New PCT application
AC Immune S.A.
Case Morphomer/Azaindol PCT
Our Ref.: S1590 PCT

CLAIMS

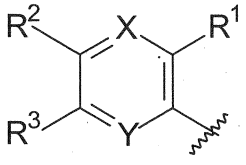
1. A compound of formula (I):

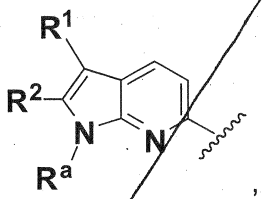
$$A–L_1–B \qquad (I)$$

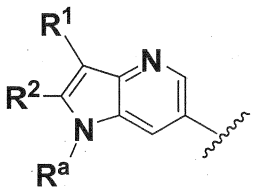
and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

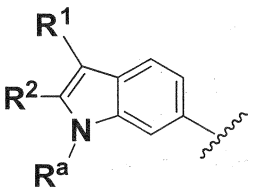
wherein

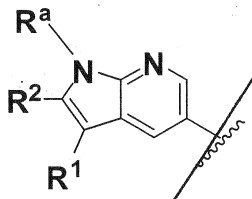
A is selected from the group consisting of

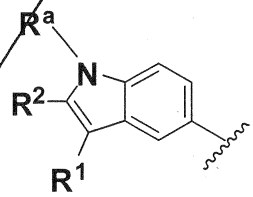

(i)

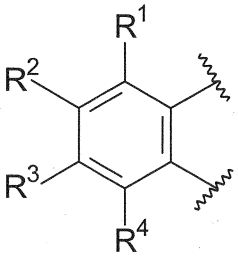

(ii)


(iii)

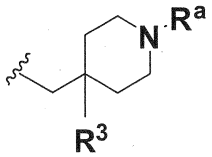

(iv)


(v)

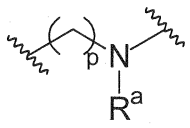

(vi)

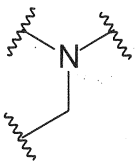

(vii)

and

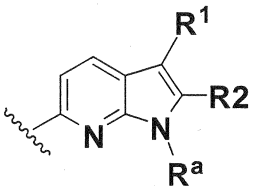

(viii)

L_1 is directionally selected from the group consisting of:

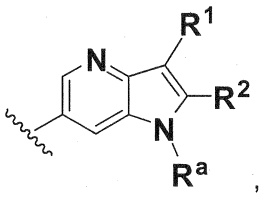


(a) and  (b) ;

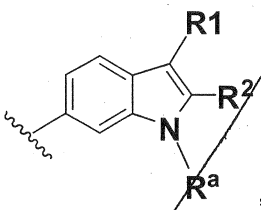
B is selected from the group consisting of:



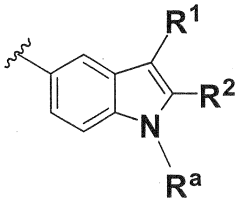
(ix) ,



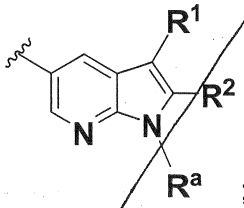
(x) ,



(xi) ,



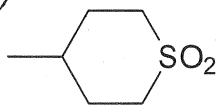
(xii) , and



(xiii) ;

wherein

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $-CONR^{30}R^{31}$, $-N(R^{30})-C(O)-R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if any of the groups $R^1/R^2/R^3/R^4$ are adjacent, they can optionally be taken together and can form a 5- to 8-membered ring containing carbon atoms and optionally one or more heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 5- to 8-membered ring may be substituted by $NR^{20}R^{21}$ or –O–alkyl, wherein the alkyl can be optionally substituted, or by



;

for each occurrence, R^a is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, $S(O)_tNR^{30}R^{31}$, $S(O)_tR^{30}$, $C(O)OR^{30}$, $C(O)R^{30}$, and $C(O)NR^{30}R^{31}$;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

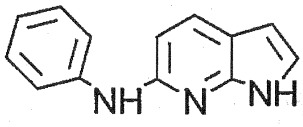
for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted, or wherein R^{20} and R^{21}, when taken together with the nitrogen to which they are attached, can form a 3- to 8-membered ring containing carbon atoms and optionally one or more further heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 3- to 8-membered ring may be optionally substituted;

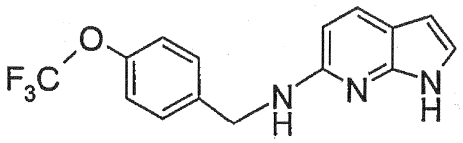
X and Y are each independently selected from the group consisting of CR^b and N;

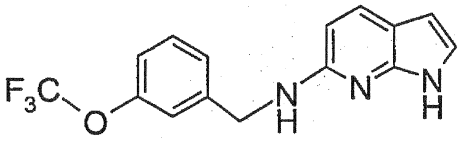
t is 1 or 2; and

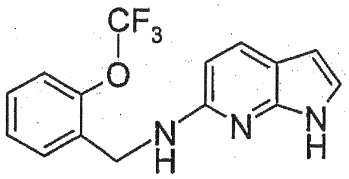
p is 0, 1 or 2

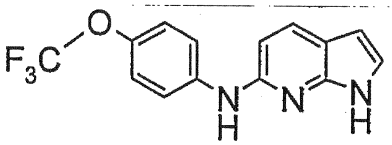
with the proviso that the following compounds are excluded:

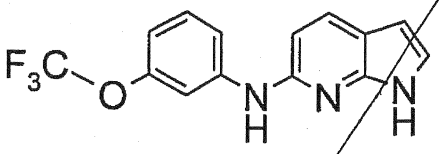


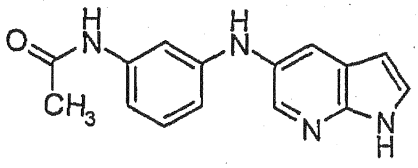


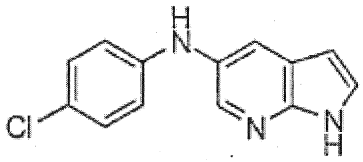


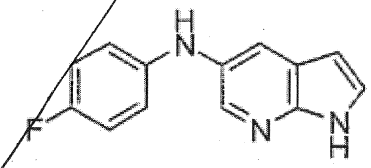


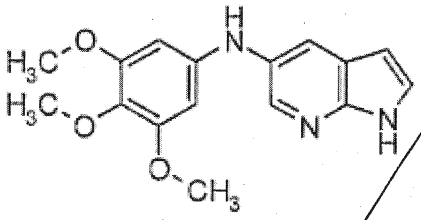


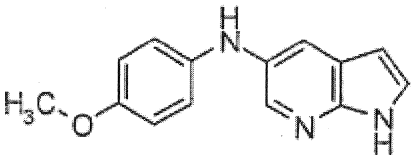


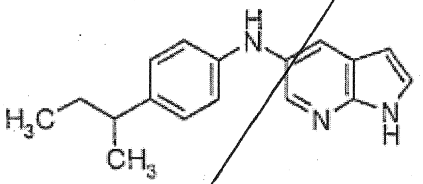


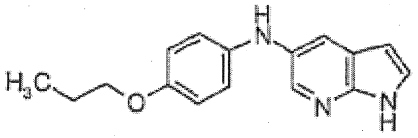


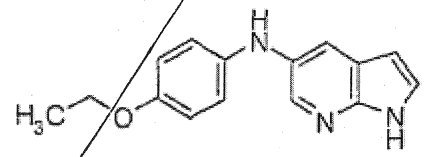


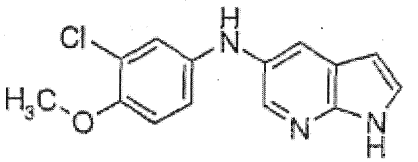


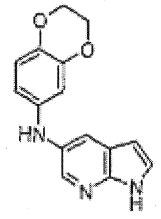
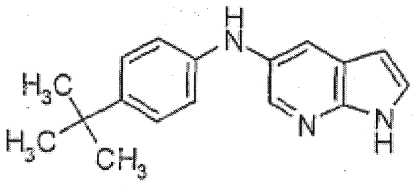
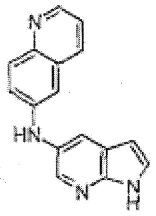
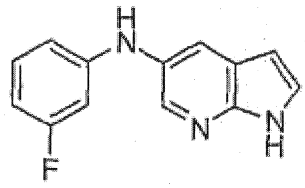
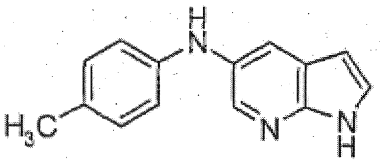
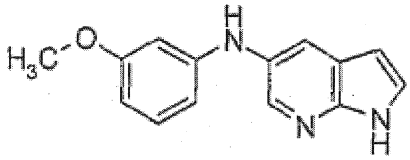
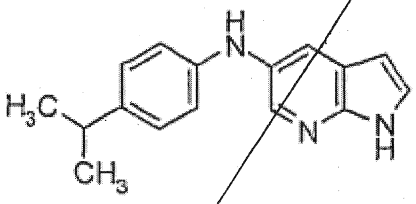
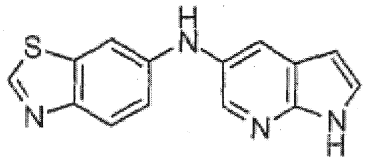
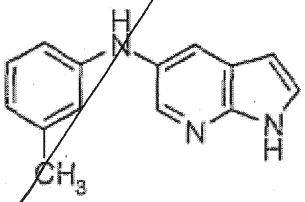
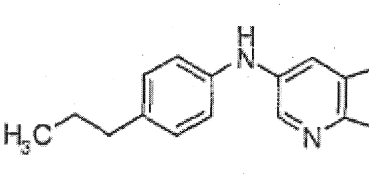


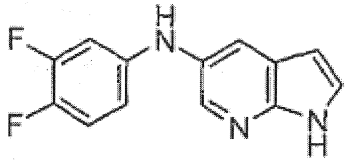
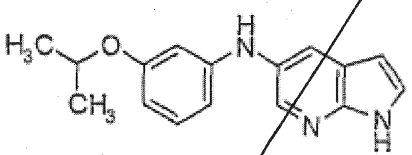
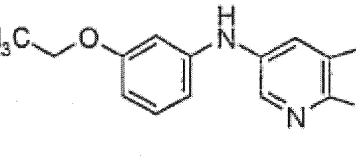


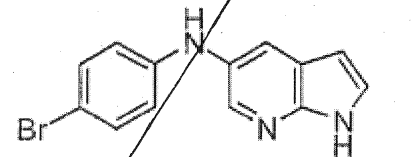


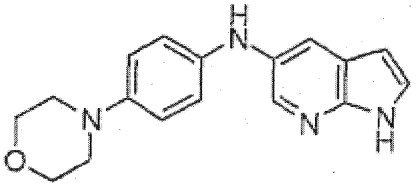


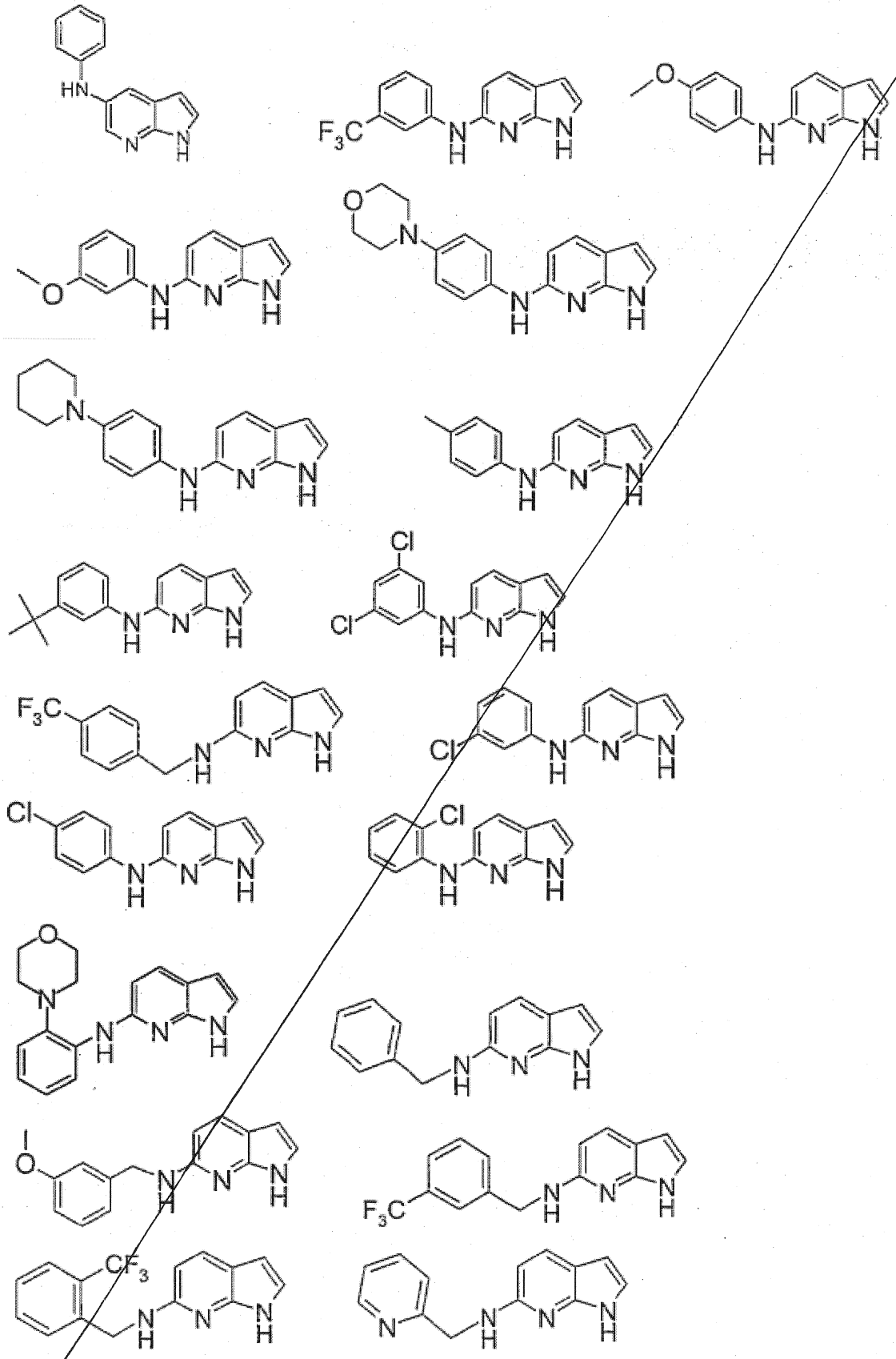


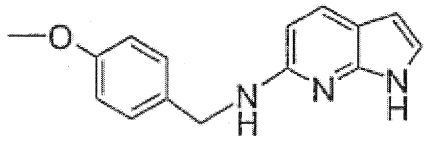
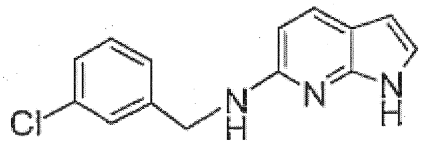
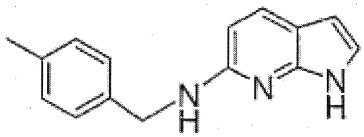
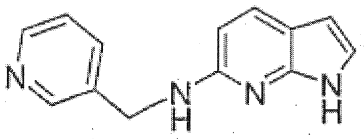
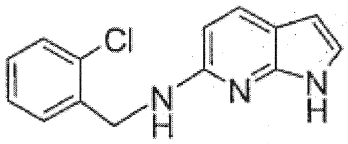
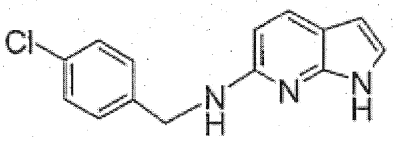
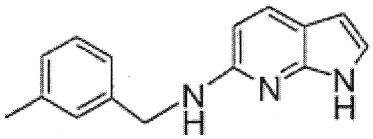
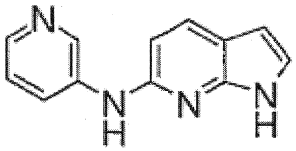
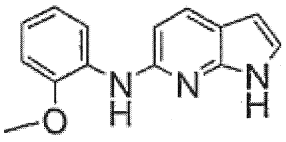
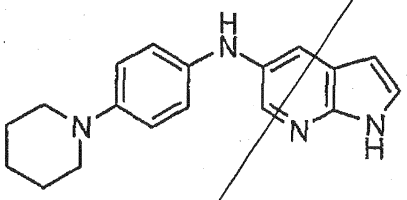
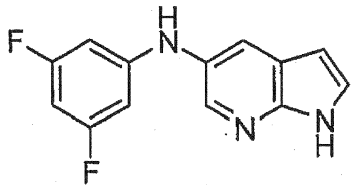
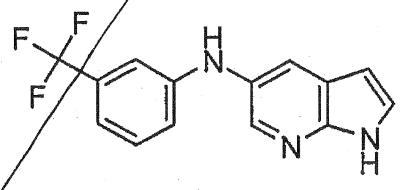













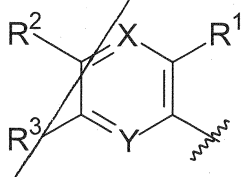
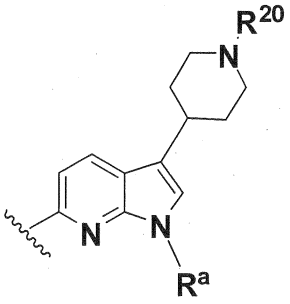
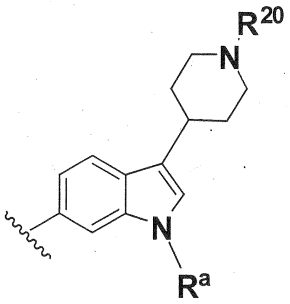


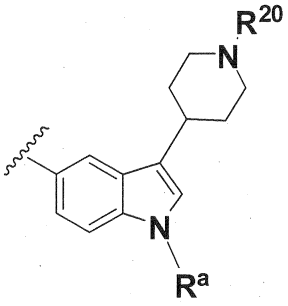
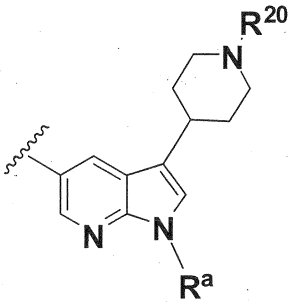
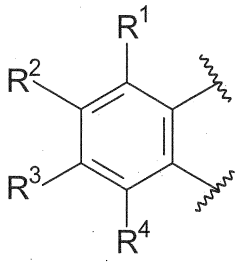













and


2. The compound of claim 1, wherein

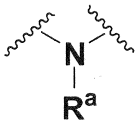
A is selected from the group consisting of:


,

,

,

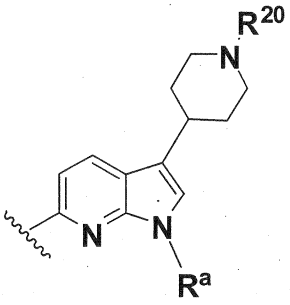
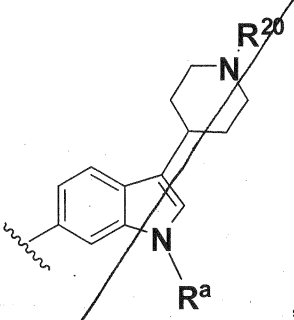
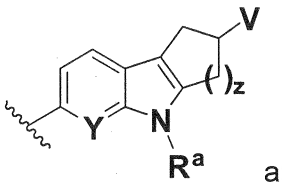
and

L_1 is

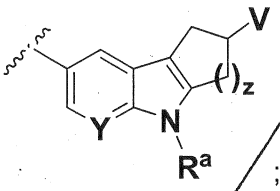


;

B is selected from the group consisting of:

and

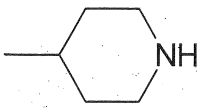
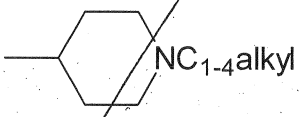
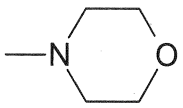


;

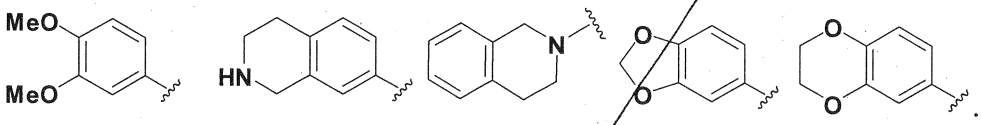
wherein:

R^1, R^2, R^3, R^4, R^a, R^{20}, X and Y have the same meanings as in claim 1;
V is absent or $NR^{20}R^{21}$ and
z is 1 or 2.

3. The compound of any of the preceding claims, wherein L_1 has the formula (a) and preferably p is 0.

4. The compound of any of the preceding claims, wherein R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, halogen (such as F), CN, CF_3, $CONR^{30}R^{31}$, –O–alkyl, heterocycloalkyl (such as , , or .

5. The compound of claim 1, wherein formula (vii) in A is selected from



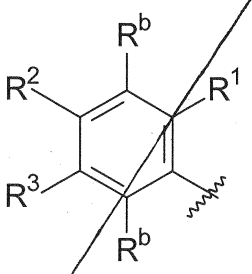
6. The compound of any of the preceding claims, wherein R^a is hydrogen or C_{1-4} alkyl.

7. The compound of claim 1 having the formula (I):

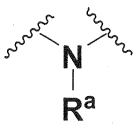
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

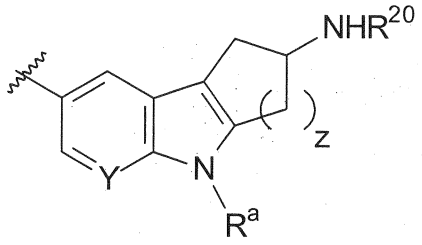
wherein A is:

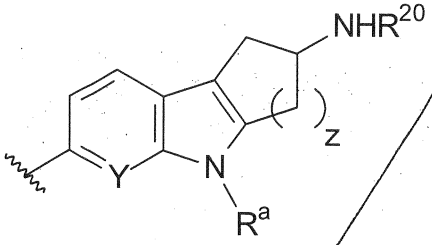


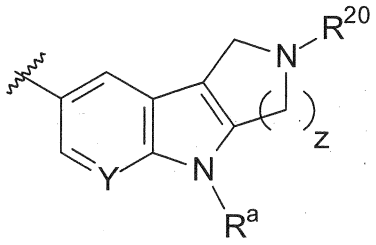
L_1 is:



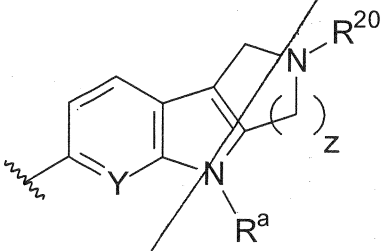
B is:







or



wherein

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if R^1 and R^2 are adjacent, they can optionally be taken together and can form a 5- or 6-membered ring containing carbon atoms and optionally one or two heteroatoms selected from O, S, or N or the heteroatom-containing moiety NR^{50};

R^3 is hydrogen or halogen;

R^a is hydrogen or alkyl;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

R^{50} is for each occurrence R^{20}, $S(O)_tNR^{20}R^{21}$, $S(O)_tR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$;

Y is each independently CH or N

t is 1 or 2; and

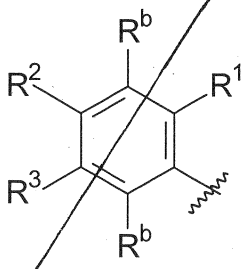
z is 1 or 2.

8. A compound of claim 1 having the formula (I):

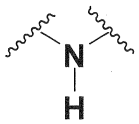
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

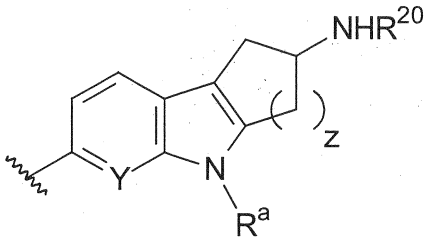
wherein A is:



L_1 is:



B is:



wherein

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if R^1 and R^2 are adjacent, they can optionally be taken together and can form a 5- or 6-membered ring containing carbon atoms and optionally one or two heteroatoms selected from O, S, or N or the heteroatom-containing moiety NR^{50};

R^3 is hydrogen or halogen;

R^a is hydrogen or alkyl;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl,

heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

R^{50} is, for each occurrence, R^{20}, $S(O)_tNR^{20}R^{21}$, $S(O)_tR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$;

Y is each independently CH or N;

t is 1 or 2; and

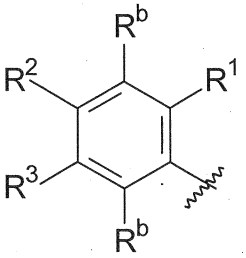
z is 1 or 2.

9. A compound of claim 1 having the formula (I):

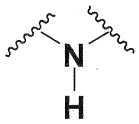
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

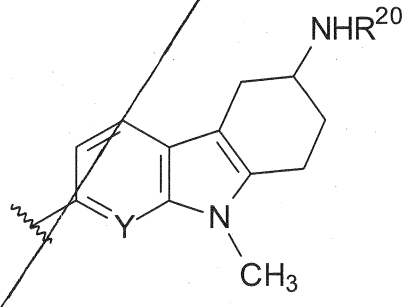
wherein A is:



L_1 is:



B is:



wherein

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$,alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if R^1 and R^2 are adjacent, they can optionally be taken together and can form a 5- or 6-membered ring containing carbon atoms and optionally one or two heteroatoms selected from O, S, or N or the heteroatom-containing moiety NR^{50};

R^3 is hydrogen or halogen;

R^a is hydrogen or alkyl;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

R^{50} is, for each occurrence, R^{20}, $S(O)_tNR^{20}R^{21}$, $S(O)_tR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$;

Y is each independently CH or N; and

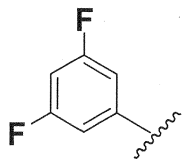
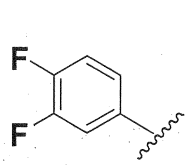
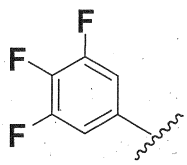
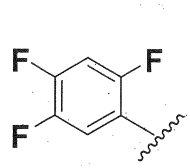
t is 1 or 2.

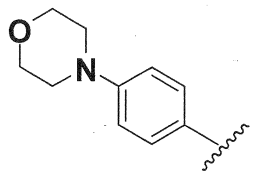
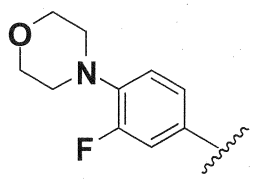
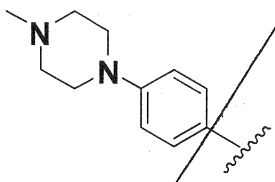
10. A compound of claim 1 having the formula (I):

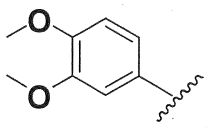
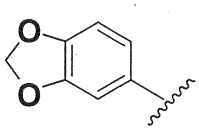
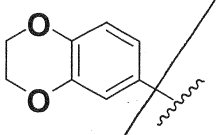
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

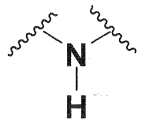
wherein A is:

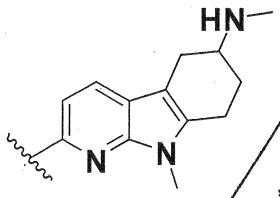
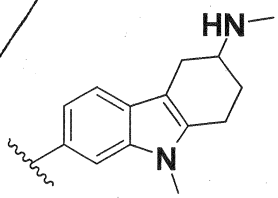


,or


L_1 is:

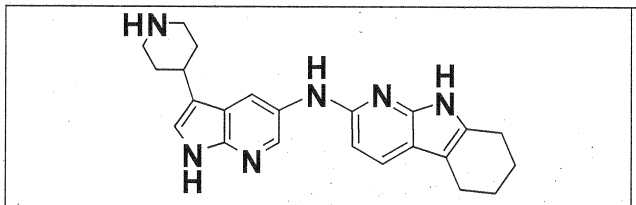


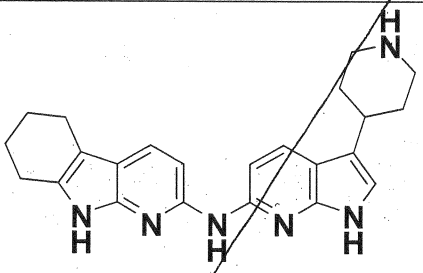
and

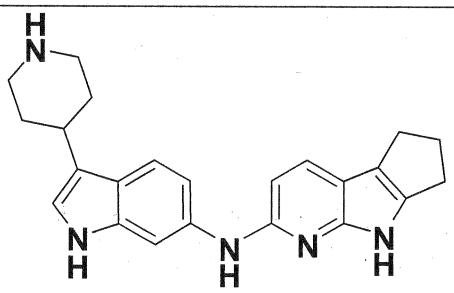
B is:

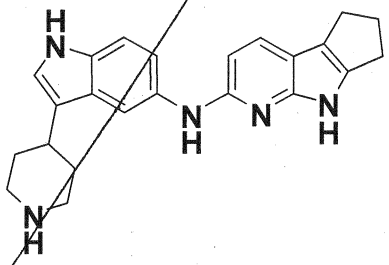

, or


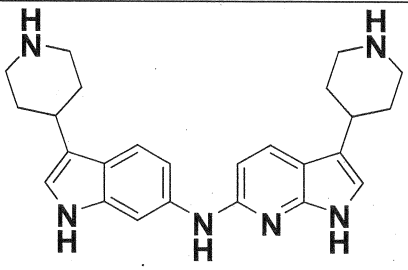
11. The compound of any of the preceding claims, wherein the compound is selected from the group consisting of

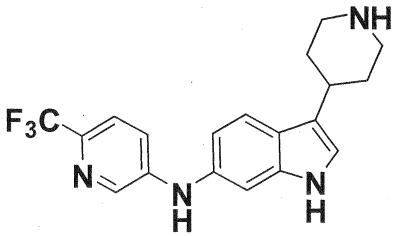


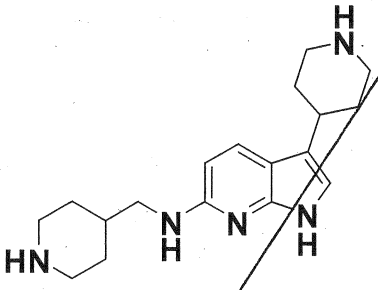


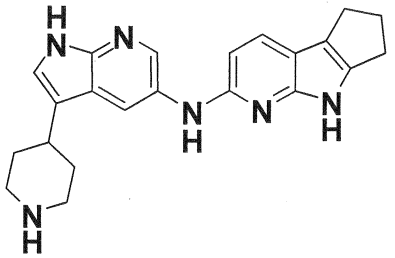


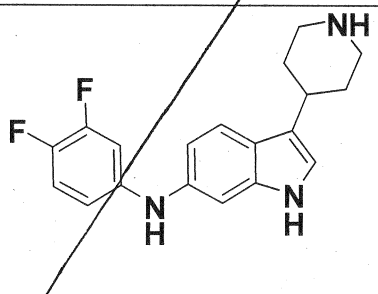


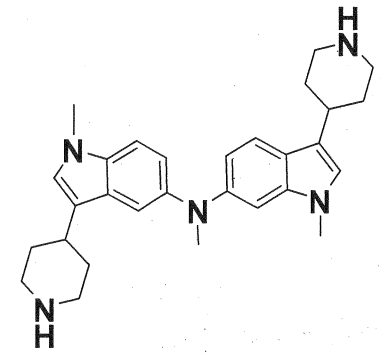
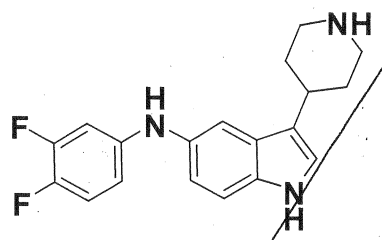
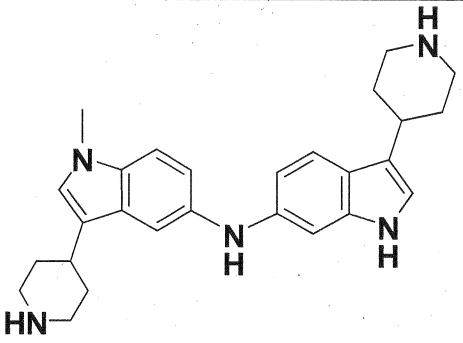
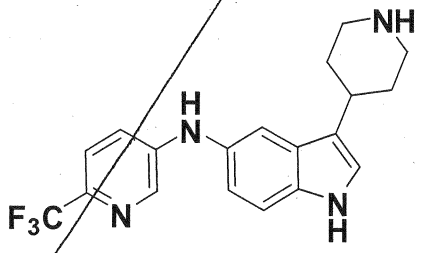
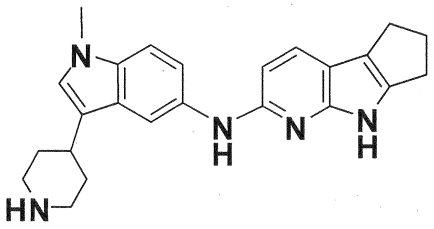
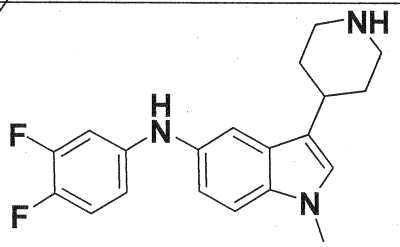
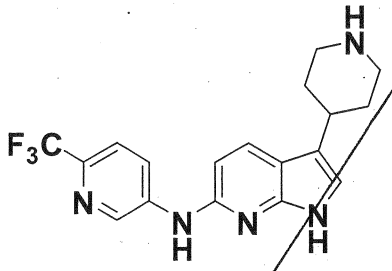
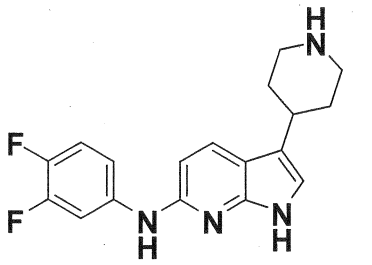
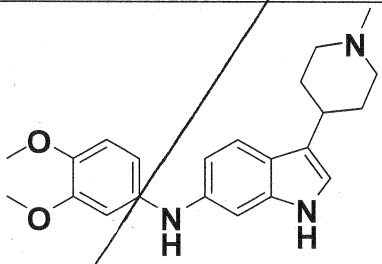
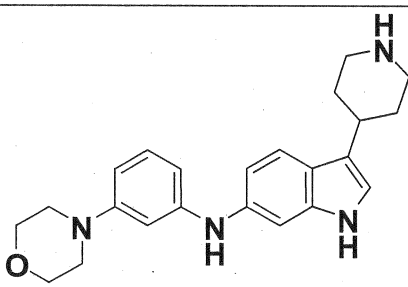


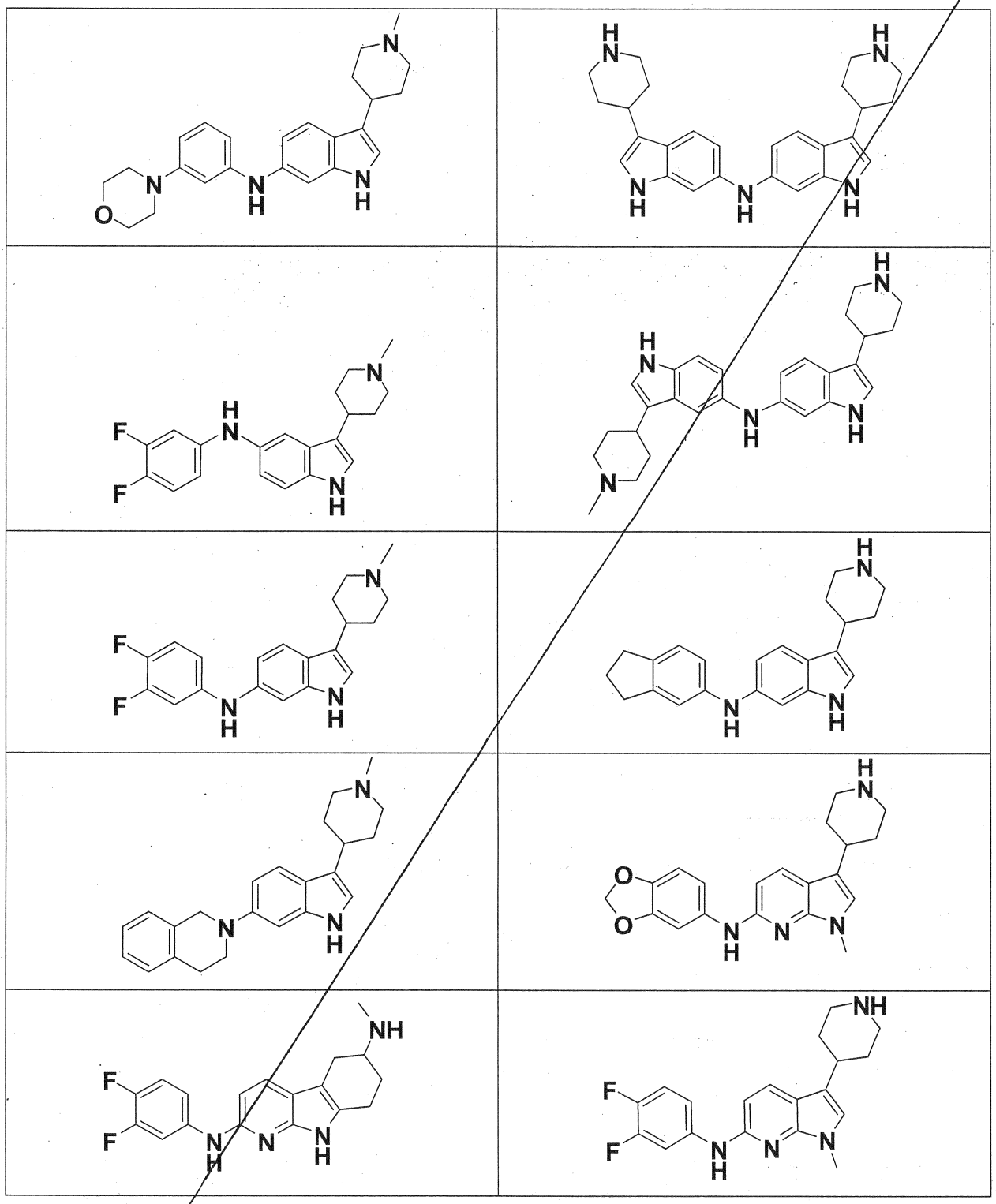


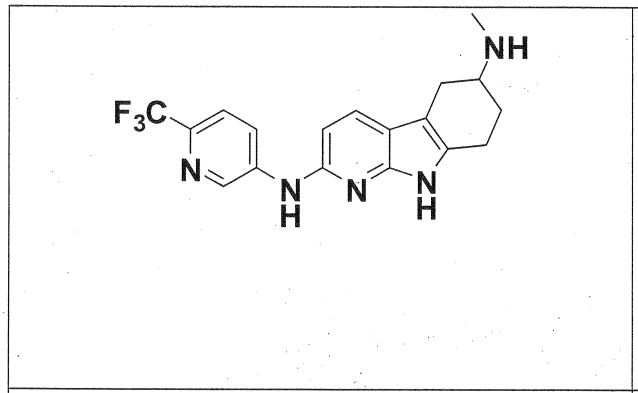


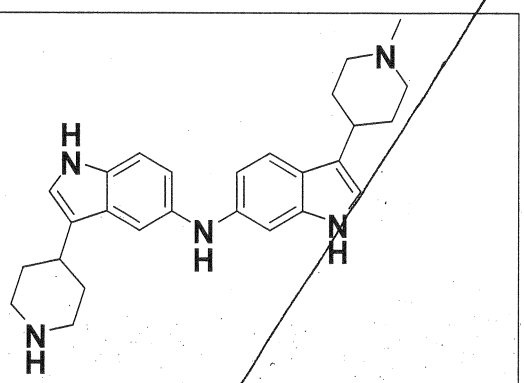


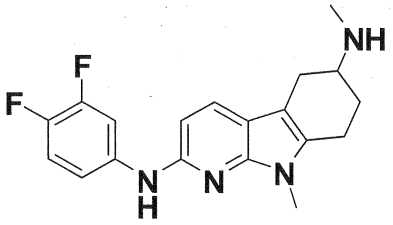


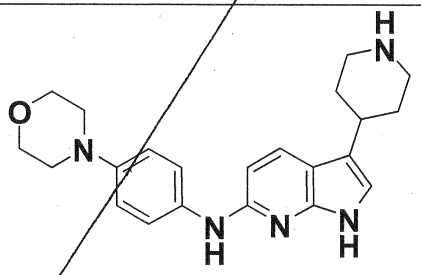
	
	
	
	
	

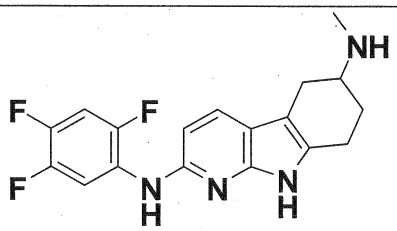


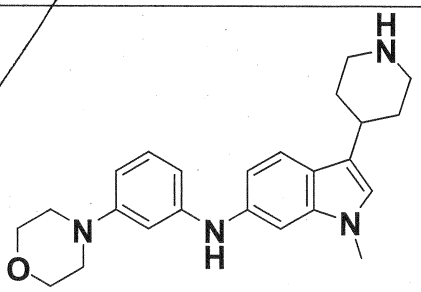


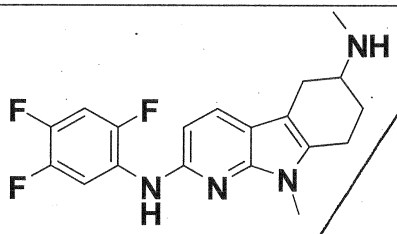


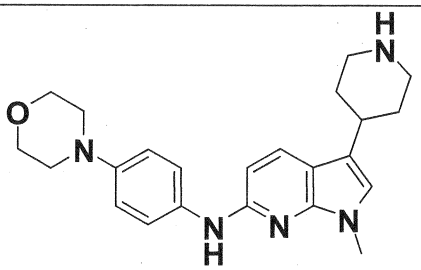


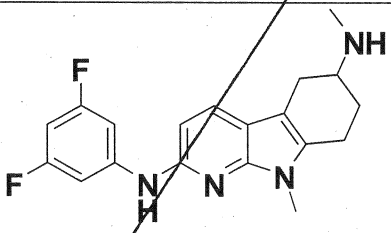


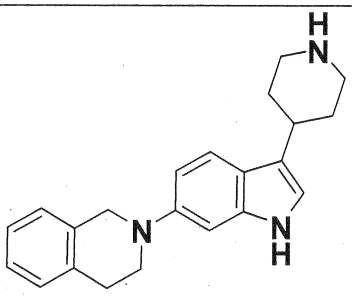


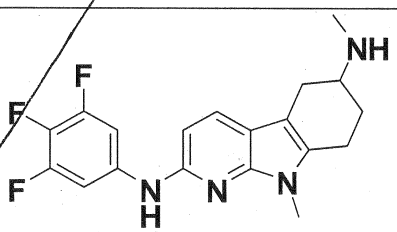


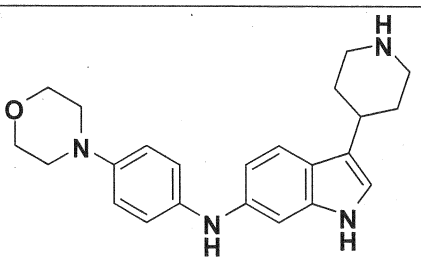


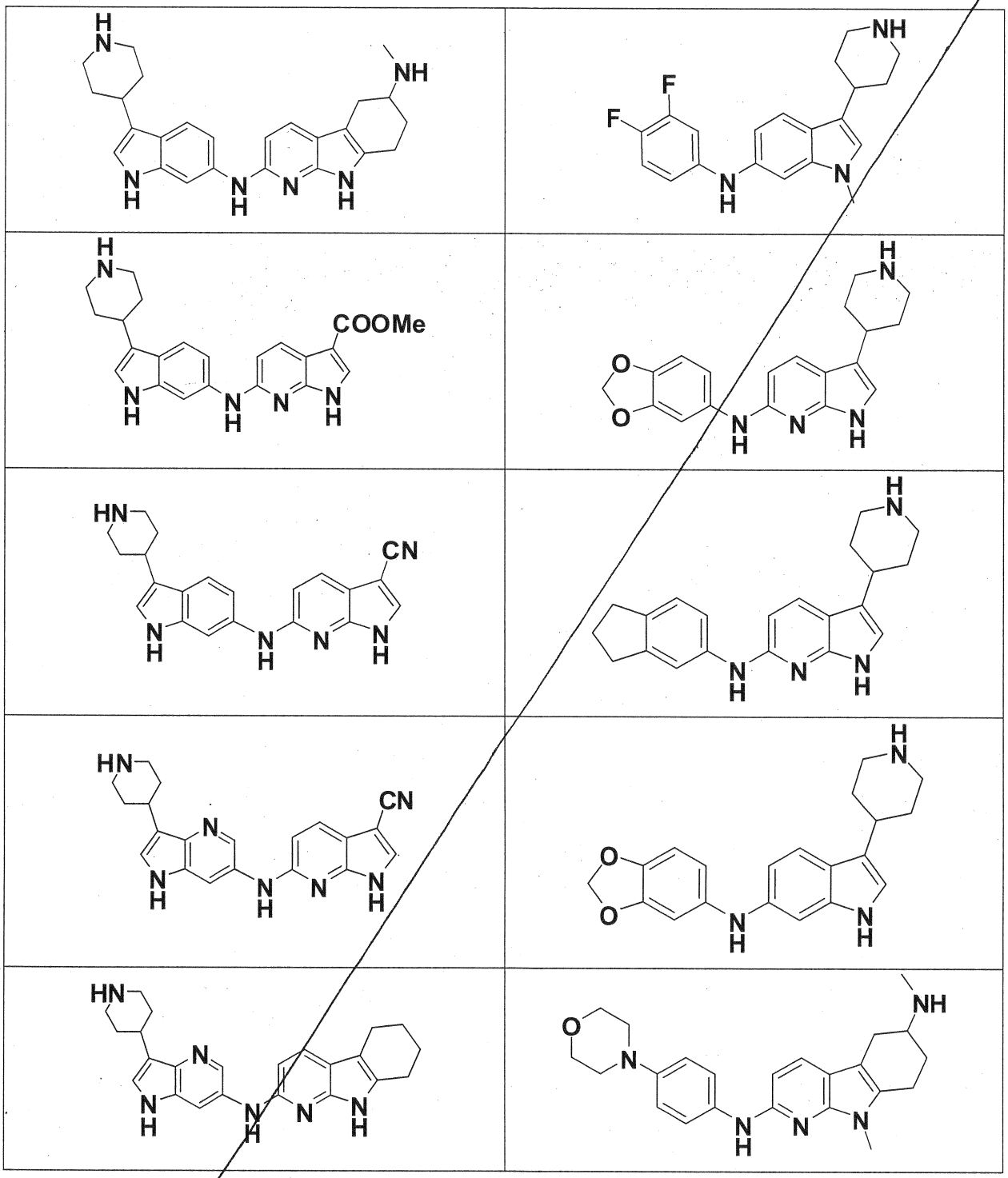


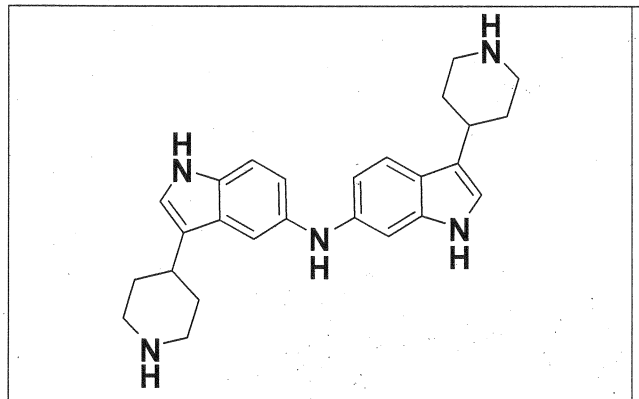


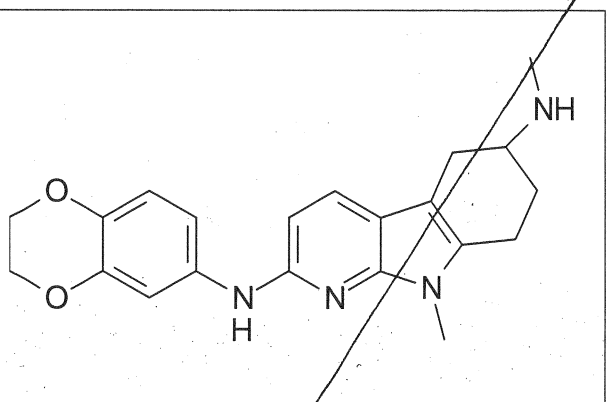


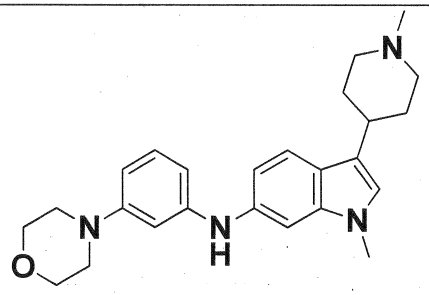


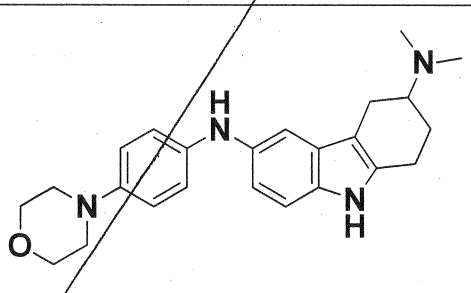


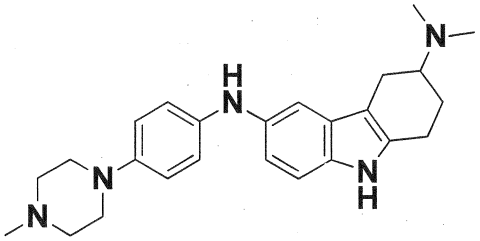


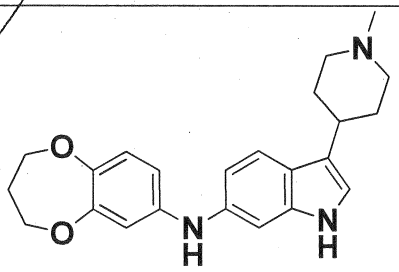


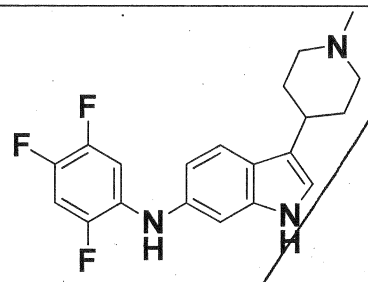


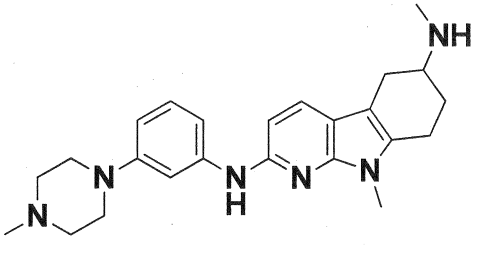


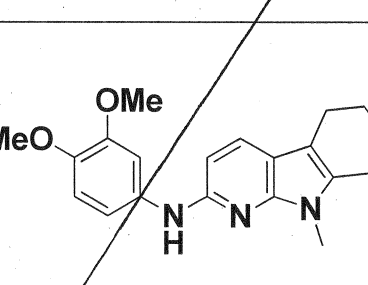


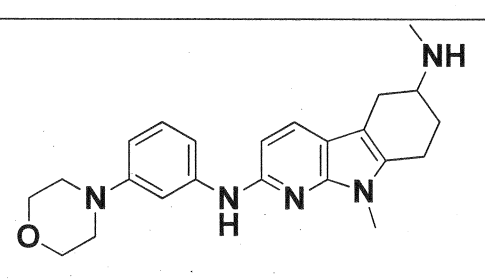


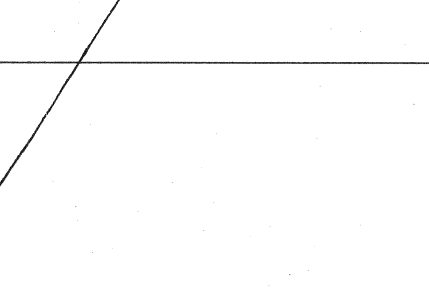


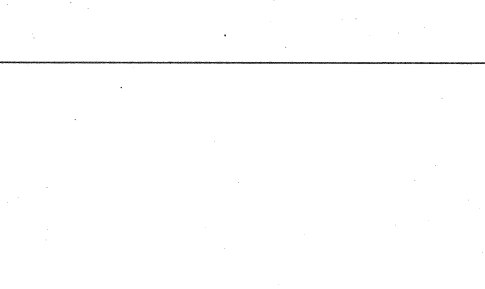


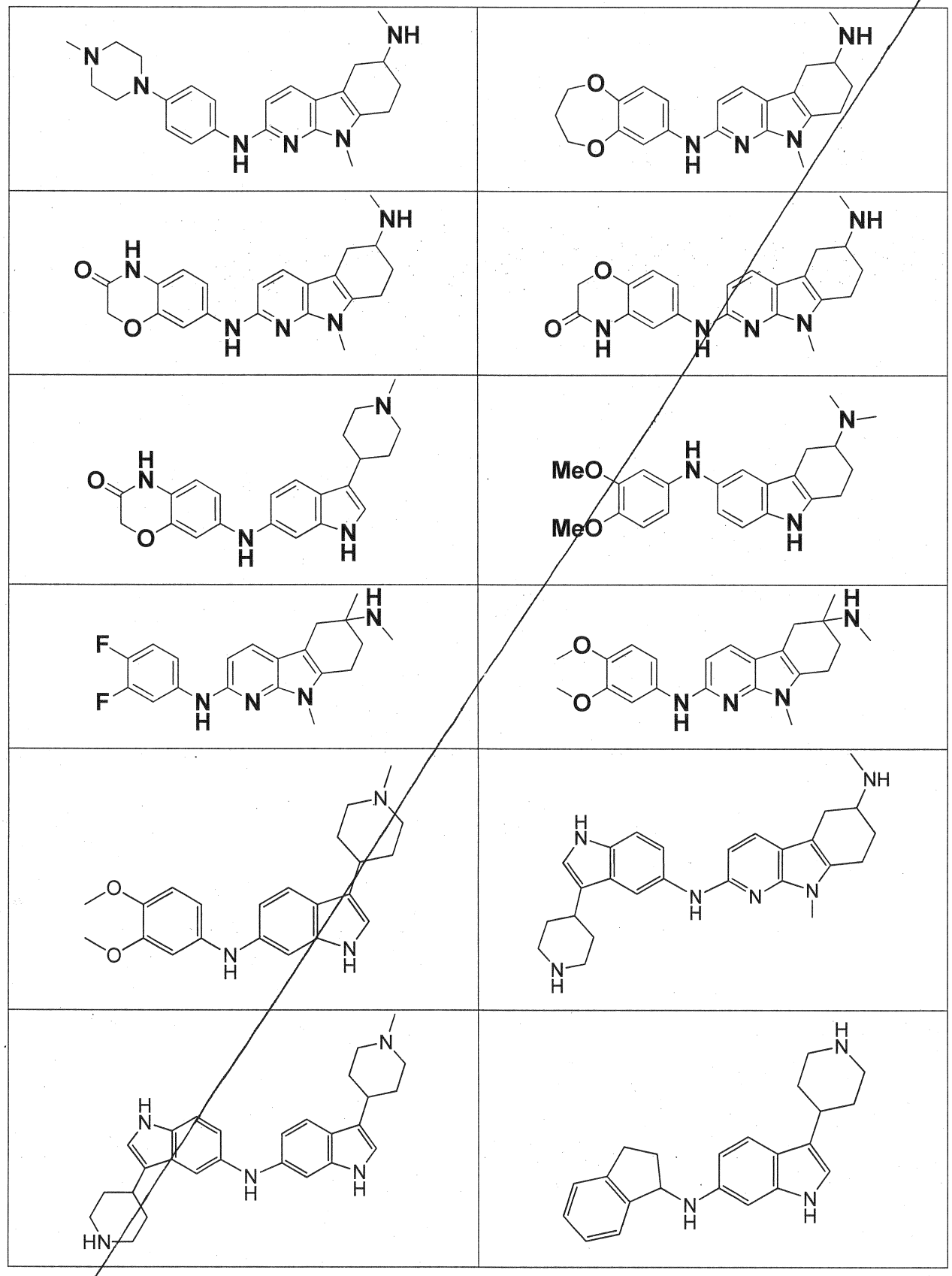


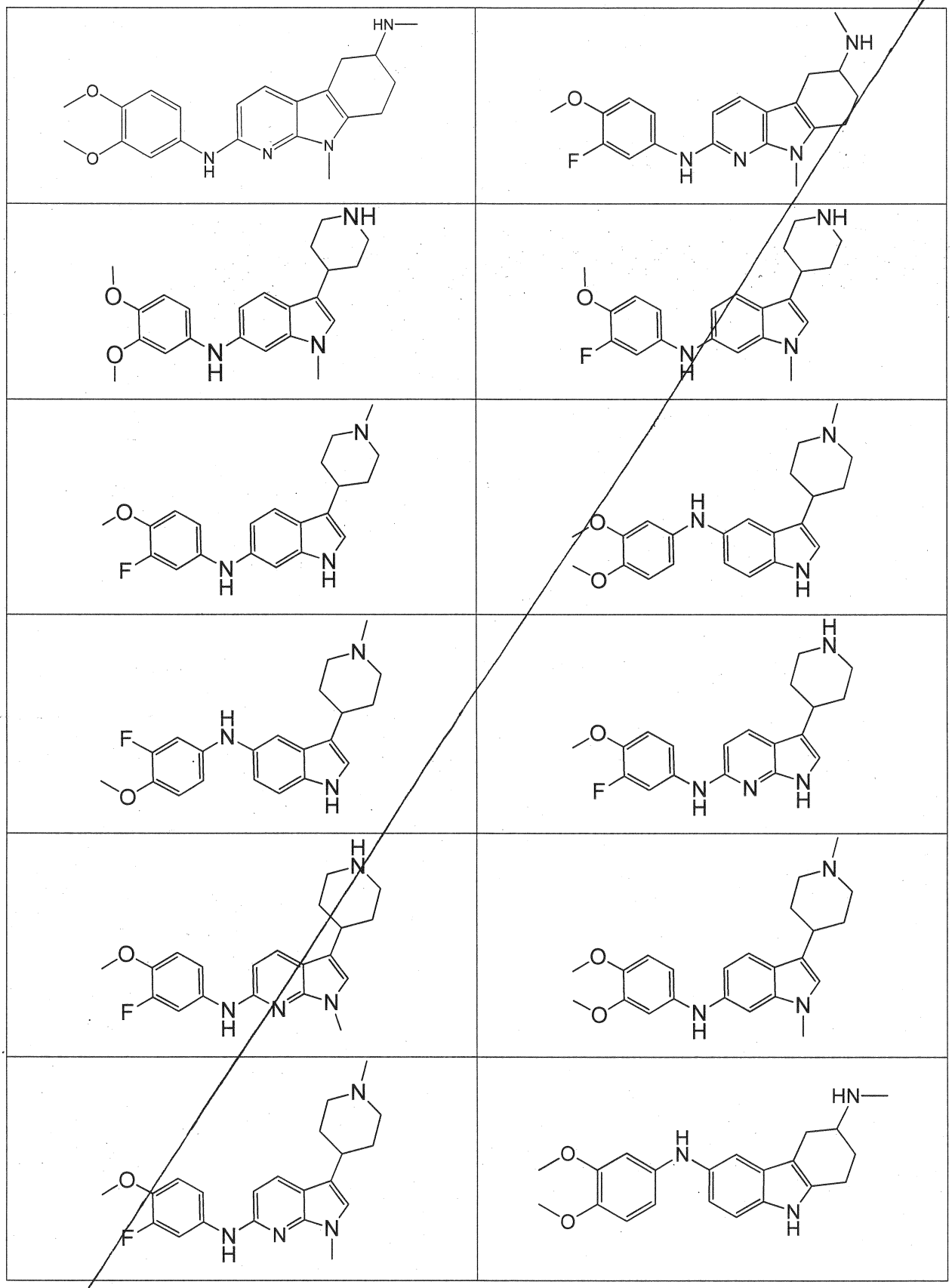


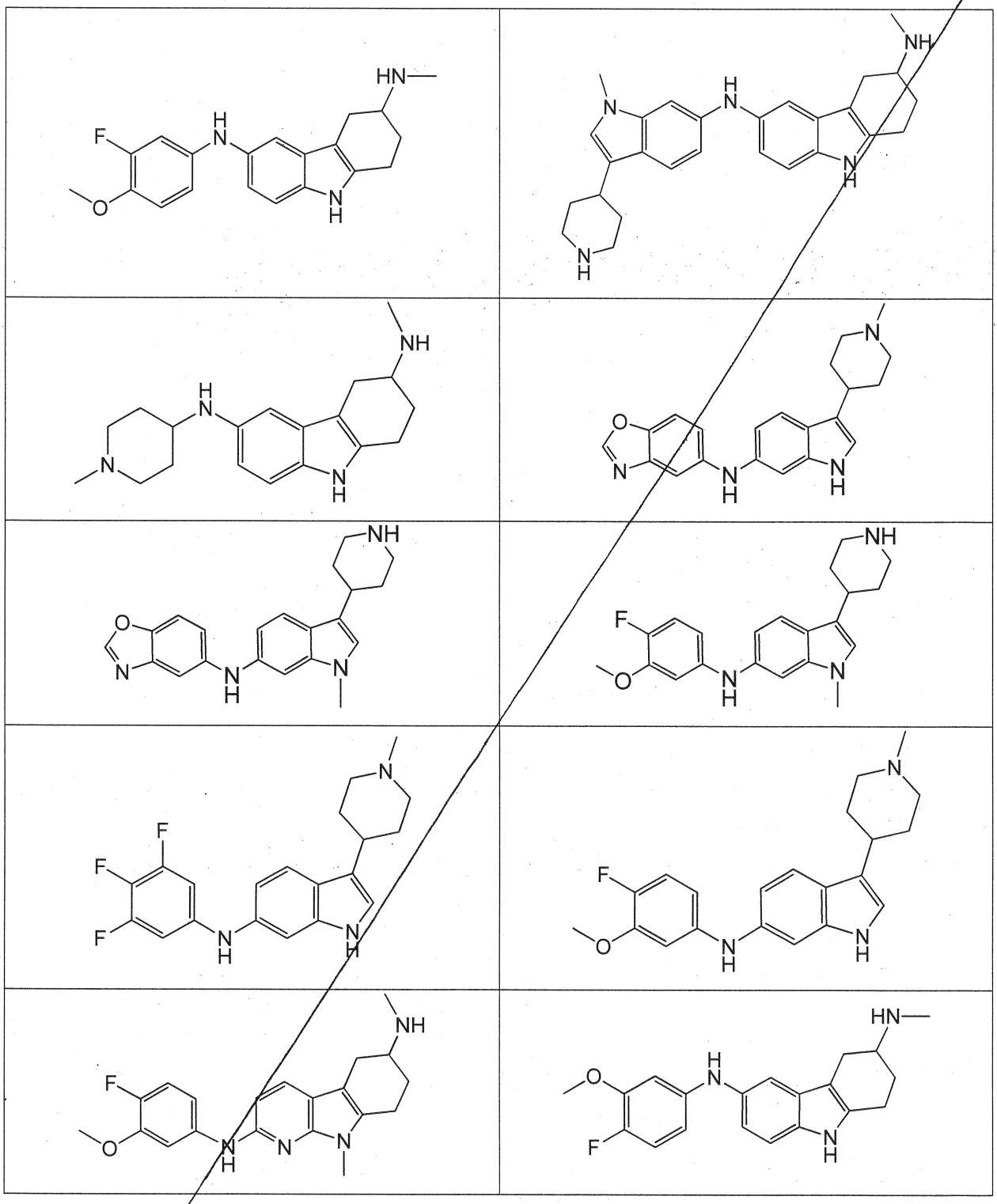


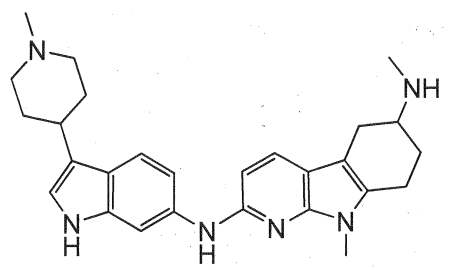
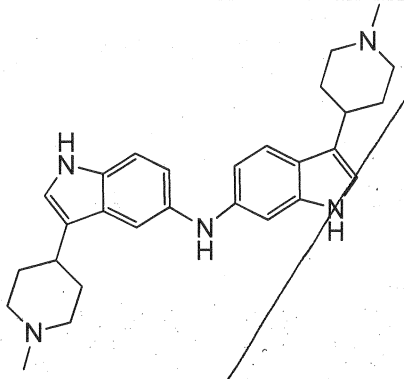
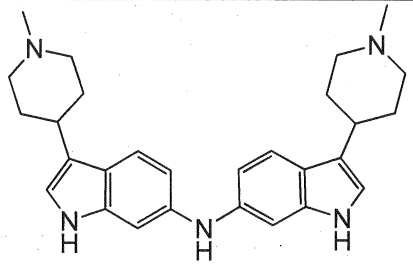
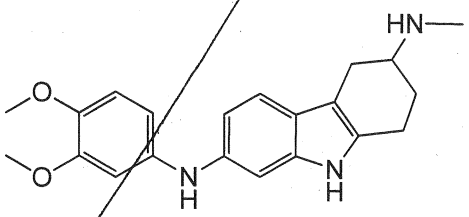
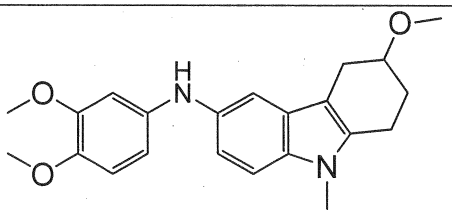
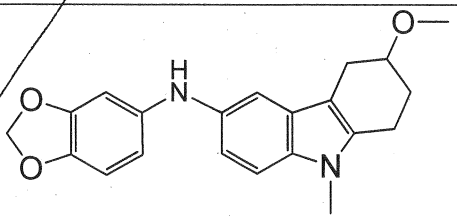
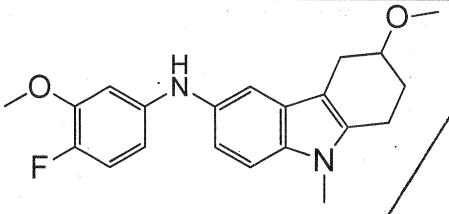
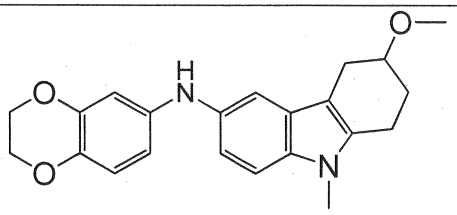
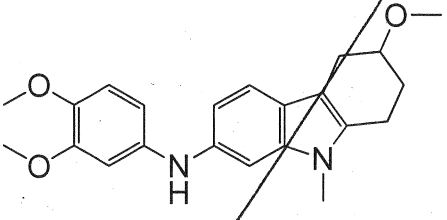
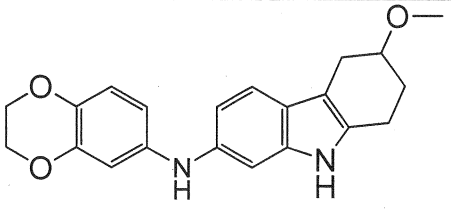
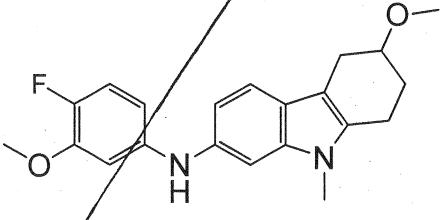
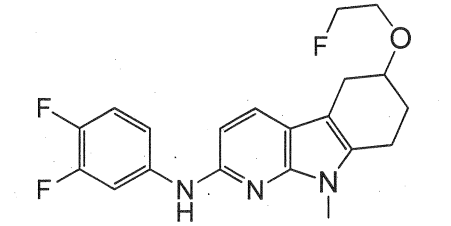


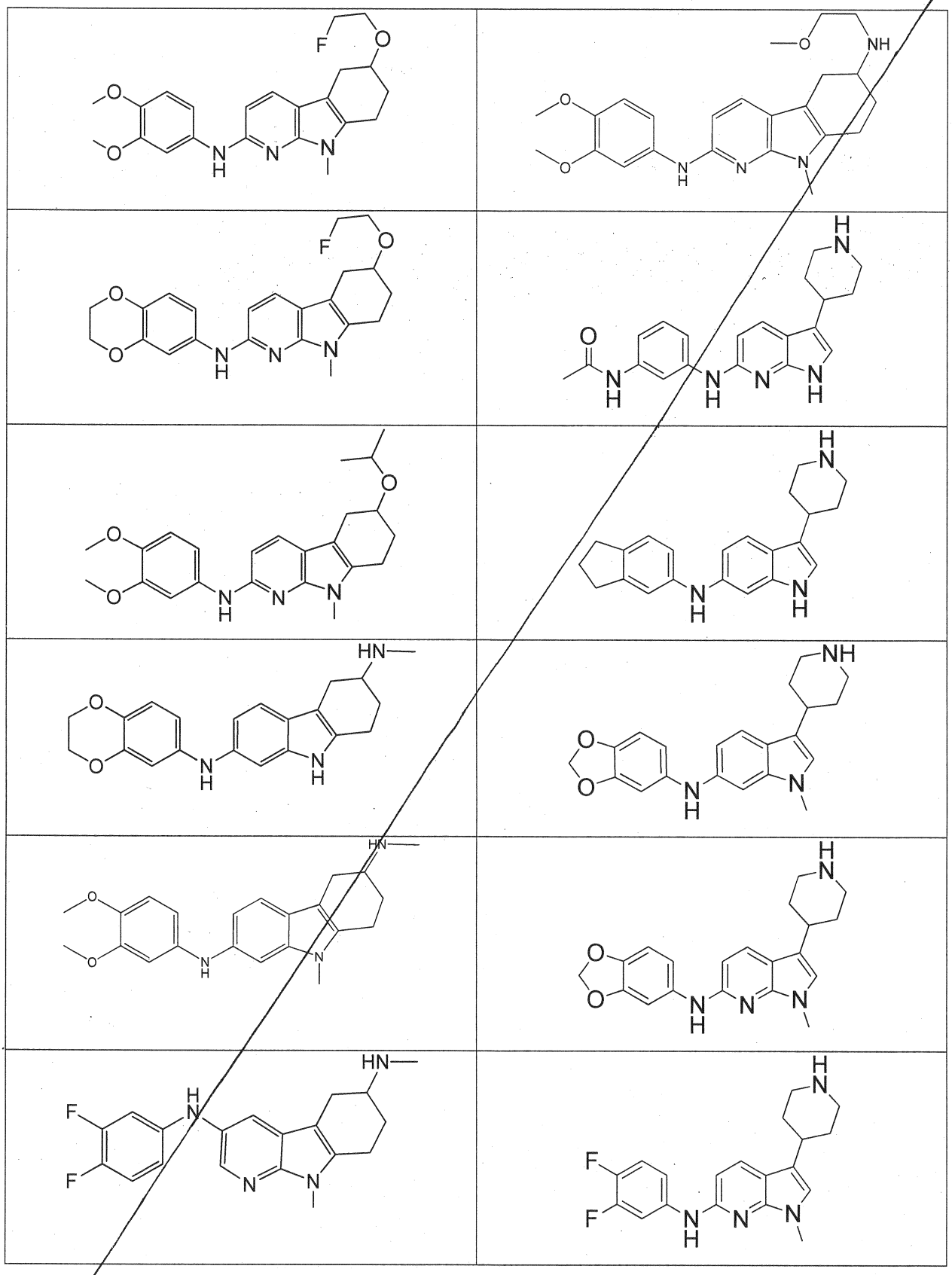


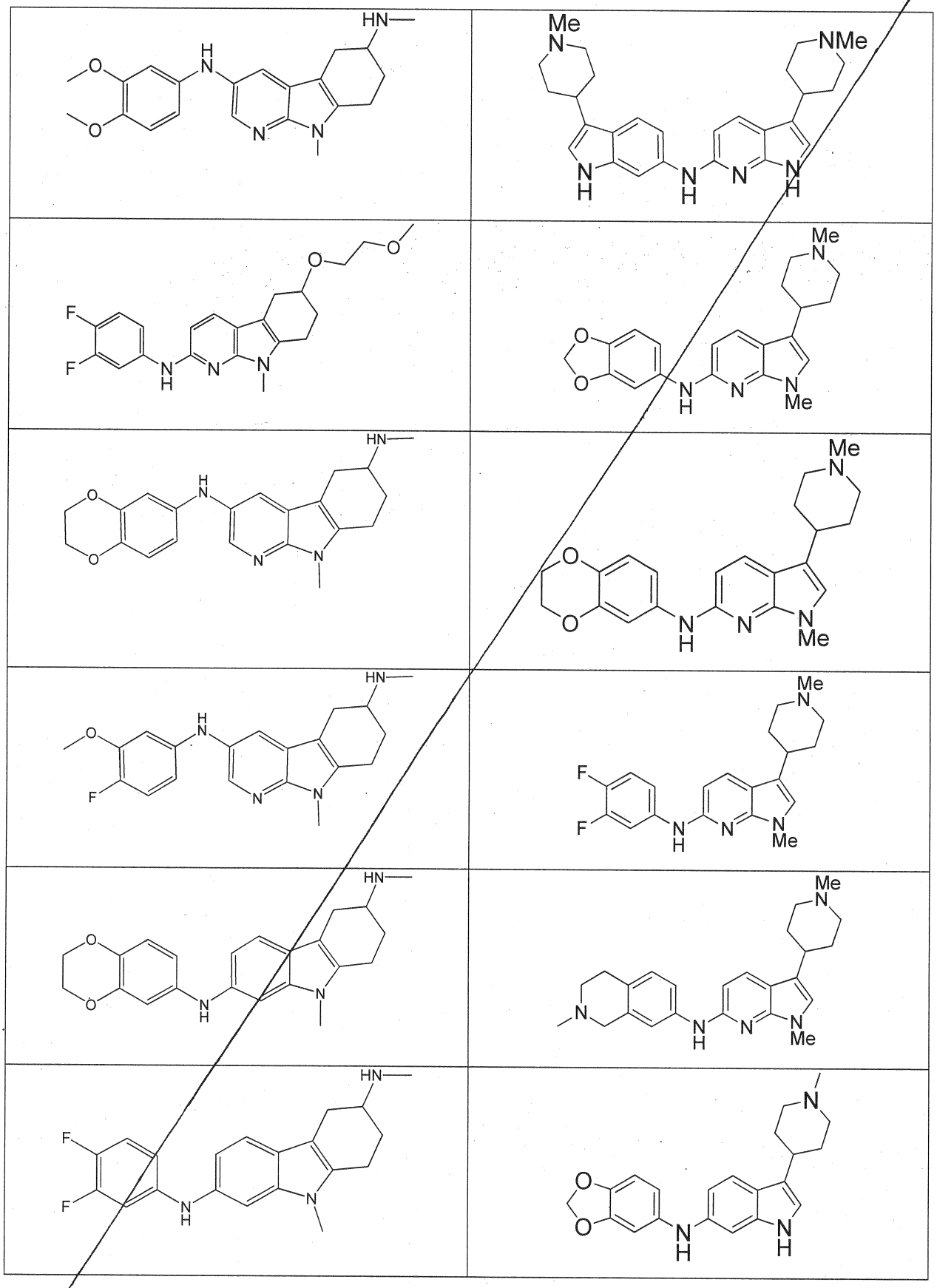


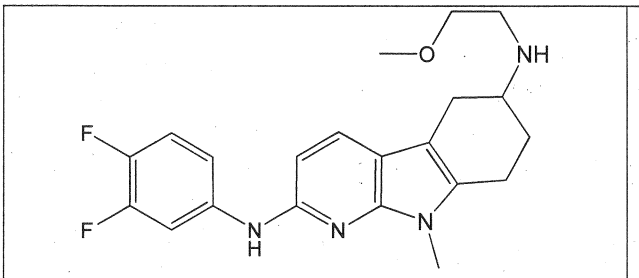


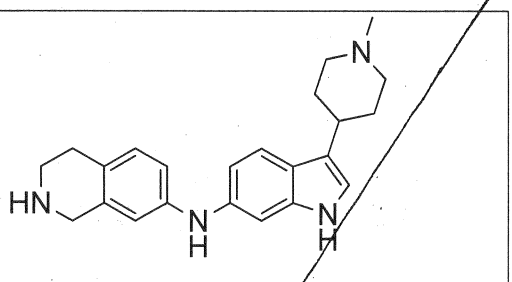


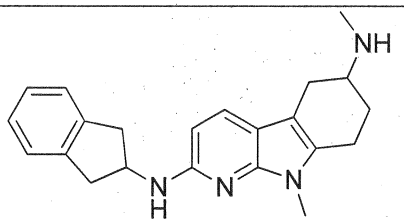
	
	
	
	
	
	

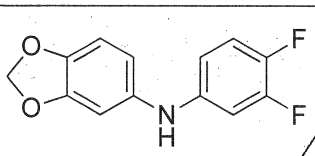


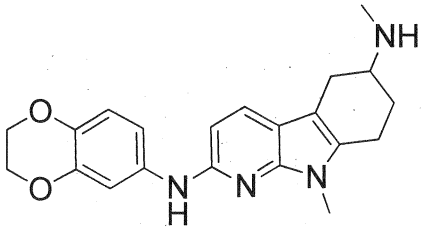


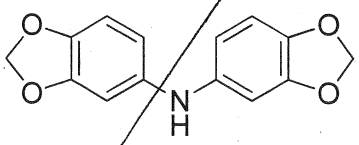


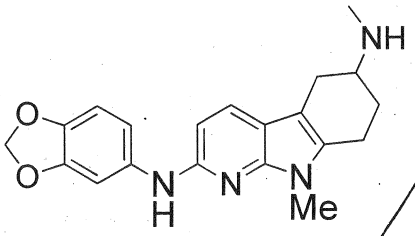


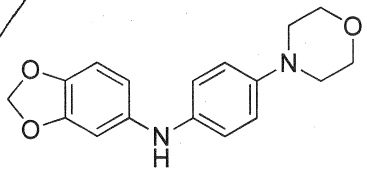


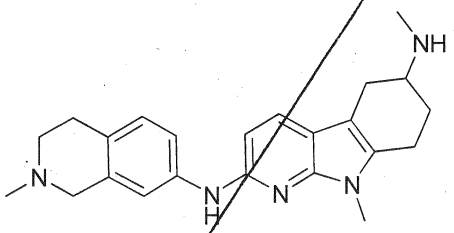


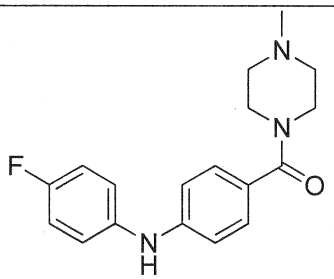


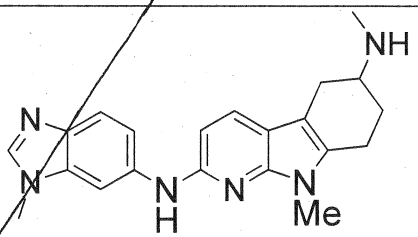


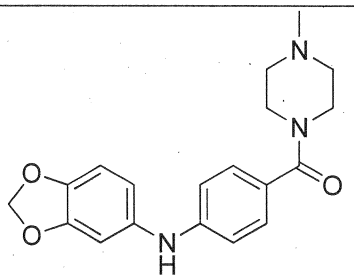


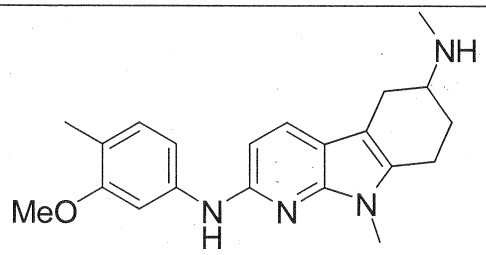
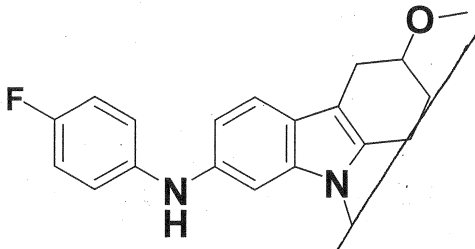
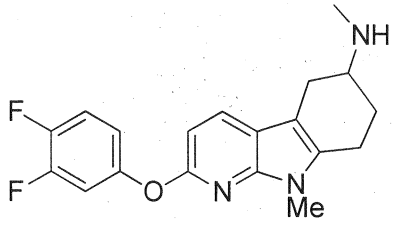
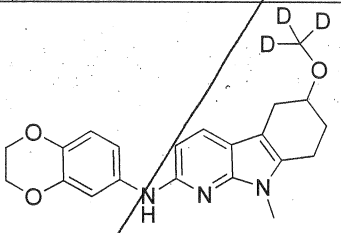
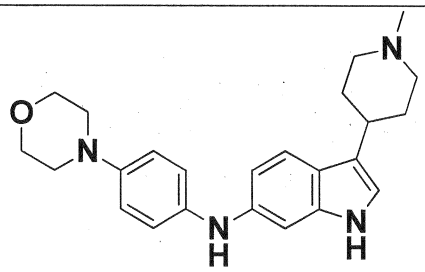
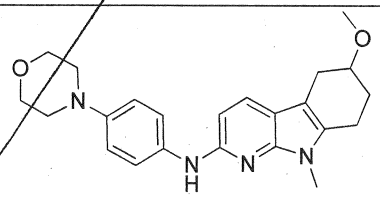
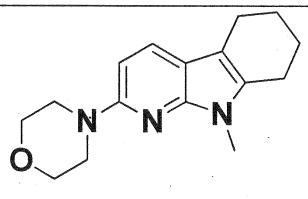
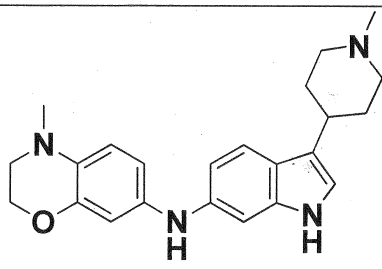
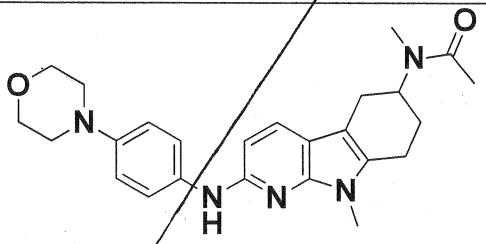
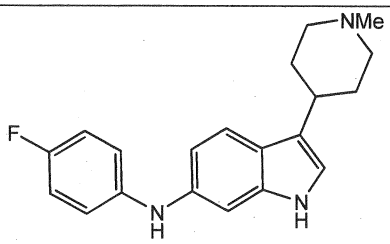


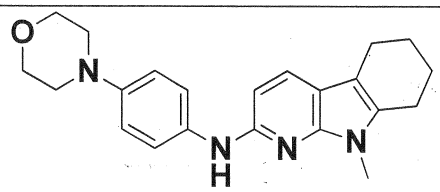
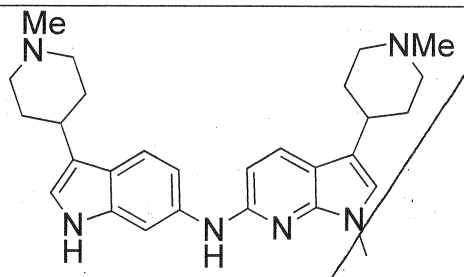
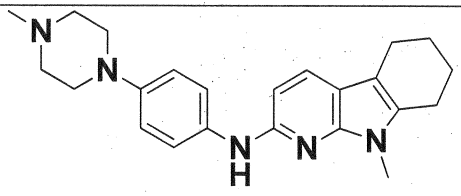
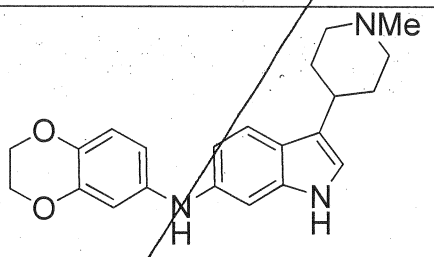
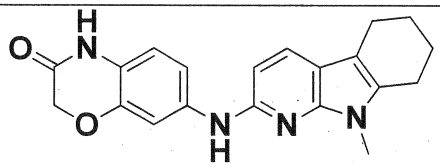
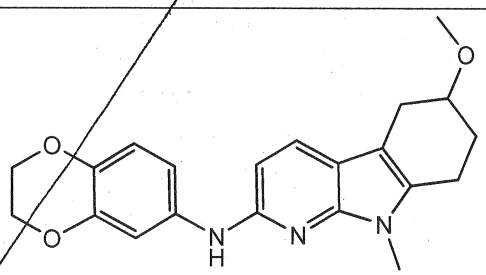
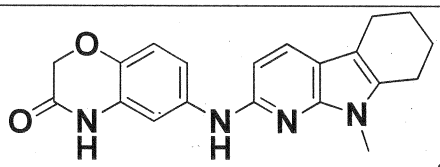
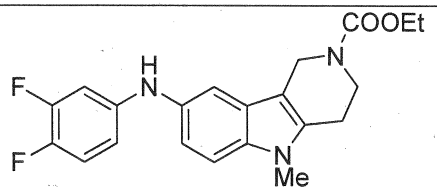
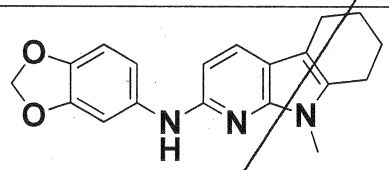
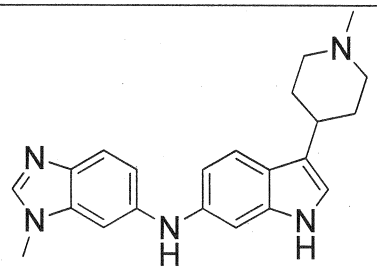
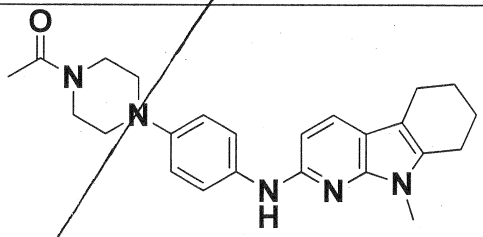
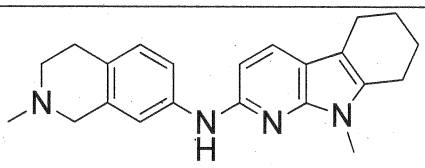


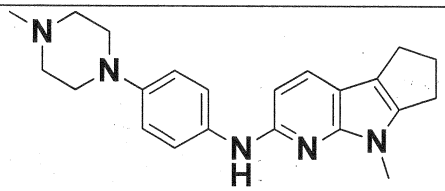
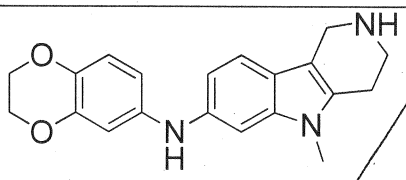
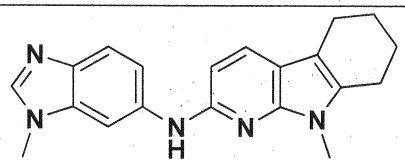
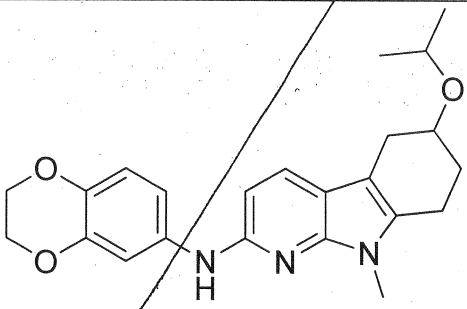
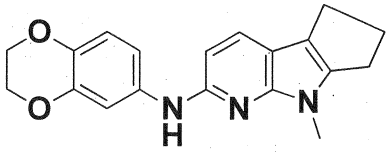
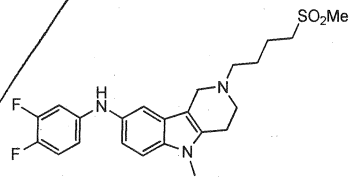
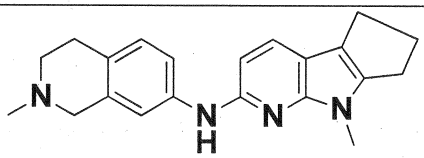
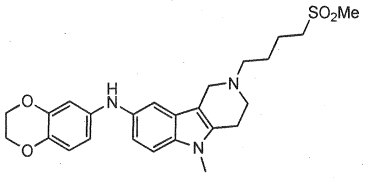
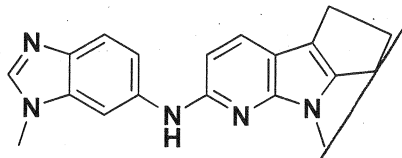
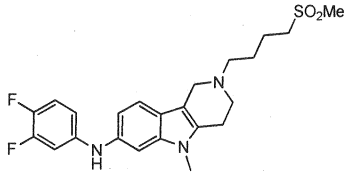
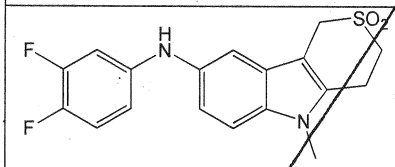
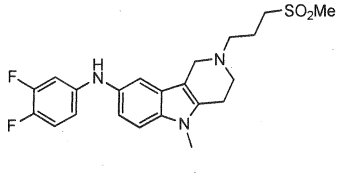
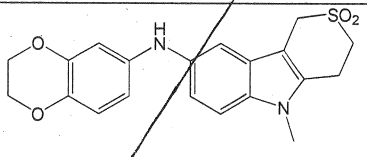
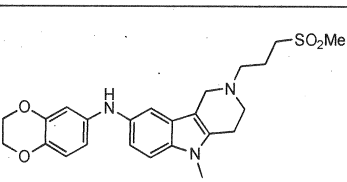


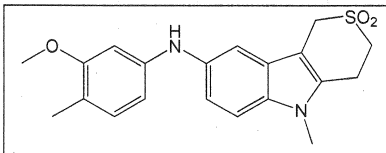
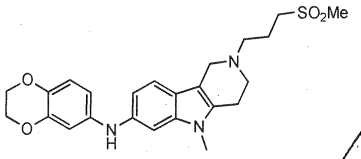
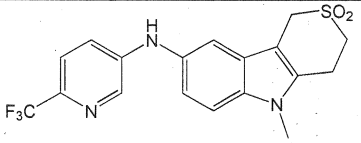
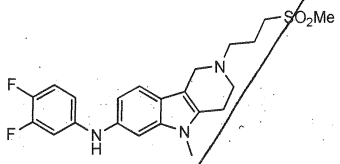
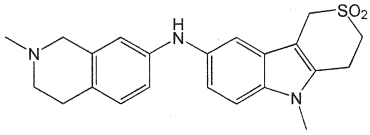
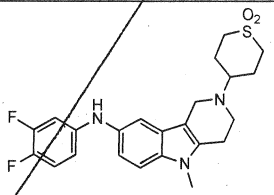
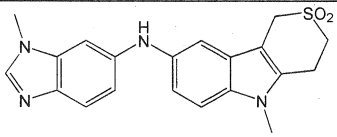
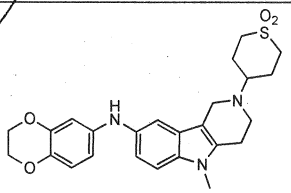
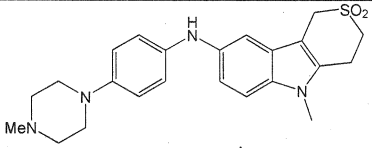
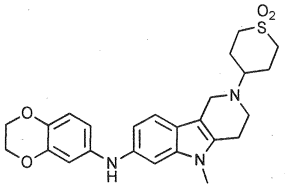
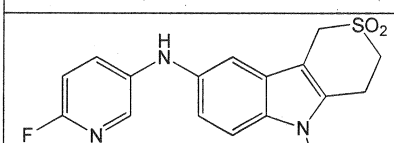
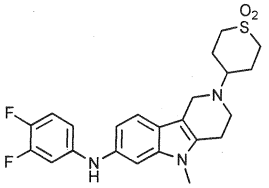
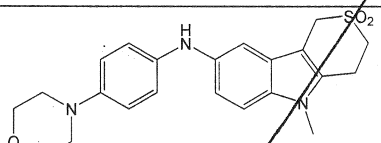
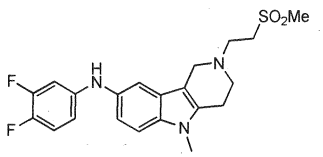
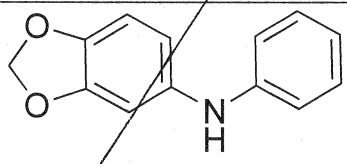
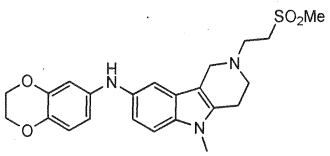


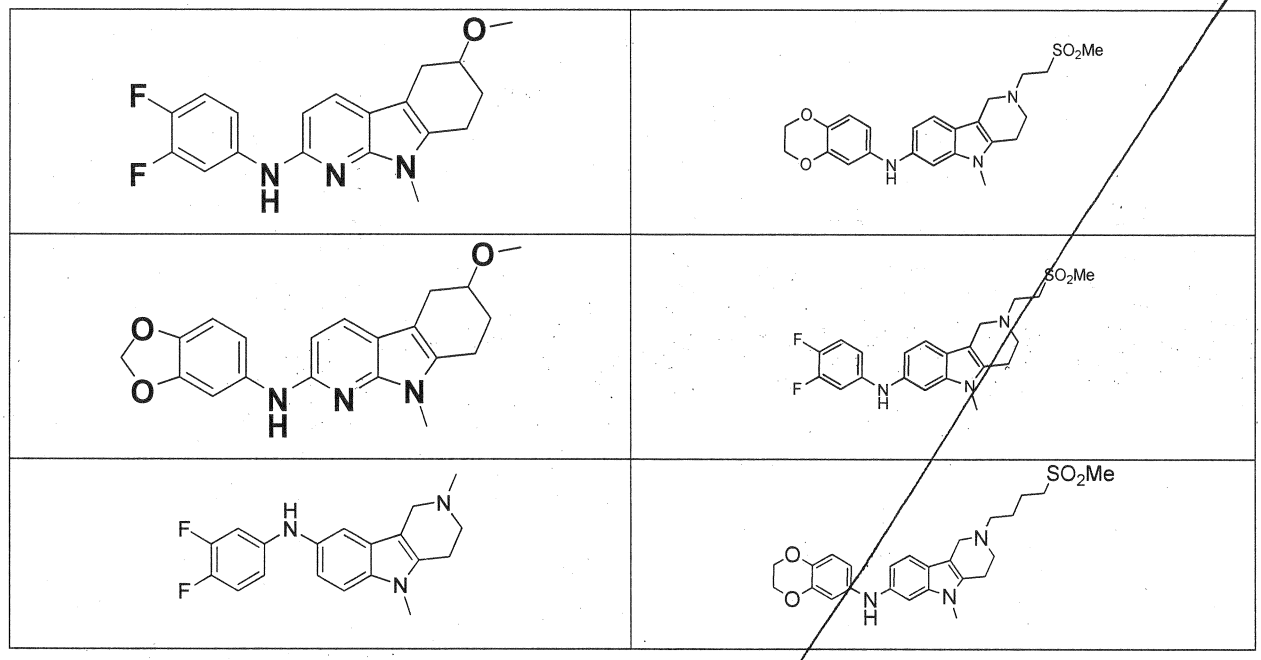




12. A compound as defined in any one of claims 1 to 11 comprising a radionuclide wherein the compounds disclaimed in claim 1 are disclaimed.

13. A radiopharmaceutical formulation comprising a compound as defined in any one of claims 1 to 11 comprising a radionuclide wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed.

14. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or excipient.

15. Use of the compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for the preparation of a medicament for treating or preventing a disease or condition associated with an amyloid and/or amyloid-like protein.

16. The use of claim 15, wherein the disease is a neurological disorder selected from the group consisting of

Alzheimer's disease (AD), Lewy body dementia (LBD), Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type), the Guam Parkinson-Dementia complex or mild cognitive impairment (MCI) or wherein the disease is progressive supranuclear palsy, multiple sclerosis, inclusion-body myositis (IBM), Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, amyotropic lateral sclerosis (ALS), inclusion-body myositis (IBM), adult onset diabetis, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

17. The use of claim 16, wherein the neurological disorder is Alzheimer's disease.

18. The compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for use in the treatment or prevention a disease or condition associated with an amyloid and/or amyloid-like protein.

19. The compound of claim 18, wherein the disease is a neurological disorder selected from the group consisting of Alzheimer's disease (AD), Lewy body dementia (LBD), Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type), the Guam Parkinson-Dementia complex or mild cognitive impairment (MCI) or wherein the disease is progressive supranuclear palsy, multiple sclerosis, inclusion-body myositis (IBM), Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, amyotropic lateral sclerosis (ALS), inclusion-body myositis (IBM), adult onset diabetis, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

20. The compound of claim 19, wherein the neurological disorder is Alzheimer's disease.

21. A mixture comprising a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed and optionally at least one further biologically active compound and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

22. The mixture according to claim 21, wherein the further biologically active compound is a compound used in the treatment of amyloidosis.

23. The mixture according to claim 21 or 22, wherein the further biologically active compound is selected from the group consisting of antibodies, vaccines, compounds against oxidative stress, anti-apoptotic compounds, metal chelators, inhibitors of DNA repair such as pirenzepin and metabolites, 3-amino-1-propanesulfonic acid (3APS), 1,3-propanedisulfonate (1,3PDS), α-secretase activators, β- and γ-secretase inhibitors, tau proteins, neurotransmitters, β-sheet breakers, attractants for amyloid beta clearing / depleting cellular components, inhibitors of N-terminal truncated amyloid beta including pyroglutamated amyloid beta 3-42, anti-inflammatory molecules, or cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine, M1 agonists and other drugs including any amyloid or tau modifying drug and nutritive supplements.

24. The mixture according to claim 23, wherein the further biologically active compound is a cholinesterase inhibitor (ChEI).

25. A method of collecting data for the diagnosis of an amyloid-associated disease or condition in a sample comprising:
    (a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed;
    (b) allowing the compound to bind to the amyloid protein;
    (c) detecting the compound bound to the protein; and
    (d) optionally correlating the presence or absence of compound binding with the amyloid protein with the presence or absence of amyloid protein in the sample.

26. A method of determining the extent of amyloidogenic plaque burden in a tissue and/or a body fluid comprising:
    (a) providing a sample representative of the tissue and/or body fluid under investigation;
    (b) testing the sample for the presence of amyloid protein with a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed;
    (c) determining the amount of compound bound to the amyloid protein; and

(d) calculating the plaque burden in the tissue and/or body fluid.

27. The method according to claim 26, wherein the determination in step (c) is conducted such that presence or absence of the compound binding with the amyloid protein correlates with presence or absence of amyloid protein.

28. A method of collecting data for determining a predisposition to an amyloid-associated disease or condition in a patient comprising detecting the specific binding of a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed to an amyloid protein in a sample or *in situ* which comprises the steps of:

(a) bringing the sample suspected to contain the amyloid protein into contact with the compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample or; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

29. A method of collecting data for monitoring minimal residual disease in a patient following treatment with an antibody or a vaccine composition, wherein the method comprises:

(a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined in any one of claims 1 to 11wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

30. A method of collecting data for predicting responsiveness of a patient being treated with an antibody or a vaccine composition comprising:

(a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

31. A test kit for detection and/or diagnosis of an amyloid-associated disease or condition comprising a compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed.

32. Use of the compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for the preparation of a medicament for treating or preventing an ocular disease or condition associated with a pathological abnormality/change in the tissue of the visual system, particularly associated with an amyloid-beta-related pathological abnormality/change in the tissue of the visual system.

33. The use of claim 32, wherein the ocular disease or condition is selected from the group consisting of neuronal degradation, cortical visual deficits, glaucoma, cataract due to beta-amyloid deposition, ocular amyloidosis, primary retinal degeneration, macular degeneration, for example age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

34. A compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for use in the treatment or prevention of an ocular disease or condition associated with a pathological abnormality/change in the

tissue of the visual system, particularly associated with an amyloid-beta-related pathological abnormality/change in the tissue of the visual system.

35. The compound of claim 34, wherein the ocular disease or condition is selected from the group consisting of neuronal degradation, cortical visual deficits, glaucoma, cataract due to beta-amyloid deposition, ocular amyloidosis, primary retinal degeneration, macular degeneration, for example age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

36. A compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for use in inhibiting protein aggregation, in particular for use in inhibiting Aβ1-42 aggregation, Tau aggregation or alpha-synuclein aggregation.

37. Use of the compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for the preparation of a medicament for (a) reducing the β-amyloid plaque load, and/or (b) inhibiting the formation of β-amyloid plaques and/or (c) retarding the increase of amyloid load in the brain of a patient.

38. A compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for use in (a) the reduction of the β-amyloid plaque load, and/or (b) the inhibition of the formation of β-amyloid plaques and/or (c) the retardation of the increase of amyloid load in the brain of a patient.

39. The use of claim 37 or the compound of claim 38, wherein reducing the β-amyloid plaque load, inhibiting the formation of β-amyloid plaques and/or retarding the increase of amyloid load lead to a reduction and/or amelioration of the effects of a disease or condition caused by or associated with the formation and deposition of β-amyloid plaques in the brain.

40. Use of the compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for the preparation of a medicament for retaining or increasing cognitive memory capacity in a subject suffering from memory impairment.

41. A compound as defined in any one of claims 1 to 11 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for use in the retention or increase of cognitive memory capacity in a subject suffering from memory impairment.

42. The use of claim 15 or the compound of claim 16, wherein the amyloid-associated condition is characterized by a loss of cognitive memory capacity and the treatment of the amyloid-associated condition leads to an increase in the retention of cognitive memory capacity or a complete restoration of cognitive memory capacity.

CLAIMS

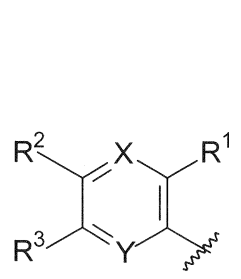
1. A compound of formula (I):

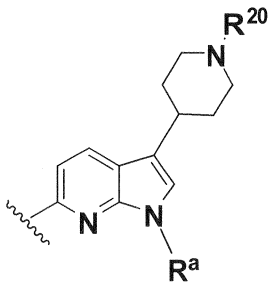
$$A–L_1–B \qquad (I)$$

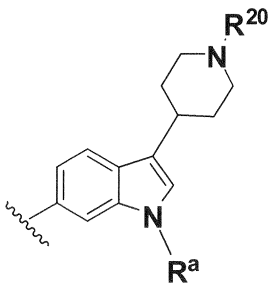
and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

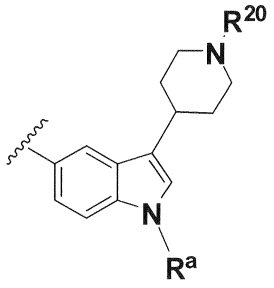
wherein

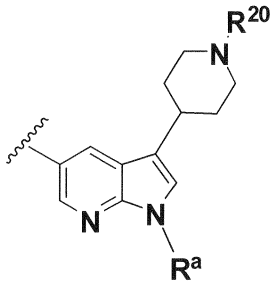
A is selected from the group consisting of:

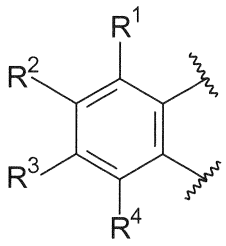


,


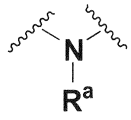
,


,


,


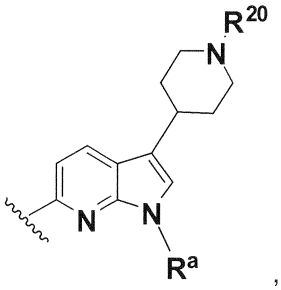
and


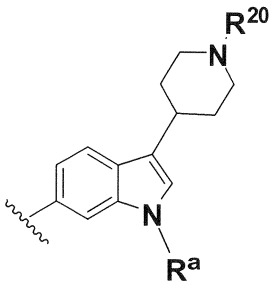
L_1 is

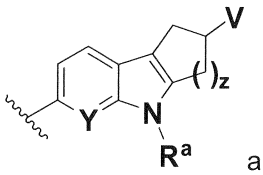


;

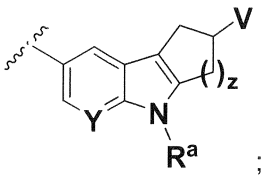
B is selected from the group consisting of:



,


,


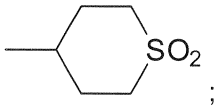
and



;

wherein

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $-CONR^{30}R^{31}$, $-N(R^{30})-C(O)-R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if any of the groups $R^1/R^2/R^3/R^4$ are adjacent, they can optionally be taken together and can form a 5- to 8-membered ring containing carbon atoms and optionally one or more heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 5- to 8-membered ring may be substituted by $NR^{20}R^{21}$ or –O–alkyl, wherein the alkyl can be optionally substituted, or by



;

for each occurrence, R^a is independently selected from the group consisting of hydrogen, alkyl, haloalkyl, $S(O)_tNR^{30}R^{31}$, $S(O)_tR^{30}$, $C(O)OR^{30}$, $C(O)R^{30}$, and $C(O)NR^{30}R^{31}$;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted, or wherein R^{20} and R^{21}, when taken together with the nitrogen to which they are attached, can form a 3- to 8-membered ring containing carbon atoms and optionally one or more further heteroatoms selected from O, S, or N or optionally one or more heteroatom (e.g., N, O and/or S)-containing moieties and wherein the 3- to 8-membered ring may be optionally substituted;

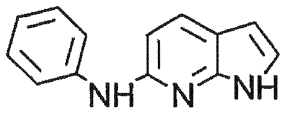
X and Y are each independently selected from the group consisting of CR^b and N;

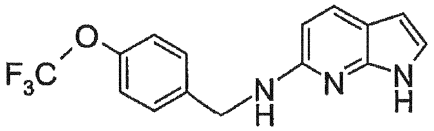
t is 1 or 2; and

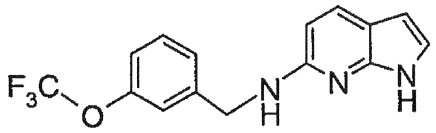
p is 0, 1 or 2

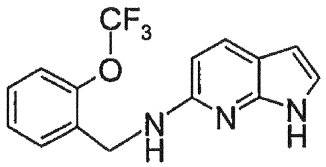
V is absent or $NR^{20}R^{21}$
z is 1 or 2, and

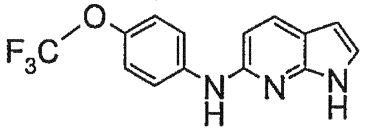
with the proviso that the following compounds are excluded:

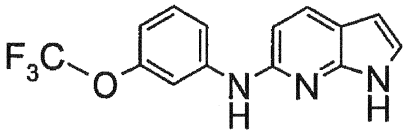


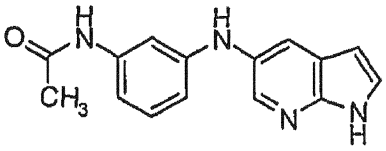


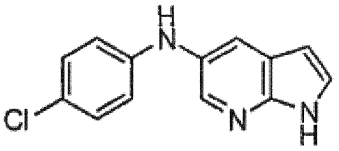


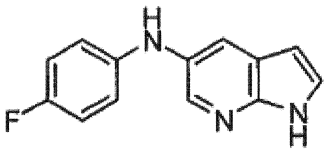


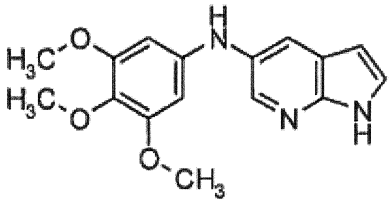


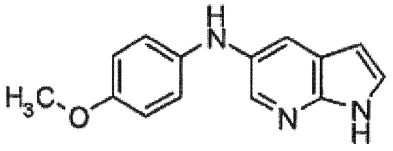


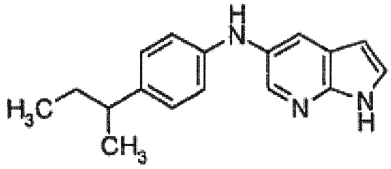


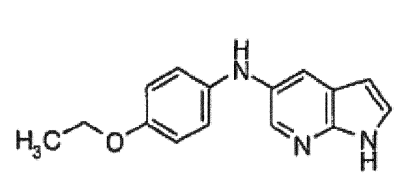


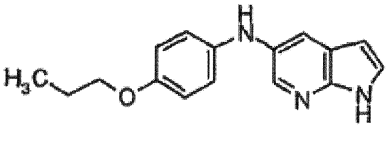


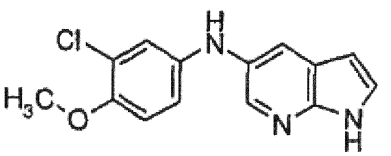


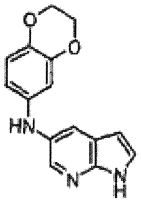


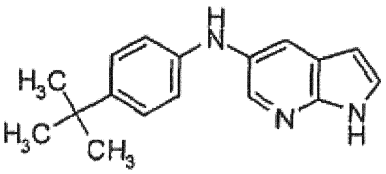


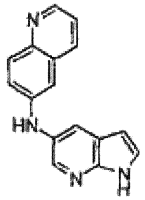


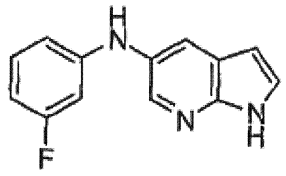


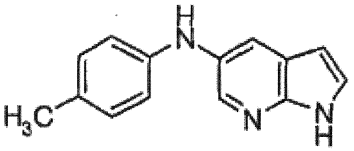


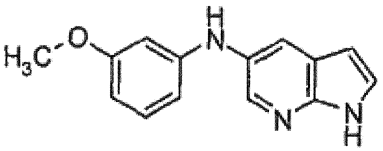


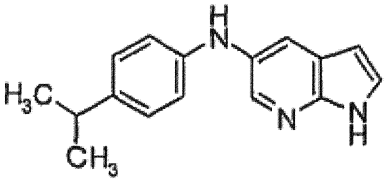


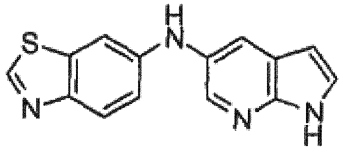


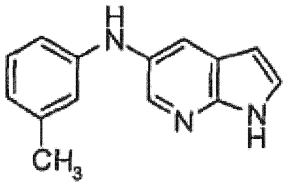


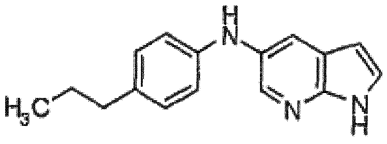


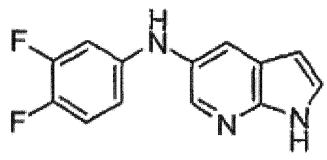


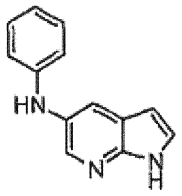
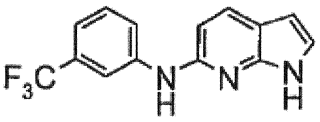
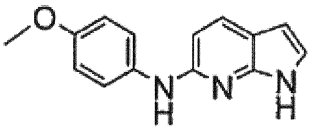
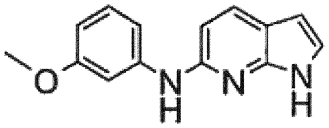
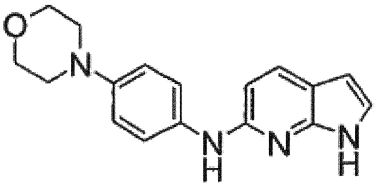
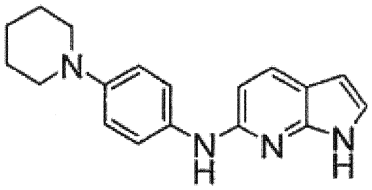
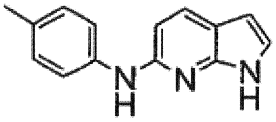
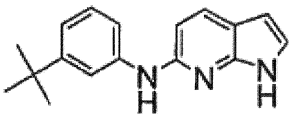
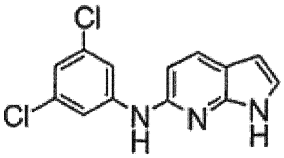
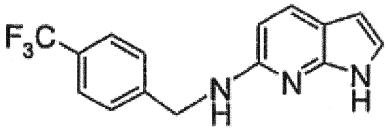
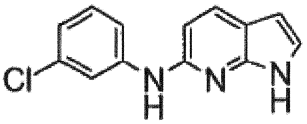
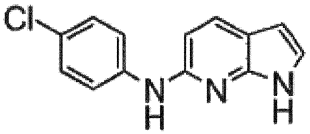
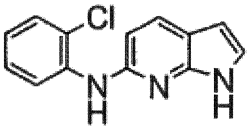
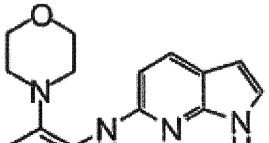
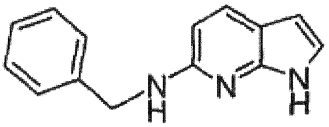
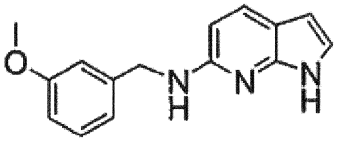
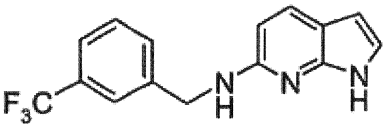
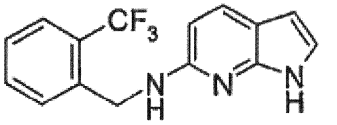
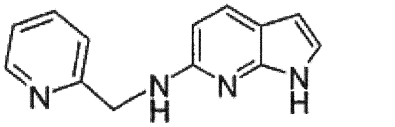


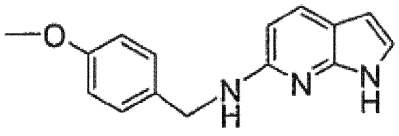
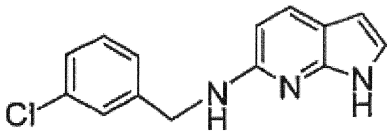
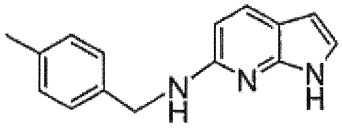
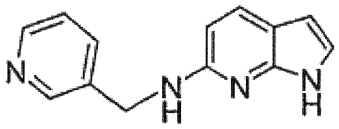
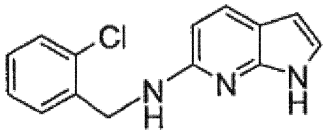
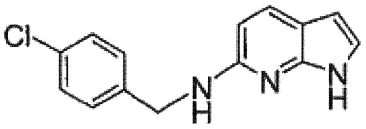
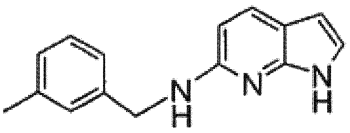
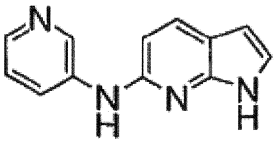
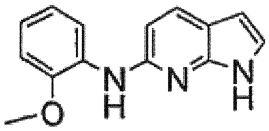
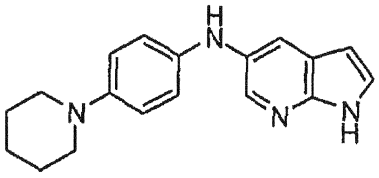
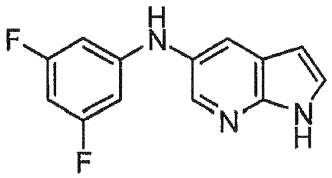
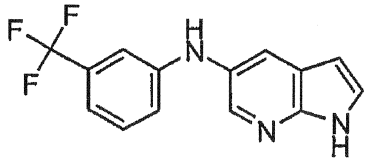






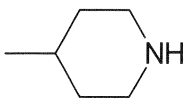
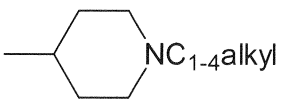
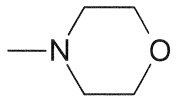


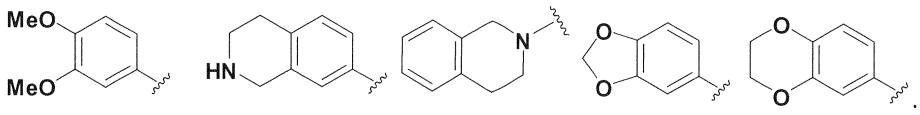













and .

2. The compound of claim 1, wherein L_1 has the formula (a) and preferably p is 0.

3. The compound of any of the preceding claims, wherein R^1, R^2, R^3 and R^4 are each independently selected from hydrogen, halogen (such as F), CN, CF_3, $CONR^{30}R^{31}$, –O–alkyl, heterocycloalkyl (such as ,  or .

4. The compound of claim 1, wherein formula (vii) in A is selected from



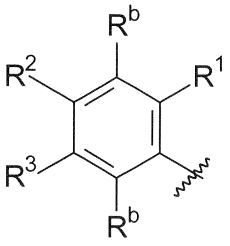
5. The compound of any of the preceding claims, wherein R^a is hydrogen or C_{1-4} alkyl.

6. The compound of claim 1 having the formula (I):

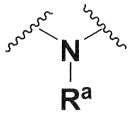
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

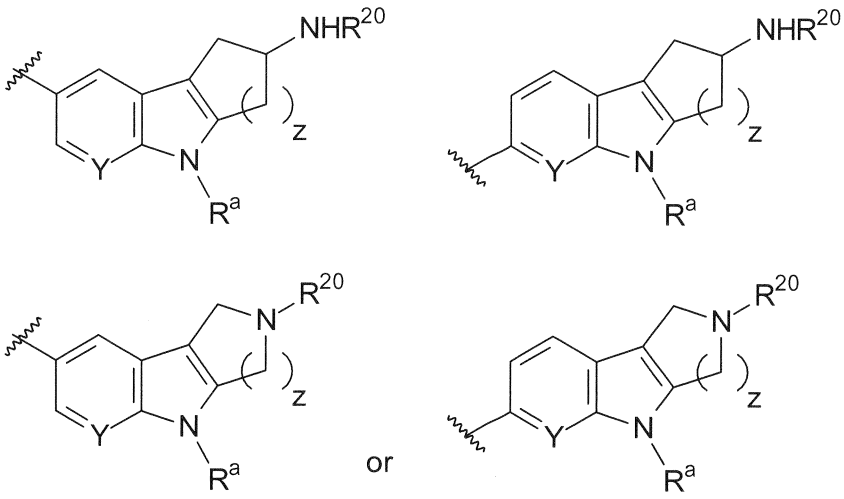
wherein A is:



L_1 is:



B is:



wherein

R^2 and R^3 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, R^2 and R^3 can optionally be taken together and can form a 5- or 6-membered ring containing carbon atoms and optionally one or two heteroatoms selected from O, S, or N or the heteroatom-containing moiety NR^{50};

R^1 is hydrogen or halogen;

R^a is hydrogen or alkyl;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

R^{50} is for each occurrence R^{20}, $S(O)_tNR^{20}R^{21}$, $S(O)_tR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$;

Y is each independently CH or N

t is 1 or 2; and

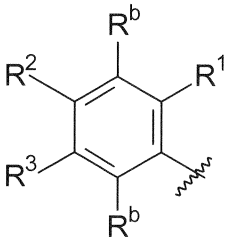
z is 1 or 2.

7. A compound of claim 1 having the formula (I):

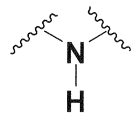
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

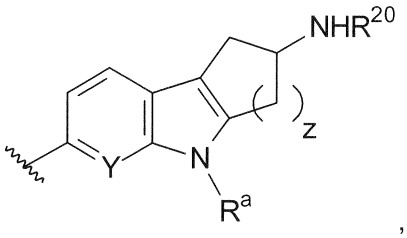
wherein A is:



L_1 is:



B is:



,

wherein

R^2 and R^3 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if R^1 and R^2 are adjacent, they can optionally be taken together and can form a 5- or 6-membered ring containing carbon atoms and optionally one or two heteroatoms selected from O, S, or N or the heteroatom-containing moiety NR^{50};

R^1 is hydrogen or halogen;

R^a is hydrogen or alkyl;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence, R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl,

heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

R^{50} is, for each occurrence, R^{20}, $S(O)_tNR^{20}R^{21}$, $S(O)_tR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$;

Y is each independently CH or N;

t is 1 or 2; and

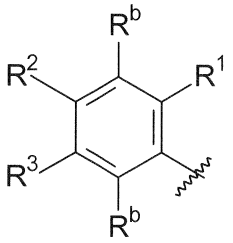
z is 1 or 2.

8. A compound of claim 1 having the formula (I):

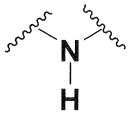
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

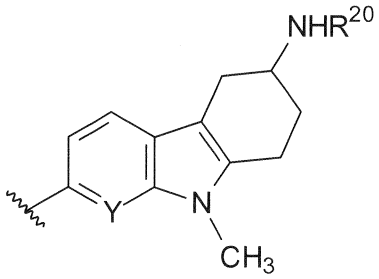
wherein A is:



L_1 is:



B is:



wherein

R^1 and R^2 are each independently selected from the group consisting of hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$,alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl can be optionally substituted, or if R^1 and R^2 are adjacent, they can optionally be taken together and can form a 5- or 6-membered ring containing carbon atoms and optionally one or two heteroatoms selected from O, S, or N or the heteroatom-containing moiety NR^{50};

R^3 is hydrogen or halogen;

R^a is hydrogen or alkyl;

for each occurrence, R^b is independently selected from the group consisting of: hydrogen, halogen, CN, CF_3, $CONR^{30}R^{31}$, alkyl, –O–alkyl, –C(O)O–alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

for each occurrence R^{30}, R^{31}, R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl, wherein alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, fluoroalkyl, heterocycloalkylalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and aminoalkyl can be optionally substituted;

R^{50} is, for each occurrence, R^{20}, $S(O)_tNR^{20}R^{21}$, $S(O)_tR^{20}$, $C(O)OR^{20}$, $C(O)R^{20}C(=NR^a)NR^{20}R^{21}$, $C(=NR^{20})NR^{21}R^a$, $C(=NOR^{20})R^{21}$ or $C(O)NR^{20}R^{21}$;

Y is each independently CH or N; and

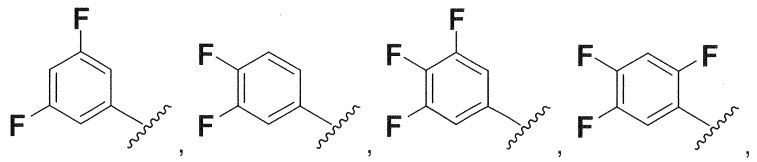
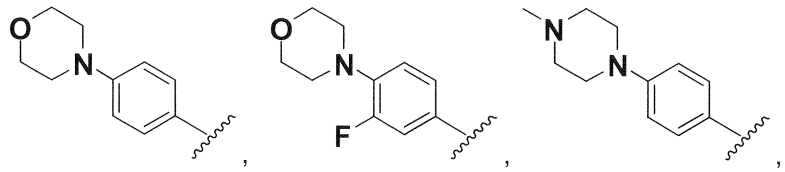
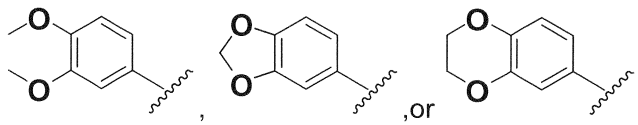
t is 1 or 2.

9. A compound of claim 1 having the formula (I):

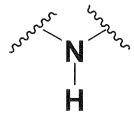
$$A–L_1–B \qquad (I)$$

and all stereoisomers, racemic mixtures, pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof;

wherein A is:

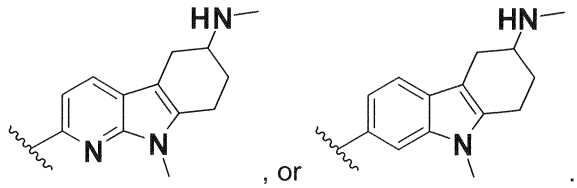



,or

L_1 is:



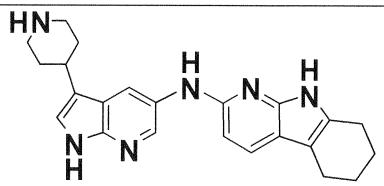
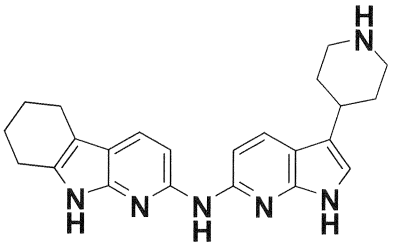
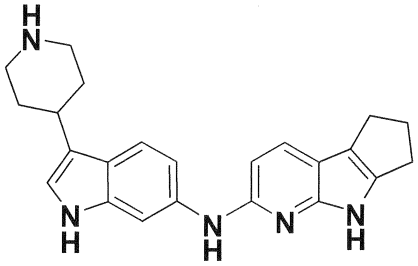
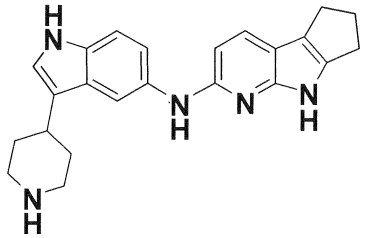
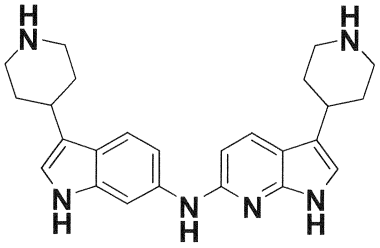
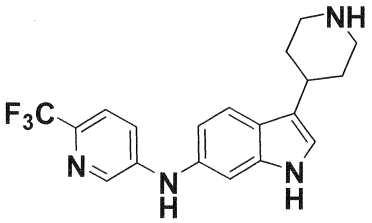
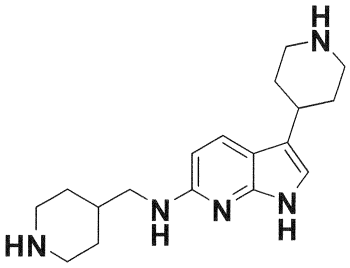
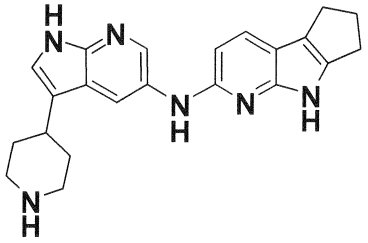
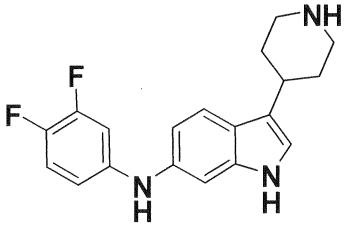
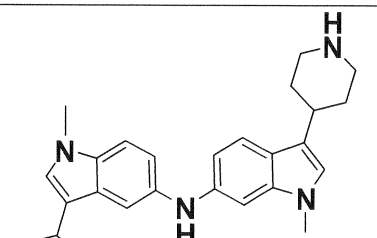
and

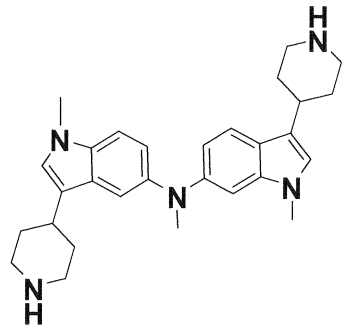
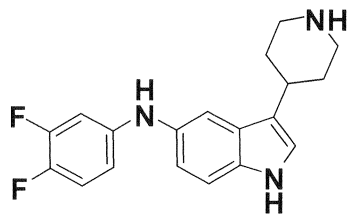
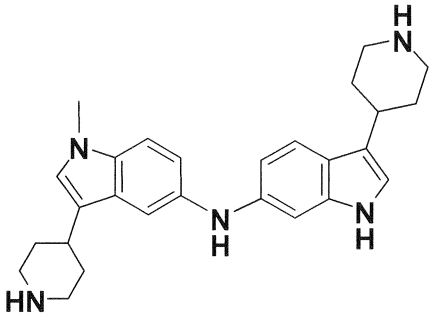
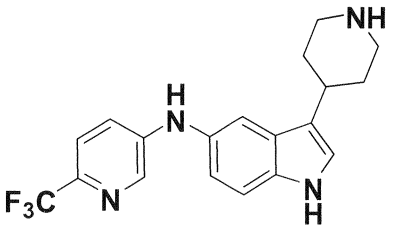
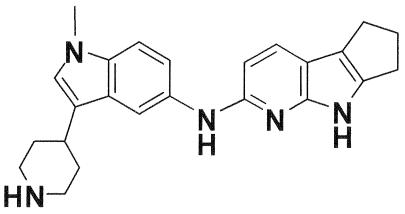
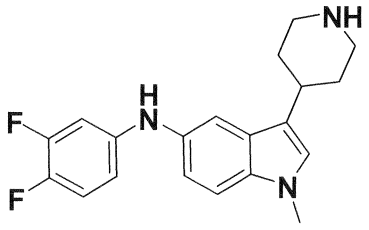
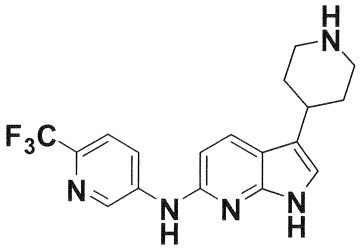
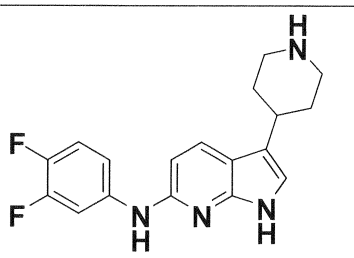
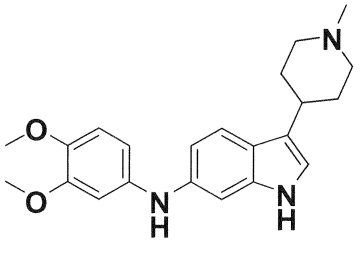
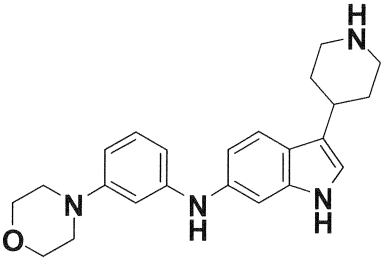
B is:

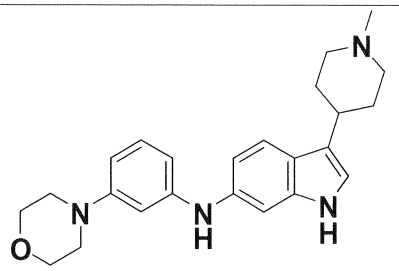
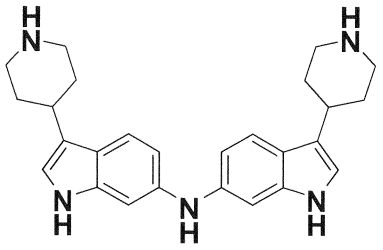
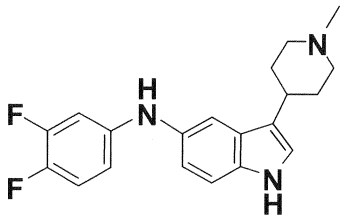
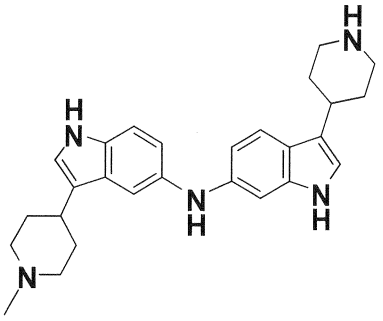
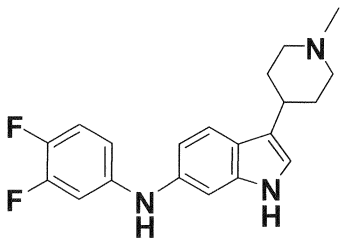
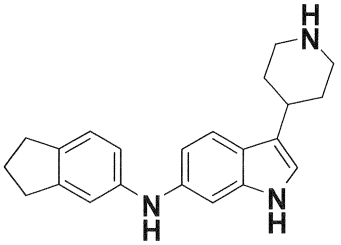
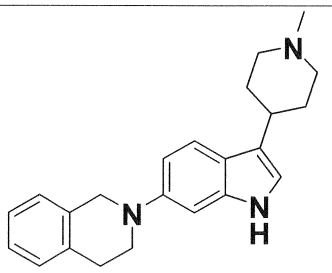
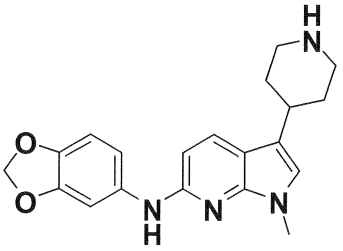
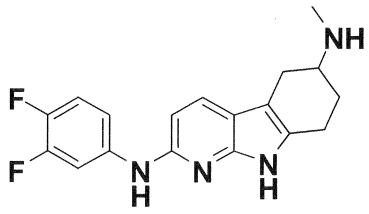
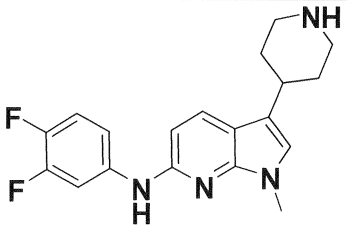

, or

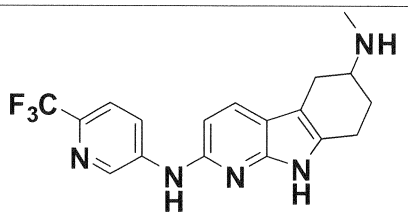
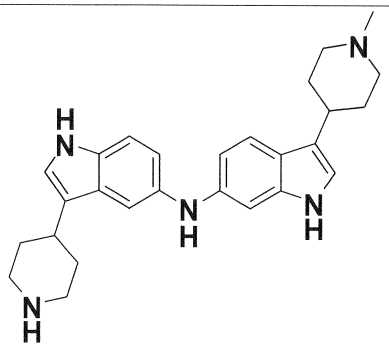
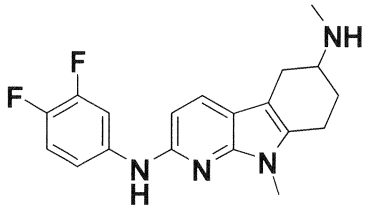
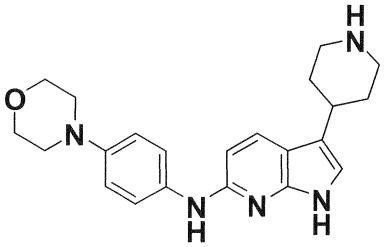
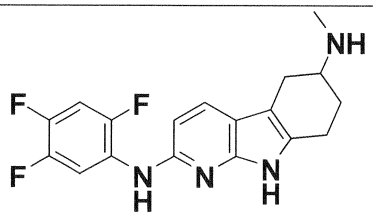
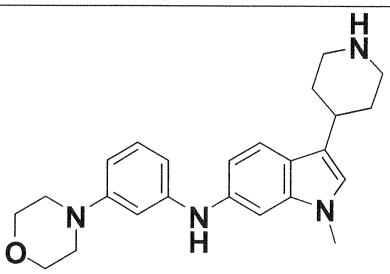
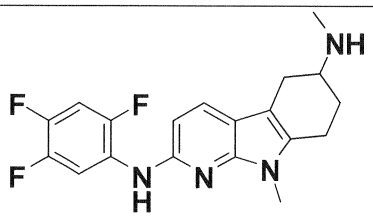
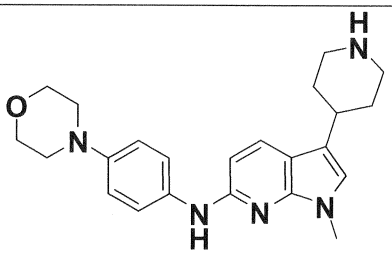
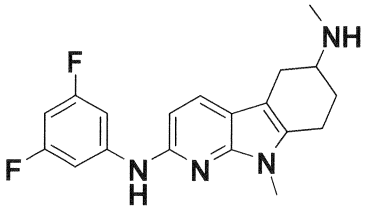
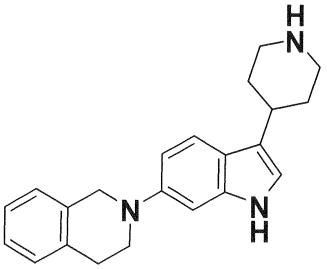
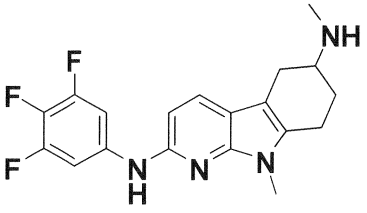
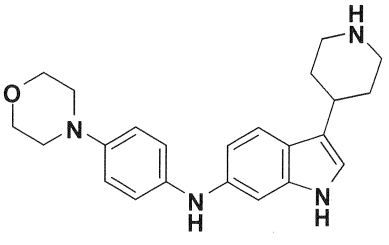
.

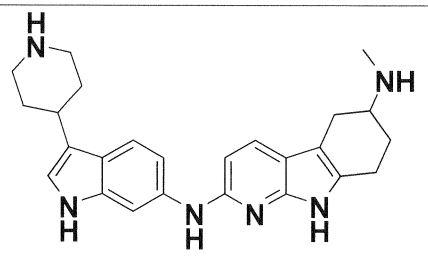
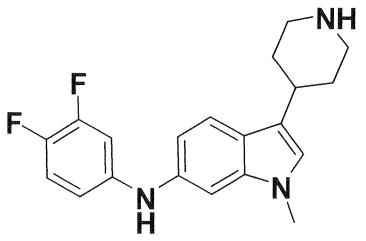
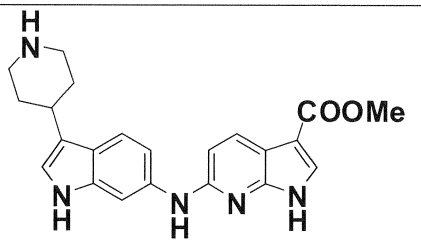
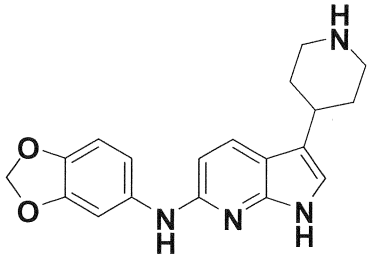
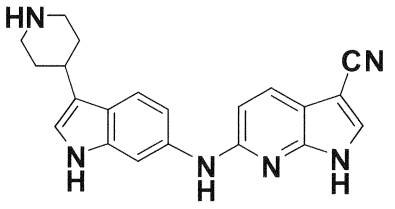
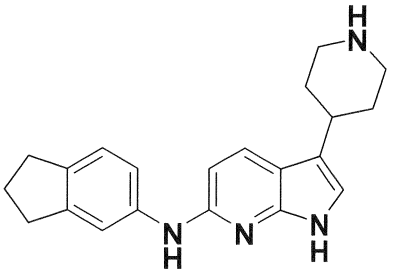
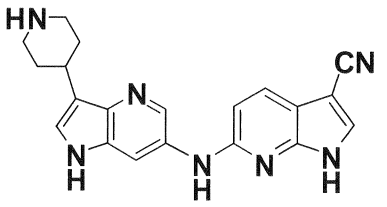
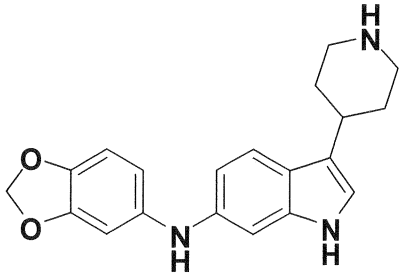
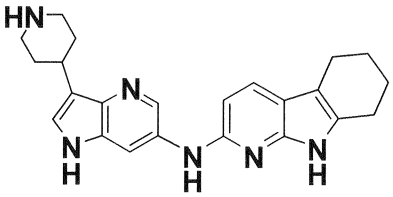
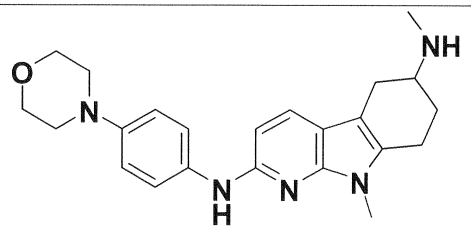
10. The compound of any of the preceding claims, wherein the compound is selected from the group consisting of

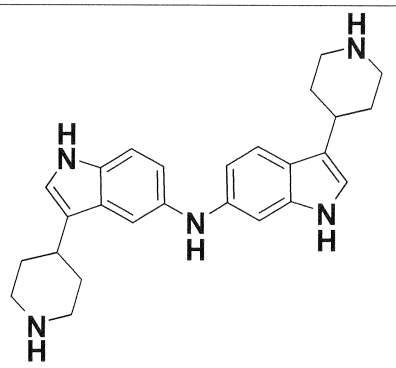
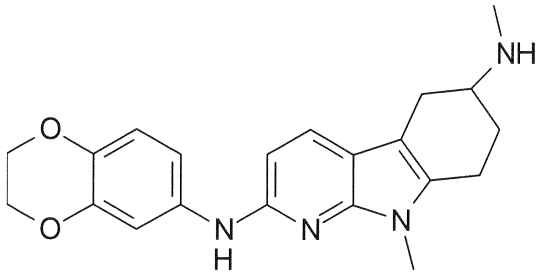
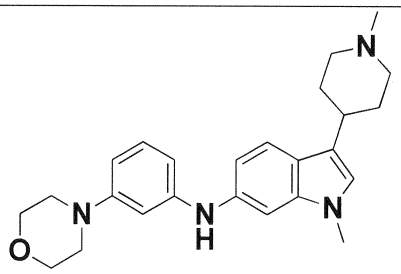
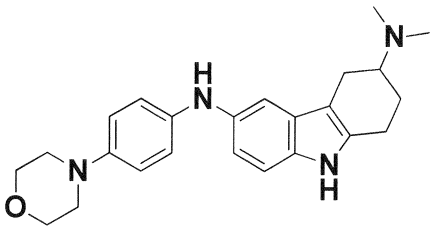
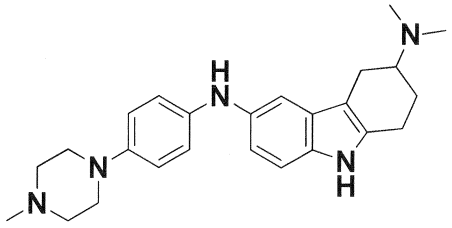
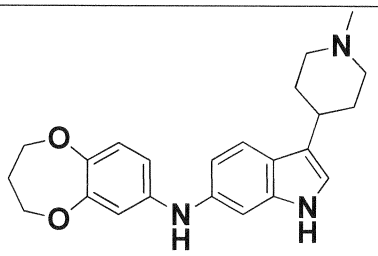
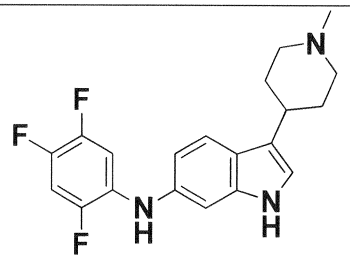
	
	
	
	
	

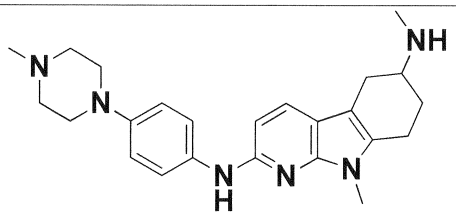
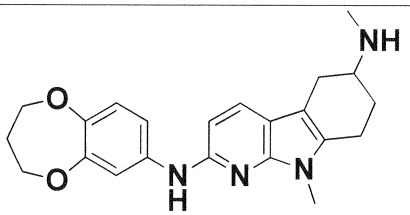
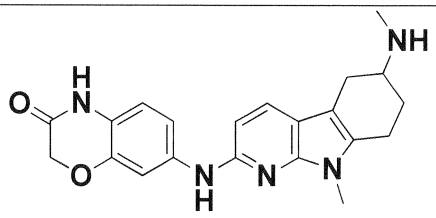
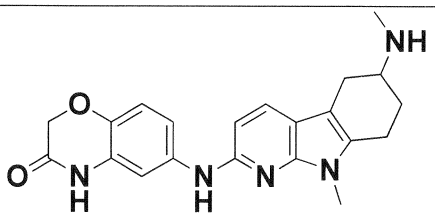
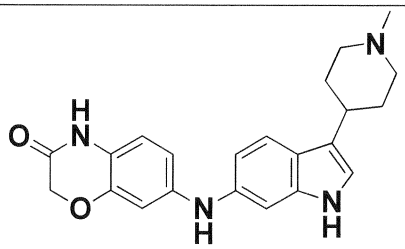
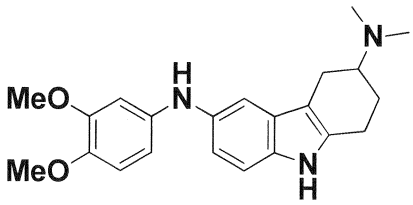
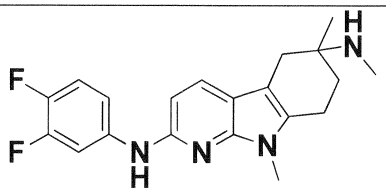
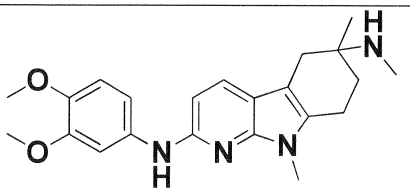
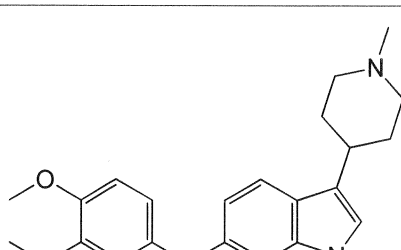
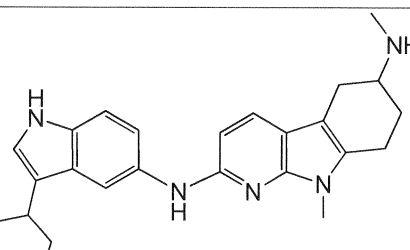
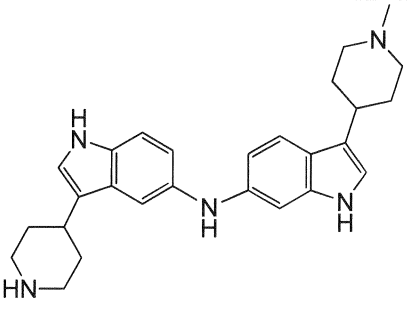
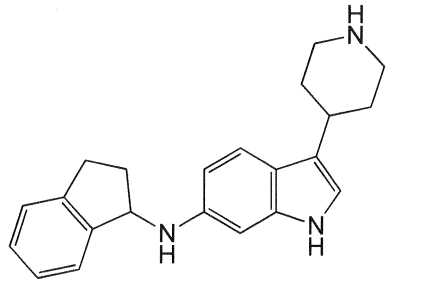
	
	
	
	
	

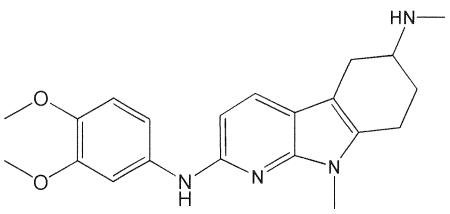
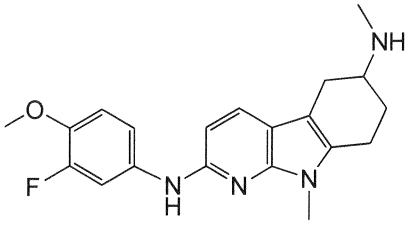
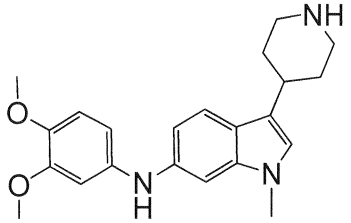
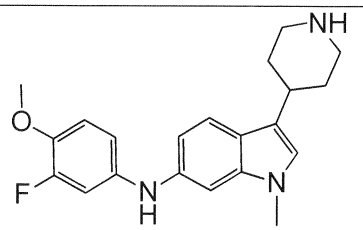
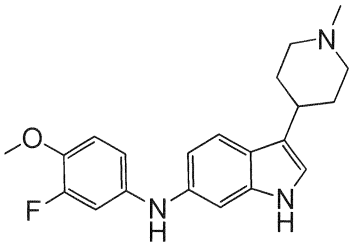
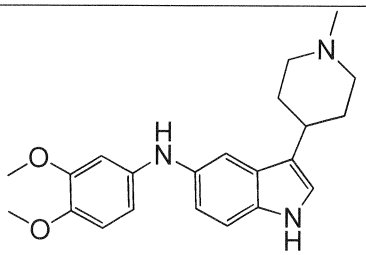
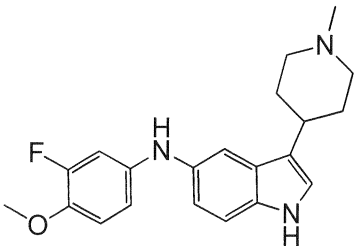
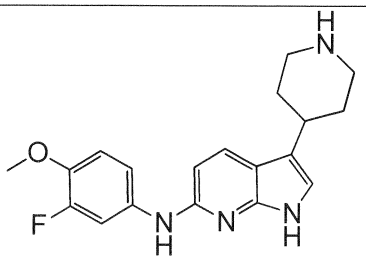
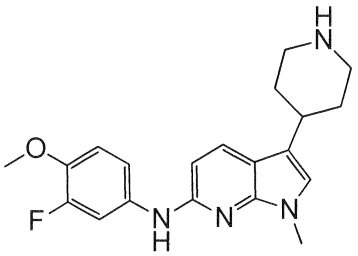
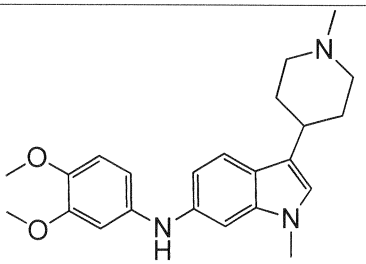
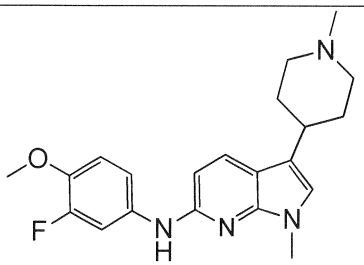
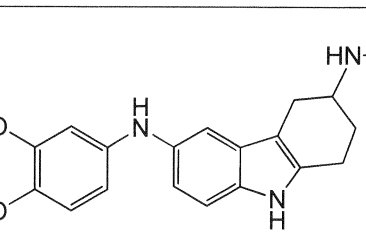
	
	
	
	
	

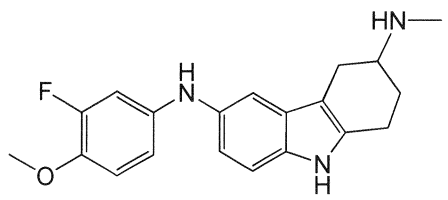
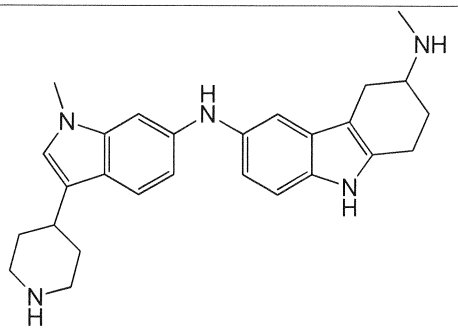
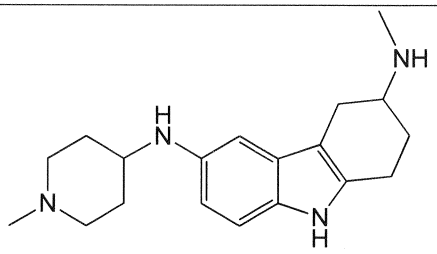
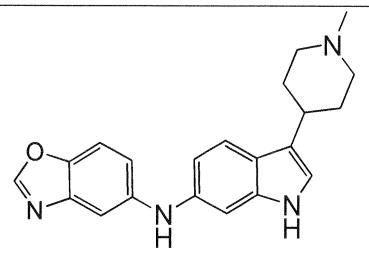
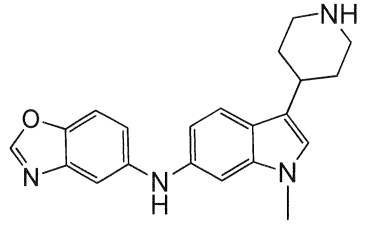
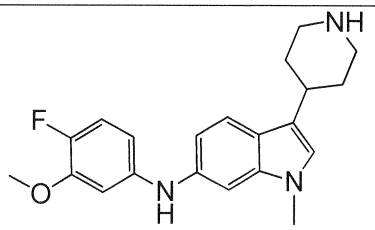
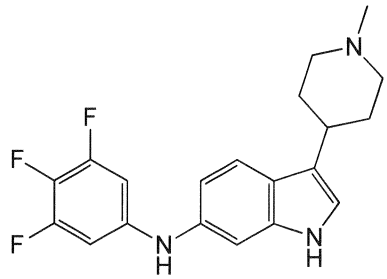
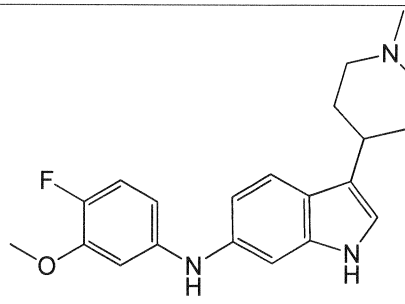
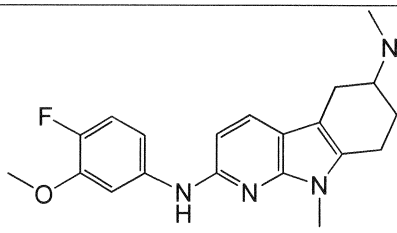
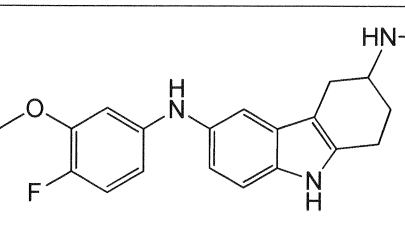
	
	
	
	
	
	

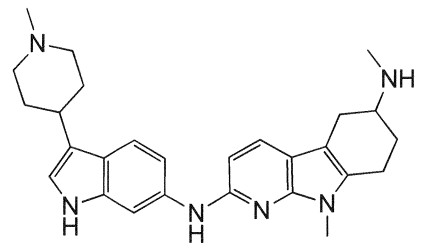
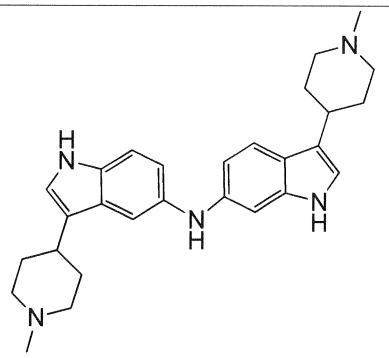
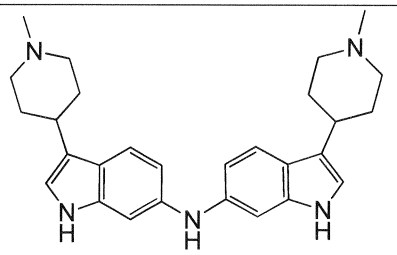
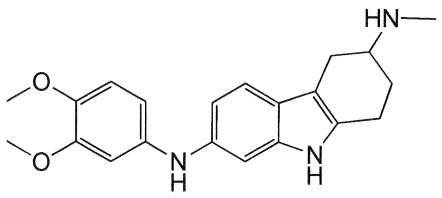
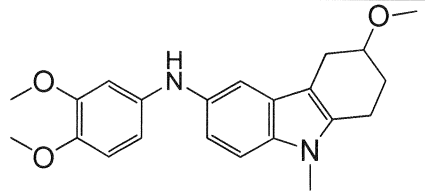
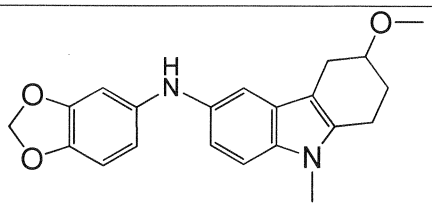
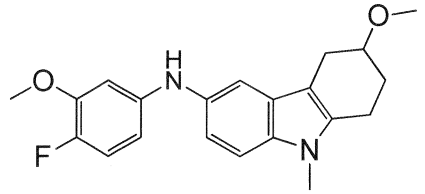
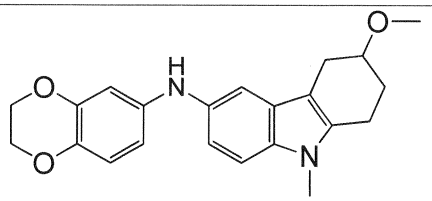
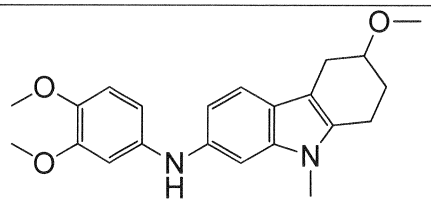
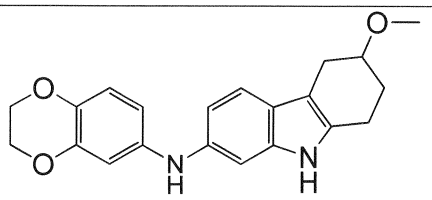
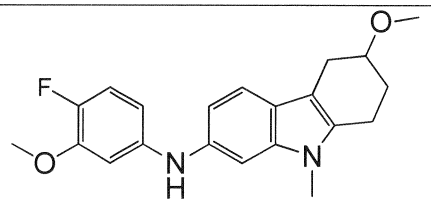
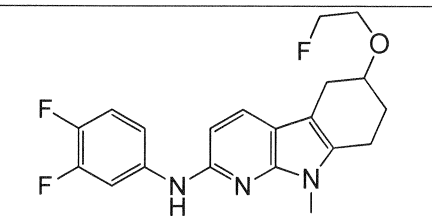
	
	
	
	
	

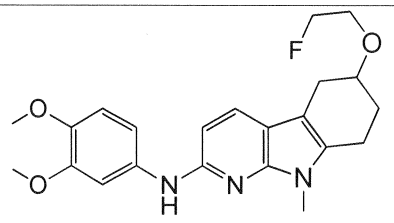
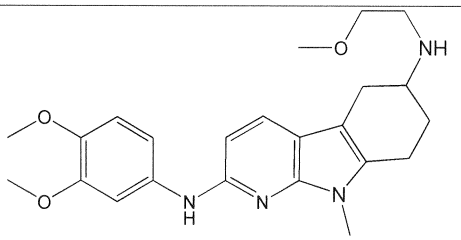
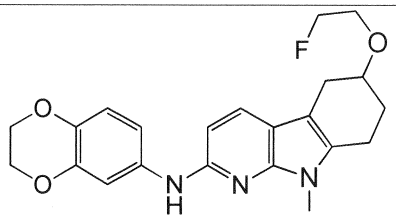
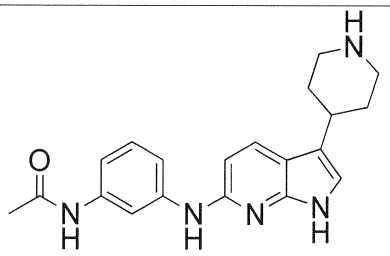
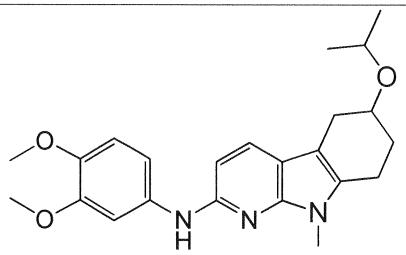
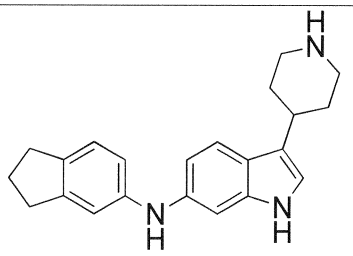
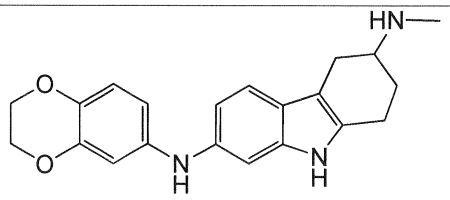
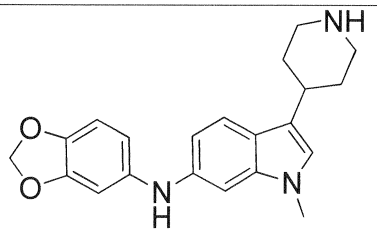
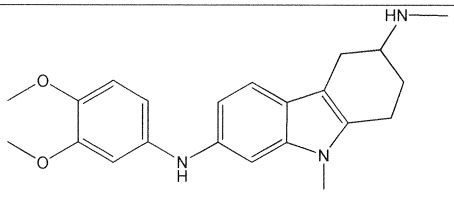
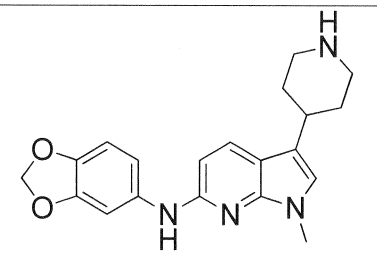
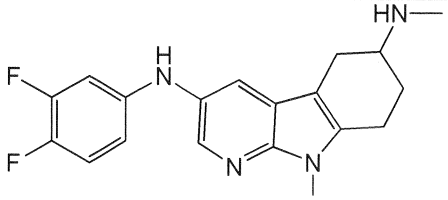
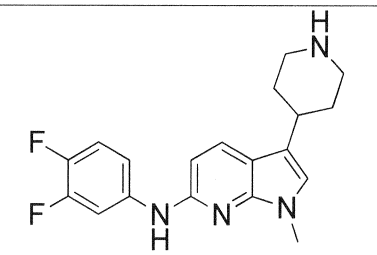
	
	
	
	

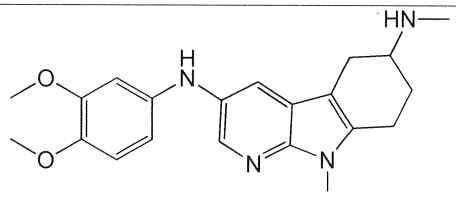
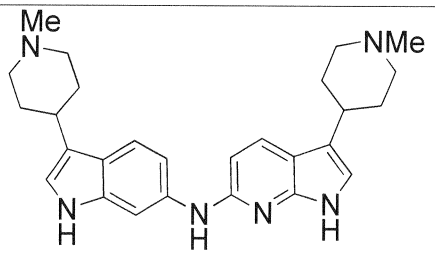
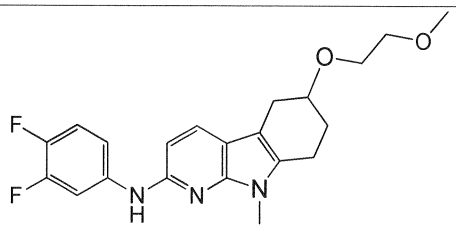
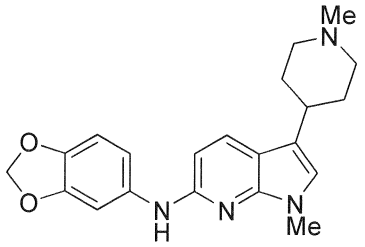
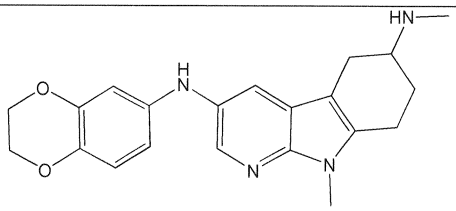
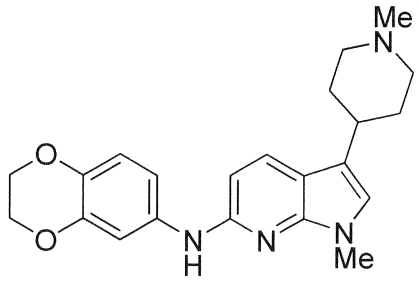
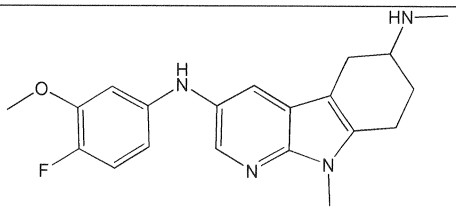
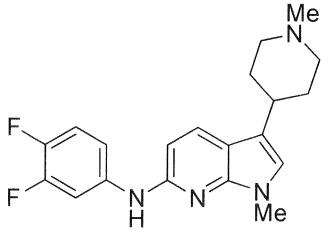
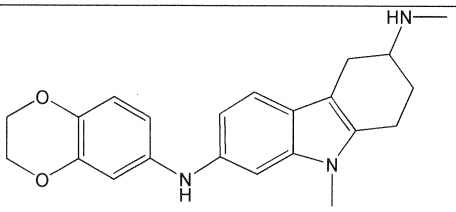
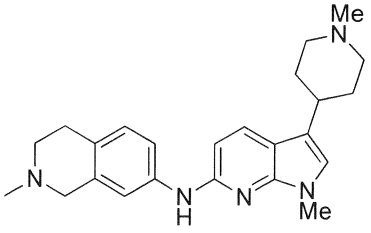
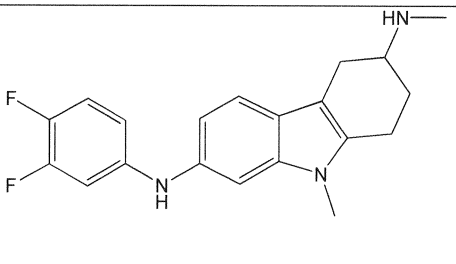
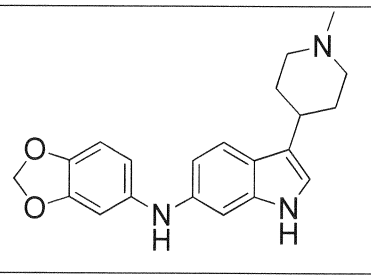
	
	
	
	
	
	
	

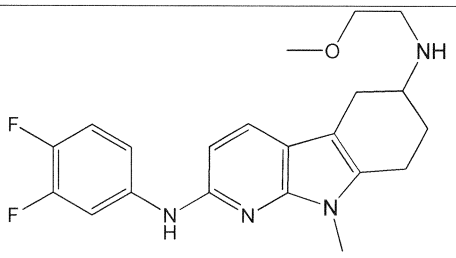
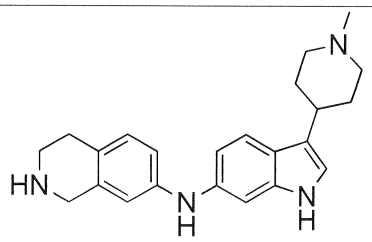
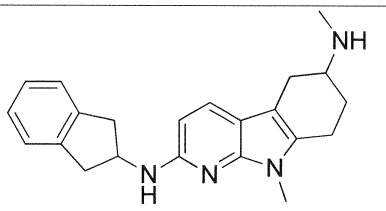
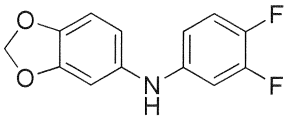
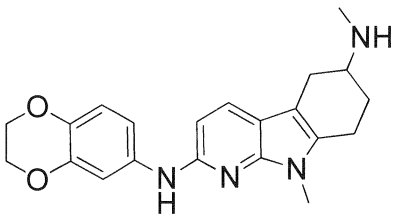
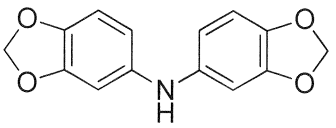
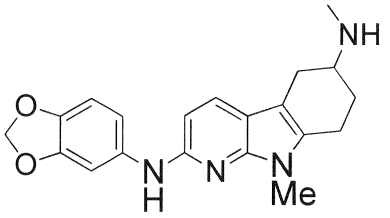
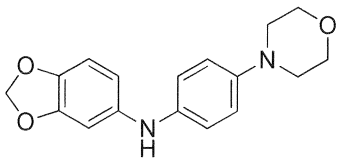
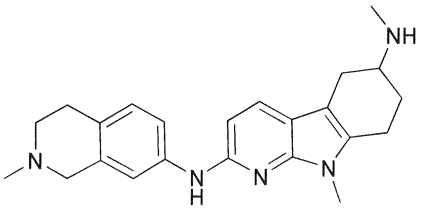
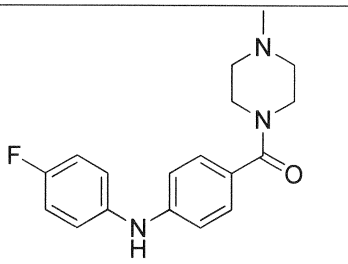
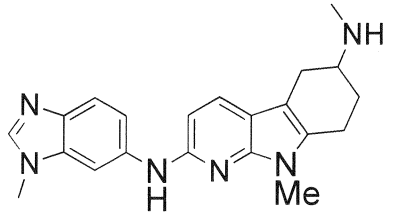
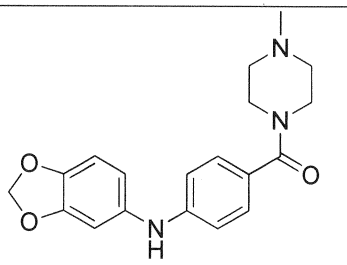
	
	
	
	
	
	

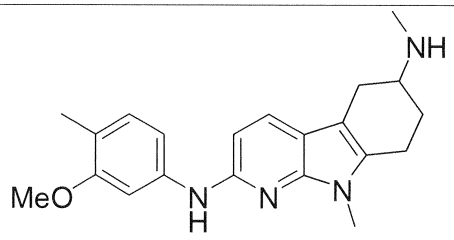
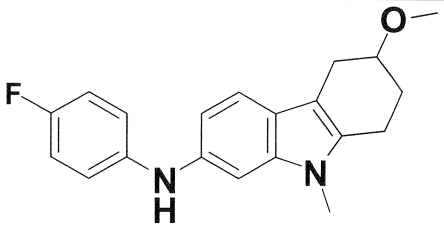
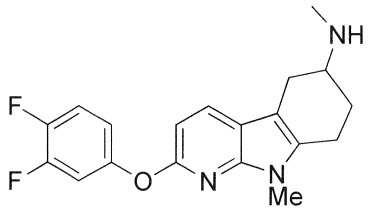
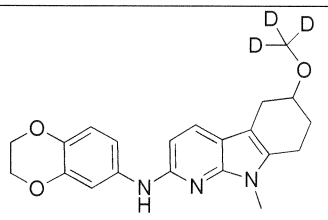
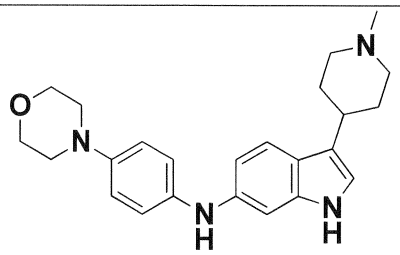
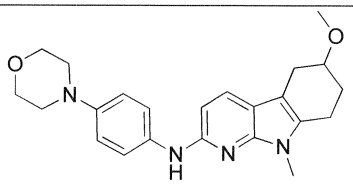
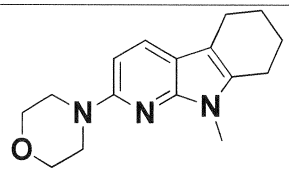
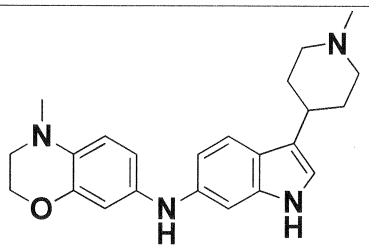
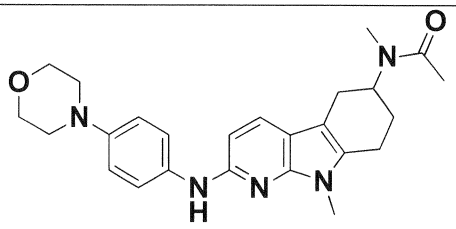
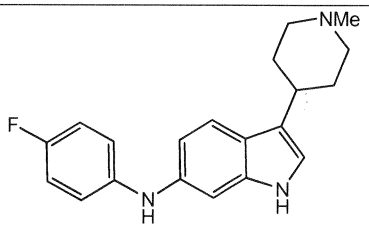
	
	
	
	
	

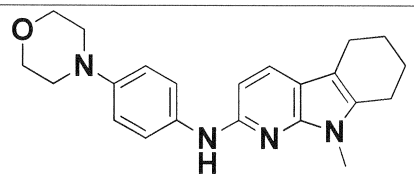
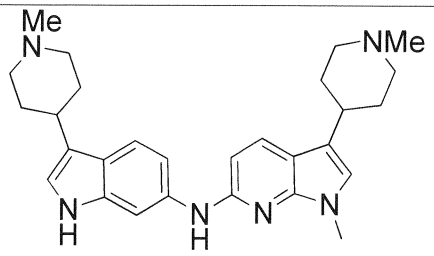
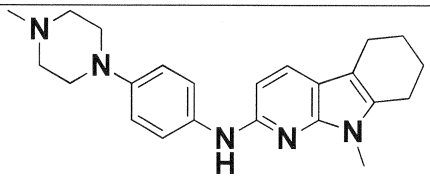
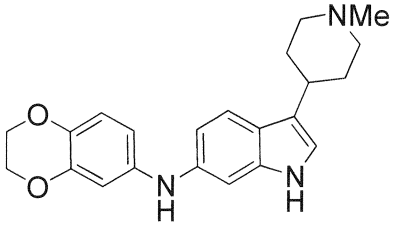
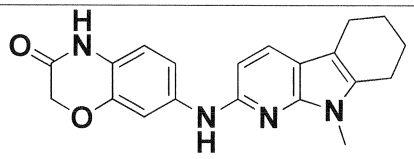
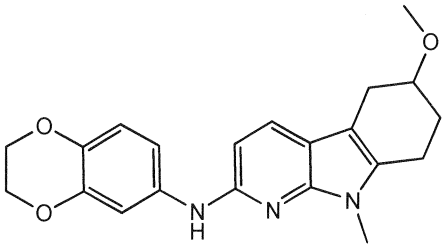
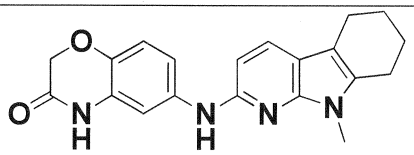
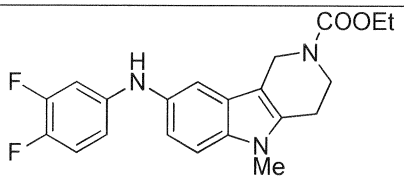
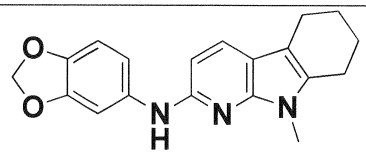
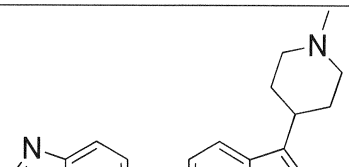
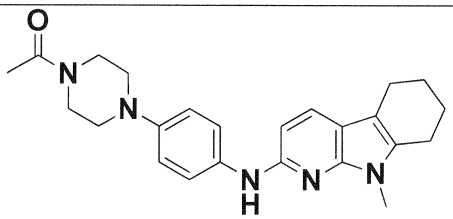
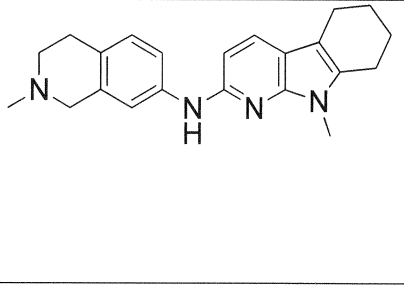
	
	
	
	
	
	

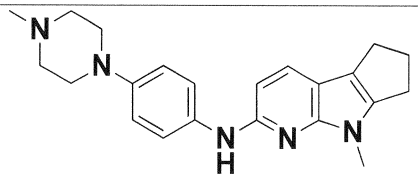
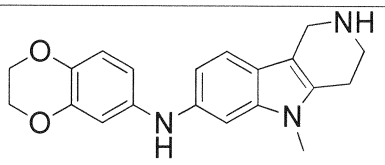
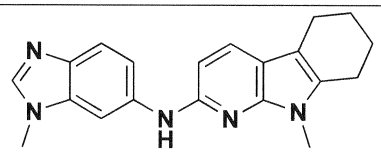
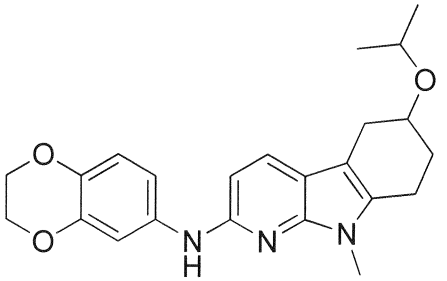
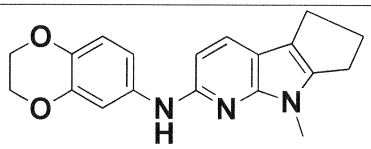
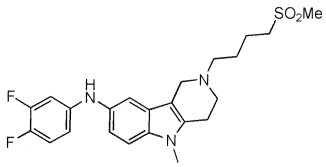
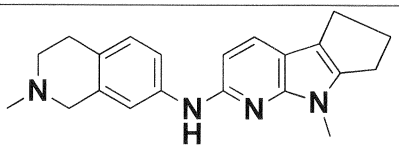
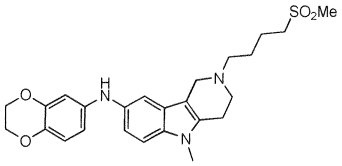
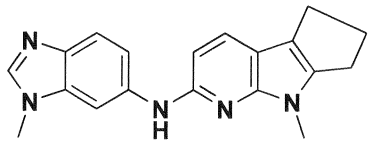
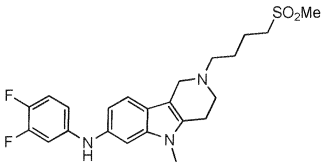
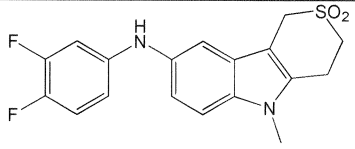
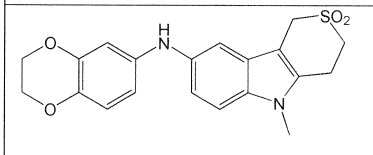
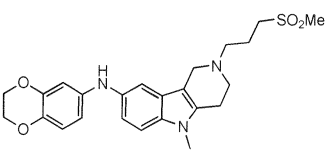
	
	
	
	
	
	

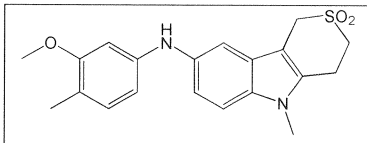
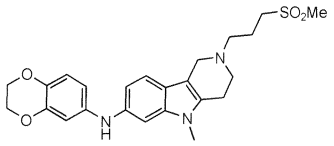
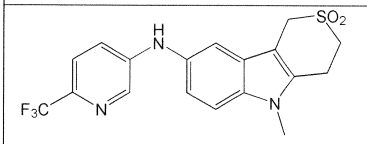
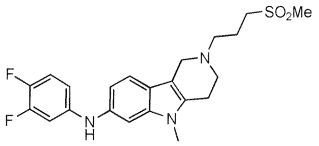
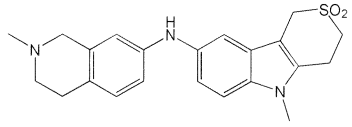
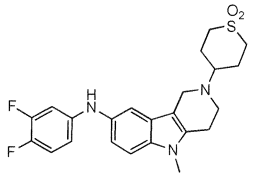
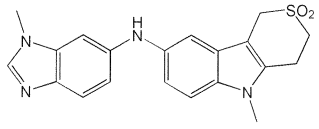
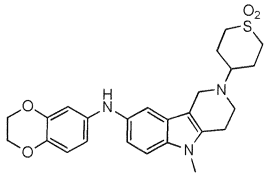
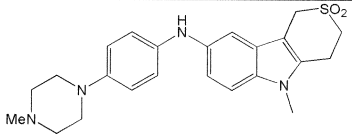
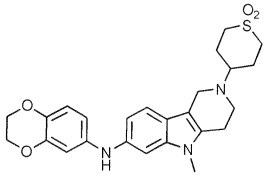
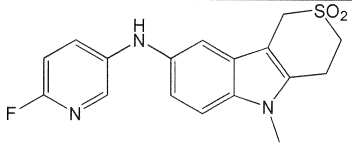
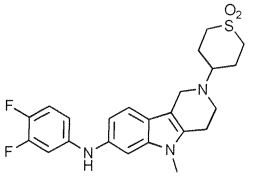
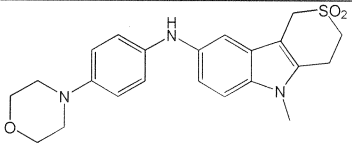
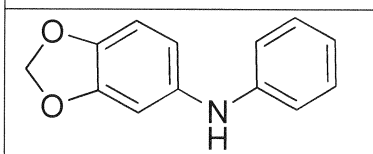
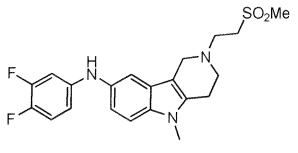
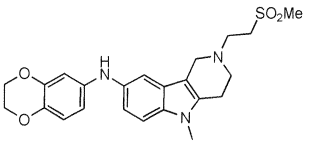
	
	
	
	
	
	

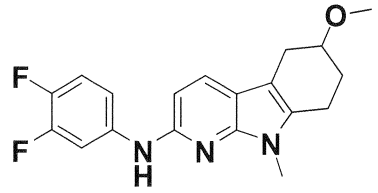
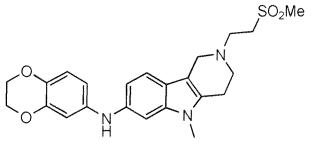
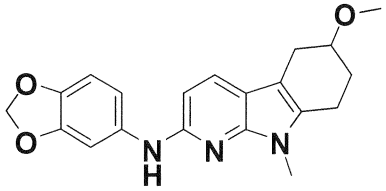
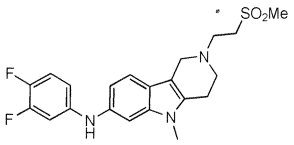
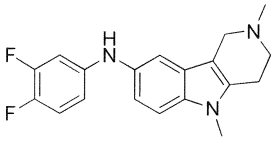
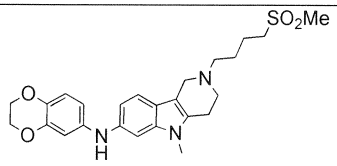
	
	
	
	
	
	

11. A compound as defined in any one of claims 1 to 10 comprising a radionuclide wherein the compounds disclaimed in claim 1 are disclaimed.

12. A radiopharmaceutical formulation comprising a compound as defined in any one of claims 1 to 10 comprising a radionuclide wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed.

13. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier or excipient.

14. Use of the compound as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, for the preparation of a medicament for treating or preventing a disease or condition associated with an amyloid and/or amyloid-like protein, wherein the disease is a neurological disorder selected from the group consisting of

Alzheimer's disease (AD), Lewy body dementia (LBD), Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type), the Guam Parkinson-Dementia complex or mild cognitive impairment (MCI) or wherein the disease is progressive supranuclear palsy, multiple sclerosis, inclusion-body myositis (IBM), Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, amyotropic lateral sclerosis (ALS), inclusion-body myositis (IBM), adult onset diabetes, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

15. The use of claim 14, wherein the neurological disorder is Alzheimer's disease.

16. The compound, as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, for use in the treatment or prevention of a disease or condition associated with an amyloid and/or amyloid-like protein.

17. The compound of claim 16, wherein the disease is a neurological disorder selected from the group consisting of Alzheimer's disease (AD), Lewy body dementia (LBD), Down's syndrome, hereditary cerebral hemorrhage with amyloidosis (Dutch type), the Guam Parkinson-Dementia complex or mild cognitive impairment (MCI) or wherein the disease is progressive supranuclear palsy, multiple sclerosis, inclusion-body myositis (IBM), Creutzfeld Jacob disease, Parkinson's disease, HIV-related dementia, amyotropic lateral sclerosis (ALS), inclusion-body myositis (IBM), adult onset diabetis, senile cardiac amyloidosis, endocrine tumors, glaucoma, ocular amyloidosis, primary retinal degeneration, macular degeneration (such as age-related macular degeneration (AMD)), optic nerve drusen, optic neuropathy, optic neuritis, or lattice dystrophy.

18. The compound of claim 17, wherein the neurological disorder is Alzheimer's disease.

19. A mixture comprising a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed and optionally at least one further biologically active compound and/or a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

20. The mixture according to claim 19, wherein the further biologically active compound is a compound for treating of amyloidosis.

21. The mixture according to claim 19 or 20, wherein the further biologically active compound is selected from the group consisting of antibodies, vaccines, compounds against oxidative stress, anti-apoptotic compounds, metal chelators, inhibitors of DNA repair such as pirenzepin and metabolites, 3-amino-1-propanesulfonic acid (3APS), 1,3-propanedisulfonate (1,3PDS), α-secretase activators, β- and γ-secretase inhibitors, tau proteins, neurotransmitters, β-sheet breakers, attractants for amyloid beta clearing / depleting cellular components, inhibitors of N-terminal truncated amyloid beta including pyroglutamated amyloid beta 3-42, anti-inflammatory molecules, or cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine, M1 agonists and other drugs including any amyloid or tau modifying drug and nutritive supplements.

22. The mixture according to claim 21, wherein the further biologically active compound is a cholinesterase inhibitor (ChEI).

23. An *in vitro* method of collecting data for the diagnosis of an amyloid-associated disease or condition in a sample comprising:
    (a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed;
    (b) allowing the compound to bind to the amyloid protein;
    (c) detecting the compound bound to the protein; and
    (d) optionally correlating the presence or absence of compound binding with the amyloid protein with the presence or absence of amyloid protein in the sample.

24. An *in vitro* method of determining the extent of amyloidogenic plaque burden in a tissue and/or a body fluid comprising:
    (a) providing a sample representative of the tissue and/or body fluid under investigation;
    (b) testing the sample for the presence of amyloid protein with a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed;
    (c) determining the amount of compound bound to the amyloid protein; and

(d) calculating the plaque burden in the tissue and/or body fluid.

25. The method according to claim 24, wherein the determination in step (c) is conducted such that presence or absence of the compound binding with the amyloid protein correlates with presence or absence of amyloid protein.

26. An *in vitro* method of collecting data for determining a predisposition to an amyloid-associated disease or condition in a patient comprising detecting the specific binding of a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed to an amyloid protein in a sample which comprises the steps of:

(a) bringing the sample suspected to contain the amyloid protein into contact with the compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample or; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

27. An *in vitro* method of collecting data for monitoring minimal residual disease in a patient following treatment with an antibody or a vaccine composition, wherein the method comprises:

(a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, which compound specifically binds to the amyloid protein;

(b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;

(c) detecting the formation of the compound/protein complex;

(d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample; and

(e) optionally comparing the amount of the compound/protein complex to a normal control value.

28. An *in vitro* method of collecting data for predicting responsiveness of a patient being treated with an antibody or a vaccine composition comprising:
    (a) bringing a sample suspected to contain an amyloid protein into contact with a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, which compound specifically binds to the amyloid protein;
    (b) allowing the compound to bind to the amyloid protein to form a compound/protein complex;
    (c) detecting the formation of the compound/protein complex;
    (d) optionally correlating the presence or absence of the compound/protein complex with the presence or absence of amyloid protein in the sample; and
    (e) optionally comparing the amount of the compound/protein complex to a normal control value.

29. A test kit for *in vitro* detection and/or diagnosis of an amyloid-associated disease or condition comprising a compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed.

30. Use of the compound as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, for the preparation of a medicament for treating or preventing an ocular disease or condition associated with a pathological abnormality/change in the tissue of the visual system, particularly associated with an amyloid-beta-related pathological abnormality/change in the tissue of the visual system, wherein the ocular disease or condition is selected from the group consisting of neuronal degradation, cortical visual deficits, glaucoma, cataract due to beta-amyloid deposition, ocular amyloidosis, primary retinal degeneration, macular degeneration, for example age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

31. A compound as defined in any one of claims 1 to 10 wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed for use in the treatment or prevention of an ocular disease or condition associated with a pathological abnormality/change in the

tissue of the visual system, particularly associated with an amyloid-beta-related pathological abnormality/change in the tissue of the visual system.

32. The compound of claim 31, wherein the ocular disease or condition is selected from the group consisting of neuronal degradation, cortical visual deficits, glaucoma, cataract due to beta-amyloid deposition, ocular amyloidosis, primary retinal degeneration, macular degeneration, for example age-related macular degeneration, optic nerve drusen, optic neuropathy, optic neuritis, and lattice dystrophy.

33. A compound as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, for use in inhibiting protein aggregation, in particular for use in inhibiting Aβ1-42 aggregation, Tau aggregation or alpha-synuclein aggregation.

34. A compound as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, for use in (a) the reduction of the β-amyloid plaque load, and/or (b) the inhibition of the formation of β-amyloid plaques and/or (c) the retardation of the increase of amyloid load in the brain of a patient.

35. The compound of claim 34, wherein reducing the β-amyloid plaque load, inhibiting the formation of β-amyloid plaques and/or retarding the increase of amyloid load lead to a reduction and/or amelioration of the effects of a disease or condition caused by or associated with the formation and deposition of β-amyloid plaques in the brain.

36. A compound as defined in any one of claims 1 to 10, wherein the compounds disclaimed in claim 1 are disclaimed or are not disclaimed, for use in the retention or increase of cognitive memory capacity in a subject suffering from memory impairment.

37. The compound of claim 16, wherein the amyloid-associated condition is characterized by a loss of cognitive memory capacity and the treatment of the amyloid-associated condition leads to an increase in the retention of cognitive memory capacity or a complete restoration of cognitive memory capacity.