Title: NAPHTHYRIDINONE ANALOGS AS MGLUR5 POSITIVE ALLOSTERIC MODULATORS

Abstract: In one aspect, the invention relates to naphthyridinone analogs, derivatives thereof, and related compounds, which are useful as positive 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.
NAPHTHYRIDINONE ANALOGS AS MGLUR5 POSITIVE ALLOSTERIC MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Application No. 61/428,746, filed December 30, 2010, which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Glutamate (L-glutamic acid) is the major excitatory transmitter in the mammalian central nervous system, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlus) belong to family C (also known as family 3) of the G-protein-coupled receptors (GPCRs). They are characterized by a seven transmembrane (7TM) cc-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 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 Gccq, a process that results in 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 Gcci, 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 neurotransmitter release.

[0003] Without wishing to be bound by a particular theory, metabotropic glutamate receptors, including mGluR5, have been implicated in a wide range of biological functions, indicating a potential role for the mGluR5 receptor in a variety of disease processes in mammals. Ligands of metabotropic glutamate receptors can be used for the treatment or prevention of acute and/or chronic neurological and/or psychiatric disorders associated with glutamate dysfunction, such as psychosis, schizophrenia, age-related cognitive decline, and the like. Further, 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 Fmrl knockout mouse have identified a connection between the fragile X phenotype and mGluR signaling.

[0004] The identification of small molecule mGluR agonists 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 agonists were designed as analogs of glutamate, they typically lack the 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 agonists lack selectivity among the various mGluRs.

[0005] Selective positive allosteric modulators ("PAMs") are compounds that do not directly activate receptors by themselves, but binding of these compounds potentiates the response of the receptor to glutamate or other orthosteric agonists by increasing the affinity of an orthosteric agonist at the orthosteric binding site. PAMs are thus an attractive mechanism for enhancing appropriate physiological receptor activation.

[0006] Unfortunately, there is a scarcity of selective positive allosteric modulators for the mGluR5 receptor. Further, conventional mGluR5 receptor modulators typically lack satisfactory aqueous solubility and exhibit poor oral bioavailability. Therefore, there remains a need for methods and compositions that overcome these deficiencies and that effectively provide selective positive allosteric modulators for the mGluR5 receptor.

SUMMARY

[0007] 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 positive allosteric modulators (i.e., potentiatior) of the metabotropic glutamate receptor subtype 5 (mGluR5), methods of making same, pharmaceutical compositions comprising same, and methods of treating neurological and psychiatric disorders associated with glutamate dysfunction using same.

[0008] Disclosed are compounds having a structure represented by a formula:

![Chemical Structure](image)

wherein each $\cdots$ is independently an optional covalent bond, wherein valence is satisfied;
wherein one of \( Y^1 \) and \( Y^2 \) is \( N \), and the other is \( C-R^{3a} \); wherein one of \( Z^1 \) and \( Z^2 \) is \( C-L-Ar^1 \), and the other is \( C-R^{1b} \); wherein \( L \) is \(-0-C(R^{1a}R^{1b})-\) or \(-C(R^{1a}R^{1b})-0;\) wherein \( Ar^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, \( C1-C4 \) alkyl, and \( C1-C4 \) alkyloxy, or \( Ar^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, \( C1-C4 \) alkyl, and \( C1-C4 \) alkyloxy; wherein each of \( R^{1a} \) and \( R^{1b} \) is independently selected from hydrogen and \( C1-C4 \) alkyl; wherein \( R^2 \) is selected from hydrogen; \( C1-C6 \) alkyl; \( (C1-C6 \) alkyloxy) \( Cl-C6 \) alkyl; \( C3-C8 \) cycloalkyl; \( (C3-C8 \) cycloalkyl) \( C1-C6 \) alkyl; \( C2-C5 \) heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, \( C1-C4 \) alkyl, and \( C1-C4 \) alkyloxy; \( (C1-C2 \) alkyl) phenyl with 0-3 substituents selected from halogen, cyano, \( C1-C4 \) alkyl, and \( C1-C4 \) alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, \( C1-C4 \) alkyl, and \( C1-C4 \) alkyloxy; wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and \( C1-C4 \) alkyl; wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and \( C1-C4 \) alkyl, or \( R^{3a} \) and \( R^{3b} \) are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( R^{4a} \) is selected from hydrogen and \( C1-C4 \) alkyl; wherein \( R^{4b} \), when present, is selected from hydrogen and \( C1-C4 \) alkyl, or \( R^{4a} \) and \( R^{4b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein \( R^{5a} \) is selected from hydrogen and \( C1-C4 \) alkyl; wherein \( R^{5b} \), when present, is selected from hydrogen and \( C1-C4 \) alkyl, or \( R^{5a} \) and \( R^{5b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein \( R^{4a} \) and \( R^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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.

[0009] The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined herein and a pharmaceutically acceptable carrier or excipient. Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.
Furthermore, the invention relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as described herein.

Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:

![Chemical Structure]

wherein $R^{3a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein $R^{3b}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or $R^{3a}$ and $R^{3b}$ are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein $R^{4a}$ is selected from hydrogen and C1-C4 alkyl; wherein $R^{5a}$ is selected from hydrogen and C1-C4 alkyl; and wherein $R^{4a}$ and $R^{5a}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, (b) halogenating to yield a compound having a structure represented by a formula:

![Chemical Structure]

wherein X is a halogen, and (c) reacting with a compound having a structure represented by a formula:

![Chemical Structure]

wherein $Ar^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or $Ar^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and wherein each of $R^{1a}$ and $R^{1b}$ is independently selected from hydrogen and C1-C4 alkyl.

Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:
wherein \( R^1 \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^2 \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^3 \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( R^3 \) and \( R^3 \) are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( R^4 \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^4 \) is selected from hydrogen and C1-C4 alkyl, or \( R^4 \) and \( R^4 \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein \( R^5 \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^5 \) is selected from hydrogen and C1-C4 alkyl, or \( R^5 \) and \( R^5 \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein \( R^6 \) and \( R^6 \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) reacting with \( \text{Ar}^1 \text{OH} \), wherein \( \text{Ar}^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or \( \text{Ar}^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy.

Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:

![Image](image_url)

wherein \( X^2 \) is halogen; wherein \( R \) is cyano or ester; wherein \( \text{Ar}^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or \( \text{Ar}^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein \( R^3 \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; and wherein \( R^3 \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, and (b) coupling with an allyl(trialkyl)tin reagent having a structure represented by a formula:
wherein \( R^4 \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^5 \) is selected from hydrogen and C1-C4 alkyl; and wherein \( R^4 \) and \( R^5 \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl.

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

\[
\begin{array}{c}
\text{X}^1 \\
\text{R}^{3a} \\
\text{R}^{3b} \\
\text{O} \\
\text{R}^{4a} \\
\text{R}^{5a} \\
\end{array}
\]

wherein wherein \( X^1 \) is halogen; wherein \( R \) is alkyl; wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{4a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^{5a} \) is selected from hydrogen and C1-C4 alkyl; and wherein \( R^{4a} \) and \( R^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) cyclizing with \( \text{H}_2\text{NPMB} \).

[0015] Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:

\[
\begin{array}{c}
\text{R}^{3a} \\
\text{R}^{3b} \\
\text{O} \\
\text{R} \\
\end{array}
\]

wherein \( R \) is alkyl; wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; and wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, and (b) cyclizing with \( \text{H}_2\text{NPMB} \).

[0016] Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:
wherein \( R \) is alkyl; wherein \( \text{Ar}^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or \( \text{Ar}^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of \( R^{1a} \) and \( R^{1b} \) is independently selected from hydrogen and C1-C4 alkyl; wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{3a} \) is selected from hydrogen and C1-C4 alkyl; and wherein \( R^{3a} \) and \( R^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) cyclization in the presence of \( \text{H}_2\text{NR}^2 \), wherein \( R^2 \) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocycl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, to yield a compound having a structure represented by a formula:

\[
\begin{align*}
\text{Ar}^1 & \quad R^{1a} \quad R^{1b} \\
& \quad R^{3a} \quad R^{3b} \\
& \quad R^{4a} \quad R^{5a} \\
& \quad R^2
\end{align*}
\]

[0017] Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:

\[
\begin{align*}
& \quad R^{1a} \quad R^{1b} \\
& \quad R^{3a} \quad R^{3b} \\
& \quad R^{4a} \quad R^{5a} \\
& \quad R^2
\end{align*}
\]

wherein each \( R \) is independently alkyl; wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( R^{3a} \) and \( R^{3b} \) are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( R^{4a} \) is selected from hydrogen.
and C1-C4 alkyl; wherein R\textsuperscript{5a} is selected from hydrogen and C1-C4 alkyl; and wherein R\textsuperscript{4a} and R\textsuperscript{5a} are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) cyclization in the presence of H\textsubscript{2}N\textsubscript{R}\textsuperscript{2} to yield a compound having a structure represented by a formula:

\[
\begin{align*}
\text{wherein } R^2 \text{ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyl)O-C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.}
\end{align*}
\]

[0018] Also disclosed are synthetic methods comprising the steps of: (a) providing a compound having a structure represented by a formula:

\[
\begin{align*}
\text{wherein } R\textsuperscript{3a} \text{ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein } R\textsuperscript{3b} \text{ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or } R\textsuperscript{3a} \text{ and } R\textsuperscript{3b} \text{ are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein } R\textsuperscript{4a} \text{ is selected from hydrogen and C1-C4 alkyl; wherein } R\textsuperscript{5a} \text{ is selected from hydrogen and C1-C4 alkyl; and wherein } R\textsuperscript{4a} \text{ and } R\textsuperscript{5a} \text{ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, (b) halogenating to yield a compound having a structure represented by a formula:}
\end{align*}
\]

\[
\begin{align*}
\text{wherein } X \text{ is a halogen, and (c) reacting with a compound having a structure represented by a formula:}
\end{align*}
\]
wherein \( \text{Ar}^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or \( \text{Ar}^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and wherein each of \( \text{R}^{1a} \) and \( \text{R}^{1b} \) is independently selected from hydrogen and C1-C4 alkyl.

[0019] Also disclosed are methods for the treatment of a neurological and/or psychiatric disorder associated with glutamate dysfunction 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:

![Chemical structure](image)

wherein each \( \ldots \) is independently an optional covalent bond, wherein valence is satisfied; wherein one of \( Y^1 \) and \( Y^2 \) is N, and the other is C-R\(^3\); wherein one of \( Z^1 \) and \( Z^2 \) is C-L-Ar\(^1\), and the other is C-R\(^3\); wherein \( L \) is -0-C(\( R^{1a} R^{1b} \)) or -C(\( R^{1a} R^{1b} \))0-; wherein \( \text{Ar}^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or \( \text{Ar}^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein each of \( \text{R}^{1a} \) and \( \text{R}^{1b} \) is independently selected from hydrogen and C1-C4 alkyl; wherein \( \text{R}^2 \) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein \( \text{R}^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( \text{R}^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( \text{R}^{3a} \) and \( \text{R}^{3b} \) are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( \text{R}^{4a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( \text{R}^{4b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( \text{R}^{4a} \) and \( \text{R}^{4b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;
wherein \( R^{3a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^{5b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( R^{3a} \) and \( R^{5b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein \( R^{4a} \) and \( R^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0020] Also disclosed are methods for the treatment of a disorder of uncontrolled cellular proliferation 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:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}^{2} \\
\text{R}^{3a} \\
\text{R}^{5a} \\
\text{R}^{5b} \\
\text{R}^{4a} \\
\text{Z}^{1} \\
\text{Z}^{2} \\
\end{array}
\]

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of \( Y^{1} \) and \( Y^{2} \) is N, and the other is C-\( R^{3a} \); wherein one of \( Z^{1} \) and \( Z^{2} \) is C-L-Ar \(^{1}\), and the other is C-\( R^{3b} \); wherein \( L = -0-(R^{1}aR^{1b})- \) or \(-0-((R^{1}aR^{1b})-0-\); wherein \( Ar^{1} \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or \( Ar^{1} \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein each of \( R^{1a} \) and \( R^{1b} \) is independently selected from hydrogen and C1-C4 alkyl; wherein \( R^{2} \) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocycyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( R^{3a} \) and \( R^{3b} \) are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( R^{4a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^{4b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( R^{4a} \) and \( R^{4b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;
wherein R³ is selected from hydrogen and C1-C4 alkyl; wherein R⁵b, when present, is selected from hydrogen and C1-C4 alkyl, or R³ and R⁵b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R⁴b and R⁵a are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0021] Additionally, the invention relates to a compound as defined herein for use in the treatment or in the prevention of disorders of uncontrolled cellular proliferation.

[0022] Also disclosed are methods for potentiation of 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:

\[
\begin{align*}
&\text{wherein each} \quad \cdots \quad \text{is independently an optional covalent bond, wherein valence is satisfied;} \\
&\text{wherein one of } Y_1 \text{ and } Y_2 \text{ is } N, \text{ and the other is } C-R_3^a; \text{ wherein one of } Z_1 \text{ and } Z_2 \text{ is } C-L-Ar^1, \text{ and the other is } C-R_3^b; \text{ wherein } L \text{ is } -0-C(R^1_{1a}R^1_{1b})- \text{ or } -C(R^1_{1a}R^1_{1b})-0--; \text{ wherein } Ar^1 \text{ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar}^1 \text{ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of } R^1_{1a} \text{ and } R^1_{1b} \text{ is independently selected from hydrogen and C1-C4 alkyl; wherein } R^2 \text{ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein } R^3a \text{ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein } R^3b \text{ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or } R^3a \text{ and } R^3b \text{ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein } R^4b \text{ is selected from hydrogen and C1-C4 alkyl; wherein } R^4b, \text{ when present, is selected from hydrogen and C1-C4 alkyl, or } R^4a \text{ and } R^4b \text{ are covalently bonded and, together with the }
\end{align*}
\]
intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R³⁸ is selected from hydrogen and C1-C4 alkyl; wherein R₄⁰, when present, is selected from hydrogen and C1-C4 alkyl, or R³⁸ and R₄⁰ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R⁴⁰ and R⁵⁵ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0023] Also disclosed are methods for partial agonism of 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 each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y¹ and Y² is N, and the other is C-R³⁸; wherein one of Z¹ and Z² is C-L-Ar ¹, and the other is C-R³⁸; wherein L is -0-C(R¹R²)- or -C(R¹R²)-0--; wherein Ar¹ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar¹ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R¹ and R² is independently selected from hydrogen and C1-C4 alkyl; wherein R² is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R³⁸ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R³⁸ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R³⁸ and R⁴⁰ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R⁴⁰ is selected from hydrogen and C1-C4 alkyl; wherein R⁴⁰, when present, is selected from hydrogen and C1-C4 alkyl, or R³⁸ and R⁴⁰ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;
wherein R^3a is selected from hydrogen and C1-C4 alkyl; wherein R^5b, when present, is selected from hydrogen and C1-C4 alkyl, or R^3a and R^5b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R^4b and R^5a are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0024] Also disclosed are methods for enhancing cognition in a mammal comprising the step of administering to the mammal an effective amount of at least one compound having a structure represented by a formula:

![Chemical Structure Image]

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y^1 and Y^2 is N, and the other is C-R^3a; wherein one of Z^1 and Z^2 is C-L-Ar^1, and the other is C-R^1b; wherein L is -0-C(R^1aR^1b)- or -C(R^1aR^1b)-0-; wherein Ar^1 is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar^1 is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R^1a and R^1b is independently selected from hydrogen and C1-C4 alkyl; wherein R^2 is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R^3a is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R^5b is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R^3a and R^5b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyln, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R^4a is selected from hydrogen and C1-C4 alkyl; wherein R^4b, when present, is selected from hydrogen and C1-C4 alkyl, or R^4a and R^4b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R^3a is selected from hydrogen and C1-C4 alkyl; wherein R^5b, when present, is
selected from hydrogen and C1-C4 alkyl, or R⁵a and R⁵b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R⁴a and R⁴b are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0025] Also disclosed are methods for modulating mGluR5 activity in a mammal comprising the step of administering to the mammal an effective amount of at least one compound having a structure represented by a formula:

\[ \text{Structure} \]

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y¹ and Y² is N, and the other is C-R³; wherein one of Z¹ and Z² is C-L-Ar¹, and the other is C-R³; wherein L is -O-C(R¹aR¹b)- or -C(R¹aR¹b)-O--; wherein Ar¹ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxylo; and C1-C4 alkyl; wherein each of R¹a and R¹b is independently selected from hydrogen and C1-C4 alkyl; wherein R² is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein R³ is selected from hydroen, halogen, cyano, and C1-C4 alkyl; wherein R⁴ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R³a and R³b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R⁴a is selected from hydrogen and C1-C4 alkyl; wherein R⁴b, when present, is selected from hydrogen and C1-C4 alkyl, or R⁴a and R⁴b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R³a is selected from hydrogen and C1-C4 alkyl; wherein R³b, when present, is selected from hydrogen and C1-C4 alkyl, or R³a and R³b are covalently bonded and, together
with the intermediate carbon, comprise an optionally substituted 3- to 7-membered
spirocycloalkyl; and wherein R⁴b and R⁵a are optionally covalently bonded and, together
with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused
cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0026] 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 at least one
compound having a structure represented by a formula:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}^2 \\
\text{R}^4 \\
\text{R}^5a \\
\end{array}
\]

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied;
wherein one of Y¹ and Y² is N, and the other is C-R³a; wherein one of Z¹ and Z² is C-L-Ari, and
the other is C-R³b; wherein L is -0-C(R¹aR³b)- or -C(R¹aR³b)-0-; wherein Ar¹ is phenyl
with 0-3 substituents selected from halogen, cyano, C¹-C⁴ alkyl, and C¹-C⁴ alkyloxy, or Ar¹
is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C¹-C⁴ alkyl,
and C¹-C⁴ alkyloxy; wherein each of R¹a and R³b is independently selected from hydrogen
and C¹-C⁴ alkyl; wherein R² is selected from hydrogen; C¹-C⁶ alkyl; (C¹-C⁶ alkyloxy) C¹-
C⁶ alkyl; C³-C⁸ cycloalkyl; (C³-C⁸ cycloalkyl) C¹-C⁶ alkyl; C²-C⁵ heterocyclyl; phenyl
with 0-3 substituents selected from halogen, cyano, C¹-C⁴ alkyl, and C¹-C⁴ alkyloxy; (C¹-C²
alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C¹-C⁴ alkyl, and C¹-C⁴
alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano,
C¹-C⁴ alkyl, and C¹-C⁴ alkyloxy; wherein R³a is selected from hydrogen, halogen, cyano, and
C¹-C⁴ alkyl; wherein R³b is selected from hydrogen, halogen, cyano, and C¹-C⁴ alkyl, or R³a
and R³b are substituted on adjacent carbons and are covalently bonded and, together with the
intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-
membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R⁴a is
selected from hydrogen and C¹-C⁴ alkyl; wherein R⁴b, when present, is selected from
hydrogen and C¹-C⁴ alkyl, or R⁴a and R⁴b are covalently bonded and, together with the
intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;
wherein R⁵a is selected from hydrogen and C¹-C⁴ alkyl; wherein R⁵b, when present, is
selected from hydrogen and C¹-C⁴ alkyl, or R⁵a and R⁵b are covalently bonded and, together
with the intermediate carbon, comprise an optionally substituted 3- to 7-membered
spirocycloalkyl; and wherein R₁ and R₂ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[0027] Also disclosed are kits 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 instructions for treating a disorder associated with glutamate dysfunction.

[0028] Additionally, the invention also relates to a product comprising a compound as described herein and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of neurological and psychiatric disorders and diseases.

[0029] 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. Additionally, the invention relates to a compound as defined herein for use as a medicament, and to a compound as defined herein for use in the treatment or in the prevention of neurological and psychiatric disorders and diseases.

[0030] Also disclosed are uses 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.

[0031] 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

[0032] 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.

[0033] Figure 1 shows a schematic of the NMDA receptor.

[0034] Figure 2 shows a schematic illustrating that activation of mGluR5 potentiates NMDA receptor function.

[0035] Figure 3 illustrates allosteric modulation of mGluR5.

[0036] Figure 4 shows a representative study demonstrating the dose-dependent reversal of amphetamine-induced hyperlocomotion by a representative disclosed compound.

[0037] Figure 5 shows a representative study demonstrating the dose-dependent reversal of amphetamine-induced hyperlocomotion by a representative disclosed compound.

[0038] 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 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

[0039] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0040] 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.

[0041] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. 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 can be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0042] 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, EIZ 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.).

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0048] As used herein, the term "allosteric site" refers to a ligand binding site that is topographically distinct from the orthosteric binding site.

[0049] As used herein, the term "modulator" refers to a molecular entity (e.g., but not limited to, a ligand and a disclosed compound) that modulates the activity of the target receptor protein.

[0050] As used herein, the term "ligand" refers to a natural or synthetic molecular entity that is capable of associating or binding to a receptor to form a complex and mediate, prevent or modify a biological effect. Thus, the term "ligand" encompasses allosteric modulators, inhibitors, activators, agonists, antagonists, natural substrates and analogs of natural substrates.

[0051] As used herein, the terms "natural ligand" and "endogenous ligand" are used interchangeably, and refer to a naturally occurring ligand, found in nature, which binds to a receptor.

[0052] 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.

[0053] As used herein, the term "mGluR5 receptor positive allosteric modulator" refers to any exogenously administered compound or agent that directly or indirectly augments the activity of the mGluR5 receptor in the presence or in the absence of glutamate in an animal, in particular a mammal, for example a human. In one aspect, a mGluR5 receptor positive allosteric modulator increases the activity of the mGluR5 receptor in a cell in the presence of extracellular glutamate. The cell can be human embryonic kidney cells transfected with human mGluR5. The cell can be human embryonic kidney cells transfected with rat mGluR5. The cell can be human embryonic kidney cells transfected with a mammalian mGluR5. The term "mGluR5 receptor positive allosteric modulator" includes a compound that is a
"mGluR5 receptor allosteric potentiator" or a "mGluR5 receptor allosteric agonist," as well as a compound that has mixed activity comprising pharmacology of both an "mGluR5 receptor allosteric potentiator" and an "mGluR5 receptor allosteric agonist". The term "mGluR5 receptor positive allosteric modulator also includes a compound that is a "mGluR5 receptor allosteric enhancer."

[0054] As used herein, the term "mGluR5 receptor allosteric potentiator" refers to any exogenously administered compound or agent that directly or indirectly augments the response produced by the endogenous ligand (such as glutamate) when the endogenous ligand binds to the orthosteric site of the mGluR5 receptor in an animal, in particular a mammal, for example a human. The mGluR5 receptor allosteric potentiator binds to a site other than the orthosteric site, that is, an allosteric site, and positively augments the response of the receptor to an agonist or the endogenous ligand. In one aspect, an allosteric potentiator does not induce desensitization of the receptor, activity of a compound as an mGluR5 receptor allosteric potentiator provides advantages over the use of a pure mGluR5 receptor allosteric agonist. Such advantages can include, for example, increased safety margin, higher tolerability, diminished potential for abuse, and reduced toxicity.

[0055] As used herein, the term "mGluR5 receptor allosteric enhancer" refers to any exogenously administered compound or agent that directly or indirectly augments the response produced by the endogenous ligand in an animal, in particular a mammal, for example a human. In one aspect, the allosteric enhancer increases the affinity of the natural ligand or agonist for the orthosteric site. In another aspect, an allosteric enhancer increases the agonist efficacy. The mGluR5 receptor allosteric enhancer binds to a site other than the orthosteric site, that is, an allosteric site, and positively augments the response of the receptor to an agonist or the endogenous ligand. An allosteric enhancer has no effect on the receptor by itself and requires the presence of an agonist or the natural ligand to realize a receptor effect.

[0056] As used herein, the term "mGluR5 receptor allosteric agonist" refers to any exogenously administered compound or agent that directly activates the activity of the mGluR5 receptor in the absence of the endogenous ligand (such as glutamate) in an animal, in particular a mammal, for example a human. The mGluR5 receptor allosteric agonist binds to a site that is distinct from the orthosteric glutamate site of the mGluR5. Because it does not require the presence of the endogenous ligand, activity of a compound as an mGluR5
receptor allosteric agonist provides advantages over the use of a pure mGluR5 receptor allosteric potentiator, such as more rapid onset of action.

[0057] As used herein, the term "mGluR5 receptor neutral allosteric ligand" refers to any exogenously administered compound or agent that binds to an allosteric site without affecting the binding or function of agonists or the natural ligand at the orthosteric site in an animal, in particular a mammal, for example a human. However, a neutral allosteric ligand can block the action of other allosteric modulators that act via the same site.

[0058] 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 positive 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 agonism of metabotropic glutamate receptor activity prior to the administering step.

[0059] 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.).

[0060] 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.

[0061] 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. For example, the term "diagnosed with a need for positive 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 positive allosteric modulation of metabotropic glutamate receptor activity. For example, "diagnosed with a need for partial agonism of metabotropic glutamate receptor activity" 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 partial agonism 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 associated with glutamate dysfunction.

[0062] 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. 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.

[0063] 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 art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraural 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 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.

[0064] The term "contacting" as used herein refers to bringing a disclosed compound and a cell, 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.

[0065] 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 affects. 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.

[0066] As used herein, "kit" means a collection of at least two components constituting the kit. Together, the components constitute a functional unit for a given purpose. Individual member components may be physically packaged together or separately. For example, a kit comprising an instruction for using the kit may or may not physically include the instruction with other individual member components. Instead, the instruction can be supplied as a separate member component, either in a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation.

[0067] As used herein, "instruction(s)" means documents describing relevant materials or methodologies pertaining to a kit. These materials may include any combination of the following: background information, list of components and their availability information (purchase information, etc.), brief or detailed protocols for using the kit, trouble-shooting, references, technical support, and any other related documents. Instructions can be supplied with the kit or as a separate member component, either as a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation. Instructions can comprise one or multiple documents, and are meant to include future updates.
As used herein, the terms "therapeutic agent" include any synthetic or naturally occurring biologically active compound or composition of matter which, when administered to an organism (human or nonhuman animal), induces a desired pharmacologic, immunogenic, and/or physiologic effect by local and/or systemic action. The term therefore encompasses those compounds or chemicals traditionally regarded as drugs, vaccines, and biopharmaceuticals including molecules such as proteins, peptides, hormones, nucleic acids, gene constructs and the like. Examples of therapeutic agents are described in well-known literature references such as the Merck Index (14 th edition), the Physicians' Desk Reference (64 th edition), and The Pharmacological Basis of Therapeutics (12 th edition), and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances that affect the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. For example, the term "therapeutic agent" includes compounds or compositions for use in all of the major therapeutic areas including, but not limited to, adjuvants; anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations, anorexics, anti-inflammatory agents, anti-epileptics, local and general anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergics, antiarrhythmics, antihypertensive agents, hormones, and nutrients, antiarthritics, antiasthmatic agents, anticonvulsants, antihistamines, antinauseants, antineoplastics, antipruritics, antipyretics; antispasmosics, cardiovascular preparations (including calcium channel blockers, beta-blockers, beta-agonists and antiarrythmics), antihypertensives, diuretics, vasodilators; central nervous system stimulants; cough and cold preparations; decongestants; diagnostics; hormones; bone growth stimulants and bone resorption inhibitors; immunosuppressives; muscle relaxants; psychostimulants; sedatives; tranquilizers; proteins, peptides, and fragments thereof (whether naturally occurring, chemically synthesized or recombinantly produced); and nucleic acid molecules (polymeric forms of two or more nucleotides, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) including both double- and single-stranded molecules, gene constructs, expression vectors, antisense molecules and the like), small molecules (e.g., doxorubicin) and other biologically active macromolecules such as, for example, proteins and enzymes. The agent may be a biologically active agent used in medical, including veterinary, applications and in
agriculture, such as with plants, as well as other areas. The term therapeutic agent also includes without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of disease or illness; or substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a predetermined physiological environment.

[0069] As used herein, "EC<sub>50</sub>" is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% activation or enhancement of a biological process, or component of a process. For example, EC<sub>50</sub> can refer to the concentration of agonist that provokes a response halfway between the baseline and maximum response in an in vitro assay. For example, an EC<sub>50</sub> for mGluR5 receptor can be determined in an in vitro or cell-based assay system. Such in vitro assay systems frequently utilize a cell line that either expresses endogenously a target of interest, or has been transfected with a suitable expression vector that directs expression of a recombinant form of the target such as mGluR5. For example, the EC<sub>50</sub> for mGluR5 can be determined using human embryonic kidney (HEK) cells transfected with human mGluR5. Alternatively, the EC<sub>50</sub> for mGluR5 can be determined using human embryonic kidney (HEK) cells transfected with rat mGluR5. In another example, the EC<sub>50</sub> for mGluR5 can be determined using human embryonic kidney (HEK) cells transfected with a mammalian mGluR5.

[0070] As used herein, "IC<sub>50</sub>" 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. For example, IC<sub>50</sub> refers to the half maximal (50%) inhibitory concentration (IC) of a substance as determined in a suitable assay. For example, an IC<sub>50</sub> for mGluR5 receptor can be determined in an in vitro or cell-based assay system. Frequently, receptor assays, including suitable assays for mGluR5, make use of a suitable cell-line, e.g. a cell line that either expresses endogenously a target of interest, or has been transfected with a suitable expression vector that directs expression of a recombinant form of the target such as mGluR5. For example, the IC<sub>50</sub> for mGluR5 can be determined using human embryonic kidney (HEK) cells transfected with human mGluR5. Alternatively, the IC<sub>50</sub> for mGluR5 can be determined using human embryonic kidney (HEK) cells transfected with rat mGluR5. In another example, the IC<sub>50</sub> for mGluR5 can be determined using human embryonic kidney (HEK) cells transfected with a mammalian mGluR5.
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.

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.

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. 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 microencapsule 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 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.

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 -OCH₂CH₂O- 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(CH₂)₆CO- moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

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).

In defining various terms, "A₁," "A²," "A³," and "A⁴" 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.

The term "aliphatic" or "aliphatic group," as used herein, denotes a hydrocarbon
moiety that may be straight-chain (i.e., unbranched), branched, or cyclic (including fused,
bridging, and spirofused polycyclic) and may be completely saturated or may contain one or
more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic
groups contain 1-20 carbon atoms. Aliphatic groups include, but are not limited to, linear or
branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl,
(cycloalkeny)alkyl or (cycloalkyl)alkenyl.

The term "alkyl" as used herein is a branched or unbranched saturated
hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, w-propyl, isopropyl, n-
butyl, isobutyl, s-butyl, i-butyl, w-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. The term
alkyl group can also be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-
C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like up to and
including a C1-C24 alkyl.

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. Alternatively, the term "monohaloalkyl" specifically refers to an alkyl group that is
substituted with a single halide, e.g. fluorine, chlorine, bromine, or iodine. The term
"polyhaloalkyl" specifically refers to an alkyl group that is independently substituted with two
or more halides, i.e. each halide substituent need not be the same halide as another halide
substituent, nor do the multiple instances of a halide substituent need to be on the same
carbon. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with
one or more alkoxy groups, as described below. The term "aminoalkyl" specifically refers to
an alkyl group that is substituted with one or more amino groups. The term "hydroxyalkyl"
specifically refers to an alkyl group that is substituted with one or more hydroxy groups.
When "alkyl" is used in one instance and a specific term such as "hydroxyalkyl" is used in
another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "hydroxyalkyl" and the like.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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 —OA¹—OA² or —OA¹—(OA²)ₐ—OA³, where "a" is an integer of from 1 to 200 and A¹, A², and A³ are alkyl and/or cycloalkyl groups.

[0084] 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 (A¹A²)C=C(A³A⁴) 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 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.

[0085] 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, \(i.e.,\) C=\(\text{C}\). Examples of cycloalkenyl groups include, but are not limited to, cyclopropanenyl, 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.

[0086] 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.

[0087] 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, cyclononylnyl, 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, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

The term "aromatic group" as used herein refers to a ring structure having cyclic clouds of delocalized \( \pi \) electrons above and below the plane of the molecule, where the \( \pi \) clouds contain \((4n+2)\) \( \pi \) electrons. A further discussion of aromaticity is found in Morrison and Boyd, Organic Chemistry, (5th Ed., 1987), Chapter 13, entitled "Aromaticity," pages 477-497, incorporated herein by reference. The term "aromatic group" is inclusive of both aryl and heteroaryl groups.

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, anthracene, and the like. 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, alkylnyl, cycloalkynyl, aryl, heteroaryl, aldehyde, —NH\(_2\), 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." In addition, the aryl group can be a single ring structure or comprise multiple ring structures that are either fused ring structures or attached via one or more bridging groups such as a carbon-carbon bond. For example, 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.

The term "aldehyde" as used herein is represented by the formula —C(\( \text{O} \))H.

Throughout this specification "C(\( \text{O} \))" is a short hand notation for a carbonyl group, \( i.e., \ C=\text{O}. \)

The terms "amine" or "amino" as used herein are represented by the formula —NA\(^1\)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. A specific example of amino is —NH\(_2\).

The term "alkylamino" as used herein is represented by the formula —NH(-alkyl) where alkyl is a 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.
The term "dialkylamino" as used herein is represented by the formula —N(-alkyl)$_2$ where alkyl is a 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.

The term "carboxylic acid" as used herein is represented by the formula —C(0)OH.

The term "ester" as used herein is represented by the formula —OC(0)A$_1$ or —C(0)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 —(A$_1$$^0$C(0)A$^2$C(0))$_a$ or —(A$_1$$^0$C(0)A$^2$OC(0))$_a$, where A$_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 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.

The term "ether" as used herein is represented by the formula A$^1$A$^2$, 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 —(A$_1$$^0$O-A$^2$$^0$)$_a$—, where A$_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.

The terms "halo," "halogen," or "halide," as used herein can be used interchangeably and refer to F, Cl, Br, or I.

The terms "pseudohalide," "pseudohalogen" or "pseudohalo," as used herein can be used interchangeably and refer to functional groups that behave substantially similar to halides. Such functional groups include, by way of example, cyano, thiocyanato, azido, trifluoromethyl, trifluoromethoxy, perfluoroalkyl, and perfluoroalkoxy groups.

The term "heteroalkyl," as used herein refers to an alkyl group containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S,
wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. Heteroalkyls can be substituted as defined above for alkyl groups.

[00100] The term "heteroaryl," as used herein refers to 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, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. The heteroaryl group can be substituted or unsubstituted. The heteroaryl 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. Heteroaryl groups can be monocyclic, or alternatively fused ring systems. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, quinolyl, isoquinolyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridazinyl, pyrazinyl, benzo[1,2,3]thiadiazolyl, benzothiophenyl, benzothiophenyl, indolyl, indazolyl, benzimidazolyl, imidazopyridinyl, pyrazolopyridinyl, and pyrazolopyrimidinyl. Further not limiting examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, pyrazolyl, pyrazolyl, benzo[J]oxazolyl, benzo[J]thiazolyl, quinolyl, quinazinolyl, indazolyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazolyl, and pyrido[2,3-b]pyrazinyl.

[00101] The terms "heterocycle" or "heterocyclyl," as used herein can be used interchangeably and refer to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Thus, the term is inclusive of, but not limited to, "heterocycloalkyl," "heteroaryl," "bicyclic heterocycle" and "polycyclic heterocycle." 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, pyridazine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydrofuran, tetrahydrofuran, dioxane, and the like. The term heterocyclyl group can also be a C2 heterocyclyl, C2-C3 heterocyclyl, C2-C4 heterocyclyl, C2-C5 heterocyclyl, C2-C6 heterocyclyl, C2-C7 heterocyclyl, C2-C8
heterocyclyl, C2-C9 heterocyclyl, C2-C10 heterocyclyl, C2-C11 heterocyclyl, and the like up to and including a C2-C18 heterocyclyl. For example, a C2 heterocyclyl comprises a group which has two carbon atoms and at least one heteroatom, including, but not limited to, aziridinyl, diazetidinyl, dihydropyrazetyl, oxiranyl, thiiranyl, and the like. Alternatively, for example, a C5 heterocyclyl comprises a group which has five carbon atoms and at least one heteroatom, including, but not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, diazepanyl, pyridinyl, and the like. It is understood that a heterocyclyl group may be bound either through a heteroatom in the ring, where chemically possible, or one of carbons comprising the heterocyclyl ring.

[00102] The term "bicyclic heterocycle" or "bicyclic heterocyclyl," as used herein refers to a ring system in which at least one of the ring members is other than carbon. Bicyclic heterocyclyl encompasses ring systems wherein an aromatic ring is fused with another aromatic ring, or wherein an aromatic ring is fused with a non-aromatic ring. Bicyclic heterocyclyl encompasses ring systems wherein a benzene ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms or wherein a pyridine ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms. Bicyclic heterocyclic groups include, but are not limited to, indolyl, indazolyl, pyrazolo[1,5-a]pyridinyl, benzofuranyl, quinolinyl, quinoxalinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-chromenyl, 1H-pyrazolo[4,3-c]pyridin-3-yl; 1H-pyrrolo[3,2-b]pyridin-3-yl; and 1H-pyrazolo[3,2-b]pyridin-3-yl.

[00103] The term "heterocycloalkyl" as used herein refers to an aliphatic, partially unsaturated or fully saturated, 3- to 14-membered ring system, including single rings of 3 to 8 atoms and bi- and tricyclic ring systems. The heterocycloalkyl ring-systems include one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein a nitrogen and sulfur heteroatom optionally can be oxidized and a nitrogen heteroatom optionally can be substituted. Representative heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

[00104] The term "hydroxyl" or "hydroxy" as used herein is represented by the formula \(-\text{OH}\).

[00105] The term "ketone" as used herein is represented by the formula \(\text{A}^{(0)} \text{A}^2\), where \(\text{A}^1\) and \(\text{A}^2\) can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl,
cycloalkynyl, aryl, or heteroaryl group as described herein.

[00106] The term "azide" or "azido" as used herein is represented by the formula —N₃.

[00107] The term "nitro" as used herein is represented by the formula —NO₂.

[00108] The term "nitrile" or "cyano" as used herein is represented by the formula —CN.

[00109] The term "silyl" as used herein is represented by the formula —SiA₁A₂A₃, where A₁, A₂, and A₃ can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[00110] The term "sulfo-oxo" as used herein is represented by the formulas —S(0)A₁, —S(0)₂A₁, —OS(O)₂A₁, or —OS(0)₂OA₁, where A₁ 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 —S(O)₂A₁, where A₁ 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 A₁S(0)₂A₂, where A₁ and A₂ 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 A₁S(O)₂, where A₁ and A₂ can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[00111] The term "thiol" as used herein is represented by the formula —SH.

[00112] "R¹," "R²," "R³," "R₄," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R¹ 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.

[00113] 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. In 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).

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.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; -(CH<sub>2</sub>)<sub>α</sub>OR<sup>°</sup>; -(CH<sub>3</sub>)OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>; -(CH<sub>2</sub>)OR<sup>°</sup>-0-(CH<sub>2</sub>)OR<sup>°</sup>-OR<sup>°</sup>.
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.

[00116] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, -\((\text{CH}_2)_{0-2}\)R*, -(haloR*), -\((\text{CH}_2)_{0-2}\)OH, -\((\text{CH}_2)_{0-2}\)OR*, -(CH)\(_2\)o.

\[\text{2CH(OR*)}_2; -\text{O(haloR')}, -\text{CN}, -\text{N}_3, -\text{(CH)_{0-2}C(0)R*}, -\text{(CH)_{0-2}C(0)OH}, -(\text{CH})_{0-2}o.\]

\[\text{2C(0)OR*}, -\text{(CH)_{0-2}SR*}, -(\text{CH}_{2})_{0-2}\text{SH}, -(\text{CH})_{0-2}\text{NH}_2, -(\text{CH}_{2})_{0-2}\text{NHR*}, -(\text{CH}_{2})_{0-2}\text{NR*}_{2}, -\text{N0}_{2}, -\text{SiR*}_{3}, -\text{OSiR*}_{3}, -\text{C(0)SR*}, -(\text{C}_{1-4} \text{ straight or branched alkylene})\text{C(0)OR*}, \text{ or } -\text{SSR*} \]

wherein each R* 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\(_2\)Ph, -0(CH)\(_2\)iPh, 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 =0 and =S.

[00117] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =0, =S, =NNR*\(_2\), =NNHC(0)R*, =NNHC(0)OR*, =NNHS(0)\(_2\)R*, =NR*, =NOR*, -0(C(R*)\(_2\))\(_2\)\(_0\), or -S(C(R*)\(_2\))\(_2\)\(_3\)S*, wherein each independent occurrence of R* 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: -0(CR*)\(_2\)\(_2\)\(_3\)\(_0\), wherein each independent occurrence of R* 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.

[00118] Suitable substituents on the aliphatic group of R° include halogen, -R*, -(haloR*), -OH, -OR*, -O(haloR*), -CN, -C(0)OH, -C(0)OR*, -NH\(_2\), -NHR*, -NR*\(_2\), or -N0\(_2\), wherein each R* is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C\(_{1-4}\) aliphatic, -CH\(_2\)Ph, -0(CH)\(_2\)iPh, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00119] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include -R†, -NR†\(_2\), -C(0)R†, -C(0)OR†, -C(0)C(0)R†, -C(0)CH\(_2\)C(0)OR†, -
S(0) 2 R†, -S(0) 2 NR†, -C(S)NR† 2, -C(NH)NR† 2, or -N(R*)S(0) 2 R†; wherein each R† is independently hydrogen, C1-6 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†, 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.

Suitable substituents on the aliphatic group of R† are independently halogen, -R*, -(haloR*), -OH, -OR*, -O(haloR*), -CN, -C(0)OH, -C(0)OR*, -NH2, -NHR*, -NR* 2, or -N0 2, wherein each R* is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C1-4 aliphatic, -CH2Ph, -0(CH2)0-4Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

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, and brosylate.

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).

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.

[00124] 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.

[00125] "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, aeyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohalkyl, alkoxy, substituted alkoxy, haloalkyl, halolalkoxy, ary, 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.
"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.

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.

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.

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.

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 \(^2\)H, \(^3\)H, \(^{13}\)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 \(^3\)H and \(^{14}\)C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., \(^3\)H, 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., \(^2\)H, 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.

[00131] 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 solvent 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.

[00132] 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 anhydrates 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.

[00133] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an a-hydrogen can exist in an equilibrium of the keto form and the enol form.

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\[ \text{keto form} \quad \leftrightarrow \quad \text{enol form} \]
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Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. As another example, pyridinones can exist in two tautomeric forms, as shown below.

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\[ \text{imidic acid form} \quad \leftrightarrow \quad \text{imidic acid form} \]
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Unless stated to the contrary, the invention includes all such possible tautomers.
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.

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

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

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 Supplemental (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 Laroc’s Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

The following abbreviations are used herein. DCM: Dichloromethane. DDQ: 2,3-dichloro-5,6-dicyanobenzoquinone. DIAD: diisopropyl azodicarboxylate. DMF: N,N-dimethyl formamide. DMSO: dimethylsulfoxide. EtOAc: ethyl acetate. EtOH: ethanol. h:

[00138] 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.

[00139] 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 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 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 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.

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 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. COMPOUNDS

In one aspect, the invention relates to compounds useful as positive allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5). More specifically, 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.

In one aspect, the disclosed compounds exhibit positive allosteric modulation of mGluR5 response to glutamate as an increase 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.

In one aspect, the compounds of the invention are 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.

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

In one aspect, the invention relates to a compound having a structure represented by a formula:
wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y_1 and Y_2 is N, and the other is C-R^3; wherein one of Z_1 and Z_2 is C-L-Ar, and the other is C-R^3b; wherein L is -O-C(R^1A-R^1b)- or -C(R^1A-R^1b)-0-; wherein Ar^1 is phenyl with 0-3 substituents selected from halogen, cyano, C_1-C_4 alkyl, and C_1-C_4 alkoxy, or Ar^1 is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C_1-C_4 alkyl, and C_1-C_4 alkoxy; wherein each of R^1a and R^1b is independently selected from hydrogen and C_1-C_4 alkyl; wherein R^2 is selected from hydrogen; C_1-C_6 alkyl; (C_1-C_6 alkoxy) C_1-C_6 alkyl; C_3-C_8 cycloalkyl; (C_3-C_8 cycloalkyl) C_1-C_6 alkyl; C_2-C_5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C_1-C_4 alkyl, and C_1-C_4 alkoxy; (C_1-C_2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C_1-C_4 alkyl, and C_1-C_4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C_1-C_4 alkyl, and C_1-C_4 alkoxy; wherein R^3a is selected from hydrogen, halogen, cyano, and C_1-C_4 alkyl; wherein R^3b is selected from hydrogen, halogen, cyano, and C_1-C_4 alkyl, or R^3a and R^3b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R^4a is selected from hydrogen and C_1-C_4 alkyl; wherein R^4b, when present, is selected from hydrogen and C_1-C_4 alkyl, or R^4a and R^4b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R^5a is selected from hydrogen and C_1-C_4 alkyl; wherein R^5b, when present, is selected from hydrogen and C_1-C_4 alkyl, or R^5a and R^5b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R^6a and R^6b are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt,
solvent, polymorph, hydrate or the stereochemical isomeric form thereof.

In a further aspect, the invention relates to a compound having a structure represented by a formula:

wherein one of $Y^1$ and $Y^2$ is N, and the other is C-R$^{3a}$; wherein one of $Z^1$ and $Z^2$ is $C$-$L$-$Ar^1$, and the other is C-R$^{3b}$; wherein $L$ is -0-$(R^{1a}R^{1b})$- or -0-$(R^{1a}R^{1b})$-0-; wherein $Ar^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or $Ar^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of $R^{1a}$ and $R^{1b}$ is independently selected from hydrogen and C1-C4 alkyl; wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein $R^{3a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein $R^{3b}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or $R^{3a}$ and $R^{3b}$ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein each of $R^{4a}$ and $R^{4b}$ is independently selected from hydrogen and C1-C4 alkyl; or $R^{4a}$ and $R^{4b}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein each of $R^{5a}$ and $R^{5b}$ is independently selected from hydrogen and C1-C4 alkyl; or $R^{5a}$ and $R^{5b}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein $R^{4a}$ and $R^{5a}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

In one aspect, the invention relates to a compound having a structure represented by a formula:

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of $Y^1$ and $Y^2$ is N, and the other is C-$R^{3a}$; wherein one of $Z^1$ and $Z^2$ is C-L-Ar, and the other is C-$R^{3b}$; wherein L is -O-C($R^{1a}$)$R^{1b}$) or -C($R^{1a}$)$R^{1b}$)-0-; wherein Ar is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or Ar is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein each of $R^{1a}$ and $R^{1b}$ is independently selected from hydrogen and C1-C4 alkyl; wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein $R^{3a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkoxy; wherein $R^{3b}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein $R^{4a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or $R^{3a}$ and $R^{3b}$ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein $R^{4a}$ is selected from hydrogen and C1-C4 alkyl; wherein $R^{5a}$ is selected from hydrogen and C1-C4 alkyl; wherein $R^{5b}$, when present, is selected from hydrogen and C1-C4 alkyl; and wherein $R^{4a}$ and $R^{5a}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the
stereochemically isomeric form thereof.

[00148] In a further aspect, the invention relates to a compound having a structure represented by a formula:

![Chemical Structure](image)

wherein L is selected from —CH₂0— or —OCH₂—; wherein Ar¹ is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R² is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R³a is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein R³b is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein each of R⁴a and R⁴b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R⁵a and R⁵b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

[00149] In a further aspect, the invention relates to a compound having a structure represented by a formula:

![Chemical Structure](image)

wherein L is selected from —CH₂0— or —OCH₂—; wherein Ar¹ is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R² is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; pyridinyl with 0-2 substituents selected from...
fluoro, chloro, cyano, —CH₂, —OCH₃; wherein R³a is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein R³b is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein each of R⁴a and R⁴b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R⁵a and R⁵b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

[00150] In a further aspect, the invention relates to a compound having a structure represented by a formula:

![Chemical Structure](image)

wherein Ar¹ is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R² is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R³a is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein R³b is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein each of R⁴a and R⁴b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R⁵a and R⁵b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

[00151] In a further aspect, the invention relates to a compound having a structure represented by a formula:
wherein L is selected from —CH₂0— or —OCH₂—; wherein Ar¹ is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R² is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein each of R₄ and R₅ is independently selected from hydrogen, —CH₃, —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

[00152] In a further aspect, the invention relates to a compound having a structure represented by a formula:

wherein Ar¹ is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R² is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein each of R₄ and R₅ is independently selected from hydrogen, halogen, cyano, —CH₃, —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R₅ and R₅ is independently selected from hydro
independently selected from hydrogen, —CH₃, and —CH₂CH₃; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

[00153] In a further aspect, the invention relates to a compound having a structure represented by a formula:

![Chemical structure](image)

wherein L is selected from —CH₂0 — or —OCH₂—; wherein Ar¹ is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R² is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, —OCH₃; wherein R³a is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein R³b is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃; wherein each of R⁴a and R⁴b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; wherein each of R⁵a and R⁵b is independently selected from hydrogen, —CH₃, and —CH₂CH₃; or a pharmaceutically acceptable salt thereof, wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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 further aspect, the compound comprises the pharmaceutically acceptable salt, solvate, polymorph, hydrate or the stereochemically isomeric form thereof.

[00154] In a further aspect, the compound has a structure represented by a formula:

![Chemical structure](image)
wherein L is selected from $-\text{CH}_2\text{O}-$ or $-\text{OCH}_2-$; Ar$^1$ is phenyl optionally monosubstituted a halo group; R$^2$ is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

In a further aspect, the compound has a structure represented by a formula:

wherein Ar$^1$ is phenyl optionally monosubstituted a halo group; R$^2$ is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

In a further aspect, the compound has a structure represented by a formula:

wherein Ar$^1$ is phenyl optionally monosubstituted a halo group; R$^2$ is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

In a further aspect, the compound has a structure represented by a formula:

wherein wherein L is selected from $-\text{CH}_2\text{O}-$ or $-\text{OCH}_2-$; Ar$^1$ is phenyl optionally monosubstituted a halo group; R$^2$ is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a $-\text{F}$ group; benzyl optionally substituted with a 1-2 groups selected from $-\text{F}$, $-\text{Cl}$, $-\text{CF}_3$, and $-\text{OCH}_3$; and pyridinyl optionally monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.
[00158] In a further aspect, the compound has a structure represented by a formula:

wherein $\text{Ar}^1$ is phenyl optionally monosubstituted a halo group; $\text{R}^2$ is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a $-\text{F}$ group; benzyl optionally substituted with a 1-2 groups selected from $-\text{F}$, $-\text{Cl}$, $-\text{CF}_3$, and $-\text{OCH}_3$; and pyridinyl optionally monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00159] In a further aspect, the compound has a structure represented by a formula:

wherein $\text{Ar}^1$ is phenyl optionally monosubstituted a halo group; $\text{R}^2$ is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a $-\text{F}$ group; benzyl optionally substituted with a 1-2 groups selected from $-\text{F}$, $-\text{Cl}$, $-\text{CF}_3$, and $-\text{OCH}_3$; and pyridinyl optionally monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00160] In a further aspect, the compound has a structure represented by a formula:

wherein $\text{L}$ is selected from $-\text{CH}_2\text{O}$ — or $-\text{OCH}_2$ — $\text{Ar}^1$ is phenyl monosubstituted with a $-\text{F}$ or $-\text{Cl}$ group; $\text{R}^2$ is selected from hydrogen, phenyl monosubstituted with a $-\text{F}$ group; and pyridinyl monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00161] In a further aspect, the compound has a structure represented by a formula:

wherein $\text{Ar}^1$ is phenyl monosubstituted with a $-\text{F}$ or $-\text{Cl}$ group; $\text{R}^2$ is selected from hydrogen, phenyl monosubstituted with a $-\text{F}$ group; and pyridinyl monosubstituted with a $-\text{F}$
group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00162] In a further aspect, the compound has a structure represented by a formula:

\[
\begin{align*}
\text{Ar}^1 & \quad \text{O} \\
\text{N} & \quad \text{R}^2
\end{align*}
\]

wherein \(\text{Ar}^1\) is phenyl monosubstituted with a \(-\text{F}\) or \(-\text{Cl}\) group; \(\text{R}^2\) is selected from hydrogen, phenyl monosubstituted with a \(-\text{F}\) group; and pyridinyl monosubstituted with a \(-\text{F}\) group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00163] In a further aspect, the compound has a structure represented by a formula:

\[
\begin{align*}
\text{Ar}^1 & \quad \text{L} \\
\text{N} & \quad \text{R}^2
\end{align*}
\]

wherein \(\text{L}\) is selected from \(-\text{CH}_2\text{O}\) or \(-\text{OCH}_2\); \(\text{Ar}^1\) is phenyl optionally monosubstituted a halo group; \(\text{R}^2\) is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00164] In a further aspect, the compound has a structure represented by a formula:

\[
\begin{align*}
\text{Ar}^1 & \quad \text{O} \\
\text{N} & \quad \text{R}^2
\end{align*}
\]

wherein \(\text{Ar}^1\) is phenyl optionally monosubstituted a halo group; \(\text{R}^2\) is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00165] In a further aspect, the compound has a structure represented by a formula:

\[
\begin{align*}
\text{Ar}^1 & \quad \text{O} \\
\text{N} & \quad \text{R}^2
\end{align*}
\]
wherein $A_{r1}$ is phenyl optionally monosubstituted a halo group; $R_2$ is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00166] In a further aspect, the compound has a structure represented by a formula:

$$
\begin{align*}
&\text{wherein wherein L is selected from } -\text{CH}_20 - \text{or } -\text{OCH}_2; A_{r1} \text{ is phenyl optionally monosubstituted a halo group; } R_2 \text{ is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a } -\text{F group; benzyl optionally substituted with a 1-2 groups selected from } -\text{F, } -\text{Cl, } -\text{CF}_3, \text{ and } -\text{OCH}_3; \text{ and pyridinyl optionally monosubstituted with a } -\text{F group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.}
\end{align*}
$$

[00167] In a further aspect, the compound has a structure represented by a formula:

$$
\begin{align*}
&\text{wherein Ar}^1 \text{ is phenyl optionally monosubstituted a halo group; } R_2 \text{ is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a } -\text{F group; benzyl optionally substituted with a 1-2 groups selected from } -\text{F, } -\text{Cl, } -\text{CF}_3, \text{ and } -\text{OCH}_3; \text{ and pyridinyl optionally monosubstituted with a } -\text{F group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.}
\end{align*}
$$

[00168] In a further aspect, the compound has a structure represented by a formula:

$$
\begin{align*}
&\text{wherein Ar}^1 \text{ is phenyl optionally monosubstituted a halo group; } R_2 \text{ is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a } -\text{F group; benzyl optionally substituted with a 1-2 groups selected from } -\text{F, } -\text{Cl, } -\text{CF}_3, \text{ and } -\text{OCH}_3; \text{ and pyridinyl optionally monosubstituted with a } -\text{F group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.}
\end{align*}
$$
In a further aspect, the compound has a structure represented by a formula:

$$\text{Ar}^{1} - \text{L} \rightarrow \text{N} \rightarrow \text{R}^{2}$$

wherein L is selected from $-\text{CH}_2\text{O}$ or $-\text{OCH}_2$; $\text{Ar}^{1}$ is phenyl monosubstituted with a $-\text{F}$ or $-\text{Cl}$ group; $\text{R}^{2}$ is selected from hydrogen, phenyl monosubstituted with a $-\text{F}$ group; and pyridinyl monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

In a further aspect, the compound has a structure represented by a formula:

$$\text{Ar}^{1} - \text{O} \rightarrow \text{N} \rightarrow \text{R}^{2}$$

wherein $\text{Ar}^{1}$ is phenyl monosubstituted with a $-\text{F}$ or $-\text{Cl}$ group; $\text{R}^{2}$ is selected from hydrogen, phenyl monosubstituted with a $-\text{F}$ group; and pyridinyl monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

In a further aspect, the compound has a structure represented by a formula:

$$\text{Ar}^{1} - \text{O} \rightarrow \text{N} \rightarrow \text{R}^{2}$$

wherein $\text{Ar}^{1}$ is phenyl monosubstituted with a $-\text{F}$ or $-\text{Cl}$ group; $\text{R}^{2}$ is selected from hydrogen, phenyl monosubstituted with a $-\text{F}$ group; and pyridinyl monosubstituted with a $-\text{F}$ group; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.
and wherein all variables are as defined herein.

[00173] In a further aspect, the compound has a structure represented by a formula:

and wherein all variables are as defined herein.

[00174] In a further aspect, the compound has a structure represented by a formula:

and wherein all variables are as defined herein.

[00175] In a further aspect, the compound has a structure represented by a formula:
and wherein all variables are as defined herein.

[00176] In a further aspect, the compound has a structure represented by a formula:

[00177] In a further aspect, the compound has a structure represented by a formula:

[00178] In a further aspect, the compound has a structure represented by a formula:
and wherein all variables are as defined herein.

[00179] In a further aspect, the compound has a structure represented by a formula:

\[
\text{[Image of chemical structures]}
\]

and wherein all variables are as defined herein,

a. **L GROUPS**

[00180] In one aspect, L is is -O-C(\text{R}^{1a}R^{1b})- or -C(\text{R}^{1a}R^{1b})-0-. Thus, in a further aspect, L has a structure represented by a formula:

\[
\text{[Image of chemical structures]}
\]

[00181] In a yet further aspect, L has a structure represented by a formula:

\[
\text{[Image of chemical structures]}
\]

[00182] In a further aspect, L is is -O-CH_{2} or -CH_{2}-0-. Thus, in a still further aspect, L has a structure represented by a formula:
In a yet further aspect, L has a structure represented by a formula:

\[ \text{b. Y}^1 \text{AND Y}^2 \text{GROUPS} \]

In one aspect, one of \( Y^1 \) and \( Y^2 \) is N, and the other is C-R\(^3\). For example, in certain compounds, \( Y^1 \) can be selected as N, while \( Y^2 \) is C-R\(^3\). In further aspects, \( Y^1 \) can be selected as C-R\(^3\), while \( Y^2 \) is N.

In a further aspect, \( Y^1 \) is N and \( Y^2 \) is CH. In still further aspects, \( Y^1 \) can be selected as C-R\(^3\), while \( Y^2 \) is C-H.

In a further aspect, Z\(^1\) has a structure represented by a formula:

\[ \text{c. Z}^1 \text{AND Z}^2 \text{GROUPS} \]

In one aspect, one of \( Z^1 \) and \( Z^2 \) is C-L-Ar\(^1\), and the other is C-R\(^3\). For example, in certain compounds, \( Z^1 \) can be selected as C-L-Ar\(^1\), while \( Z^2 \) is C-R\(^3\). In further aspects, \( Z^1 \) can be selected as C-R\(^3\), while \( Z^2 \) is C-L-Ar\(^1\).

Thus, in a further aspect, \( Z^1 \) can have a structure represented by a formula:

\[ \text{while } Z^2 \text{ is C-R\(^3\).} \]

In a yet further aspect, \( Z^2 \) has a structure represented by a formula:

\[ \text{while } Z^1 \text{ is C-R\(^3\).} \]

In one aspect, one of \( Z^1 \) and \( Z^2 \) is C-O-CH\(^\text{Ar} \text{ or C-CH}\_2\text{-0-Ar}\)\(^1\), and the other is C-R\(^3\). For example, in certain compounds, \( Z^1 \) can be selected as C-O-CH\(^\text{Ar} \text{ or C-CH}\_2\text{-0-Ar}\)\(^1\), while \( Z^2 \) is C-R\(^3\). In further aspects, \( Z^1 \) can be selected as C-R\(^3\), while \( Z^2 \) is C-O-CH\(^\text{Ar} \text{ or C-CH}\_2\text{-0-Ar}.\)

In a further aspect, \( Z^1 \) can have a structure represented by a formula:

\[ \text{while } Z^2 \text{ is C-R\(^3\).} \]

In a further aspect, \( Z^2 \) has a structure represented by a formula:
while Z₁ is C-R₃ᵇ.

[00194] In a further aspect, Z₁ can have a structure represented by a formula:

![Chemical Structure](image1)

while Z₂ is C-R₃ᵇ.

[00195] In a further aspect, Z₂ has a structure represented by a formula:

![Chemical Structure](image2)

while Z₁ is C-R₃ᵇ.

[00196] In a further aspect, Z₁ can have a structure represented by a formula:

![Chemical Structure](image3)

while Z₂ is C-R₃ᵇ.

[00197] In a further aspect, Z₂ has a structure represented by a formula:

![Chemical Structure](image4)

while Z₁ is C-R₃ᵇ.

[00198] In a further aspect, Z₁ can have a structure represented by a formula:

![Chemical Structure](image5)

while Z₂ is C-R₃ᵇ.

[00199] In a further aspect, Z₂ has a structure represented by a formula:

![Chemical Structure](image6)

while Z₁ is C-R₃ᵇ.
In a further aspect, $Z^2$ has a structure represented by a formula:

![Chemical Structure](image)

while $Z^1$ is C-R.$^3b$.

In a further aspect, $Z^1$ can have a structure represented by a formula:

![Chemical Structure](image)

while $Z^2$ is C-R.$^3b$.

In a further aspect, $Z^2$ has a structure represented by a formula:

![Chemical Structure](image)

while $Z^1$ is C-R.$^3b$.

**d. $A R^1$ GROUPS**

In one aspect, $A r^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or $A r^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

In a further aspect, $A r^1$ is unsubstituted. In a still further aspect, $A r^1$ has 1, 2, or 3 substituents. In a yet further aspect, $A r^1$ is phenyl. In an even further aspect, $A r^1$ is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

In a further aspect, $A r^1$ is substituted with 1-3 groups independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, $A r^1$ is substituted with 1-3 groups independently selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In an even further aspect, $A r^1$ is substituted with 1-3 groups independently selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

In a further aspect, $A r^1$ is substituted with 1-3 halogens. In a yet further aspect, $A r^1$ is substituted with 0-3 halogens. In a still further aspect, $A r^1$ is substituted with 0-2 halogens. In an even further aspect, $A r^1$ is substituted with 0-1 halogens. In a still further aspect, $A r^1$ is optionally monosubstituted a halo group. In a yet further aspect, $A r^1$ is monosubstituted a halo group.
In a further aspect, Ar is substituted with 1-3 groups independently selected from —F and —Cl. In a yet further aspect, Ar is substituted with 0-3 groups independently selected from —F and —Cl. In a still further aspect, Ar is substituted with 0-2 groups independently selected from —F and —Cl. In an even further aspect, Ar is substituted with 0-1 groups independently selected from —F and —Cl. In a still further aspect, Ar is optionally monosubstituted with group selected from —F or —Cl. In a yet further aspect, Ar is monosubstituted with a —F or —Cl group.

In a further aspect, Ar is phenyl substituted with 1-3 halogens. In a yet further aspect, Ar is phenyl substituted with 0-3 halogens. In a still further aspect, Ar is phenyl substituted with 0-2 halogens. In an even further aspect, Ar is phenyl substituted with 0-1 halogens. In a still further aspect, Ar is phenyl optionally monosubstituted a halo group. In a yet further aspect, Ar is phenyl monosubstituted a halo group.

In a further aspect, Ar is phenyl substituted with 1-3 groups independently selected from —F and —Cl. In a yet further aspect, Ar is phenyl substituted with 0-3 groups independently selected from —F and —Cl. In a still further aspect, Ar is phenyl substituted with 0-2 groups independently selected from —F and —Cl. In an even further aspect, Ar is phenyl substituted with 0-1 groups independently selected from —F and —Cl. In a still further aspect, Ar is phenyl optionally monosubstituted with group selected from —F or —Cl. In a yet further aspect, Ar is phenyl monosubstituted with a —F or —Cl group.

In a further aspect, Ar is phenyl with 0-3 substituents selected from fluoro, chloro, cyano, —CH₃, and —OCH₃. In a yet further aspect, Ar is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, and —OCH₃. In an even further aspect, Ar is phenyl with 0-1 substituents selected from fluoro, chloro, cyano, —CH₃, and —OCH₃. In a still further aspect, Ar is phenyl monosubstituted with a group selected from fluoro, chloro, cyano, —CH₃, and —OCH₃.

In a further aspect, Ar is phenyl monosubstituted with a halogen. In a yet further aspect, Ar is phenyl monosubstituted with a —F. In a yet further aspect, Ar is phenyl monosubstituted with a —Cl. In an even further aspect, Ar is unsubstituted phenyl.

In a further aspect, Ar is selected from:

![Chemical structures](image)

In a further aspect, Ar is selected from:
In one aspect, each of R₁ᵃ and R₁ᵇ is independently selected from hydrogen and C₁-C₄ alkyl. In a further aspect, R₁ᵃ and R₁ᵇ are each hydrogen. In a yet further aspect, R₁ᵃ and R₁ᵇ is independently selected from hydrogen and C₁-C₃ alkyl. In a still further aspect, R₁ᵃ and R₁ᵇ is independently selected from hydrogen and C₁-C₂ alkyl.

In a further aspect, each of R₁ᵃ, R₁ᵇ, R₃ᵃ, and R₃ᵇ is hydrogen. In a still further aspect, each of R₁ᵃ, R₁ᵇ, R₃ᵃ, R₃ᵇ, R₄ᵃ, and R₄ᵇ, when present, is hydrogen. In a yet further aspect, each of R₁ᵃ, R₁ᵇ, R₃ᵃ, R₃ᵇ, R₄ᵃ, R₄ᵇ, when present, R₅ᵃ, and R₅ᵇ, when present, is hydrogen. In an even further aspect, each of R₁ᵃ, R₁ᵇ, R₃ᵃ, R₃ᵇ, R₄ᵃ, and R₅ᵇ is hydrogen.

f. R² GROUPS

In one aspect, R² is is selected from hydrogen; C₁-C₆ alkyl; (C₁-C₆ alkyl) C₁-C₆ alkyl; C₃-C₈ cycloalkyl; (C₃-C₈ cycloalkyl) C₁-C₆ alkyl; C₂-C₅ heterocyclil; phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy.

In various aspects, R² is selected from hydrogen; C₁-C₆ alkyl; (C₁-C₆ alkyl) C₁-C₆ alkyl; C₃-C₈ cycloalkyl; (C₃-C₈ cycloalkyl) C₁-C₆ alkyl; C₂-C₅ heterocyclil; phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; (C₁-C₂ alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein R₃ᵃ is selected from hydrogen, halogen, cyano, and C₁-C₄ alkyl.

In various aspects, R² is selected from hydrogen; C₁-C₆ alkyl; (C₁-C₆ alkyl) C₁-C₆ alkyl; C₃-C₈ cycloalkyl; (C₃-C₈ cycloalkyl) C₁-C₆ alkyl; C₂-C₅ heterocyclil; phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; benzyl
with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R\textsuperscript{39} is selected from hydrogen, halogen, cyano, and C1-C4 alkyl.

[00221] In a still further aspect, R\textsuperscript{2} is selected from hydrogen, C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; monohalo C1-C6 alkyl; polyhalo C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; and C2-C5 heterocyclyl. In a still further aspect, R\textsuperscript{2} is selected from C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; monohalo C1-C6 alkyl; polyhalo C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; and C2-C5 heterocyclyl. In an even further aspect, R\textsuperscript{2} is hydrogen. In a still further aspect, R\textsuperscript{2} is selected from hydrogen and C1-C6 alkyl. In a yet further aspect, R\textsuperscript{2} is selected from hydrogen, methyl, trifluoromethyl, ethyl, propyl, butyl, pentyl, and hexyl. In an even further aspect, R\textsuperscript{2} is selected from methyl, trifluoromethyl, ethyl, propyl, butyl, pentyl, and hexyl. In a still further aspect, R\textsuperscript{2} is selected from hydrogen, methyl, ethyl, (cyclobutyl)methyl, and (cyclopropyl)methyl.

[00222] In a further aspect, R\textsuperscript{2} is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH\textsubscript{3}, and —OCH\textsubscript{3}; benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH\textsubscript{3}, and —OCH\textsubscript{3}; and pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH\textsubscript{3}, and —OCH\textsubscript{3}. In an even further aspect, R\textsuperscript{2} is selected from hydrogen, C1-C6 alkyl, (C3-C8 cycloalkyl) C1-C6 alkyl; phenyl optionally substituted with a halo group; benzyl optionally substituted with a 1-2 halo groups; pyridinyl optionally substituted with a halo group. In a still further aspect, R\textsuperscript{2} is selected from hydrogen; methyl; (cyclobutyl)methyl; phenyl optionally monosubstituted with a —F group; benzyl optionally substituted with a 1-2 groups selected from —F, —Cl, —CF\textsubscript{3}, and —OCH\textsubscript{3}; and pyridinyl optionally monosubstituted with a —F group. In a yet further aspect, R\textsuperscript{2} is selected from hydrogen, phenyl monosubstituted with a —F group; and pyridinyl monosubstituted with a —F group.

[00223] In a further aspect, R\textsuperscript{2} is selected from phenyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and heteroaryl having 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R\textsuperscript{2} is selected from phenyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl; benzyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and heteroaryl having 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a yet further aspect, R\textsuperscript{2} is selected from phenyl with 0-2 substituents independently selected
from halogen, cyano, C1-C4 alkyl; benzyl with 0-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and pyridinyl having 0-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

[00224] In a further aspect, R² is phenyl. In a still further aspect, R² is phenyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, R² is phenyl with 0-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is phenyl with 0-1 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a yet further aspect, R² is phenyl with 1-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, R² is phenyl monosubstituted with a group selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, and —OCH₃. In an even further aspect, R² is phenyl with 0-2 substituents selected from fluoro, chloro, cyano, —CF₃, —CH₃, and —OCH₃. In a yet further aspect, R² is phenyl optionally substituted with a halo group. In an even further aspect, R² is phenyl optionally substituted with a 1-2 halo groups. In a still further aspect, R² is phenyl optionally monosubstituted with a fluoro group. In an even further aspect, R² is phenyl optionally monosubstituted with a chloro group. In a yet further aspect, R² is phenyl optionally substituted with a 1-2 groups selected from fluoro, chloro, —CF₃, and —OCH₃. In a still further aspect, R² is phenyl optionally substituted with a 1-2 groups selected from fluoro, chloro, —CH₃, —CF₃, and —OCH₃. In an even further aspect, R² is phenyl monosubstituted with a fluoro group.

[00225] In a further aspect, R² is benzyl. In a still further aspect, R² is benzyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is benzyl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, R² is benzyl with 0-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is benzyl with 0-1 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a yet further aspect, R² is benzyl with 1-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, R² is benzyl monosubstituted with a group selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is benzyl with 0-2
substituents selected from fluoro, chloro, cyano, —CH₃, and —OCH₃. In an even further aspect, R² is benzyl with 0-2 substituents selected from fluoro, chloro, cyano, —CF₃, —CH₃, and —OCH₃. In a yet further aspect, R² is benzyl optionally substituted with a halo group. In an even further aspect, R² is benzyl optionally substituted with a 1-2 halo groups. In a still further aspect, R² is benzyl optionally monosubstituted with a fluoro group. In an even further aspect, R² is benzyl optionally monosubstituted with a chloro group. In a yet further aspect, R² is benzyl optionally substituted with a 1-2 groups selected from fluoro, chloro, —CF₃, and —OCH₃. In a still further aspect, R² is benzyl optionally substituted with a 1-2 groups selected from fluoro, chloro, —CH₃, —CF₃, and —OCH₃. In an even further aspect, R² is benzyl monosubstituted with a fluoro group.

[00226] In a further aspect, R² is heteroaryl. In a still further aspect, R² is heteroaryl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is heteroaryl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, R² is heteroaryl with 0-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is heteroaryl with 0-1 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a yet further aspect, R² is heteroaryl with 1-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, R² is heteroaryl monosubstituted with a group selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, R² is heteroaryl with 0-2 substituents selected from fluoro, chloro, cyano, —CH₃, and —OCH₃. In an even further aspect, R² is heteroaryl with 0-2 substituents selected from fluoro, chloro, cyano, —CF₃, —CH₃, and —OCH₃. In a yet further aspect, R² is heteroaryl optionally substituted with a halo group. In an even further aspect, R² is heteroaryl optionally substituted with a 1-2 halo groups. In a still further aspect, R² is heteroaryl optionally monosubstituted with a fluoro group. In an even further aspect, R² is heteroaryl optionally monosubstituted with a chloro group. In a yet further aspect, R² is heteroaryl optionally substituted with a 1-2 groups selected from fluoro, chloro, —CF₃, and —OCH₃. In a still further aspect, R² is heteroaryl optionally substituted with a 1-2 groups selected from fluoro, chloro, —CH₃, —CF₃, and —OCH₃. In an even further aspect, R² is heteroaryl monosubstituted with a fluoro group.

[00227] In a further aspect, R² is pyridinyl. In a still further aspect, R² is pyridinyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.
In a still further aspect, \( R^2 \) is pyridinyl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In an even further aspect, \( R^2 \) is pyridinyl with 0-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, \( R^2 \) is pyridinyl with 0-1 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a yet further aspect, \( R^2 \) is pyridinyl with 1-2 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

In an even further aspect, \( R^2 \) is pyridinyl monosubstituted with a group selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy. In a still further aspect, \( R^2 \) is pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, \(-\text{CH}_3\), and \(-\text{OCH}_3\). In an even further aspect, \( R^2 \) is pyridinyl with 0-2 substituents selected from fluoro, chloro, cyano, \(-\text{CF}_3\), \(-\text{CH}_3\), and \(-\text{OCH}_3\). In a yet further aspect, \( R^2 \) is pyridinyl optionally substituted with a halo group. In an even further aspect, \( R^2 \) is pyridinyl optionally substituted with a 1-2 halo groups. In a still further aspect, \( R^2 \) is pyridinyl optionally monosubstituted with a fluoro group. In an even further aspect, \( R^2 \) is pyridinyl optionally monosubstituted with a chloro group. In a yet further aspect, \( R^2 \) is pyridinyl optionally substituted with a 1-2 groups selected from fluoro, chloro, \(-\text{CF}_3\), and \(-\text{OCH}_3\). In a still further aspect, \( R^2 \) is pyridinyl optionally substituted with a 1-2 groups selected from fluoro, chloro, \(-\text{CH}_3\), \(-\text{CF}_3\), and \(-\text{OCH}_3\). In an even further aspect, \( R^2 \) is pyridinyl monosubstituted with a fluoro group.

**g. \( R^3 \) GROUPS**

[00228] In one aspect, \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl. In a further aspect, \( R^{3a} \) is hydrogen. In a still further aspect, \( R^{3a} \) is C1-C4 alkyl. In a yet further aspect, \( R^{3a} \) is selected from methyl, ethyl, propyl, and butyl. In a still further aspect, \( R^{3a} \) is selected from halogen and C1-C4 alkyl. In a yet further aspect, \( R^{3a} \) is selected from hydrogen and C1-C4 alkyl. In an even further aspect, \( R^{3a} \) is selected from hydrogen, halogen, cyano, \(-\text{CH}_3\), and \(-\text{CH}_2\text{CH}_3\). In a yet further aspect, \( R^{3a} \) is selected from hydrogen, \(-\text{CH}_3\), and \(-\text{CH}_2\text{CH}_3\). In a still further aspect, \( R^{3a} \) is selected from hydrogen and \(-\text{CH}_3\). In an even further aspect, \( R^{3a} \) and \( R^{3b} \) are both hydrogen. In a further aspect, \( R^{3a} \) and \( R^{3b} \) are not substituted on adjacent carbons.

[00229] In a further aspect, \( R^{3a} \) and \( R^{3b} \) are substituted on adjacent carbons. In a still further aspect, \( R^{3a} \) and \( R^{3b} \) are substituted on adjacent carbons and are both hydrogen. In an even further aspect, \( R^{3a} \) and \( R^{3b} \) are substituted on adjacent carbons, and \( R^{3a} \) and \( R^{3b} \) are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered
heteroaryl, and 6-membered aryl. In a further aspect, R^3a and R^3b are substituted on adjacent carbons, and R^3c and R^3d are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl and the fused cycloalkyl is unsubstituted. In a further aspect, R^3a and R^3b are substituted on adjacent carbons, and R^3c and R^3d are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl and the fused cycloalkyl is substituted with 1 or 2 groups independently selected from halogen and C1-C4 alkyl.

In a further aspect, each of R^3a, R^3b, R^4a, and R^4b, when present, is hydrogen. In a yet further aspect, each of R^3a, R^3b, R^4a, R^4b, when present, R^5a, and R^5b, when present, is hydrogen. In an even further aspect, each of R^3a, R^3b, R^4a, and R^5a is hydrogen.

h. R^3b GROUPS

In one aspect, R^3b is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R^3a and R^3b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl.

In one aspect, R^3b is selected from hydrogen, halogen, cyano, and C1-C4 alkyl. In a further aspect, R^3b is hydrogen. In a still further aspect, R^3b is C1-C4 alkyl. In a yet further aspect, R^3b is selected from methyl, ethyl, propyl, and butyl. In a still further aspect, R^3b is selected from halogen, cyano, and C1-C4 alkyl. In a yet further aspect, R^3b is selected from hydrogen and C1-C4 alkyl. In an even further aspect, R^3b is selected from hydrogen, halogen, cyano, —CH₃, and —CH₂CH₃. In a yet further aspect, R^3b is selected from hydrogen, —CH₃, and —CH₂CH₃. In a still further aspect, R^3b is selected from hydrogen and —CH₃.

In a further aspect, each of R^3a and R^3b, when present, is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, wherein R^3a and R^3b, when present, are both hydrogen.

i. R^4a GROUPS

In one aspect, R^4a is selected from hydrogen and C1-C4 alkyl. In a further aspect, R^4a is hydrogen. In a still further aspect, R^4a is C1-C4 alkyl. In a yet further aspect, R^4a is selected from hydrogen and C1-C3 alkyl. In an even further aspect, R^4a is selected from hydrogen and C1-C2 alkyl. In a further aspect, R^4a is selected from methyl, ethyl, propyl, and butyl. In a still further aspect, R^4a is methyl.
In a further aspect, R⁴ and R⁵ are not directly covalently bonded. In a yet further aspect, R⁺⁴ and R⁻⁵ are each methyl.

In a further aspect, R⁴⁺ and R⁻⁵ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl. In a still further aspect, R⁺⁴ and R⁻⁵ are directly covalently bonded to comprise, together with the intermediate atoms, a 3-, 4-, 5-, 6-, or 7-membered fused cycloalkyl. In yet further aspect, R⁺⁴ and R⁻⁵ are directly covalently bonded to comprise, together with the intermediate atoms, a substituted 3-, 4-, 5-, 6-, or 7-membered fused cycloalkyl. In an even further aspect, R⁺⁴ and R⁻⁵ are directly covalently bonded to comprise, together with the intermediate atoms, a substituted 3-, 4-, 5-, 6-, or 7-membered fused cycloalkyl, and the the fused cycloalkyl is substituted with 1 or 2 groups independently selected from methyl, ethyl, and propyl.

In a further aspect, each of R⁺⁴ and R⁻⁴, when present, is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, R⁺⁴ and R⁻⁴, when present, are both hydrogen. In a yet further aspect, each of R⁺⁴ and R⁻⁴, when present, is independently selected from hydrogen, —CH₃, and —CH₂CH₃.

In a yet further aspect, each of R⁺⁴, R⁻⁴, when present, R⁻⁵, and R⁺⁵, when present, is hydrogen. In an even further aspect, each of R⁺⁴ and R⁻⁵ is hydrogen.

**j. R⁺⁴ Groups**

In one aspect, R⁺⁴, when present, is selected from hydrogen and C1-C4 alkyl, or R⁺⁴ and R⁻⁴ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl. In a further aspect, R⁻⁴, when present, is hydrogen. In a still further aspect, R⁻⁴, when present, is C1-C4 alkyl. In a yet further aspect, R⁻⁴, when present, is C1-C3 alkyl. In an even further aspect, R⁻⁴, when present, is C1-C2 alkyl. In a yet further aspect, R⁻⁴, when present, is selected from methyl, trifluoromethyl, ethyl, propyl, and butyl.

In a further aspect, R⁻⁴ is present, and R⁺⁴ and R⁻⁴ are covalently bonded and, together with the intermediate carbon, comprise a 3- to 7-membered spirocycloalkyl. In a still further aspect, R⁻⁴ is present, and R⁺⁴ and R⁻⁴ are covalently bonded and, together with the intermediate carbon, comprise a substituted 3- to 7-membered spirocycloalkyl. In a still further aspect, R⁻⁴ is present, and R⁺⁴ and R⁻⁴ are covalently bonded and, together with the intermediate carbon, comprise a substituted 3- to 7-membered spirocycloalkyl, and the
spirocycloalkyl is substituted with 1 or 2 groups independently selected from methyl, ethyl, and propyl.

k. $R^5A$ GROUPS

[00241] In one aspect, $R^5A$ is selected from hydrogen and C1-C4 alkyl. In a further aspect, $R^5A$ is hydrogen. In a still further aspect, $R^5A$ is methyl. In a yet further aspect, $R^5A$ is C1-C4 alkyl. In an even further aspect, $R^5A$ is C1-C3 alkyl. In a further aspect, $R^5A$ is C1-C2 alkyl. In a yet further aspect, $R^5A$ is selected from methyl, trifluoromethyl, ethyl, propyl, and butyl.

[00242] In a further aspect, $R^{sa}$ and $R^{sb}$, when present, are both hydrogen. In a yet further aspect, each of $R^{sa}$ and $R^{sb}$, when present, is independently selected from hydrogen and C1-C4 alkyl. In a still further aspect, each of $R^{sa}$ and $R^{sb}$ is independently selected from hydrogen, -CH$_3$, and -CH$_2$CH$_3$.

l. $R^{sb}$ GROUPS

[00243] In one aspect, $R^{sb}$, when present, is selected from hydrogen and C1-C4 alkyl, or $R^{sa}$ and $R^{sb}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl. In a further aspect, $R^{sb}$, when present, is hydrogen. In a still further aspect, $R^{sb}$, when present, is C1-C4 alkyl. In a yet further aspect, $R^{sb}$, when present, is selected from methyl, trifluoromethyl, ethyl, propyl, and butyl.

[00244] In a further aspect, $R^{sb}$ is present, and $R^{sa}$ and $R^{sb}$ are covalently bonded and, together with the intermediate carbon, comprise a 3- to 7-membered spirocycloalkyl. In a yet further aspect, $R^{sb}$ is present, and $R^{sa}$ and $R^{sb}$ are covalently bonded and, together with the intermediate carbon, comprise a substituted 3- to 7-membered spirocycloalkyl. In a still further aspect, $R^{sb}$ is present, and $R^{sa}$ and $R^{sb}$ are covalently bonded and, together with the intermediate carbon, comprise a substituted 3- to 7-membered spirocycloalkyl, and the spirocycloalkyl is substituted with 1 or 2 groups independently selected from methyl, ethyl, and propyl.

m. HALOGEN (X)

[00245] In one aspect, halogen is fluoro, chloro, bromo or iodo. In a further aspect, halogen is fluoro, chloro, or bromo. In a yet further aspect, halogen is fluoro or chloro. In a further aspect, halogen is chloro or bromo. In a further aspect, halogen is fluoro. In an even further aspect, halogen is chloro. In a yet further aspect, halogen is iodo. In a still further aspect, halogen is bromo.
It is also contemplated that pseudohalogens (e.g. triflate, mesylate, brosylate, etc.) can be used as leaving groups in place of halogens in certain aspects.

2. EXAMPLE COMPOUNDS

In one aspect, a compound can be present as:
In one aspect, a compound can be present as:
[00249] In one aspect, a compound can be present as:
[00250] In one aspect, a compound can be present as:
In one aspect, a compound can be present as:
In one aspect, a compound can be present as:

[Diagram 1]

In one aspect, a compound can be present as:

[Diagram 2]

In one aspect, a compound can be present as:

[Diagram 3]
In yet a further aspect, the compound produced exhibits positive allosteric modulation of mGluR5 response to glutamate as an increase 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 yet a further aspect, the compound produced exhibits positive allosteric modulation of mGluR5 after contacting a cell expressing mGluR5.

In a further aspect, the disclosed compounds are allosteric modulators of mGluR5, in particular, positive allosteric modulators of mGluR5. The disclosed compounds can potentiate glutamate responses by binding to an allosteric site other than the glutamate orthosteric binding site. The response of mGluR5 to a concentration of glutamate is increased when the disclosed compounds are present. In a further aspect, the disclosed compounds can have their effect substantially at mGluR5 by virtue of their ability to enhance the function of the receptor.

Compounds are shown above are depicted having a basic group or acidic group and named as the free base acid. Depending on the reaction and purification conditions, various compounds having a basic group were isolated in either the free base form, or as a salt (e.g. HCl salt), or in both free base and salt forms.

It is contemplated that one or more compounds can optionally be omitted from the disclosed invention.
3. POSITIVE ALLOSTERIC MODULATION OF MGLUR5 RESPONSE

Generally, the disclosed compounds exhibit potentiation of mGluR5 response to glutamate as an increase 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. For example, a compound can exhibit positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. In a further aspect, the mGluR5 is rat mGluR5. In a still further aspect, the mGluR5 is human mGluR5.

In one aspect, the disclosed compounds exhibit potentiation of mGluR5 response to glutamate as an increase in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, the transfected cell line is the H10H cell line. In a yet further aspect, the transfected cell line is the H12H cell line. For example, a compound can exhibit positive allosteric modulation of transfected human mGluR5 with an EC$_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM.

In one aspect, the disclosed compounds exhibit potentiation of mGluR5 response to glutamate as an increase 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. For example, a compound can exhibit positive allosteric modulation of transfected rat mGluR5 with an EC$_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM.

C. METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

The utility of the compounds in accordance with the present invention as potentiators 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 mGluR5 were plated in clear bottom assay plates for assay in a Functional Drug Screening System (FDSS). In the alternative assay, HEK cells transfected with human mGluR5 were plated for assay in the FDSS. In some cases the HEK cells transfected with human mGluR5 were the H10H cell line. Alternatively, the HEK cells transfected with
human mGluR5 were the H12H cell line. Rat assay results were found to correlate well with human assay results. 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. After establishment of a fluorescence baseline for twelve seconds, the compounds of the present invention were added to the cells, and the response in cells was measured. Alternatively, in various further aspects, after establishment of a fluorescence baseline for about three seconds, the compounds of the present invention were added to the cells, and the response in cells was measured. Five minutes later, an mGluR5 agonist (e.g., glutamate, 3,5-dihydroxyphenylglycine, or quisqualate) was added to the cells, and the response of the cells was measured. Potentiation of the agonist response of mGluR5 by the compounds in the present invention was observed as an increase 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.

The above described assay operated in two modes. In the first mode, a range of concentrations of the present compounds were added to cells, followed by a single fixed concentration of agonist. If a compound acted as a potentiator, an EC\(_{50}\) value for potentiation and a maximum extent of potentiation by the compound at this concentration of agonist was determined by non-linear curve fitting. In the second mode, 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 non-linear 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 potentiation 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.

In one aspect, the disclosed compounds exhibit potentiation of mGluR5 response to glutamate as an increase in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with a mammalian mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. For example, human embryonic kidney cells can be transfected with human mGluR5. For
example, human embryonic kidney cells can be transfected with rat mGluR5. For example, a compound can exhibit positive allosteric modulation of mGluR5 (e.g., rmGluR5) with an EC$_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. Alternatively, the disclosed compounds exhibit potentiation of mGluR5 response to glutamate as an increase in response to non-maximal concentrations of glutamate in human embryonic kidney cells transfected with human mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, the transfected cell line is the H10H cell line. In a yet further aspect, the transfected cell line is the H12H cell line. For example, a compound can exhibit positive allosteric modulation of mGluR5 (e.g., hmGluR5) with an EC$_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM.

[00265] In particular, the disclosed compounds exhibit activity in potentiating the mGluR5 receptor in the aforementioned assays, generally with an EC$_{50}$ for potentiation of less than about 10 μM. Preferred compounds within the present invention had activity in potentiating the mGluR5 receptor with an EC$_{50}$ for potentiation of less than about 500 nM. Preferred compounds further caused a leftward shift of the agonist EC$_{50}$ by greater than 3-fold. These compounds did not cause mGluR5 to respond in the absence of agonist, and they did not elicit a significant increase in the maximal response of mGluR5 to agonists. These compounds are positive allosteric modulators (potentiators) of human and rat mGluR5. In various aspects, the compounds can be selective for mGluR5 compared to the other seven subtypes of metabotropic glutamate receptors.

[00266] In vivo efficacy for disclosed compounds can be measured in a number of preclinical rat behavioral model where known, clinically useful antipsychotics display similar positive responses. For example, disclosed compounds can reverse amphetamine-induced hyperlocomotion in male Sprague-Dawley rats at doses ranging from 1 to 100 mg/kg p.o.

D. METHODS OF MAKING THE COMPOUNDS

[00267] In one aspect, the invention relates to methods of making compounds useful as positive 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.
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.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations known in the literature or to one skilled in the art. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

In a further aspect, the disclosed compounds comprise the products of the disclosed methods. 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.

1. **ROUTE I**

In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.

Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below. In one aspect, ethers of type 1.5 and 1.6 can be prepared starting from methyl 2-bromonicotinate. Stille or Suzuki coupling followed by Michael addition using p-methoxybenzyl amine and ring closure gives Intermediate 1.2. Oxidation and Polonovski rearrangement using POCl₃ affords chloride 1.3. Displacement with an alcohol and protecting group removal using 2,3-
dichloro-5,6-dicyanobenzoquinone (DDQ) give unsubstituted lactams of type 1.5. Optional alkylation or arylation using a Cu(I) or Pd(0) source gives additional examples of type 1.6.

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

wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( R^{3a} \) and \( R^{3b} \) are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( R^{4a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^{5a} \) is selected from hydrogen and C1-C4 alkyl; and wherein \( R^{3a} \) and \( R^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, (b) halogenating to yield a compound having a structure represented by a formula:
wherein \( X \) is a halogen, and (c) reacting with a compound having a structure represented by a formula:

\[
\begin{align*}
&\text{R}^{1a} \quad \text{O} \\
&\text{Ar}^{1} \\
&\text{H}
\end{align*}
\]

wherein \( \text{Ar}^{1} \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or \( \text{Ar}^{1} \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and wherein each of \( \text{R}^{1a} \) and \( \text{R}^{1b} \) is independently selected from hydrogen and C1-C4 alkyl.

[00274] In a further aspect, the prepared compound has a structure represented by a formula:

\[
\begin{align*}
&\text{R}^{1a} \quad \text{R}^{3a} \\
&\text{O} \\
&\text{N} \\
&\text{H} \\
&\text{R}^{5a}
\end{align*}
\]

[00275] In a further aspect, the providing is reacting \( \text{NH}_{2}\text{PMB} \) with a compound having a structure represented by a formula:

\[
\begin{align*}
&\text{R}^{2b} \\
&\text{R}^{3a} \\
&\text{O} \\
&\text{R} \\
&\text{R}^{5a}
\end{align*}
\]

[00276] In a further aspect, the method further comprises the steps of deprotection and alkylation or arylation to yield a compound having a structure represented by a formula:

\[
\begin{align*}
&\text{R}^{2} \\
&\text{R}^{3b} \\
&\text{R}^{3a} \\
&\text{O} \\
&\text{N} \\
&\text{H} \\
&\text{R}^{5a}
\end{align*}
\]

wherein \( \text{R}^{2} \) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.
2. ROUTE II

[00277] In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.

[00278] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

[00279] In one aspect, ethers of type 2.5 through 2.7 can be prepared starting from compound 2.1, 2-chloro-7,8-dihydro-1,6-naphthyridin-5(6H)-one. (see WO 2010/052222, pg 67 and also Intermediate 1.1 described under Route I above) protection with p-methoxybenzyl chloride affords Intermediate 2.2. Vinylation using Pd(0) catalysis, following by ozonolysis and reduction provides Intermediate 2.4. Mitsunobu reaction with A^OH-phenols gives p-methoxybenzyl (PMB) example compounds 2.5; deprotection gives additional examples of type 2.6 and finally alkylation or optional arylation using a Cu(I) or Pd(0) source gives examples of type 2.7.
Thus, in one aspect, the invention relates to a method of making a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:

\[
\begin{align*}
\text{R}^{1a} & \quad \text{R}^{1b} \\
\text{R}^{2a} & \quad \text{R}^{2b} \\
\text{R}^{3a} & \quad \text{R}^{3b} \\
\text{R}^{4a} & \quad \text{R}^{4b} \\
\text{R}^{5a} & \quad \text{R}^{5b}
\end{align*}
\]

wherein \( \text{R}^{1a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( \text{R}^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \( \text{R}^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( \text{R}^{3a} \) and \( \text{R}^{3b} \) are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( \text{R}^{4a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( \text{R}^{4b} \) is selected from hydrogen and C1-C4 alkyl, or \( \text{R}^{4a} \) and \( \text{R}^{4b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein \( \text{R}^{5a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( \text{R}^{5b} \) is selected from hydrogen and C1-C4 alkyl, or \( \text{R}^{5a} \) and \( \text{R}^{5b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein \( \text{R}^{4a} \) and \( \text{R}^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) reacting with \( \text{Ar}^{1a} \text{OH} \), wherein \( \text{Ar}^{1a} \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or \( \text{Ar}^{1a} \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

In a further aspect, the prepared compound has a structure represented by a formula:

\[
\begin{align*}
\text{R}^{1a} & \quad \text{R}^{1b} \\
\text{R}^{2a} & \quad \text{R}^{2b} \\
\text{R}^{3a} & \quad \text{R}^{3b} \\
\text{R}^{4a} & \quad \text{R}^{4b} \\
\text{R}^{5a} & \quad \text{R}^{5b}
\end{align*}
\]

In a further aspect, the providing is hydroxymethylation of a compound having \( \Sigma \) structure represented by a formula:
wherein X is halogen. In a still further aspect, the hydroxymethylation comprises the steps of vinylation, ozonolysis, and reduction. In a yet further aspect, the hydroxymethylation comprises the steps of formylation and reduction.

[00283] In a further aspect, the method further comprises the steps of deprotection and alkylation or arylation to yield a compound having a structure represented by a formula:

wherein R2 is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

3. ROUTE III

[00284] In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.

[00285] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.
In one aspect, ethers of type 3.7 containing a 2,7-disubstituted-6,7-dihydro-1,7-naphthyridin-8(5H)-one can be prepared according the general route outlined above. Dichloronicotinic acid 3.1 is first reduced to alcohol 3.2 followed by selective cyanation to give 3.3. Mitsunobu alkylation gives ether 3.4. Nitrile hydrolysis, allyl coupling, and oxidative cleavage using OsO₄ and sodium periodate gives penultimate intermediate 3.6. Reductive amination with a primary amine and cyclization provides examples of type 3.7.

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

\[
\text{R}^{3a} \quad \text{N} \quad \text{R}^{3b}
\]

wherein \(X^2\) is halogen; wherein \(R\) is cyano or ester; wherein \(\text{Ar}^1\) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or \(\text{Ar}^1\) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein \(\text{R}^{3a}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; and wherein \(\text{R}^{3b}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, and (b) coupling with an allyl(trialkyl)tin reagent having a structure represented by a formula:

\[
\text{R}^{4a} \quad \text{Sn(alkyl)₃}
\]
wherein $R^{4a}$ is selected from hydrogen and C1-C4 alkyl; wherein $R^{5a}$ is selected from hydrogen and C1-C4 alkyl; and wherein $R^{4b}$ and $R^{5b}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl.

[00288] In a further aspect, the prepared compound has a structure represented by a formula:

![Chemical structure](attachment:image)

[00289] In a further aspect, the providing comprises the steps of: (a) reduction of a compound having a structure represented by a formula:

![Chemical structure](attachment:image)

wherein $X^1$ and $X^2$ are independently halogen, (b) reaction with $Ar^1OH$, and (c) conversion of $X^1$ to cyano.

[00290] In a further aspect, the method further comprises the steps of: (a) oxidative cleavage of the vinyl group; and (b) cyclization in the presence of $3\alpha NR$, wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, to yield a compound having a structure represented by a formula:

![Chemical structure](attachment:image)

[00291] In a further aspect, each of $R^4$ and $R^5$ are hydrogen.

4. ROUTE IV

[00292] In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.
Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below. In one aspect, ethers of type 4.5-4.7 are prepared as described in the reaction schemes above. The acid 4.1 is first converted to ester 4.2, followed by selective vinylation using Molander Suzuki coupling conditions to give 4.3. Cyclization, Cu promoted etherification, PMB removal, and final alkylation or N-arylation gives examples 4.7.

Thus, in one aspect, the invention relates to a method of making a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:
wherein $X_1$ is halogen; wherein $R$ is alkyl; wherein $R^{3a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein $R^{3b}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein $R^{4a}$ is selected from hydrogen and C1-C4 alkyl; wherein $R^{5a}$ is selected from hydrogen and C1-C4 alkyl; and wherein $R^{4a}$ and $R^{5a}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) cyclizing with $\text{H}_2\text{NPMB}$.

[00295] In a further aspect, the prepared compound has a structure represented by a formula:

![Chemical structure](image1)

[00296] In a further aspect, the providing is vinylation of a compound having a structure represented by a formula:

![Chemical structure](image2)

wherein $X_1$ and $X_2$ are independently halogen. In a still further aspect, $X_1$ is Br, and wherein $X_2$ is chloro. In a yet further aspect, vinylation is performed with a reagent having a structure represented by a formula:

![Chemical structure](image3)

[00297] In a further aspect, the method further comprises the step of etherification with a compound having a structure represented by a formula:

![Chemical structure](image4)

wherein $\text{Ar}^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or $\text{Ar}^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, to yield a compound having a structure.
represented by a formula:

![Chemical Structure](image)

[00298] In a still further aspect, the foregoing method further comprises the steps of deprotection and alkylation or arylation to yield a compound having a structure represented by a formula:

![Chemical Structure](image)

wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy.

[00299] In a further aspect, each of $R^4$ and $R^5$ are hydrogen.

5. ROUTE V

[00300] In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.

![Synthetic Route](image)

[00301] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below. In one aspect, ethers of type 5.5-5.7 are prepared as described in the synthetic reaction sequence above. Starting from ester 5.1, double Suzuki or Stille coupling gives 5.2. Selective Michael addition using p-methoxybenzyl amine and ring closure gives 5.3. Ozonolysis and reduction gives alcohol 5.4. Ether formation using a Mitsunobu reaction gives PMB examples of type 5.5. PMB removal provides examples of type 5.6 and optional alkylation using an alkyl
halide or optional arylation using a copper or palladium catalyst with an appropriate aryl halide provides additional examples of type 5.7.

[00302] Thus, in one aspect, the invention relates to a method of making a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:

![Chemical Structure](image)

wherein R is alkyl; wherein R^{3a} is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; and wherein R^{3b} is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, and (b) cyclizing with H_2NPMB.

[00303] In a further aspect, the prepared compound has a structure represented by a formula:

![Chemical Structure](image)

[00304] In a further aspect, the providing is vinylation, under Stille or Suzuki conditions, of a compound having a structure represented by a formula:
wherein $X^1$ and $X^2$ are independently halogen. In a still further aspect, $X^1$ is Br, and wherein $X^2$ is chloro.

[00305] In a further aspect, the method further comprises the steps of ozonolysis, Mitsunobu reaction, and alkylation or arylation to yield a compound having a structure represented by a formula:

wherein $Ar^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or $Ar^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

6. ROUTE VI

[00306] In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.

[00307] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.
In one aspect, ethers of type 6.5 can be prepared starting from commercially available 6.1. A sequence involving first phenol alkylation or Mitsunobu alkylation followed by allylation, oxidative cleavage and tandem reductive amination and ring closure generates examples of type 6.5.

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

wherein R is alkyl; wherein Ar\(^{1}\) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar\(^{1}\) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R\(^{1a}\) and R\(^{1b}\) is independently selected from hydrogen and C1-C4 alkyl; wherein R\(^{3a}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R\(^{3b}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R\(^{4a}\) is selected from hydrogen and C1-C4 alkyl; wherein R\(^{5a}\) is selected from hydrogen and C1-C4 alkyl; and wherein R\(^{4a}\) and R\(^{5a}\) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and (b) cyclization in the presence of H\(_2\)NR\(^2\), wherein R\(^{2}\) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, to yield a compound having a structure represented by a formula:
In a further aspect, the providing comprises ozonolysis of a compound having a structure represented by a formula:

In a still further aspect, the providing further comprises coupling a compound having a structure represented by a formula:

wherein $X^2$ is halogen, with an allyl(trialkyl)tin reagent having a structure represented by a formula:

In a further aspect, each of $R^4$ and $R^5$ are hydrogen.

7. ROUTE VII

In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.
Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

[00314] In one aspect, examples of type 7.5 can be prepared starting from diester 7.1. Lithiation and alkylation generates allyl intermediate 7.2. Ozonolysis and reductive workup can provide 7.3. Reductive alkylation and ring closure with an amine, followed by ester reduction and ether formation via either Mitsunobu or a two-step activation-alkylation sequence can prepare examples 7.5.

[00315] Thus, in one aspect, the invention relates to a method of making a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:

\[
\begin{array}{c}
\text{R}^4 \text{N} \text{R}^5 \text{O} \text{R}^6 \\
\text{R}^a \text{R}^b \text{R}^\text{c} \text{R}^\text{d}
\end{array}
\]

wherein each R is independently alkyl; wherein R^{3a} is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R^{3b} is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R^{3a} and R^{3b} are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R^{4a} is selected from hydrogen and C1-C4 alkyl; wherein R^{5a} is selected from hydrogen and C1-C4 alkyl; and wherein R^{4a} and R^{5a} are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, and cyclization in the presence of 3\text{a}NR \text{R}^2 to yield a compound having a structure represented by a formula:
wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8
cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents
selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl
having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

[00317] In a further aspect, the providing comprises ozonolysis of a compound having a
structure represented by a formula:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

[00318] In a still further aspect, the providing further comprises the sequential steps of: (a)
deprotonation of a compound having a structure represented by a formula:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

and, (b) reaction with a compound having a structure represented by a formula:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

wherein $X$ is halogen or pseudohalogen. In a yet further aspect, deprotonation is lithiation.

[00319] In a further aspect, the method further comprises the steps of reduction and
etherification to form a compound having a structure represented by a formula:

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

[00320] In a still further aspect, etherification is performed under Mitsunobu conditions
with $A^\text{OH}$. 

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In a further aspect, $R_3^{\text{b}}$ is hydrogen. In a still further aspect, each of $R_4$ and $R_5$ are hydrogen.

8. **ROUTE VIII**

In one aspect, substituted naphthyridinone analogs of the present invention can be prepared as shown below.

[00323] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

[00324] In one aspect, ethers of type 8.5 and 8.6 can be prepared starting from the commercially available compound, methyl 2-bromonicotinate. A Stille or Suzuki coupling is carried out on the starting material, followed by Michael addition using p-methoxybenzyl amine and ring closure gives Intermediate 8.2. Oxidation and Polonovski rearrangement using $\text{POCl}_3$ affords chloride 8.3. Displacement with an alcohol and protecting group removal using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) yields unsubstituted lactams of
type 8.5. Optional alkylation or arylation using a Cu(I) or Pd(0) source gives additional examples of type 8.6.

[00325] Thus, in one aspect, the invention relates to a method of making a compound comprising the steps of: (a) providing a compound having a structure represented by a formula:

\[
\begin{align*}
H & \quad N \\
\text{PMB} & \quad N \\
R^3a & \quad R^3a \\
R^4a & \quad R^5a
\end{align*}
\]

wherein \(R^{3a}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein \(R^{3b}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \(R^{3a}\) and \(R^{3b}\) are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \(R^{4a}\) is selected from hydrogen and C1-C4 alkyl; wherein \(R^{5a}\) is selected from hydrogen and C1-C4 alkyl; and wherein \(R^{3a}\) and \(R^{5a}\) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl, (b) halogenating to yield a compound having a structure represented by a formula:

\[
\begin{align*}
& \quad X \\
\text{PMB} & \quad N \\
R^3a & \quad R^3a \\
R^4a & \quad R^5a
\end{align*}
\]

wherein \(X\) is a halogen, and (c) reacting with a compound having a structure represented by a formula:

\[
\begin{align*}
\text{Ar}^{1a} & \quad \text{Ar}^{1b} \\
\text{O} & \quad \text{H}
\end{align*}
\]

wherein \(\text{Ar}^1\) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or \(\text{Ar}^1\) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and wherein each of \(R^{1a}\) and \(R^{1b}\) is independently selected from hydrogen and C1-C4 alkyl.

[00326] In a further aspect, the prepared compound has a structure represented by a formula:
In a further aspect, the providing comprises reacting $\text{NH}_{2}\text{PMB}$ with a compound having a structure represented by a formula:

![Chemical Structure](image)

In a further aspect, the method further comprises the steps of deprotection and alkylation or arylation to yield a compound having a structure represented by a formula:

![Chemical Structure](image)

wherein $R^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy.

In a further aspect, $X$ is chloro.

In a further aspect, the compound produced exhibits positive allosteric modulation of mGluR5 response to glutamate as an increase 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 positive allosteric modulation of mGluR5 (e.g., rmGluR5) with an $EC_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. In a still further aspect, the compound produced exhibits potentiation of mGluR5 response to glutamate as an increase in response to non-maximal concentrations of glutamate.
in human embryonic kidney cells transfected with human mGluR5 in the presence of the compound, compared to the response to glutamate in the absence of the compound. In a further aspect, the transfected cell line is the H10H cell line. In a still further aspect, the transfected cell line is the H12H cell line. In a yet further aspect, the compound produced exhibits positive allosteric modulation of mGluR5 (e.g., hmGluR5) with an EC$_{50}$ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM.

In particular, the compound produced exhibits activity in potentiating the mGluR5 receptor in the disclosed assays, generally with an EC$_{50}$ for potentiation of less than about 10 µM. Preferred compounds within the present invention had activity in potentiating the mGluR5 receptor with an EC$_{50}$ for potentiation of less than about 500 nM. Preferred compounds further caused a leftward shift of the agonist EC$_{50}$ by greater than 3-fold. These compounds did not cause mGluR5 to respond in the absence of agonist, and they did not elicit a significant increase in the maximal response of mGluR5 to agonists. These compounds are positive allosteric modulators (potentiators) of human and rat mGluR5. In various aspects, the compounds can be selective for mGluR5 compared to the other seven subtypes of metabotropic glutamate receptors.

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.

Table 1 below lists specific compounds as well as experimentally determined 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 human mGluR5. The compounds in Table 1 were synthesized with methods identical or analogous to those shown herein. The column labeled "Rxn" and the data thereunder indicated in Table 1 refers to the Reaction Scheme number described above. The requisite starting materials were commercially available, described in the literature, or readily synthesized by one skilled in the art of organic synthesis.
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<th>EC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
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<td>EC_{50} (nM)</td>
<td>E_{Max} (%)</td>
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E. PHARMACEUTICAL COMPOSITIONS

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 or at least one product of a disclosed method and a pharmaceutically acceptable carrier.

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 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.

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 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'-dibenzylethlenediamine, 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.
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, pamoic, pantothentic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

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.

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.

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.

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 standard aqueous or nonaqueous techniques.

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 agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

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 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.

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.
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.

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.

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.

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.

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 miligrams 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.

[00351] 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.

[00352] 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 comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[00353] The disclosed pharmaceutical compositions can further comprise other therapeutically active compounds, which are usually applied in the treatment of the above mentioned pathological conditions.

[00354] It is understood that the disclosed compositions can be prepared from the disclosed 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

[00355] 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 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, including, but not limited to, schizophrenia general psychosis and cognitive deficits, 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 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.

The second class of glutamate receptor, termed metabotropic glutamate receptors, (mGlurRs), 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 mGlurRs 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 mGlurRs have been identified, cloned and sequenced. Based on structural similarity, primary coupling to intracellular signaling pathways and pharmacology, the mGlurRs 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 mGlurRs are coupled through G_{e/11} to increase inositol phosphate and metabolism and resultant increases in intracellular calcium. Group I mGlurRs 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) mGlurRs are primarily located pre-synaptically where they regulate the release of neurotransmitters, such as glutamate. Group II and Group III mGlurRs are coupled to G_{e/i} and its associated effectors such as adenylate cyclase.

Post-synaptic mGlurRs are known to functionally interact with post-synaptic ionotopic glutamate receptors, such as the NMDA receptor. For example, activation of

Phencyclidine (PCP) and other NMDA receptor antagonists induce a psychotic state in humans similar to schizophrenia. In schizophrenia patients, PCP and ketamine exacerbate/precipitate preexisting positive and negative symptoms in stable patients. Treatment with NMDA receptor co-agonists can improve positive and negative symptoms. A schematic of the NMDA receptor is shown in Figure 1. Activation of mGluR5 potentiates NMDA receptor function as shown in Figure 2. Orthosteric ligands lack subtype selectivity and can cause unwanted side effects. Allosteric modulators (see Figure 3) that can target transmembrane domains offer a pharmacologically attractive alternative. In one aspect, transmembrane domains can be significantly less conserved than extracellular loop regions.

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

In another aspect, the subject compounds can be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), 5-HT2 antagonists, GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbitol, and salts thereof and combinations thereof.

In another aspect, the subject compound can be used in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor), anticholinergics such as biperiden, COMT inhibitors such as entacapone, A2a adenosine antagonists, cholinergic agonists, NMDA receptor antagonists and dopamine agonists.

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

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.

Examples of disorders associated with glutamate dysfunction include: autism, 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.

[00366] Epilepsy can be treated or prevented by the compositions disclosed herein,
including absence epilepsy. In various aspects, the compositisons disclosed herein can have
a protective role for spike and wave discharges associated with absence seizures.
Metabotropic glutamate (mGlu) receptors positioned at synapses of the cortico-thalamo-
cortical circuitry that generates spike-and-wave discharges (SWDs) associated with absence
seizures. Thus, without wishing to be bound by a particular theory, mGluR receptors are
therapeutic targets for the treatment of absence epilepsy (e.g., see Epilepsia, 52(7): 121 1-1222,
2011; Neuropharmacology 60 (2011) 1281el291; and abstract from 7th International
conference on metabotropic glutamate receptors, Oct 2-6, 2011 Taormina, Italy,
"Pharmacological activation of metabotropic glutamate receptor subtype reduces Spike and
Wave Discharges in the WAG/Rij rat model of absence epilepsy," I. Santolini, V. D'Amore,

[00367] 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.

[00368] Thus, in some aspects of the disclosed method, the disorder is dementia, delirium,
amnestic disorders, age-related cognitive decline, schizophrenia, including positive and
negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis
including schizophrenia, schizoaffective disorder, schizoaffective disorder, delusional
disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy,
chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep
disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar
disorder, and psychotic depression.
Thus, provided is a method for treating or prevention schizophrenia, 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 schizophrenia and
related disorders.

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.

a. TREATMENT OF A NEUROLOGICAL AND/OR PSYCHIATRIC DISORDER ASSOCIATED WITH GLUTAMATE DYSFUNCTION

In one aspect, the invention relates to a method for the treatment of a disorder
associated with mGluR5 activity in a mammal comprising the step of administering to the
mammal at least one disclosed compound or at least one disclosed product in a dosage and
amount effective to treat the disorder in the mammal. In a further aspect, the mammal is a
human. In a further aspect, the mammal has been diagnosed with a need for treatment of the
disorder prior to the administering step. In a further aspect, the method further comprises the
step of identifying a mammal in need of treatment of the disorder.

In one aspect, the invention relates to a method for the treatment of a neurological
and/or psychiatric disorder associated with glutamate dysfunction 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 each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of $Y^1$ and $Y^2$ is N, and the other is C-R$^{3a}$; wherein one of $Z^1$ and $Z^2$ is C-L-Ar$^1$, and the other is C-R$^{3b}$; wherein $L$ is -0-C(R$^1$R$^{1b}$)- or -C(R$^1$R$^{1b}$)-0-; wherein Ar$^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar$^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R$^{1a}$ and R$^{1b}$ is independently selected from hydrogen and C1-C4 alkyl; wherein R$^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R$^{3a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R$^{3b}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R$^{3a}$ and R$^{3b}$ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R$^{4a}$ is selected from hydrogen and C1-C4 alkyl; wherein R$^{4b}$, when present, is selected from hydrogen and C1-C4 alkyl, or R$^{4a}$ and R$^{4b}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R$^{5a}$ is selected from hydrogen and C1-C4 alkyl; wherein R$^{5b}$, when present, is selected from hydrogen and C1-C4 alkyl, or R$^{5a}$ and R$^{5b}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R$^{4a}$ and R$^{5a}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00373] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00374] In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 10,000 nM. In a still further aspect, the compound
exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of about 100 nM.

[00375] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of treatment of the disorder.

[00376] In a further aspect, the disorder is a neurological and/or psychiatric disorder associated with mGluR5 dysfunction. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof, and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, 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, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer’s disease, and mild cognitive impairment.
b. TREATMENT OF A DISORDER OF UNCONTROLLED CELLULAR PROLIFERATION

In one aspect, the invention relates to a method for the treatment of a disorder of uncontrolled cellular proliferation 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:

![Chemical Structure]

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y¹ and Y² is N, and the other is C-R³ᵇ; wherein one of Z¹ and Z² is C-L-Ar¹, and the other is C-R³ᵇ; wherein L is -0-C(R¹ᵃR¹ᵇ)- or -C(R¹ᵃR¹ᵇ)-0-; wherein Ar¹ is phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy, or Ar¹ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein each of R¹ᵃ and R¹ᵇ is independently selected from hydrogen and C₁-C₄ alkyl; wherein R² is selected from hydrogen; C₁-C₆ alkyl; (C₁-C₆ alkyloxy) C₁-C₆ alkyl; C₃-C₈ cycloalkyl; (C₃-C₈ cycloalkyl) C₁-C₆ alkyl; C₂-C₅ heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; (C₁-C₂ alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein R³ᵃ is selected from hydrogen, halogen, cyano, and C₁-C₄ alkyl; wherein R³ᵇ is selected from hydrogen, halogen, cyano, and C₁-C₄ alkyl, or R³ᵃ and R³ᵇ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R⁴ᵃ is selected from hydrogen and C₁-C₄ alkyl; wherein R⁴ᵇ, when present, is selected from hydrogen and C₁-C₄ alkyl, or R⁴ᵃ and R⁴ᵇ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R⁵ᵃ is selected from hydrogen and C₁-C₄ alkyl; wherein R⁵ᵇ, when present, is selected from hydrogen and C₁-C₄ alkyl, or R⁵ᵃ and R⁵ᵇ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R⁴ᵃ and R⁵ᵃ are optionally covalently bonded and, together with
the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused
cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00378] In a further aspect, the compound administered is a disclosed compound or a
product of a disclosed method of making a compound.

[00379] In one aspect, the mammal is human. In a further aspect, the mammal has been
diagnosed with a need for treatment of a disorder of uncontrolled cellular proliferation 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 of uncontrolled cellular proliferation.
In a yet further aspect, the disorder of uncontrolled cellular proliferation is associated with
mGluR5 dysfunction.

[00380] In a further aspect, the disorder of uncontrolled cellular proliferation is cancer. In
a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer,
and colorectal cancer. In a yet further aspect, the disorder is selected from lymphoma,
cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer,
larinx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma. In an even
further aspect, the disorder is selected from breast cancer, renal cancer, gastric cancer,
colorectal cancer, lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic
system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, and malignant
melanoma.

c. POTENTIATION OF METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00381] In one aspect, the invention relates to a method for potentiation of mGluR5
activity in a mammal comprising the step of administering to the mammal at least one
disclosed compound or at least one disclosed product in a dosage and amount effective to
increase mGluR5 activity in the mammal either in the presence or absence of the endogenous
ligand. In a further aspect, the mammal is a human. In a further aspect, the mammal has been
diagnosed with a need for increasing mGluR5 activity prior to the administering step. In a
further aspect, the mammal has been diagnosed with a need for treatment of a disorder related
to mGluR5 activity prior to the administering step. In a further aspect, the method further
comprises the step of identifying a mammal in need of increasing mGluR5 activity.

[00382] In one aspect, the invention relates to a method for potentiation of 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 each $\ldots$ is independently an optional covalent bond, wherein valence is satisfied; wherein one of $Y^1$ and $Y^2$ is N, and the other is C-R$^{3a}$; wherein one of $Z^1$ and $Z^2$ is C-L-Ar$^1$, and the other is C-R$^{3b}$; wherein L is -O-C(R$^{1a}$R$^{1b}$)- or -C(R$^{1a}$)-0-; wherein Ar$^1$ is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar$^1$ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R$^{1a}$ and R$^{1b}$ is independently selected from hydrogen and C1-C4 alkyl; wherein R$^2$ is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R$^{3a}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R$^{3b}$ is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R$^{3a}$ and R$^{3b}$ are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R$^{4a}$ is selected from hydrogen and C1-C4 alkyl; wherein R$^{4b}$, when present, is selected from hydrogen and C1-C4 alkyl, or R$^{4a}$ and R$^{4b}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R$^{5a}$ is selected from hydrogen and C1-C4 alkyl; wherein R$^{5b}$, when present, is selected from hydrogen and C1-C4 alkyl, or R$^{5a}$ and R$^{5b}$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R$^{4b}$ and R$^{5a}$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00383] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00384] In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 10,000 nM. In a still further aspect, the compound
exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 100 nM.

[00385] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for potentiation of metabotropic glutamate receptor activity prior to the administering step. In a further aspect, the method further comprises comprising the step of identifying a mammal in need for potentiation of metabotropic glutamate receptor activity. In a further aspect, the metabotropic glutamate receptor is mGluR5.

[00386] In a yet further aspect, the potentiation of mGluR5 activity treats a disorder associated with mGluR5 activity in the mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In an even further aspect, treatment further comprises the step of identifying a mammal in need of treatment of the disorder.

[00387] In a further aspect, potentiation of metabotropic glutamate receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with mGluR5 dysfunction. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, 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, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer’s disease, and mild cognitive impairment.

[00388] In a further aspect, potentiation of metabotropic glutamate receptor activity in a mammal is associated with the treatment of a disorder associated with uncontrolled cellular proliferation. In a further aspect, the disorder associated with uncontrolled cellular proliferation is cancer. In a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In a yet further aspect, the disorder 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. In an even further aspect, the disorder is selected from breast cancer, renal cancer, gastric cancer, colorectal cancer, lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, and malignant melanoma.

d. PARTIAL AGONISM OF METABOTROPIC GLUTAMATE RECEPTOR ACTIVITY

[00389] In one aspect, the invention relates to a method for partial agonism of metabotropic glutamate receptor activity in a mammal. In a further aspect, the method relates to a method for partial agonism of metabotropic glutamate receptor activity in a mammal by contacting at least one cell in the mammal, comprising the step of contacting the at least one cell with at least one disclosed compound or at least one disclosed product in an amount effective to inhibit mGluR5 activity in the at least one cell.

[00390] In one aspect, the invention relates to a method for partial agonism of 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 each is independently an optional covalent bond, wherein valence is satisfied; wherein one of \(Y^1\) and \(Y^2\) is \(N\), and the other is \(C-R^3\); wherein one of \(Z^1\) and \(Z^2\) is \(C-L-Ar\), and the other is \(C-R^{ib}\); wherein \(L\) is \(-O-(R^1R^{ib})\)- or \(-C(R^{1b}R^{ib})-O\)-; wherein \(Ar^1\) is phenyl with 0-3 substituents selected from halogen, cyano, \(C_1-C_4\) alkyl, and \(C_1-C_4\) alkyloxy, or \(Ar^1\) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, \(C_1-C_4\) alkyl, and \(C_1-C_4\) alkyloxy; wherein each of \(R^1a\) and \(R^{ib}\) is independently selected from hydrogen and \(C_1-C_4\) alkyl; wherein \(R^2\) is selected from hydrogen; \(C_1-C_6\) alkyl; \((C_1-C_6\) alkyloxy) \(C_1-C_6\) alkyl; \(C_3-C_8\) cycloalkyl; \((C_3-C_8\) cycloalkyl) \(C_1-C_6\) alkyl; \(C_2-C_5\) heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, \(C_1-C_4\) alkyl, and \(C_1-C_4\) alkyloxy; \((C_1-C_2\) alkyl) phenyl with 0-3 substituents selected from halogen, cyano, \(C_1-C_4\) alkyl, and \(C_1-C_4\) alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, \(C_1-C_4\) alkyl, and \(C_1-C_4\) alkyloxy; wherein \(R^{3a}\) is selected from hydrogen, halogen, cyano, and \(C_1-C_4\) alkyl; wherein \(R^{3b}\) is selected from hydrogen, halogen, cyano, and \(C_1-C_4\) alkyl, or \(R^{3a}\) and \(R^{3b}\) are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \(R^{4a}\) is selected from hydrogen and \(C_1-C_4\) alkyl; wherein \(R^{4b}\), when present, is selected from hydrogen and \(C_1-C_4\) alkyl, or \(R^{4a}\) and \(R^{4b}\) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein \(R^{5a}\) is selected from hydrogen and \(C_1-C_4\) alkyl; wherein \(R^{5b}\), when present, is selected from hydrogen and \(C_1-C_4\) alkyl, or \(R^{5a}\) and \(R^{5b}\) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein \(R^{4b}\) and \(R^{5a}\) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00391] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00392] In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an \(EC_{50}\) of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an \(EC_{50}\) of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an \(EC_{50}\) of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an \(EC_{50}\) of less than about 500 nM. In a yet further
aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC\textsubscript{50} of less than about 100 nM.

[00393] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for partial agonism 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 for partial agonism of metabotropic glutamate receptor activity. In a yet further aspect, the metabotropic glutamate receptor is mGluR5.

[00394] In a further aspect, partial agonism of metabotropic glutamate receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with mGluR5 dysfunction. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, 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, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer’s disease, and mild cognitive impairment.

[00395] In a further aspect, partial agonism of metabotropic glutamate receptor activity in a mammal is associated with the treatment of a disorder associated with uncontrolled cellular
proliferation. In a further aspect, the disorder associated with uncontrolled cellular proliferation is cancer. In a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In a yet further aspect, the disorder 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. In an even further aspect, the disorder is selected from breast cancer, renal cancer, gastric cancer, colorectal cancer, lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, and malignant melanoma.

**e. ENHANCING COGNITION**

[00396] In one aspect, the invention relates to a method for enhancing cognition in a mammal comprising the step of administering to the mammal an effective amount of at least one disclosed compound.

[00397] In one aspect, the invention relates to a method for enhancing cognition in a mammal comprising the step of administering to the mammal an effective amount of at least one compound having a structure represented by a formula:

![Chemical Structure](image)

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y<sup>1</sup> and Y<sup>2</sup> is N, and the other is C-R<sup>3a</sup>; wherein one of Z<sup>1</sup> and Z<sup>2</sup> is C-L-Ar<sup>1</sup>, and the other is C-R<sup>1b</sup>; wherein L is -O-C(R<sup>1a</sup>R<sup>1b</sup>)<sub>2</sub>- or -C(R<sup>1a</sup>R<sup>1b</sup>)<sub>3</sub>-; wherein Ar<sup>1</sup> is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar<sup>1</sup> is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R<sup>1a</sup> and R<sup>1b</sup> is independently selected from hydrogen and C1-C4 alkyl; wherein R<sup>2</sup> is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) Cl-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R<sup>3a</sup> is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R<sup>3b</sup> is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R<sup>3a</sup>...
and \( R^{3b} \) are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein \( R^{4a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^{4b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( R^{4a} \) and \( R^{4b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein \( R^{5a} \) is selected from hydrogen and C1-C4 alkyl; wherein \( R^{5b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( R^{5a} \) and \( R^{5b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein \( R^{4a} \) and \( R^{5a} \) are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00398] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00399] In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 100 nM.

[00400] In one aspect, the mammal is a human. In one aspect, the mammal has been diagnosed with a need for cognition enhancement prior to the administering step. In a still further aspect, the method further comprises the step of identifying a mammal in need of cognition enhancement prior to the administering step. In a further aspect, the cognition enhancement is a statistically significant increase in Novel Object Recognition. In a further aspect, the cognition enhancement is a statistically significant increase in performance of the Wisconsin Card Sorting Test.

f. MODULATING MGLUR5 ACTIVITY IN MAMMALS

[00401] In one aspect, the invention relates to a method for modulating mGluR5 activity in a mammal comprising the step of administering to the mammal an effective amount of at least one disclosed compound.
In one aspect, the invention relates to a method for modulating mGluR5 activity in a mammal comprising the step of administering to the mammal an effective amount of at least one compound having a structure represented by a formula:

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y1 and Y2 is N, and the other is C-R3a; wherein one of Z1 and Z2 is C-L-Ar1, and the other is C-R3b; wherein L is -0-C(R1aR1b)- or -C(R1aR1b)-0-; wherein Ar1 is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy, or Ar1 is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein each of R1a and R1b is independently selected from hydrogen and C1-C4 alkyl; wherein R2 is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkoxy; wherein R3a is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R3b is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R3a and R3b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R4a is selected from hydrogen and C1-C4 alkyl; wherein R4b, when present, is selected from hydrogen and C1-C4 alkyl, or R4a and R4b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R5a is selected from hydrogen and C1-C4 alkyl; wherein R5b, when present, is selected from hydrogen and C1-C4 alkyl, or R5a and R5b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R4b and R5a are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.
In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC$_{50}$ of less than about 100 nM.

In one aspect, modulating is increasing. In a further aspect, modulating is potentiation. In a further aspect, modulating is partial agonism.

In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for modulating mGluR5 activity prior to the administering step. In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to mGluR5 activity prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of increasing mGluR5 activity.

In one aspect, an effective amount is a therapeutically effective amount. In a further aspect, an effective amount is a prophylactically effective amount.

In one aspect, modulating mGluR5 activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with mGluR5 dysfunction. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating
disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, 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, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer's disease, and mild cognitive impairment.

In a further aspect, modulating mGluR5 activity in a mammal is associated with the treatment of a disorder associated with uncontrolled cellular proliferation. In a further aspect, the disorder associated with uncontrolled cellular proliferation is cancer. In a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In a yet further aspect, the disorder 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. In an even further aspect, the disorder is selected from breast cancer, renal cancer, gastric cancer, colorectal cancer, lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, and malignant melanoma.

g. MODULATING mGLU5 ACTIVITY IN CELLS

In one aspect, the invention relates to a method for modulating mGluR5 activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of at least one disclosed compound.

In one aspect, the invention relates to a method for modulating mGluR5 activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of at least one compound having a structure represented by a formula:

![Chemical Structure](image)

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y1 and Y2 is N, and the other is C-R3a; wherein one of Z1 and Z2 is C-L-Ar1, and the other is C-R3b; wherein L is -O-(R1aR1b)- or -C(R1aR1b)-O--; wherein Ar1 is phenyl...
with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or Ar is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein each of R1 and R2 is independently selected from hydrogen and C1-C4 alkyl; wherein R3 is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; wherein R3a is selected from hydrogen, halogen, cyano, and C1-C4 alkyl; wherein R3b is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R3a and R3b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R4a is selected from hydrogen and C1-C4 alkyl; wherein R4b, when present, is selected from hydrogen and C1-C4 alkyl, or R4a and R4b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R5a is selected from hydrogen and C1-C4 alkyl; wherein R5b, when present, is selected from hydrogen and C1-C4 alkyl, or R5a and R5b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R4a and R5a are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof.

[00412] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound.

[00413] In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mGluR5 with an EC50 of less than about 100 nM.
In one aspect, modulating is increasing. In a further aspect, modulating is potentiation. In a further aspect, modulating is partial agonism.

In one aspect, the cell is mammalian. In a further aspect, the cell is human. In a further aspect, the cell has been isolated from a mammal prior to the contacting step.

In a further aspect, contacting is via administration to a mammal. In a further aspect, the mammal has been diagnosed with a need for modulating mGluR5 activity prior to the administering step. In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to mGluR5 activity prior to the administering step.

In one aspect, modulating mGluR5 activity in at least one cell treats a neurological and/or psychiatric disorder. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, 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, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer’s disease, and mild cognitive impairment.

In a further aspect, modulating mGluR5 activity in at least one cell treats a disorder associated with uncontrolled cellular proliferation. In a further aspect, the disorder
associated with uncontrolled cellular proliferation is cancer. In a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In a yet further aspect, the disorder 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. In an even further aspect, the disorder is selected from breast cancer, renal cancer, gastric cancer, colorectal cancer, lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, and malignant melanoma.

2. MANUFACTURE OF A MEDICAMENT

[00419] In one aspect, the invention relates to a method for the manufacture of a medicament for potentiation of metabotropic glutamate receptor activity in a mammal comprising combining a therapeutically effective amount of a disclosed compound or product of a disclosed method with a pharmaceutically acceptable carrier or diluent.

3. USE OF COMPOUNDS

[00420] In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method. In a further aspect, a use relates to the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal. In a further aspect, the disorder is a neurological and/or psychiatric disorder. In a further aspect, the disorder is a disease of uncontrolled cellular proliferation. In a further aspect, a use relates to treatment of a neurological and/or psychiatric disorder associated with glutamate dysfunction in a mammal.

[00421] In a further aspect, a use relates to potentiation of metabotropic glutamate receptor activity in a mammal. In a further aspect, a use relates to partial agonism of metabotropic glutamate receptor activity in a mammal. In a further aspect, a use relates to enhancing cognition in a mammal. In a further aspect, a use relates to modulating mGluR5 activity in a mammal. In a further aspect, a use relates to modulating mGluR5 activity in a cell.

[00422] In one aspect, a use is treatment of a neurological and/or psychiatric disorder associated with mGluR5 dysfunction. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia,
obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, 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, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer’s disease, and mild cognitive impairment.

In one aspect, a use is associated with the treatment of a disorder associated with uncontrolled cellular proliferation. In a further aspect, the disorder is cancer. In a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In a further aspect, the disorder 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.

In one 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 further aspect, the disorder is a neurological and/or psychiatric disorder. In a further aspect, the disorder is a disease of uncontrolled cellular proliferation.

4. KITS

In one aspect, the invention relates to a kit comprising a disclosed compound or a product of a disclosed method 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 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.

[00426] In a further aspect, the kit o comprised a disclosed compound or a product of a disclosed method.

[00427] In a further aspect, the at least one compound and the at least one agent are co-formulated. In a still further aspect, the at least one compound and the at least one agent are co-packaged.

[00428] 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.

[00429] 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.

5. NON-MEDICAL USES

[00430] 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 potentiators 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 potentiators 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

[00431] 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.

[00432] 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.

[00433] The following exemplary compounds of the invention were synthesized. The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. The Examples are typically depicted in free base form, according to the IUPAC naming convention. However, some of the Examples were obtained or isolated in salt form.

[00434] As indicated, some of the Examples were obtained as racemic mixtures of one or more enantiomers or diastereomers. The compounds may be separated by one skilled in the art to isolate individual enantiomers. Separation can be carried out by the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. A racemic or diastereomeric mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases.

1. GENERAL METHODS

[00435] H NMR spectra were recorded either on a Bruker DPX-400 or on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 400 MHz and 500 MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard.

[00436] Microwave assisted reactions were performed in a single-mode reactor: Emrys™ Optimizer microwave reactor (Personal Chemistry A.B., currently Biotage).

[00437] Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Open column chromatography was performed on silica gel, particle size 60 A, mesh = 230-400 (Merck) under standard techniques. Flash column chromatography was performed using ready-to-connect cartridges from Merck, on irregular silica gel, particle size 15-40 μη (normal layer disposable flash columns) on a FLASH system from Armen Instrument.
In addition analytical HPLC was performed on an HP1 100 with UV detection at 214 and 254 nm along with ELSD detection and low resolution mass spectra using an Agilent 1200 series 6130 mass spectrometer.

Reversed phase UPLC was carried out on a BEH-C18 column (1.7 μm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50 °C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40 % A, 60 % B in 3.8 minutes, to 5 % A, 95 % B in 4.6 minutes, kept till 5.0 minutes. Injection volume 2.0 μl. Reversed phase Agilent LC-MS was performed using a YMC J-Sphere ODS H80 C18, 3.0 x 50 mm, 4 μm column, 4.1 min gradient, 5% CH₃CN/H₂O (with 0.05%TFA in both mobile phases) to 100% CH₃CN/H₂O (0.05%TFA).

Preparative RP-HPLC purification: Purification by RP-HPLC was performed on a custom HP1 100 automated purification system with collection triggered by mass detection or using a Gilson Inc. preparative UV-based system using a Phenomenex Luna C18 column (50 x 30 mm I.D., 5 μm) with an acetonitrile (unmodified)-water (0.1% TFA) custom gradient.

2. LC-MS METHODS

LC-MS analytical procedures and methods: LC-MS: [M+H], means the protonated mass of the free base of the compound and where indicated Rₜ means retention time (in minutes). The UPLC (Ultra Performance Liquid Chromatography) measurement was performed using an Acquity UPLC (Waters) system comprising a sampler organizer, a binary pump with degasser, a four column's oven, a diode-array detector (DAD) and a column as specified in the respective methods below. Column flow was used without split to the MS detector. The MS detector was configured with an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode. Data acquisition was performed with MassLynx-Openlynx software.
3. PREPARATION OF 2-CHLORO-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(Ω)-ONE.

a. STEP 1: PREPARATION OF 2-CHLORO-6-METHOXY-NICOTINIC ACID.

Potassium tert-butoxide (220 g, 1956 mmol) was added to a solution of 2,6-dichloronicotinic acid (180 g, 938 mmol) in MeOH (3000 mL). The mixture was stirred at 80 °C for 48 h. The solvent was evaporated *in vacuo*. The crude product was dissolved in H₂O and treated with HCl (until the pH was 1). The solid was filtered and dried *in vacuo* to yield 2-chloro-6-methoxy-nicotinic acid as hydrochloride salt (130 g, 70% yield) as a white solid.

b. STEP 2: PREPARATION OF 2-CHLORO-6-METHOXY-NICOTINOYL CHLORIDE.

A mixture of 2-chloro-6-methoxy-nicotinic acid hydrochloride salt (360 g, 1925 mmol) in thionyl chloride (500 mL) was stirred at 80 °C for 5 h. The solvent was evaporated *in vacuo* to yield 2-chloro-6-methoxy-nicotinoyl chloride (340 g, 85%).

c. STEP 3: PREPARATION OF 2-CHLORO-6-METHOXY-NICOTINIC ACID METHYL ESTER.

A mixture of 2-chloro-6-methoxy-nicotinoyl chloride (340 g, 1650 mmol) in MeOH (4500 mL) was stirred at RT for 1 h. The solvent was evaporated *in vacuo*. The mixture was basified with a saturated solution of NaHCO₃ and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; petroleum ether/EtOAc 10/1). The desired fractions were collected and the solvents evaporated in vacuo to yield 2-chloro-6-methoxy-nicotinic acid methyl ester (280 g, 90%) as a solid.
d. **STEP 4: PREPARATION OF 6-METHOXY-2-VINYL-NICOTINIC ACID METHYL ESTER.**

![Chemical Structure]

A mixture of 2-chloro-6-methoxy-nicotinic acid methyl ester (10 g, 49.8 mmol), tributyl(vinyl)tin (15.8 g, 49.8 mmol), 2,6-di-tert-butyl-4-methylphenol (0.3 g, 1.36 mmol) and trans-bis(triphenylphosphine)palladium(II) chloride (0.5 g, 0.71 mmol) was added to DMF (50 mL) under nitrogen. The mixture was stirred at 80 °C for 16 h. The solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica; petroleum ether/EtOAc 50/1). The desired fractions were collected and the solvents evaporated *in vacuo* to yield 6-methoxy-2-vinyl-nicotinic acid methyl ester (5.12 g, 54%) as an oil.

e. **STEP 5: PREPARATION OF 2-METHOXY-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.**

![Chemical Structure]

A mixture of 6-methoxy-2-vinyl-nicotinic acid methyl ester (130 g, 674 mmol) in 7M solution of NH₃ in MeOH (500 mL) was added to a sealed vessel. The mixture was stirred at 100 °C for 24 h. The solvent was evaporated *in vacuo*. The crude product was diluted with MeOH and the mixture was stirred at rt. The solid was filtered and dried in vacuo to yield 2-methoxy-7,8-dihydro-1,6-naphthyridin-5((5 H)-one (75 g, 63%) as a solid.

f. **STEP 6: PREPARATION OF 2-HYDROXY-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.**

![Chemical Structure]

2-Methoxy-7,8-dihydro-6H-[1,6]naphthyridin-5-one (18 g, 101.1 mmol) was added to a mixture of HBr/CH₃CO₂H (60 mL). The mixture was stirred at 60 °C for 16 h. The solvent was evaporated in vacuo to yield 2-hydroxy-7,8-dihydro-1,6-naphthyridin-5((5 H)-one (17 g, 68%) as an oil.
g. **STEP 7: PREPARATION OF 2-CHLORO-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6\(H\))-ONE.**

![Chemical Structure](image)

[00448] A mixture of 2-hydroxy-7,8-dihydro-6H-\([1,6]\)naphthyridin-5-one (17 g, 73.1 mmol) in phosphorus oxychloride (30 mL) was stirred at 100 °C for 8 h. The solvent was evaporated in vacuo. The mixture was basified with a saturated solution of NaHCO\(_3\) and extracted with EtOAc. The organic layer was separated, dried (Na\(_2\)SO\(_4\)), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; petroleum ether/EtOAc 1/1). The desired fractions were collected and the solvents evaporated *in vacuo* to yield 2-chloro-7,8-dihydro-1,6-naphthyridin-5(6\(H\))-one (4.81 g, 36%) as a solid.

4. **PREPARATION OF 2-CHLORO-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6\(H\))-ONE.**

![Chemical Structure](image)

[00449] 2-chloro-7,8-dihydro-6H-\([1,6]\)naphthyridin-5-one, (1.6 g, 8.77 mmol) was dissolved in DMF (20 mL) and treated with KOTBu (1.3 g, 10.7 mmol), followed by p-methoxybenzyl chloride (1.6 mL, 1.8 mmol). The mixture was heated to 60 °C for 2 h, concentrated and purified by silica chromatography (0 to 100% EtOAc in Hexanes) to give the compound. LC-MS (M+H) = 303.2.

5. **PREPARATION OF 3-BROMO-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6\(H\))-ONE.**

a. **STEP 1: PREPARATION OF METHYL 5-BROMO-2-CHLORONICOTINATE.**

![Chemical Structure](image)

[00450] To 0.5 L flask charged with 5-Bromo-2-chloronicotinic acid (25.0 g, 106.4 mmol) in MeOH (250 mL) was added H\(_2\)SO\(_4\) (5 mL). The mixture was heated to 60 °C, stirred for 1.5 day. LC-MS indicated full conversion of starting material at this time. The reaction was cooled to RT and the volatile components removed in vacuo. The crude residue was dissolved
in EtOAc (300 mL), quenched with sat. aqueous Na(HCO₃)₂ (200 mL). The organic layer was separated, washed with brine, dried over MgSO₄ and concentrated to afford the compound, methyl-5-bromo-2-chloronicotinate, as a white solid (quantitative yield). LC-MS (M+H) = 250.1.

b. **STEP 2: PREPARATION OF METHYL 5-BROMO-2-VINYLNicotinate.**

![Chemical Structure](image)

[00451] Methyl 5-bromo-2-chloronicotinate (500 mg, 2.0 mmol) was dissolved in EtOH (20 mL) with potassium vinyltrifluoroborate (269 mg, 2.0 mmol), TEA (0.28 mL, 2.0 mmol), and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (PdCl₂(dppf)) (29 mg, 0.04 mmol). The reaction was heated at 80 °C for 1h, filtered through a Celite pad. The filtrate was concentrated, partitioned between EtOAc (50 mL) and H₂O (50 mL). The organic layer was separated, dried over MgSO₄ and concentrated. Purification over silica gel using automated flash chromatography (EtOAc/hexanes 0-20%) affords the compound, methyl-5-bromo-2-vinylnicotinate, as a white solid (484 mg, 76%). LC-MS (M+H) = 242.1.

c. **STEP 3: PREPARATION OF BROMO -6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5 (Ο/Η)-ONE.**

![Chemical Structure](image)

[00452] In a 2 mL microwave vial methyl 5-bromo-2-vinylnicotinate (110 mg, 0.46 mmol) and (4-methoxyphenyl)methanamine (70.0 μL, 0.50 mmol) were mixed in DMA (1.0 mL). The reaction was subjected to microwave irradiation at 180 °C for 20 min, then diluted with H₂O (6 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were concentrated and purified by column chromatography (EtOAc/hexanes 0-30%). The compound was obtained as sticky oil (115 mg, 73%). LC-MS (M+H) = 347.1.

6. **PREPARATION OF 2-((3-FLUOROBENZYL)OXY)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(Ο/Η)-ONE.**
3-Fluorobenzyl alcohol (1.66 g, 13.14 mmol) was dissolved into DMF (25 mL) and treated with KOTBu (3.2 g, 26.29 mmol) and stirred for 30 min. The mixture was treated with 2-chloro-7,8-dihydro-1,6-naphthyridin-5(6H)-one and heated to 100 °C overnight. The mixture was adsorbed onto silica and purified (0 to 80% EtOAc /Hexanes) to give a semi-pure solid. This material was further purified on RP-HPLC (eluting with 40-90% MeCN/H$_2$O with 0.1% TFA modifier) to give 840 mg of the compound, 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one.  

**7. PREPARATION OF 6-(3-CHLORO-2-FLUOROBENZYL)-2-((3-FLUOROBENZYL)OXY)-7,8-DIHYDRO-L,6-NAPHTHYRIDIN-5(6H)-ONE.**

![Image]

A solution of 2-((3-fluorobenzyl)oxy)-7,8-dihydro- 1,6-naphthyridin-5(6H)-one (20 mg, 0.05 mmol, prepared above as in Example 1.1) in DMSO (1 mL) was treated with 3-fluoro-2-chlorobenzyl bromide (20 mg 0.12 mmol) and KOTBu (20 mg, 0.18 mmol). The reaction mixture was stirred at RT overnight and then purified directly by RP-HPLC to give indicated compound. LC-MS (M+H) = 415.3.

**8. PREPARATION OF 2-((3-FLUOROBENZYL)OXY)-6-(3-METHOXY-4-(TRIFLUOROMETHYL)BENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5 (6H)-ONE.**

![Image]

Prepared in a manner similar to that described above for 6-(3-chloro-2-fluorobenzyl)-2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one to give the compound. LC-MS (M+H) = 461.1.
9. PREPARATION OF 2-((3-FLUOROBENZYL)OXY)-6-(3-FLUOROPHENYL)-7,8-DIHYDRO -1,6-NAPHTHYRIDIN-5 (ß40-ONE).

[00456] 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (30 mg, 0.11 mmol) was dissolved into DCM (2 mL) and treated with 3-fluorophenylboronic acid (30 mg, 0.22 mmol), Cu(OAc)$_2$ (22 mg, 0.13 mmol), and triethylamine (50 µL). The reaction was stirred for 2 days at RT and concentrated to an oil and purified by RP-HPLC (10-90% gradient CH$_3$CN in water with 0.1% TFA modifier) to give the compound, 2-((3-fluorobenzyl)oxy)-6-(3-fluorophenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. LC-MS (M+H) = 367.2.

10. PREPARATION OF 2-((3-FLUOROBENZYL)OXY)-6-(5-FLUOROPYRIDIN-2-YL)-7,8-DIHYDRO -1,6-NAPHTHYRIDIN-5 (ß40)-ONE.

[00457] 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (20 mg, 0.07 mmol) was dissolved into DMF (1 mL) and treated with 2-bromo-5-fluoropyridine (17 mg, 0.1 mmol), 1,2-diaminocyclohexane (4 mg, 0.04 mmol) and Cul (2 mg, 0.01 mmol). The reaction was stirred at 100 °C over 72 h and then poured onto 3M LiCl and EtOAc (5 mL each). The organic layers were dried over Na$_2$SO$_4$, concentrated and the residue purified RP-HPLC to give the compound, 2-((3-fluorobenzyl)oxy)-6-(5-fluoropyridin-2-yl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one. LC-MS (M+H) = 368.1.

11. PREPARATION OF 2-((3-FLUOROPHENOXY)METHYL)-6-(4-FLUOROPHENYL)-7,8-DIHYDRO -1,6-NAPHTHYRIDIN-5 (ß40)-ONE.

a. STEP 1: PREPARATION OF 6-(4-METHOXYBENZYL)-2- VINYL -7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5 (ß40)-ONE.
2-chloro-6-(4-methoxybenzyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one, (1.5 g, 4.97 mmol) was dissolved in EtOH with potassium vinyltrifluoroborate (865 mg, 6.46 mmol), Cs$_2$CO$_3$ (2.42 g, 7.46 mmol) and Pd(PPh$_3$)$_4$ (115 mg, 0.01 mmol). The reaction was heated in a microwave synthesizer at 150 °C for 1 h. It was then concentrated and purified over silica gel (EtOAc/hexanes) to give after solvent removal and drying *in vacuo* the compound as an off-white solid (1.1 g, 76%). LC-MS (M+H) = 295.2.

**b. STEP 2: PREPARATION OF 2-(HYDROXYMETHYL)-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.**

6-(4-Methoxybenzyl)-2-vinyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one (1 g, 4.49 mmol) from above was dissolved in a 1:1 mixture of DCM:MeOH,(50mL) and cooled to -78 °C. Ozone was bubbled through for 30 min. The reaction was warmed to 0 °C then NaBH$_4$ (400mg, 10.8mmol) was added and the cold bath removed. After 10 min, the reaction mixture was quenched with Rochelle’s Salt (20% solution, 50 mL) and diluted with EtOAc (100 mL). The organics were dried and concentrated to give 980 mg (96%). LC-MS (M+H) = 299.1.

**c. STEP 3: PREPARATION OF 2-((3-FLUOROPHENOXY)METHYL)-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.**

2-(Hydroxymethyl)-6-(4-methoxybenzyl)-7,8-dihydro- 1,6-naphthyridin-5(6H)-one (270 mg, 0.9 mmol) from above and 3 equiv of 3-fluorophenol was dissolved in THF (10 mL). To this mixture was added polystyrene bound-PPh$_3$ (3 equiv) and diisopropylazodicarboxylate (3 equiv) in THF (2 mL) dropwise. The mixture was allowed to warm to RT and stirred for 6 h. The residue was loaded directly onto a silica and eluted with EtOAc/hexanes to give the compound (310 mg, 88%). LC-MS (M+H) = 393.2.
d. **STEP 4**: PREPARATION OF 2-((3-FLUOROPHENOXY)METHYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.

![Chemical Structure](image)

2-((3-Fluorophenoxy)methyl)-6-(4-methoxybenzyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (300 mg, 0.77 mmol) from above was dissolved in CH$_3$CN (5mL) and water (2mL) added. Cerium ammonium nitrate (419 mg, 0.77 mmol) was added and after 15min, the reaction was partitioned between EtOAc (10mL) and brine (10mL). The organic layers were concentrated and purified by RP-HPLC (0 to 90% CH$_3$CN). Product containing fractions were treated with PS-TsNHNH$_2$ (2equiv) to give the compound as a solid (74 mg, 76%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.38 (1H, d, J=8), 7.56 (1H, d, J=8), 7.27 (1H, dd, J=16, 7.6), 6.77 (1H, dd, J=13.2, 2.0), 6.71 (2H, m), 5.96 (1H, br s), 5.20 (2H, s), 3.67 (2H, t, J=6.2Hz), 3.24 (2H, t, J=6.8Hz); LC-MS (M+H) = 273.2.

e. **STEP 5**: PREPARATION OF 2-((3-FLUOROPHENOXY)METHYL)-6-(4-FLUOROPHENYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.

![Chemical Structure](image)

2-((3-Fluorophenoxy)methyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one from above (10mg, 0.04 mmol) was dissolved into dioxane (400 μL) and treated with 4-fluorobromobenzene (10 mg, 0.06 mmol) followed by Cul (5 mg, 0.03 mmol) and N,N”-dimethylethlenediamine (6.2 mL, 0.04 mmol). The mixture was heated in a microwave synthesizer at 150 °C for 2 h, cooled to RT and diluted with DMSO and purified by RP-HPLC to give the compound (5 mg, 34%). $^1$H NMR (400MHz, CDC$_1$$_3$) δ 8.46 (IH, d, J=8Hz), 7.59 (IH, d, J=8Hz), 7.37 (2H, m), 7.27 (IH, dd, J=16, 7.6Hz), 7.16 (2H, m), 6.80 (IH, dd, J=7.6, 1.6), 6.74 (2H, m), 5.25 (2H, s), 4.10 (2H, t, J=6.8Hz), 3.38 (2H, t, J=6.8Hz); LC-MS (M+H) = 367.2.
12. PREPARATION OF 2-((3-FLUOROPHENOXY)METHYL)-6-(5-FLUOROPYRIDIN-2-YL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5 (ON)-ONE

Prepared in a manner similar to the preceding example, 2-((3-fluorophenoxy)methyl)-6-(4-fluorophenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one, using the common intermediate 2-((3-fluorophenoxy)methyl)-7,8-dihydro-1,6-naphthyridin-5(5H)-one as described above and 2-bromo-5-fluoropyridine.

H NMR (400MHz, CDCl₃) δ 8.49 (1H, d, J=8), 8.32 (1H, d, J=3), 8.03 (1H, dd, J=9.2, 4.0), 7.60 (1H, d, J=23, 8), 7.28 (1H, dd, J=16, 7.6), 6.80 (1H, dd, J=7.6, 1.6), 5.26 (1H, s), 4.41 (2H, t, J=6.8), 3.38 (2H, t, J=6.8); LC-MS (M+H) = 368.2.

13. PREPARATION OF 7-(4-FLUOROPHENYL)-3-(PHENOXYMETHYL)-6,7-DIHYDRO-1,7-NAPHTHYRIDIN-8(ON)-ONE.

a. STEP 1: PREPARATION OF (5,6-DICHLORO-PYRIDIN-3-YL)-METHANOL.

Borane tetrahydrofuran complex (15.4 mL, 15.4 mmol) was added to a stirred solution of 5,6-dichloronicotinic acid (2.46 g, 12.8 mmol) in anhydrous THF (15 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min while the mixture became orange in color and then at RT for 3 h. An additional portion of borane tetrahydrofuran complex (15.4 mL, 15.4 mmol) was added and the mixture was stirred at RT for 16 h. The mixture was then carefully poured into a cold 1 N aqueous HC1 solution and extracted with DCM. The organic layer was dried (Na₂SO₄), filtered and the solvents evaporated to yield 5,6-dichloro-pyridin-3-yl)-methanol (1.64 g, 68%) as a pale yellow wax which was used in next reaction without further purification.

b. STEP 2. PREPARATION OF 3-CHLORO-5-HYDROXYMETHYL-PYRIDINE-2-CARBONITRILE.
Tetrakis (triphenylphosphine) palladium (0) (1.5 g, 1.3 mmol) was added to a stirred mixture of 5,6-dichloro-pyridin-3-yl)-methanol (2.44 g, 13.0 mmol) and zinc cyanide (1.24 g, 10.42 mmol) in DMF (50 mL). The mixture was stirred at 100 °C for 3 h. The mixture was diluted with EtOAc and filtered through a diatomaceous earth pad. The filtrate was concentrated in vacuo and the crude product was purified by flash column chromatography (silica; EtOAc in heptane 0/100 to 70/30). The desired fractions were collected and the solvents evaporated in vacuo to yield 3-chloro-5-hydroxymethyl-pyridine-2-carbonitrile (1.23 g, 56%) as a white solid.

c. STEP 3: PREPARATION OF 3-CHLORO-5-PHENOXYMETHYL-PYRIDINE-2-CARBOXYLIC ACID.

[00466] Di-tert-butyl azodicarboxylate (174 mg, 0.76 mmol) was added to a stirred solution of 3-chloro-5-hydroxymethyl-pyridine-2-carbonitrile (71 mg, 0.42 mmol), phenol (79 mg, 0.84 mmol) and triphenylphosphine (199 mg, 0.76 mmol) in anhydrous THF (3.3 mL) at 0 °C. The mixture was stirred at 120 °C for 30 minutes under microwave irradiation. Then, the mixture was diluted with EtOAc and washed with a saturated solution of NaHCO₃ and brine. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 20/80). The desired fractions were collected and the solvents evaporated in vacuo to yield 3-chloro-5-phenoxy methyl-pyridine-2-carbonitrile (83 mg, 80%) as a white solid.

d. STEP 4: PREPARATION OF 3-CHLORO-5-PHENOXYMETHYL-PYRIDINE-2-CARBOXYLIC ACID.

[00467] A 10% aqueous solution of NaOH (2.5 mL) was added to a stirred solution of 3-chloro-5-phenoxy methyl-pyridine-2-carbonitrile (40 mg, 0.16 mmol) in EtOH (1.5 mL) in a sealed tube. The mixture was stirred at 115 °C for 3 h. The solvent was evaporated in vacuo and the crude product was neutralized with a 6 N aqueous solution of HCl and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated
in vacuo to yield 3-chloro-5-phenoxymethyl-pyridine-2-carboxylic acid (43 mg, quantitative) which was used in the next step without further purification.

e. **STEP 5: PREPARATION OF 3-CHLORO-5-PHENOXYMETHYL-PYRIDINE-2-CARBOXYLIC ACID METHYL ESTER.**

![Chemical Structure](image)

Iodomethane (0.4 mL, 6.39 mmol) was added to a suspension of 3-chloro-5-phenoxymethyl-pyridine-2-carboxylic acid (265 mg, 1.92 mmol) and K₂CO₃ (265 mg, 1.92 mmol) in DMF (15 mL) in a sealed tube. The mixture was stirred at RT for 16 h. The solvent was evaporated in vacuo and the mixture was diluted with H₂O and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 70/30). The desired fractions were collected and the solvents evaporated in vacuo to yield 3-chloro-5-phenoxymethyl-pyridine-2-carboxylic acid methyl ester (258 mg, 73%) as a colorless oil.

f. **STEP 6: PREPARATION OF 3-ALLYL-5-PHENOXYMETHYL-PYRIDINE-2-CARBOXYLIC ACID METHYL ESTER.**

![Chemical Structure](image)

Tetrakis (triphenylphosphine) palladium (0) (54 mg, 0.046 mmol) was added to a stirred solution of 3-chloro-5-phenoxymethyl-pyridine-2-carboxylic acid methyl ester (130 mg, 0.47 mmol) and allyltri-n-butyltin (0.25 mL, 0.79 mmol) in degassed toluene (1.5 mL) under nitrogen. The mixture was stirred at 125 °C for 20 h. Then further tetrakis (triphenylphosphine) palladium (0) (54 mg, 0.046 mmol) and allyltri-n-butyltin (0.25 mL, 0.79 mmol) were added and the mixture was stirred at 125 °C for 16 h. The mixture was diluted with EtOAc, filtered through a diatomaceous earth pad. The filtrate was evaporated in vacuo. The crude product was purified by flash column chromatography (silica; EtOAc in DCM 0/100 to 100/0). The desired fractions were collected and the solvents evaporated in vacuo to yield 3-allyl-5-phenoxymethyl-pyridine-2-carboxylic acid methyl ester (111 mg, 84% yield) as a yellow oil.
g. **STEP 7: PREPARATION OF 3-(2-OXO-ETHYL)-5-PHENOXYMETHYL-PYRIDINE-2-CARBOXYLIC ACID METHYL ESTER.**

![Chemical Structure](image)

[S00470] Sodium metaperiodate (304 mg, 1.42 mmol) was added to a stirred solution of 3-allyl-5-phenoxymethyl-pyridine-2-carboxylic acid methyl ester (161 mg, 0.57 mmol) and osmium tetraoxide (0.37 mL, 0.028 mmol; 2.5% in tert-butanol) in H₂O (3 mL) and THF (6 mL) at 0 °C. The mixture was stirred at RT for 2 h. The mixture was diluted with H₂O and extracted with EtOAc. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo to yield 3-(2-oxo-ethyl)-5-phenoxymethyl-pyridine-2-carboxylic acid methyl ester (200 mg, 60% purity, 74%) as a black residue which was used in the next step without further purification.

h. **STEP 8: PREPARATION OF 7-(4-FLUOROPHENYL)-3-(PHENOXYMETHYL)-6,7-DIHYDRO-1,7-NAPHTHYRIDIN-8(1,7)-ONE.**

![Chemical Structure](image)

[S00471] 4-Fluoroaniline (0.032 mL, 0.34 mmol) was added to a stirred solution of 3-(2-oxo-ethyl)-5-phenoxymethyl-pyridine-2-carboxylic acid methyl ester (80 mg, 0.28 mmol, from step 7) in DCM (4 mL). The mixture was stirred at RT for 1 h. Sodium triacetoxyborohydride (89 mg, 0.42 mmol) was added and the mixture was stirred at RT for additional 20 h. The mixture was diluted with DCM and washed with a saturated solution of NaHCO₃ and brine. The organic layer was separated, dried (Na₂SO₄), filtered and the solvents evaporated in vacuo. The crude product was purified by flash column chromatography (silica; 7N solution of ammonia in methanol in DCM 0/100 to 4/96). The desired fractions were collected and the solvents evaporated in vacuo to yield an impure fraction which was repurified by RP-HPLC on (C18 XBridge, 19 x 100, 5 µm; 80% /0.1% NH₄CO₃/H/NH₄OH pH 9 solution in water, 20% CH₃CN to 0%/ 0.1% NH₄CO₃/H/NH₄OH pH 9 solution in water, 100% CH₃CN), to yield 7-(4-fluoro-phenyl)-3-phenoxyethyl-6,7-dihydro-...
naphthyridin-8(5H)-one (14.86 mg, 15% yield) as a white solid: ¹H NMR (500 MHz, CDCl₃) δ 3.22 (t, J=6.4, 2 H), 4.01 (t, J=6.4, 2 H), 5.17 (s, 2 H), 6.98 (d, J=7.8, 2 H), 7.01 (t, J=7.5, 1 H), 7.07 - 7.16 (m, 2 H), 7.29 - 7.35 (m, 2 H), 7.36 - 7.42 (m, 2 H), 7.76 (br. s, 1 H), 8.78 (d, J=1.7, 1 H); LC-MS (M+H) = 349.1.

14. PREPARATION OF -(3-FLUOROPHENOXY)METHYL)-6-(4-METHOXYBENZYL)-7,8-DIHYDRO -1,6-NAPHTHYRIDIN-5 (αβδ)-ONE.

a. STEP 1: PREPARATION OF METHYL 2,5-DIVINYLNICOTINATE.

[00472] Methyl 5-bromo-2-chloronicotinate (6.9 g, 27.6 mmol) was dissolved into toluene (100 mL). Tributyl(vinyl)tin (19.7 g, 62.1 mmol) was added, followed by tetrakistriphenylphosphinopalladium (2.5 g, 2.1 mmol), and the reaction heated at 110 °C for 3h. The reaction mixture was poured onto 2 N HCl (100 mL) and stirred for 30 min, then neutralized with saturated sodium bicarbonate. The organic layer was removed, concentrated and purified over silica gel using automated chromatography to give 4.5 g (86%) of the compound. LC-MS (M+H) = 190.1.

b. STEP 2: PREPARATION OF 6-(4-METHOXYBENZYL)-3-VINYL-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5 (αβδα)-ONE.

[00473] Methyl 2,5-divinylnicotinate (2.1 g, 11.1 mmol) was combined with p-methoxybenzylamine (2 mL, 15 mmol) and dimethylacetamide (7 mL) and heated for 20 min in a microwave reactor at 150 °C. The reaction mixture was concentrated and purified over silica gel (0-100% EtOAc/hexanes) using automated chromatography. The product containing fractions were combined and evaporated under reduced pressure to give the compound (2.99 g, 92%). LC-MS (M+H) = 295.1.
c. **STEP 3: PREPARATION OF 3-(HYDROXYMETHYL)-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(^¾)-ONE.**

![Chemical Structure](image)

[00474] 6-(4-Methoxybenzyl)-3-vinyl-7,8-dihydro-1,6-naphthyridin-5(6H)-one (800 mg, 4.23 mmol) was dissolved in 1:1 MeOH:DCM (50 mL) and cooled in a dry ice/acetone bath. A stream of O₂ was bubbled through for 20 min. At this time LC-MS indicated complete consumption of starting material. Oxygen was passed through the solution for 20 min, and then NaBH₄ (500 mg) was added to the solution and the cold bath removed. After 20 min, Rochelle’s salt (20%, 5 mL) was added to the reaction mixture. The mixture was concentrated and re-suspended into EtOAc (50 mL) and dried over MgSO₄. The filtrate was concentrated and used directly in the next step without further purification (800 mg, 98%). LC-MS (M+H) = 299.1.

d. **STEP 4: PREPARATION OF 3-((3-FLUOROPHENOXY)METHYL)-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(^¾)-ONE.**

![Chemical Structure](image)

[00475] 3-(Hydroxymethyl)-6-(4-methoxybenzyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (250 mg, .84 mmol) from the preceding step was combined with polymer supported PPh₃ (600 mg, 1.8 mmol), and 3-fluorophenol (200 mg, 1.8 mmol) in THF (10 mL). The mixture was gently stirred and treated dropwise with diisopropylazodicaboxylate (400 µL, 2 mmol). After 1 h the reaction mixture was filtered and concentrated onto silica and purified using an EtOAc/hexanes gradient to give the compound (326 mg, 90%). 1H NMR (400 MHz, CDCl₃) δ 8.96 (1H, d, J=1.6), 8.49 (1H, d, J=1.6), 7.28 (3H, m) 6.91 (2H, d, J=7.2), 6.79 (1H, dd, J=8.2) 6.72 (2H, m), 5.12 (2H, s), 4.76 (2H, s), 3.82 (3H, s), 3.60 (2H, t, J=6.8), 3.18 (2H, t, J=6.8); LC-MS (M+H) = 393.1.
15. PREPARATION OF 3-(BENZYLXO)-6-(4-METHOXYBENZYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(¼)-ONE.

3-Bromo-6-(4-methoxybenzyl)-7,8-dihydro-1,6-naphthyridin-5(6 H)-one (1.2 g, 3.5 mmol), benzyl alcohol (3.62 mL, 35.0 mmol), CuI (67.0 mg, 0.35 mmol), 1,10-phenanthroline (127.0 mg, 0.7 mmol) were mixed with Cs₂CO₃ (1.69 g, 5.2 mmol) in toluene (15.0 mL). The reaction was degassed, sealed in a microwave tube, heated to 110 °C for 1.5 day. The reaction mixture was passed through a Celite pad, diluted with H₂O (50.0 mL), extracted with EtOAc (40.0 x 3 mL). The organic layers were combined, dried over MgSO₄, concentrated in vacuo and purified by automated silica gel column chromatography (EtOAc/hexanes 0-60%). The compound was obtained as a sticky oil (1.08g, 83%).

1H NMR (400MHz, CDCl₃) δ 8.39 (br s, 1H), 8.01 (d, J = 3.2 Hz, 1H), 7.48-7.37 (overlapped, 5H), 7.30-7.27 (overlapped, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H), 4.74 (s, 2H), 3.82 (s, 3H), 3.55 (t, J = 6.8 Hz, 2H), 3.08 (t, J = 6.8 Hz, 2H); LC-MS (M+H) = 375.1.

16. PREPARATION OF 3-(BENZYLXO)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(¼)-ONE.

3-(Benzyloxy)-6-(4-methoxybenzyl)-7,8-dihydro-1,6-naphthyridin-5(<5H)-one (1.05 g, 2.8 mmol) was dissolved in MeCN (50 mL). To the solution cerium ammonium nitrate (15.4 g, 28 mmol) in water (50 mL) was added slowly at room temperature. The reaction was stirred for 1 h at the same temperature, partitioned between EtOAc (200 mL) and brine (200 mL). The organic layers were dried, concentrated and purified by column chromatography (MeOH, DCM 0-5%). The compound was obtained as an off white solid (293 mg, 41%).

1H NMR (400MHz, CDCl₃) δ 8.44 (d, J = 2.8, 1H), 7.94 (d, J = 2.8, 1H), 7.47-7.35 (overlapped, 5H), 6.05 (br s, NH), 5.16 (s, 2H), 4.74 (s, 2H), 3.82 (s, 3H), 3.66 (td, J = 6.8, 2.4, 2H), 3.17 (td, J = 6.8, 2.4, 2H); LC-MS (M+H) = 255.1
17. PREPARATION OF 3-(BENZYLOXY)-6-METHYL-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE.

![Chemical Structure]

3-(Benzyloxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (10.0 mg, 0.04 mmol) was dissolved in DMF (0.5 mL). NaH (2.0 mg, 0.08 mmol) was added into the solution and stirred at room temperature. After 30 min, Mel (5.0 µL) was added into the mixture and allowed to stir for another hour. Reaction was then quenched with H₂O (2.0 mL) and extracted with EtOAc (3.0 mL x 3). The organic layers were combined and concentrated to afford pure product as a white solid (9.2 mg, 87%). LC-MS (M+H) = 267.1.

18. PREPARATION OF 3-(BENZYLOXY)-6-(PYRIDIN-2-YL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(5H)-ONE.

![Chemical Structure]

3-(Benzyloxy)-7,8-dihydro-1,6-naphthyridin-5(5H)-one, example 1.15, (10.0 mg, 0.04 mmol), 2-bromopyridine (8.0 µL, 0.08 mmol), Cul (1.1 mg, 0.006 mmol) and K₂CO₃ (11.0 mg, 0.08 mmol) were mixed in DMF (0.5 mL), and heated to 150°C for 2 days. The reaction was then partitioned between EtOAc (10 mL) and brine (10 mL). The organics were dried and concentrated and purified by RP-HPLC to afford the compound. LC-MS (M+H) = 332.1.

19. GENERATION OF HUMAN MGLUR5 STABLE CELL LINE

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").

20. CELL-BASED FUNCTIONAL ASSAY

HEK cells transfected with the human mGluR5a receptor (H10H or H12H cell line) were plated at 15,000 cells/well in clear-bottomed poly-D-lysine-coated assay plates (BD Falcon) in glutamate-glutamine-free growth medium and incubated overnight at 37°C.
and 5% C0₂. Cell-lines used were either the HIOH or H12H cell-lines expressing the human mGluR5 receptor. The following day, the growth medium was removed and the cells were washed with assay buffer containing 1X Hank's balanced salt solution (Invitrogen, Carlsbad, CA), 20 mM HEPES, 2.5 mM probenecid, pH 7.4 and left with 20 μL of this reagent. Following this step, the cells were loaded with calcium indicator dye, fluo-4 AM, to a final concentration of 2 μM and incubated for 40-45 min at 37 °C. The dye solution was removed and replaced with assay buffer. Cell plates were held for 10-15 min at room temperature and were then loaded into the Functional Drug Screening System 6000 (FDSS 6000, 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 1.7 minutes. 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. Potentiation of the agonist response of the mGluR5 receptor in the present invention was observed as an increase in response to submaximal concentrations of glutamate in the presence of compound compared to the response to glutamate in the absence of compound.

21. DATA ANALYSIS

The concentration-response curves of compounds of the present invention, obtained in the presence of EC₂₀ of mGluR5 receptor agonist glutamate to determine positive allosteric modulation, were generated using Microsoft Excel with IGBS XLfit add-ins. 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/F₀) for each measurement of the total 350 values per well divided by each well's initial value. Data was then reduced as to peak amplitudes (Max - Initial Min) using a time range that starts approximately 1 second after the glutamate EC₂₀ 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 %E₅ₐₓ by multiplying each amplitude by 100 and then dividing the product by the mean of the amplitudes derived.
from the glutamate ECMax-treated wells. pEC$_{50}$ 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. Individual values falling outside the 95% prediction limits of the curve fit were automatically excluded from the fit. A compound was designated as a positive allosteric modulator if the compound showed a concentration-dependent increase in the glutamate EC$_{20}$ addition. %EM$_{ax}$ for compounds may be estimated using the resulting corresponding parameter value determined using the curve fit or by taking an average of the overall maximum response at a single concentration. These two methods are in good agreement for curves with a clear plateau at the high concentration range. For data that show an increase in the EC$_{20}$ response, but, do not hit a plateau, the average of the maximum response at a single concentration is preferred. For consistency purposes across the range of potencies observed, all EM$_{ax}$ values reported in this application are calculated using the maximum average response at a single concentration. The %EM$_{ax}$ value for each compound reported in this application is defined as the maximum % effect obtained in a concentration-response curve of that compound expressed as a percent of the response of a maximally effect concentration of glutamate.

Table I above shows the pharmacological data obtained for a selected set of compounds.

For compounds showing a lower potency (e.g. as indicated by a lack of a plateau in the concentration response curve), but with a greater than a 20% increase in glutamate response, a potency of > 10 µM (pEC$_{50}$ < 5) was estimated.

22. PROSPECTIVE IN VIVO EFFECTS

Generally clinically relevant antipsychotic agents (both typical and atypical) display efficacy in preclinical behavior challenge models. The compounds described in the preceding examples are expected to show in vivo effects in various animal behavioural challenge models known to the skilled person, such as amphetamine-induced or phencyclidine (PCP)-induced hyperlocomotion, and other models, such as NMDA receptor antagonist MK-801-induced locomotor activity conducted in rodent, such as rat or mouse, but may be conducted in other animal species as is convenient to the study goals. Compounds, products, and compositions disclosed herein are expected to show in vivo effects in various animal behavioural challenge models known to the skilled person, such as amphetamine-induced or phencyclidine (PCP)-induced hyperlocomotion in rodent, and other models, such as NMDA receptor antagonist MK-801-induced locomotor activity. 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.

[00486] Compounds of the present invention are expected as a class to show in vivo efficacy in a preclinical rat behavioral model, where known, clinically useful antipsychotics display similar positive responses. For example, 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one, which is viewed as representative of the compounds of the present invention was tested in reverse amphetamine-induced hyperlocomotion in male Sprague-Dawley rates at doses ranging from 3 to 100 mg/kg by oral gavage (see discussion below). For example, compounds having a structure represented by a formula:

![Chemical Structure](image)

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y₁ and Y₂ is N, and the other is C-R₃--; wherein one of Z₁ and Z₂ is C-L-Ar₁, and the other is C-R₃--; wherein L is -0-C(R₁-R₁b)- or -C(R₁-R₁b)-0--; wherein Ar₁ is phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy, or Ar₁ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein each of R₁a and R₁b is independently selected from hydrogen and C₁-C₄ alkyl; wherein R₂ is selected from hydrogen; C₁-C₆ alkyl; (C₁-C₆ alkoxy) Cl-C₆ alkyl; C₃-C₈ cycloalkyl; (C₃-C₈ cycloalkyl) C₁-C₆ alkyl; C₂-C₅ heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; (C₁-C₂ alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein R₃a is selected from hydrogen, halogen, cyano, and C₁-C₄ alkyl; wherein R₃b is selected from hydrogen, halogen, cyano, and C₁-C₄ alkyl, or R₃a and R₃b are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R₄a is selected from hydrogen and C₁-C₄ alkyl; wherein R₄b, when present, is selected from hydrogen and C₁-C₄ alkyl, or R₄a and R₄b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R₅a is selected from hydrogen and C₁-C₄ alkyl; wherein R₅b, when present, is
selected from hydrogen and C1-C4 alkyl, or R⁵a and R⁵b are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R⁴a and R⁵a are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt thereof, are expected to show such \textit{in vivo} effects. Moreover, compounds prepared using the disclosed synthetic methods are also expected to show such \textit{in vivo} effects.

23. 2-((3-FLUOROBENZYL)OXY)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE

\textbf{ACTIVITY IN INDUCED HYPERLOCOMOTION ANIMAL MODEL}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{Chemical structure of 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one.}
\end{figure}

[00487] Locomotor activity was assessed as mean distance traveled (cm) in standard 16 x 16 photocell testing chambers measuring 43.2 cm (Length) x 43.2 cm (Width) x 30.5 cm (Height) (Med Associates, St. Albans, VT). Animals were habituated to individual activity chambers for at least 30 min prior to drug administration. Following administration of drug or vehicle, activity was recorded for a 90 minute time period. Data was expressed as the mean (+ SEM) distance traveled recorded in 5 min intervals over the test period. The data were analyzed using repeated measures analysis of variance (ANOVA) followed by post-hoc testing using Dunnett's test, when appropriate. A difference was considered significant when p <0.05.

[00488] Amphetamine sulfate was obtained from Sigma (Cat#A5880-IG; St. Louis, MO) and 10 mg was dissolved in 10 ml of water. Test compound, 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one, was formulated in a volume of 10 ml with an amount of drug appropriate to the dosage indicated. The appropriate amount of compound was mixed into a 20% 2-hydroxypropyl -P-cyclodextrin (2- HP-β-CD; indicated as "BCD" in Figure 4) solution. The solution was formulated so that animals were injected with a volume equal to about 10X body weight. The mixture was then ultrahomogenized on ice for 2-3 minutes using the Dismembrator (Fisher Scientific Model 150T). Then the pH was checked using 0-14 EMD strips and adjusted to a pH of 6-7 if necessary. The mixture was then vortexed and stored in a warm sonication bath until time to be injected. Animals were administered samples of the following: (a) Amphetamine sulfate, 1 mg/kg, administered subcutaneously;
and, (b) 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one, at the doses as indicated in Figure 4, was administered by oral gavage.

The study was carried out using male Sprague-Dawley rats weighing 225g-275g, between 2-3 months old (Harlan, Inc., Indianapolis, IN), were used. The number of animals used is as indicated in Figure 4. They were kept in the animal care facility certified by the American Association for the Accreditation of Laboratory Animal Care (AALAC) under a 12-hour light/dark cycle (lights on: 6 a.m.; lights off: 6 p.m.) and had free access to food and water. The experimental protocols performed during the light cycle were approved by the Institutional Animals Care and Use Committee of Vanderbilt University and conformed to the guidelines established by the National Research Council Guide for the Care and Use of Laboratory Animals.

The animals were habituated in Smart Open Field locomotor activity test chambers (Hamilton-Kinder, San Diego, CA) with 16 x 16 photobeams to automatically record locomotor activity for 30 min and then dosed with vehicle or test compound. The rats were then placed into cages. At 60 min, all rats were injected subcutaneously with 1 mg/kg amphetamine or vehicle and then monitored for an additional 60 min. Animals are monitored for a total of 120 minutes. Data are expressed as changes in ambulation defined as total number of beam breaks per 5 min periods.

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 amphetamine group. The calculations were performed using JMP IN 8 (SAS Institute, Cary, NC) statistical software and graphed using SigmaPlot9 (Saugua, MA). Results for reversal of amphetamine-induced hyperlocomotion by 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one are shown in Figure 4. The following abbreviations are used: (a) "Test compound" refers to 2-((3-fluorobenzyl)oxy)-7,8-dihydro-1,6-naphthyridin-5(6H)-one; (b) subcutaneous administration of compound is indicated by "sc"; (c) oral gavage administration is indicated by "po"; and (d) amphetamine sulfate is indicated as "amphetamine." The time of administration of amphetamine sulfate is indicated in Figure 4 by "AMP" and the corresponding arrow. The vehicle for test compound is 20% wt/v HP-β-CD (indicated as "BCD" in Figure 4), and the vehicle for amphetamine is sterile water.
24. 2-(BENZYLOXY)-6-(4-FLUOROPHENYL)-7,8-DIHYDRO-1,6-NAPHTHYRIDIN-5(6H)-ONE ACTIVITY IN INDUCED HYPERLOCOMOTION ANIMAL MODEL

Activity in the induced hyperlocomotion animal model was determined as described in the examples above for the test compound was 2-(benzyloxy)-6-(4-fluorophenyl)-7,8-dihydro-1,6-naphthyridin-5(6H)-one (see Figure 5). The test compound was dosed at 10 mg/kg in the same vehicle as described above. The apparent reversal was 35%. The data were analyzed using repeated measures analysis of variance (ANOVA) followed by post-hoc testing using Dunnett’s test, and statistically significant data points (p <0.05) are indicated with a “#” symbol in Figure 5.

25. PROPHETIC PHARMACEUTICAL COMPOSITION EXAMPLES

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

wherein each ----- is independently an optional covalent bond, wherein valence is satisfied; wherein one of Y¹ and Y² is N, and the other is C-R³a; wherein one of Z¹ and Z² is C-L-Ar¹, and the other is C-R³b; wherein L is -O-C(R¹aR³b)- or -C(R¹aR³b)-O-; wherein Ar¹ is phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy, or Ar¹ is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein each of R¹a and R³b is independently selected from hydrogen and C₁-C₄ alkyl; wherein R² is selected from hydrogen; C₁-C₆ alkyl; (C₁-C₆ alkyloxy) C₁-C₆ alkyl; C₃-C₈ cycloalkyl; (C₃-C₈ cycloalkyl) C₁-C₆ alkyl; C₂-C₅ heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; (C₁-C₂ alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C₁-C₄ alkyl, and C₁-C₄ alkyloxy; wherein R³a is selected from hydrogen, halogen, cyano, and
C1-C4 alkyl; wherein R is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or R and R3 are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl; wherein R4 is selected from hydrogen and C1-C4 alkyl; wherein R4, when present, is selected from hydrogen and C1-C4 alkyl, or R4 and R4 are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; wherein R5 is selected from hydrogen and C1-C4 alkyl; wherein R5, when present, is selected from hydrogen and C1-C4 alkyl, or R5 and R5 are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and wherein R4 and R5 are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl; or a pharmaceutically acceptable salt, solvate, polymorph, hydrate and the stereochemically isomeric form thereof. The following examples of the formulation of the 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**

A tablet can be prepared as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>5 to 50 mg</td>
</tr>
<tr>
<td>Di-calcium phosphate</td>
<td>20 mg</td>
</tr>
<tr>
<td>Lactose</td>
<td>30 mg</td>
</tr>
<tr>
<td>Talcum</td>
<td>10 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Potato starch</td>
<td>add to make total weight 200 mg</td>
</tr>
</tbody>
</table>

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.
b. **SUSPENSION**

[00496] 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**

[00497] 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**

[00498] An ointment can be prepared as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>5 to 1000 mg</td>
</tr>
<tr>
<td>Stearyl alcohol</td>
<td>3 g</td>
</tr>
<tr>
<td>Lanoline</td>
<td>5 g</td>
</tr>
<tr>
<td>White petroleum</td>
<td>15 g</td>
</tr>
<tr>
<td>Water</td>
<td>add to make total weight 100 g</td>
</tr>
</tbody>
</table>

[00499] 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.

[00500] 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.
What is claimed is:

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

   \[
   \begin{array}{c}
   \text{\textbf{Diagram}}
   \end{array}
   \]

   wherein each ---- is independently an optional covalent bond, wherein valence is satisfied;

   wherein one of \(Y^1\) and \(Y^2\) is \(N\), and the other is \(C-R^3\);

   wherein one of \(Z^1\) and \(Z^2\) is \(C-L\cdot \text{Ar}^1\), and the other is \(C-R^3\);

   wherein \(L\) is \(-0-(R^{1a}R^{1b})\) and \(-C(R^{1a}R^{1b})-0\);

   wherein \(\text{Ar}^1\) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or \(\text{Ar}^1\) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy;

   wherein each of \(R^{1a}\) and \(R^{1b}\) is independently selected from hydrogen and C1-C4 alkyl;

   wherein \(R^2\) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkoxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy;

   wherein \(R^{3a}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl;

   wherein \(R^{3b}\) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \(R^{3a}\) and \(R^{3b}\) are substituted on adjacent carbons and are covalently bonded and, together with the
intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl;

wherein $R^4$ is selected from hydrogen and C1-C4 alkyl;

wherein $R^4$, when present, is selected from hydrogen and C1-C4 alkyl, or $R^4$ and $R^4b$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;

wherein $R^5a$ is selected from hydrogen and C1-C4 alkyl;

wherein $R^5b$, when present, is selected from hydrogen and C1-C4 alkyl, or $R^5a$ and $R^5b$ are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and

wherein $R^4a$ and $R^5a$ are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl;

or a pharmaceutically acceptable salt thereof,

wherein the compound exhibits potentiation of mGluR5 response to glutamate as an increase 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.

2. The compound of claim 1, wherein $Ar^1$ is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

3. The compound of claim 1, wherein $Ar^1$ is substituted with 1-3 groups independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

4. The compound of claim 1, wherein $Ar^1$ is substituted with 1-3 groups independently selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

5. The compound of claim 1, wherein $R^2$ is selected from hydrogen and C1-C6 alkyl.
6. The compound of claim 1, wherein $R^2$ is selected from C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; monohalo C1-C6 alkyl; polyhalo C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; and C2-C5 heterocyclyl.

7. The compound of claim 1, wherein $R^3$ is selected from phenyl with 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and heteroaryl having 0-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

8. The compound of claim 1, wherein $R^2$ is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy.

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

$$\text{Ar}^1 \quad \text{Ar}^2 \quad \text{R}^{1a} \quad \text{R}^{2a} \quad \text{R}^{3a} \quad \text{N} \quad \text{R}^{4a} \quad \text{R}^{5a} \quad \text{R}^{6a}$$

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

$$\text{Ar}^1 \quad \text{Ar}^2 \quad \text{R}^{1b} \quad \text{R}^{2b} \quad \text{R}^{3b} \quad \text{N} \quad \text{R}^{4b} \quad \text{R}^{5b} \quad \text{R}^{6b}$$

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

$$\text{Ar}^1 \quad \text{Ar}^2 \quad \text{R}^{1c} \quad \text{R}^{2c} \quad \text{R}^{3c} \quad \text{N} \quad \text{R}^{4c} \quad \text{R}^{5c} \quad \text{R}^{6c}$$

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

![Chemical Structure](image1)

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

![Chemical Structure](image2)

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

![Chemical Structure](image3)

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

![Chemical Structure](image4)

17. A method for the treatment of a neurological and/or psychiatric disorder associated with glutamate dysfunction 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:

![Chemical Structure](image5)

wherein each ---- is independently an optional covalent bond, wherein valence is
satisfied;

wherein one of \( Y^1 \) and \( Y^2 \) is N, and the other is C-R\(^{3a} \);

wherein one of \( Z^1 \) and \( Z^2 \) is C-L-Ar \(^1 \), and the other is C-R\(^{3b} \);

wherein \( L \) is -0-C(R\(^{1a} R\(^{1b} \))- or -C(R\(^{1a} R\(^{1b} \))-0-;

wherein \( \text{Ar}^1 \) is phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy, or \( \text{Ar}^1 \) is monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy;

wherein each of \( R^{1a} \) and \( R^{1b} \) is independently selected from hydrogen and C1-C4 alkyl;

wherein \( R^2 \) is selected from hydrogen; C1-C6 alkyl; (C1-C6 alkyloxy) C1-C6 alkyl; C3-C8 cycloalkyl; (C3-C8 cycloalkyl) C1-C6 alkyl; C2-C5 heterocyclyl; phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; (C1-C2 alkyl) phenyl with 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy; and monocyclic heteroaryl having 0-3 substituents selected from halogen, cyano, C1-C4 alkyl, and C1-C4 alkyloxy;

wherein \( R^{3a} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl;

wherein \( R^{3b} \) is selected from hydrogen, halogen, cyano, and C1-C4 alkyl, or \( R^{3a} \) and \( R^{3b} \) are substituted on adjacent carbons and are covalently bonded and, together with the intermediate carbons, comprise an optionally substituted fused ring selected from 4- to 7-membered cycloalkenyl, 5- to 7-membered heteroaryl, and 6-membered aryl;

wherein \( R^{4a} \) is selected from hydrogen and C1-C4 alkyl;

wherein \( R^{4b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( R^{4a} \) and \( R^{4b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;

wherein \( R^{5a} \) is selected from hydrogen and C1-C4 alkyl;

wherein \( R^{5b} \), when present, is selected from hydrogen and C1-C4 alkyl, or \( R^{5a} \) and \( R^{5b} \) are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl;
are covalently bonded and, together with the intermediate carbon, comprise an optionally substituted 3- to 7-membered spirocycloalkyl; and

wherein R^{4a} and R^{5a} are optionally covalently bonded and, together with the intermediate atoms, comprise an optionally substituted 3- to 7-membered fused cycloalkyl;

or a pharmaceutically acceptable salt thereof.

18. The method of claim 17, wherein the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step.

19. The method of claim 17, wherein the disorder is a neurological and/or psychiatric disorder associated with mGluR5 dysfunction.

20. The method of claim 17, wherein the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression.
FIG. 3

N-TERMINAL EXTRACELLULAR
LIGAND-BINDING DOMAIN

NH₂

CYSTEINE-RICH DOMAIN

7TM DOMAIN

INTRACELLULAR
C-TERMINAL DOMAIN

NON-COMPETITIVE
ANTAGONISTS

COMPETITIVE
AGONISTS/ANTAGONISTS

COOH
Dose-Dependent Reversal of Amphetamine-induced Hyperlocomotion

![Graph showing ambulations over time with different compound treatments.](image)

**FIG. 4**
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 471/02 (2012.01)
USPC - 546/123

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07D 471/02 (2012.01)
USPC - 546/123

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/303; 546/122 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest, Google Patent, Google Scholar (fused, valence, composition, potentiator, schizophrenia, alkoxy, neuro, metabotropic, mgur5, glutamate, metabotropic, formula, cyano, receptor, isoquinoline, pyridine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>MALHERBE et al. Mutational Analysis and Molecular Modeling of the Binding Pocket of the Metabotropic Glutamate 5 Receptor Negative Modulator 2-Methyl-6-(phenylethynyl)pyridine; MOLECULAR PHARMACOLOGY, 2003, Vol. 64, No. 4, pp 8237832. Downloaded from: molpharm.aspetjournals.org pg 829, col 1, para 2 to pg 831, col 1, para 1; Table 4; Fig 5</td>
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Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search 12 April 2012 (12.04.2012)

Date of mailing of the international search report 30 APR 2012

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PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)