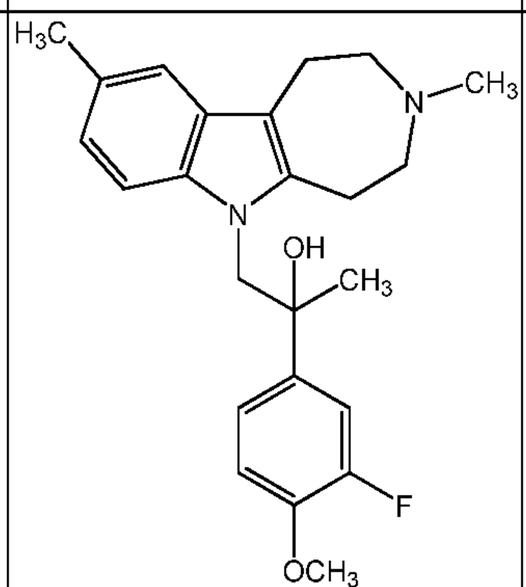
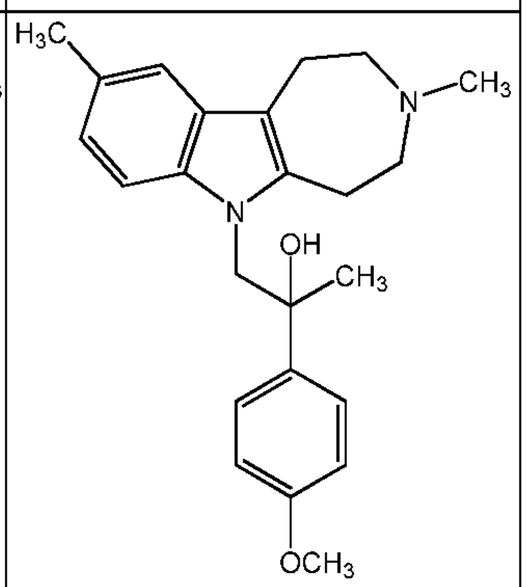


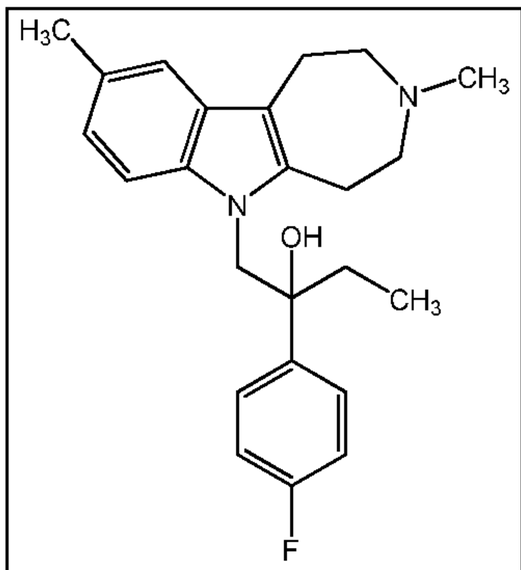
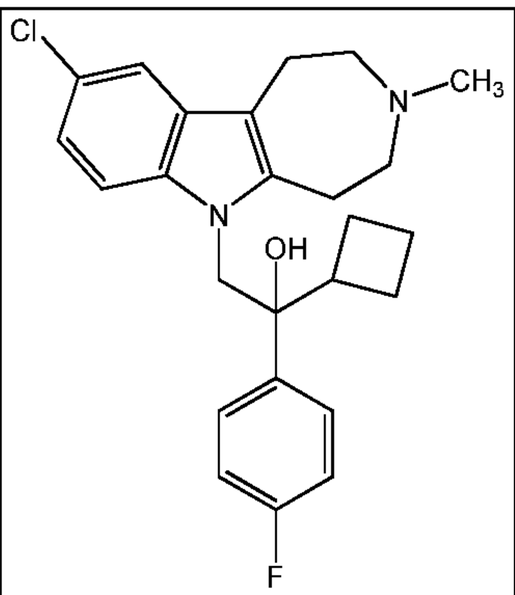
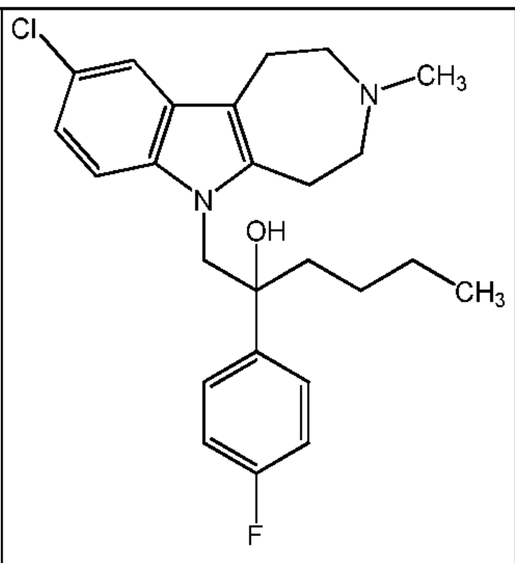
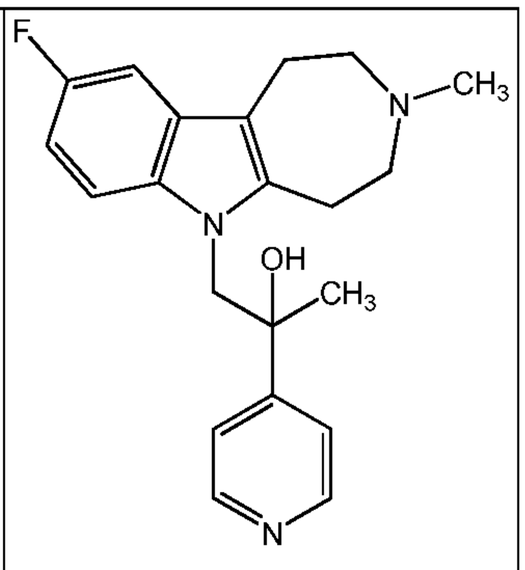
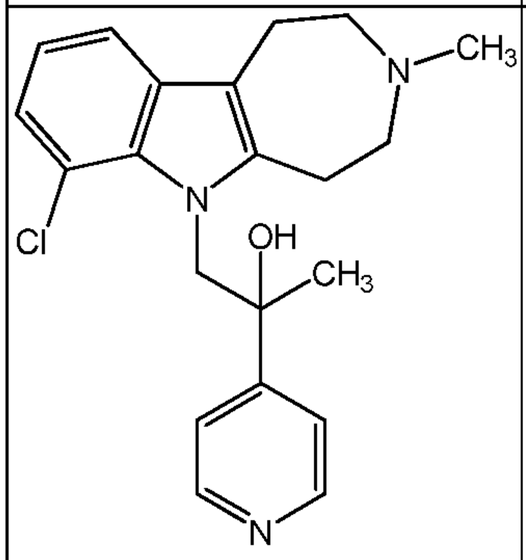
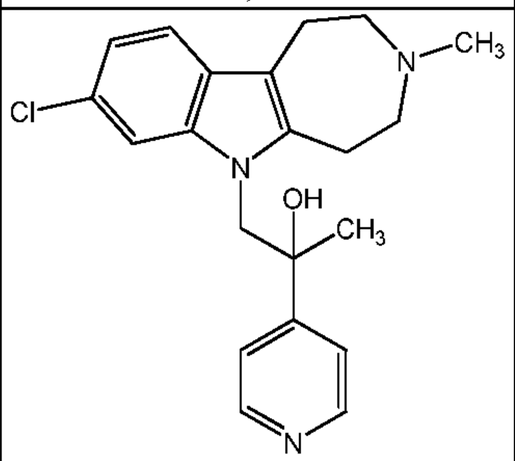
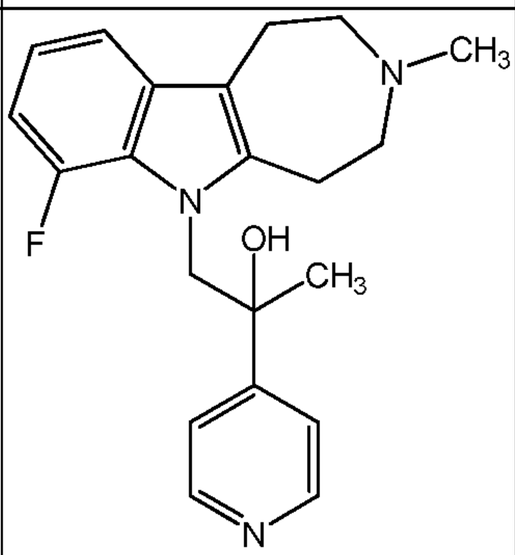
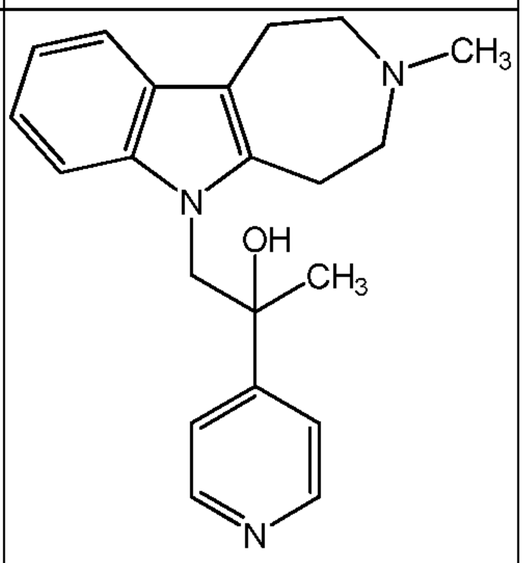
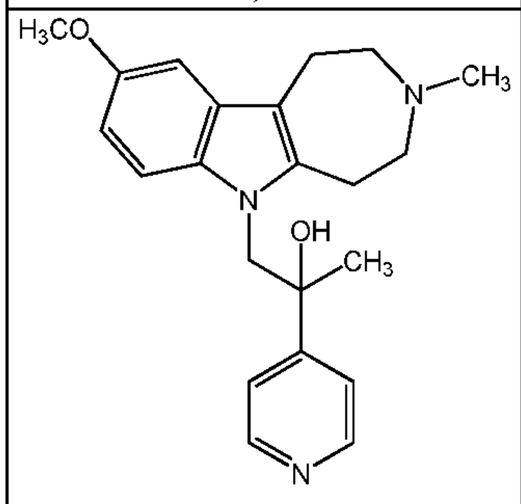
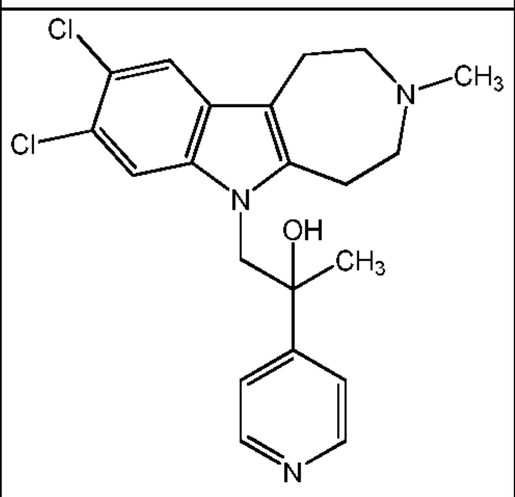
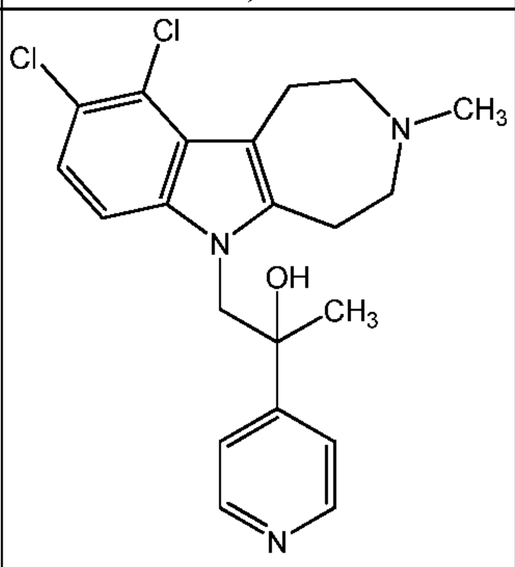
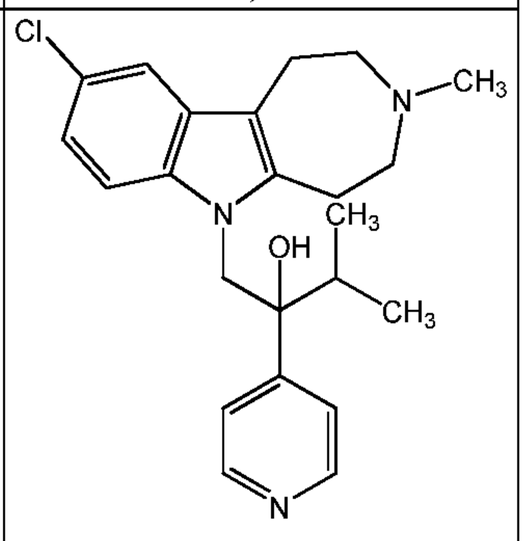
III-96
III-96a, III-96b

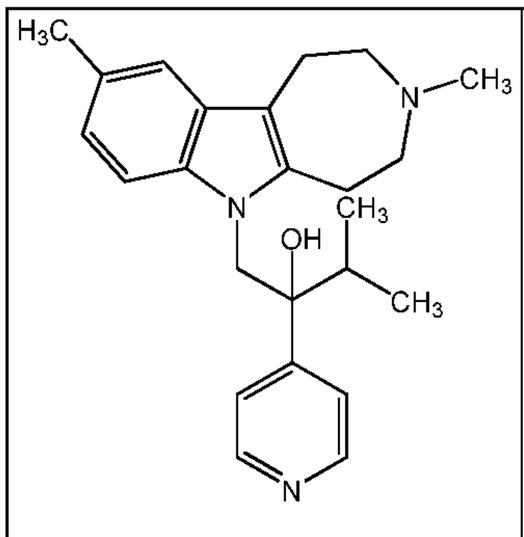
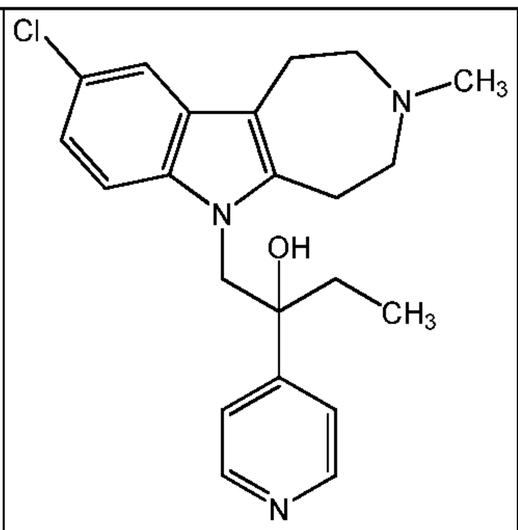
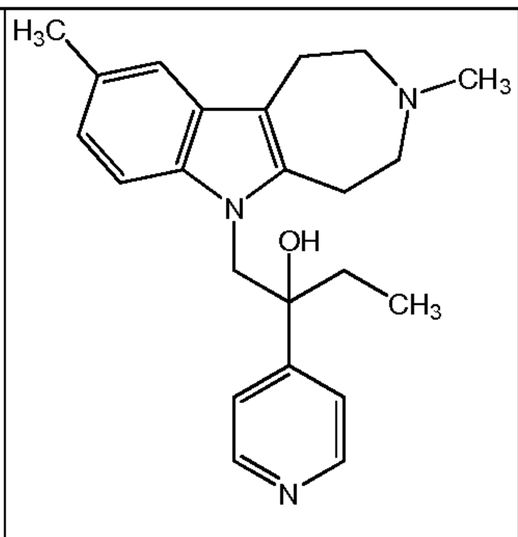
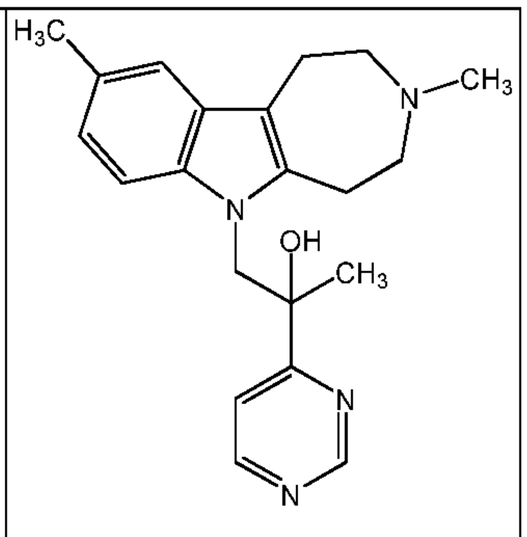
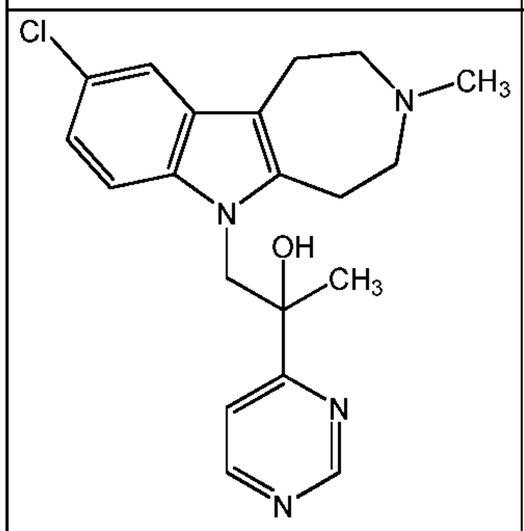
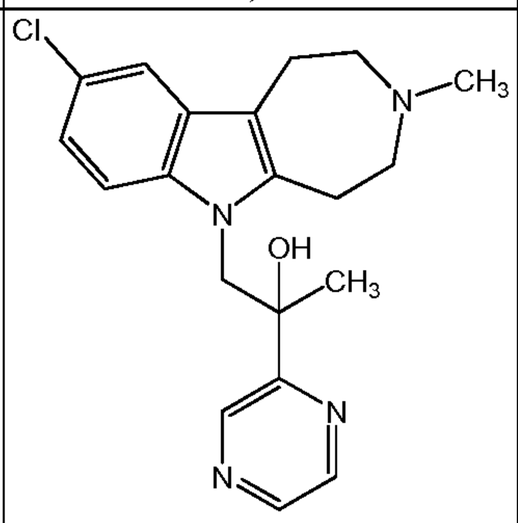
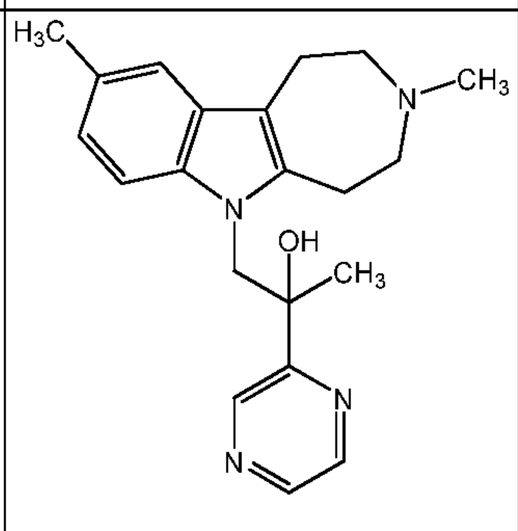
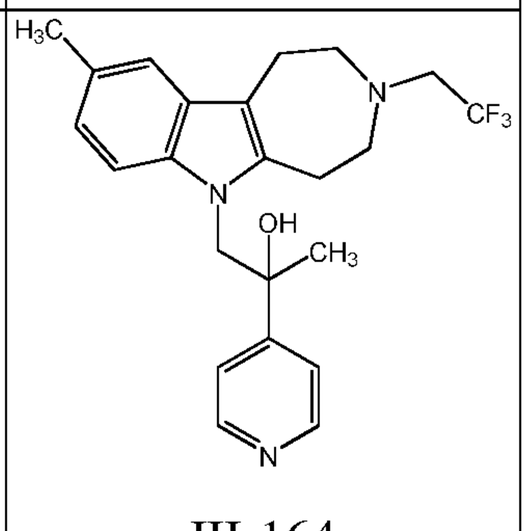
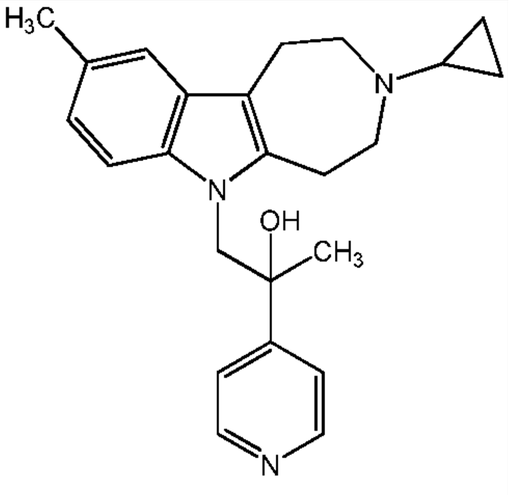
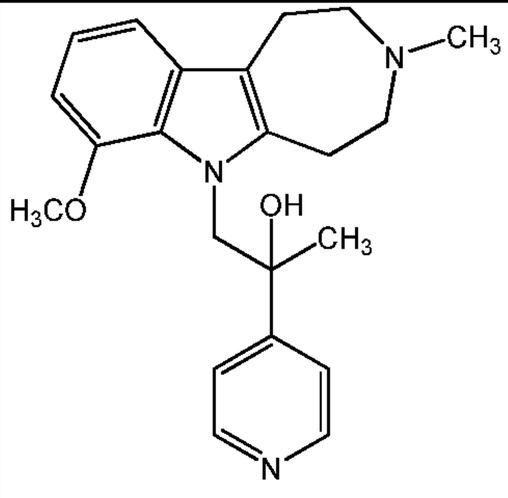
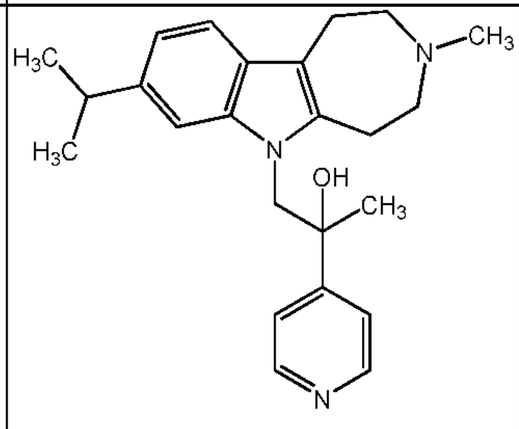
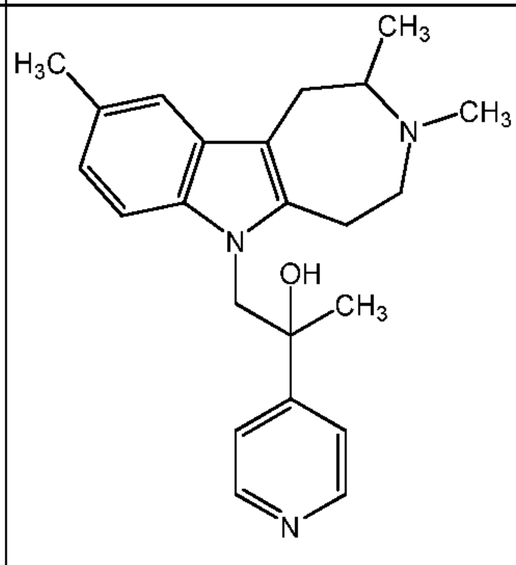
 III-97 III-97a, III-97b	 III-98 III-98a, III-98b	 III-99 III-99a, III-99b, III-99c, III-99d	 III-100 III-100a, III-100b, III-100c, III-100d
 III-101 III-101a, III-101b, III-101c, III-101d	 III-102 III-102a, III-102b, III-102c, III-102d	 III-103 III-103a, III-103b, III-103c, III-103d	 III-104 III-104a, 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

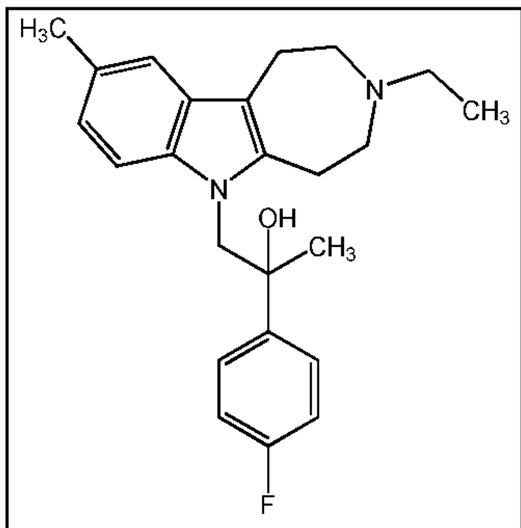
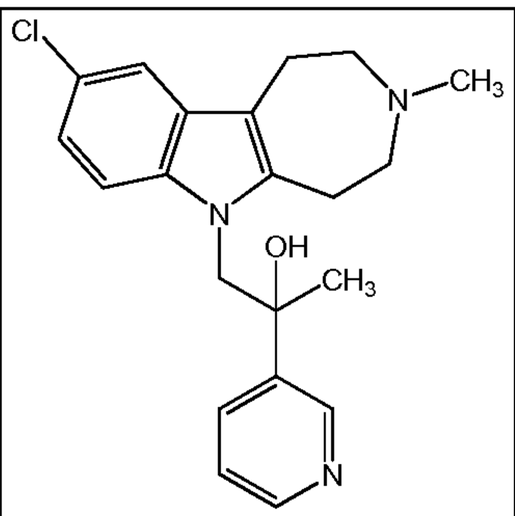
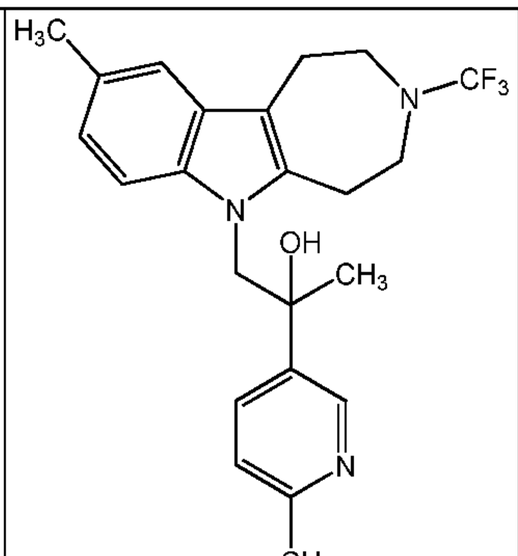
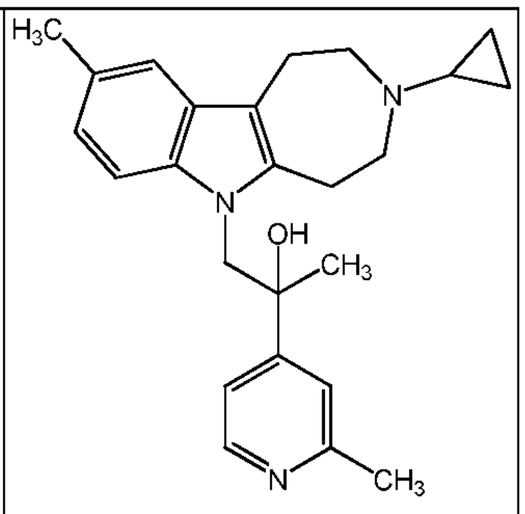
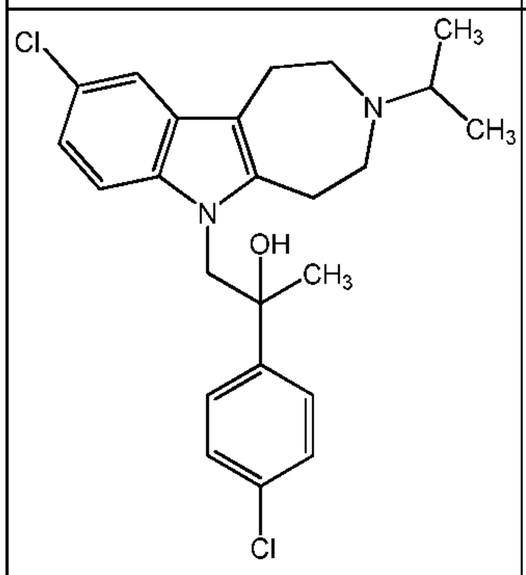
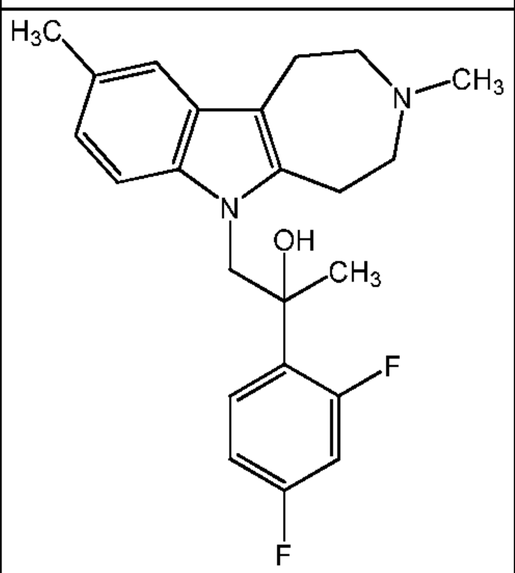
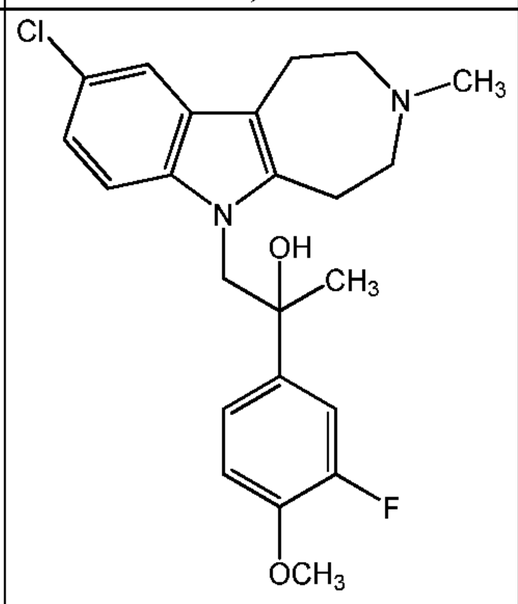
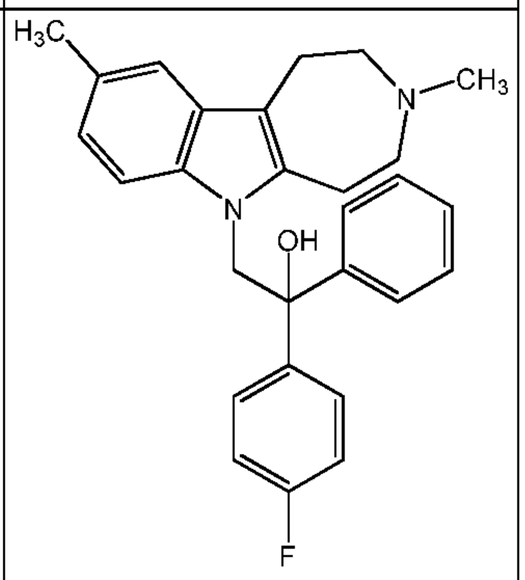
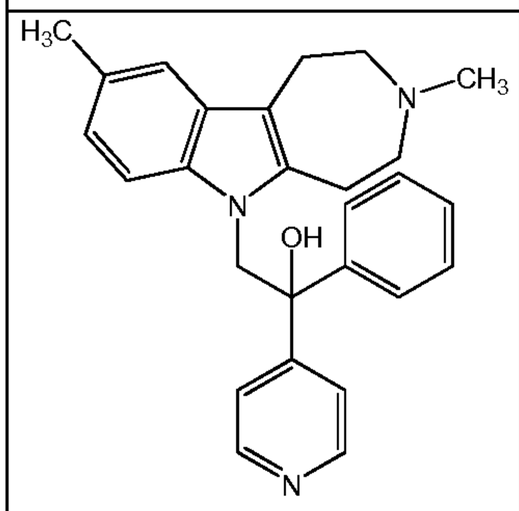
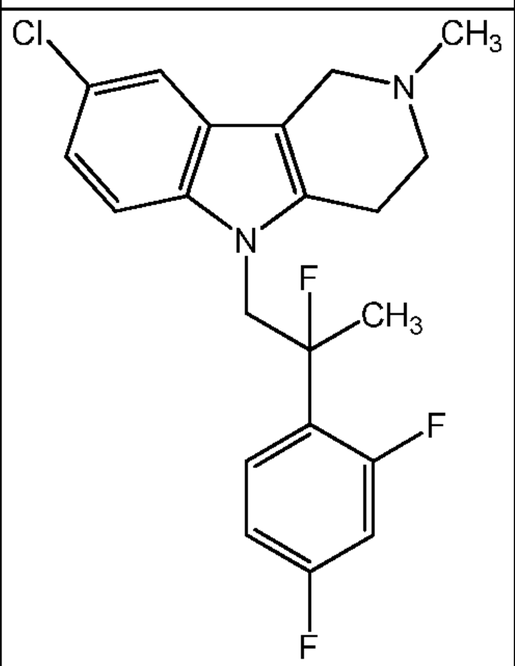
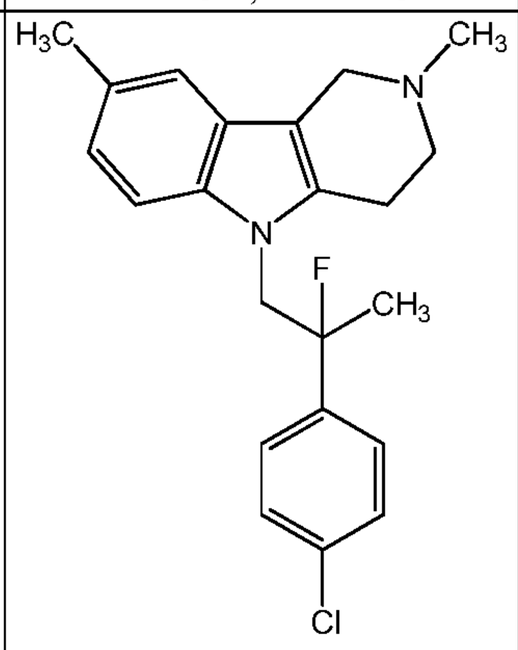
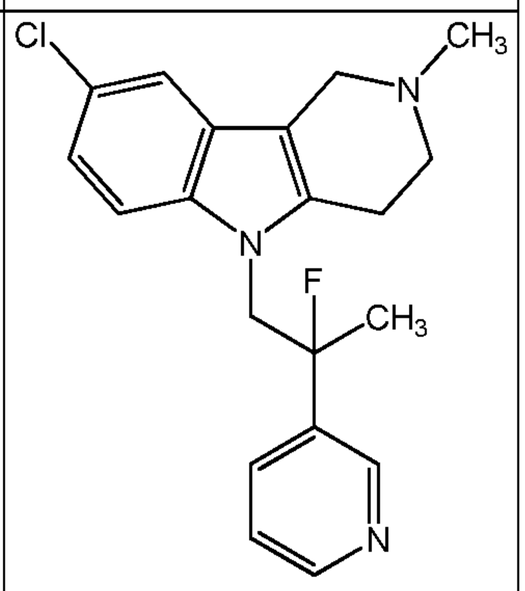
 III-109 III-109a, III-109b, III-109c, III-109d	 III-110 III-110a, III-110b, III-110c, III-110d	 III-111 III-111a, III-111b, III-111c, III-111d	 III-112 III-112a, III-112b, III-112c, III-112d
 III-113 III-113a, III-113b, III-113c, III-113d	 III-114 III-114a, III-114b, III-114c, III-114d	 III-115 III-115a, 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

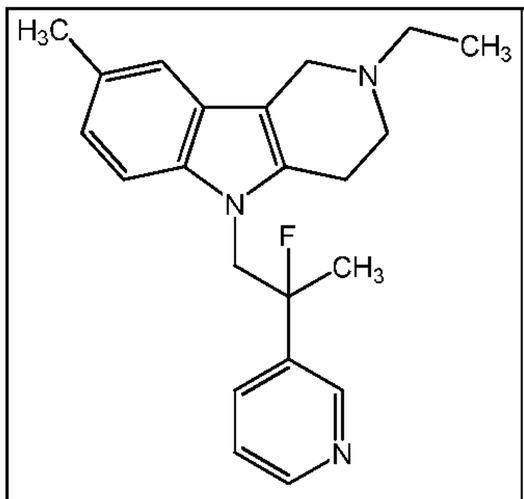
 III-121 III-121a, III-121b, III-121c, III-121d	 III-122 III-122a, III-122b, III-122c, III-122d	 III-123 III-123a, III-123b, III-123c, III-123d	 III-124 III-124a, III-124b, III-124c, III-124d
 III-125 III-125a, III-125b, III-125c, III-125d	 III-126 III-126a, III-126b, III-126c, III-126d	 III-127 III-127a, 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

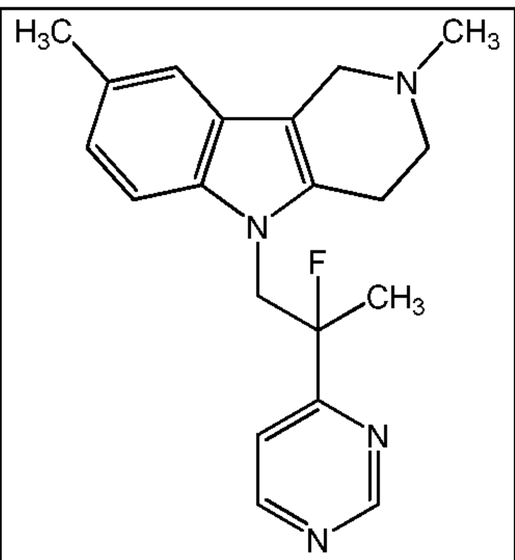
 III-145 III-145a, III-145b	 III-146 III-146a, III-146b	 III-147 III-147a, III-147b	 III-148 III-148a, III-148b
 III-149 III-149a, III-149b	 III-150 III-150a, III-150b	 III-151 III-151a, III-151b	 III-152 III-152a, III-152b
 III-153 III-153a, III-153b	 III-154 III-154a, III-154b	 III-155 III-155a, III-155b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

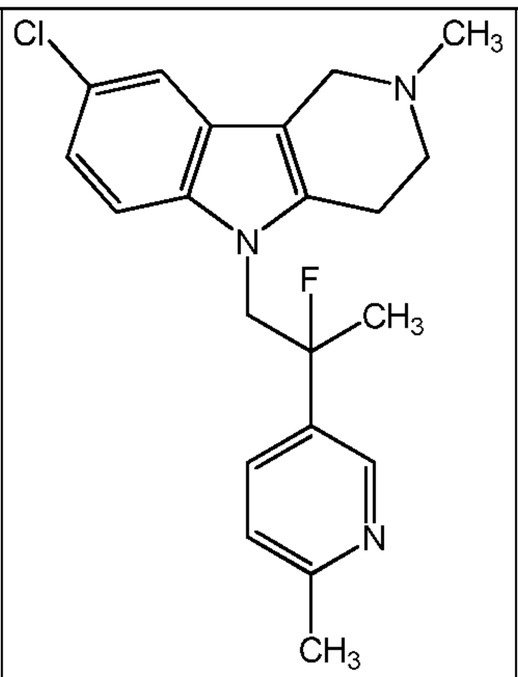
 III-169 III-169a, III-169b	 III-170 III-170a, III-170b	 III-171 III-171a, III-171b	 III-172 III-172a, III-172b
 III-173 III-173a, III-173b	 III-174 III-174a, III-174b	 III-175 III-175a, III-175b	 III-176 III-176a, III-176b
 III-177 III-177a, III-177b	 III-178 III-178a, III-178b	 III-179 III-179a, III-179b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



III-181
III-181a, III-181b



III-182
III-182a, III-182b



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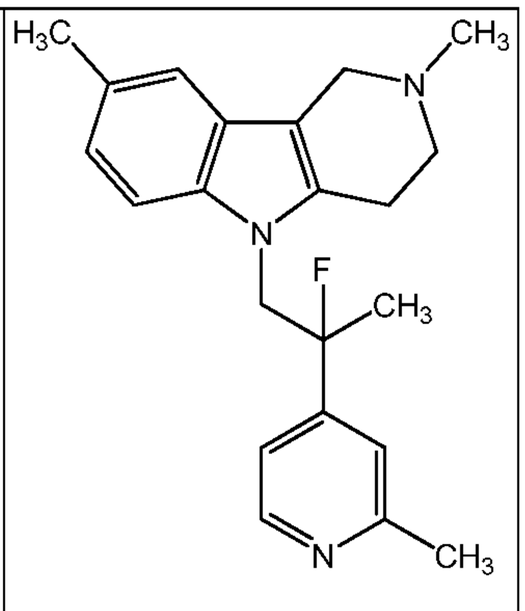
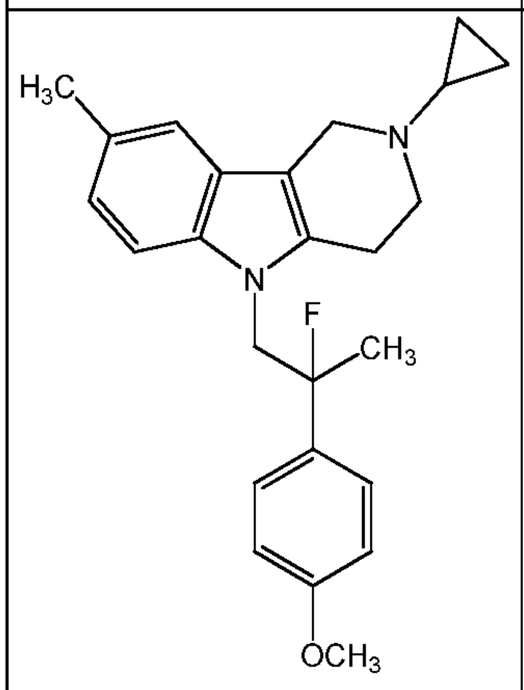
III-183a, III-183b



III-184
III-184a, III-184b



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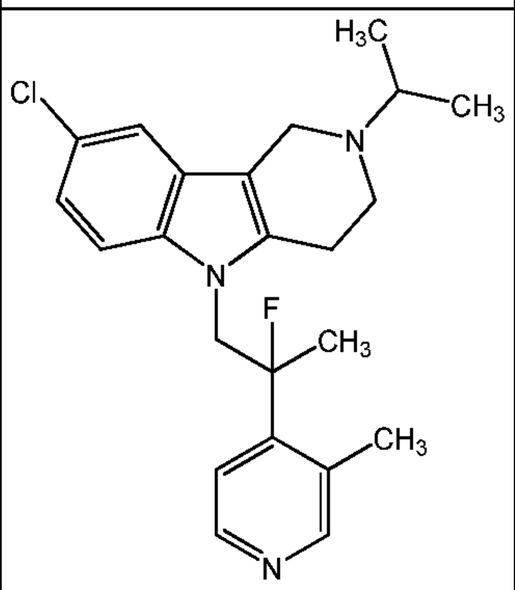
III-185a, III-185b



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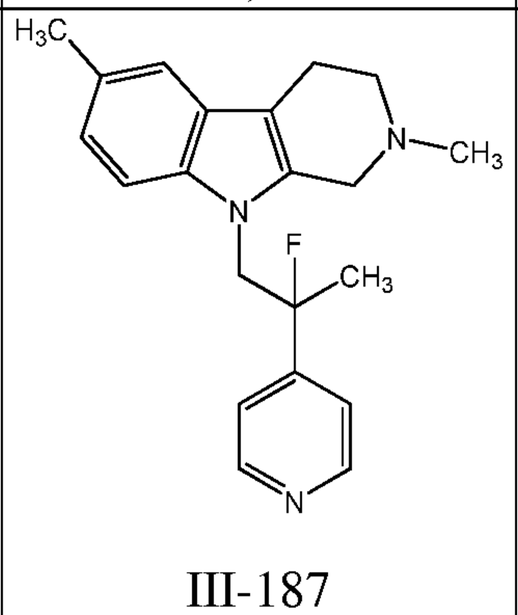
III-186a, III-186b



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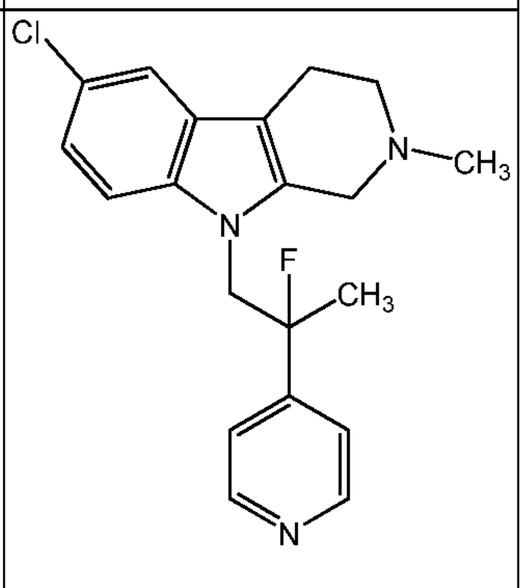
III-187a, III-187b



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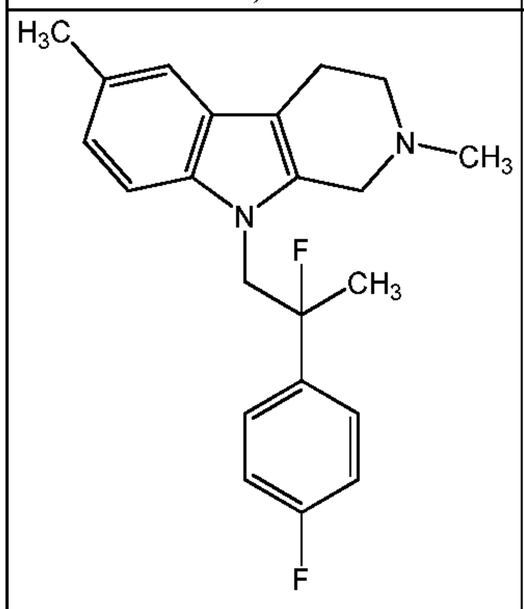
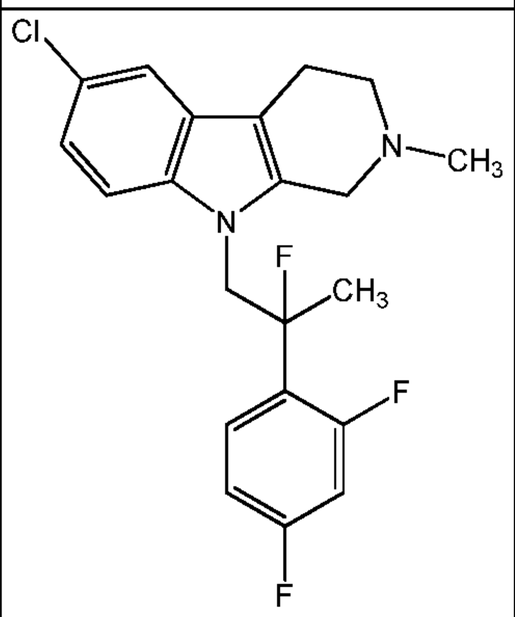
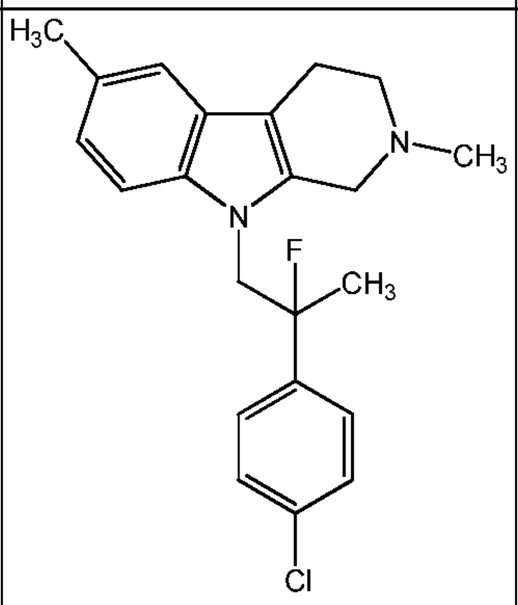
III-188a, III-188b



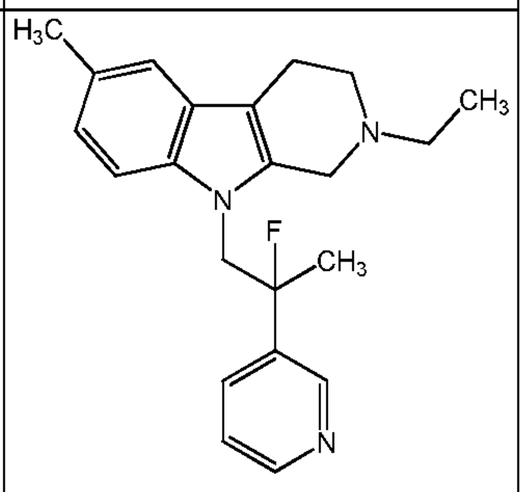
III-189
III-189a, III-189b



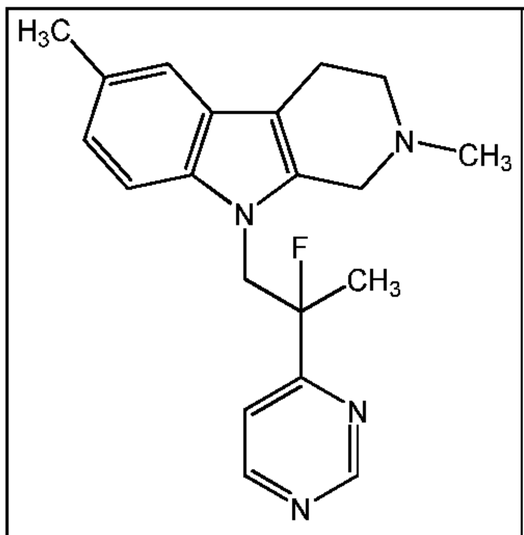
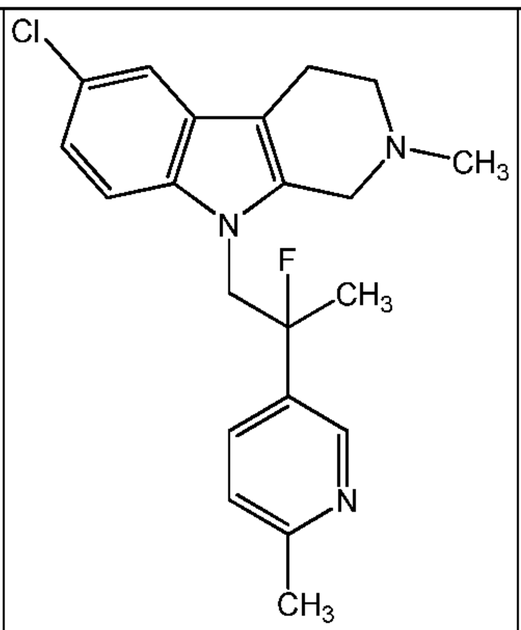
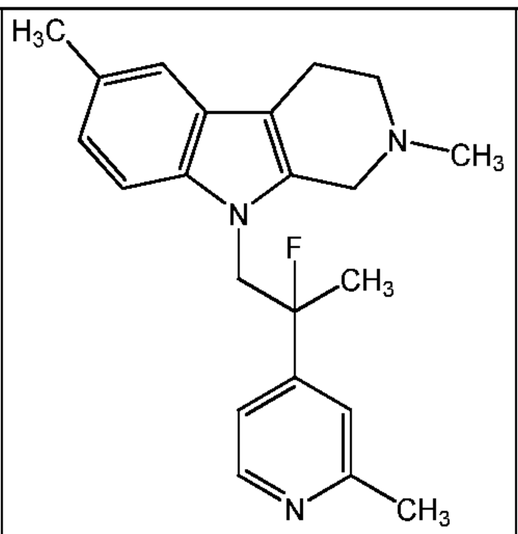
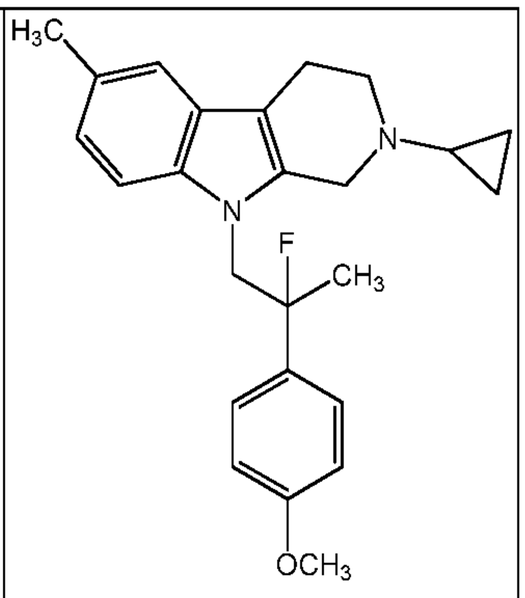
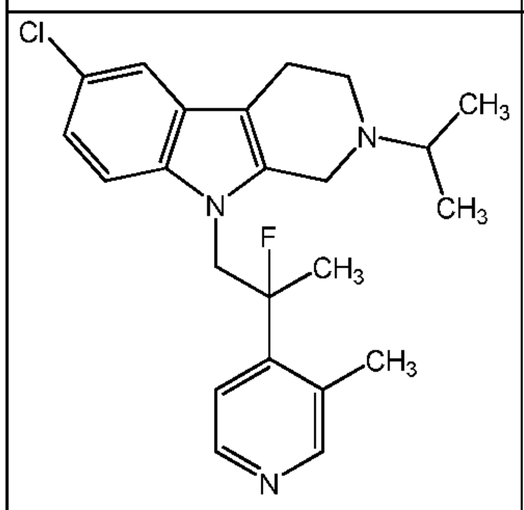
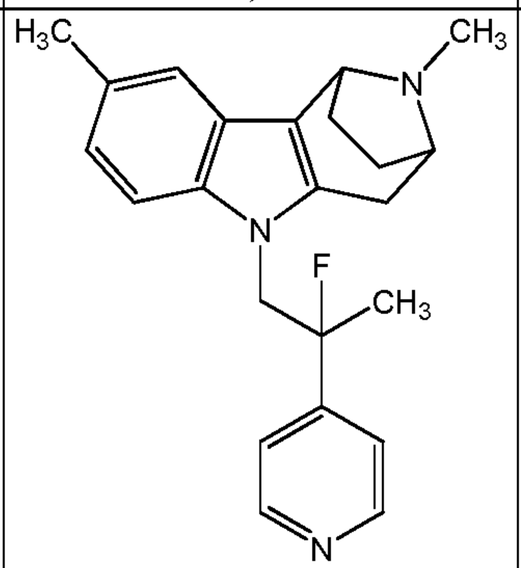
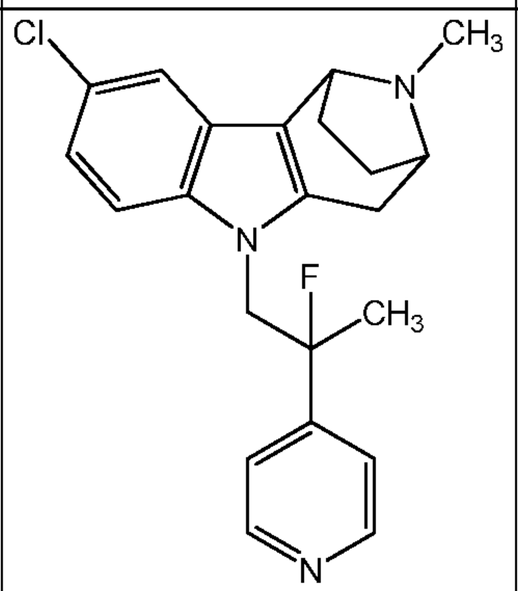
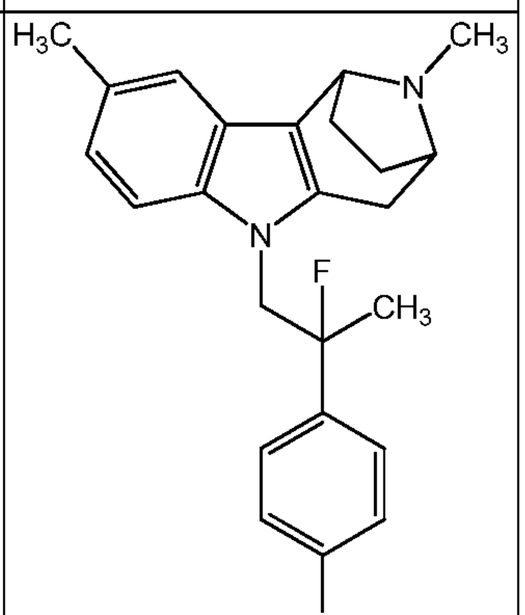
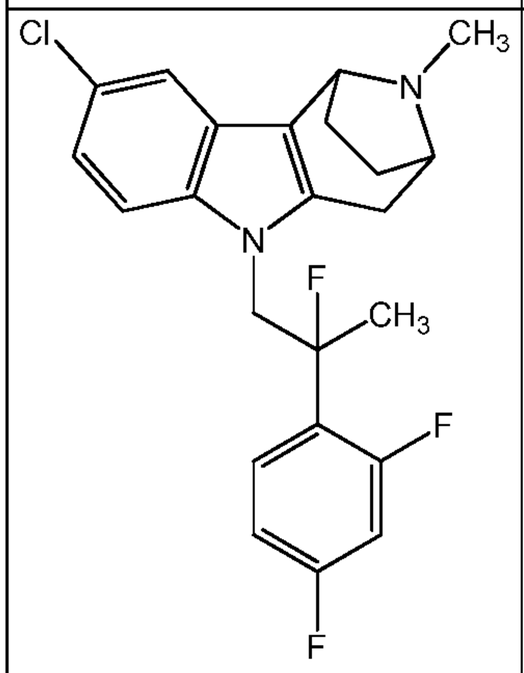
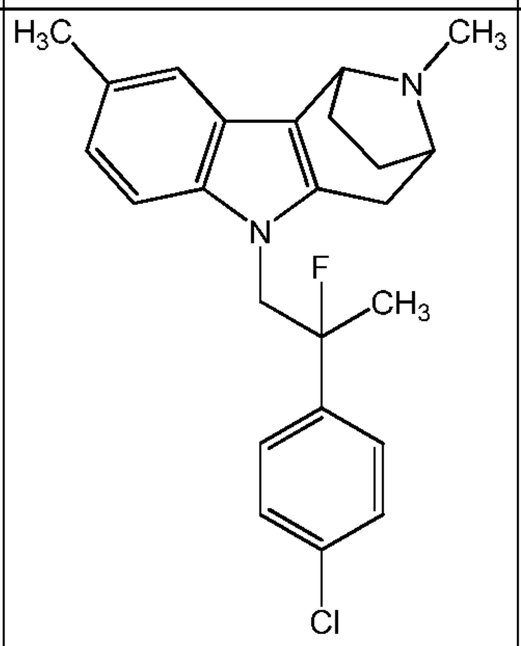
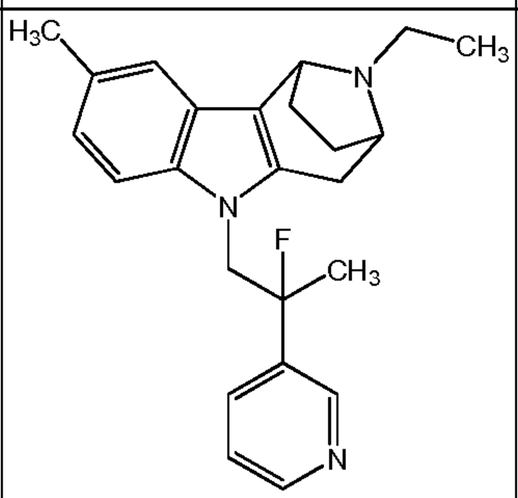
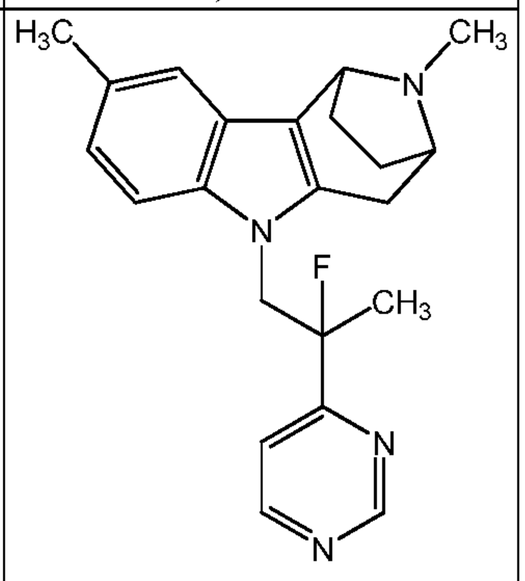
III-190
III-190a, III-190b

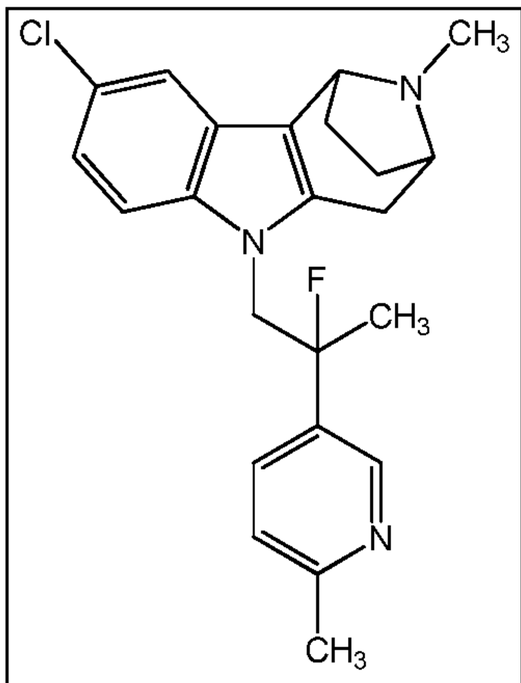


III-191
III-191a, III-191b



III-192
III-192a, III-192b

 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



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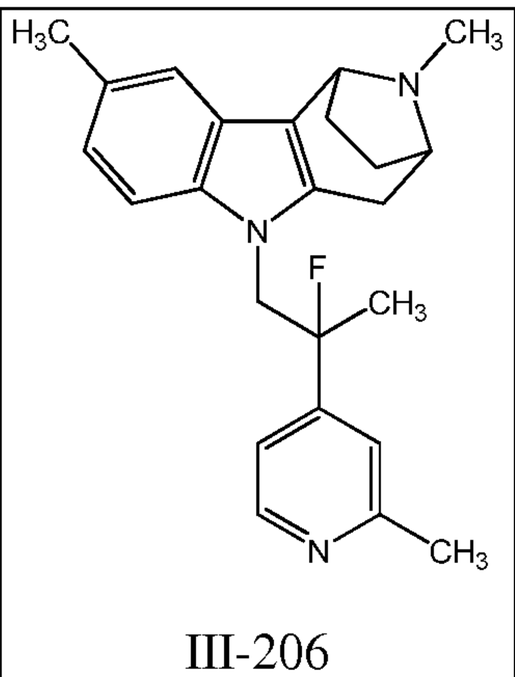
III-205a, III-205b, III-205c, III-205d



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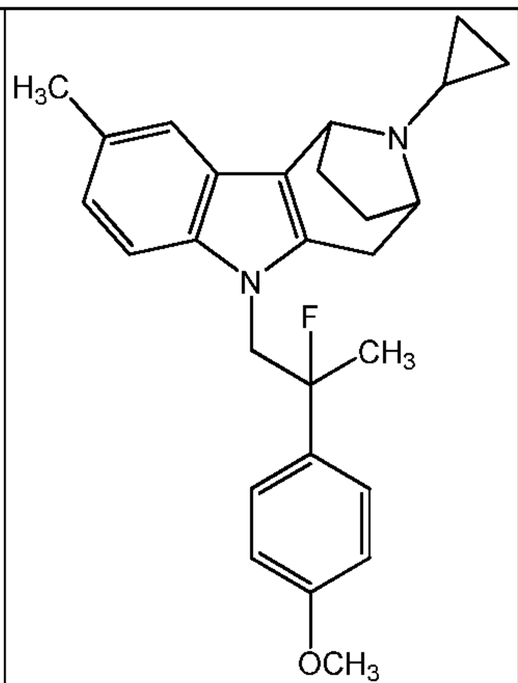
III-206a, III-206b, III-206c, III-206d



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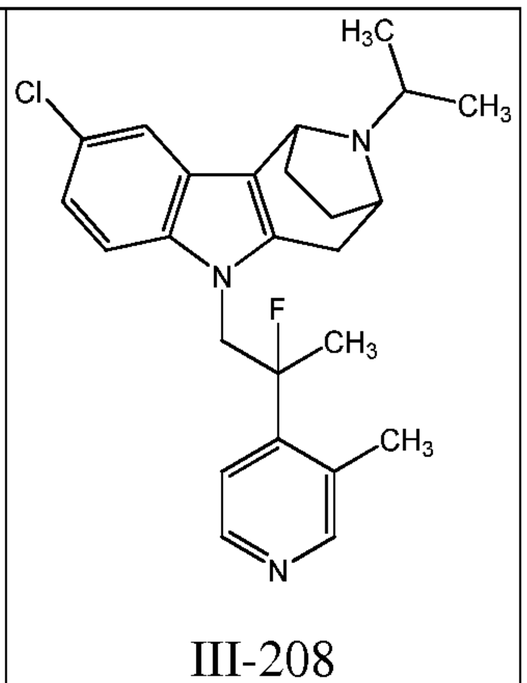
III-207a, III-207b, III-207c, III-207d



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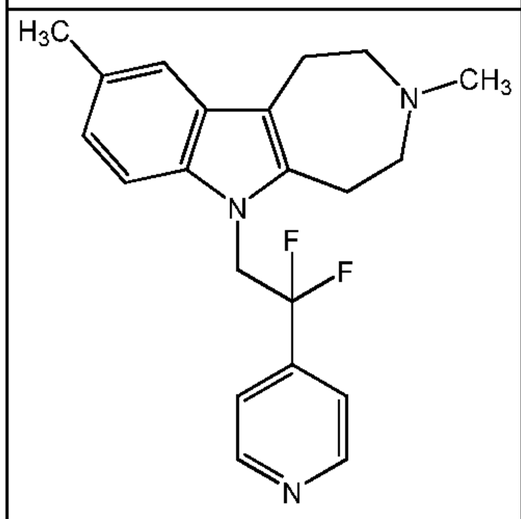
III-208a, III-208b, III-208c, III-208d



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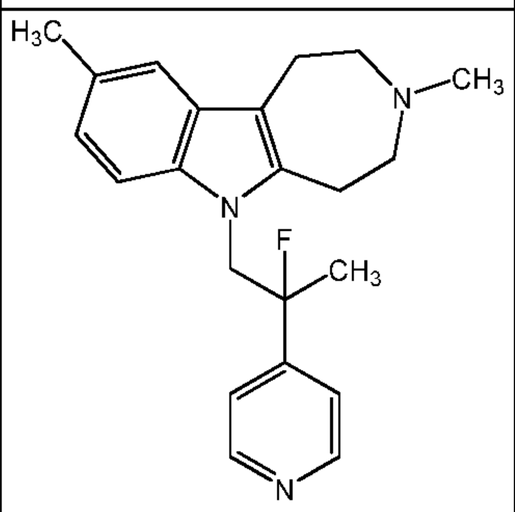

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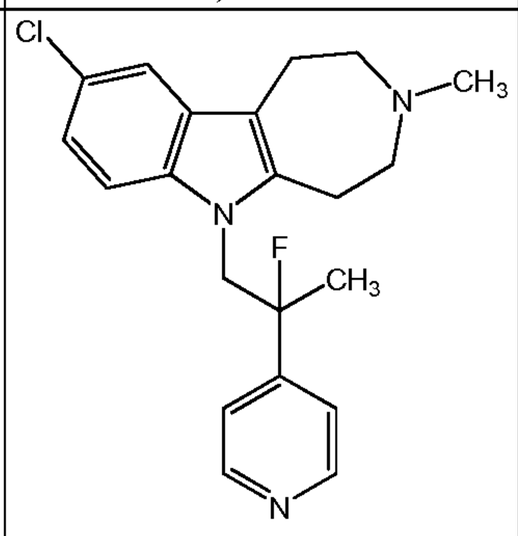
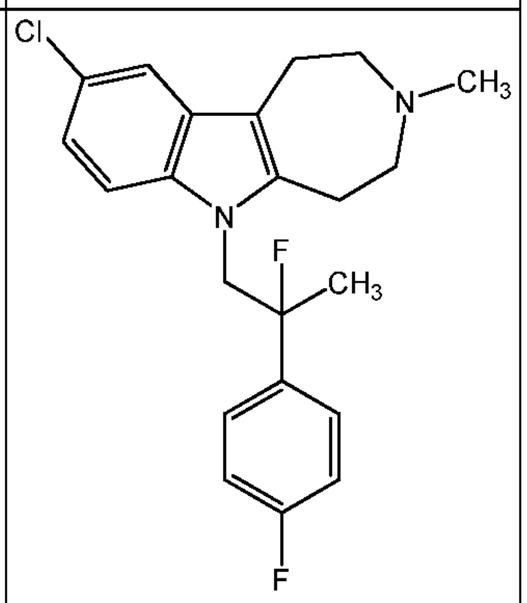
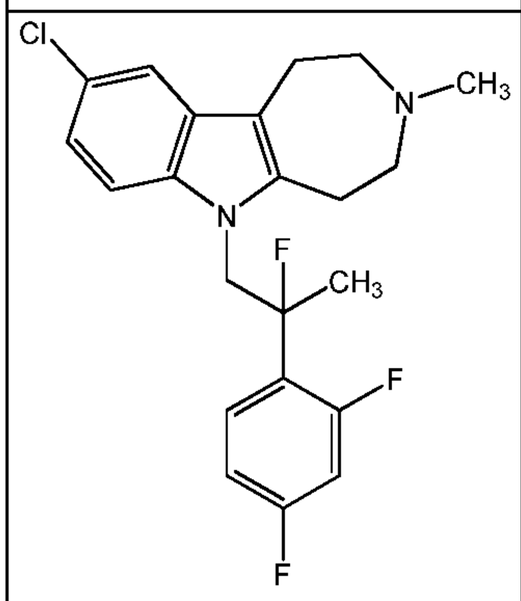
III-210a, III-210b



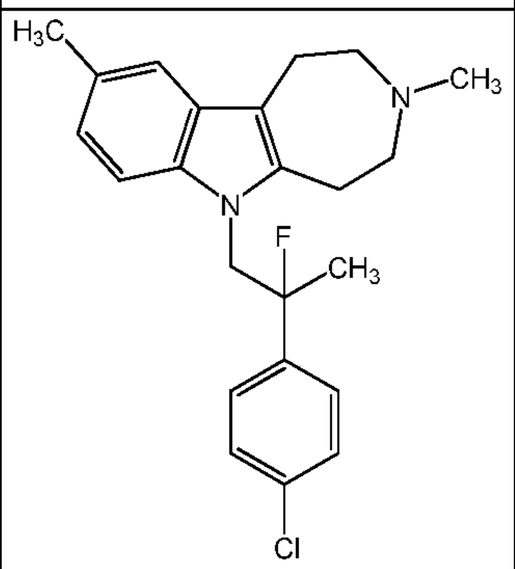
III-211
III-211a, III-211b



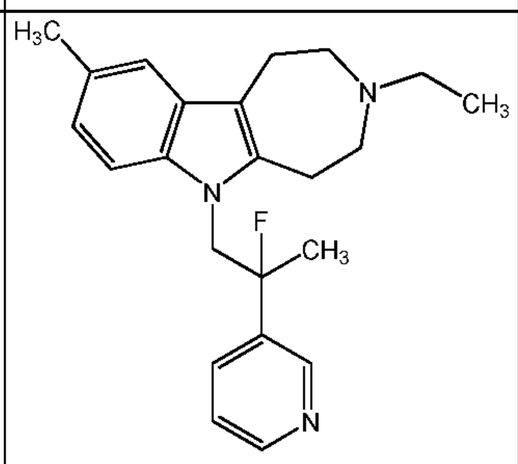
III-212
III-212a, III-212b



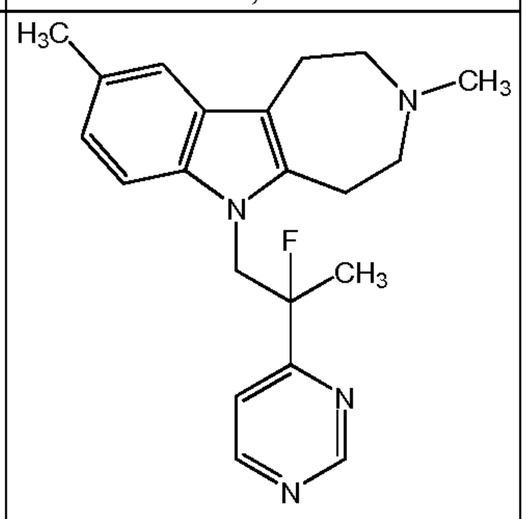
III-213
III-213a, III-213b



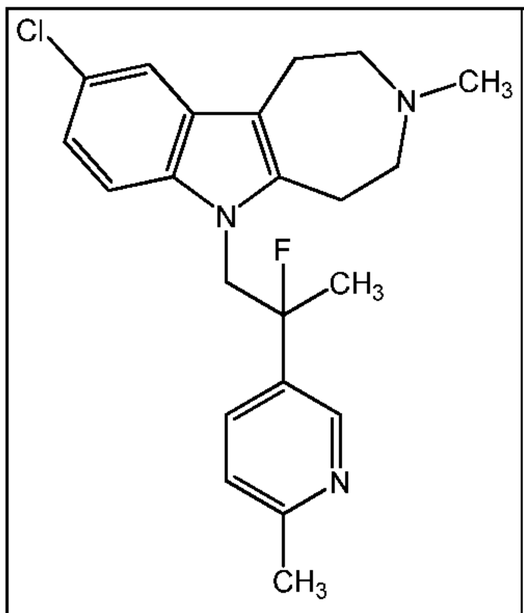
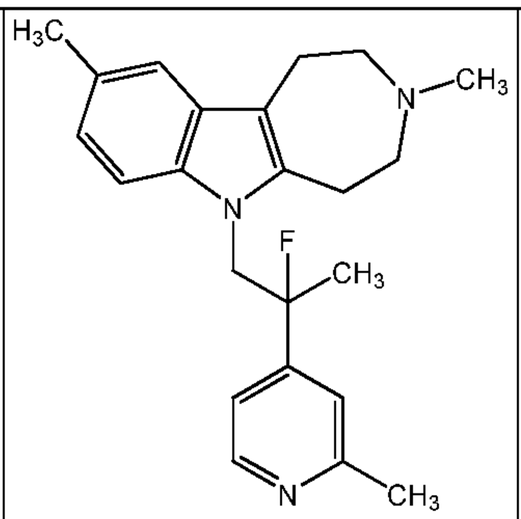
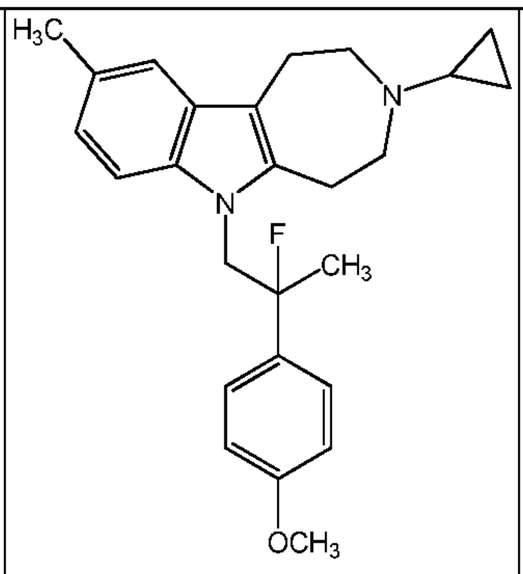
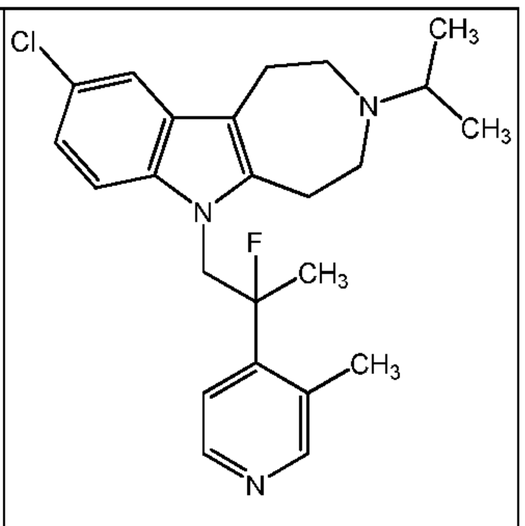
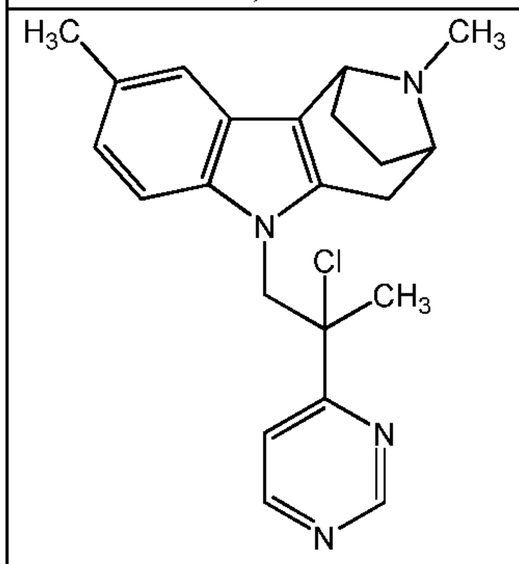
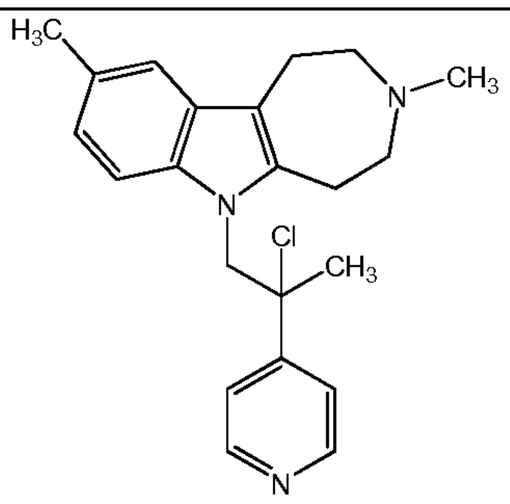
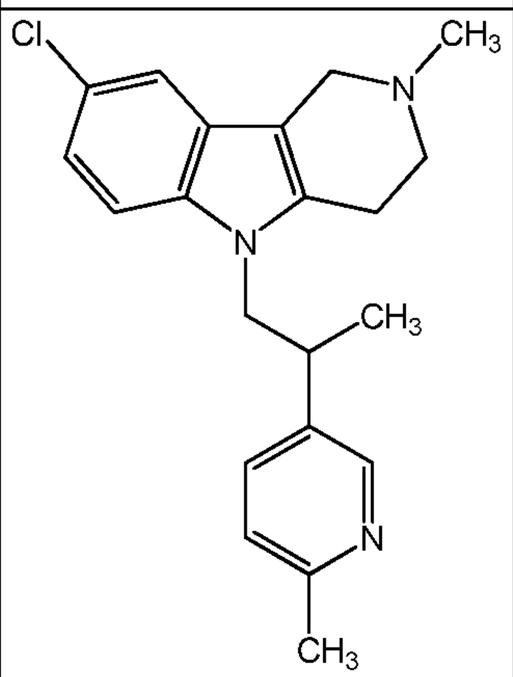
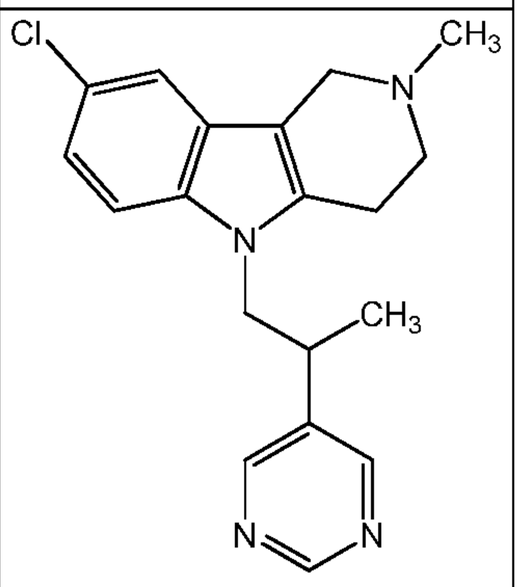
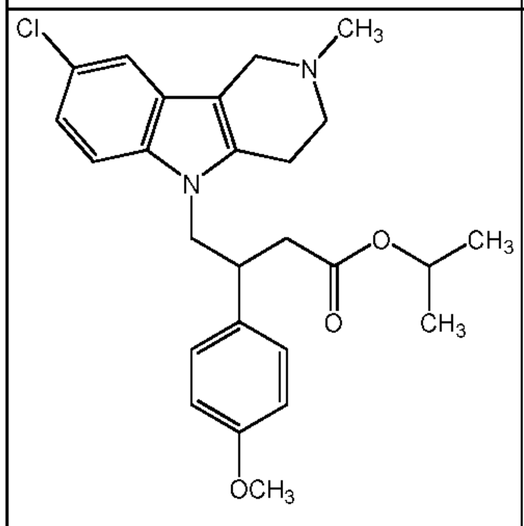
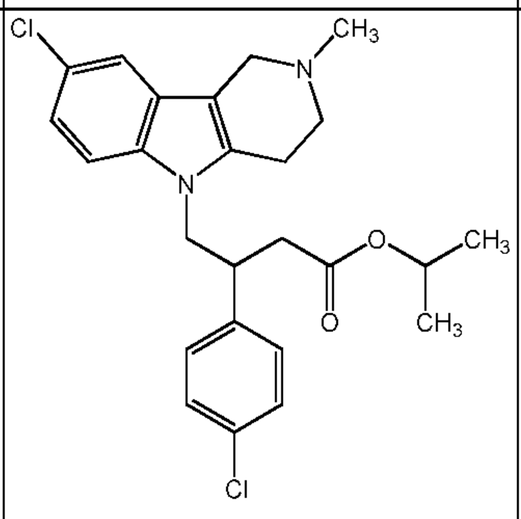
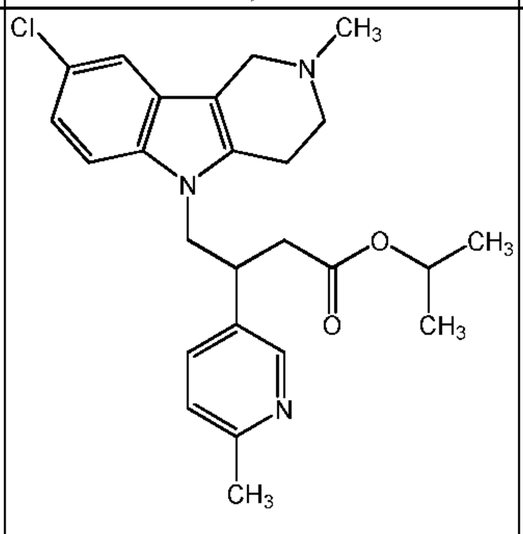
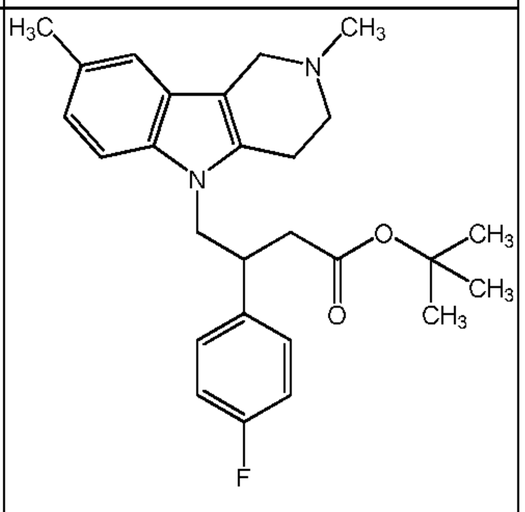
III-214
III-214a, III-214b

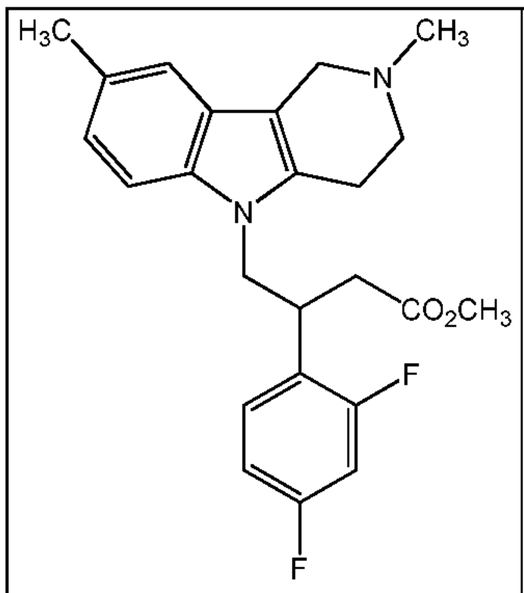


III-215
III-215a, III-215b



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



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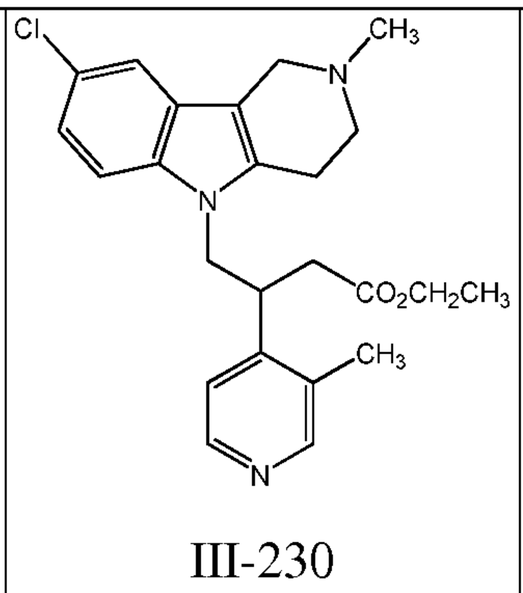
III-229a, III-229b



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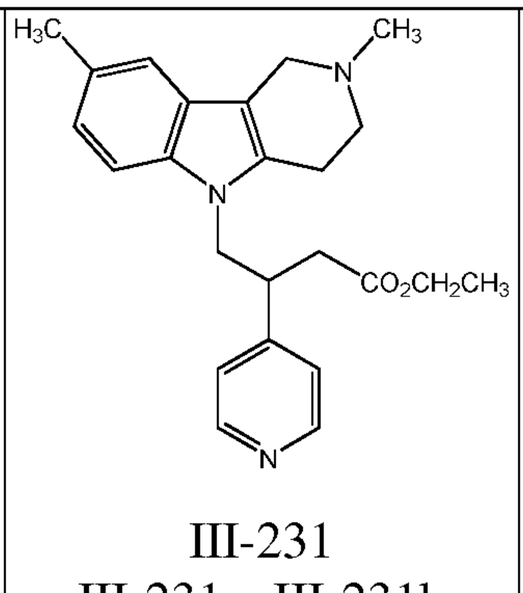

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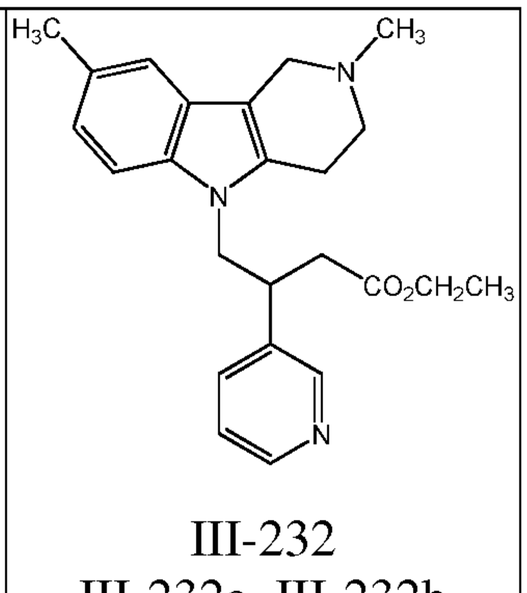

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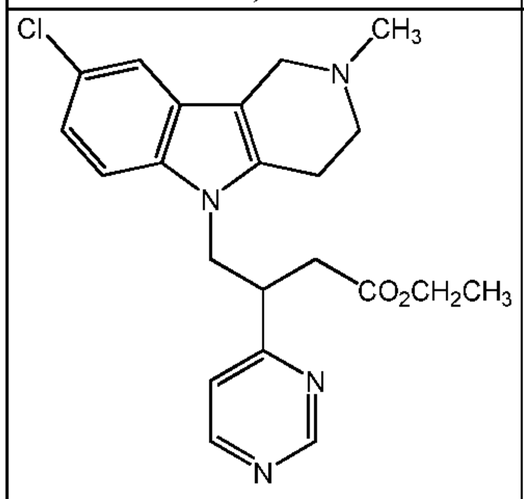

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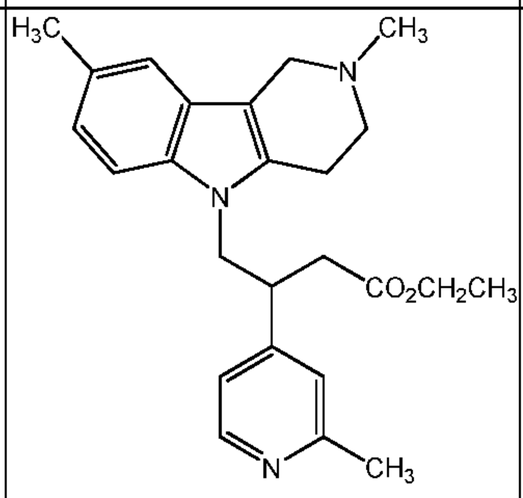
III-233a, III-233b



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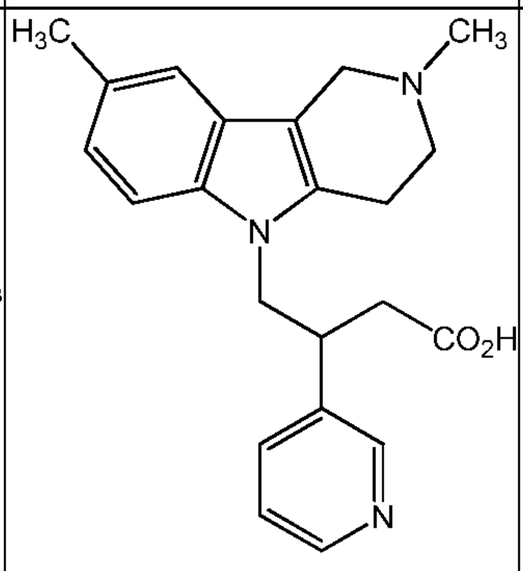

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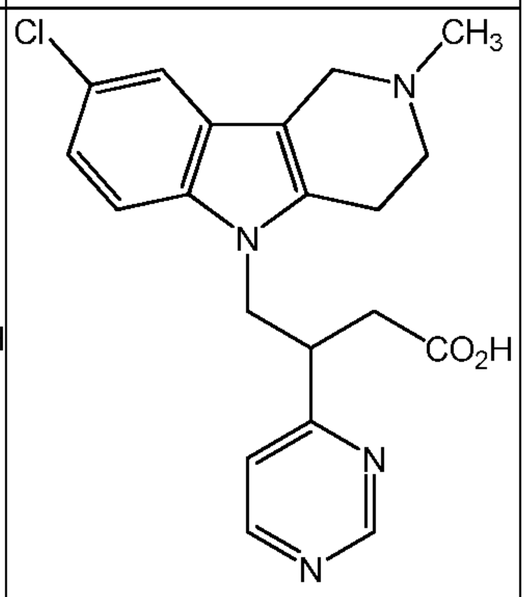

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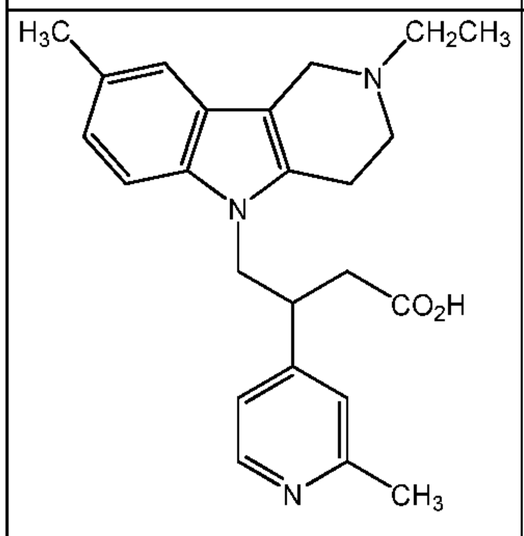
III-236a, III-236b



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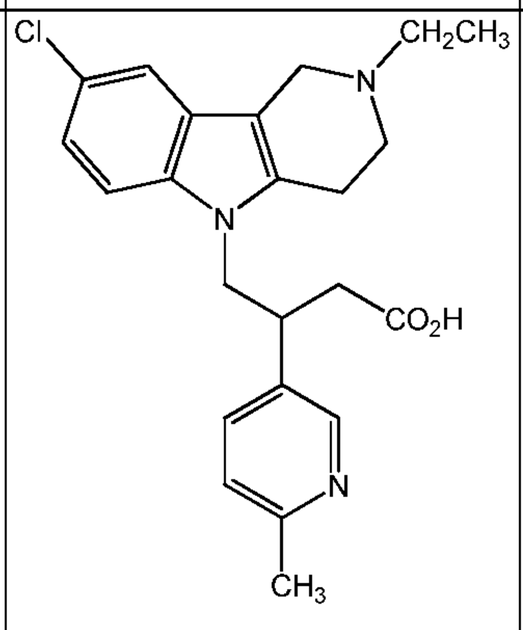

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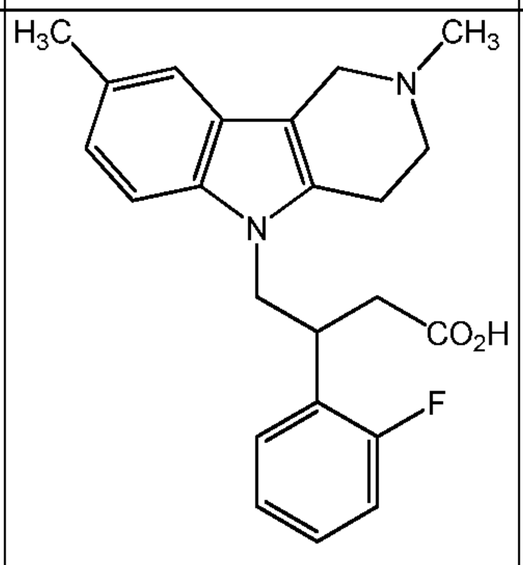

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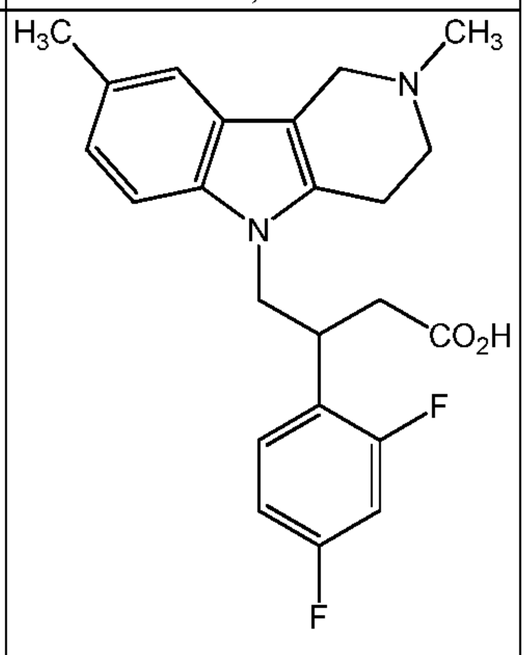

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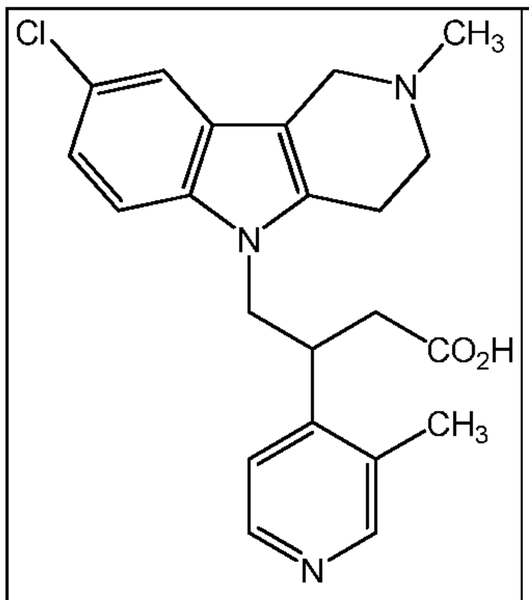

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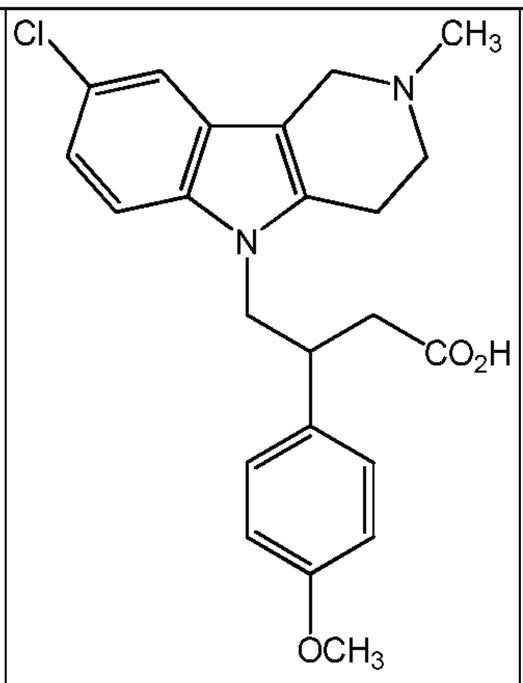

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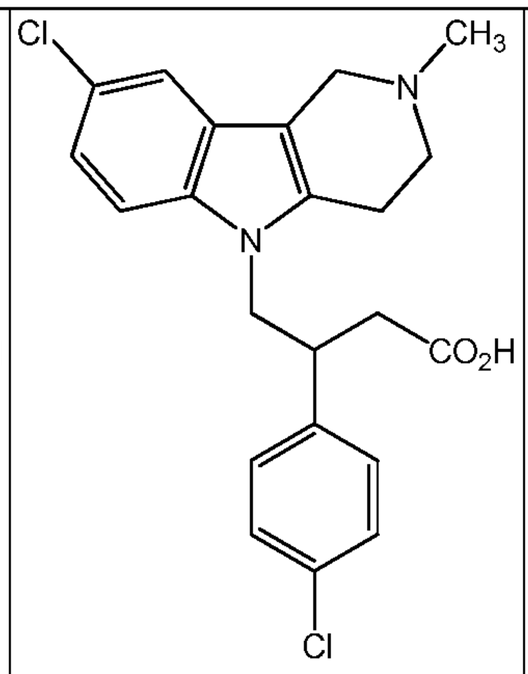

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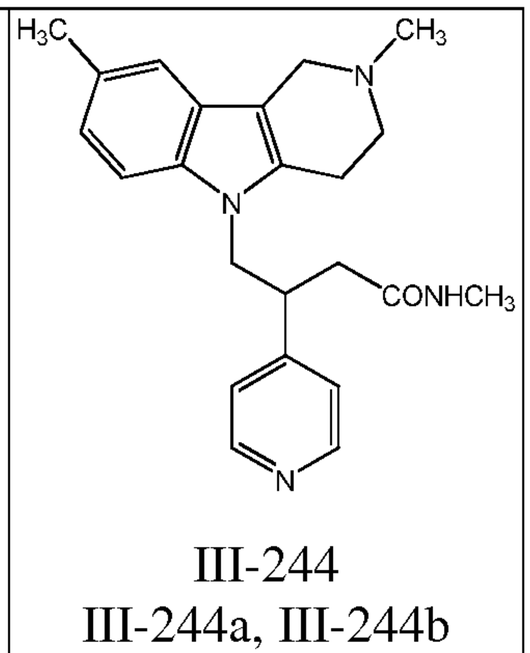
III-243a, III-243b



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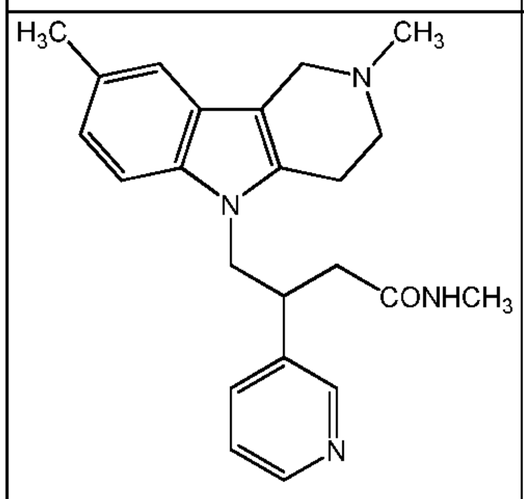

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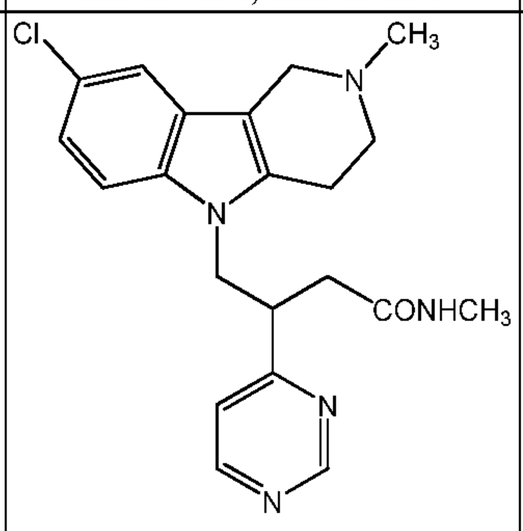

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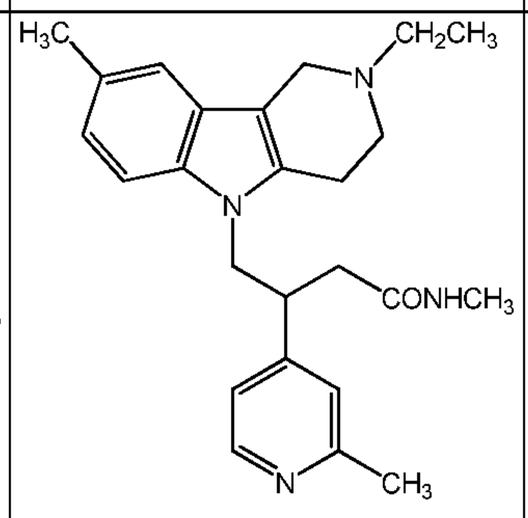

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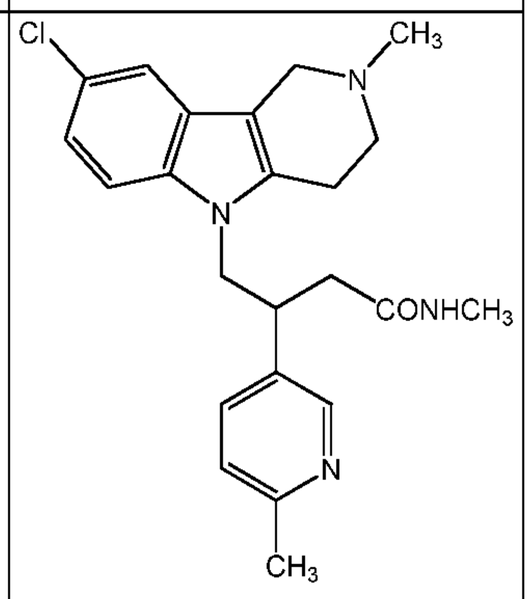

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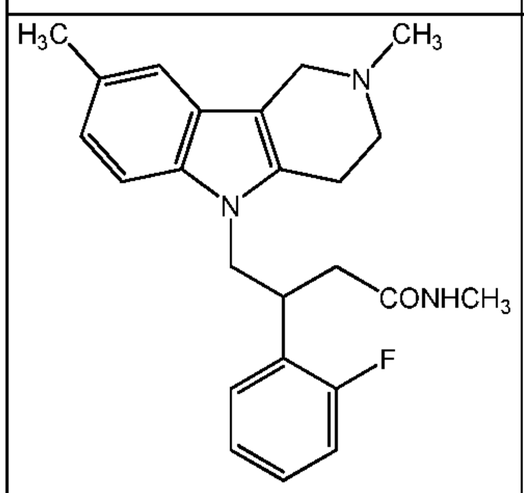

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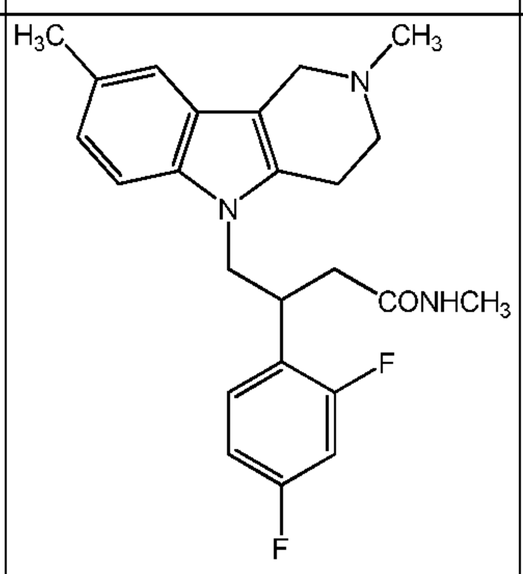

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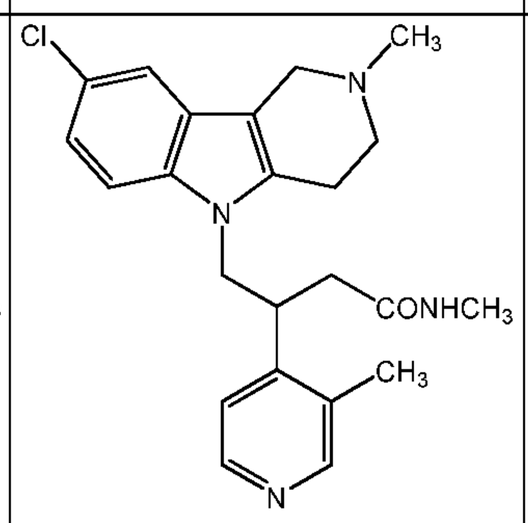

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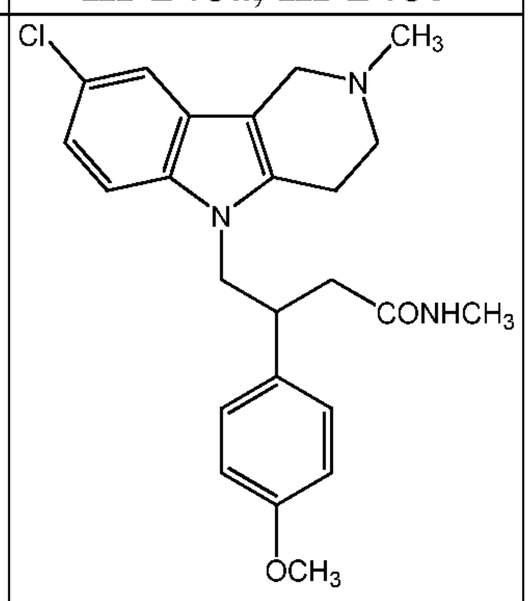
III-251a, III-251b



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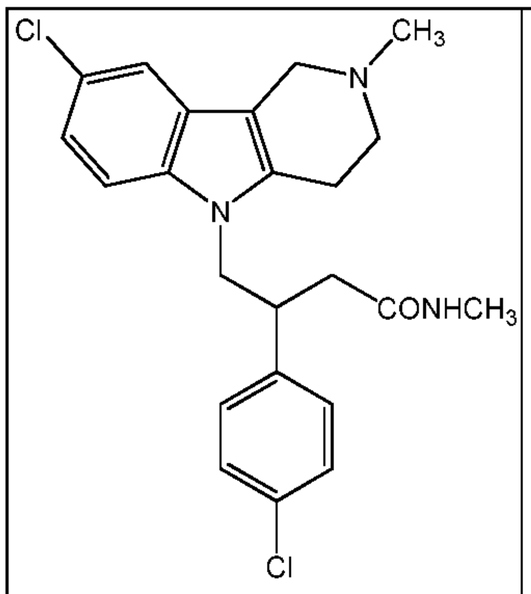
III-252a, III-252b



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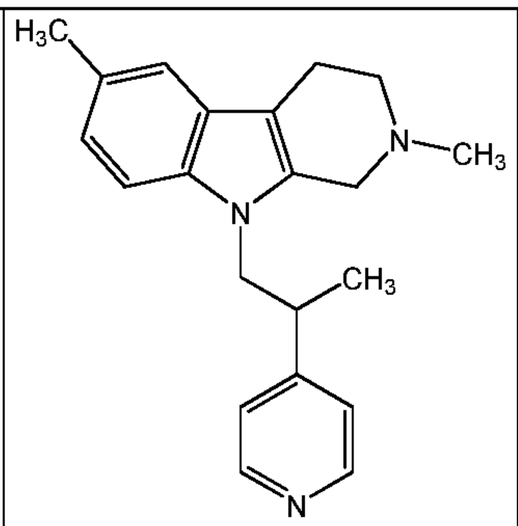
III-253a, III-253b



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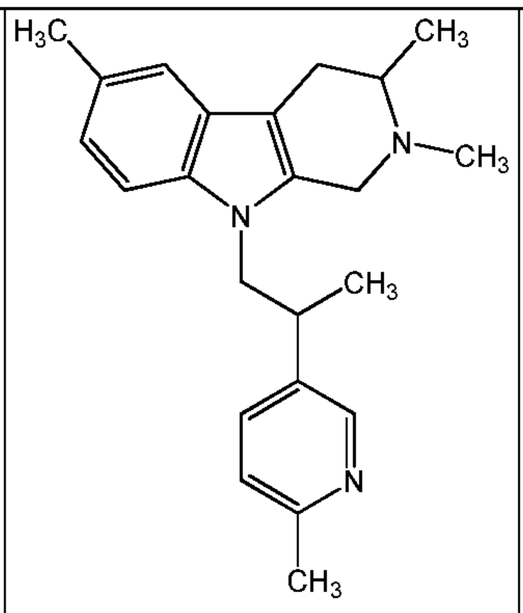
III-254a, III-254b



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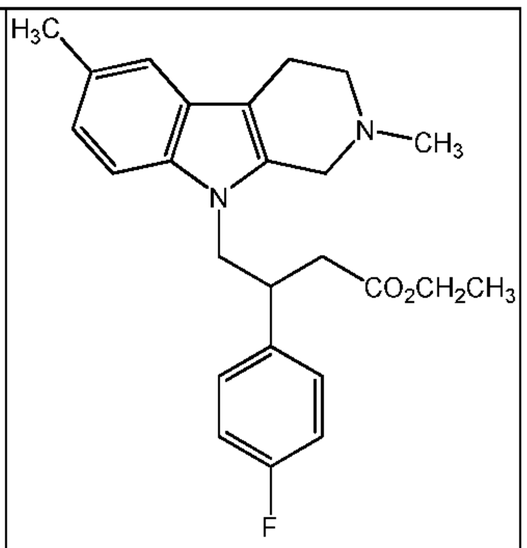

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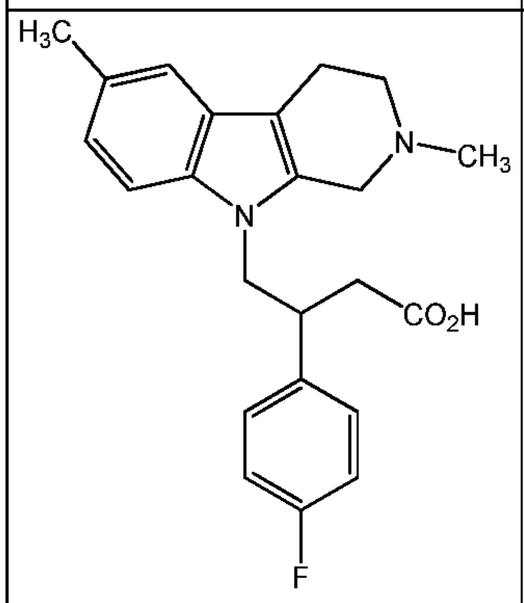
III-256a, III-256b



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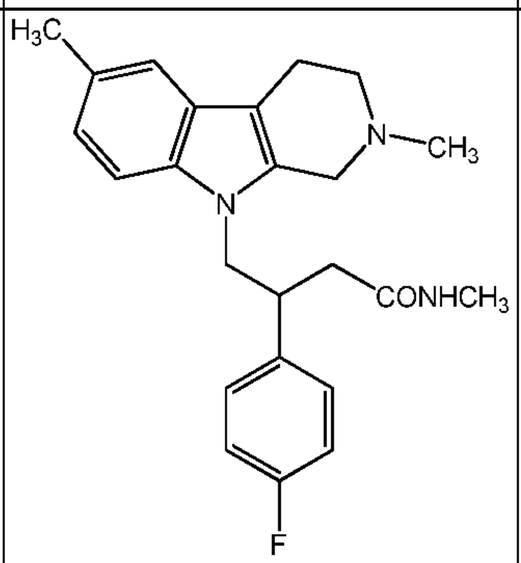

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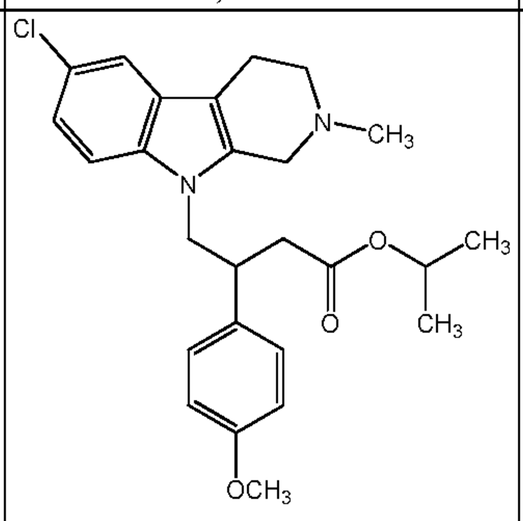
III-258a, III-258b



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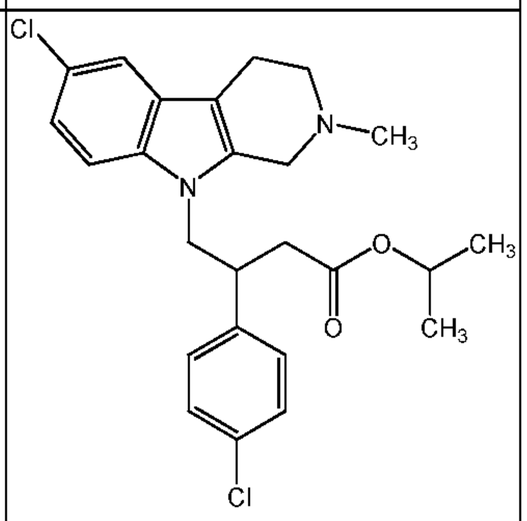
III-259a, III-259b



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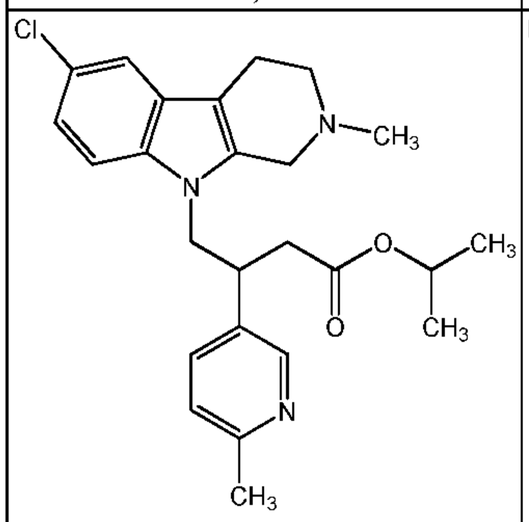

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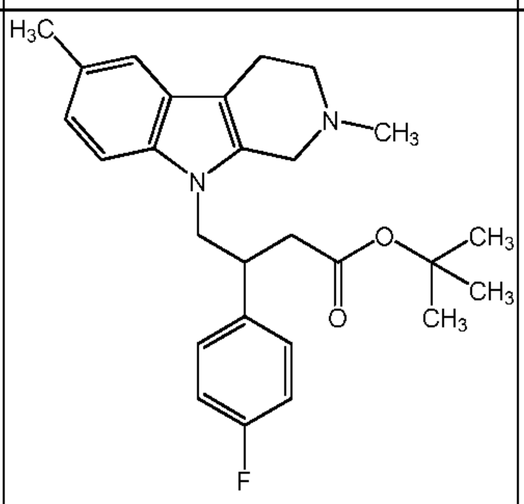
III-261a, III-261b



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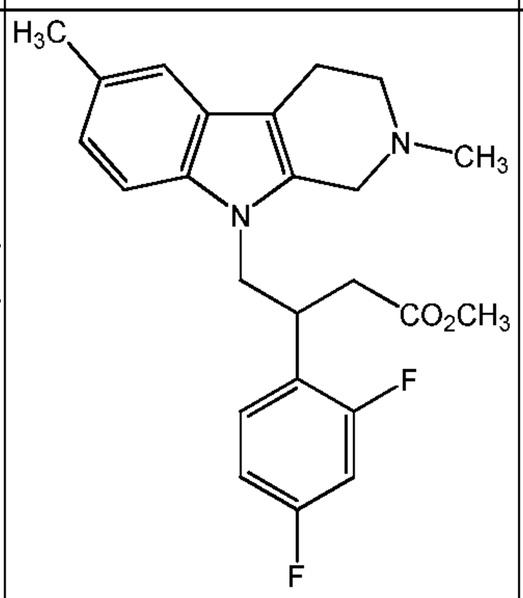
III-262a, III-262b



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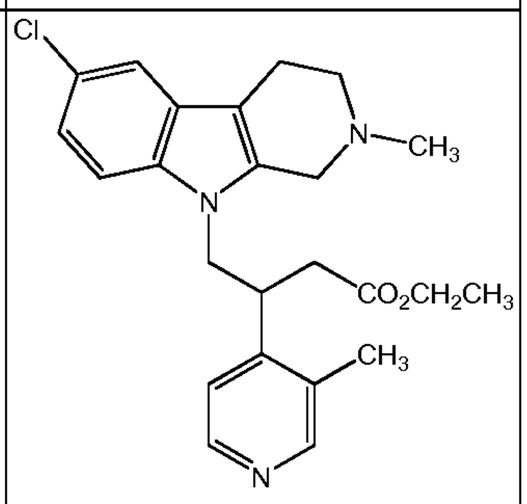
III-263a, III-263b



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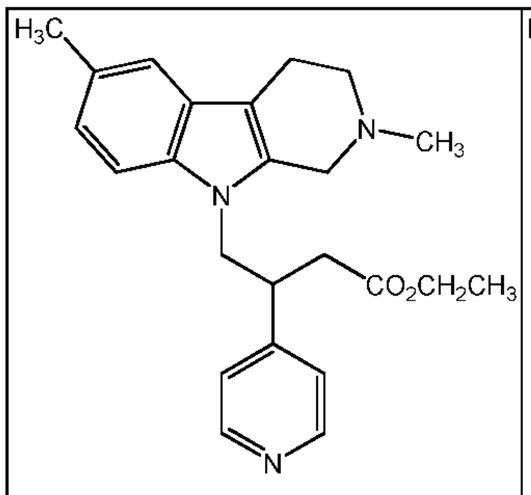
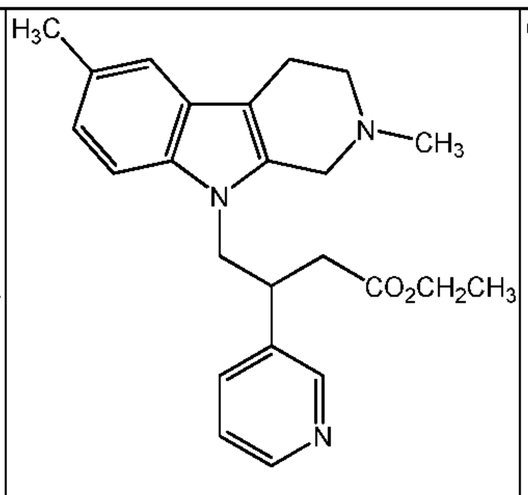
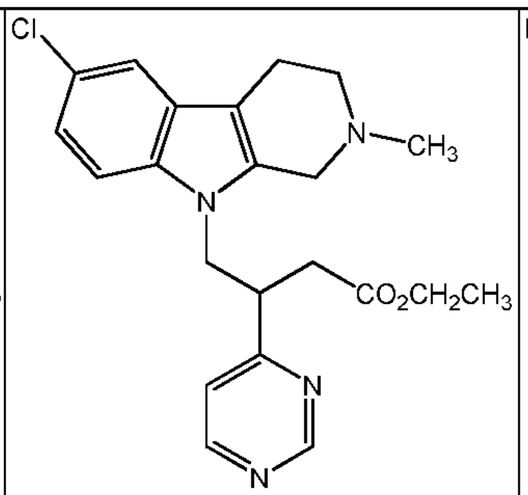
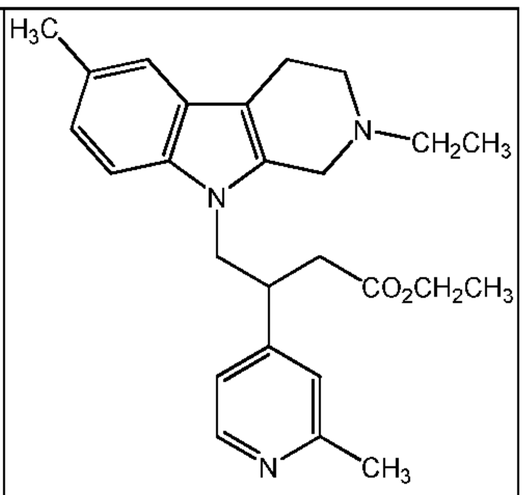
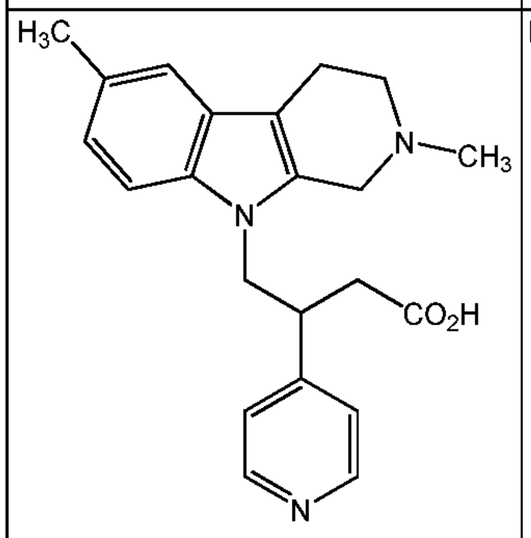
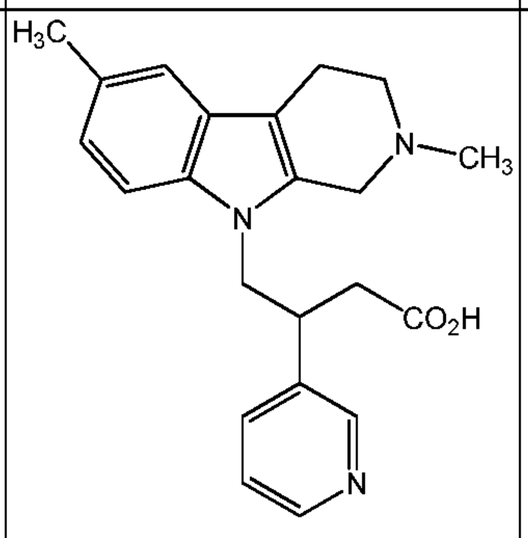
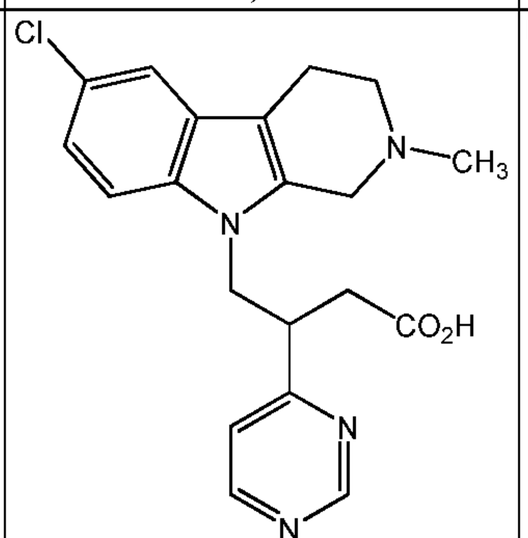
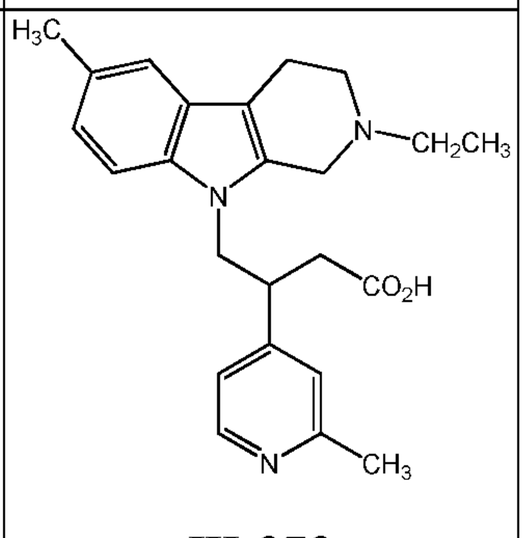
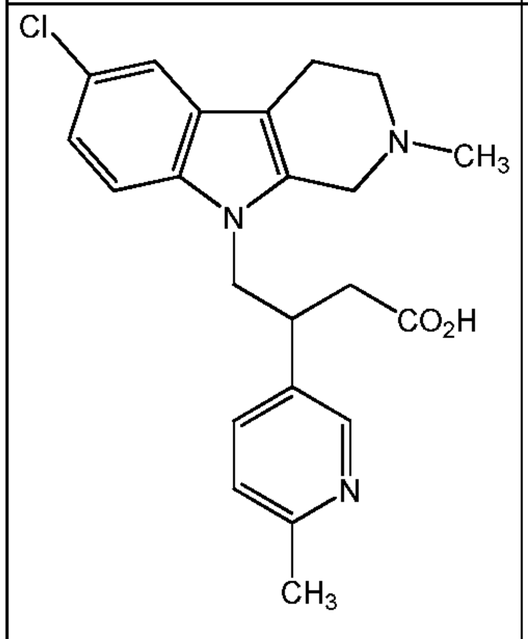
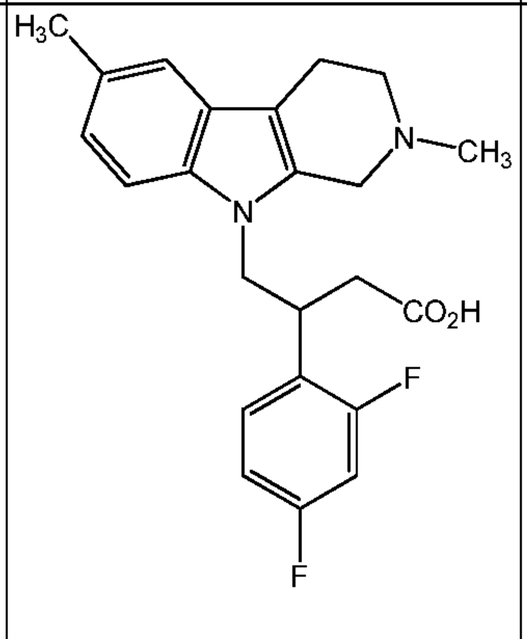
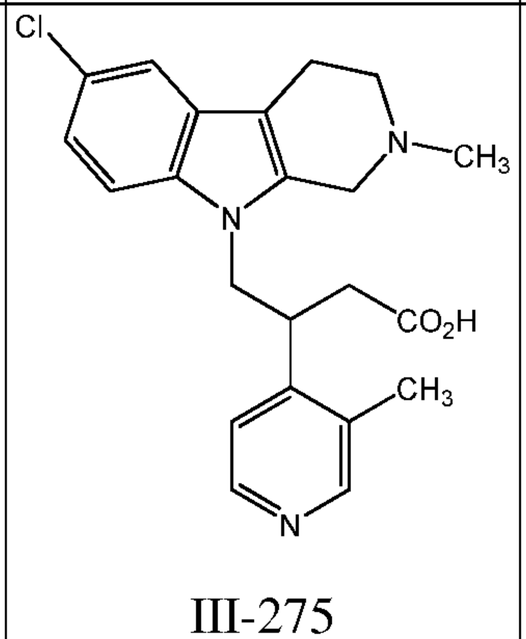
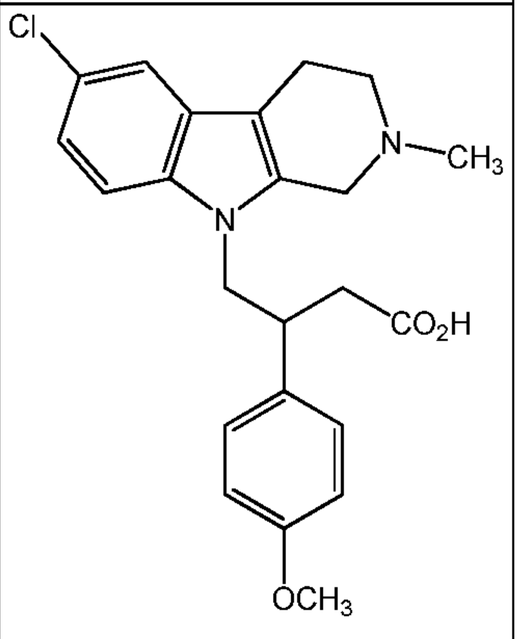
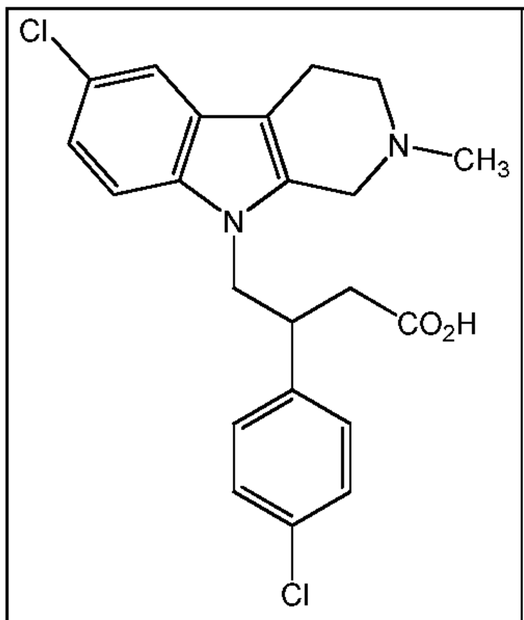
III-264a, III-264b

 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



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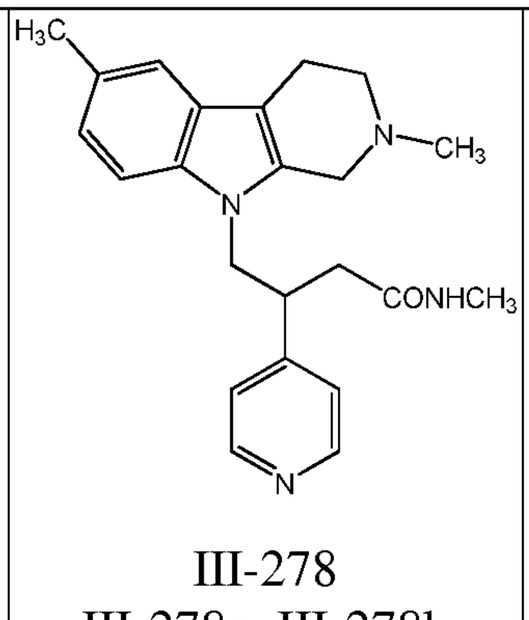
III-277a, III-277b



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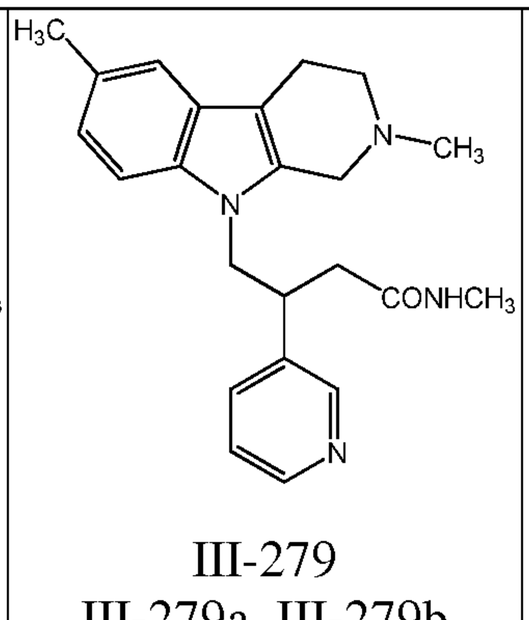

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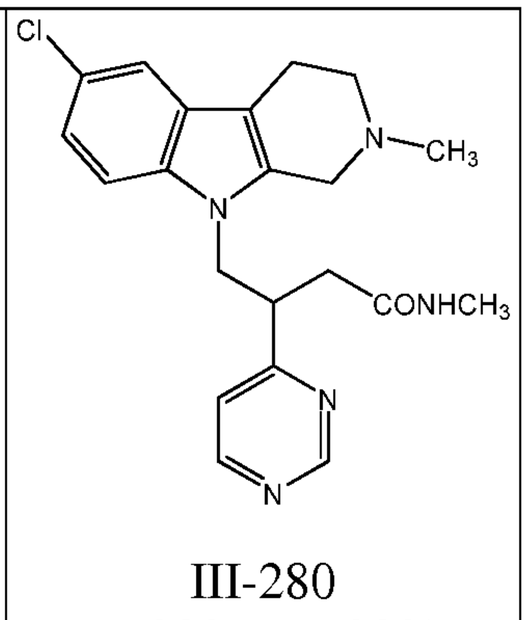

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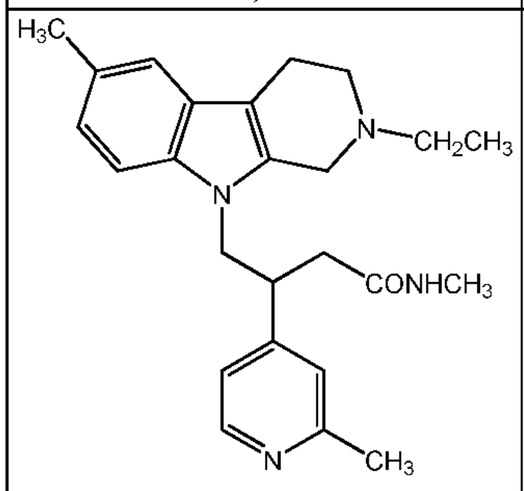
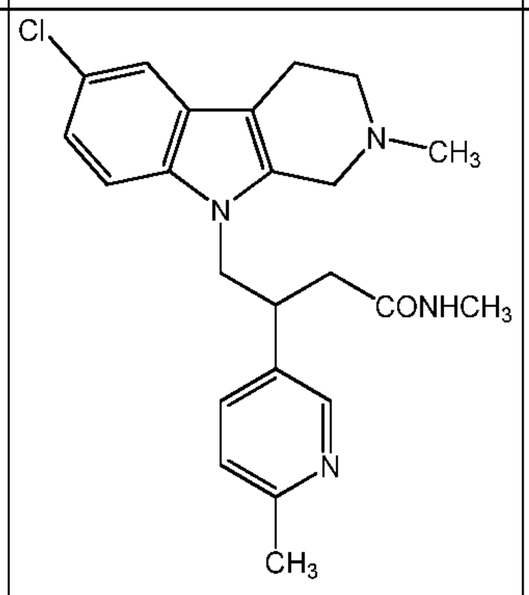
III-280a, III-280b



III-281
III-281a, III-281b



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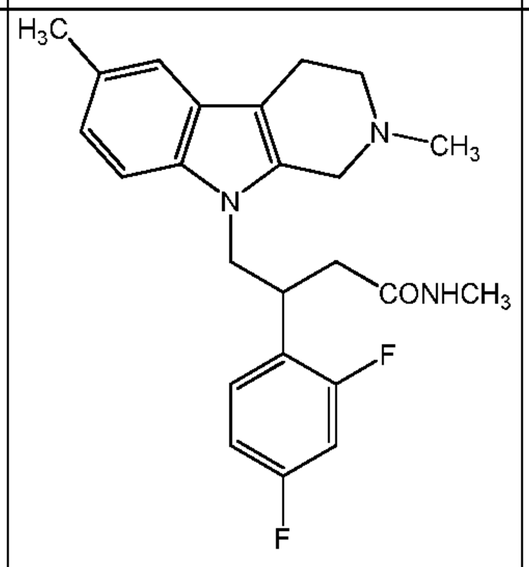

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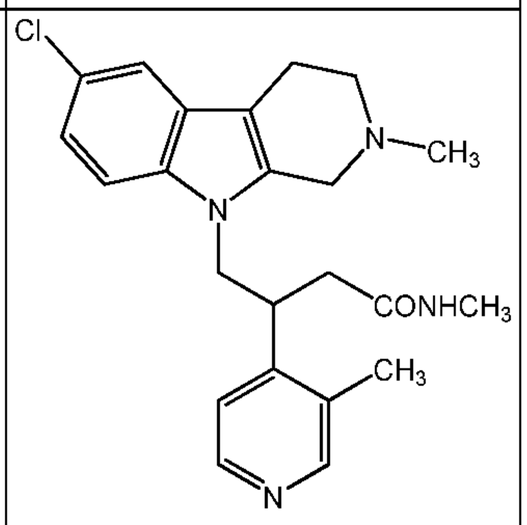

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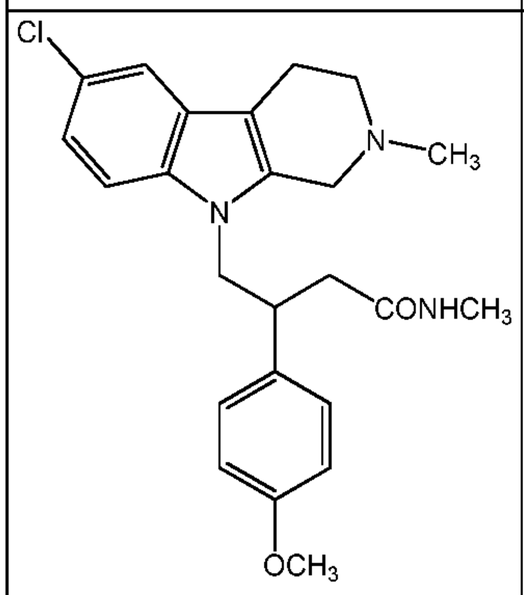

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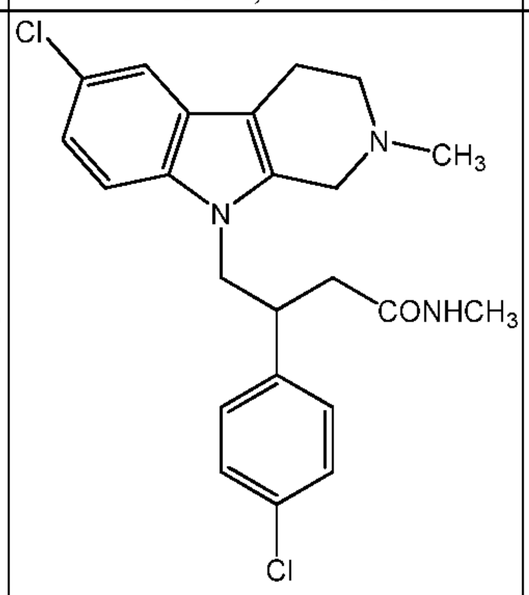

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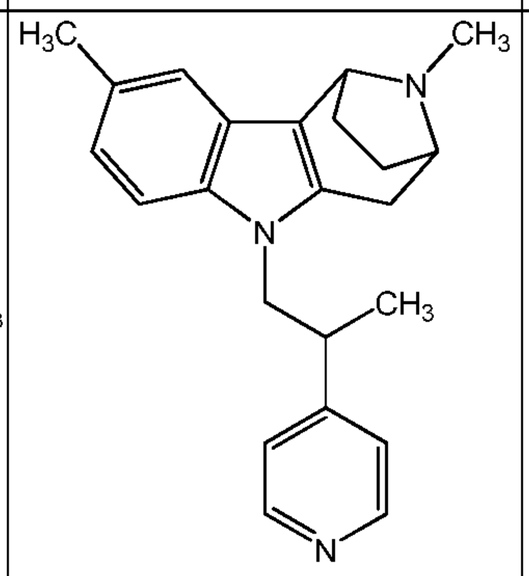

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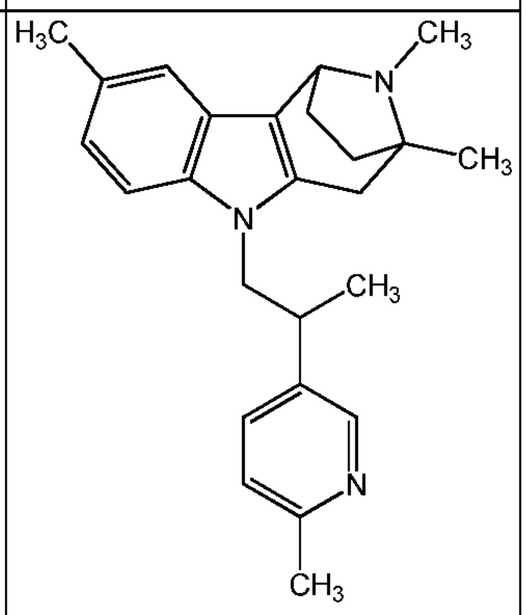

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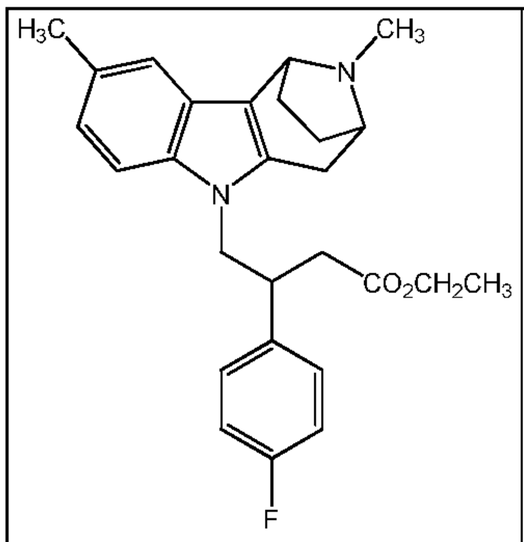
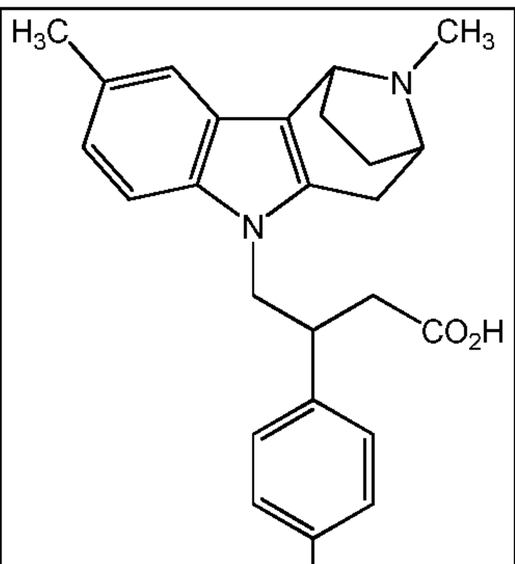
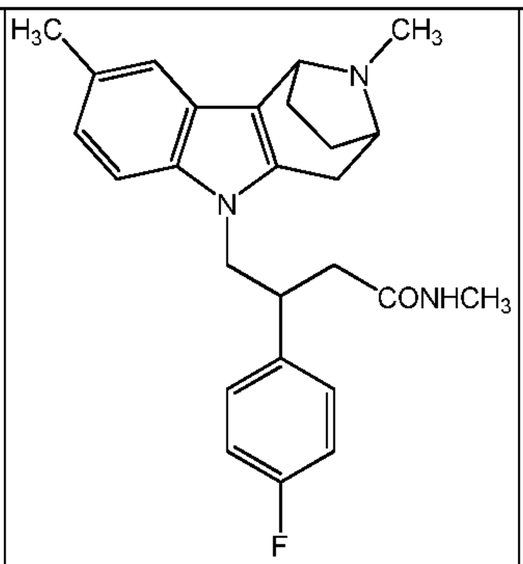
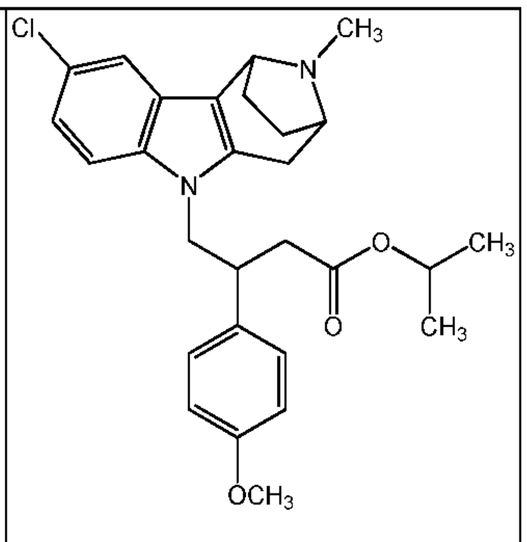
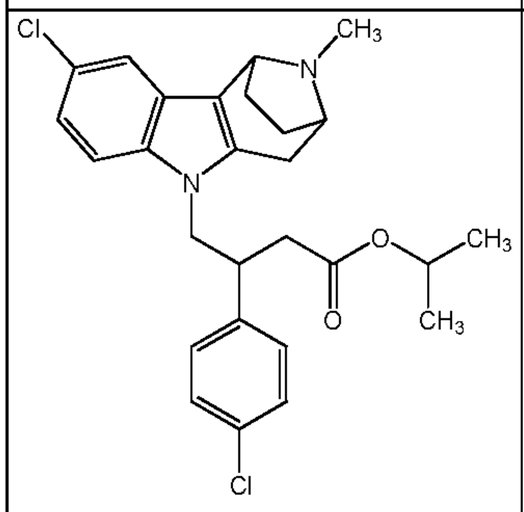
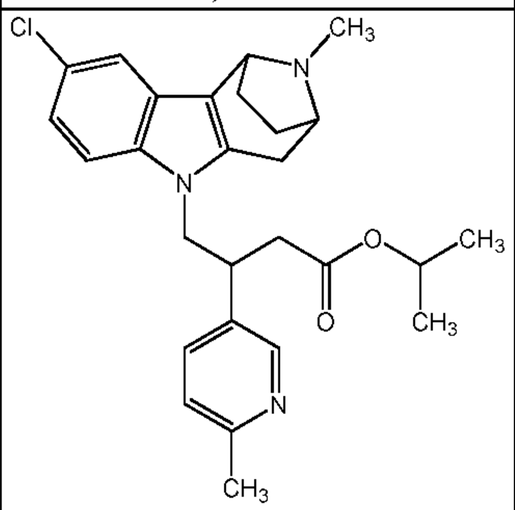
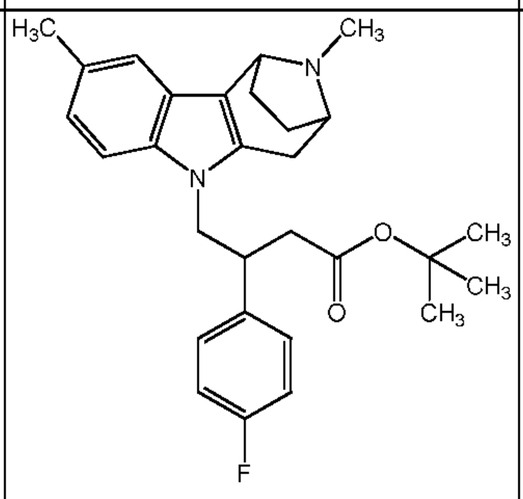
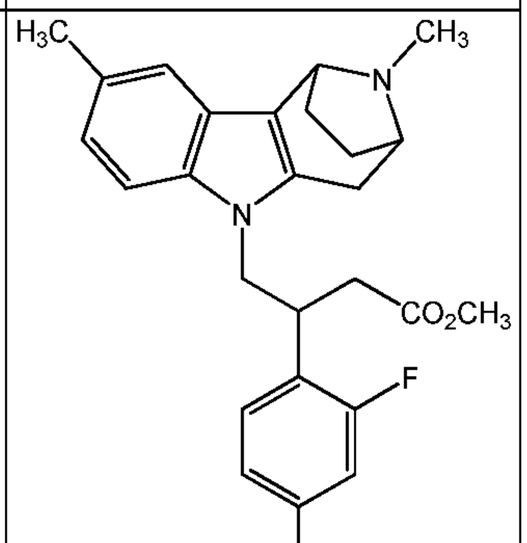
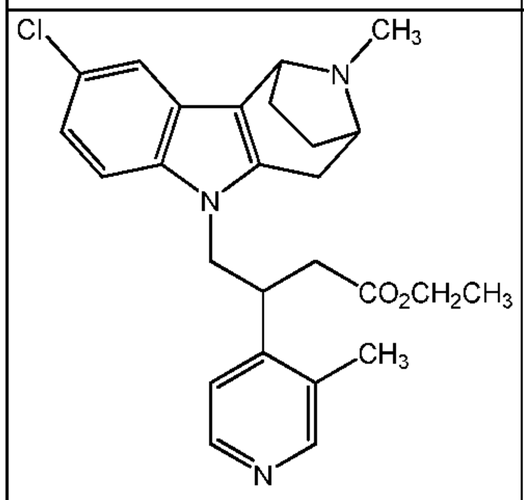
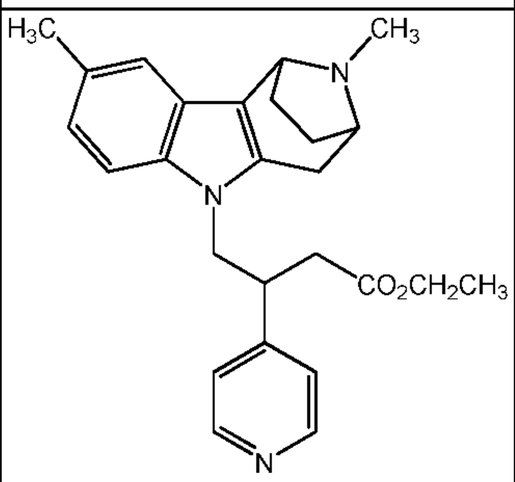
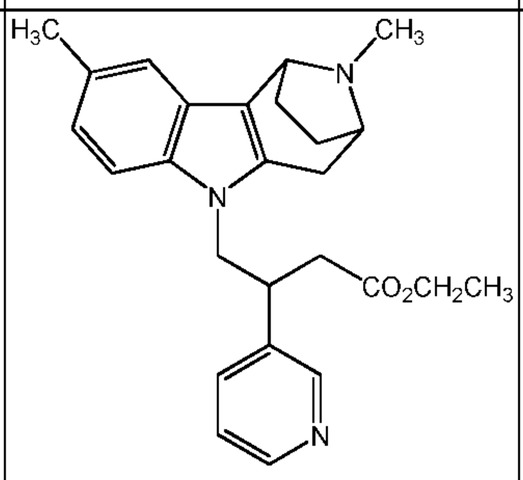
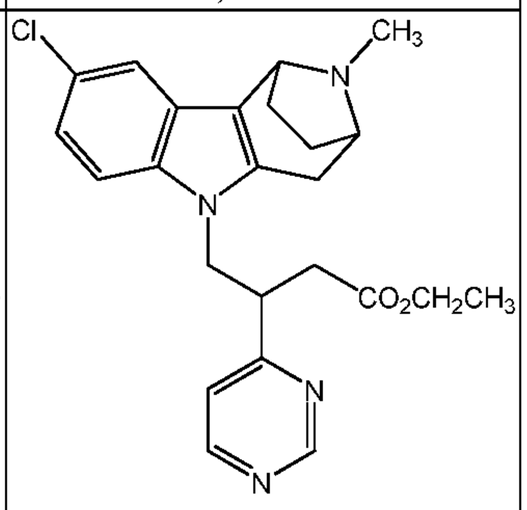
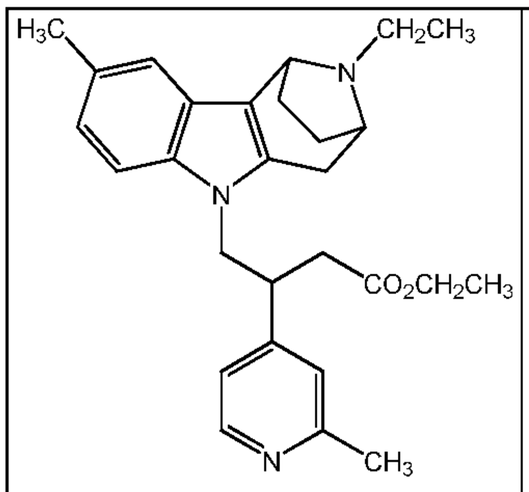
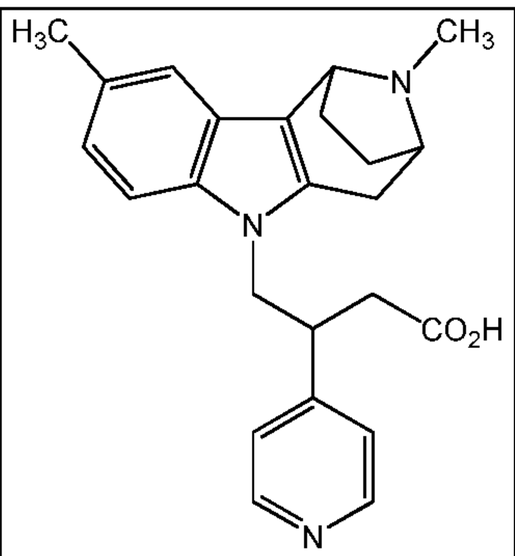
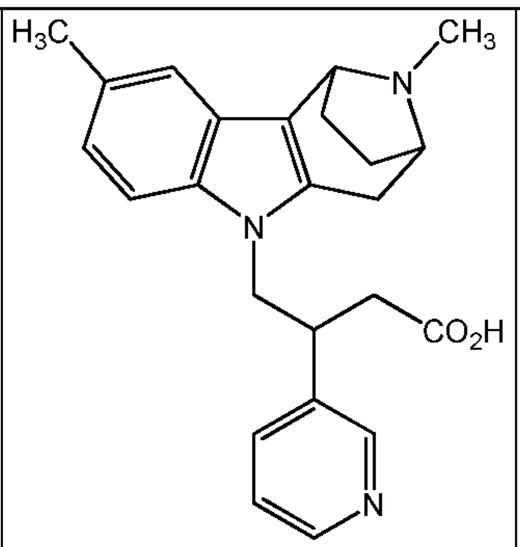
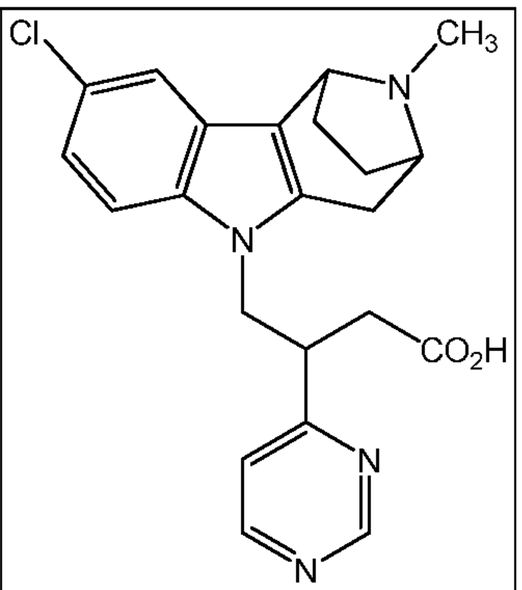
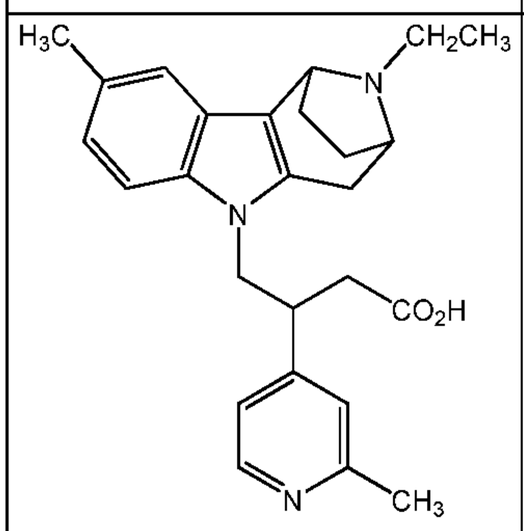
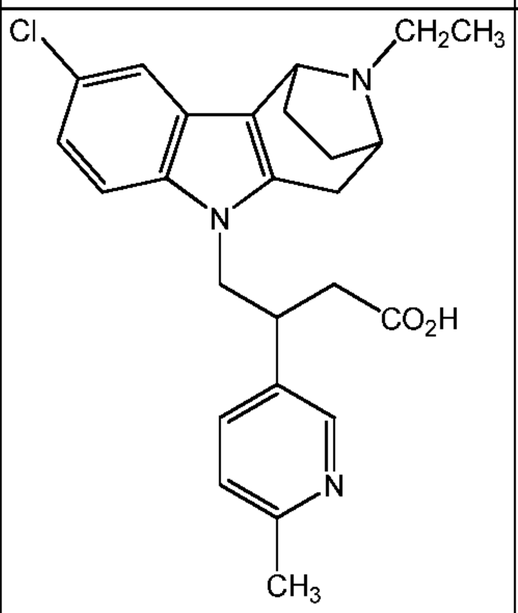
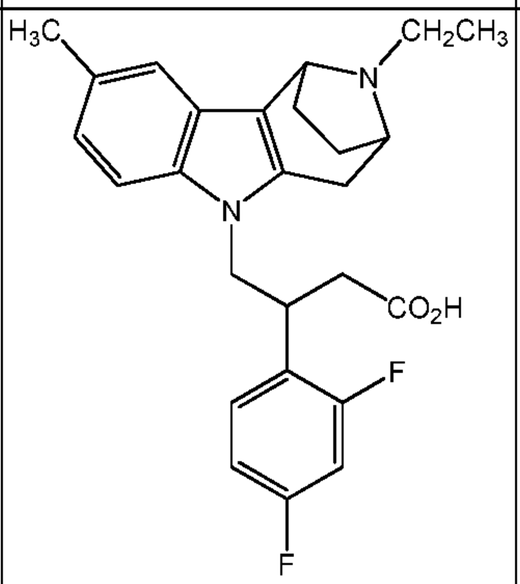
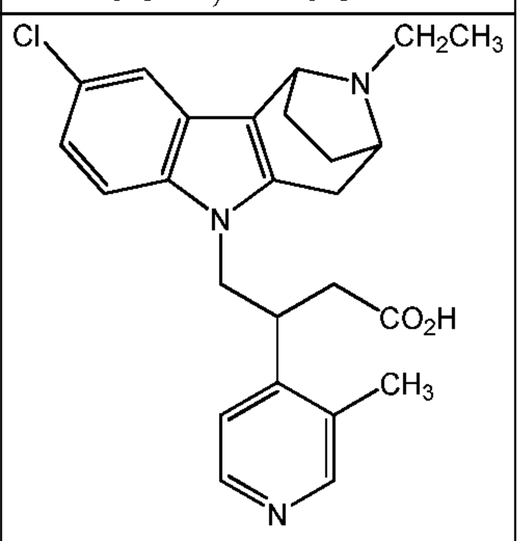
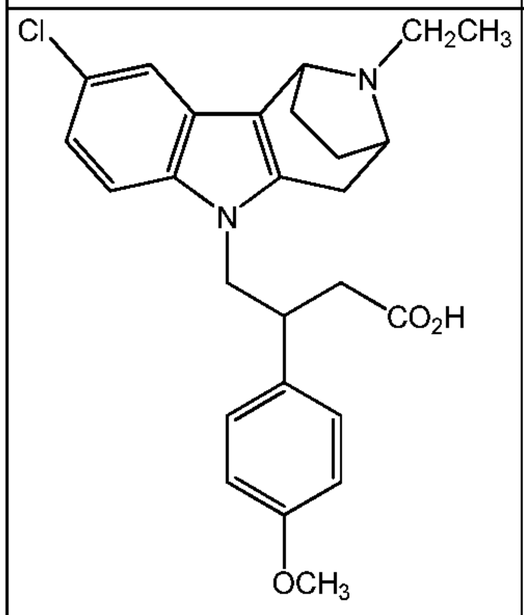
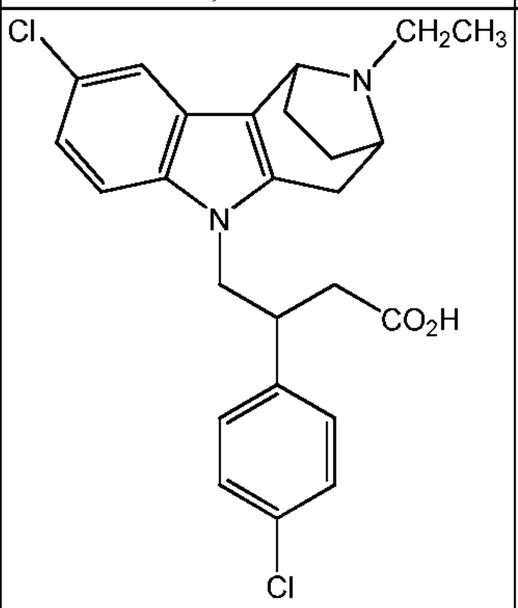
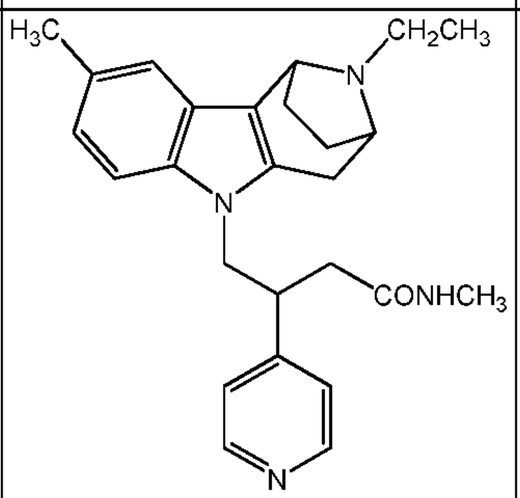
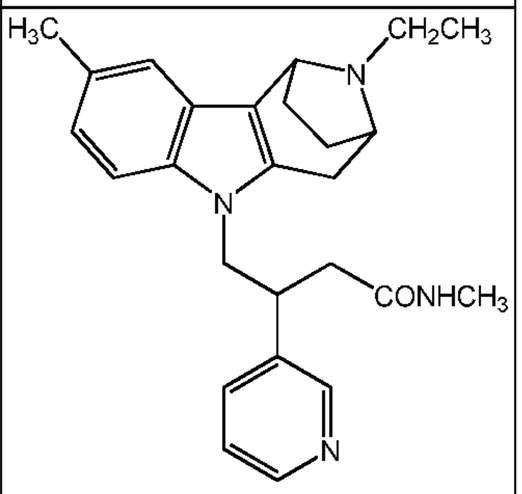
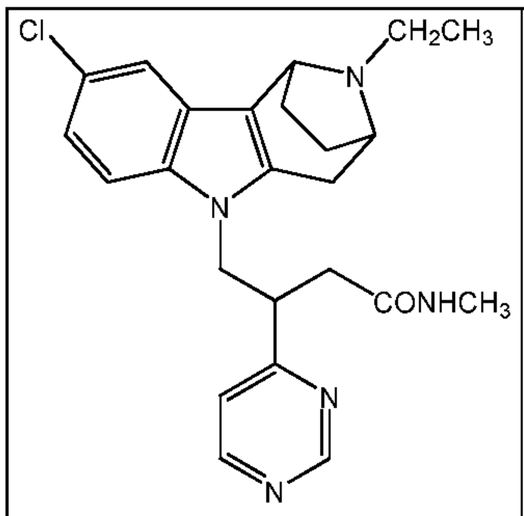
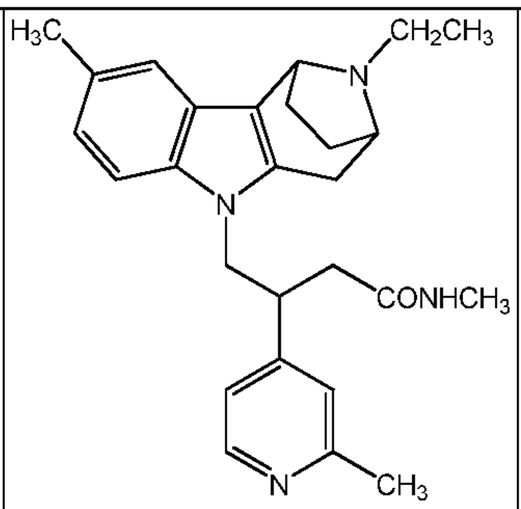
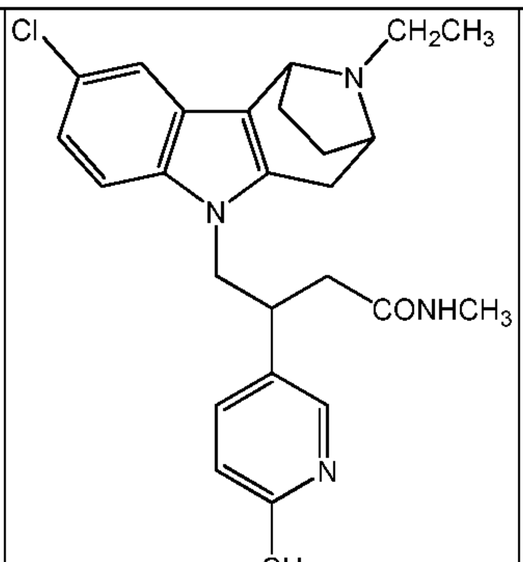
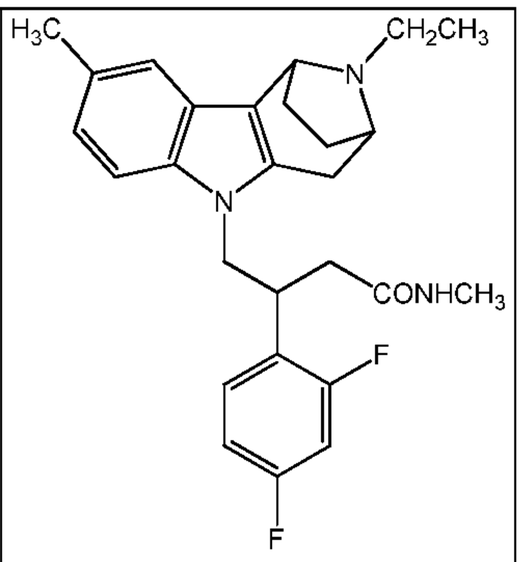
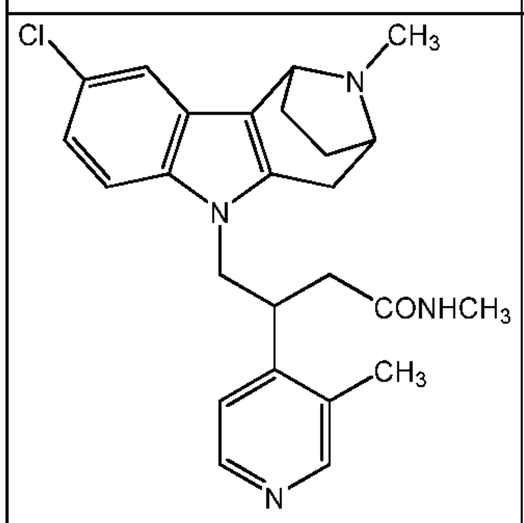
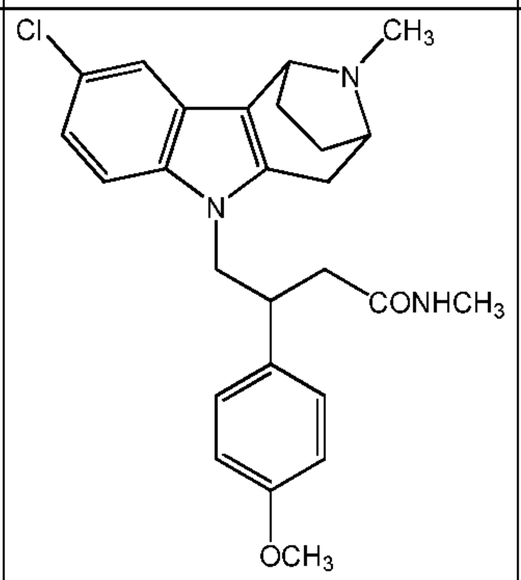
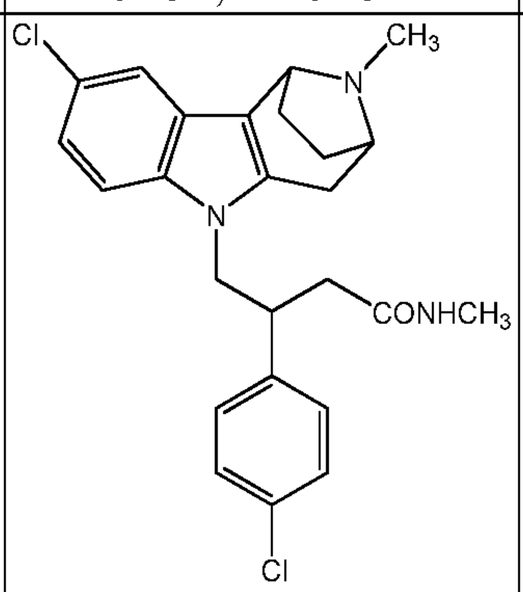
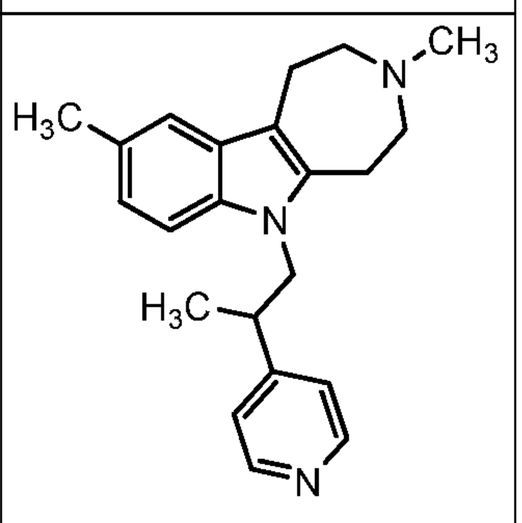
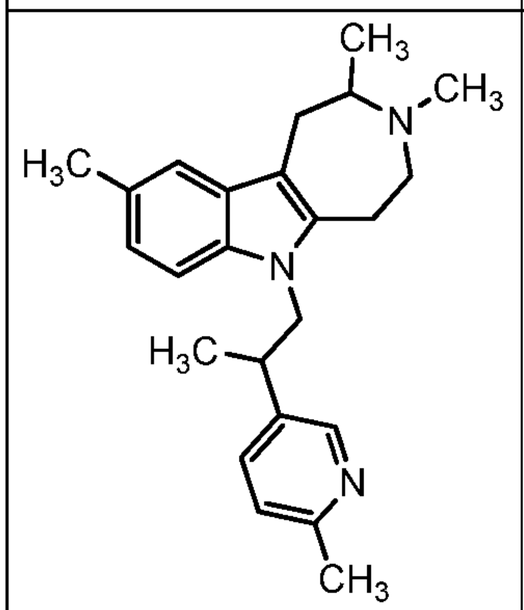
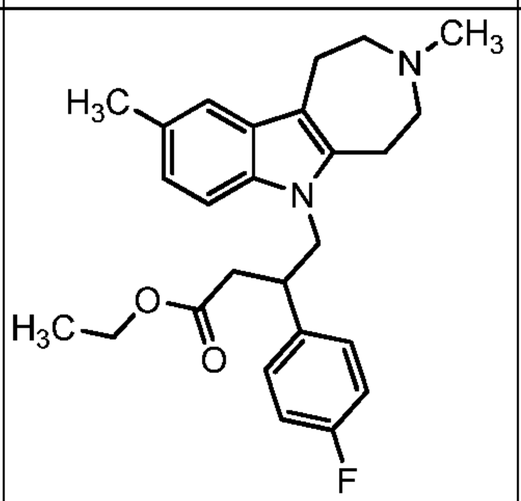
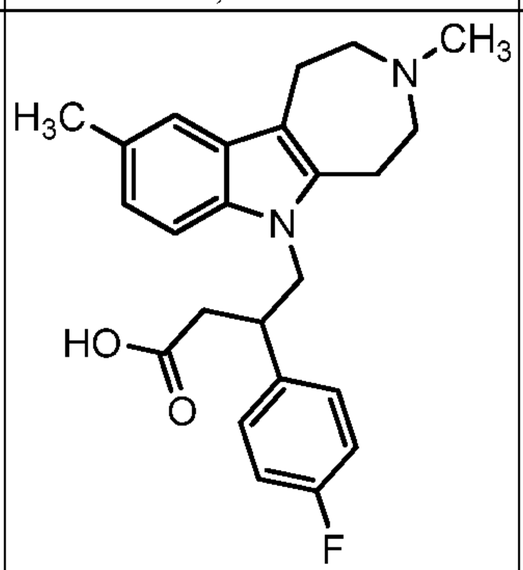
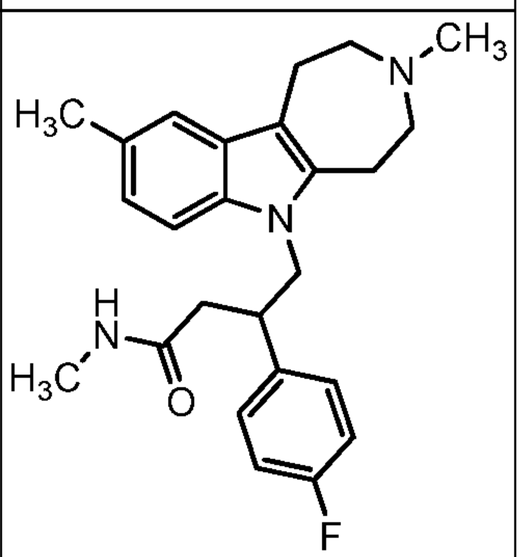
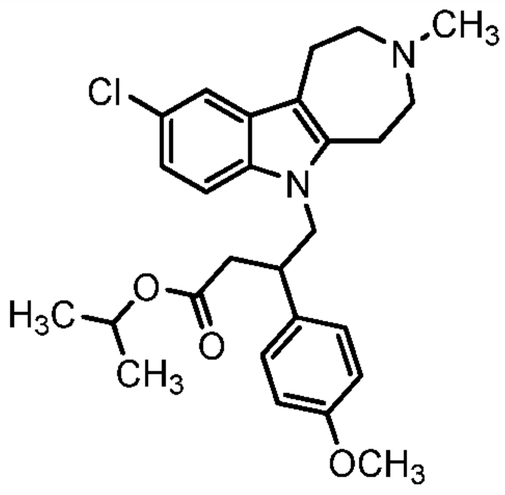
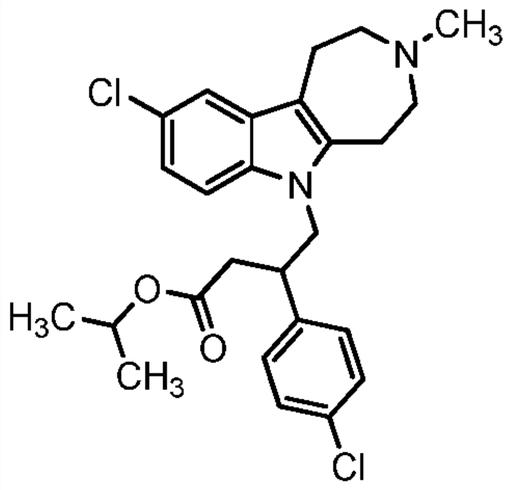
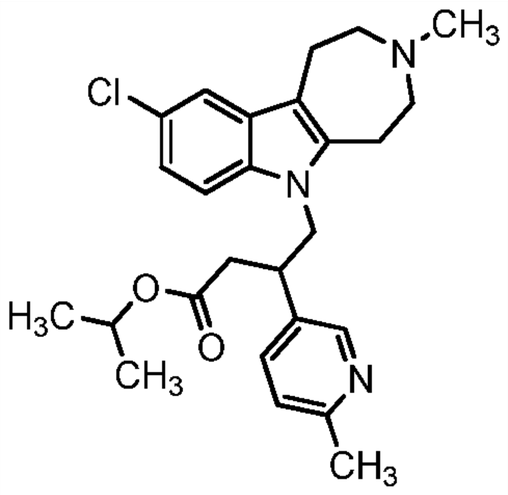
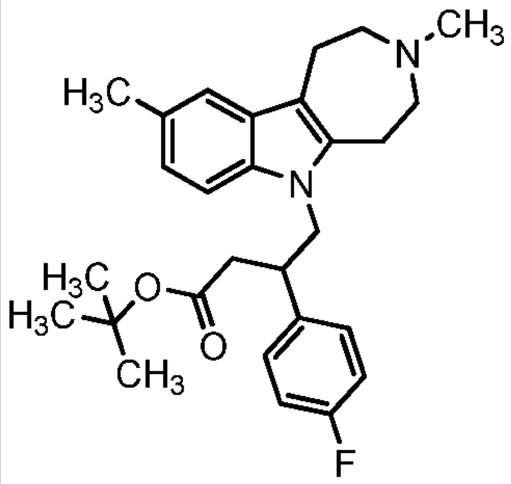
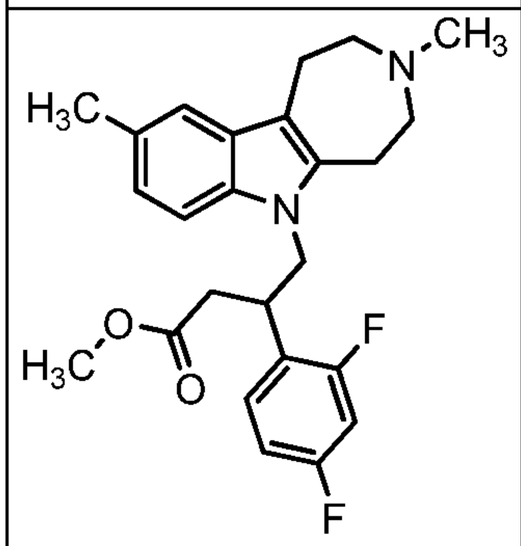
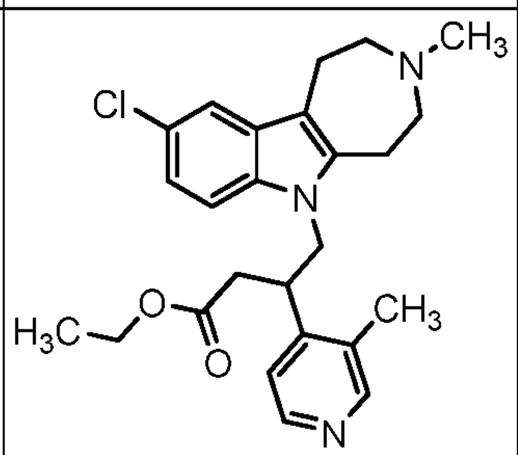
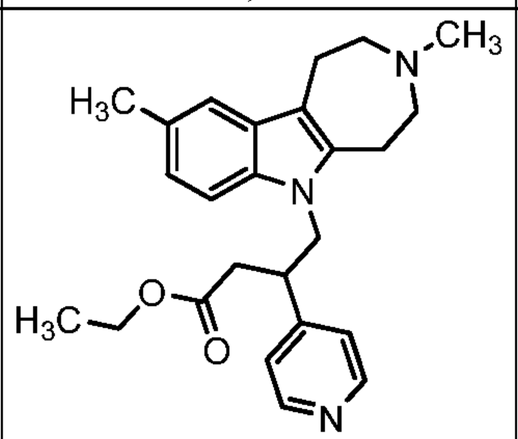
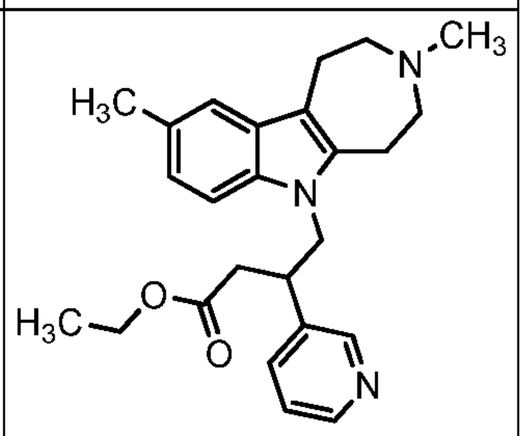
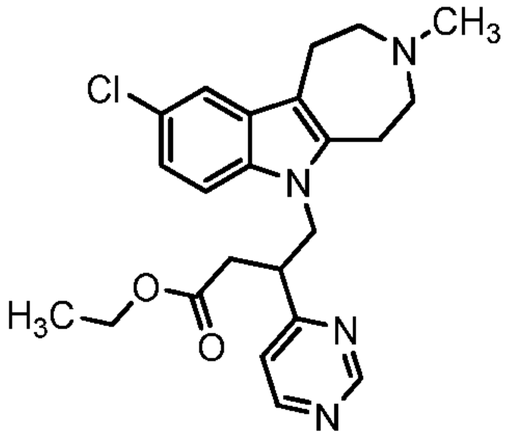
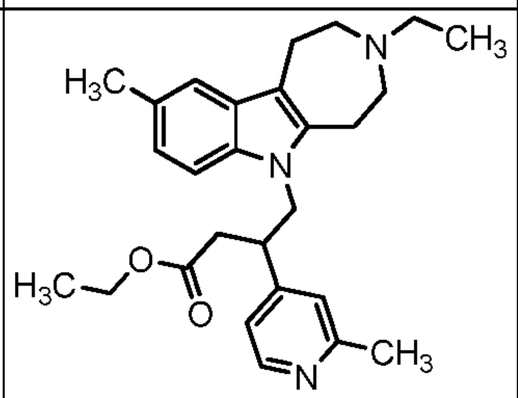
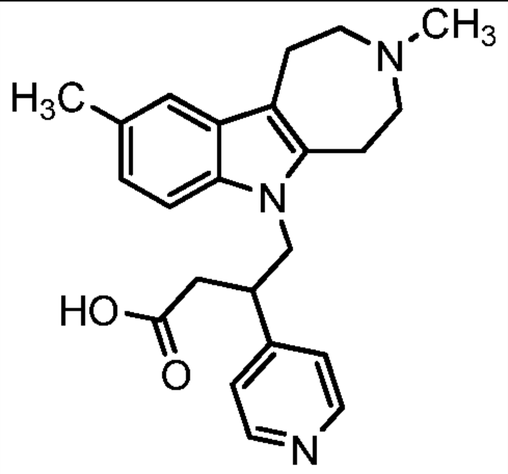
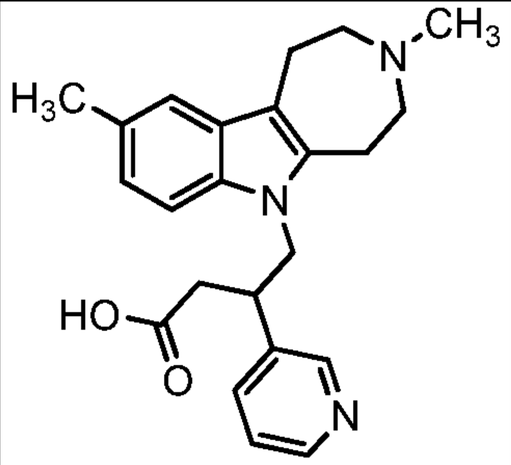
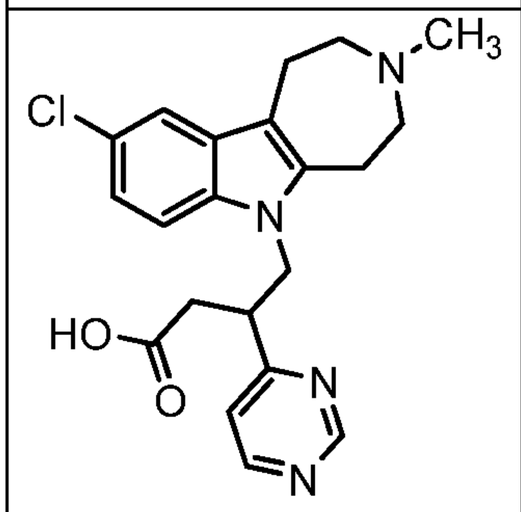
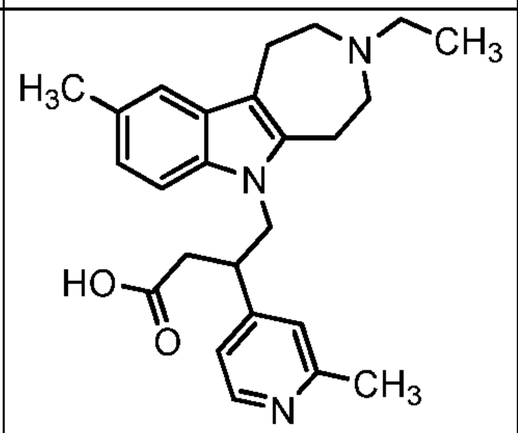
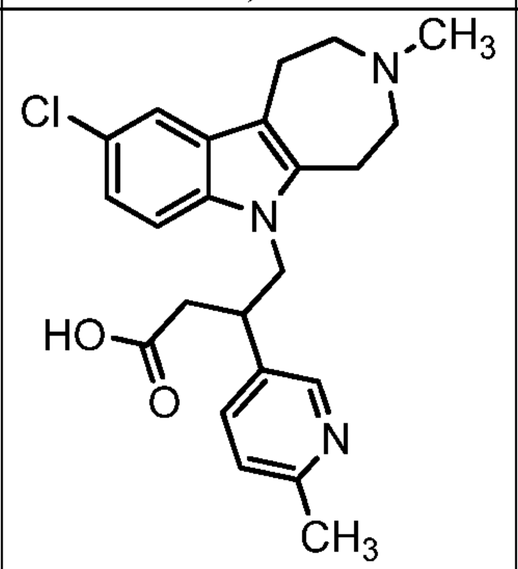
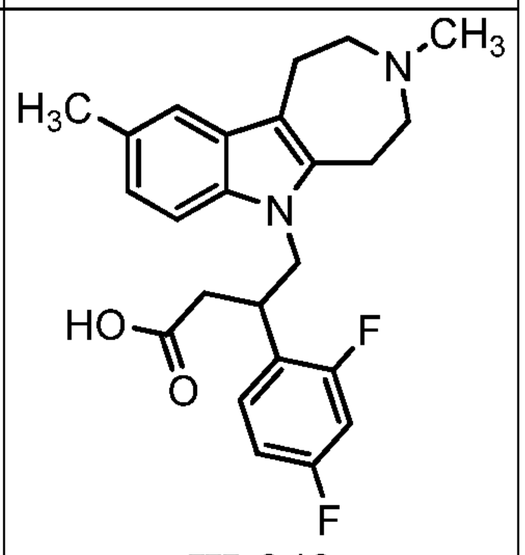
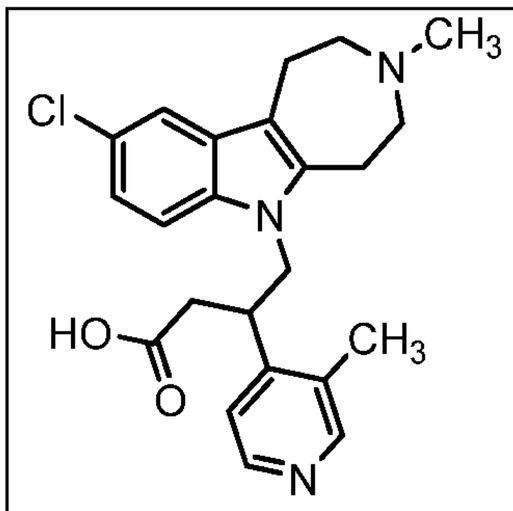
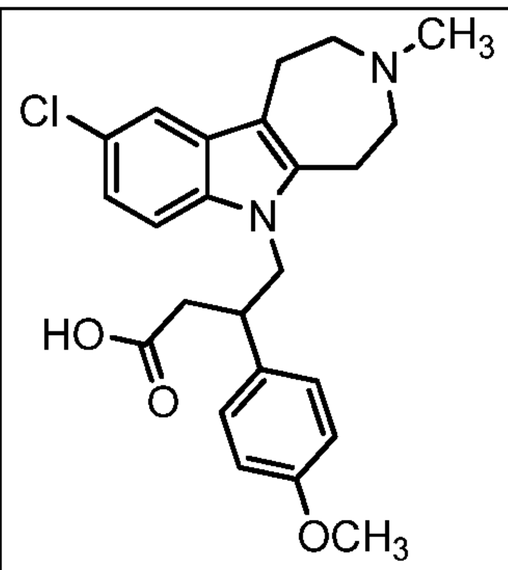
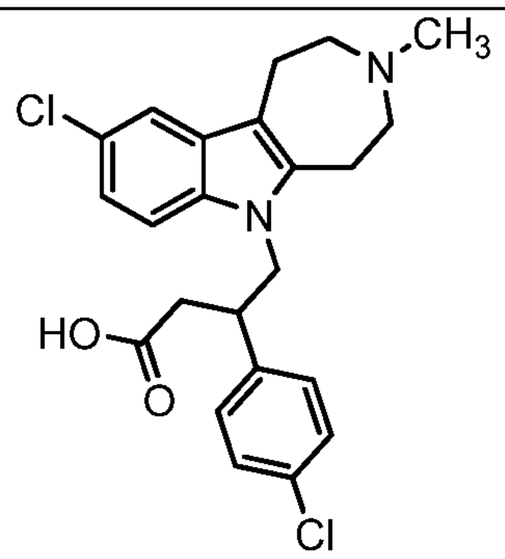
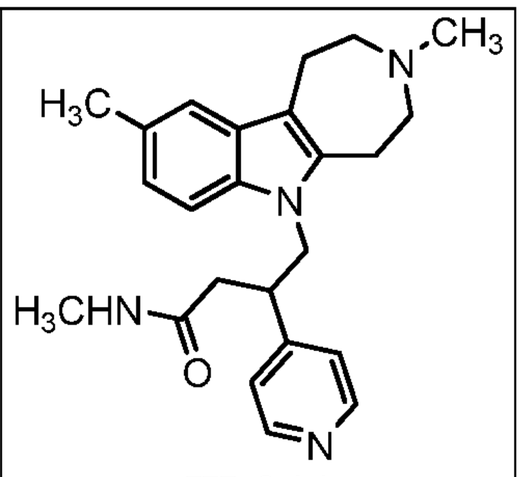
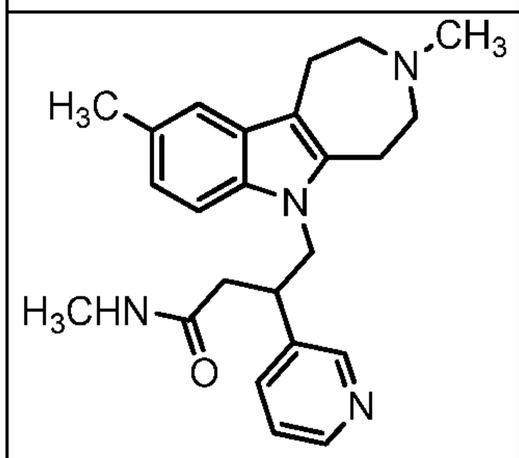
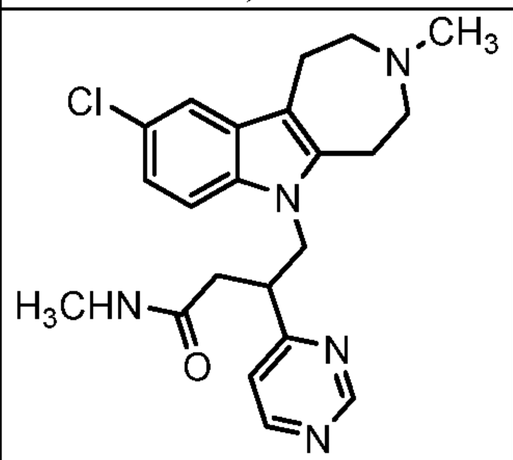
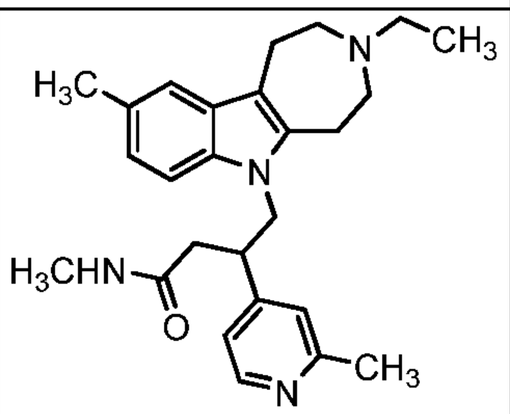
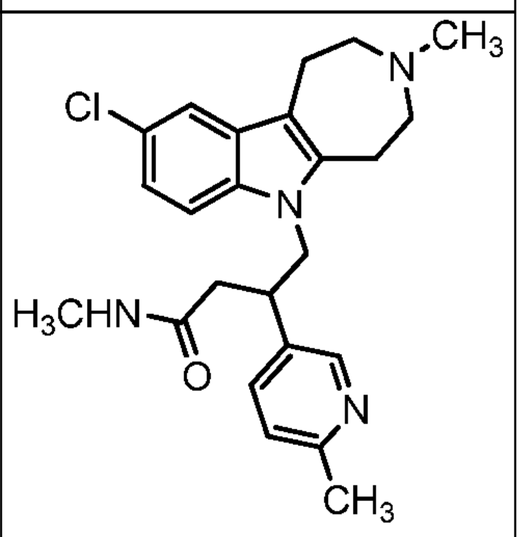
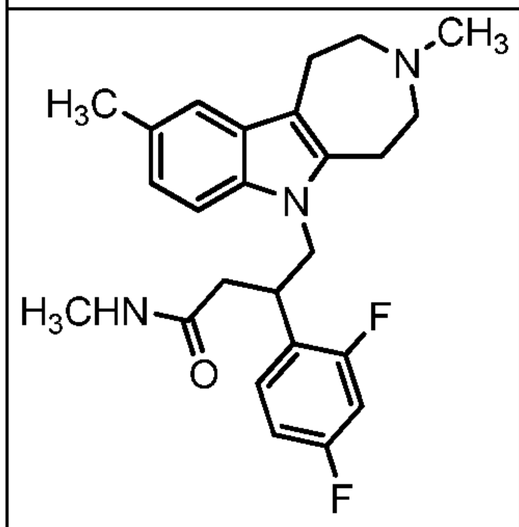
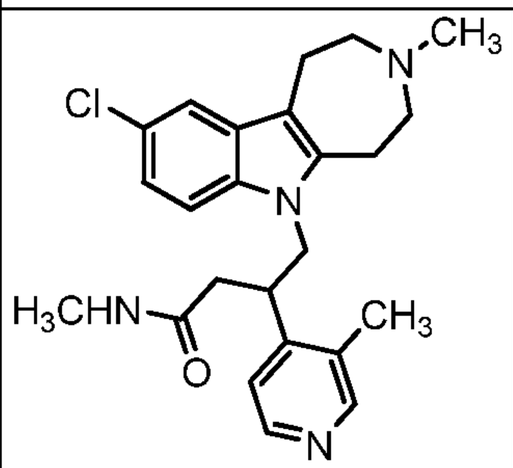
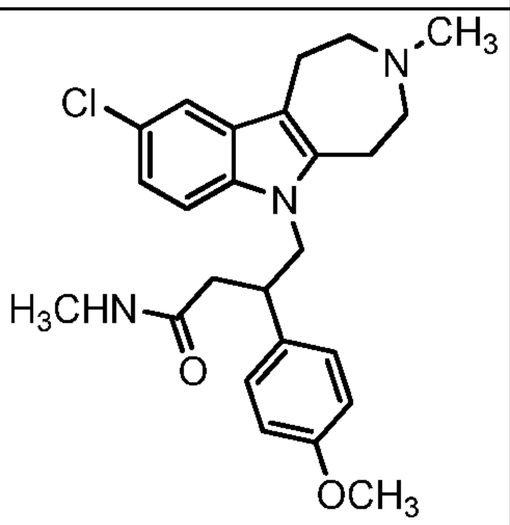
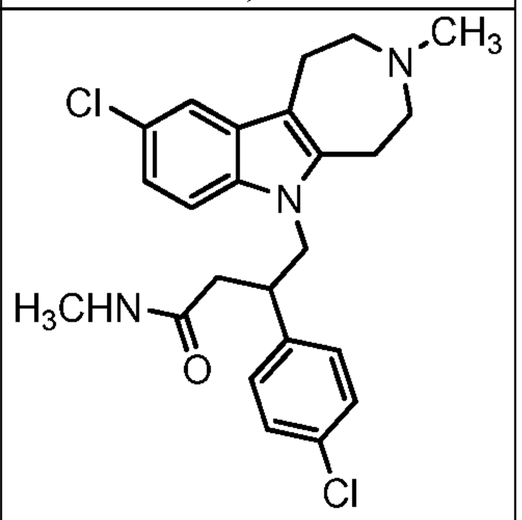
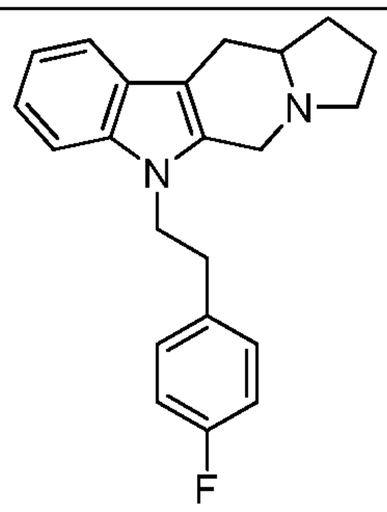
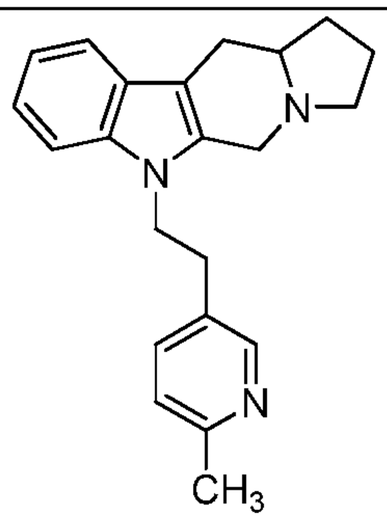
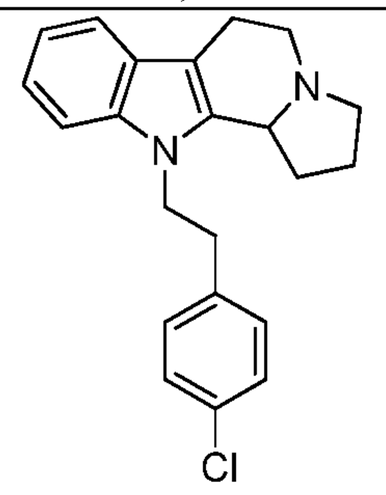
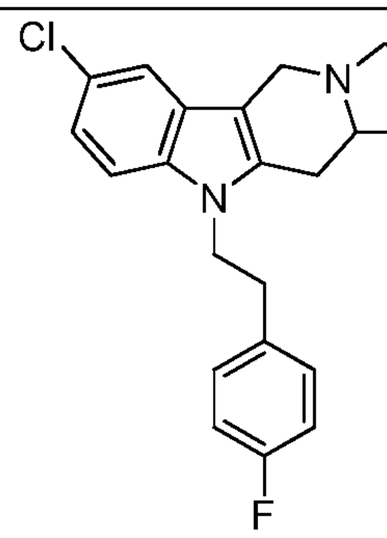
 III-289 III-289a, III-289b, III-289c, III-289d	 III-290 III-290a, III-290b, III-290c, III-290d	 III-291 III-291a, III-291b, III-291c, III-291d	 III-292 III-292a, III-292b, III-292c, III-292d
 III-293 III-293a, III-293b, III-293c, III-293d	 III-294 III-294a, III-294b, III-294c, III-294d	 III-295 III-295a, 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

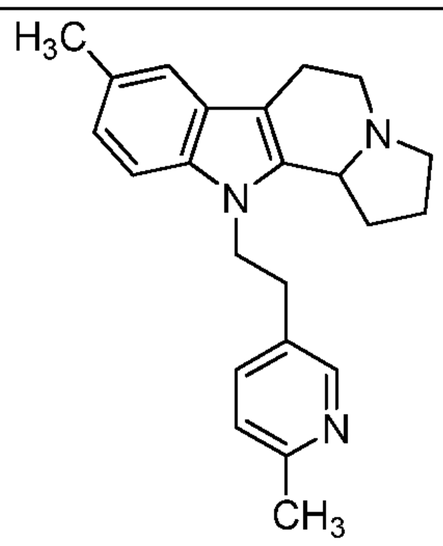
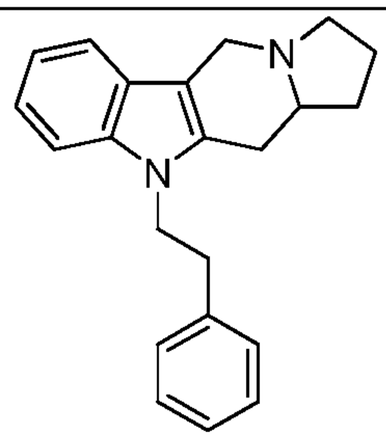
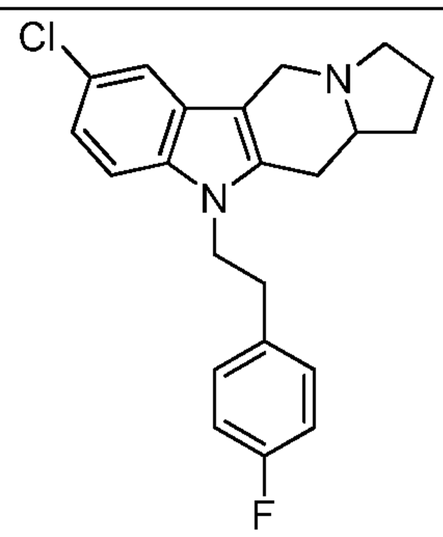
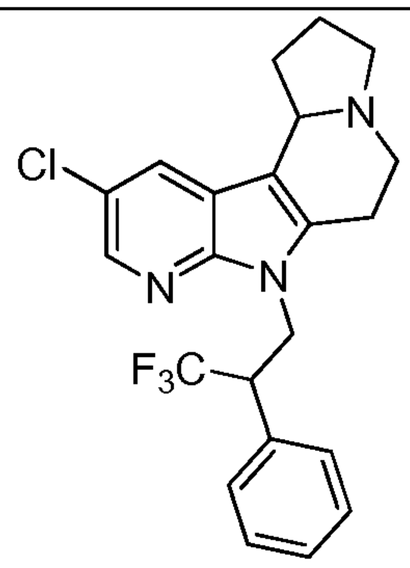
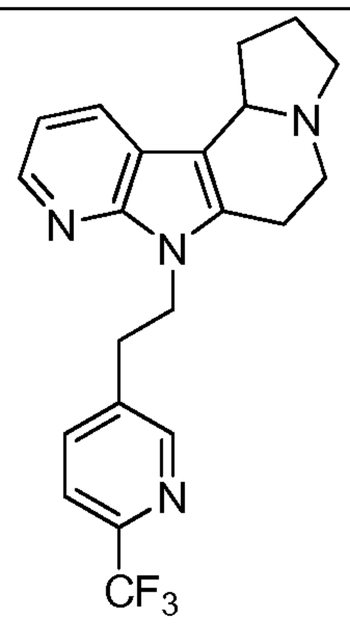
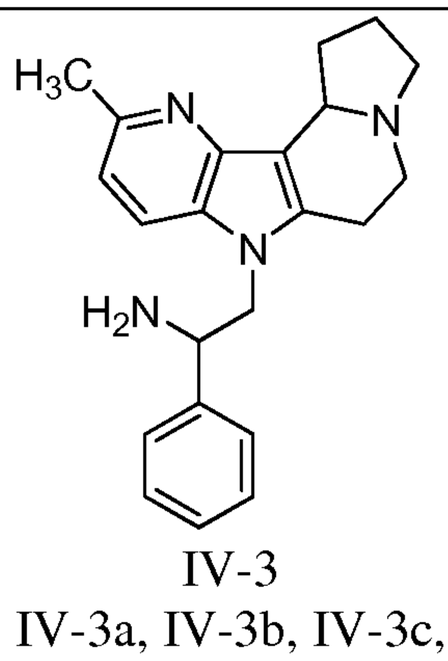
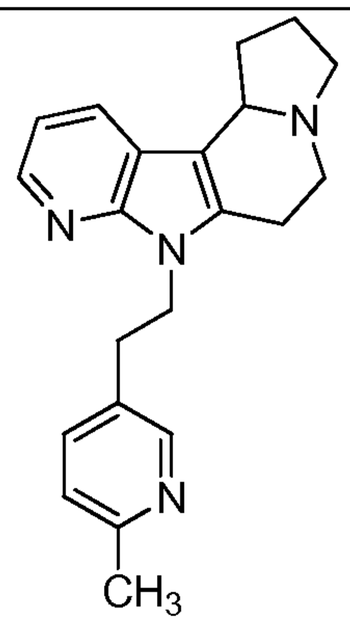
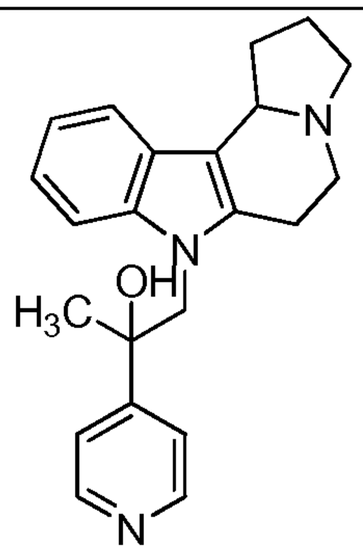
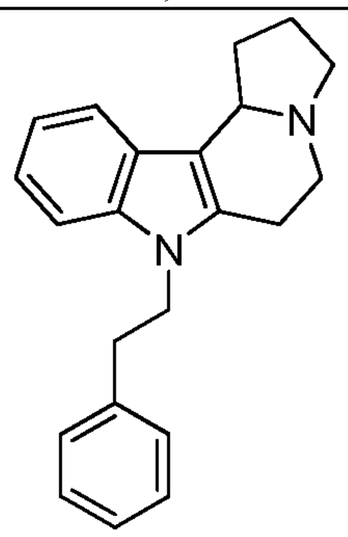
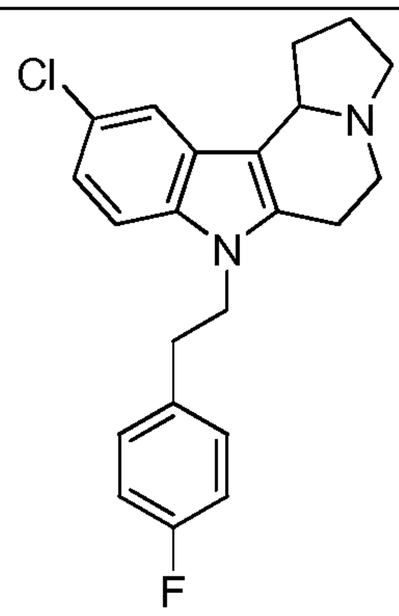
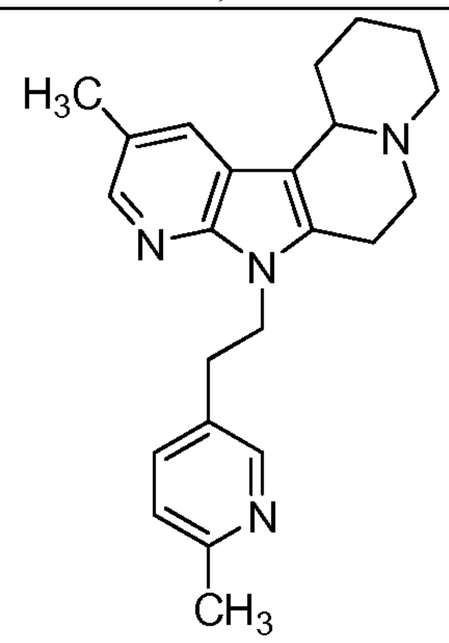
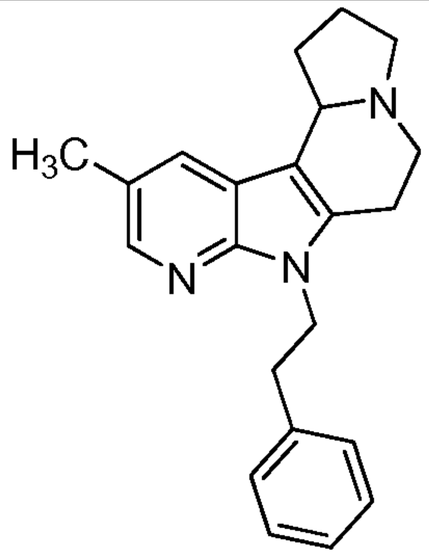
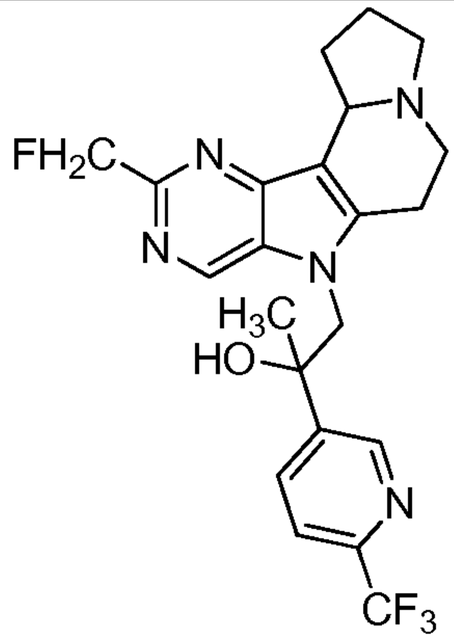
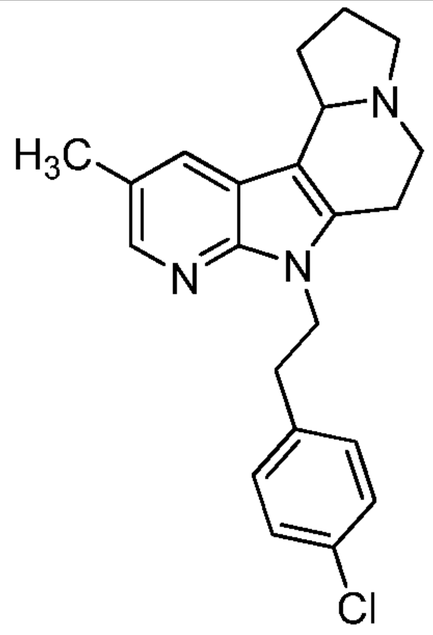
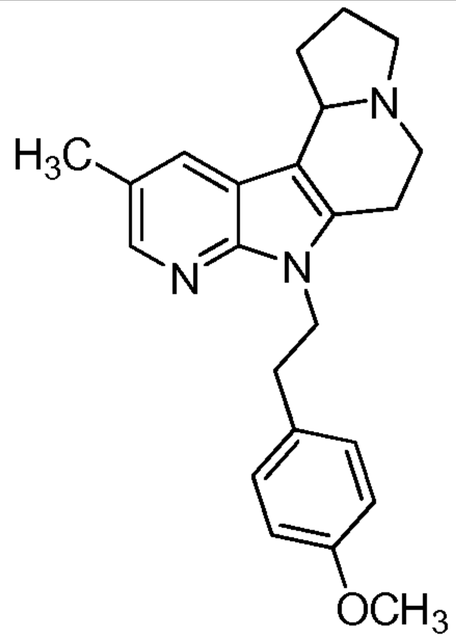
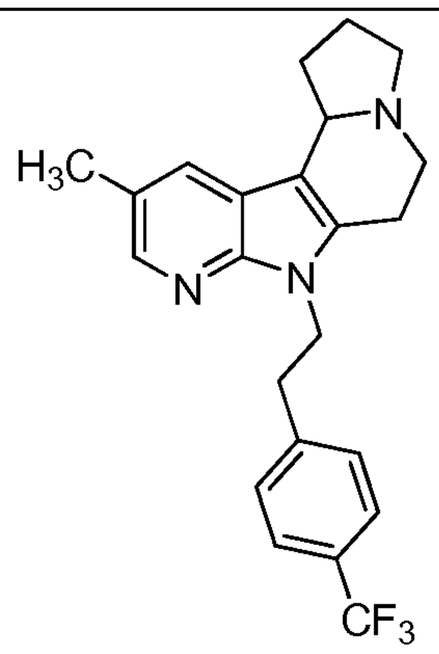
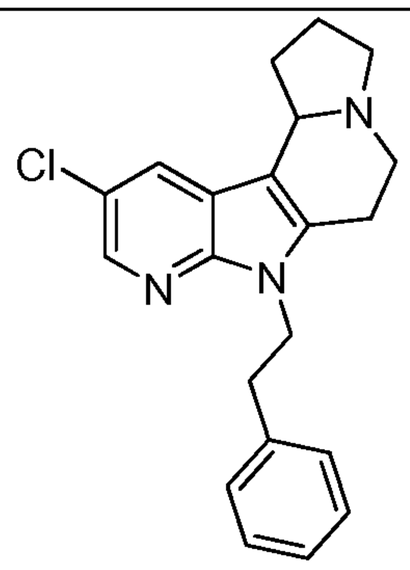
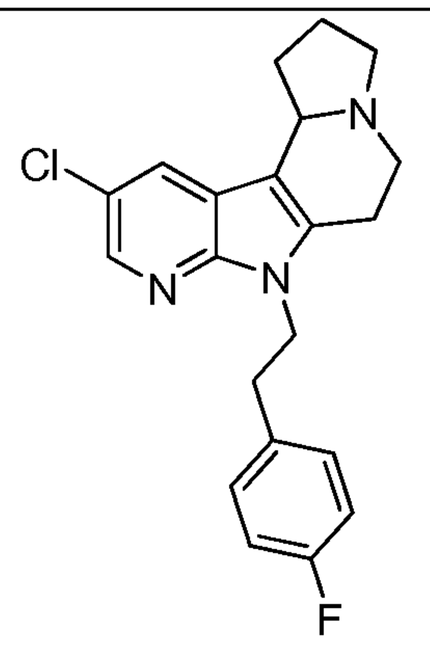
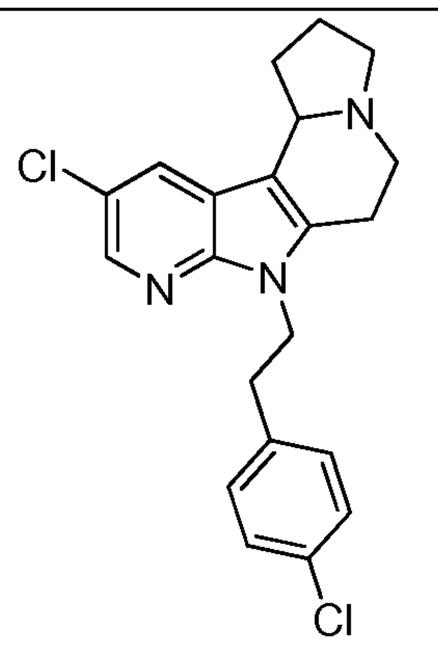
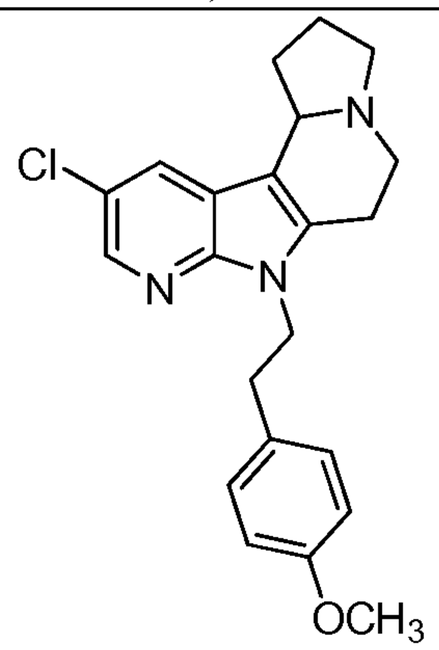
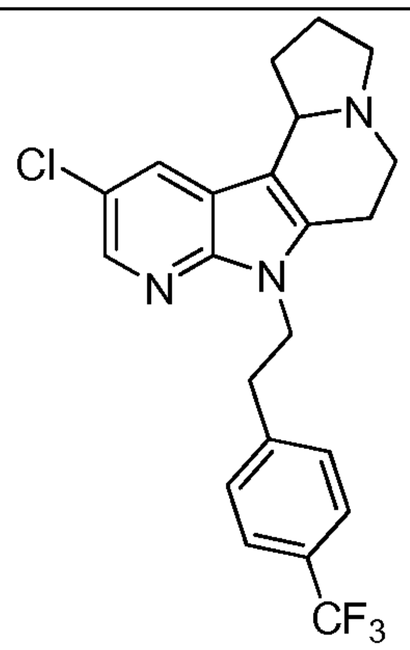
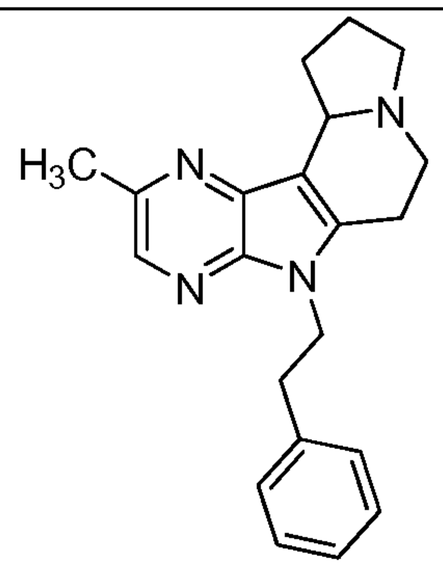
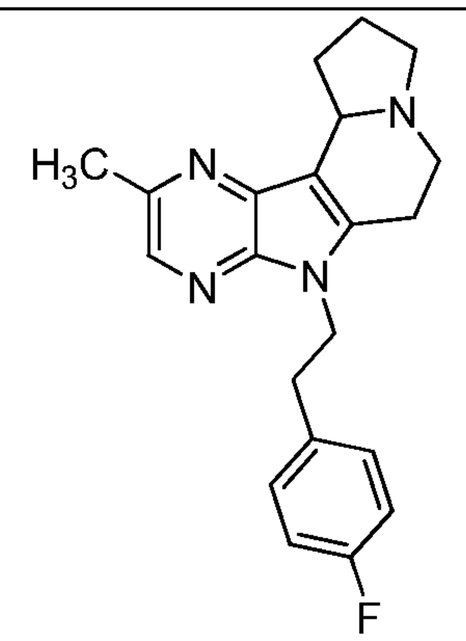
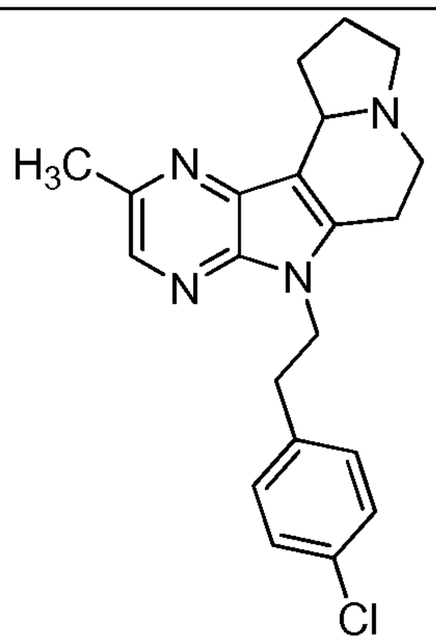
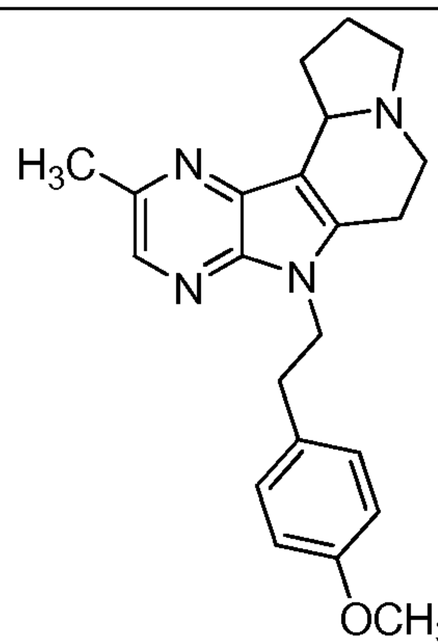
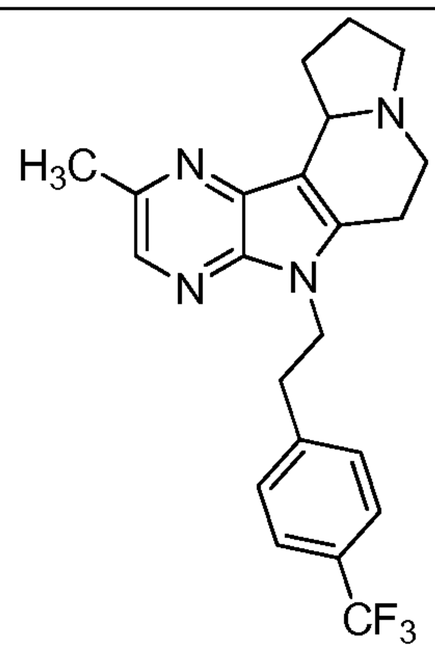
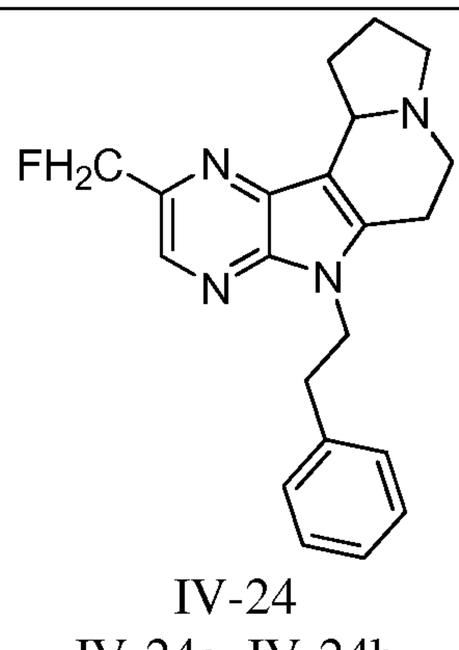
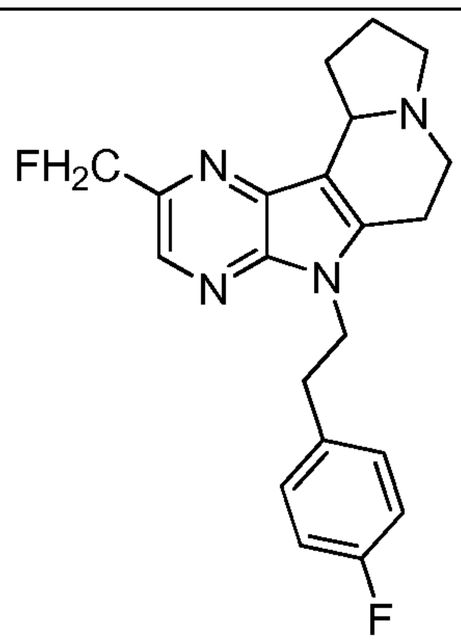
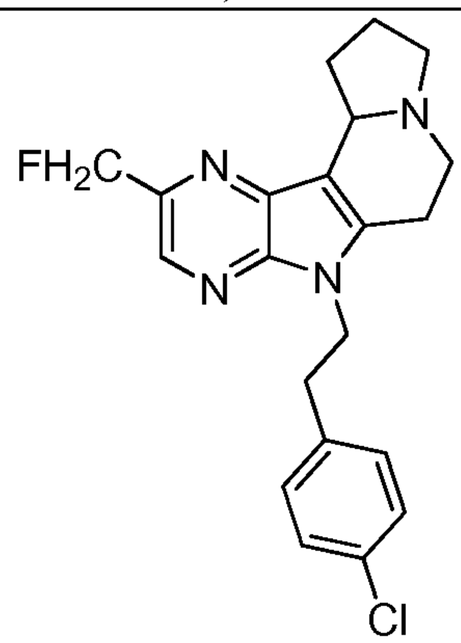
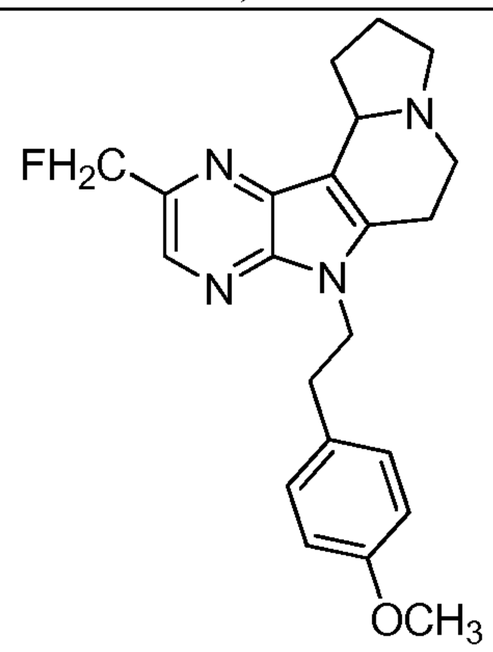
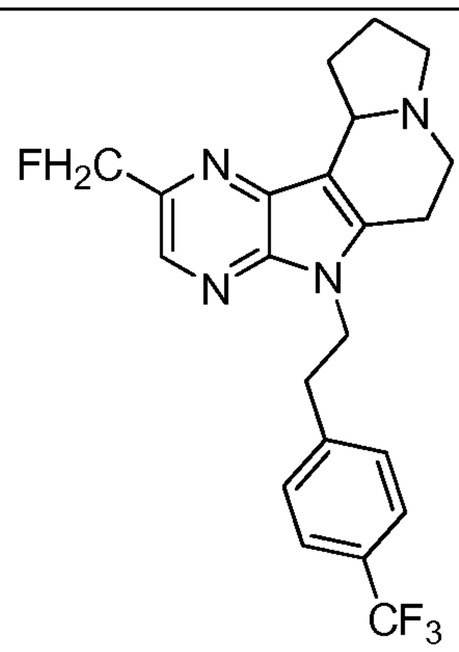
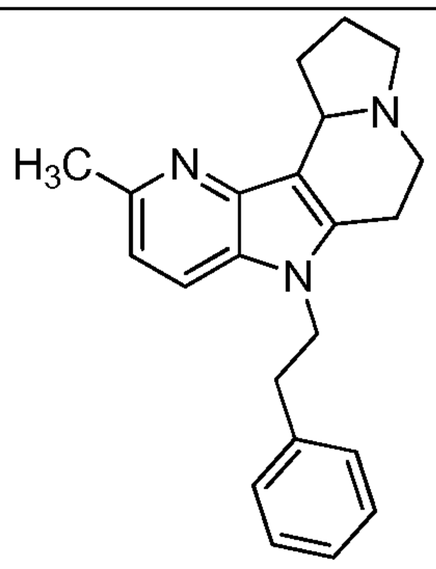
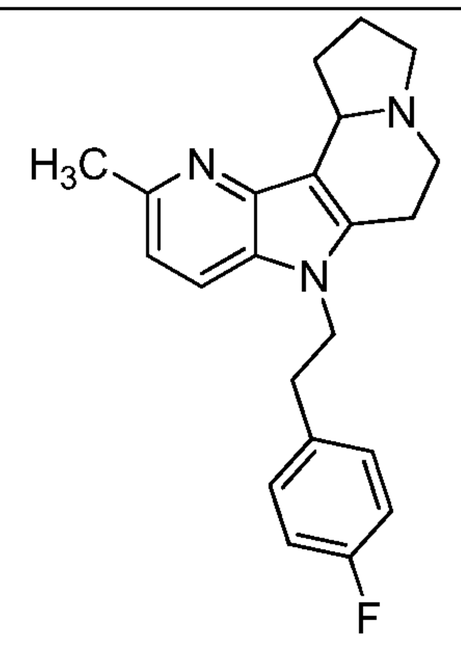
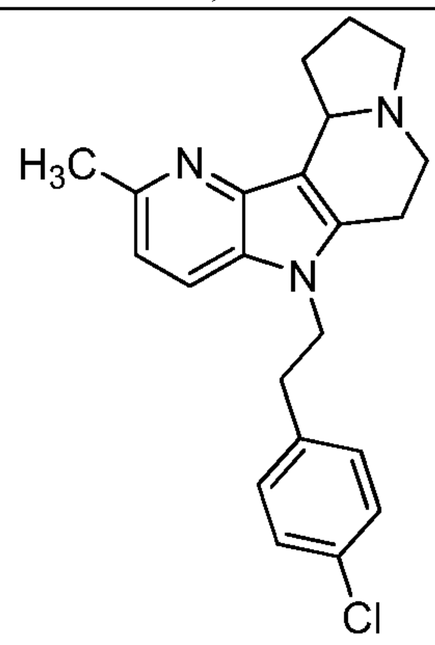
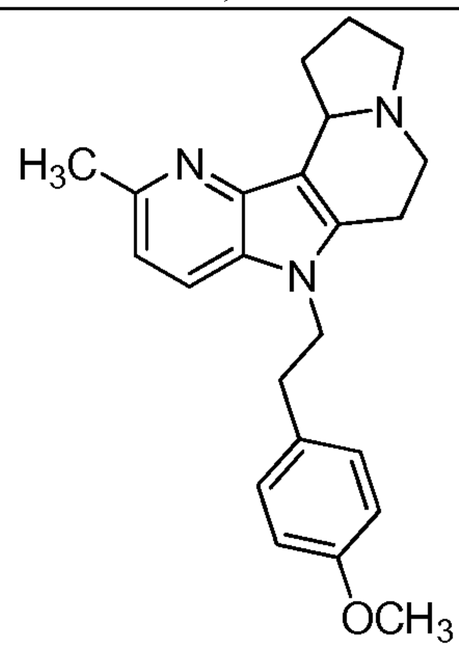
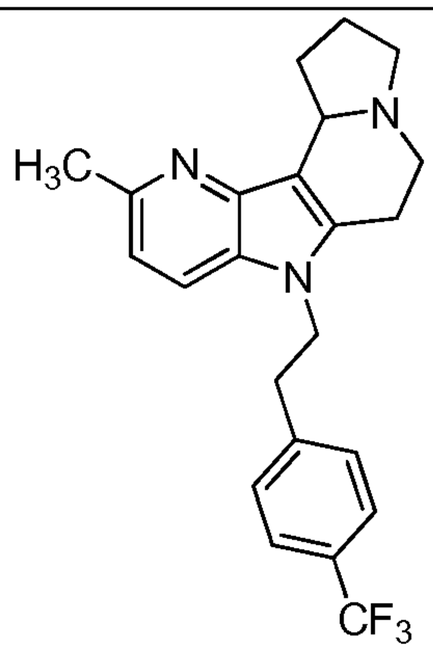
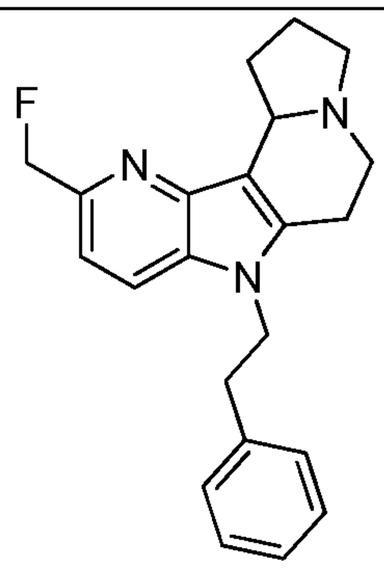
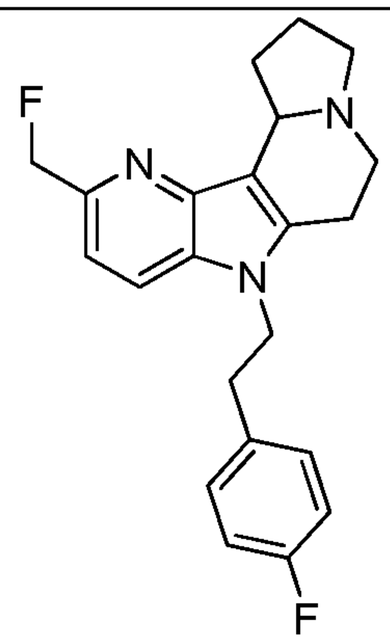
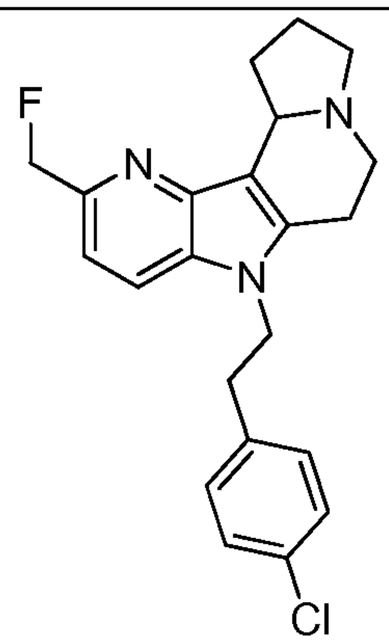
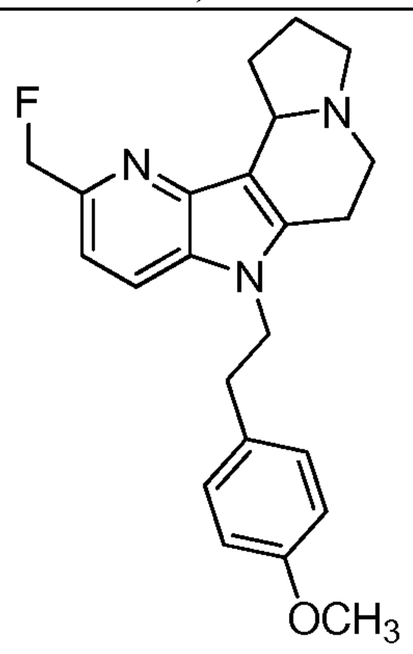
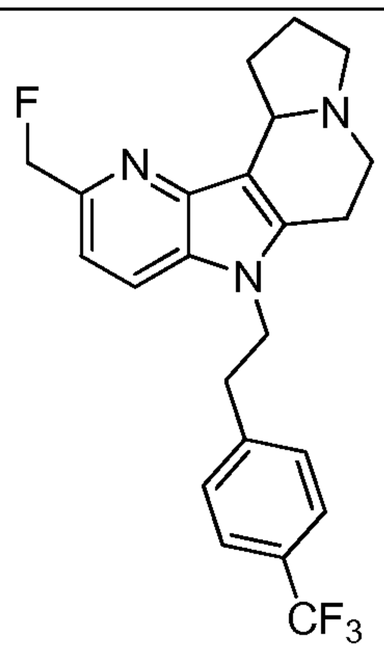
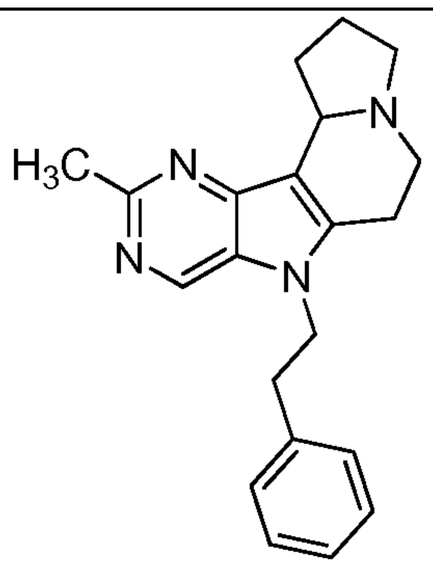
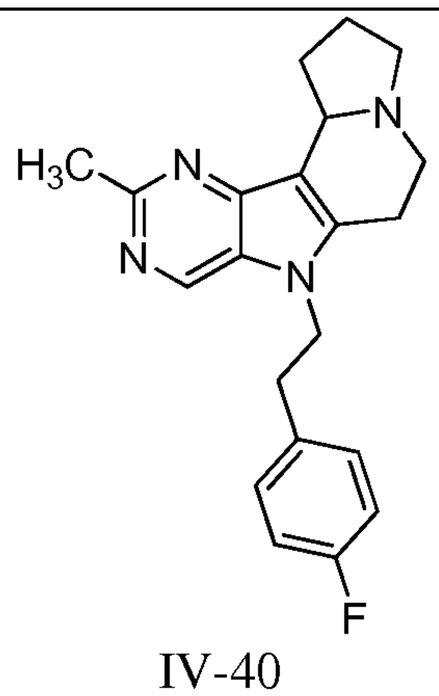
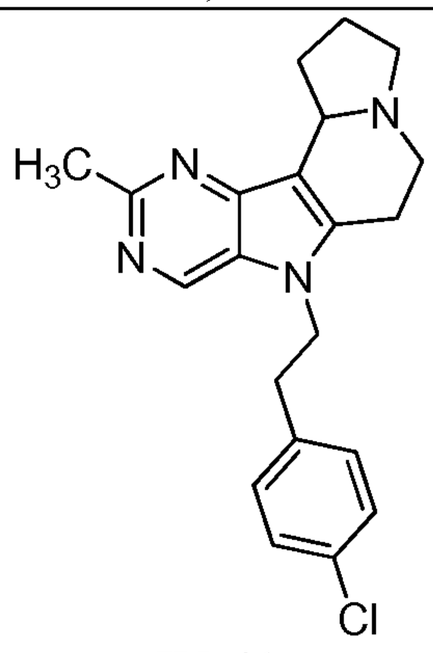
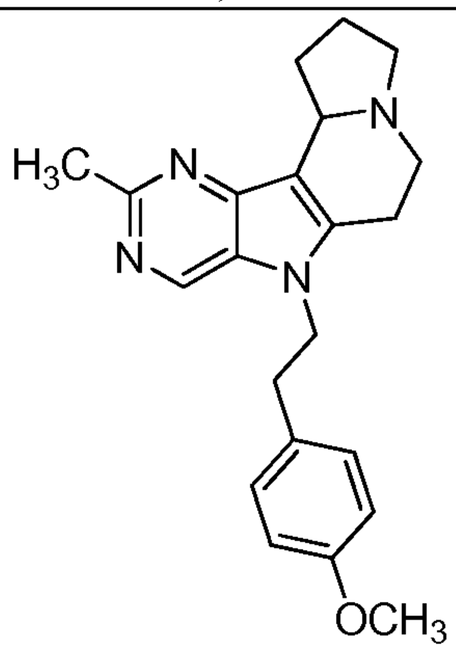
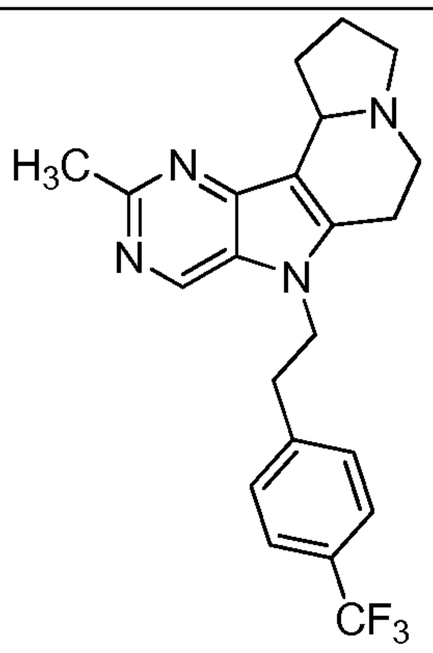
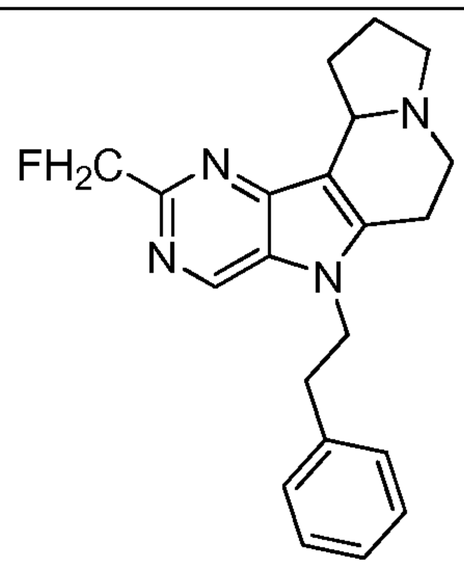
 III-357 III-357a, III-357b	 III-358 III-358a, III-358b	 III-359 III-359a, III-359b	

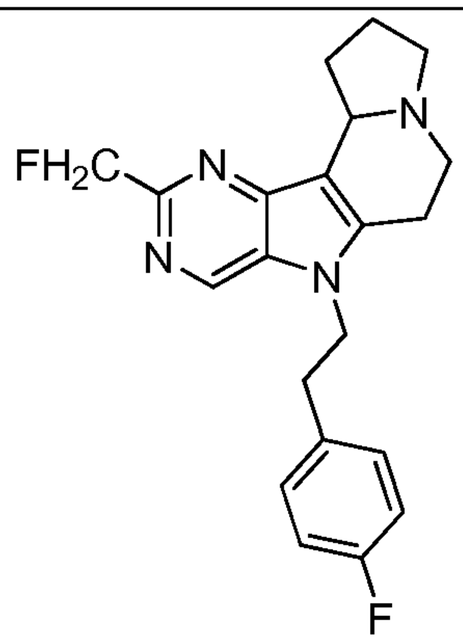
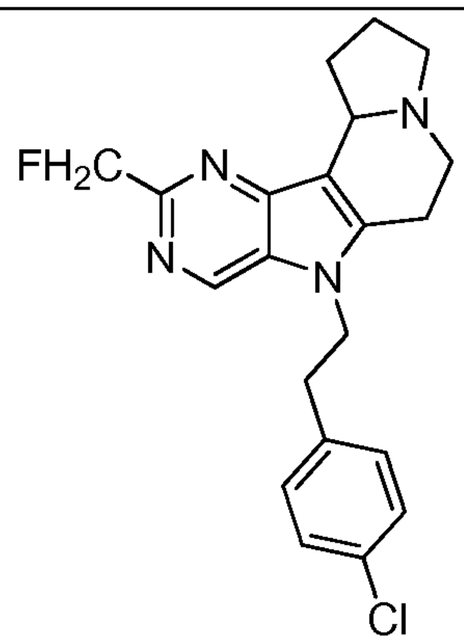
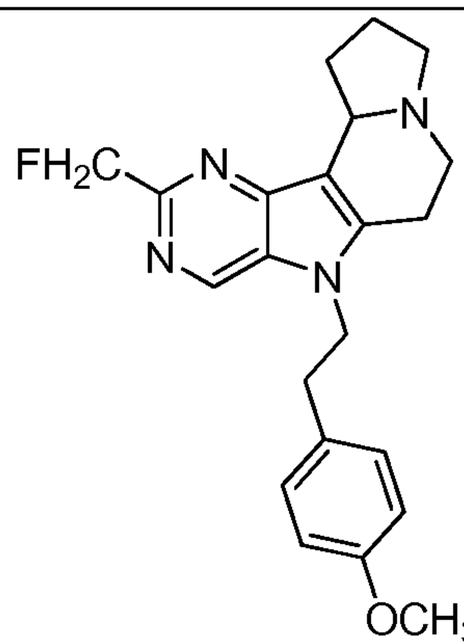
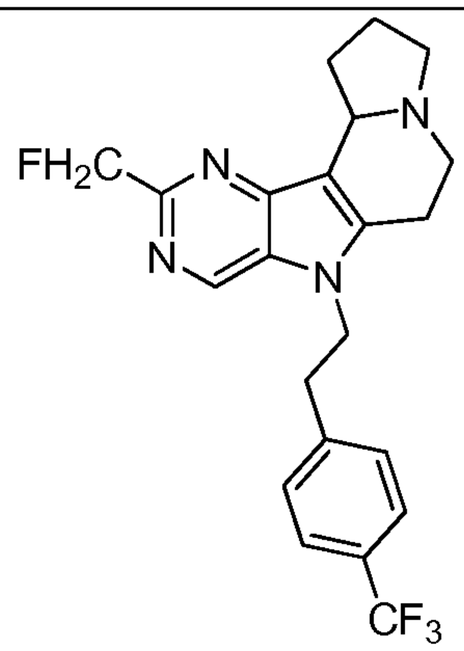
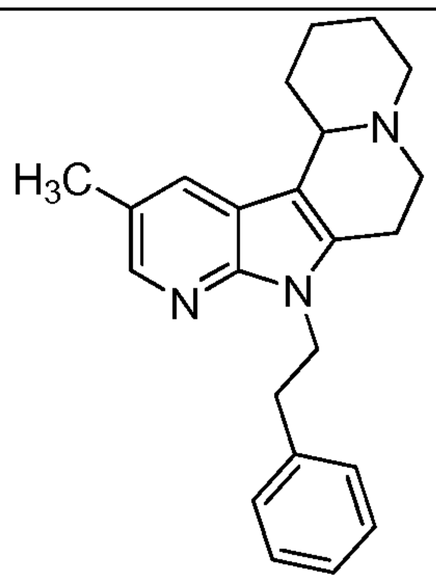
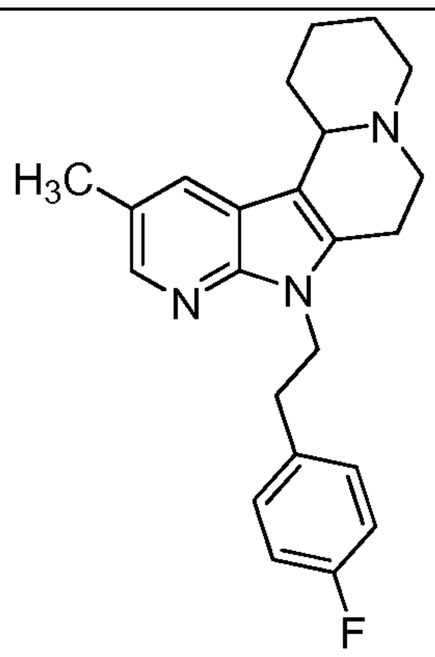
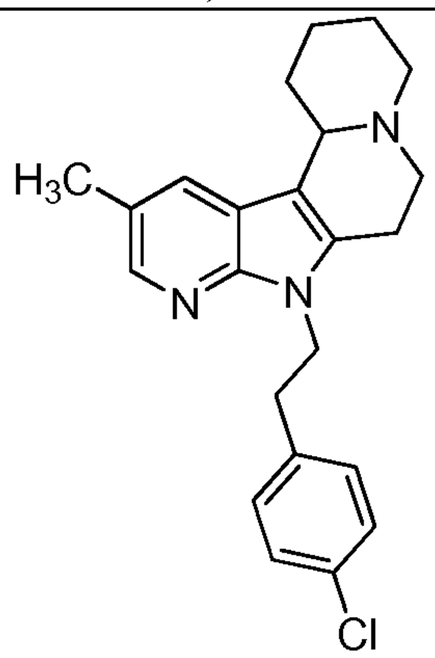
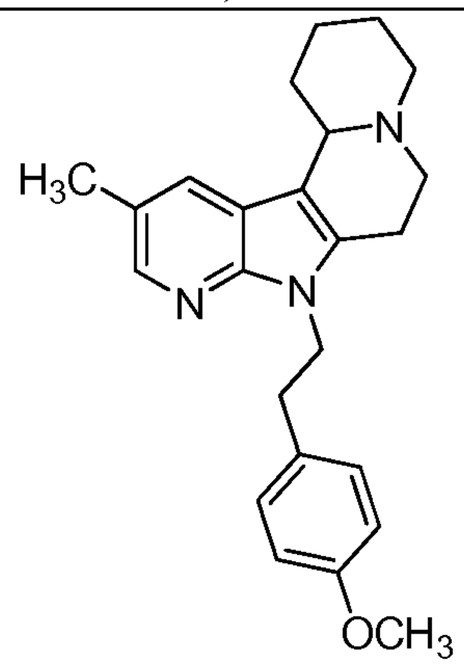
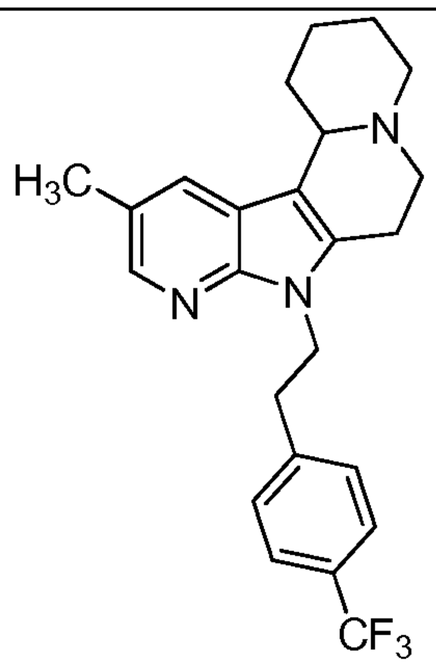
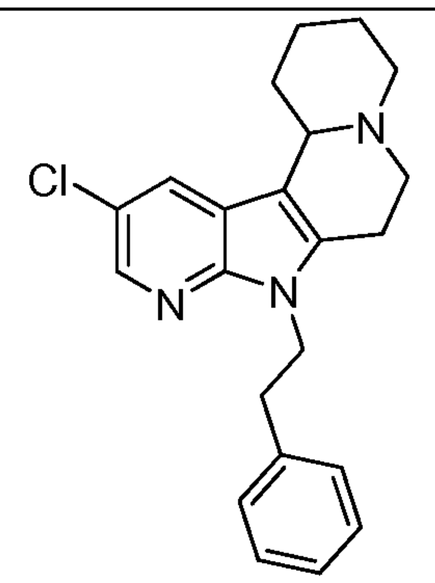
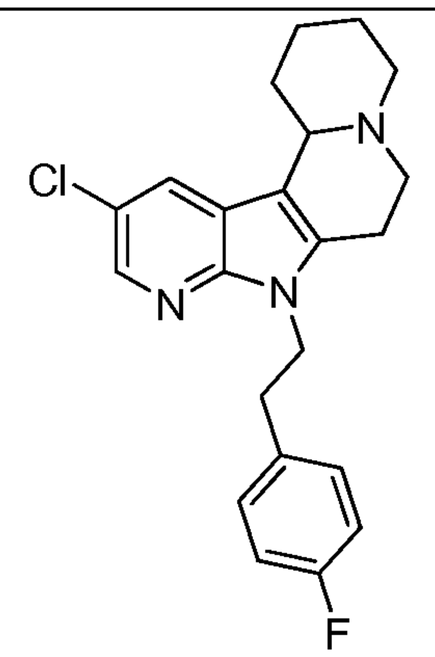
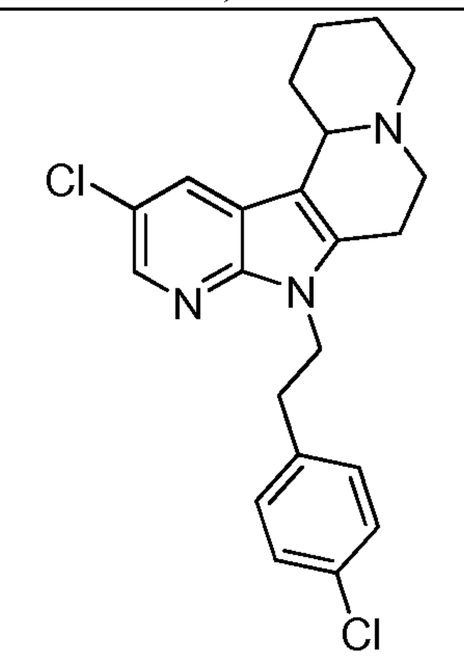
Table 4. Representative Compounds of the Invention

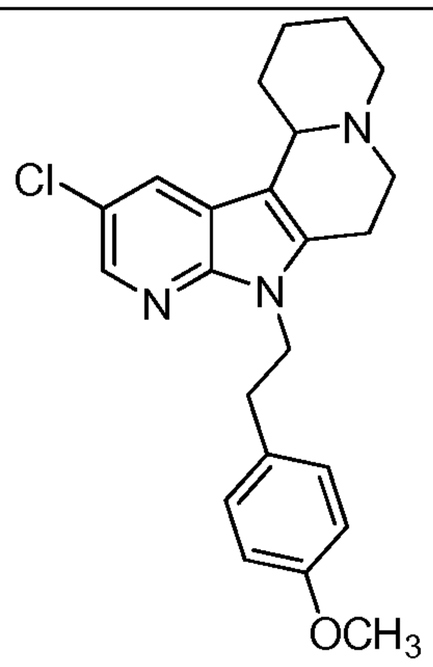
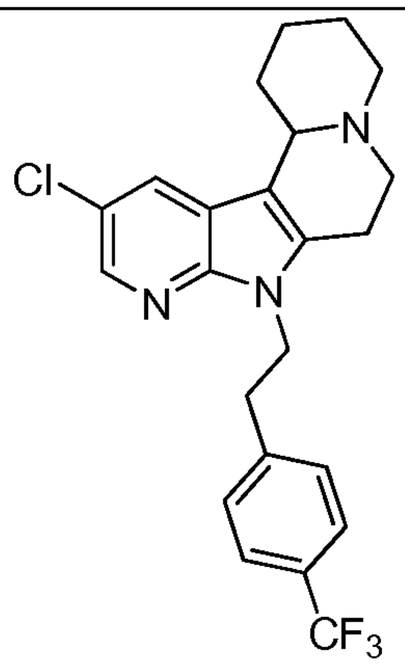
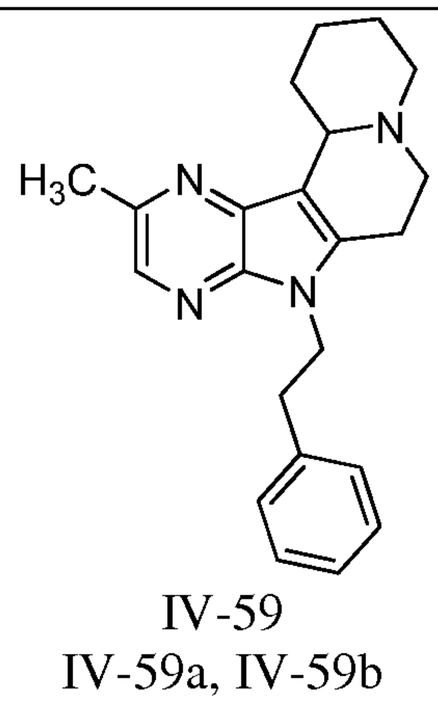
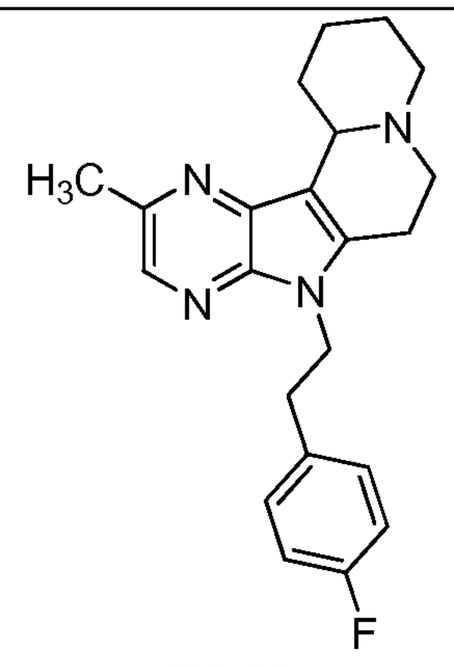
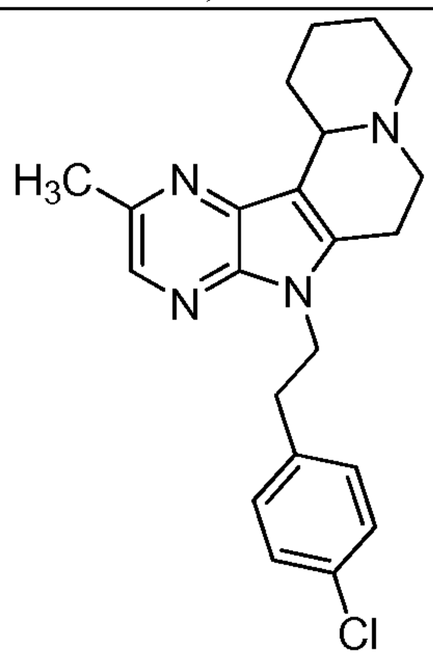
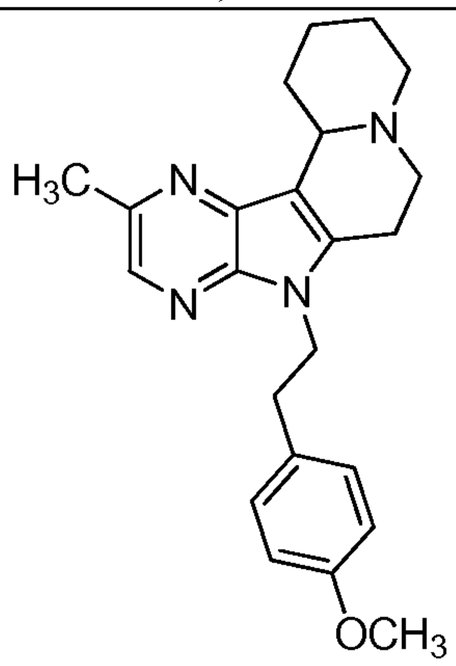
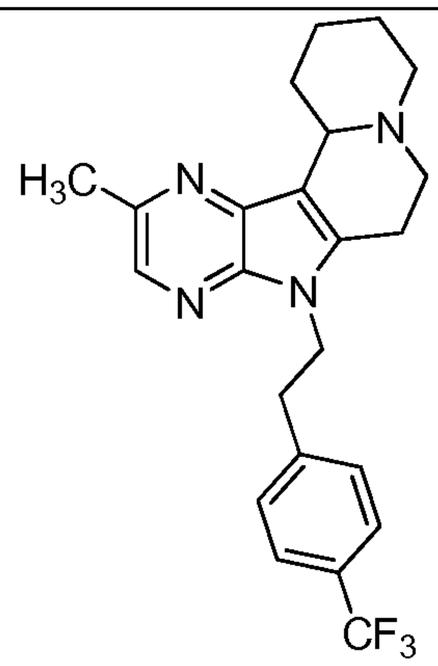
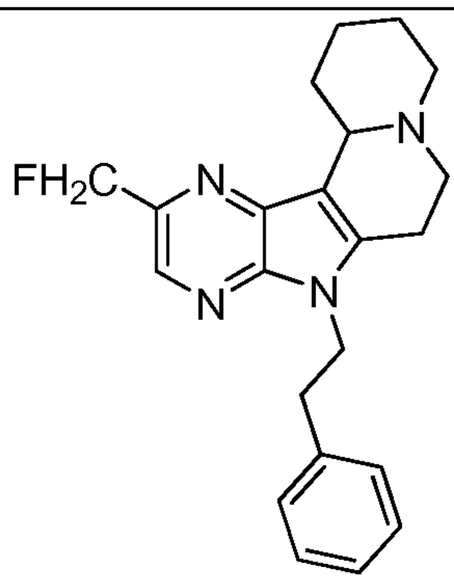
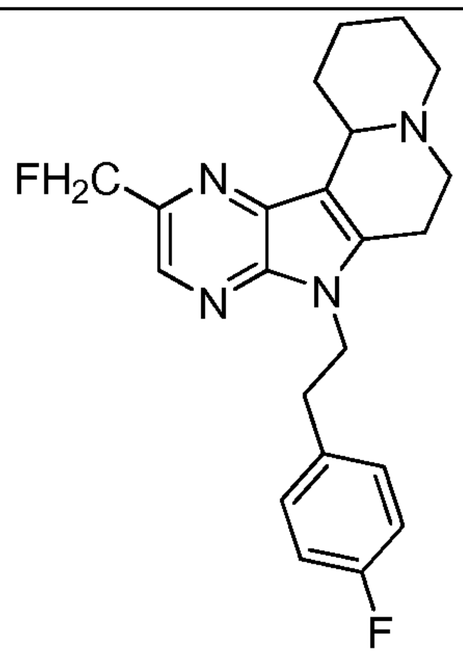
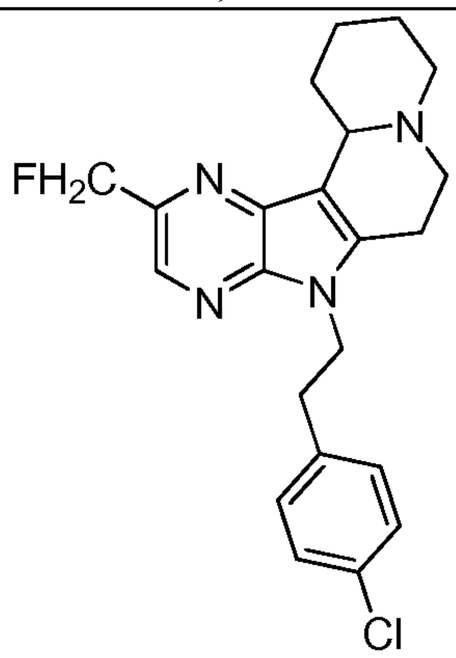
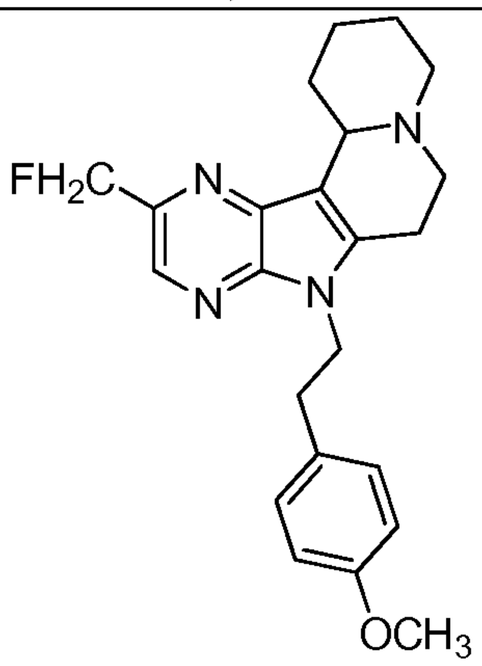
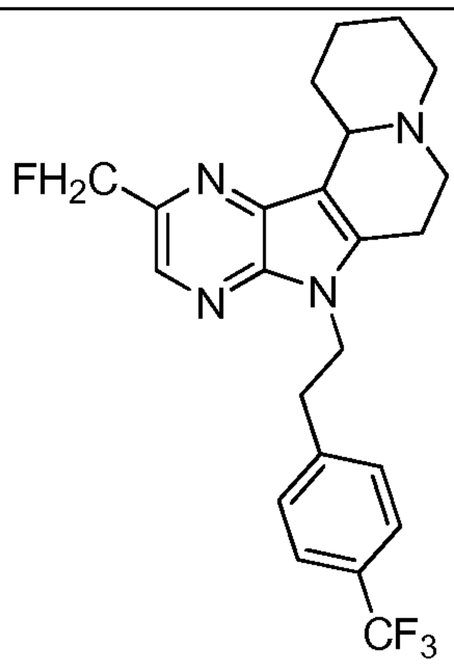
 IV-1 IV-1a, IV-1b	 IV-2 IV-2a, IV-2b	 IV-3 IV-3a, IV-3b, IV-3c, IV-3d	 IV-4 IV-4a, IV-4b
 IV-5 IV-5a, IV-5b, IV-5c, IV-5d	 IV-6 IV-6a, IV-6b	 IV-7 IV-7a, IV-7b	 IV-8 IV-8a, IV-8b

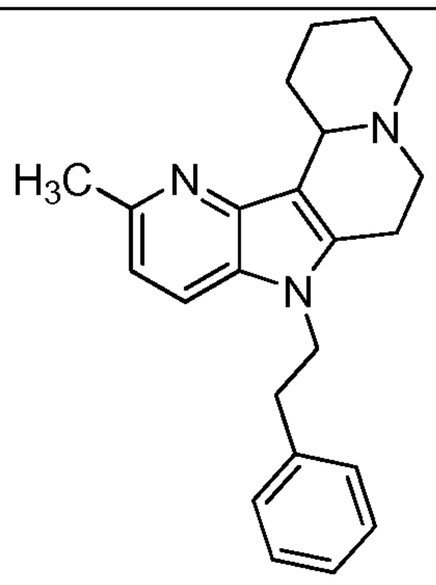
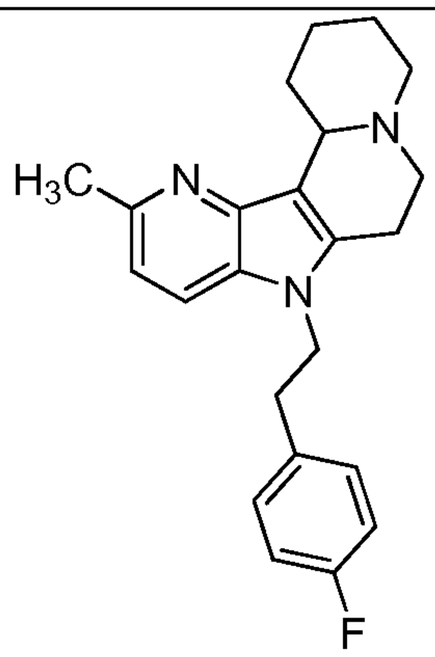
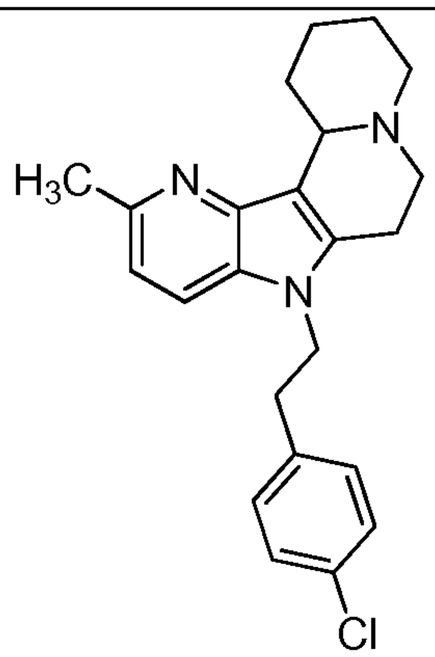
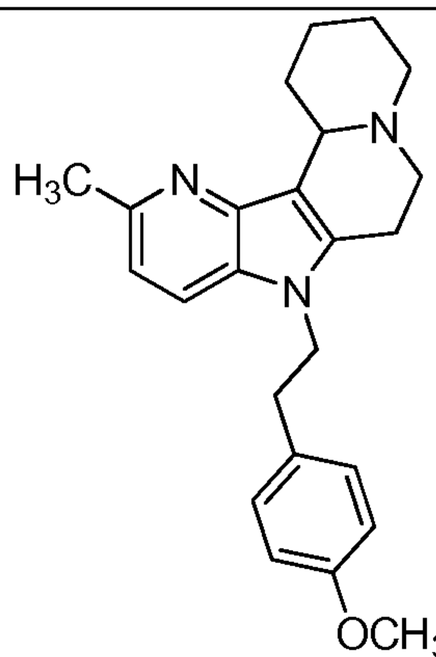
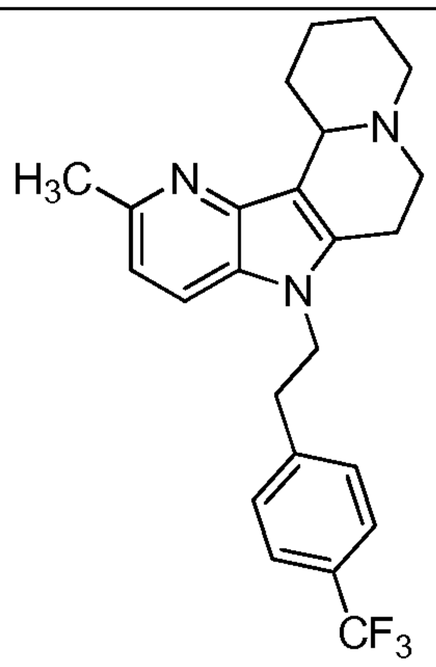
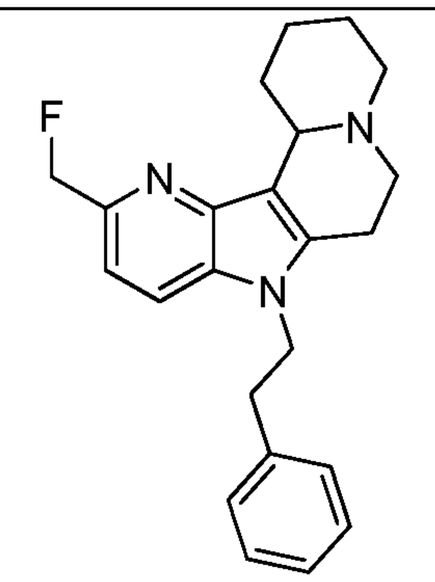
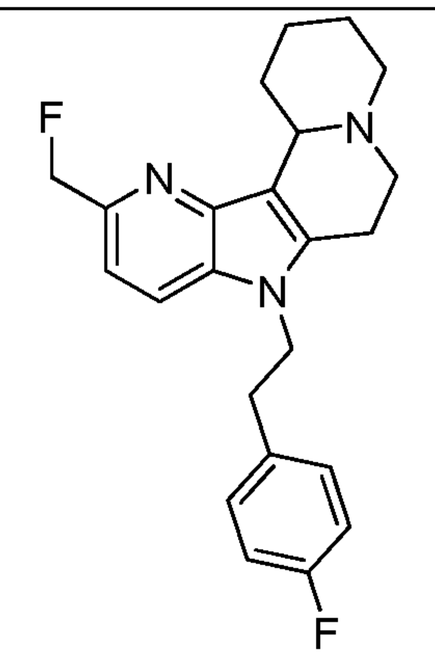
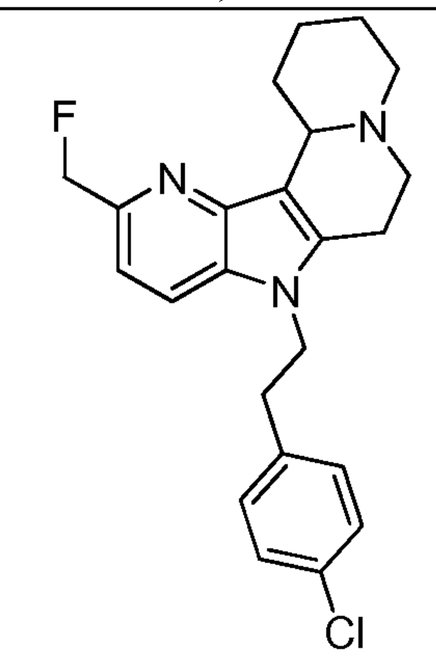
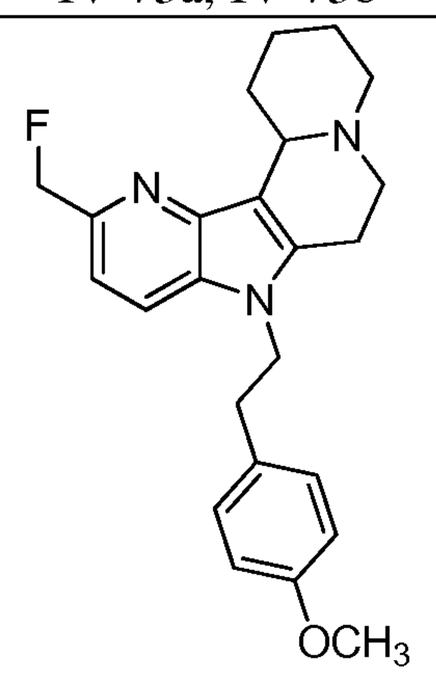
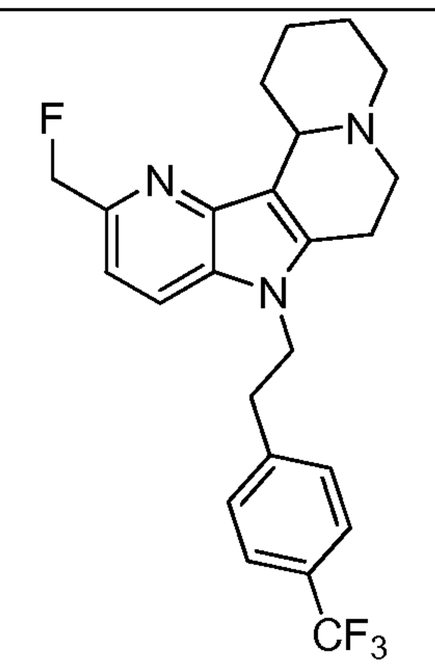
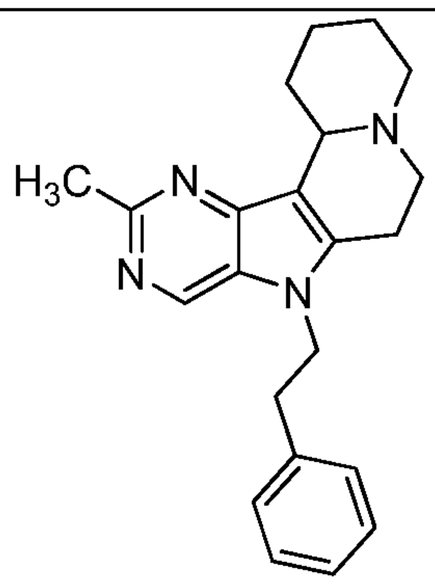
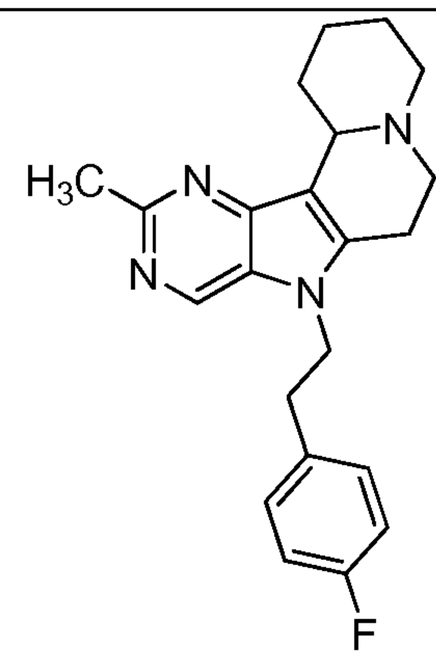
 IV-9 IV-9a, IV-9b	 IV-10 IV-10a, IV-10b, IV-10c, IV-10d	 IV-11 IV-11a, IV-11b	 IV-12 IV-12a, IV-12b
 IV-13 IV-13a, IV-13b	 IV-14 IV-14a, IV-14b	 IV-15 IV-15a, IV-15b	 IV-16 IV-16a, IV-16b
 IV-17 IV-17a, IV-17b	 IV-18 IV-18a, IV-18b	 IV-19 IV-19a, IV-19b	 IV-20 IV-20a, IV-20b

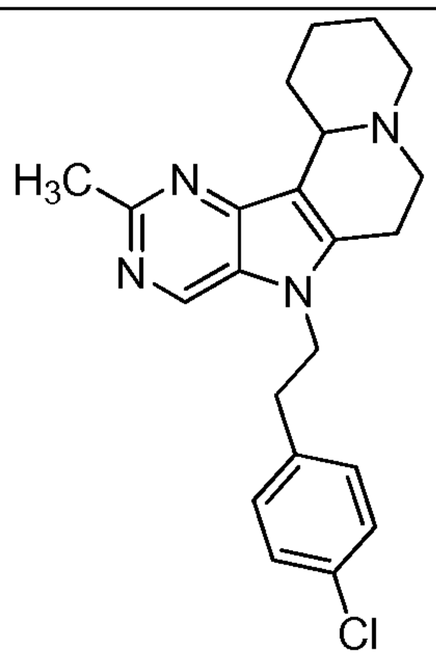
 IV-21 IV-21a, IV-21b	 IV-22 IV-22a, IV-22b	 IV-23 IV-23a, IV-23b	 IV-24 IV-24a, IV-24b
 IV-25 IV-25a, IV-25b	 IV-26 IV-26a, IV-26b	 IV-27 IV-27a, IV-27b	 IV-28 IV-28a, IV-28b
 IV-29 IV-29a, IV-29b	 IV-30 IV-30a, IV-30b	 IV-31 IV-31a, IV-31b	 IV-32 IV-32a, IV-32b

 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

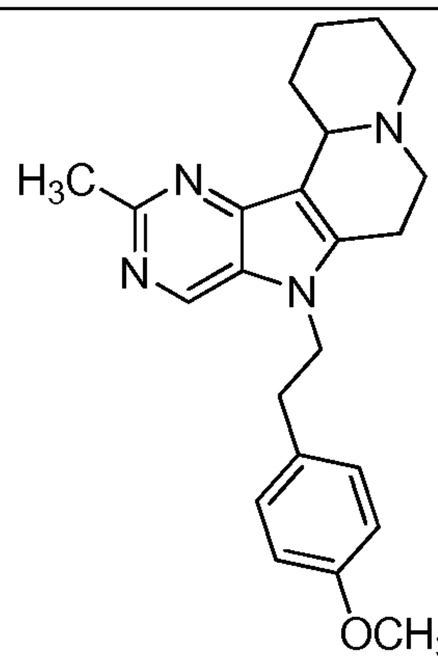
 IV-45 IV-45a, IV-45b	 IV-46 IV-46a, IV-46b	 IV-47 IV-47a, IV-47b	 IV-48 IV-48a, IV-48b
 IV-49 IV-49a, IV-49b	 IV-50 IV-50a, IV-50b	 IV-51 IV-51a, IV-51b	 IV-52 IV-52a, IV-52b
 IV-53 IV-53a, IV-53b	 IV-54 IV-54a, IV-54b	 IV-55 IV-55a, IV-55b	 IV-56 IV-56a, IV-56b

 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

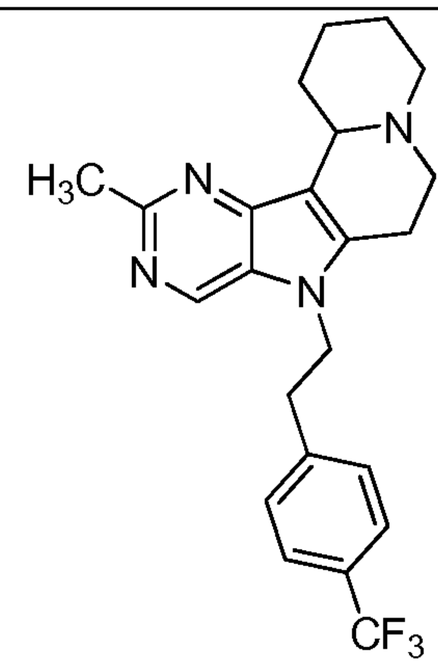
 IV-69 IV-69a, IV-69b	 IV-70 IV-70a, IV-70b	 IV-71 IV-71a, IV-71b	 IV-72 IV-72a, IV-72b
 IV-73 IV-73a, IV-73b	 IV-74 IV-74a, IV-74b	 IV-75 IV-75a, IV-75b	 IV-76 IV-76a, IV-76b
 IV-77 IV-77a, IV-77b	 IV-78 IV-78a, IV-78b	 IV-79 IV-79a, IV-79b	 IV-80 IV-80a, IV-80b



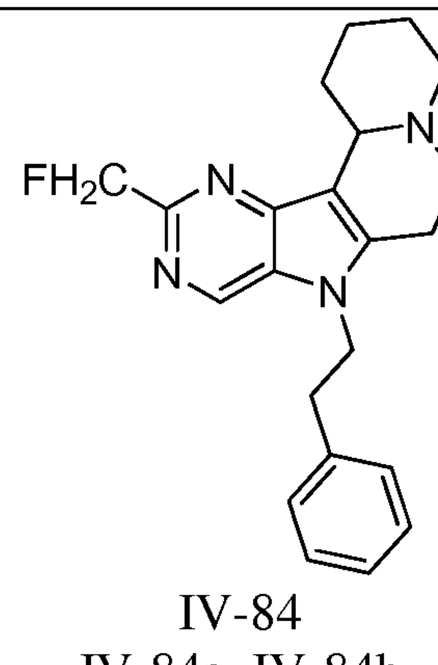
IV-81
IV-81a, IV-81b



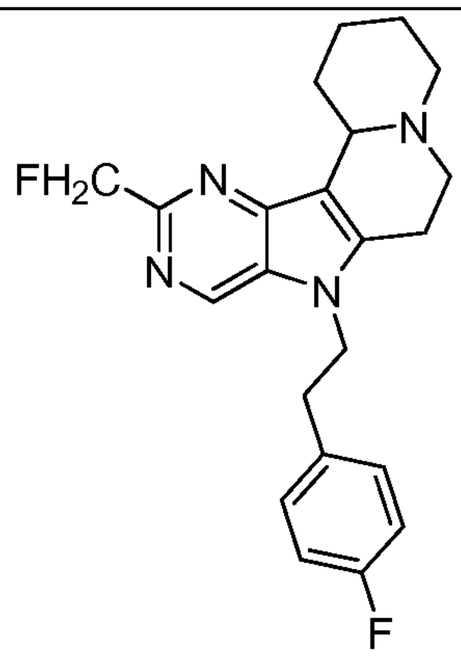
IV-82
IV-82a, IV-82b



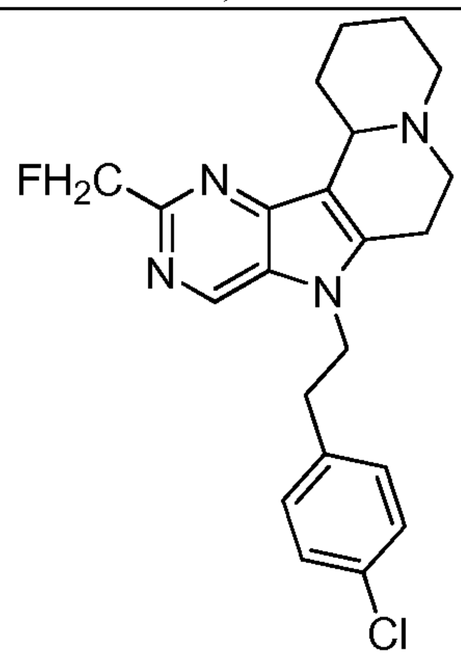
IV-83
IV-83a, IV-83b



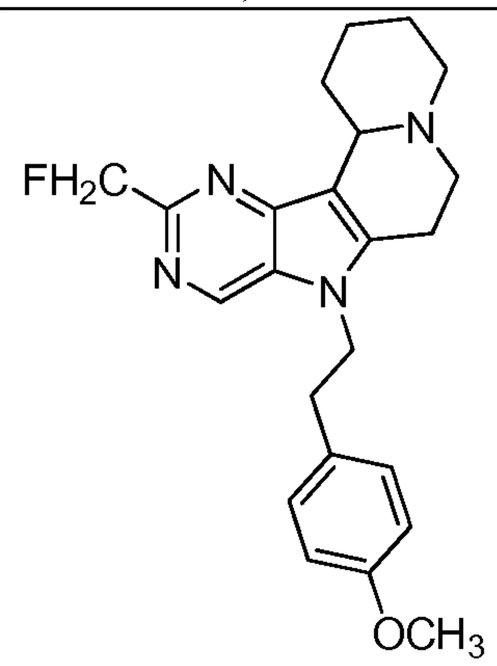
IV-84
IV-84a, IV-84b



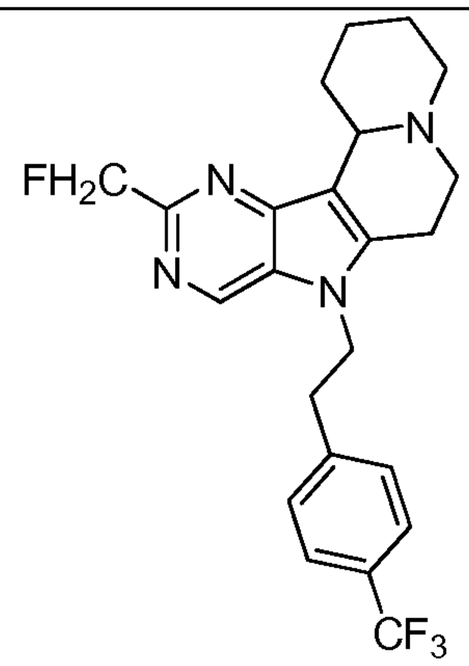
IV-85
IV-85a, IV-85b



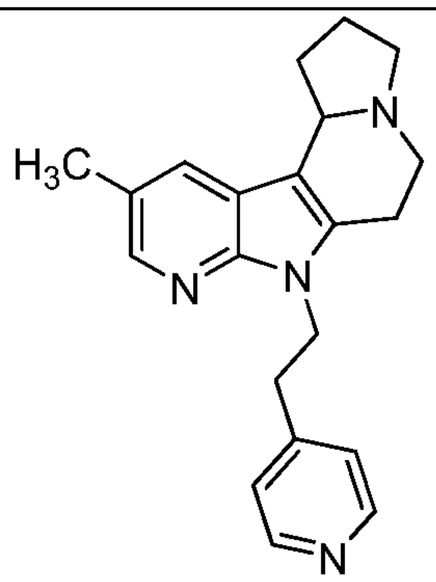
IV-86
IV-86a, IV-86b



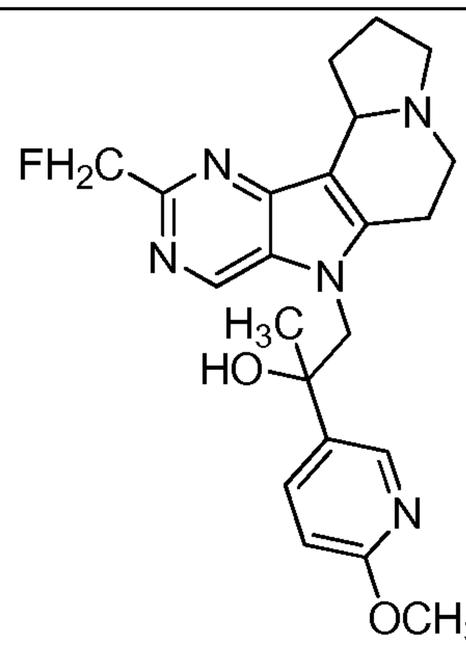
IV-87
IV-87a, IV-87b



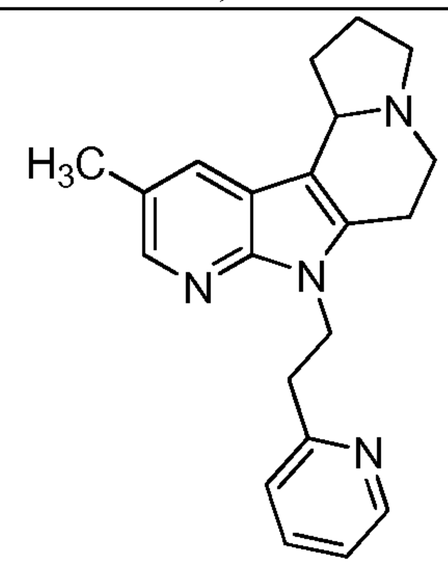
IV-88
IV-88a, IV-88b



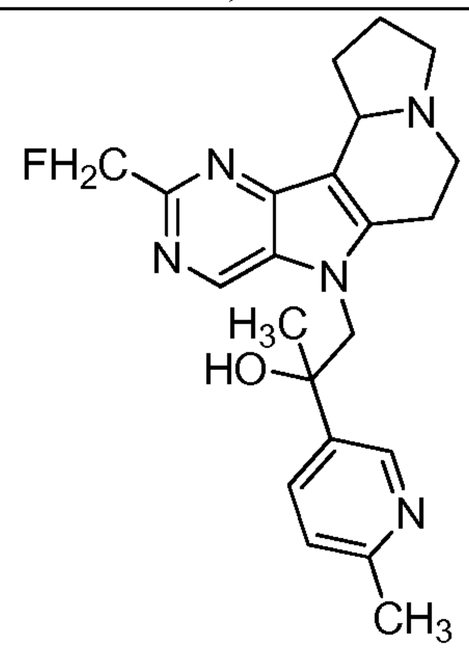
IV-89
IV-89a, IV-89b



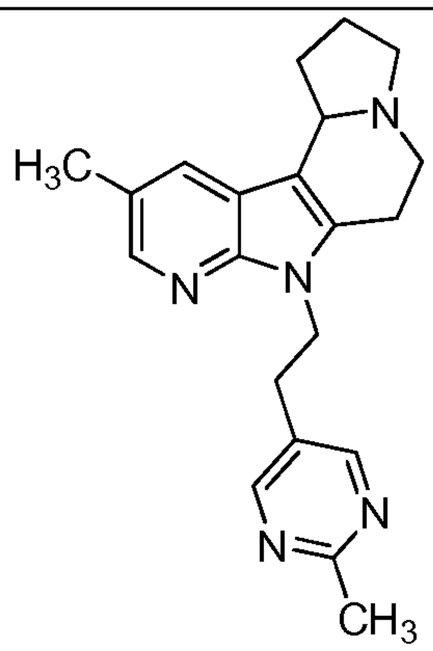
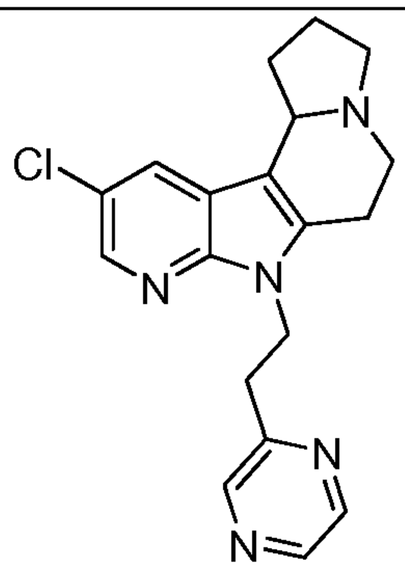
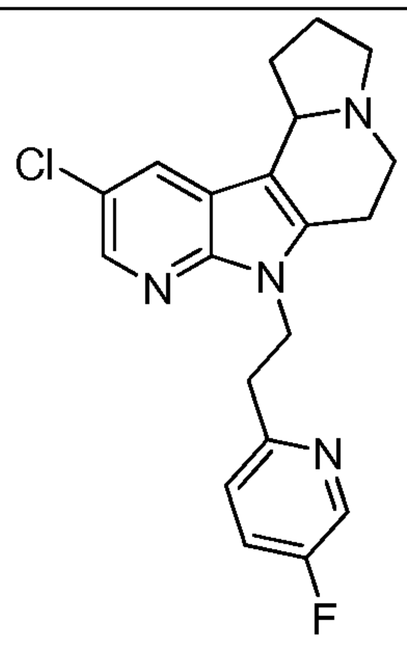
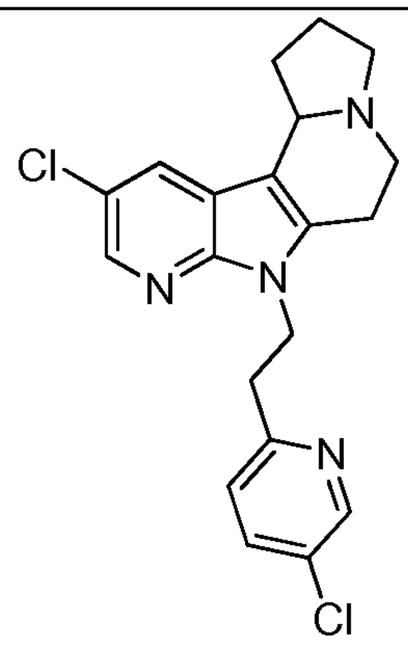
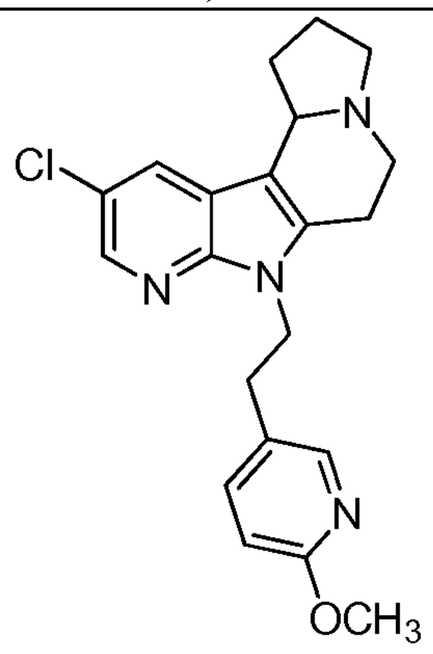
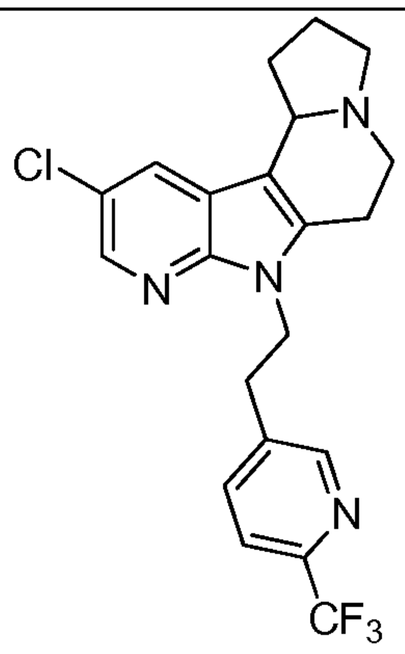
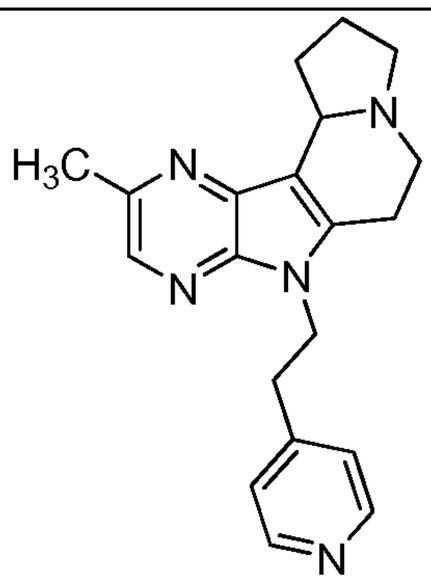
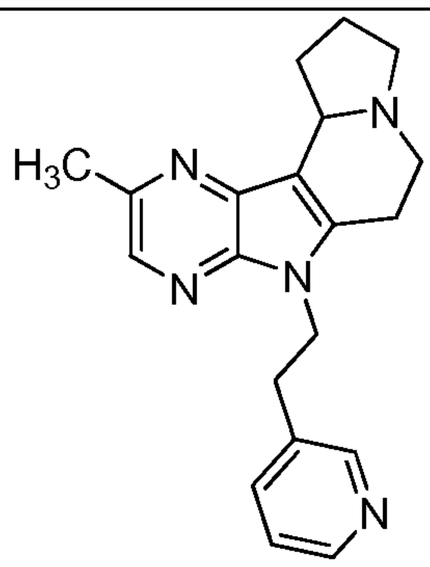
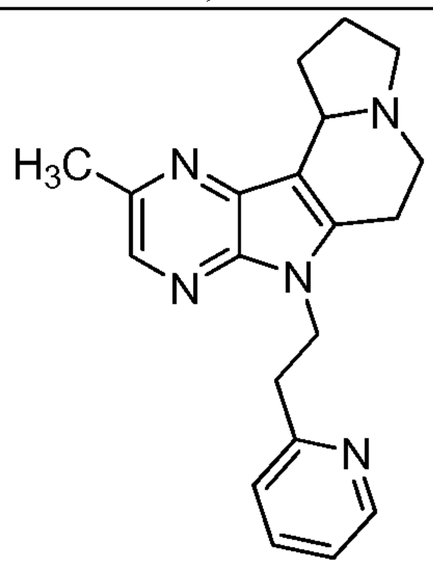
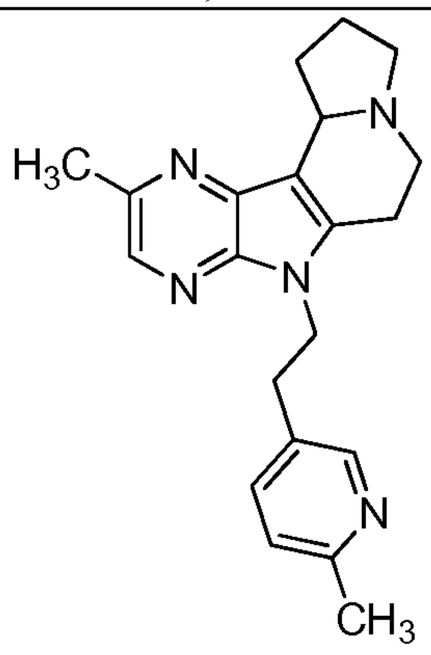
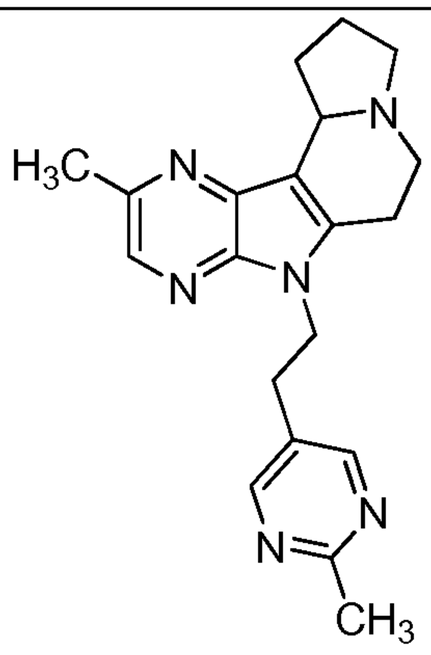
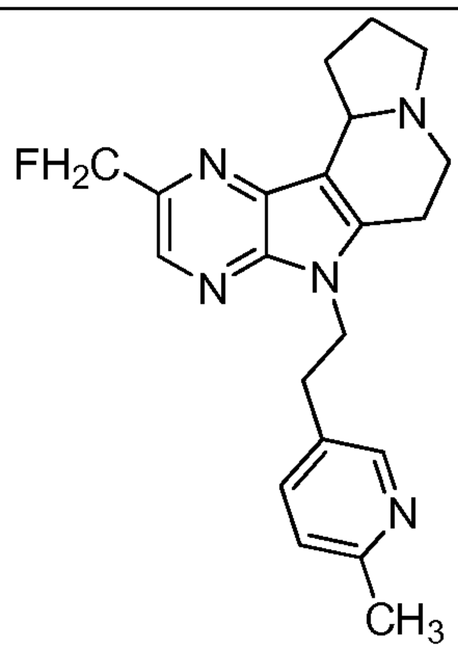
IV-90
IV-90a, IV-90b, IV-90c, IV-90d

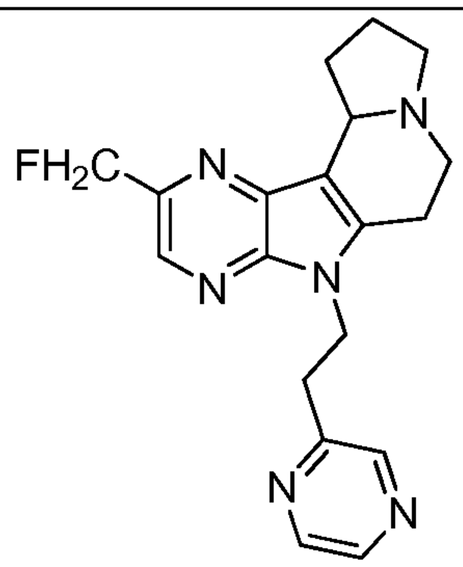
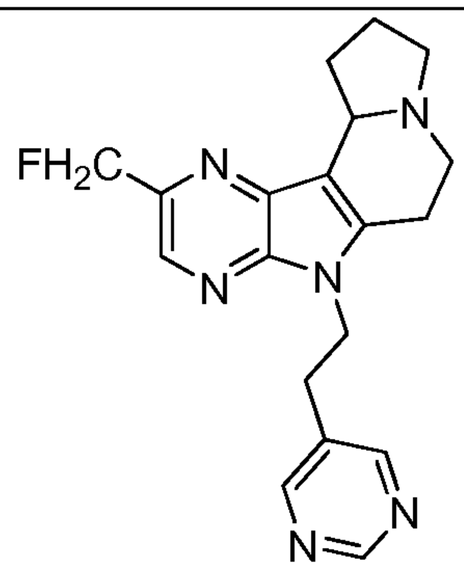
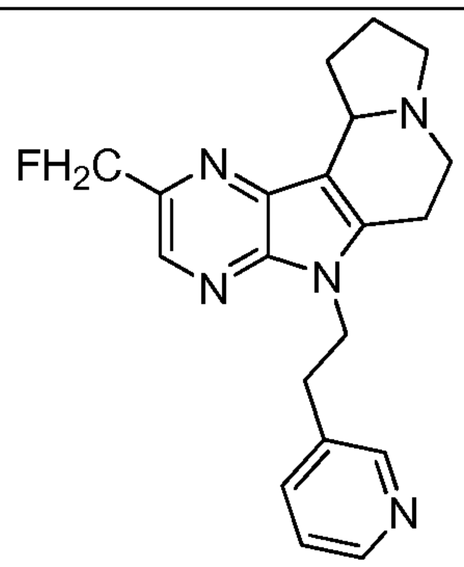
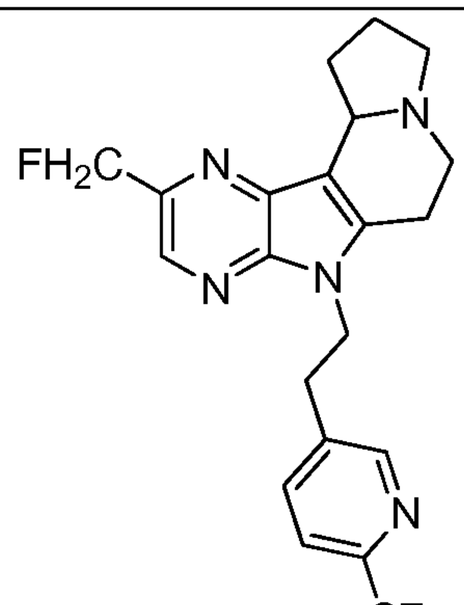
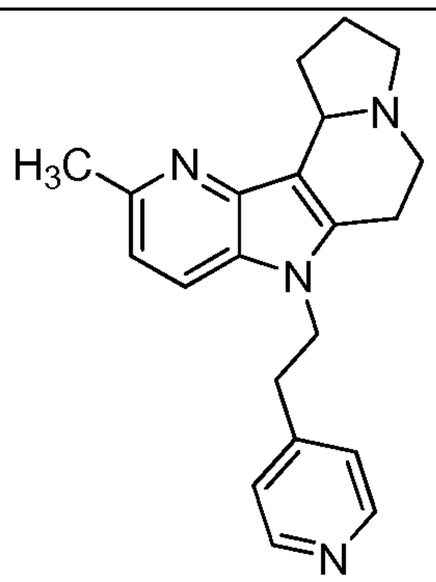
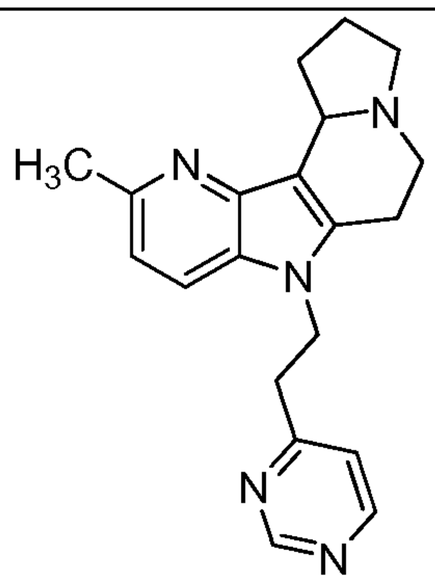
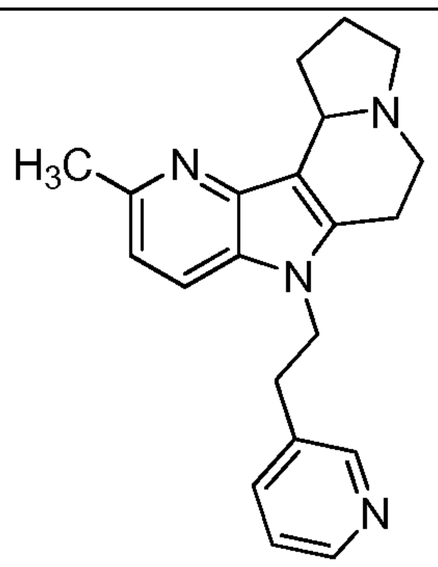
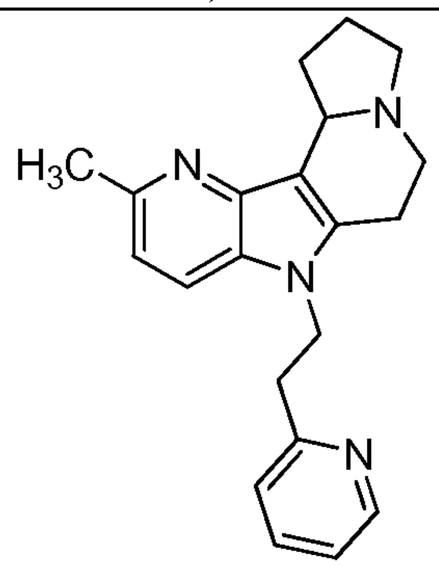
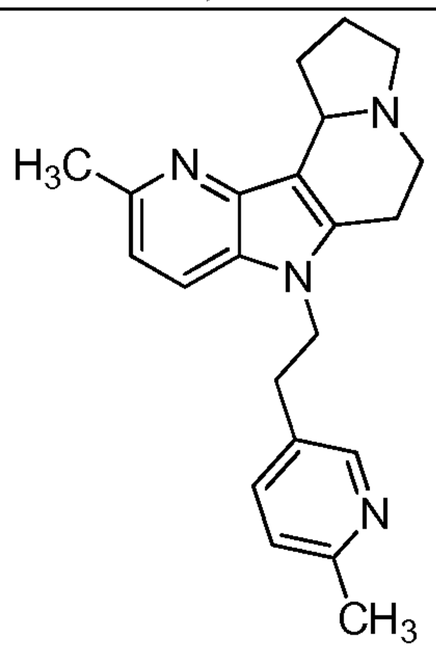
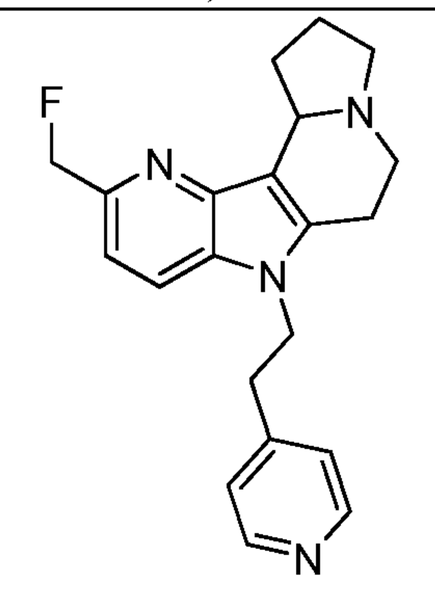
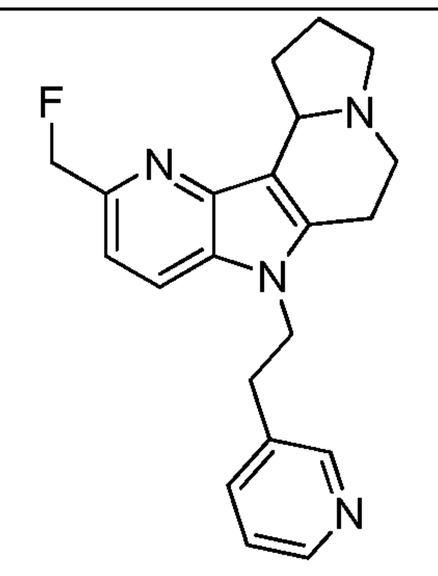
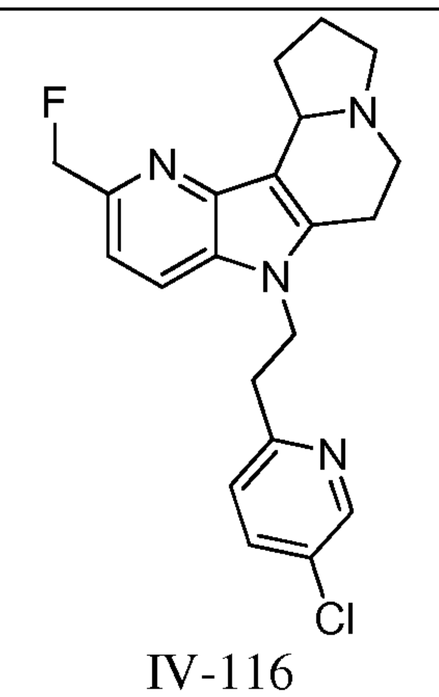


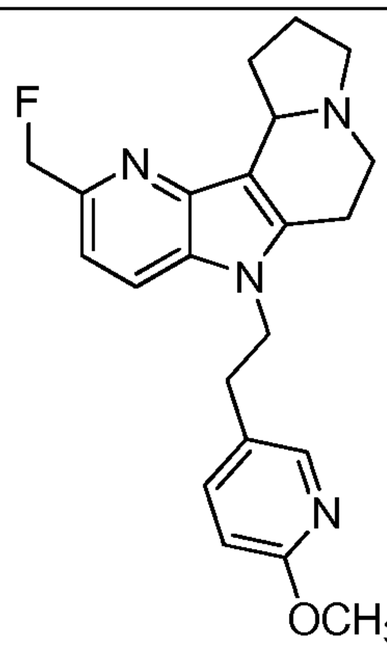
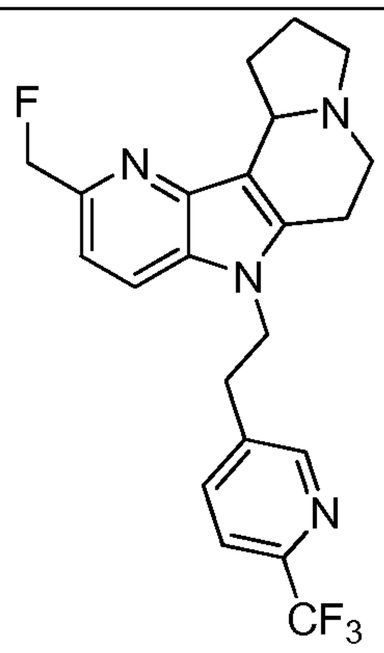
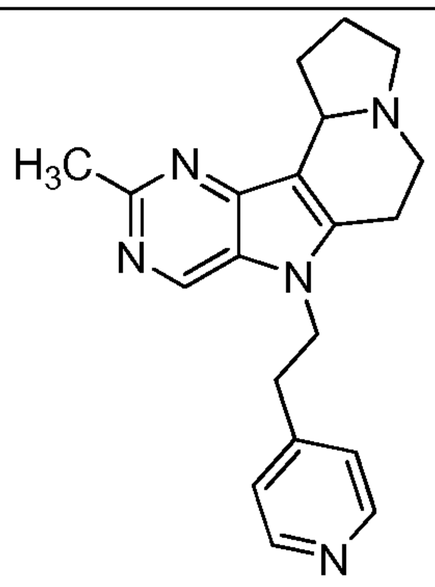
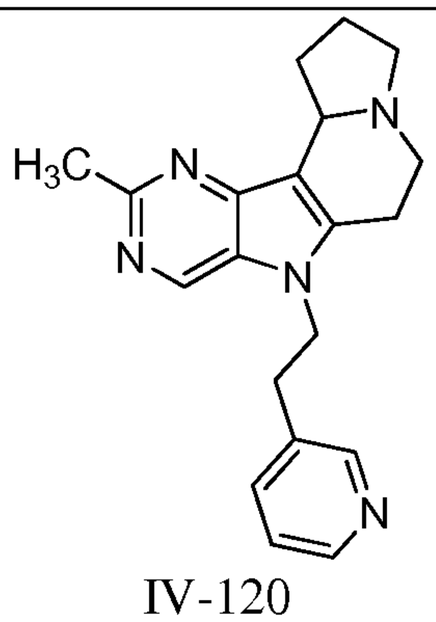
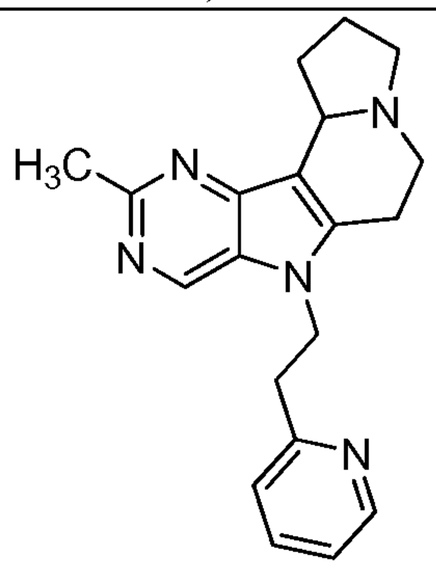
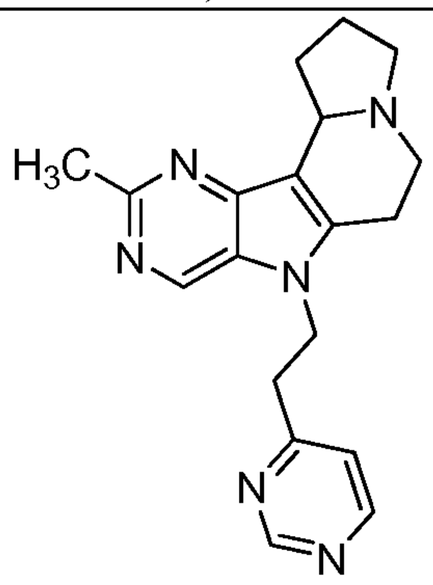
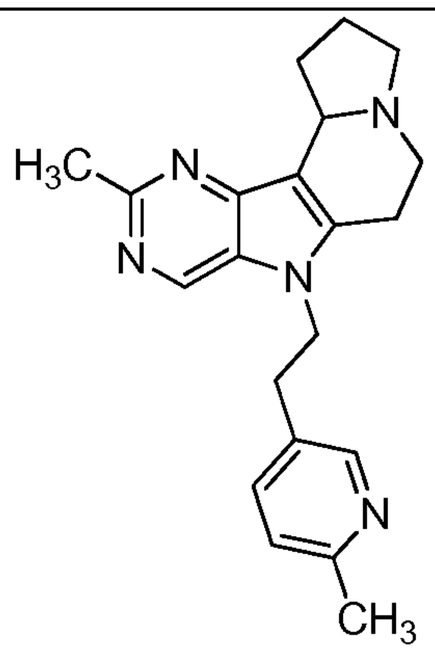
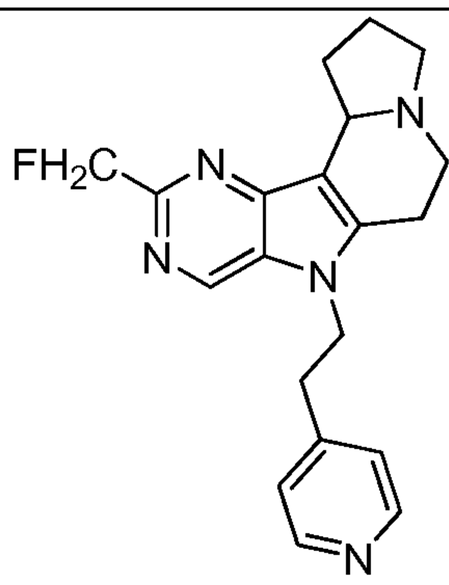
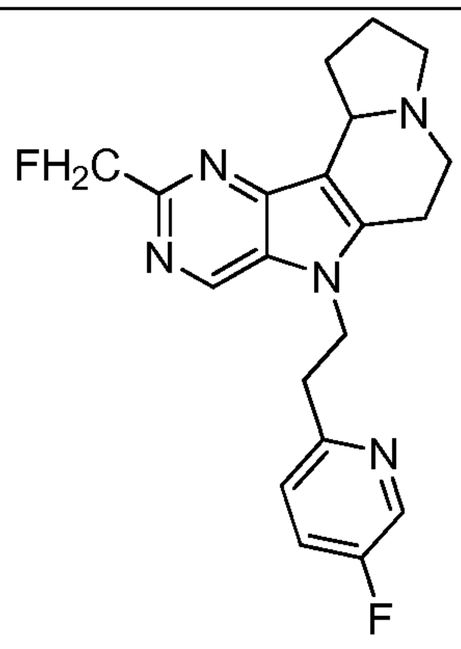
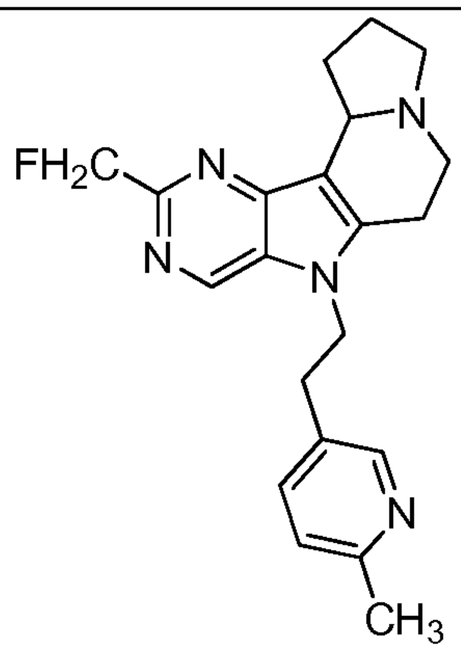
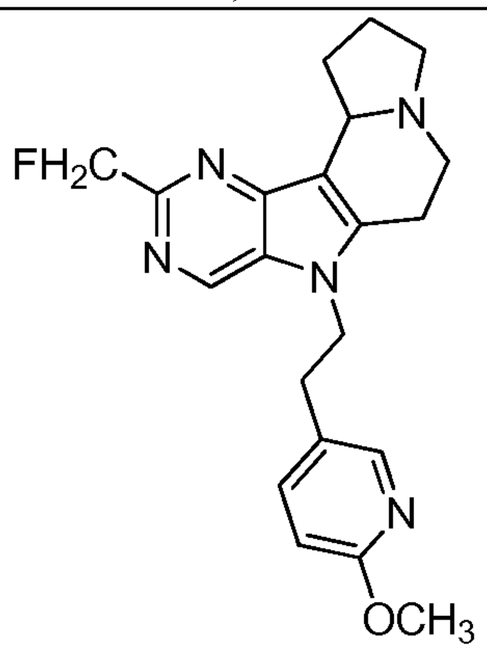
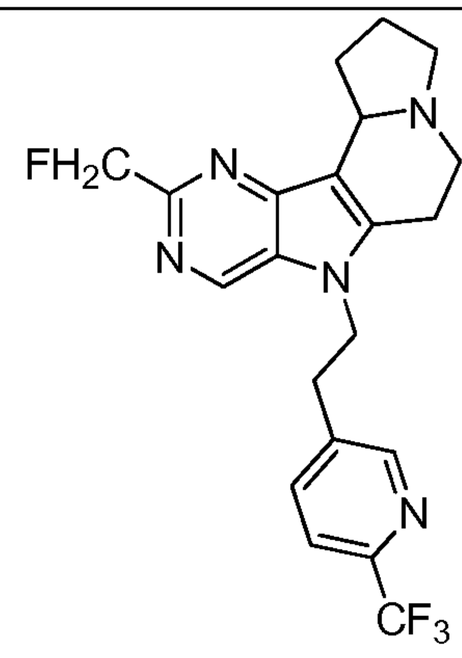
IV-91
IV-91a, IV-91b

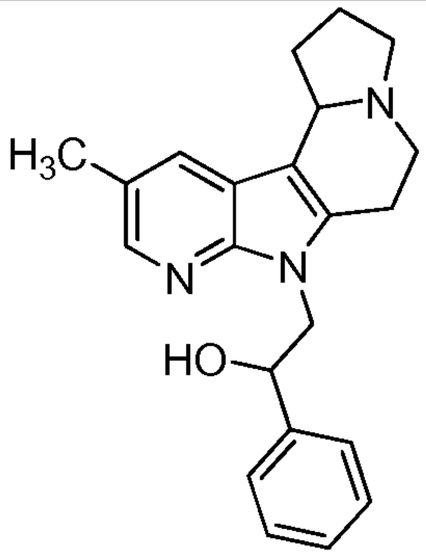
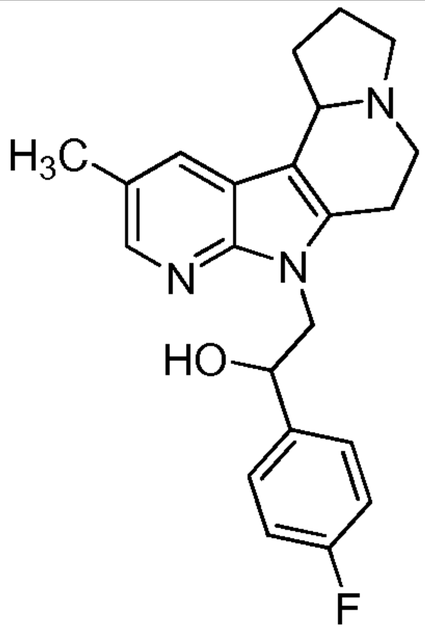
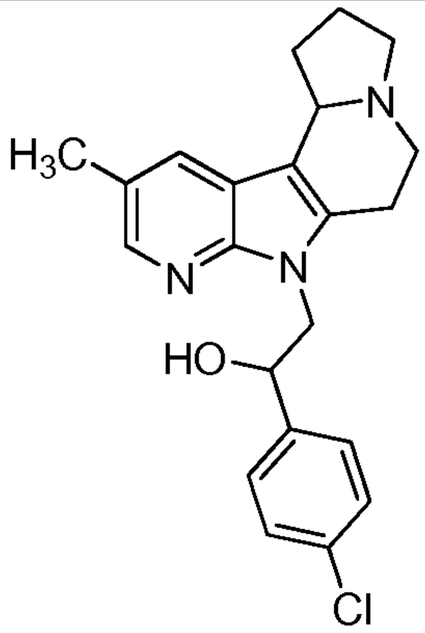
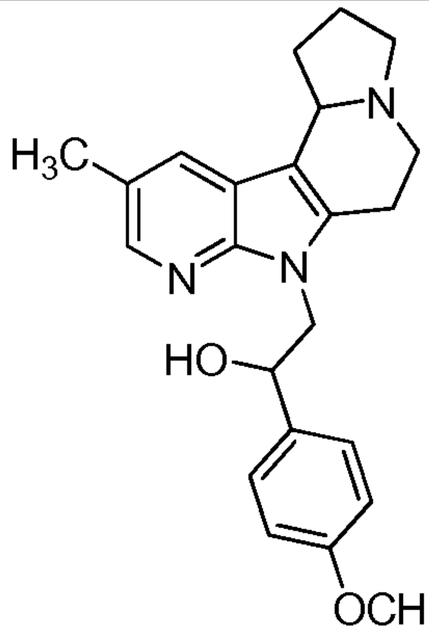
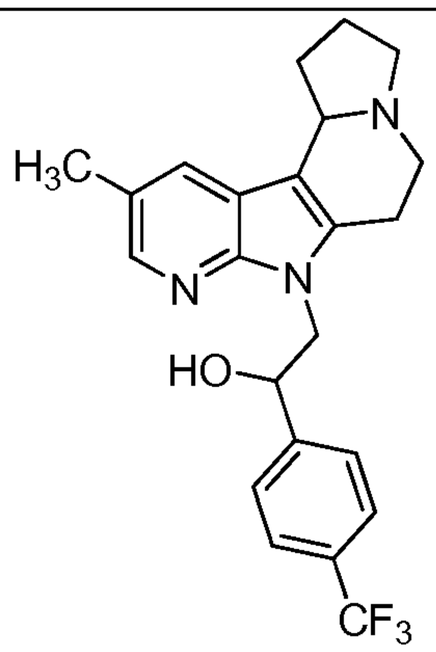
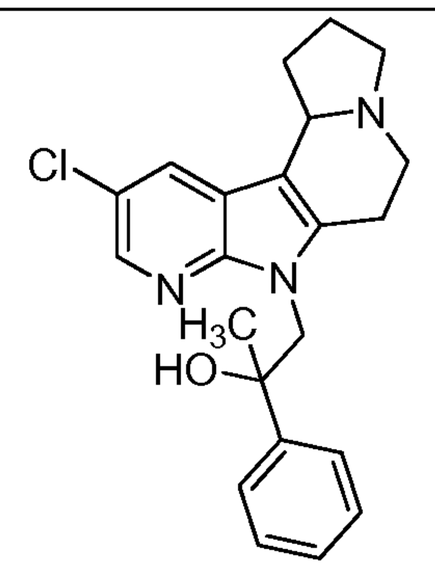
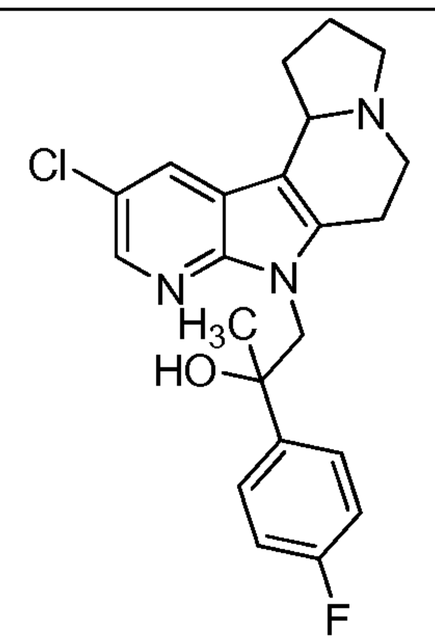
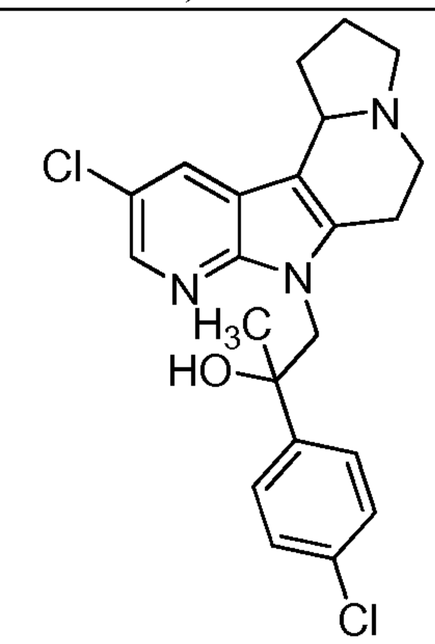
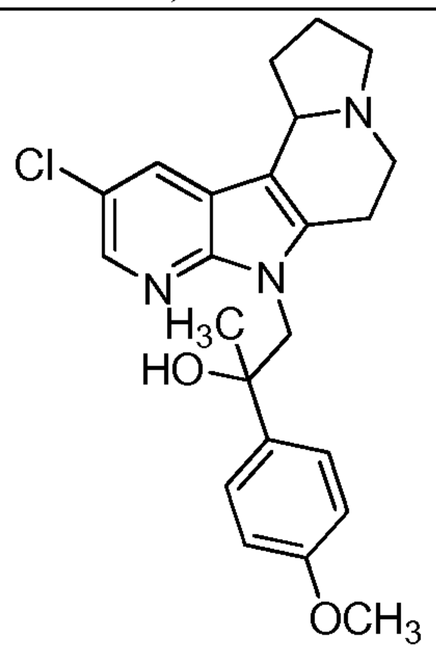
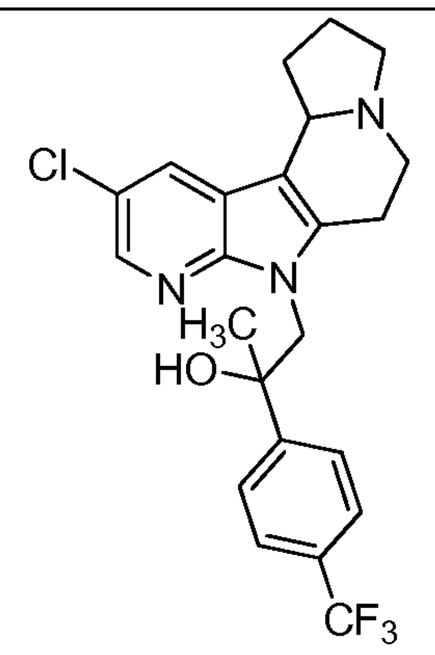
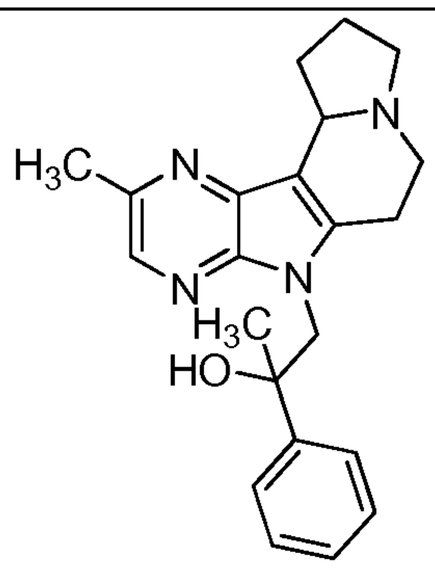
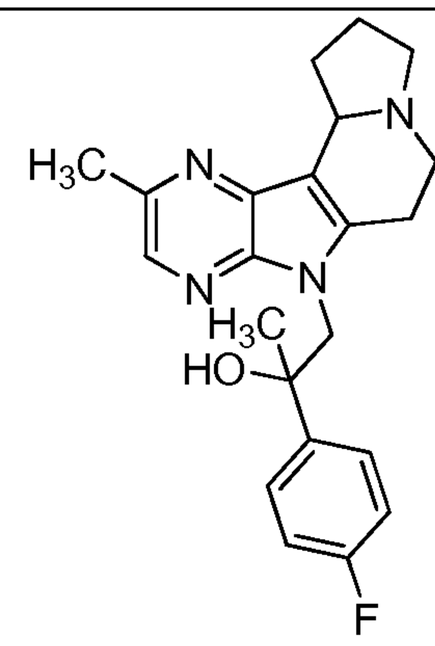


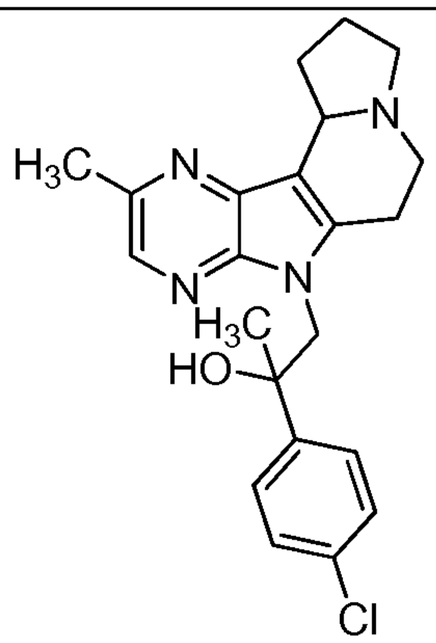
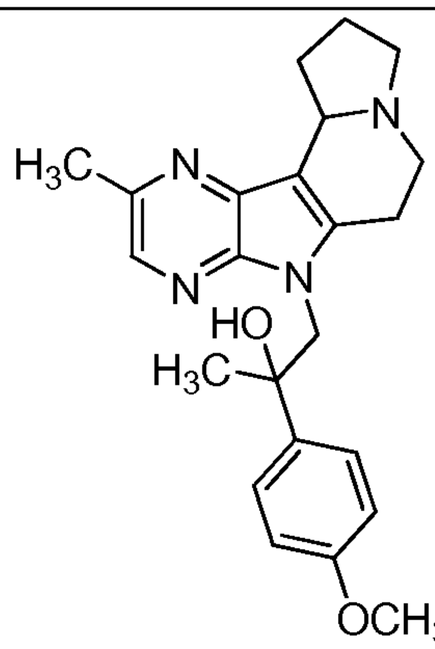
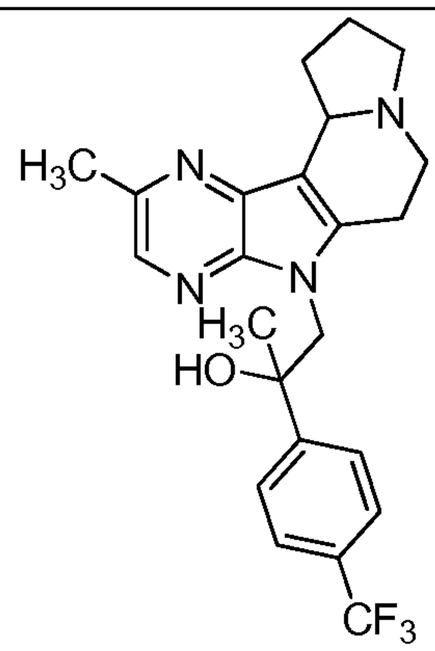
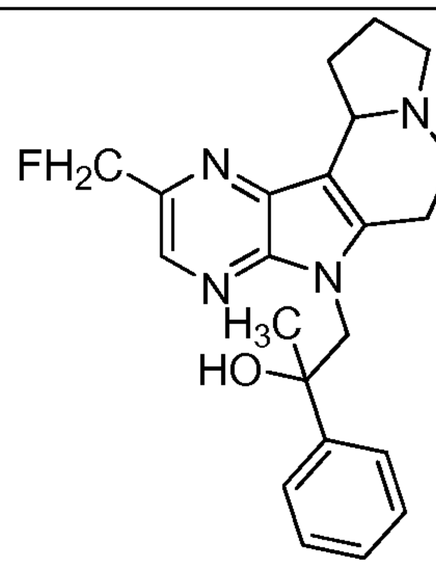
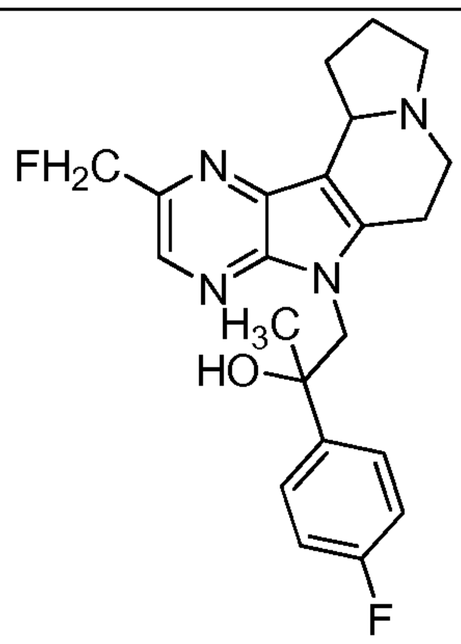
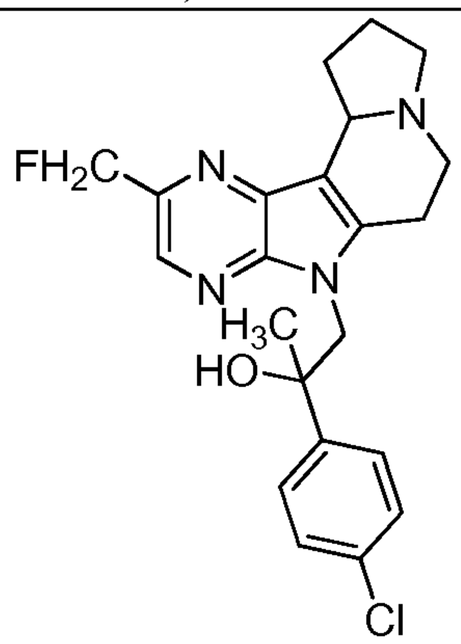
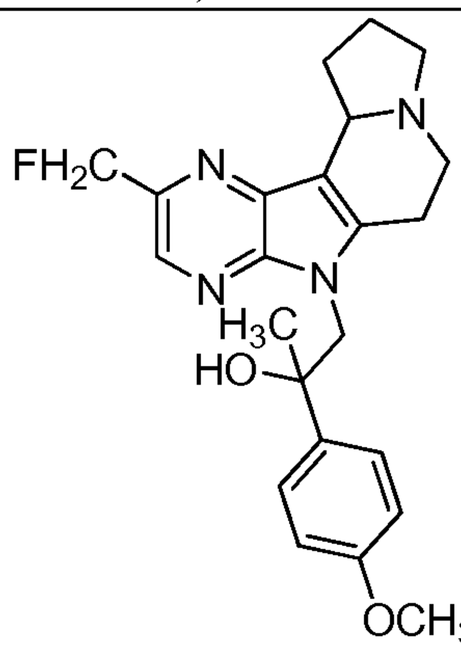
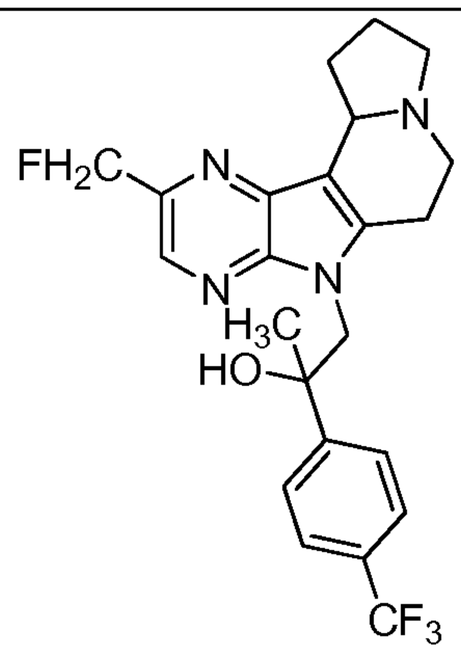
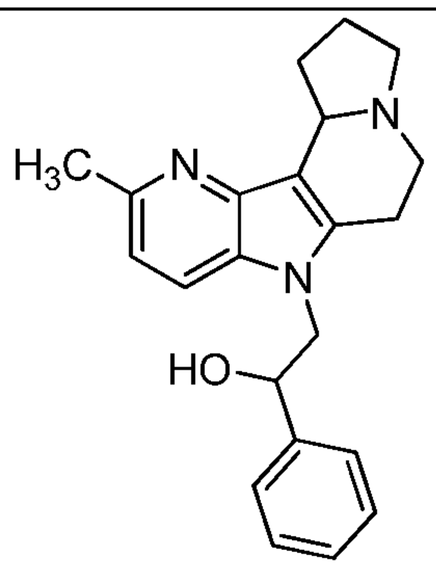
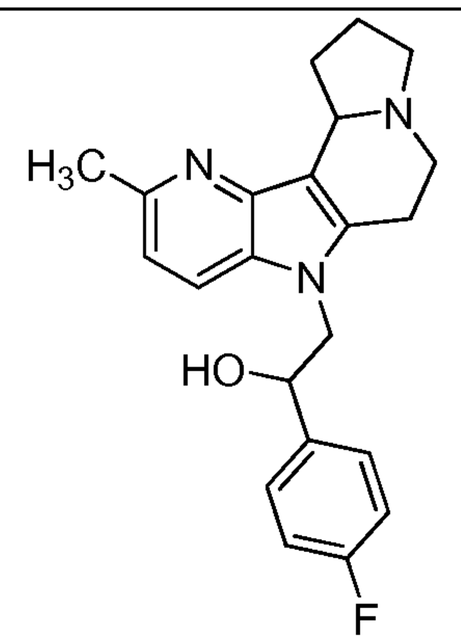
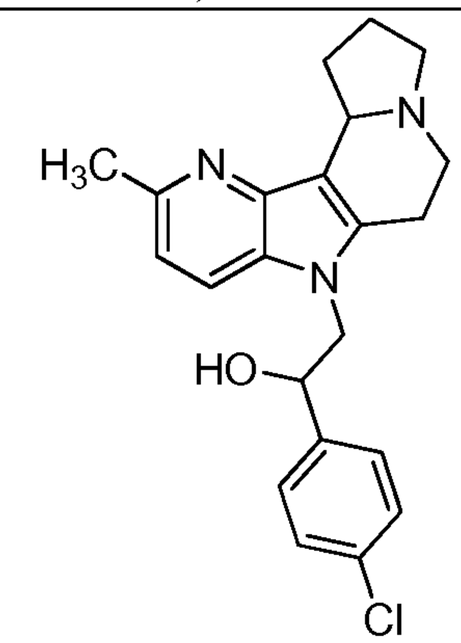
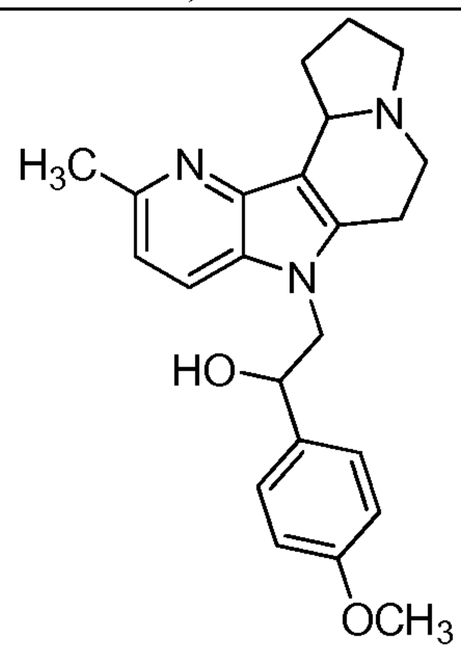
IV-92
IV-92a, IV-92b, IV-92c, IV-92d

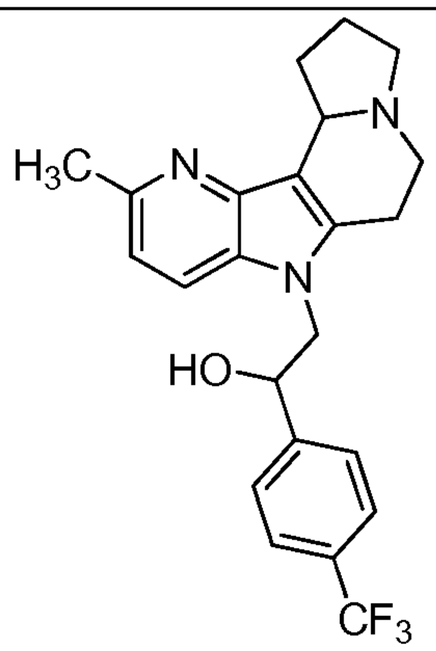
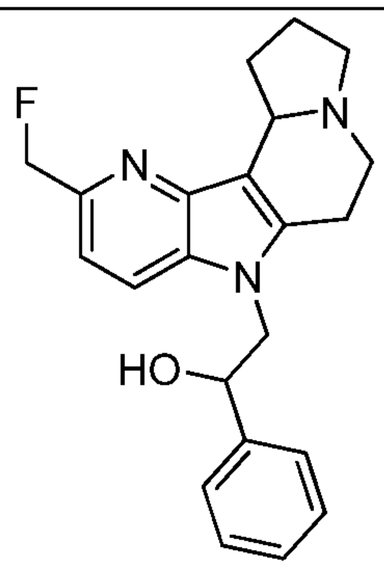
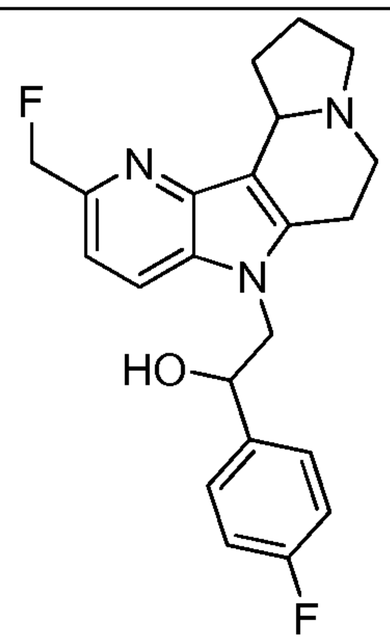
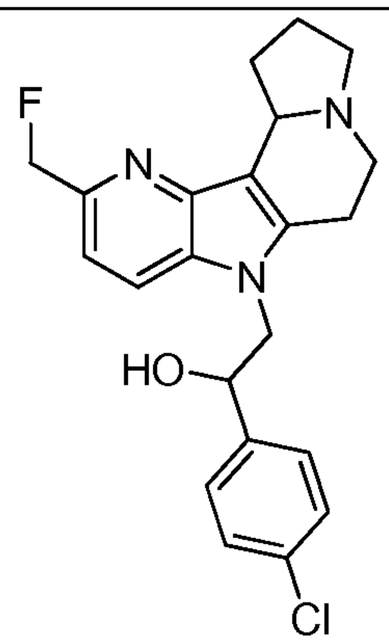
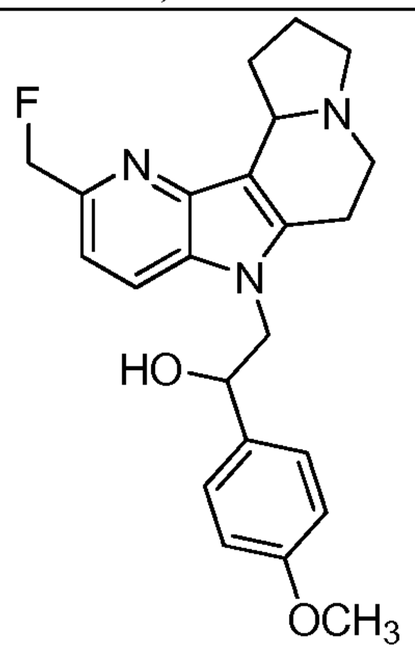
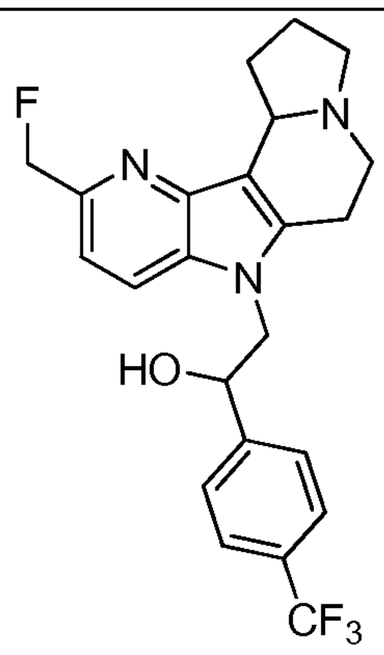
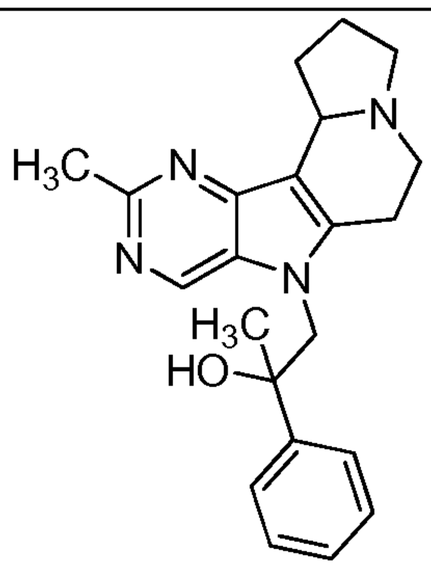
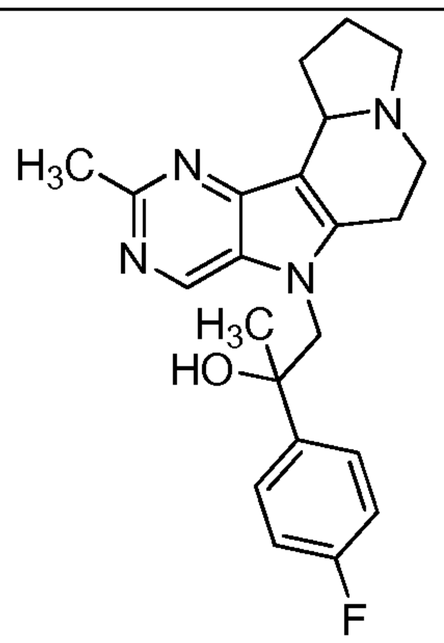
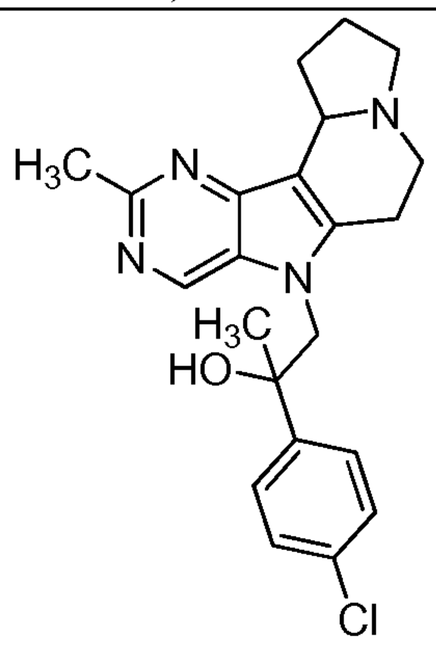
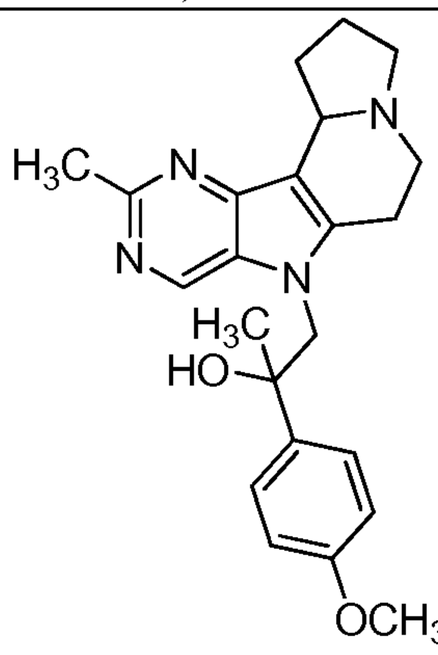
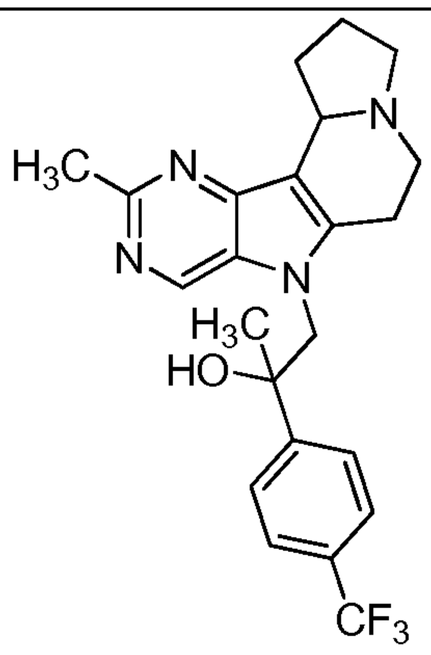
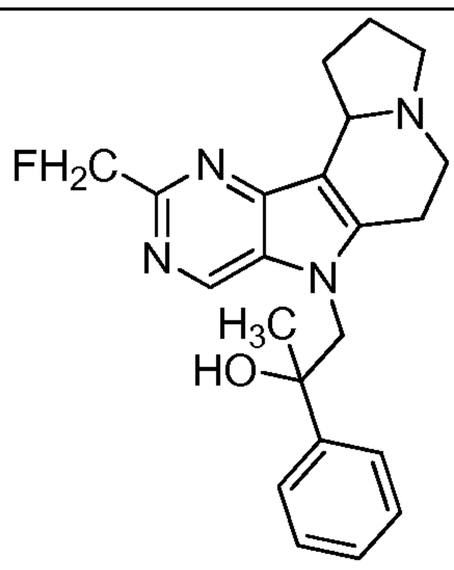
 IV-93 IV-93a, IV-93b	 IV-94 IV-94a, IV-94b	 IV-95 IV-95a, IV-95b	 IV-96 IV-96a, IV-96b
 IV-97 IV-97a, IV-97b	 IV-98 IV-98a, IV-98b	 IV-99 IV-99a, IV-99b	 IV-100 IV-100a, IV-100b
 IV-101 IV-101a, IV-101b	 IV-102 IV-102a, IV-102b	 IV-103 IV-103a, IV-103b	 IV-104 IV-104a, IV-104b

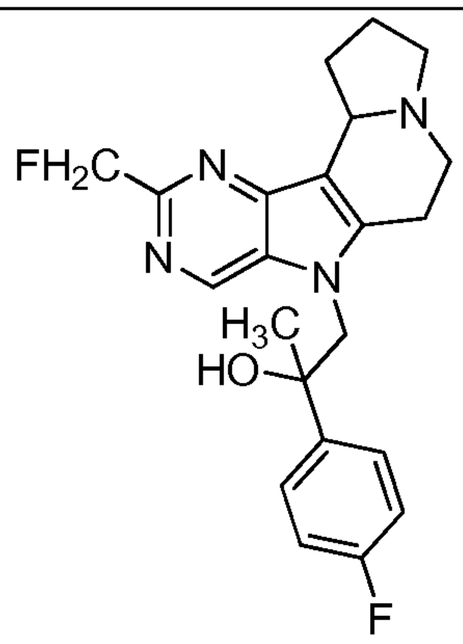
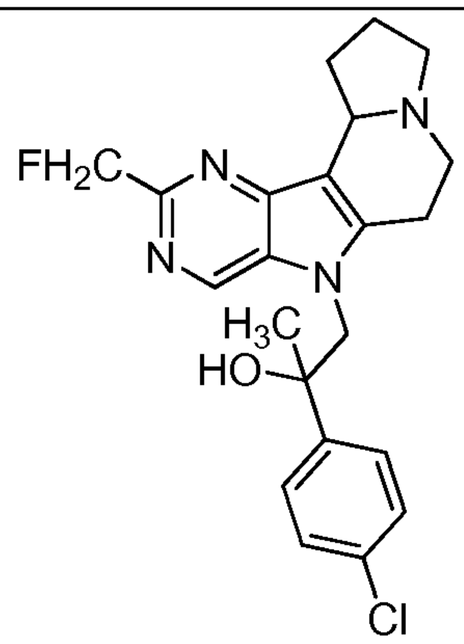
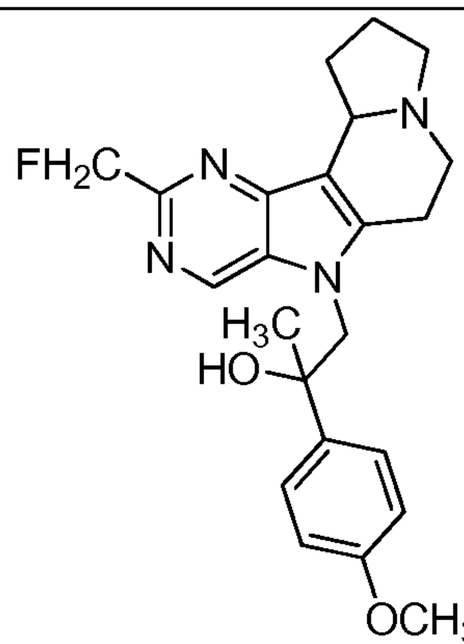
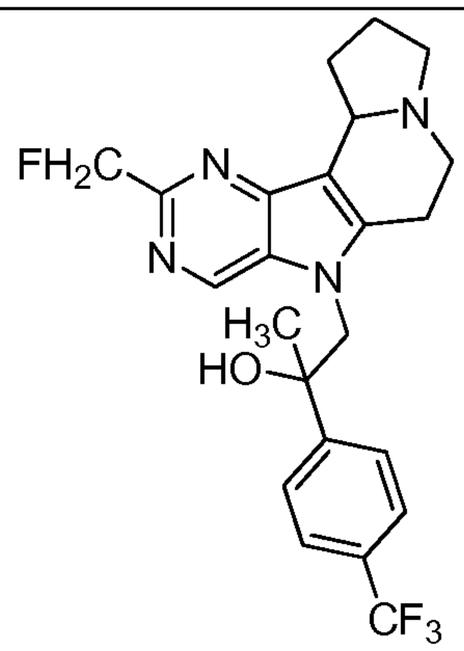
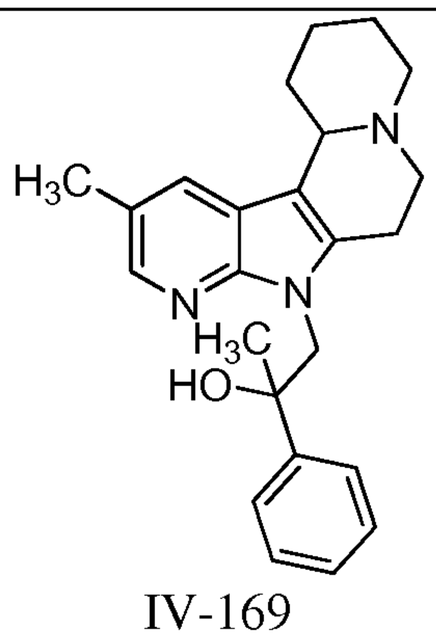
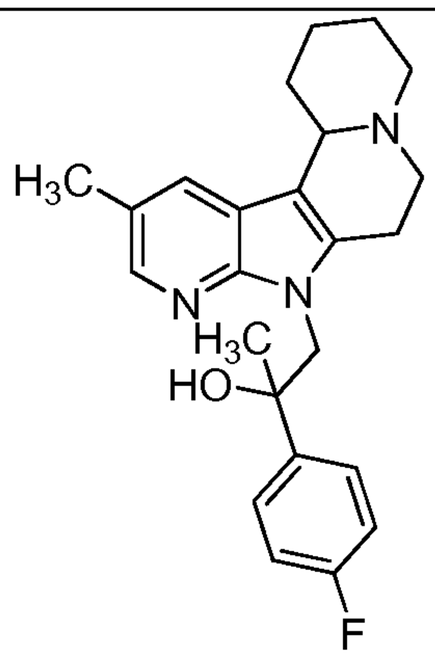
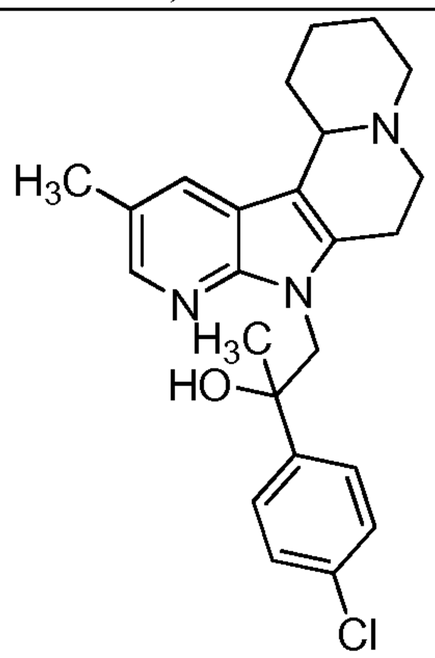
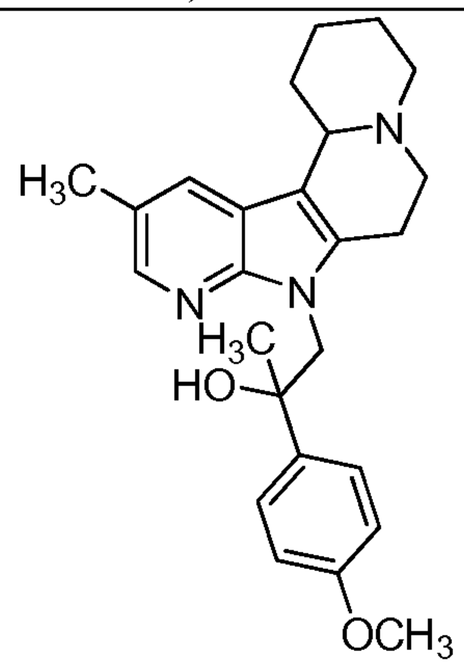
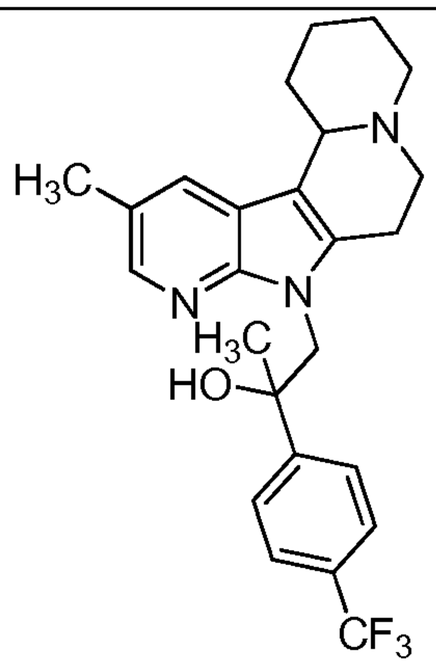
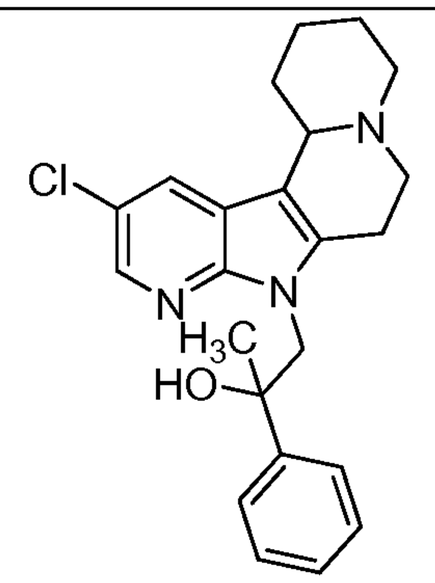
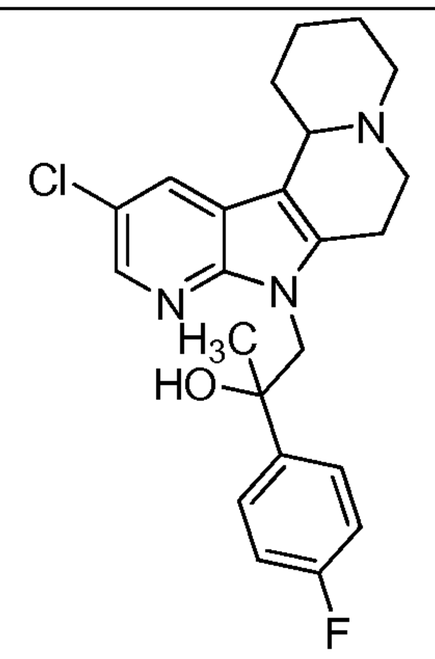
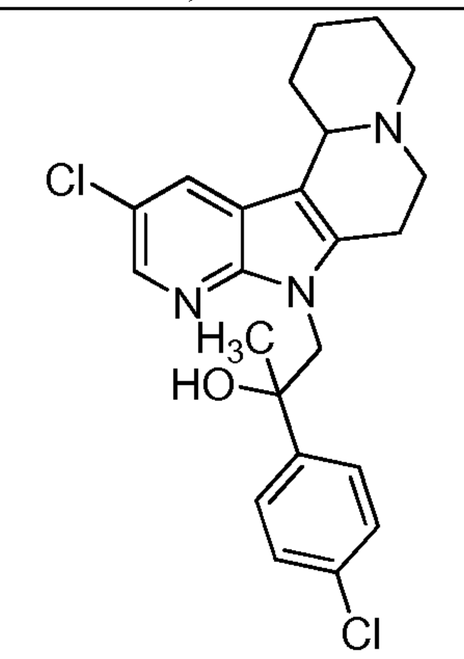
 IV-105 IV-105a, IV-105b	 IV-106 IV-106a, IV-106b	 IV-107 IV-107a, IV-107b	 IV-108 IV-108a, IV-108b
 IV109 IV-109a, IV-109b	 IV-110 IV-110a, IV-110b	 IV-111 IV-111a, IV-111b	 IV-112 IV-112a, IV-112b
 IV-113 IV-113a, IV-113b	 IV-114 IV-114a, IV-114b	 IV-115 IV-115a, IV-115b	 IV-116 IV-116a, IV-116b

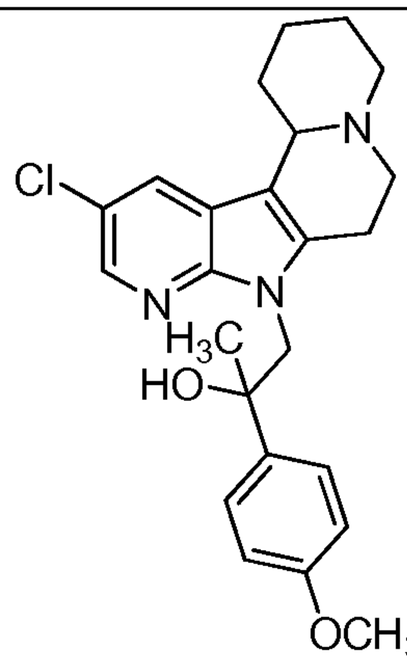
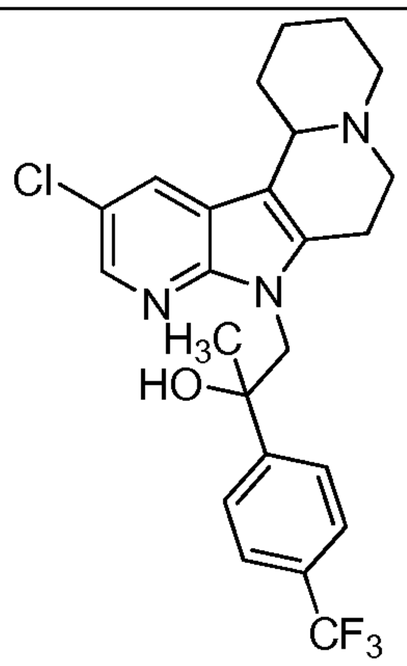
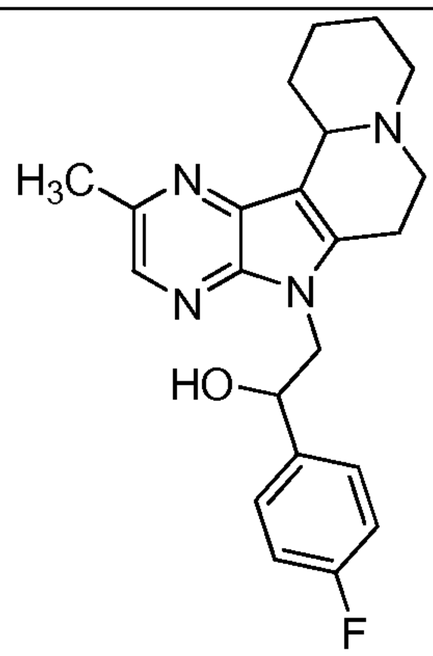
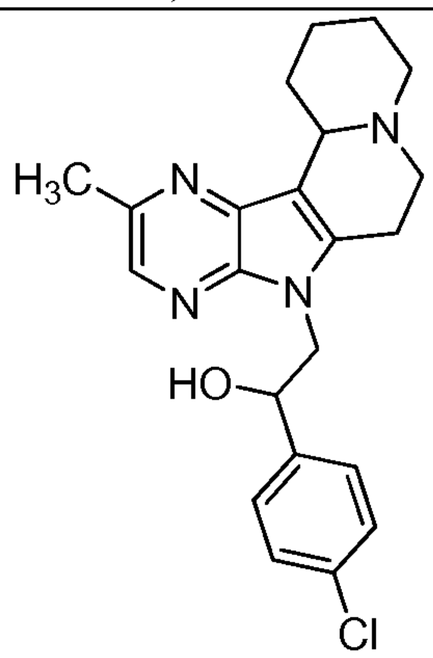
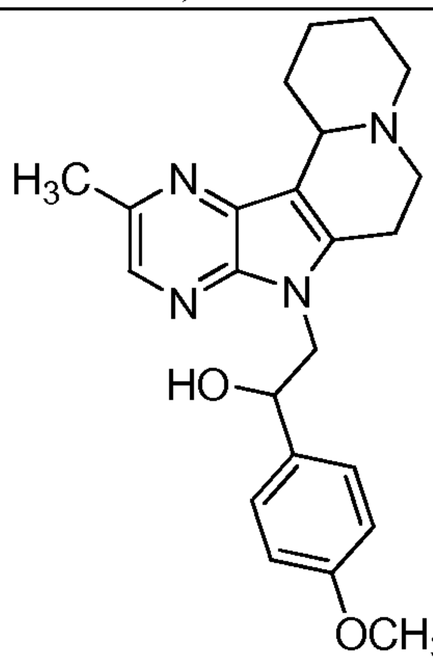
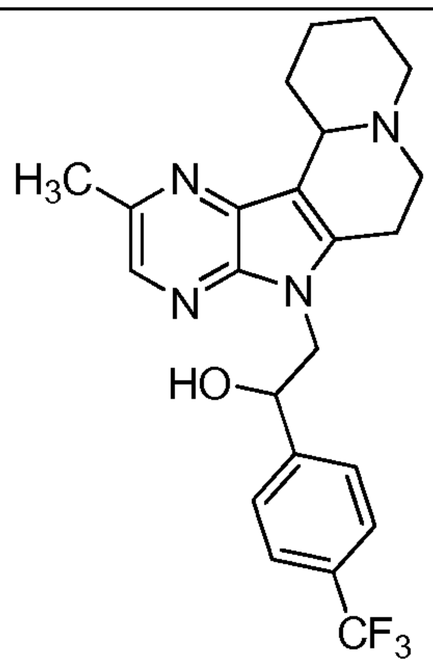
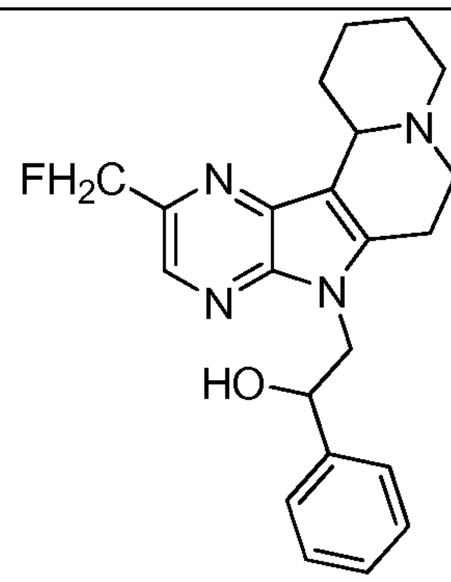
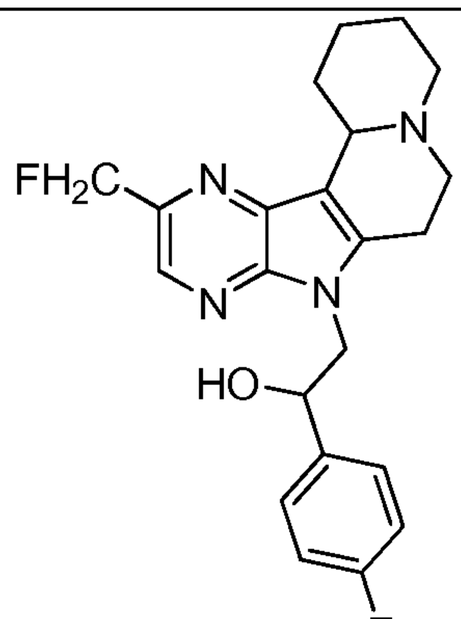
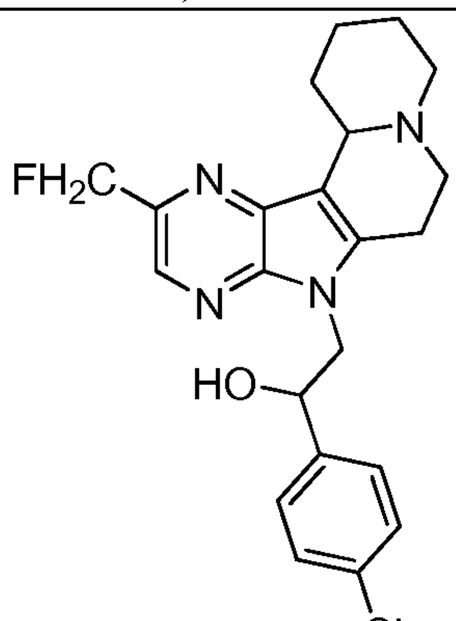
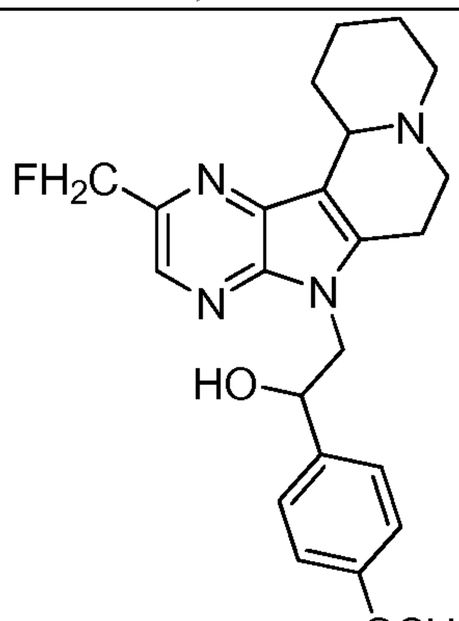
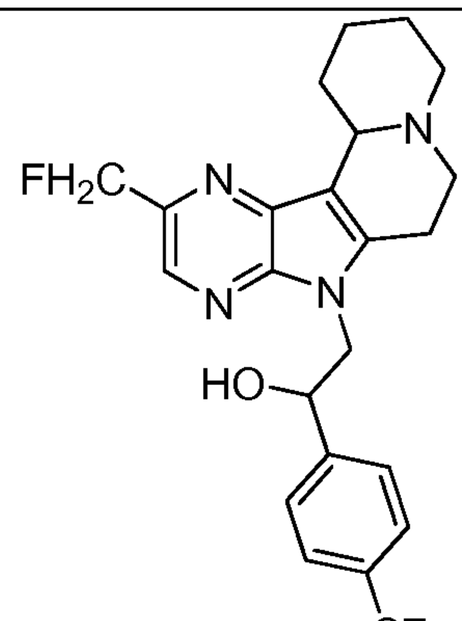
 IV-117 IV-117a, IV-117b	 IV-118 IV-118a, IV-118b	 IV-119 IV-119a, IV-119b	 IV-120 IV-120a, IV-120b
 IV-121 IV-121a, IV-121b	 IV-122 IV-122a, IV-122b	 IV-123 IV-123a, IV-123b	 IV-124 IV-124a, IV-124b
 IV-125 IV-125a, IV-125b	 IV-126 IV-126a, IV-126b	 IV-127 IV-127a, IV-127b	 IV-128 IV-128a, IV-128b

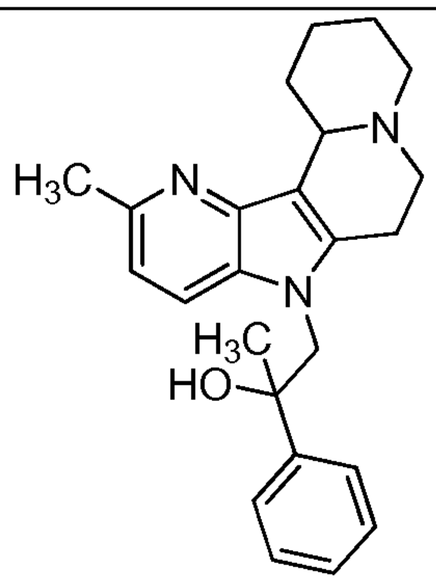
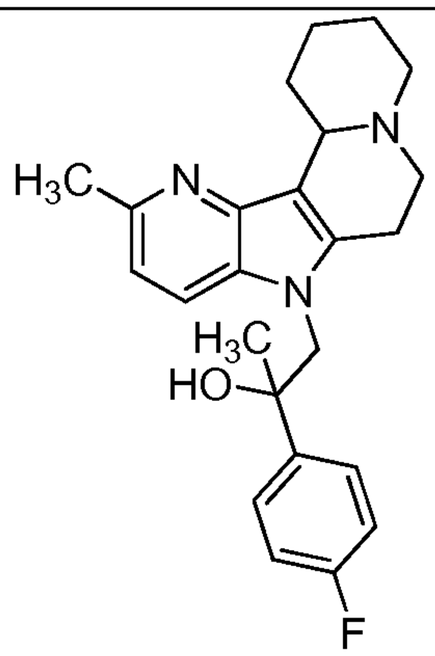
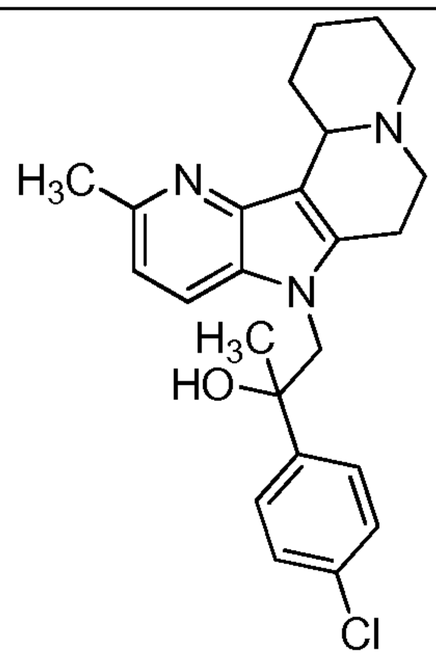
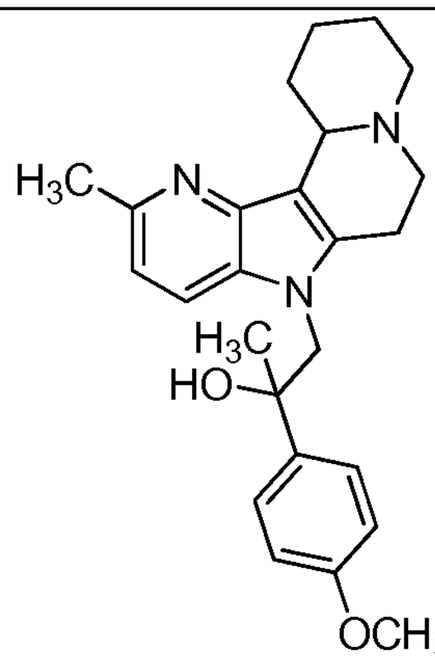
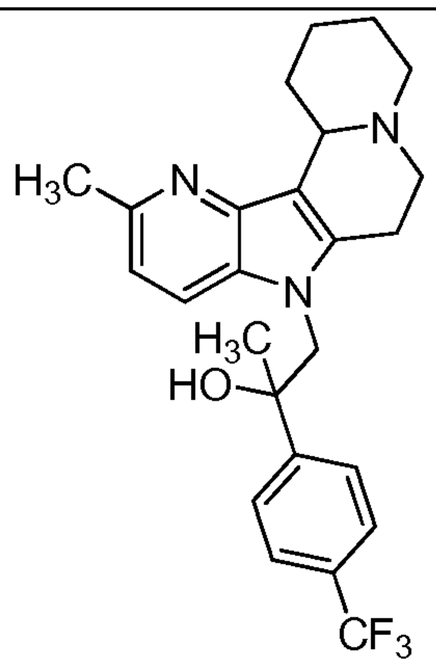
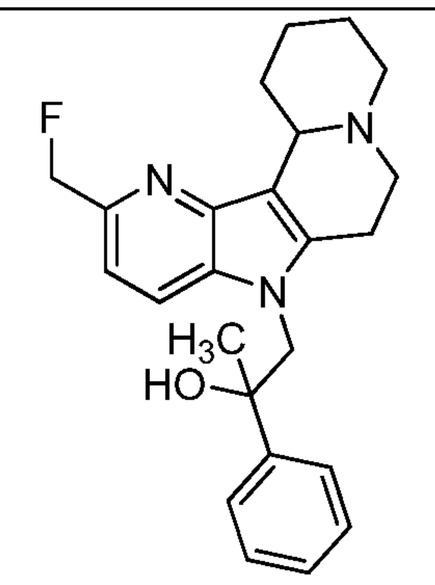
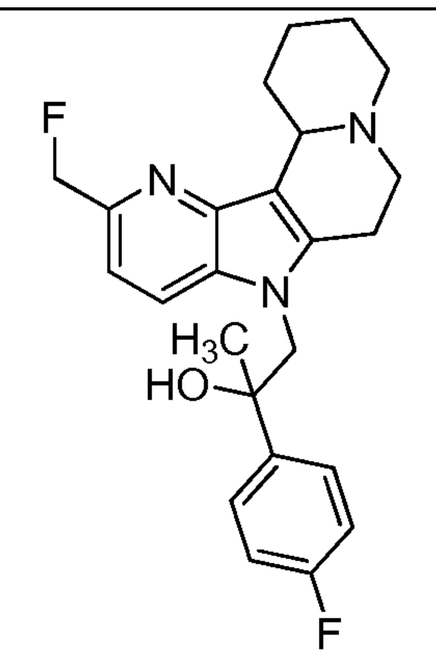
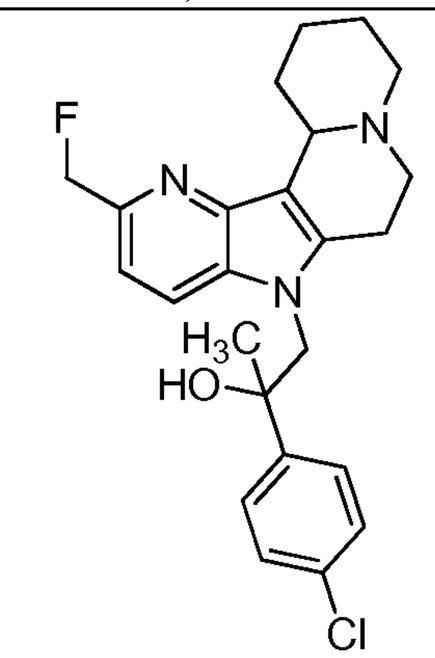
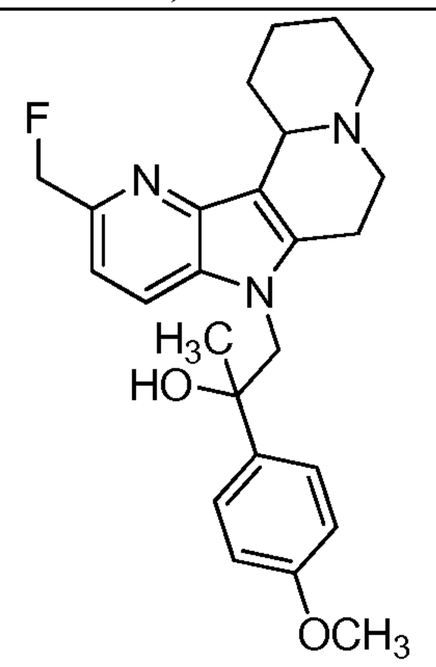
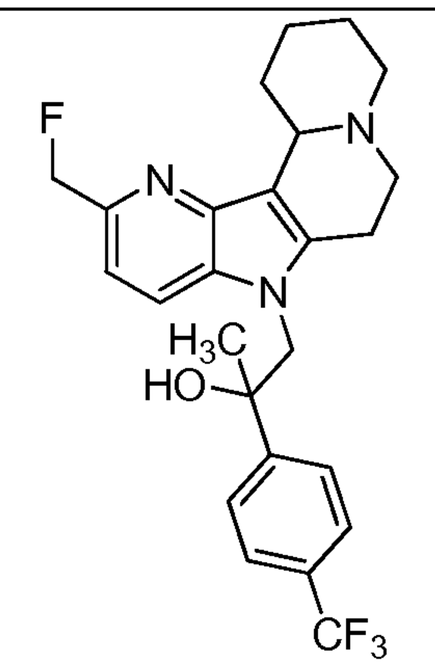
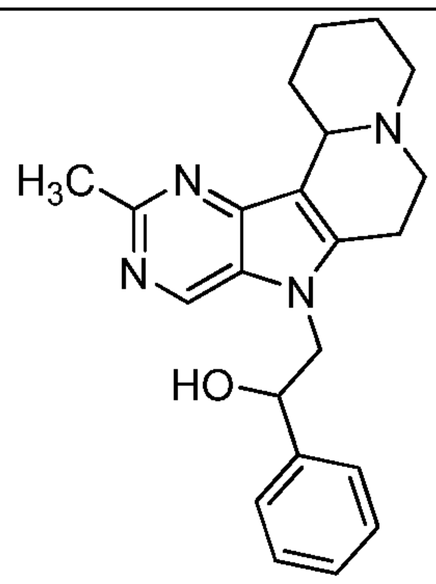
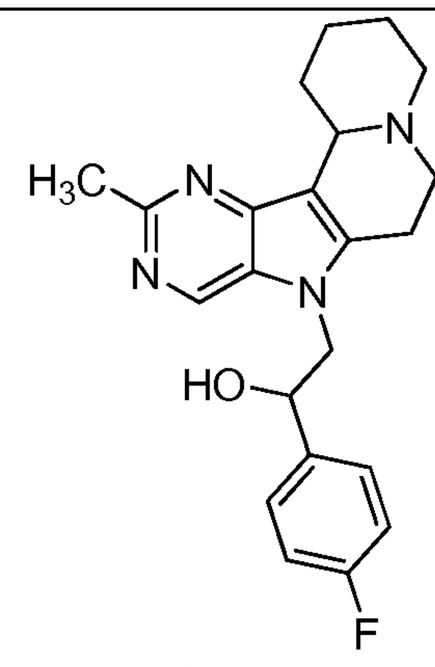
 IV-129 IV-129a, IV-129b, IV-129c, IV-129d	 IV-130 IV-130a, IV-130b, IV-130c, IV-130d	 IV-131 IV-131a, IV-131b, IV-131c, IV-131d	 IV-132 IV-132a, IV-132b, IV-132c, IV-132d
 IV-133 IV-133a, IV-133b, IV-133c, IV-133d	 IV-134 IV-134a, IV-134b, IV-134c, IV-134d	 IV-135 IV-135a, IV-135b, IV-135c, IV-135d	 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

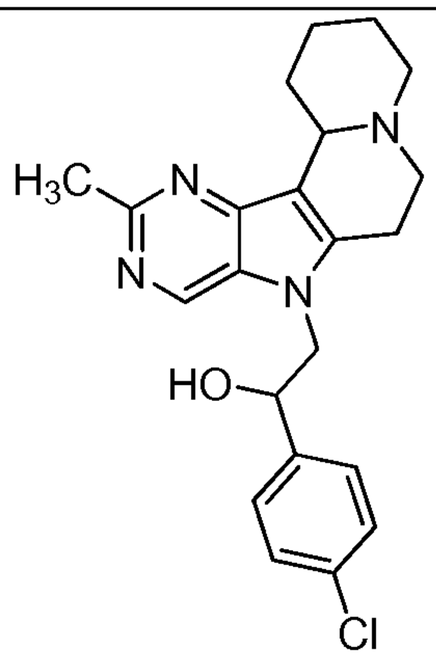
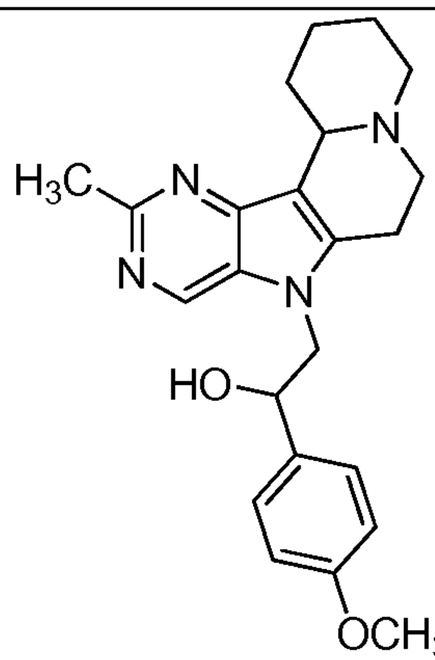
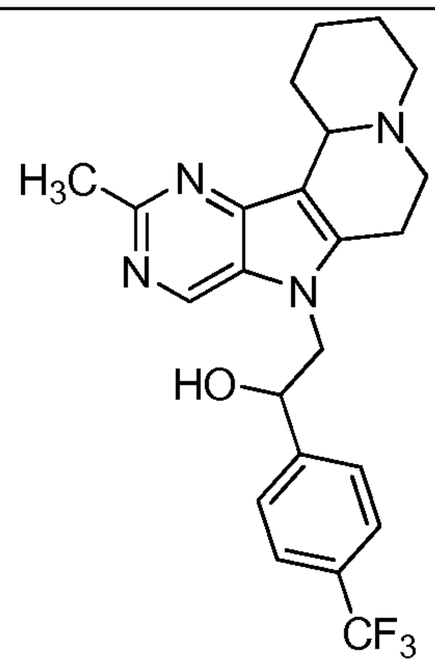
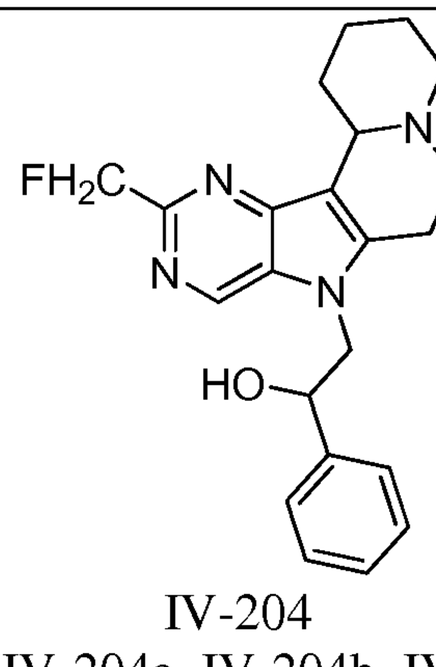
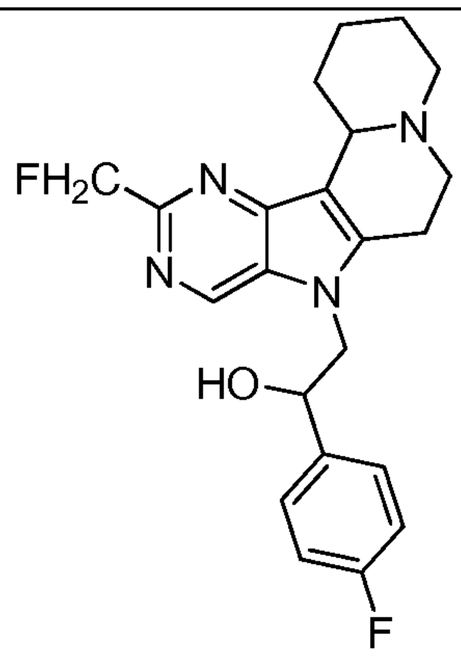
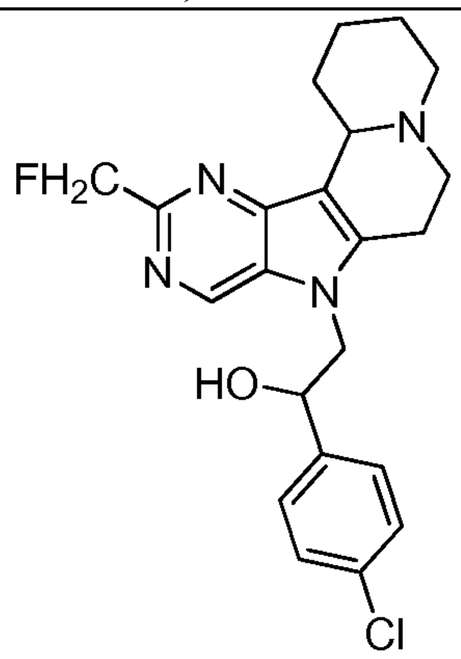
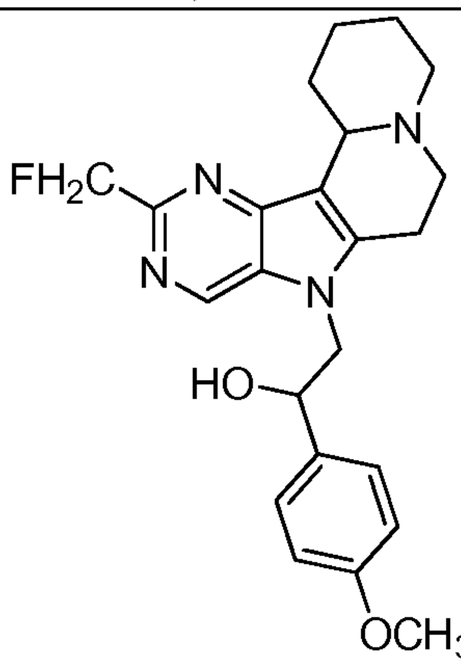
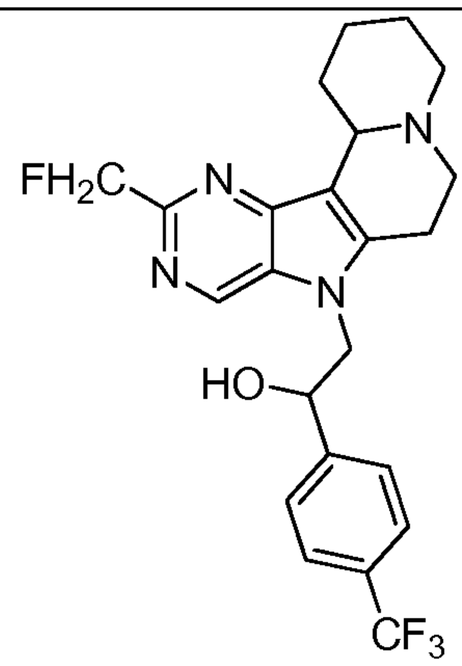
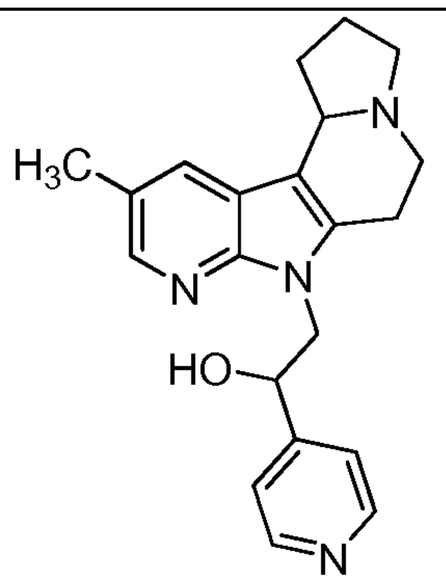
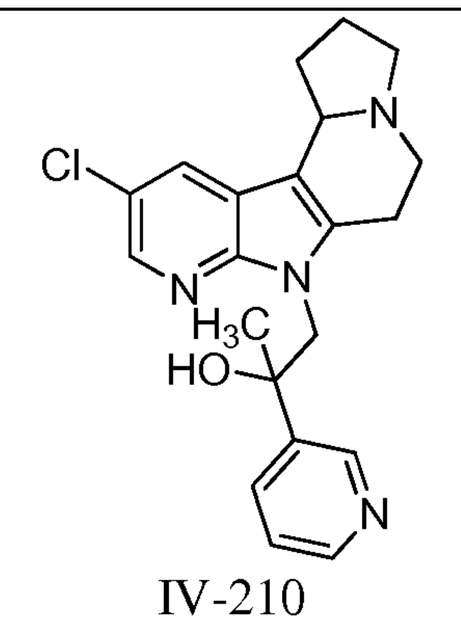
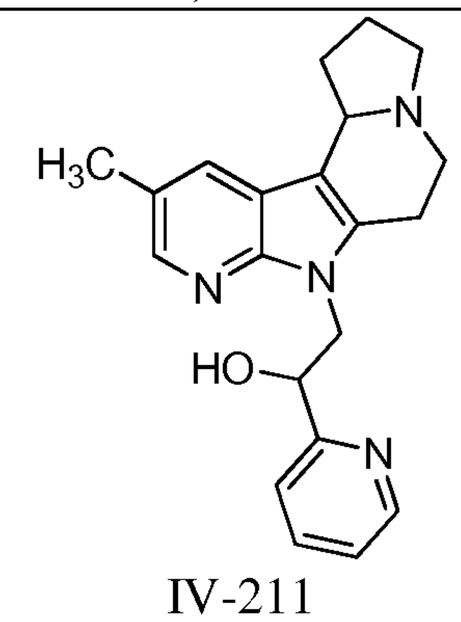
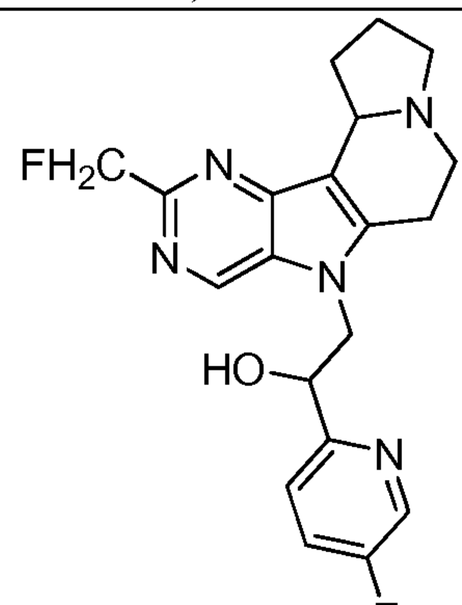
 IV-141 IV-141a, IV-141b, IV-141c, IV-141d	 IV-142 IV-142a, IV-142b, IV-142c, IV-142d	 IV-143 IV-143a, IV-143b, IV-143c, IV-143d	 IV-144 IV-144a, IV-144b, IV-144c, IV-144d
 IV-145 IV-145a, IV-145b, IV-145c, IV-145d	 IV-146 IV-146a, IV-146b, IV-146c, IV-146d	 IV-147 IV-147a, IV-147b, IV-147c, IV-147d	 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

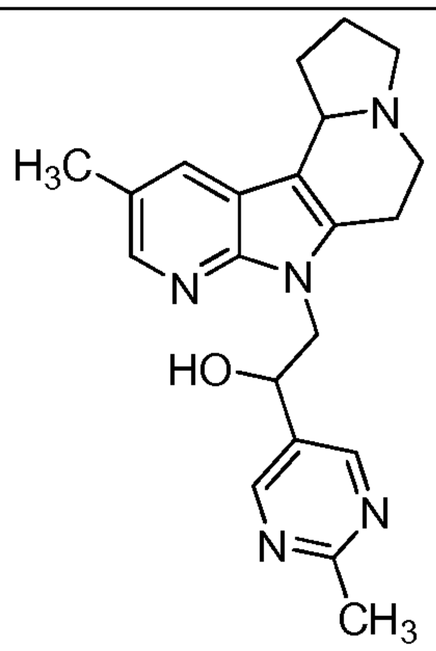
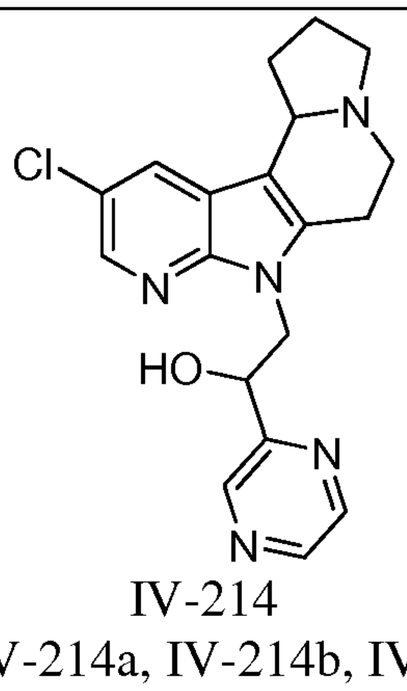
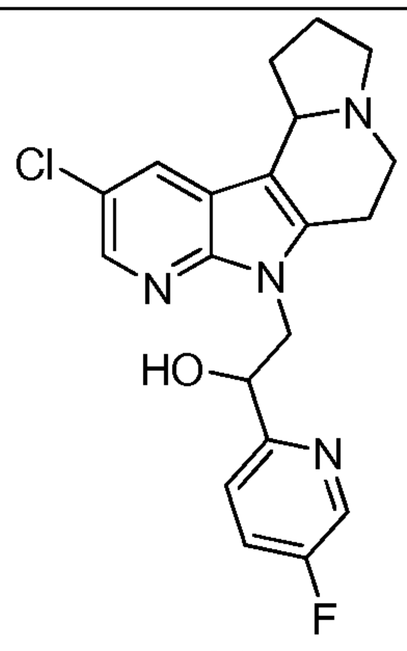
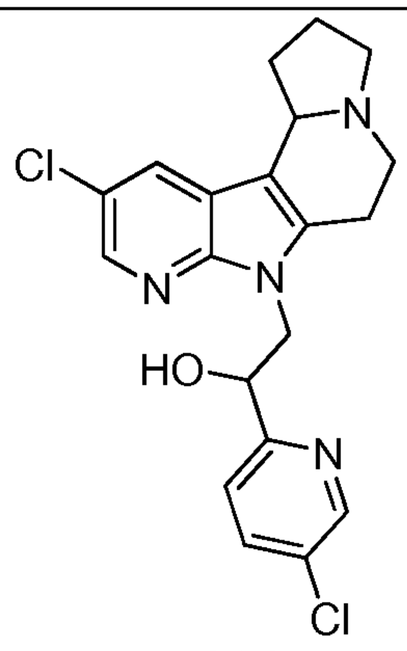
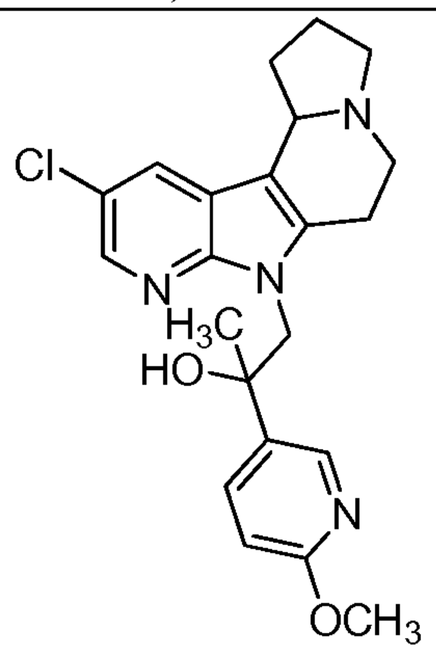
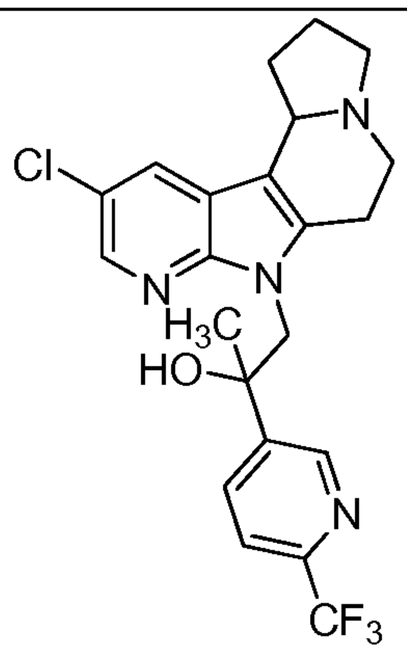
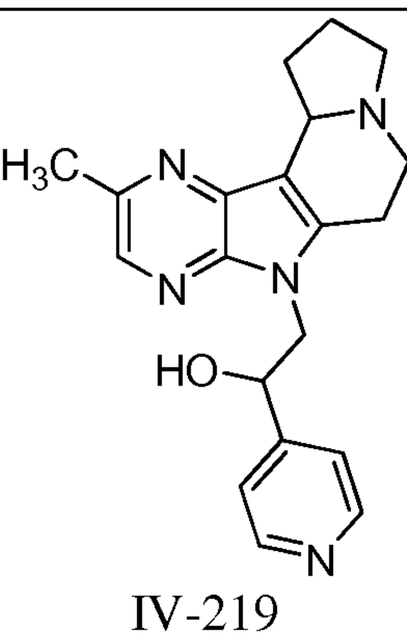
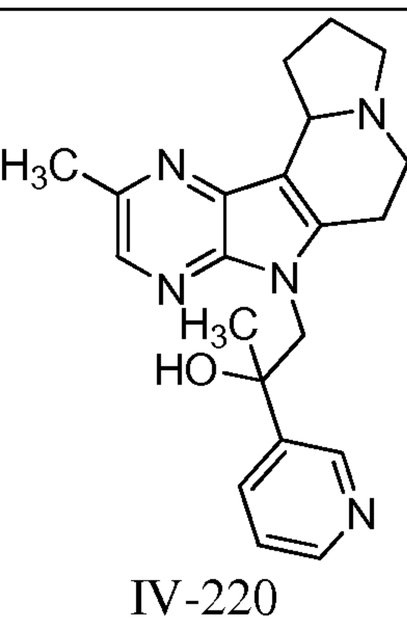
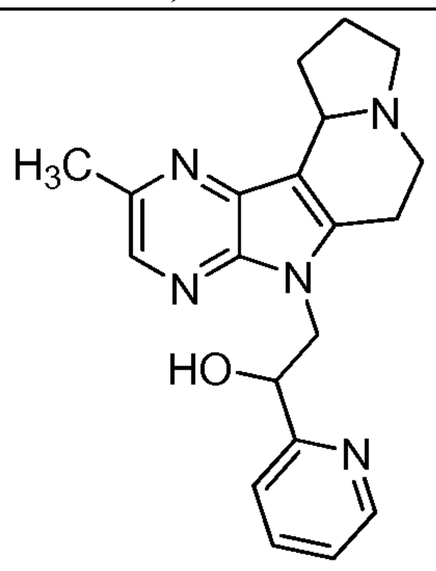
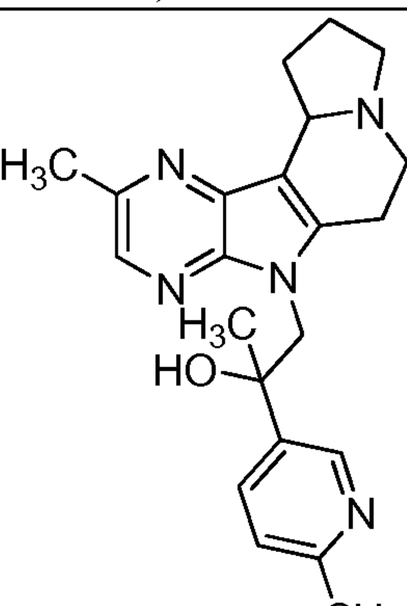
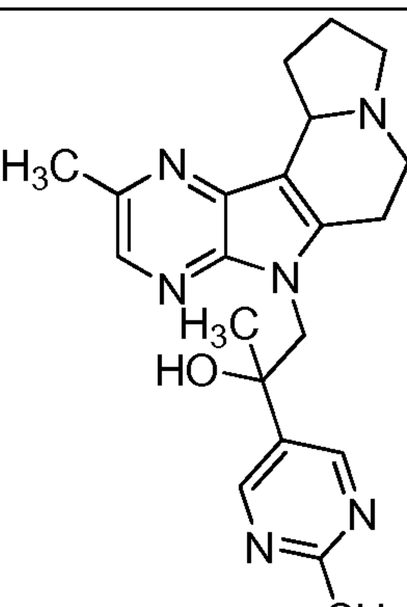
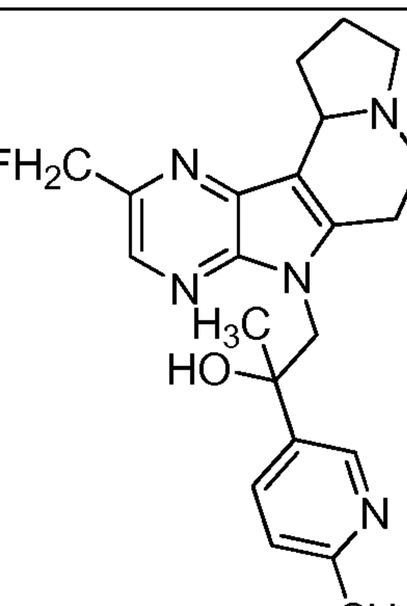
 IV-153 IV-153a, IV-153b, IV-153c, IV-153d	 IV-154 IV-154a, IV-154b, IV-154c, IV-154d	 IV-155 IV-155a, IV-155b, IV-155c, IV-155d	 IV-156 IV-156a, IV-156b, IV-156c, IV-156d
 IV-157 IV-157a, IV-157b, IV-157c, IV-157d	 IV-158 IV-158a, IV-158b, IV-158c, IV-158d	 IV-159 IV-159a, IV-159b, IV-159c, IV-159d	 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

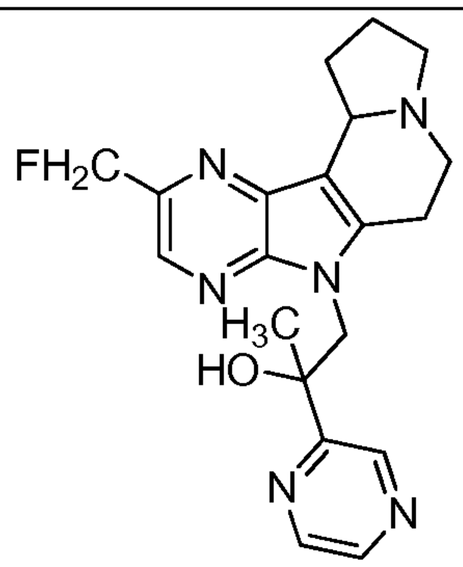
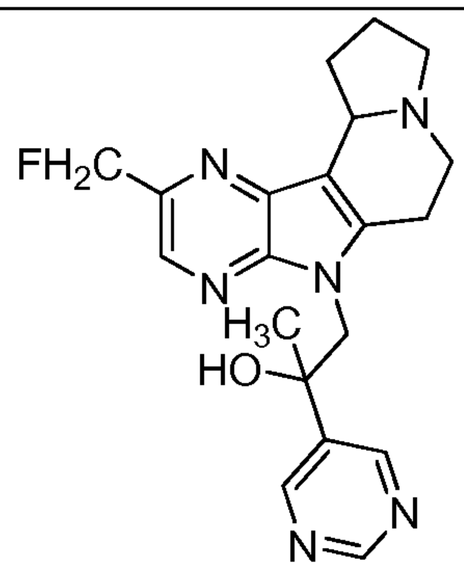
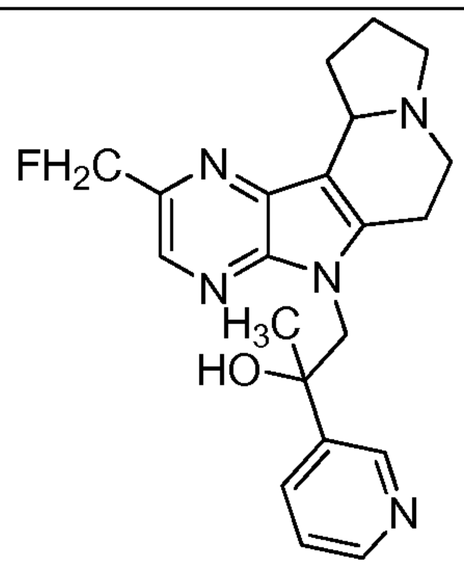
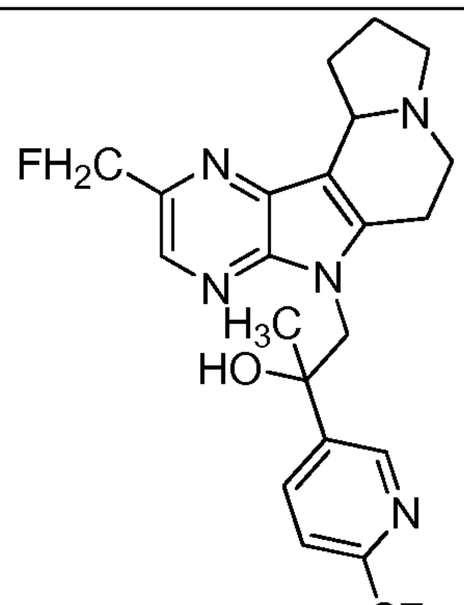
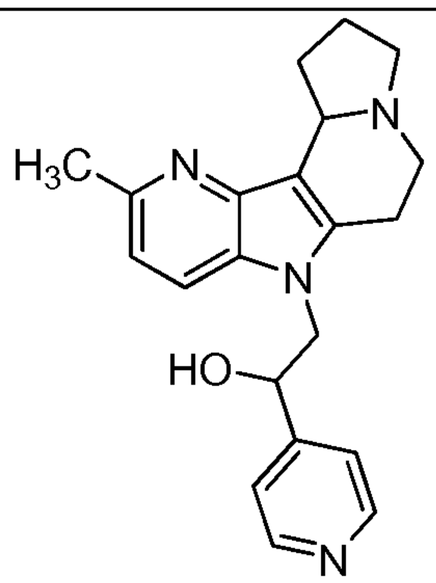
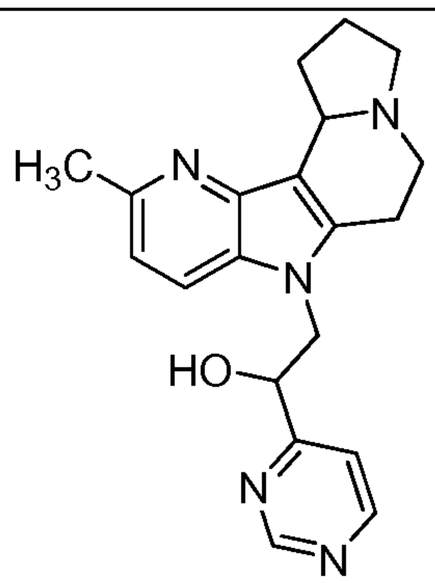
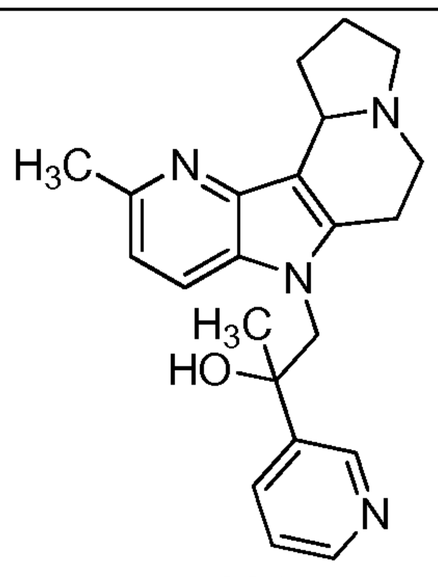
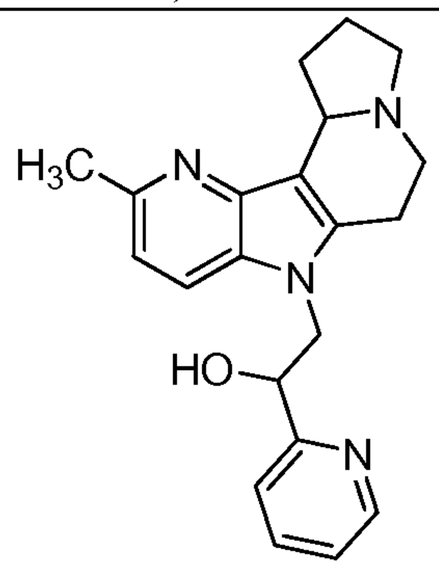
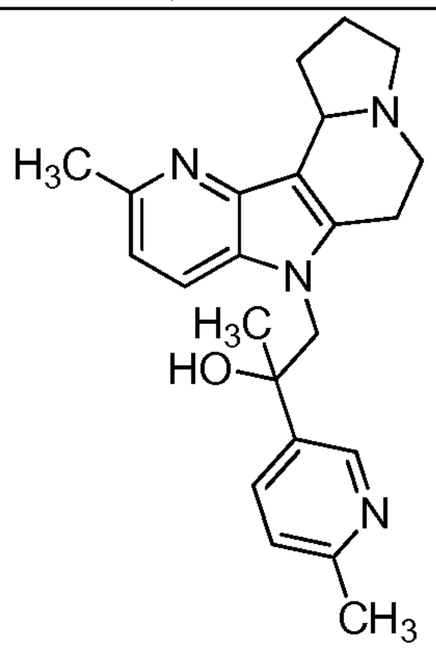
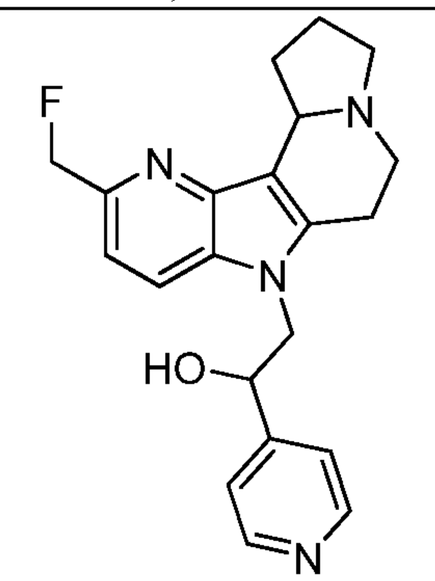
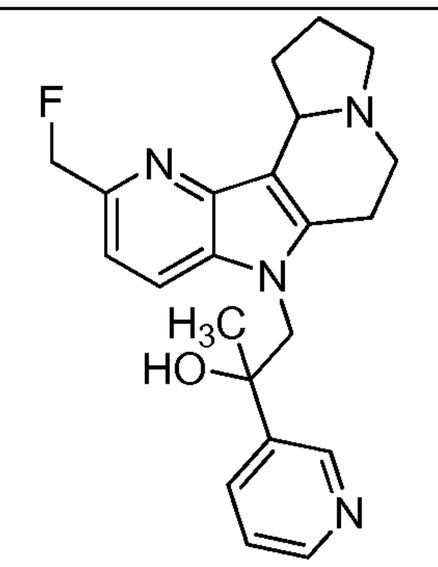
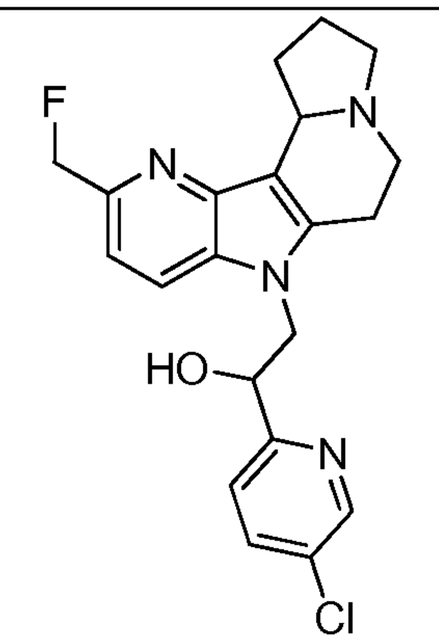
 IV-165 IV-165a, IV-165b, IV-165c, IV-165d	 IV-166 IV-166a, IV-166b, IV-166c, IV-166d	 IV-167 IV-167a, IV-167b, IV-167c, IV-167d	 IV-168 IV-168a, IV-168b, IV-168c, IV-168d
 IV-169 IV-169a, IV-169b, IV-169c, IV-169d	 IV-170 IV-170a, IV-170b, IV-170c, IV-170d	 IV-171 IV-171a, IV-171b, IV-171c, IV-171d	 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

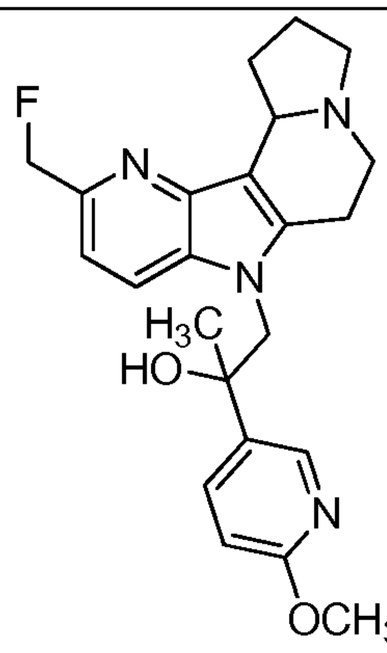
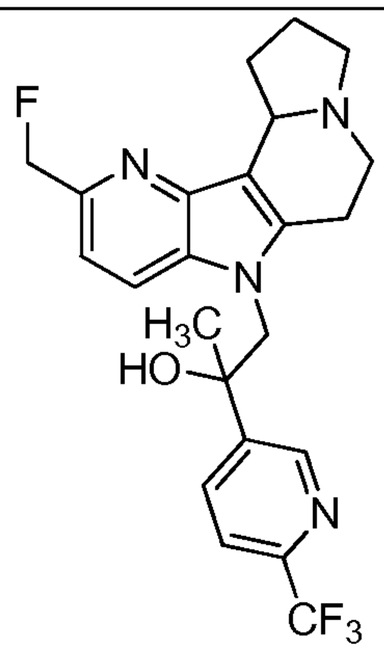
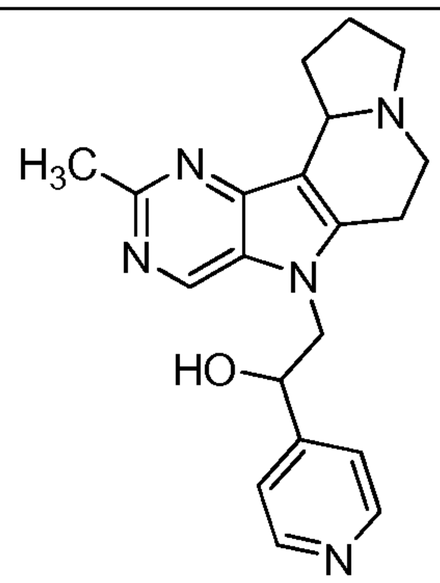
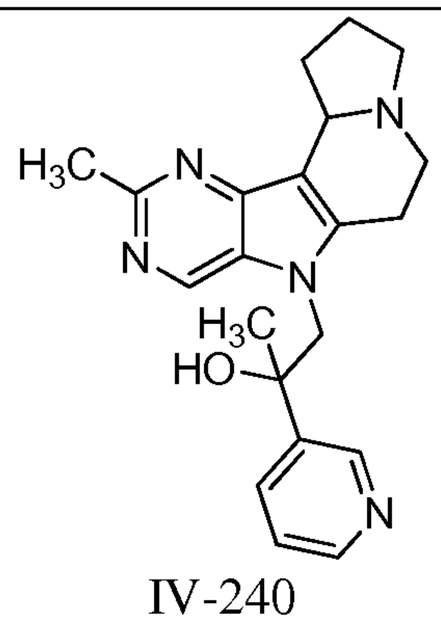
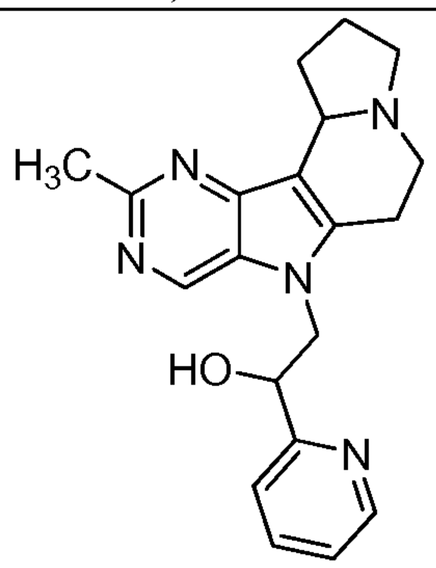
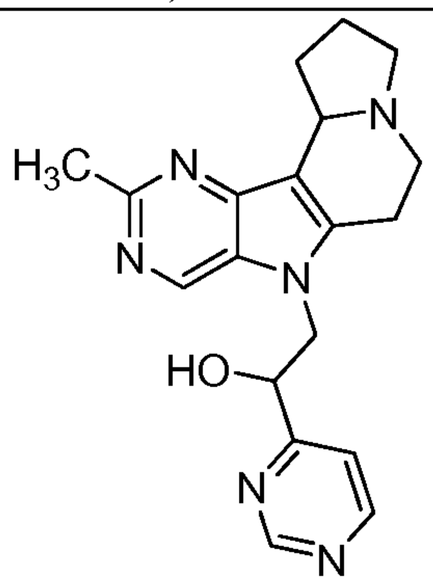
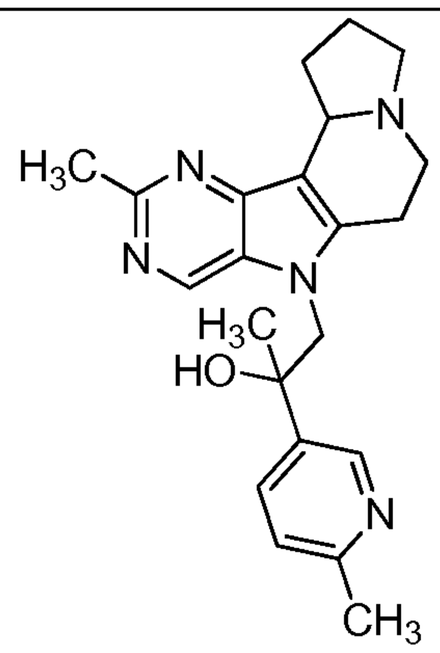
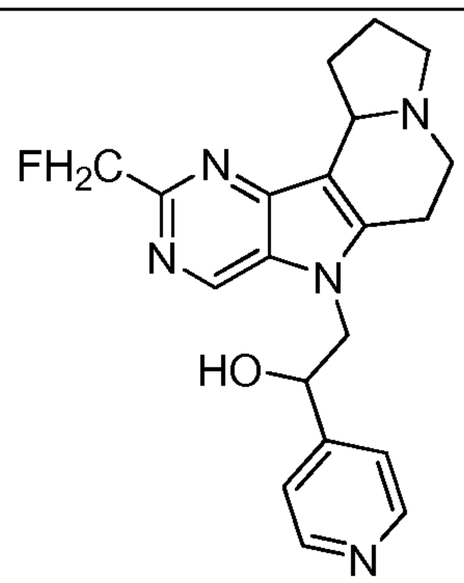
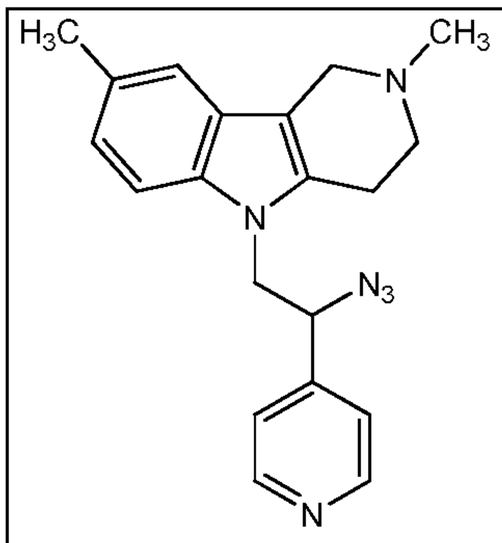
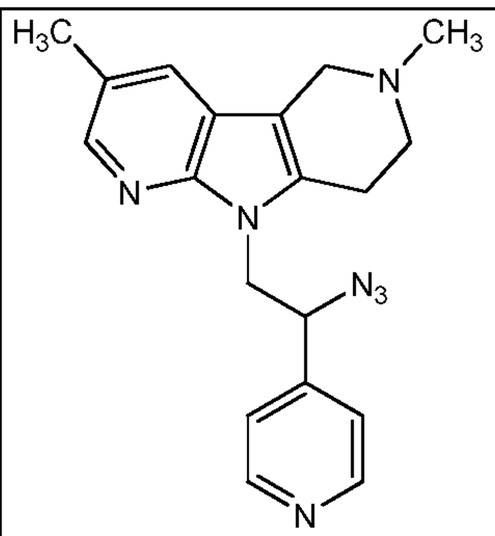
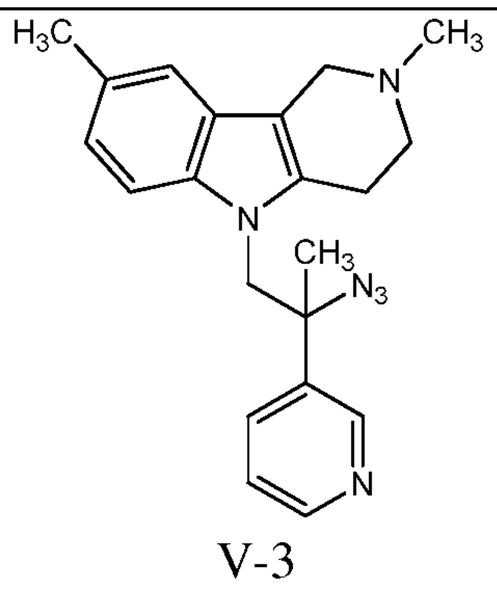
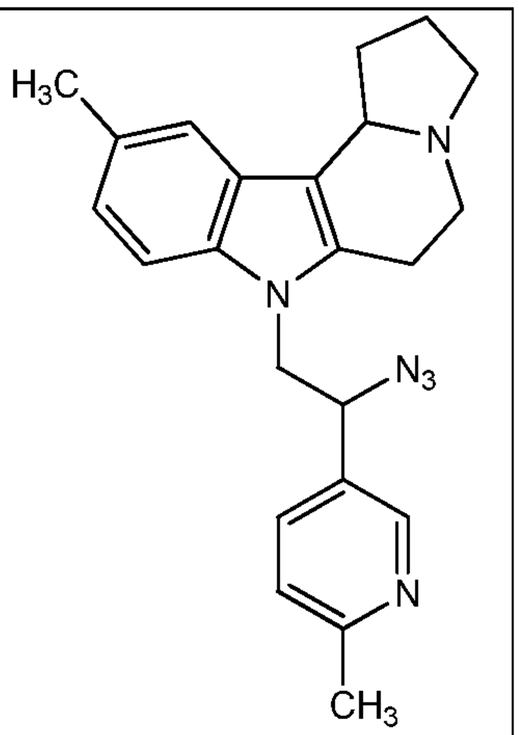
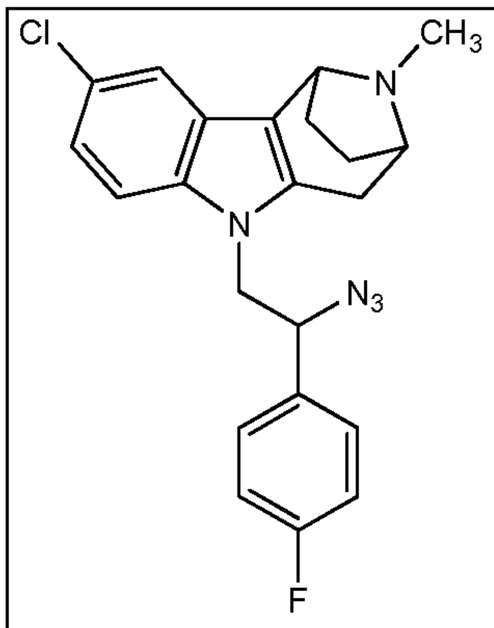
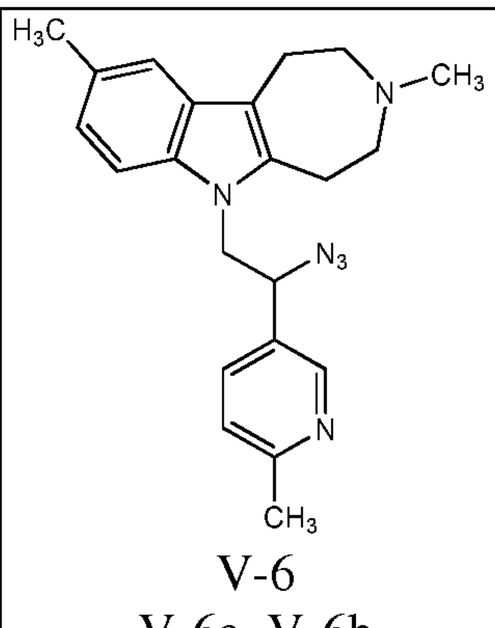
 IV-237 IV-237a, IV-237b, IV-237c, IV-237d	 IV-238 IV-238a, IV-238b, IV-238c, IV-238d	 IV-239 IV-239a, IV-239b, IV-239c, IV-239d	 IV-240 IV-240a, IV-240b, IV-240c, IV-240d
 IV-241 IV-241a, IV-241b, IV-241c, IV-241d	 IV-242 IV-242a, IV-242b, IV-242c, IV-242d	 IV-243 IV-243a, IV-243b, IV-243c, IV-243d	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

Table 5. Representative Compounds of the Invention

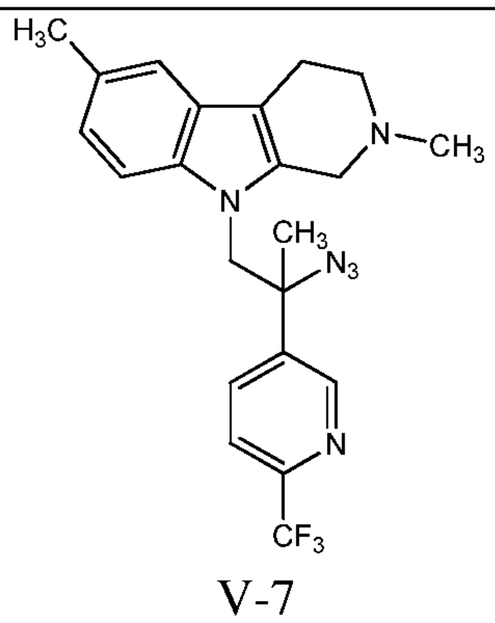
 V-1 V-1a, V-1b	 V-2 V-2a, V-2b	 V-3 V-3a, V-3b	 V-4 V-4a, V-4b, V-4c,V-4d



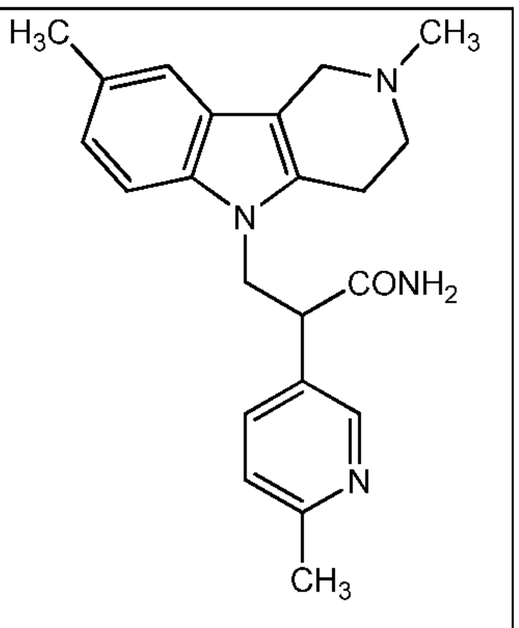
V-5
V-5a, V-5b, V-5c, V-5d



V-6
V-6a, V-6b



V-7
V-7a, V-7b



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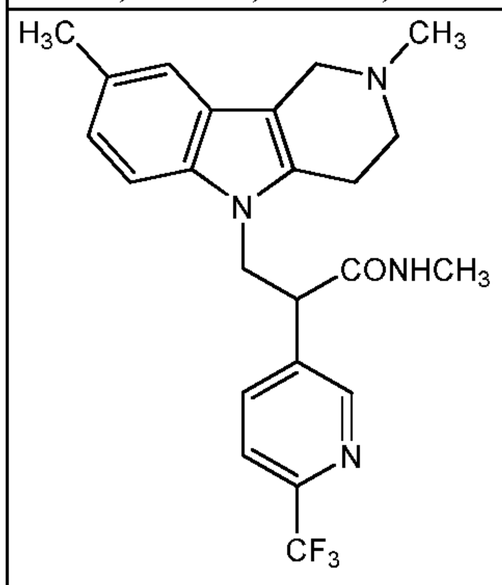
V-8a, V-8b



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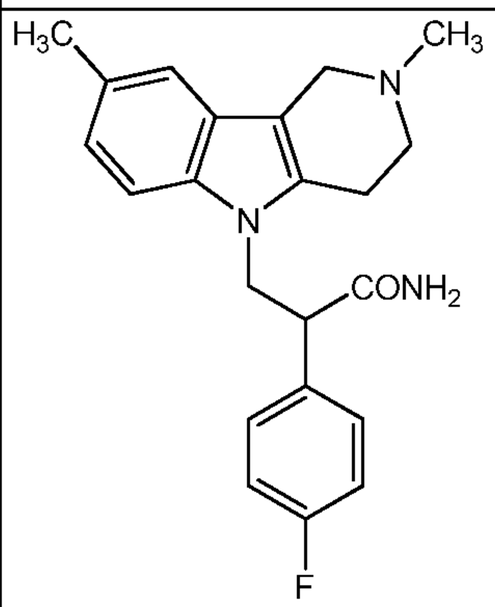
V-9a, V-9b



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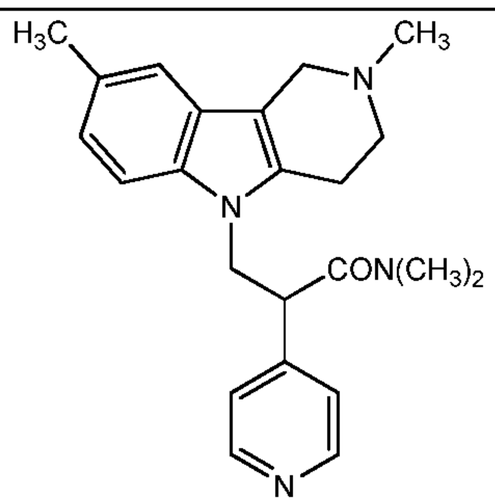
V-10a, V-10b



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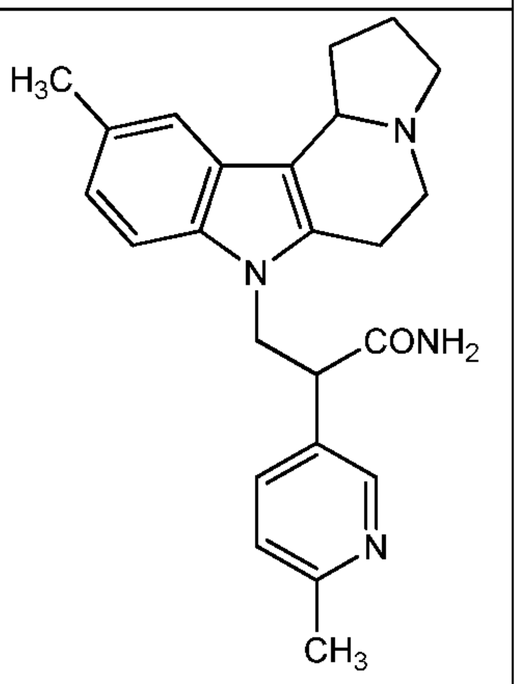
V-11a, V-11b



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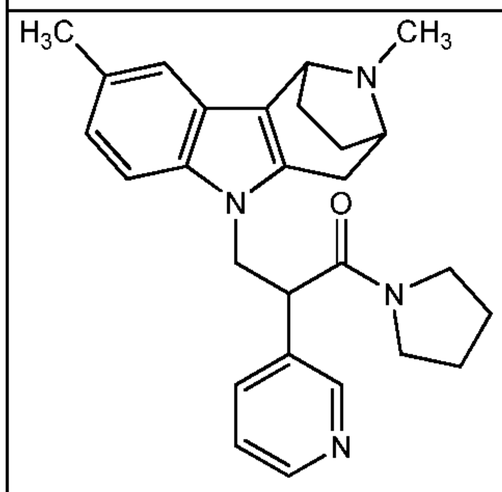
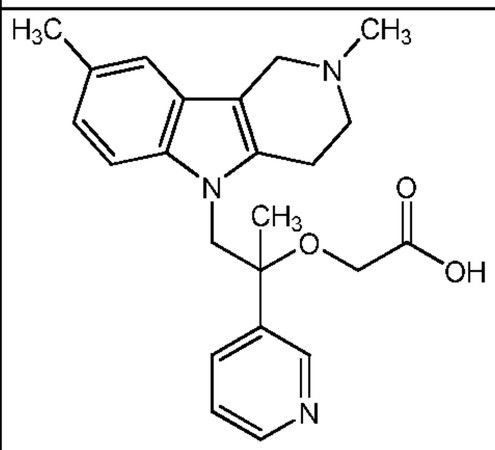
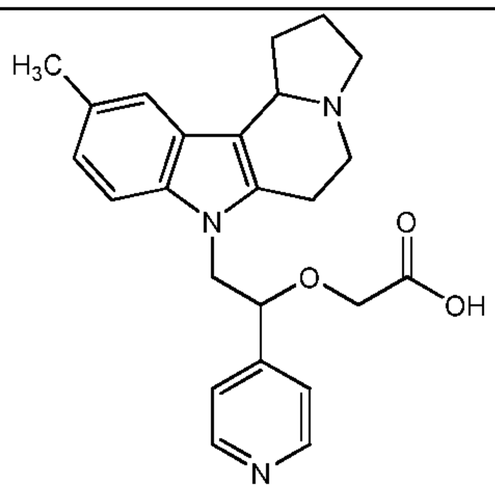
V-12a, V-12b, V-12c, V-12d



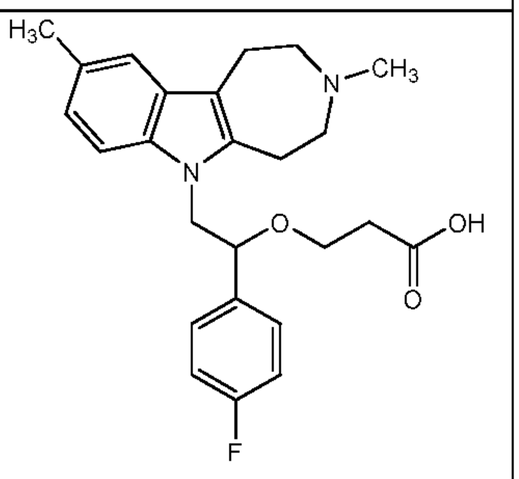
V-13
V-13a, V-13b, V-13c, V-13d



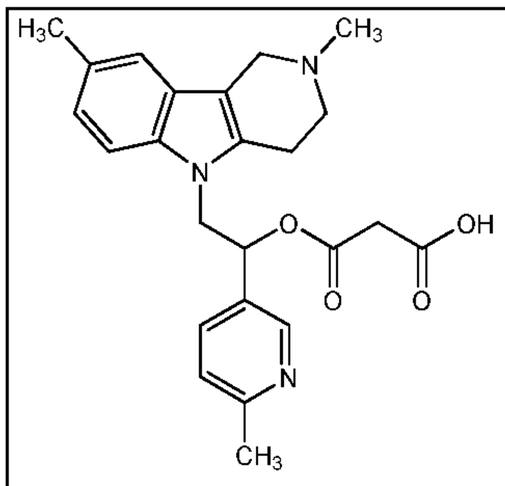
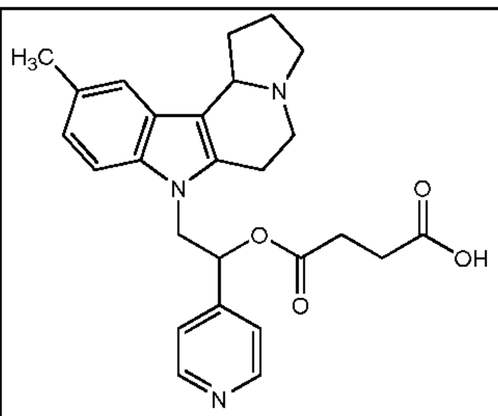
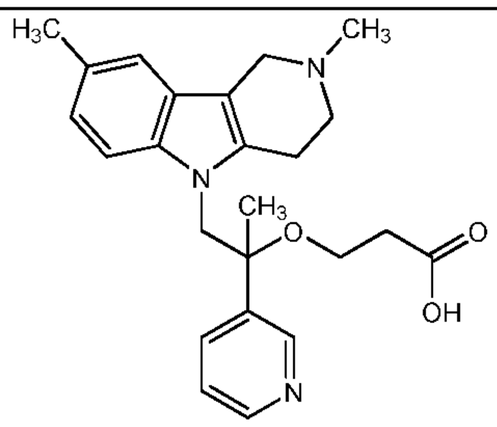
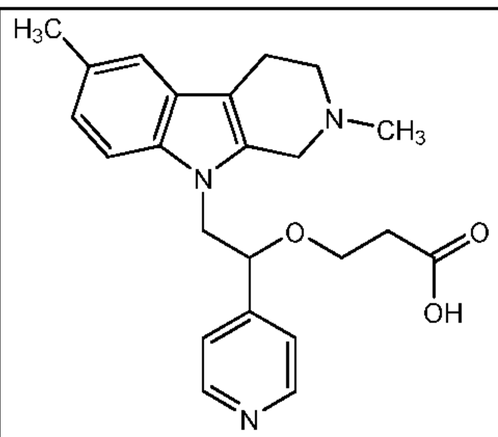
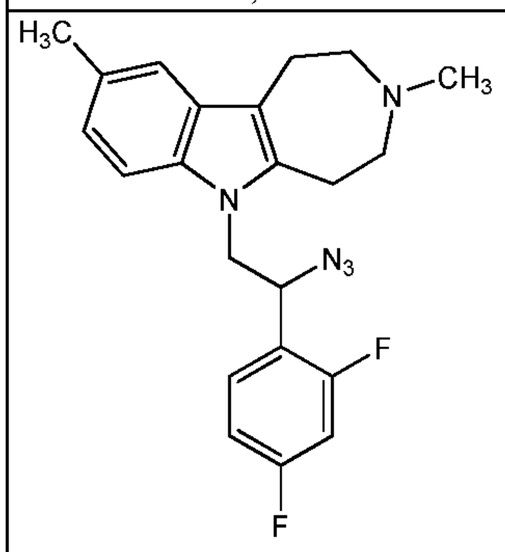
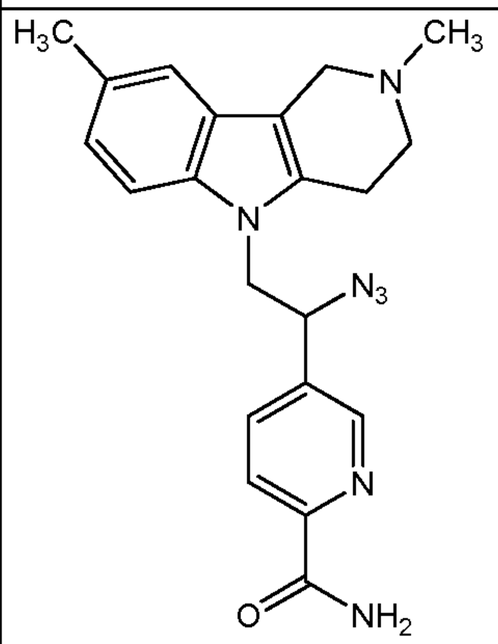
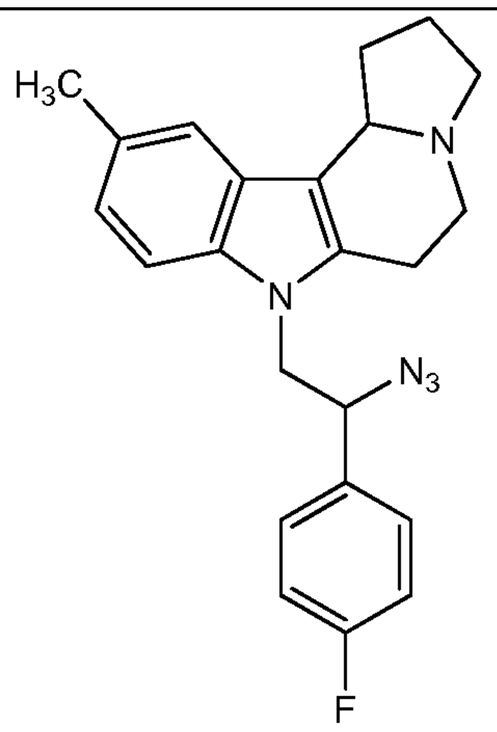
V-14
V-14a, V-14b



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.

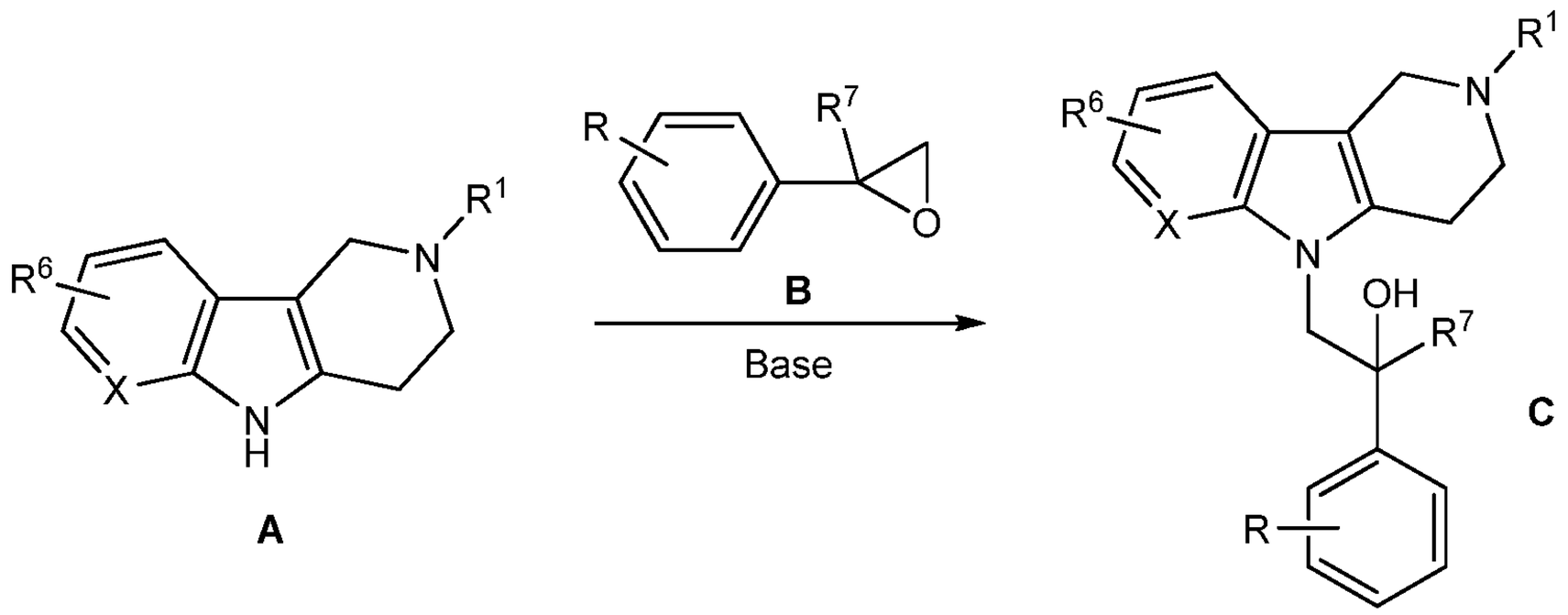
Column: Chiral PAK-AD-H. Column ID: 20*250mm, 5µ. Mobile Phase: Hexane (0.2% diethylamine):Isopropanol - 93:7. Flow rate: 15 mL/min. Solubility: 40 mg/mL in MeOH.

[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. ^1H 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 No. 3a; (-)31.32 (c 1, Chloroform, 94.1% HPLC purity); Compound No. 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. ^1H 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 No. 4a, (+)47.31 (c 0.58, Chloroform, 96.26% HPLC purity); Compound No. 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 No. 5a, (-)39.27 (c 0.43, Chloroform, 99.69% HPLC purity); Compound No. 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 No. 10a, (-)34.60 (c 0.55, Chloroform, 99.16% HPLC purity); Compound No. 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 No. 11a, (-)25.66 (c 0.56, Chloroform, 96.42% HPLC purity); Compound No. 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 No. 12a, (+)121.78 (c 0.53, Chloroform, 97.32% HPLC purity); Compound No. 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 No. 13a, (-)5.03 (c 0.56, Chloroform, 99.17% HPLC purity); Compound No. 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 No. 14a, (+)31.28 (c 0.58, Chloroform, 96.04% HPLC purity); Compound No. 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 No. 16a, (-)5.77 (c 0.52, Chloroform, 98.11% HPLC purity); Compound No. 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 No. 17a, (+)50.54 (c 0.56, Chloroform, 99.31% HPLC purity); Compound No. 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

No. 18a, (-)6.97 (c 0.56, Chloroform, 89.35% HPLC purity); Compound No. 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 No. 19a, (+)22.35 (c 0.58, Chloroform, 98.36% HPLC purity); Compound No. 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 No. 20a, (-)10.20 (c 0.58, Chloroform, 99.61% HPLC purity); Compound No. 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 No. 21a, (-)12.41 (c 0.56, Chloroform, 97.75% HPLC purity); Compound No. 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 No. 22a, (-)58.57 (c 0.57, Chloroform, 98.5% HPLC purity); Compound No. 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 No. 23a, (-)52.54 (c 0.55, Chloroform, 95.4% HPLC purity); Compound No. 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 No. 24a, (+)25.89 (c 0.58, Chloroform, 96.39% HPLC purity); Compound No. 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 No. 28a, (+)26.78 (c 0.54, Chloroform, 98.11% HPLC purity); Compound No. 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 No. 59a, (-)16.42 (c 0.54, Chloroform, 99.96% HPLC purity); Compound No. 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. ^{1}H 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. ^{1}H 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. ^{1}H 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 No. 129 (90 mg), which was separated by chiral prep HPLC to give compounds 129a, 129b, 129c and 129d. Compound No. 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 No. 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 No. 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 No. 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.

DEMANDE OU BREVET VOLUMINEUX

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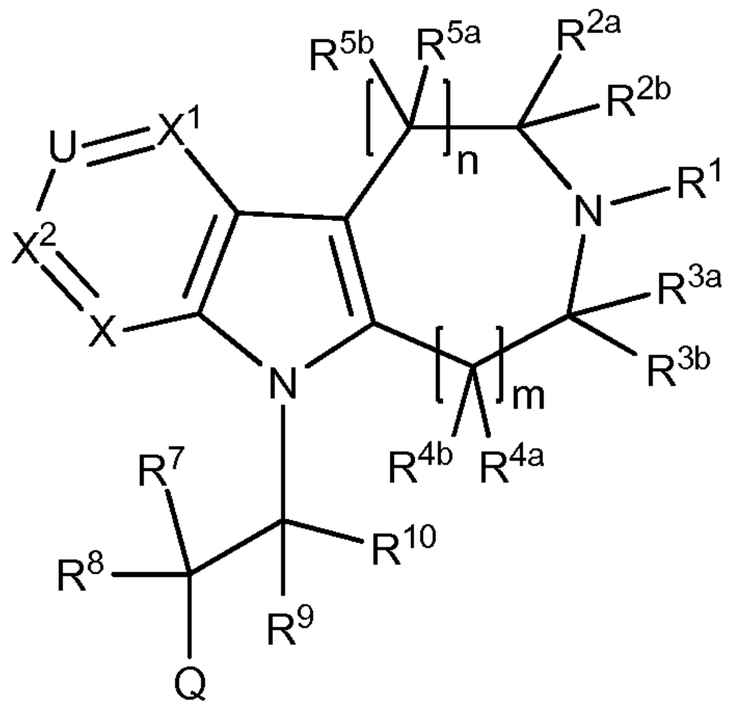
CLAIMS

What is claimed is:

1. A method of regulating blood glucose levels 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; 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

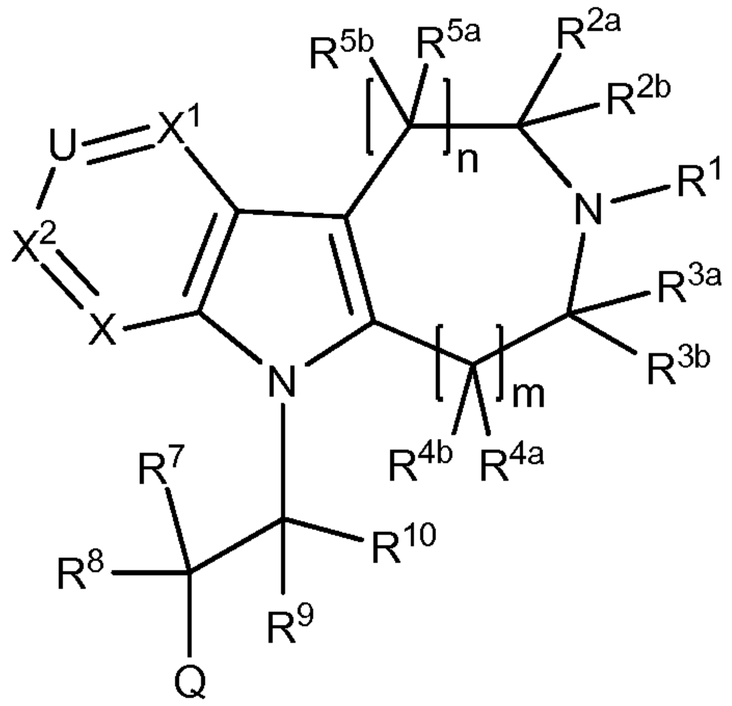
Q is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

2. The method of claim 1, wherein the method reduces blood glucose level in the individual.

3. The method of claim 2, wherein the method reduces blood glucose level in the individual for a period of more than 0.5 hours following administration.

4. The method of any one of claims 1 to 3, wherein the method stabilizes of blood glucose level in the individual.

5. A method of (i) increasing insulin secretion, and/or (ii) promoting insulin release into the blood stream, 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; 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 method increases insulin secretion.

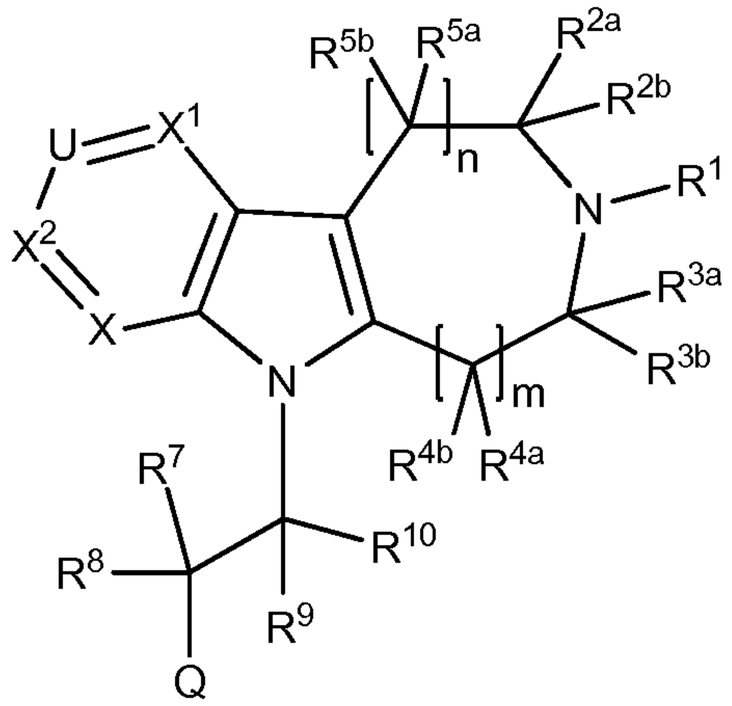
7. The method of claim 5, wherein the method promotes insulin release into the blood stream.

8. The method of any one of claims 1 to 7, wherein the individual has a disease or condition that involves impaired insulin secretion.

9. The method of any one of claims 1 to 8, wherein the individual has one or more risk factors for developing a disease or condition that involves impaired insulin secretion.

10. The method of any one of claims 1 to 9, wherein the administration results in decrease of blood pressure in the individual.

11. A method of treating a disease or condition that is responsive to an increase in insulin secretion, 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;

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;

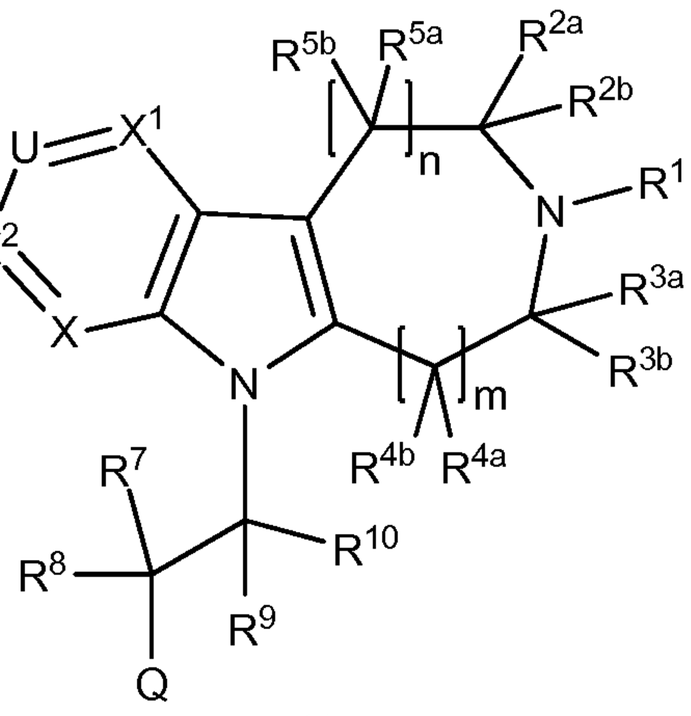
R^{13} is H or optionally substituted C_1-C_5 alkyl;

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.

12. A method of delaying the onset of a disease or condition that is responsive to an increase in insulin secretion, 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;

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.

13. The method of claims 11 or 12, wherein the disease or condition is type 2 diabetes.

14. The method of claim 13, wherein the individual is not responsive to standard treatment of type 2 diabetes.

15. The method of claims 11 or 12, wherein the disease or condition is glucose intolerance.

16. The method of claims 11 or 12, wherein the disease or condition is metabolic syndrome.

17. The method of any one of claims 11 to 16, further comprising administering to the individual in need thereof one or more anti-diabetic agents.

18. The method of claim 17, wherein at least one of the anti-diabetic agents is an insulin sensitizer.

19. The method of any one of claims 1-18, wherein one of X^1, X^2, X and U is N, and the other three of X^1, X^2, X and U are independently CR^6.

20. The method of any one of claims 1-18, wherein two of X^1, X^2, X and U is N, and the other two of X^1, X^2, X and U are independently CR^6.

21. The method of any one of claims 1-18, wherein each X^1, X^2, X and U is independently CR^6.

22. The method of any one of claims 1-21, wherein Q is:

unsubstituted aryl;

unsubstituted heteroaryl;

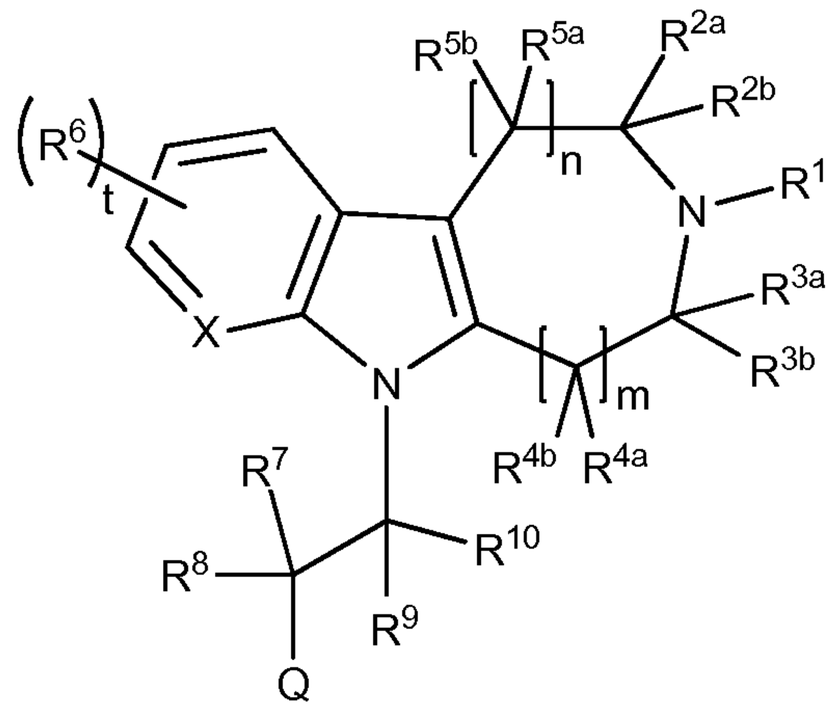
aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, hydroxyl, C_1-C_5 alkyl, C_3-C_8 cycloalkyl, halo-substituted C_1-C_5 alkyl, halo-substituted C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, C_3-C_8 cycloalkoxy, cyano, carboxyl, aminoacyl, $N(R^{16})(R^{17})$, $-C(O)OR^{18}$, SR^{18}, $S(O)R^{18}$ and SO_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.

23. The method of any one of claims 1-18, 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.

24. The method of claim 23, wherein X is CR^{6a}, wherein each R^{6a} is independently H, halo or C_1-C_5 alkyl.

25. The method of claim 24, wherein R^{6a} is H.

26. The method of any one of claims 23 to 25, wherein each R^6 is independently H, halo or C_1-C_5 alkyl.

27. The method of claim 23, wherein X is N.

28. The method of any one of claims 23-27, wherein R^1 is H or C_1-C_5 alkyl.

29. The method of any one of claims 23-28, wherein each R^{2a} and R^{3a} is H.

30. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl.

31. The method of any one of claims 23-30, wherein, R^8 is H, hydroxyl, $N(R^{11})R^{12}$ or -$OC(O)C_1$-C_5 alkyl.

32. The method of claim 31, wherein R^8 is hydroxyl.

33. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl, and R^8 is H, hydroxyl, $N(R^{11})R^{12}$ or -$OC(O)C_1$-C_5 alkyl.

34. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is H, hydroxyl, $N(R^{11})R^{12}$ or -$OC(O)C_1$-C_5 alkyl.

35. The method of any one of claims 23-29, wherein R^7 is C_1-C_5 alkyl, and R^8 is H, hydroxyl, $N(R^{11})R^{12}$ or -$OC(O)C_1$-C_5 alkyl.

36. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl, and R^8 is H or hydroxyl.

37. The method of any one of claims 23-29, wherein R^7 is H or C_1-C_5 alkyl, and R^8 is hydroxyl.

38. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is hydroxyl.

39. The method of any one of claims 23-29, wherein R^7 is methyl, and R^8 is hydroxyl.

40. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is NH_2.

41. The method of any one of claims 23-29, wherein R^7 is H, and R^8 is -OC(O)C_1-C_5 alkyl.

42. The method of any one of claims 23-41, wherein R^9 is H or C_1-C_5 alkyl.

43. The method of any one of claims 23-42, wherein R^{10} is H or C_1-C_5 alkyl.

44. The method of any one of claims 23-41, wherein each R^9 and R^{10} is H.

45. The method of any one of claims 23-41, wherein one of R^9 and R^{10} is H and the other is C_1-C_5 alkyl.

46. The method of any one of claims 23-45, wherein Q is:

unsubstituted pyridyl;

unsubstituted pyrimidyl;

unsubstituted pyrazinyl;

unsubstituted phenyl;

unsubstituted imidazolyl;

unsubstituted triazolyl;

pyridyl substituted with 1 to 3 substituents independently selected 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;

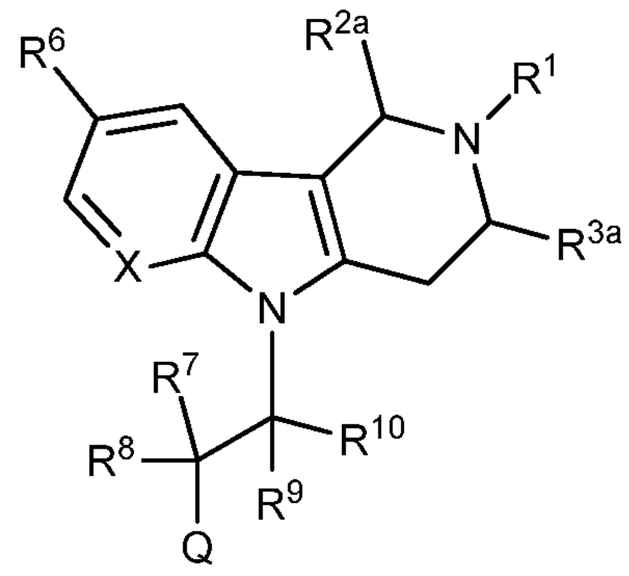
pyrazinyl substituted with 1 to 3 substituents independently selected form the group consisting of halo, C_1-C_5 alkyl, halo-substituted C_1-C_5 alkyl, carboxyl and –C(O)$NR^{16}R^{17}$, wherein each R^{16} and R^{17} is independently H or optionally substituted C_1-C_5 alkyl;

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.

47. The method of any one of claims 1-18, 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.

48. The method of claim 47, wherein X is CH.

49. The method of claim 47, wherein X is N.

50. The method of any one of claims 47-49, wherein R^1 is H or CH_3.

51. The method of any one of claims 47-50, wherein R^{2a} is H or is taken together with R^1 to form a propylene ($-CH_2CH_2CH_2-$) moiety.

52. The method of any one of claims 47-51, wherein R^{3a} is H.

53. The method of any one of claims 47-52, wherein each R^6 and R^{6a} is independently H, halo or C_1-C_5 alkyl.

54. The method of any one of claims 47-53, wherein R^7 is H or CH_3.

55. The method of any one of claims 47-54, wherein R^8 is hydroxyl.

56. The method of any one of claims 47-55, wherein Q is:

unsubstituted pyridyl;

unsubstituted pyrimidyl;

unsubstituted pyrazinyl;

unsubstituted phenyl;

unsubstituted imidazolyl;

unsubstituted triazolyl;

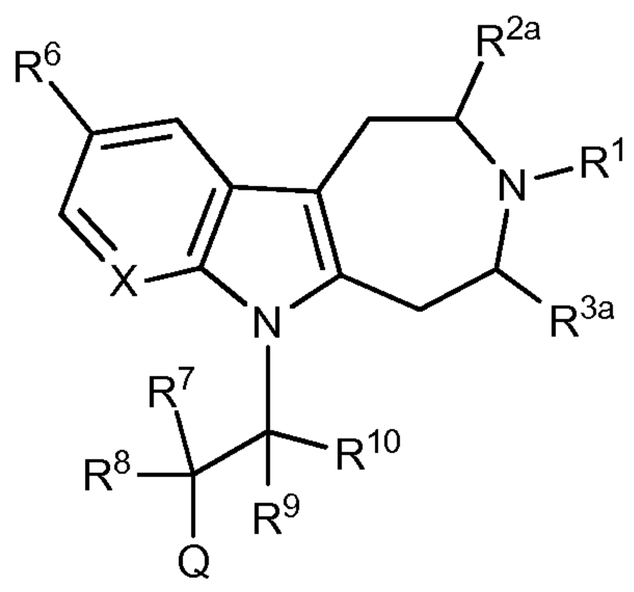
pyridyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3;

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.

57. The method of any one of claims 1-18, 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.

58. The method of claim 57, wherein X is CH.

59. The method of claim 57 or 58, wherein R^1 is H or CH_3.

60. The method of any one of claims 57-59, wherein each R^6 and R^{6a} is independently H, halo or C_1-C_5 alkyl.

61. The method of any one of claims 57-60, wherein R^7 is H or CH_3.

62. The method of any one of claims 57-61, wherein R^8 is hydroxyl.

63. The method of any one of claims 57-62, wherein Q is:

unsubstituted pyridyl;

unsubstituted pyrimidyl;

unsubstituted pyrazinyl;

unsubstituted phenyl;

unsubstituted imidazolyl;

unsubstituted triazolyl;

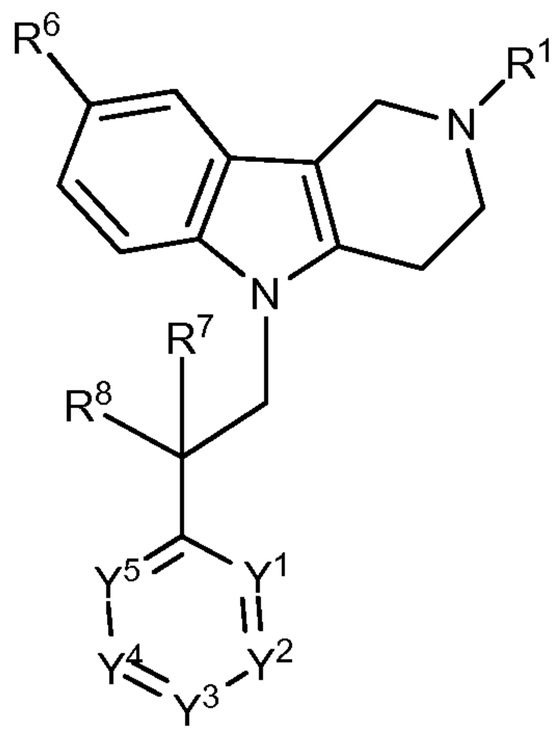
pyridyl substituted with halo, CH_3, CF_3, $CONH_2$, OH, or OCH_3;

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.

64. The method of any one of claims 1-18, 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.

65. The method of claim 64, wherein one of Y^1, Y^2, Y^3, Y^4 and Y^5 is N and the other four of Y^1, Y^2, Y^3, Y^4 and Y^5 are independently CR^4.

66. The method of claim 64, wherein Y^5 is CH, and each Y^1, Y^2, Y^3 and Y^4 is independently N or CR^4 such that two of Y^1, Y^2, Y^3 and Y^4 are N.

67. The method of any one of claims 64-66, wherein each R^4 is independently H, halo, CH_3, CF_3, or OCH_3.

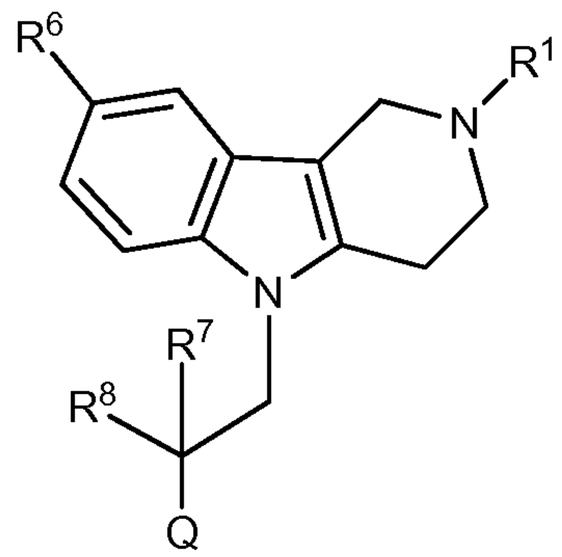
68. The method of any one of claims 64-67, wherein R^1 is H or CH_3.

69. The method of any one of claims 64-68, wherein R^6 is CH_3 or chloro.

70. The method of any one of claims 64-69, wherein R^7 is H or CH_3.

71. The method of any one of claims 64-70, wherein R^8 is hydroxyl.

72. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (A-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;

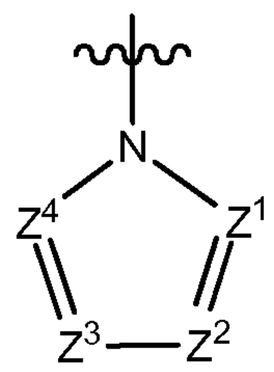
R^8 is H, halo, hydroxyl, $N(R^{11})R^{12}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, -OC(O)$N(R^{14})R^{15}$, -OC(O)-aryl, -OC(O)-heteroaryl, or -OC(O)C_1-C_5 alkyl optionally substituted with amino, or is taken together with R^7 and the carbon atom to which they are attached to form a dioxolane ring or a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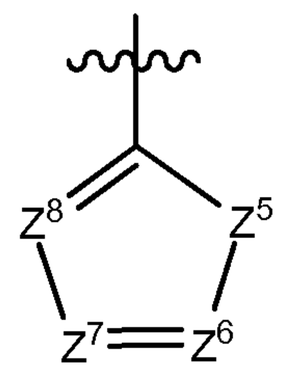

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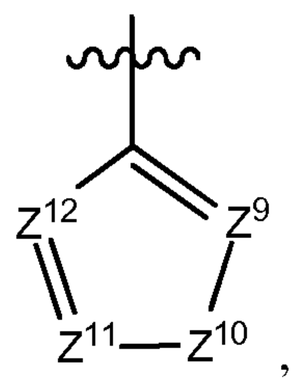


,

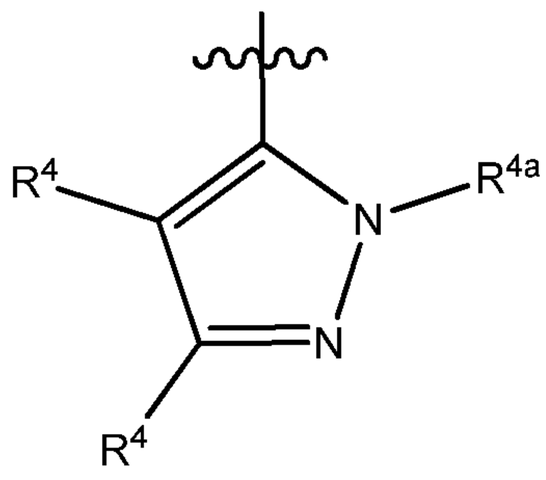
wherein

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.

73. The method of claim 72, wherein Q is selected from the group consisting of: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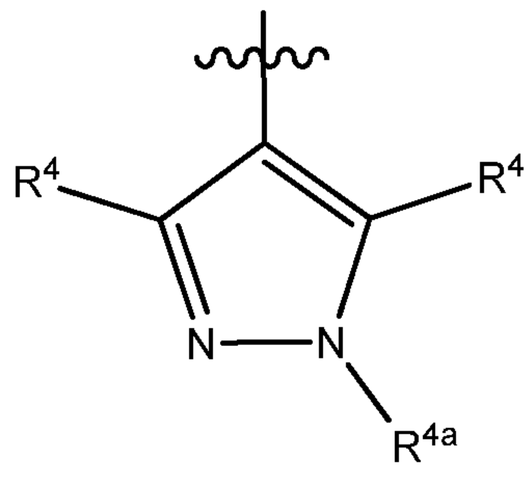
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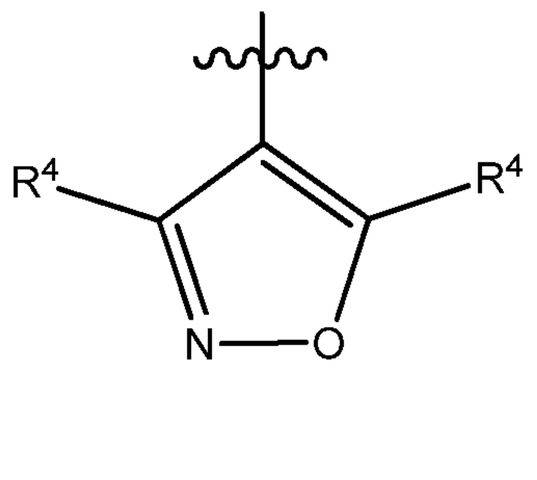
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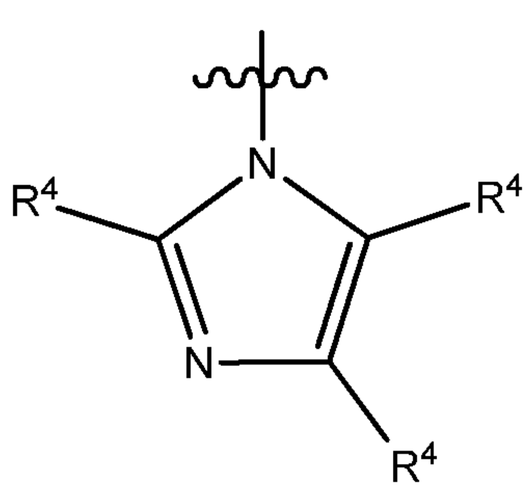
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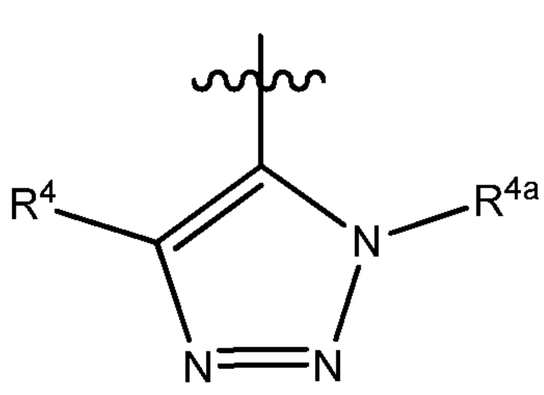
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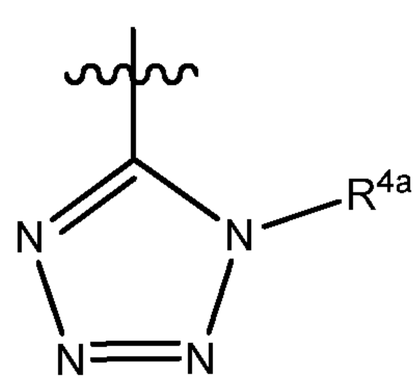
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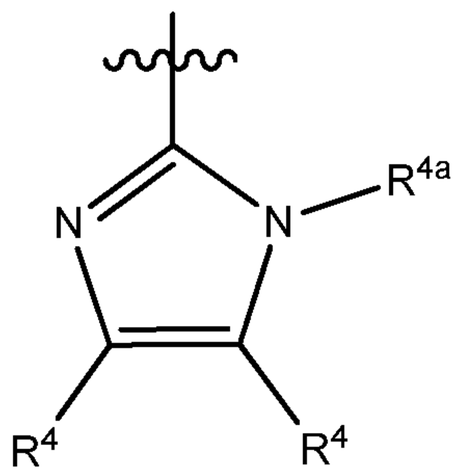
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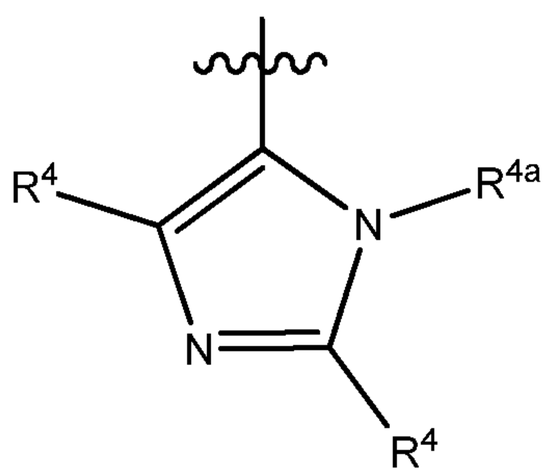
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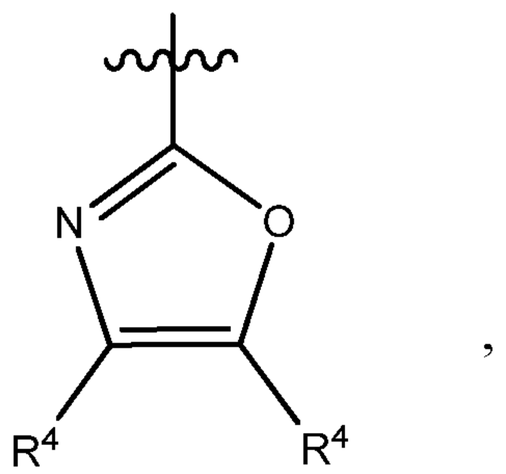
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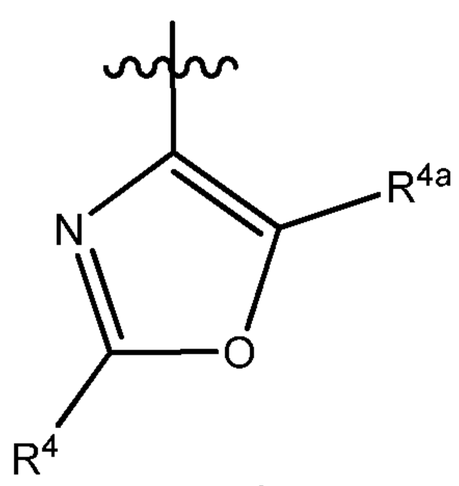
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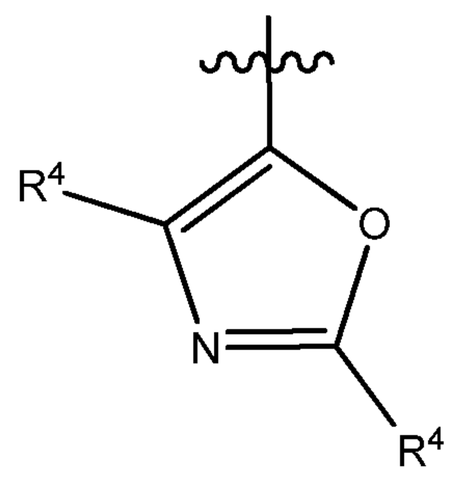
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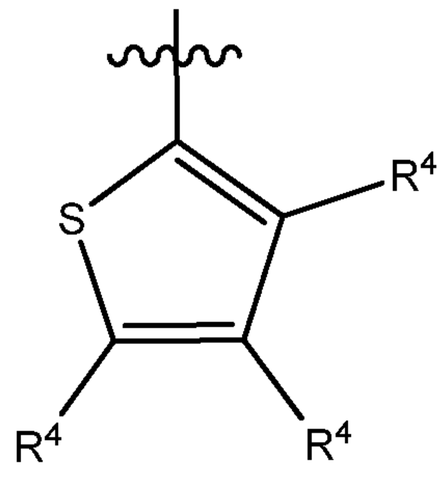
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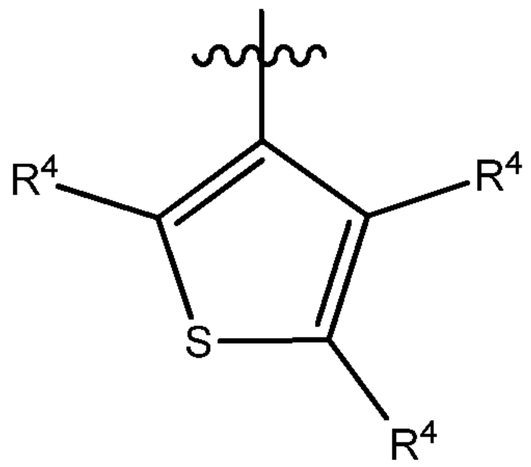


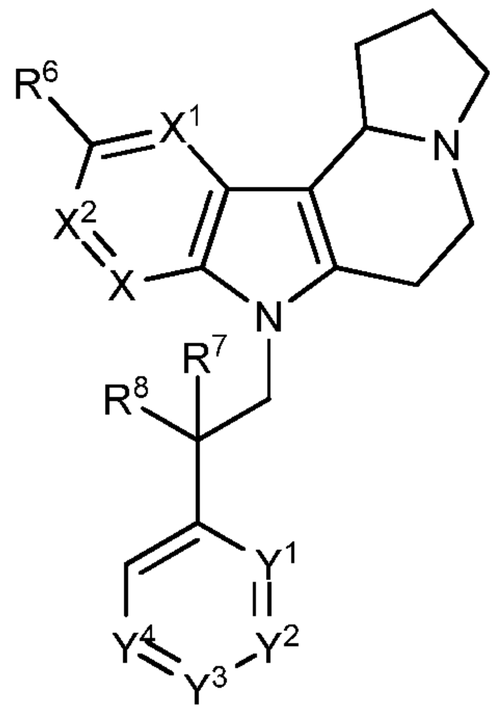
74. The method of claim 72 or 73, wherein R^1 is H or CH_3.

75. The method of any one of claims 72-74, wherein R^6 is CH_3 or chloro.

76. The method of any one of claims 72-75, wherein R^7 is H or CH_3.

77. The method of any one of claims 72-76, wherein R^8 is hydroxyl.

78. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (C-IA):



(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.

79. The method of claim 78, wherein each of X^1, X^2 and X is CH.

80. The method of claim 78 or 79, wherein R^6 is CH_3 or chloro.

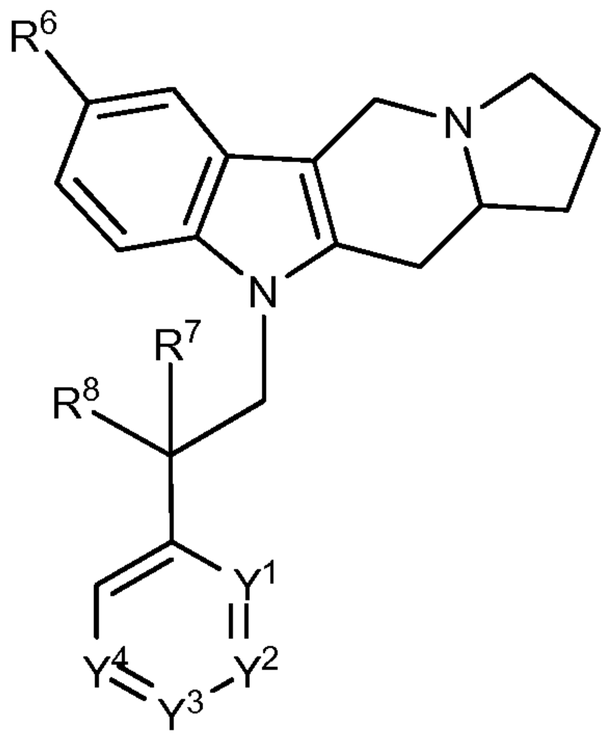
81. The method of any one of claims 78-80, wherein R^7 and R^8 are H.

82. The method of any one of claims 78-81, wherein one of Y^1, Y^2, Y^3 and Y^4 is N and the remaining three of Y^1, Y^2, Y^3 and Y^4 are CR^4, and wherein each R^4 is independently H, halo, CH_3, CF_3, or OCH_3.

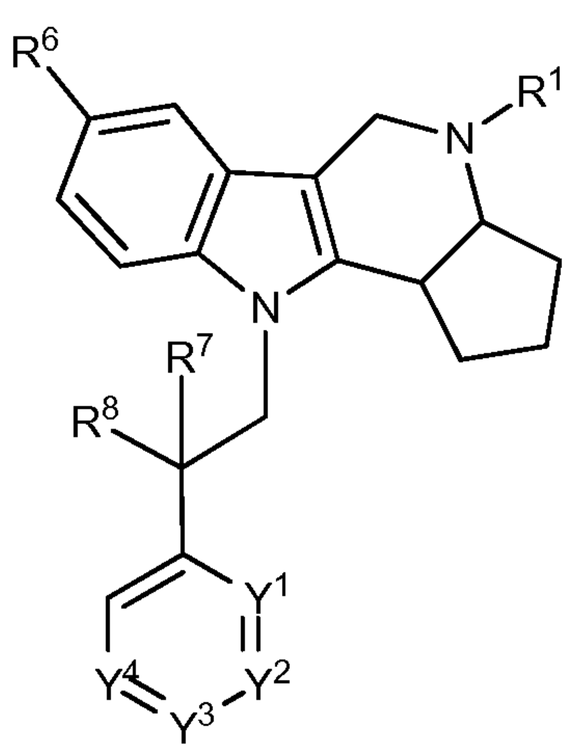
83. The method of any one of claims 78-82, wherein each of Y^1, Y^3 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^2 is N.

84. The method of any one of claims 78-82, wherein each of Y^1, Y^2 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^3 is N.

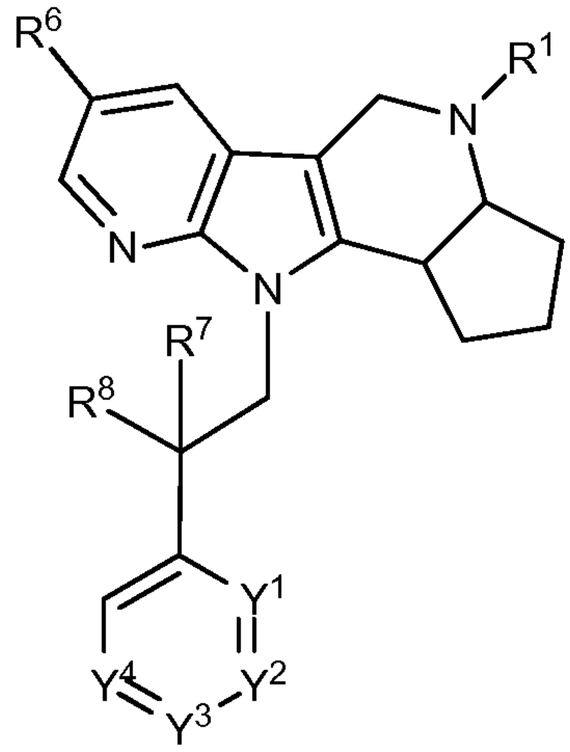
85. The method of any one of claims 1-18, wherein the compound of formula (I) is a compound of formula (D-IIA-1), (E-IIA-1), (E-IIA-2), (F-IIA-1), (F-IIA-2), (G-IIA-1), or (G-IIA-2):



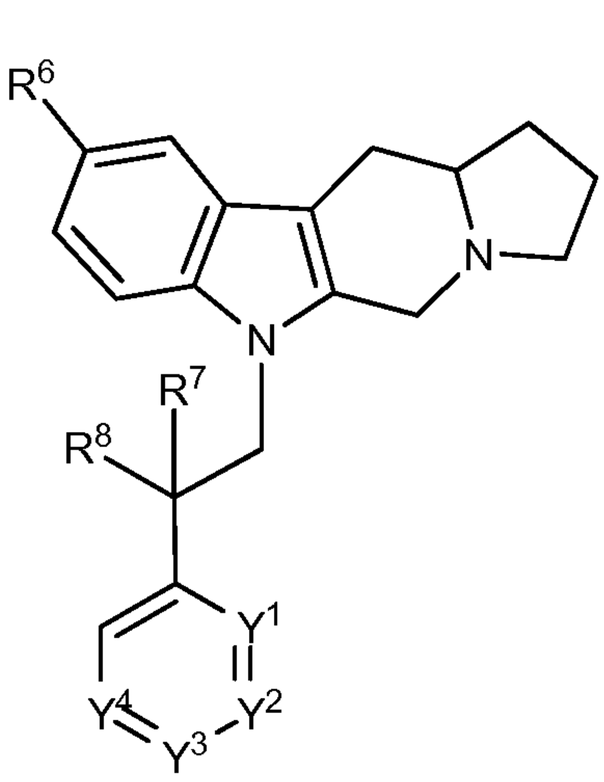
(D-IIA-1),



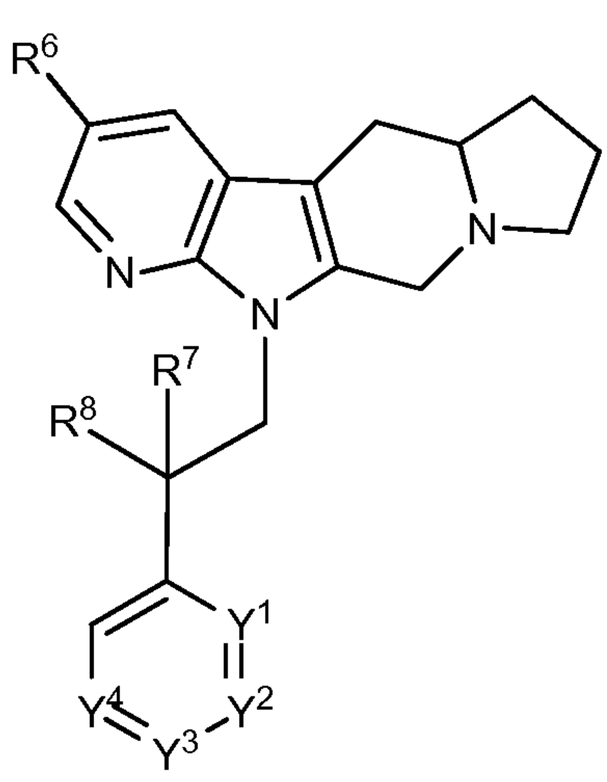
(E-IIA-1),



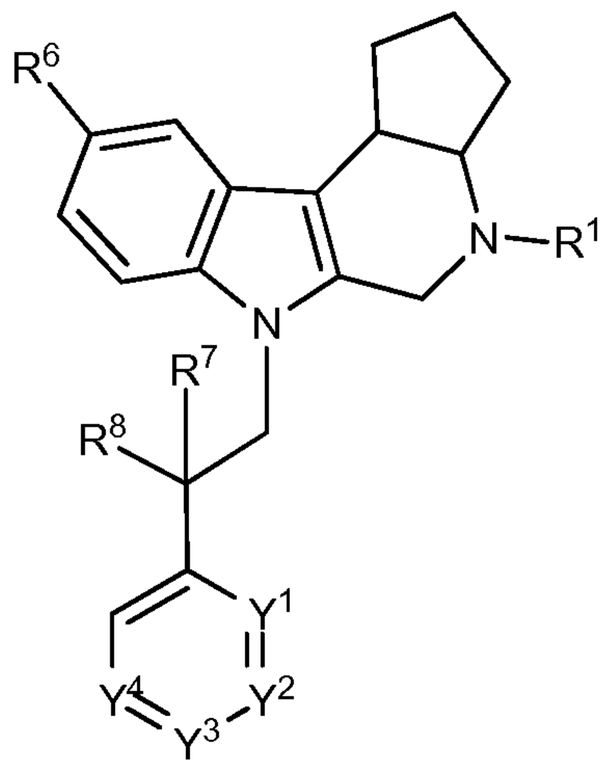
(E-IIA-2),



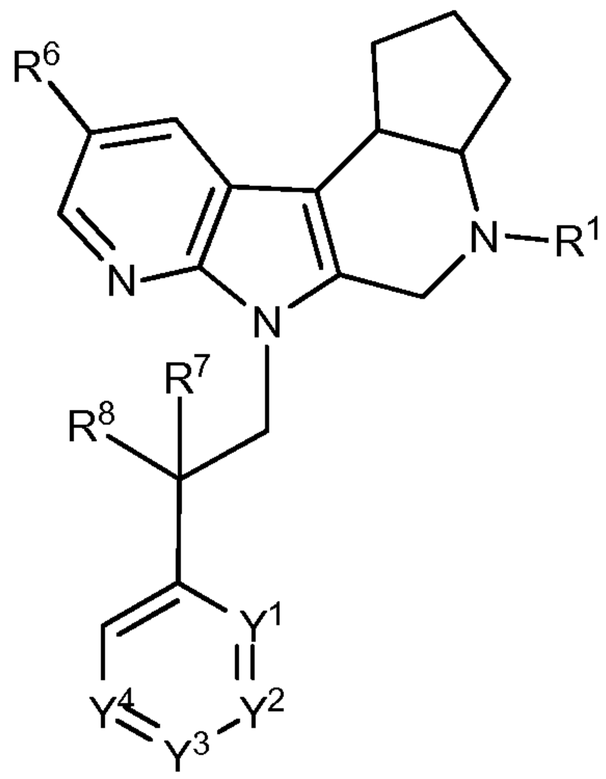
(F-IIA-1),



(F-IIA-2),



(G-IIA-1),



(G-IIA-2)

or ,

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.

86. The method of claim 85, wherein R^6 is unsubstituted C_1-C_5 alkyl or halo.

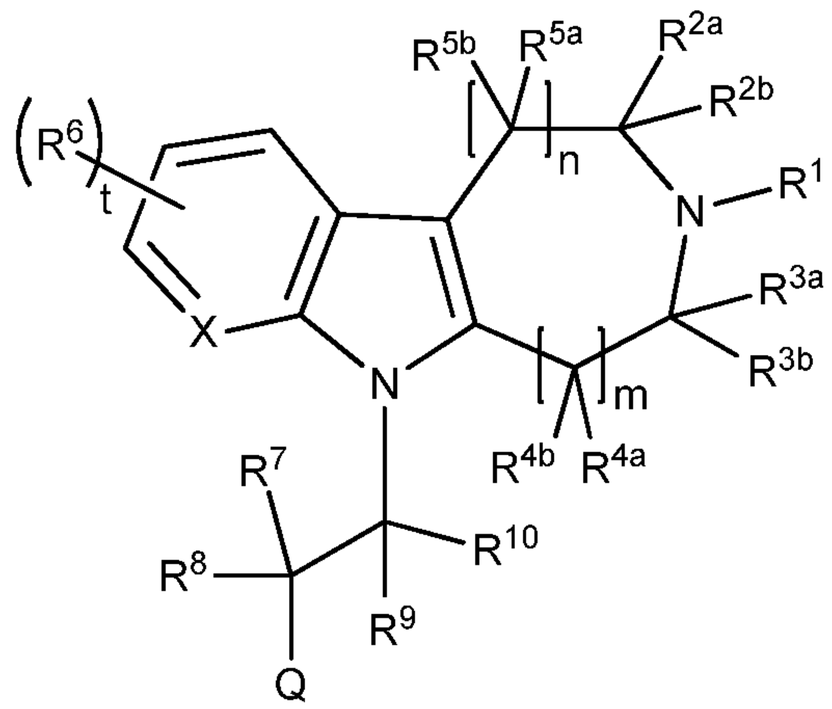
87. The method of claim 85 or 86, wherein R^7 and R^8 are H.

88. The method of any one of claims 85-87, wherein one of Y^1, Y^2, Y^3 and Y^4 is N and the remaining three of Y^1, Y^2, Y^3 and Y^4 are CR^4, and wherein each R^4 is independently H, halo, CH_3, CF_3, or OCH_3.

89. The method of any one of claims 85-88, wherein each of Y^1, Y^3 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^2 is N.

90. The method of any one of claims 85-88, wherein each of Y^1, Y^2 and Y^4 is independently CR^4, wherein R^4 is H or CH_3, and Y^3 is N.

91. The method of any one of claims 1-18, 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.

92. The method of claim 91, wherein X is CR^{6a}, wherein each R^{6a} is independently H, halo or C_1-C_5 alkyl.

93. The method of claim 91 or 92, wherein each R^6 is independently H, halo or C_1-C_5 alkyl.

94. The method of claim 91, wherein X is N.

95. The method of any one of claims 91-94, wherein R^1 is H or C_1-C_5 alkyl.

96. The method of any one of claims 91-95, wherein each R^{2a} and R^{3a} is H.

97. The method of any one of claims 91-96, wherein R^7 is H or optionally substituted C_1-C_5 alkyl.

98. The method of any one of claims 91-97, wherein, R^8 is azido.

99. The method of any one of claims 91-98, wherein R^9 is H or C_1-C_5 alkyl.

100. The method of any one of claims 91-99, wherein R^{10} is H or C_1-C_5 alkyl.

101. The method of any one of claims 91-100, wherein Q is:

unsubstituted aryl;

unsubstituted heteroaryl;

aryl substituted with 1 to 3 substituents independently selected from the group consisting of halo, C_1-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.

102. The method of any one of claims 1-18, wherein the compound is selected from Table I, Table II, Table III, Table IV or Table V; or a salt, solvate or N-oxide thereof.

103. The method of any one of claims 1-18, wherein the compound is Compound No. 1 to 343, II-1 to II-265, III-1 to III-368, IV-1 to IV-244 or V-1 to V-23; or a salt, solvate or N-oxide thereof.

104. The method of any one of claims 1-18, wherein the compound is Compound No. 129d; or a salt, solvate or N-oxide thereof.

105. The method of any one of claims 1-18, wherein the compound is selected from the group consisting of Compound Nos. 3a, 3b, 4a, 4b, 5a, 5b, 6, 7a, 7b, 8a, 8b, 9, 9a, 9b, 10, 10a, 10b, 11, 11a, 11b, 12, 12a, 12b, 13a, 13b, 14, 14a, 14b, 15a, 15b, 16, 16a, 16b, 17, 17a, 17b, 18, 18a, 18b, 19, 19a, 19b, 20, 20a, 20b, 21, 21a, 21b, 22a, 22b, 23, 23a, 23b, 24, 24a, 24b, 25, 25a, 25b, 26, 26a, 26b, 26c, 26d, 27, 27a, 27b, 28, 28a, 28b, 29a, 29b, 30a, 30b, 31a, 31b, 36, 37, 37c, 37d, 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.

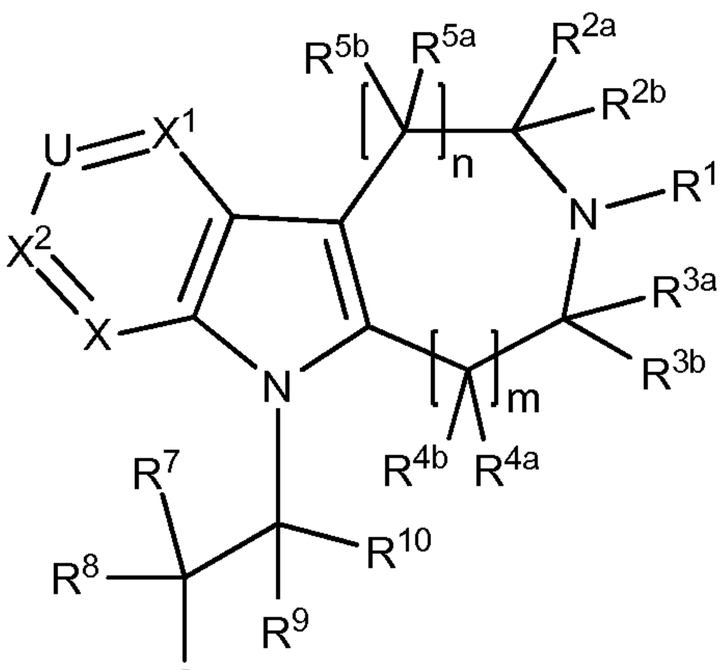
106. The method of any one of claims 1 to 105, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2A} and, wherein the compound either (a) also binds to and is an antagonist of the adrenergic receptor α_{2B} or (b) the compound is not an antagonist of the adrenergic receptor α_{2B} and the compound is administered in conjunction with a second agent that reduces blood pressure in the individual.

107. The method of claim 106, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{2B}.

108. The method of claims 106 or 107, wherein the compound binds to and is an antagonist of the adrenergic receptor α_{1B}.

109. The method of claim 106, wherein the compound is not an antagonist of the adrenergic receptor α_{2B} and the compound is administered in conjunction with a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist, a beta blocker, a calcium channel blocker, or any combination thereof.

110. 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;

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;

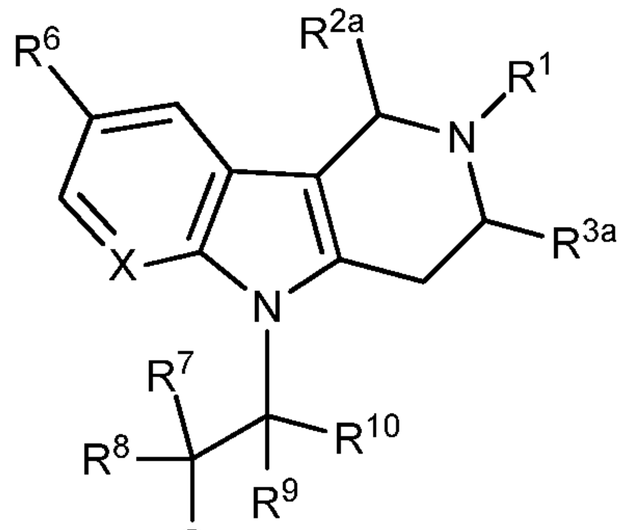
each R^{14} and R^{15} is independently H or optionally substituted C_1-C_5 alkyl; or R^{14} and R^{15} are taken together to form a C_3-C_5 alkylene;

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,

or a pharmaceutically acceptable salt thereof, and (ii) instructions for use according to the method of any one of claims 1-18.

111. 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 according to the method of any one of claims 47-56.

112. A compound selected from the group consisting of Compound No. 6, 9 to 12, 14, 16 to 21, 23 to 28, 39 to 42, 44 to 59, 63 to 72, 75 to 82, 104, 108 to 131, 133 to 171, 173 to 179, 187 to 193, 195 to 198, 220, 269 to 271, 273 to 287, 290 to 38, 340 to 343, II-1 to II-265, III-1 to III-368, IV-1, IV-3, IV-8 to IV-244, or V-1 to V-23, or a salt thereof.

113. A pharmaceutical composition comprising a compound of claim 112, and a pharmaceutically acceptable carrier.

114. A kit comprising (i) a compound of claim 112 or a pharmaceutically acceptable salt thereof, and (ii) instructions for use in regulating blood glucose in an individual in need

thereof, increasing insulin secretion in an individual in need thereof, and/or in treating a disease or condition that is responsive to an increase in insulin secretion.

115. The kit of claim 114, wherein the disease or condition is selected from the group consisting of the disease or condition is selected from the group consisting of type 2 diabetes, glucose intolerance and metabolic syndrome.

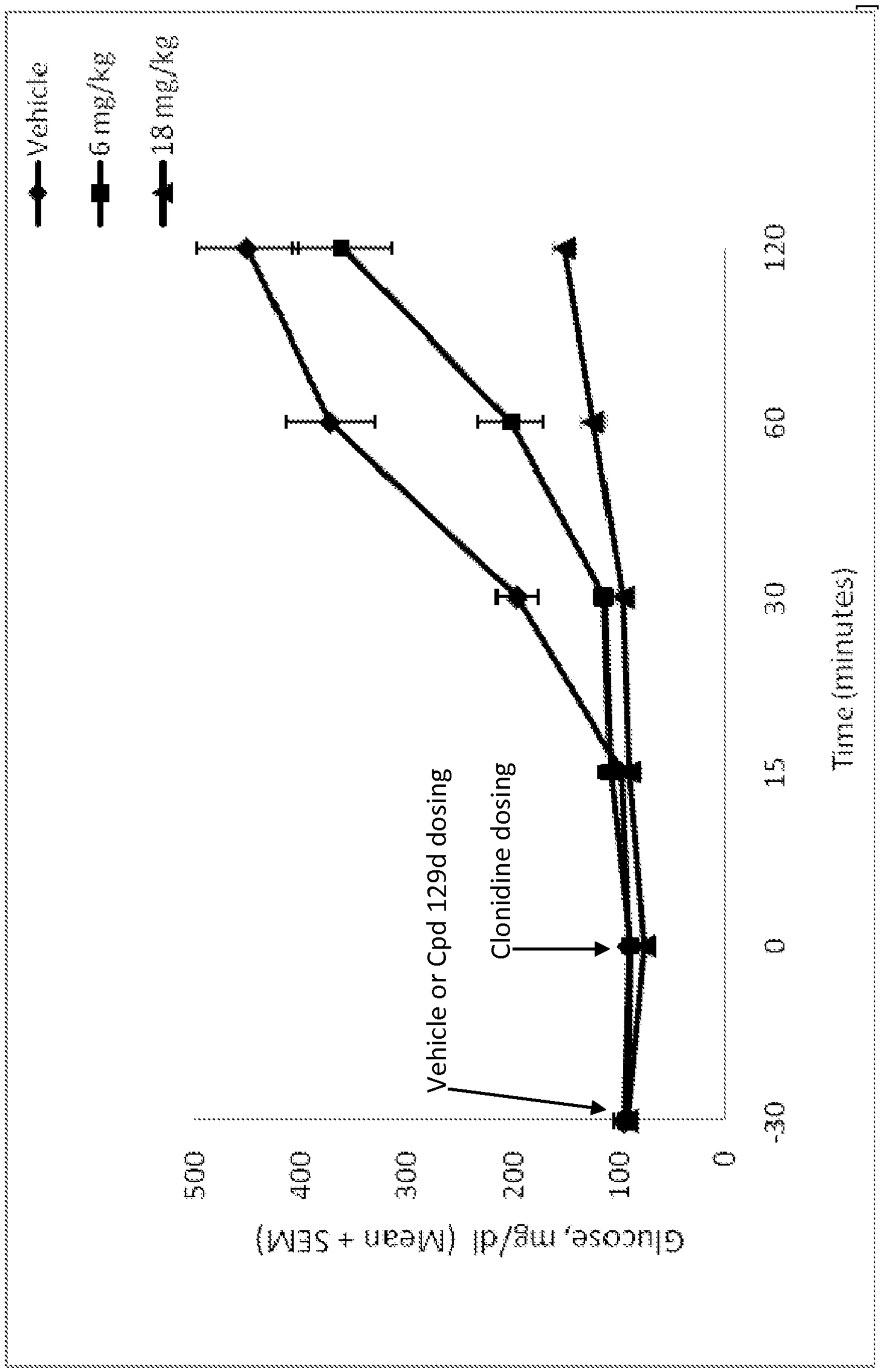

Vehicle
6 mg/kg
18 mg/kg
Vehicle or Cpd 129d dosing
Clonidine dosing
Glucose, mg/dl (Mean + SEM)
500
400
300
200
100
0
-30
0
15
30
60
120
Time (minutes)

Figure 1

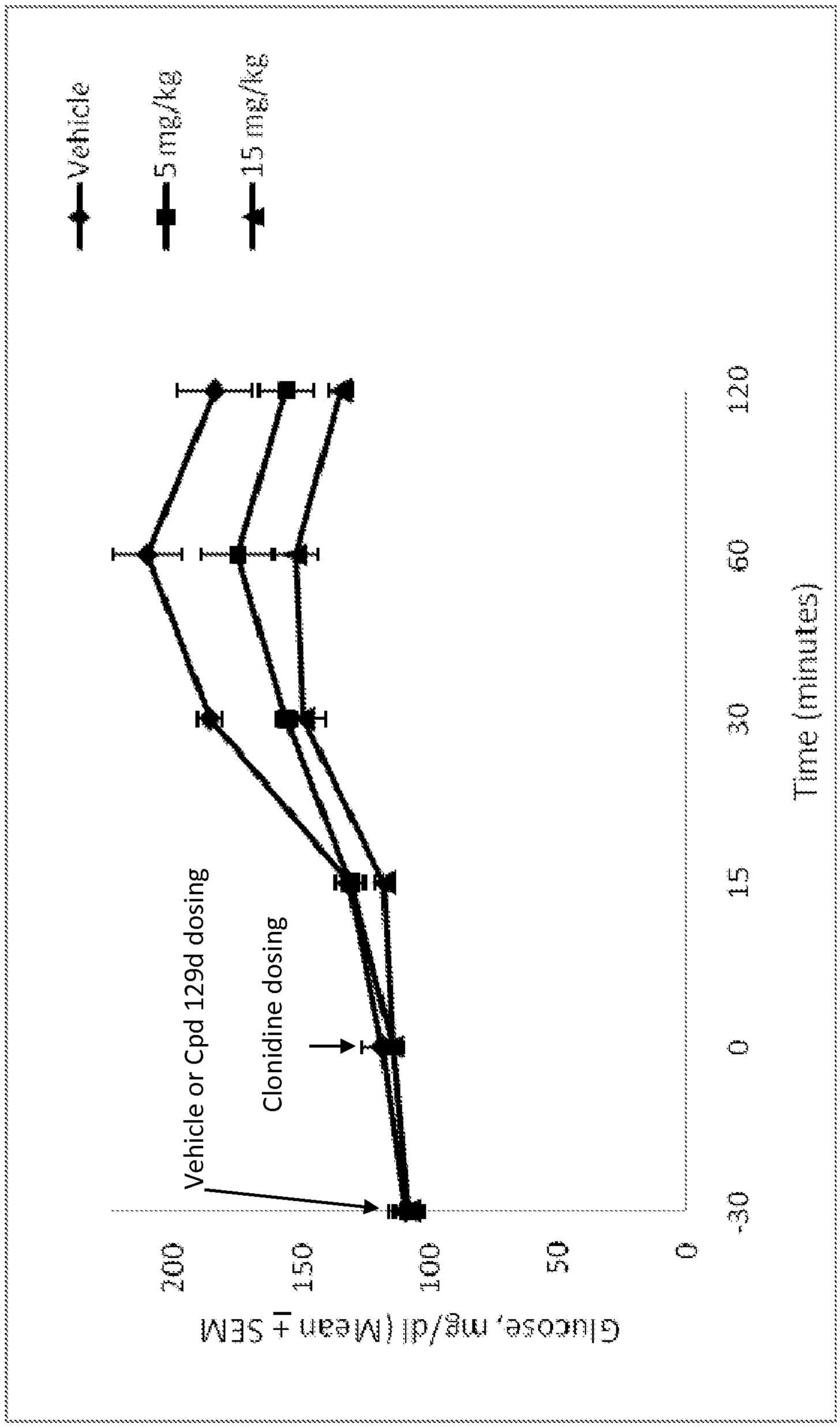

Vehicle
5 mg/kg
15 mg/kg
Vehicle or Cpd 129d dosing
Clonidine dosing
Glucose, mg/dl (Mean ± SEM
200
150
100
50
0
-30
0
15
30
60
120
Time (minutes)

Figure 2

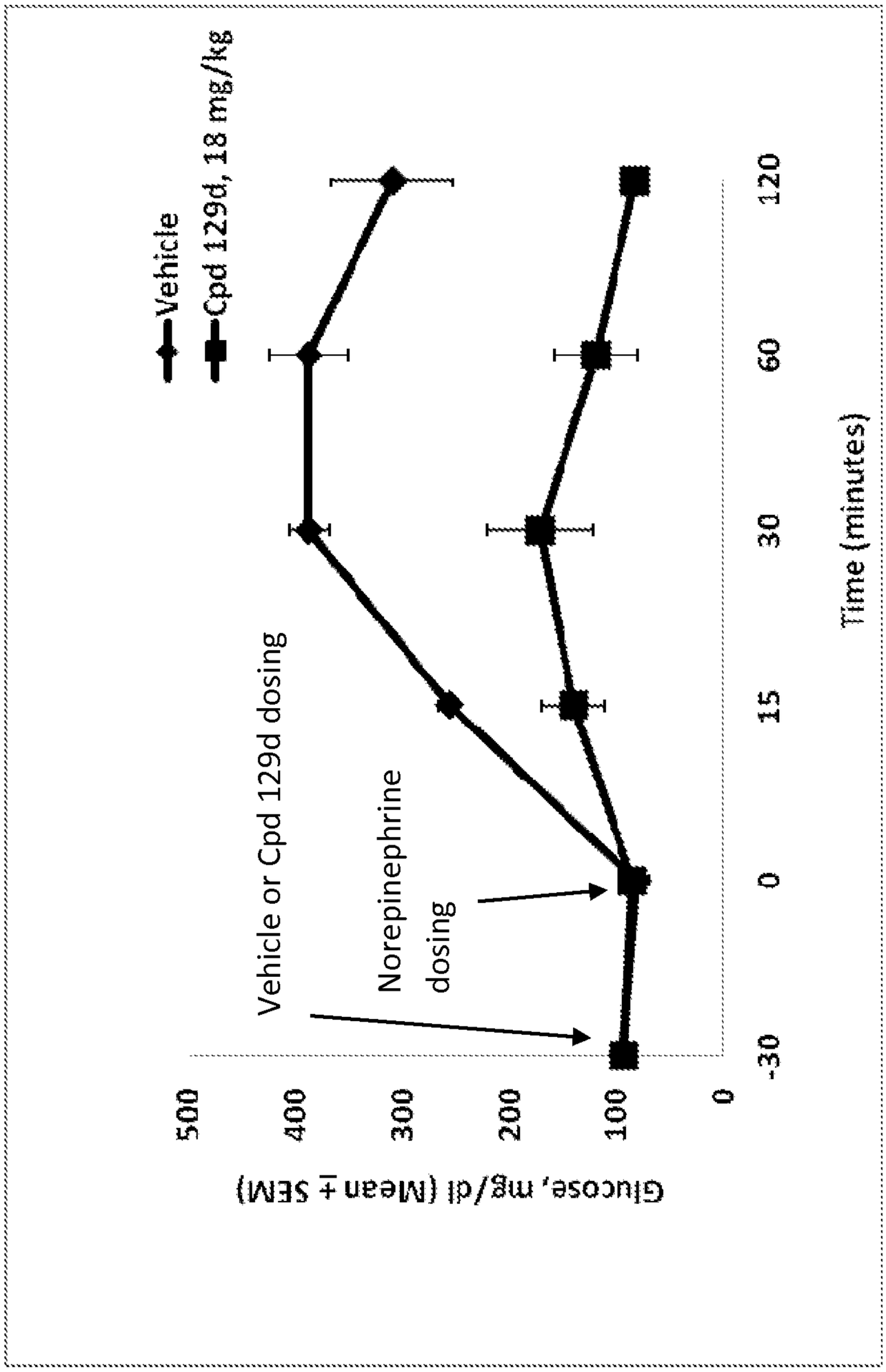

Vehicle
Cpd 129d, 18 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
Glucose, mg/dl (Mean ± SEM)
500
400
300
200
100
0
-30
0
15
30
60
120
Time (minutes)

Figure 3

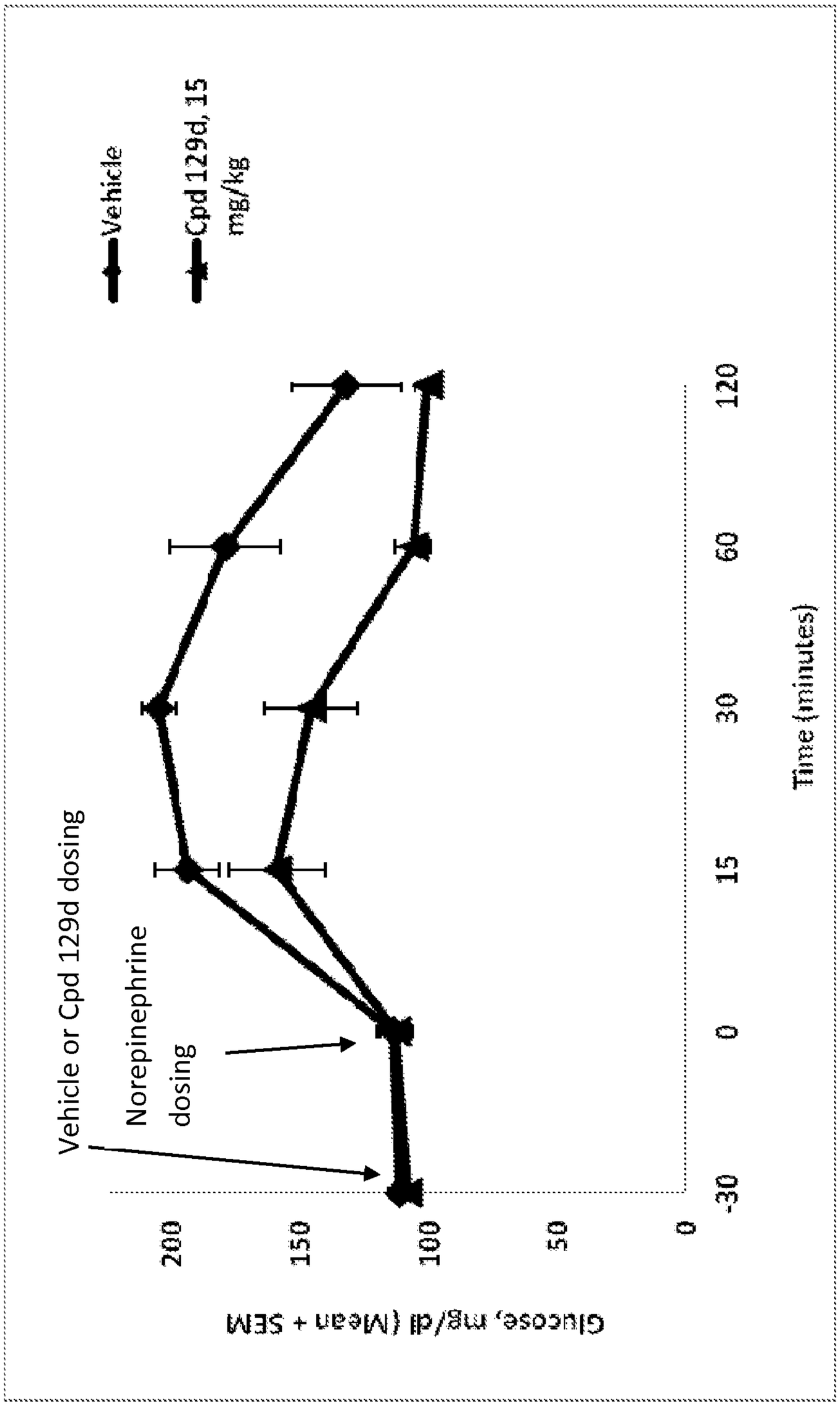

Vehicle
Cpd 129d, 15 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
Glucose, mg/dl (Mean + SEM
200
150
100
50
0
-30
0
15
30
60
120
Time (minutes)

Figure 4

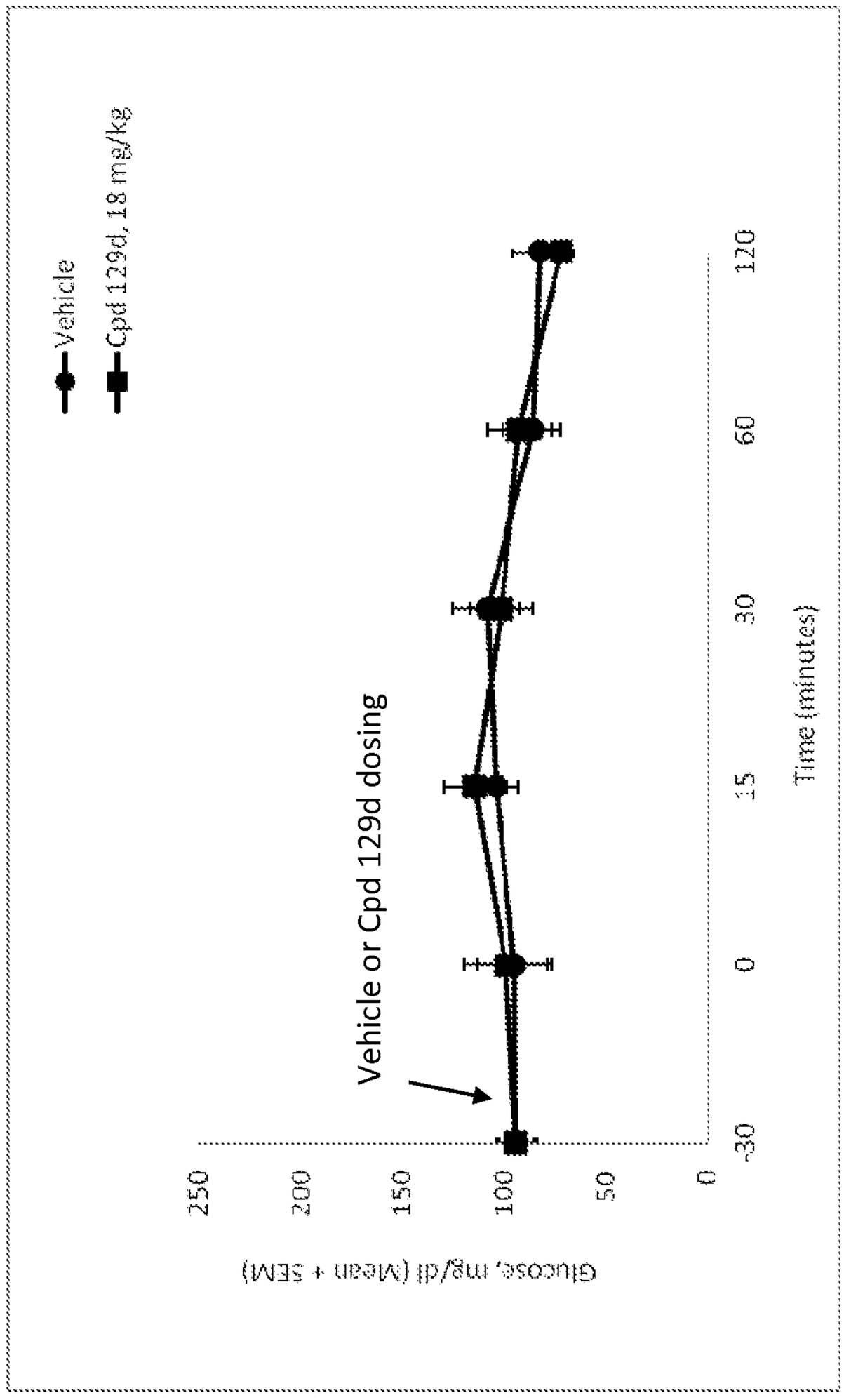

Vehicle
Cpd 129d, 18 mg/kg
Vehicle or Cpd 129d dosing
Glucose, mg/dl (Mean + SEM)
250
200
150
100
50
0
-30
0
15
30
60
120
Time (minutes)

Figure 5

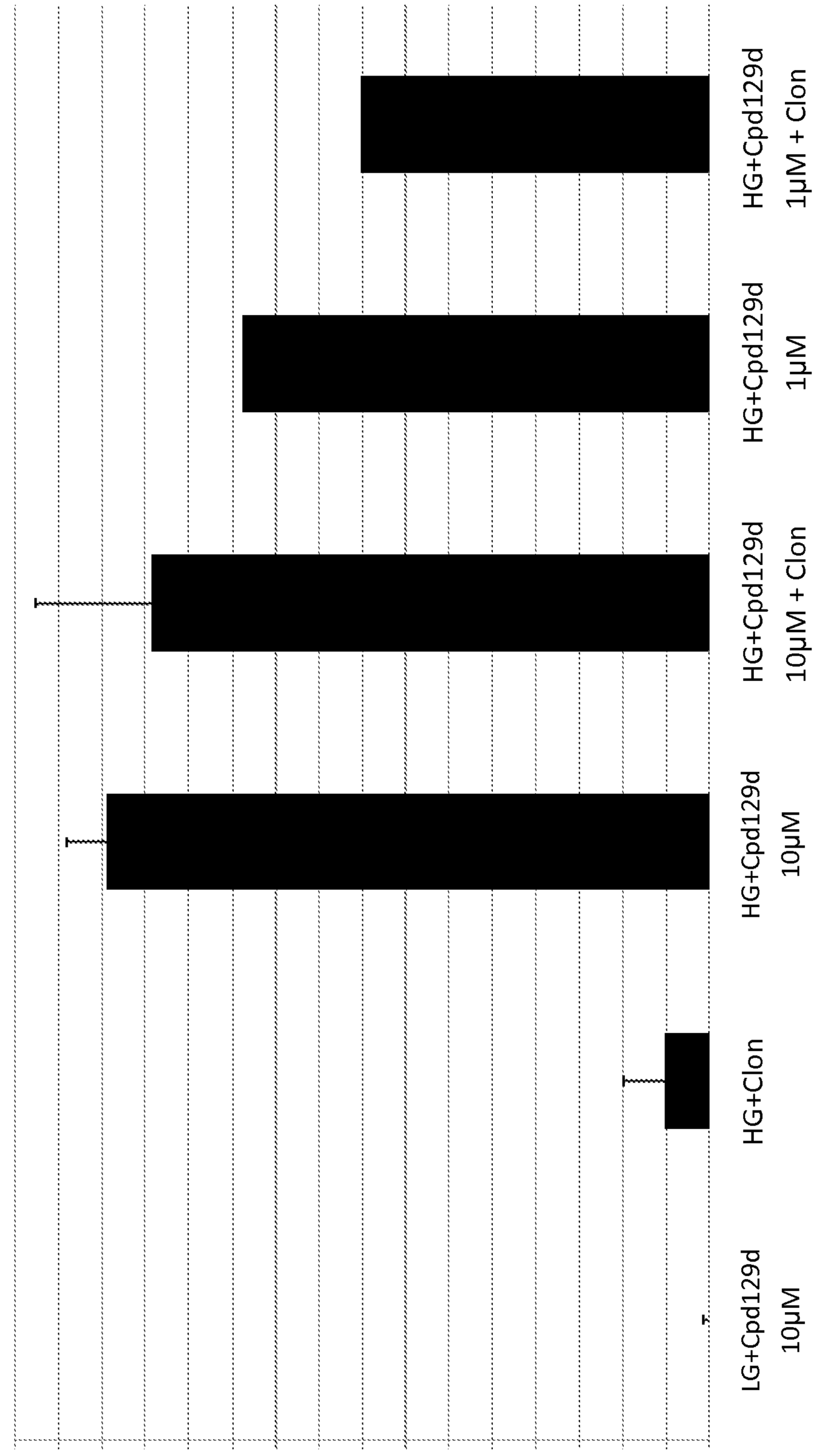

Percentage increase
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
LG+Cpd129d 10μM
HG+Clon
HG+Cpd129d 10μM
HG+Cpd129d 1μM
HG+Cpd129d 10μM + Clon
HG+Cpd129d 1μM + Clon

Figure 6

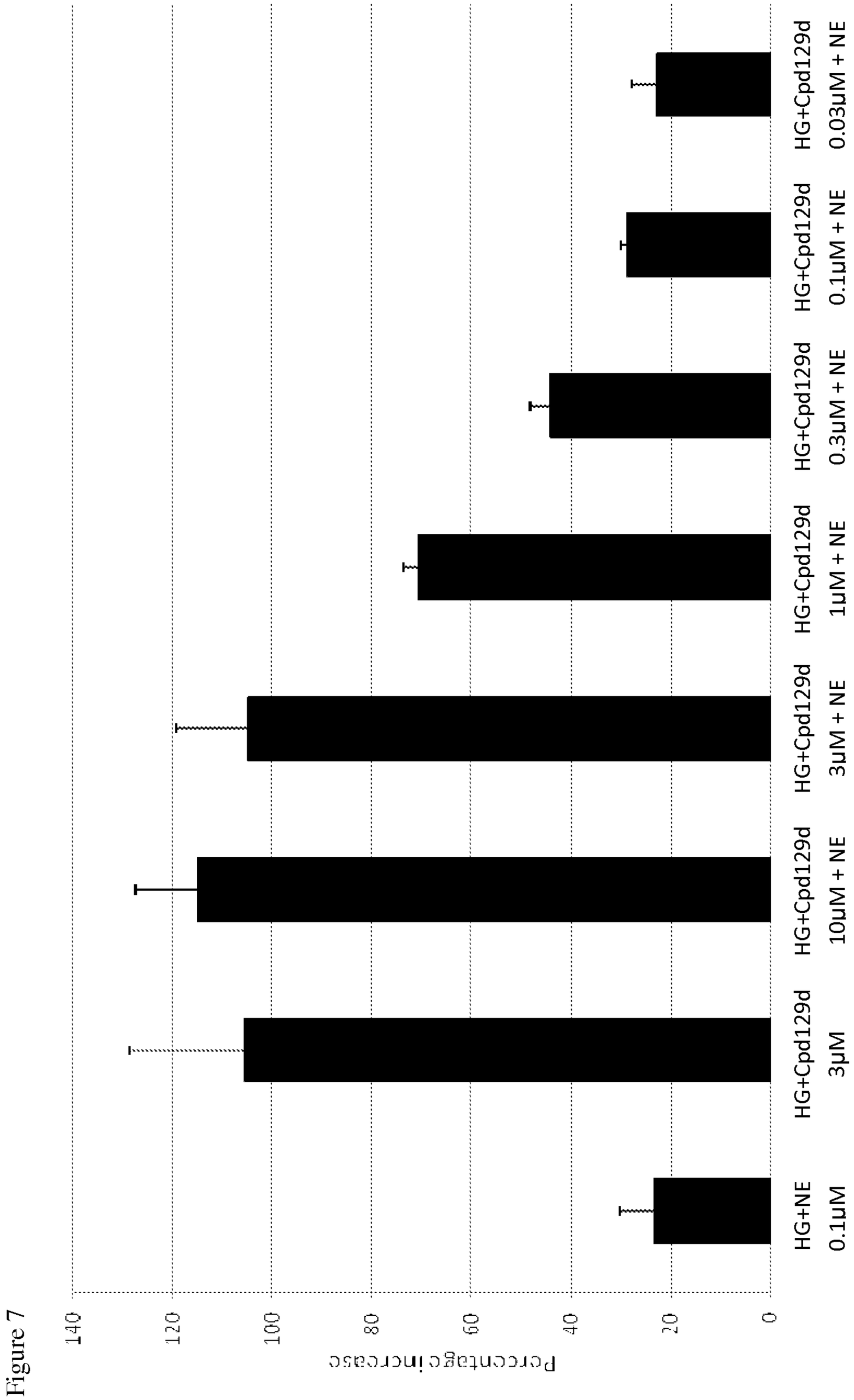
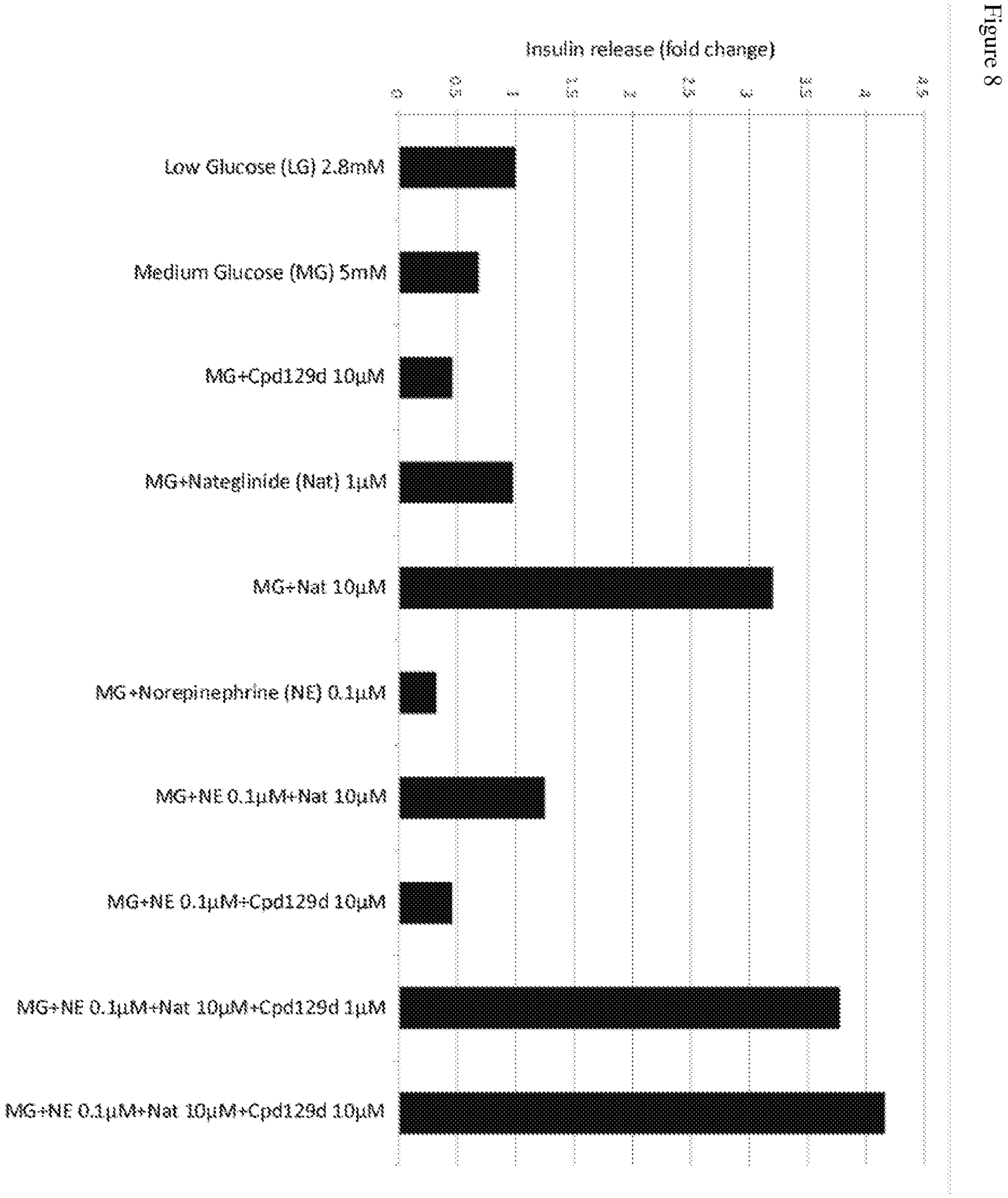

Percentage increase
140
120
100
80
60
40
20
0
HG+Cpd129d 3μM
HG+Cpd129d 10μM + NE
HG+Cpd129d 3μM + NE
HG+Cpd129d 1μM + NE
HG+Cpd129d 0.3μM + NE
HG+Cpd129d 0.1μM + NE
HG+Cpd129d 0.03μM + NE
HG+NE 0.1μM

Figure 7

Figure 8


Insulin release (fold change)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Low Glucose (LG) 2.8mM
Medium Glucose (MG) 5mM
MG+Cpd129d 10μM
MG+Nateglinide (Nat) 1μM
MG+Nat 10μM
MG+Norepinephrine (NE) 0.1μM
MG+NE 0.1μM+Nat 10μM
MG+NE 0.1μM+Cpd129d 10μM
MG+NE 0.1μM+Nat 10μM+Cpd129d 1μM
MG+NE 0.1μM+Nat 10μM+Cpd129d 10μM

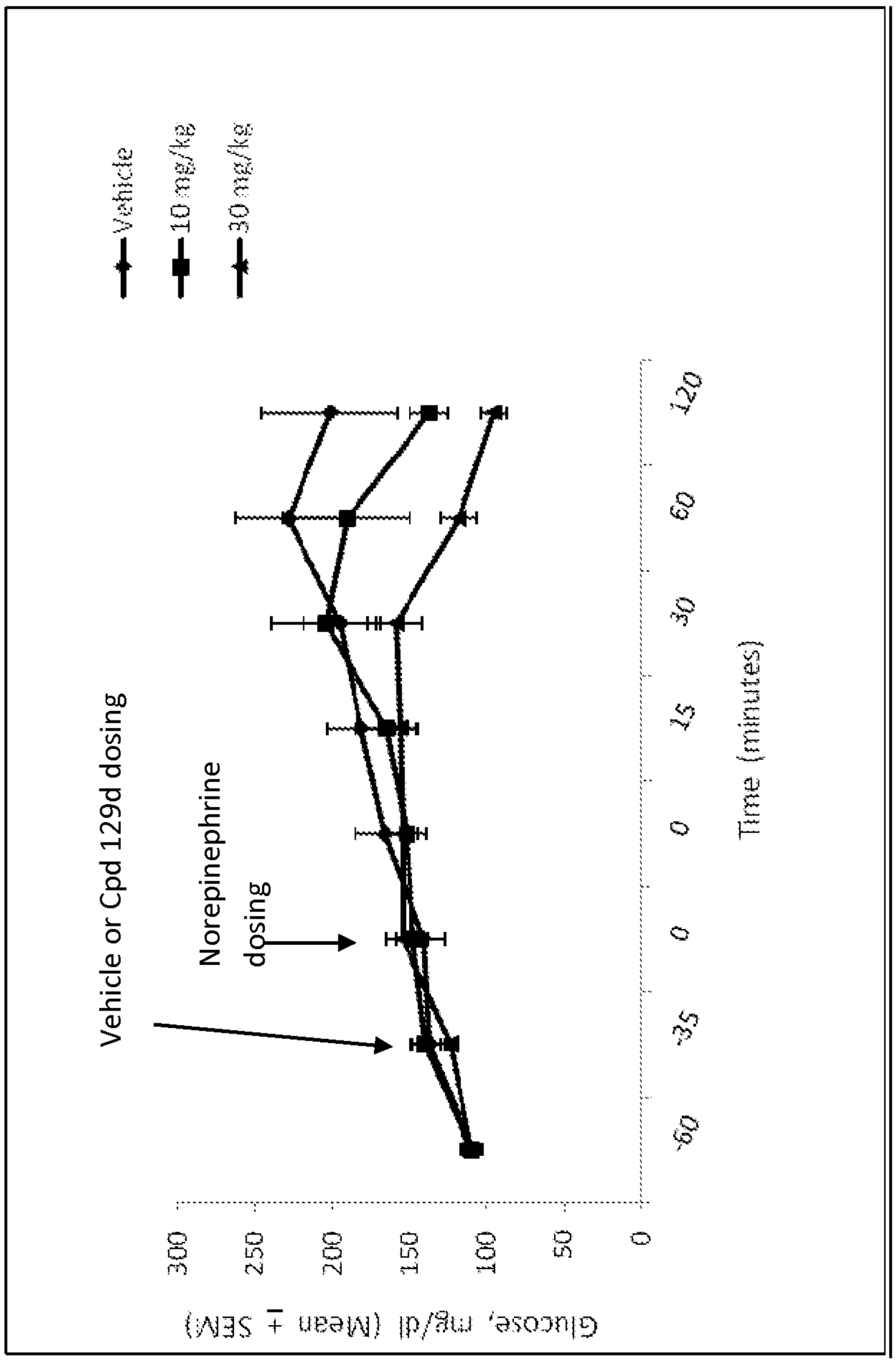

Vehicle
10 mg/kg
30 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
-35
0
15
30
60
120
Time (minutes)
300
250
200
150
100
50
0
Glucose, mg/dl (Mean ± SEM)

Figure 9

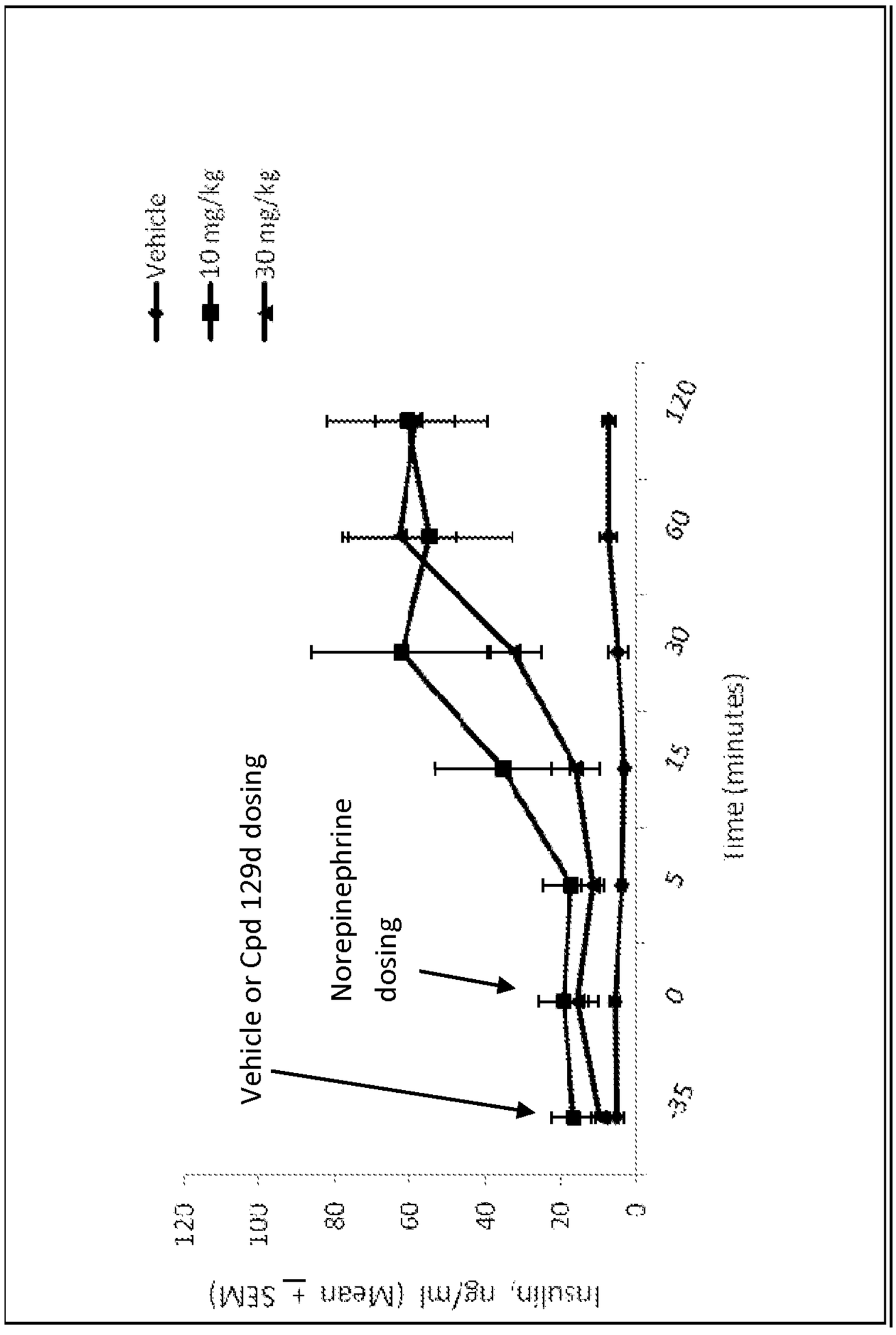

Vehicle
10 mg/kg
30 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
0
5
15
30
60
120
time (minutes)
120
100
80
60
40
20
0
Insulin, ng/ml (Mean ± SEM)

Figure 10

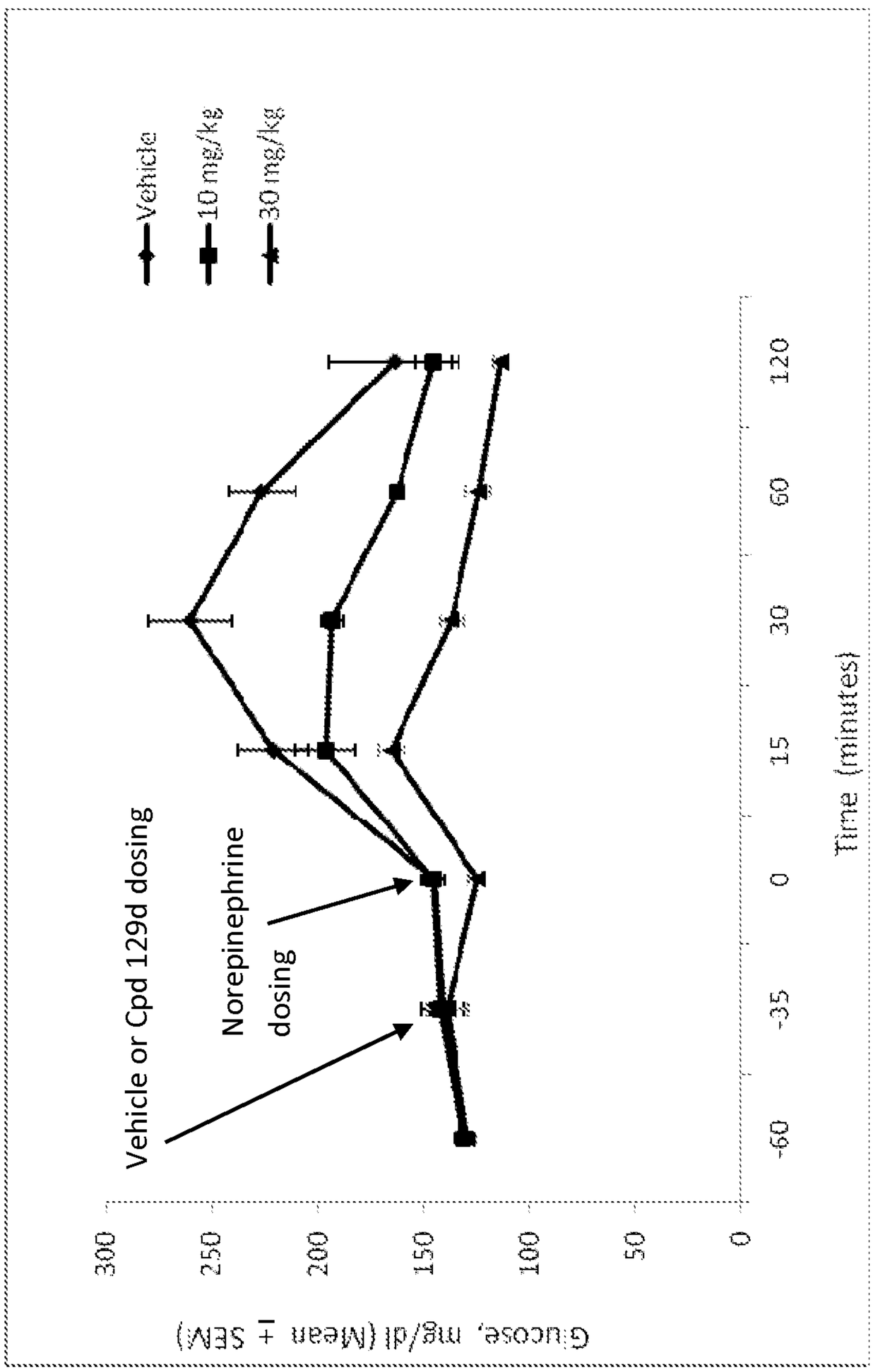

Vehicle
10 mg/kg
30 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
300
250
200
150
100
50
0
-60
-35
0
15
30
60
120
Time (minutes)
Glucose, mg/dl (Mean + SEM)

Figure 11

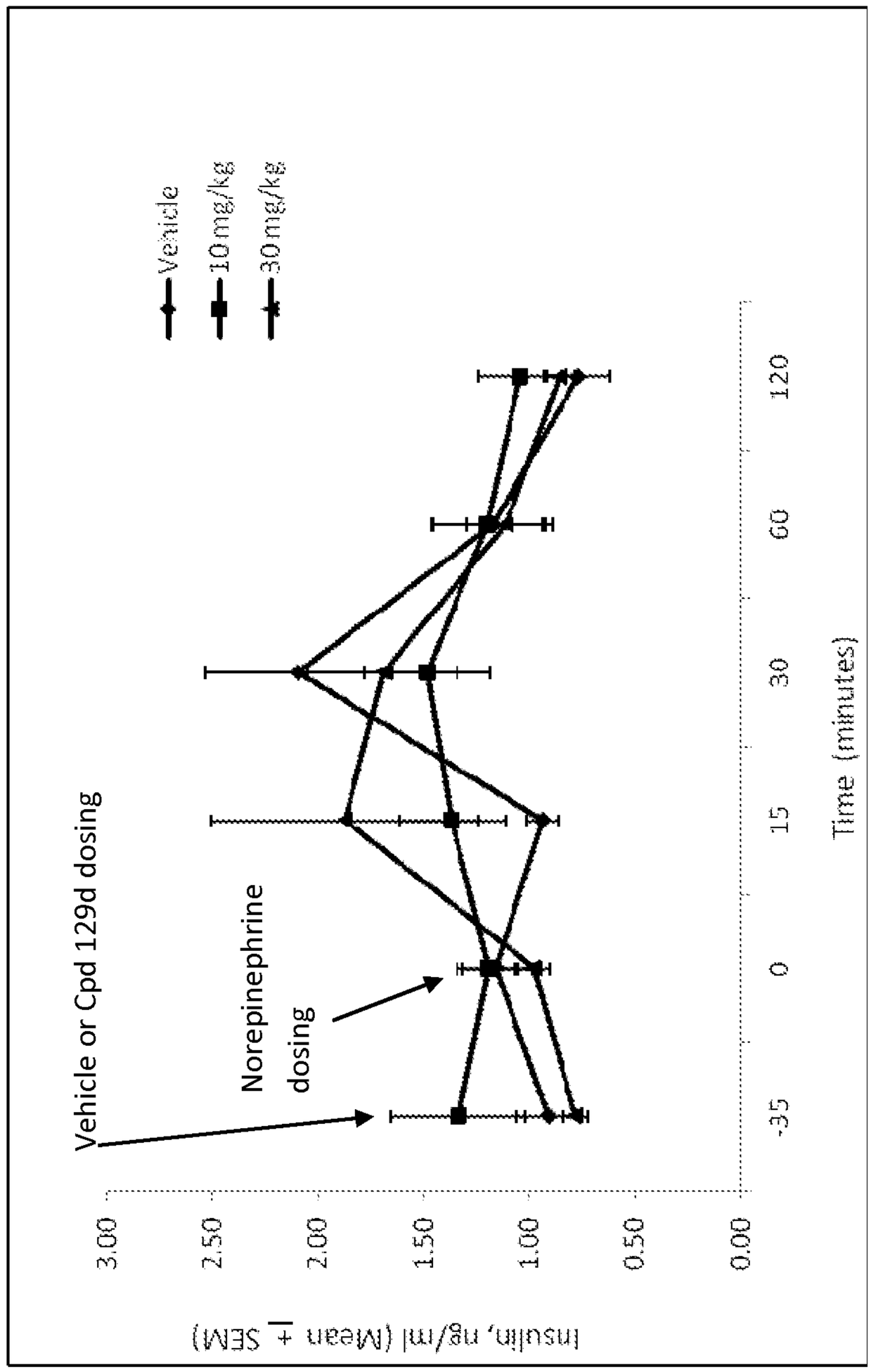

Vehicle
10 mg/kg
30 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
-35
0
15
30
60
120
Time (minutes)
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Insulin, ng/ml (Mean ± SEM)

Figure 12

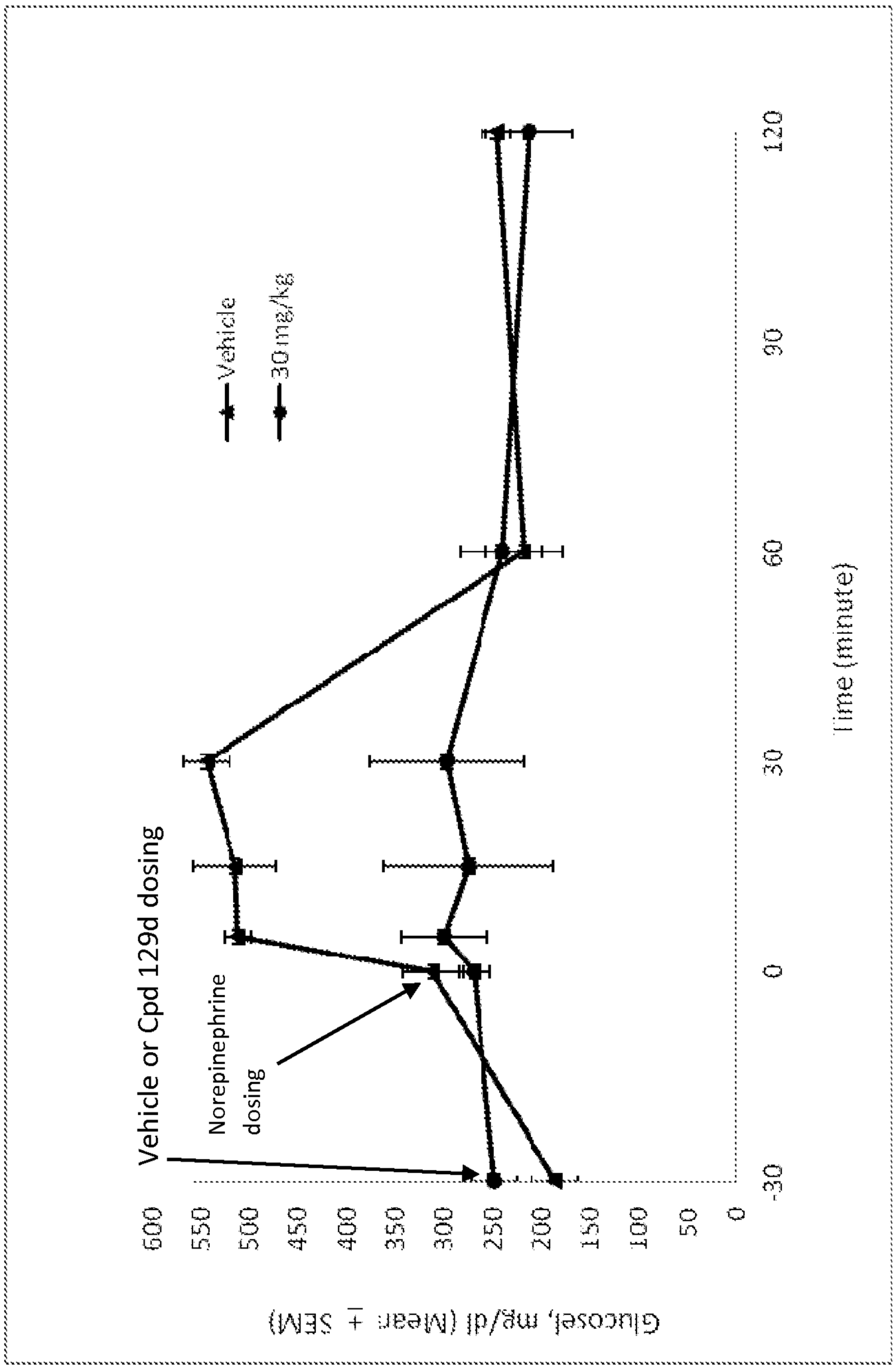

Vehicle
30 mg/kg
Vehicle or Cpd 129d dosing
Norepinephrine dosing
Glucose, mg/dl (Mean + SEM)
600
550
500
450
400
350
300
250
200
150
100
50
0
-30
0
30
60
90
120
Time (minute)

Figure 13

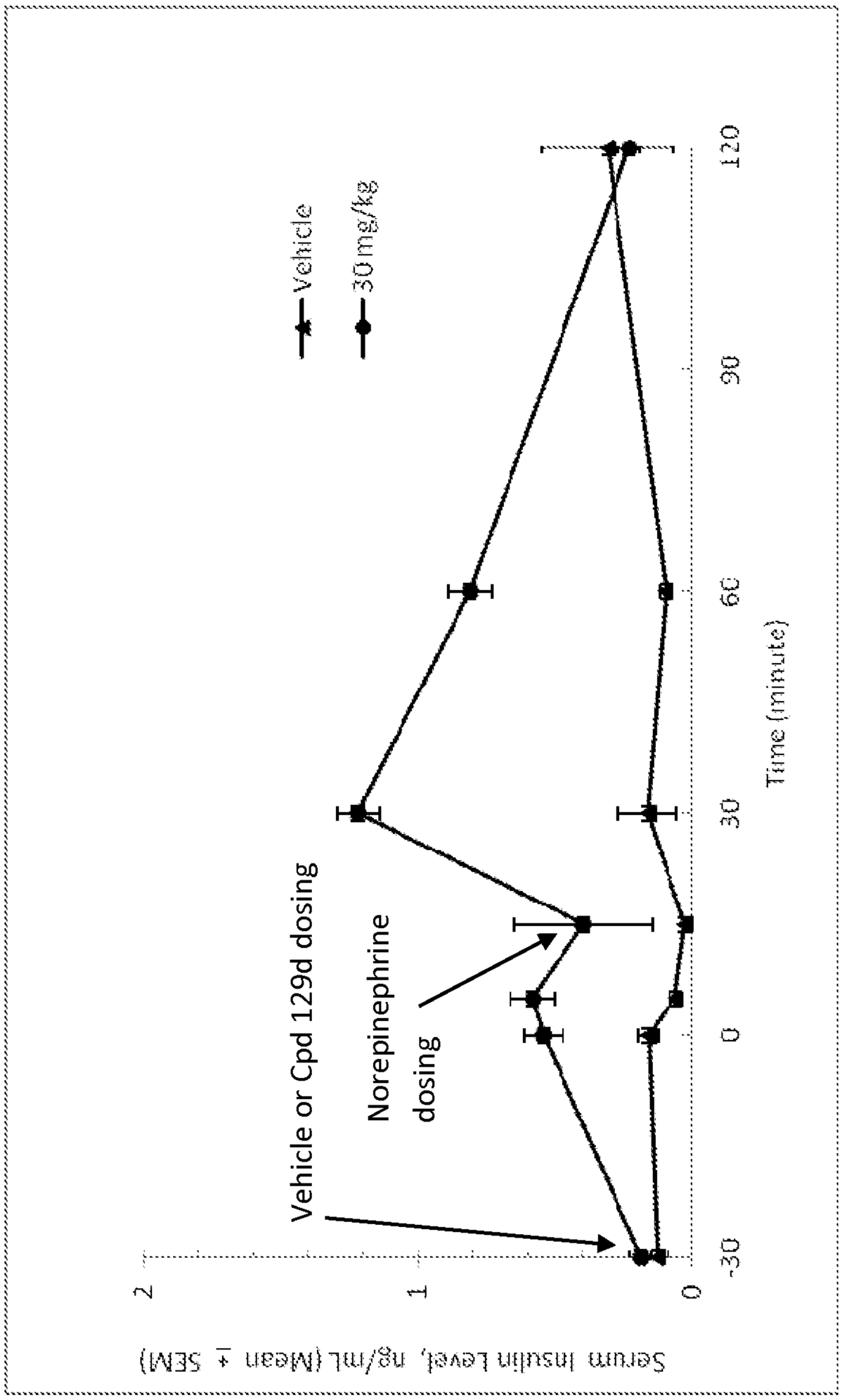

Vehicle
30 mg/kg
120
90
60
30
0
Time (minute)
Norepinephrine dosing
Vehicle or Cpd 129d dosing
2
1
0
-30
Serum Insulin Level, ng/mL (Mean ± SEM)

Figure 14

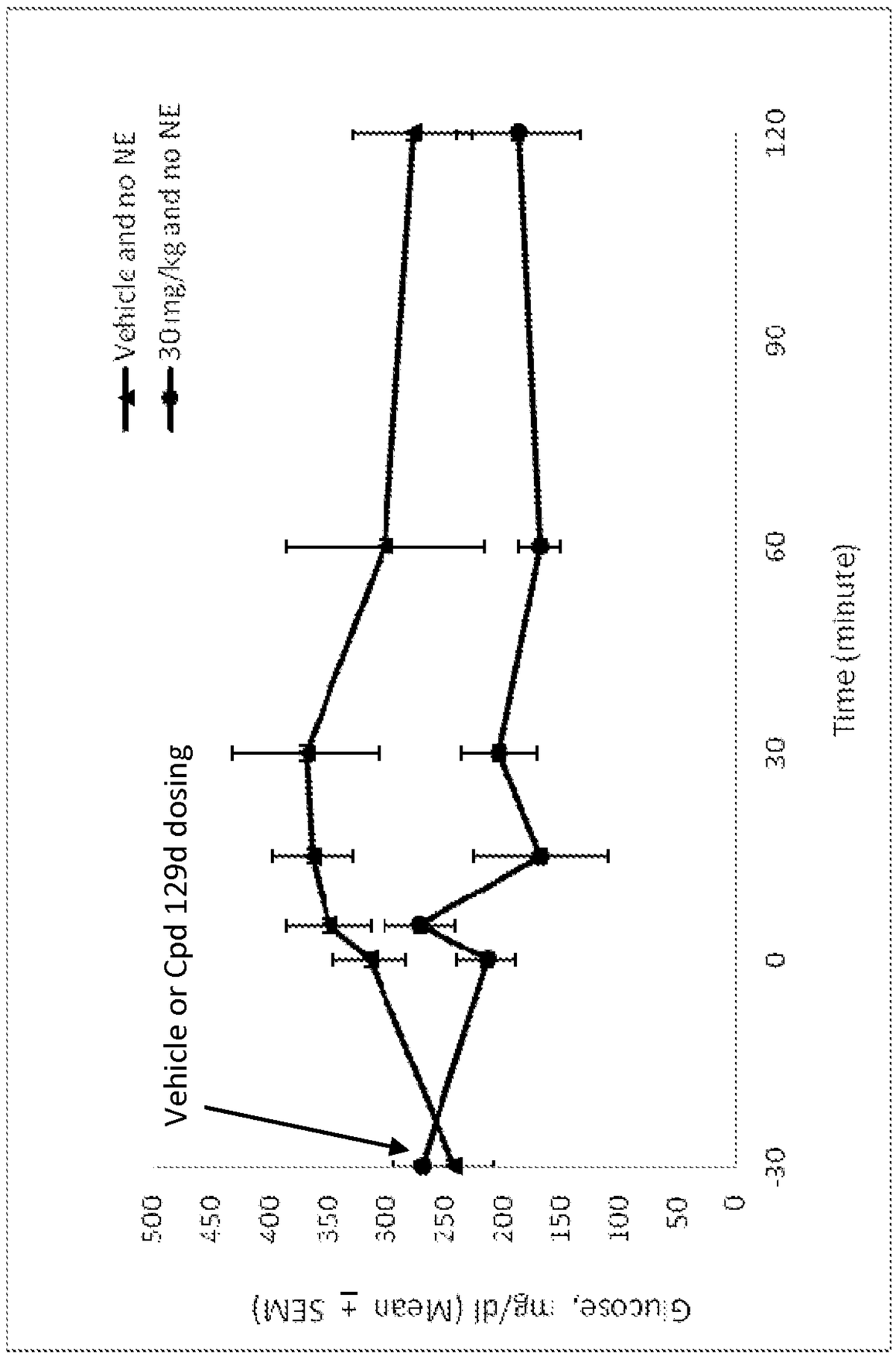

Vehicle and no NE
30 mg/kg and no NE
Glucose, mg/dl (Mean ± SEM)
500
450
400
350
300
250
200
150
100
50
0
-30
0
30
60
90
120
Time (minute)
Vehicle or Cpd 129d dosing

Figure 15

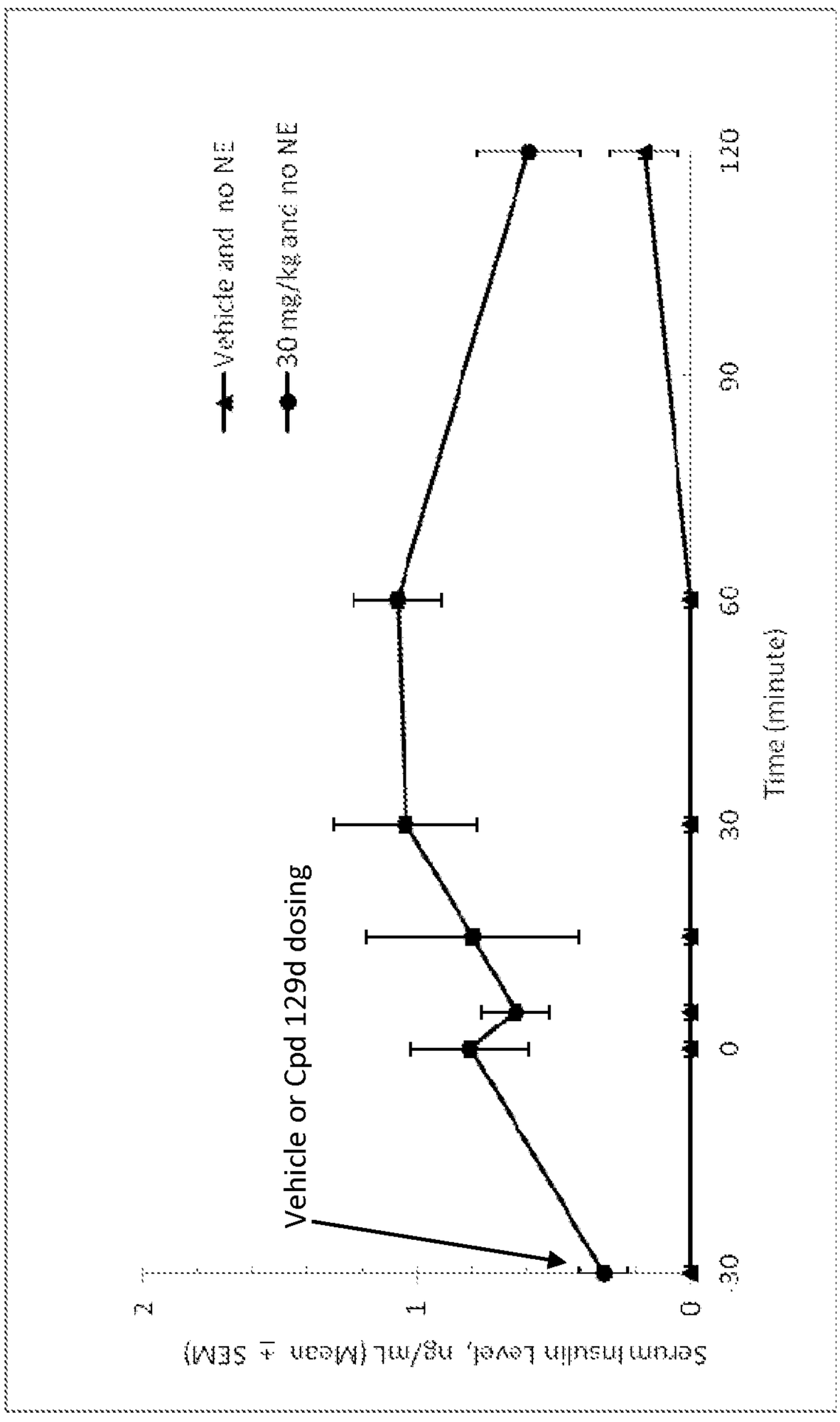

Vehicle and no NE
30 mg/kg and no NE
Vehicle or Cpd 129d dosing
Serum Insulin Level, ng/mL (Mean ± SEM)
2
1
0
-30
0
30
60
90
120
Time (minute)

Figure 16

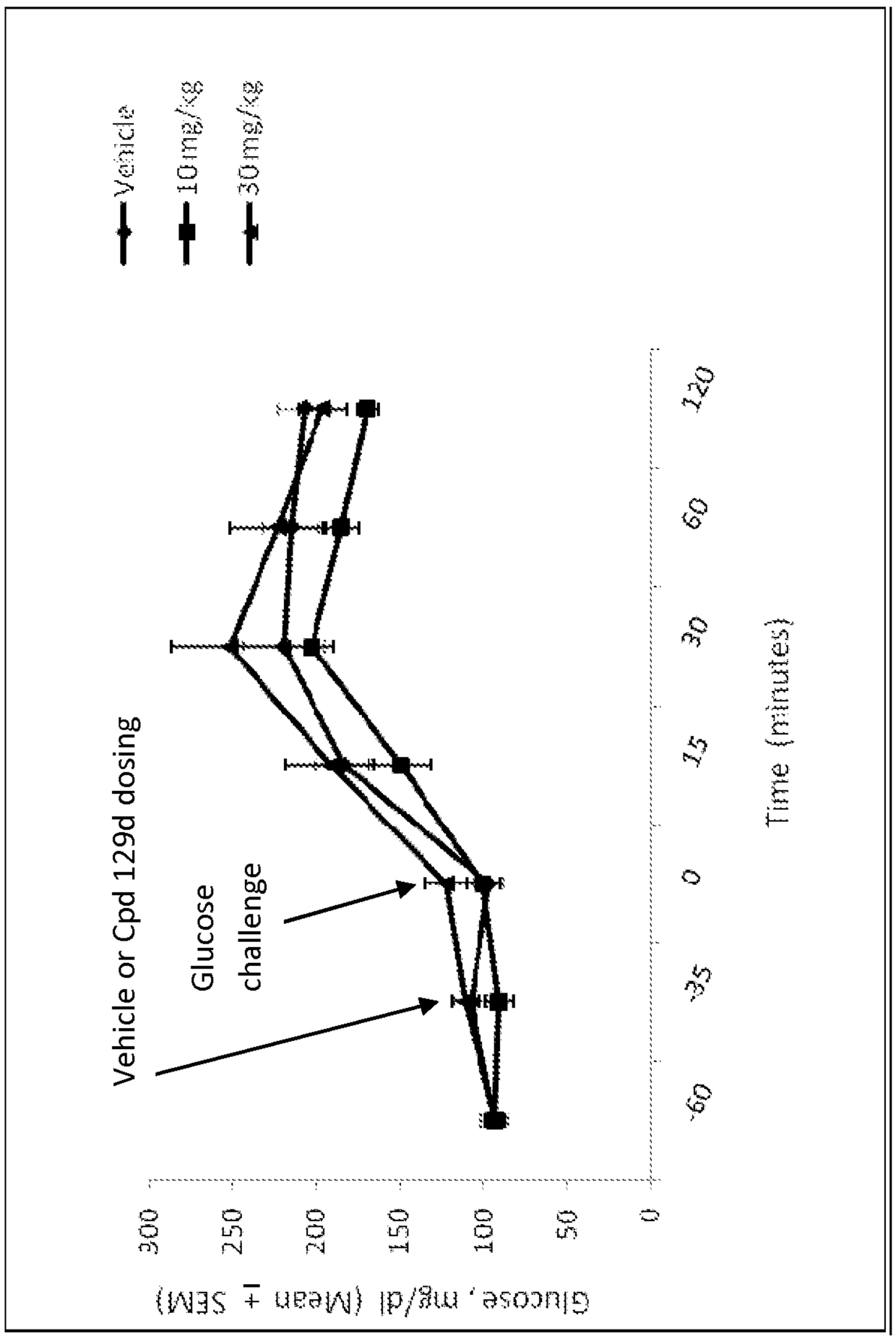

Vehicle
10mg/kg
30mg/kg
Vehicle or Cpd 129d dosing
Glucose challenge
-60
-35
0
15
30
60
120
Time (minutes)
0
50
100
150
200
250
300
Glucose, mg/dl (Mean + SEM)

Figure 17

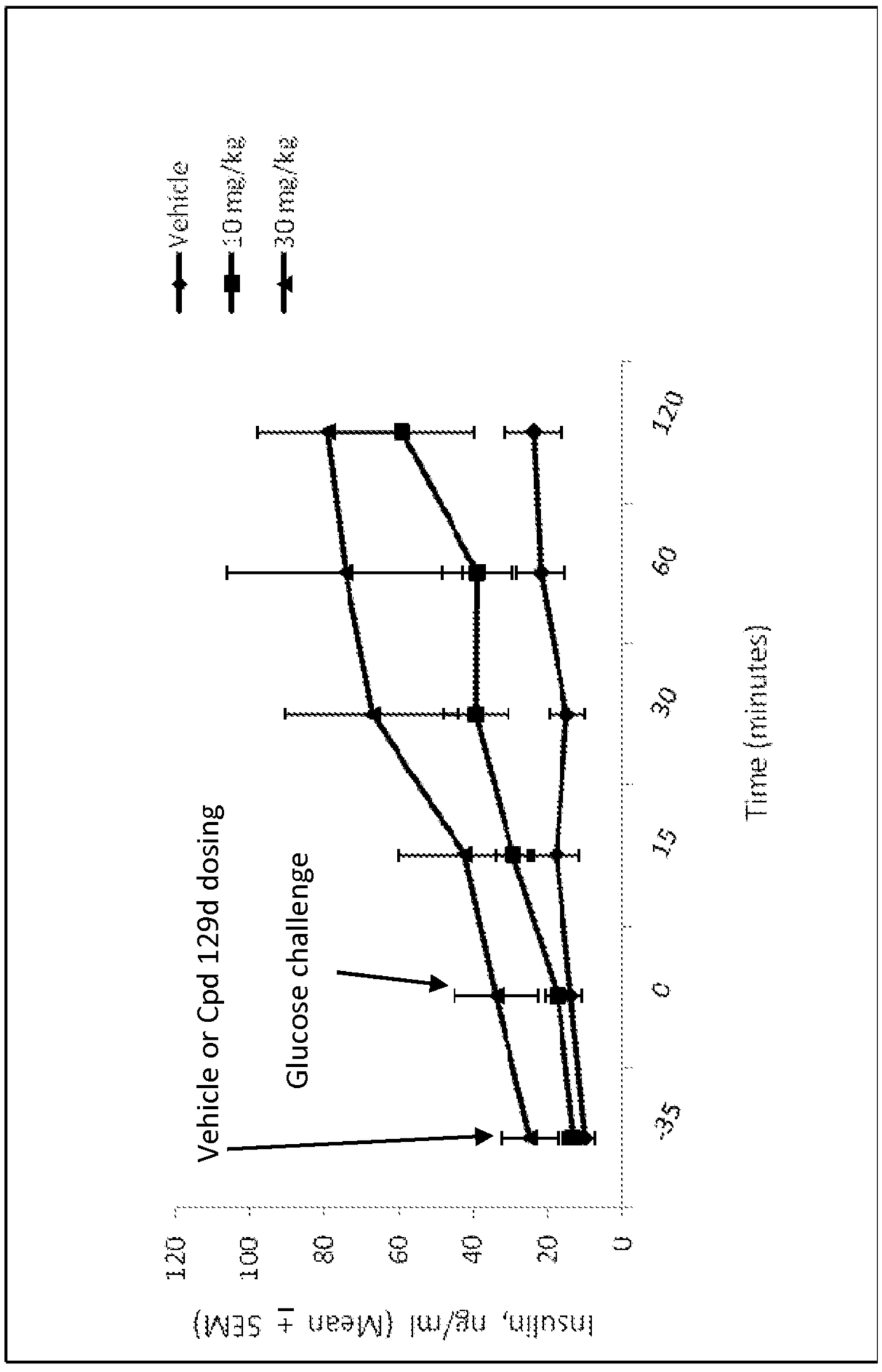

Vehicle
10 mg/kg
30 mg/kg
Vehicle or Cpd 129d dosing
Glucose challenge
Insulin, ng/ml (Mean + SEM)
120
100
80
60
40
20
0
-35
0
15
30
60
120
Time (minutes)

Figure 18

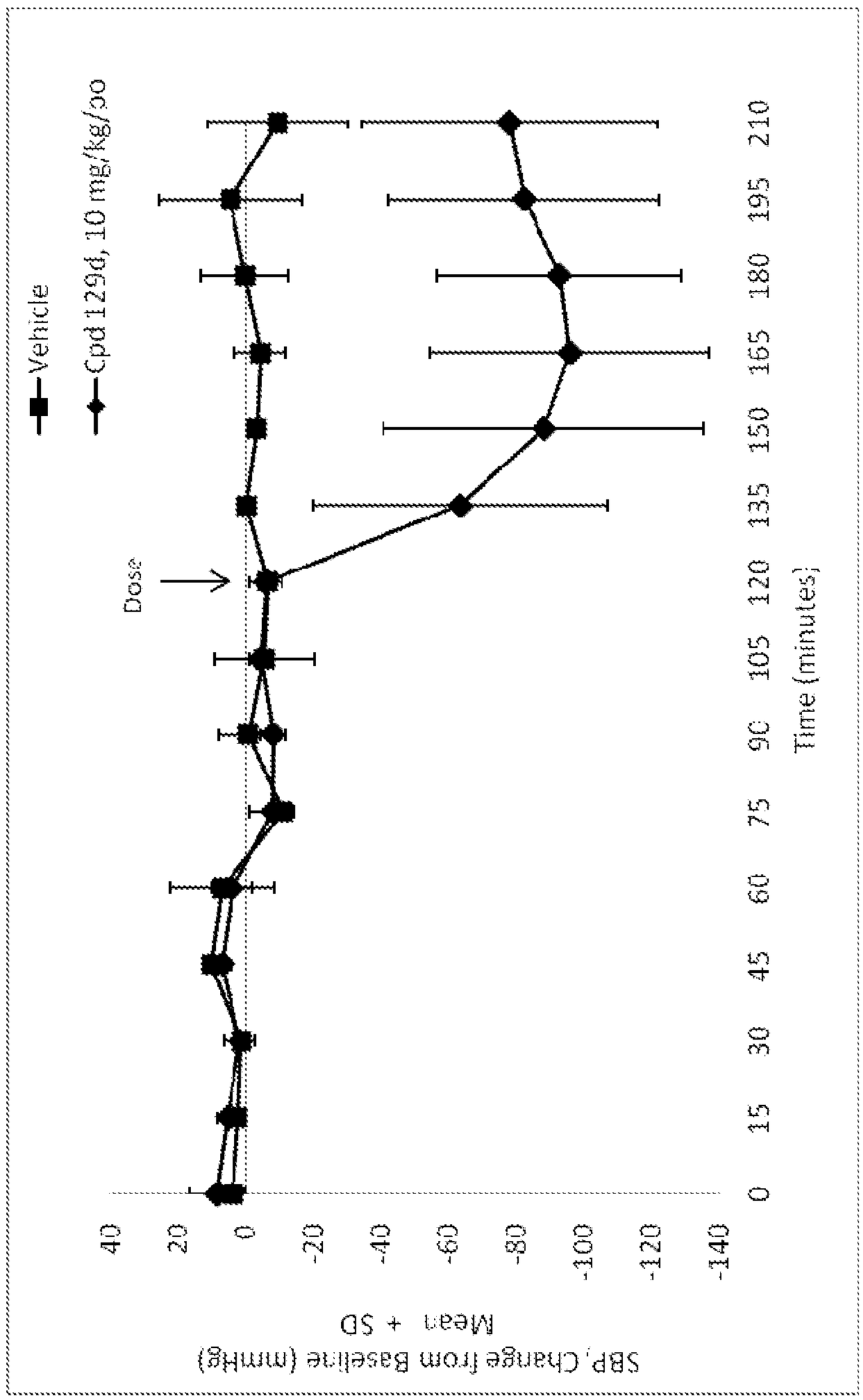

Vehicle
Cpd 129d, 10 mg/kg/po
Dose
SBP, Change from Baseline (mmHg)
Mean + SD
Time (minutes)
40
20
0
-20
-40
-60
-80
-100
-120
-140
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210

Figure 19

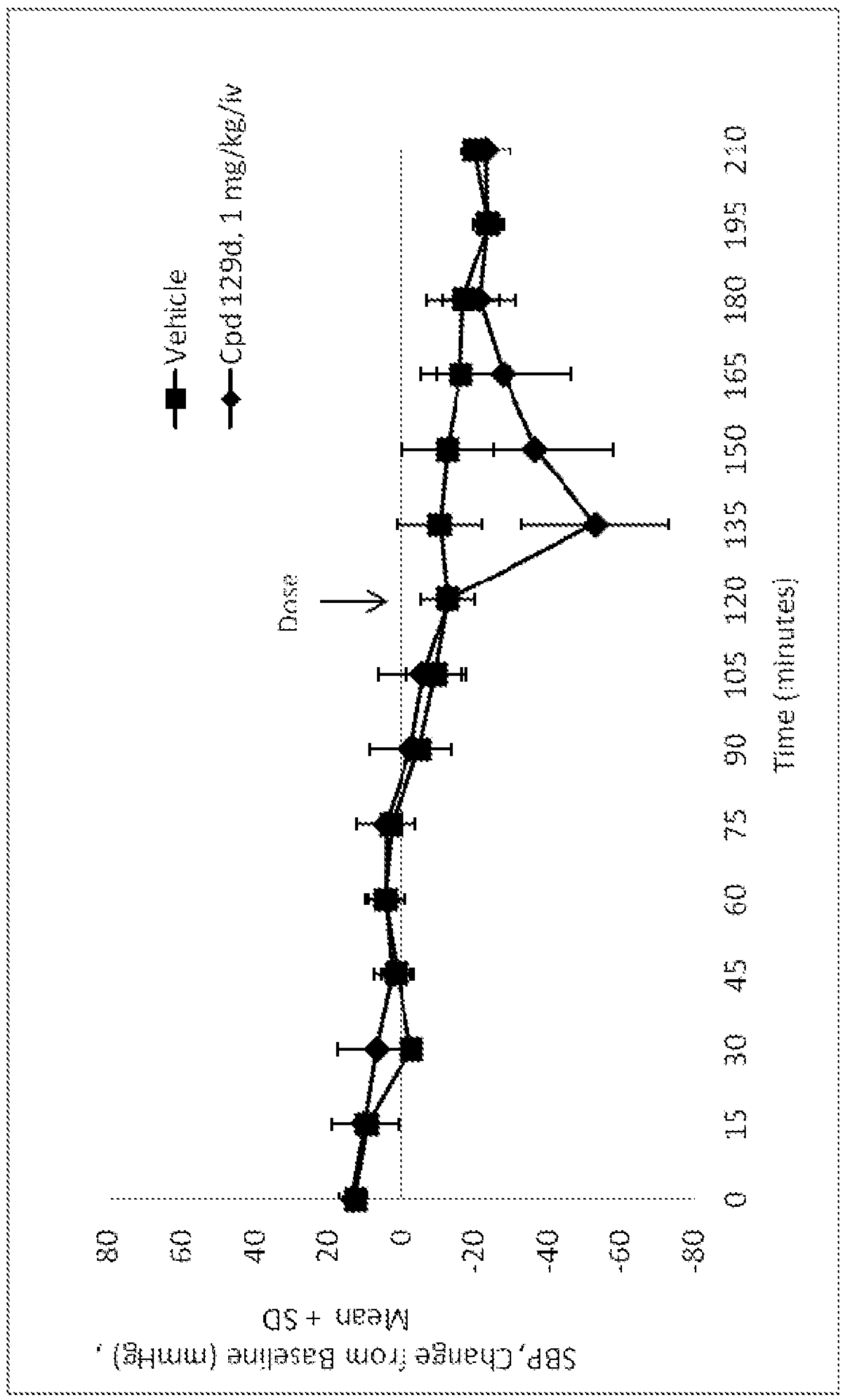

Vehicle
Cpd 129d, 1 mg/kg/iv
Dose
SBP, Change from Baseline (mmHg) , Mean + SD
80
60
40
20
0
-20
-40
-60
-80
15
30
45
60
75
90
105
120
135
150
165
180
195
210
Time (minutes)

Figure 20

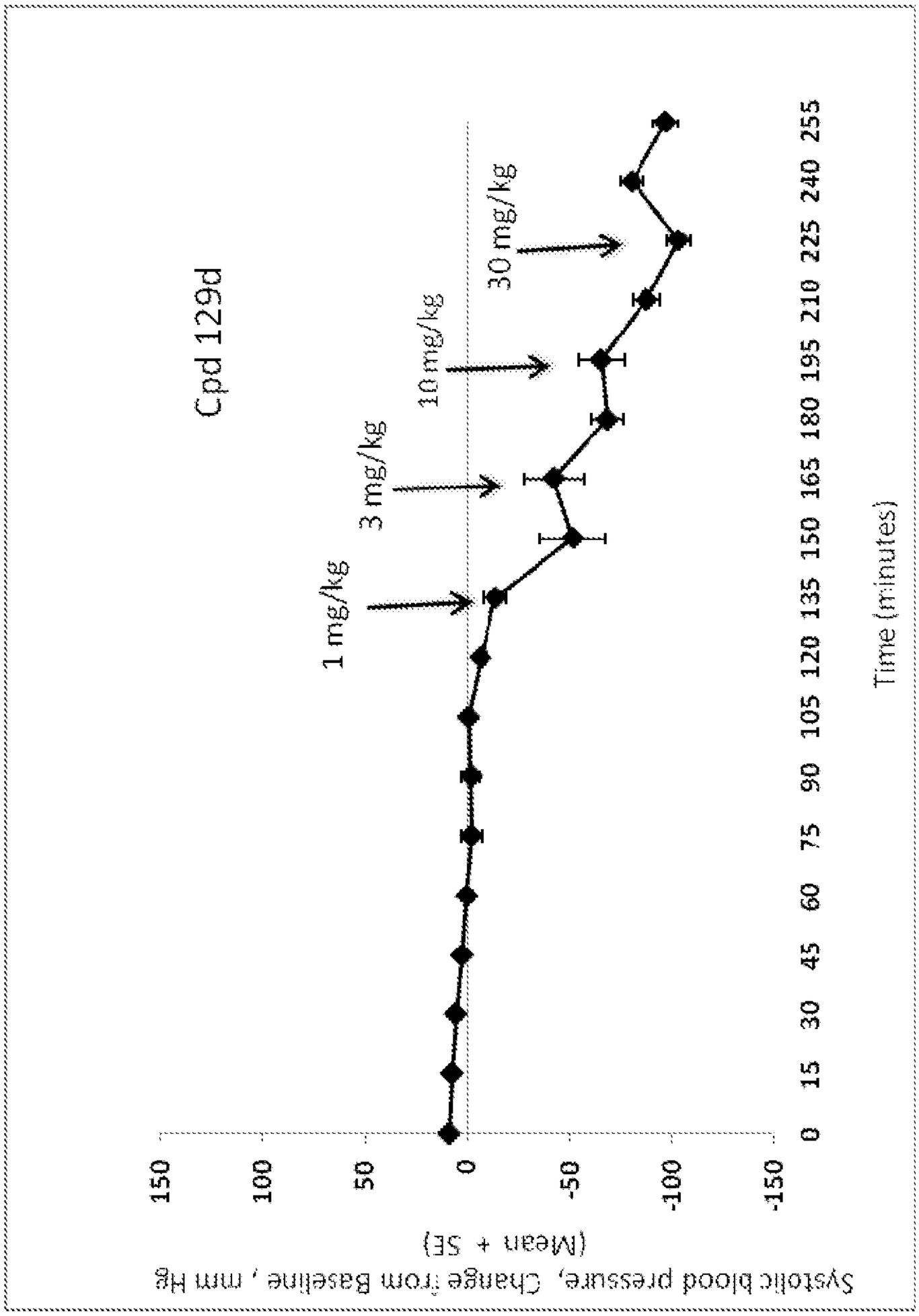

Cpd 129d
1 mg/kg
3 mg/kg
10 mg/kg
30 mg/kg
0 15 30 45 60 75 90 105 120 135 150 165 180 195 210 225 240 255
Time (minutes)
150 100 50 0 -50 -100 -150
Systolic blood pressure, Change from Baseline , mm Hg
(Mean + SE)

Figure 21

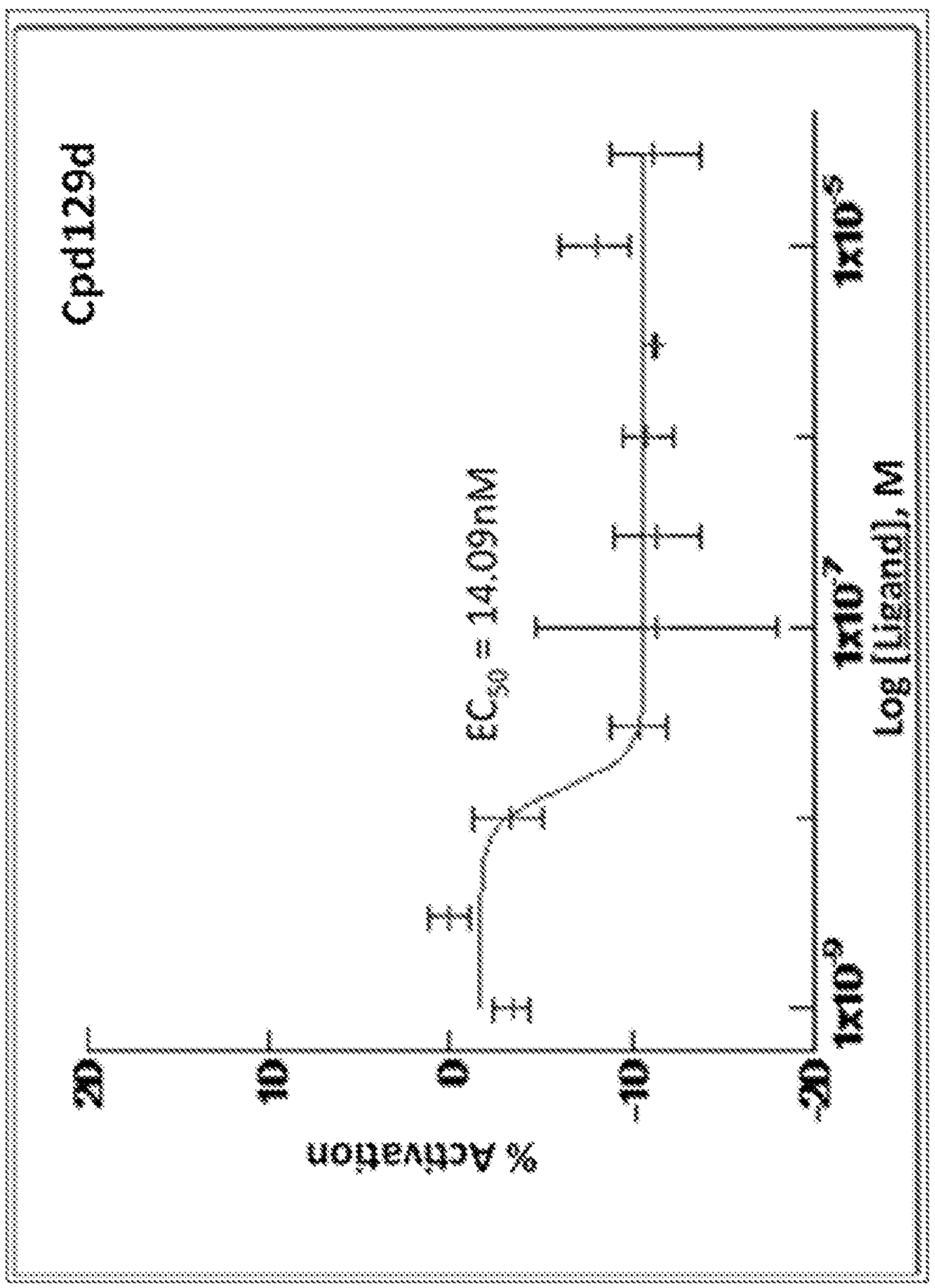
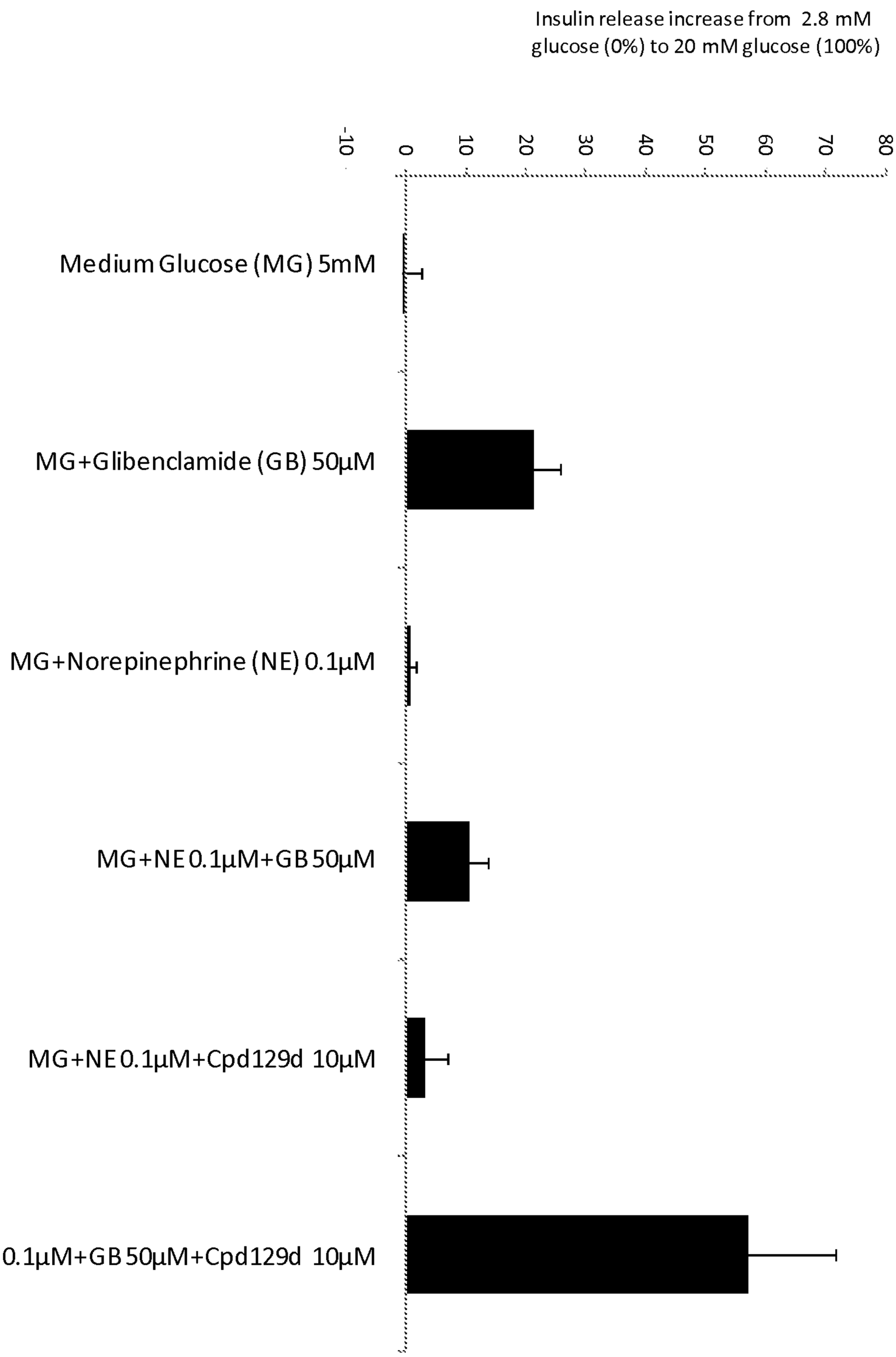

Cpd129d
% Activation
20
10
0
-10
-30
1x10-9
1x10-8
1x10-7
1x10-6
1x10-5
Log [Ligand], M
EC50 = 14.09nM

Figure 22

Figure 23


Insulin release increase from 2.8 mM glucose (0%) to 20 mM glucose (100%)
-10
0
10
20
30
40
50
60
70
80
Medium Glucose (MG) 5mM
MG+Glibenclamide (GB) 50µM
MG+Norepinephrine (NE) 0.1µM
MG+NE 0.1µM+GB 50µM
MG+NE 0.1µM+Cpd129d 10µM
MG+NE 0.1µM+GB 50µM+Cpd129d 10µM

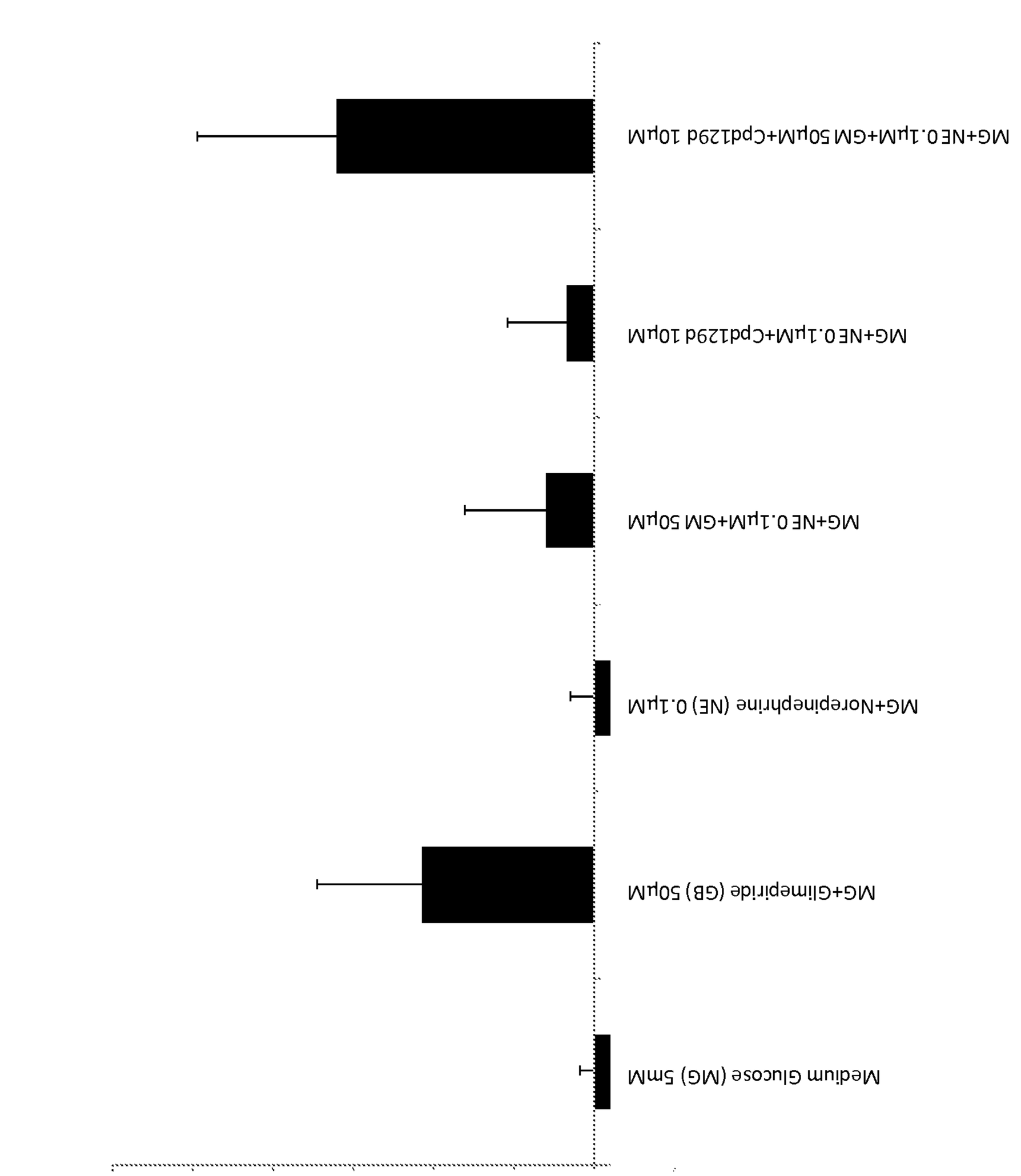

MG+NE 0.1μM+GM 50μM+Cpd129d 10μM
MG+NE 0.1μM+Cpd129d 10μM
MG+NE 0.1μM+GM 50μM
MG+Norepinephrine (NE) 0.1μM
MG+Glimepiride (GB) 50μM
Medium Glucose (MG) 5mM
insulin release increase from 2.8 mM glucose (0%) to 20 mM glucose (100%)
120
100
80
60
40
20
0
-20

Figure 24

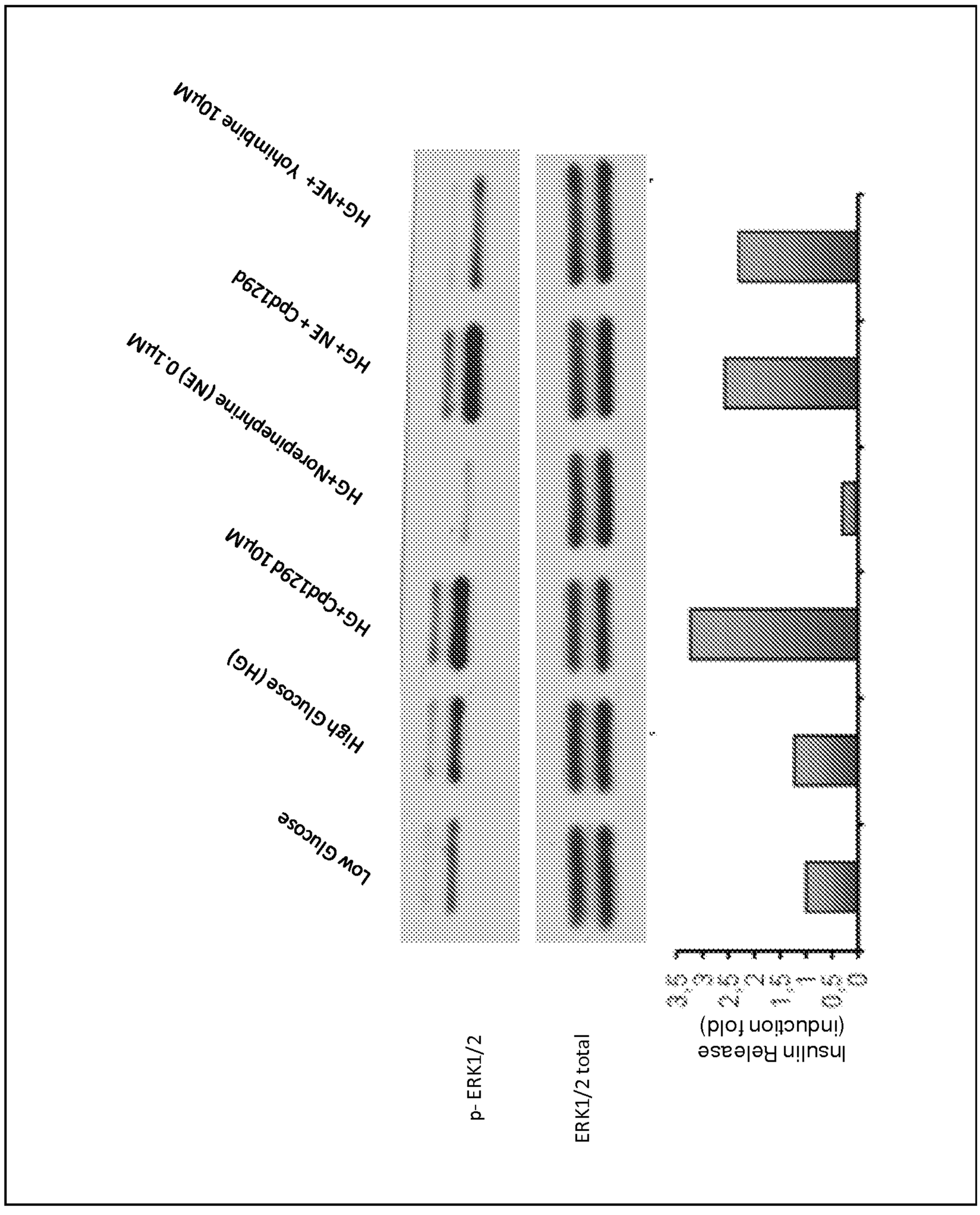
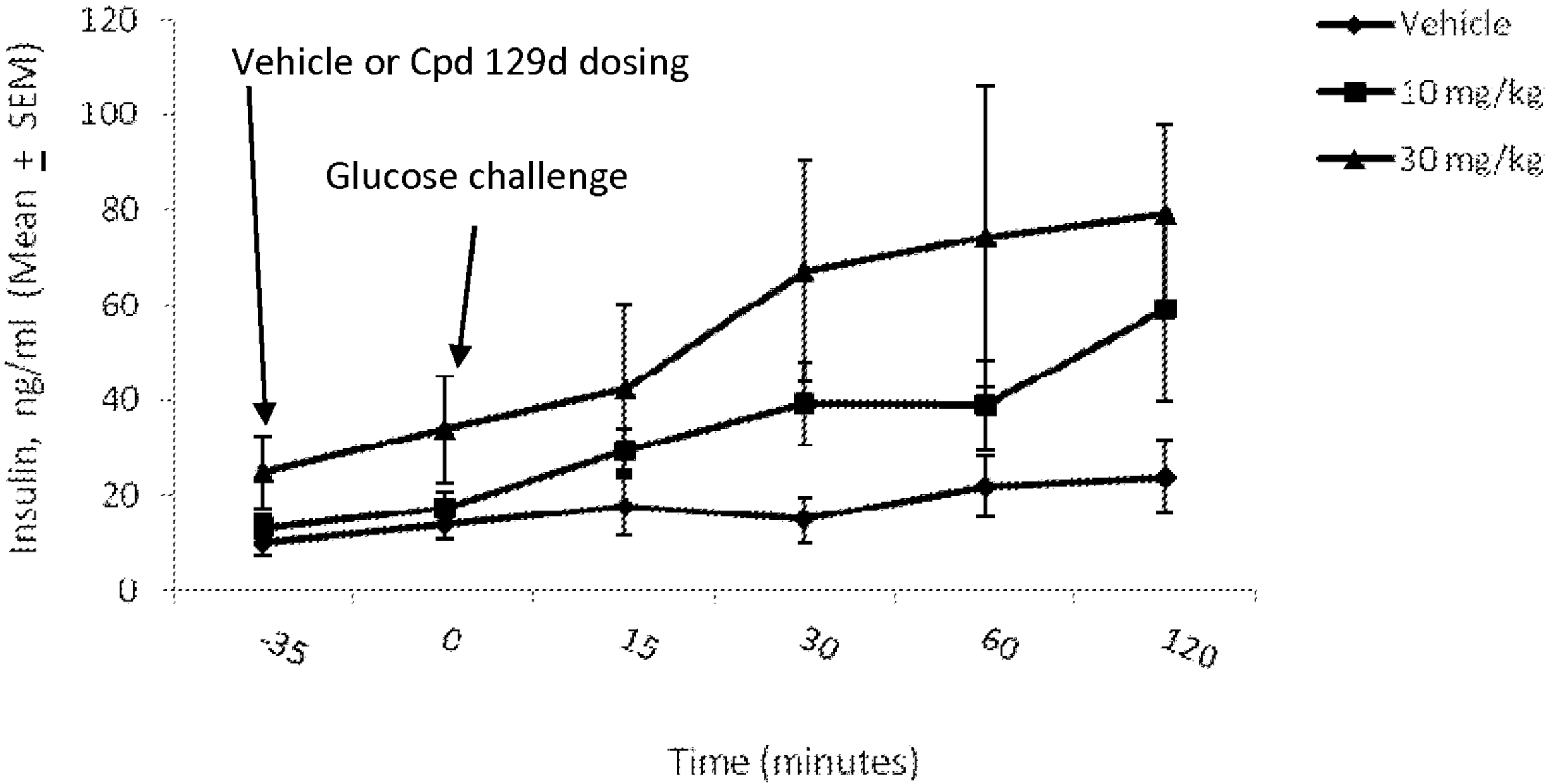

Insulin Release
(induction fold)
0
2
4
6
8
p- ERK1/2
ERK1/2 total
Low Glucose
High Glucose (HG)
HG+Cpd129d 10μM
HG+Norepinephrine (NE) 0.1μM
HG+NE+ Cpd129d
HG+NE+ Yohimbine 10μM

Figure 25

Figure 18


Vehicle or Cpd 129d dosing
Glucose challenge
Insulin, ng/ml (Mean +1 SEM)
120
100
80
60
40
20
0
-35
0
15
30
60
120
Time (minutes)
Vehicle
10 mg/kg
30 mg/kg