

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
7 September 2012 (07.09.2012)



(10) International Publication Number
WO 2012/118563 A2

(51) International Patent Classification:

A61K 31/513 (2006.01) C07D 401/14 (2006.01)

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(21) International Application Number:

PCT/US2012/000119

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(22) International Filing Date:

5 March 2012 (05.03.2012)

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/449,017 3 March 2011 (03.03.2011) US

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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))



WO 2012/118563 A2

(54) Title: 6-ALKYL-N-(PYRIDIN-2-YL)-4-ARYLOXYPICOLINAMIDE ANALOGS AS MGLUR5 NEGATIVE ALLOSTERIC MODULATORS AND METHODS OF MAKING AND USING THE SAME

(57) Abstract: Disclosed are negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5); synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of treating neurological and psychiatric disorders associated with glutamate dysfunction using the compounds and compositions. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

**6-ALKYL-N-(PYRIDIN-2-YL)- 4-ARYLOXYPICOLINAMIDE ANALOGS AS MGLUR5
NEGATIVE ALLOSTERIC MODULATORS AND METHODS OF MAKING AND USING THE
SAME**

CROSS-REFERENCE TO RELATED APPLICATIONS

- 5 [0001] This application claims benefit of U.S. Provisional Application No. 61/449,017, filed on March 3, 2011, which is hereby incorporated by reference in its entirety.

ACKNOWLEDGMENT

- [0002] This invention was made with government support under Grant no. 2R01-MH062646-12 awarded by the National Institute of Mental Health (NIMH), under Grant no. 5R01-MH073676-04
10 awarded by the NIMH, under Grant no. 5R01-NS031373-15 awarded by the National Institute of Neurological Disorders and Stroke (NINDS), and Grant no. 1R01-DA023947-01 awarded by the National Institute on Drug Abuse (NIDA). The United States government has certain rights in the invention.

BACKGROUND

- [0003] Glutamate (L-glutamic acid) is the major excitatory transmitter in the mammalian central
15 nervous system, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGluRs) belong to family C (also known as family 3) of the G-protein-coupled receptors (GPCRs). They are characterized by a seven transmembrane (7TM) α -helical domain connected via a cysteine rich-region to a large bi-lobed extracellular amino-terminal domain (Figure 1). While the orthosteric binding site is contained in the amino-terminal domain, currently known allosteric
20 binding sites reside in the 7TM domain. The mGluR family comprises eight known mGluRs receptor types (designated as mGluR1 through mGluR8). Several of the receptor types are expressed as specific splice variants, e.g. mGluR5a and mGluR5b or mGluR8a, mGluR8b and mGluR8c. The family has been classified into three groups based on their structure, preferred signal transduction mechanisms, and pharmacology. Group I receptors (mGluR1 and mGluR5) are coupled to $G_{\alpha q}$, a process that results in
25 stimulation of phospholipase C and an increase in intracellular calcium and inositol phosphate levels. Group II receptors (mGluR2 and mGluR3) and group III receptors (mGluR4, mGluR6, mGluR7, and mGluR8) are coupled to $G_{\alpha i}$, which leads to decreases in cyclic adenosine monophosphate (cAMP) levels. While the Group I receptors are predominately located postsynaptically and typically enhance postsynaptic signaling, the group II and III receptors are located presynaptically and typically have inhibitory effects on
30 neurotransmitter release. Without wishing to be bound by theory, increasing evidence indicates mGluRs play an important role in lasting changes in synaptic transmission, and studies of synaptic plasticity in the *Fmr1* knockout mouse have identified a connection between the fragile X phenotype and mGluR signaling.

[0004] The identification of small molecule mGluR antagonists that bind at the orthosteric site has greatly increased the understanding of the roles played by these receptors and their corresponding relation to disease. Because the majority of these antagonists were designed as analogs of glutamate, they typically lack desired characteristics for drugs targeting mGluR such as oral bioavailability and/or distribution to the central nervous system (CNS). Moreover, because of the highly conserved nature of the glutamate binding site, most orthosteric antagonists lack selectivity among the various mGluRs.

[0005] A more recent strategy that has been able to successfully deal with the aforementioned issues has been the design of compounds that bind the mGluR at a site that is topographically distinct from the orthosteric binding site, or an allosteric binding site. Selective negative allosteric modulators (NAMs) are compounds that do not directly deactivate receptors by themselves, but decrease the affinity of a glutamate-site agonist at its extracellular N-terminal binding site. Negative allosteric modulation is thus an attractive mechanism for inhibiting appropriate physiological receptor activation. Among the most studied and characterized small molecules are the mGluR5 NAMs, 2-methyl-6-(phenylethynyl) pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP). Both MPEP and MTEP have proven efficacious in numerous rodent models of disease, including those for drug addiction and pain as well as anxiety. The compounds were also able to inhibit transient lower esophageal sphincter relaxation (TLESR), the major cause of gastroesophageal reflux disease (GERD), in dogs and ferrets. In addition, MPEP was efficacious in mouse models of fragile X syndrome (FXS) and Parkinson's disease (PD) as well as a baboon model of binge-eating disorder.

[0006] Although the utility of MPEP and MTEP as tool compounds has been clearly demonstrated, both molecules have issues that complicate or prevent their further development as therapeutic molecules. MPEP has been shown to directly inhibit the *N*-methyl-D-aspartate (NMDA) receptor activity at higher concentrations and is a positive allosteric modulator of mGluR4. While these selectivity issues are mitigated with MTEP, it is a potent inhibitor of cytochrome P450 1A2 and is efficiently cleared following intravenous administration to rhesus monkeys.

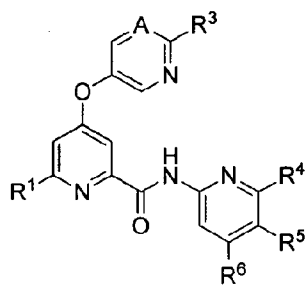
[0007] Potential adverse effects of known mGluR5 NAMs, however, could reduce their ultimate therapeutic utility. Further, conventional mGluR5 receptor modulators which target the orthosteric binding site can lack satisfactory aqueous solubility, exhibit poor oral bioavailability, and/or exhibit adverse effects. Therefore, there remains a need for methods and compositions that overcome these deficiencies and that effectively provide selective negative allosteric modulators for the mGluR5 receptor.

SUMMARY

[0008] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5), methods of making same, pharmaceutical

compositions comprising same, and methods of treating disorders associated with glutamate dysfunction using same.

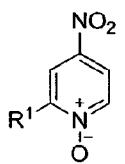
[0009] Disclosed are compounds having a structure represented by a formula:



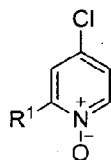
- 5 wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.

15 [0010] Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

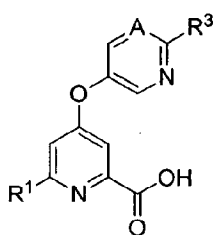
[0011] Also disclosed are methods for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:



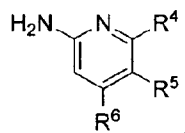
- 20 wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and (b) chlorinating by reacting with concentrated HCl under reflux conditions, thereby forming a compound having a structure represented by a formula:



[0012] Also disclosed are methods for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:

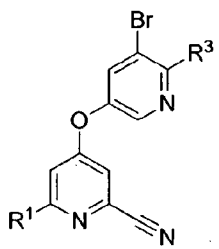


- 5 wherein wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and (b) coupling the compound with a compound represented by the formula:



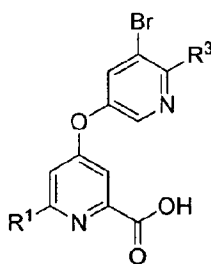
- 10 wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.

[0013] Also disclosed are methods for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:

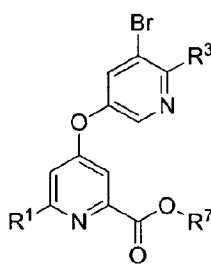


- 15 wherein wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3

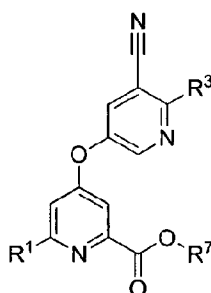
polyhaloalkyl, and C3 cycloalkyl; and (b) reacting with aqueous hydroxide, thereby providing a compound represented by the formula:



[0014] Also disclosed are methods for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:



wherein wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and wherein R7 is C1-C5 alkyl; and (b) performing a cyanation reaction, thereby providing a compound having a structure represented by a formula:

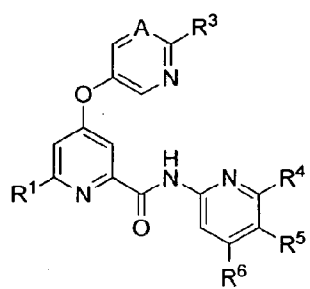


[0015] Also disclosed are products of the disclosed methods.

[0016] Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed product and a pharmaceutically acceptable carrier.

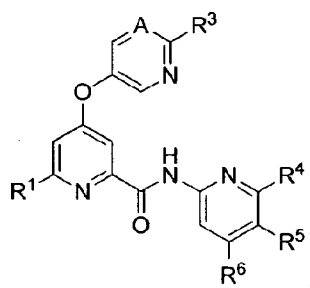
[0017] Also disclosed are methods for manufacturing a medicament comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[0018] Also disclosed are methods for the treatment of a disorder associated with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of a compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

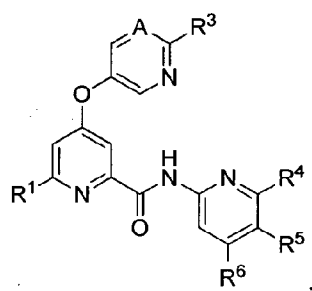
[0019] Also disclosed are methods for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently

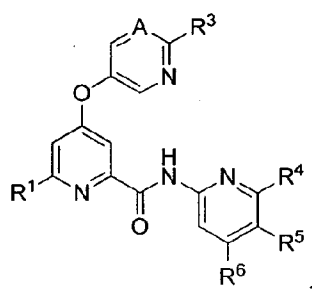
selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0020] Also disclosed are methods for inhibiting metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



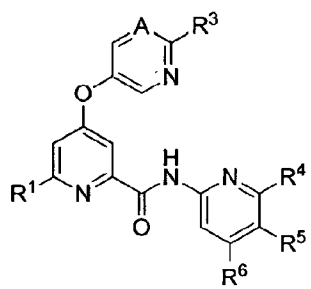
wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0021] Also disclosed are methods for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



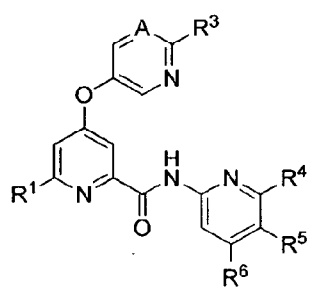
wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0022] Also disclosed are methods for partial antagonism of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



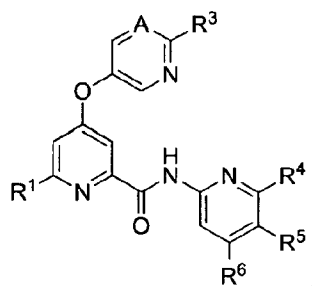
- 5 wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0023] Also disclosed are methods for modulating mGluR5 activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



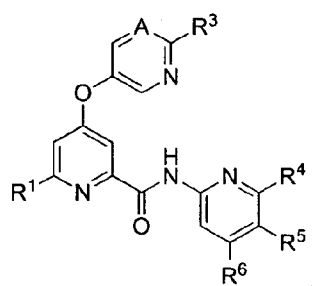
- 15 wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0024] Also disclosed are methods for modulating mGluR5 activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of least one compound having a structure represented by a formula:



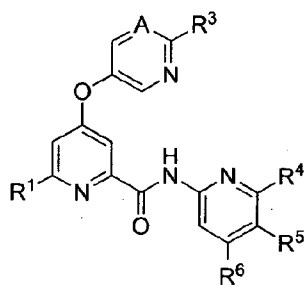
- 5 wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3
10 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0025] Also disclosed are methods for inhibiting mGluR5 activity in at least one cell, comprising the step of contacting the at least one cell with at least one compound having a structure represented by a formula:



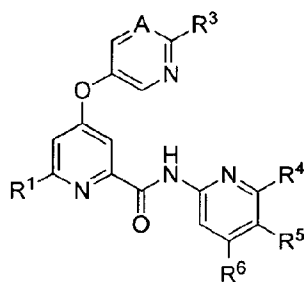
- 15 wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3
20 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0026] Also disclosed are uses of a compound having a structure represented by a formula:



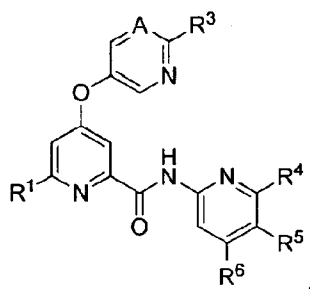
wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal.

10 [0027] Also disclosed are pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0028] Also disclosed are kit comprising at least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to increase mGluR5 activity; (b) at least one agent known to decrease mGluR5 activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; (d) at least one agent known to treat a disease of uncontrolled cellular proliferation; or (e) instructions for treating a disorder associated with glutamate dysfunction.

[0029] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

BRIEF DESCRIPTION OF THE FIGURES

[0030] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0031] Figure 1 is a schematic representation of an mGluR.

[0032] Figure 2 illustrates allosteric modulation of mGluR5.

[0033] Figure 3 shows representative data of the effect of an exemplary compound (test compound 2, which corresponds to Compound (2) described herein) in a mouse model of anxiolytic behavior.

5 [0034] Figure 4 shows representative data of the effect of an exemplary compound (test compound 2, which corresponds to Compound (2) described herein) in a mouse model of anxiolytic behavior.

[0035] Figure 5 shows representative data of the effect of an exemplary compound (test compound 1, which corresponds to Compound (11) described herein) in a mouse model of anxiolytic behavior.

10 [0036] Figure 6 shows representative data of the effect of an exemplary compound (test compound 1, which corresponds to Compound (11) described herein) in a mouse model of anxiolytic behavior.

[0037] Figures 7A-7C and 8A-8C show representative data of the effect of test compounds 1 and 2 (Compounds (11) and (2) as described herein) as studied in the FvB Audiogenic Seizure (AGS) test.

[0038] Figures 9A-9C and Figures 10A-10B show exemplary pharmacological data for two test compounds (Compounds (23) and (7) as described herein).

15 [0039] Figure 11 shows representative data for test compounds (1) and (2) (Compounds (11) and (2) as described herein) as measured in the elevated plus maze, which is a model of anxiolytic behavior.

[0040] Additional advantages of the invention 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. The advantages of the invention will be realized and attained by means of the elements and combinations
20 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, as claimed.

DESCRIPTION

[0041] The present invention can be understood more readily by reference to the following detailed
25 description of the invention and the Examples and Figures included herein.

[0042] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects

only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

5 [0043] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

15 [0044] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

25 [0045] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for stereochemistry can be employed to designate stereochemical priority, *E/Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAW™ (Cambridgesoft Corporation, U.S.A.).

30 [0046] As used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a functional group,” “an alkyl,” or “a residue” includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0047] Ranges can be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0048] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0049] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

[0050] As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance can or can not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0051] As used herein, the term “orthosteric site” refers to the primary binding site on a receptor that is recognized by the endogenous ligand or agonist for that receptor. For example, the orthosteric site in the mGluR5 receptor is the site that glutamate binds.

[0052] As used herein, the term “mGluR5 receptor negative allosteric modulator” refers to any exogenously administered compound or agent that directly or indirectly inhibits the activity of the mGluR5 receptor in the presence of the endogenous ligand (such as glutamate) in an animal, in particular a mammal, for example a human. The term is synonymous with the terms “mGluR5 receptor allosteric inhibitor,” “mGluR5 receptor noncompetitive inhibitor,” “mGluR5 receptor allosteric antagonist,” and “mGluR5 receptor noncompetitive antagonist.”

[0053] As used herein, the term “subject” can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a

particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more neurological and/or psychiatric disorder associated with glutamate dysfunction prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for negative allosteric modulation of metabotropic glutamate receptor activity prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for partial antagonism of metabotropic glutamate receptor activity prior to the administering step.

10 [0054] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0055] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0056] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, "diagnosed with a disorder treatable by modulation of mGluR5" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by

a compound or composition that can modulate mGluR5. As a further example, "diagnosed with a need for modulation of mGluR5" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition characterized by mGluR5 activity. Such a diagnosis can be in reference to a disorder, such as a neurodegenerative disease, and the like, as discussed herein.

5 For example, the term "diagnosed with a need for negative allosteric modulation of metabotropic glutamate receptor activity" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by negative allosteric modulation of metabotropic glutamate receptor activity. For example, "diagnosed with a need for partial antagonism of metabotropic glutamate receptor activity" means having been subjected to a
10 physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by partial antagonism of metabotropic glutamate receptor activity. For example, "diagnosed with a need for treatment of one or more neurological and/or psychiatric disorder associated with glutamate dysfunction" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have one or more neurological and/or psychiatric disorder
15 associated with glutamate dysfunction.

[0057] As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to mGluR5 activity) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder.
20 It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0058] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the
25 art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous
30 administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0059] The term "contacting" as used herein refers to bringing a disclosed compound and a cell,
35 target metabotropic glutamate receptor, or other biological entity together in such a manner that the

compound can affect the activity of the target (e.g., spliceosome, cell, etc.), either directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[0060] As used herein, the terms “effective amount” and “amount effective” refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a “therapeutically effective amount” refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a “prophylactically effective amount”; that is, an amount effective for prevention of a disease or condition.

[0061] As used herein, “EC₅₀,” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC₅₀ can refer to the concentration of a substance that is required for 50% agonism *in vivo*, as further defined elsewhere herein. In a further aspect, EC₅₀ refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response. In a yet further aspect, the response is *in vitro*. In a still further aspect, the response is in a human embryonic kidney cell transfected with human mGluR5. In a yet further aspect, the response is in a human embryonic kidney cell transfected with rat mGluR5. In an even further aspect, the response is in a human embryonic kidney cell transfected with a mammalian mGluR5.

[0062] As used herein, “IC₅₀,” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC₅₀ can refer to the concentration of a substance that is required for 50% inhibition *in vivo*, as further defined elsewhere

herein. In a further aspect, IC_{50} refers to the half maximal (50%) inhibitory concentration (IC) of a substance. In a yet further aspect, the inhibition is measured *in vitro*. In a still further aspect, the inhibition is measured in a human embryonic kidney cell transfected with human mGluR5. In a yet further aspect, the inhibition is measured in a human embryonic kidney cell transfected with rat mGluR5. In an even further aspect, the inhibition is measured in a human embryonic kidney cell transfected with a mammalian mGluR5.

[0063] The term “pharmaceutically acceptable” describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

10 [0064] As used herein, the term “derivative” refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0065] As used herein, the term “pharmaceutically acceptable carrier” refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents.

20 Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be

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dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0066] A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $-CO(CH_2)_8CO-$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0067] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0068] In defining various terms, " A^1 ," " A^2 ," " A^3 ," and " A^4 " are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0069] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can

be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms.

[0070] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, e.g., fluorine, chlorine, bromine, or iodine. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "alkylamino" specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When "alkyl" is used in one instance and a specific term such as "alkylalcohol" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "alkylalcohol" and the like.

[0071] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, e.g., an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, e.g., a "halogenated alkoxy," a particular substituted alkenyl can be, e.g., an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[0072] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0073] The term "polyalkylene group" as used herein is a group having two or more CH₂ groups linked to one another. The polyalkylene group can be represented by the formula —(CH₂)_a—, where "a" is an integer of from 2 to 500.

[0074] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as —OA¹ where A¹ is alkyl or

cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as $\text{—OA}^1\text{—OA}^2$ or $\text{—OA}^1\text{—(OA}^2\text{)}_a\text{—OA}^3$, where "a" is an integer of from 1 to 200 and A^1 , A^2 , and A^3 are alkyl and/or cycloalkyl groups.

[0075] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(\text{A}^1\text{A}^2)\text{C}=\text{C}(\text{A}^3\text{A}^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol $\text{C}=\text{C}$. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0076] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bond, *i.e.*, $\text{C}=\text{C}$. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term "heterocycloalkenyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0077] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0078] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bond. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononyl, and the like. The term "heterocycloalkynyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkynyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The

cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0079] The term “aryl” as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term “aryl” also includes “heteroaryl,” which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term “non-heteroaryl,” which is also included in the term “aryl,” defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term “biaryl” is a specific type of aryl group and is included in the definition of “aryl.” Biaryl refers to two aryl groups that are bound together *via* a fused ring structure, as in naphthalene, or are attached *via* one or more carbon-carbon bonds, as in biphenyl.

[0080] The term “aldehyde” as used herein is represented by the formula —C(O)H . Throughout this specification “C(O)” is a short hand notation for a carbonyl group, *i.e.*, C=O .

[0081] The terms “amine” or “amino” as used herein are represented by the formula $\text{—NA}^1\text{A}^2$, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0082] The term “alkylamino” as used herein is represented by the formula —NH(—alkyl) where alkyl is as described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0083] The term “dialkylamino” as used herein is represented by the formula —N(—alkyl)_2 where alkyl is as described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

[0084] The term “carboxylic acid” as used herein is represented by the formula —C(O)OH .

[0085] The term “ester” as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1 , where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “polyester” as used herein is represented by the formula $\text{—(A}^1\text{O(O)C—A}^2\text{—OC(O))}_a\text{—}$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an interger from 1 to 500. “Polyester” is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0086] The term “ether” as used herein is represented by the formula A^1OA^2 , where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term “polyether” as used herein is represented by the formula $\text{—(A}^1\text{O—A}^2\text{O)}_a\text{—}$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0087] The term “halide” as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

[0088] The term “heterocycle,” as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycle includes pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like.

[0089] The term “hydroxyl” as used herein is represented by the formula —OH .

[0090] The term “ketone” as used herein is represented by the formula $\text{A}^1\text{C(O)A}^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0091] The term “azide” as used herein is represented by the formula —N_3 .

[0092] The term “nitro” as used herein is represented by the formula —NO_2 .

[0093] The term "nitrile" as used herein is represented by the formula —CN .

[0094] The term "silyl" as used herein is represented by the formula $\text{—SiA}^1\text{A}^2\text{A}^3$, where A^1 , A^2 , and A^3 can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

5 [0095] The term "sulfo-oxo" as used herein is represented by the formulas —S(O)A^1 , $\text{—S(O)}_2\text{A}^1$, $\text{—OS(O)}_2\text{A}^1$, or $\text{—OS(O)}_2\text{OA}^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O . The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula $\text{—S(O)}_2\text{A}^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula $\text{A}^1\text{S(O)}_2\text{A}^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula $\text{A}^1\text{S(O)A}^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

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[0096] The term "thiol" as used herein is represented by the formula —SH .

[0097] " R^1 ," " R^2 ," " R^3 ," " R^n ," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

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[0098] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. It is also contemplated that, in certain aspects,

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unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0099] The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[00100] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group is independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 5–6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3–12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[00101] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), is independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each R^\bullet is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6-membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[00102] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=O$, $=S$, $=NNR^{\bullet}_2$, $=NNHC(O)R^{\bullet}$, $=NNHC(O)OR^{\bullet}$, $=NNHS(O)_2R^{\bullet}$, $=NR^{\bullet}$, $=NOR^{\bullet}$, $-O(C(R^{\bullet}_2))_{2-3}O-$, or $-S(C(R^{\bullet}_2))_{2-3}S-$, wherein each independent occurrence of R^{\bullet} is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-O(CR^{\bullet}_2)_{2-3}O-$, wherein each independent occurrence of R^{\bullet} is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00103] Suitable substituents on the aliphatic group of R^{\bullet} include halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each R^{\bullet} is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00104] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each R^{\dagger} is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^{\dagger} , taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00105] Suitable substituents on the aliphatic group of R^{\dagger} is independently halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each R^{\bullet} is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

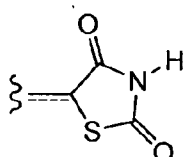
[00106] The term “leaving group” refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include halides and sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, brosylate, and halides.

[00107] The terms “hydrolysable group” and “hydrolysable moiety” refer to a functional group capable of undergoing hydrolysis, e.g., under basic or acidic conditions. Examples of hydrolysable residues

include, without limitation, acid halides, activated carboxylic acids, and various protecting groups known in the art (see, for example, "Protective Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

[00108] The term "organic residue" defines a carbon containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[00109] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[00110] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide,

substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[00111] "Inorganic radicals," as the term is defined and used herein, contain no carbon atoms and therefore comprise only atoms other than carbon. Inorganic radicals comprise bonded combinations of atoms selected from hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in their chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include, but not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and like commonly known inorganic radicals. The inorganic radicals do not have bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Inorganic radicals do not comprise metalloids elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, or the noble gas elements, unless otherwise specifically indicated elsewhere herein.

[00112] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[00113] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[00114] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or

(+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

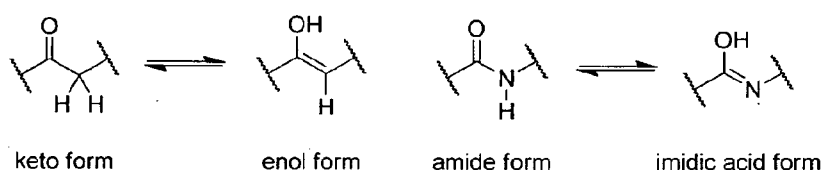
[00115] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labelled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labelled reagent for a non- isotopically labelled reagent.

[00116] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by

crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvate or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[00117] The term "co-crystal" means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrides or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarasson, O., et al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

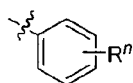
[00118] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α -hydrogen can exist in an equilibrium of the keto form and the enol form.



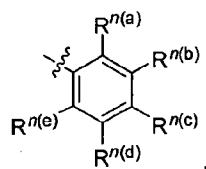
Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. Unless stated to the contrary, the invention includes all such possible tautomers.

[00119] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00120] In some aspects, a structure of a compound can be represented by a formula:



which is understood to be equivalent to a formula:



wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, $R^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

[00121] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00122] The following abbreviations are used herein. AcOEt: ethyl acetate. AcOH: acetic acid. ACN: acetonitrile. BuOH: 1-butanol. DIPEA or DIEA: diisopropylethylamine. DMAP: 4-dimethylaminopyridine. DCM: dichloromethane. DCE: 1,2-dichloroethane. DIPE: diisopropylether. DIPEA: N,N-diisopropylethylamine. DMF: N,N-dimethyl formamide. DMSO: dimethylsulfoxide. EDC: 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride. EtOAc: ethyl acetate. EtOH: ethanol. h: Hours. HPLC: high-performance liquid chromatography. HOBt: 1-hydroxybenzotriazole. iPrOH: 2-propanol. LC-MS or LCMS: liquid chromatography/mass spectrometry. $[M+H]^+$: protonated mass of the free base of the compound. M. p.: melting point. MeCN: Acetonitrile. MeOH: methanol. Min: Minutes. NMR: nuclear magnetic resonance. RP: reversed phase. Rt: retention time (in minutes). RT: Room temperature. TEA: triethylamine. THF: tetrahydrofuran. TMEDA: N,N,N',N'-tetramethylethylenediamine.

[00123] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order

be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

5 **[00124]** Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds can not be explicitly disclosed, each is specifically
10 contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a
15 combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the
20 invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00125] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that
25 there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. MGLUR5 NEGATIVE ALLOSTERIC MODULATORS

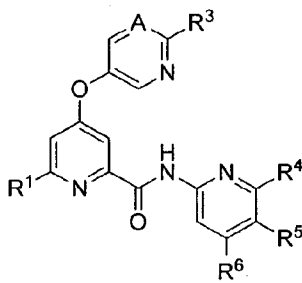
[00126] In one aspect, the invention relates to compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5). Negative allosteric modulators are non-
30 competitive antagonists and can include a range of maximal antagonist activity from partial antagonists to inverse agonists. In one aspect, the present invention relates to compounds that allosterically modulate mGluR5 receptor activity, affecting the sensitivity of mGluR5 receptors to agonists without acting as orthosteric agonists themselves. The compounds can, in one aspect, exhibit subtype selectivity. The compounds of the invention can be useful in the treatment neurological and psychiatric disorders

associated with glutamate dysfunction and other diseases in which metabotropic glutamate receptors are involved, as further described herein. Generally, the disclosed compounds exhibit negative allosteric modulation of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In further aspect, the human embryonic kidney cells are transfected with human mGluR5. In yet a further aspect, human embryonic kidney cells are transfected with mGluR5 of a mammal.

[00127] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. STRUCTURE

[00128] In one aspect, the invention relates to compounds, or pharmaceutically acceptable salts thereof, having a structure represented by a formula:



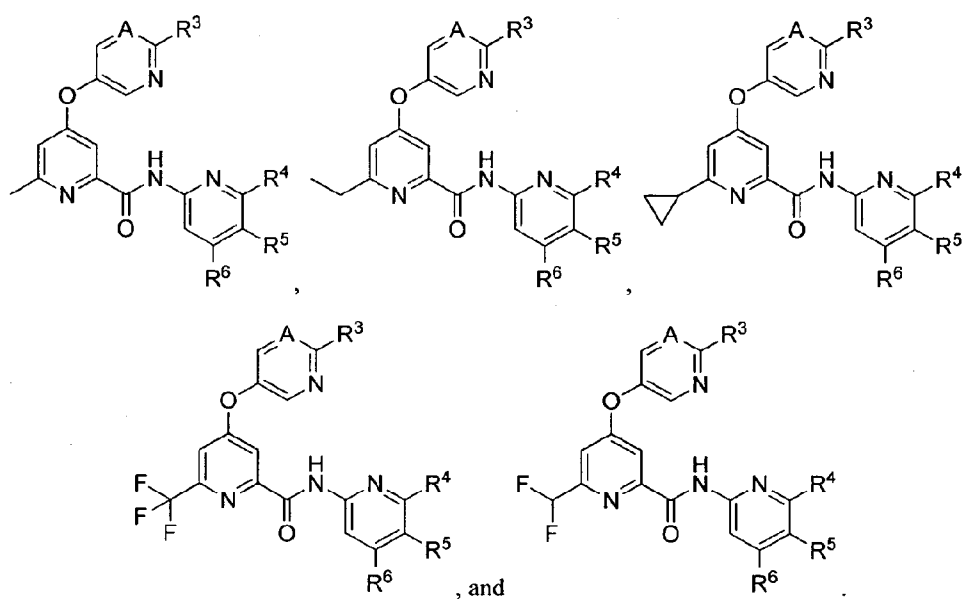
wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.

[00129] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response. In a yet further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶. In an even

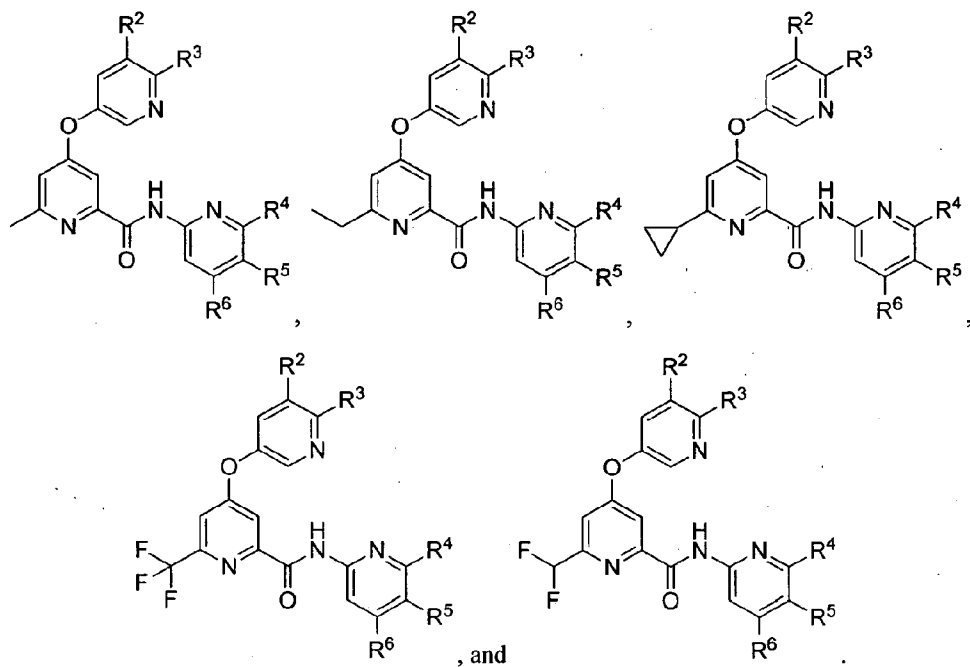
further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} . In a further aspect, the mGluR5 is rat mGluR5. In a still further aspect, the mGluR5 is human mGluR5.

[00130] In a further aspect, a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or product of a disclosed method of making and a pharmaceutically acceptable carrier.

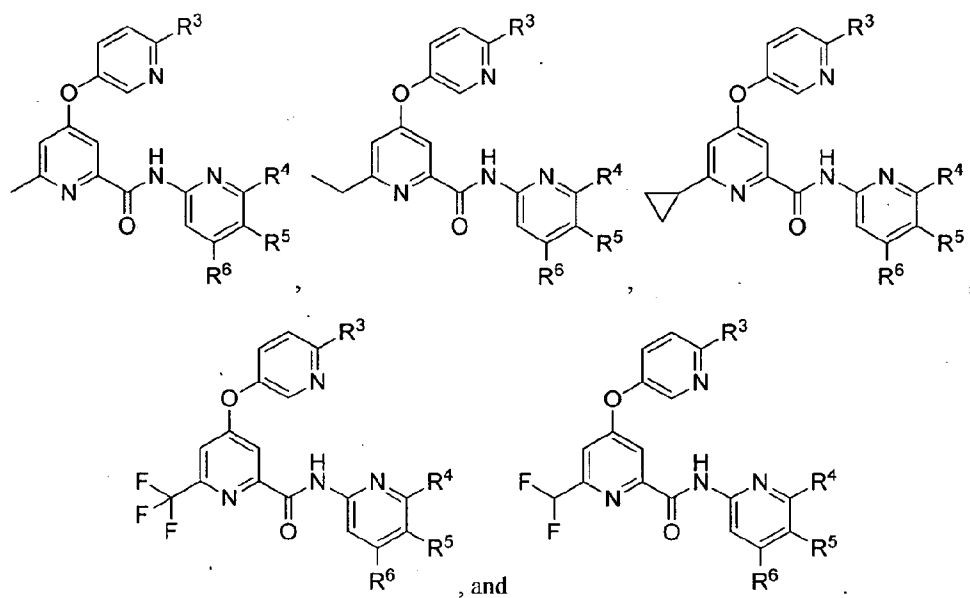
[00131] In a further aspect, a compound has a structure selected from:



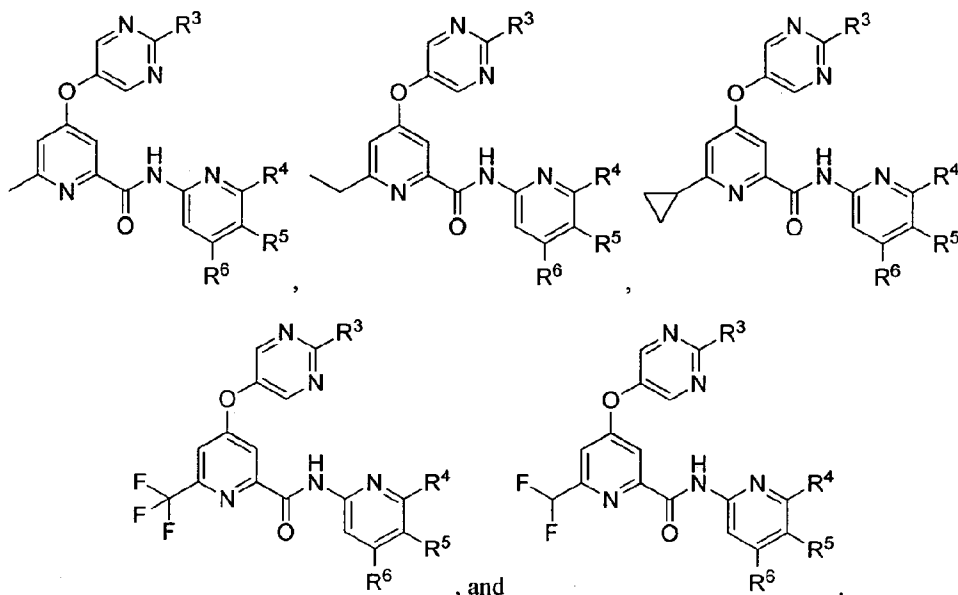
[00132] In a further aspect, a compound has a structure selected from:



[00133] In a further aspect, a compound has a structure selected from:



[00134] In a further aspect, a compound has a structure selected from:



a. A GROUPS

5 [00135] In one aspect, A is CR² or N. In a further aspect, A is N. In a still further aspect, A is CR².

b. R¹ GROUPS

[00136] In one aspect, R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl

10 [00137] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is methyl. In an even further aspect, R¹ is ethyl. In a still further aspect, R¹ is CHF₂. In a yet further aspect, R¹ is CF₃. In a yet further aspect, R¹ is cyclopropyl. In an even further aspect, R¹ is selected from methyl and ethyl. In a still further aspect, R¹ is selected from methyl, ethyl, or CHF₂. In an even further aspect, methyl, ethyl, CHF₂, and CF₃.

15 **c. R² GROUPS**

[00138] In one aspect, R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl

[00139] In a further aspect, R² is selected from hydrogen, CN, halogen, and methyl. In a still further aspect, R² is hydrogen. In a yet further aspect, R² is methyl. In an even further aspect, R² is CN.

[00140] In a further aspect, R^2 is halogen. In a still further aspect, the halogen is chloro or fluoro. In a yet further aspect, the halogen is chloro. In an even further aspect, the halogen is fluoro.

[00141] In a further aspect, R^2 is selected from hydrogen, CN, chloro, fluoro and methyl. In a still further aspect, R^2 is selected from C1-C2 alkyl, C1-C2 haloalkyl, and C1-C2 polyhaloalkyl.

5 [00142] In a further aspect, one of R^2 , when present, and R^3 must be hydrogen.

d. R^3 GROUPS

[00143] In one aspect, R^3 is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.

10 [00144] In a further aspect, R^3 is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R^3 is selected from hydrogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.

[00145] In a further aspect, R^3 is selected from hydrogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R^3 is selected from hydrogen, methyl, trifluoromethyl, and cyclopropyl.

15 e. R^4 GROUPS

[00146] In one aspect, each of R^4 , R^5 , and R^6 is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.

20 [00147] In a further aspect, the halogen is selected from chloro and fluoro. In a yet further aspect, the halogen is chloro. In a still further aspect, the halogen is fluoro. In an even further aspect, the halogen is selected from fluoro, chloro and bromo.

[00148] In a further aspect, R^4 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a yet further aspect, R^4 is selected from hydrogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R^4 is selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R^4 is hydrogen. In
25 a further aspect, wherein R^4 is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.

[00149] In a further aspect, R^4 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R^4 is selected from hydrogen, halogen, and C1-C3 alkyl. In a yet further aspect, R^4 is selected from hydrogen, chloro, fluoro, methyl and ethyl. In an even further

aspect, R⁴ is selected from hydrogen, methyl and ethyl. In a still further aspect, R⁴ is selected from hydrogen, chloro, and fluoro.

[00150] In a further aspect, each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.

5 [00151] In a further aspect, one of R⁴, R⁵, and R⁶ must be hydrogen. In a still further aspect, two of R⁴, R⁵, and R⁶ must be hydrogen. In a yet further aspect, R⁴ and R⁵ are both hydrogen. In an even further aspect, R⁴ and R⁶ are both hydrogen.

[00152] In a further aspect, R⁴ is hydrogen, and each of R⁵ and R⁶ is independently selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a still further
10 aspect, R⁴ is hydrogen, and each of R⁵ and R⁶ is independently selected from halogen, CN, and C1-C3 alkyl. In a yet further aspect, R⁴ is hydrogen, and each of R⁵ and R⁶ is independently selected from chloro, fluoro, CN, methyl and ethyl. In an even further aspect, R⁴ is hydrogen, and each of R⁵ and R⁶ is independently selected from fluoro, CN, methyl and ethyl.

f. R⁵ GROUPS

15 [00153] In one aspect, R⁵ is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a further aspect, R⁵ is hydrogen. In a yet further aspect, R⁵ and R⁶ are both hydrogen.

[00154] In a further aspect, the halogen is selected from chloro and fluoro. In a yet further aspect, the halogen is chloro. In a still further aspect, the halogen is fluoro. In an even further aspect, the halogen is
20 selected from fluoro, chloro and bromo.

[00155] In a further aspect, R⁵ is selected from hydrogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R⁵ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.

[00156] In a further aspect, R⁵ is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R⁵ is selected from hydrogen, halogen, and C1-C3 alkyl.
25 In a yet further aspect, R⁵ is selected from hydrogen, chloro, fluoro, CN, methyl, trifluoromethyl, and ethyl. In an even further aspect, R⁵ is selected from hydrogen, methyl, trifluoromethyl, and ethyl. In a still further aspect, wherein R⁵ is selected from hydrogen, CN, chloro, and fluoro.

[00157] In a further aspect, R⁵ is hydrogen, and each of R⁴ and R⁶ is independently selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a still further
30 aspect, R⁵ is hydrogen, and each of R⁴ and R⁶ is independently selected from halogen, CN, and C1-C3

alkyl. In a yet further aspect, R⁵ is hydrogen, and each of R⁴ and R⁶ is independently selected from chloro, fluoro, CN, methyl and ethyl. In an even further aspect, R⁵ is hydrogen, and each of R⁴ and R⁶ is independently selected from fluoro, CN, methyl and ethyl.

g. R⁶ GROUPS

- 5 [00158] In one aspect, R⁶ is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R⁶ is hydrogen.

[00159] In a further aspect, the halogen is selected from chloro and fluoro. In a yet further aspect, the halogen is chloro. In a still further aspect, the halogen is fluoro. In an even further aspect, the halogen is selected from fluoro, chloro and bromo.

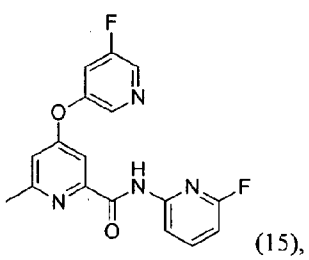
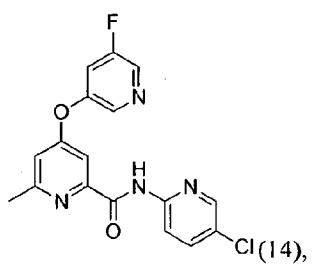
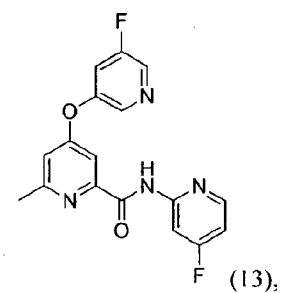
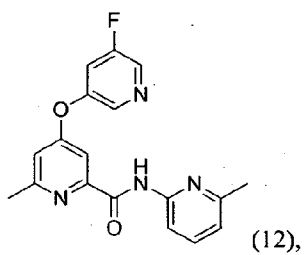
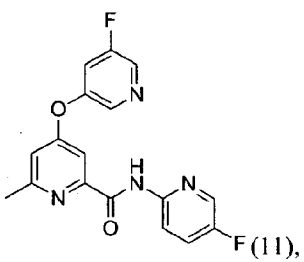
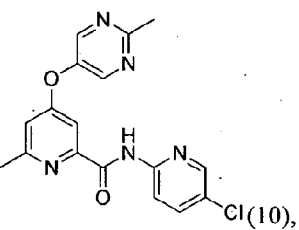
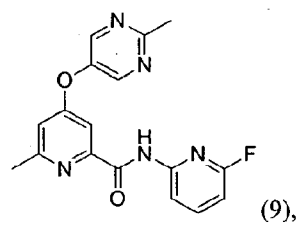
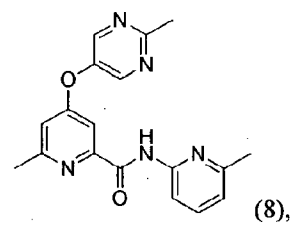
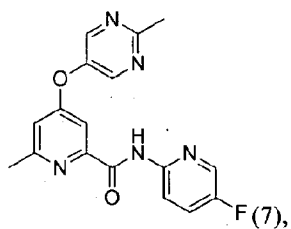
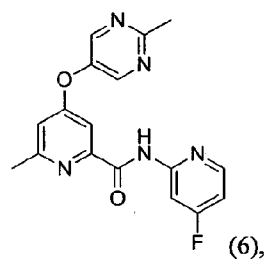
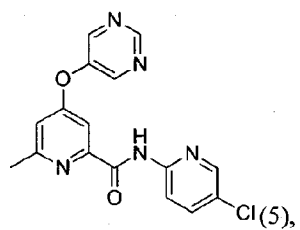
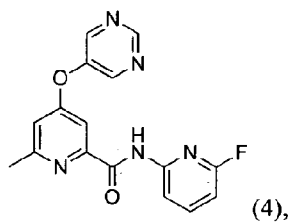
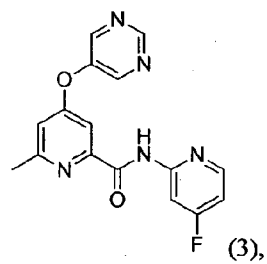
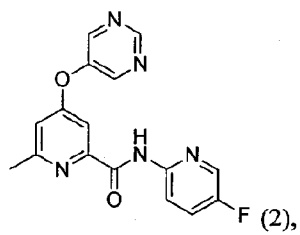
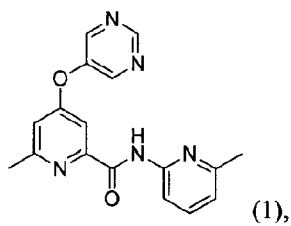
- 10 [00160] In a further aspect, R⁶ is selected from hydrogen, halogen, CN, and C1-C3 alkyl. In a yet further aspect, R⁶ is selected from hydrogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R⁶ is selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In an even further aspect, R⁶ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.

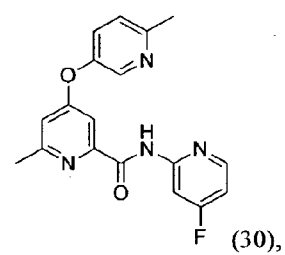
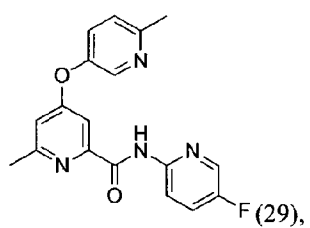
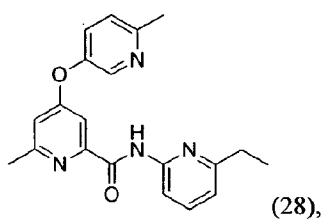
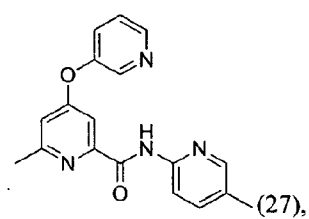
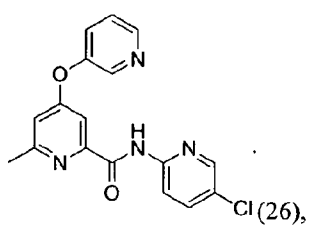
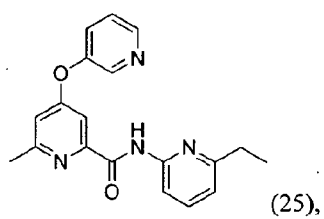
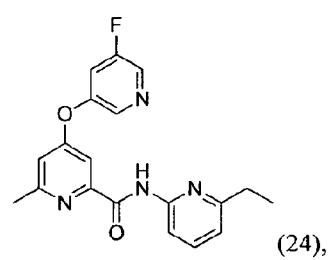
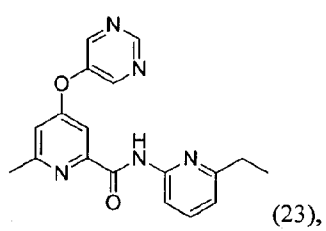
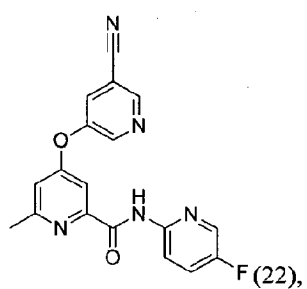
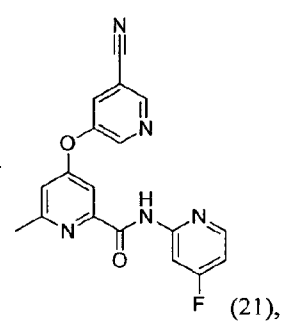
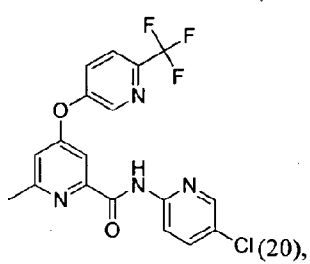
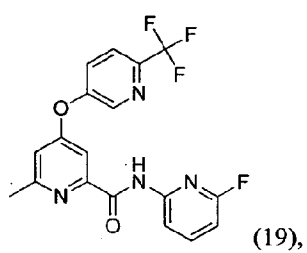
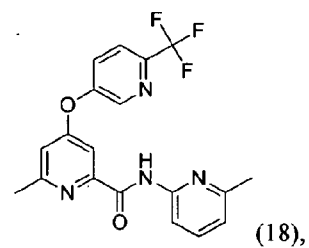
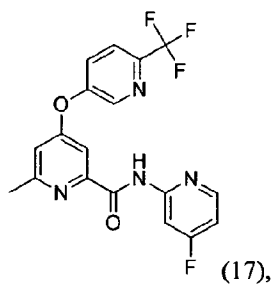
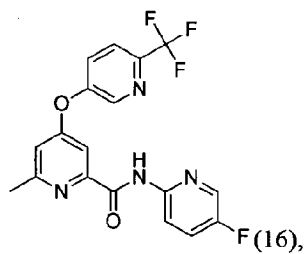
- 15 [00161] In a further aspect, R⁶ is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl. In a still further aspect, R⁶ is selected from hydrogen, halogen, and C1-C3 alkyl. In a yet further aspect, R⁶ is selected from hydrogen, chloro, fluoro, CN, and methyl. In an even further aspect, R⁶ is selected from hydrogen, fluoro, CN, and methyl. In a still further aspect, R⁶ is selected from hydrogen, CN, and methyl. In a yet further aspect, R⁶ is selected from hydrogen, CN, chloro, and fluoro.
- 20 In an even further aspect, R⁶ is selected from hydrogen, CN, and fluoro. In a yet further aspect, R⁶ is selected from hydrogen, CN, fluoro, and methyl. In a still further aspect, R⁶ is selected from hydrogen, CN, chloro, fluoro, and methyl.

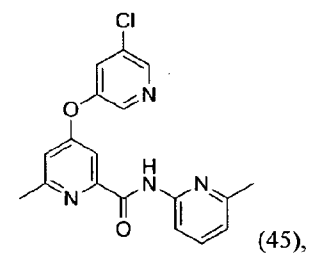
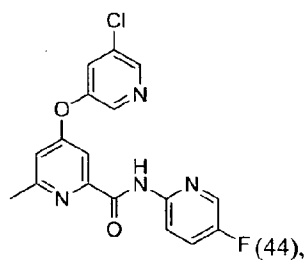
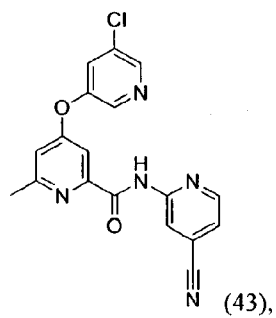
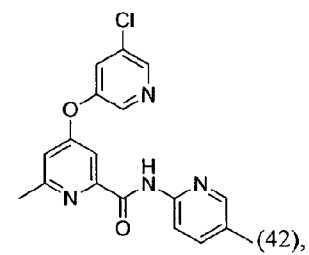
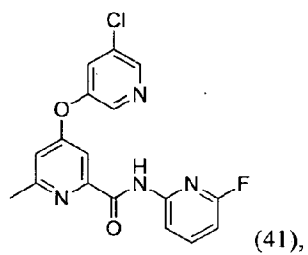
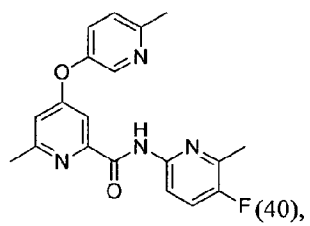
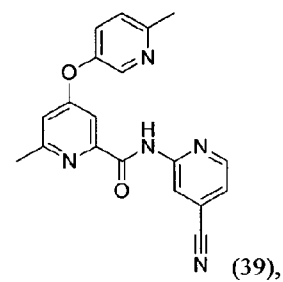
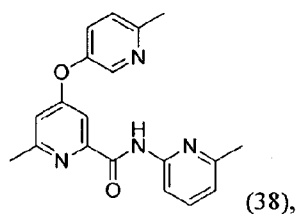
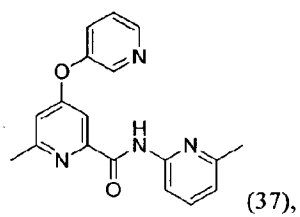
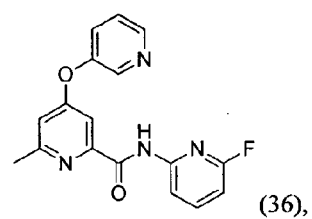
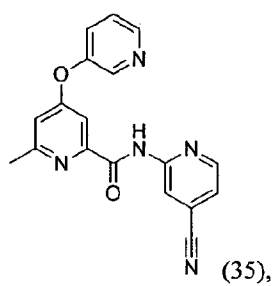
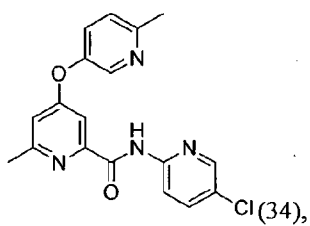
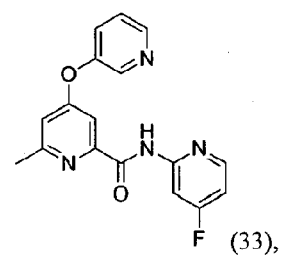
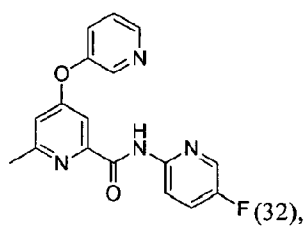
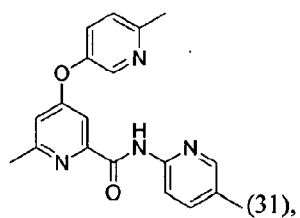
- [00162] In a further aspect, R⁶ is hydrogen, and each of R⁴ and R⁵ is independently selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R⁶ is hydrogen, and each of R⁴ and R⁵ is independently selected from halogen, CN, and C1-C3 alkyl. In a yet further aspect, R⁶ is hydrogen, and each of R⁴ and R⁵ is independently selected from halogen, CN, and C1-C3 alkyl. In an even further aspect, R⁶ is hydrogen, and each of R⁴ and R⁵ is independently selected from fluoro, CN, methyl and ethyl.
- 25

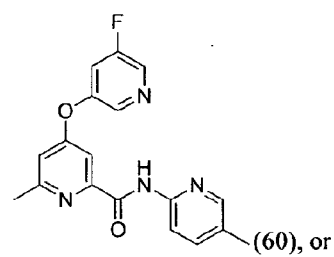
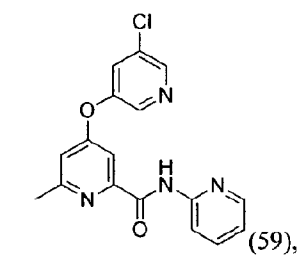
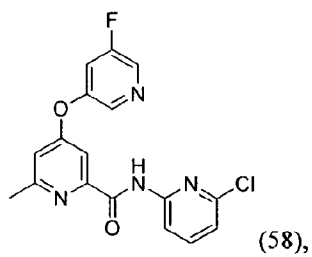
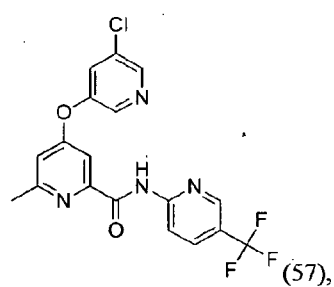
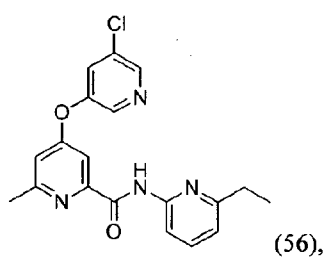
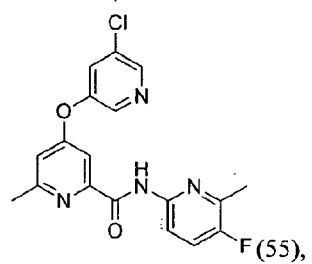
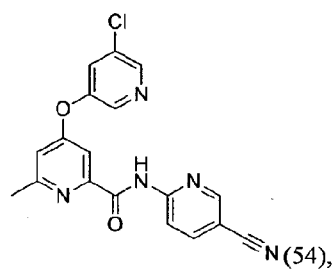
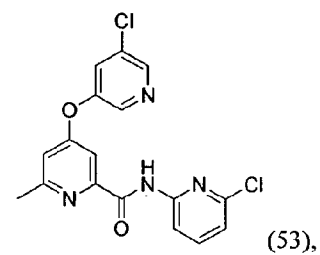
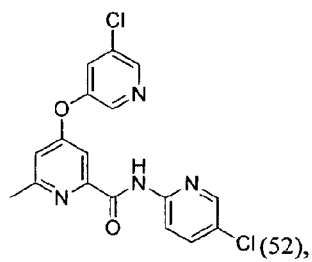
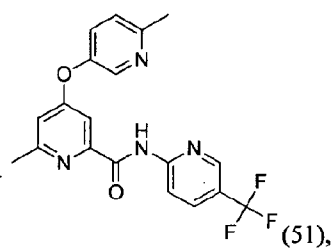
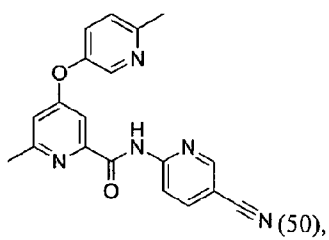
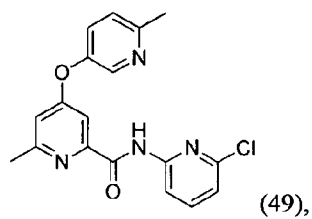
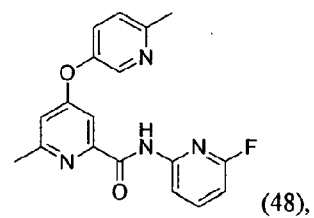
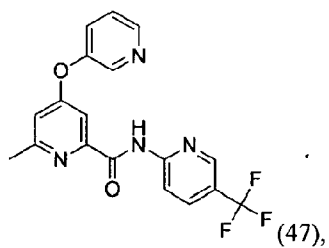
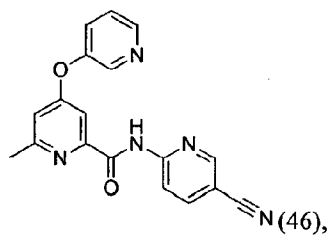
2. EXAMPLE STRUCTURES

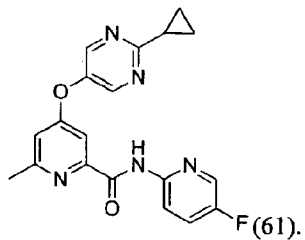
[00163] In one aspect, a compound can be present as:



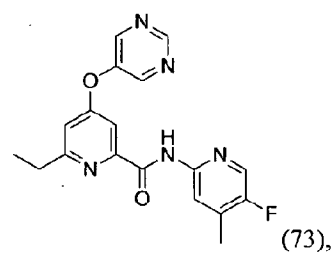
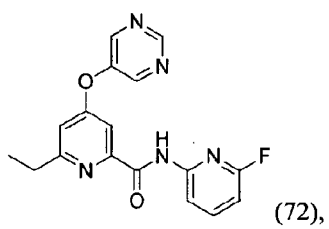
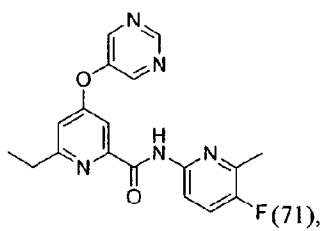
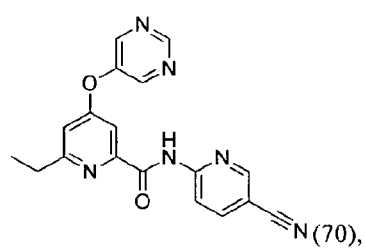
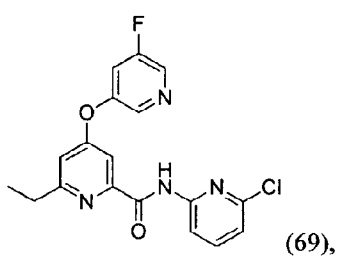
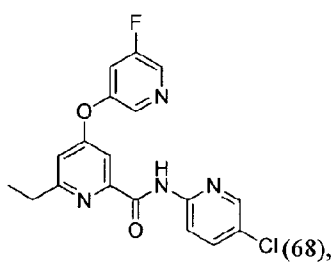
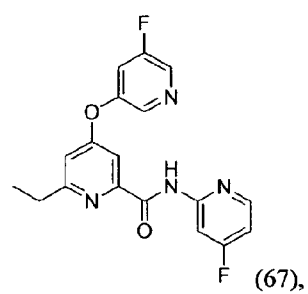
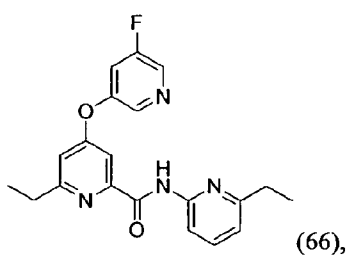
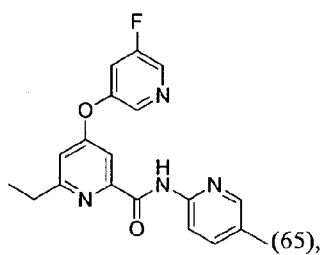
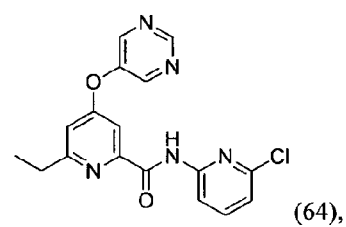
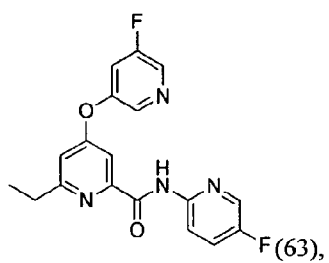
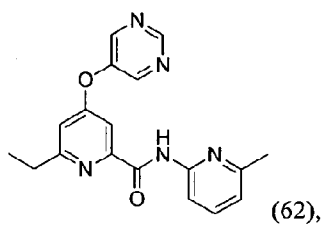


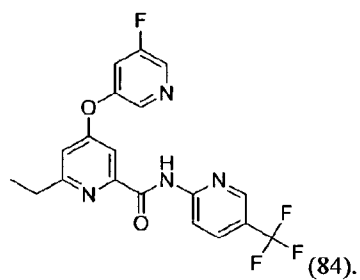
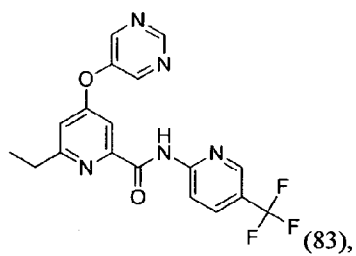
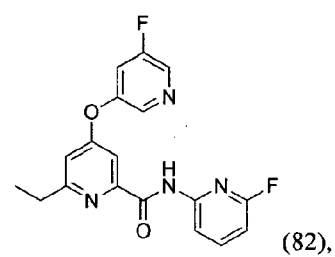
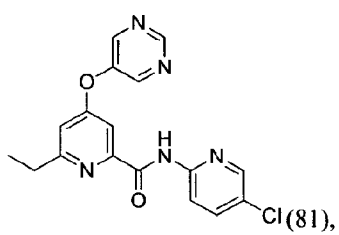
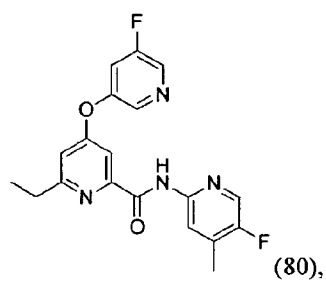
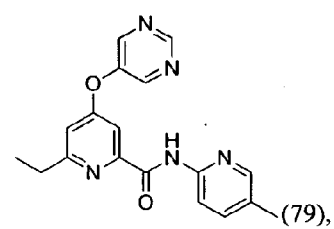
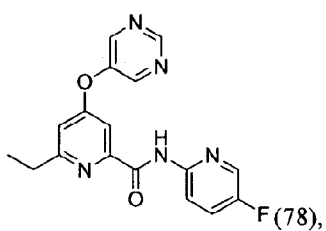
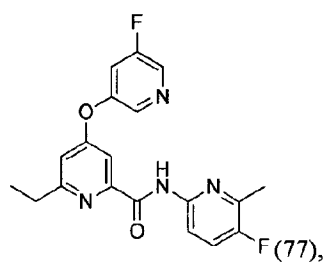
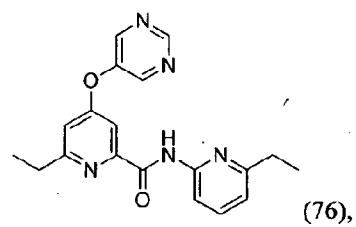
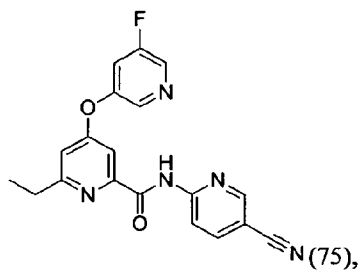
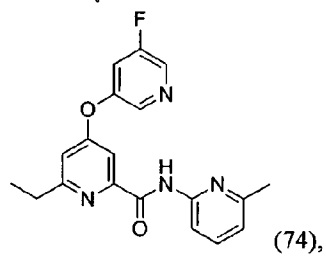






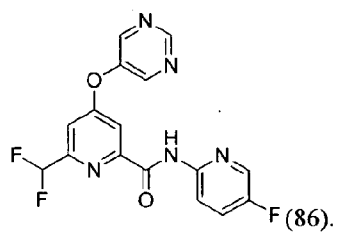
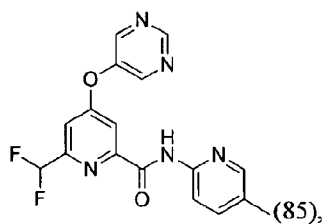
[00164] In a further aspect, a compound can be present as:





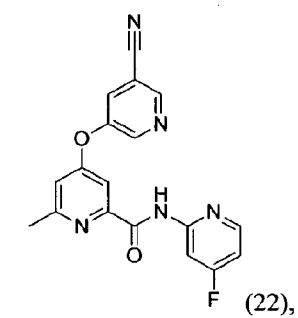
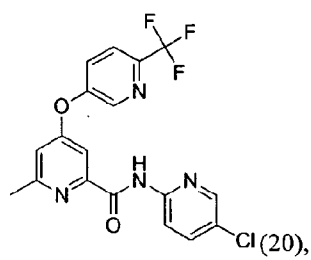
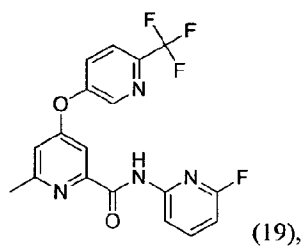
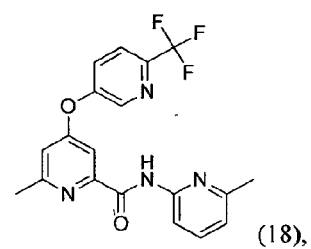
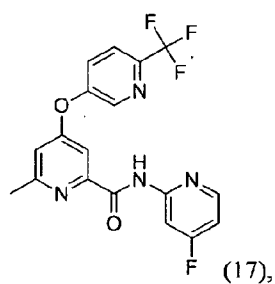
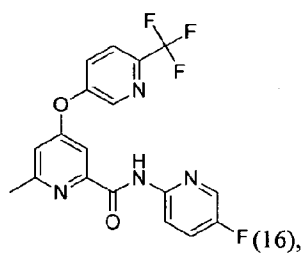
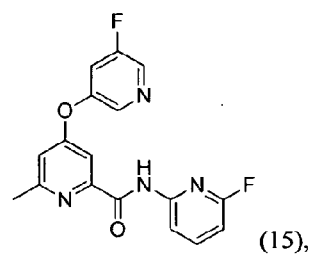
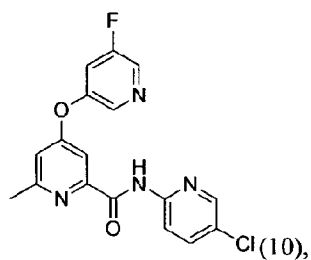
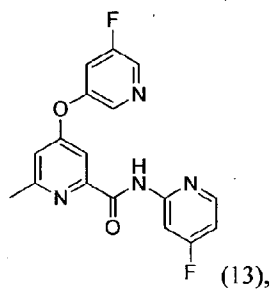
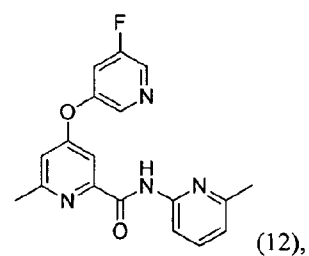
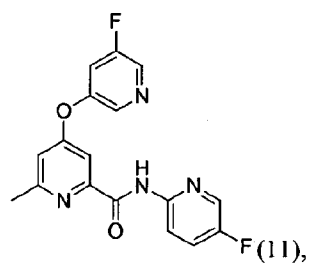
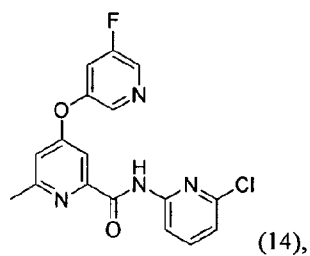
or

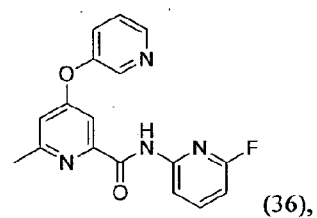
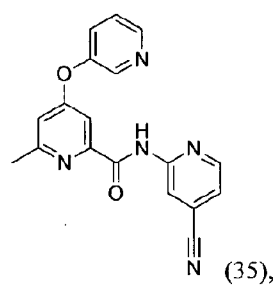
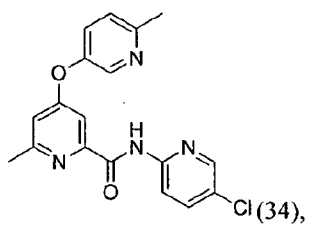
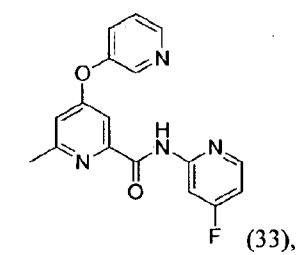
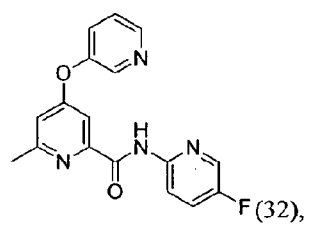
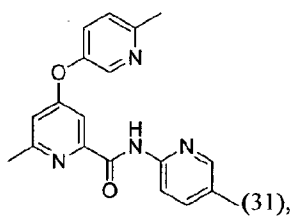
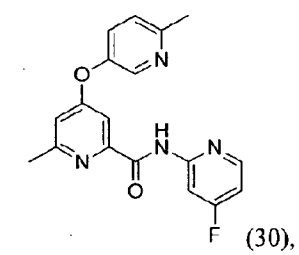
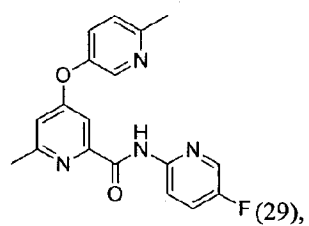
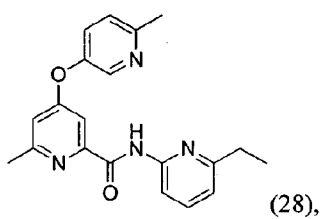
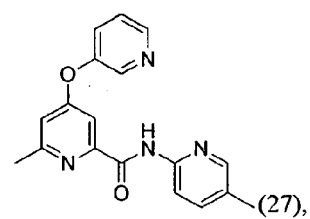
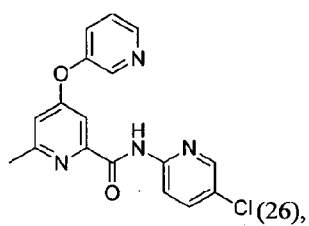
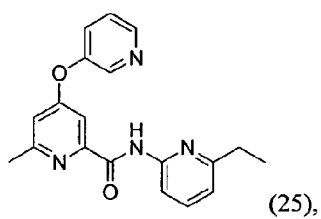
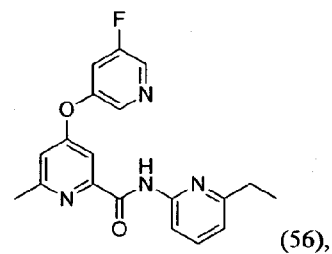
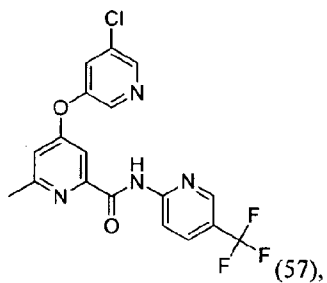
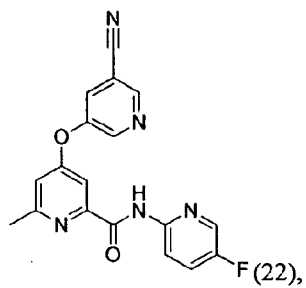
[00165] In a yet further aspect, a compound can be present as:

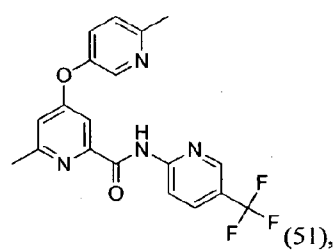
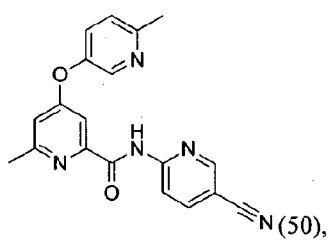
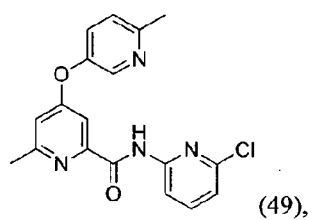
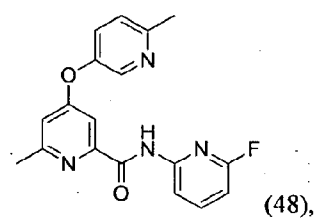
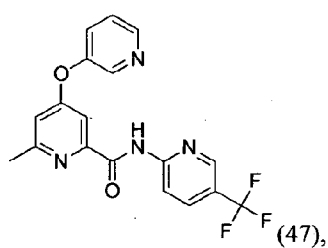
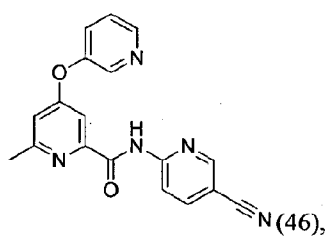
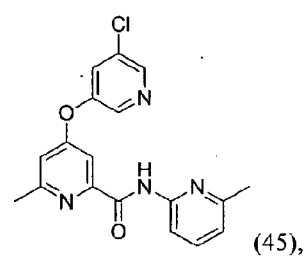
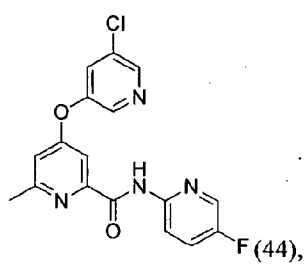
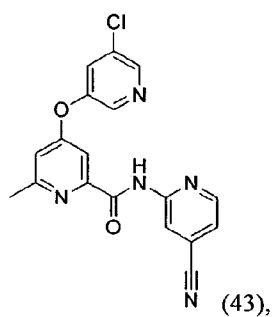
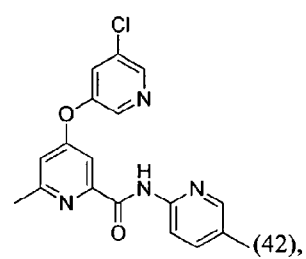
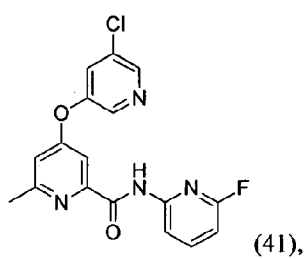
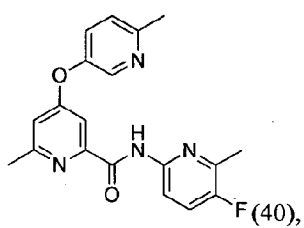
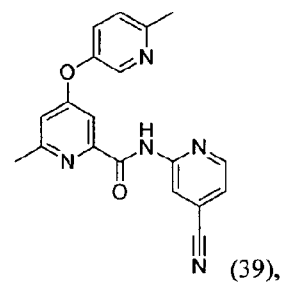
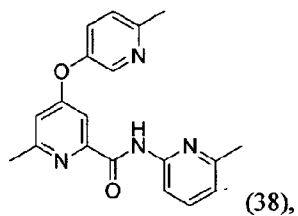
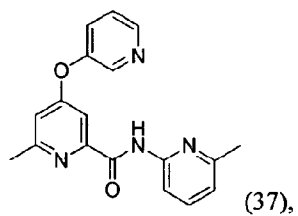


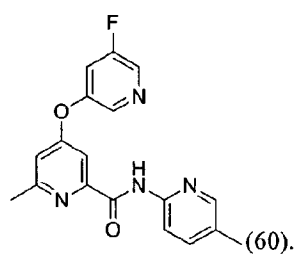
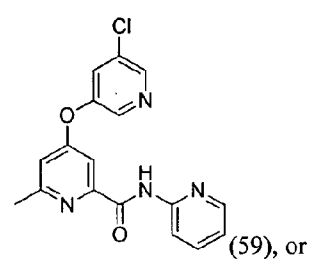
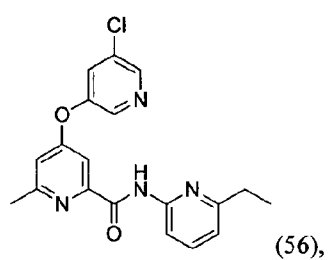
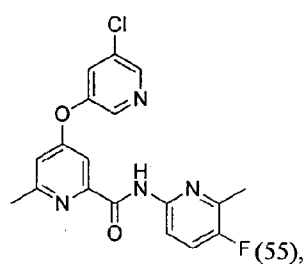
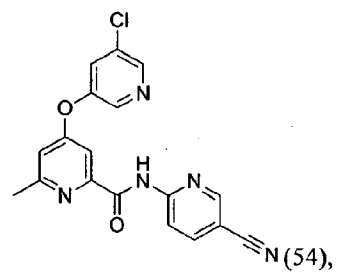
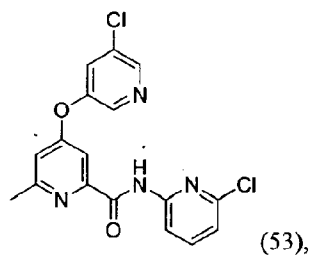
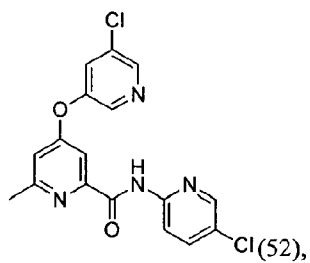
or

[00166] In a still further aspect, a compound can be present as:

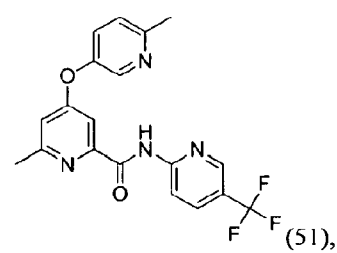
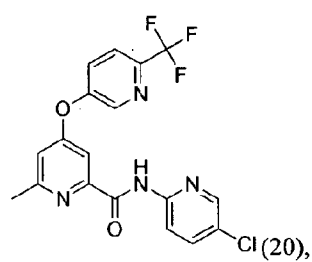
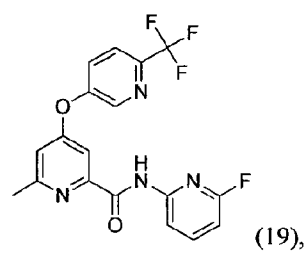
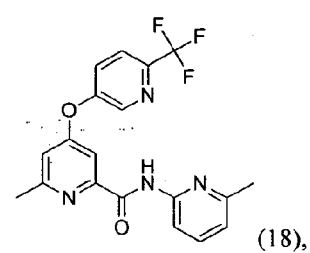
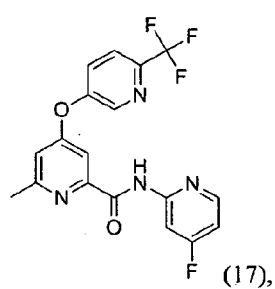
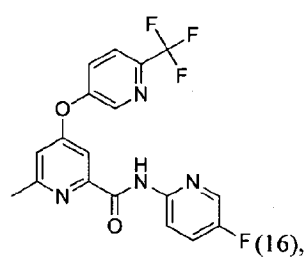


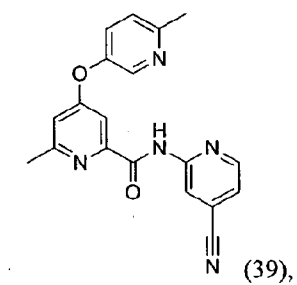
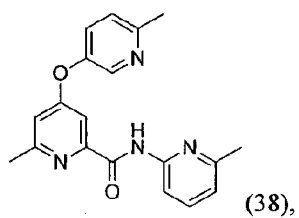
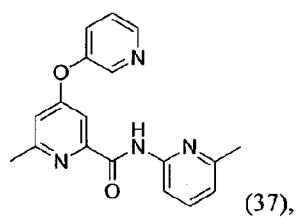
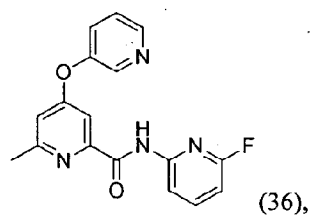
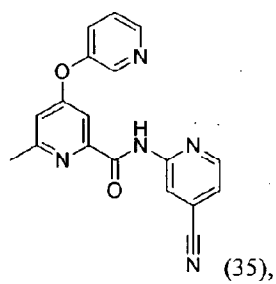
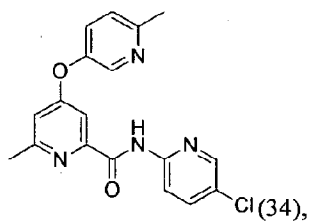
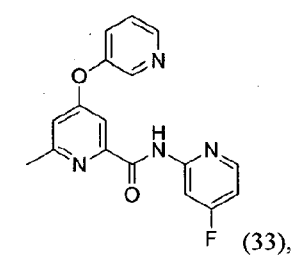
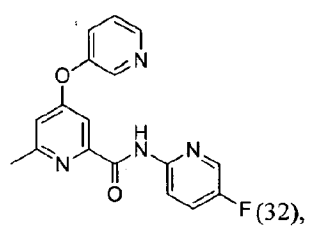
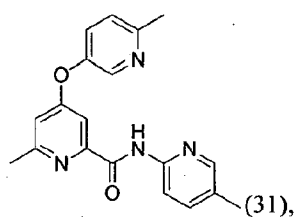
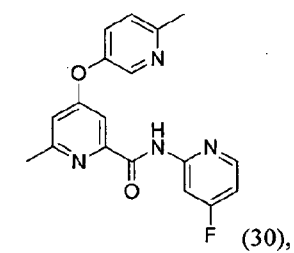
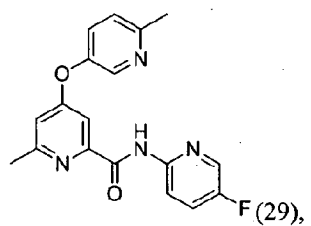
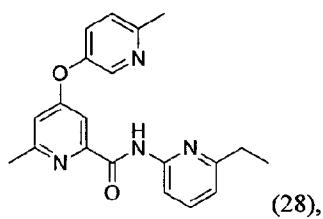
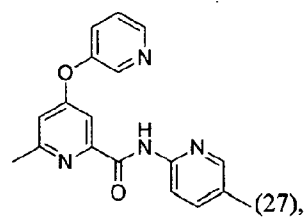
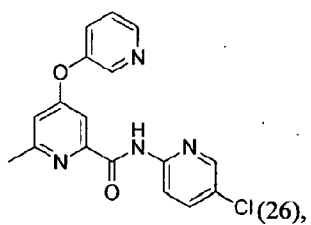
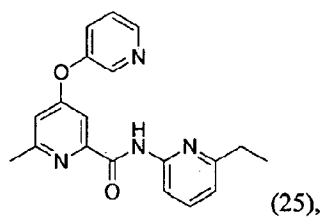


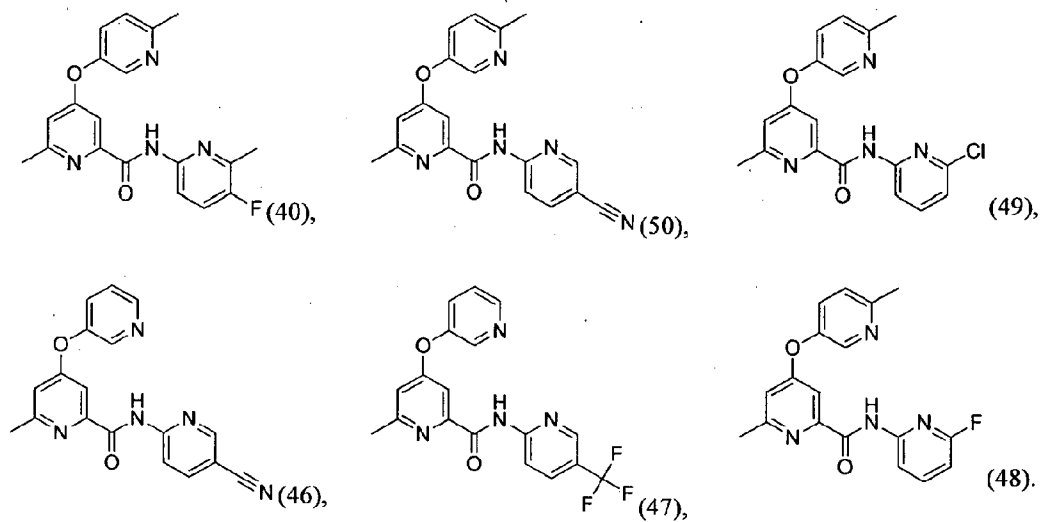




[00167] In an even further aspect, a compound can be present as:

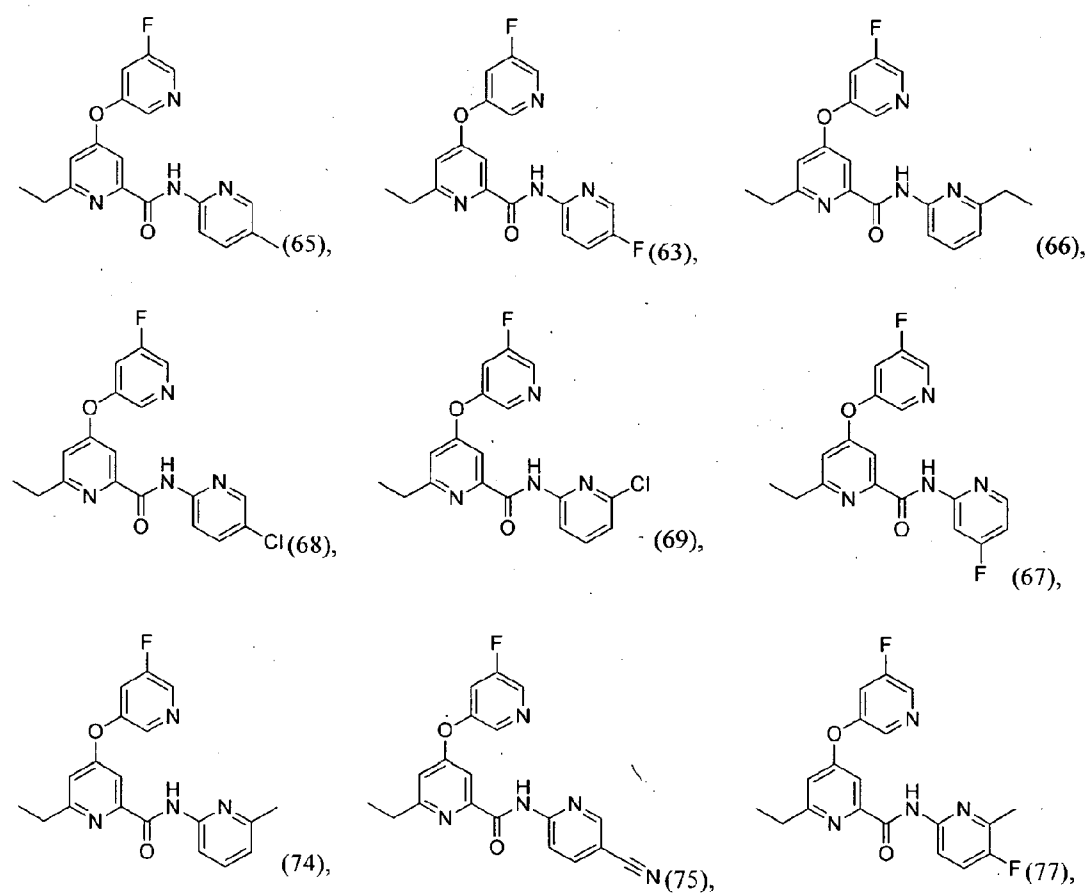


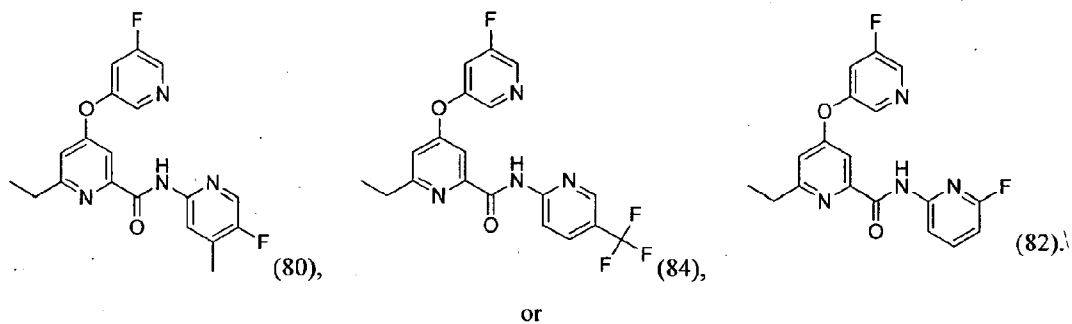




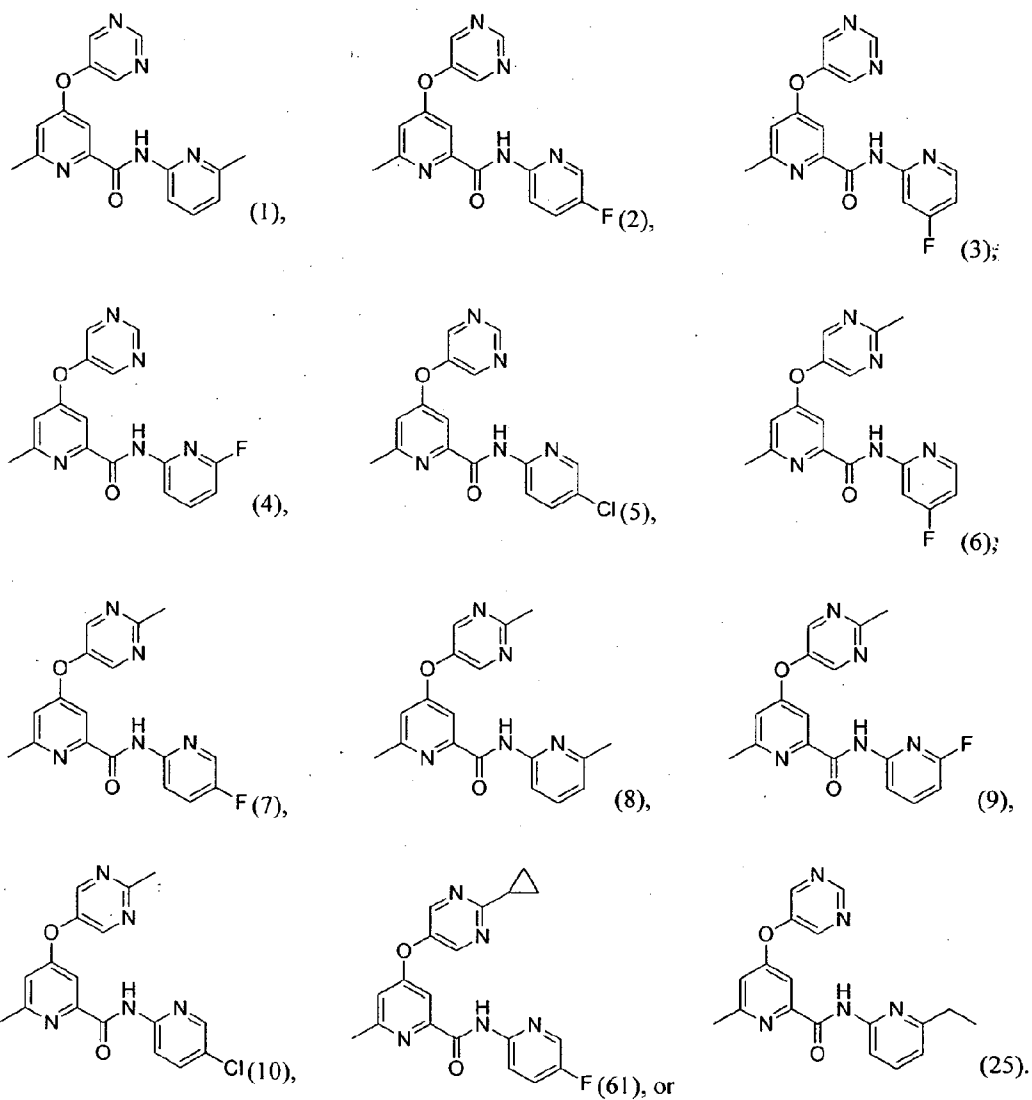
or

[00168] In a further aspect, a compound can be present as:

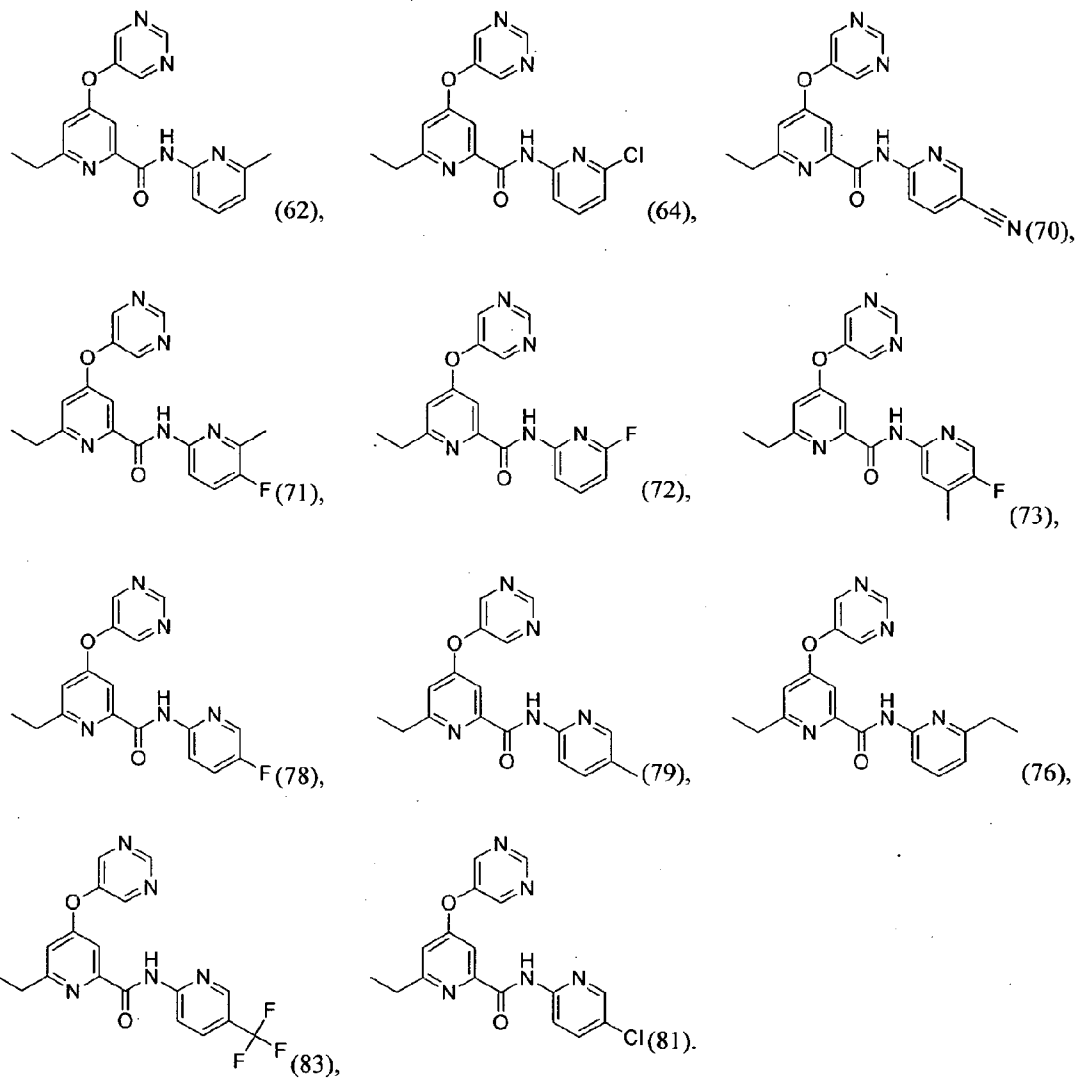




[00169] In a yet further aspect, a compound can be present as:

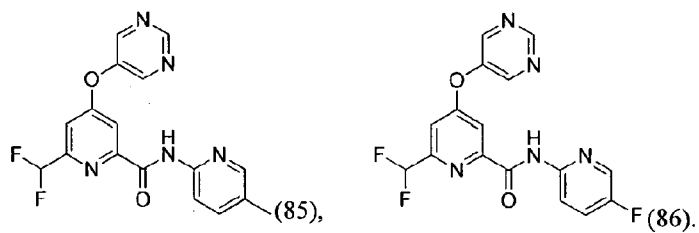


[00170] In a still further aspect, a compound can be present as:



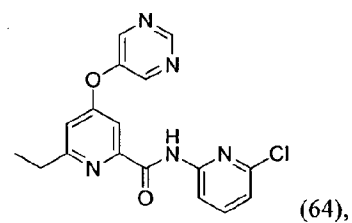
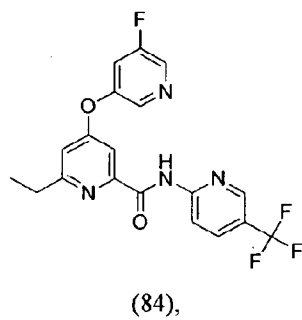
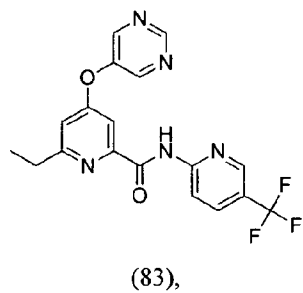
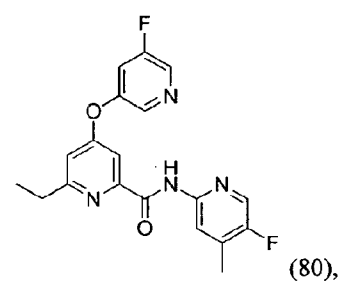
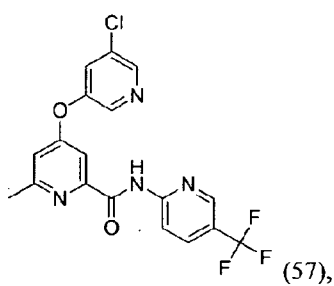
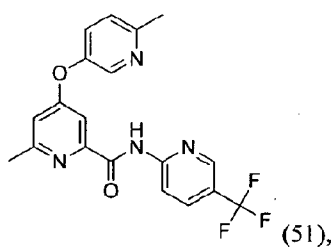
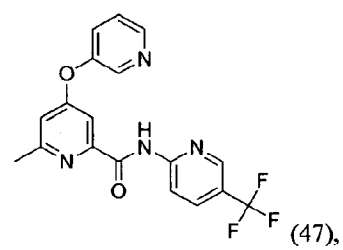
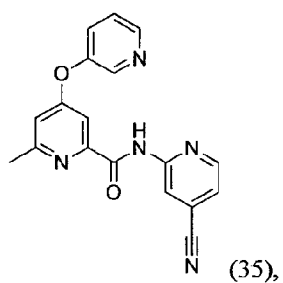
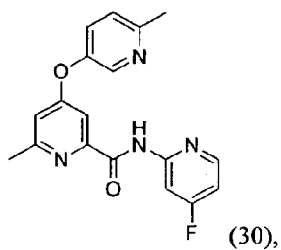
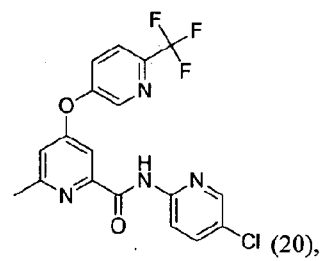
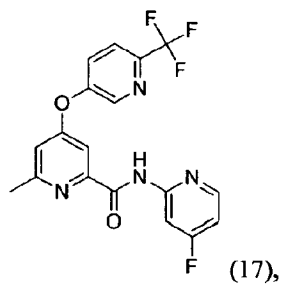
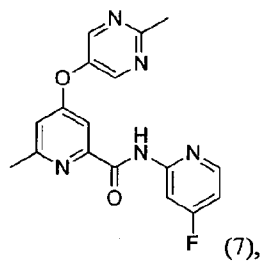
or

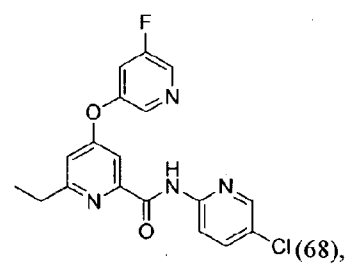
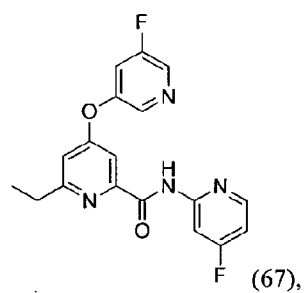
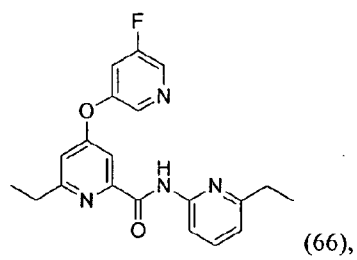
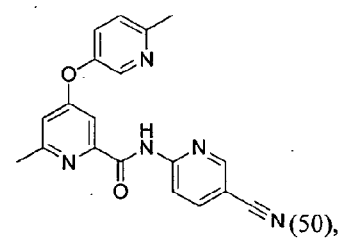
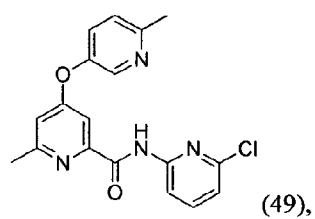
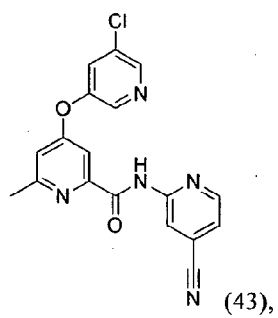
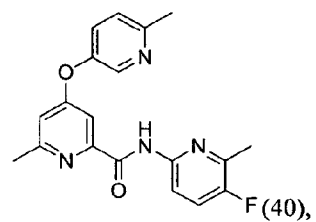
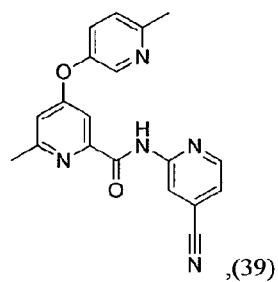
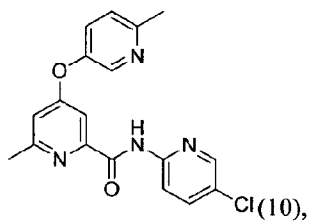
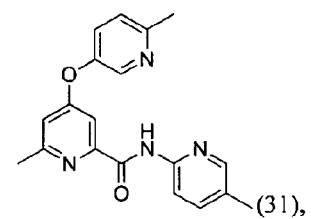
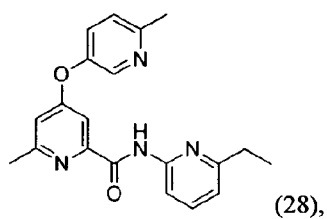
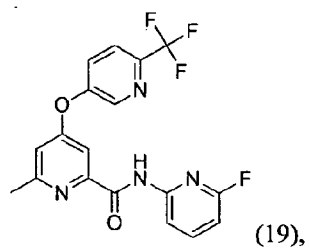
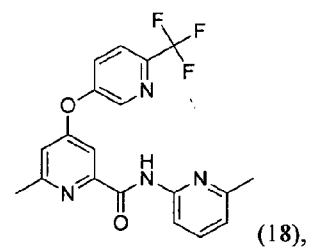
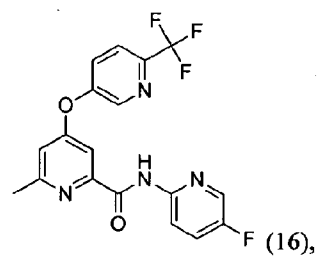
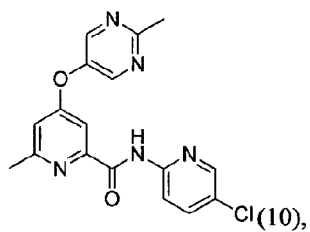
[00171] In an even further aspect, a compound can be present as:

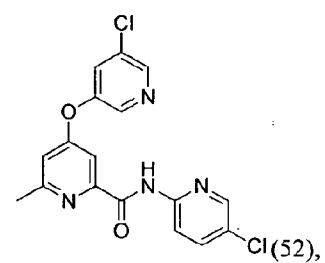
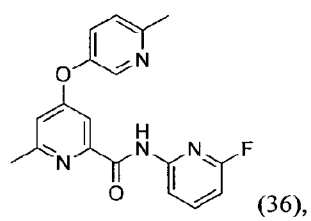
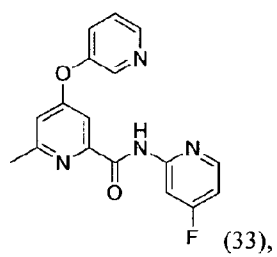
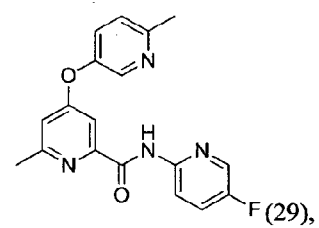
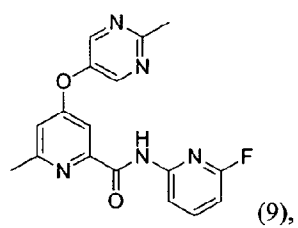
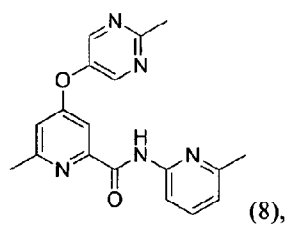
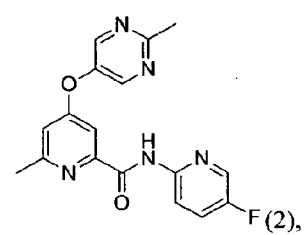
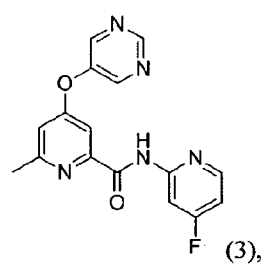
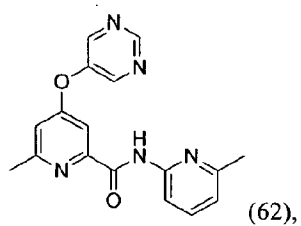
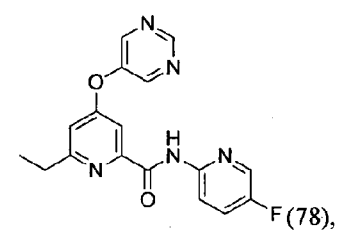
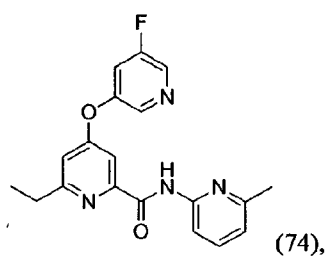
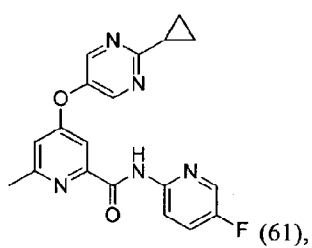
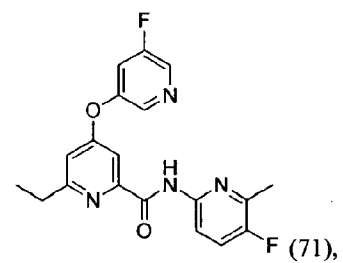
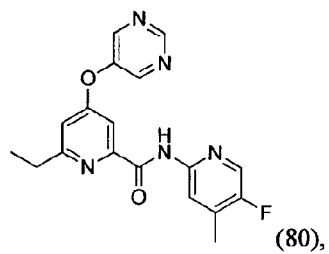
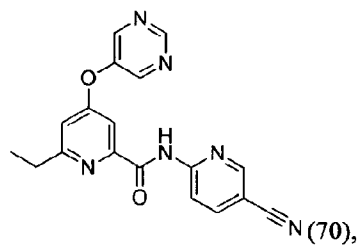


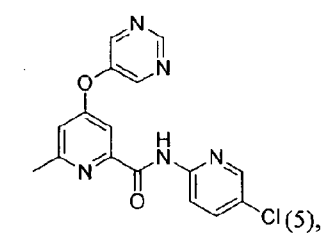
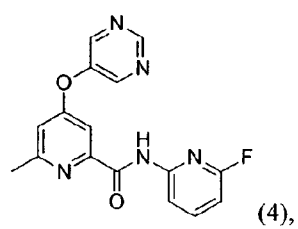
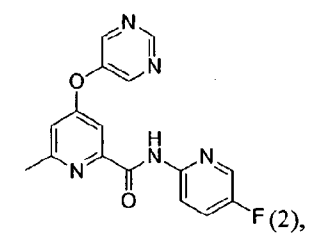
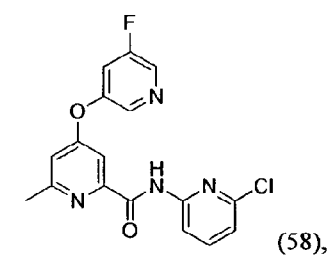
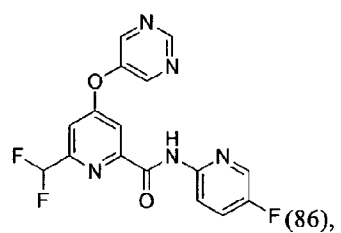
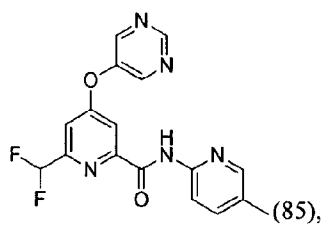
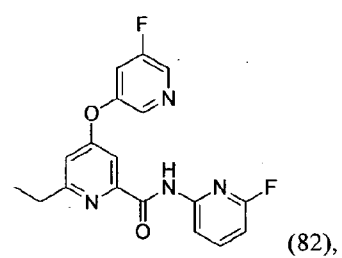
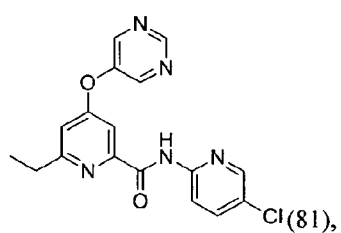
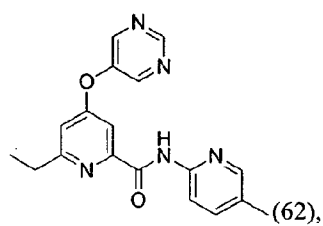
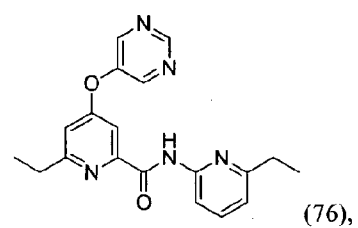
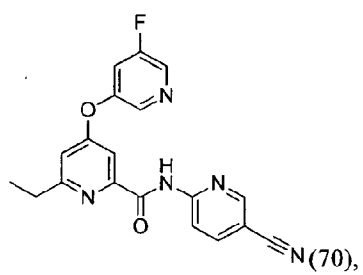
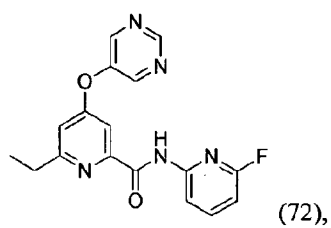
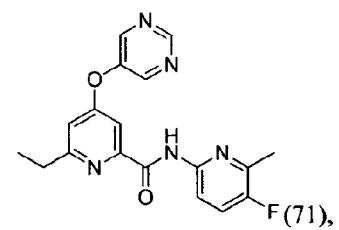
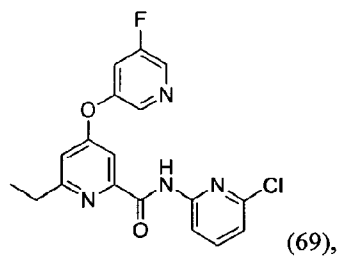
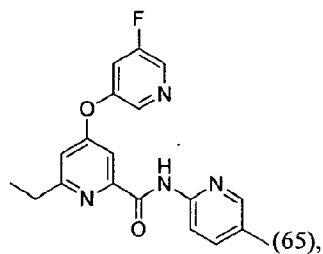
or

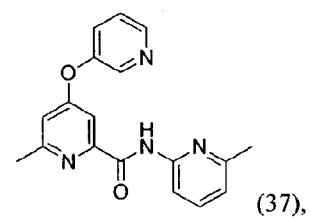
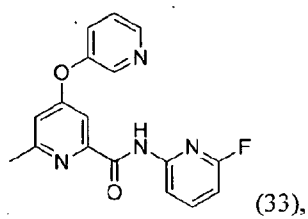
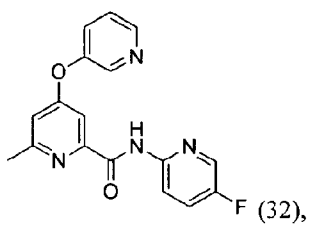
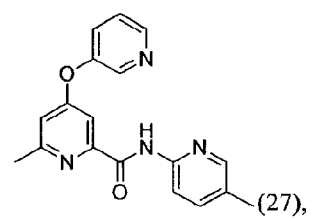
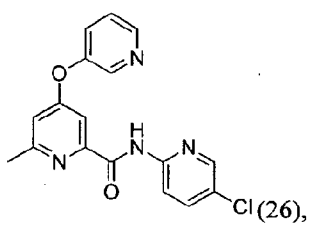
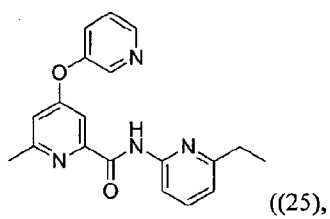
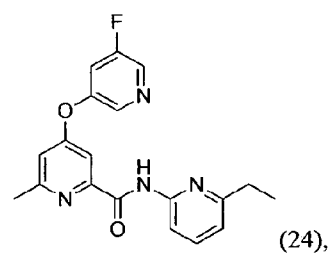
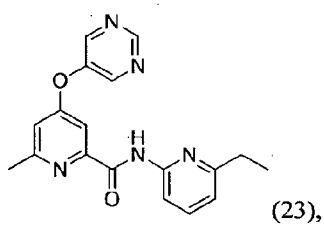
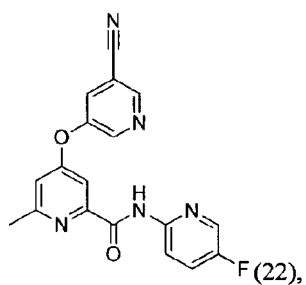
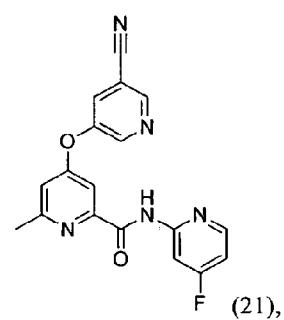
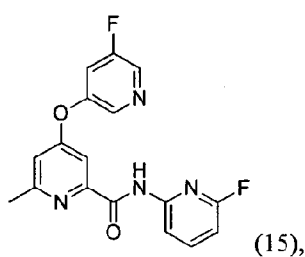
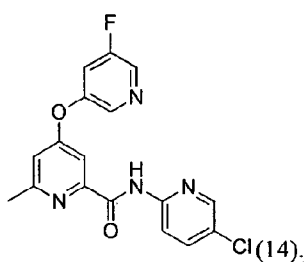
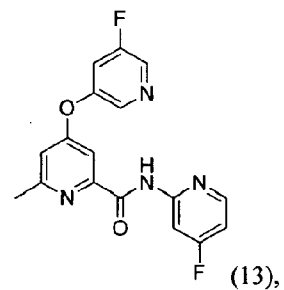
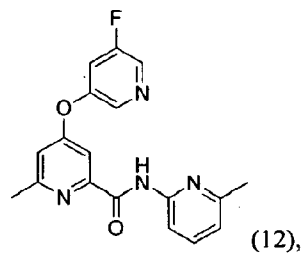
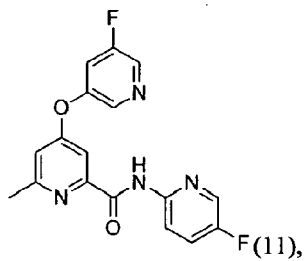
[00172] In a further aspect, a compound can be present as:

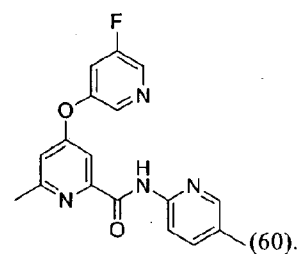
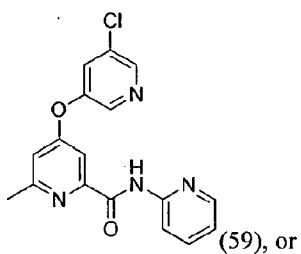
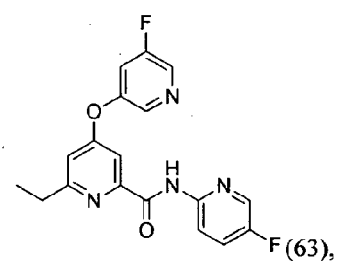
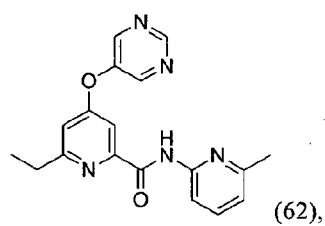
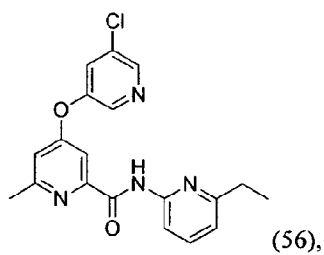
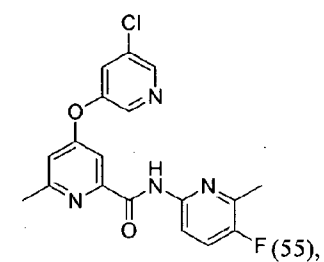
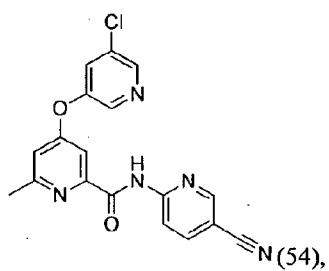
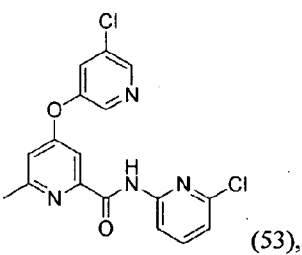
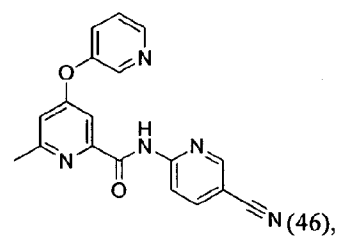
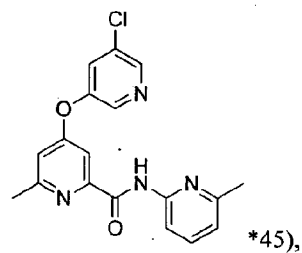
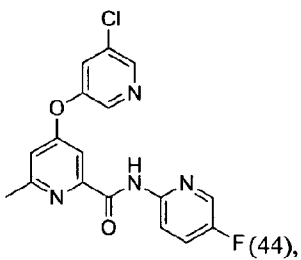
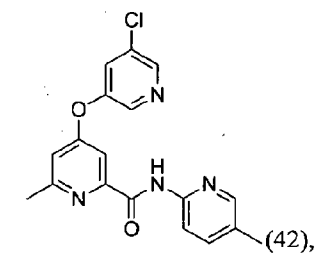
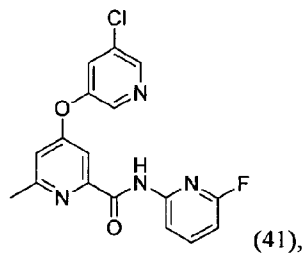
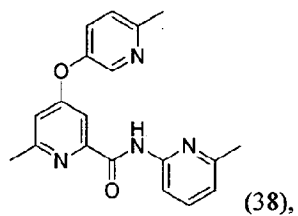




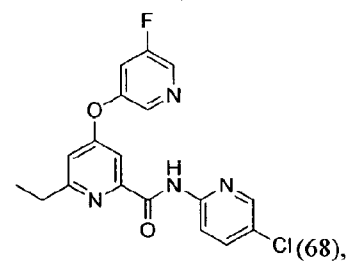
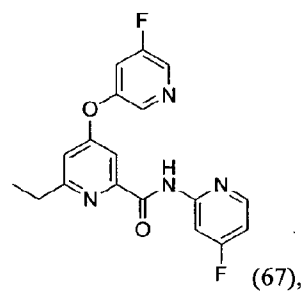
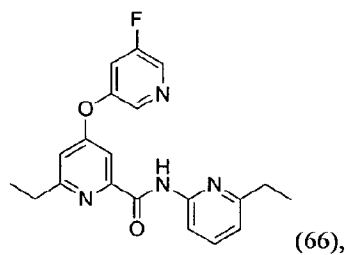
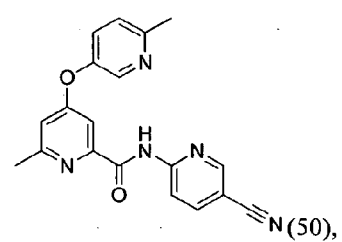
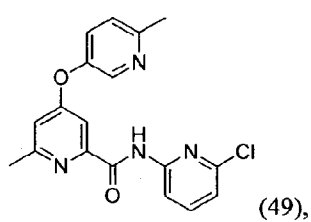
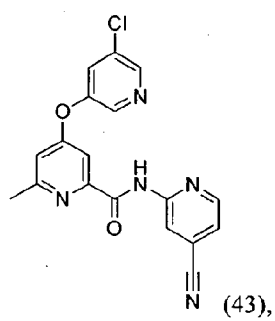
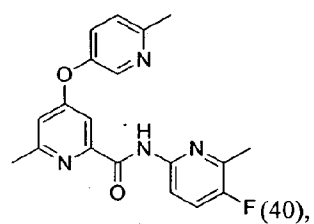
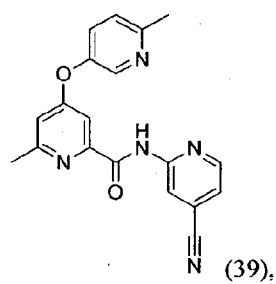
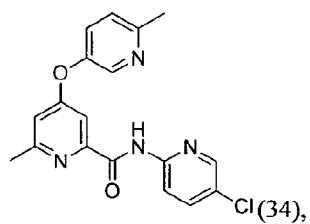
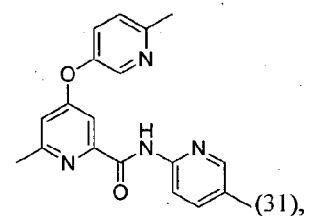
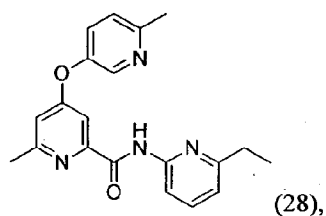
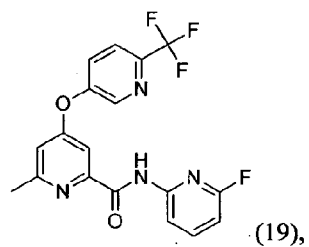
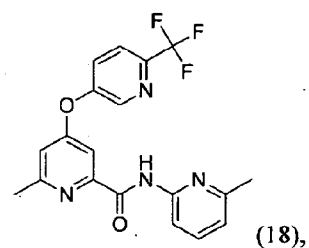
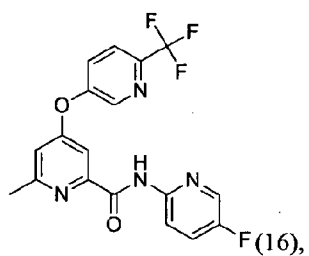
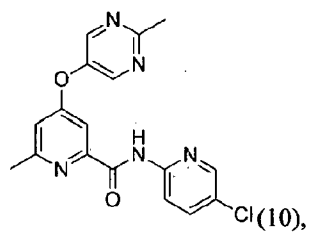


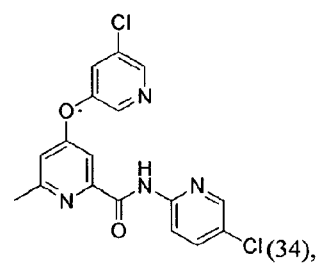
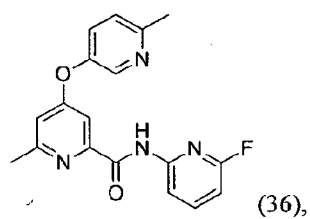
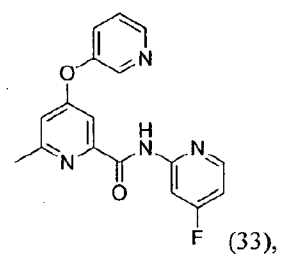
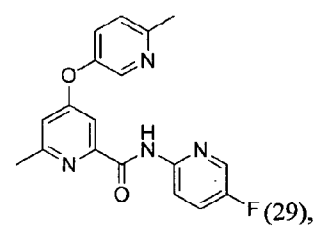
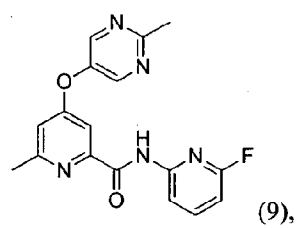
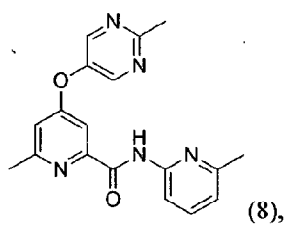
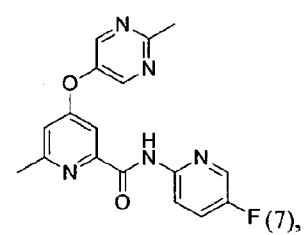
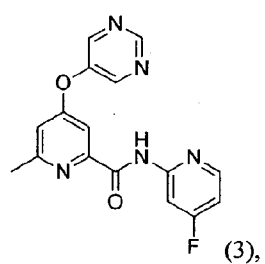
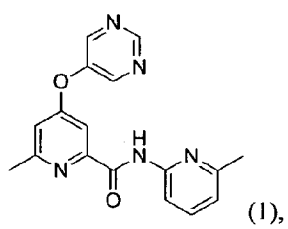
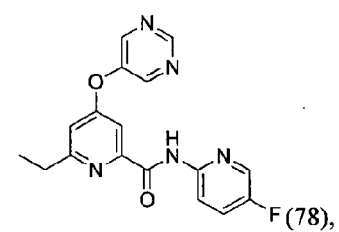
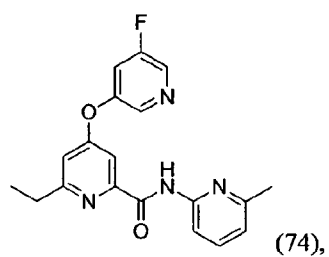
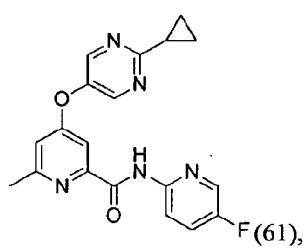
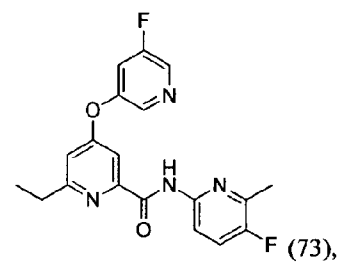
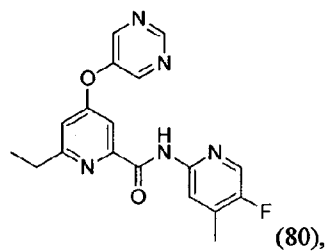
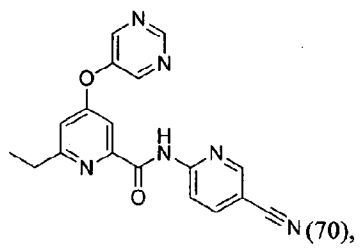


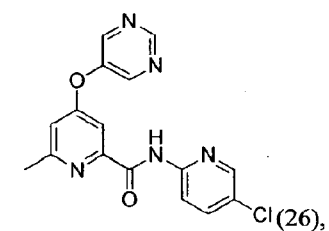
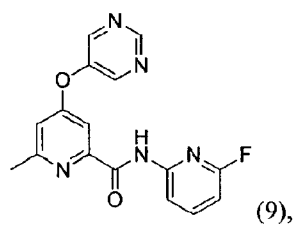
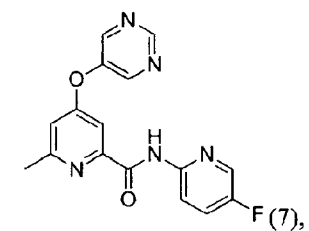
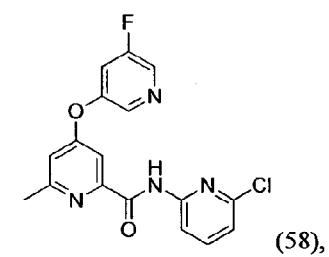
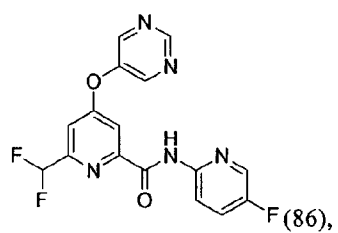
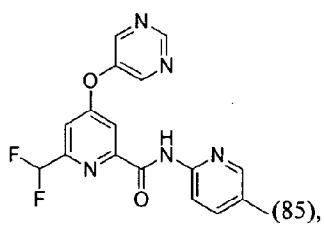
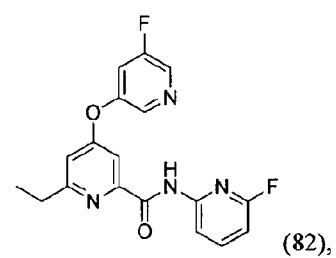
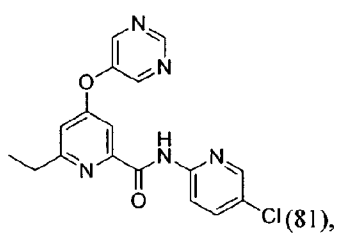
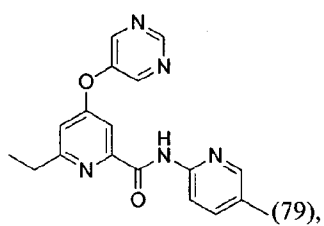
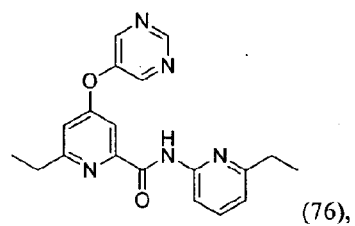
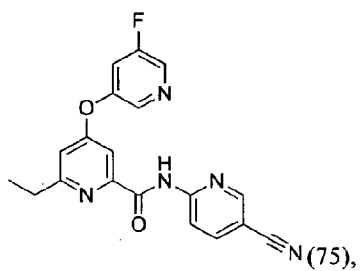
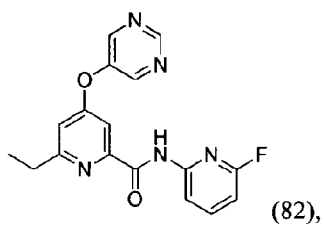
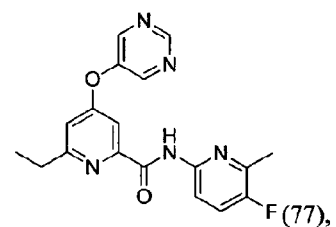
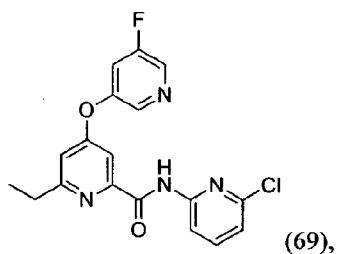
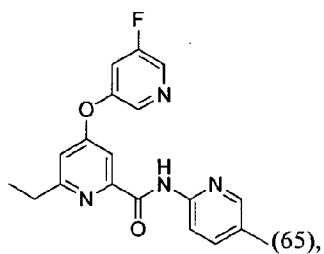


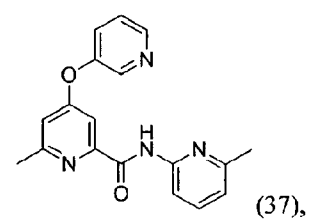
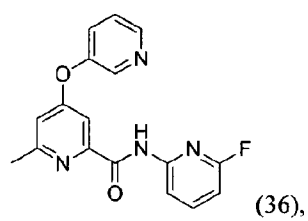
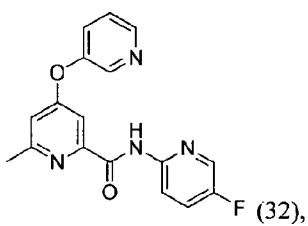
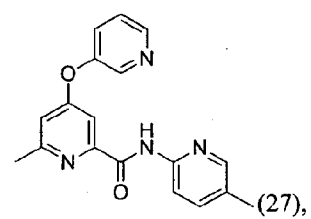
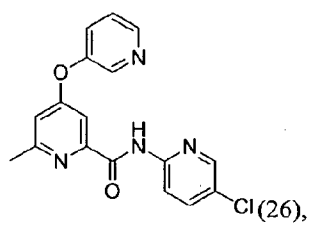
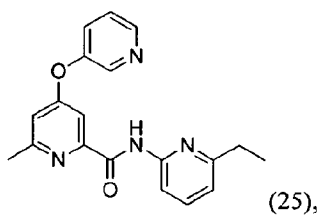
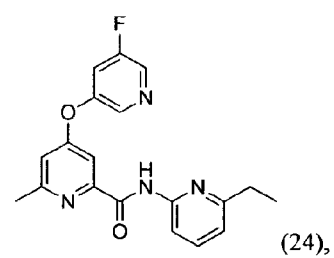
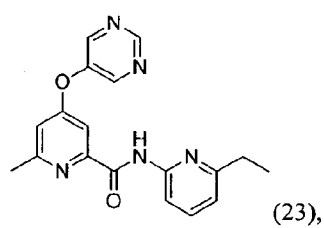
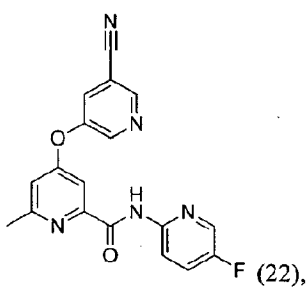
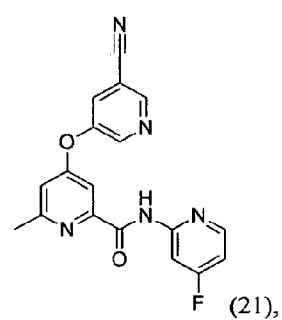
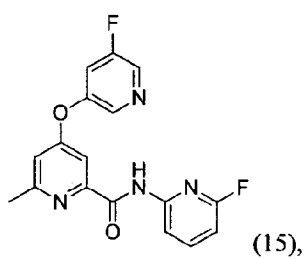
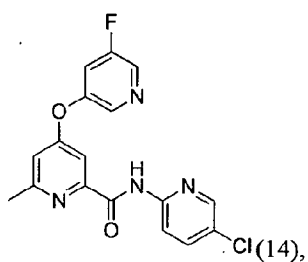
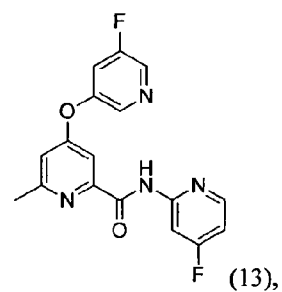
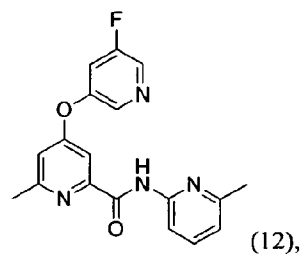
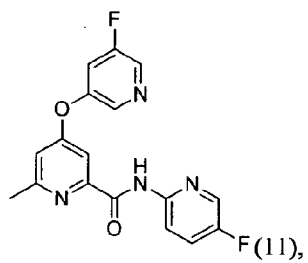


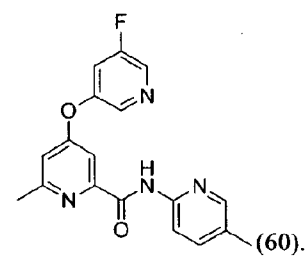
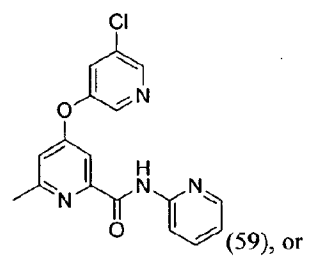
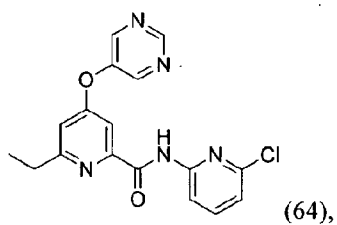
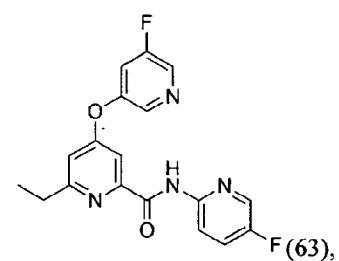
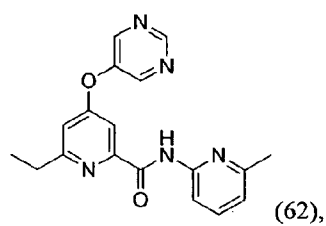
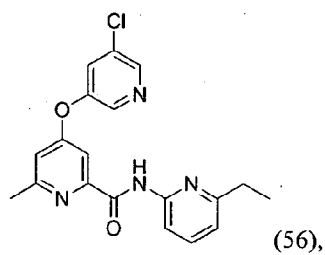
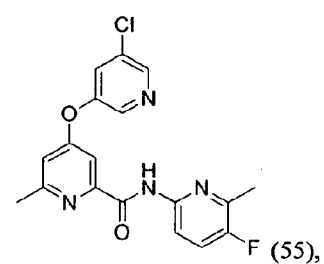
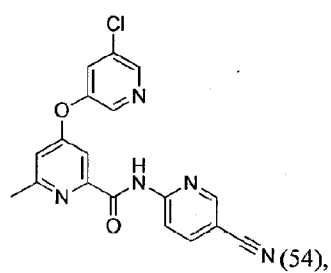
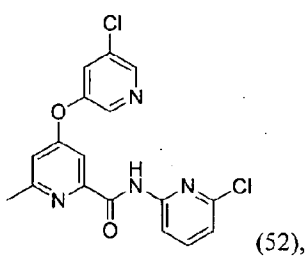
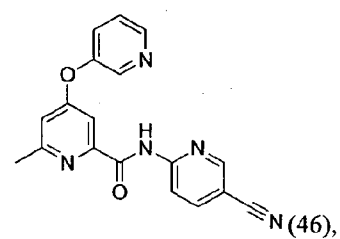
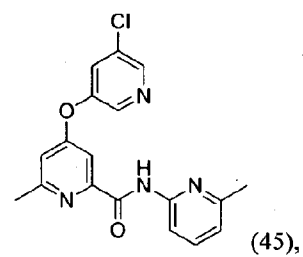
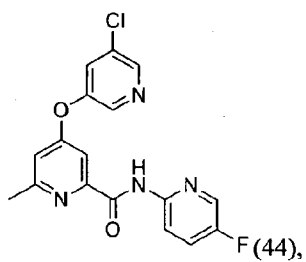
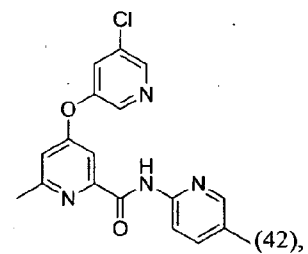
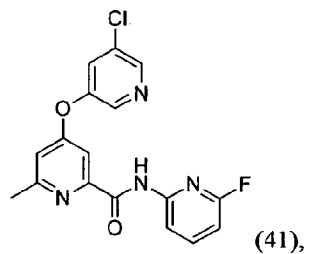
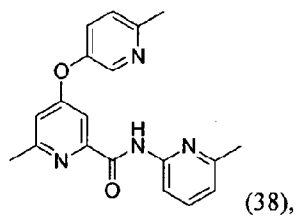
[00173] In a yet further aspect, a compound can be present as:



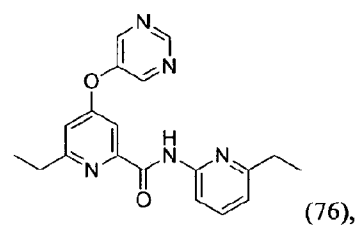
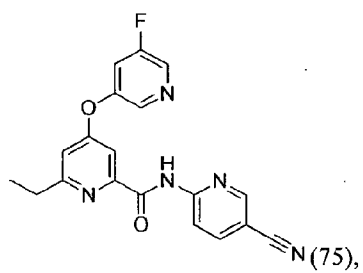
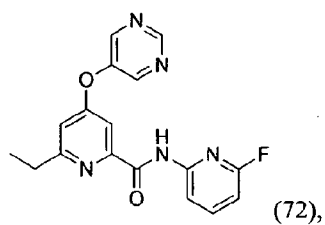
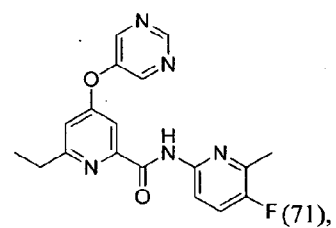
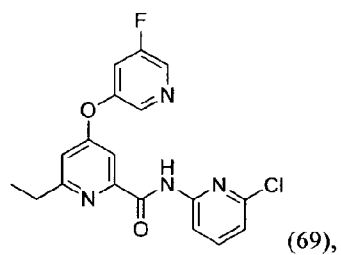
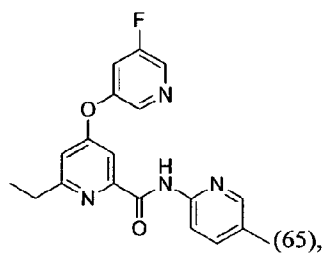
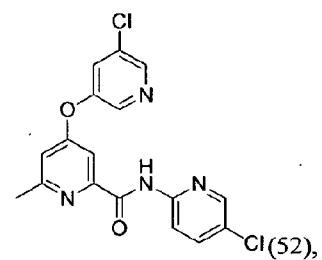
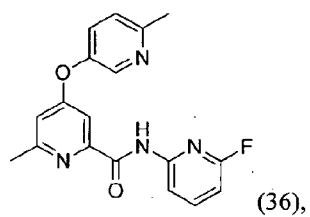
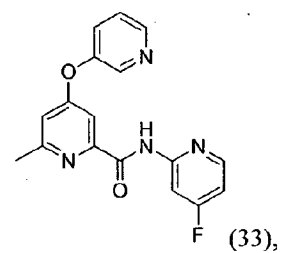
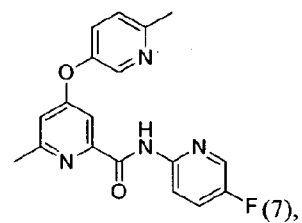
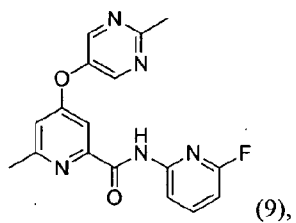
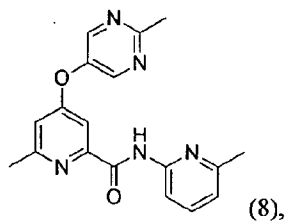
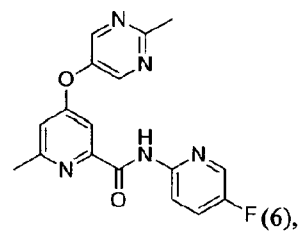
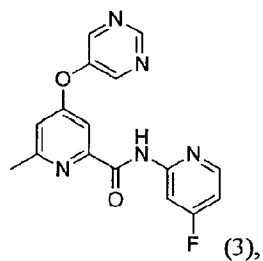
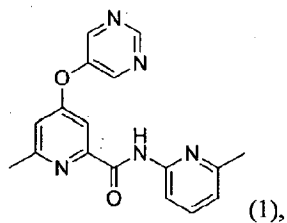


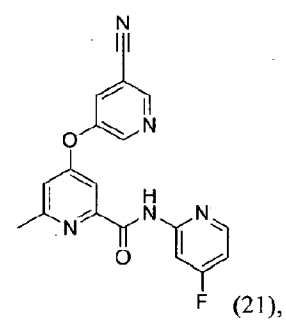
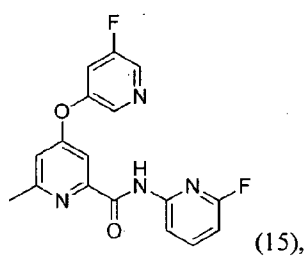
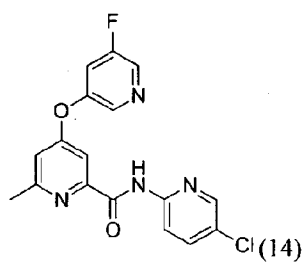
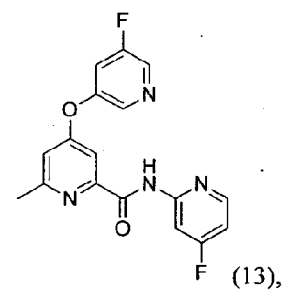
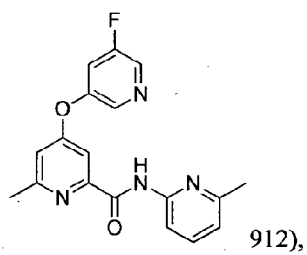
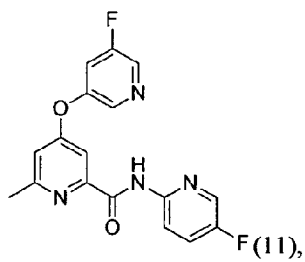
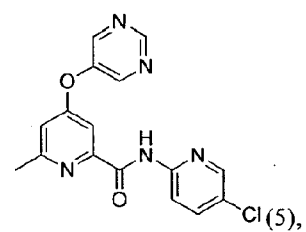
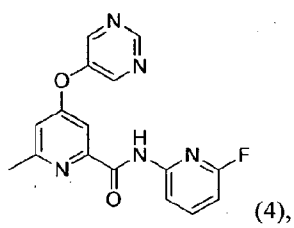
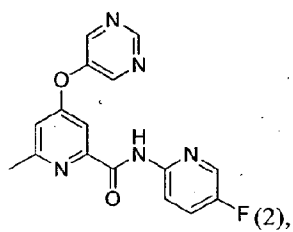
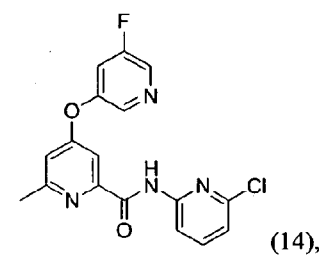
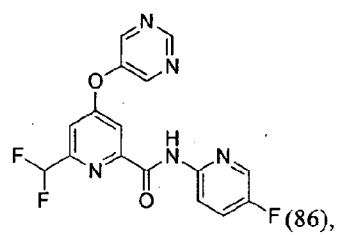
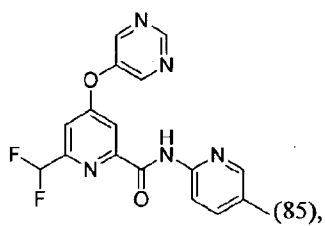
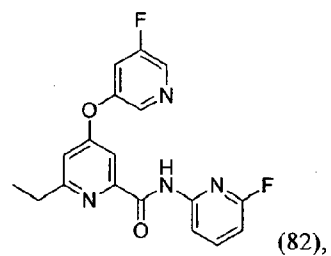
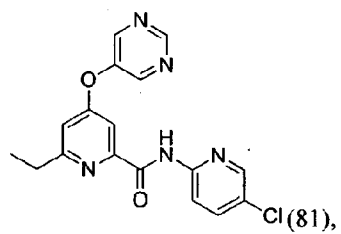
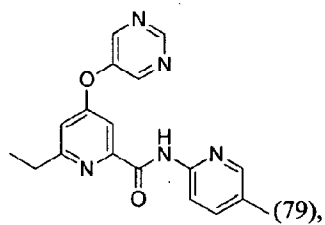


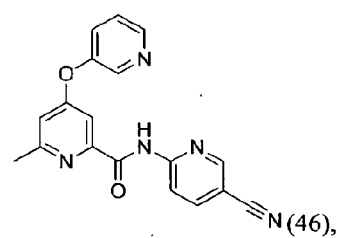
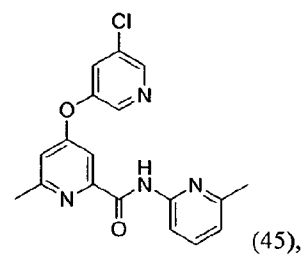
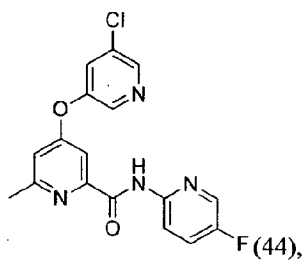
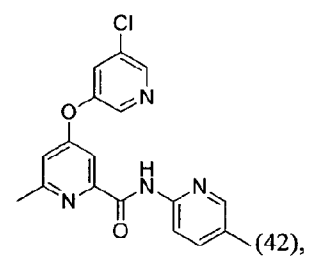
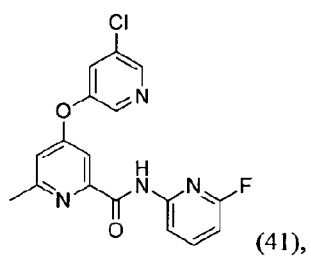
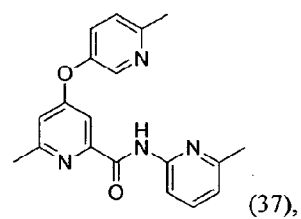
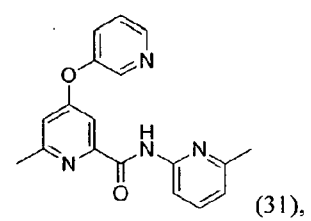
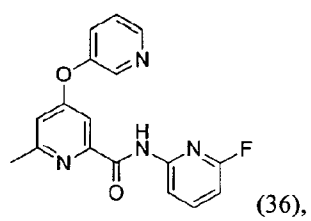
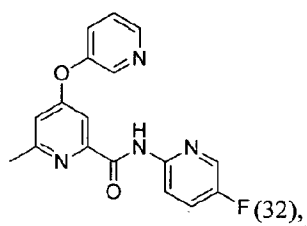
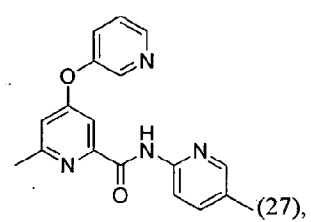
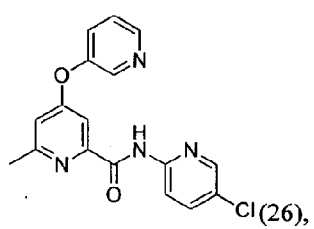
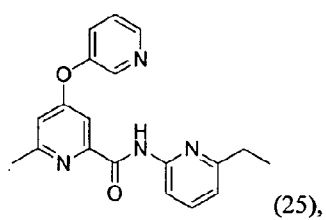
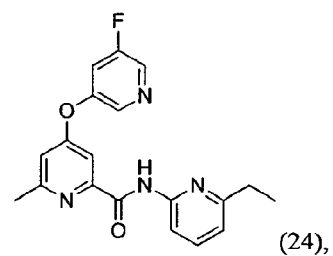
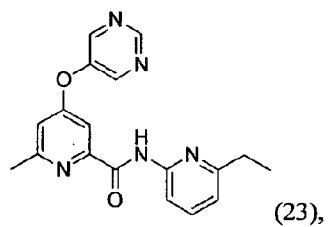
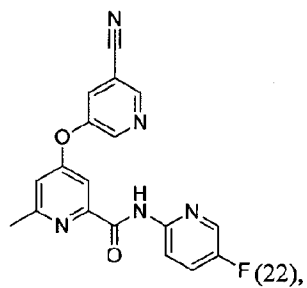


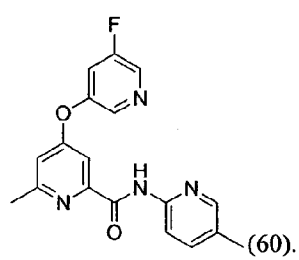
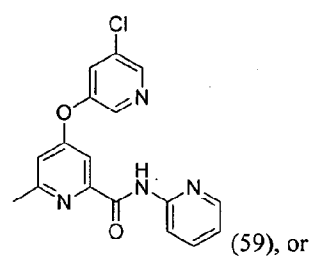
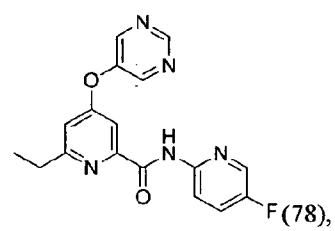
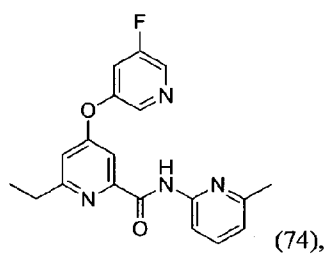
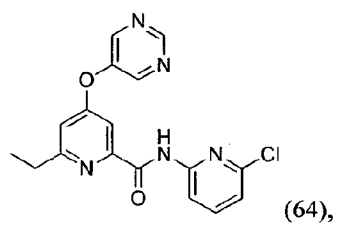
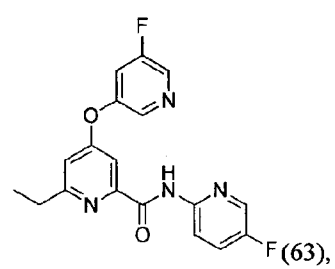
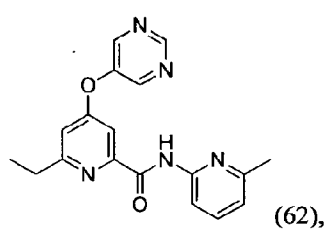
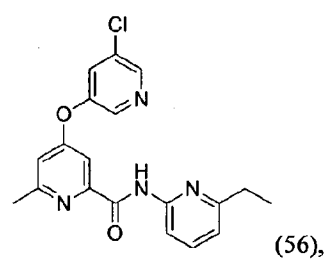
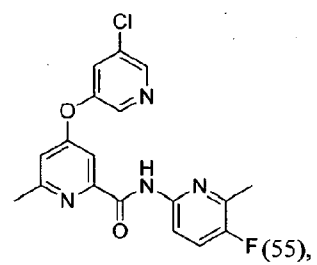
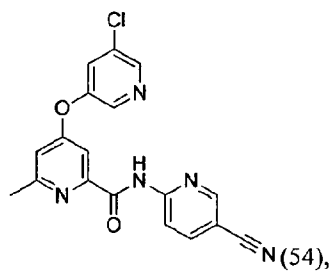
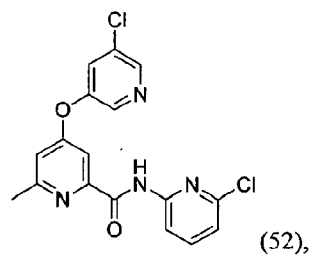


[00174] In an even further aspect, a compound can be present as:

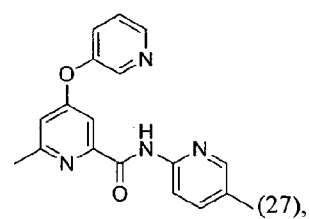
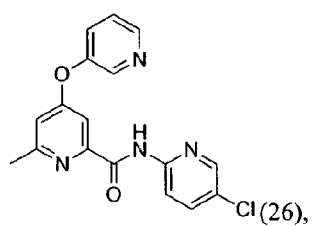
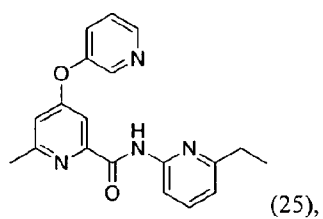
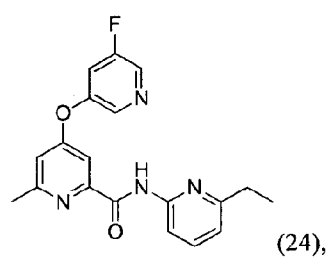
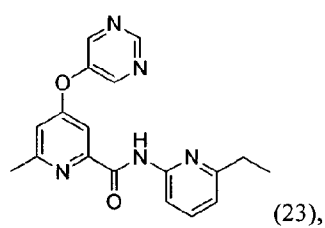
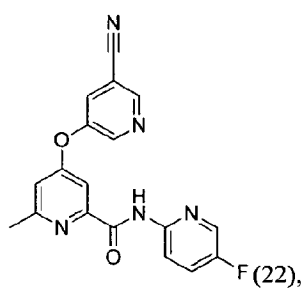
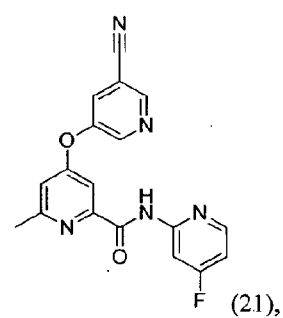
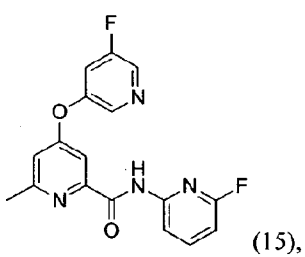
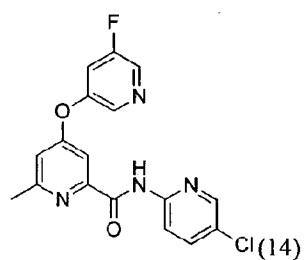
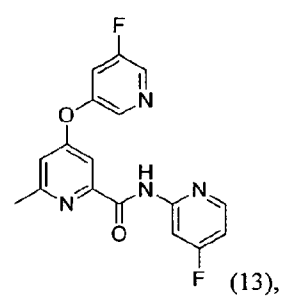
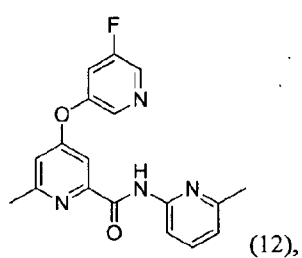
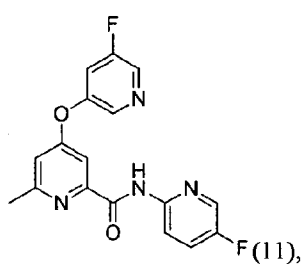
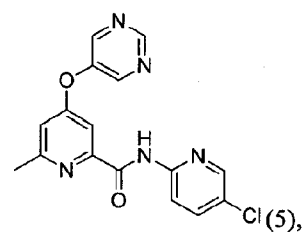
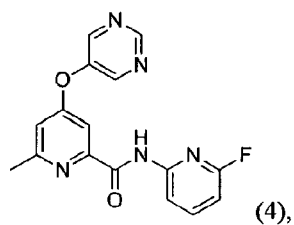
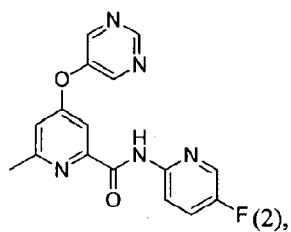


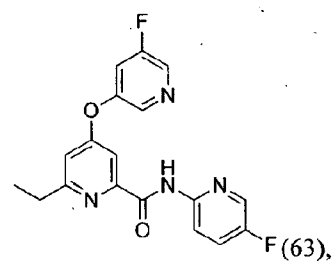
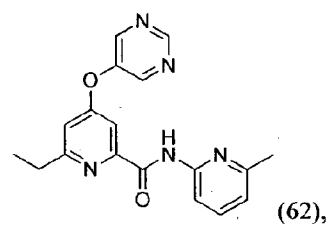
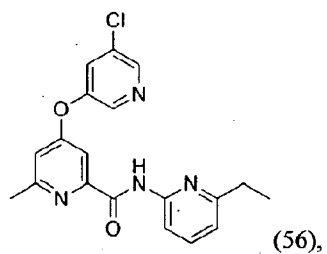
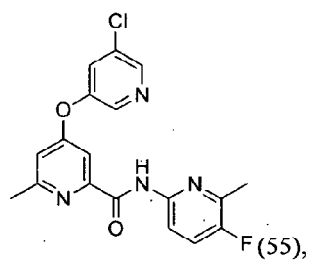
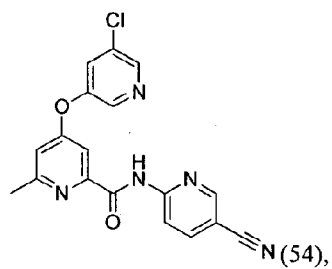
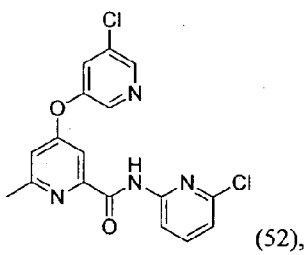
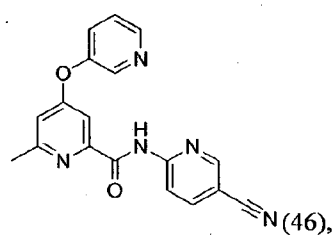
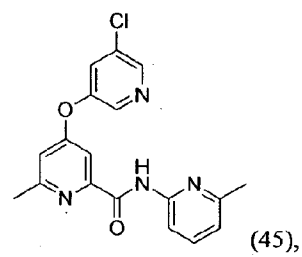
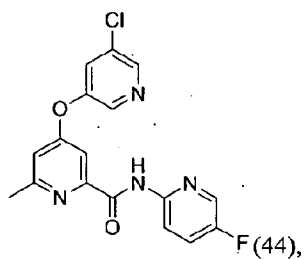
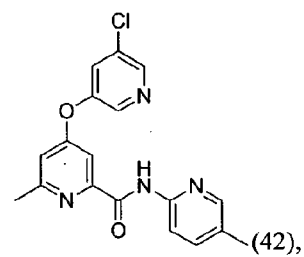
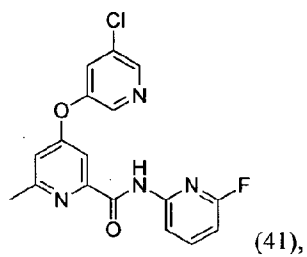
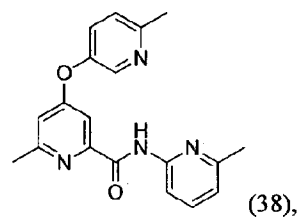
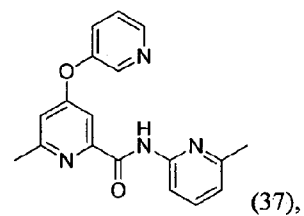
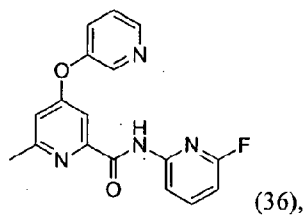
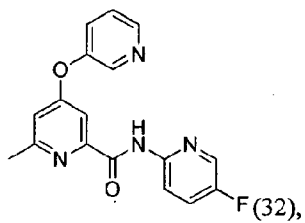


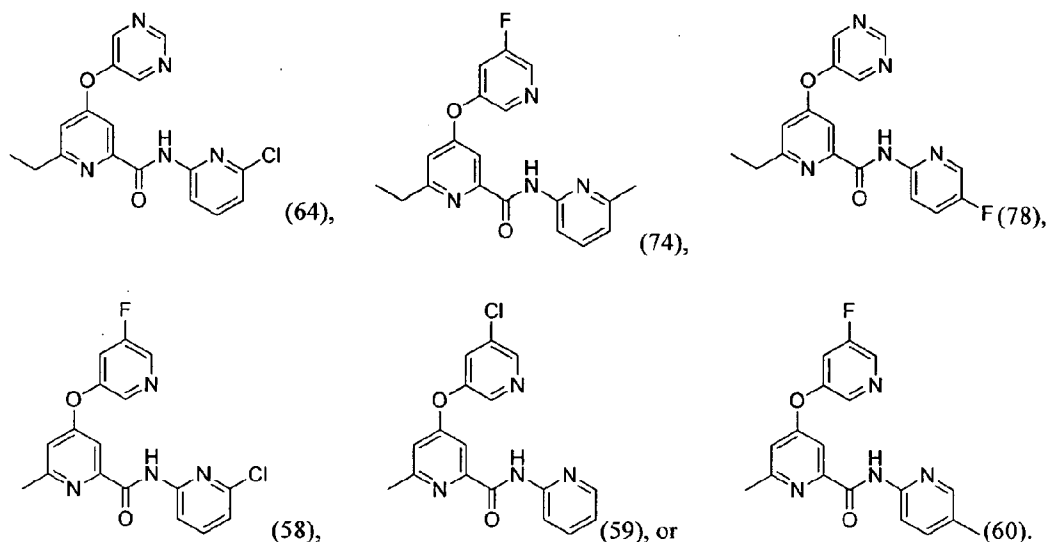




[00175] In a further aspect, a compound can be present as:







[00176] In yet a further aspect, the compound exhibits negative allosteric modulation of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, human embryonic kidney cells are transfected with human mGluR5. In yet a further aspect, human embryonic kidney cells are transfected with mammalian mGluR5. In a further aspect, the compound exhibits partial or total inhibition of mGluR5 in response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human, rat or mammalian mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In yet a further aspect, the compound exhibits negative allosteric modulation of mGluR5 after contacting a cell expressing mGluR5. In a further aspect, the compound produced exhibits partial or total inhibition of mGluR5 after contacting a cell expressing mGluR5.

[00177] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response. In a yet further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In an even further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} . In a further aspect, the mGluR5 is rat mGluR5. In a still further aspect, the mGluR5 is human mGluR5.

[00178] In a further aspect, a pharmaceutical composition comprising a therapeutically effective amount of the compound and a pharmaceutically acceptable carrier.

[00179] It is contemplated that one or more example structures can be optionally omitted from the disclosed invention.

5 3. ATROPISOMERIC FORMS

[00180] Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. Atropisomers display axial chirality, but differ from other chiral compounds in that they can be equilibrated thermally, whereas in the other forms of chirality isomerization is usually only possible chemically. In certain
10 aspects, the disclosed compounds can be provided as atropisomeric compounds. For example, disclosed compounds can be provided as single atropisomers or as a mixture of atropisomers.

[00181] It is contemplated that one atropisomer can exhibit greater negative allosteric modulation of mGluR5 response to glutamate than another, otherwise structurally identical, atropisomer. Thus, individual atropisomers of disclosed compounds can be isolated and used in disclosed methods.
15 Separation of atropisomers can be achieved by chiral resolution methods such as selective crystallization.

[00182] In an atropo-enantioselective or atropselective synthesis, one atropisomer is formed at the expense of the other. Thus, it is also contemplated that a specific atropisomer can be preferentially prepared: atroposelective synthesis can be carried out by use of chiral auxiliaries or by approaches based on thermodynamic equilibration when an isomerization reaction favors one atropisomer over the other.

20 4. NEGATIVE ALLOSTERIC MODULATION OF mGLUR5 RESPONSE

[00183] In one aspect, the compounds exhibit negative allosteric modulation of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, the compound exhibits partial inhibition of
25 mGluR5 response. In a further aspect, the compound exhibits total inhibition of mGluR5 response. In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} , of less than about 1.0×10^{-7} , of less than about 1.0×10^{-8} or of less than about 1.0×10^{-9} . In
30 further aspect, the human embryonic kidney cells are transfected with human mGluR5. In yet a further aspect, human embryonic kidney cells are transfected with mGluR5 of a mammal.

C. METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00184] The utility of the compounds in accordance with the present invention as negative allosteric modulators of metabotropic glutamate receptor activity, in particular mGluR5 activity, can be demonstrated by methodology known in the art. Human embryonic kidney (HEK) cells transfected with rat or human mGluR5 were plated in clear bottom assay plates for assay in a Functional Drug Screening System (FDSS). The cells were loaded with a Ca^{2+} -sensitive fluorescent dye (e.g., Fluo-4), and the plates were washed and placed in the FDSS instrument. Test compound was applied to cells 3 seconds after baseline readings were taken. Cells were incubated with the test compounds for 140 seconds and then stimulated with an EC_{20} concentration of an mGluR5 agonist (e.g., glutamate, 3,5-dihydroxyphenylglycine, or quisqualate); 60-80 seconds later an EC_{80} concentration of agonist was added and readings taken for an additional 40 seconds. Data were collected at 1 Hz. Negative allosteric modulation of the agonist response of mGluR5 by the compounds in the present invention was observed as a decrease in response to non-maximal concentrations of agonist (here, glutamate) in the presence of compound compared to the response to agonist in the absence of compound. Concentration response curves were generated using a four parameter logistical equation.

[00185] The above described assay was operated in two modes. In the first mode (utilizing a triple add protocol), a range of concentrations of the present compounds were added to cells, followed by two single fixed concentrations of agonist (EC_{20} followed by EC_{80}). If a compound acted as a potentiator, an EC_{50} value for potentiation of the EC_{20} response and a maximum extent of potentiation by the compound at this concentration of agonist was determined by non-linear curve fitting. If a compound acted as an antagonist, an IC_{50} value for antagonism of the EC_{80} response and a maximum extent of antagonism by the compound at this concentration of agonist was determined by non-linear curve fitting. In the second mode (utilizing a double add protocol), several fixed concentrations of the present compounds were added to various wells on a plate, followed by a range of concentrations of agonist for each concentration of present compound; the EC_{50} values for the agonist at each concentration of compound were determined by nonlinear curve fitting. A decrease in the EC_{50} value of the agonist with increasing concentrations of the present compounds (a leftward shift of the agonist concentration-response curve) is an indication of the degree of mGluR5 positive allosteric modulation at a given concentration of the present compound. An increase in the EC_{50} value of the agonist with increasing concentrations of the present compounds (a rightward shift of the agonist concentration response curve) is an indication of the degree of mGluR5 antagonism at a given concentration of the present compound. The second mode also indicates whether the present compounds also affect the maximum response to mGluR5 to agonists. Exemplary data are provided in Table 1 below.

[00186] In particular, the disclosed compounds had activity in modulating the mGluR5 receptor in the aforementioned assays, generally with an IC_{50} for modulation of less than about 30 μM . Preferred compounds within the present invention had activity in modulating the mGluR5 receptor with an IC_{50} for

negative allosteric modulation of less than about 500 nM. Preferred compounds reduced the response to an EC₈₀ concentration of glutamate to less than 50% of the maximal response and also induced a rightward and downward shift of the glutamate concentration response curve. These compounds are negative allosteric modulators of human and rat mGluR5 and were selective for mGluR5 compared to the other six subtypes of metabotropic glutamate receptors.

D. METHODS OF MAKING THE COMPOUNDS

[00187] In one aspect, the invention relates to methods of making compounds useful as negative allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5), which can be useful in the treatment neurological and psychiatric disorders associated with glutamate dysfunction and other diseases in which metabotropic glutamate receptors are involved.

[00188] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

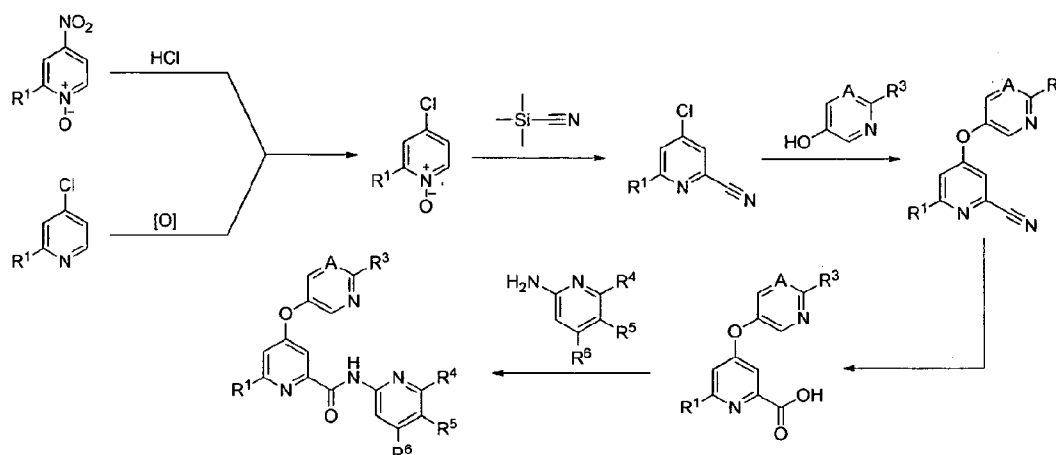
[00189] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, as described and exemplified below. In certain specific examples, the disclosed compounds can be prepared by Route I and Route II, as described and exemplified below. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[00190] In one aspect, the disclosed compounds comprise the products of the synthetic methods described herein. In a further aspect, the disclosed compounds comprise a compound produced by a synthetic method described herein. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

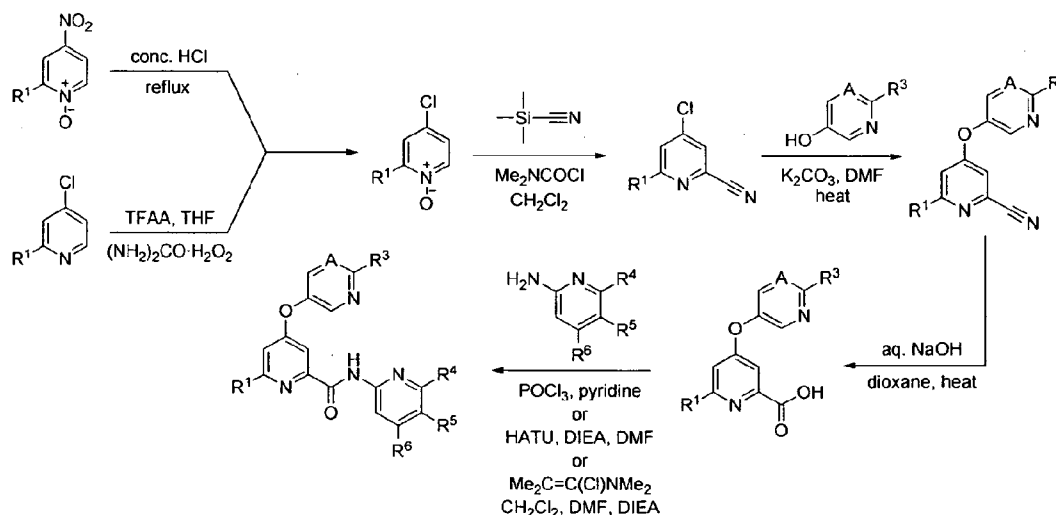
[00191] In a further aspect, the compound produced exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.

1. ROUTE I

[00192] In one aspect, substituted 6-alkyl-*N*-(pyridin-2-yl)-4-aryloxypicolinamide analogs can be prepared as shown below.

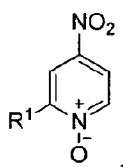


5 [00193] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

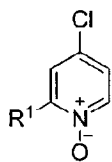


[00194] In one aspect, Route I begins with a substituted 4-nitropyridine *N*-oxide. Such 4-nitropyridine *N*-oxides are commercially available or can be readily prepared by one skilled in the art according to methods described in the literature (Taylor, E. C. Jr.; Crovetti, A. J. *Organic Syntheses* **1956**, 36). Reaction in concentrated HCl at reflux temperature yields a substituted 4-chloro-nitropyridine *N*-oxide. Alternatively, Route I begins with a commercially available substituted 4-chloropyridine. Reaction with an oxidizing reagent provides the substituted 4-chloro-nitropyridine *N*-oxide. An example of a

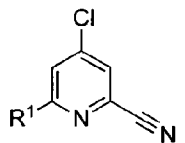
- suitable oxidizing reagent includes but is not limited to urea hydrogen peroxide/trifluoroacetic acid anhydride (Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299-2302). Treatment of the intermediate *N*-oxide with trimethylsilylcyanide affords the substituted 4-chloropicolinonitrile (Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375-1377). It will be appreciated that additives may or may not be used in the cyanation reaction. Examples of suitable additives include but are not limited to dimethylcarbamoyl chloride and benzoyl chloride. Reaction of the intermediate 4-chloropicolinonitrile with a heteroaryl alcohol under basic conditions results in S_NAr displacement of the aryl chloride and yields a biaryl ether. The resulting intermediate nitrile can be treated with aqueous sodium hydroxide to provide the substituted picolinic acid. Coupling of the carboxylic acid with a substituted or unsubstituted 2-aminopyridine can yield the amide product. Such coupling reactions are generally well known. For example, carboxylic acids can be treated with activating reagents such as 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate methanaminium (HATU), Ghosez's Reagent (1-chloro-*N,N*,2-trimethyl-1-propenylamine), and phosphorous oxychloride/pyridine including mixtures thereof, and then reacted with the amine. Functional group transformation of the remaining substituents can yield further analogs.
- 15 [00195] Thus, in one aspect, the invention relates to a method for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:



- wherein R^1 is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and (b) chlorinating by reacting with concentrated HCl under reflux conditions, thereby forming a compound having a structure represented by a formula:

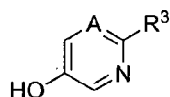


- [00196] In a further aspect, R^1 is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R^1 is selected from methyl, ethyl, CHF_2 , CF_3 , and cyclopropyl. In a yet further aspect, R^1 is methyl. In an even further aspect, R^1 is ethyl.
- 25 [00197] In a further aspect, the method further comprises the step of cyanation of the compound formed, thereby forming a compound having a structure represented by a formula:

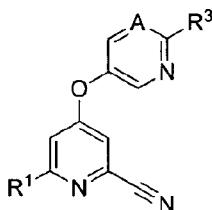


In a yet further aspect, cyanation is reacting with trimethylsilylcyanide. In a still further aspect, cyanation comprises an additive selected from dimethylcarbamoyl chloride and benzoyl chloride.

[00198] In a further aspect, the method further comprises the step of reacting the product formed from cyanation with a compound represented by a formula:

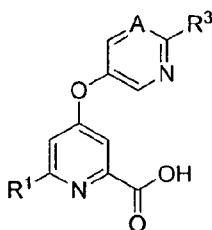


In a still further aspect, the product formed from this reaction has a structure represented by a formula:

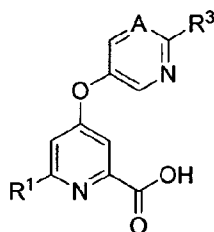


In a yet further aspect, the reaction is performed in the presence of base. In an even further aspect, A is CR². In a still further aspect, A is N.

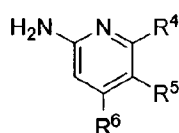
[00199] In a further aspect, the method further comprises the step of reacting the compound formed above with aqueous hydroxide, thereby forming a compound represented by a formula:



[00200] Thus, in one aspect, the invention relates to a method for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:



wherein wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and (b) coupling the compound with a compound represented by the
5 formula:

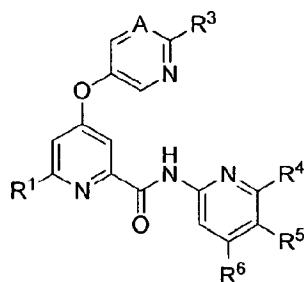


wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.

[00201] In a further aspect, providing is reaction of the compound provided with an activating agent.

10 In a still further aspect, the activating agent is selected from 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluoro-phosphate methanaminium, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, *O*-(6-chlorobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, 1-chloro-*N,N*,2-trimethyl-1-propenylamine, oxalyl chloride, thionyl chloride, and phosphorous oxychloride.
15

[00202] In a further aspect, the compound formed above is represented by the formula:



[00203] In a further aspect, the compound produced exhibits negative allosteric modulation of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in
20 human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to

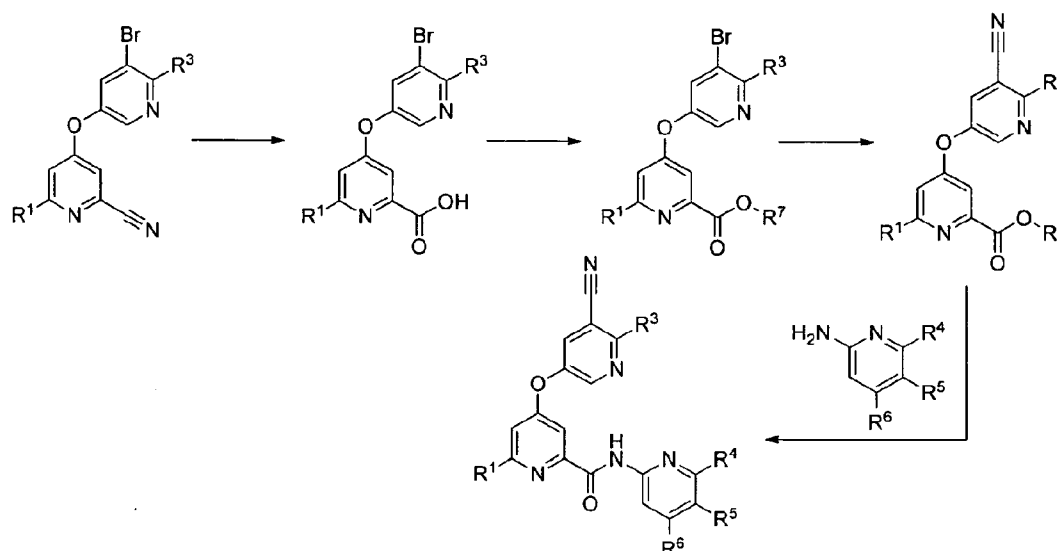
the response to glutamate in the absence of the compound. In a further aspect, human embryonic kidney cells are transfected with human mGluR5. In yet a further aspect, human embryonic kidney cells are transfected with mammalian mGluR5. In a further aspect, the compound produced exhibits partial or total inhibition of mGluR5 in response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human, rat or mammalian mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In yet a further aspect, the compound produced exhibits negative allosteric modulation of mGluR5 after contacting a cell expressing mGluR5. In a further aspect, the compound produced exhibits partial or total inhibition of mGluR5 after contacting a cell expressing mGluR5.

10 [00204] In a further aspect, the compound produced exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound produced exhibits total inhibition of mGluR5 response. In a yet further aspect, the compound produced exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In an even further aspect, the compound produced exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In a still further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a yet further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In an even further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} . In a further aspect, the mGluR5 is rat mGluR5. In a still further aspect, the mGluR5 is human mGluR5.

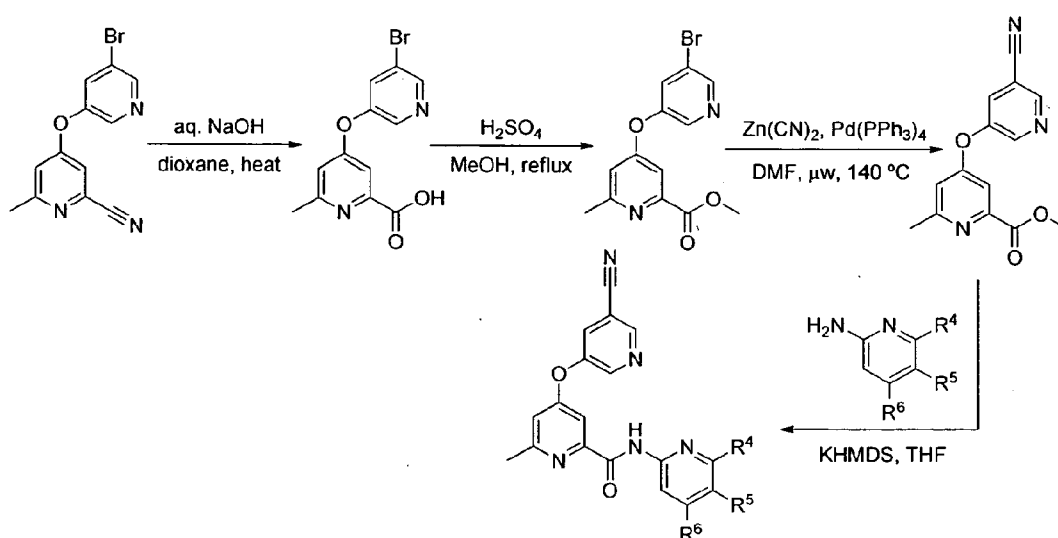
20 [00205] In a further aspect, a compound produced is a component in a pharmaceutical composition. In a still further aspect, a pharmaceutical composition comprises a therapeutically effective amount of a compound produced and a pharmaceutically acceptable carrier. In a still further aspect, a compound produced is a component is used in the manufacture of a medicament comprising combining at least one compound produced with a pharmaceutically acceptable carrier or diluent.

2. ROUTE II

[00206] In one aspect, substituted heteroarylamine analogs can be prepared as shown below.



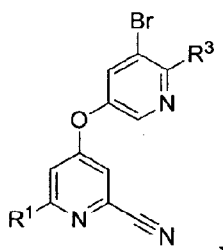
[00207] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.



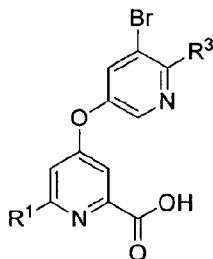
[00208] In one aspect, Route II begins with a substituted or unsubstituted 4-((5-bromopyridin-3-yl)oxy)-6-alkylpicolinonitrile, prepared according to methods described in Route I. The substituted picolinonitrile can be treated with aqueous sodium hydroxide to provide the substituted picolinic acid.

Refluxing in alcoholic solvent in the presence of acid can be used to provide the ester. It will be appreciated that other well known methods for preparing the ester may be employed. A palladium

- catalyzed cyanation reaction can be used to generate the heteroaryl nitrile compound from the heteroaryl bromide intermediate. It will be appreciated that a variety of palladium catalysts, ligands, and cyanide sources may be suitable for this coupling reaction (see *Synthetic Comm.* 2007, 37, 431-438 and references therein). Examples of potentially useful palladium catalysts for this coupling include but are not limited to tris(di-benzylideneacetone)-dipalladium(0), palladium acetate, and tetrakis(triphenylphosphine)-palladium. Examples of potentially useful phosphine ligands for this coupling include but are not limited to triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, and 1,4-bis(diphenylphosphino)butane. Examples of potentially useful cyanide sources for this coupling include but are not limited to zinc cyanide, potassium ferricyanide, trimethylsilyl cyanide, and potassium cyanide. The ester can be treated with a substituted or unsubstituted 2-aminopyridine and a suitable base to afford the amide product. It will be appreciated that a number of bases may be suitable for this type of transformation. Examples of potentially suitable bases include but are not limited to potassium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium hydride, and sodium hydride. Functional group transformation of the remaining substituents can yield further analogs.
- 15 [00209] Thus, in one aspect, the invention relates to a method for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:



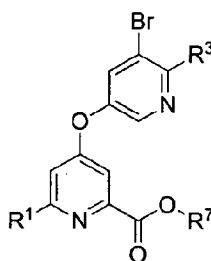
- wherein wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and (b) reacting with aqueous hydroxide, thereby providing a compound represented by the formula:



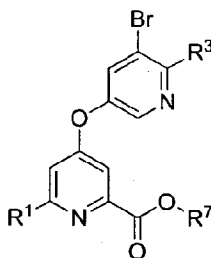
[00210] In a further aspect, R^1 is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R^1 is selected from methyl, ethyl, CHF_2 , CF_3 , and cyclopropyl. In a yet further aspect, R^1 is methyl. In an even further aspect, R^1 is ethyl.

[00211] In a further aspect, the method further comprises the step of comprising the step of reacting the compound formed with a $R^7\text{OH}$ in the presence of acid at reflux temperature thereby forming an ester, wherein R^7 is C1-C5 alkyl.

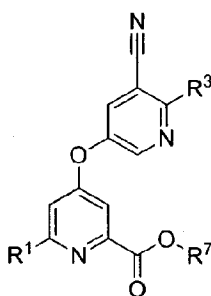
[00212] In a further aspect, the the ester formed is a compound represented by the formula:



[00213] Thus, in a further aspect, the invention relates to a method for preparing a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:



wherein wherein R^1 is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R^2 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and wherein R^7 is C1-C5 alkyl; and (b) performing a cyanation reaction, thereby providing a compound having a structure represented by a formula:

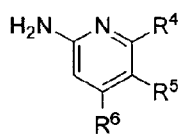


[00214] In a further aspect, the cyanation reaction is carried in the presence of a palladium catalyst. In a yet further aspect, wherein the palladium catalyst is selected from tris(di-benzylideneacetone)-dipalladium(0), palladium acetate, and tetrakis(triphenylphosphine)-palladium.

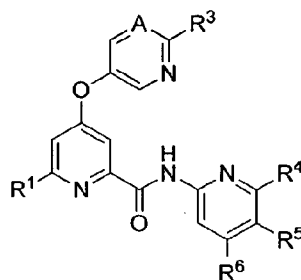
[00215] In a further aspect, wherein the cyanation reaction is carried out in the presence of a ligand. In an even further aspect, the ligand is selected from triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, and 1,4-bis(diphenyl-phosphino)butane.

[00216] In a further aspect, the cyanation reaction is carried out in the presence of cyanide source. In a still further aspect, the cyanide source is selected from zinc cyanide, potassium ferricyanide, trimethylsilyl cyanide, and potassium cyanide.

- 10 [00217] In a further aspect, the method further comprises the step of reacting the product formed with a compound having a structure represented by a formula:



- wherein each of R^4 , R^5 , and R^6 is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, the reaction is carried out in the presence of a base. In yet further aspect, the base is selected from bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium hydride, and sodium hydride. In an even further aspect, the compound formed is represented by the formula:



- [00218] In a further aspect, the compound produced exhibits negative allosteric modulation of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, human embryonic kidney cells are transfected with human mGluR5. In yet a further aspect, human embryonic kidney cells are transfected with mammalian mGluR5. In a further aspect, the compound produced exhibits partial or total

inhibition of mGluR5 in response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human, rat or mammalian mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In yet a further aspect, the compound produced exhibits negative allosteric modulation of mGluR5 after contacting a cell expressing mGluR5. In a further aspect, the compound produced exhibits partial or total inhibition of mGluR5 after contacting a cell expressing mGluR5.

[00219] In a further aspect, the compound produced exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound produced exhibits total inhibition of mGluR5 response. In a yet further aspect, the compound produced exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In an even further aspect, the compound produced exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In a still further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a yet further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In an even further aspect, the compound produced exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} . In a further aspect, the mGluR5 is rat mGluR5. In a still further aspect, the mGluR5 is human mGluR5.

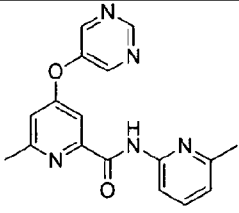
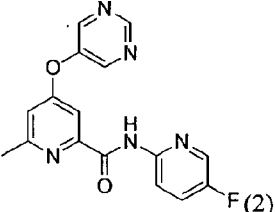
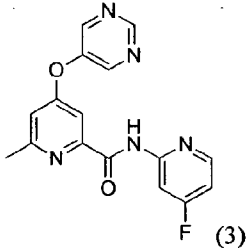
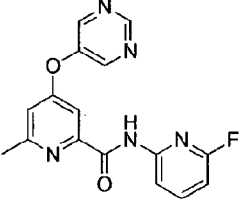
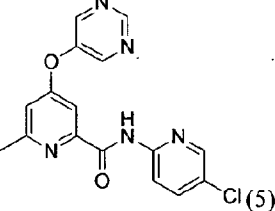
[00220] In a further aspect, a compound produced is a component in a pharmaceutical composition. In a still further aspect, a pharmaceutical composition comprises a therapeutically effective amount of a compound produced and a pharmaceutically acceptable carrier. In a still further aspect, a compound produced is a component is used in the manufacture of a medicament comprising combining at least one compound produced with a pharmaceutically acceptable carrier or diluent.

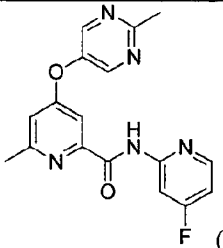
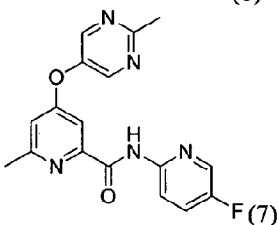
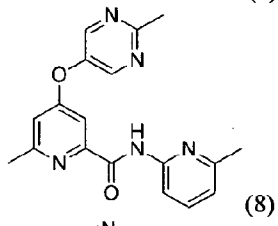
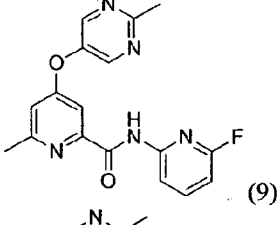
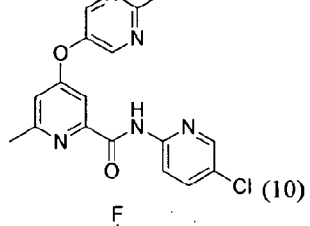
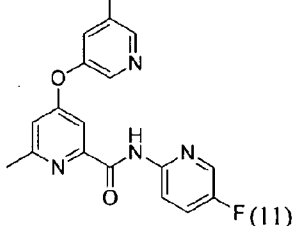
[00221] It is contemplated that each disclosed methods can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed methods can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

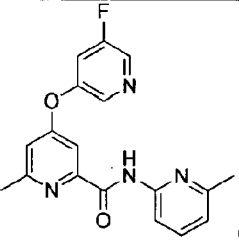
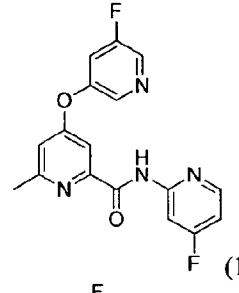
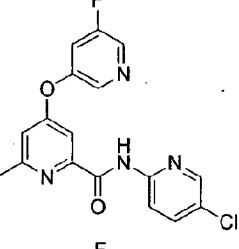
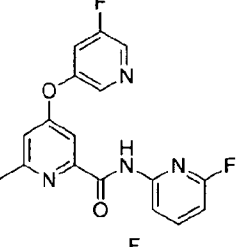
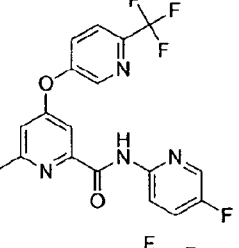
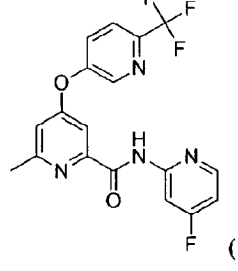
[00222] Table I below lists specific compounds as well as a preferred route for its synthesis, experimentally determined molecular mass, and mGluR5 activity determined in a cell-based assay. The mGluR5 activity was determined using the metabotropic glutamate receptor activity assays in human embryonic kidney cells as described herein, wherein the human embryonic kidney cells were transfected with rat mGluR5. The mGluR5 activity data for some compounds are shown as the average of at least three experiments with the standard error in these cases. If no error is indicated for the mGluR5 activity, the values given represent the results from a single experiment or the average of two experiments. The

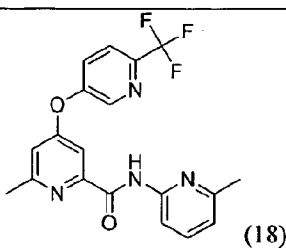
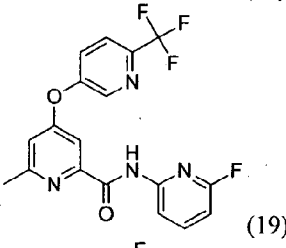
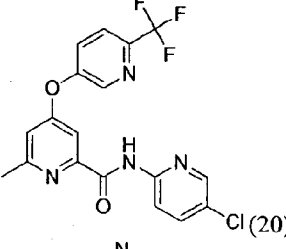
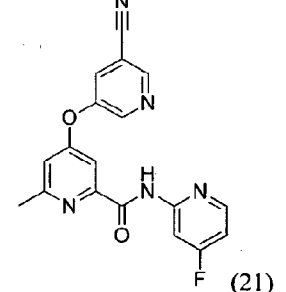
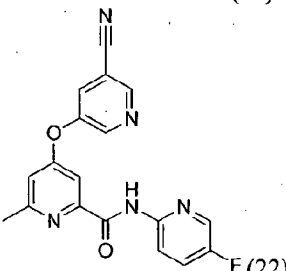
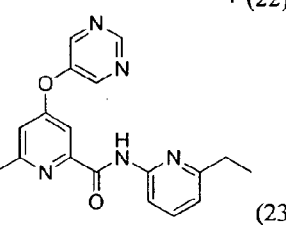
compounds in Table 1 were synthesized with methods identical or analogous to those shown herein. The requisite starting materials were commercially available, described in the literature, or readily synthesized by one skilled in the art of organic synthesis.

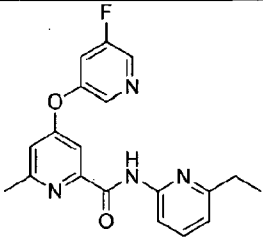
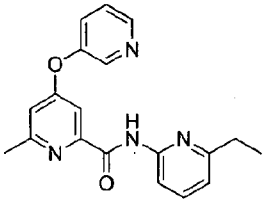
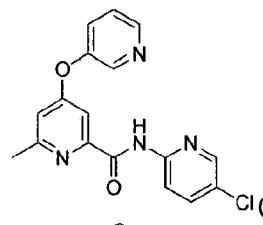
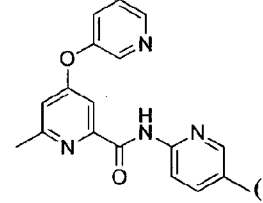
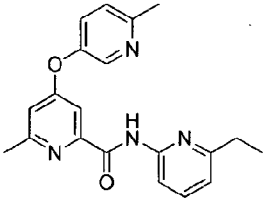
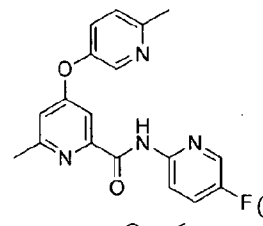
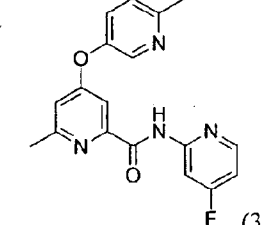
TABLE 1

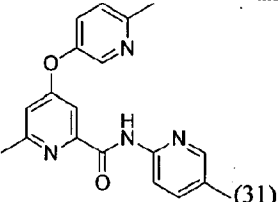
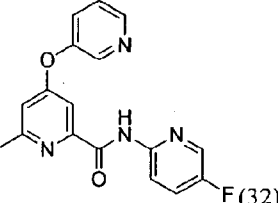
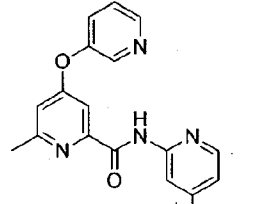
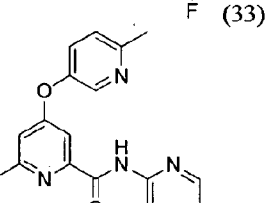
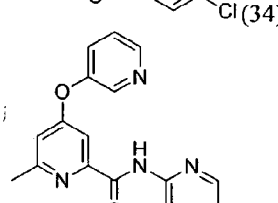
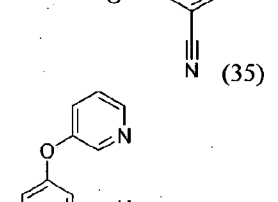
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (1)	22	322.2	I
 (2)	7.7 ± 0.7	326.2	I
 (3)	24 (n=2)	326.2	I
 (4)	6.0	326.1	I
 (5)	5.1	342.1	I

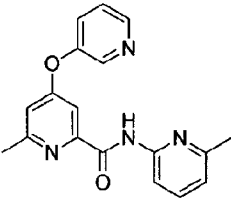
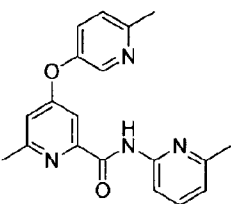
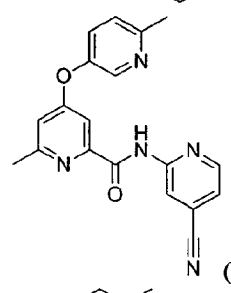
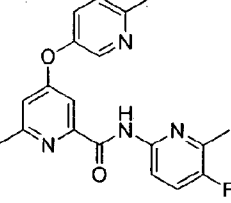
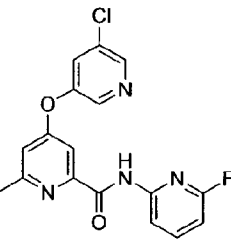
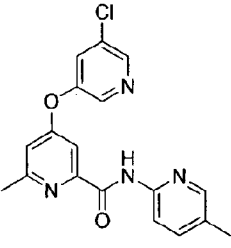
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (6)	1890	340.2	I
 (7)	33	340.2	I
 (8)	20	336.2	I
 (9)	21	340.2	I
 (10)	209	356.2	I
 (11)	3.4 ± 0.3	343.1	I

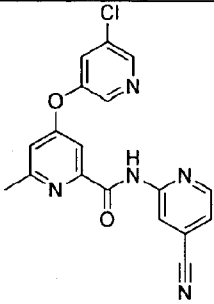
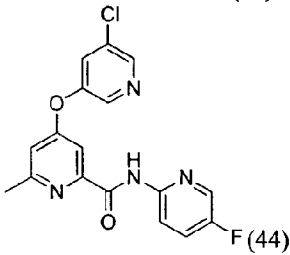
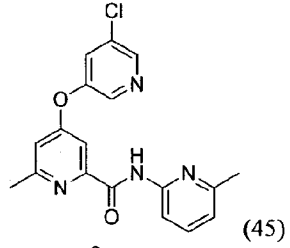
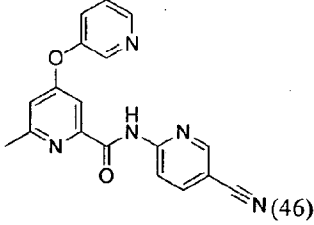
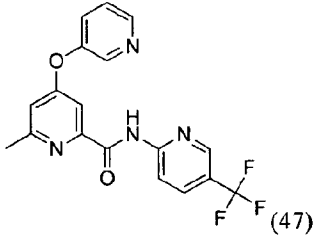
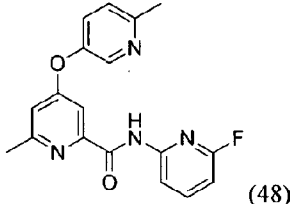
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (12)	7.9	339.2	I
 (13)	12 (n=2)	343.2	I
 (14)	5.5	359.1	I
 (15)	4.5 (n=2)	343.2	I
 (16)	255	393.2	I
 (17)	4880	393.2	I

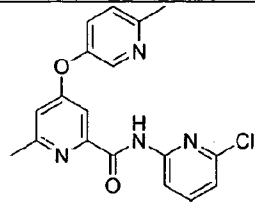
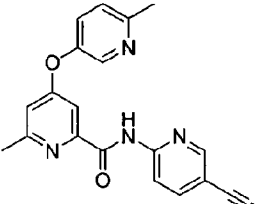
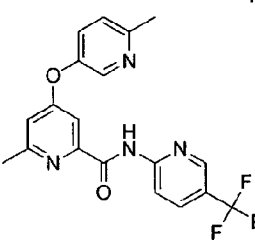
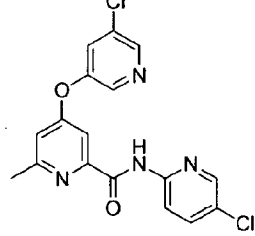
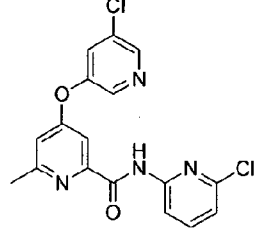
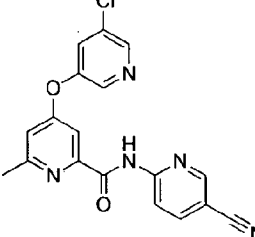
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (18)	177	389.2	I
 (19)	397	393.1	I
 (20)	>30,000	409.1	I
 (21)	15	350.2	II
 (22)	5.4	350.1	II
 (23)	12	336.1	I

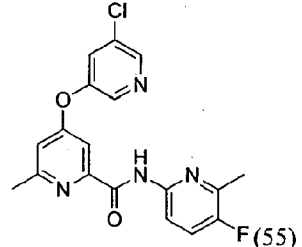
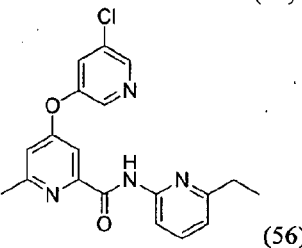
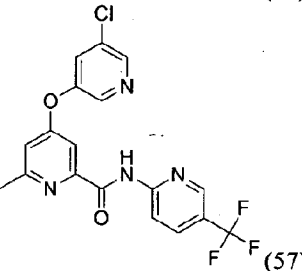
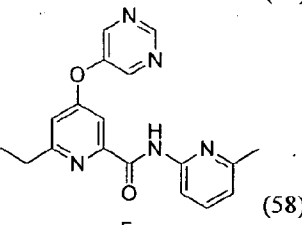
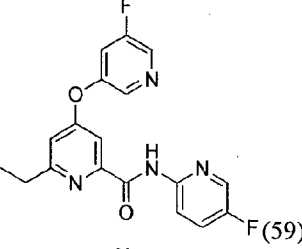
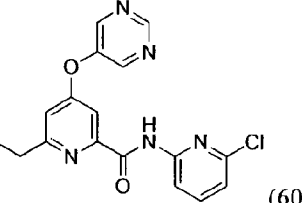
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (24)	7.9	353.2	I
 (25)	13	335.1	I
 (26)	5.5	341.1	I
 (27)	10	321.1	I
 (28)	152	349.2	I
 (29)	97	339.1	I
 (30)	1800	339.1	I

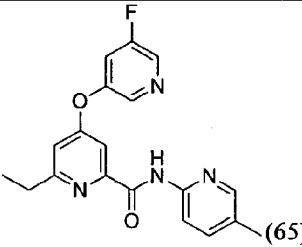
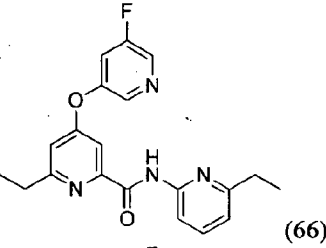
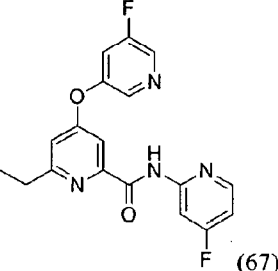
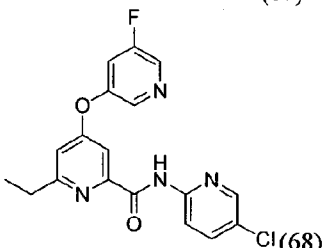
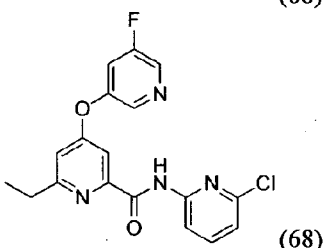
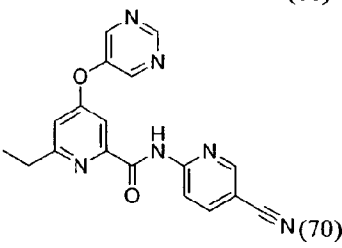
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (31)	966	335.1	I
 (32)	4.1	325.1	I
 (33)	26	325.1	I
 (34)	635	355.1	I
 (35)	>10,000	332.1	I
 (36)	3.4	325.1	I

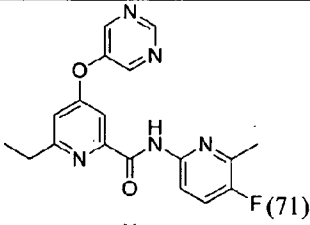
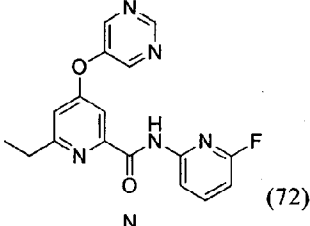
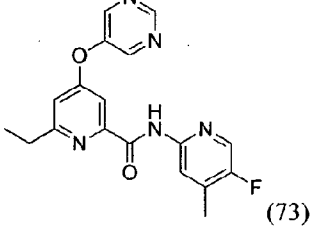
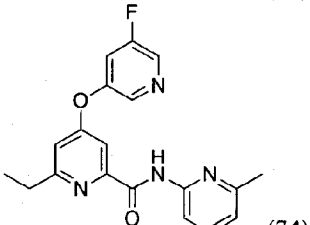
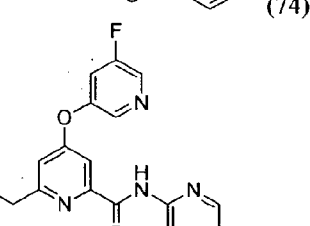
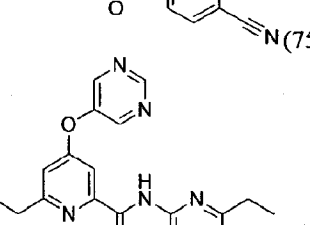
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (37)	4.4	321.1	I
 (38)	13	335.1	I
 (39)	387	346.1	I
 (40)	328	353.1	I
 (41)	5.3	359.0	I
 (42)	6.4	355.0	I

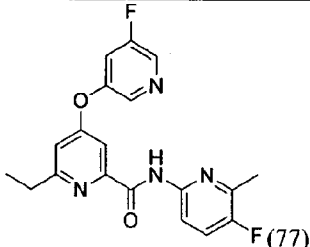
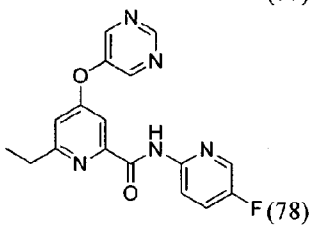
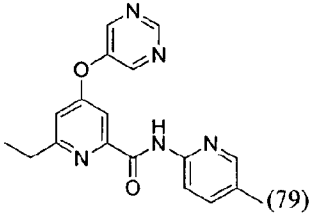
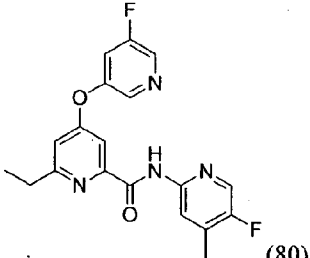
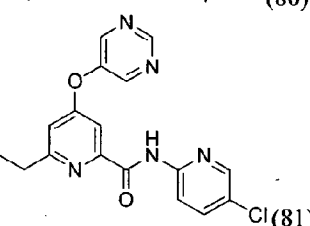
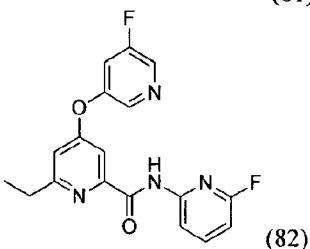
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (43)	548	366.0	I
 (44)	4.2	359.1	I
 (45)	6.7	355.0	I
 (46)	14	332.1	I
 (47)	1110	375.1	I
 (48)	64	339.1	I

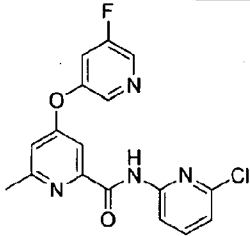
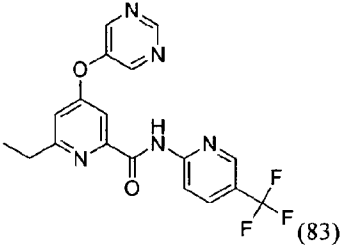
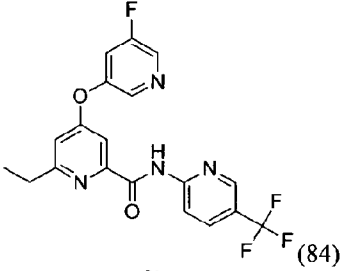
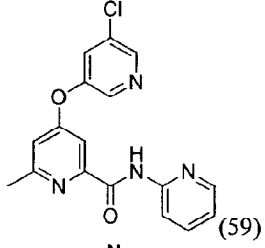
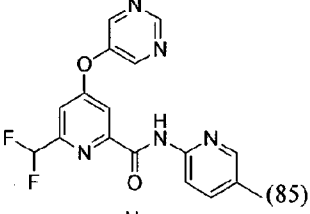
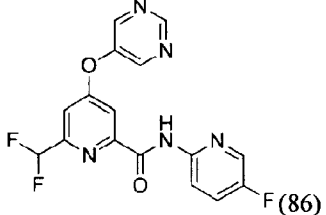
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (49)	172	355.1	I
 (50)	693	346.1	I
 (51)	>30,000	389.1	I
 (52)	18	375.0	I
 (53)	14	375.0	I
 (54)	11	366.0	I

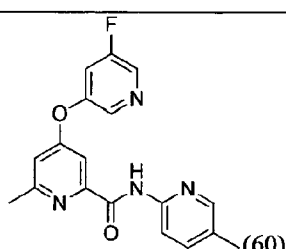
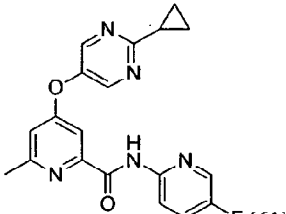
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (55)	14	373.0	I
 (56)	14	369.0	I
 (57)	>10,000	409.0	I
 (58)	6.1	336.1	I
 (59)	11	357.1	I
 (60)	14	356.1	I

Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
	41	353.1	I
	468	367.1	I
	333	357.1	I
	333	373.1	I
	59	373.1	I
	156	347.1	I

Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (71)	27	354.1	I
 (72)	24	340.1	I
 (73)	677	354.1	I
 (74)	13	353.1	I
 (75)	108	364.1	I
 (76)	19	350.2	I

Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (77)	159	371.1	I
 (78)	9.3	340.1	I
 (79)	27	336.1	I
 (80)	>30,000	371.1	I
 (81)	25	356.1	I
 (82)	18	357.1	I

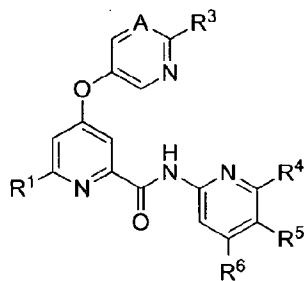
Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (14)	8.2	359.1	I
 (83)	>30,000	390.1	I
 (84)	>30,000	407.1	I
 (59)	2.2	341.1	I
 (85)	72	358.1	I
 (86)	45	362.1	I

Structure	mGluR5 IC ₅₀ (nM)	M +1	Synthetic Route Reference
 (60)	6.8	339.1	I
 (61)	186	366.2	I

E. PHARMACEUTICAL COMPOSITIONS

[00223] In one aspect, the invention relates to pharmaceutical compositions comprising the disclosed compounds. That is, a pharmaceutical composition can be provided comprising a therapeutically effective amount of at least one disclosed compound, at least one product of a disclosed method, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof, and a pharmaceutically acceptable carrier.

[00224] In one aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently

selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00225] In a further aspect, the effective amount is a therapeutically effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

5 [00226] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00227] In a further aspect, the pharmaceutical composition comprises a disclosed compound. In a yet
10 further aspect, the pharmaceutical composition comprises a product of a disclosed method of making.

[00228] In a further aspect, the pharmaceutical composition comprises a compound that exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further
15 aspect, the the human embryonic kidney cells transfected with rat mGluR5. In a yet further aspect, the human embryonic kidney cells transfected with human mGluR5.

[00229] In certain aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The
20 instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

25 [00230] As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (-ic and -ous), ferric, ferrous, lithium, magnesium, manganese (-ic
30 and -ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically

acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[00231] As used herein, the term "pharmaceutically acceptable non-toxic acids", includes inorganic acids, organic acids, and salts prepared therefrom, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[00232] In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, and/or pharmaceutically acceptable salt(s) thereof, can also be administered by controlled release means and/or delivery devices. The compositions can be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[00233] Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[00234] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and

stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

5 [00235] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by
10 standard aqueous or nonaqueous techniques

[00236] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing
15 agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[00237] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant
20 compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

25 [00238] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

30 [00239] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be

preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00240] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00241] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

[00242] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[00243] In the treatment conditions which require negative allosteric modulation of metabotropic glutamate receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day and can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably 0.5 to 100 mg/kg per day. A suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5.0 or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900 and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage of the patient to be treated. The compound can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosing regimen can be adjusted to provide the optimal therapeutic response.

[00244] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the type and severity of the particular disease undergoing therapy.

5 [00245] The present invention is further directed to a method for the manufacture of a medicament for modulating glutamate receptor activity (*e.g.*, treatment of one or more neurological and/or psychiatric disorder associated with glutamate dysfunction) in mammals (*e.g.*, humans) comprising combining one or more disclosed compounds, products, or compositions with a pharmaceutically acceptable carrier or diluent. Thus, in one aspect, the invention relates to a method for manufacturing a medicament
10 comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[00246] The disclosed pharmaceutical compositions can further comprise other therapeutically active compounds, which are usually applied in the treatment of the above mentioned pathological conditions.

[00247] It is understood that the disclosed compositions can be prepared from the disclosed
15 compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

F. METHODS OF USING THE COMPOUNDS AND COMPOSITIONS

[00248] The amino acid L-glutamate (referred to herein simply as glutamate) is the principal excitatory neurotransmitter in the mammalian central nervous system (CNS). Within the CNS, glutamate plays a key
20 role in synaptic plasticity (*e.g.*, long term potentiation (the basis of learning and memory)), motor control and sensory perception. It is now well understood that a variety of neurological and psychiatric disorders are associated with dysfunctions in the glutamatergic system. Thus, modulation of the glutamatergic system is an important therapeutic goal. Glutamate acts through two distinct receptors: ionotropic and metabotropic glutamate receptors. The first class, the ionotropic glutamate receptors, is comprised of
25 multi-subunit ligand-gated ion channels that mediate excitatory post-synaptic currents. Three subtypes of ionotropic glutamate receptors have been identified, and despite glutamate serving as agonist for all three receptor subtypes, selective ligands have been discovered that activate each subtype. The ionotropic glutamate receptors are named after their respective selective ligands: kainite receptors, AMPA receptors and NMDA receptors.

30 [00249] The second class of glutamate receptor, termed metabotropic glutamate receptors, (mGluRs), are G-protein coupled receptors (GPCRs) that modulate neurotransmitter release or the strength of synaptic transmission, based on their location (pre-or post-synaptic). The mGluRs are family C GPCR, characterized by a large (~560 amino acid) "venus fly trap" agonist binding domain in the amino-terminal

domain of the receptor. This unique agonist binding domain distinguishes family C GPCRs from family A and B GPCRs wherein the agonist binding domains are located within the 7-strand transmembrane spanning (7TM) region or within the extracellular loops that connect the strands to this region. To date, eight distinct mGluRs have been identified, cloned and sequenced. Based on structural similarity, primary coupling to intracellular signaling pathways and pharmacology, the mGluRs have been assigned to three groups: Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8). Group I mGluRs are coupled through Gαq/11 to increase inositol phosphate and metabolism and resultant increases in intracellular calcium. Group I mGluRs are primarily located post-synaptically and have a modulatory effect on ion channel activity and neuronal excitability. Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8) mGluRs are primarily located pre-synaptically where they regulate the release of neurotransmitters, such as glutamate. Group II and Group III mGluRs are coupled to Gαi and its associated effectors such as adenylate cyclase.

[00250] Post-synaptic mGluRs are known to functionally interact with post-synaptic ionotropic glutamate receptors, such as the NMDA receptor. For example, activation of mGluR5 by a selective agonist has been shown to increase post-synaptic NMDA currents (Mannaioni et al., *J. Neurosci.* 21:5925-5934 (2001)). Therefore, modulation of mGluRs is an approach to modulating glutamatergic transmission. Numerous reports indicate that mGluR5 plays a role in a number of disease states including anxiety (Spooren et al., *J. Pharmacol. Exp. Therapeut.* 295:1267-1275 (2000), Tatarczynska et al., *Br. J. Pharmacol.* 132:1423-1430 (2001)), addiction to cocaine (Chiamulera et al., *Nature Neurosci.* 4:873-874 (2001)), Parkinson's disease (Awad et al., *J. Neurosci.* 20:7871-7879 (2000), Ossowska et al., *Neuropharmacol.* 41: 413-420 (2001), pain (Salt and Binns, *Neurosci.* 100:375-380 (2001)), and Fragile X syndrome (FXS) (see, e.g., de Vrij FMS, Levenga J, van der Linde HC, Koekkoek SK, De Zeeuw CI, Nelson DL, Oostra BA, Willemsen R: Rescue of behavioral phenotype and neuronal protrusion morphology in *Fmr1* KO mice. *Neurobiol Disease* (2008) 31(1):127-132; Yan QJ, Rammal M, Tranfaglia M, Bauchwitz RP: Suppression of two major Fragile X Syndrome mouse model phenotypes by the mGluR5 antagonist MPEP. *Neuropharmacol* (2005) 49(7):1053-1066.).

[00251] The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which compounds of formula I or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping

schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound will be more efficacious than either as a single agent.

[00252] In one aspect, the subject compounds can be coadministered with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, muscarinic agonists, muscarinic potentiators, HMG-CoA reductase inhibitors, NSAIDs and anti-amyloid antibodies.

[00253] In a further aspect, the subject compounds can be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, anti-epileptics, selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), tricyclic antidepressant drugs, monoamine oxidase inhibitors (MAOIs), 5-HT₂ agonists or antagonists, GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, olanzapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbital, and salts thereof and combinations thereof.

[00254] In a further aspect, the subject compound can be used in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor), anti-cholinergics such as biperiden, COMT inhibitors such as entacapone, A_{2a} adenosine antagonists, cholinergic agonists, NMDA receptor agonists or antagonists and dopamine agonists.

[00255] In a further aspect, the subject compound can be administered in combination with opiate agonists or antagonists, calcium channel antagonists, sodium channel antagonists, COX-2 selective inhibitors, NK₁ antagonists, non-steroidal anti-inflammatory drugs ("NSAID"), GABA-A receptor modulators, dopamine agonists or antagonists, norepinephrine modulators, nicotinic agonists or antagonists including nicotine, and muscarinic agonists or antagonists. In a yet further aspect, the subject compound can be administered in combination with heroin substituting drugs such as methadone, levo-alpha-acetylmethadol, buprenorphine and naltrexone, and disulfiram and acamprosate. In a further aspect, the subject compound can be administered in combination with L-DOPA, buspirone, valproate, and gabapentin.

[00256] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

1. TREATMENT METHODS

[00257] The compounds disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with glutamate dysfunction. Thus, provided is a method of treating or preventing a disorder in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical

composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[00258] Also provided is a method for the treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[00259] Examples of disorders associated with glutamate dysfunction include: acute and chronic neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, addictive behavior, including addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), obesity, psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

[00260] Anxiety disorders that can be treated or prevented by the compositions disclosed herein include generalized anxiety disorder, panic disorder, and obsessive compulsive disorder. Addictive behaviors include addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.) and substance tolerance.

[00261] Also provided is a method for treating or prevention anxiety, comprising: administering to a subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without agoraphobia, agoraphobia without history of panic

disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified.

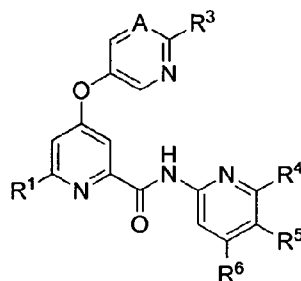
[00262] Further disorders that can be treated or prevented by the compositions disclosed herein include
5 Autism spectrum disorders, which are neuropsychiatric conditions characterized by widespread abnormalities of social interactions and communication, as well as severely restricted interests and highly repetitive behavior. Autism spectrum disorders include Autism, Asperger syndrome, Childhood Disintegrative Disorders, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, and Rett Syndrome. Fragile X syndrome (FXS) is a single gene disorder
10 almost universally associated with symptoms of autism spectrum disorder, the most common form of inherited mental retardation, and the most common known cause of autism, affecting 1 in 6,000 births. Therapeutic agents for treatment of patients with FXS are among the most critical of unmet medical needs, and there are very few proven effective treatment strategies for this patient population. Again, without wishing to be bound by theory, increasing evidence has identified a connection between the fragile X
15 phenotype and mGluR signaling

[00263] Compounds of the invention can be used, for example, for the treatment of fragile X syndrome and autism spectrum disorder in a manner that can improve symptoms (e.g., reduce anxiety and irritability; increase cognitive function, communication and/or social interaction). Thus, the methods of the invention can provide an effective manner to treat a subject having fragile X syndrome or autism spectrum disorder.

20 **a. TREATING A DISORDER ASSOCIATED WITH METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY**

[00264] In one aspect, the invention relates to a method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal an amount of at least one disclosed compound, at least one disclosed product in a dosage, or at least one
25 product of a disclosed method of making a compound. In a further aspect, the amount administered to the mammal is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with metabotropic glutamate receptor activity. In a yet further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00265] Thus, in one aspect, the invention relates to a method for the treatment of a disorder associated
30 with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of a compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00266] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00267] In a further aspect, the compound administered is any disclosed compound or at least one product of a disclosed method.

[00268] In a further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00269] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

[00270] In a further aspect, the compound exhibits non-competitive antagonism of metabotropic glutamate receptor activity. In a yet further aspect, the compound exhibits negative allosteric modulation of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits non-competitive inhibition of metabotropic glutamate receptor activity. In an even further aspect, the compound exhibits inhibition of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits antagonism of metabotropic glutamate receptor activity.

[00271] In a further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶. In a still further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶. In a yet further aspect, the compound exhibits partial or total inhibition

with an IC_{50} of less than about 1.0×10^{-6} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .

5 [00272] In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of the disorder.

[00273] In a yet further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step. In a still further aspect,
10 the method further comprises the step of identifying a mammal in need of treating a metabotropic glutamate receptor activity dysfunction. In a yet further aspect, the treating metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal.

[00274] In a further aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from
15 addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelmans's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down
20 Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

25 [00275] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

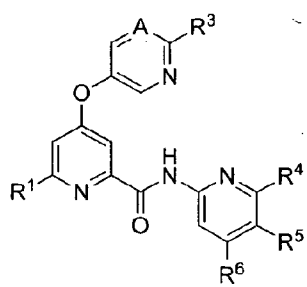
[00276] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still
30 further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is

selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

b. DECREASING METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00277] In one aspect, the invention relates to a method for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal an amount of at least one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the amount administered to the mammal is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with metabotropic glutamate receptor activity. In a yet further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5

[00278] Thus, in one aspect, the invention relates to a method for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00279] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00280] In a further aspect, the compound administered is any disclosed compound or at least one product of a disclosed method.

[00281] In a further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00282] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

5 [00283] In a further aspect, decreasing metabotropic glutamate receptor activity is non-competitive antagonism. In a yet further aspect, decreasing metabotropic glutamate receptor activity is negative allosteric modulation. In a still further aspect, decreasing metabotropic glutamate receptor activity is non-competitive inhibition. In an even further aspect, decreasing metabotropic glutamate receptor activity is inhibition. In a yet further aspect, decreasing metabotropic glutamate receptor activity is antagonism.

10 [00284] In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In a still further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .

[00285] In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

20 [00286] In a further aspect, the mammal has been diagnosed with a need for decreasing metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of decreasing metabotropic glutamate receptor activity. In an even further aspect, the decrease in metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal. In a yet further aspect, 25 the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

[00287] In a further aspect, the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelmans's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down 30

Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN harmartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

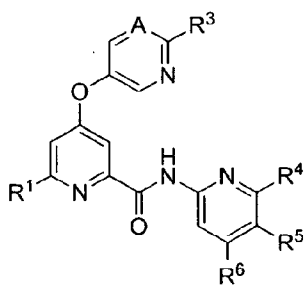
[00288] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00289] In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

c. INHIBITING METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00290] In one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal an amount of at least one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the amount administered to the mammal is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with metabotropic glutamate receptor activity. In a yet further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00291] Thus, in one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00292] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00293] In a further aspect, the compound administered is any disclosed compound or at least one product of a disclosed method.

[00294] In a further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00295] In a further aspect, inhibiting is non-competitive antagonism. In a still further aspect, inhibiting is negative allosteric modulation. In a yet further aspect, inhibiting is non-competitive inhibition. In an even further aspect, inhibiting is antagonism.

[00296] In a further aspect, mGluR5 activity is partially inhibited. In a further aspect, mGluR5 activity is totally inhibited. In a further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶. In a still further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶. In a yet further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁶. In an even further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷. In a still further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁸. In a yet further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁹.

[00297] In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

[00298] In a further aspect, the mammal has been diagnosed with a need for inhibiting metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of inhibiting metabotropic glutamate receptor activity. In an even further aspect, the inhibition of metabotropic glutamate receptor activity treats a disorder

associated with metabotropic glutamate receptor activity in the mammal. In a yet further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

[00299] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelmans's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpatic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

[00300] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

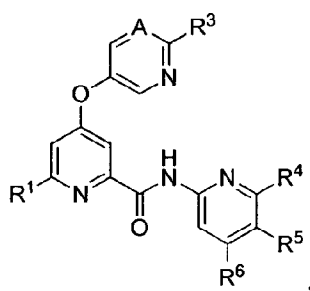
[00301] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

d. NEGATIVE ALLOSTERIC MODULATION OF METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00302] In one aspect, the invention relates to a method for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal an amount of at least one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the amount administered to the mammal is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is

associated with metabotropic glutamate receptor activity. In a yet further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00303] Thus, in one aspect, the invention relates to a method for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal
5 a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently
10 selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00304] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
15 In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00305] In a further aspect, the compound administered is any disclosed compound or at least one product of a disclosed method.

[00306] In a further aspect, the mammal is a human. In a still further aspect, the metabotropic
20 glutamate receptor is mGluR5.

[00307] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

[00308] In a further aspect, the compound exhibits negative allosteric modulation of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits non-competitive antagonism of
25 metabotropic glutamate receptor activity. In a yet further aspect, the compound decreases metabotropic glutamate receptor activity. In an even further aspect, the compound exhibits non-competitive inhibition

of metabotropic glutamate receptor activity. In a yet further aspect, the compound exhibits inhibition of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits antagonism of metabotropic glutamate receptor activity.

5 [00309] In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In a still further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In a yet further aspect, the compound exhibits
10 partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .

[00310] In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

15 [00311] In a further aspect, the mammal has been diagnosed with a need for negative allosteric modulation of metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of negative allosteric modulation of metabotropic glutamate receptor activity. In an even further aspect, the negative allosteric modulation of metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal. In a yet further aspect, the mammal has been diagnosed with a
20 need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

[00312] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the
25 neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive
30 illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

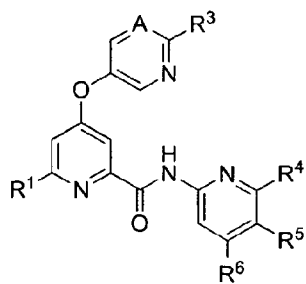
[00313] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

- 5 [00314] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain,
 10 genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

e. NON-COMPETITIVE ANTAGONISM OF METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

- [00315] In one aspect, the invention relates to a method for non-competitive antagonism of
 15 metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal an amount of at least one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the amount administered to the mammal is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with metabotropic glutamate receptor activity. In a yet further aspect, the mammal is a human.
 20 In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00316] Thus, in one aspect, the invention relates to a method for non-competitive antagonism of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



- 25 wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently

selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00317] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.

5 In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00318] In a further aspect, the compound administered is any disclosed compound or at least one product of a disclosed method.

10 [00319] In a further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00320] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

15 [00321] In a further aspect, the compound exhibits non-competitive antagonism of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits negative allosteric modulation of metabotropic glutamate receptor activity. In a yet further aspect, the compound decreases metabotropic glutamate receptor activity. In an even further aspect, the compound exhibits non-competitive inhibition of metabotropic glutamate receptor activity. In a yet further aspect, the compound exhibits inhibition of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits antagonism of metabotropic receptor activity.

20 [00322] In a further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶. In a still further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶. In a yet further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁶. In an even further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷. In a still further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁸. In a yet further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁹.

[00323] In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

30 [00324] In a further aspect, the mammal has been diagnosed with a need for partial antagonism of metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the

method further comprises the step of identifying a mammal in need of partial antagonism of metabotropic glutamate receptor activity. In an even further aspect, the partial antagonism of metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal. In a yet further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

[00325] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelmans's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpatic neuropathic pain, psychotic disorders, PTEN harmartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

[00326] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

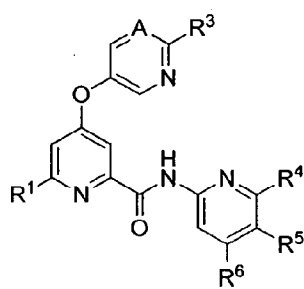
[00327] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

f. MODULATING METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00328] In one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal an amount of at least one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the amount administered to the mammal is a

therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with metabotropic glutamate receptor activity. In a yet further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00329] Thus, in one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00330] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00331] In a further aspect, the compound administered is any disclosed compound or at least one product of a disclosed method.

[00332] In a further aspect, the mammal is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5.

[00333] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

[00334] In a further aspect, the compound exhibits non-competitive antagonism of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits negative allosteric modulation of metabotropic glutamate receptor activity. In a yet further aspect, the compound decreases metabotropic

glutamate receptor activity. In an even further aspect, the compound exhibits non-competitive inhibition of metabotropic glutamate receptor activity. In a still further aspect, the compound exhibits inhibition of metabotropic receptor activity. In a yet further aspect, the compound exhibits antagonism of metabotropic receptor activity.

- 5 [00335] In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In a still further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a still further aspect, the compound exhibits partial
10 or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .

[00336] In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

- 15 [00337] In a further aspect, the mammal has been diagnosed with a need for modulation of metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of modulation of metabotropic glutamate receptor activity. In an even further aspect, the modulation of metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal. In a yet
20 further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

- [00338] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome,
25 gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders,
30 epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

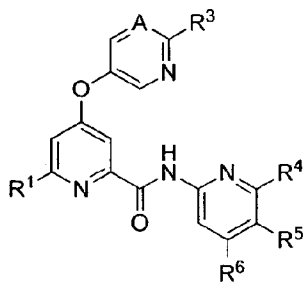
[00339] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

- 5 [00340] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain,
 10 genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

g. MODULATING METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY IN CELLS

- [00341] In one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting the at least one cell with an amount
 15 of at least one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the cell is in a mammal. In a still further aspect, the mammal is human. In an even further aspect, the amount contacting the cell is effective to inhibit mGluR5 activity in the at least one cell. In a yet further aspect, the amount contacting the cell is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with
 20 metabotropic glutamate receptor activity in at least one cell. In a further aspect, the metabotropic glutamate receptor is mGluR5.

[00342] Thus, in one aspect, the invention relates to a method for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of least one compound having a structure represented by a formula:



25

wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3

haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

5 [00343] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00344] In a further aspect, the compound contacting the cell is any disclosed compound or at least one product of a disclosed method.

10 [00345] In a further aspect, the cell is mammalian. In a still further aspect, the cell is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5. In a yet further aspect, the cell has been isolated from a mammal prior to the contacting step. In a further aspect, modulating metabotropic glutamate receptor activity in the at least one cell modulates metabotropic glutamate receptor activity in the mammal. In a yet further aspect, modulating metabotropic glutamate receptor activity in the mammal
15 treats a disorder associated with mGluR5 activity in the mammal.

[00346] In a further aspect, modulating is non-competitive antagonism. In a yet further aspect, modulating is negative allosteric modulation. In a still further aspect, modulating is non-competitive inhibition. In an even further aspect, modulating is inhibition. In a still further aspect, modulating is antagonism. In a yet further aspect, modulating is decreasing activity.

20 [00347] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

[00348] In a further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶. In a still further aspect, the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶. In a yet further aspect, the compound exhibits partial or total inhibition
25 with an IC₅₀ of less than about 1.0×10⁻⁶. In an even further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷. In a still further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁸. In a yet further aspect, the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁹.

[00349] In a further aspect, contacting is via administration to a mammal. In a further aspect, the
30 mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

[00350] In a further aspect, the mammal has been diagnosed with a need for modulation of metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of modulation of metabotropic glutamate receptor activity. In an even further aspect, the modulation of metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal. In a yet further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

[00351] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpatic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

[00352] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

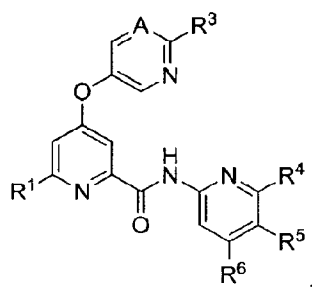
[00353] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

h. INHIBITING METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY IN CELLS

[00354] In one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting the at least one cell with an amount of at least

one disclosed compound, at least one disclosed product in a dosage, or at least one product of a disclosed method of making a compound. In a further aspect, the cell is in a mammal. In a still further aspect, the mammal is human. In an even further aspect, the amount contacting the cell is effective to inhibit mGluR5 activity in the at least one cell. In a yet further aspect, the amount contacting the cell is a therapeutically effective amount to treat a disorder in the mammal, wherein the disorder is associated with metabotropic glutamate receptor activity in at least one cell. In a further aspect, the metabotropic glutamate receptor is mGluR5.

[00355] Thus, in one aspect, the invention relates to a method for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting the at least one cell with at least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00356] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00357] In a further aspect, the compound contacting the cell is any disclosed compound or at least one product of a disclosed method.

[00358] In a further aspect, the cell is mammalian. In a still further aspect, the cell is a human. In a still further aspect, the metabotropic glutamate receptor is mGluR5. In a yet further aspect, the cell has been isolated from a mammal prior to the contacting step. In a further aspect, inhibiting metabotropic glutamate receptor activity in the at least one cell inhibits metabotropic glutamate receptor activity in the mammal. In

a yet further aspect, inhibiting metabotropic glutamate receptor activity in the mammal treats a disorder associated with mGluR5 activity in the mammal.

[00359] In a further aspect, inhibiting is non-competitive inhibition. In a still further aspect, inhibiting is non-competitive antagonism. In an even further aspect, inhibiting is negative allosteric modulation. In an even further aspect, inhibiting is antagonism.

[00360] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

[00361] In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In a still further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .

[00362] In a further aspect, contacting is via administration to a mammal. In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of treatment of a disorder.

[00363] In a further aspect, the mammal has been diagnosed with a need for inhibition of metabotropic glutamate receptor activity prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of inhibition of metabotropic glutamate receptor activity. In an even further aspect, the inhibition of metabotropic glutamate receptor activity treats a disorder associated with metabotropic glutamate receptor activity in the mammal. In a yet further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.

[00364] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders,

epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpatic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

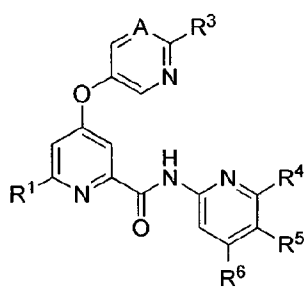
[00365] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder. In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

10 [00366] In a further aspect, the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation. In a still further aspect, the disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain,
15 genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

2. USE OF COMPOUNDS

[00367] Also provided are the uses of the disclosed compounds and products. In one aspect, the use relates to a treatment of a disorder in a mammal. In one aspect, the use is characterized in that the mammal
20 is a human. In one aspect, the use is characterized in that the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction. In one aspect, the use relates to negative allosteric modulation of metabotropic glutamate receptor activity in a mammal.

[00368] In one aspect, the invention relates to use of a compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-

C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof.

5 [00369] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00370] In a further aspect, the compound is any disclosed compound or at least one product of a
10 disclosed method.

[00371] In a further aspect, compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect, human embryonic kidney cells
15 transfected with rat mGluR5. In a yet further aspect, human embryonic kidney cells transfected with human mGluR5.

[00372] In a further aspect, the compound treats a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a still further aspect, neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease,
20 and pain. In a yet further aspect, the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-
25 induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

[00373] In a further aspect, the neurological and/or psychiatric disorder is an autism spectrum disorder.
30 In a still further aspect, the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.

[00374] In a further aspect, the compound treats a disease of uncontrolled cellular proliferation. In a still further aspect, disease of uncontrolled cellular proliferation is cancer. In a yet further aspect, the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In an even further aspect, the disease of uncontrolled cellular proliferation is
5 selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

[00375] In a further aspect, the compound exhibits partial inhibition of mGluR5 response. In a still further aspect, the compound exhibits total inhibition of mGluR5 response.

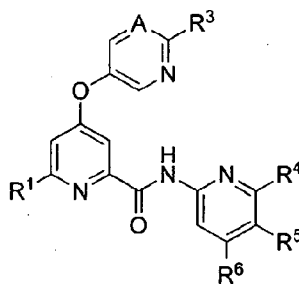
[00376] In a further aspect, the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} . In a still further aspect, the compound exhibits negative allosteric modulation with an
10 IC_{50} of less than about 10×10^{-6} . In a yet further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} . In an even further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} . In a still further aspect, the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} . In a yet further aspect, the compound exhibits
15 partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .

[00377] In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal. In a still further aspect, the disorder is a neurological and/or psychiatric disorder. In a yet further aspect, the disorder is a disease of uncontrolled cellular proliferation.

20 3. KITS

[00378] In one aspect, the invention relates to a kit comprising at least one disclosed compound or at least one disclosed product and one or more of at least one agent known to increase mGluR5 activity; at least one agent known to decrease mGluR5 activity; at least one agent known to treat a neurological and/or psychiatric disorder; at least one agent known to treat a disease of uncontrolled cellular proliferation; or
25 instructions for treating a disorder associated with glutamate dysfunction. In a further aspect, the at least one compound or the at least one product and the at least one agent are co-formulated. In a further aspect, the at least one compound or the at least one product and the at least one agent are co-packaged.

[00379] In one aspect, the invention relates to a kit comprising at least one compound having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent known to increase mGluR5 activity; (b) at least one agent known to decrease mGluR5 activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; (d) at least one agent known to treat a disease of uncontrolled cellular proliferation; or (e) instructions for treating a disorder associated with glutamate dysfunction.

[00380] In a further aspect, R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl. In a still further aspect, R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl. In a yet further aspect, R¹ is selected from methyl and ethyl. In an even further aspect, R¹ is methyl. In a still further aspect, R¹ is ethyl.

[00381] In a further aspect, the kit comprises any disclosed compound or at least one product of a disclosed method of making.

[00382] In a further aspect, the pharmaceutical composition comprises a compound that exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a still further aspect, the the human embryonic kidney cells transfected with rat mGluR5. In a yet further aspect, the human embryonic kidney cells transfected with human mGluR5.

[00383] In a further aspect, the at least one agent is selected from an antipsychotic, a selective serotonin reuptake inhibitor, a central sympathomimetic, an imidazoline receptor agonists, a propionic acid derivative, a benzodiazepine, sympathomimetics, a fatty acid derivative, a vitamin or multivitamin (with or without minerals), a piperazine derivative, an anilide, a lipid modifying agent, an aminoalkyl ether analogue, a macrolide, a melatonin receptor agonist, a penicillin derivative, a tetracycline analogue, an

expectorant, an antihistamine, an azaspirodecanedione derivative, a central acting agent, a carboxamide, an opium alkaloid or derivative, an antidepressant, an antiepileptic, a beta blocker, a psychostimulant, a proton pump inhibitor, a 5HT3 antagonist, a vitamin D analogue, a diazepam, an indole derivative, an HMG CoA reductase inhibitor, a topical antibiotic, a progesterone analogue, an estrogen analogue, an angiotensin-converting enzyme inhibitor, an anesthetic, an antifungal, an antidiarrheal, an oxazepam, a thiazepam, a vaccine, a sulfonamide, a leukotriene receptor antagonist, a lincosamide, a neuroamidase inhibitor, a non-selective monoamine reuptake inhibitor, and a salicylic acid analogue.

[00384] In a further aspect, the at least one agent is selected from Aripiprazole, Acetaminophen, Acetylcarnitine, Acetylsalicylic acid, Alprazolam, Amitriptyline, Amoxicillin, Augmentin, Azithromycin, Baclofen, Benzylpenicillin, Bupropion, Buspirone, Carbamazepine, Cetirizine, Cimetidine, Ciprofloxacin, Citalopram, Clonidine, Clozapine, Contac, Dexamfetamine, Dexmethylphenidate, Dextromethorphan, Diazepam, Dimetapp, Diphenhydramine, Donepezil, Drospirenone with ethinylestradiol, Ergocalciferol, Escitalopram, Excedrin, Fish oil, Fluoxetine, Fluvoxamine, Guaifenesin, Guanfacine, Haloperidol, Ibuprofen, Imipramine, Lamotrigine, Lansoprazole, Levoceterizine, Lisdexamfetamine, Loratadine, Lorazepam, Melatonin, Methylphenidate, Midazolam, Minocycline, Modafinil, Mupirocin, Naproxen, Obetrol, Olanzapine, Omega-3 TG, Omeprazole, Ondansetron, Oxcarbazepine, Paliperidone, Paracetamol, Pediacare, Phenobarbital, Phenylephrine, Phenytoin, Promethazine with codeine, Propranolol, Pseudoephedrine, Risperidone, Sertraline, Simvastatin, Statins, Topiramate, Trazodone, Tricyclic AD, Valproate, Venlafaxine, Ziprasidone, and Zonisamide.

[00385] In a further aspect, the at least one compound and the at least one agent are co-formulated.

[00386] In a further aspect, the at least one compound and the at least one agent are co-formulated, wherein the at least one agent is selected from an antipsychotic, a selective serotonin reuptake inhibitor, a central sympathomimetic, an imidazoline receptor agonists, a propionic acid derivative, a benzodiazepine, sympathomimetics, a fatty acid derivative, a vitamin or multivitamin (with or without minerals), a piperazine derivative, an anilide, a lipid modifying agent, an aminoalkyl ether analogue, a macrolide, a melatonin receptor agonist, a penicillin derivative, a tetracycline analogue, an expectorant, an antihistamine, an azaspirodecanedione derivative, a central acting agent, a carboxamide, an opium alkaloid or derivative, an antidepressant, an antiepileptic, a beta blocker, a psychostimulant, a proton pump inhibitor, a 5HT3 antagonist, a vitamin D analogue, a diazepam, an indole derivative, an HMG CoA reductase inhibitor, a topical antibiotic, a progesterone analogue, an estrogen analogue, an angiotensin-converting enzyme inhibitor, an anesthetic, an antifungal, an antidiarrheal, an oxazepam, a thiazepam, a vaccine, a sulfonamide, a leukotriene receptor antagonist, a lincosamide, a neuroamidase inhibitor, a non-selective monoamine reuptake inhibitor, and a salicylic acid analogue.

[00387] In a further aspect, the at least one compound and the at least one agent are co-formulated, wherein the at least one agent is selected from Aripiprazole, Acetaminophen, Acetylcarnitine, Acetylsalicylic acid, Alprazolam, Amitriptyline, Amoxicillin, Augmentin, Azithromycin, Baclofen, Benzylpenicillin, Bupropion, Buspirone, Carbamazepine, Cetirizine, Cimetidine, Ciprofloxacin, Citalopram, Clonidine, Clozapine, Contac, Dexamfetamine, Dexmethylphenidate, Dextromethorphan, Diazepam, Dimetapp, Diphenhydramine, Donepezil, Drospirenone with ethinylestradiol, Ergocalciferol, Escitalopram, Excedrin, Fish oil, Fluoxetine, Fluvoxamine, Guaifenesin, Guanfacine, Haloperidol, Ibuprofen, Imipramine, Lamotrigine, Lansoprazole, Levoceterizine, Lisdexamfetamine, Loratadine, Lorazepam, Melatonin, Methylphenidate, Midazolam, Minocycline, Modafinil, Mupirocin, Naproxen, Obetrol, Olanzapine, Omega-3 TG, Omeprazole, Ondansetron, Oxcarbazepine, Paliperidone, Paracetamol, Pediacare, Phenobarbital, Phenylephrine, Phenytoin, Promethazine with codeine, Propranolol, Pseudoephedrine, Risperidone, Sertraline, Simvastatin, Statins, Topiramate, Trazodone, Tricyclic AD, Valproate, Venlafaxine, Ziprasidone, and Zonisamide.

[00388] In a further aspect, the at least one compound and the at least one agent are co-packaged..

[00389] In a further aspect, the at least one compound and the at least one agent are co-packaged, wherein the at least one agent is selected from an antipsychotic, a selective serotonin reuptake inhibitor, a central sympathomimetic, an imidazoline receptor agonists, a propionic acid derivative, a benzodiazepine, sympathomimetics, a fatty acid derivative, a vitamin or multivitamin (with or without minerals), a piperazine derivative, an anilide, a lipid modifying agent, an aminoalkyl ether analogue, a macrolide, a melatonin receptor agonist, a penicillin derivative, a tetracycline analogue, an expectorant, an antihistamine, an azaspirodecanedione derivative, a central acting agent, a carboxamide, an opium alkaloid or derivative, an antidepressant, an antiepileptic, a beta blocker, a psychostimulant, a proton pump inhibitor, a 5HT3 antagonist, a vitamin D analogue, a diazepam, an indole derivative, an HMG CoA reductase inhibitor, a topical antibiotic, a progesterone analogue, an estrogen analogue, an angiotensin-converting enzyme inhibitor, an anesthetic, an antifungal, an antidiarrheal, an oxazepam, a thiazepam, a vaccine, a sulfonamide, a leukotriene receptor antagonist, a lincosamide, a neuroamidase inhibitor, a non-selective monoamine reuptake inhibitor, and a salicylic acid analogue.

[00390] In a further aspect, the at least one compound and the at least one agent are co-packaged, wherein the at least one agent is selected from Aripiprazole, Acetaminophen, Acetylcarnitine, Acetylsalicylic acid, Alprazolam, Amitriptyline, Amoxicillin, Augmentin, Azithromycin, Baclofen, Benzylpenicillin, Bupropion, Buspirone, Carbamazepine, Cetirizine, Cimetidine, Ciprofloxacin, Citalopram, Clonidine, Clozapine, Contac, Dexamfetamine, Dexmethylphenidate, Dextromethorphan, Diazepam, Dimetapp, Diphenhydramine, Donepezil, Drospirenone with ethinylestradiol, Ergocalciferol, Escitalopram, Excedrin, Fish oil, Fluoxetine, Fluvoxamine, Guaifenesin, Guanfacine, Haloperidol, Ibuprofen, Imipramine, Lamotrigine, Lansoprazole, Levoceterizine, Lisdexamfetamine, Loratadine,

Lorazepam, Melatonin, Methylphenidate, Midazolam, Minocycline, Modafinil, Mupirocin, Naproxen, Obetrol, Olanzapine, Omega-3 TG, Omeprazole, Ondansetron, Oxcarbazepine, Paliperidone, Paracetamol, Pediacare, Phenobarbital, Phenylephrine, Phenytoin, Promethazine with codeine, Propranolol, Pseudoephedrine, Risperidone, Sertraline, Simvastatin, Statins, Topiramate, Trazodone, Tricyclic AD, Valproate, Venlafaxine, Ziprasidone, and Zonisamide.

[00391] The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

10 [00392] It is contemplated that the disclosed kits can be used in connection with the disclosed methods of making, the disclosed methods of using, and/or the disclosed compositions.

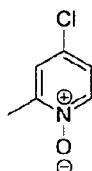
4. NON-MEDICAL USES

[00393] Also provided are the uses of the disclosed compounds and products as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of agonists and antagonists of mGluR related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of mGluR. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of agonists and antagonists of mGluR5 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of mGluR5.

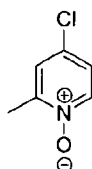
G. EXPERIMENTAL

[00394] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

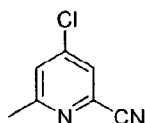
[00395] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein. All ¹H NMR spectra were obtained on instrumentation at a field strength of 300 to 500 MHz.

1. ROUTE I**a. PREPARATION OF 4-CHLORO-2-METHYLPYRIDINE 1-OXIDE (METHOD 1).**

[00396] 2-methyl-4-nitropyridine 1-oxide (5.0 g, 32 mmol, 1.0 eq) was dissolved in concentrated HCl (80 mL) and refluxed for 3 days. The reaction was cooled and the excess concentrated HCl was removed in vacuo. The viscous oil was neutralized with 10% K₂CO₃ and extracted with CH₂Cl₂ (5x). The combined organics were dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel afforded 3.49 g (75%) of the title compound as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.23 (d, *J* = 7.0 Hz, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 7.40 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.32 (s, 3H); ES-MS [M+1]⁺: 144.2.

b. PREPARATION OF 4-CHLORO-2-METHYLPYRIDINE 1-OXIDE (METHOD 2).

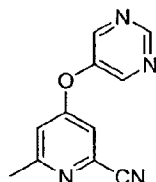
[00397] 4-Chloro-2-methylpyridine (5.0 g, 39 mmol, 1.0 eq) and hydrogen peroxide-urea adduct (7.37 g, 78.4 mmol, 2.00 eq) were dissolved in THF (196 mL) and cooled to 0 °C. Trifluoroacetic anhydride (12 mL, 86.3 mmol, 2.2 eq) was added dropwise over 15 minutes and the reaction was allowed to warm to room temperature. After determination of the completion of the reaction by LCMS (approximately 45 minutes), the reaction was cooled to 0 °C and quenched with a 10% aqueous solution of NaS₂O₃. The reaction was extracted with EtOAc (3x), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel afforded 5.63 g (99%) of the title compound as a white solid.

c. PREPARATION OF 4-CHLORO-6-METHYLPICOLINONITRILE.

[00398] 4-chloro-2-methylpyridine-N-oxide (8.97g, 62.5 mmol, 1.00 eq) was dissolved in CH₂Cl₂ and dried over MgSO₄. The solution was added to a flame-dried round-bottom flask and CH₂Cl₂ was added to

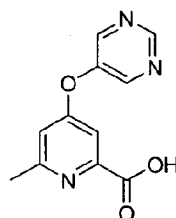
give a total volume of 188 mL. TMS-cyanide (10 mL, 75 mmol, 1.2 eq) was added and the reaction stirred for 15 minutes. Dimethylcarbamyl chloride (6.9 mL, 75 mmol, 1.2 eq) was added dropwise over 20 minutes, and the reaction was stirred for 24 hours. An additional one equivalent each of TMS-cyanide and dimethylcarbamyl chloride were added and the reaction was stirred for another 72 hours. The reaction was made basic with 10% K₂CO₃ and extracted with CH₂Cl₂ (3x). The combined organics were dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel afforded 7.2 g (75%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.13 (d, *J* = 1.6 Hz, 1H), 7.82 (d, *J* = 1.7 Hz, 1H), 2.52 (s, 3H); ES-MS [M+1]⁺: 153.2.

d. PREPARATION OF 6-METHYL-4-(PYRIMIDIN-5-YLOXY)PICOLINONITRILE.



[00399] 4-chloro-6-methylpicolinonitrile (4.0 g, 26 mmol, 1.0 eq), 5-hydroxypyrimidine (5.56 g, 57.9 mmol, 2.20 eq), K₂CO₃ (7.24 mg, 52.4 mmol, 2.0 eq) and DMF (66 mL) were added to a reaction vessel and heated at 80 °C for 16 hours. The reaction was filtered and concentrated on silica gel (25 g). The silica gel was loaded on top of a fresh bed of silica gel and washed with 50% ethyl acetate/hexane. The solvents were removed in vacuo and the crude solid was purified by flash chromatography on silica gel to afford 4.31 g (77%) of the title compound as a pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.17 (s, 1H), 8.85 (s, 2H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 2.48 (s, 3H); ES-MS [M+1]⁺: 213.2.

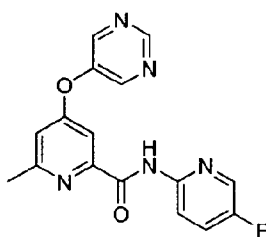
e. PREPARATION OF 6-METHYL-4-(PYRIMIDIN-5-YLOXY)PICOLINIC ACID.



[00400] 6-methyl-4-(pyrimidin-5-yloxy)picolinonitrile (4.31 g, 20.3 mmol, 1.00 eq) was dissolved in dioxane (90 mL), and 2N NaOH (45 mL) was added. The mixture was refluxed for 18 h and after cooling the reaction was neutralized with 2N HCl (45 mL). The water and solvent were removed in vacuo and the crude reaction was dissolved in 10% MeOH/CH₂Cl₂. The undissolved salt was filtered off and the

solvents were removed in vacuo to afford 4.65g (99%) of the title compound as a white solid which was used without further purification.

f. PREPARATION OF N-(5-FLUOROPYRIDIN-2-YL)-6-METHYL-4-(PYRIMIDIN-5-YLOXY)PICOLINAMIDE.



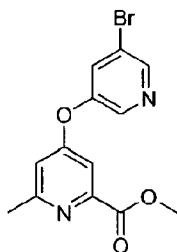
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[00401] 6-methyl-4-(pyrimidin-5-yloxy)picolinic acid (610 mg, 2.64 mmol, 1 eq) and 5-fluoro-2-aminopyridine (296 mg, 2.64 mmol, 1 eq) were dissolved in pyridine (40 mL) in a flame-dried round-bottom flask. The reaction was cooled to -15 °C and phosphorus oxychloride (270 µL, 2.90 mmol, 1.1 eq) was added dropwise while keeping the temperature below -15 °C. After stirring for 30 minutes at -15 °C and the reaction was quenched with ice-water and neutralized with 10% K₂CO₃. The mixture was extracted with EtOAc (3x) and the combined organics were dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel afforded 310 mg (36%) of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.48 (s, 1H), 9.18 (s, 1H), 8.88 (s, 2H), 8.40 (d, *J* = 3.0 Hz, 1H), 8.27 (dd, *J* = 9.2 Hz, 4.10 Hz, 1H), 7.86 (td, *J* = 8.6, 3.1 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 2.58 (s, 3H); ES-MS [M+1]⁺: 326.2.

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2. ROUTE II

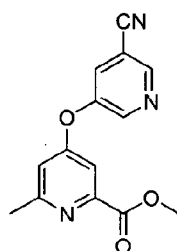
a. PREPARATION OF METHYL 4-(5-BROMOPYRIDIN-3-YLOXY)-6-METHYLPICOLINATE.



20 [00402] 4-(5-bromopyridin-3-yloxy)-6-methylpicolinic (75 mg, 0.24 mmol, 1 eq) was dissolved in methanol (1.2 mL) in a microwave vial and H₂SO₄ (0.12 mL) was added dropwise. The vial was capped and heated at 75 °C for 3 hours. The reaction was cooled to room temperature and neutralized with saturated NaHCO₃. The reaction was extracted with EtOAc (2x), dried (MgSO₄), filtered, and

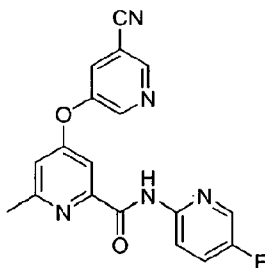
concentrated in vacuo. Purification by flash chromatography on silica gel afforded 62 mg (79%) of the title compound as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.68 (d, $J=1.8$ Hz, 1H), 8.55 (d, $J=2.4$ Hz, 1H), 8.12 (t, $J=2.1$ Hz, 1H), 7.40 (d, $J=2.3$ Hz, 1H), 7.19 (d, $J=2.3$ Hz, 1H), 3.84 (s, 1H), 2.48 (s, 3H); $[\text{M}+1]^+$: 323.0.

5 **b. PREPARATION OF METHYL 4-(5-CYANOPYRIDIN-3-YLOXY)-6-METHYLPICOLINATE.**



[00403] Methyl 4-(5-bromopyridin-3-yloxy)-6-methylpicolinate (313 mg, 0.969 mmol, 1.00 eq), Tetrakis(triphenylphosphine)palladium(0) (112 mg, 0.0969 mmol, 0.1 eq), $\text{Zn}(\text{CN})_2$ (125 mg, 1.06 mmol, 1.1 eq), and DMF (5 mL) were added to a microwave vial and heated at 140 °C for 10 minutes. The reaction was filtered and concentrated on silica gel (2g). The silica gel was loaded on top a fresh bed of silica gel and washed with 50% ethyl acetate/hexane. The solvents were removed in vacuo and the crude solid was purified by flash chromatography on silica gel to afford 210 mg (81%) of the title compound as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.97 (d, $J=1.5$ Hz, 1H), 8.84 (d, $J=2.7$ Hz, 1H), 8.35-8.34 (m, 1H), 7.45 (d, $J=2.2$ Hz, 1H), 7.21 (d, $J=2.2$ Hz, 1H), 3.85 (s, 3H), 2.49 (s, 3H); $[\text{M}+1]^+$: 270.1.

15 **c. PREPARATION OF 4-(5-CYANOPYRIDIN-3-YLOXY)-N-(5-FLUOROPYRIDIN-2-YL)-6-METHYLPICOLINAMIDE.**



[00404] 2-Amino-5-fluoropyridine (34.3 mg, 0.306 mmol, 1.10 eq) was dissolved in THF (0.7 mL) in a flame-dried round bottom flask. A 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (0.613 mL, 0.306 mmol, 1.10 eq) was added dropwise and the reaction was stirred for 5 minutes. Methyl 4-(5-cyanopyridin-3-yloxy)-6-methylpicolinate (75 mg, 0.28 mmol, 1.0 eq) was added as a solution in THF (0.7 mL) and the reaction was stirred for 30 minutes. The reaction was diluted with EtOAc, neutralized

with 1N HCl, and washed with water. The organic layer was dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel afforded 45 mg (46%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 10.48 (s, 1H), 8.99 (s, 1H), 8.87 (d, *J* = 2.4 Hz, 1H), 8.41-8.39 (m, 2H), 8.27 (dd, *J* = 9.1, 4.1 Hz, 1H), 7.86 (td, *J* = 8.7, 2.8 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.28 (d, *J* = 1.7 Hz, 1H), 2.58 (s, 3H); [M+1]⁺: 350.2.

3. GENERATION OF MGLUR5 STABLE CELL LINES

[00405] Typically, the mGluR5 activity of the disclosed compounds is determined a stable cell line transfected with rat mGluR5. The preparation of rat mGluR5 stable cell-lines is as previously described (e.g. see Romano et al. J Biol Chem. 1996 Nov 8; 271(45):28612-6). Data generated using this cell-line in the mGluR5 assay (described below) are shown in Table 1.

[00406] mGluR5 activity of the disclosed cell-lines can also be determined using a stable cell-line transfected with human mGluR5. Briefly, human mGluR5a cDNA in pCMV6-XL6 mammalian expression plasmid was purchased from OriGene Technologies, Inc. (catalogue number SC326357) and subcloned into pcDNA3.1(-). Human embryonic kidney (HEK)293A cells were then transfected with human mGluR5a pcDNA3.1(-) using LipofectAmine2000 (Invitrogen) and monoclones were selected and tested for functional response using a Ca²⁺ mobilization assay. Monoclones were named for the species ("H" for human) plus the location on the plate (e.g. "10H").

4. METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY: CALCIUM MOBILIZATION ASSAY

[00407] HEK 293A cells stably expressing rat mGluR5 were plated in black-walled, clear-bottomed, poly-D-lysine coated 384-well plates in 20 μL of assay medium (DMEM containing 10% dialyzed FBS, 20 mM HEPES, and 1 mM sodium pyruvate) at a density of 20K cells/well. The cells were grown overnight at 37 °C in the presence of 5% CO₂. The next day, medium was removed and the cells incubated with 20 μL of 2 μM Fluo-4, AM prepared as a 2.3 mM stock in DMSO and mixed in a 1:1 ratio with 10% (w/v) pluronic acid F-127 and diluted in assay buffer (Hank's balanced salt solution, 20 mM HEPES, and 2.5 mM probenecid) for 45 minutes at 37 °C. Dye was removed, 20 μL of assay buffer was added, and the plate was incubated for 10 minutes at room temperature.

[00408] Ca²⁺ flux was measured using the Functional Drug Screening System (FDSS6000, Hamamatsu, Japan). After establishment of a fluorescence baseline for about 3 seconds, the compounds of the present invention were added to the cells, and the response in cells was measured. 2.3 minutes later an EC₂₀ concentration of the mGluR5 receptor agonist glutamate was added to the cells, and the response of the cells was measured for about 1.2 minutes; an EC₈₀ concentration of agonist was added and readings taken for an additional 40 seconds. All test compounds were dissolved and diluted to a concentration of 10 mM in 100% DMSO and then serially diluted into assay buffer for a 2x stock solution in 0.6% DMSO; stock compounds were then added to the assay for a final DMSO concentration of 0.3% after the first

addition to the assay well. Calcium fluorescence measures were recorded as fold over basal fluorescence; raw data was then normalized to the maximal response to glutamate. Antagonism of the agonist response of the mGluR5 receptor in the present invention was observed as a decrease in response to nearly maximal concentrations of glutamate in the presence of compound compared to the response to glutamate in the absence of compound.

[00409] The raw data file containing all time points was used as the data source in the analysis template. This was saved by the FDSS as a tab-delimited text file. Data were normalized using a static ratio function (F/F_0) for each measurement of the total 250 values per well divided by each well's initial value. Data were then reduced as to peak amplitudes ($\text{Max} - \text{Initial Min}$) using a time range that starts approximately 3 seconds prior to the glutamate EC_{80} addition and continues for approximately 40 seconds. This is sufficient time to capture the peak amplitude of the cellular calcium response. Individual amplitudes were expressed as % E_{Max} by multiplying each amplitude by 100 and then dividing the product by the mean of the amplitudes derived from the glutamate EC_{Max} -treated wells. EC_{50} values for test compounds were generated by fitting the normalized values versus the log of the test compound concentration (in mol/L) using a 4 parameter logistic equation where none of the parameters were fixed. Each of the three values collected at each concentration of test compound were weighted evenly. A compound was designated as a negative allosteric modulator if the compound showed a concentration-dependent decrease in the glutamate EC_{80} addition. Potency (IC_{50}) and maximum response (% Glu Max) for compounds were determined using a four parameter logistical equation. For data that show a decrease in the EC_{80} response, but do not hit a plateau, the average of the maximum response at a single concentration (30 μM) was determined and potencies were not quantified.

[00410] The above described assay was also operated in a second mode where an appropriate fixed concentration of the present compounds were added to the cells after establishment of a fluorescence baseline for about 3 seconds, and the response in cells was measured. 2.3 min later the appropriate concentration of agonist was added and readings taken for an additional 2.6 minutes. Data were reduced as described above and the EC_{50} values for the agonist in the presence of test compound were determined by nonlinear curve fitting. A decrease in the EC_{50} value of the agonist with increasing concentrations of the present compounds (a leftward shift of the agonist concentration-response curve) is an indication of the degree of mGluR5 positive allosteric modulation at a given concentration of the present compound. An increase in the EC_{50} value of the agonist with increasing concentrations of the present compounds (a rightward shift of the agonist concentration response curve) is an indication of the degree of mGluR5 antagonism at a given concentration of the present compound. The second mode also indicates whether the present compounds also affect the maximum response to mGluR5 to agonists.

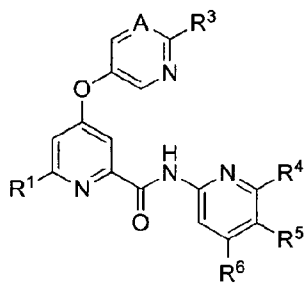
5. PROSPECTIVE METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY: RADIOLIGAND BINDING ASSAY

[00411] The following examples of the *in vitro* effects of the disclosed compounds are prophetic. An example of an *in vitro* assay method for assessing the receptor ligand binding activity of the disclosed compounds is given below.

[00412] Competition binding studies can be performed with the allosteric the allosteric antagonist [³H]methoxyPEPy to determine if the disclosed compounds interact with the well-characterized allosteric binding site for the mGluR5 NAM MPEP.

[00413] The allosteric antagonist MPEP analog [³H]methoxyPEPy is used to evaluate the ability of test compounds to interact with the MPEP site on mGluR5 (Cosford et al., 2003a). Membranes are prepared from rat mGluR5 HEK293 cells (Rodriguez et al., 2005). Compounds are diluted in assay buffer (50 mM Tris/0.9% NaCl, pH 7.4) to a 5x stock and 100 μ L test compound is added to each well of a 96 deep-well assay plate. 300 μ L aliquots of membranes diluted in assay buffer (40 μ g/well) are added to each well. 100 μ L [³H]methoxyPEPy (2 nM final concentration) is added and the reaction is incubated at room temperature for 1 hour with shaking. After the incubation period, the membrane-bound ligand is separated from free ligand by filtration through glass-fiber 96 well filter plates (Unifilter-96, GF/B, PerkinElmer Life and Analytical Sciences, Boston, MA). The contents of each well are transferred simultaneously to the filter plate and washed 3-4 times with assay buffer using a cell harvester (Brandel Cell Harvester, Brandel Inc., Gaithersburg, MD). 40 μ L scintillation fluid is added to each well and the membrane-bound radioactivity determined by scintillation counting (TopCount, PerkinElmer Life and Analytical Sciences). Non-specific binding is estimated using 5 μ M MPEP. Concentration response curves were generated using a four parameter logistical equation in GraphPad Prism (GraphPad Software, Inc., La Jolla, CA).

[00414] For example, compounds having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3

haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, are expected to show at least partial displacement of [³H]methoxyPEPy in the radioligand binding assay. Moreover, compounds prepared using the disclosed synthetic methods are also expected to show such effects.

6. PROSPECTIVE METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY: SELECTIVITY ASSAYS

[00415] The following examples of the *in vitro* effects of the disclosed compounds are prophetic. Typical examples of *in vitro* assay methods for assessing the receptor selectivity of the disclosed compounds are given below.

a. RAT MGLUR1 ASSAY

[00416] Compound activity at the group II and group III mGluRs can be assessed in the assay described herein. HEK293A cells stably expressing rat mGluR1 are cultured and assayed as described above for mGluR5-expressing cells. For these assays, after establishment of a fluorescence baseline for about 3 seconds, the compounds of the present invention are added to the cells at 2x final concentration, and the response in cells is measured. 2.3 min later the appropriate concentration of agonist is added at 5x the final concentration and readings taken for an additional 2.6 minutes. Data are analyzed as described for mGluR5 assays.

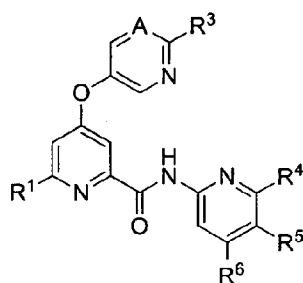
b. RAT MGLU RECEPTORS 2, 3, 4, 7, AND 8, AND HUMAN MGLUR6 ASSAYS

[00417] Compound activity at the group II and group III mGluRs can be assessed using thallium flux through G-protein-coupled inwardly rectifying potassium (GIRK) channels, a method that has been described in detail (Niswender et al. (2008) Mol. Pharmacol. 73, 1213–1224). These cell lines are grown in growth media containing 45% DMEM, 45% F-12, 10% FBS, 20 mM HEPES, 2 mM L-glutamine, antibiotic/antimycotic, nonessential amino acids, 700 µg/mL G418, and 0.6 µg/mL puromycin at 37 °C in the presence of 5% CO₂. Briefly, HEK/GIRK cells expressing the mGluR subtype 2, 3, 4, 6, 7, or 8 are plated into 384 well, black-walled, clear-bottom poly-D-lysine coated plates at a density of 15,000 cells/20 µL/well in assay medium and incubated overnight at 37 °C in the presence of 5% CO₂. The following day, the medium from the cells and 20 µL/well of 1.7 µM concentration of the indicator dye BTC-AM (Invitrogen, Carlsbad, CA) in assay buffer is added. Cells are incubated for 1 hour at room temperature and the dye is replaced with 20 µL/well of assay buffer. After establishment of a fluorescence baseline for about 3 seconds, the compounds of the present invention are added to the cells at 2x final concentration, and the response in cells is measured. 2.3 min later the appropriate concentration of agonist is added and readings taken for an additional 2.6 minutes. Agonists are diluted in thallium buffer (125 mM sodium

bicarbonate, 1 mM magnesium sulfate, 1.8 mM calcium sulfate, 5 mM glucose, 12 mM thallium sulfate, 10 mM HEPES) at 5x the final concentration to be assayed. Data are analyzed as described in Niswender et al. 2008.

c. PROSPECTIVE ACTIVITY OF THE DISCLOSED COMPOUNDS AND PRODUCTS OF THE DISCLOSED METHODS OF MAKING

[00418] It is anticipated that compounds having a structure represented by a formula:



[00419] wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, are expected to show selective inhibition of mGluR5 compared to rat mGlu receptors R1, R2, R3, R4, R7, and R8, and Human mGluR6.

[00420] In one aspect, the disclosed compounds are anticipated to show at least about 1.5 fold greater selectivity for rat mGluR5 compared rat mGlu receptors R1, R2, R3, R4, R7, and R8, and Human mGluR6 based on IC₅₀. In a further aspect, the disclosed compounds are anticipated to show about at least 5 fold greater selectivity for rat mGluR5 compared rat mGlu receptors R1, R2, R3, R4, R7, and R8, and Human mGluR6 based on IC₅₀. In a still further aspect, the disclosed compounds are anticipated to show at least about 10 fold greater selectivity for rat mGluR5 compared rat mGlu receptors R1, R2, R3, R4, R7, and R8, and Human mGluR6 based on IC₅₀. In an even further aspect, the disclosed compounds are anticipated to show at least about 50 fold greater selectivity for rat mGluR5 compared rat mGlu receptors R1, R2, R3, R4, R7, and R8, and Human mGluR6 based on IC₅₀. In a still further aspect, the disclosed compounds are anticipated to show at least about 100 fold greater selectivity for rat mGluR5 compared rat mGlu receptors R1, R2, R3, R4, R7, and R8, and Human mGluR6 based on IC₅₀. Moreover, compounds prepared using the disclosed synthetic methods are also expected to show such effects.

[00421]

7. MOUSE MODEL OF OF ANXIOLYTIC BEHAVIOR: INHIBITION OF MARBLE BURYING ACTIVITY IN MICE

- [00422] It is well known that mice will bury foreign objects such as glass marbles in deep bedding (Deacon, R. M. J. *Nature Protocols* **2006**, *1*, 122-124). Low doses of anxiolytic benzodiazepines have been demonstrated to inhibit this behavior (Njung'e, K.; Handley, S. L. *Brit. J. Pharmacol.* **1991**, *104*, 105-112; Broekkamp, C. L.; Rijk, H. W.; Joly-Gelouin, D.; Lloyd, K. L. *Eur. J. Pharmacol.* **1986**, *126*, 223-229). Moreover, the known mGlu₅ NAMs MPEP (3-((2-Methyl-4-thiazolyl)ethynyl)-pyridine) and fenobam (1-(3-chlorophenyl)-3-(1-methyl-4-oxo-4,5-dihydro-1*H*-imidazol-2-yl)urea) are effective in this model (Spooren W. P. J. M.; Vassout A.; Neijt H. C.; Kuhn R.; Gasparini F.; Roux S.; Porsolt R. D.; Gentsch C. J. *Pharmacol. Exp. Ther.* **2000**, *295*, 1267-1275; Nicolas, L. B.; Kolb, Y.; Prinssen, E. P. M. *Eur. J. Pharmacol.* **2006**, *547*, 106-115). These facts along with the relative convenience of this assay make it a useful *in vivo* screening tool.
- [00423] Doses of compound were suspended in vehicle (10% Tween 80 for intraperitoneal dosing and 0.5% methylcellulose for oral dosing), vortexed vigorously, heated gently with a Master Heat Gun (Master Appliance Corp., Racine, WI), and sonicated at 37°C for 30 minutes. The pH was checked using 0-14 EMD strips and adjusted to approximately 7. All doses were administered at approximately 10 mL/kg.
- [00424] Studies were conducted using male Harlan CD-1 mice (Harlan Sprague Dawley, Indianapolis, IN), weighing 30 to 35 grams. Subjects were housed in a large colony room under a 12 hour light/dark cycle (lights on at 6:00 a.m.) with food and water provided *ad libitum*. Test sessions were performed between 10:00 a.m. and 4:00 p.m. All dose groups consisted of ≥ 10 mice. All experiments were conducted in accordance with the National Institute of Health regulations of animal care covered in Principles of Laboratory Animal Care (National Institutes of Health publication 85-23, revised 1985) and were approved by the Institutional Animal Care and Use Committee.
- [00425] Plexiglass cages (32 x 17 x 14 cm) were arranged on top of a large, round table. Mice were transported from the colony room to the testing room and allowed to habituate for 30 minutes. Mice were pretreated with a dose of a standard compound (MTEP, 2-methyl-4-(pyridin-3-ylethynyl)thiazole) or novel compound for 15 or 30 minutes and individually placed in the cages in which 12 black glass marbles (14 mm diameter) had been evenly distributed (spaced 6.4 cm vertically and 4.25 cm horizontally from each other and the walls of the cage) on top of 2.5 cm Diamond Soft Bedding (Harlan Teklad, Madison, WI). The novel compound and comparator were evaluated in a counterbalanced design, in which all doses of compounds were tested in each session. Mice receiving the same dose were placed in cages on opposite sides of the table to control for effects of lighting and context. Clear, perforated plastic lids were set on top of each cage and the amount of marble burying was recorded over a 30 minute interval. The mice were then removed from the cages and the number of buried marbles was counted using the criteria of greater

than 2/3 covered by bedding. Each session was videotaped with a Sony MiniDV camcorder equipped with a Sony wide-angle lens mounted on a 1.5 m tripod.

[00426] The data for the dose-response studies were analyzed by a between-group analysis of variance. If there was a main effect of dose, then each dose group was compared with the vehicle control group using a Dunnett's comparison. The calculations were performed using JMP IN 8 (SAS Institute, Cary, NC) statistical software and graphed using SigmaPlot9 (Sasgaa, MA).

8. INHIBITION OF MARBLE BURYING IN MICE BY *N*-(5-FLUOROPYRIDIN-2-YL)-6-METHYL-4-(PYRIMIDIN-5-YLOXY)PICOLINAMIDE

[00427] Dose response activity of *N*-(5-fluoropyridin-2-yl)-6-methyl-4-(pyrimidin-5-yloxy)picolinamide in the marble burying assay as described above is shown in Figures 3 and 4, and was carried out as described above. *N*-(5-fluoropyridin-2-yl)-6-methyl-4-(pyrimidin-5-yloxy)picolinamide is indicated as "Test Compound" in the figures. In Figure 3, the assay was carried out by via intraperitoneal ("IP") injection of animals at the doses indicated (mg/kg). Activity of the compound is compared to a positive control compound, MTEP, at the dose indicated.

[00428] In Figure 4, the assay was carried out by oral ("PO") dosing of animals at the doses indicated (mg/kg). Activity of the compound is compared to a positive control compound, MTEP, at the dose indicated. Statistically significant results ($p < 0.05$) are indicated by an asterisk above the bar.

[00429] A second set of experiments also shown in Figure 3 using WT and *Fmr1* KO mice on the C57BL/6J background ($n = 10-12$ per group). These mice were 8-12 weeks of age. The reference compound (STX107) was administered at a dose of (10 mg/kg-Free Base) in 0.5% methylcellulose after overnight stirring (IP 60 min. ptx). The test compound (2) was administered in in 0.5%MC, pH ~ 6-7, administered PO 15 min. prior to testing. The burying time was 30 minutes. In WT and KO animals, inhibition of marble burying was observed at 3 and 10 mg/kg treatment groups and the STX107 positive control vs. vehicle.

9. INHIBITION OF MARBLE BURYING IN MICE BY *N*-(5-FLUOROPYRIDIN-2-YL)-4-((5-FLUOROPYRIDIN-3-YL)OXY)-6-METHYLPICOLINAMIDE

[00430] Dose response activity of *N*-(5-fluoropyridin-2-yl)-4-((5-fluoropyridin-3-yl)oxy)-6-methylpicolinamide in the marble burying assay as described above is shown in Figures 5 and 6, and was carried out as described above. *N*-(5-fluoropyridin-2-yl)-4-((5-fluoropyridin-3-yl)oxy)-6-methylpicolinamide as "Test Compound" in the figures. In Figure 5, the assay was carried out by via intraperitoneal ("IP") injection of animals at the doses indicated (mg/kg). Activity of the compound is compared to a positive control compound, MTEP, at the dose indicated. In Figure 6, the assay was carried out by oral ("PO") dosing of animals at the doses indicated (mg/kg). Activity of the compound is

compared to a positive control compound, MTEP, at the dose indicated. Statistically significant results ($p < 0.05$) are indicated by an asterick above the bar.

[00431] A second set of experiments is also shown in Figure 6 under similar conditions to those described in Figure 3. These experiments employed test compound 1 (in 10%Tween80/0.5%MC, pH ~ 6-7, administered PO 15 min. prior to testing). In this experiment in WT and KO animals inhibition was observed at 30 mg/kg and positive control groups for both genotypes, as well as the 10 mg/kg KO animals vs. vehicle.

[00432] Figure 7A shows the structures of the compounds used in the FvB Audiogenic Seizure (AGS) studies shown in Figures 7B and 7C. This study is known in the art and is described in, e.g., Musumeci et al., *Experimental Neurology*, 203(1):233-240 (January 2007), and Yan et al., *Neuropharmacology*, 2005 49(7):1053-1066 (December 2005). These studies employed FvB WT & Fmr1 KO male mice (62 days of age), and either vehicle or the test compound in 0.5% methylcellulose (Pharmatek Formulation) was administered at dosages of 1, 3, or 10 mg/kg (QD, 15min PO gavage, 10ml/kg). In these studies, animals with an AGS score of greater than 2 counted as positive for seizures. Each of the three dosage levels was effective at reducing the occurrence of seizures in the KO mice.

[00433] Figure 8A shows the structures of compounds used in a second set of AGS studies shown in Figures 8B and 8C. In these studies, the test compound was administered at dosages of 3, 10, and 30 mg/kg.

[00434] Figures 9A-9B show selected pharmacological data for test Compound (3), the structure of which is shown in Figure 9A. These studies were conducted according to methods known in the art. In studies, brain concentration of this compound at 1 hour post dose (10 mg/kg PO) was 617 nM ($n=2$), and plasma concentration at 1 hour post dose (10 mg/kg PO) was 843 ± 308 nM ($n=4$, B/P = 0.73). Figure 9C shows the results of marble burying studies conducted according to methods similar to those described above.

[00435] Similarly, Figure 10A shows exemplary pharmacological data for a fourth test compound, and Figure 10B shows marble burying data obtained following administration of this compound.

[00436] Additional physicochemical and pharmacological data are provided below in Tables 2-4 for Test Compounds 1 and 2 (Compounds (1) and (2) as described herein). These data were obtained using standard procedures known in the art.

Table 2

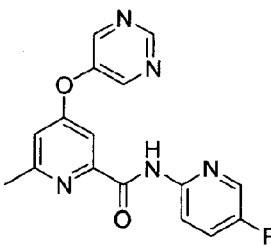
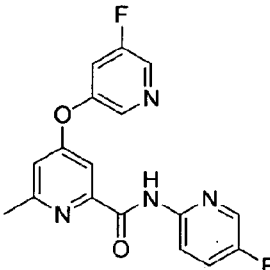
structure		
MW	325	342
cLogP	1.77	2.53
mGluR5 IC ₅₀ (nM)	7.8 ± 1.4 NAM	3.4 ± 0.4 NAM
Solubility	205 µg/mL SGF, pH 1.6 47 µg/mL FaSSIF, pH 6.5	70 µg/mL SGF, pH 1.6 7 µg/mL FaSSIF, pH 6.5
Permeability/efflux	Predicted high & no efflux	Predicted high & no efflux
Human PPB, %	91.4	98.5

Table 3

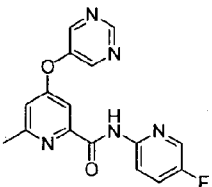
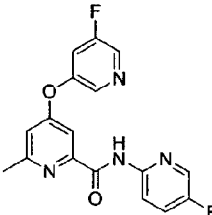
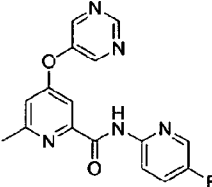
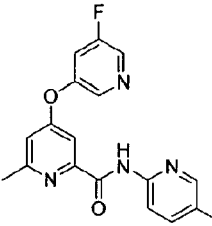
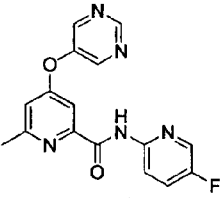
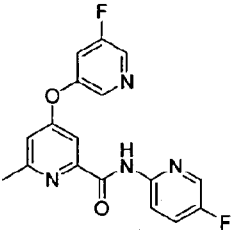
	Rat IV/PO					
	CL (mL/min/kg)	t _½ (hr)	V _{ss} (L/kg)	PO T _{max} (hr)	PO C _{max} (nM)	F (%)
	19.2	0.47	1.78	0.5	2170	30-76
	9.15	4.7	1.89	1.5	3330	67-75
	Cynomolgus monkey IV/PO					
	CL (mL/min/kg)	t _½ (hr)	V _{ss} (L/kg)	PO T _{max} (hr)	PO C _{max} (nM)	F (%)
	15.4	6.04	2.50	3.0	858	42-45
	13.2	9.38	3.95	2.0	1360	25-45

Table 4

								
mGluR5 IC ₅₀ (nM)	7.8 ± 1.4				3.3 ± 0.6			
Mouse BHB (%)	92.2				98.5			
Mouse PO PK	10 mg/kg				10 mg/kg			
Time (h)	0.25	0.5	1	3	0.25	0.5	1	3
Plasma Concentration (nM)	33.2	77.4	BLQ	BLQ	48.3	30.7	BLQ	3.2
Brain Concentration (nM)	195	345	9.9	9.2	176	143	BLQ	19.6
Free Brain Concentration (nM)	15.2	26.9	0.8	0.7	2.6	2.1	—	0.3
Brain to Plasma Ratio	5.9				4.7			

[00437] Figure 11 shows the results of studies employing the elevated plus maze, which can test for
 5 anxiolytic or anxiogenic compounds. Test compounds (1) and (2) were administrated at the 10 mg/kg and
 30 mg/kg doses described in this figure. The 30 mg/kg doses of each test compound was shown to provide
 a statistically significant increase in the time spent in the open arms. In measurements of the total distance
 traveled, both the 10 and 30 mg/kg doses of Compound (1) had a statistically significant beneficial effect,
 as did the 30 mg/kg dose of Compound (2).

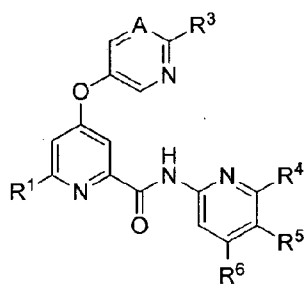
10 PROSPECTIVE *IN VIVO* EFFECTS

[00438] The following examples of the *in vivo* effects of the disclosed compounds are prophetic.
 Typical examples of study methods for assessing the *in vivo* effects of the disclosed compounds are given
 below.

[00439] Generally clinically relevant antipsychotic agents (both typical and atypical) display efficacy in preclinical behavior challenge models. *In vivo* effects of the compounds described in the preceding examples are expected to be shown in various animal models of disorders associated with metabotropic glutamate receptor dysfunction known to a person skilled in the art, such as models of stress and anxiety (e.g. the marble burying assay as described herein; or alternatively, elevated plus maze, shock probe burying, social interaction, passive avoidance, open field behavior, elevated plus maze, Y-maze, Hole-Board and stress-induced hyperthermia models in rodent), models of addictive behavior (e.g. reinstatement of ethanol-seeking behavior by drug-associated cues in rator the alcohol deprivation effect in long-term ethanol-consuming rat) and reversal or amelioration of Fragile X phenotypes in FMR1 knockout mice or FMR1 transgenic mice (e.g. susceptibility to audiogenic seizures, learning deficits, and growth oabnormalities of dendritic spines). These models are typically conducted in rodent, such as rat or mouse, but may be conducted in other animal species as is convenient to the study goals.

[00440] Compounds, products, and compositions disclosed herein are expected to show *in vivo* effects in various animal models of disorders associated with metabotropic glutamate receptor dysfunction known to the skilled person, such as models of stress and anxiety (e.g. the marble burying assay as described herein; or alternatively, elevated plus maze, shock probe burying, social interaction, passive avoidance, open field behavior, elevated plus maze, Y-maze, Hole-Board and stress-induced hyperthermia models in rodent), models of addictive behavior (e.g. reinstatement of ethanol-seeking behavior by drug-associated cues in rator the alcohol deprivation effect in long-term ethanol-consuming rat) and reversal or amelioration of Fragile X phenotypes in FMR1 knockout mice or FMR1 transgenic mice (e.g. susceptibility to audiogenic seizures, learning deficits, and growth oabnormalities of dendritic spines). These models are typically conducted in rodent, such as rat or mouse, but may be conducted in other animal species as is convenient to the study goals.

[00441] For example, compounds having a structure represented by a formula:

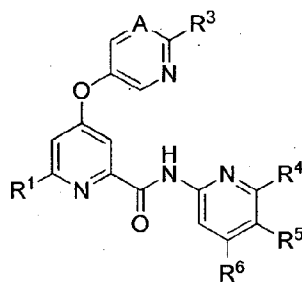


wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3

haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof, are expected to show such *in vivo* effects. Moreover, compounds prepared using the disclosed synthetic methods are also expected to show such *in vivo* effects.

11. PROPHETIC PHARMACEUTICAL COMPOSITION EXAMPLES

[00442] “Active ingredient” as used throughout these examples relates to one or more compounds having a structure represented by a formula:



wherein A is CR² or N; wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; or a pharmaceutically acceptable salt thereof. The following examples of the formulation of the disclosed compounds of the present invention in tablets, suspension, injectables and ointments are prophetic. Typical examples of recipes for the formulation of the invention are as given below.

a. TABLETS

[00443] A tablet can be prepared as follows:

Component	Amount
Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5
Potato starch	add to make total weight 200 mg

[00444] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

5 **b. SUSPENSION**

[00445] An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

c. INJECTABLE

10 [00446] A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol in water.

d. OINTMENT

[00447] An ointment can be prepared as follows:

Component	Amount
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	add to make total
	weight 100 g

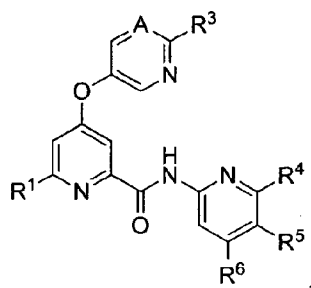
15 [00448] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

20 [00449] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof,

wherein the compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with rat mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.

2. The compound of claim 1, wherein the compound exhibits partial inhibition of mGluR5 response.
3. The compound of claim 1, wherein the compound exhibits total inhibition of mGluR5 response.
4. The compound of claim 1, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶.

5. The compound of claim 1, wherein the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} .
6. The compound of claim 1, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} .
7. The compound of claim 1, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} .
8. The compound of claim 1, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} .
9. The compound of claim 1, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .
10. The compound of any of claims 1-9, wherein A is CR^2 .
11. The compound of claim 10, wherein R^2 is selected from hydrogen, CN, halogen, and methyl.
12. The compound of claim 11, wherein R^2 is hydrogen.
13. The compound of claim 11, wherein R^2 is methyl.
14. The compound of claim 11, wherein R^2 is CN.
15. The compound of claim 11, wherein R^2 is halogen.
16. The compound of claim 15, wherein the halogen is chloro or fluoro.
17. The compound of claim 15, wherein the halogen is chloro.
18. The compound of claim 15, wherein the halogen is fluoro.
19. The compound of claim 10, wherein R^2 is selected from hydrogen, CN, chloro, fluoro and methyl.
20. The compound of claim 10, wherein R^2 is selected from C1-C2 alkyl, C1-C2 haloalkyl, and C1-C2 polyhaloalkyl.
21. The compound of any of claims 1-9, wherein A is N.
22. The compound of any of claims 1-20, wherein R^1 is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.

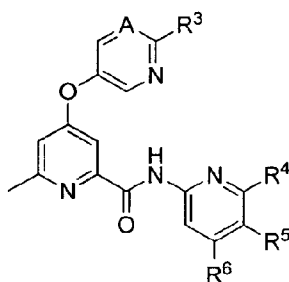
23. The compound of claim 22 wherein R^1 is selected from methyl, ethyl, CHF_2 , CF_3 , and cyclopropyl.
24. The compound of claim 23, wherein R^1 is selected from methyl, ethyl, CHF_2 , and CF_3 .
25. The compound of claim 23, wherein R^1 is selected from methyl, ethyl, CHF_2 , and cyclopropyl.
26. The compound of claim 23, wherein R^1 is selected from methyl, ethyl, and CHF_2 .
27. The compound of claim 23, wherein R^1 is selected from methyl, ethyl, and CF_3 .
28. The compound of claim 23, wherein R^1 is selected from methyl, ethyl, and cyclopropyl.
29. The compound of claim 23, wherein R^1 is methyl.
30. The compound of claim 23, wherein R^1 is ethyl.
31. The compound of claim 23, wherein R^1 is CHF_2 .
32. The compound of claim 23, wherein R^1 is CF_3 .
33. The compound of claim 23, wherein R^1 is cyclopropyl.
34. The compound of any of claims 1-33, wherein R^3 is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
35. The compound of claim 34, wherein R^3 is selected from hydrogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
36. The compound of any of claims 1-33, wherein R^3 is selected from hydrogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.
37. The compound of claim 36, wherein R^3 is selected from hydrogen, methyl, trifluoromethyl, and cyclopropyl.
38. The compound of any of claims 1-33, wherein one of R^2 , when present, and R^3 must be hydrogen.
39. The compound of any of claims 1-38, wherein each of R^4 , R^5 , and R^6 is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
40. The compound of any of claims 1-39, wherein R^4 is hydrogen.
41. The compound of any of claims 1-39, wherein one of R^4 , R^5 , and R^6 must be hydrogen.
42. The compound of any of claims 1-39, wherein two of R^4 , R^5 , and R^6 must be hydrogen.

43. The compound of any of claims 42, wherein R⁴ and R⁵ are both hydrogen.
44. The compound of any of claims 42, wherein R⁴ and R⁶ are both hydrogen.
45. The compound of any of claims 42, wherein R⁵ and R⁶ are both hydrogen.
46. The compound of any of claims 1-39, wherein R⁴ is selected from hydrogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
47. The compound of any of claims 1-39, wherein R⁴ is selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
48. The method of claim 47, wherein the halogen is chloro or fluoro.
49. The compound of any of claims 1-39, wherein R⁴ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
50. The method of claim 49, wherein the halogen is chloro or fluoro.
51. The compound of any of claims 1-39, wherein R⁴ is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
52. The compound of claim 51, wherein R⁴ is selected from hydrogen, halogen, and C1-C3 alkyl.
53. The compound of claim 51, wherein the halogen is chloro or fluoro.
54. The compound of claim 51, wherein R⁴ is selected from hydrogen, chloro, fluoro, methyl and ethyl.
55. The compound of claim 51, wherein R⁴ is selected from hydrogen, methyl and ethyl.
56. The compound of claim 51, wherein R⁴ is selected from hydrogen, chloro, and fluoro.
57. The compound of any of claims 1-39, wherein R⁵ is hydrogen.
58. The compound of any of claims 1-39, wherein R⁵ is selected from hydrogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
59. The compound of any of claims 1-39, wherein R⁵ is selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
60. The method of claim 59, wherein the halogen is chloro or fluoro.
61. The compound of any of claims 1-39, wherein R⁵ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.

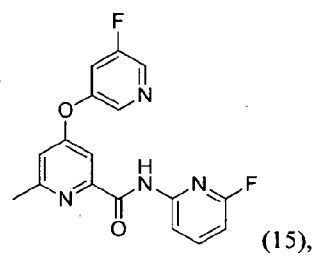
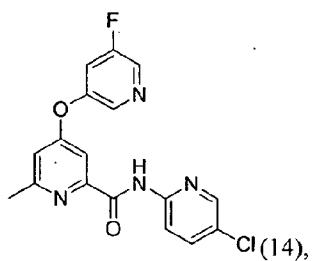
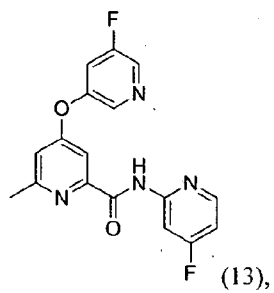
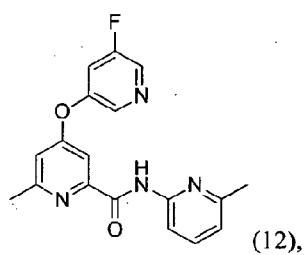
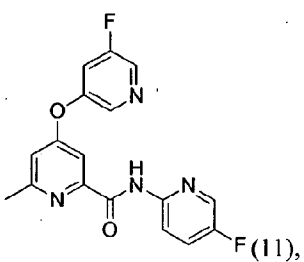
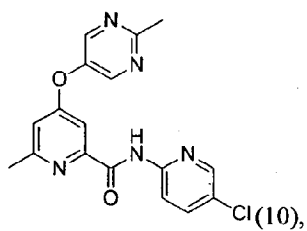
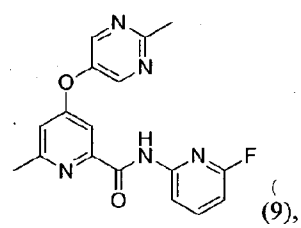
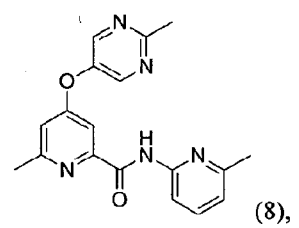
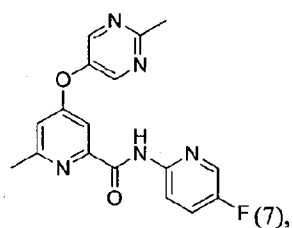
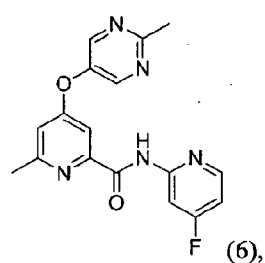
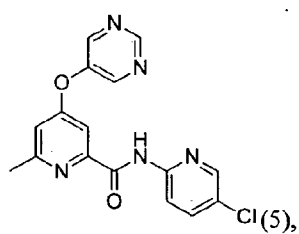
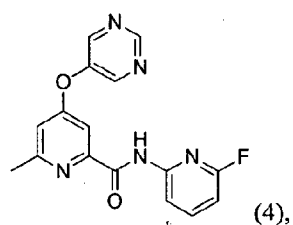
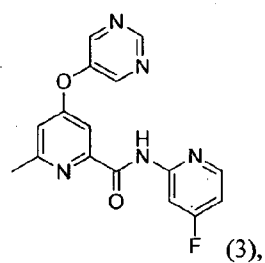
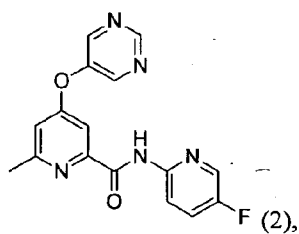
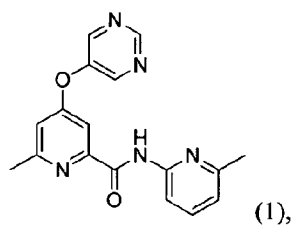
62. The method of claim 61, wherein the halogen is chloro or fluoro.
63. The compound of any of claims 1-39, wherein R^5 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
64. The compound of claim 63, wherein R^5 is selected from hydrogen, halogen, and C1-C3 alkyl.
65. The compound of claim 63, wherein the halogen is chloro or fluoro.
66. The compound of claim 63, wherein R^5 is selected from hydrogen, chloro, fluoro, CN, methyl, trifluoromethyl, and ethyl.
67. The compound of claim 63, wherein R^5 is selected from hydrogen, methyl, trifluoromethyl, and ethyl.
68. The compound of claim 63, wherein R^5 is selected from hydrogen, CN, chloro, and fluoro.
69. The compound of any of claims 1-39, wherein R^6 is hydrogen.
70. The compound of any of claims 1-39, wherein R^6 is selected from hydrogen, halogen, CN, and C1-C3 alkyl.
71. The compound of any of claims 1-39, wherein R^6 is selected from hydrogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
72. The compound of any of claims 1-39, wherein R^6 is selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
73. The method of claim 72, wherein the halogen is chloro or fluoro.
74. The compound of any of claims 1-39, wherein R^6 is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
75. The compound of claim 74, wherein the halogen is chloro or fluoro.
76. The compound of claim 74, wherein the halogen is fluoro.
77. The compound of any of claims 1-39, wherein R^6 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, and C1-C3 polyhaloalkyl.
78. The compound of claim 77, wherein R^6 is selected from hydrogen, halogen, and C1-C3 alkyl.
79. The compound of claim 77, wherein the halogen is chloro or fluoro.
80. The compound of claim 77, wherein the halogen is fluoro.

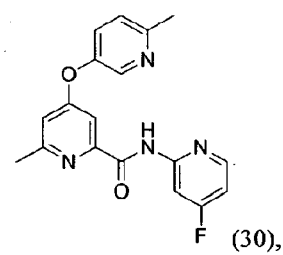
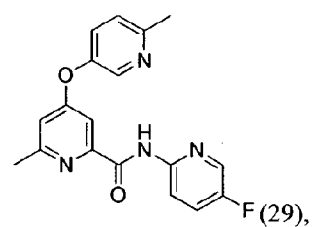
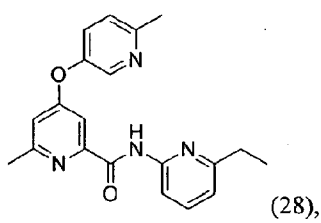
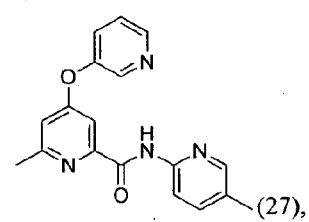
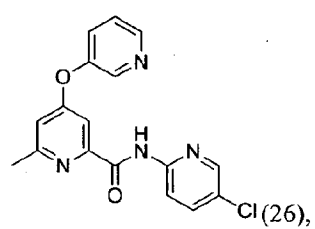
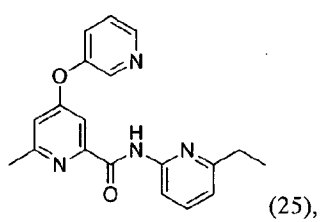
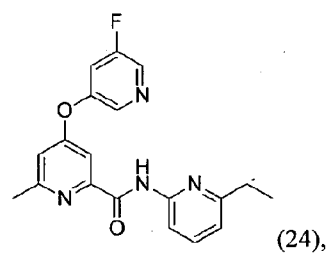
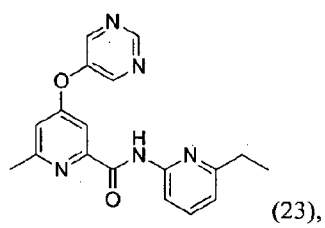
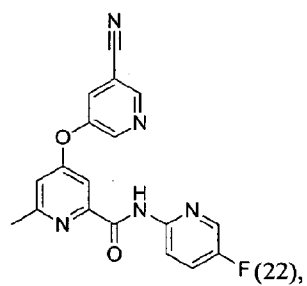
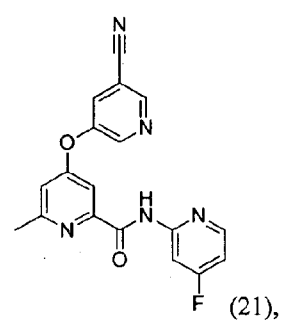
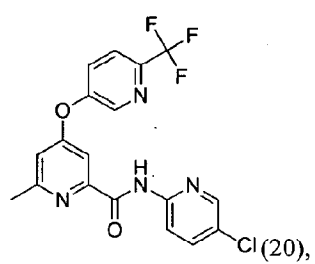
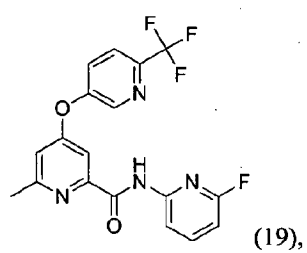
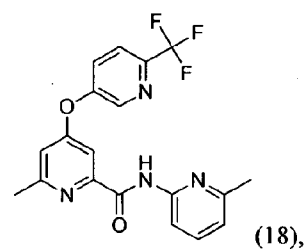
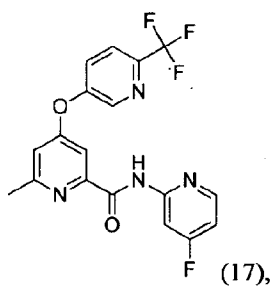
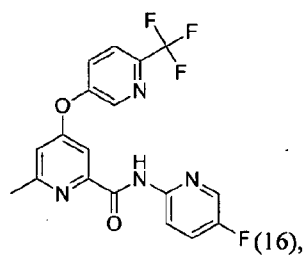
81. The compound of claim 77, wherein R⁶ is selected from hydrogen, chloro, fluoro, CN, and methyl.
82. The compound of claim 77, wherein R⁶ is selected from hydrogen, fluoro, CN, and methyl.
83. The compound of claim 77, wherein R⁶ is selected from hydrogen, CN, and methyl.
84. The compound of claim 77, wherein R⁶ is selected from hydrogen, CN, chloro, and fluoro.
85. The compound of claim 77, wherein R⁶ is selected from hydrogen, CN, and fluoro.
86. The compound of claim 77, wherein R⁶ is selected from hydrogen, CN, fluoro, and methyl.
87. The compound of claim 77, wherein R⁶ is selected from hydrogen, CN, chloro, fluoro, and methyl.
88. The compound of any of claims 1-39, wherein R⁴ is hydrogen, and wherein each of R⁵ and R⁶ is independently selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.
89. The compound of claim 88, wherein the halogen is chloro or fluoro.
90. The compound of claim 88, wherein each of R⁵ and R⁶ is independently selected from halogen, CN, and C1-C3 alkyl.
91. The compound of claim 90, wherein the halogen is chloro or fluoro.
92. The compound of claim 90, wherein each of R⁵ and R⁶ is independently selected from chloro, fluoro, CN, methyl and ethyl.
93. The compound of claim 90, wherein each of R⁵ and R⁶ is independently selected from fluoro, CN, methyl and ethyl.
94. The compound of any of claims 1-39, wherein R⁵ is hydrogen, and wherein each of R⁴ and R⁶ is independently selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.
95. The compound of claim 94, wherein the halogen is chloro or fluoro.
96. The compound of claim 94, wherein each of R⁴ and R⁶ is independently selected from halogen, CN, and C1-C3 alkyl.
97. The compound of claim 96, wherein the halogen is chloro or fluoro.

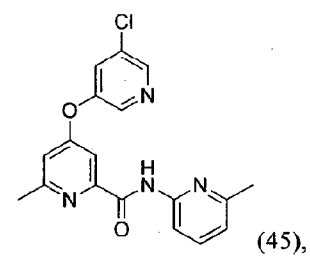
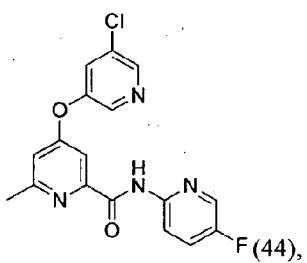
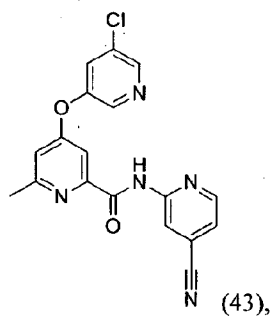
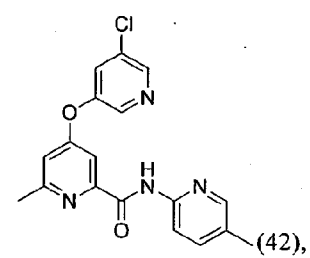
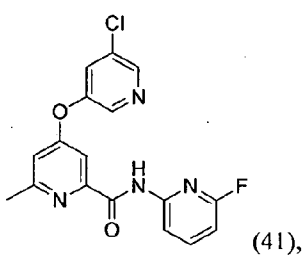
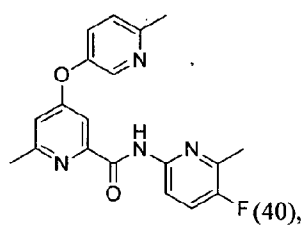
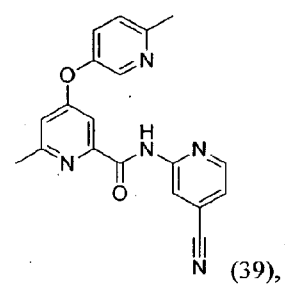
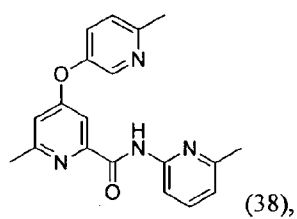
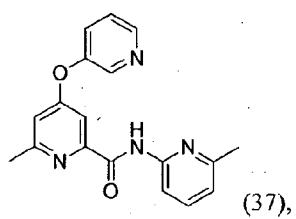
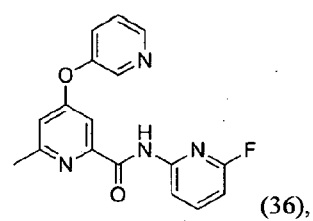
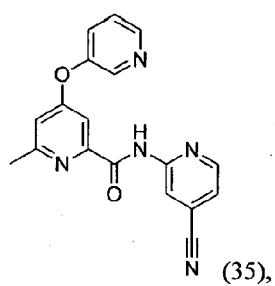
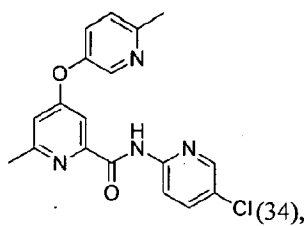
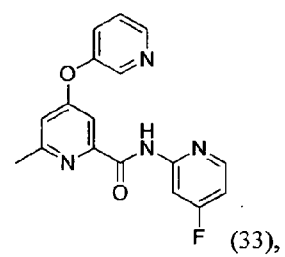
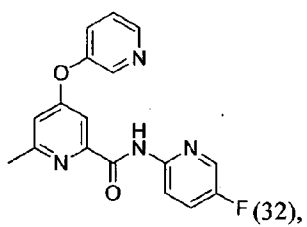
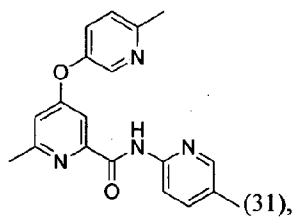
98. The compound of claim 96, wherein each of R^4 and R^6 is independently selected from chloro, fluoro, CN, methyl and ethyl.
99. The compound of claim 96, wherein each of R^4 and R^6 is independently selected from fluoro, CN, methyl and ethyl.
100. The compound of any of claims 1-39, wherein R^6 is hydrogen, and wherein each of R^4 and R^5 is independently selected from halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.
101. The compound of claim 100, wherein the halogen is chloro or fluoro.
102. The compound of claim 100, wherein each of R^4 and R^5 is independently selected from halogen, CN, and C1-C3 alkyl.
103. The compound of claim 102, wherein the halogen is chloro or fluoro.
104. The compound of claim 102, wherein each of R^4 and R^5 is independently selected from halogen, CN, and C1-C3 alkyl.
105. The compound of claim 102, wherein each of R^4 and R^5 is independently selected from fluoro, CN, methyl and ethyl.
106. The compound of claim 1, having a structure represented by a formula:

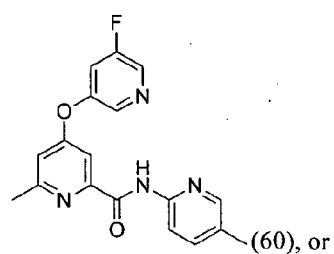
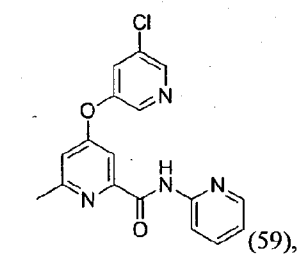
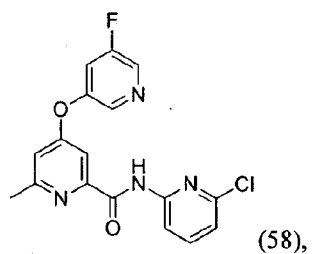
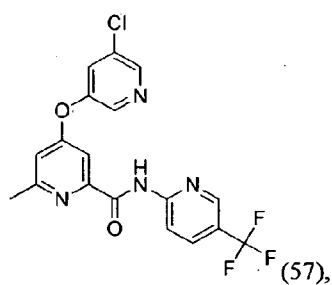
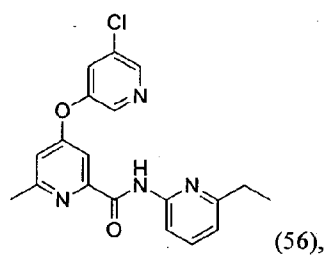
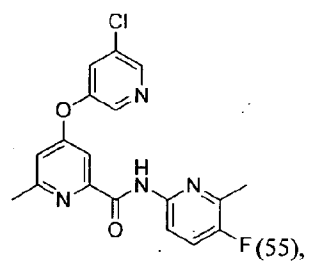
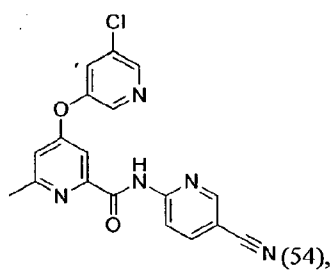
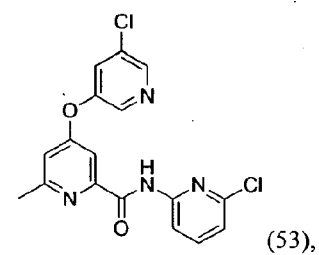
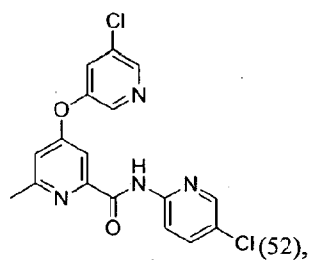
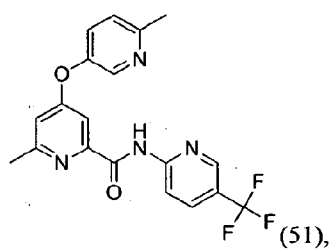
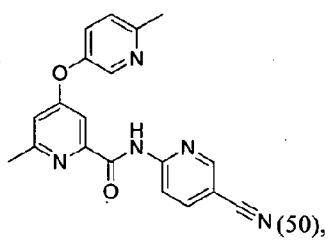
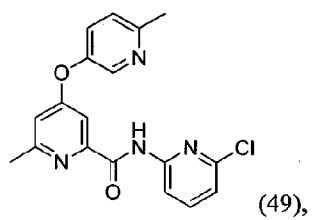
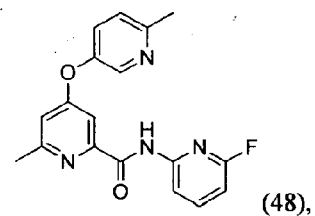
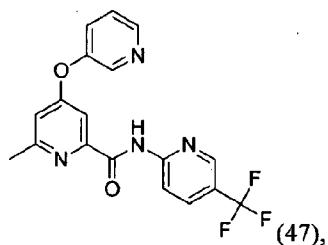
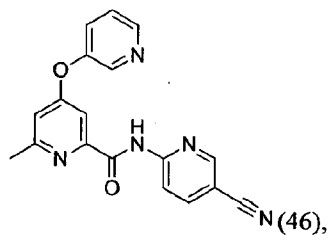


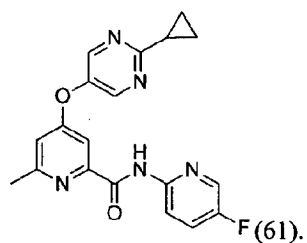
107. The compound of claim 106, selected from:



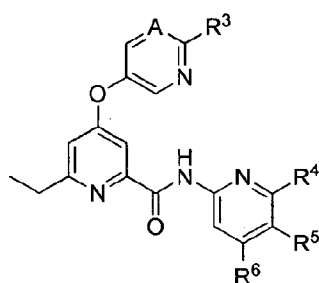




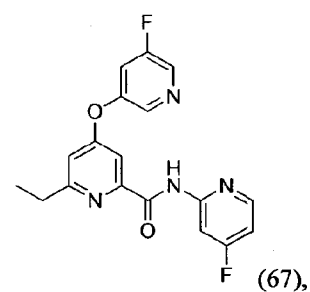
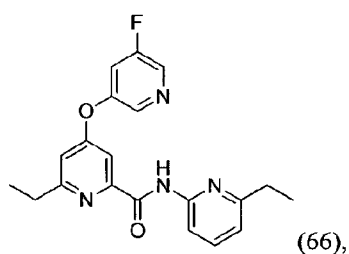
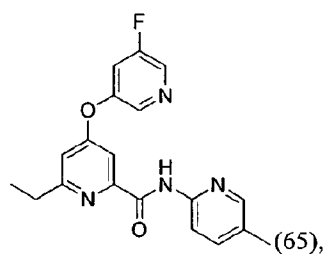
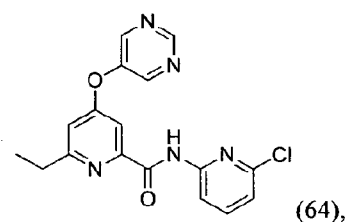
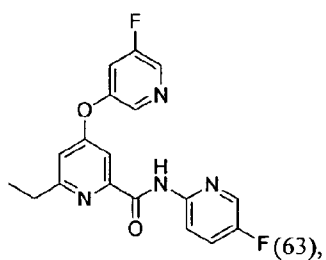
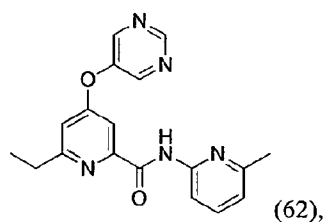


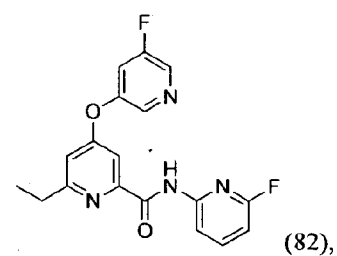
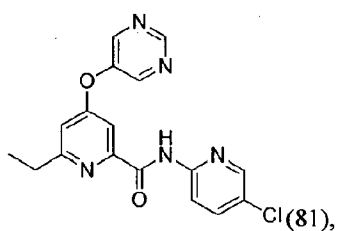
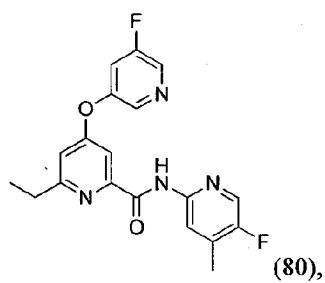
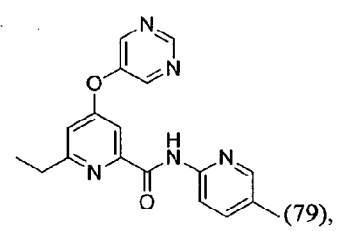
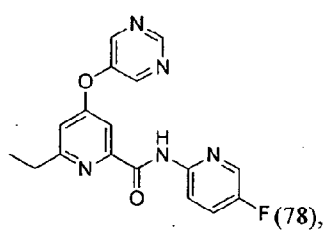
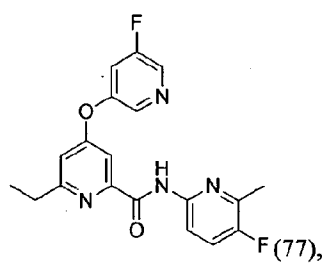
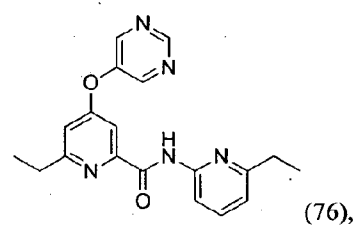
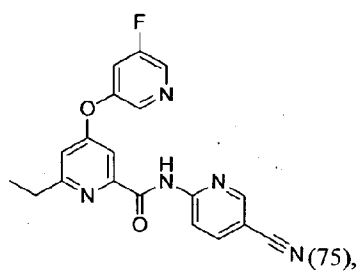
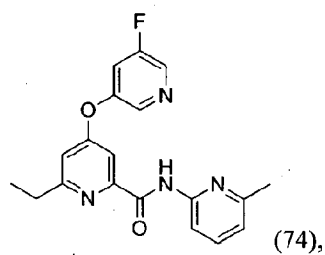
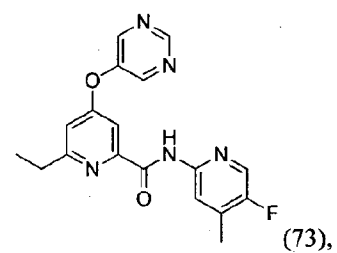
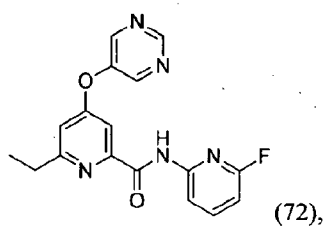
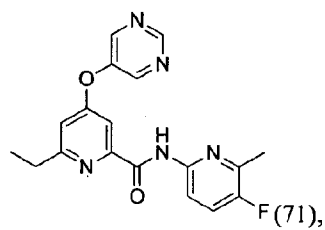
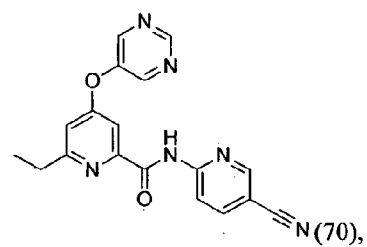
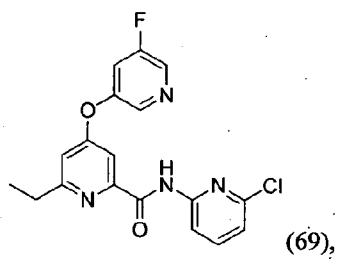
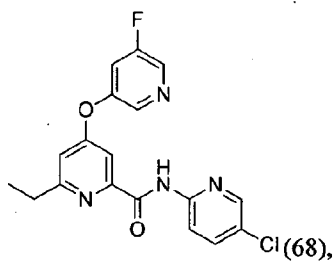


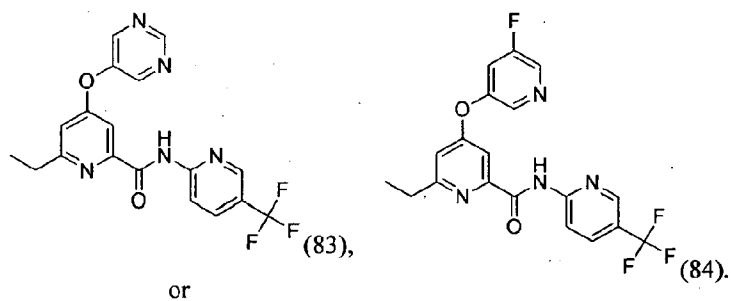
108. The compound of claim 1, having a structure represented by a formula:



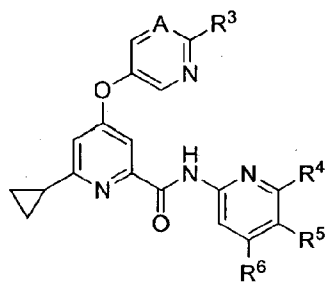
109. The compound of claim 108, selected from:



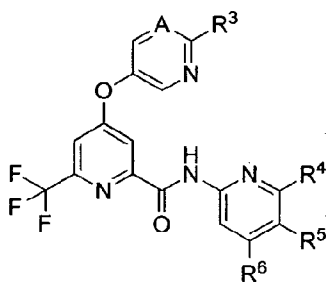




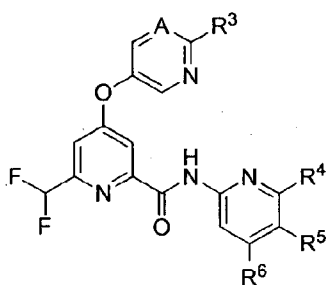
110. The compound of claim 1, having a structure represented by a formula:



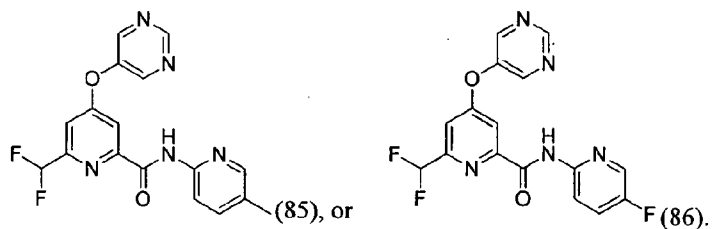
111. The compound of claim 1, having a structure represented by a formula:



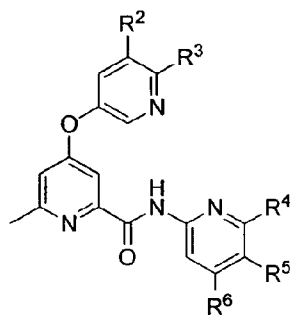
112. The compound of claim 1, having a structure represented by a formula:



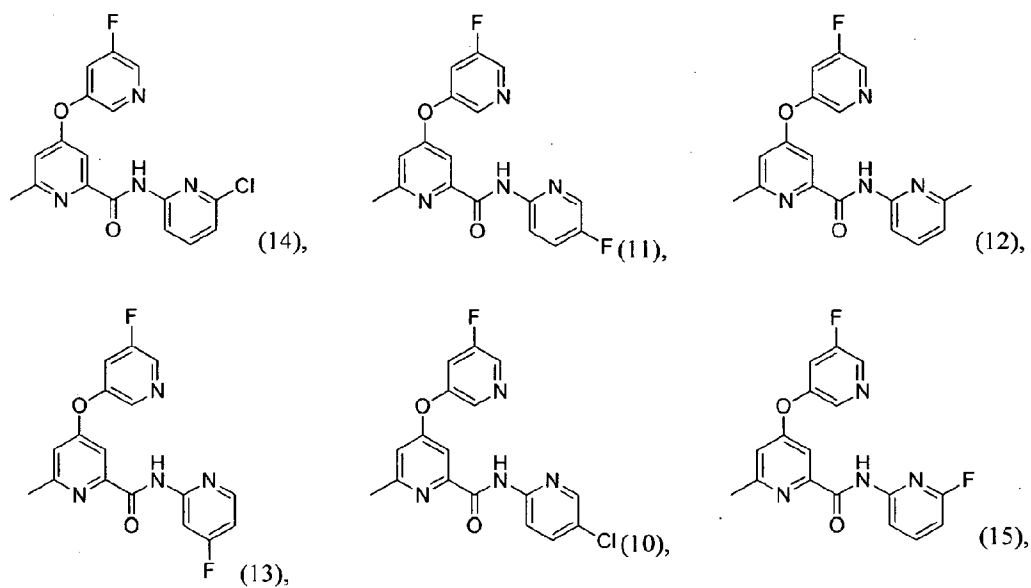
113. The compound of claim 112, selected from:

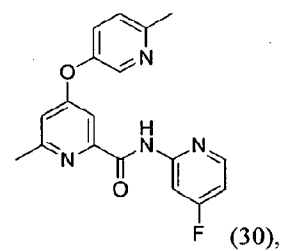
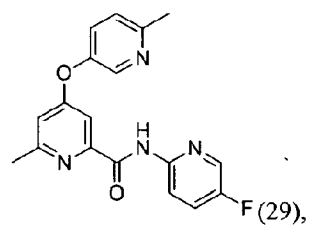
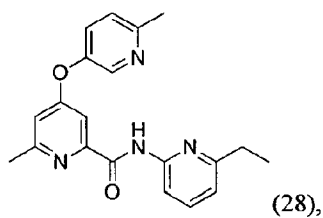
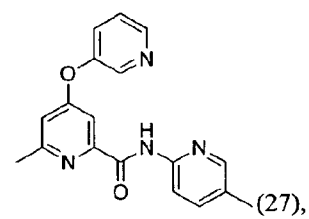
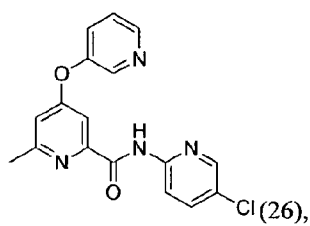
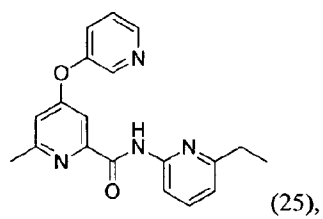
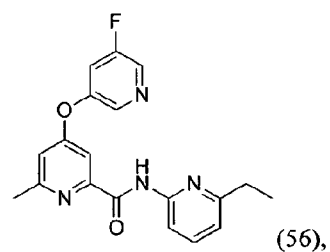
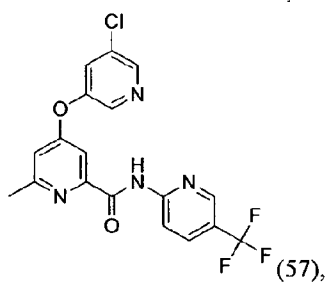
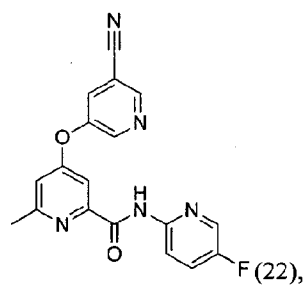
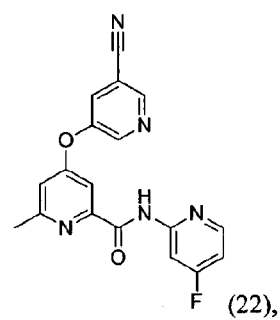
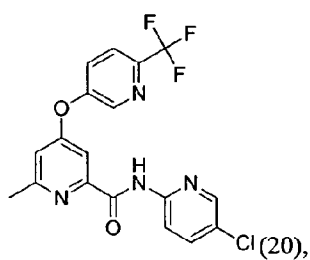
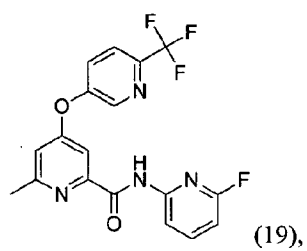
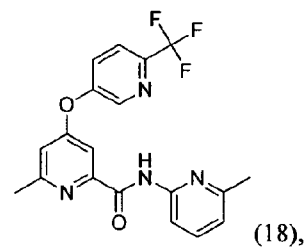
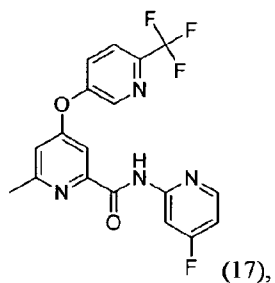
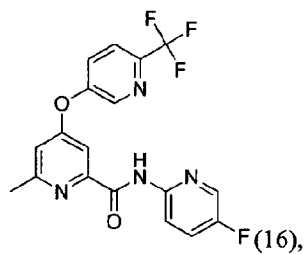


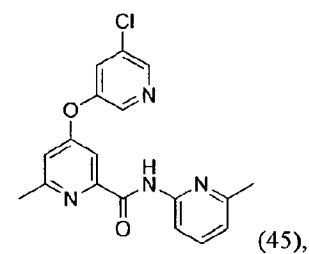
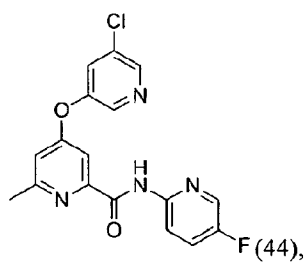
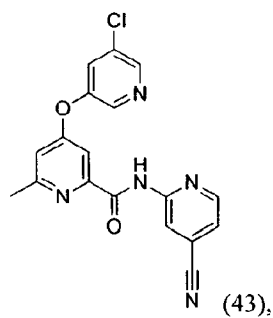
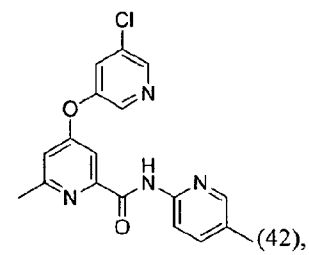
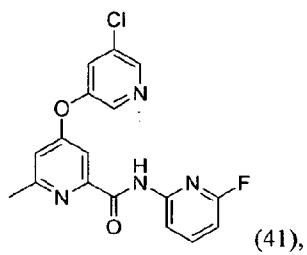
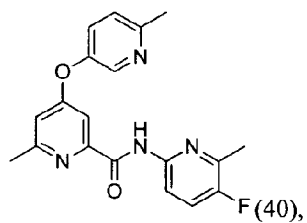
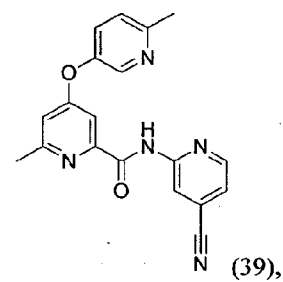
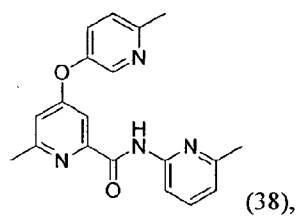
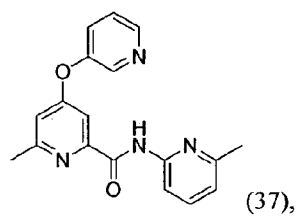
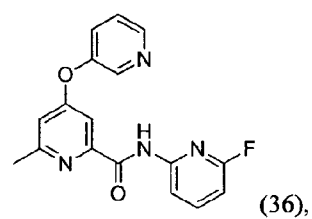
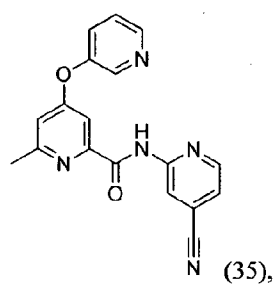
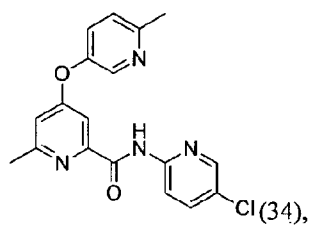
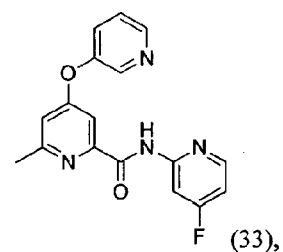
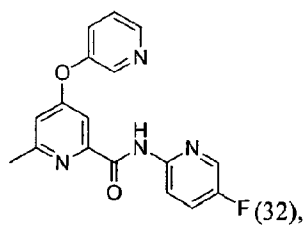
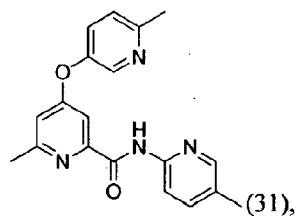
114. The compound of claim 1, having a structure represented by a formula:

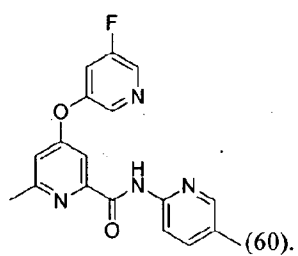
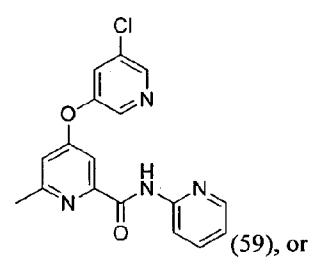
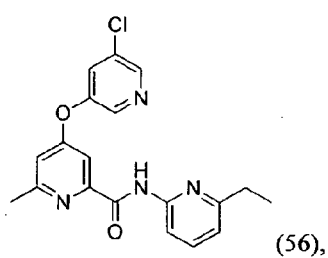
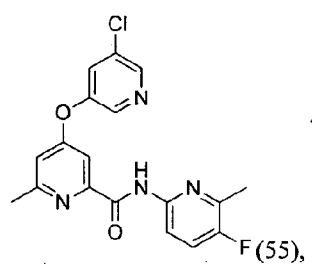
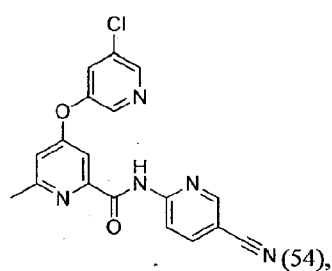
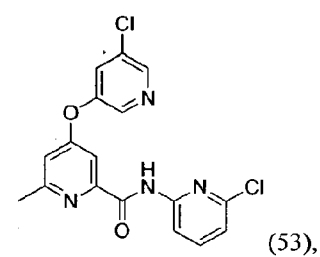
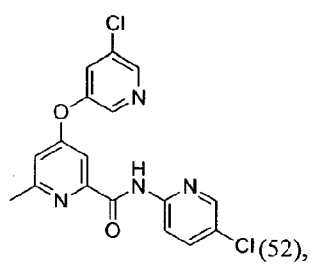
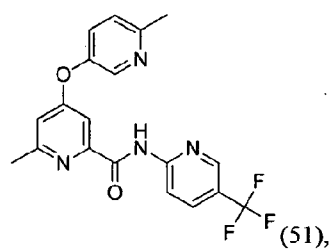
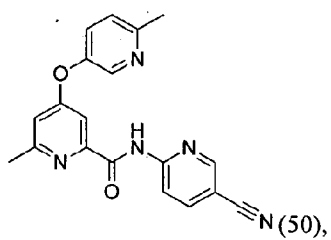
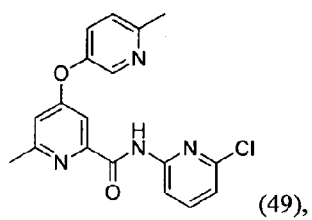
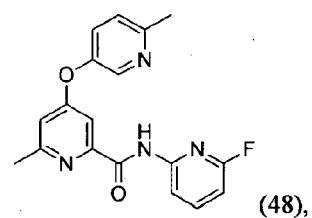
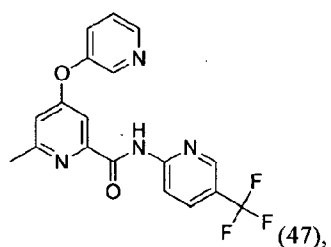
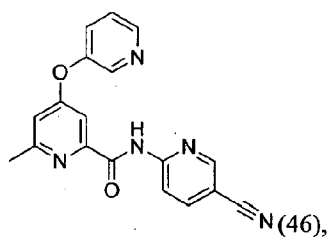


115. The compound of claim 0, selected from:

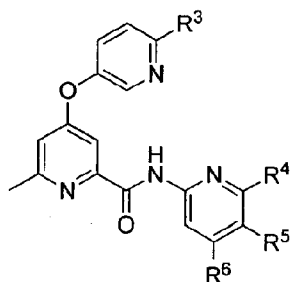




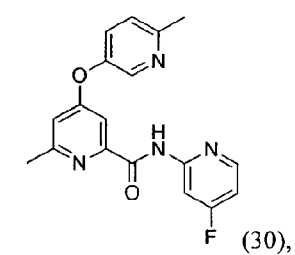
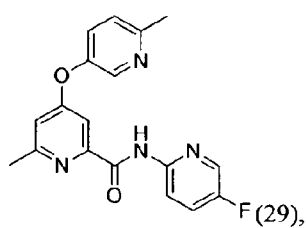
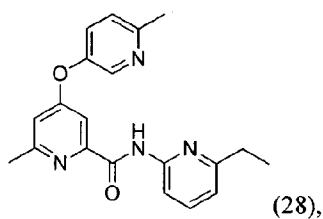
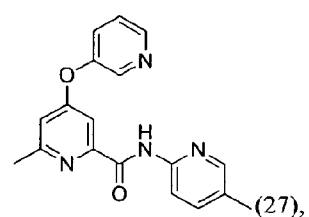
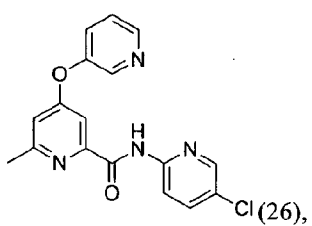
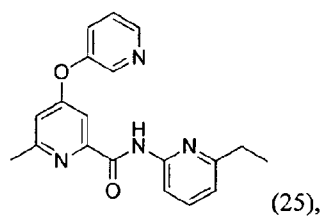
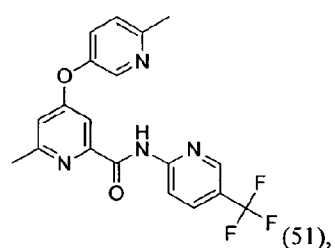
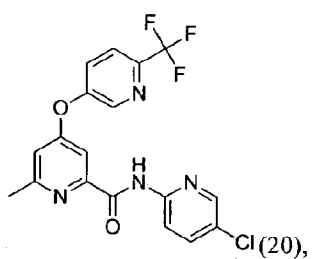
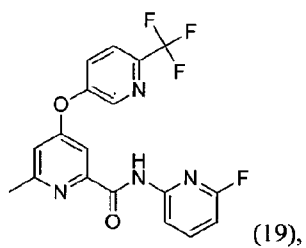
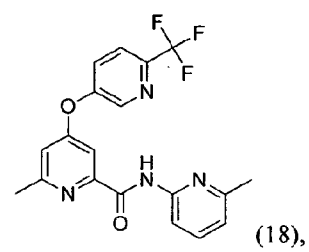
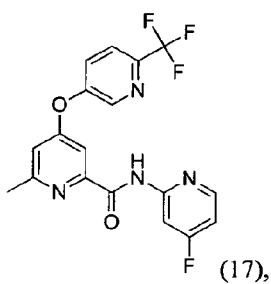
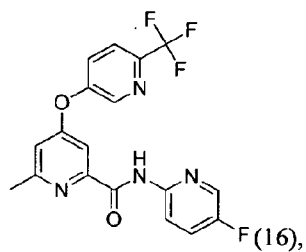


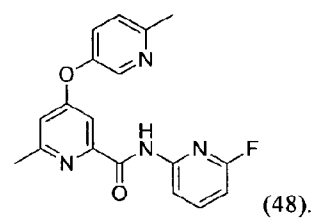
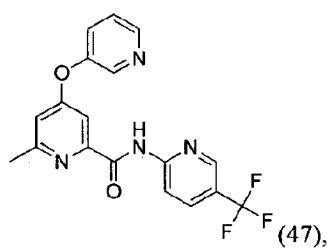
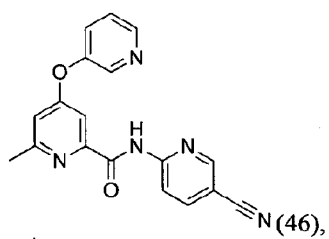
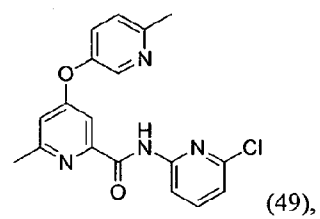
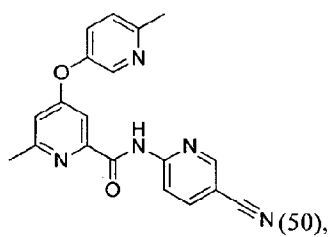
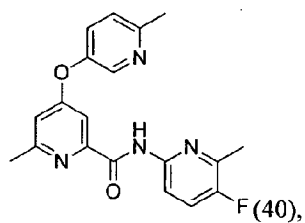
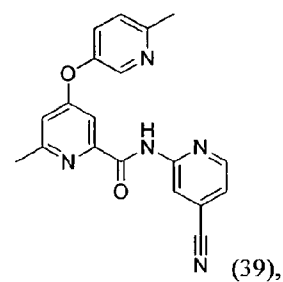
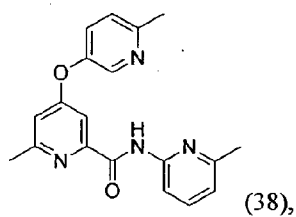
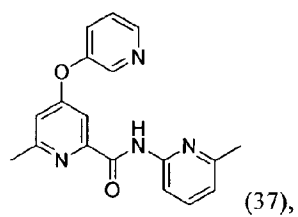
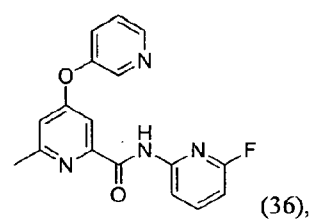
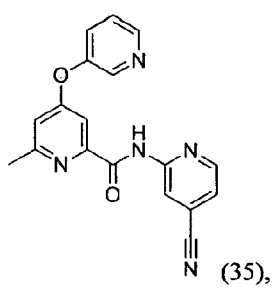
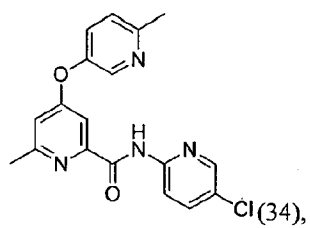
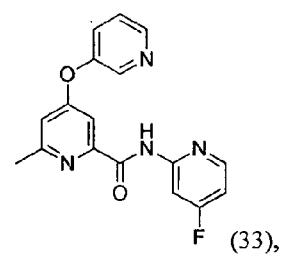
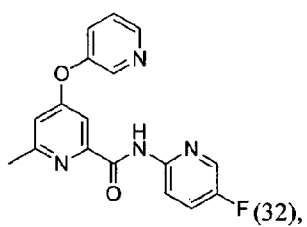
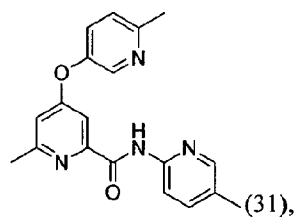


116. The compound of claim 0, having a structure represented by a formula:



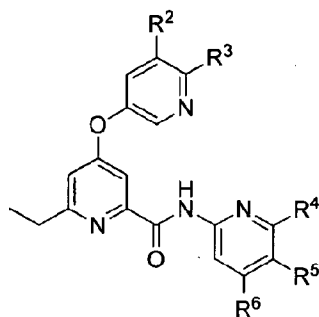
117. The compound of claim 116, selected from:



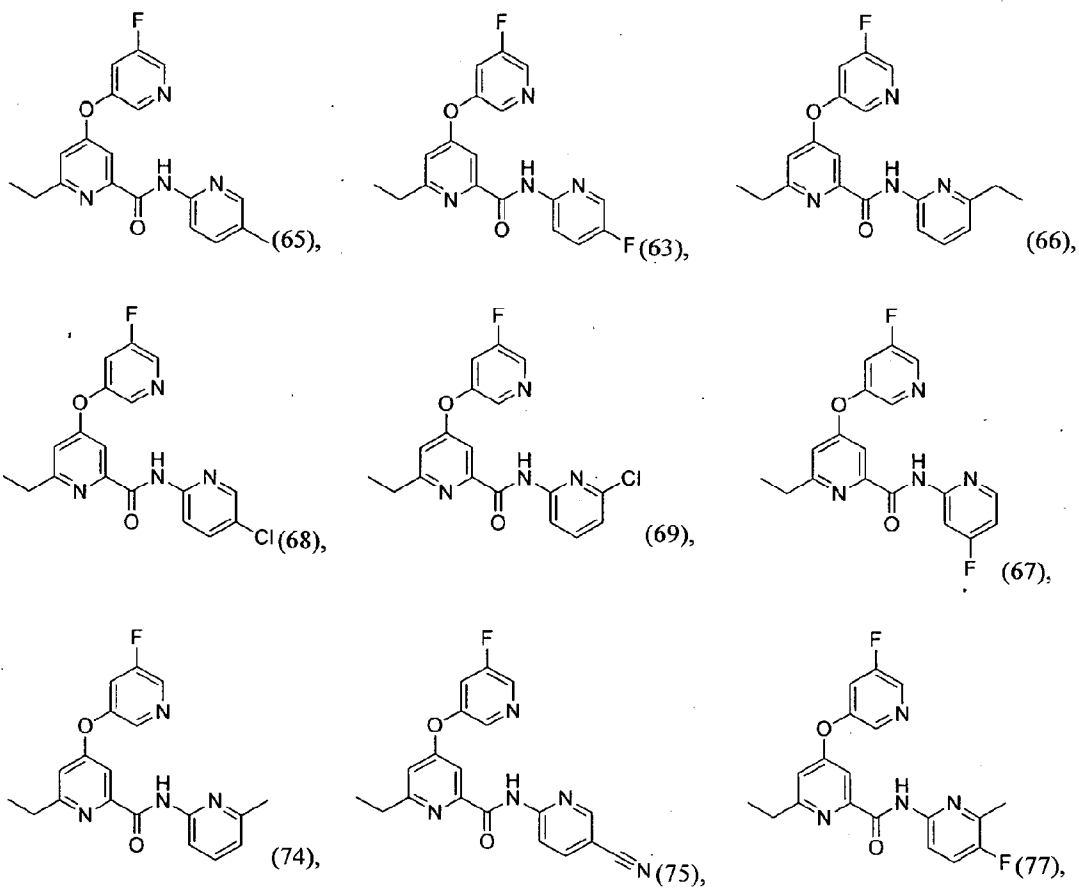


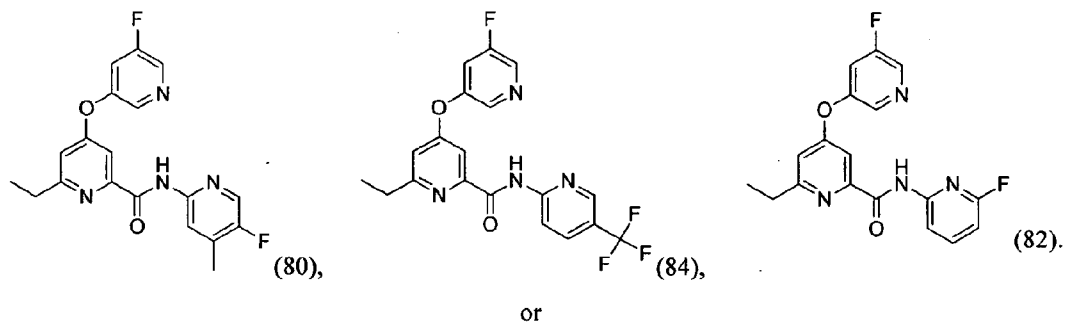
or

118. The compound of claim 1, having a structure represented by a formula:

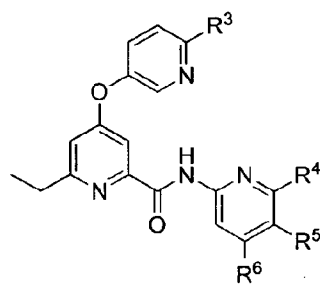


119. The compound of claim 118, selected from:

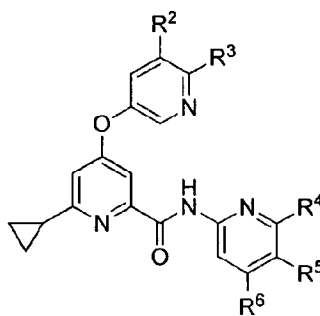




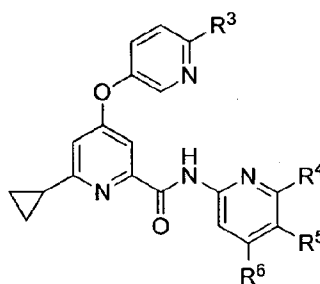
120. The compound of claim 118, having a structure represented by a formula:



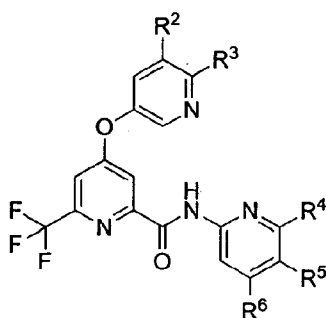
121. The compound of claim 1, having a structure represented by a formula:



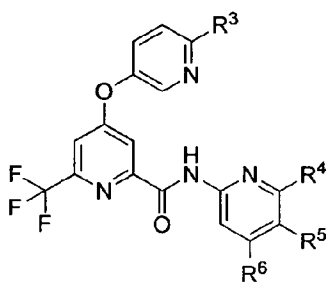
122. The compound of claim 121, having a structure represented by a formula:



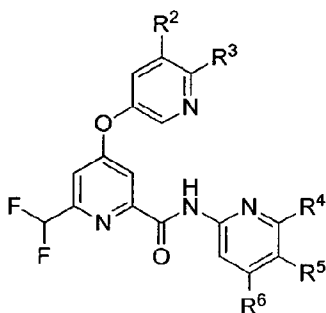
123. The compound of claim 1, having a structure represented by a formula:



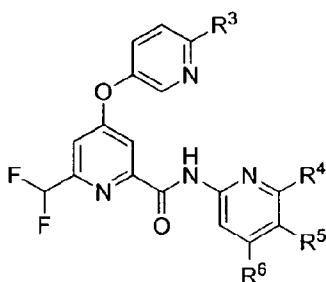
124. The compound of claim 123, having a structure represented by a formula:



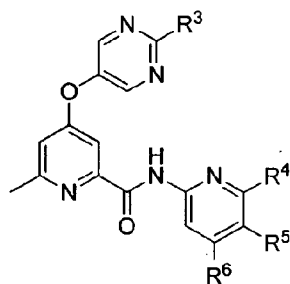
125. The compound of claim 1, having a structure represented by a formula:



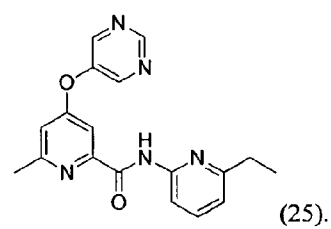
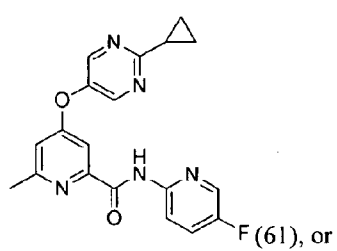
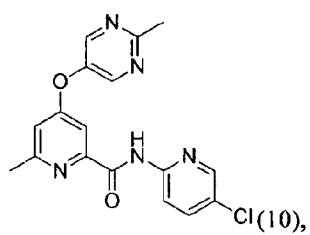
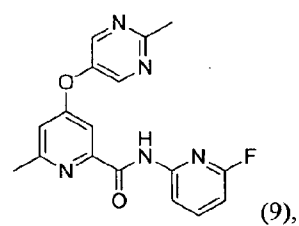
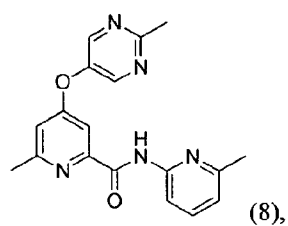
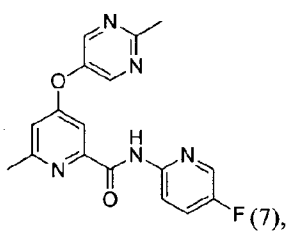
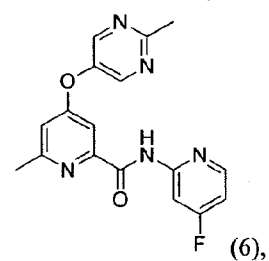
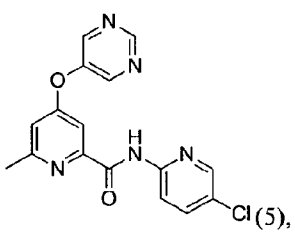
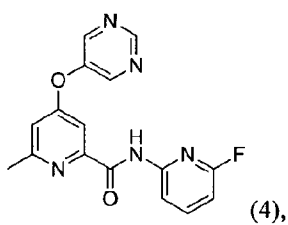
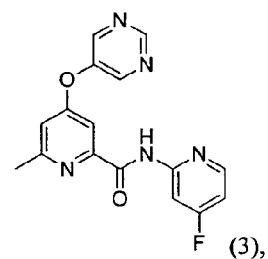
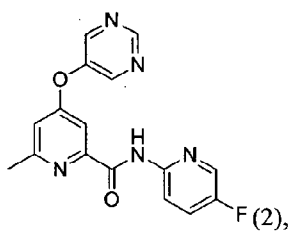
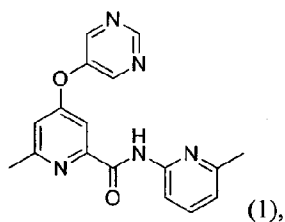
126. The compound of claim 125, having a structure represented by a formula:



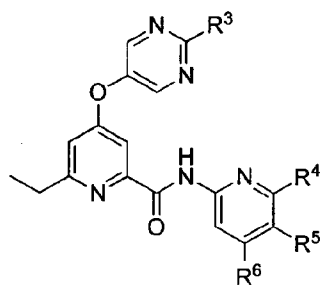
127. The compound of claim 1, having a structure represented by a formula:



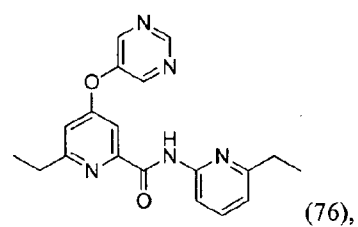
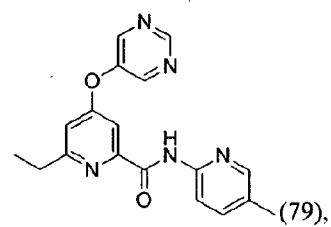
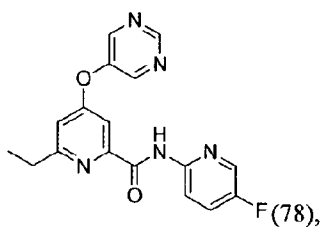
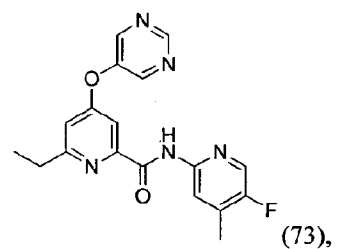
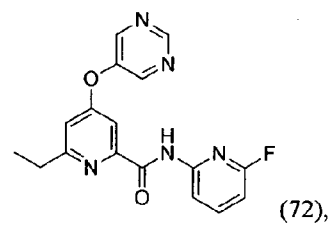
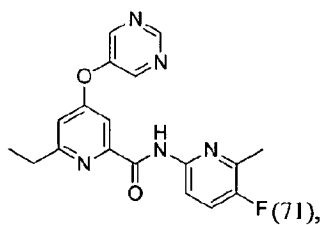
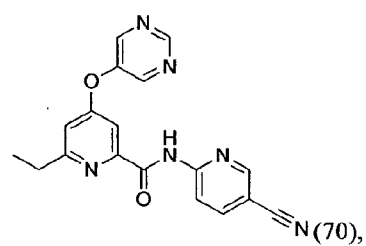
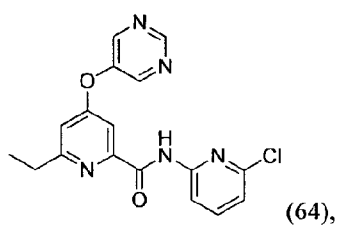
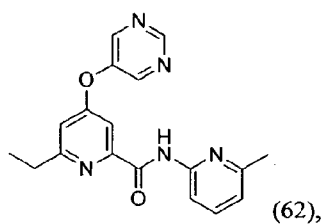
128. The compound of claim 127, selected from:

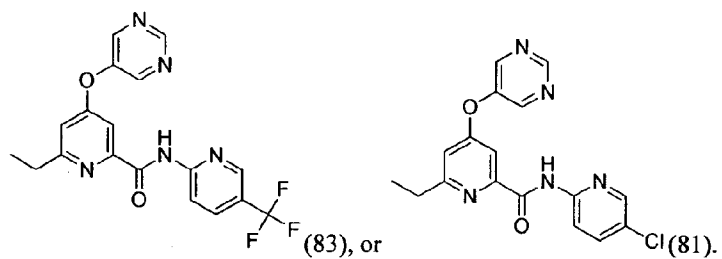


129. The compound of claim 1, having a structure represented by a formula:

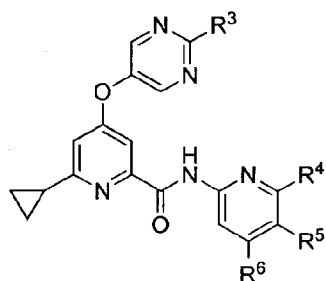


130. The compound of claim 129, selected from:

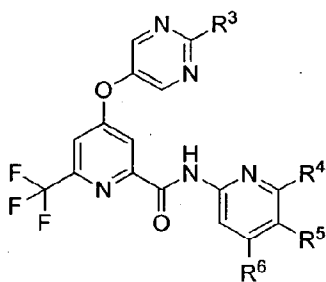




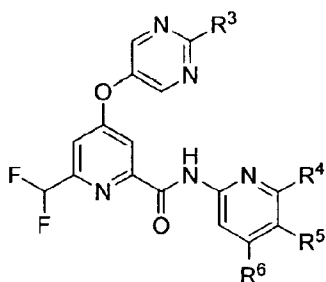
131. The compound of claim 1, having a structure represented by a formula:



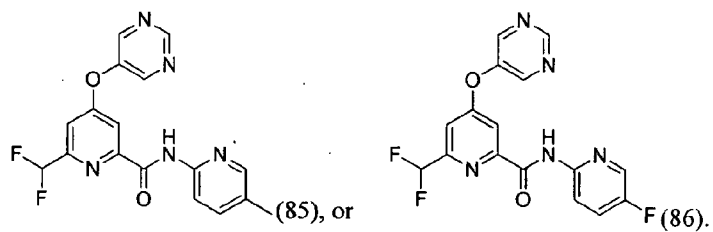
132. The compound of claim 1, having a structure represented by a formula:



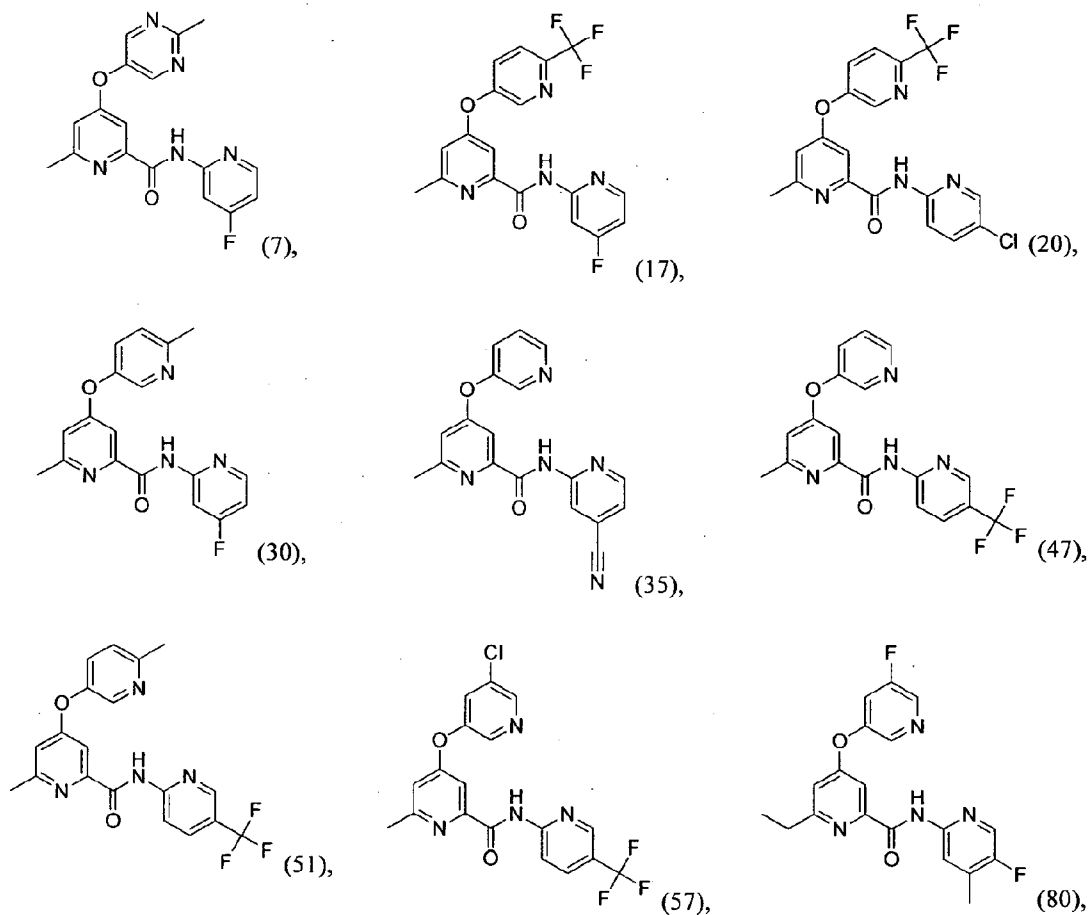
133. The compound of claim 1, having a structure represented by a formula:

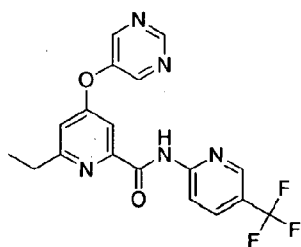


134. The compound of claim 133, selected from:

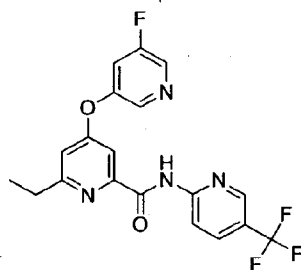


135. The compound of claim 1, selected from:

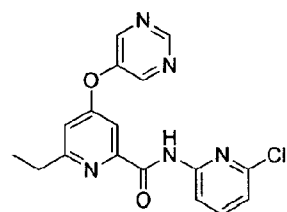




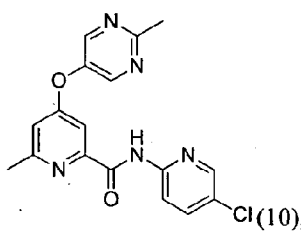
(83),



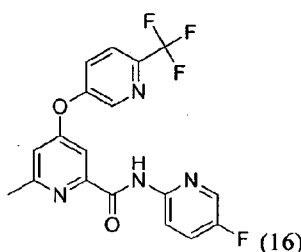
(84),



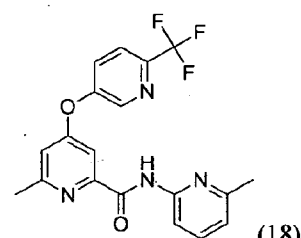
(64),



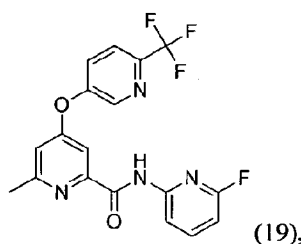
(10),



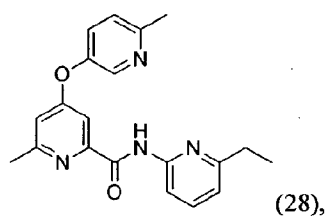
(16),



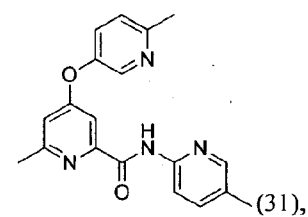
(18),



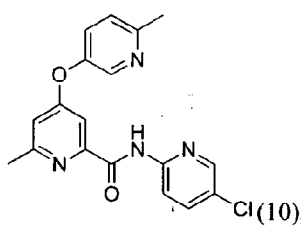
(19),



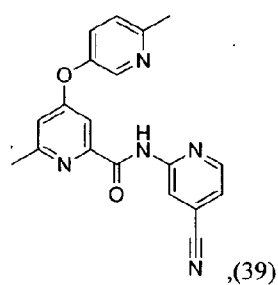
(28),



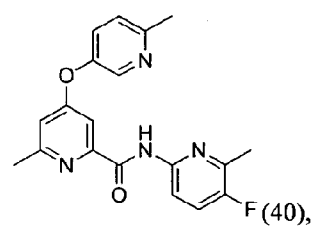
(31),



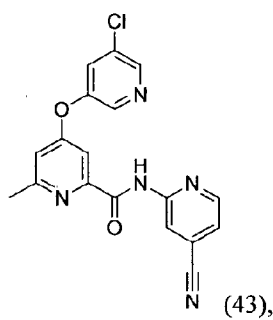
(10),



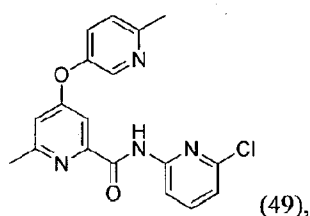
(39)



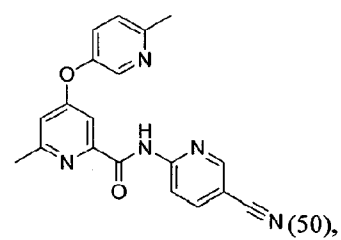
(40),



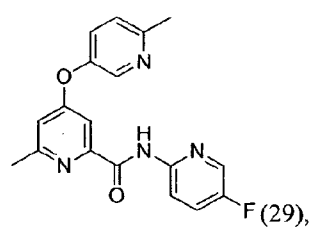
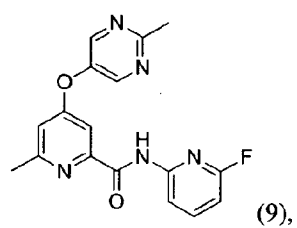
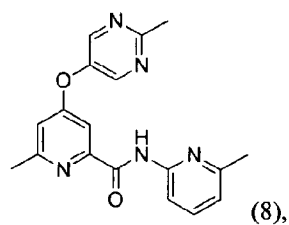
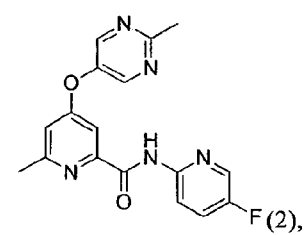
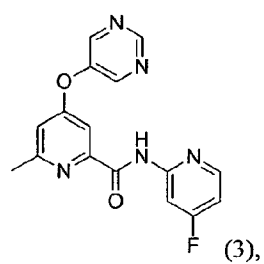
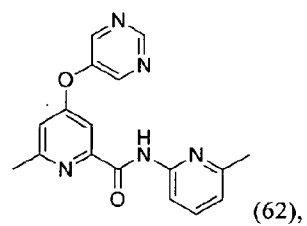
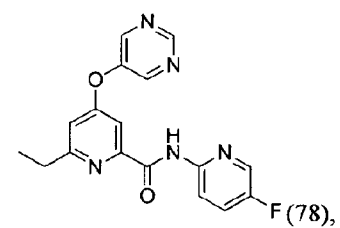
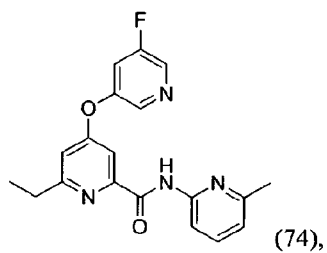
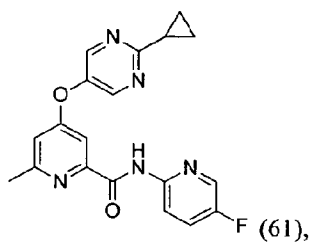
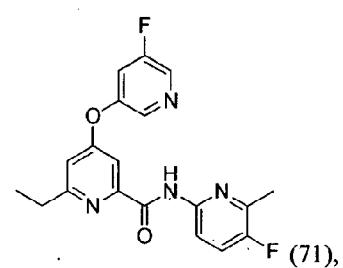
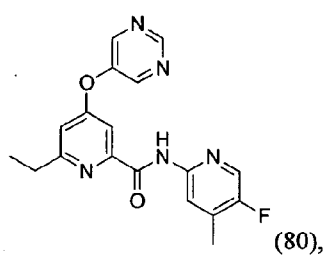
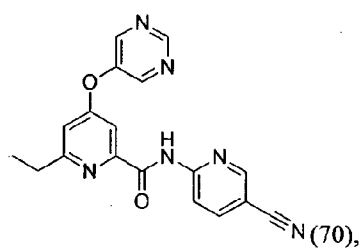
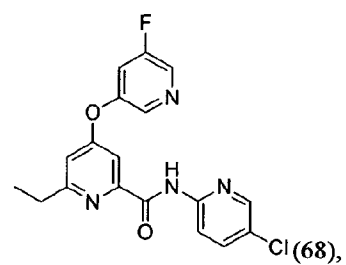
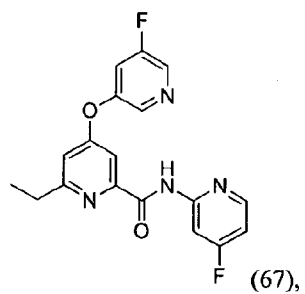
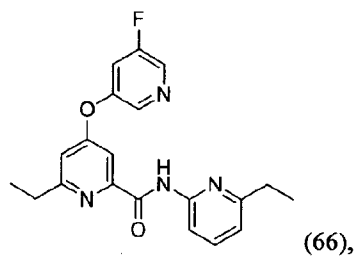
(43),

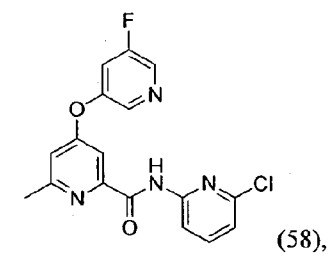
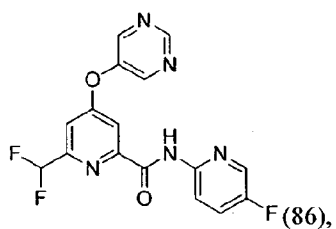
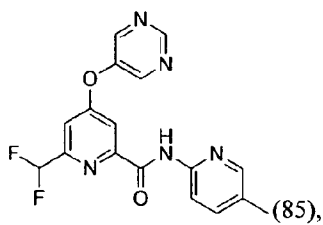
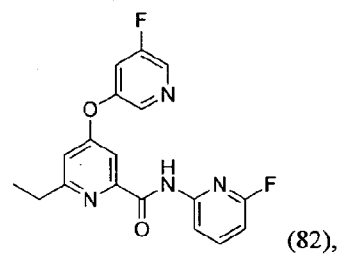
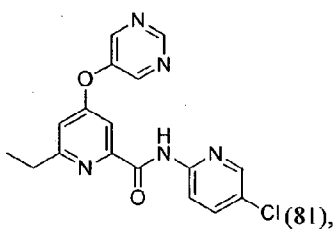
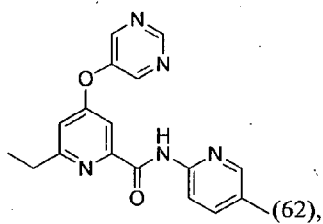
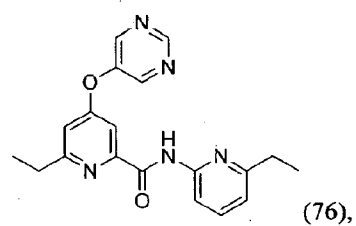
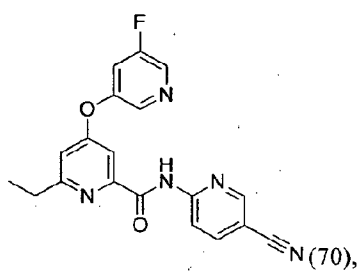
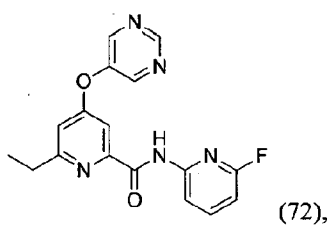
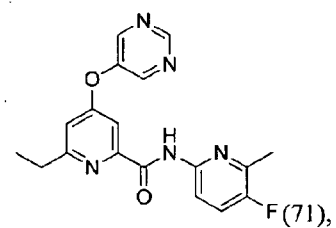
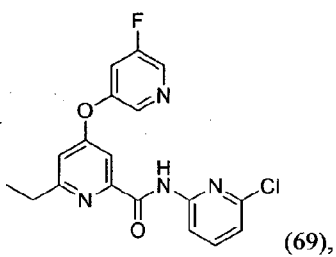
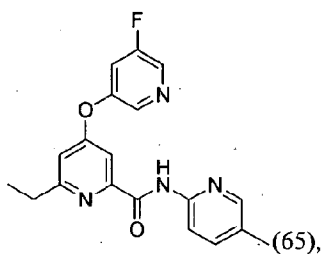
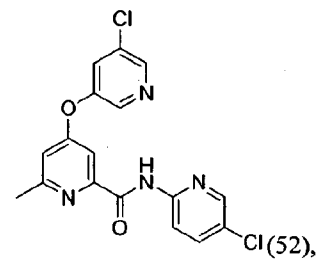
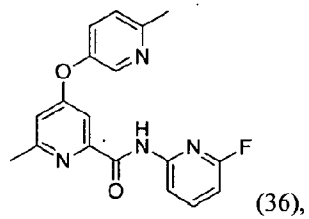
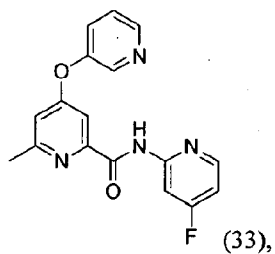


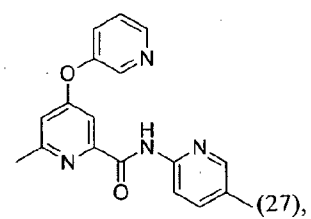
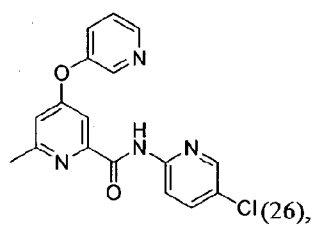
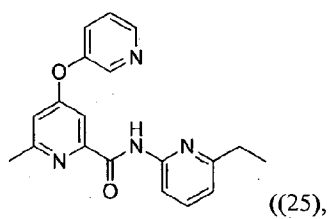
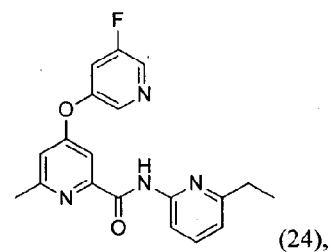
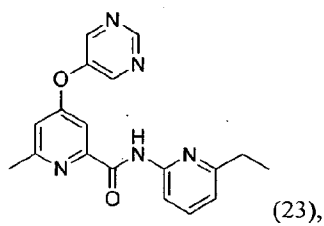
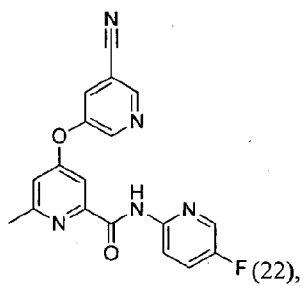
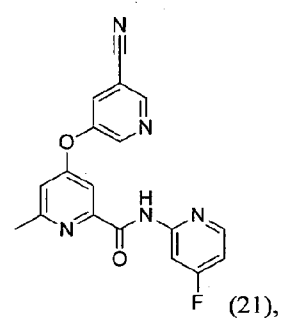
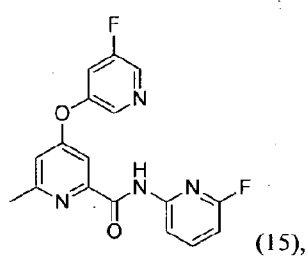
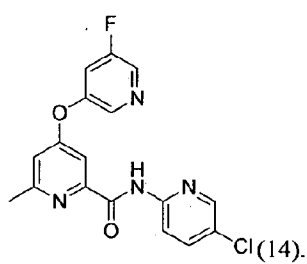
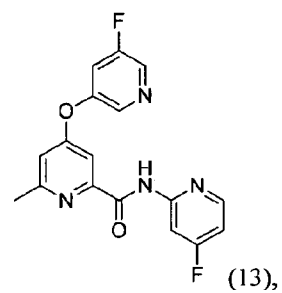
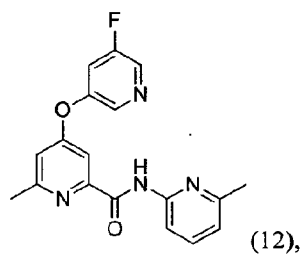
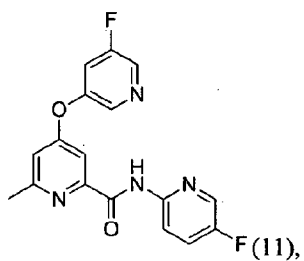
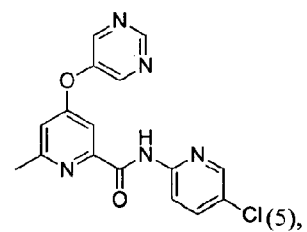
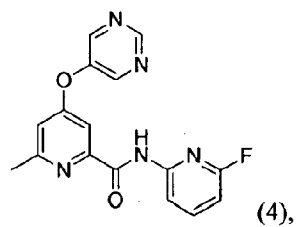
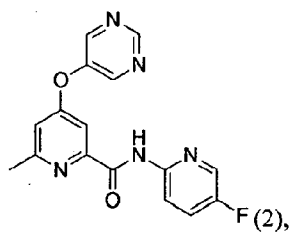
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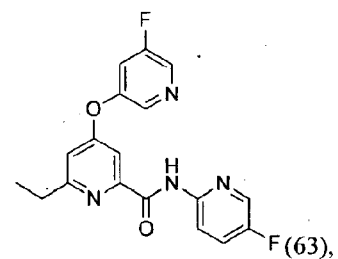
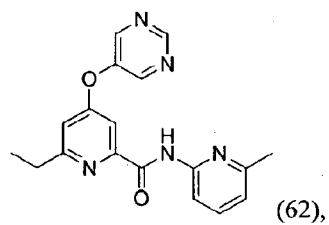
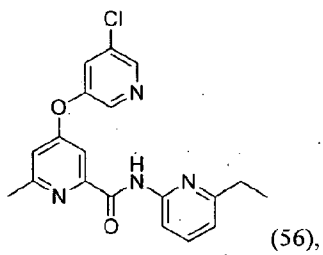
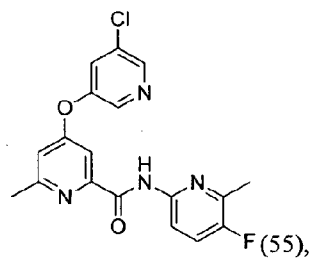
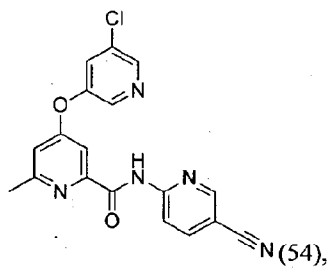
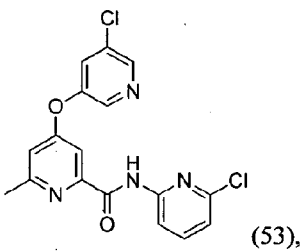
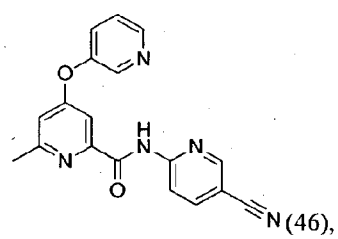
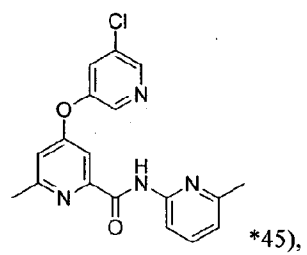
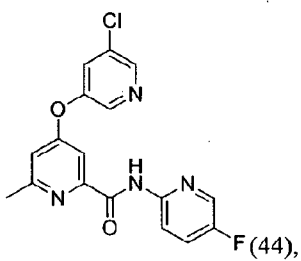
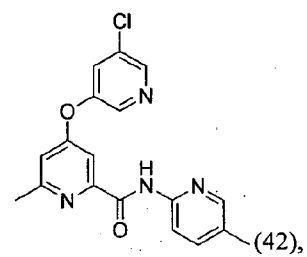
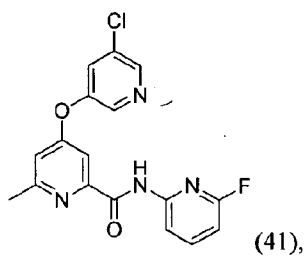
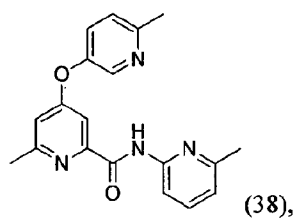
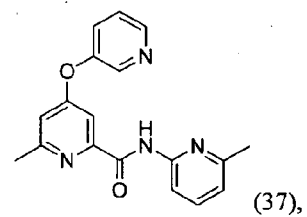
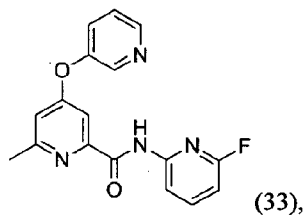
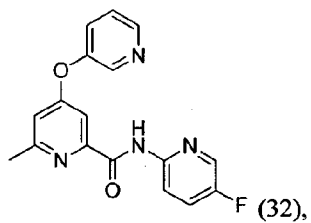


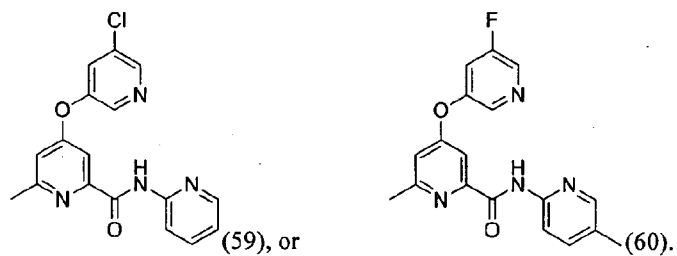
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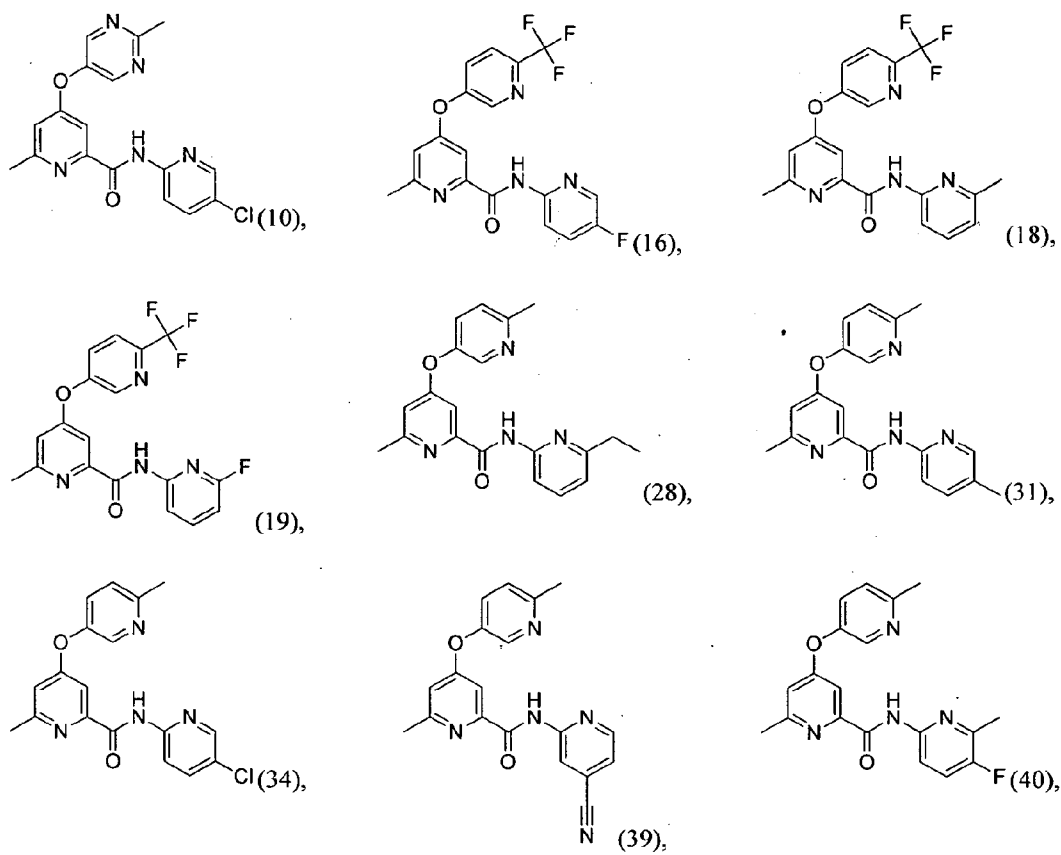


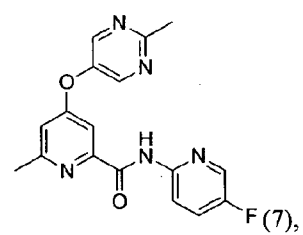
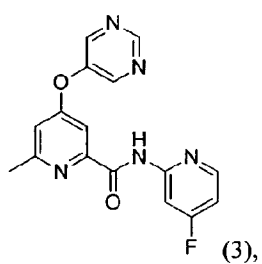
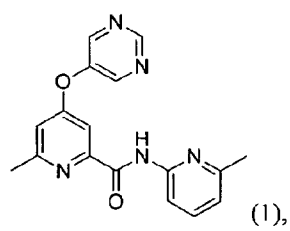
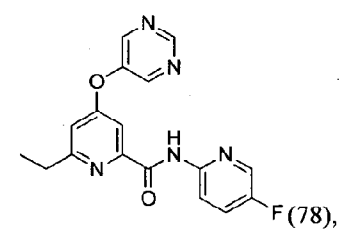
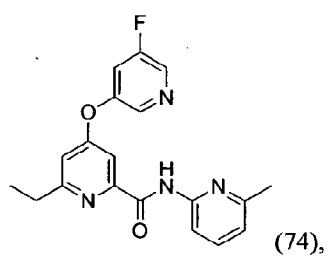
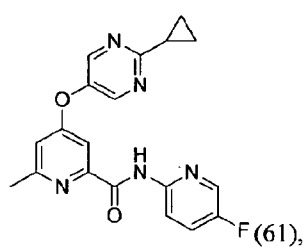
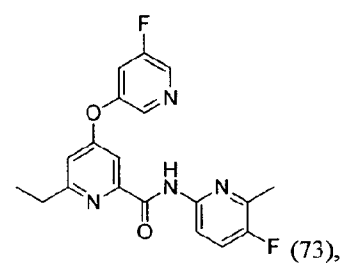
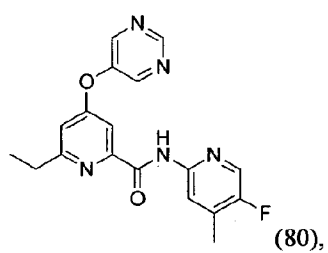
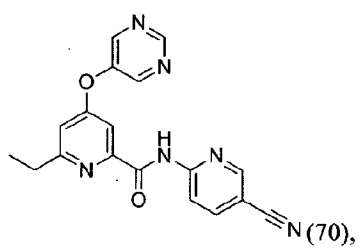
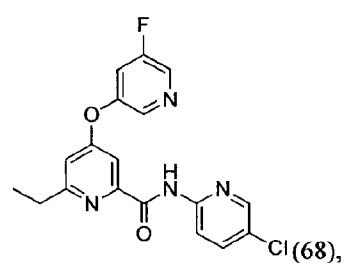
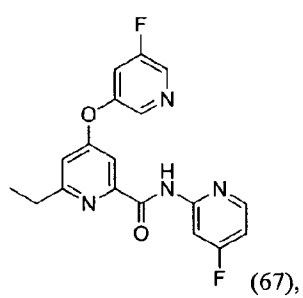
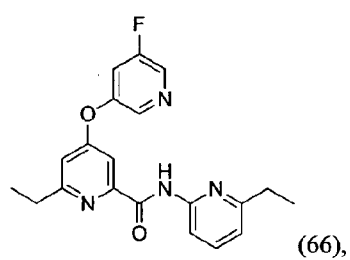
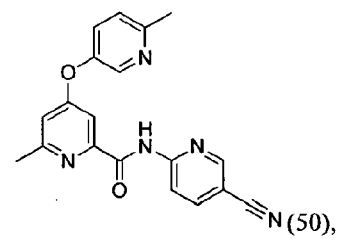
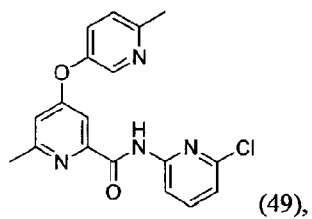
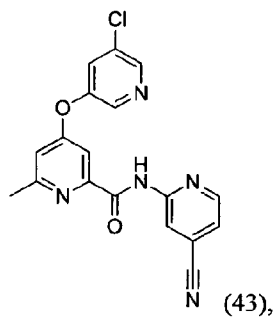


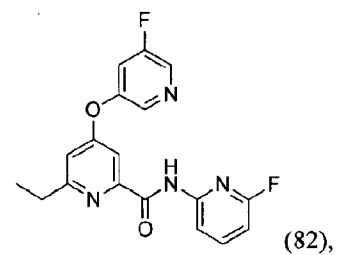
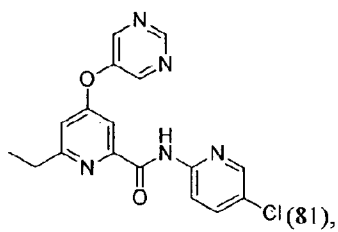
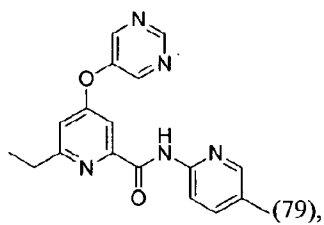
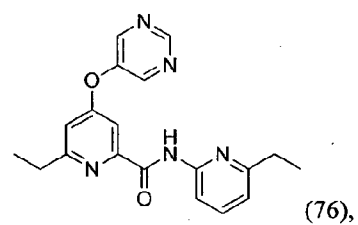
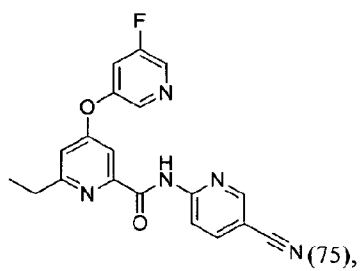
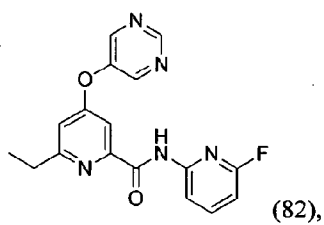
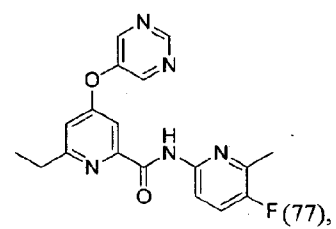
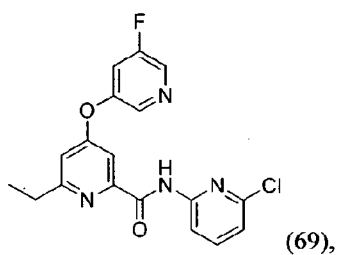
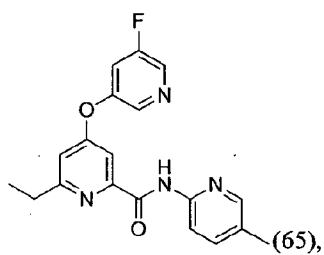
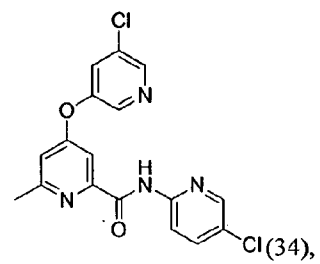
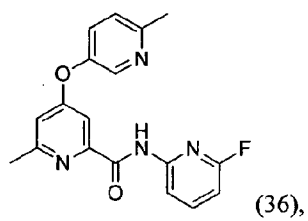
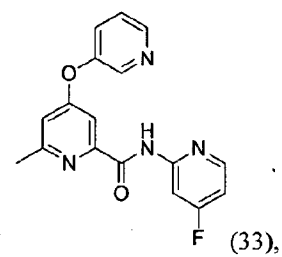
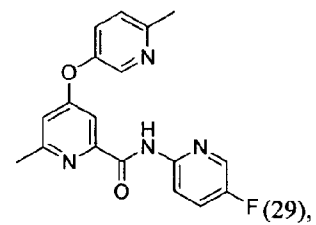
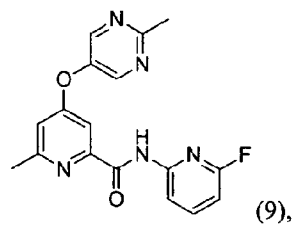
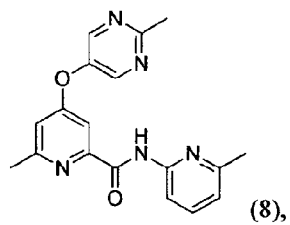


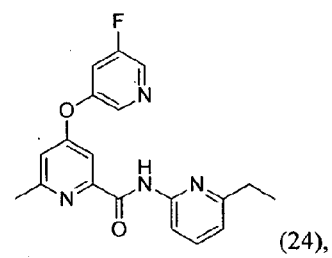
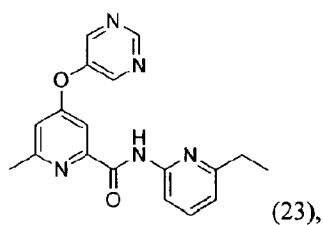
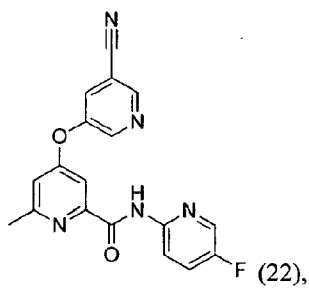
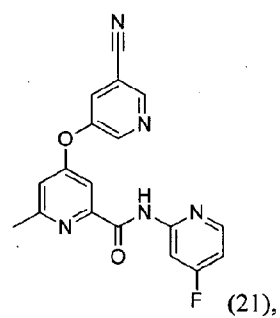
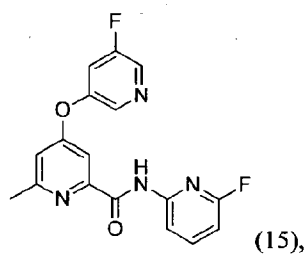
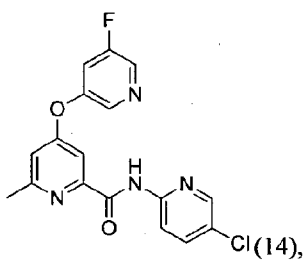
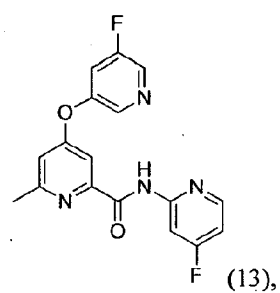
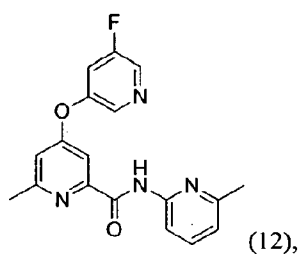
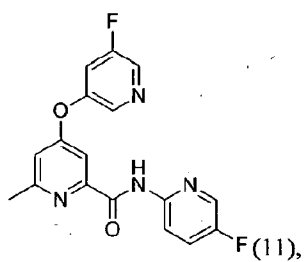
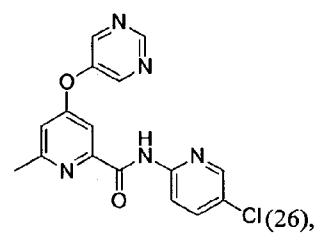
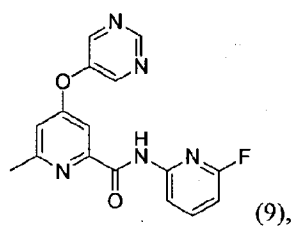
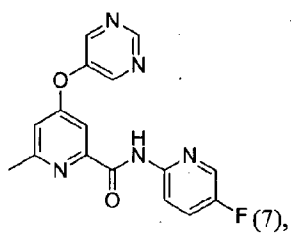
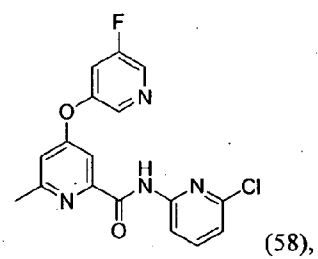
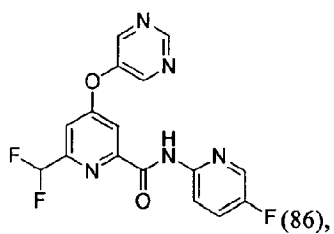
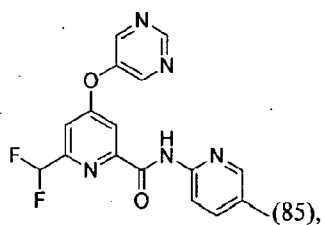


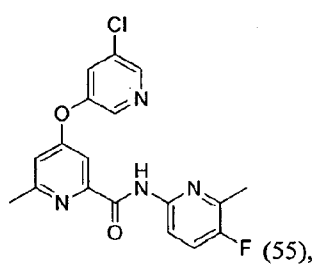
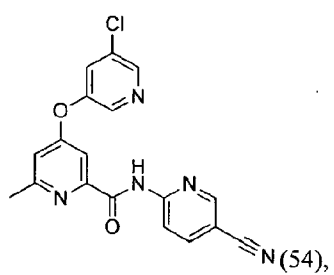
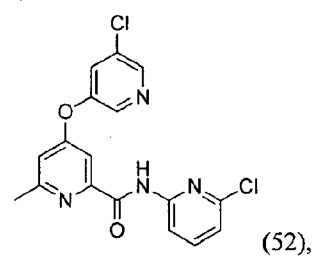
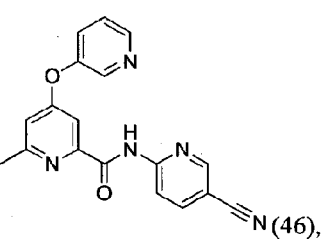
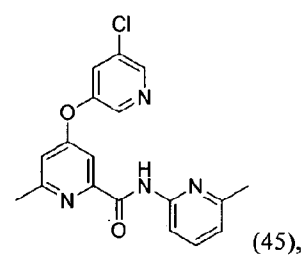
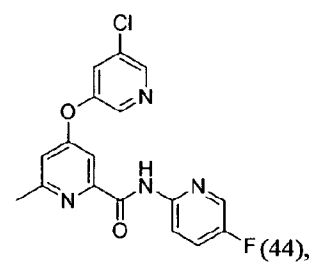
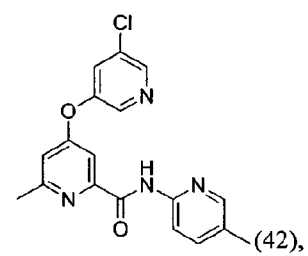
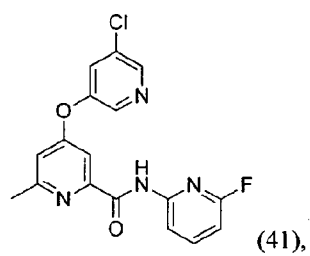
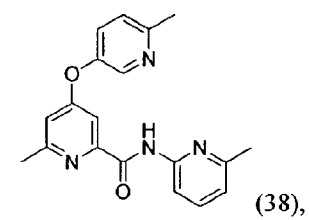
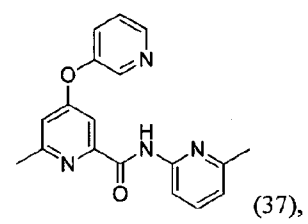
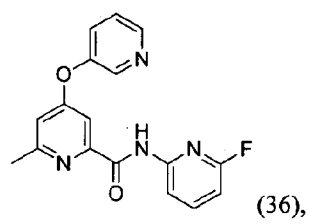
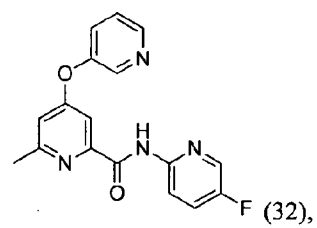
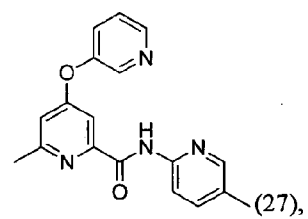
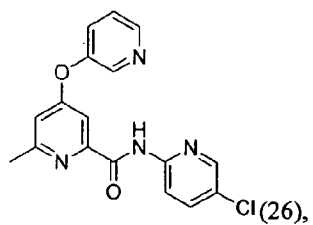
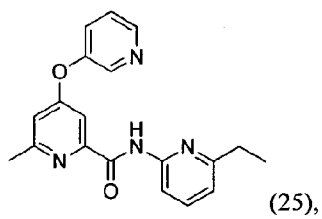
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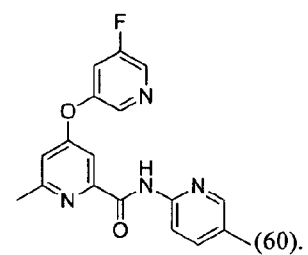
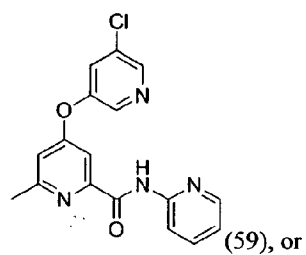
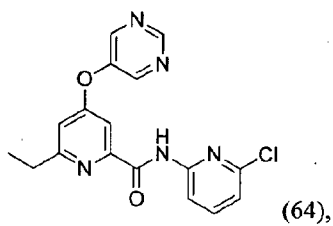
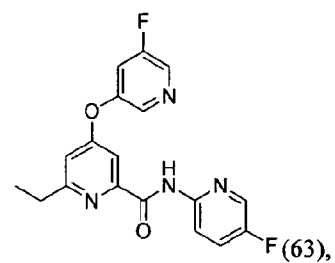
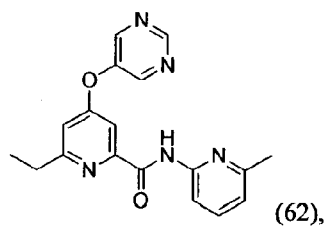
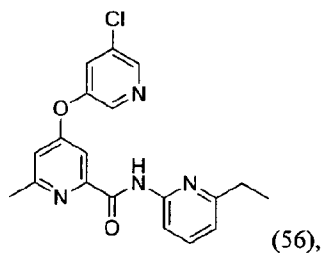




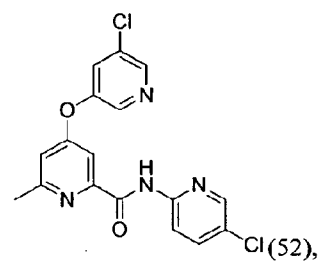
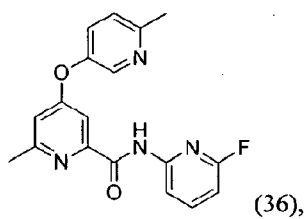
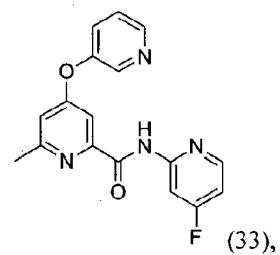
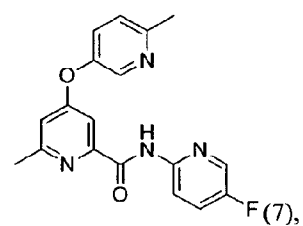
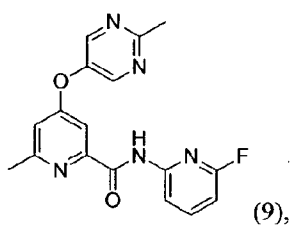
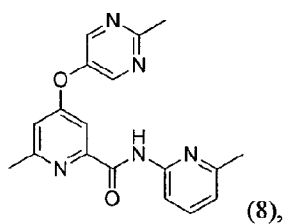
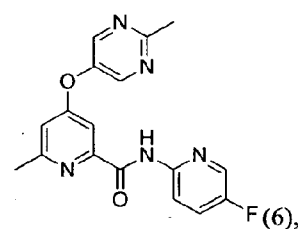
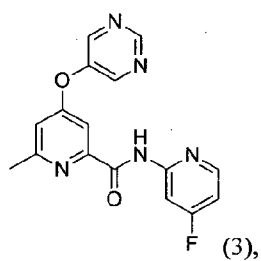
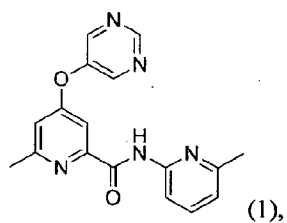


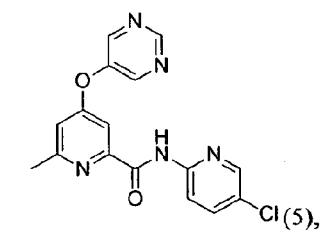
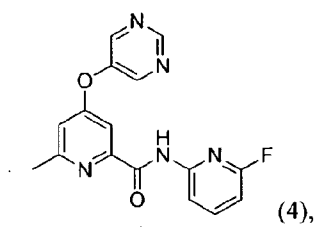
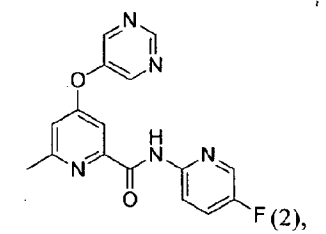
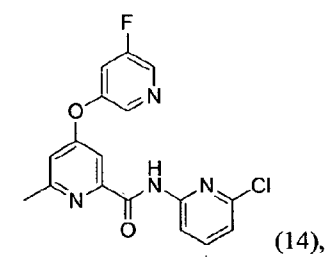
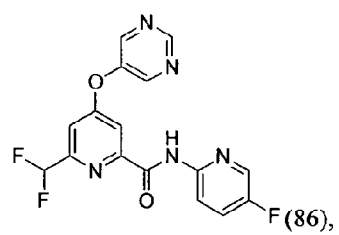
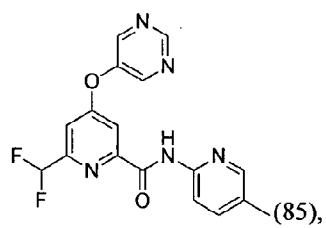
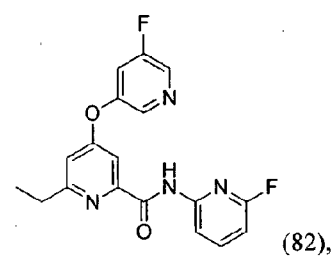
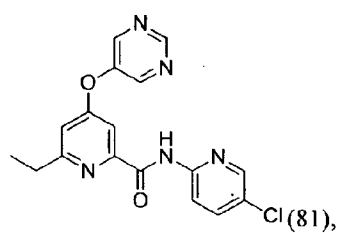
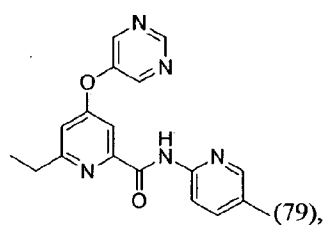
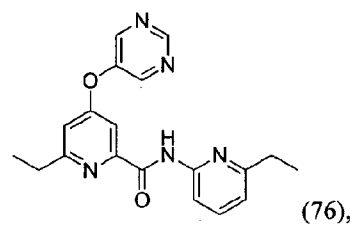
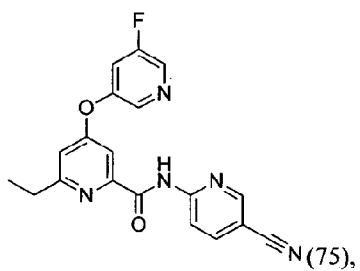
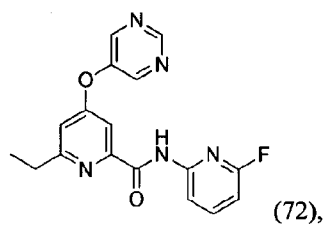
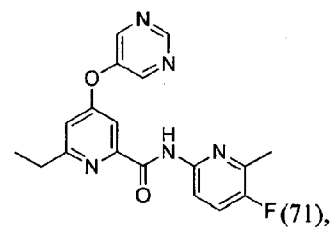
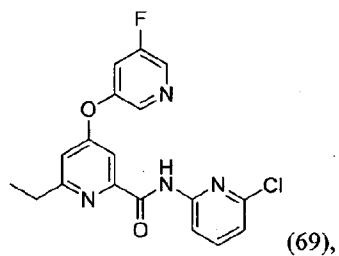
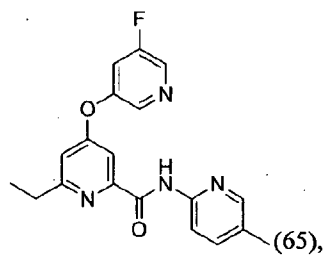


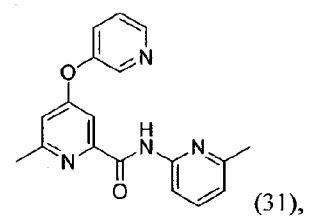
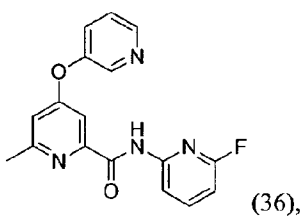
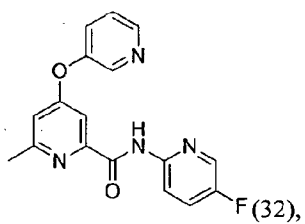
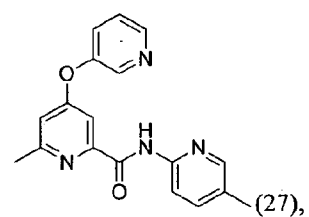
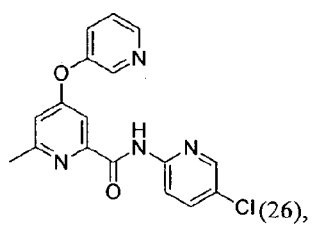
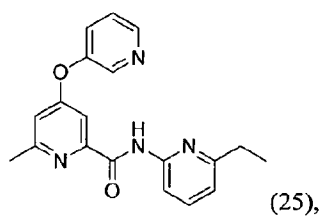
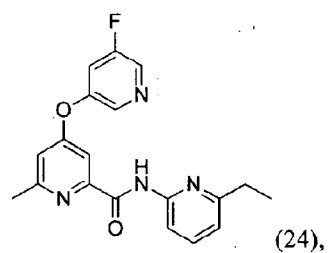
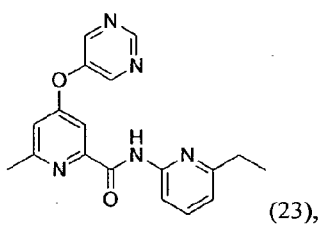
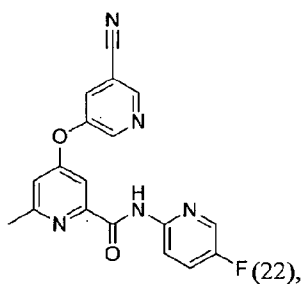
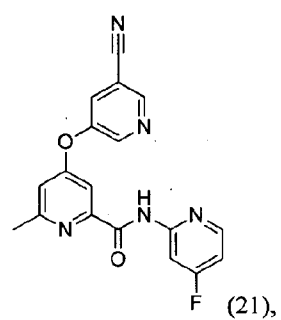
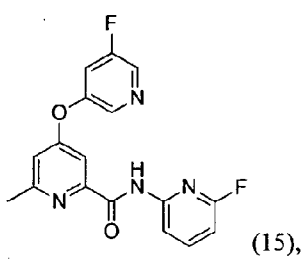
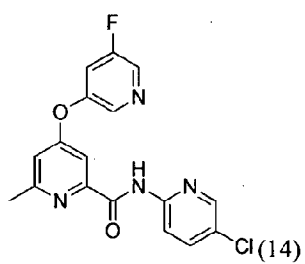
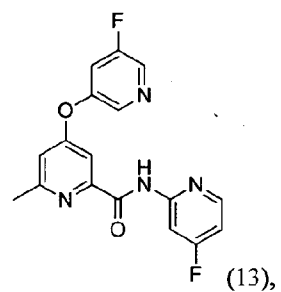
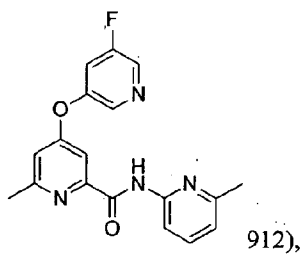
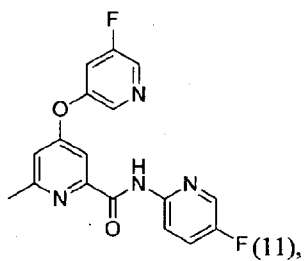


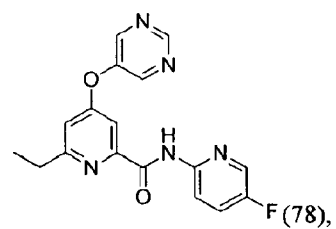
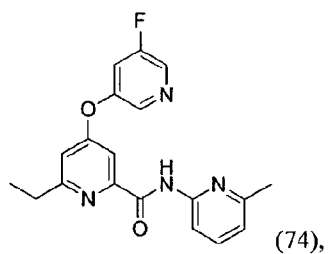
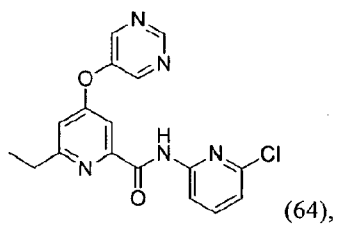
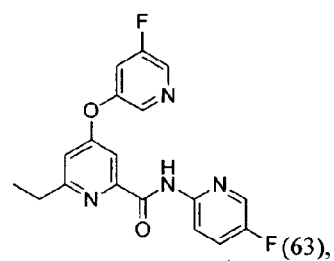
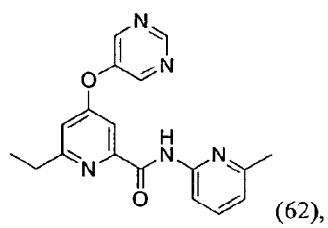
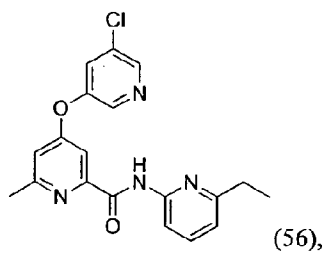
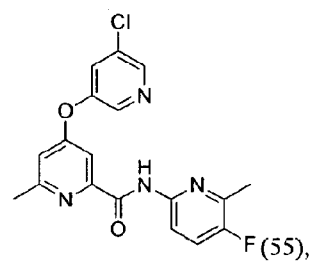
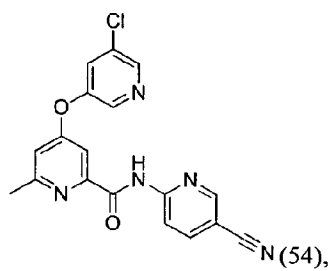
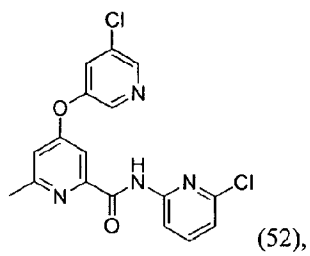
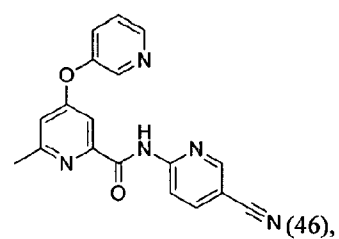
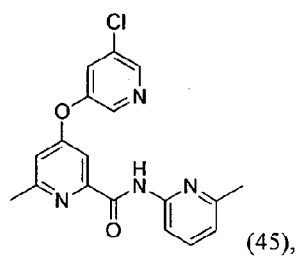
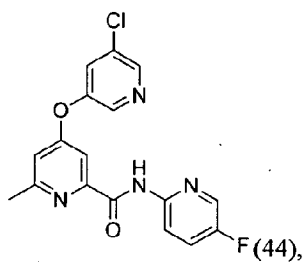
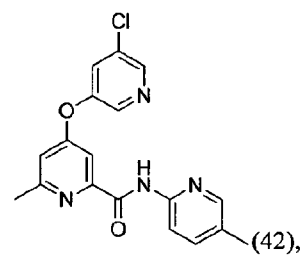
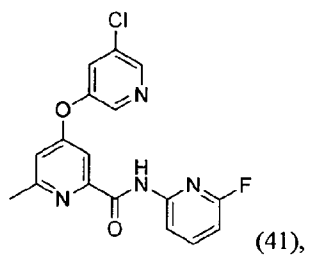
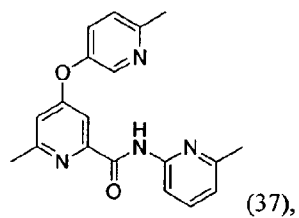


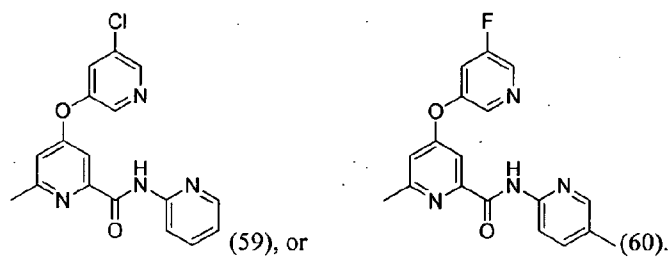
137. The compound of claim 1, selected from:



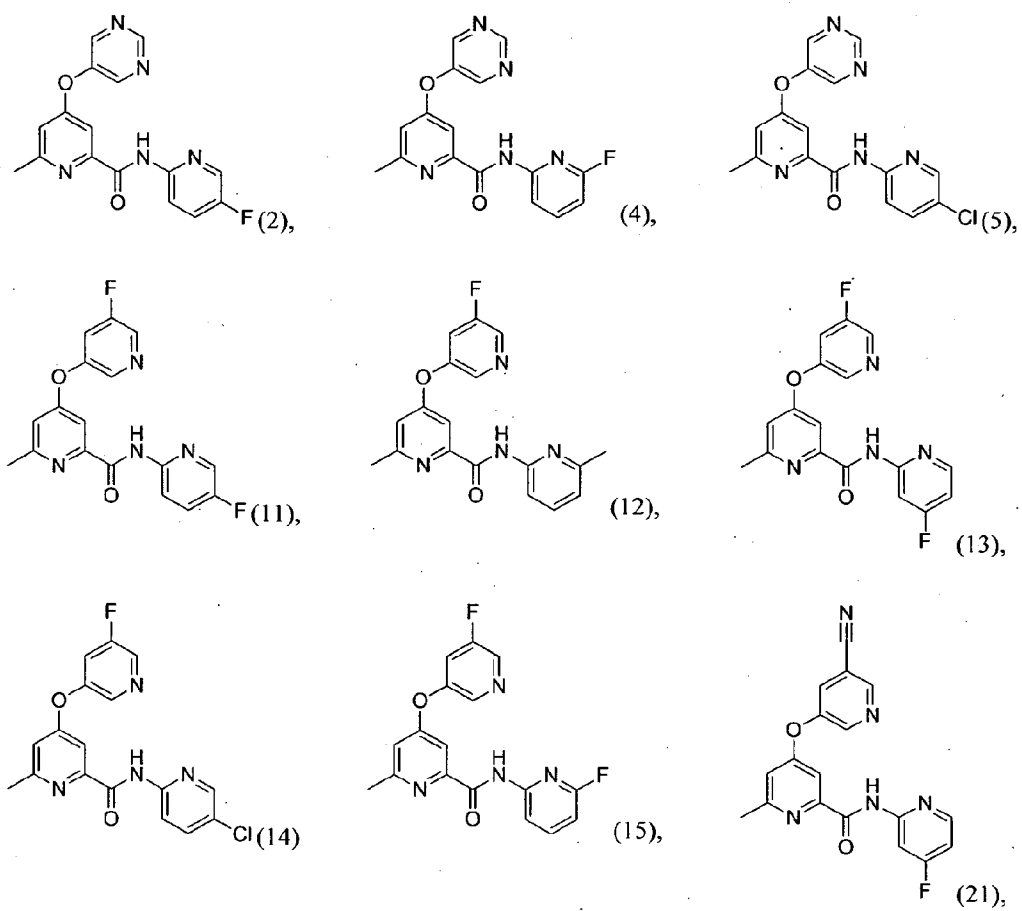


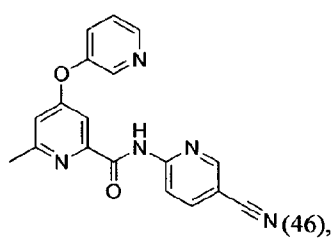
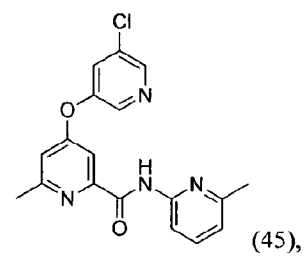
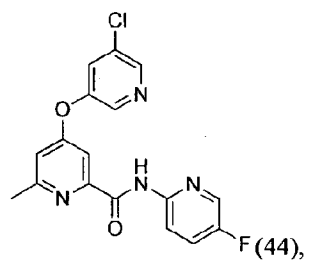
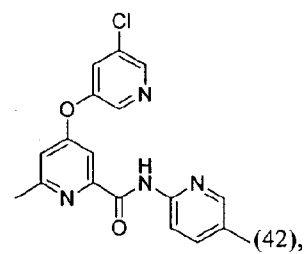
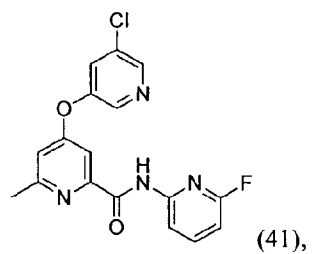
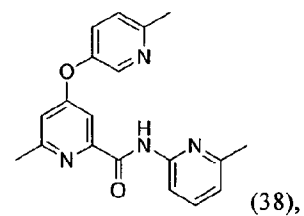
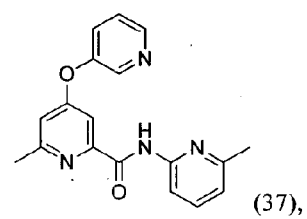
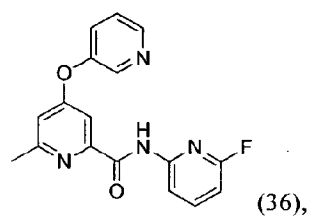
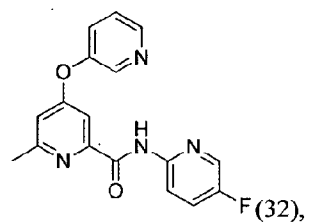
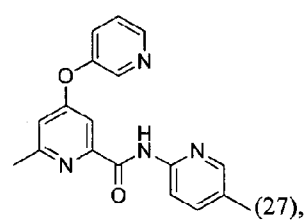
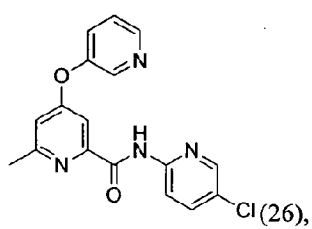
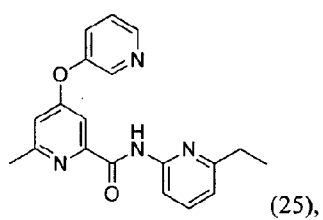
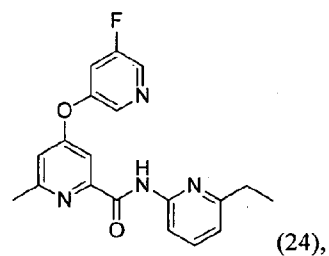
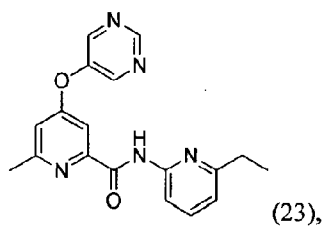
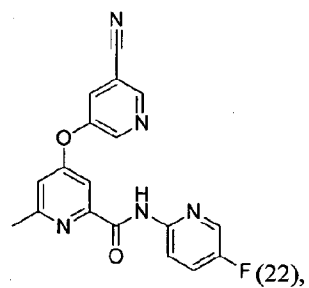


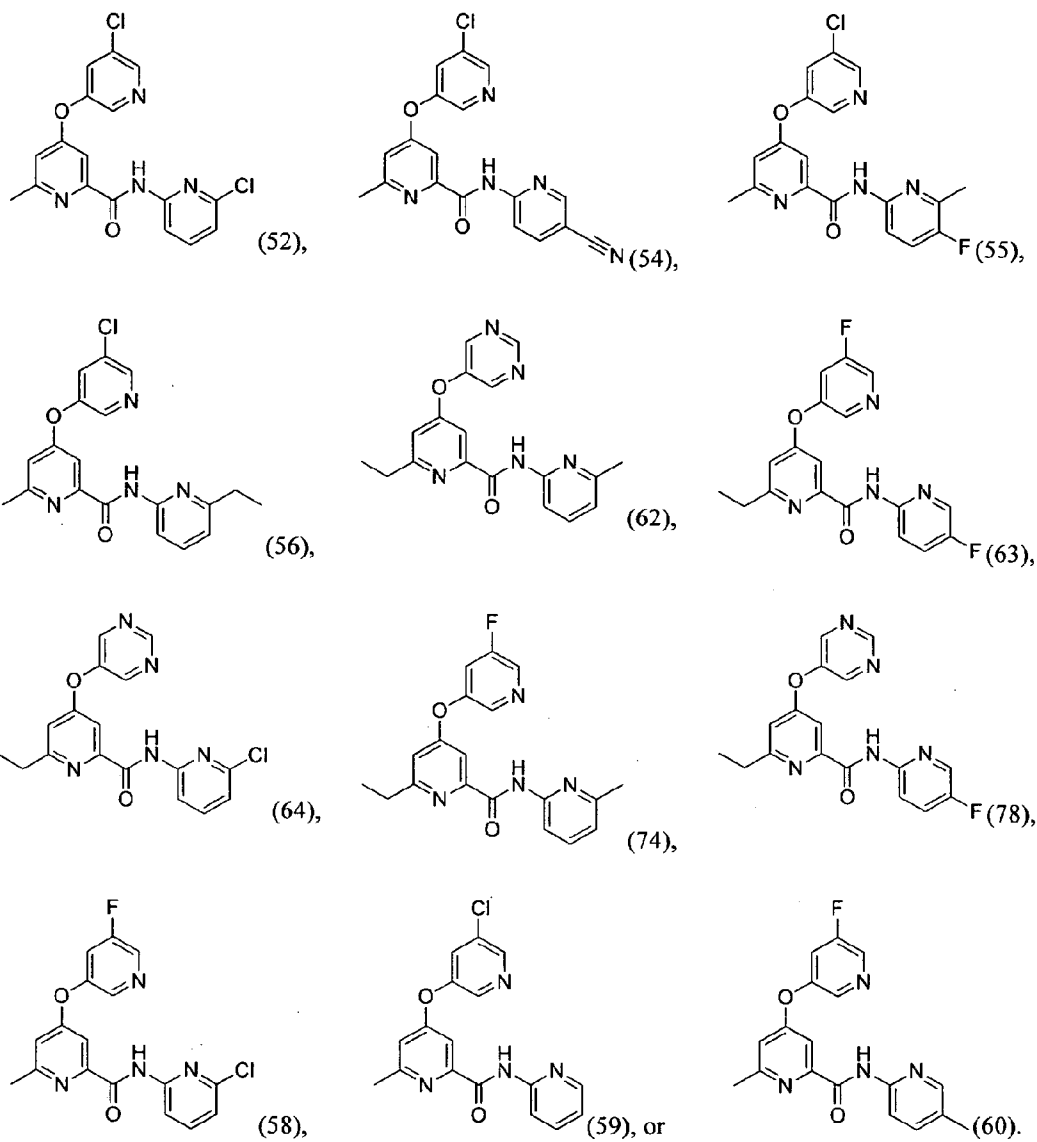




138. The compound of claim 1, selected from:



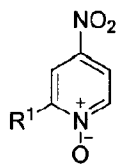




139. The compound of any of claims 1-138, wherein the mGluR5 is rat mGluR5.
140. The compound of any of claims 1-138, wherein the mGluR5 is human mGluR5.
141. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-140 and a pharmaceutically acceptable carrier.

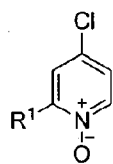
142. A method for preparing a compound comprising the steps of:

(a) providing a compound having a structure represented by a formula:



wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;
and

(b) chlorinating by reacting with concentrated HCl under reflux conditions, thereby forming a compound having a structure represented by a formula:



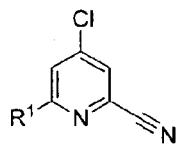
143. The method of claim 142, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.

144. The method of claim 143, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.

145. The method of claim 143, wherein R¹ is methyl.

146. The method of claim 143, wherein R¹ is ethyl.

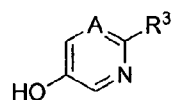
147. The method of claim 142, further comprising the step of cyanation of the compound formed, thereby forming a compound having a structure represented by a formula:



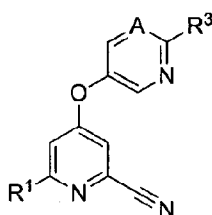
148. The method of claim 147, wherein cyanation is reacting with trimethylsilylcyanide.

149. The method of claim 147, wherein cyanation comprises an additive selected from dimethylcarbamoyl chloride and benzoyl chloride.

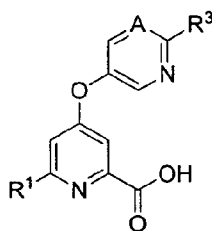
150. The method of claim 147, further comprising the step of reacting the compound formed with a compound represented by a formula:



151. The method of claim 150, wherein the compound formed has a structure represented by a formula:

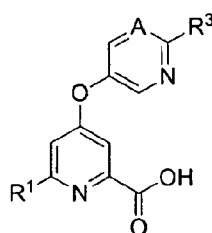


152. The method of claim 150, wherein the reaction is performed in the presence of base.
153. The method of claim 150, wherein A is CR².
154. The method of claim 150, wherein A is N.
155. The method of claim 150, further comprising the step of reacting the compound formed with aqueous hydroxide, thereby forming a compound represented by a formula:



156. A method for preparing a compound comprising the steps of:

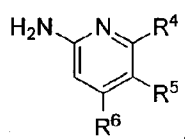
(a) providing a compound having a structure represented by a formula:



wherein wherein R^1 is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and

wherein R^2 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and

(b) coupling the compound with a compound represented by the formula:

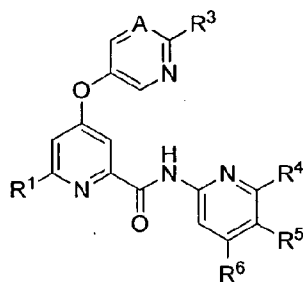


wherein each of R^4 , R^5 , and R^6 is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.

157. The method of claim 156, wherein providing is reaction of the compound provided with an activating agent.

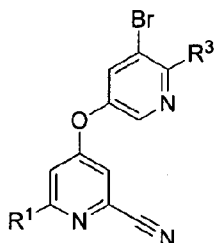
158. The method of claim 157, wherein the activating agent is selected from 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluoro-phosphate methanaminium, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, *O*-(6-chlorobenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, 1-chloro-*N,N,N*-trimethyl-1-propenylamine, oxalyl chloride, thionyl chloride, and phosphorous oxychloride..

159. The method of claim 157, wherein the compound formed is represented by the formula:



160. A method for preparing a compound comprising the steps of:

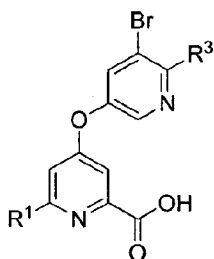
(a) providing a compound having a structure represented by a formula:



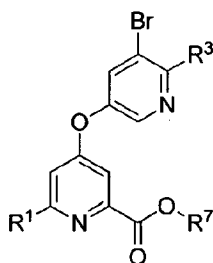
wherein wherein R^1 is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and

wherein R^2 is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and

(b) reacting with aqueous hydroxide, thereby providing a compound represented by the formula:

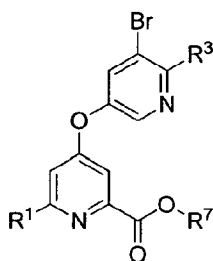


161. The method of claim 160, wherein R^1 is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
162. The method of claim 161, wherein R^1 is selected from methyl, ethyl, CHF_2 , CF_3 , and cyclopropyl.
163. The method of claim 161, wherein R^1 is methyl.
164. The method of claim 161, wherein R^1 is ethyl.
165. The method of claim 160, further comprising the step of reacting the compound formed with a $R^7\text{OH}$ in the presence of acid at reflux temperature thereby forming an ester, wherein R^7 is C1-C5 alkyl.
166. The method of claim 165, wherein the ester formed is a compound represented by the formula:



167. A method for preparing a compound comprising the steps of:

(a) providing a compound having a structure represented by a formula:

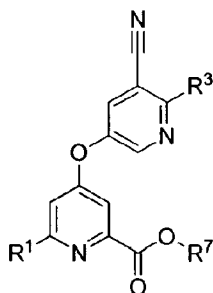


wherein wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl; and

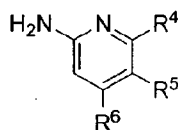
wherein R⁷ is C1-C5 alkyl; and

(b) performing a cyanation reaction, thereby providing a compound having a structure represented by a formula:



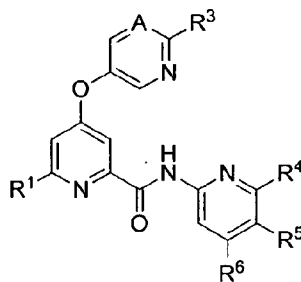
168. The method of claim 167, wherein the cyanation reaction is carried in the presence of a palladium catalyst.

169. The method of claim 168, wherein the palladium catalyst is selected from tris(di-benzylideneacetone)-dipalladium(0), palladium acetate, and tetrakis(triphenylphosphine)-palladium.
170. The method of claim 167, wherein the cyanation reaction is carried out in the presence of a ligand.
171. The method of claim 170, wherein the ligand is selected from triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, and 1,4-bis(diphenyl-phosphino)butane.
172. The method of claim 167, wherein the cyanation reaction is carried out in the presence of cyanide source.
173. The method of claim 172, wherein the cyanide source is selected from zinc cyanide, potassium ferricyanide, trimethylsilyl cyanide, and potassium cyanide.
174. The method of claim 167, further comprising the step of reacting the product formed with a compound having a structure represented by a formula:



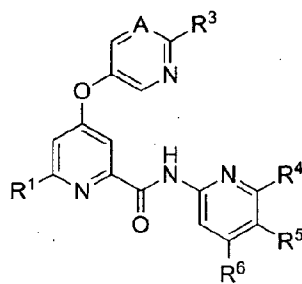
wherein each of R^4 , R^5 , and R^6 is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl.

175. The method of claim 174, wherein the reaction is carried out in the presence of a base.
176. The method of claim 174, wherein the base is selected from bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium hydride, and sodium hydride.
177. The method of claim 174, wherein the compound formed is represented by the formula:



178. The product of the method of any of claims [0011]-177.

179. A pharmaceutical composition comprising a therapeutically effective amount of the product of claim 179 and a pharmaceutically acceptable carrier.
180. A method for manufacturing a medicament comprising combining at least one compound of any of claims 1-138 or at least one product of claim 178 with a pharmaceutically acceptable carrier or diluent.
181. A method for the treatment of a disorder associated with metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of a compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

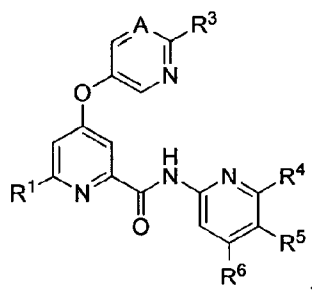
or a pharmaceutically acceptable salt thereof.

182. The method of claim 181, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
183. The method of claim 182, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
184. The method of claim 182, wherein R¹ is selected from methyl and ethyl.

185. The method of claim 182, wherein R¹ is methyl.
186. The method of claim 182, wherein R¹ is ethyl.
187. The method of claim 181, wherein the compound administered is a compound of any of claims 1-138 or at least one product of claim 178.
188. The method of claim 181, wherein the mammal is a human.
189. The method of claim 181, wherein the metabotropic glutamate receptor is mGluR5.
190. The method of claim 181, wherein the compound exhibits partial inhibition of mGluR5 response.
191. The method of claim 181, wherein the compound exhibits total inhibition of mGluR5 response.
192. The method of claim 181, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶.
193. The method of claim 181, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶.
194. The method of claim 181, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁶.
195. The method of claim 181, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷.
196. The method of claim 181, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁸.
197. The method of claim 181, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁹.
198. The method of claim 181, wherein the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step.
199. The method of claim 181, further comprising the step of identifying a mammal in need of treatment of the disorder.
200. The method of claim 199, wherein the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction.

201. The method of claim 200, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
202. The method of claim 200, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelmans's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
203. The method of claim 200, wherein the neurological and/or psychiatric wherein the disorder is an autism spectrum disorder.
204. The method of claim 203, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
205. The method of claim 199, wherein the disorder is a disease of uncontrolled cellular proliferation.
206. The method of claim 205, wherein the disease of uncontrolled cellular proliferation is cancer.
207. The method of claim 205, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
208. The method of claim 205, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

209. A method for decreasing metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

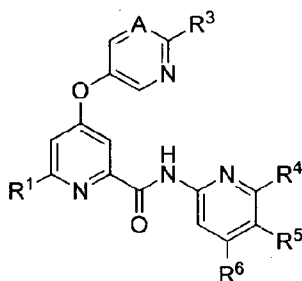
or a pharmaceutically acceptable salt thereof.

210. The method of claim 209, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
211. The method of claim 210, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
212. The method of claim 210, wherein R¹ is selected from methyl and ethyl.
213. The method of claim 210, wherein R¹ is methyl.
214. The method of claim 210, wherein R¹ is ethyl.
215. The method of claim 209, wherein the compound administered is a compound of any of claims 1-138 or at least one product of claim 178.

216. The method of claim 209, wherein the mammal is a human.
217. The method of claim 209, wherein the metabotropic glutamate receptor is mGluR5.
218. The method of claim 209, wherein the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} .
219. The method of claim 209, wherein the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} .
220. The method of claim 209, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} .
221. The method of claim 209, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} .
222. The method of claim 209, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} .
223. The method of claim 209, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .
224. The method of claim 209, wherein the mammal has been diagnosed with a need for decreasing metabotropic glutamate receptor activity prior to the administering step.
225. The method of claim 209, further comprising the step of identifying a mammal in need of decreasing metabotropic glutamate receptor activity.
226. The method of claim 209, wherein the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.
227. The method of claim 226, wherein the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction.
228. The method of claim 227, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
229. The method of claim 227, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression,

diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levadopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

230. The method of claim 227, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
231. The method of claim 230, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
232. The method of claim 226, wherein the disorder is a disease of uncontrolled cellular proliferation.
233. The method of claim 232, wherein the disease of uncontrolled cellular proliferation is cancer.
234. The method of claim 232, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
235. The method of claim 232, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
236. A method for inhibiting metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

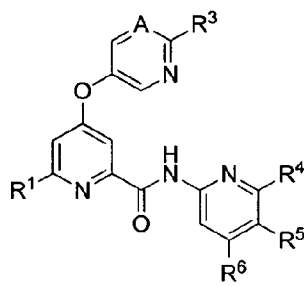
wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

237. The method of claim 236, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
238. The method of claim 237, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
239. The method of claim 237, wherein R¹ is selected from methyl and ethyl.
240. The method of claim 237, wherein R¹ is methyl.
241. The method of claim 237, wherein R¹ is ethyl.
242. The method of claim 236, wherein the compound administered is a compound of any of claims 1-138 or at least one product of claim 178.
243. The method of claim 236, wherein the mammal is a human.
244. The method of claim 236, wherein the metabotropic glutamate receptor is mGluR5.
245. The method of claim 236, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶.
246. The method of claim 236, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶.
247. The method of claim 236, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁶.
248. The method of claim 236, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷.
249. The method of claim 236, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁸.

250. The method of claim 236, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .
251. The method of claim 236, wherein the mammal has been diagnosed with a need for inhibiting metabotropic glutamate receptor activity prior to the administering step.
252. The method of claim 236, further comprising the step of identifying a mammal in need of inhibiting metabotropic glutamate receptor activity.
253. The method of claim 236, wherein the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.
254. The method of claim 253, wherein the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction.
255. The method of claim 254, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
256. The method of claim 254, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
257. The method of claim 254, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
258. The method of claim 257, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
259. The method of claim 253, wherein the disorder is a disease of uncontrolled cellular proliferation.
260. The method of claim 259, wherein the disease of uncontrolled cellular proliferation is cancer.

261. The method of claim 259, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
262. The method of claim 259, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
263. A method for negative allosteric modulation of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

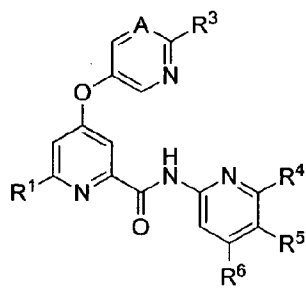
wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

264. The method of claim 263, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
265. The method of claim 264, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
266. The method of claim 264, wherein R¹ is selected from methyl and ethyl.

267. The method of claim 264, wherein R¹ is methyl.
268. The method of claim 264, wherein R¹ is ethyl.
269. The method of claim 263, wherein the compound administered is a compound of any of claims 1-138 or at least one product of claim 178.
270. The method of claim 263, wherein the mammal is a human.
271. The method of claim 263, wherein the metabotropic glutamate receptor is mGluR5.
272. The method of claim 263, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶.
273. The method of claim 263, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶.
274. The method of claim 263, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁶.
275. The method of claim 263, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷.
276. The method of claim 263, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁸.
277. The method of claim 263, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁹.
278. The method of claim 263, wherein the mammal has been diagnosed with a need for negative allosteric modulation of metabotropic glutamate receptor activity prior to the administering step.
279. The method of claim 263, further comprising the step of identifying a mammal in need of negative allosteric modulation of metabotropic glutamate receptor activity.
280. The method of claim 263, wherein the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.
281. The method of claim 280, wherein the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction.

282. The method of claim 281, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
283. The method of claim 281, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelmans's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN harmartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
284. The method of claim 281, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
285. The method of claim 284, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
286. The method of claim 280, wherein the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation.
287. The method of claim 286, wherein the disease of uncontrolled cellular proliferation is cancer.
288. The method of claim 286, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
289. The method of claim 286, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
290. A method for partial antagonism of metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

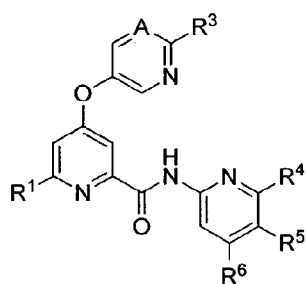
or a pharmaceutically acceptable salt thereof.

291. The method of claim 290, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
292. The method of claim 291, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
293. The method of claim 291, wherein R¹ is selected from methyl and ethyl.
294. The method of claim 291, wherein R¹ is methyl.
295. The method of claim 291, wherein R¹ is ethyl.
296. The method of claim 290, wherein the compound administered is a compound of any of claims 1-138 or at least one product of claim 178.
297. The method of claim 290, wherein the mammal is a human.
298. The method of claim 290, wherein the metabotropic glutamate receptor is mGluR5.

299. The method of claim 290, wherein the compound exhibits negative allosteric modulation with an IC_{50} of less than about 30×10^{-6} .
300. The method of claim 290, wherein the compound exhibits negative allosteric modulation with an IC_{50} of less than about 10×10^{-6} .
301. The method of claim 290, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} .
302. The method of claim 290, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} .
303. The method of claim 290, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} .
304. The method of claim 290, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .
305. The method of claim 290, wherein the mammal has been diagnosed with a need for partial antagonism metabotropic glutamate receptor activity prior to the administering step.
306. The method of claim 290, further comprising the step of identifying a mammal in need of partial antagonism metabotropic glutamate receptor activity.
307. The method of claim 290, wherein the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.
308. The method of claim 307, wherein the disorder is a neurological and/or psychiatric disorder associated with glutamate dysfunction.
309. The method of claim 308, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
310. The method of claim 308, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia,

Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.

311. The method of claim 308, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
312. The method of claim 311, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
313. The method of claim 307, wherein the disorder related to metabotropic glutamate receptor is a disease of uncontrolled cellular proliferation.
314. The method of claim 313, wherein the disease of uncontrolled cellular proliferation is cancer.
315. The method of claim 313, wherein disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
316. The method of claim 313, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
317. A method for modulating metabotropic glutamate receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

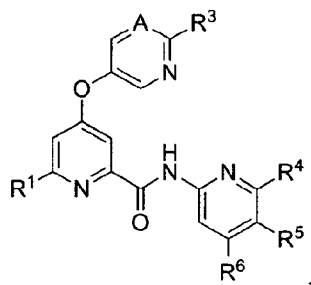
wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

318. The method of claim 317, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
319. The method of claim 318, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
320. The method of claim 318, wherein R¹ is selected from methyl and ethyl.
321. The method of claim 318, wherein R¹ is methyl.
322. The method of claim 318, wherein R¹ is ethyl.
323. The method of claim 317, wherein the compound administered is a compound of any of claims 1-138 or at least one product of claim 178.
324. The method of claim 317, wherein the mammal is a human.
325. The method of claim 317, wherein the metabotropic glutamate receptor is mGluR5.
326. The method of claim 317, wherein modulating is decreasing.
327. The method of claim 317, wherein modulating is non-competitive inhibition.
328. The method of claim 317, wherein modulating is non-competitive antagonism.
329. The method of claim 317, wherein modulating is negative allosteric modulation.
330. The method of claim 317, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶.
331. The method of claim 317, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶.

332. The method of claim 317, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-6} .
333. The method of claim 317, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-7} .
334. The method of claim 317, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} .
335. The method of claim 317, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .
336. The method of claim 317, wherein the mammal has been diagnosed with a need for partial antagonism metabotropic glutamate receptor activity prior to the administering step.
337. The method of claim 317, further comprising the step of identifying a mammal in need of partial antagonism metabotropic glutamate receptor activity.
338. The method of claim 317, wherein the mammal has been diagnosed with a need for treatment of a disorder related to metabotropic glutamate receptor activity prior to the administering step.
339. The method of claim 338, wherein the disorder related to metabotropic glutamate receptor activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction.
340. The method of claim 339, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
341. The method of claim 339, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
342. The method of claim 339, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.

343. The method of claim 342, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
344. The method of claim 338, wherein the disorder related to metabotropic glutamate receptor activity is a disease of uncontrolled cellular proliferation.
345. The method of claim 341, wherein the disease of uncontrolled cellular proliferation is cancer.
346. The method of claim 341, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
347. The method of claim 341, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
348. A method for modulating metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

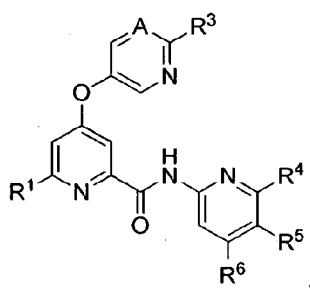
wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

349. The method of claim 348, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
350. The method of claim 349, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
351. The method of claim 349, wherein R¹ is selected from methyl and ethyl.
352. The method of claim 349, wherein R¹ is methyl.
353. The method of claim 349, wherein R¹ is ethyl.
354. The method of claim 348, wherein the compound is a compound of any of claims 1-138 or at least one product of claim 178.
355. The method of claim 348, wherein the cell is mammalian.
356. The method of claim 348, wherein the cell is a human.
357. The method of claim 348, wherein the metabotropic glutamate receptor is mGluR5.
358. The method of claim 348, wherein modulating is inhibition.
359. The method of claim 348, wherein modulating is non-competitive inhibition.
360. The method of claim 348, wherein modulating is non-competitive antagonism
361. The method of claim 348, wherein modulating is negative allosteric modulation.
362. The method of claim 348, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10⁻⁶.
363. The method of claim 348, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10⁻⁶.
364. The method of claim 348, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁶.
365. The method of claim 348, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10⁻⁷.

366. The method of claim 348, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-8} .
367. The method of claim 348, wherein the compound exhibits partial or total inhibition with an IC_{50} of less than about 1.0×10^{-9} .
368. The method of claim 348, wherein contacting is via administration to a mammal.
369. The method of claim [00349], wherein the mammal has been diagnosed with a need for modulating mGluR5 activity prior to the administering step.
370. The method of claim [00349], wherein the mammal has been diagnosed with a need for treatment of a disorder related to mGluR5 activity prior to the administering step
371. The method of claim 370, wherein the disorder related to mGluR5 activity prior is a neurological and/or psychiatric disorder associated with glutamate dysfunction.
372. The method of claim 371, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
373. The method of claim 371, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnestic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
374. The method of claim 371, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
375. The method of claim 374, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
376. The method of claim 370, wherein the disorder related to mGluR5 activity prior is a disease of uncontrolled cellular proliferation.

377. The method of claim 376, wherein the disease of uncontrolled cellular proliferation is cancer.
378. The method of claim 376, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
379. The method of claim 376, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
380. A method for inhibiting metabotropic glutamate receptor activity in at least one cell, comprising the step of contacting the at least one cell with at least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

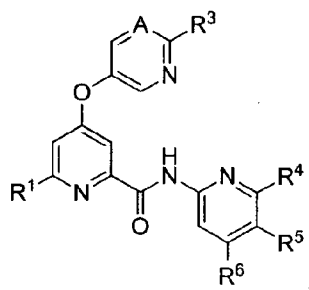
wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

381. The method of claim 380, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
382. The method of claim 381, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.

383. The method of claim 381, wherein R¹ is selected from methyl and ethyl.
384. The method of claim 381, wherein R¹ is methyl.
385. The method of claim 381, wherein R¹ is ethyl.
386. The method of claim 380, wherein the compound is a compound of any of claims 1-138 or at least one product of claim 178.
387. The method of claim 380, wherein the cell is mammalian.
388. The method of claim 380, wherein the cell is a human.
389. The method of claim 380, wherein the metabotropic glutamate receptor is mGluR5.
390. The method of claim 380, wherein inhibiting is antagonism.
391. The method of claim 380, wherein inhibiting is non-competitive antagonism.
392. The method of claim 380, wherein inhibiting is negative allosteric modulation.
393. The method of claim 380, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 30×10^{-6} .
394. The method of claim 380, wherein the compound exhibits negative allosteric modulation with an IC₅₀ of less than about 10×10^{-6} .
395. The method of claim 380, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10^{-6} .
396. The method of claim 380, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10^{-7} .
397. The method of claim 380, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10^{-8} .
398. The method of claim 380, wherein the compound exhibits partial or total inhibition with an IC₅₀ of less than about 1.0×10^{-9} .
399. The method of claim 380, wherein contacting is via administration to a mammal.
400. The method of claim 380, wherein the mammal has been diagnosed with a need for inhibiting mGluR5 activity prior to the administering step.

401. The method of claim 380, wherein the mammal has been diagnosed with a need for treatment of a disorder related to mGluR5 activity prior to the administering step
402. The method of claim 401, wherein the disorder related to mGluR5 activity is a neurological and/or psychiatric disorder associated with glutamate dysfunction.
403. The method of claim 402, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
404. The method of claim 402, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamartoma syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
405. The method of claim 402, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
406. The method of claim 405, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
407. The method of claim 401, wherein the disorder related to mGluR5 activity is a disease of uncontrolled cellular proliferation.
408. The method of claim 404, wherein the disease of uncontrolled cellular proliferation is cancer.
409. The method of claim 404, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.
410. The method of claim 404, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
411. Use of a compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

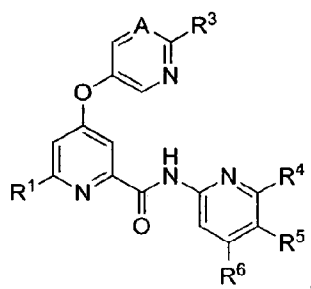
or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal.

412. The use of claim 411, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
413. The use of claim 412, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
414. The use of claim 412, wherein R¹ is selected from methyl and ethyl.
415. The use of claim 412, wherein R¹ is methyl.
416. The use of claim 412, wherein R¹ is ethyl.
417. The use of claim 411, wherein the compound is a compound of any of claims 1-138 or at least one product of claim 178.

418. The use of claim 411, wherein the compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.
419. The use of claim 418, wherein the human embryonic kidney cells transfected with rat mGluR5.
420. The use of claim 418, wherein the human embryonic kidney cells transfected with human mGluR5.
421. The use of claim 411, wherein the compound treats a neurological and/or psychiatric disorder associated with glutamate dysfunction.
422. The use of claim 421, wherein the neurological and/or psychiatric disorder is selected from addiction, anxiety, fragile x syndrome, gastroesophageal reflux disease (GERD), Parkinson's disease, and pain.
423. The use of claim 421, wherein the neurological and/or psychiatric disorder is selected from affective disorder, age-related cognitive decline, Alzheimer's disease, amnesic disorders, amyotrophic lateral sclerosis, anxiety disorders, Angelman's syndrome, Asperger's syndrome, attention deficit hyperactivity disorder, bipolar disorder, brain edema, chronic pain, delirium, dementia, depression, diabetes, Down Syndrome, dystonia, eating disorders, epilepsy, fibromyalgia, Huntington's-related chorea, levodopa-induced dyskinesia, manic-depressive illness, migraine, movement disorders, multiple sclerosis, narcolepsy, neurofibromatosis type 1, neuropathic pain, obesity, pain, paranoia, Parkinson's disease, post-herpetic neuropathic pain, psychotic disorders, PTEN hamman-Richards syndrome, senile dementia, sleep disorder, substance-related disorder, or unipolar depression.
424. The use of claim 421, wherein the neurological and/or psychiatric disorder is an autism spectrum disorder.
425. The use of claim 424, where the autism spectrum disorder is selected from autism, classical autism, Asperger syndrome, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), sometimes called atypical autism, Fragile X syndrome, Rett syndrome, and Childhood Disintegrative Disorder.
426. The use of claim 411, wherein the compound treats a disease of uncontrolled cellular proliferation.
427. The use of claim 426, wherein the disease of uncontrolled cellular proliferation is cancer.
428. The use of claim 426, wherein the disease of uncontrolled cellular proliferation is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer.

429. The use of claim 426, wherein the disease of uncontrolled cellular proliferation is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.
430. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

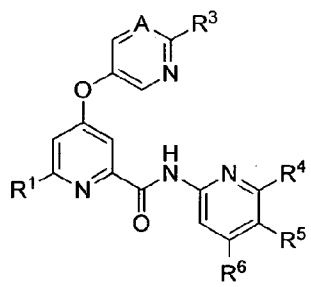
wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

431. The composition of claim 430, wherein the effective amount is a therapeutically effective amount.
432. The composition of claim 430, wherein the effective amount is a prophylactically effective amount.
433. The composition of claim 430, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
434. The composition of claim 433, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.

435. The composition of claim 433, wherein R¹ is selected from methyl and ethyl.
436. The composition of claim 433, wherein R¹ is methyl.
437. The composition of claim 433, wherein R¹ is ethyl.
438. The composition of claim 430 wherein the compound is a compound of any of claims 1-138 or at least one product of claim 178.
439. The composition of claim 430, wherein the compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.
440. The composition of claim 439, wherein the human embryonic kidney cells transfected with rat mGluR5.
441. The composition of claim 439, wherein the human embryonic kidney cells transfected with human mGluR5.
442. A kit comprising at least one compound having a structure represented by a formula:



wherein A is CR² or N;

wherein R¹ is selected from C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R² is selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein R³ is selected from hydrogen, halogen, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

wherein each of R⁴, R⁵, and R⁶ is independently selected from hydrogen, halogen, CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, and C3 cycloalkyl;

or a pharmaceutically acceptable salt thereof,

and one or more of:

- (a) at least one agent known to increase mGluR5 activity;
- (b) at least one agent known to decrease mGluR5 activity;
- (c) at least one agent known to treat a neurological and/or psychiatric disorder;
- (d) at least one agent known to treat a disease of uncontrolled cellular proliferation; or
- (e) instructions for treating a disorder associated with glutamate dysfunction.

443. The kit of claim 442, wherein R¹ is selected from C1-C2 alkyl, C1-C2 haloalkyl, C1-C2 polyhaloalkyl, and C3 cycloalkyl.
444. The kit of claim 443, wherein R¹ is selected from methyl, ethyl, CHF₂, CF₃, and cyclopropyl.
445. The kit of claim 443, wherein R¹ is selected from methyl and ethyl.
446. The kit of claim 443, wherein R¹ is methyl.
447. The kit of claim 443, wherein R¹ is ethyl.
448. The kit of claim 442 wherein the compound is a compound of any of claims 1-138 or at least one product of claim 178.
449. The kit of claim 442, wherein the compound exhibits partial or total inhibition of mGluR5 response to glutamate as a decrease in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound.
450. The kit of claim 449, wherein the human embryonic kidney cells are transfected with rat mGluR5.
451. The kit of claim 449, wherein the human embryonic kidney cells are transfected with human mGluR5.
452. The kit of claim 442, wherein the at least one agent is selected from an antipsychotic, a selective serotonin reuptake inhibitor, a central sympathomimetic, an imidazoline receptor agonists, a propionic

acid derivative, a benzodiazepine, sympathomimetics, a fatty acid derivative, a vitamin or multivitamin (with or without minerals), a piperazine derivative, an anilide, a lipid modifying agent, an aminoalkyl ether analogue, a macrolide, a melatonin receptor agonist, a penicillin derivative, a tetracycline analogue, an expectorant, an antihistamine, an azaspirodecanedione derivative, a central acting agent, a carboxamide, an opium alkaloid or derivative, an antidepressant, an antiepileptic, a beta blocker, a psychostimulant, a proton pump inhibitor, a 5HT3 antagonist, a vitamin D analogue, a diazepam, an indole derivative, an HMG CoA reductase inhibitor, a topical antibiotic, a progesterone analogue, an estrogen analogue, an angiotensin-converting enzyme inhibitor, an anesthetic, an antifungal, an antidiarrheal, an oxazepam, a thiazepam, a vaccine, a sulfonamide, a leukotriene receptor antagonist, a lincosamide, a neuroamidase inhibitor, a non-selective monoamine reuptake inhibitor, and a salicylic acid analogue.

453. The kit of claim 442 or claim 452, wherein the at least one agent is selected from Aripiprazole, Acetaminophen, Acetylcarnitine, Acetylsalicylic acid, Alprazolam, Amitriptyline, Amoxicillin, Augmentin, Azithromycin, Baclofen, Benzylpenicillin, Bupropion, Buspirone, Carbamazepine, Cetirizine, Cimetidine, Ciprofloxacin, Citalopram, Clonidine, Clozapine, Contac, Dexamfetamine, Dexmethylphenidate, Dextromethorphan, Diazepam, Dimetapp, Diphenhydramine, Donepezil, Drospirenone with ethinylestradiol, Ergocalciferol, Escitalopram, Excedrin, Fish oil, Fluoxetine, Fluvoxamine, Guaifenesin, Guanfacine, Haloperidol, Ibuprofen, Imipramine, Lamotrigine, Lansoprazole, Levoceterizine, Lisdexamphetamine, Loratadine, Lorazepam, Melatonin, Methylphenidate, Midazolam, Minocycline, Modafinil, Mupirocin, Naproxen, Obetrol, Olanzapine, Omega-3 TG, Omeprazole, Ondansetron, Oxcarbazepine, Paliperidone, Paracetamol, Pediacare, Phenobarbital, Phenylephrine, Phenytoin, Promethazine with codeine, Propranolol, Pseudoephedrine, Risperidone, Sertraline, Simvastatin, Statins, Topiramate, Trazodone, Tricyclic AD, Valproate, Venlafaxine, Ziprasidone, and Zonisamide.

454. The kit of claim 442, wherein the at least one compound and the at least one agent are co-formulated.

455. The kit of claim 454, wherein the at least one agent is selected from wherein the at least one agent is selected from an antipsychotic, a selective serotonin reuptake inhibitor, a central sympathomimetic, an imidazoline receptor agonists, a propionic acid derivative, a benzodiazepine, sympathomimetics, a fatty acid derivative, a vitamin or multivitamin (with or without minerals), a piperazine derivative, an anilide, a lipid modifying agent, an aminoalkyl ether analogue, a macrolide, a melatonin receptor agonist, a penicillin derivative, a tetracycline analogue, an expectorant, an antihistamine, an azaspirodecanedione derivative, a central acting agent, a carboxamide, an opium alkaloid or derivative, an antidepressant, an antiepileptic, a beta blocker, a psychostimulant, a proton pump inhibitor, a 5HT3 antagonist, a vitamin D analogue, a diazepam, an indole derivative, an HMG CoA reductase inhibitor,

a topical antibiotic, a progesterone analogue, an estrogen analogue, an angiotensin-converting enzyme inhibitor, an anesthetic, an antifungal, an antidiarrheal, an oxazepine, a thiazepine, a vaccine, a sulfonamide, a leukotriene receptor antagonist, a lincosamide, a neuroamidase inhibitor, a non-selective monoamine reuptake inhibitor, and a salicylic acid analogue.

456. The kit of claim 455, wherein the at least one agent is selected from Aripiprazole, Acetaminophen, Acetylcarnitine, Acetylsalicylic acid, Alprazolam, Amitriptyline, Amoxicillin, Augmentin, Azithromycin, Baclofen, Benzylpenicillin, Bupropion, Buspirone, Carbamazepine, Cetirizine, Cimetidine, Ciprofloxacin, Citalopram, Clonidine, Clozapine, Contac, Dexamfetamine, Dexmethylphenidate, Dextromethorphan, Diazepam, Dimetapp, Diphenhydramine, Donepezil, Drospirenone with ethinylestradiol, Ergocalciferol, Escitalopram, Excedrin, Fish oil, Fluoxetine, Fluvoxamine, Guaifenesin, Guanfacine, Haloperidol, Ibuprofen, Imipramine, Lamotrigine, Lansoprazole, Levoceterizine, Lisdexamfetamine, Loratadine, Lorazepam, Melatonin, Methylphenidate, Midazolam, Minocycline, Modafinil, Mupirocin, Naproxen, Obetrol, Olanzapine, Omega-3 TG, Omeprazole, Ondansetron, Oxcarbazepine, Paliperidone, Paracetamol, Pediacare, Phenobarbital, Phenylephrine, Phenytoin, Promethazine with codeine, Propranolol, Pseudoephedrine, Risperidone, Sertraline, Simvastatin, Statins, Topiramate, Trazodone, Tricyclic AD, Valproate, Venlafaxine, Ziprasidone, and Zonisamide.

457. The kit of claim 442, wherein the at least one compound and the at least one agent are co-packaged.

458. The kit of claim 457, wherein the at least one agent is selected from wherein the at least one agent is selected from an antipsychotic, a selective serotonin reuptake inhibitor, a central sympathomimetic, an imidazoline receptor agonists, a propionic acid derivative, a benzodiazepine, sympathomimetics, a fatty acid derivative, a vitamin or multivitamin (with or without minerals), a piperazine derivative, an anilide, a lipid modifying agent, an aminoalkyl ether analogue, a macrolide, a melatonin receptor agonist, a penicillin derivative, a tetracycline analogue, an expectorant, an antihistamine, an azaspirodecanedione derivative, a central acting agent, a carboxamide, an opium alkaloid or derivative, an antidepressant, an antiepileptic, a beta blocker, a psychostimulant, a proton pump inhibitor, a 5HT3 antagonist, a vitamin D analogue, a diazepam, an indole derivative, an HMG CoA reductase inhibitor, a topical antibiotic, a progesterone analogue, an estrogen analogue, an angiotensin-converting enzyme inhibitor, an anesthetic, an antifungal, an antidiarrheal, an oxazepine, a thiazepine, a vaccine, a sulfonamide, a leukotriene receptor antagonist, a lincosamide, a neuroamidase inhibitor, a non-selective monoamine reuptake inhibitor, and a salicylic acid analogue.

459. The kit of claim 458, wherein the at least one agent is selected from Aripiprazole, Acetaminophen, Acetylcarnitine, Acetylsalicylic acid, Alprazolam, Amitriptyline, Amoxicillin, Augmentin,

Azithromycin, Baclofen, Benzylpenicillin, Bupropion, Buspirone, Carbamazepine, Cetirizine, Cimetidine, Ciprofloxacin, Citalopram, Clonidine, Clozapine, Contac, Dexamfetamine, Dexmethylphenidate, Dextromethorphan, Diazepam, Dimetapp, Diphenhydramine, Donepezil, Drospirenone with ethinylestradiol, Ergocalciferol, Escitalopram, Excedrin, Fish oil, Fluoxetine, Fluvoxamine, Guaifenesin, Guanfacine, Haloperidol, Ibuprofen, Imipramine, Lamotrigine, Lansoprazole, Levoceterizine, Lisdexamfetamine, Loratadine, Lorazepam, Melatonin, Methylphenidate, Midazolam, Minocycline, Modafinil, Mupirocin, Naproxen, Obetrol, Olanzapine, Omega-3 TG, Omeprazole, Ondansetron, Oxcarbazepine, Paliperidone, Paracetamol, Pediacare, Phenobarbital, Phenylephrine, Phenytoin, Promethazine with codeine, Propranolol, Pseudoephedrine, Risperidone, Sertraline, Simvastatin, Statins, Topiramate, Trazodone, Tricyclic AD, Valproate, Venlafaxine, Ziprasidone, and Zonisamide.

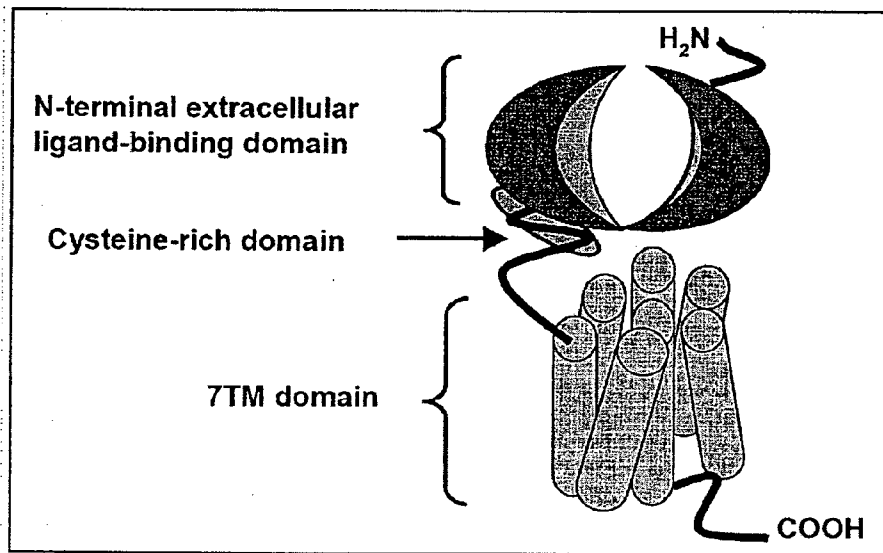


FIGURE 1

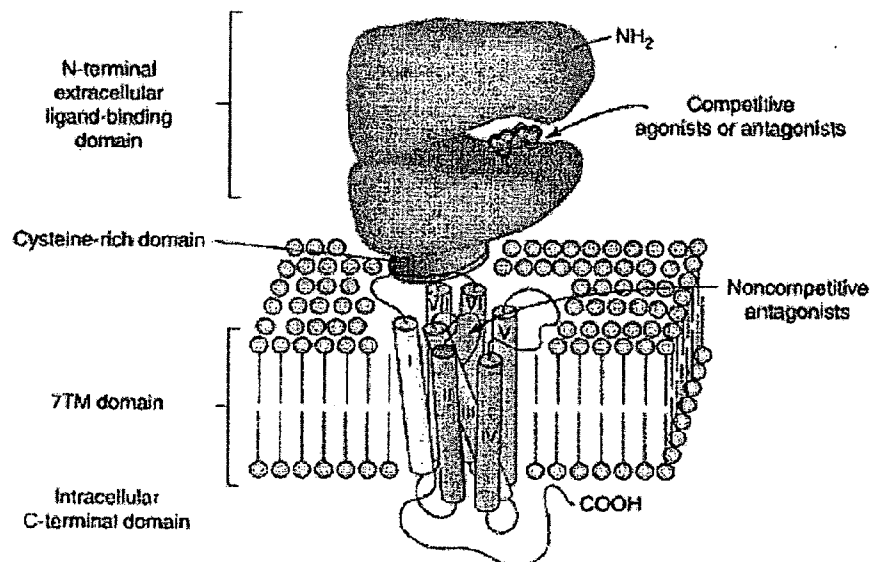


FIGURE 2

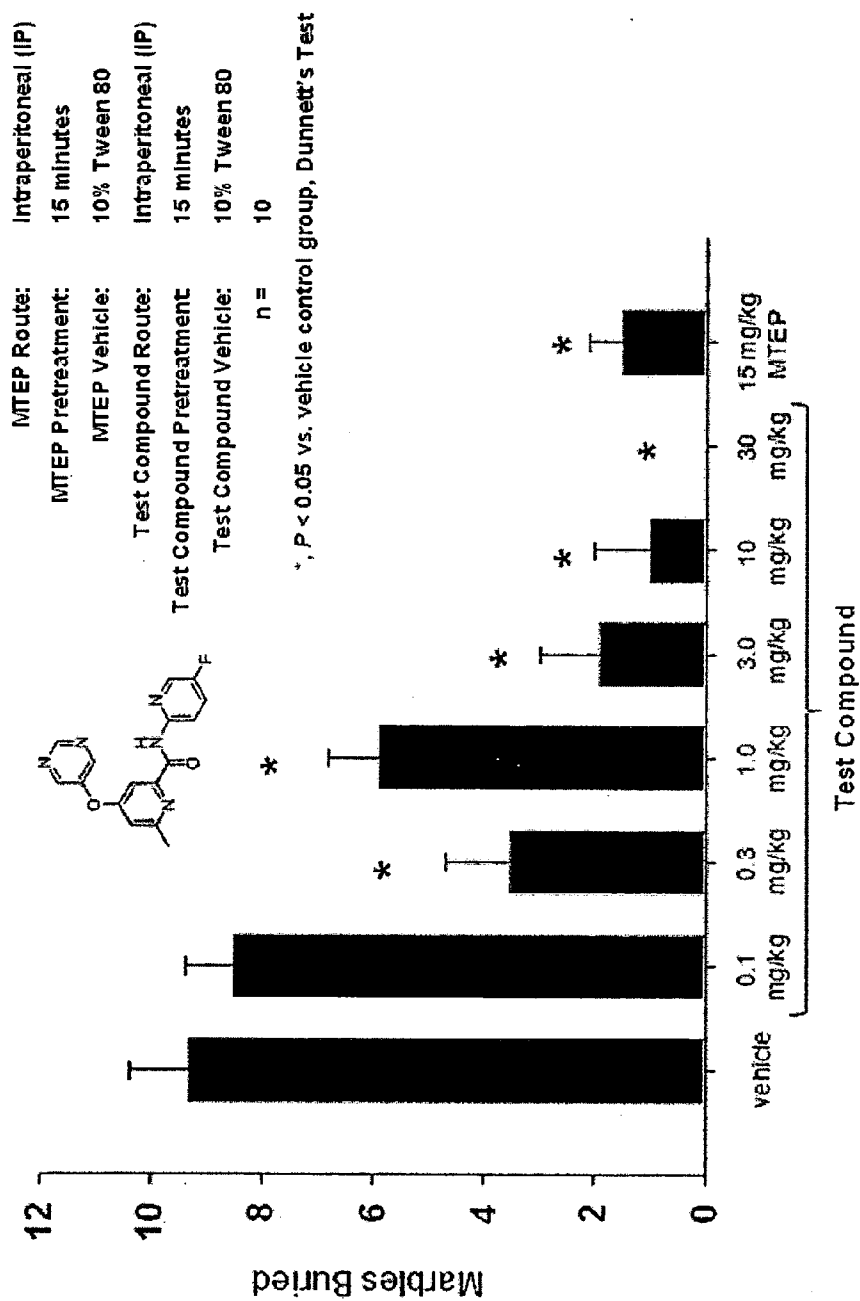


Figure 3

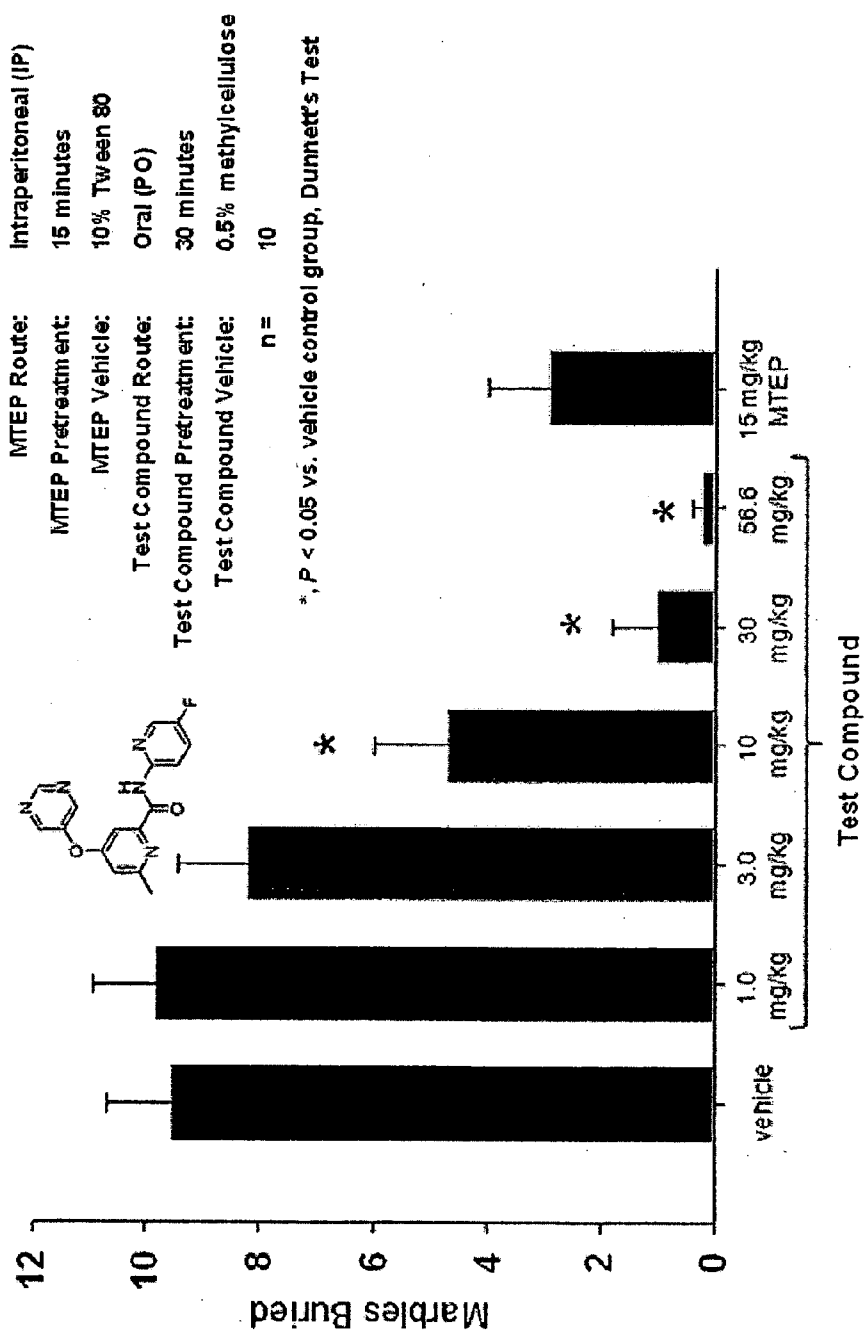
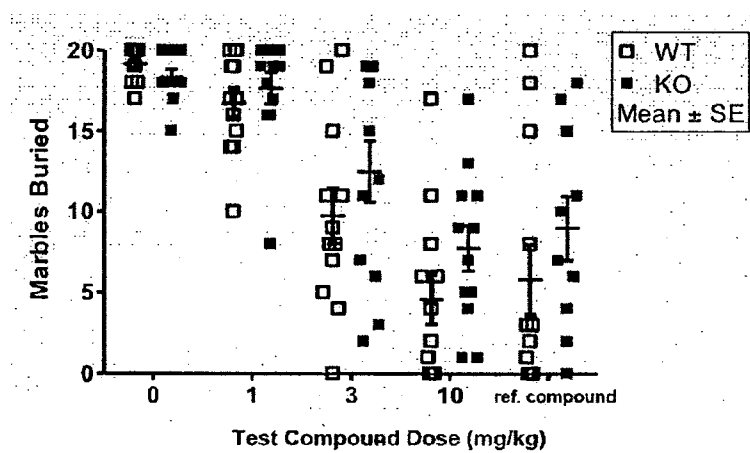
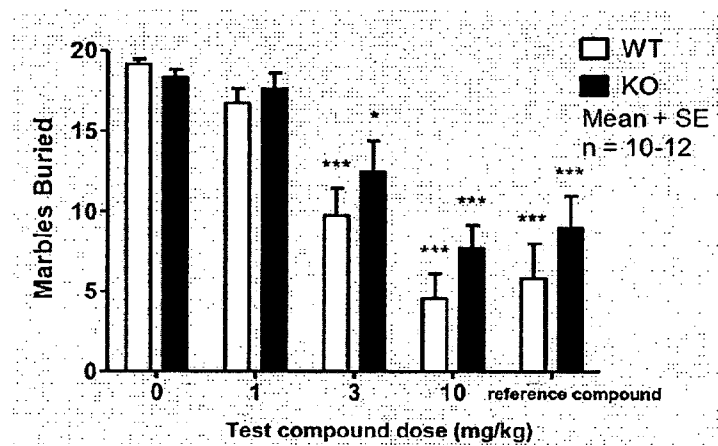
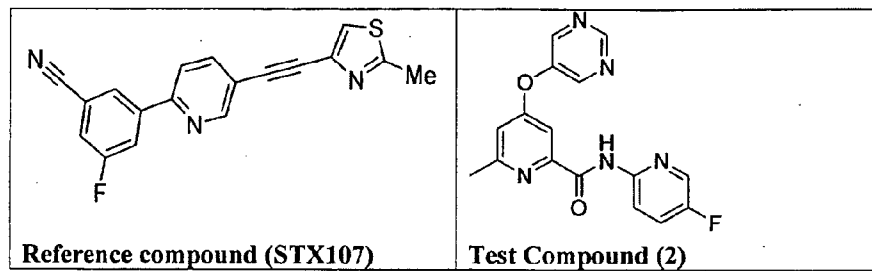


Figure 4

Fig. 4 (con't)



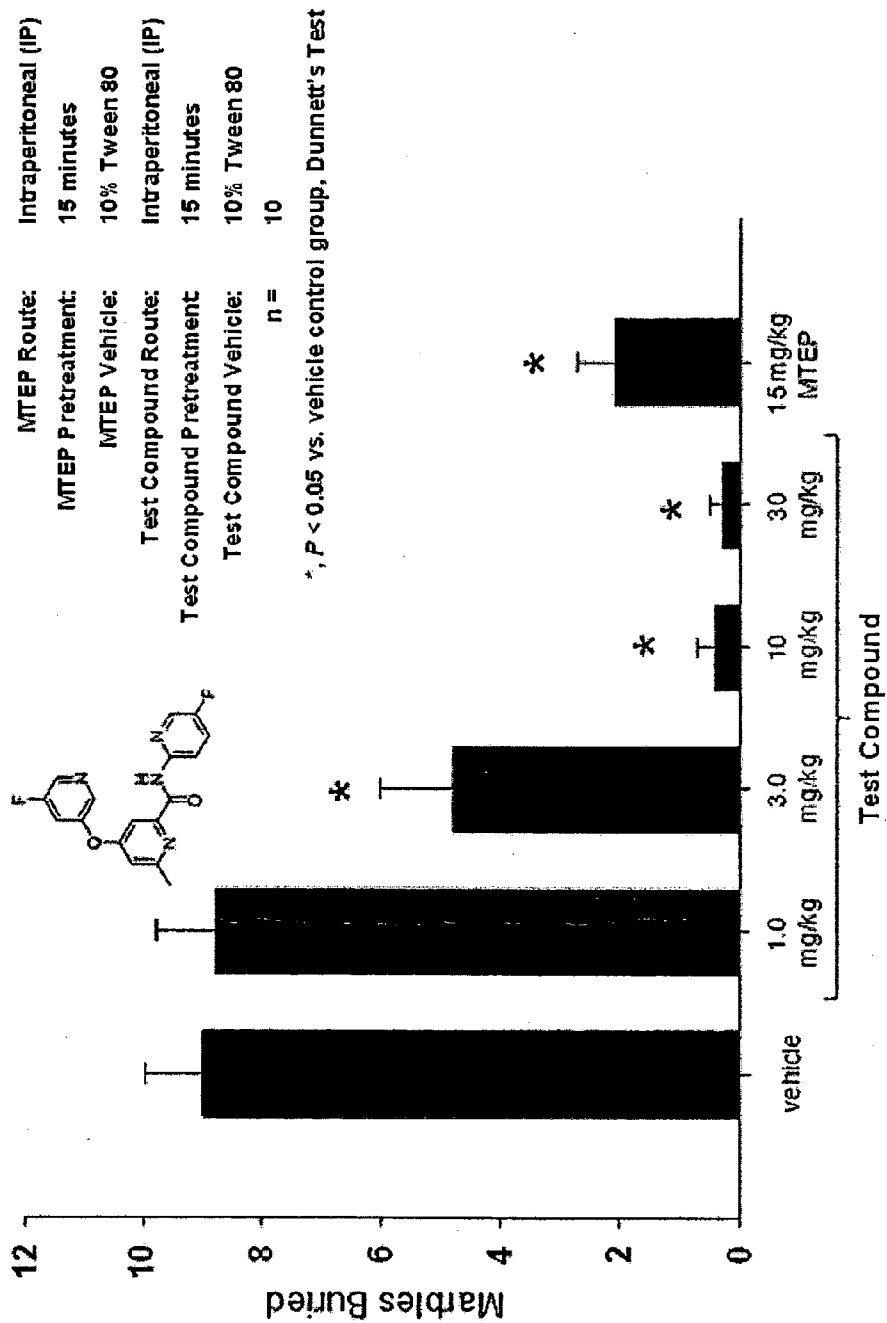


Figure 5

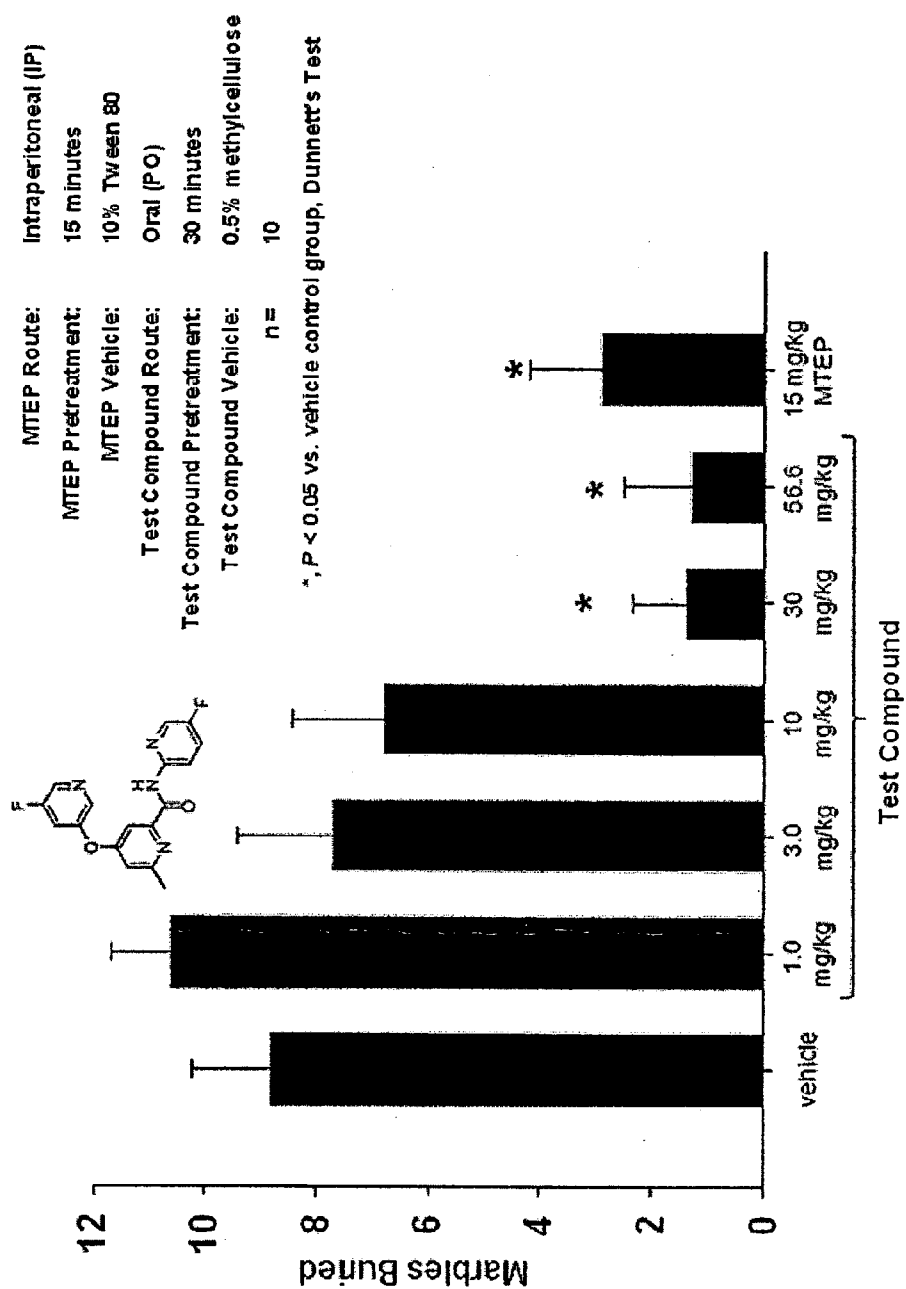


Figure 6

Fig. 6 (con't)

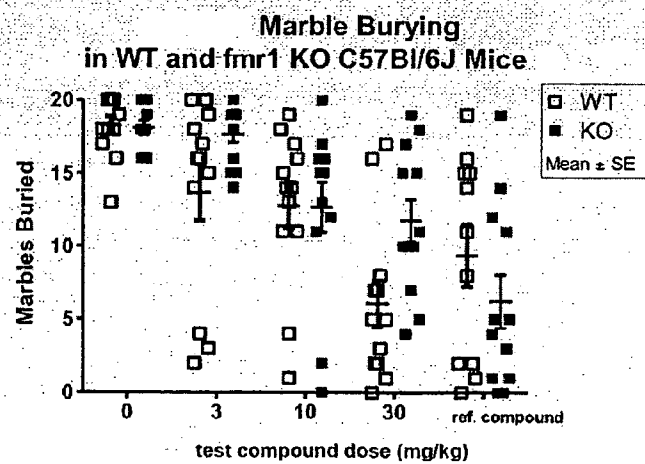
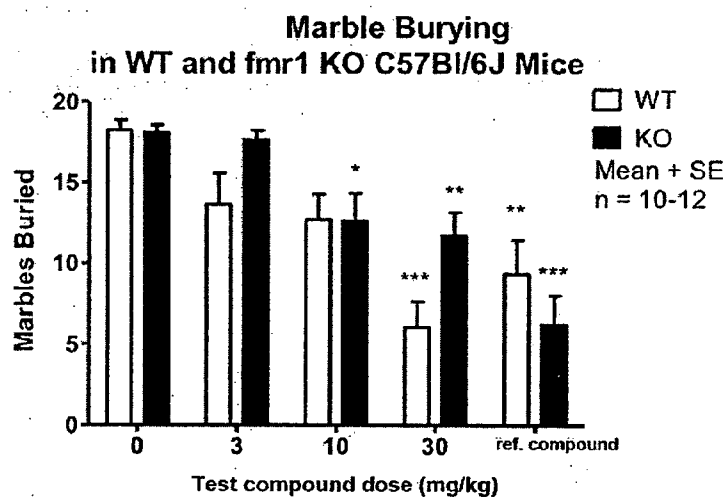
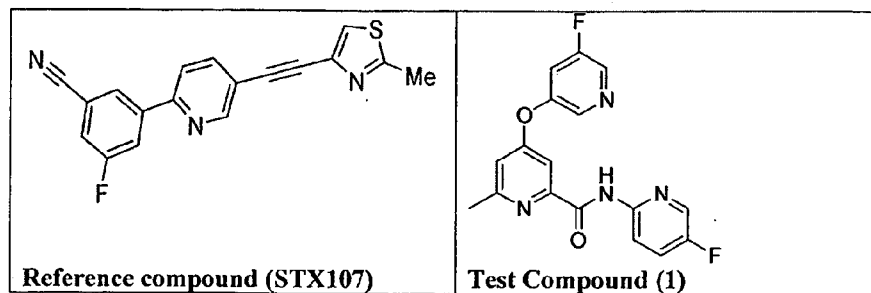


Fig. 7A

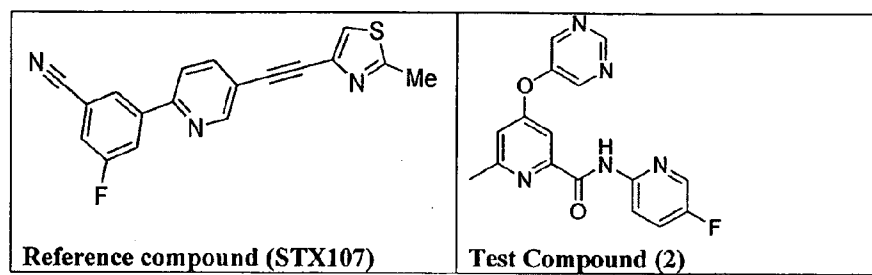
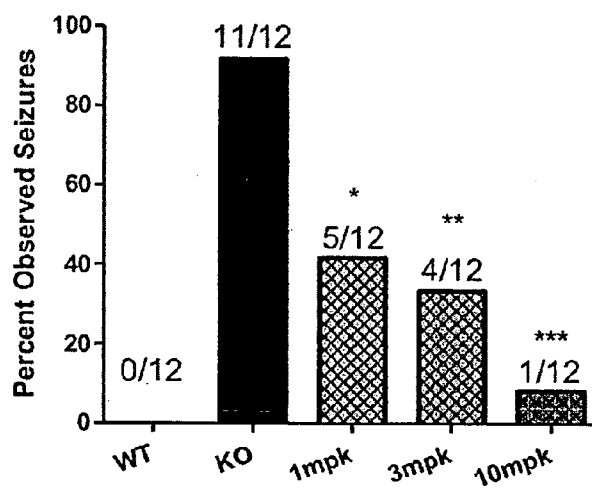
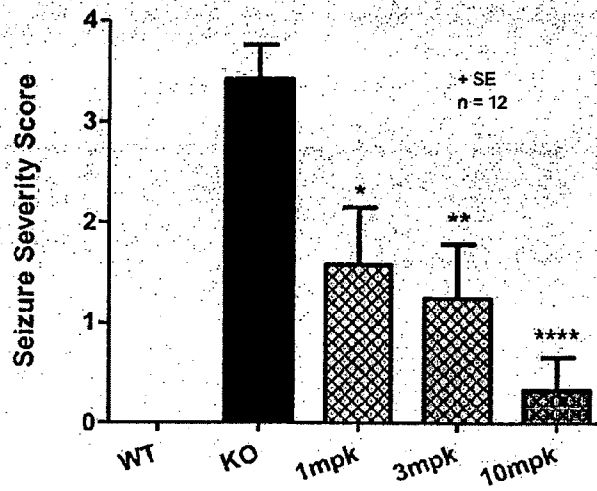


Fig. 7B



SSS	Type of Seizure
1	Wild running (WR)
2	Clonic seizure
3	Tonic seizure
4	Respiratory arrest

Fig. 7C



SSS	Type of Seizure
1	Wild running (WR)
2	Clonic seizure
3	Tonic seizure
4	Respiratory arrest

Fig. 8A

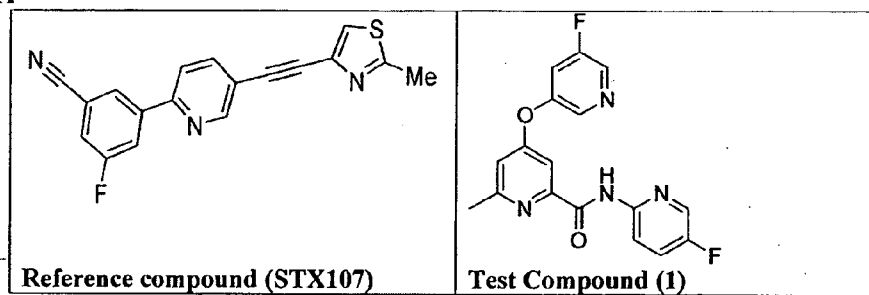
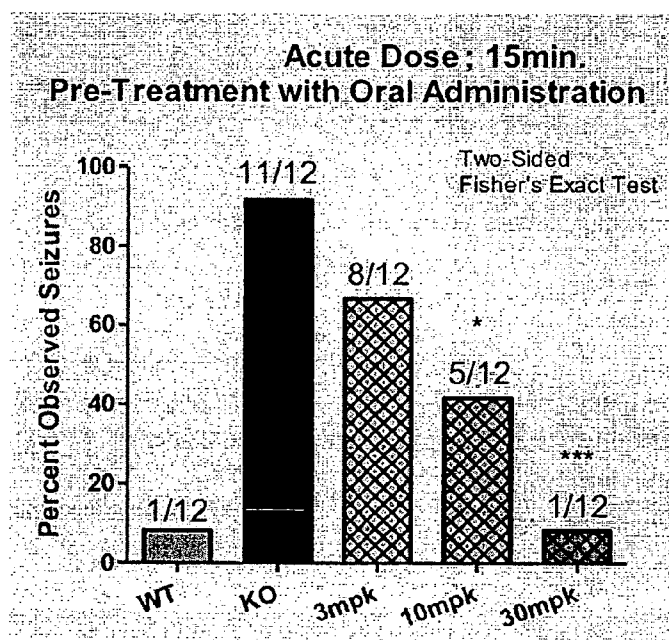
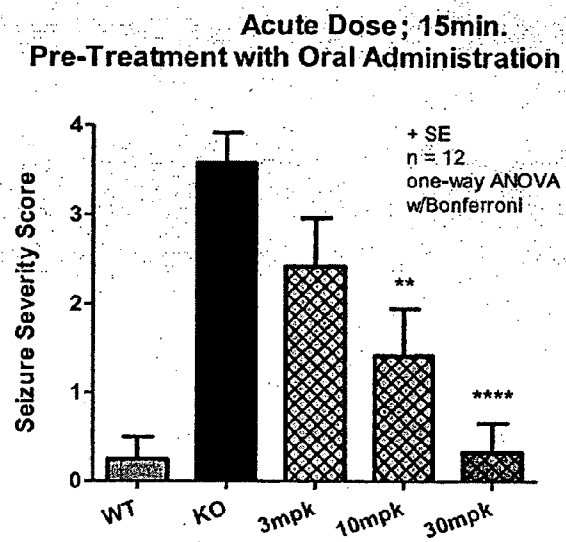


Fig. 8B



SSS	Type of Seizure
1	Wild running (WR)
2	Clonic seizure
3	Tonic seizure
4	Respiratory arrest

Fig. 8C



SSS	Type of Seizure
1	Wild running (WR)
2	Clonic seizure
3	Tonic seizure
4	Respiratory arrest

Fig. 9A

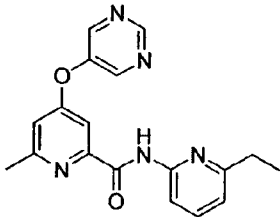
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Key Data	
MW	335
cLogP	2.80
mGluR5 IC ₅₀ (nM)	11 (n=2)
Protein Binding (percent bound)	
Human PPB	96.6
Rat PPB	97.3
CYP450 Inhibition (IC₅₀ values in μM)	
CYP3A4	> 30
CYP2D6	> 30
CYP2C9	1.8
CYP1A2	0.89

Fig. 9B

Rat PK Data	
half-life	404
MRT	80
Clearance	43.8
V _{ss}	6.6
PO C _{max}	2250
Bioavailability	39

Fig. 9C

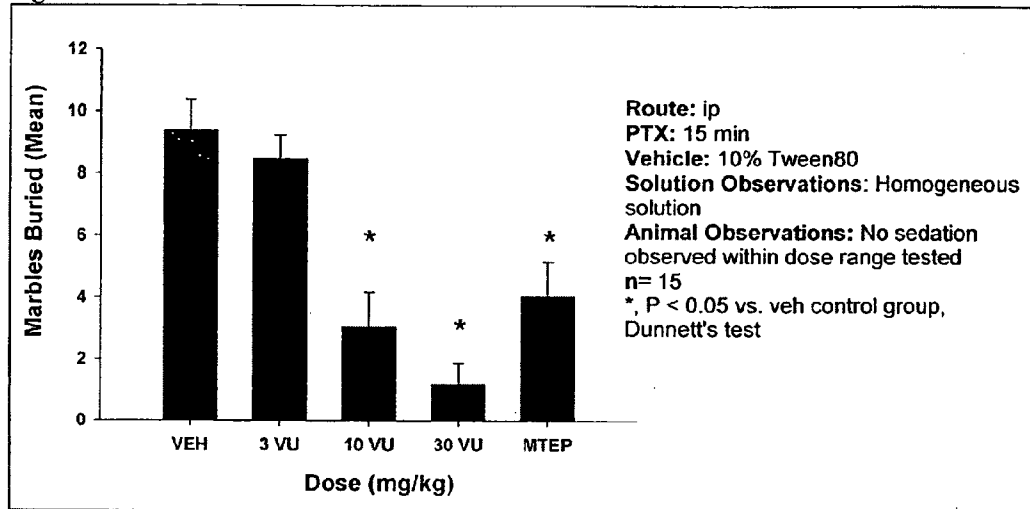


Fig. 10A

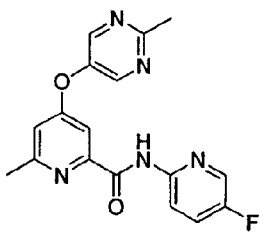
Structure (Test Compound 4)		
<i>Calculated Properties</i>		
MW	cLogP	339
<i>In Vitro Pharmacology</i>		
mGluR5 IC ₅₀ (nM)		36 (n=2)
<i>Protein Binding (percent bound)</i>		
Human Plasma	Mouse Brain	
<i>CYP450 Inhibition Profile (IC₅₀ values in μM)</i>		
3A4	2D6	
2C9	1A2	
<i>Rat IV PK (1.0 mg/kg)</i>		
half-life (minutes)		229
clearance (mL/min/kg)		
V _{ss} (L/kg)		1.2
<i>Rat PO Snapshot PK (10 mg/kg – one hour time point)</i>		
systemic plasma concentration (nM)		4820
brain concentration (nM)		3220

Fig. 10B

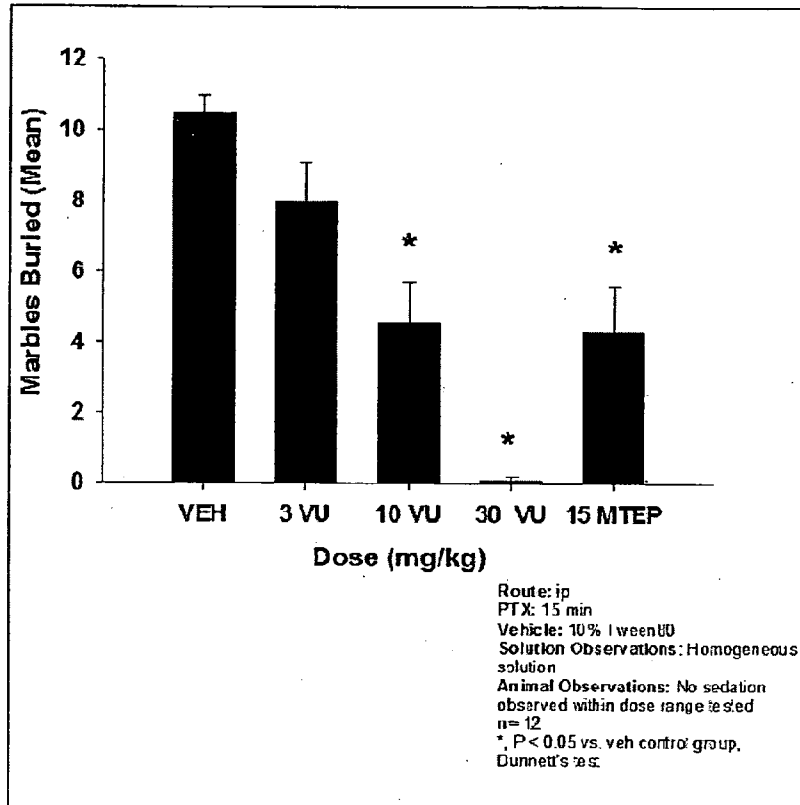
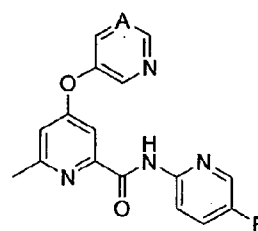
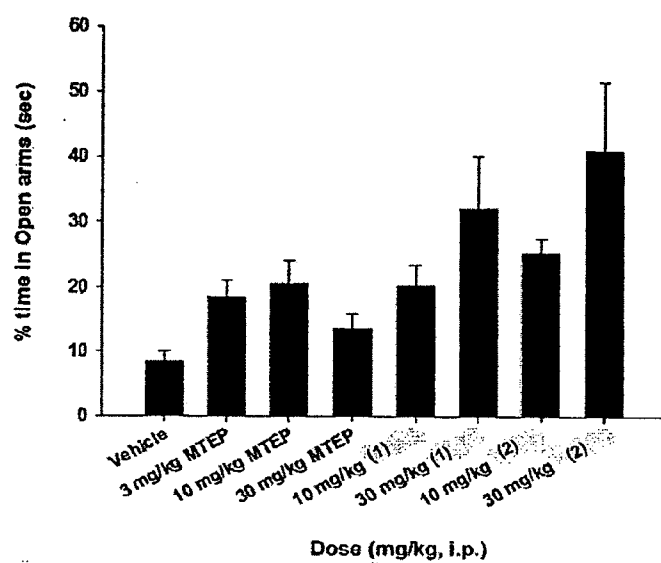
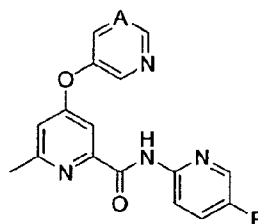
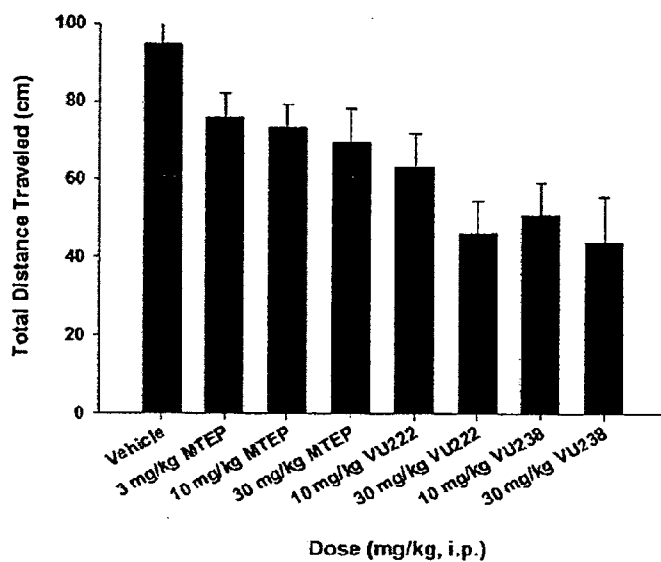


Fig. 11



- (1) A = CF
(2) A = N



- (1) A = CF
(2) A = N