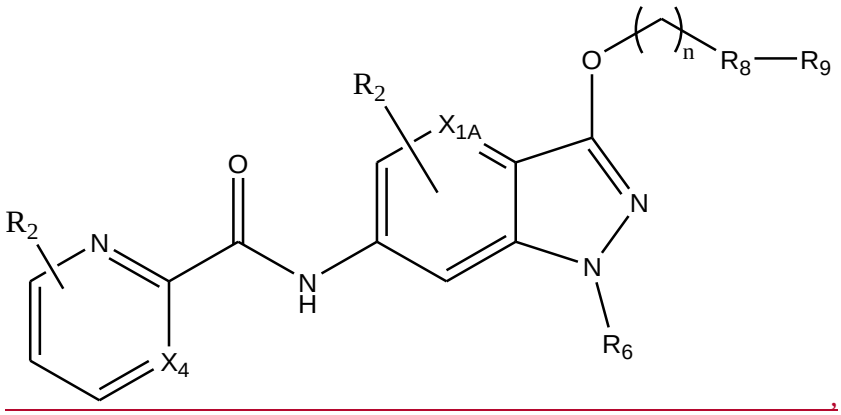
2016; Jones et al. *JPET* 2012). Thus, mGluR4 PAMs may be useful as adjunct therapy in schizophrenia to reduce and/or eliminate catalepsy and potentially delay the onset and/or prevent TD.

[008] Despite advances in mGluR4 research, there is still a scarcity of compounds that effectively potentiate mGluR4 which are also effective in the treatment of neurological and psychiatric disorders associated with glutamatergic neurotransmission dysfunction and diseases, as well as inflammatory central nervous system disorders, medulloblastomas, metabolic disorders and taste enhancing associated with glutamatergic dysfunction and diseases in which mGluR4 receptor is involved. Further, conventional mGluR4 receptor modulators typically lack satisfactory aqueous solubility and exhibit poor oral bioavailability. These needs and other needs are satisfied by the present invention.

SUMMARY

[009] In accordance with the purpose(s) of the ~~invention~~disclosure, as embodied and broadly described herein, the ~~invention~~disclosure, in one ~~aspect~~example, relates to compounds useful as allosteric modulators of mGluR4 receptor activity, methods of making same, pharmaceutical compositions comprising same, and methods of treating neurological and psychiatric disorders associated with glutamate dysfunction, for example Parkinson's disease, using same. Further disclosed are methods and pharmaceutical compositions useful for treating a disease related to mGluR4 activity. In one ~~aspect~~example, the disclosed compounds can affect the sensitivity of mGluR4 receptors to agonists without binding to the orthosteric agonist binding site or acting as orthosteric agonists themselves. A "receptor allosteric agonist-PAM", as used herein, is generally defined as a ligand that functions as both an allosteric modulator and as an agonist on its own (though the latter is usually only at higher concentrations). The presence of allosteric agonist-PAM (Ago-PAM) activity may offer advantages in various CNS and neurological disorders where the basal glutamatergic tone is low in given brain regions.

[009a] In one aspect, there is provided a compound of the following formula:



,

wherein:

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, CH_3 or CD_3;

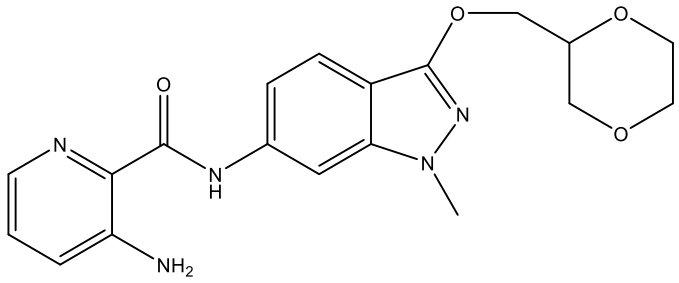
R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;

n is 0-6;

or a pharmaceutically acceptable salt thereof.

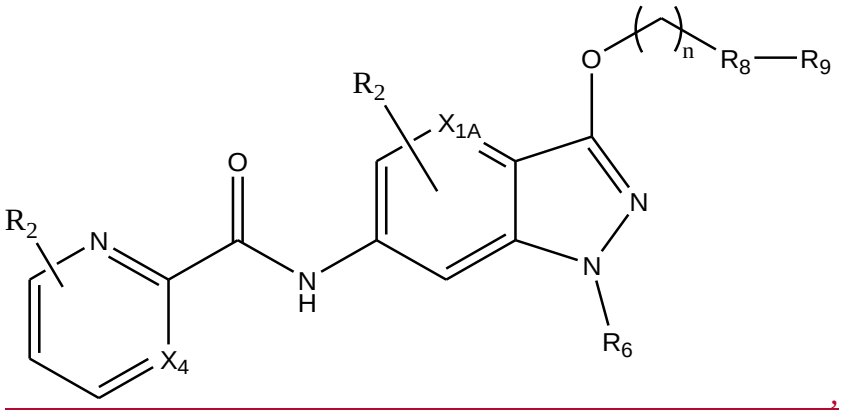
[009b] In another aspect, there is provided a compound as described above, of the following formula:



;

or a pharmaceutically acceptable salt thereof.

[009c] In another aspect, there is provided a use of at least one compound having a structure represented by a compound of the following formula:



wherein:

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, CH_3 or CD_3;

R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

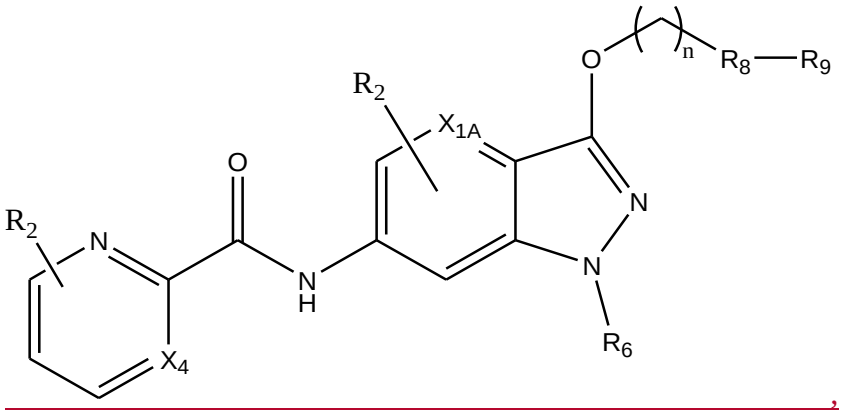
R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;

n is 0-6;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for the treatment of Parkinson's disease, wherein the at least one compound is to be administered to the mammal in a dosage and amount effective to treat Parkinson's disease in the mammal.

[009d] In another aspect, there is provided a pharmaceutical composition comprising a compound having a structure represented by a compound of the following formula:



,

wherein:

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, CH_3 or CD_3;

R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;

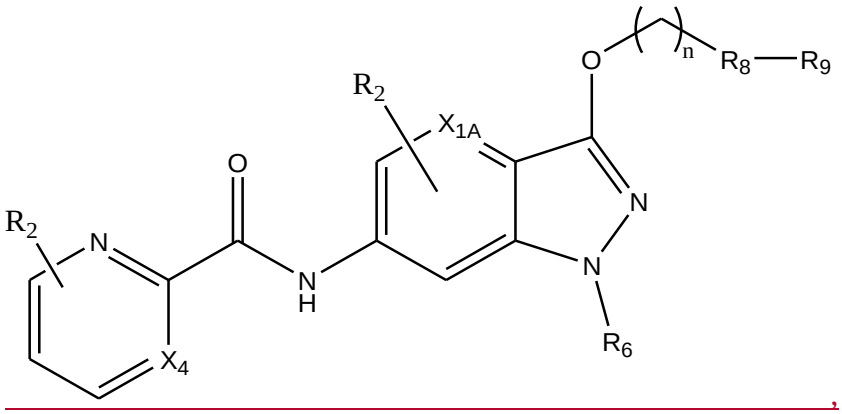
n is 0-6;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[009e] In another aspect, there is provided a pharmaceutical composition comprising a compound as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[009f] In another aspect, there is provided a pharmaceutical composition comprising a compound as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[009g] In another aspect, there is provided a use of a compound having a structure represented by a compound of the following formula:



,

wherein:

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, CH_3 or CD_3;

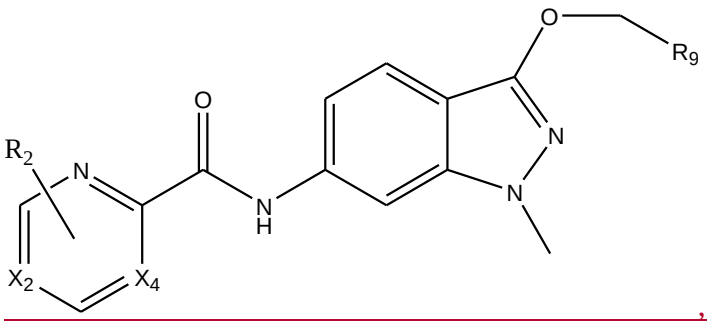
R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;

n is 0-6;

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of Parkinson's disease; wherein the compound is to be co-administered with a drug having a known side-effect of treating Parkinson's disease; and wherein the compound is to be co-administered in a dosage and amount effective to treat Parkinson's disease in the mammal.

[009h] In another aspect, there is provided a compound of the following formula:



, wherein

X_2 is CH;

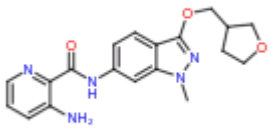
X_4 is CR_1;

R_1 is NH_2;

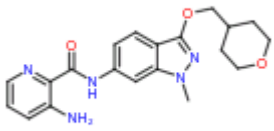
R_2 is optionally present, and chosen from fluorine;

R_9 is heterocycloalkyl, oxygen-containing heterocycle.

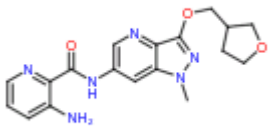
[009i] In another aspect, there is provided a compound as described above, of the following formula:



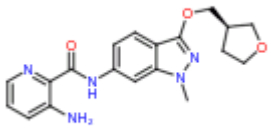
,

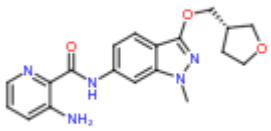


,

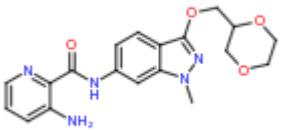


,

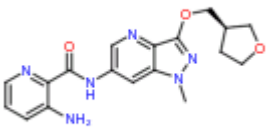




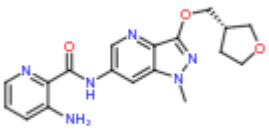
,



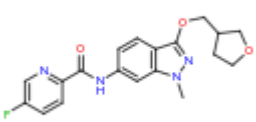
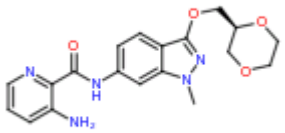
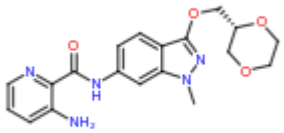
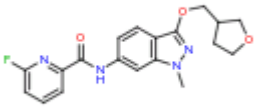
,



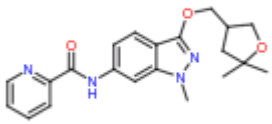
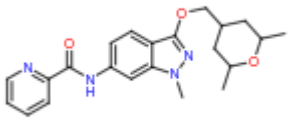
,



,

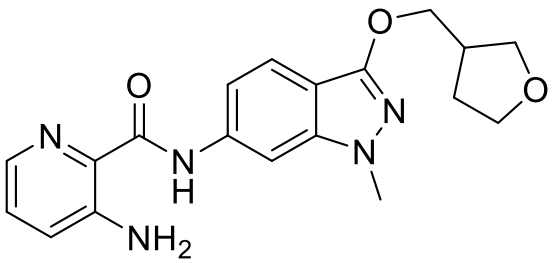





, , , ,

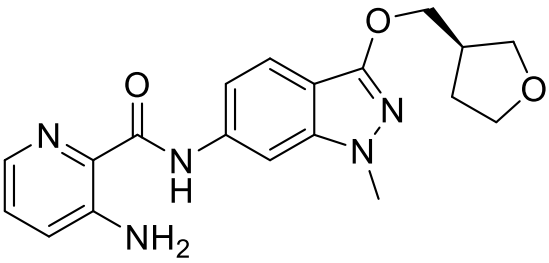
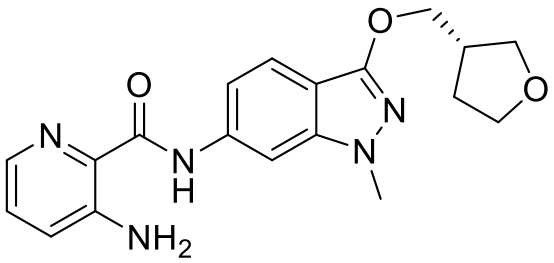



, or ; or a pharmaceutically acceptable salt thereof.

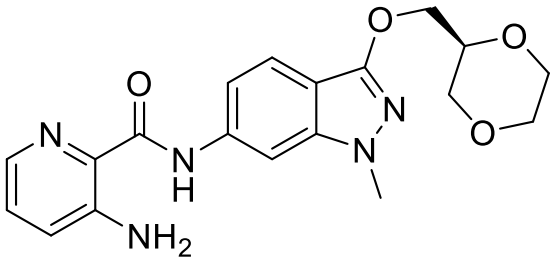
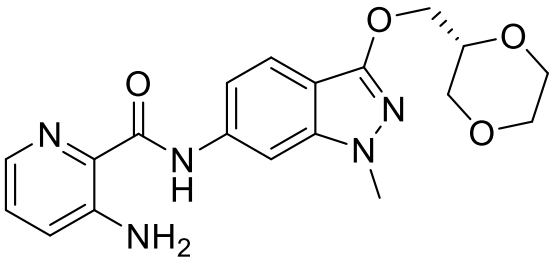
[009j] In another aspect, there is provided a compound as described above, of the following formula:



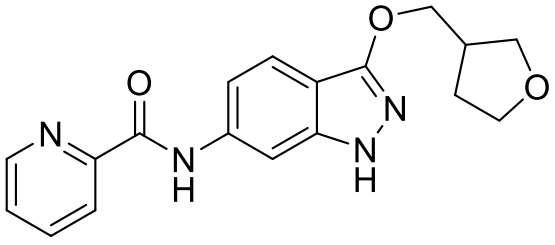
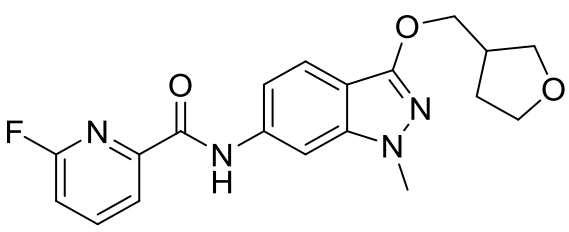
,

, , , , ,

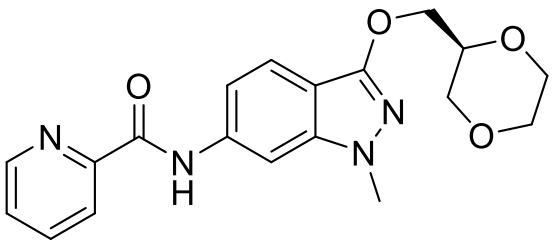
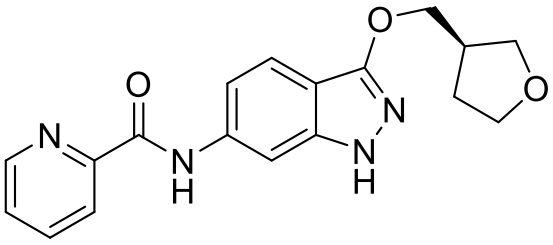



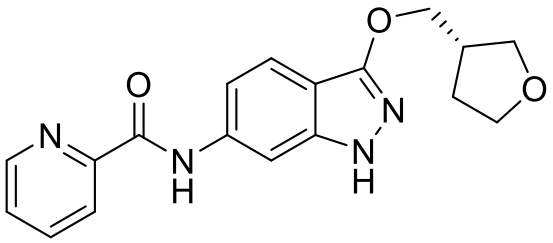
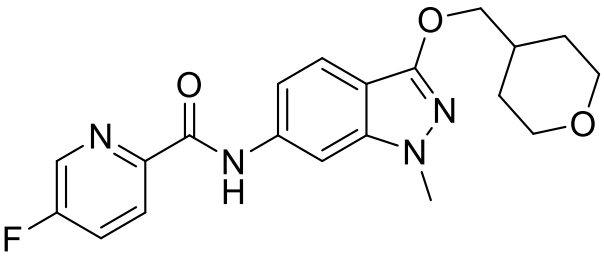
, ,

, ,

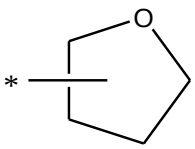
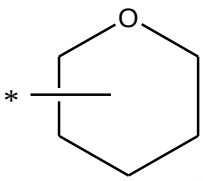
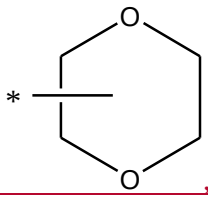
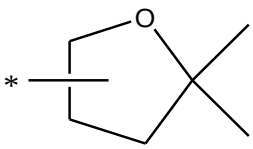
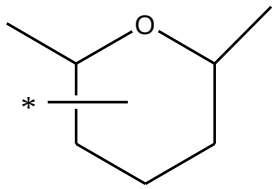
3f

 ,  ,

 ,  ;

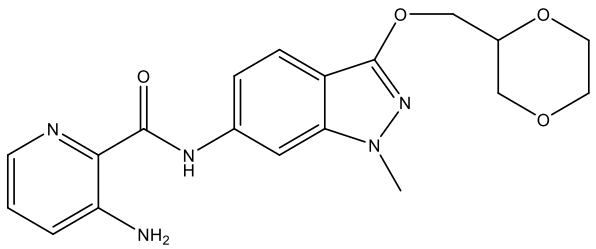
or a pharmaceutically acceptable salt thereof.

[009k] In another aspect, there is provided a compound as described above, wherein R_9 is:

 ,  ,  ,  , or  ;

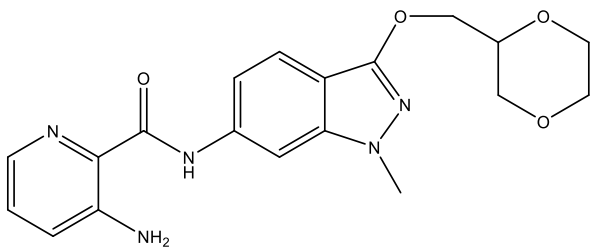
or a pharmaceutically acceptable salt thereof.

[009l] In another aspect, there is provided a compound of the following formula:

 ;

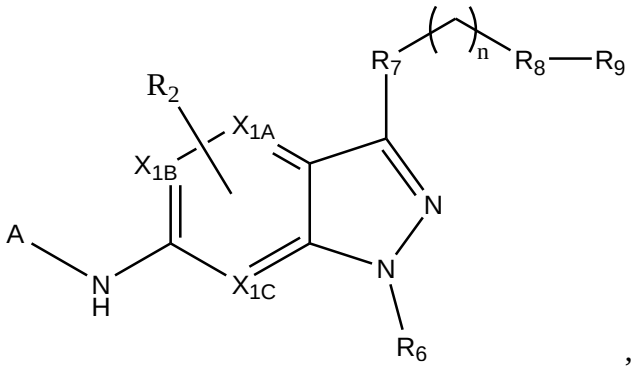
or a pharmaceutically acceptable salt thereof.

[009m] In another aspect, there is provided a pharmaceutical composition comprising a compound having a structure represented by a compound of the following formula:

 ;

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0010] Disclosed are methods for the treatment of a neurotransmission dysfunction or other disease state associated with mGluR4 activity in a mammal comprising the step of administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by the following formula:

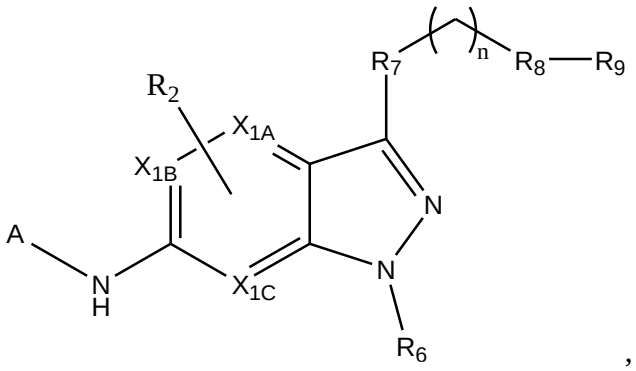


,

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof with a drug known to treat the neurotransmission dysfunction or other disease states.

[0027] Also disclosed are kits comprising a compound of the present ~~invention~~disclosure.

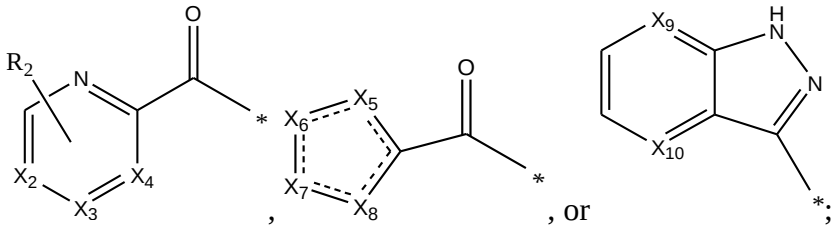
[0028] Also disclosed are methods for the treatment of a neurotransmission dysfunction and other disease states associated with mGluR4 activity in a mammal comprising the step of co-administering to the mammal at least one compound in a dosage and amount effective to treat the dysfunction in the mammal, the compound having a structure represented by a compound of following formula:



,

wherein:

A is chosen from



, , or

X_{1A}: CH, CR_1, or N;

X_{1B}: CH, CR_1, or N;

X_{1C}: CH, CR_1, or N;

X_2: CH, CR_1, or N;

X_3: CH, CR_1, or N;

X_4: CH, CR_1, or N;

X_5: CH, CR_1, S, O, NH, NCH_3, or N;

X_6: CH, CR_1, S, NH, or N;

X_7: CH, CR_1, or NH, N;

X_8: CH, CR_1, NH, N, S, or O;

X_9: CH, CR_1, or N;

X_{10}: CH, CR_1, or N;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, CH_3 or CD_3;

R_7 is O or –CO–;

R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from H, heteroaryl, aryl, heterocycloalkyl, oxygen-containing heterocycle, cycloalkyl, CD_3, CF_2, CD_2-CH_3, alkyl, CH_3,

n is 0-6;

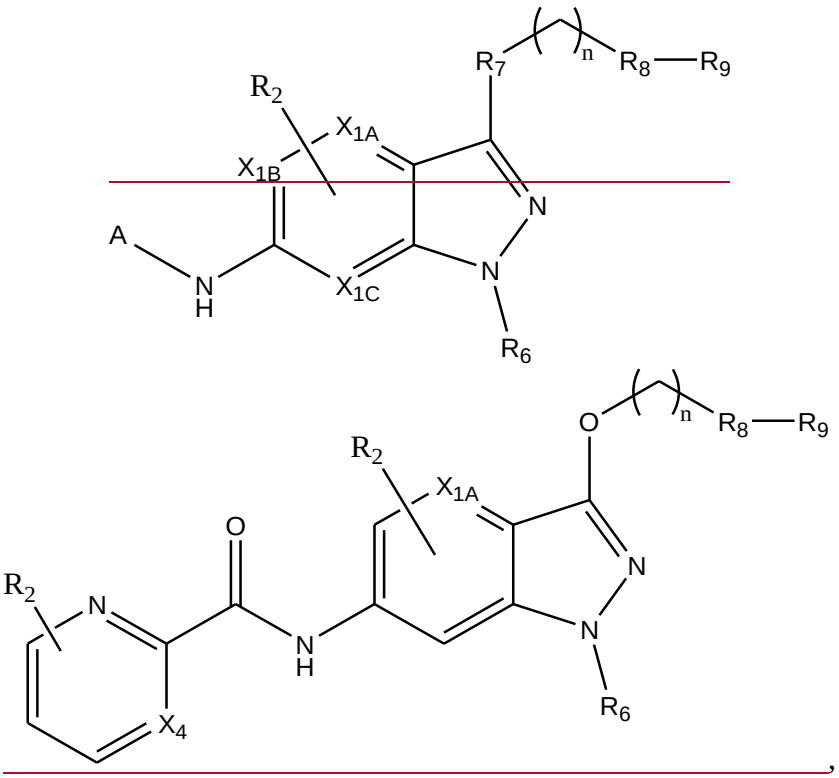
wherein each heteroaryl, aryl, heterocycloalkyl, cycloalkyl, when chosen, can be optionally substituted with one or more of the following: H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof, and one or more of a drug having a known side-effect of increasing metabotropic glutamate receptor activity, a drug known to treat a disorder associated with increasing metabotropic glutamate receptor activity, and/or a drug known to treat the neurotransmission dysfunction.

[0029] Additional advantages of the ~~invention~~ disclosure will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the ~~invention~~disclosure. The advantages of the ~~invention~~ disclosure will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the ~~invention~~disclosure, as claimed.

CLAIMS

What is claimed is:

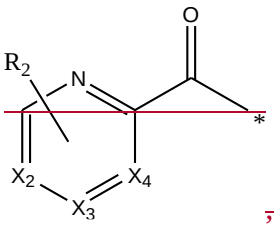
1. A compound of the following formula:



,

wherein:

~~A is chosen from~~



~~,~~

X_{1A}: CH~~;~~, CR_1, or N;

~~X_{1B}: CH;~~

~~X_{1C}: CH;~~

~~X_2: CH, or CR_1,;~~

~~X_3: CH, or CR_1;~~

X_4: CH, ~~or~~ CR_1, or N;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, ~~or~~ F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, ~~or~~ CH_3 or CD_3;

~~R_7 is O;~~

R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane~~heteroaryl, aryl, heterocycloalkyl, oxygen-containing heterocycle,~~;

n is 0-6;

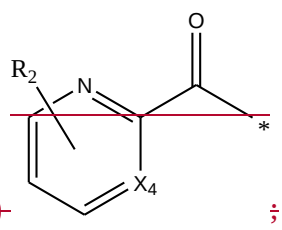
~~wherein each heteroaryl, aryl, heterocycloalkyl, cycloalkyl, when chosen, can be optionally substituted with one or more of the following: H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;~~

or a pharmaceutically acceptable salt thereof~~ or a pharmaceutically acceptable derivative thereof~~.

2. The compound of claim 1, wherein R_9 is 1,4-dioxane.

~~2. The compound of claim 1,~~

~~wherein A is:~~



~~(i)~~ ~~;~~

~~wherein~~

~~X_4 is CR_1; and~~

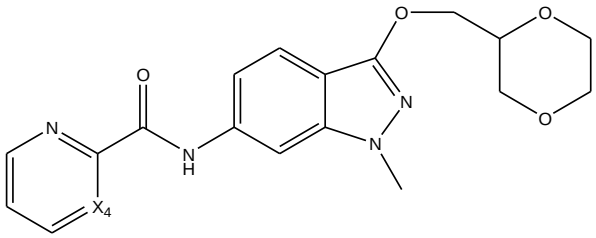
~~R_1 is NH_2, F, or OH.~~

~~3. The compound of claim 1, wherein~~

~~R_9 is heterocycloalkyl.~~

~~4. The compound of one of claims 1 or 3, wherein heterocycloalkyl is 1,4-dioxane, tetrahydropyran, dimethyl-tetrahydropyran, tetrahydrofuran, dimethyl-tetrahydrofuran.~~

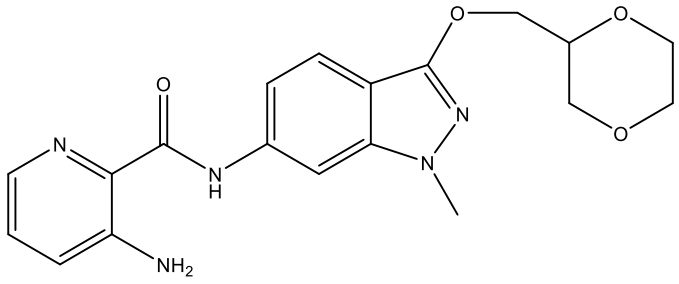
~~5~~3. The compound of claim 1, of the following formula:



;

wherein X_4 is CH or C-NH_2; or a pharmaceutically acceptable salt thereof.

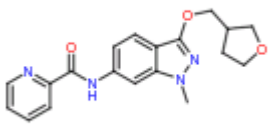
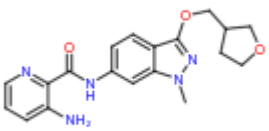
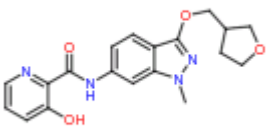
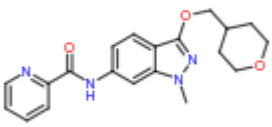
4. A compound of claim 1, of the following formula:

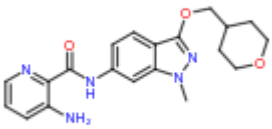
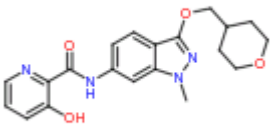
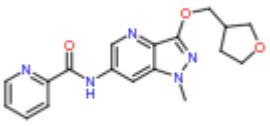
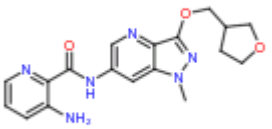


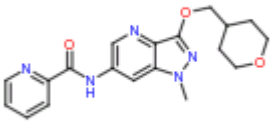
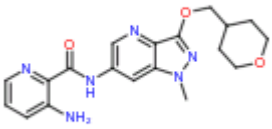
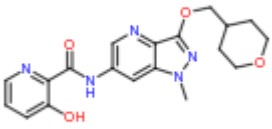
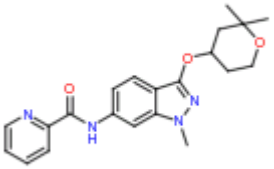
;

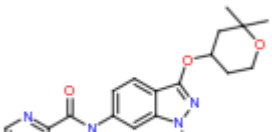
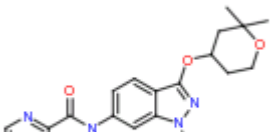
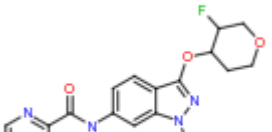
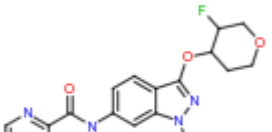
or a pharmaceutically acceptable salt thereof

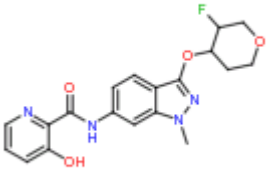
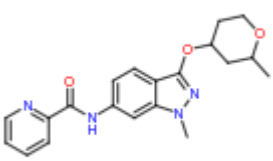
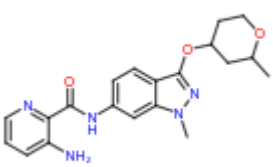
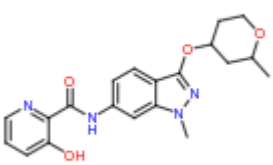
~~6~~5. The compound of claim 1, of the following formula:

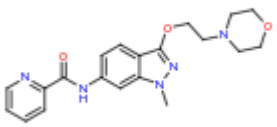
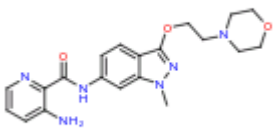
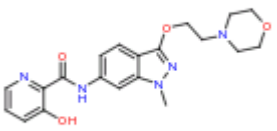
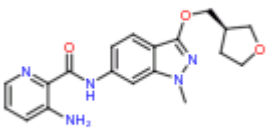

,

,

,

,


,

,

,

,

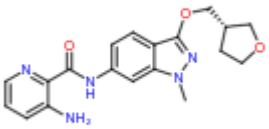
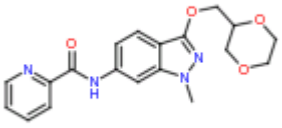
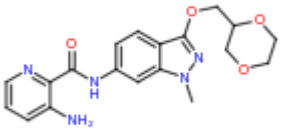
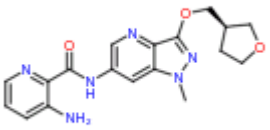

,

,

,

,


,

,

,

,

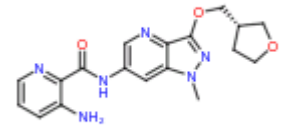
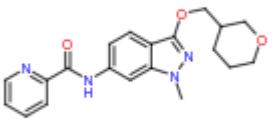
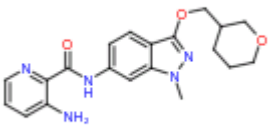
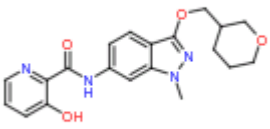

,

,

,

,

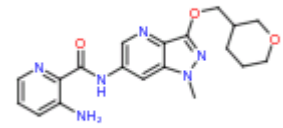
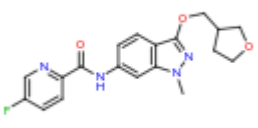
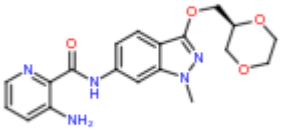
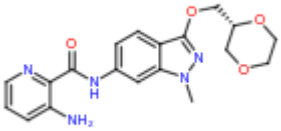
,

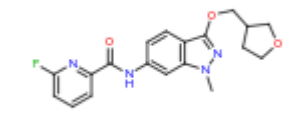
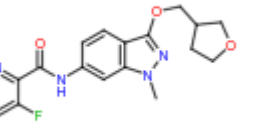
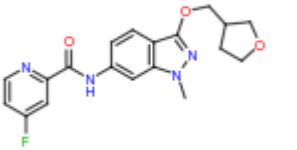
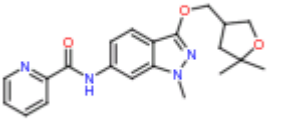
,

,

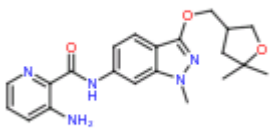
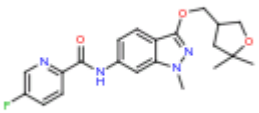
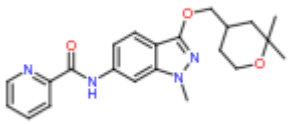
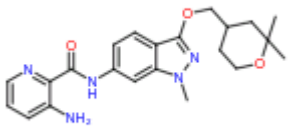





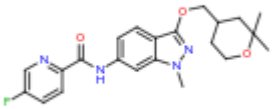
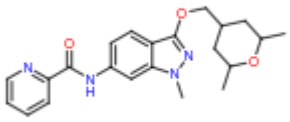
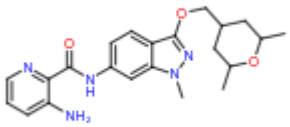
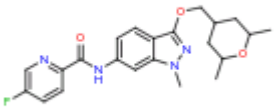
,

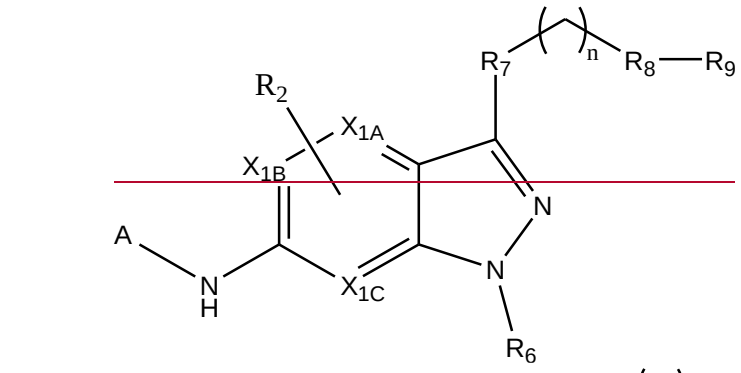
,

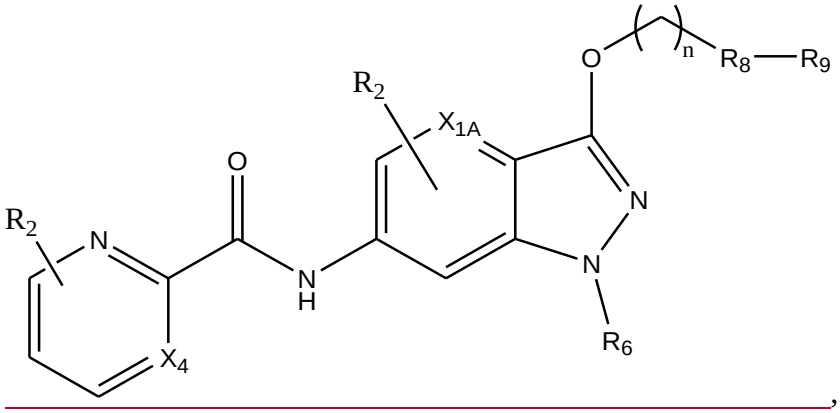
,


,

,

,

,


,

,

, or

.

~~7~~6. Use of at least one compound having a structure represented by a compound of the following formula:

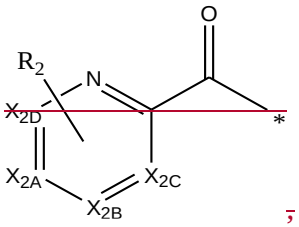




,

wherein:

~~A is chosen from~~



,

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N~~X_{1B}: CH;~~

~~X_{1C}: CH;~~

~~X_{2A}: CH, or CR_1;~~

~~X_{2B}: CH, or CR_1;~~

~~X_{2C}: CH, or CR_1;~~

~~X_{2D}: CH, CR_1~~;

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5,~~or~~ F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, ~~or~~ CH_3 or CD_3;

~~R_7 is O;~~

R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;~~heteroaryl, aryl, heterocycloalkyl, oxygen-containing heterocycle, ,~~

n is 0-6;

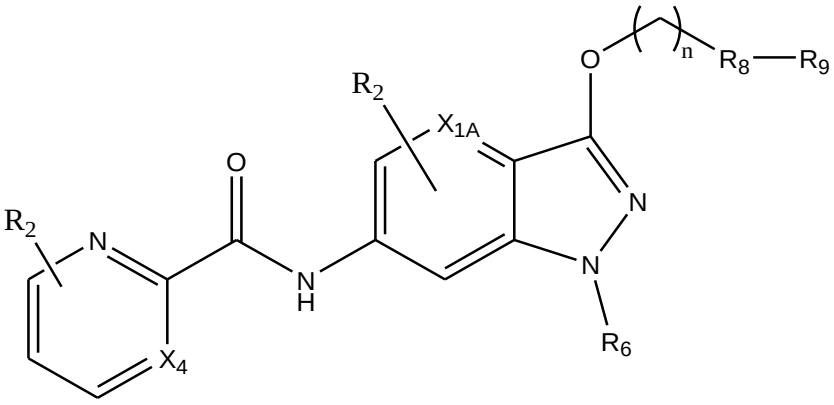
~~wherein each heteroaryl, aryl, heterocycloalkyl, cycloalkyl, when chosen, can be optionally substituted with one or more of the following: H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;~~

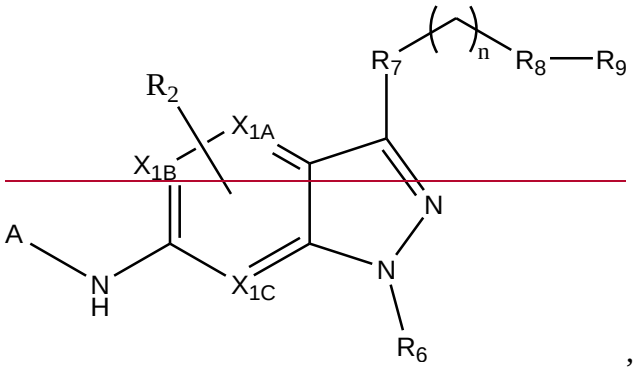
~~-~~or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~;

in the manufacture of a medicament for the treatment of Parkinson's disease, wherein the at least one compound is to be administered to the mammal in a dosage and amount effective to treat Parkinson's disease in the mammal.

~~8~~7. The use of claim ~~7~~6, wherein the mammal is a human.

~~9~~8. A pharmaceutical composition comprising a compound having a structure represented by a compound of the following formula:

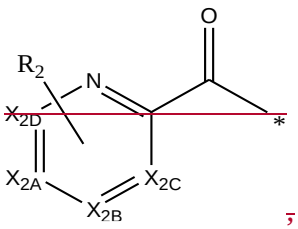




,

wherein:

~~A is chosen from~~



,

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N;

~~X_{1B}: CH;~~

~~X_{1C}: CH;~~

~~X_{2A}: CH, or CR_1;~~

~~X_{2B}: CH, or CR_1;~~

~~X_{2C}: CH, or CR_1;~~

~~X_{2D}: CH, CR_1;~~

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, ~~or~~ F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, ~~or~~ CH_3 or CD_3;

~~R_7 is O;~~

R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;~~heteroaryl, aryl, heterocycloalkyl, oxygen-containing heterocycle,~~

n is 0-6;

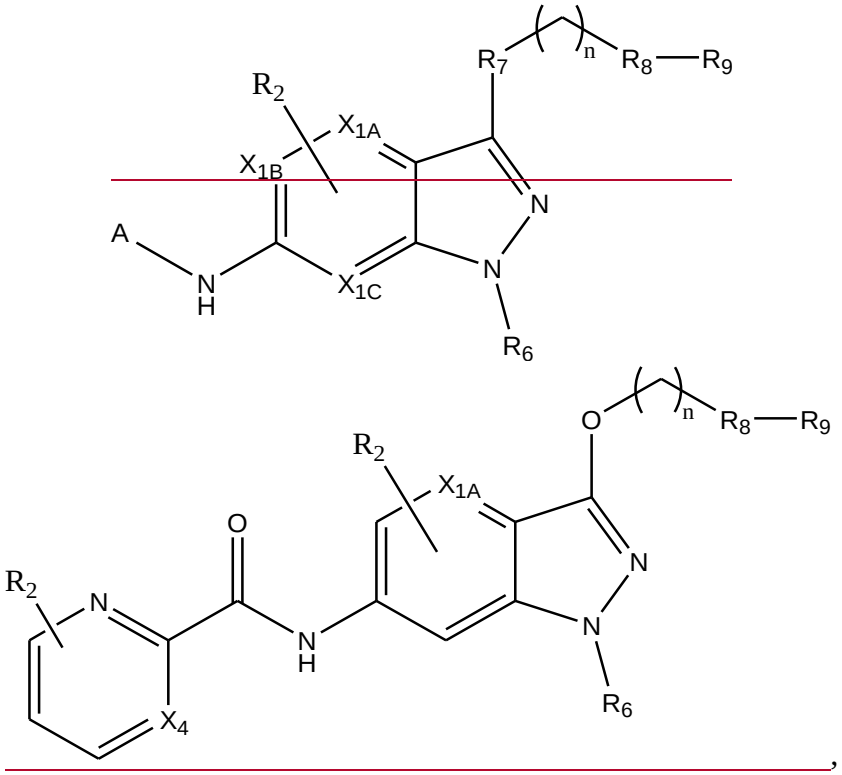
~~wherein each heteroaryl, aryl, heterocycloalkyl, cycloalkyl, when chosen, can be optionally substituted with one or more of the following: H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;~~

or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~, and a pharmaceutically acceptable carrier.

~~10~~9. A pharmaceutical composition comprising a compound of one of claims 1-~~6~~5, or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~, and a pharmaceutically acceptable carrier.

~~11~~10. A pharmaceutical composition comprising a compound of claim ~~6~~4, or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~, and a pharmaceutically acceptable carrier.

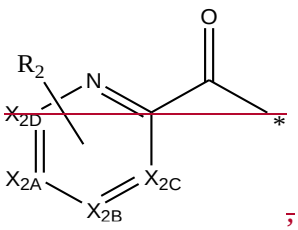
~~12~~11. Use of a compound having a structure represented by a compound of the following formula:



,

wherein:

~~A is chosen from~~



~~,~~

X_{1A}: CH, CR_1, or N;

X_4: CH, CR_1, or N;

~~X_{1B}: CH;~~

~~X_{1C}: CH;~~

~~X_{2A}: CH, or CR_1;~~

~~X_{2B}: CH, or CR_1;~~

~~X_{2C}: CH, or CR_1;~~

~~X_{2D}: CH, CR_1;~~

each R_1 is independent and chosen from H, D, OH, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

each R_2 is optionally present, independent and chosen from H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, ~~or~~ F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, cycloalkyl, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;

R_3 is chosen from H, alkyl, alkoxy, or OH;

R_4 is chosen from H, alkyl, alkoxy, or OH;

R_5 is chosen from H, or alkyl;

R_6 is H, ~~or~~ CH_3 or CD_3;

~~R_7 is O;~~

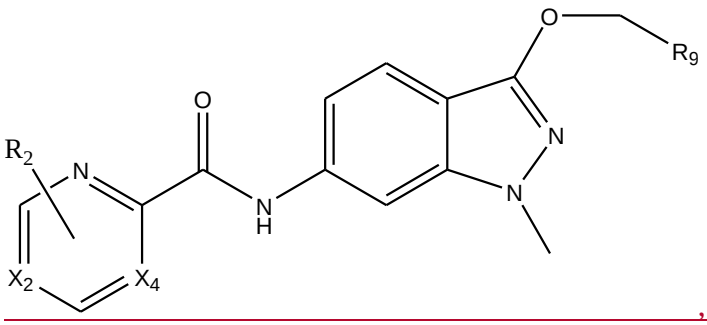
R_8 is a bond, alkyl, -NH-, -O-, alkyl-O-;

R_9 is substituted or unsubstituted and chosen from cycloalkyl, tetrahydrofuran, tetrahydropyran, 1,4 dioxane;~~heteroaryl, aryl, heterocycloalkyl, oxygen-containing heterocycle, cycloalkyl,~~

n is 0-6;

~~wherein each heteroaryl, aryl, heterocycloalkyl, cycloalkyl, when chosen, can be optionally substituted with one or more of the following: H, D, OH, $CONH_2$, NH_2, NR_3R_4, OR_5, F, CHF_2, CF_3, halogen, F, alkyl, Me, O-Me, alkyl-O-Me, CD_3, CN, methoxy, alkoxy, alkyl-methoxy, or alkyl-alkoxy;~~ or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~ in the manufacture of a medicament for the treatment of Parkinson's disease; wherein the compound is to be co-administered with a drug having a known side-effect of treating Parkinson's disease; and wherein the compound is to be co-administered in a dosage and amount effective to treat Parkinson's disease in the mammal.

12. A compound of the following formula:



, wherein

X_2 is CH;

X_4 is CR_1;

R_1 is NH_2;

R_2 is optionally present, and chosen from fluorine;

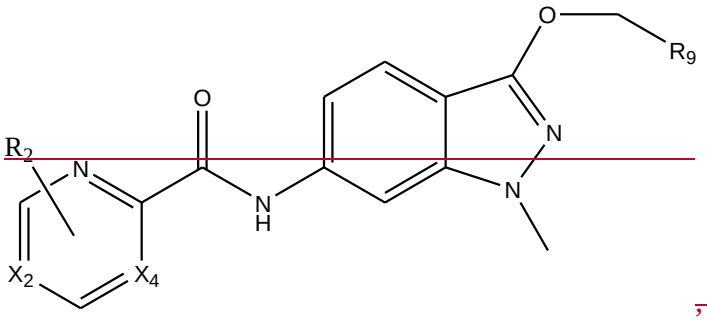
R_9 is heterocycloalkyl, oxygen-containing heterocycle.

13. The compound of claim 12, wherein heterocycloalkyl is 1,4-dioxane, tetrahydropyran, dimethyl-tetrahydropyran, tetrahydrofuran, dimethyl-tetrahydrofuran.

~~13. The use of claim 12, wherein co-administration is sequential.~~

~~14. The use of claim 12, wherein the mammal is a human.~~

~~15. A compound of claim 1, of the following formula:~~



~~, wherein~~

~~X_2 is CH;~~

~~X_4 is CR_1;~~

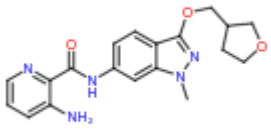
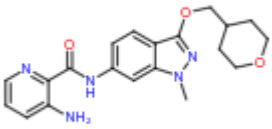
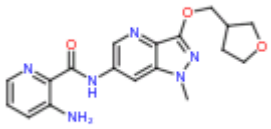
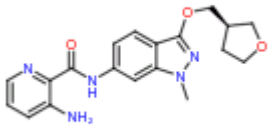
~~R_1 is NH_2;~~

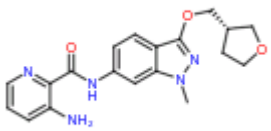
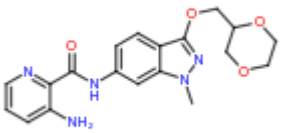
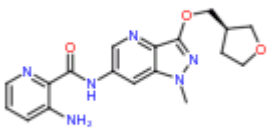
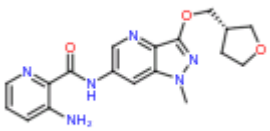
~~R_2 is optionally present, and chosen from fluorine;~~

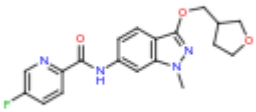
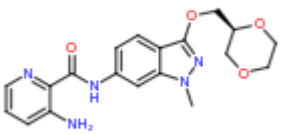
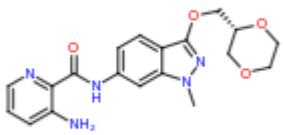
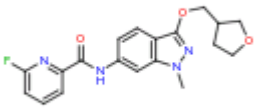
~~R_9 is heteroaryl, aryl, heterocycloalkyl, oxygen-containing heterocycle, cycloalkyl.~~

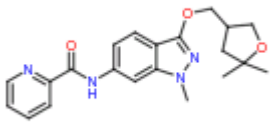
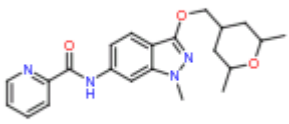
~~16. The compound of claim 15, wherein heterocycloalkyl is 1,4-dioxane, tetrahydropyran, dimethyl-tetrahydropyran, tetrahydrofuran, dimethyl-tetrahydrofuran.~~

~~17~~14. A compound of claim 1, of the following formula:


, 
, 


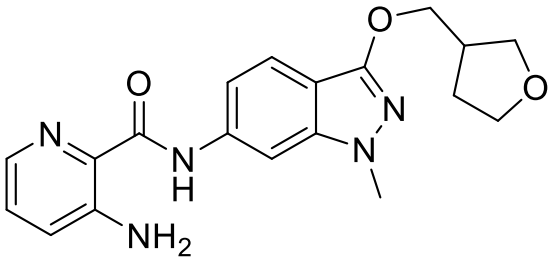

, 
, 


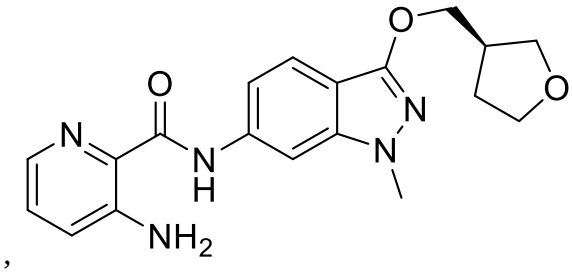

, 
, 
, 
,

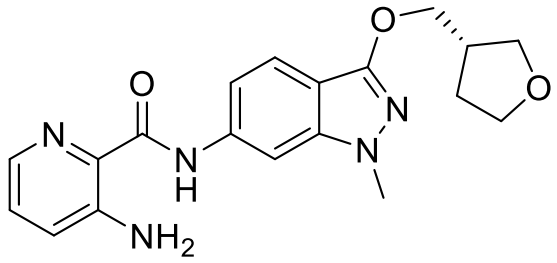



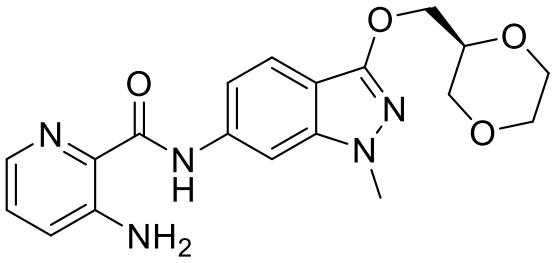
, or ; or a pharmaceutically acceptable salt thereof.

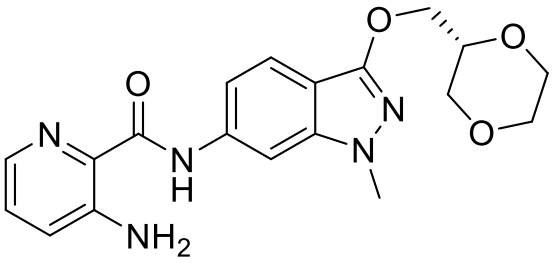
~~18~~15. A compound of claim 1, of the following formula:

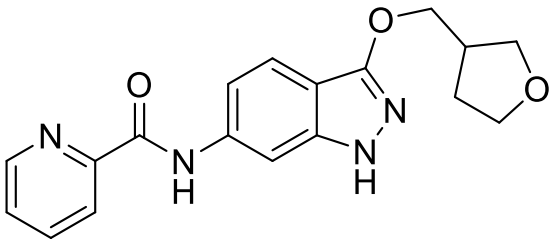

,

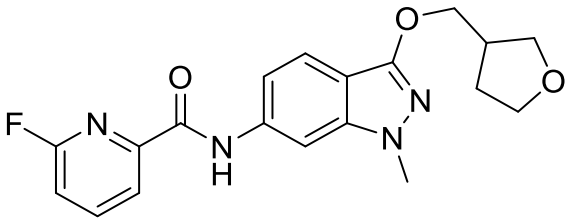

,

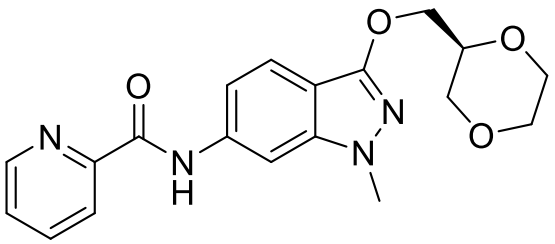

, , ,

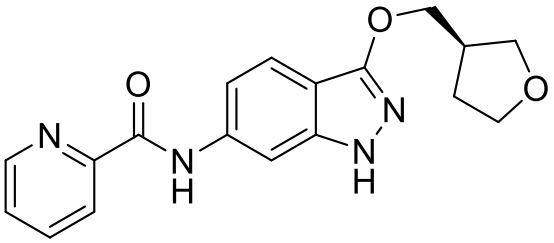

,

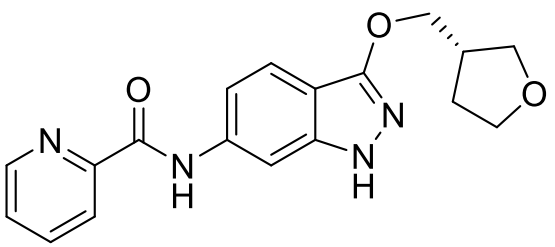

,

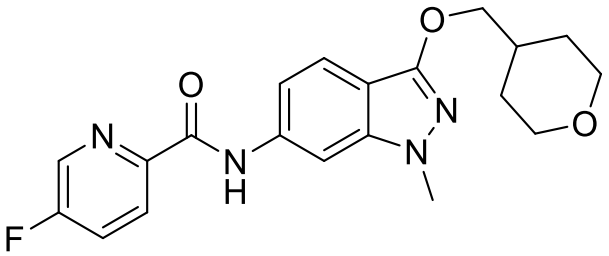

,


,


,

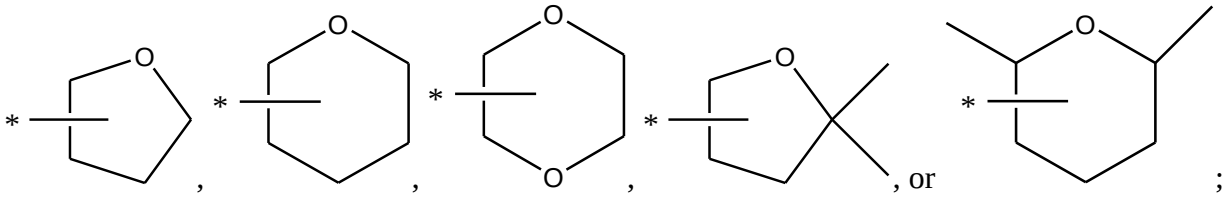

,


,


;

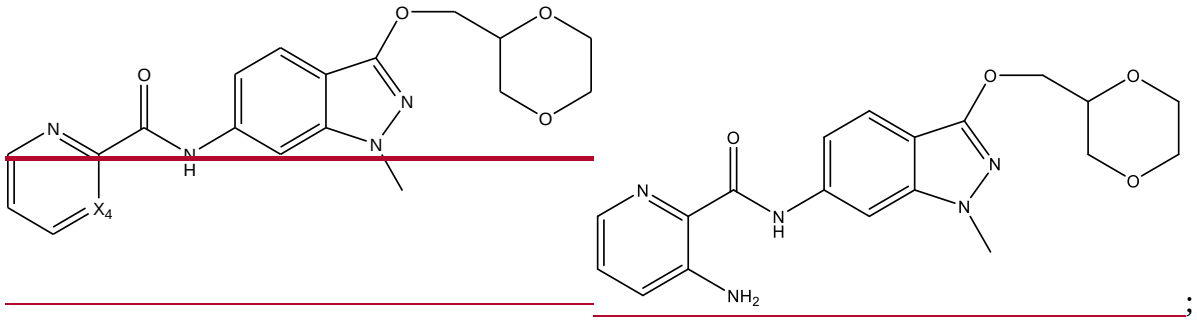
or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~.

~~19~~16. A compound of claim 1, wherein R_9 is:



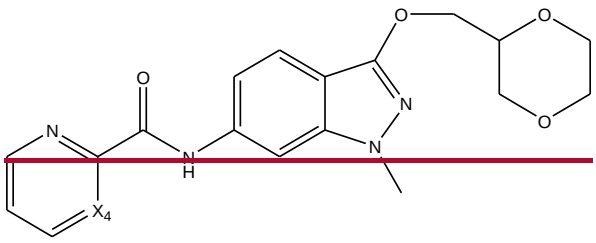
or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~.

~~20~~17. A compound of the following formula:



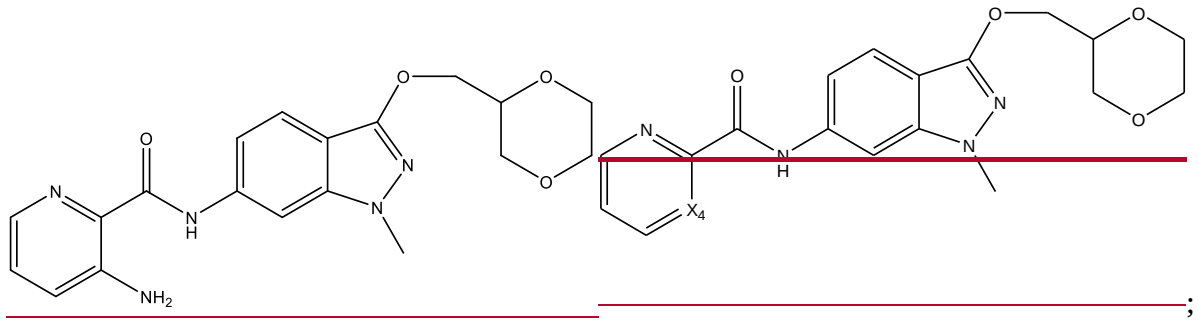
~~wherein X_4 is C-NH_2;~~ or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~.

~~21. Use of at least one compound having a structure represented by a compound of the following formula:~~



~~wherein X_4 is C-NH_2; or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable derivative thereof; in the manufacture of a medicament for the treatment of Parkinson's disease in a mammal, wherein the at least one compound is to be administered to the mammal in a dosage and amount effective to treat Parkinson's disease in the mammal.~~

~~22~~18. A pharmaceutical composition comprising a compound having a structure represented by a compound of the following formula:



;

~~wherein X_4 is C-NH_2;~~ or a pharmaceutically acceptable salt thereof ~~or a pharmaceutically acceptable derivative thereof~~, and a pharmaceutically acceptable carrier.