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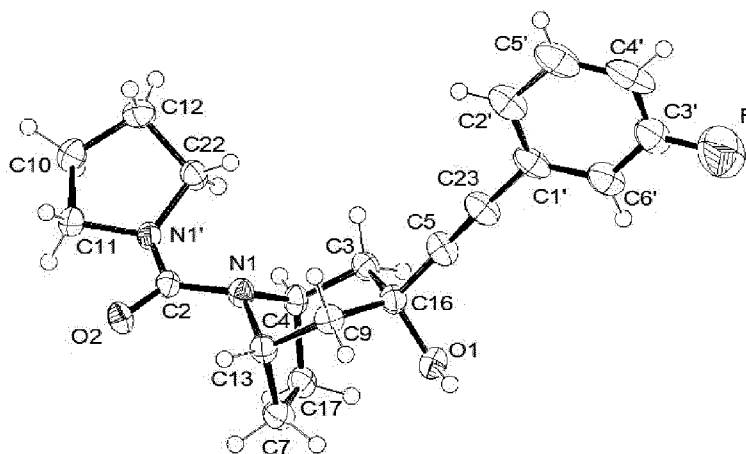
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(54) Title: METABOTROPIC GLUTAMATE RECEPTOR MODULATORS



(57) Abstract: The invention relates to heterocyclic derivatives as well as their pharmaceutically acceptable salts. The invention further relates to a process for the preparation of such compounds. The compounds of the invention are mGluR5 modulators and are therefore useful for the control and prevention of acute and/or chronic neurological disorders.

Figure 1 – Crystal Structure of (3r)-3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone

WO 2012/152854 A1



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, **Published:**
ML, MR, NE, SN, TD, TG).

— *with international search report (Art. 21(3))*

Metabotropic Glutamate Receptor Modulators

FIELD OF THE INVENTION

[0001] The present invention relates to heterocyclic derivatives, which may act as novel metabotropic glutamate receptor (mGluR) modulators, methods for their synthesis and the treatment and/or prevention of various diseases and disorders, including neurological disorders, by administration of such derivatives.

BACKGROUND OF THE INVENTION

[0002] Neuronal stimuli are transmitted by the central nervous system (CNS) through the interaction of a neurotransmitter released by a neuron, which neurotransmitter has a specific effect on a neuroreceptor of another neuron. L-glutamic acid is considered to be a major excitatory neurotransmitter in the mammalian CNS, consequently playing a critical role in a large number of physiological processes. Glutamate-dependent stimulus receptors are divided into two main groups. The first group comprises ligand-controlled ion channels whereas the other comprises metabotropic glutamate receptors (mGluR). Metabotropic glutamate receptors are a subfamily of G-protein-coupled receptors (GPCR). There is increasing evidence for a peripheral role of both ionotropic and metabotropic glutamate receptors outside the CNS e.g. in chronic pain states.

[0003] At present, eight different members of these mGluRs are known. On the basis of structural parameters such as sequence homology, the second messenger system utilized by these receptors and their different affinity to low-molecular weight compounds, these eight receptors may be divided into three groups. mGluR1 and mGluR5 belong to Group I which are positively coupled to phospholipase C and their activation leads to a mobilization of intracellular calcium ions. mGluR2 and mGluR3 belong to Group II and mGluR4, mGluR6, mGluR7 and mGluR8 belong to Group III,

both of which are negatively coupled to adenylyl cyclase, i.e., their activation causes a reduction in second messenger cAMP and thus a dampening of neuronal activity.

[0004] The mGluR5 modulators have been shown to modulate the effects of the presynaptically released neurotransmitter glutamate via postsynaptic mechanisms (receptors). Moreover, as these modulators may be both positive and/or negative mGluR5 modulators, such modulators may increase or inhibit the effects mediated through these metabotropic glutamate receptors.

[0005] Modulators which are negative mGluR5 modulators decrease the effects mediated through metabotropic glutamate receptors. Since a variety of pathophysiological processes and disease states affecting the CNS are thought to be related to abnormal glutamate neurotransmission, and mGluR5 receptors are shown to be expressed in many areas of the CNS and in PNS (peripheral nervous system), modulators of these receptors could be therapeutically beneficial in the treatment of diseases involving CNS and PNS.

[0006] Therefore, mGluR5 positive or negative modulators may be administered to provide neuroprotection and/or disease modification in the following acute or chronic pathological conditions or to provide a symptomatological effect on the following conditions: Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis (ALS), multiple system atrophy, olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, cognitive deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest or stroke or bypass operations or transplants, convulsions, epileptic convulsions, epilepsy,

temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, inner ear insult in tinnitus, tinnitus, sound- or drug-induced inner ear insult, sound- or drug-induced tinnitus, hyperacusis, L-DOPA-induced dyskinesias, L-DOPA-induced dyskinesias in Parkinson's disease therapy, dyskinesias, dyskinesia in Huntington's disease, drug
5 induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, neuroleptics-induced dyskinesia, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential
10 tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity
15 in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, HIV-1 encephalopathy, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, major depressive disorder, major depression, depression, depression resulting from Borna virus infection, major depression resulting from Borna virus infection,
20 bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, fragile-X syndrome, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer pain, posttraumatic stress disorder
25 (PTSD), schizophrenia, positive or cognitive or negative symptoms of schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), gastrointestinal dysfunction, lower esophageal sphincter (LES) disease, functional gastrointestinal disorders,
30 dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity, obesity-related disorders, obesity abuse, food addiction, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders, substance-induced
35 anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform

disorder, substance-induced psychotic disorder, or delirium, diabetes, hyperammonemia and liver failure, and sleep disturbances.

[0007] mGluR5 negative or positive modulators may also be administered to provide inhibition of tumour cell growth, migration, invasion, adhesion and toxicity in the peripheral tissues, peripheral nervous system and CNS. MGlur5 modulators may be administered to provide therapeutic intervention in neoplasia, hyperplasia, dysplasia, cancer, carcinoma, sarcoma, oral cancer, squamous cell carcinoma (SCC), oral squamous cell carcinoma (SCC), lung cancer, lung adenocarcinoma, breast cancer, prostate cancer, gastric cancer, liver cancer, colon cancer, colorectal carcinoma, rhabdomyosarcoma, brain tumour, tumour of a nerve tissue, glioma, malignant glioma, astrogloma, neuroglioma, neuroblastoma, glioblastoma, medulloblastoma, cancer of skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, and other tumours.

[0008] mGluR5 positive or negative modulators may also be administered to provide disease modification and/or to provide a symptomatological effect on the following conditions: diabetes, hyperammonemia and liver failure.

[0009] Further indications for mGluR5 negative or positive modulators include those indications wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, for example cognitive enhancement, learning impairment and/or neuroprotection.

[0010] Positive modulators may be particularly useful in the treatment of positive and negative symptoms in schizophrenia and cognitive deficits in various forms of dementia and mild cognitive impairment.

[0011] Moreover, mGluR modulators may have activity when administered in combination with other substances exhibiting neurological effects via different mechanisms.

[0012] Simultaneous administration of Group I mGluR modulators and NMDA receptor antagonists has also been shown to provide neuroprotection in animal models

(Zieminska et al. *Acta Neurobiol. Exp.*, **2006**, 66, 301-309; Zieminska et al. *Neurochemistry International*, **2003**, 43, 481-492; and Zieminska et al. *Neurochemistry International*, **2006**, 48, 491-497).

[0013] Simultaneous administration of Group I mGluR modulators and compounds such as L-DOPA, dopaminomimetics, and/or neuroleptics may be useful in treating various conditions including drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias.

[0014] In the literature, several types of modulators of mGluR5 have already been described.

THE PRESENT INVENTION

[0015] It now has been found that certain heterocyclic derivatives are potent mGluR5 modulators. Therefore, these substances may be therapeutically beneficial in the treatment of conditions which involve abnormal glutamate neurotransmission or in which modulation of mGluR5 receptors results in therapeutic benefit. These substances may be administered in the form of a pharmaceutical composition, wherein they are present together with one or more pharmaceutically acceptable diluents, carriers, or excipients.

OBJECTS OF THE INVENTION

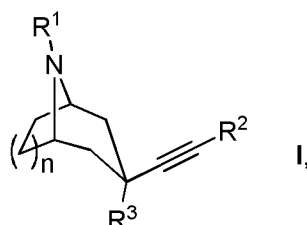
[0016] It is an object of the present invention to provide novel pharmaceutical compounds which are mGluR5 modulators and pharmaceutical compositions thereof. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, modifying, or ameliorating undesirable CNS disorders which involve abnormal glutamate neurotransmission, and/or to provide symptomological effects, by employing a compound of the invention or a pharmaceutical composition containing the same.

[0017] An additional object of the invention is the provision of processes for producing the heterocyclic derivatives.

SUMMARY OF THE INVENTION

[0018] What we therefore believe to be comprised by our invention may be summarized inter alia in the following words:

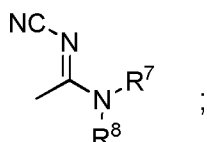
A compound selected from those of Formula I



wherein

n represents 1 or 2;

R¹ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆alkylsulfonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylsulfonyl, -C(O)R⁴, or



R² represents aryl, heteroaryl, cycloC₃₋₁₂alkyl, or heterocyclyl;

R³ represents H, F, OH, C₁₋₆alkoxy;

R⁴ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkyl, heterocyclyl, C₁₋₆alkoxy which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or -NR⁵R⁶;

R⁵ and R⁶ which may be the same or different represent H or C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or

5

R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two additional heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, and oxo;

10

R⁷ and R⁸ which may be the same or different represent H or C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, or

15

R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two additional heteroatoms selected from sulfur, oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, and oxo;

20

and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

25

[0019] A further aspect of the invention relates to a compound of Formula **I**, wherein R¹ represents -C(O)R⁴.

[0020] Such a compound of Formula **I**, wherein R⁴ represents C₁₋₆alkyl, C₁₋₆alkoxy optionally substituted by one or more halogen atoms, C₃₋₆cycloalkyl which may be optionally substituted by C₁₋₆alkyl, heterocyclyl, or -NR⁵R⁶.

30

[0021] Such a compound of Formula I, wherein R^4 represents $-NR^5R^6$, wherein R^5 and R^6 each represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached form pyrrolidino.

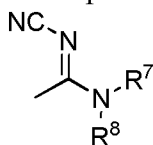
5 [0022] A further aspect of the invention relates to a compound of Formula I, wherein R^1 represents C_{1-6} alkylsulfonyl.

[0023] A further aspect of the invention relates to a compound of Formula I, wherein R^1 represents heteroaryl.

10

[0024] Such a compound of Formula I, wherein R^1 represents pyridyl optionally substituted by one or more substituents selected from cyano, halogen, and C_{1-6} alkyl.

[0025] A further aspect of the invention relates to a compound of Formula I, wherein



15 R^1 represents

[0026] Such a compound of Formula I, wherein R^7 and R^8 each represent C_{1-6} alkyl (e.g., methyl).

20 [0027] A further aspect of the invention relates to a compound of Formula I, wherein R^2 represents aryl or heteroaryl.

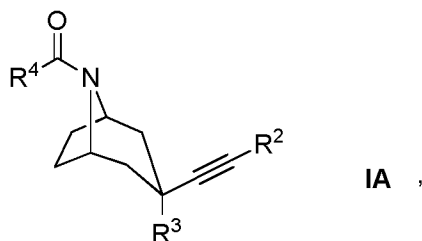
[0028] Such a compound of Formula I, wherein R^2 represents phenyl which is optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, cyano, C_{1-6} alkoxy, and trifluoromethoxy; pyridyl which is optionally substituted by one or more substituents selected from C_{1-6} alkyl, amino, and C_{1-6} alkoxy; or imidazopyridinyl (e.g., imidazo[1,2-a]pyridin-6-yl).

25 [0029] A further aspect of the invention relates to a compound of Formula I, wherein n represents 1.

30

[0030] A further aspect of the invention relates to a compound of Formula I, wherein R^3 represents OH or C_{1-6} alkoxy (e.g., methoxy).

[0031] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IA**



wherein R^2 , R^3 , and R^4 are as defined above for Formula **I**,

and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

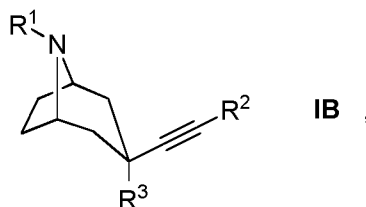
[0032] Such a compound of Formula **IA**, wherein R^2 represents aryl or heteroaryl and R^3 represents OH or C_{1-6} alkoxy (e.g., methoxy).

[0033] Such a compound of Formula **IA**, wherein R^2 represents phenyl which is optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, cyano, C_{1-6} alkoxy, and trifluoromethoxy; pyridyl which is optionally substituted by one or more substituents selected from C_{1-6} alkyl, amino, and C_{1-6} alkoxy; or imidazopyridinyl (e.g., imidazo[1,2-a]pyridin-6-yl).

[0034] Such a compound of Formula **IA**, wherein R^4 represents C_{1-6} alkyl, C_{1-6} alkoxy optionally substituted by one or more halogen atoms, C_{3-6} cycloalkyl which may be optionally substituted by C_{1-6} alkyl, heterocyclcyl, or $-NR^5R^6$.

[0035] Such a compound of Formula **IA**, wherein R^5 and R^6 each represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached form pyrrolidino.

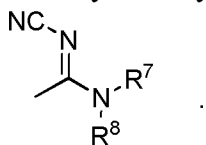
[0036] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IB**



wherein R^1 - R^3 are as defined above for Formula **I**,

and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0037] Such a compound of Formula **IB**, wherein R^1 represents heteroaryl, C_{1-6} alkylsulfonyl, $-C(O)R^4$, or



[0038] Such a compound of Formula **IB**, wherein R^4 represents C_{1-6} alkyl, C_{1-6} alkoxy optionally substituted by one or more halogen atoms, C_{3-6} cycloalkyl which may be optionally substituted by C_{1-6} alkyl, heterocyclyl, or $-NR^5R^6$.

[0039] Such a compound of Formula **IB**, wherein R^5 and R^6 each represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached form pyrrolidino.

[0040] Such a compound of Formula **IB**, wherein R^2 represents aryl or heteroaryl.

[0041] Such a compound of Formula **IB**, wherein R^2 represents phenyl which is optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, cyano, C_{1-6} alkoxy, and trifluoromethoxy; pyridyl which is optionally substituted by one or more substituents selected from C_{1-6} alkyl, amino, and C_{1-6} alkoxy; or imidazopyridinyl (e.g., imidazo[1,2-a]pyridin-6-yl).

[0042] Such a compound of Formula **IB**, wherein R^3 represents OH or C_{1-6} alkoxy (e.g., methoxy).

[0043] Specific compounds of Formula I within the present invention include, but are not limited to, the following compounds:

(3*r*)-Methyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

5 (3*r*)-Methyl 3-((4-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

10 (3*r*)-Methyl 3-((3-cyanophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

15 (3*r*)-Methyl 3-((3-cyano-5-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-hydroxy-3-((6-methylpyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-((6-aminopyridin-2-yl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

20 (3*r*)-Methyl 3-hydroxy-3-((6-methoxypyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone,

1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropan-1-one,

25 1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2,2-dimethylpropan-1-one,

((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(1-methylcyclopropyl)methanone,

30 1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylbutan-1-one,

(3*r*)-Ethyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-3-Hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide,

35 (3*r*)-*N,N*-Diethyl-3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide,

- (3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone,
(3*r*)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone,
5 (3*r*)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone,
(3*r*)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone,
(3*r*)-Ethyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-
10 carboxylate,
(3*r*)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide,
(3*r*)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide,
15 (3*r*)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide,
(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)nicotinonitrile,
Azetidin-1-yl((3*r*)-3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)methanone,
20 (3*r*)-Methyl 3-hydroxy-3-(imidazo[1,2-*a*]pyridin-6-ylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-8-(Methylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol,
(3*r*)-Isopropyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
25 (3*r*)-Isopropyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-Isopropyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-*N'*-Cyano-3-hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-
30 8-carboximidamide,
(3*r*)-Methyl 3-methoxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-Methyl 3-hydroxy-3-(imidazo[1,2-*a*]pyridin-6-ylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-8-(Methylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol,

(3*r*)-8-Isopropyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-Methyl 3-methoxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-Isopropyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
5 (3*r*)-Isopropyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-*N*-Cyano-3-hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboximidamide,
10 (3*r*)-8-(Isopropylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol,
(3*r*)-1,1,1-Trifluoro-2-methylpropan-2-yl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-Methyl 3-hydroxy-3-(phenylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(3-methyloxetan-3-yl)methanone,
15 (3*r*)-Methyl 3-hydroxy-3-((3-(trifluoromethoxy)phenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

20 [0044] In a further aspect, the invention relates to a compound of Formula **I** as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for use in therapy.

25 [0045] Moreover, the invention relates to a compound of Formula **I** as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the treatment and/or prevention of a condition or disease associated with abnormal glutamate neurotransmission, including a condition or disease which is affected or facilitated by modulation of the mGluR5 receptor, including for the
30 conditions or diseases selected from those described earlier in the description.

[0046] In a further aspect, the invention relates to a compound of Formula **I** as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the treatment and/or prevention of a CNS disorder. Moreover,
35 the invention relates to a compound of Formula **I** as defined above or an optical isomer,

pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the treatment and/or prevention of abnormal glutamate neurotransmission. The invention additionally relates to a compound of Formula I as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for modulation of the mGluR5 receptor. The invention furthermore relates to such a compound for treatment, prevention and or modulation of a condition or disease selected from those described earlier in the description. The invention still further relates to such a compound for treatment, prevention and or modulation of a physiological parameter, such as cognitive disorder, whether or not a specific identifiable condition exists.

[0047] A further aspect of the invention relates to a compound of Formula I as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the treatment and/or prevention of a condition associated with abnormal glutamate neurotransmission or in which modulation of mGluR5 receptors results in therapeutic benefit. The conditions which may be treated have already been described above. Such conditions and indications include:

a) For mGluR5 modulators: chronic pain, neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-DOPA-induced dyskinesias, dopaminomimetic-induced dyskinesias, L-DOPA-induced dyskinesias in Parkinson's disease therapy, dopaminomimetic-induced dyskinesias in Parkinson's disease therapy, tardive dyskinesias, Parkinson's disease, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), generalized anxiety disorder, substance-induced anxiety disorder, eating disorders, obesity, binge eating disorders, Huntington's chorea, epilepsy, Alzheimer's disease, positive and negative symptoms of schizophrenia, cognitive impairment, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), migraine, irritable bowel syndrome (IBS), or for cognitive enhancement and/or neuroprotection.

b) Negative modulation of mGluR5 may be particularly useful for: chronic pain, neuropathic pain, diabetic neuropathic pain (DNP), cancer pain, pain related to rheumatic arthritis, inflammatory pain, L-DOPA-induced

dyskinesias, dopaminomimetic-induced dyskinesias, L-DOPA-induced dyskinesias in Parkinson's disease therapy, dopaminomimetic-induced dyskinesias in Parkinson's disease therapy, tardive dyskinesias, Parkinson's disease, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), generalized anxiety disorder, substance-induced anxiety disorder, eating disorders, obesity, binge eating disorders, migraine, irritable bowel syndrome (IBS), functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Huntington's chorea and/or epilepsy.

- c) Positive modulation of mGluR5 may be particularly useful for: Alzheimer's disease, positive and/or negative symptoms of schizophrenia, cognitive impairment, or for cognitive enhancement and/or neuroprotection.

[0048] A further aspect of the invention relates to a compound of Formula I as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the treatment of binge eating disorders.

[0049] Further, the invention relates to the use of a compound of Formula I as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for the preparation of a medicament for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission. Such a use includes the use of such a compound for the preparation of a medicament for the prevention and/or treatment of a condition or disease in an animal including a human being which condition or disease is affected or facilitated by modulation of the mGluR5 receptor.

[0050] Moreover, the invention relates to a method for treating or preventing a condition associated or disease associated with abnormal glutamate neurotransmission, including a condition or disease which is affected or facilitated by modulation of the mGluR5 receptor, including for the conditions or diseases selected from those described earlier in the description.

[0051] Further, the invention relates to a pharmaceutical composition comprising as active ingredient at least one compound of Formula **I** as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients.

5 [0052] Moreover, the mGluR modulators as described above are expected to have a high activity when administered in combination with other substances exhibiting neurological effects via different mechanisms.

10 [0053] In a yet further aspect, the invention thus relates to a compound of Formula **I** as defined above or an optical isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof for neuroprotection and/or for cognitive enhancement in combination with at least one NMDA receptor antagonist such as Memantine.

15 [0054] A further aspect of the invention relates to a pharmaceutical composition comprising at least two different active ingredients, selected from least one compound of Formula **I** as defined above, and, additionally, at least one NMDA-antagonist, together with one or more pharmaceutically acceptable excipients. These compositions may be used for the treatment of CNS-related diseases, cognitive enhancement and for neuro-protection. The invention thus additionally provides a composition comprising at
20 least two different active ingredients, selected from least one compound of Formula **I** as defined above, and, additionally, at least one NMDA-antagonist for the treatment of any of the conditions indicated herein, including CNS-related diseases, cognitive enhancement and for neuro-protection.

25 [0055] This invention also relates to a pharmaceutical composition comprising a combination of a compound of Formula **I** as described above and an NMDA receptor antagonist, including compositions wherein the NMDA receptor antagonist is e.g. Memantine and pharmaceutically acceptable salts, polymorphs, hydrates and solvates thereof.

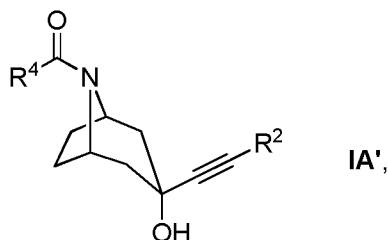
30 [0056] The invention also relates to a pharmaceutical composition comprising at least two different active ingredients, selected from at least one compound of Formula **I** as defined above, and, additionally, at least one active ingredient selected from L-DOPA, other dopaminomimetics (such as antiparkinsonian dopaminomimetics, including
35 bromocriptine, cabergolin, ropinirole, pramipexole, pergolide, rotigotine), and

neuroleptics (such as classical neuroleptics, including haloperidol, perphenazin, chlorpromazine, metoclopramide).

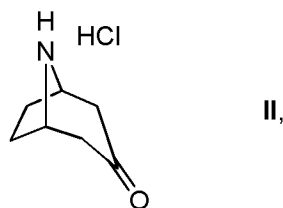
[0057] The invention also relates to a method of providing neuroprotection in a living animal, including a human, comprising the step of administering to a living animal, including a human, a therapeutically effective amount of a composition as described above.

[0058] Furthermore, the invention relates to the use of a composition as described above for the manufacture of a medicament to provide neuroprotection in an animal, including a human.

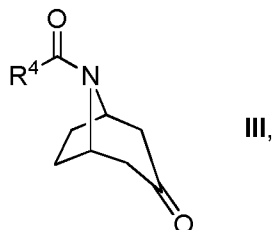
[0059] The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA'**



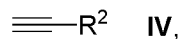
or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R² is as defined above for Formula **I**, wherein nortropinone hydrochloride of Formula **II**



is treated with a substituted carbonyl chloride (such as a carboxylic acid chloride, an alkyl chloroformate, or a dialkylcarbamic chloride) under basic conditions to yield a compound of Formula **III**



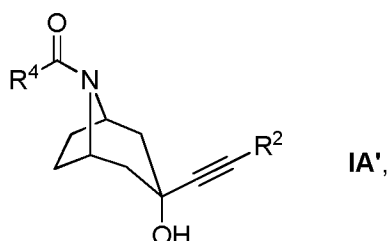
which is reacted with a compound of Formual **IV**



and deprotonated by a strong base such as *n*-butyllithium, to yield the compound of Formula **IA'**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

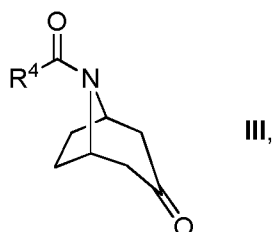
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[0060] The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA'**

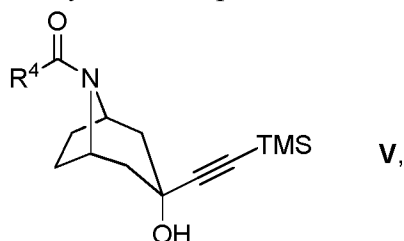


or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R² is as defined above for Formula **I**, wherein the compound of Formula **III**

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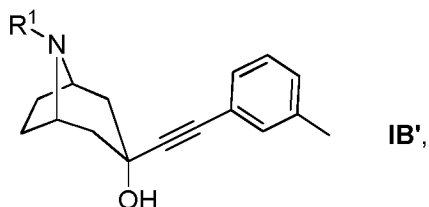
is treated with TMS-acetylene to yield a compound of Formula **V**



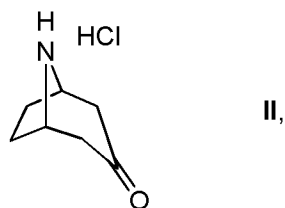
15 which is reacted with an aryl halide under Sonogashira coupling conditions to yield a compound of Formula **IA'**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

[0061] The invention also relates to a process for the synthesis or preparation of a compound of Formula **IB'**

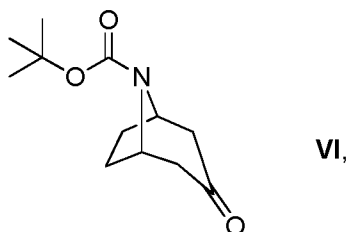
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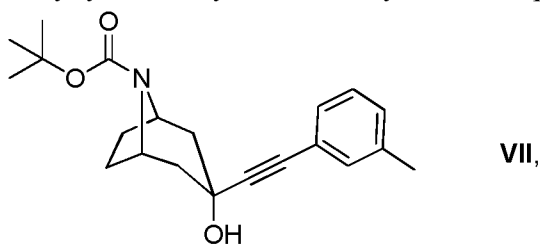
or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R^1 is as defined above for Formula I, wherein nortropinone hydrochloride of Formula II



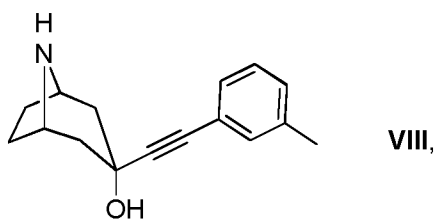
is treated with di-*tert*-butyl dicarbonate to yield the BOC-protected intermediate of Formula VI



which is reacted with 1-ethynyl-3-methylbenzene to yield a compound of Formula VII



which is deprotected under appropriate conditions (e.g., HCl/dioxane) to yield a compound of formula VIII



which is treated with an acid chloride, carbamoyl chloride, chloroformate, or carboxylic acid (in the presence of a suitable coupling agent), to yield the compound of

Formula **IB'**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

BRIEF DESCRIPTION OF THE DRAWINGS

- 5 [0062] **Figure 1** shows the crystal structure of (3*r*)-3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone.

DETAILED DESCRIPTION OF THE INVENTION

- 10 [0063] For the purpose of the present invention, in the compounds of Formula **I** the carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, (C₁₋₃)alkyl refers to alkyl of one to three carbon atoms (i.e. 1, 2 or 3 carbon atoms), inclusive, (i.e., methyl, ethyl, propyl, and isopropyl), straight and
15 branched forms thereof, (C₁₋₆) for instance refers to a radical of one to six carbon atoms (i.e. 1, 2, 3, 4, 5 or 6 carbon atoms).

- [0064] As used herein, the following definitions are applicable unless otherwise described, the term "C₁₋₆alkyl" represents straight or branched chain alkyl groups.
20 Examples of such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

[0065] The term "C₂₋₆alkenyl" represents straight or branched chain alkenyl groups.

- 25 [0066] The term "C₁₋₆alkoxy" represents straight or branched chain -O-C₁₋₆alkyl groups. Examples of such alkoxy groups include methoxy, ethoxy, n-propoxy, and isopropoxy, *sec*-butoxy, *tert*-butoxy.

- 30 [0067] The term "cycloC₃₋₁₂alkyl" represents monocyclic or bicyclic, or tricyclic alkyl groups, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl and adamantanyl, which may be optionally substituted by one or more (e.g., 1, 2, 3, 4, or 5) substituents, which may be the same or different, selected independently from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, cyano, C₁₋₆alkoxycarbonyl, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋

alkylcarbonylamino, oxo, C₁₋₆alkoxyimino, *N*-C₁₋₆alkylaminocarbonyl, *N,N*-di-(C₁₋₆alkyl)aminocarbonyl, arylC₁₋₆alkoxycarbonyl, and C₁₋₆alkylenedioxy.

[0068] The term "cycloC₃₋₆alkyl" represents monocyclic alkyl groups, including cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, which may be optionally substituted by one or more (e.g., 1, 2, 3, 4, or 5) substituents, which may be the same or different, selected independently from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, cyano, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyl, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, oxo, C₁₋₆alkoxyimino, *N*-C₁₋₆alkylaminocarbonyl, *N,N*-di-(C₁₋₆alkyl)aminocarbonyl, arylC₁₋₆alkoxycarbonyl, and C₁₋₆alkylenedioxy.

[0069] The term "aryl" represents phenyl or naphthyl, wherein the phenyl or naphthyl group is optionally substituted by one or more (e.g., 1, 2, 3, 4, or 5) substituents, which may be the same or different, selected independently from halogen, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆alkylthio, C₁₋₆alkoxyC₁₋₆alkyl, amino, hydroxy, nitro, cyano, formyl, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyloxy, C₁₋₆alkylcarbonyloxyC₁₋₆alkyl, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, cycloC₃₋₁₂alkylamino, C₁₋₆alkylcarbonylamino, phenylcarbonylamino, aminocarbonyl, *N*-C₁₋₆alkylaminocarbonyl, *N,N*-di-(C₁₋₆alkyl)aminocarbonyl, pyrrolidinyl, piperidinyl, morpholinyl, oxetanyl, piperazinyl, cycloC₃₋₁₂alkyl, pyridyl, and C₁₋₆alkylenedioxy.

[0070] The term "heteroaryl" represents an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, or a bicyclic group comprising a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heteroaryl group may be optionally substituted by one or more (e.g., 1, 2, 3, 4, or 5) substituents, which may be the same or different, selected independently from halogen, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆alkylthio, amino, hydroxy, nitro, cyano, C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, C₁₋₆alkoxycarbonyloxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino,

cycloC₃₋₁₂alkylamino, C₁₋₆alkylcarbonylamino, aminocarbonyl, N-C₁₋₆alkylaminocarbonyl, N,N-di-(C₁₋₆alkyl)aminocarbonyl, pyrrolidinyl, piperidinyl, morpholinyl, oxetanyl, cycloC₃₋₁₂alkyl, C₁₋₆alkylenedioxy, aryl, and pyridyl. Representative heteroaryl groups include furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, pyrazolyl, triazolyl, thiadiazolyl, thiazolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, triazinyl, purinyl, benzofuryl, benzothienyl, indolyl, indoliziny, isoindolyl, indolinyl, indazolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, isoquinolinyl, quinoliziny, phthalazinyl, and pteridinyl.

[0071] The term "heterocyclyl" represents a saturated or unsaturated non-aromatic 3 to 12 membered ring comprising one to four heteroatoms selected from oxygen, sulfur and nitrogen, and a saturated or unsaturated non-aromatic bicyclic ring system having 3 to 12 members comprising one to six heteroatoms selected from oxygen, sulfur and nitrogen, wherein the heterocyclic ring or ring system may be optionally substituted by one or more (e.g., 1, 2, 3, 4, or 5) substituents, which may be the same or different, selected independently from halogen, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, amino, hydroxy, nitro, cyano, C₁₋₆alkoxycarbonyl, C₁₋₆alkylcarbonyl, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonylamino, oxo, C₁₋₆alkoxyimino, N-C₁₋₆alkylaminocarbonyl, N,N-di-(C₁₋₆alkyl)aminocarbonyl, arylC₁₋₆alkoxycarbonyl, and C₁₋₆alkylenedioxy; examples of such heterocyclyl groups include piperidinyl, morpholinyl, thiomorpholinyl, imidazoliny, imidazolidinyl, pyrazoliny, pyrazolidinyl, pyrroliny, pyrrolidinyl, or piperazinyl, wherein the heterocyclic ring or ring system is linked to the group to which it is attached optionally via nitrogen or a carbon atom.

[0072] The term "halogen" represents fluorine, chlorine, bromine and iodine.

[0073] The compounds of the present invention are usually named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "min" for minute or minutes, "h" for hour or hours, and "rt" for room temperature).

[0074] Memantine, also known as 1-amino-3,5-dimethyladamantane, is disclosed, U.S. Patent Nos. 4,122,193; 4,273,774; and 5,061,703, the subject matter of which patents is hereby incorporated by reference.

5 [0075] Memantine is a systemically-active noncompetitive NMDA receptor antagonists having moderate affinity for the receptor. It exhibits strong voltage dependent characteristics and fast blocking/unblocking kinetics (see e.g. Görtelmeyer et al., *Arzneim-Forsch/Drug Res.*, 1992, 42:904-913; Winblad et al., *Int. J. Geriat. Psychiatry*, 1999, 14:135-146; Rogawski, *Amino Acids*, 2000, 19: 133-49; Danysz et
10 al., *Curr. Pharm. Des.*, 2002, 8:835-43; Jirgensons et. al. *Eur. J. Med. Chem.*, 2000, 35: 555-565).

[0076] The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a reference
15 molecule, but has been modified in a targeted and controlled manner to replace one or more specific substituents of the reference molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule. Synthesis and screening of analogs (e.g., using structural and/or biochemical analysis), to identify slightly modified versions of a known compound which may have improved
20 or biased traits (such as higher potency and/or selectivity at a specific targeted receptor type, greater ability to penetrate blood-brain barriers, fewer side effects, etc.) is a drug design approach that is well known in pharmaceutical chemistry.

[0077] In addition, using methods known to those skilled in the art, analogs and
25 derivatives of the compounds of the invention may be created which have improved therapeutic efficacy, i.e., higher potency and/or selectivity at a specific targeted receptor type, either greater or lower ability to penetrate mammalian blood-brain barriers (e.g., either higher or lower blood-brain barrier permeation rate), fewer side effects, etc.

30 [0078] The term "prodrug" is used herein in the conventional pharmaceutical sense, to refer to a molecule which undergoes a transformation *in vivo* (e.g., an enzymatic or chemical transformation) to release an active parent drug. Prodrugs of the compounds of Formula I of the present invention may be prepared by chemically modifying a functional group present in the compound of Formula I such that the chemically
35 modified compound may undergo a transformation *in vivo* (e.g., enzymatic hydrolysis)

to provide the compound of Formula I. Examples of functional groups present in the compounds of Formula I which may be modified to produce prodrugs include carboxy, hydroxy, amino, and thio groups. Prodrugs of the compounds of Formula I of the present invention may be prepared according to conventional techniques which have
5 been described in the art (see, for example, Stella V., et al., *Prodrugs: Challenges and Rewards*, AAPS Press/Springer, New York, **2007**).

[0079] The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such
10 compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). The term "pharmaceutically acceptable" may also mean approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

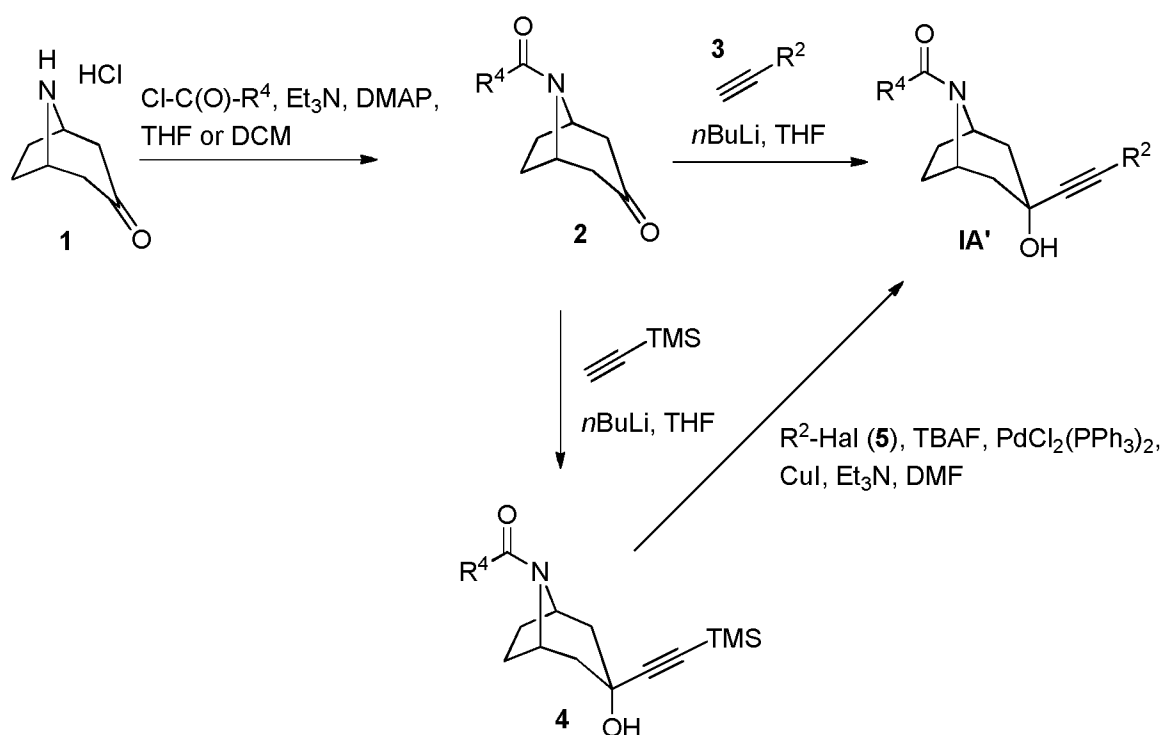
[0080] Compounds of the present invention may be in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not
15 biologically or otherwise undesirable. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

[0081] It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms.
25 Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, polymorphic, tautomeric, or stereoisomeric form, or mixture thereof, of a compound of the invention, which possesses the useful properties described herein.

[0082] The following Schemes 1-2 describe the preparation of compounds of Formula I of the present invention. All of the starting materials may be prepared by procedures described in these schemes, by procedures well known to one of ordinary skill in organic chemistry, or may be obtained commercially. All of the final compounds of the present invention may be prepared by procedures described in these charts or by
30 procedures analogous thereto, which would be well known to one of ordinary skill in

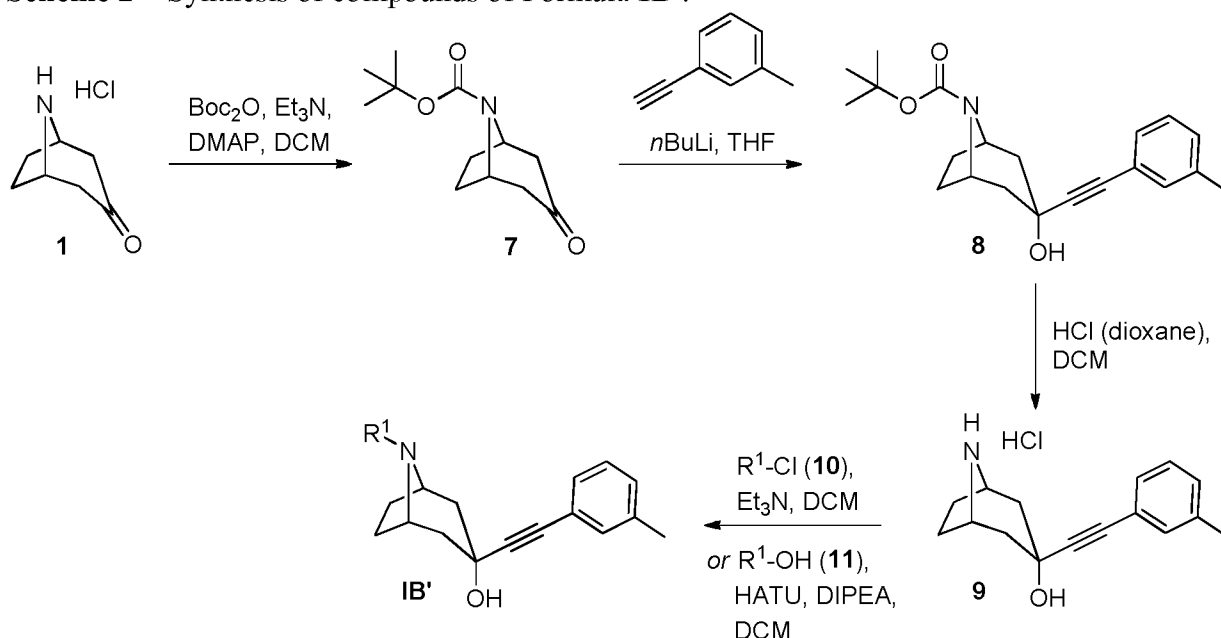
organic chemistry. All of the variables used in Schemes 1-2 are as defined below or as in the claims. Compounds containing one or more chiral centers may be prepared as racemates or mixtures of various stereoisomers and then separated. However, they also may be prepared by a special enantioselective synthesis. For several of the chiral compounds, the enantiomers differ in pharmacological activity.

Scheme 1 – Synthesis of compounds of Formula **IA'**.



[0083] Reaction of nortropinone hydrochloride (**1**) with substituted carbonyl chlorides such as carboxylic acid chlorides, alkyl chloroformates or dialkylcarbamic chlorides under basic conditions results in the formation of intermediate **2**, which is reacted with a terminal acetylene **3**, and deprotonated by a strong base such as *n*-butyllithium, to yield a compound of Formula **IA'**. Alternatively, the TMS-protected intermediate **4** may be formed from compound **2**, which is then reacted with an aryl bromide **5** via a Sonogashira reaction to provide a compound of Formula **IA'**.

[0084] Additional *N*-substituted 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol derivatives may be synthesized as shown in **Scheme 2**.

Scheme 2 – Synthesis of compounds of Formula **IB'**.

- 5 [0085] After *N*-protection of nortropinone hydrochloride (**1**) with di-*tert*-butyl dicarbonate, the BOC-protected intermediate **7** is reacted with 1-ethynyl-3-methylbenzene to give acetylene **8**. Subsequently, the BOC group is removed via treatment with 4N hydrochloride acid in dioxane. *N*-derivatisation of the secondary amine **9** may be achieved via conventional methods, such as reaction with acid
- 10 chlorides, carbamoyl chlorides or chloroformates to provide compounds of Formula **IB'**. Acyl derivatives may also be formed via reaction of intermediate **9** with carboxylic acids using suitable coupling reagents such as HATU.

- [0086] It will be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the molecule of the compound in question in
- 15 order to avoid undesirable side reactions.

- [0087] Pure stereoisomeric forms (including optical isomers) of the compounds and the intermediates of this invention may be obtained by the application of art-known procedures. Diastereomers may be separated by physical separation methods such as
- 20 selective crystallization and chromatographic techniques, e.g. liquid chromatography using chiral stationary phases. Enantiomers (optically active isomers) may be separated from each other by selective crystallization of their diastereomeric salts with optically

active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases.

[0088] Pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric form of appropriate starting materials, provided that the reaction occur stereoselectively. Stereoisomeric forms of Formula I are included within the scope of this invention.

[0089] Compounds of Formula I which are marked by radioactive atoms may be obtained using art-known procedures. Typical compounds include those where one or more hydrogens are substituted by tritium, where one or more ^{12}C are substituted by ^{14}C , where one or more fluorine atoms are substituted by ^{18}F or other isotopes. These may be used for the treatment of diseases (e.g. cancer) but also for diagnostic purposes. The radioactive atoms exchanged in the molecule are often isotopes of carbon, hydrogen, halogen, sulphur or phosphorus. Compounds of the Formula I which are marked by radioactive atoms are included within the scope of this invention.

ADDITION SALTS

[0090] For therapeutic use, salts of the compounds of Formula I are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases, which are non-pharmaceutically acceptable, may also find use, for example, in the preparation and purification of pharmaceutically acceptable compounds. All salts whether pharmaceutically acceptable or not are included within the ambit of the present invention. The pharmaceutically acceptable salts as mentioned above are meant to comprise the therapeutically active non-toxic salt forms, which the compounds of Formula I are able to form. The latter may conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, e.g. hydrohalic acids such as hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids such as acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfonic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely, the salt form may be converted by treatment with alkali into the free base form.

PHARMACEUTICAL COMPOSITIONS

[0091] The active ingredients of the compounds of the invention, together with one or more excipients such as adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions, unit dosages or dosage forms. The pharmaceutical compositions may be employed as solid dosage forms, such as powders, granules, pellets, coated or uncoated tablets or filled capsules, or liquid dosage forms, such as solutions, suspensions, emulsions, or capsules filled with the same, or semi solid dosage forms, such as gels, creams and ointments. The active ingredient(s) dissolution and release profiles of the pharmaceutical dosage forms may be varied from seconds to months.

[0092] The pharmaceutical compositions are designed for the use in animals and humans and may be applied via all application routes. Preferred application routes will be the oral route, the dermal route, the pulmonary route, the nasal route, the rectal route, the parenteral route. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional or new ingredients in conventional or special proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing one (1) to one hundred (100) milligrams of active ingredient or, more broadly, zero point five (0.5) to five hundred (500) milligrams per tablet, are accordingly suitable representative unit dosage forms.

[0093] The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is administered. Such pharmaceutical carriers may be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. A.R. Gennaro, 20th Edition, describes suitable pharmaceutical carriers in "Remington: The Science and Practice of Pharmacy".

METHOD OF TREATING

[0094] Due to their high degree of activity and their low toxicity, together presenting a most favorable therapeutic index, the active principles of the invention may be administered to a subject, e.g., a living animal (including a human) body, in need

thereof, for the treatment, alleviation, or amelioration, palliation, or elimination of an indication or condition which is susceptible thereto, or representatively of an indication or condition set forth elsewhere in this application, preferably concurrently, simultaneously, or together with one or more pharmaceutically-acceptable excipients, carriers, or diluents, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parental (including intravenous and subcutaneous) or in some cases even topical route, in an effective amount. Suitable dosage ranges are 1-1000 milligrams daily, optionally 10-500 milligrams daily, and optionally 50-500 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

[0095] The term "treat" is used herein to mean to relieve or alleviate at least one symptom of a disease in a subject. Within the meaning of the present invention, the term "treat" also denotes to arrest, delay the onset (*i.e.*, the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease.

[0096] The term "combination" is used herein to define a single pharmaceutical composition (formulation) comprising a compound of the present invention and a second active ingredient (e.g., an NMDA receptor antagonist, L-DOPA, a dopaminomimetic, or a neuroleptic), in a formulation known in the art, or two separate pharmaceutical compositions (formulations), one comprising a compound of the present invention as formulated above and one comprising a second active ingredient (e.g., an NMDA receptor antagonist, L-DOPA, a dopaminomimetic, or a neuroleptic) in a formulation known in the art, to be administered conjointly.

[0097] Within the meaning of the present invention, the term "conjoint administration" is used to refer to administration of a compound of the present invention and a second active ingredient (e.g., an NMDA receptor antagonist, L-DOPA, a dopaminomimetic, or a neuroleptic) in one composition, or simultaneously in different compositions, or sequentially. For the sequential administration to be considered "conjoint", however, the compound of the present invention and the NMDA receptor antagonist must be administered separated by a time interval that still permits the resultant beneficial effect in a mammal. For example, the compound of the present invention and the NMDA

receptor antagonist must be administered on the same day (*e.g.*, each - once or twice daily), including within an hour of each other, and including simultaneously.

[0098] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a living animal body in need thereof.

5

[0099] Compounds of the present invention may be administered orally, topically, parenterally, or mucosally (*e.g.*, buccally, by inhalation, or rectally) in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. It is usually desirable to use the oral route. The active agents may be administered orally in the form of a capsule, a tablet, or the like (see Remington: The Science and Practice of Pharmacy, 20th Edition). The orally administered pharmaceutical compositions may be administered in the form of a time-controlled release vehicle, including diffusion-controlled systems, osmotic devices, dissolution-controlled matrices, and erodible/degradable matrices.

15

[00100] For oral administration in the form of a tablet or capsule, the active drug component of Formula I may be combined with non-toxic, pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, sucrose, glucose, mannitol, sorbitol and other reducing and non-reducing sugars, microcrystalline cellulose, calcium sulfate, or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc, or silica, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like); disintegrants (*e.g.*, potato starch or sodium starch glycolate); and/or wetting agents (*e.g.*, sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like. For oral administration in liquid form, the drug components may be combined with non-toxic, pharmaceutically acceptable inert carriers (*e.g.*, ethanol, glycerol, water), suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (*e.g.*, lecithin or acacia), non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (*e.g.*, methyl or propyl-p-hydroxybenzoates or sorbic acid), and the like.

30

Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) may also be added to stabilize the dosage forms.

[00101]Tablets may be coated by methods well known in the art. Compositions of the invention containing as active compound a compound of Formula **I** may be also introduced in beads, microspheres or microcapsules, e.g., fabricated from polyglycolic acid/lactic acid (PGLA). Liquid preparations for oral administration may take the form of, for example, solutions, syrups, emulsions or suspensions, or they may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Preparations for oral administration may be suitably formulated to give controlled or postponed release of the active compound.

[00102]Compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines, as is well known.

[00103]Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. Active drugs may also be coupled with soluble polymers as targetable drug carriers. Such polymers include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropyl methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, active drug may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[00104]For administration by inhalation, the therapeutics according to the present invention containing as active compound a compound of Formula **I** may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin

for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[00105] Formulations comprising compounds of the present invention may be delivered parenterally, i.e., by intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdermal (s.d.), or intradermal (i.d.) administration, by direct injection, via, for example, bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as excipients, suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00106] Compounds of the present invention may also be formulated for rectal administration, e.g., as suppositories or retention enemas (e.g., containing conventional suppository bases such as cocoa butter or other glycerides).

[00107] Compositions containing a compound of Formula I may, if desired, be presented in a pack or dispenser device, which may contain one or more unit dosage forms containing the active ingredient and/or may contain different dosage levels to facilitate dosage titration. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[00108] As disclosed herein, the dose of the components in the compositions of the present invention is determined to ensure that the dose administered continuously or intermittently will not exceed an amount determined after consideration of the results in test animals and the individual conditions of a patient. A specific dose naturally varies depending on the dosage procedure, the conditions of a patient or a subject animal such as age, body weight, sex, sensitivity, feed, dosage period, drugs used in combination, seriousness of the disease. The appropriate dose and dosage times under certain conditions may be determined by the test based on the above-described indices but may

be refined and ultimately decided according to the judgment of the practitioner and each patient's circumstances (age, general condition, severity of symptoms, sex, etc.) according to standard clinical techniques.

- 5 [00109] Toxicity and therapeutic efficacy of the compositions of the invention may be determined by standard pharmaceutical procedures in experimental animals, e.g., by determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it may be expressed as the ratio LD₅₀/ED₅₀.
- 10 Compositions that exhibit large therapeutic indices are preferred.

- [00110] From the Examples described herein below, it is apparent that the present invention provides novel and valuable applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the
- 15 present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith.

- [00111] The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on
- 20 its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies which are responsible for and authorized to pass
- 25 judgment on such questions.

- [00112] The instant compounds of Formula I represent a novel class of mGluR5 modulators. In view of their potency, they will be useful therapeutics in a wide range of disorders, in particular CNS disorders, which involve excessive glutamate induced
- 30 excitation.

- [00113] These compounds accordingly find application in the treatment of the disorders of a living animal body, especially a human, as listed earlier in the description.

[00114] These compounds also find application in the treatment of indications in a living animal body, especially a human, wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, including cognitive enhancement.

5

[00115] Neuroprotection as well as cognitive enhancement may also be achieved by administration of the instant compounds in combination with a NMDA receptor antagonist like Memantine.

10 [00116] The method-of-treating a living animal body with a compound of the invention, for the inhibition of progression or alleviation of the selected ailment therein, is as previously stated by any normally-accepted pharmaceutical route, employing the selected dosage which is effective in the alleviation of the particular ailment desired to be alleviated. Use of the compounds of the present invention in the manufacture of a
15 medicament for the treatment of a living animal for inhibition of progression or alleviation of selected ailments or conditions, particularly ailments or conditions susceptible to treatment with a Group I mGluR modulator is carried out in the usual manner comprising the step of admixing an effective amount of a compound of the invention with a pharmaceutically-acceptable diluent, excipient, or carrier, and the
20 method-of-treating, pharmaceutical compositions, and use of a compound of the present invention in the manufacture of a medicament.

[00117] Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier,
25 include tablets, capsules, solutions for injection, liquid oral formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

EXPERIMENTAL PART

30 [00118] The compounds and their preparation of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

[00119] Hereinafter, "DCM" is defined as dichloromethane, "DEE" as diethyl ether,
35 "DIPEA" as *N,N*-diisopropylethylamine, "DMAP" as 4-dimethylaminopyridine, "DMF"

as *N,N*-dimethylformamide, "EtOAc" as ethyl acetate, "HATU" as 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, "MeOH" as methanol, "TBAF" as tetrabutylammonium fluoride, "TEA" as triethylamine, and "THF" as tetrahydrofuran.

5

General Procedure 1 – Alkynylation of cyclic ketones

[00120] *n*-Butyllithium (1.6M in hexane, 2 equiv.) is added slowly to a cooled (-20 °C) solution of the acetylene (2.1 equiv.) in THF. The reaction mixture is stirred at 0 °C for 90 min and then cooled to -78 °C. A solution of the cyclic ketone in THF is slowly added, and the reaction mixture is allowed to warm to 0-5 °C and stirred for 2 h. The reaction mixture is quenched with saturated aqueous NH₄Cl, warmed to room temperature and diluted with EtOAc. The aqueous layer is extracted twice with EtOAc, and the combined organic layers are washed with water (3x), brine, dried over Na₂SO₄ and evaporated to dryness. Purification of the residue by flash column chromatography or preparative TLC or HPLC provides final products.

15

Preparation 1

Methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate

20

[00121] To a solution of 8-azabicyclo[3.2.1]octan-3-one hydrochloride in THF are added TEA (4 equiv.) and DMAP (0.2 equiv.), and the mixture is cooled in an ice bath. Methyl chloroformate (1.5 equiv.) is added dropwise, and after complete addition the mixture is stirred at room temperature for 3 h. The reaction mixture is diluted with EtOAc, solids are filtered off, and the filtrate is washed with brine. The aqueous phase is extracted with EtOAc, and the combined organic phases are washed with water (3x), dried over Na₂SO₄ and concentrated. The crude product is purified by flash column chromatography (silica gel, EtOAc in heptane, 15 to 50%) to provide the title compound (37%) as a colorless oil.

25

¹H NMR (CDCl₃), δ_H, 1.69 (m, 2H), 2.10 (m, 2H), 2.34 (s, 1H), 2.38 (s, 1H), 2.59-2.78 (m, 2H), 3.76 (s, 3H), 4.58 (br s, 1H), 5.53 (br s, 1H).

30

LC/MS (M+H)⁺ = 184

Preparation 2

(3*r*)-Methyl 3-hydroxy-3-((trimethylsilyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00122] Synthesis is performed according to General Procedure 1 using methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate and ethynyltrimethylsilane. The crude product is purified by flash column chromatography (silica gel, 25% EtOAc to 40% EtOAc in heptane) to give the title compound (65%) as white solid.

¹H NMR (CDCl₃), δ_H, 0.12 (s, 9H), 1.67 (s, 1H), 1.74 (m, 2H), 1.79 (s, 1H), 1.83 (s, 1H), 1.91-2.09 (m, 2H), 2.11-2.24 (m, 1H), 3.57 (s, 3H), 4.10 (br s, 1H), 4.18 (br s, 1H).

General Procedure 2 – Alkynylation of aryl halides

[00123] A mixture of the acetylene, the corresponding aryl bromide or iodide (1 equiv.), and TEA (4 equiv.) in DMF is thoroughly degassed with N₂. Copper iodide (0.1 equiv.) and bis(triphenylphosphine)palladium dichloride (0.1 equiv.) are added followed by dropwise addition of TBAF (1M in THF, 1.1 equiv.). The reaction mixture is heated to 60 °C for 2 h and then stirred overnight at room temperature. The mixture is quenched with brine and extracted with EtOAc (3x). The combined organic layers are washed with brine (2x), dried with Na₂SO₄ and concentrated. The residue is purified by flash column chromatography or preparative TLC or HPLC to give final products.

General Procedure 3 – *N*-Derivatisation of 3-arylethynyl-8-azabicyclo[3.2.1]octan-3-ol derivatives

[00124] To a suspension of 3-arylethynyl-8-azabicyclo[3.2.1]octan-3-ol hydrochloride and TEA (2.0-6.0 equiv.) in DCM at 0 °C is added the acid chloride, carbamoyl chloride or chloroformate (1.5 equiv.). The reaction mixture is warmed up to room temperature and stirred overnight, then water and EtOAc are added. The layers are separated, and the aqueous layer is extracted twice with EtOAc. The organic layers are combined and washed with water and brine, dried with Na₂SO₄, and concentrated to give the crude product, which is further purified by flash column chromatography or preparative TLC or HPLC, if necessary.

Preparation 3

***tert*-Butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate**

[00125] To 8-azabicyclo[3.2.1]octan-3-one (2 g, 15.98 mmol) in DCM (80 mL) are added di-*tert*-butyl dicarbonate (5.23 g, 23.97 mmol), *N,N*-dimethylpyridin-4-amine (0.390 g, 3.20 mmol), and TEA (8.98 mL, 63.9 mmol) at 0 °C. The reaction is warmed up to room temperature and stirred for 16 h. The reaction mixture is concentrated *in vacuo*. EtOAc (250 mL) and water (250 mL) are added, and the layers are separated. The aqueous layer is extracted with EtOAc (3x 250 mL). The organic layers are combined and washed with water (250 mL) and brine (250 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue is purified by flash chromatography (silica gel, 25% EtOAc in heptane) to give the title compound (74%) as a white solid.

¹H NMR (d₆-DMSO), δ_H, 1.43 (s, 9H), 1.54 (d, 2H), 1.98 (br s, 2H), 2.21 (d, 2H), 2.49 (s, 1H), 2.55 (d, 1H), 4.31 (br s, 2H).

Preparation 4

(3*r*)-*tert*-Butyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00126] 1-Ethynyl-3-methylbenzene (0.551 mL, 4.30 mmol) in THF (6 mL) is cooled under argon to -20 °C. *n*-Butyllithium (1.6 M, 2.96 mL, 4.73 mmol) is added, and the mixture is warmed up to 0 °C for 1 h. Then the mixture is cooled to -20 °C, and *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (484 mg, 2.15 mmol) in THF (4 mL) is added. The mixture is warmed up to 0 °C and stirred for 1 h. The mixture is quenched with saturated NH₄Cl, and EtOAc (50 mL) is added. The layers are separated, and the aqueous layer is extracted with EtOAc (2 x 50 mL). The organic layers are combined and washed with water (50 mL) and brine (50 mL), dried over Na₂SO₄ and concentrated. The residue is purified by flash chromatography (silica gel, 10 to 35% EtOAc in heptane) to give the title compound (51%) as a colorless oil.

¹H NMR (CDCl₃), δ_H, 1.48 (s, 9H), 1.91 (m, 2H), 1.96 (s, 1H), 2.01 (m, 2H), 2.17 (s, 2H), 2.28 (m, 1H), 2.31 (s, 3H), 2.41 (m, 1H), 4.20 (d, 2H), 7.12 (d, 1H), 7.17 (m, 3H).

LC/MS (M+H)⁺ = 343

Preparation 5

(3*r*)-3-(*m*-Tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride

[00127] A solution of *tert*-butyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.48 g, 4.33 mmol) in DCM (5 mL) is treated with 4N HCl in dioxane (4.33 mL, 17.34 mmol). The mixture is stirred at room temperature for 1 h. The suspension is filtered off, and the residue is rinsed with DCM.
5 After drying the title compound (56%) is obtained as a white solid.
¹H NMR (d₆-DMSO), δ_H, 1.88 (m, 2H), 2.15 (d, 2H) 2.23 (m, 2H), 2.29 (s, 3H), 2.37 (d, 2H), 3.96 (s, 2H), 5.89 (s, 1H), 7.18 (m, 3H), 7.25 (t, 1H), 9.19 (br s, 2H).

General Procedure 4 – *N*-derivatisation of nortropinone

10 [00128] To a solution of 8-azabicyclo[3.2.1]octan-3-one (nortropinone) hydrochloride in DCM or THF is added TEA or DIPEA (2-6 equiv.). This mixture is cooled in an ice-bath and the acid chloride, carbamoyl chloride or chloroformate (1.5 equiv.) is added
15 dropwise. After complete addition the reaction mixture is stirred until complete conversion is obtained according to TLC analysis. The reaction mixture is diluted with DCM or EtOAc and washed with brine. The organic layer is dried over Na₂SO₄ and concentrated to give the crude product, which is further purified by flash column chromatography, if necessary.

Example 1

(3*r*)-Methyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate

25 [00129] According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-3-fluorobenzene, and the crude product is purified by preparative TLC (EtOAc/heptane 1:6) to provide the title compound (24%) as a white solid.

¹H NMR (CDCl₃), δ_H, 1.84-1.99 (m, 3H), 2.03 (s, 1H), 2.07 (s, 1H), 2.12-2.23 (m, 2H),
30 2.23-2.48 (m, 2H), 3.72 (s, 3H), 4.27 (br s, 1H), 4.36 (br s, 1H), 7.15 (d, 1H), 6.97-7.11 (m, 2H), 7.22-7.30 (m, 1H).

LC/MS (M+H)⁺ = 304

Example 2**(3*r*)-Methyl 3-((4-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate**

5 [00130]According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-4-fluorobenzene, and the crude product is purified by preparative TLC (EtOAc/heptane 1:4) to provide the title compound (24%) as a white solid.

¹H NMR (CDCl₃), δ_H, 1.89 (s, 1H), 1.93 (m, 2H), 2.02-2.08 (m, 2H), 2.16-2.22 (m, 2H),
10 2.25-2.45 (m, 2H), 3.72 (s, 3H), 4.27 (bs, 1H), 4.35 (bs, 1H), 6.94-7.01 (m, 2H), 7.33-7.39 (m, 2H).

LC/MS (M+H)⁺ = 304

Example 3

15 **(3*r*)-Methyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate**

[00131]According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-3-chlorobenzene, and the crude product is purified
20 by preparative TLC (EtOAc/heptane 1:6) to provide the title compound (17%) as a white solid.

¹H NMR (CDCl₃), δ_H, 1.90 (m, 3H), 2.03 (s, 1H), 2.07 (s, 1H), 2.11-2.23 (m, 2H), 2.24-2.52 (m, 2H), 3.72 (s, 3H), 4.28 (br s, 1H), 4.36 (br s, 1H), 7.12-7.38 (m, 4H).

LC/MS (M+H)⁺ = 320

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Example 4**(3*r*)-Methyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

[00132]According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-3-methylbenzene, and the crude product is
30 purified by preparative TLC (EtOAc/heptane 1:4) to provide the title compound (13%) as a white solid.

¹H NMR (CDCl₃), δ_H, 1.90 (m, 3H), 2.03 (s, 1H), 2.07 (s, 1H), 2.21 (m, 2H), 2.31 (s, 3H), 2.40 (m, 1H), 3.71 (s, 3H), 4.27 (br s, 1H), 4.35 (br s, 1H), 7.11 (m, 1H), 7.17 (m,
35 3H).

LC/MS (M+H)⁺ = 300

Example 5

(3*r*)-Methyl 3-((3-cyanophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate

[00133]According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 3-ethynylbenzonitrile, and the crude product is purified by preparative TLC (EtOAc/heptane 1:6) to provide the title compound (9%) as a colorless oil.

¹H NMR (CDCl₃), δ_H, 1.89 (s, 1H), 1.90-2.01 (m, 2H), 2.07 (s, 1H), 2.11 (s, 1H), 2.16-2.50 (m, 4H), 3.72 (s, 3H), 4.29 (br s, 1H), 4.36 (br s, 1H), 7.42 (t, 1H), 7.59-7.60 (d, 2H), 7.66 (s, 1H).

LC/MS (M+H)⁺ = 311

Example 6

(3*r*)-Methyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00134]According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-3-methoxybenzene, and the crude product is purified by preparative TLC (EtOAc/heptane 1:6) to provide the title compound (19%) as a colorless oil.

¹H NMR (CDCl₃), δ_H, 1.89 (s, 1H), 1.90-1.94 (m, 2H), 2.04 (s, 1H), 2.08 (s, 1H), 2.21 (m, 2H), 2.22-2.52 (m, 2H), 3.72 (s, 3H), 3.79 (s, 3H), 4.27 (br s, 1H), 4.36 (br s, 1H), 6.82-6.90 (m, 2H), 6.96 (m, 1H), 7.20 (m, 1H).

LC/MS (M+H)⁺ = 316

[00135]In addition to the (*r*)-isomer, the corresponding (*s*)-isomer (i.e., *exo*-hydroxy isomer) (3%) is separated as colorless oil.

¹H NMR (CDCl₃), δ_H, 1.86-2.07 (m, 3H), 2.16 (m, 2H), 2.21-2.29 (m, 4H), 3.71 (s, 3H), 3.80 (s, 3H), 4.32 (br s, 1H), 4.41 (br s, 1H), 6.93 (m, 2H), 7.01 (m, 1H), 7.24 (m, 1H).

LC/MS (M+H)⁺ = 316

Example 7**(3*r*)-Methyl 3-((3-cyano-5-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate**

- 5 [00136]According to General Procedure 2, methyl 3-hydroxy-3-((trimethylsilyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 3-bromo-5-fluorobenzonitrile to provide the title compound (62%) as an orange-brown solid.
- ¹H NMR (CDCl₃), δ_H, 1.93 (m, 2H), 2.05 (m, 3H), 2.20 (m, 3H), 2.38 (m, 1H), 3.72 (s, 3H), 4.33 (m, 2H), 7.31 (m, 2H), 7.46 (s, 1H).
- 10 LC/MS (M+H)⁺ = 329

Example 8

- 15 **(3*r*)-Methyl 3-hydroxy-3-((6-methylpyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

- [00137]According to General Procedure 2, methyl 3-hydroxy-3-((trimethylsilyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 2-bromo-6-methylpyridine, and the crude product is purified by preparative TLC
- 20 (EtOAc/heptane 2:1) to provide the title compound (32%) as a colorless oil.
- ¹H NMR (CDCl₃), δ_H, 1.91 (m, 2H), 2.08 (m, 2H), 2.11-2.29 (m, 3H), 2.29-2.57 (m, 2H), 2.55 (s, 3H), 3.71 (s, 3H), 4.27 (br s, 1H), 4.35 (br s, 1H), 7.09 (d, 1H), 7.21 (d, 1H), 7.53 (t, 1H).
- LC/MS (M+H)⁺ = 301

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Example 9**(3*r*)-Methyl 3-((6-aminopyridin-2-yl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate**

- 30 [00138]According to General Procedure 2, methyl 3-hydroxy-3-((trimethylsilyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 6-bromopyridin-2-amine, and the crude product is purified by flash column chromatography (silica gel, 0.5% to 5 % MeOH in DCM) followed by preparative TLC (DCM/MeOH 97:3) to provide the title compound (15%) as a colorless oil.

¹H NMR (CDCl₃), δ_H, 1.62 (m, 2H), 2.06 (d, 2H), 2.12 (s, 1H), 2.19 (m, 2H), 2.27-2.52 (m, 2H), 3.71 (s, 3H), 4.26 (br s, 1H), 4.34 (br s, 1H), 4.52 (br s, 2H), 6.45 (d, 1H), 6.78 (d, 1H), 7.38 (m, 1H).

LC/MS (M+H)⁺ = 302

5

Example 10

(3*r*)-Methyl 3-hydroxy-3-((6-methoxypyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

10 [00139]According to General Procedure 2, methyl 3-hydroxy-3-((trimethylsilyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 2-bromo-6-methoxypyridine, and the crude product is purified by column chromatography (silica gel, EtOAc/heptane 1:4) to provide the title compound (58%) as a yellow oil.

15 ¹H NMR (CDCl₃), δ_H, 1.92 (m, 2H), 2.10 (m, 3H), 2.21 (m, 2H), 2.38 (m, 2H), 3.72 (s, 3H), 3.93 (s, 3H), 4.32 (m, 2H), 6.69 (d, 1H), 6.99 (d, 1H), 7.49 (dd, 1H).
LC/MS (M+H)⁺ = 317

Example 11

20 1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone

[00140]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with acetyl chloride to provide the title compound (86%) as a white solid.

25 ¹H NMR (CDCl₃), δ_H, 1.85-1.98 (m, 2H), 2.06 (m, 3H), 2.07 (s, 3H), 2.10-2.36 (m, 8H), 2.41 (dd, 1H), 4.13 (m, 1H), 4.70 (m, 1H), 7.10 (m, 1H), 7.17 (m, 3H).
LC/MS (M+H)⁺ = 284

Example 12

30 1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropan-1-one

[00141]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with isobutyryl chloride, and the crude product is purified by flash chromatography (silica gel, 0.5 to 2% MeOH in DCM) to provide the title compound (35%) as a white solid.

35

¹H NMR (d₆-DMSO), δ_H, 0.98 (q, 6H), 1.65-1.86 (m, 2H), 1.99-2.18 (m, 6H), 2.27 (s, 3H), 2.71 (m, 1H), 4.32 (m, 1H), 4.47 (m, 1H), 5.62 (s, 1H), 7.14-7.26 (m, 4H).

LC/MS (M+H)⁺ = 312

5 Example 13

1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2,2-dimethylpropan-1-one

[00142]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with pivaloyl chloride to provide the title compound (88%) as a white solid.

¹H NMR (d₆-DMSO), δ_H, 1.16 (s, 9H), 1.71 (m, 2H), 2.02-2.27 (m, 6H), 2.27 (s, 3H), 4.56 (m, 2H), 5.62 (s, 1H), 7.15-7.23 (m, 4H).

LC/MS (M+H)⁺ = 326

15

Example 14

((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(1-methylcyclopropyl)methanone

[00143]A mixture of 1-methylcyclopropanecarboxylic acid (33.3 mg, 0.333 mmol), HATU (158 mg, 0.416 mmol) and DIPEA (0.095 mL, 0.554 mmol) in DCM (2 mL) is stirred for 30 min. The reaction mixture is added to a stirred suspension of 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (77 mg, 0.277 mmol) and DIPEA (0.047 mL, 0.277 mmol) in DCM (2 mL). The mixture is stirred at room temperature for 2 h and concentrated. To the residue EtOAc is added, and the organic layer is washed with 1M aqueous KHSO₄ solution and saturated NaHCO₃ solution, dried with Na₂SO₄, and concentrated. Purification by flash column chromatography (silica gel, EtOAc/heptane, 30% to 50%) provided the title compound (94 mg, 83%) as a white solid.

¹H NMR (d₆-DMSO), δ_H, 0.49 (d, 2H), 0.77 (br s, 2H), 1.24 (s, 3H), 1.72 (br s, 2H), 1.99-2.15 (m, 6H), 2.27 (s, 3H), 4.49 (br s, 2H), 5.63 (s, 1H), 7.15-7.26 (m, 4H).

LC/MS (M+H)⁺ = 324

30

Example 15**1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylbutan-1-one**

- 5 [00144]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with D,L-2-methylbutyryl chloride, and the crude product is purified by flash chromatography (silica gel, 1 to 2.5% MeOH in DCM) to provide the title compound (47%) as a colorless oil.
- ¹H NMR (d₆-DMSO), δ_H, 0.80 (t, 3H), 0.97 (q, 3H), 1.29 (m, 1H), 1.46 (m, 1H), 1.58 (m, 1H), 1.69 (m, 1H), 1.85 (m, 1H), 2.00-2.19 (m, 6H), 2.27 (s, 3H), 2.55 (m, 1H), 4.38 (m, 1H), 4.51 (m, 1H), 5.66 (s, 1H), 7.12-7.26 (m, 4H).
- 10 LC/MS (M+H)⁺ = 326

Example 16

- 15 **(3*r*)-Ethyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

- [00145]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with ethyl chloroformate, and the crude product is purified by flash chromatography (silica gel, 0.5 to 2% MeOH in DCM) to provide the title compound (63%) as a colorless oil.
- 20 ¹H NMR (d₆-DMSO), δ_H, 1.18 (t, 3H), 1.79 (m, 2H), 2.04-2.12 (m, 6H), 2.27 (s, 3H), 4.04 (q, 2H), 4.14 (m, 2H), 5.62 (s, 1H), 7.14-7.26 (m, 4H).
- LC/MS (M+H)⁺ = 314

- 25 **Example 17**

(3*r*)-3-Hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide

- [00146]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with dimethylcarbamoyl chloride, and the crude product is purified by flash chromatography (silica gel, 0.5 to 2% MeOH in DCM) to provide the title compound (56%) as a white solid.
- 30 ¹H NMR (d₆-DMSO), δ_H, 1.67 (m, 2H), 2.02-2.18 (m, 6H), 2.27 (s, 3H), 2.78 (s, 6H), 3.96 (m, 2H), 5.47 (s, 1H), 7.15-7.26 (m, 4H).
- 35 LC/MS (M+H)⁺ = 313

Example 18**(3*r*)-*N,N*-Diethyl-3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide**

5

[00147]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with diethylcarbonyl chloride, and the crude product is purified by flash chromatography (silica gel, 30% EtOAc in heptane) to provide the title compound (79%) as a colorless oil.

10 ¹H NMR (CDCl₃), δ_H, 1.14 (t, 6H), 1.86-1.89 (m, 3H), 2.07-2.18 (m, 4H), 2.31 (s, 3H), 2.39-2.44 (m, 2H), 3.27 (q, 4H), 4.05-4.07 (m, 2H), 7.11-7.23 (m, 4H).
LC/MS (M+H)⁺ = 341

Example 19**(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone**

[00148]According to General Procedure 3, 3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride is reacted with pyrrolidine-1-carbonyl chloride, and the crude product is triturated with MeOH to provide the title compound (26%) as a white solid.

20 ¹H NMR (d₆-DMSO), δ_H, 1.68 (m, 2H), 1.74 (m, 4H), 1.99-2.18 (m, 6H), 2.27 (s, 3H), 3.29 (m, 4H), 4.03 (m, 2H), 5.48 (s, 1H), 7.14-7.24 (m, 4H).
LC/MS (M+H)⁺ = 339

25

Example 20**(3*r*)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone**

30 [00149]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with pyrrolidine-1-carbonyl chloride, and the crude product is purified by flash column chromatography (silica gel, DCM/MeOH 0-5%) to give 8-(pyrrolidine-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-one as a colorless solid. This intermediate product is then reacted with 1-ethynyl-3-fluorobenzene according to
35 General Procedure 1, and the crude product is purified by trituration with DCM

followed by flash column chromatography (silica gel, heptane/EtOAc 5-75%) to provide the title compound (23%) as a white solid.

^1H NMR (d_6 -DMSO), δ_{H} , 1.69 (m, 2H), 1.74 (m, 4H), 2.01-2.09 (m, 4H), 2.17 (m, 2H), 3.28 (m, 4H), 4.06 (bs, 2H), 5.52 (s, 1H), 7.21 (m, 3H), 7.40 (m, 1H).

5 LC/MS ($\text{M}+\text{H}$) $^+$ = 343

Example 21

(3*r*)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone

10

[00150]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with pyrrolidine-1-carbonyl chloride, and the crude product is purified by flash column chromatography (silica gel, DCM/MeOH 0-5%) to give 8-(pyrrolidine-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-one as a colorless solid. This

15

intermediate product is then reacted with 1-chloro-3-ethynylbenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 0-60%) to provide the title compound (37%) as a colorless solid.

20

^1H NMR (d_6 -DMSO), δ_{H} , 1.68 (m, 2H), 1.75 (m, 4H), 2.06 (m, 4H), 2.17 (m, 2H), 3.28 (t, 4H), 4.07 (bs, 2H), 5.52 (s, 1H), 7.32-7.44 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 359, 361

Example 22

(3*r*)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone

25

[00151]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with pyrrolidine-1-carbonyl chloride, and the crude product is purified by flash column chromatography (silica gel, DCM/MeOH 0-5%) to give 8-(pyrrolidine-1-carbonyl)-8-azabicyclo[3.2.1]octan-3-one as a colorless solid. This

30 intermediate product is then reacted with 1-ethynyl-3-methoxybenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 5-75%) to provide the title compound (41%) as a colorless solid.

¹H NMR (d₆-DMSO), δ_H, 1.68 (m, 2H), 1.74 (m, 4H), 1.99-2.09 (m, 4H), 2.17 (m, 2H), 3.28 (m, 4H), 3.75 (m, 3H), 4.06 (bs, 2H), 5.47 (s, 1H), 6.88 (s, 1H), 6.93 (m, 2H), 7.26 (t, 1H).

LC/MS (M+H)⁺ = 355

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Example 23

(3*r*)-Ethyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

10 [00152]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with ethyl chloroformate adding 0.2 equivalents of DMAP, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 15-40%) to give ethyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (29%) as a colorless oil. This intermediate product is then reacted with 1-ethynyl-3-

15 methoxybenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10-40%) to provide the title compound (12%) as a white foam.

¹H NMR (CDCl₃), δ_H, 1.27 (t, 3H), 1.91-1.99 (m, 3H), 2.02-2.08 (m, 2H), 2.17-2.23 (m, 2H), 2.24-2.44 (m, 2H), 3.79 (s, 3H), 4.15 (q, 2H), 4.31 (bs, 2H), 6.80-6.91 (m, 2H),

20 6.91-7.12 (m, 1H), 7.17-7.25 (m, 1H).

LC/MS (M+H)⁺ = 330

Example 24

(3*r*)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide

[00153]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with dimethylcarbamic chloride adding 0.2 equivalents of DMAP, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 15-40%) to give *N,N*-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-

30 carboxamide (41%) as an off-white solid. This intermediate product is then reacted with 1-ethynyl-3-fluorobenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10-40%) to provide the title compound (49%) as a white solid.

^1H NMR ($\text{d}_6\text{-DMSO}$), δ_{H} , 1.59-1.72 (m, 2H), 1.97-2.12 (m, 4H), 2.14-2.25 (m, 2H), 2.79 (s, 6H), 3.97 (bs, 2H), 5.52 (s, 1H), 7.15-7.28 (m, 3H), 7.32-7.46 (m, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 317

5 Example 25

(3*r*)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide

[00154]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one
10 hydrochloride is reacted with dimethylcarbamic chloride adding 0.2 equivalents of DMAP, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 15-40%) to give *N,N*-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxamide (41%) as an off-white solid. This intermediate product is then reacted with 1-chloro-3-ethynylbenzene according to General Procedure 1, and the crude product is
15 washed with DEE to provide the title compound (25%) as a white solid.

^1H NMR ($\text{d}_6\text{-DMSO}$), δ_{H} , 1.58-1.75 (m, 2H), 1.94-2.12 (m, 4H), 2.13-2.22 (m, 2H), 2.79 (s, 6H), 3.97 (bs, 2H), 5.52 (s, 1H), 7.28-7.51 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 333

20 Example 26

(3*r*)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide

[00155]According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one
25 hydrochloride is reacted with dimethylcarbamic chloride adding 0.2 equivalents of DMAP, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 15-40%) to give *N,N*-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxamide (41%) as an off-white solid. This intermediate product is then reacted with 1-ethynyl-3-methoxybenzene according to General Procedure 1, and the crude product
30 is purified by flash column chromatography (silica gel, heptane/EtOAc 10-40%) to provide the title compound (50%) as a white solid.

^1H NMR (CDCl_3), δ_{H} , 1.88 (m, 2H), 1.96 (s, 1H), 2.09 (d, 2H), 2.17 (d, 2H), 2.41 (m, 2H), 2.89 (s, 6H), 3.79 (s, 3H), 4.10 (bs, 2H), 6.86 (d, 1H), 6.91 (s, 1H), 6.99 (d, 1H), 7.26 (t, 1H).

35 LC/MS ($\text{M}+\text{H}$) $^+$ = 329

Example 27**(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)nicotinonitrile**

5 [00156] To a solution of 2-chloronicotinonitrile (857 mg, 6.19 mmol) and TEA (1.294 ml, 9.28 mmol) in dry THF (8 ml) is added 8-azabicyclo[3.2.1]octan-3-one hydrochloride (500 mg, 3.09 mmol). The reaction mixture is stirred at reflux for 3 days, then evaporated to dryness and purified by reverse phase column chromatography to give 2-(3-oxo-8-azabicyclo[3.2.1]octan-8-yl)nicotinonitrile (285 mg, 40%) as a yellow
10 oil. This intermediate product is then reacted with 1-ethynyl-3-methylbenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 0-50%) to provide the title compound (50%) as a colorless oil.

¹H NMR (d₆-DMSO), δ_H, 1.85 (m, 2H), 2.12-2.29 (m, 9H), 4.86 (bs, 2H), 5.65 (s, 1H),
15 6.81 (dd, 1H), 7.12-7.24 (m, 4H), 8.01 (dd, 1H), 8.37 (dd, 1H).

LC/MS (M+H)⁺ = 344

Example 28**(3*r*)-Methyl 3-((3-(difluoromethoxy)phenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate**

[00157] According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-(difluoromethoxy)-3-ethynylbenzene, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10-
25 40%) followed by reverse phase chromatography (C18, water/acetonitrile) to provide the title compound (11%) as a colorless oil.

¹H NMR (d₆-DMSO), δ_H, 1.67-1.89 (m, 2H), 1.97-2.21 (m, 6H), 3.61 (s, 3H), 4.16 (bs, 2H), 5.67 (s, 1H), 7.08-7.47 (m, 5H).

LC/MS (M+H)⁺ = 352

Example 29**(3*r*)-Methyl 3-hydroxy-3-(imidazo[1,2-*a*]pyridin-6-ylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate**

[00158] According to General Procedure 2, methyl 3-hydroxy-3-((trimethylsilyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 6-bromoimidazo[1,2-a]pyridine, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 0% to 60%) followed by reversed phase flash chromatography (acetonitrile/water 0% to 100%) to provide the title compound (19%) as a white solid.

^1H NMR (d_6 -DMSO), δ_{H} , 1.80 (m, 2H), 2.10 (m, 6H), 3.60 (s, 3H), 4.17 (m, 2H), 5.74 (br s, 1H), 7.58 (d, 1H), 7.77 (d, 1H), 7.98 (s, 1H), 8.10 (s, 1H), 8.95 (s, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 326

Example 30

(3*r*)-8-(Methylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol

[00159] According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with methanesulfonyl chloride, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10% to 70%) to give 8-(methylsulfonyl)-8-azabicyclo[3.2.1]octan-3-one (95%) as a white solid. This intermediate product is then reacted with 1-ethynyl-3-methylbenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10% to 60%) to provide the title compound (49%) as an off-white solid.

^1H NMR (d_6 -DMSO), δ_{H} , 1.80-1.96 (m, 2H), 2.04-2.22 (m, 6H), 2.28 (s, 3H), 2.96 (s, 3H), 4.15 (br s, 2H), 5.57 (s, 1H), 7.11-7.28 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 320

Example 31

(3*r*)-8-Isopropyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00160] According to General Procedure 4, 8-azabicyclo[3.2.1]octan-3-one hydrochloride is reacted with isopropyl carbonochloridate, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10% to 70%) to give isopropyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (83%) as a colorless oil. This intermediate product is then reacted with 1-ethynyl-3-methoxybenzene according to General Procedure 1, and the crude product is purified by flash column

chromatography (silica gel, heptane/EtOAc 10% to 70%) followed by reversed phase chromatography (C18, water/acetonitrile) to provide the title compound (26%) as a white solid.

^1H NMR (CDCl_3), δ_{H} , 1.18 (s, 3H), 1.19 (s, 3H), 1.79 (br s, 2H), 1.97-2.18 (m, 6H), 3.75 (s, 3H), 4.12 (br s, 2H), 4.79 (m, 1H), 5.61 (s, 1H), 6.82-6.99 (m, 3H), 7.20-7.30 (m, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 344

Example 32

(3*r*)-Methyl 3-methoxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00161] (3*r*)-Methyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.334 mmol, **Example 4**) is dissolved in THF (1 mL) and cooled to -78 °C. *n*BuLi (1.6M in hexanes) (209 μl , 0.334 mmol) is added, and the reaction mixture is stirred for 30 min at -78 °C. MeI (20.89 μl , 0.334 mmol) is added, and, after 1h, DMSO (119 μl , 1.670 mmol) is added. The reaction mixture is then warmed to room temperature, quenched with water and extracted with EtOAc. The yellow organic layer is dried over Na_2SO_4 , filtered and evaporated to dryness. Column chromatography (silica gel, heptane/EtOAc 0% to 33%) provides the title compound (74 mg, 71%) as a colorless oil.

^1H NMR ($\text{d}_6\text{-DMSO}$), δ_{H} , 1.80 (m, 2H), 1.95 (m, 4H), 2.20 (m, 2H), 2.27 (s, 3H), 3.34 (s, 3H), 3.62 (s, 3H), 4.14 (br s, 2H), 7.22 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 314

Example 33

(3*r*)-Isopropyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate

[00162] Isopropyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (preparation described in **Example 31**) is reacted with 1-ethynyl-3-fluorobenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc 10% to 70%) followed by reversed phase chromatography (C18, water/acetonitrile), preparative TLC (heptane/EtOAc 1:2), and preparative LCMS to provide the title compound (6%) as a white solid.

^1H NMR (CDCl_3), δ_{H} , 1.18 (s, 3H), 1.19 (s, 3H), 1.69-1.88 (m, 2H), 1.90-2.23 (m, 6H), 4.02-4.19 (m, 2H), 4.79 (m, 1H), 5.66 (s, 1H), 7.14-7.28 (m, 3H), 7.35-7.47 (m, 1H).

LC/MS (M+H)⁺ = 332

Example 34

(3*r*)-Isopropyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate

[00163]Isopropyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (preparation described in **Example 31**) is reacted with 1-ethynyl-3-chlorobenzene according to General Procedure 1, and the crude product is purified by reversed phase chromatography (C18, water/acetonitrile) followed by preparative LCMS to provide the title compound (21%) as a white solid.

¹H NMR (CDCl₃), δ_H, 1.17 (s, 3H), 1.19 (s, 3H), 1.69-1.86 (m, 2H), 1.94-2.23 (m, 6H), 4.03-4.18 (m, 2H), 4.79 (m, 1H), 5.66 (s, 1H), 7.30-7.49 (m, 4H).

LC/MS (M+H)⁺ = 348

Example 35

(3*r*)-*N*'-Cyano-3-hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboximidamide

[00164]8-Azabicyclo[3.2.1]octan-3-one hydrochloride (0.5 g, 3.09 mmol) is dissolved in DCM (30 mL). Diphenyl cyanocarbonimidate (0.811 g, 3.40 mmol) and TEA (0.862 mL, 6.19 mmol) are added, and the reaction mixture is stirred at room temperature for 2 h. Then the reaction mixture is washed with water. The water layer is extracted with DCM (10 mL). The organic layers are combined, dried over Na₂SO₄ and evaporated to dryness. The crude product is purified by column chromatography (silica gel, heptane/EtOAc 0% to 50%) to give the intermediate product phenyl *N*-cyano-3-oxo-8-azabicyclo[3.2.1]octane-8-carbimide (754 mg, 91%) as a white solid.

[00165]Phenyl *N*-cyano-3-oxo-8-azabicyclo[3.2.1]octane-8-carbimide (300 mg, 1.114 mmol) is dissolved in 2-propanol (12 mL), and dimethylamine (2M in THF) (6 mL, 12.00 mmol) is added. The mixture is divided into 3 fractions in closed vessels. The reaction mixtures are stirred at 80 °C for 3 h, then cooled to room temperature and evaporated to dryness. The residue is taken up in DCM/H₂O, and the layers are separated with a phase separator. Purification by column chromatography (silica gel,

DCM/MeOH 0% to 5%) affords *N*-cyano-*N,N*-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboximidamide (250 mg, 87%) as a yellowish solid.

[00166] According to General Procedure 1, *N*-cyano-*N,N*-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboximidamide is reacted with 1-ethynyl-3-methylbenzene, and the crude product is purified by column chromatography (silica gel, heptane/EtOAc 0% to 100%) to provide the title compound (14%) as a white solid.

¹H NMR (d₆-DMSO), δ_H, 1.80 (m, 2H), 2.10-2.24 (m, 6H), 2.27 (s, 3H), 2.96 (s, 6H), 4.15 (s, 2H), 5.59 (s, 1H), 7.15-7.26 (m, 4H).

LC/MS (M+H)⁺ = 337

Example 36

(3*r*)-8-(Isopropylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol

[00167] The intermediate product 8-(isopropylsulfonyl)-8-azabicyclo[3.2.1]octan-3-one is prepared in close analogy to the procedure described in **Example 30** using propane-2-sulfonyl chloride.

[00168] The intermediate product is then reacted with 1-ethynyl-3-methylbenzene according to General Procedure 1, and the crude product is purified by flash column chromatography (silicagel, heptane/EtOAc 10% to 60%) to provide the title compound (40%) as a yellow oil.

¹H NMR (d₆-DMSO), δ_H, 1.22 (s, 3H), 1.23 (s, 3H), 1.68-1.85 (m, 2H), 2.06-2.23 (m, 6H), 2.28 (s, 3H), 4.09 (br s, 2H), 5.58 (s, 1H), 7.12-7.29 (m, 4H).

LC/MS (M+H)⁺ = 348

Example 37

(3*r*)-1,1,1-Trifluoro-2-methylpropan-2-yl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00169] 8-Azabicyclo[3.2.1]octan-3-one hydrochloride (107 mg, 0.665 mmol) is added to a stirring solution of 3-methyl-1-((1,1,1-trifluoro-2-methylpropan-2-yloxy)carbonyl)-1*H*-imidazol-3-ium iodide (242 mg, 0.665 mmol) and TEA (185 μl, 1.329 mmol) in DCM at 0 °C. The reaction mixture is allowed to warm up to room temperature and stirred for 2 h. Then the reaction mixture is washed with water and brine, and the

organic layer is evaporated *in vacuo*. The crude product is purified by flash chromatography (silica gel, heptane/EtOAc, 0% to 40%) to give 1,1,1-trifluoro-2-methylpropan-2-yl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (73 mg, 39%) as a white solid.

[00170] According to General Procedure 1, 1,1,1-trifluoro-2-methylpropan-2-yl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-3-methylbenzene, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc, 0% to 40%) followed by flash reversed phase column chromatography (silica gel, water/acetonitrile, 0% to 100%) to provide the title compound (29%) as a colorless oil.

^1H NMR (d_6 -DMSO), δ_{H} , 1.63-1.65 (m, 6H), 1.80-1.82 (m, 2H), 2.00-2.13 (m, 6H), 2.26 (s, 3H), 4.05-4.12 (m, 2H), 5.67 (s, 1H), 7.14-7.26 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 396

Example 38

(3*r*)-Methyl 3-hydroxy-3-(phenylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00171] According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynylbenzene, and the crude product is purified by flash column chromatography (silicagel, heptane/EtOAc 10% to 60%) to provide the title compound (44%) as a light brown solid.

^1H NMR (d_6 -DMSO), δ_{H} , 1.67-1.88 (m, 2H), 1.97-2.21 (m, 6H), 3.61 (s, 3H), 4.15 (br s, 2H), 5.65 (s, 1H), 7.36 (m, 5H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 286

Example 39

(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl(3-methyloxetan-3-yl)methanone

[00172] 3-Methyloxetane-3-carboxylic acid (20 mg, 0.172 mmol) is suspended in DCM (2 mL). DIPEA (0.045 mL, 0.258 mmol) and HATU (98 mg, 0.258 mmol) are added at 0 °C, and the mixture is stirred at this temperature for 1 h. 3-(*m*-Tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (47.8 mg, 0.172 mmol, synthesis according to **Preparation 5**) is added at 0 °C, and the solution is allowed to warm up to room

temperature and stirred for 2 days. The solution is diluted with DCM and washed with saturated NaHCO_3 and brine. The organic layer is dried over Na_2SO_4 , filtered, and the filtrate is evaporated. The crude product is purified by flash chromatography (silicagel, EtOAc in heptane, 0% to 40%) to provide the title compound (30 mg, 50%) as a

^1H NMR (d_6 -DMSO), δ_{H} , 1.52 (s, 3H), 1.65-1.80 (m, 2H), 1.99-2.14 (m, 6H), 2.27 (s, 3H), 3.59 (br s, 1H), 4.26-4.28 (m, 2H), 4.54-4.56 (m, 1H), 4.68-4.84 (m, 2H), 5.65 (br s, 1H), 7.16-7.26 (m, 4H).

LC/MS $(\text{M}+\text{H})^+ = 340, 679, 701$

Example 40

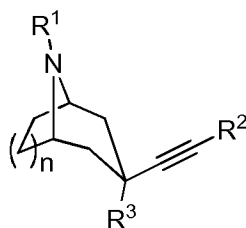
(3*r*)-Methyl 3-hydroxy-3-((3-(trifluoromethoxy)phenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate

[00173] According to General Procedure 1, methyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate is reacted with 1-ethynyl-3-(trifluoromethoxy)benzene, and the crude product is purified by flash column chromatography (silica gel, heptane/EtOAc, 0% to 50%) to provide the title compound (11%) as a colorless oil.

^1H NMR (d_6 -DMSO), δ_{H} , 1.79 (m, 2H), 2.05-2.12 (m, 6H), 3.60 (s, 3H), 4.15 (m, 2H), 5.71 (s, 1H), 7.36-7.52 (m, 4H).

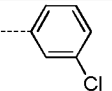
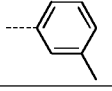
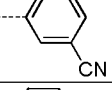
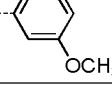
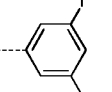
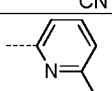
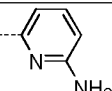
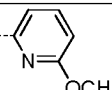
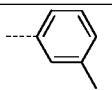
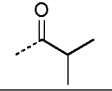
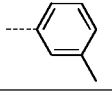
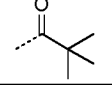
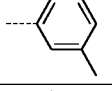
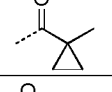
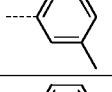
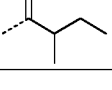
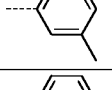
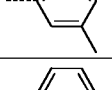
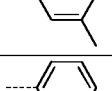
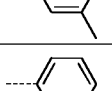
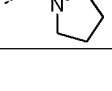
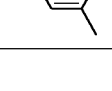
LC/MS $(\text{M}+\text{H})^+ = 370$

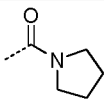
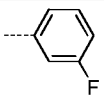
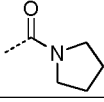
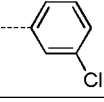
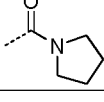
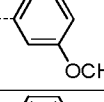
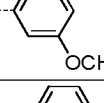
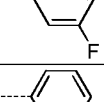
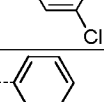
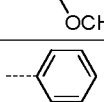
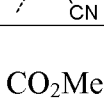
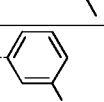
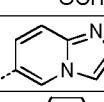
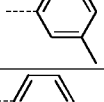
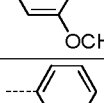
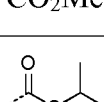
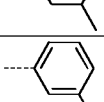
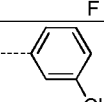
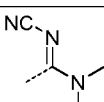
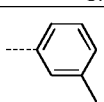
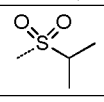
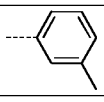
Table 1



I

Example No.	n	R ¹	R ²	R ³
1	1	CO ₂ Me		OH
2	1	CO ₂ Me		OH

3	1	CO ₂ Me		OH
4	1	CO ₂ Me		OH
5	1	CO ₂ Me		OH
6	1	CO ₂ Me		OH
7	1	CO ₂ Me		OH
8	1	CO ₂ Me		OH
9	1	CO ₂ Me		OH
10	1	CO ₂ Me		OH
11	1	C(O)Me		OH
12	1			OH
13	1			OH
14	1			OH
15	1			OH
16	1	CO ₂ Et		OH
17	1	C(O)NMe ₂		OH
18	1	C(O)NEt ₂		OH
19	1			OH

20	1			OH
21	1			OH
22	1			OH
23	1	CO ₂ Et		OH
24	1	C(O)NMe 2		OH
25	1	C(O)NMe 2		OH
26	1	C(O)NMe 2		OH
27	1			OH
28	1	CO ₂ Me		OH
29	1	CO ₂ Me		OH
30	1	SO ₂ Me		OH
31	1			OH
32	1	CO ₂ Me		OMe
33	1			OH
34	1			OH
35	1			OH
36	1			OH

37	1			OH
38	1	CO ₂ Me	Ph	OH
39	1			OH
40	1	CO ₂ Me		OH

CRYSTAL STRUCTURE DETERMINATION

5 [00174] In order to demonstrate that the compounds of Examples 1-28 are obtained in the *endo* configuration (i.e., 3*r* configuration of the pseudo-chiral center = *endo*-OH isomer), the crystal structures may be determined by means of X-ray crystallography.

10 [00175] The experimental data is collected at low temperature (T = 180 K) on X-ray single crystal diffractometer Nonius KappaCCD (Bruker AXS), using Mo K_{α1} – radiation, graphite monochromator. The crystal structure may be resolved by SIR-2004 software and refined to R factor 0.087 in anisotropic full-matrix approximation using of SHELXL-97 program.

15 **Crystal Structure of (3*r*)-3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone**

20 [00176] The crystal structure of (3*r*)-3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone (i.e., the compound of **Example 20**) was determined as described above.

[00177] The crystals are monoclinic, space group P2₁/n, unit cell parameters are: a = 9.8210 (6) Å, b = 15.314 (1) Å, c = 12.3120 (8) Å, β = 111.489 (4)°.

25 **Atomic crystallographic coordinates:**

Atoms	x/a	y/b	z/c
O2	0.058417	0.131116	0.716257

	O1	-0.417822	0.193088	0.271339
	H01	-0.422472	0.253680	0.246715
	N1'	-0.082019	0.017040	0.722712
	N1	-0.173088	0.121088	0.575393
5	C2	-0.059533	0.091112	0.673352
	C22	-0.225672	-0.019560	0.710299
	H22A	-0.253316	-0.066335	0.653219
	H22B	-0.300912	0.025107	0.687048
	C3	-0.412348	0.099044	0.427726
10	H3A	-0.456027	0.094272	0.486522
	H3B	-0.469307	0.063063	0.361922
	C4	-0.256978	0.063437	0.477953
	H4	-0.256325	0.003165	0.504890
	C5	-0.561272	0.234216	0.382046
15	C7	-0.099345	0.160311	0.419013
	H7A	0.006204	0.154003	0.447017
	H7B	-0.130743	0.197083	0.350072
	C9	-0.291916	0.248410	0.470415
	H9A	-0.279930	0.300352	0.429715
20	H9B	-0.315272	0.267182	0.536811
	C10	-0.042332	-0.085452	0.873511
	H10A	-0.000482	-0.091076	0.957804
	H10B	-0.035120	-0.141115	0.838404
	C11	0.032884	-0.013540	0.831410
25	H11A	0.065076	0.033213	0.888298
	H11B	0.116559	-0.036084	0.816318
	C12	-0.201782	-0.054005	0.832483
	H12A	-0.268032	-0.101670	0.829684
	H12B	-0.213897	-0.008169	0.882569
30	C13	-0.148117	0.198986	0.514677
	H13	-0.070438	0.235384	0.568389
	C16	-0.422145	0.194584	0.387244
	C17	-0.175203	0.070505	0.392235
	H17A	-0.243178	0.067650	0.311966
35	H17B	-0.103864	0.023992	0.405576

	C23	-0.673475	0.267570	0.377425
	C2'	-0.835382	0.336255	0.465813
	H2'	-0.765785	0.325833	0.539715
	C1'	-0.808847	0.309087	0.367496
5	C6'	-0.915409	0.324989	0.257449
	H6'	-0.900136	0.307743	0.190378
	F	-1.139515	0.381497	0.145594
	C5'	-0.966352	0.379301	0.454534
	H5'	-0.982992	0.397761	0.520565
10	C3'	-1.042311	0.366118	0.249234
	C4'	-1.070751	0.394064	0.344027
	H4'	-1.158055	0.422361	0.334885

[00178] The crystal structure of (3*r*)-3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone (i.e., the compound of **Example 20**) is shown in **Figure 1**.

EXAMPLES OF REPRESENTATIVE PHARMACEUTICAL COMPOSITIONS

[00179] In combination with commonly used solvents, excipients, auxiliary agents and carriers, the instant compounds may be processed into tablets, coated tablets, capsules, drip solutions, suppositories, injection and infusion preparations, and the like and may be therapeutically applied by the oral, rectal, parenteral, and additional routes. Representative pharmaceutical compositions according to the present invention follow:

(a) Tablets suitable for oral administration which contain the active ingredient, may be prepared by conventional tableting techniques.

(b) For suppositories, any usual suppository base may be employed for incorporation therein by usual procedure of the active ingredient, such as a polyethyleneglycol which is a solid at normal room temperature but which melts at or about body temperature.

(c) For parenteral (including intravenous and subcutaneous) sterile solutions, the active ingredient together with conventional ingredients in usual amounts are employed, such as for example sodium chloride and double-distilled water q.s., according to conventional procedure, such as filtration, aseptic filling into ampoules or IV-drip bottles, and autoclaving for sterility.

[00180]Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

5 FORMULATION EXAMPLES

[00181]The following examples are again given by way of illustration only and are not to be construed as limiting.

EXAMPLE 1

Tablet Formulation

- 10 A suitable formulation for a tablet containing 10 milligrams of active ingredient is as follows:

	mg
Active Ingredient	10
Lactose	61
Microcrystalline Cellulose	25
Talcum	2
Magnesium stearate	1
Colloidal silicon dioxide	1

EXAMPLE 2

Tablet Formulation

- 15 Another suitable formulation for a tablet containing 100 mg is as follows:

	mg
Active Ingredient	100
Polyvinylpyrrolidone, crosslinked	10
Potato starch	20
Polyvinylpyrrolidone	19
Magnesium stearate	1
Microcrystalline Cellulose	50
Film coated and colored.	
The film coating material consists of:	
Hypromellose	10
Microcryst. Cellulose	5
Talcum	5

Polyethylene glycol	2
Color pigments	5

EXAMPLE 3

Capsule Formulation

A suitable formulation for a capsule containing 50 milligrams of active ingredient is as follows:

	mg
Active Ingredient	50
Corn starch	26
Dibasic calcium phosphate	50
Talcum	2
Colloidal silicon dioxide	2

filled in a gelatin capsule.

10 **EXAMPLE 4**

Solution for injection

A suitable formulation for an injectable solution is as follows:

Active Ingredient	mg	10
Sodium chloride	mg	q.s.
Water for Injection	mL	add 1.0

EXAMPLE 5

15

Liquid oral formulation

A suitable formulation for 1 liter of a an oral solution containing 2 milligrams of active ingredient in one milliliter of the mixture is as follows:

	mg
Active Ingredient	2
Saccharose	250
Glucose	300
Sorbitol	150

Orange flavor	10
Colorant	q.s.
Purified water	add 1000 mL

EXAMPLE 6

Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 20 milligrams of
 5 active ingredient in one milliliter of the mixture is as follows:

	G
Active Ingredient	20.00
Tragacanth	7.00
Glycerol	50.00
Saccharose	400.00
Methylparaben	0.50
Propylparaben	0.05
Black currant-flavor	10.00
Soluble Red color	0.02
Purified water	add 1000 mL

EXAMPLE 7

Liquid oral formulation

Another suitable formulation for 1 liter of a liquid mixture containing 2 milligrams of
 10 active ingredient in one milliliter of the mixture is as follows:

	G
Active Ingredient	2
Saccharose	400
Bitter orange peel tincture	20
Sweet orange peel tincture	15
Purified water	add 1000 mL

EXAMPLE 8

Aerosol formulation

180 g aerosol solution contain:

	G
Active Ingredient	10

Oleic acid	5
Ethanol	81
Purified Water	9
Tetrafluoroethane	75

15 ml of the solution are filled into aluminum aerosol cans, capped with a dosing valve, purged with 3.0 bar.

5 **EXAMPLE 9**

TDS formulation

100 g solution contain:

	G
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
Dimethylsulfoxide	5.0
Hydroxyethylcellulose	0.4
Purified water	19.6

1.8 ml of the solution are placed on a fleece covered by an adhesive backing foil. The system is closed by a protective liner which will be removed before use.

EXAMPLE 10

Nanoparticle formulation

10 g of polybutylcyanoacrylate nanoparticles contain:

	G
Active Ingredient	1.00
Poloxamer	0.10
Butylcyanoacrylate	8.75
Mannitol	0.10
Sodium chloride	0.05

Polybutylcyanoacrylate nanoparticles are prepared by emulsion polymerization in a water/0.1 N HCl/ethanol mixture as polymerization medium. The nanoparticles in the suspension are finally lyophilized under vacuum.

EXAMPLE 11

Suspension formulation

1.0 g of the suspension contains the following:

5

	g
Active Ingredient	0.10
Hypromellose	0.01
Purified water	Ad 1.0 g

Hypromellose is dispersed in water homogeneously with a high speed mixer/blender. After about one hour of hydration time of the hypromellose, the active ingredient is blended homogeneously into the hypromellose solution. The viscosity of the suspension may be adjusted by the amount of hypromellose, resulting in a very stable suspension with a very slow tendency of particle sedimentation and particle agglomeration.

10

EXAMPLE 12

Solution for Injection

15 1.0 ml of solution contain:

	g
Active Ingredient	0.05
Mannitol	q.s.
DMSO	0.10
Water for injection	Ad 1.0 ml

The active ingredient is dissolved in DMSO by stirring and heating (solution 1). The mannitol is dissolved in WFI (solution 2). After cooling down to room temperature solution 1 is mixed with solution 2 by continuous stirring. The solution is sterilized by filtration of by autoclaving.

20

PHARMACOLOGY

[00182]The active principles of the present invention, and pharmaceutical compositions containing them and method of treating therewith, are characterized by unique and advantageous properties. The compounds and pharmaceutical compositions thereof

25

exhibit, in standard accepted reliable test procedures, the following valuable properties and characteristics.

METHODS

5 BINDING ASSAYS FOR THE CHARACTERIZATION OF mGluR5 ANTAGONIST PROPERTIES

**[³H]MPEP (2-methyl-6-(phenylethynyl)pyridine) binding to transmembrane
allosteric modulatory sites of mGluR5 receptors in cortical membranes**

10

Preparation of rat cortical membranes:

[00183]Male Sprague-Dawley rats (200-250 g) are decapitated and their brains are removed rapidly. The cortex is dissected and homogenized in 20 volumes of ice-cold 0.32 M sucrose using a glass-Teflon homogenizer. The homogenate is centrifuged at
15 1000 x g for 10 minutes. The pellet is discarded and the supernatant centrifuged at 20,000 x g for 20 minutes. The resulting pellet is re-suspended in 20 volumes of distilled water and centrifuged for 20 minutes at 8000 x g. Then the supernatant and the buffy coat are centrifuged at 48,000 x g for 20 minutes in the presence of 50 mM Tris-HCl, pH 8.0. The pellet is then re-suspended and centrifuged two to three more times at
20 48,000 x g for 20 minutes in the presence of 50 mM Tris-HCl, pH 8.0. All centrifugation steps are carried out at 4°C. After resuspension in 5 volumes of 50 mM Tris-HCl, pH 8.0, the membrane suspension is frozen rapidly at -80°C.

[00184]On the day of assay the membrane suspensions are thawed and washed four
25 times by resuspension in 50 mM Tris-HCl, pH 8.0, and centrifugation at 48,000 x g for 20 minutes and finally re-suspended in 50 mM Tris-HCl, pH 7.4. The amount of protein in the final membrane preparation (500-700 µg/ml) is determined according to the method of Lowry (Lowry O. H. et al. 1951. J. Biol. Chem. 193, 256-275).

30 [³H]MPEP Assay

[00185]Incubations are started by adding [³H]-MPEP (50.2 Ci/mmol, 5 nM, Tocris, GB) to vials with 125-250 µg protein (total volume 0.25 ml) and various concentrations of the agents. Alternatively, assays are performed with [³H]-MMPEP (2-(3-methoxyphenylethynyl)-6-methylpyridine hydrochloride) as radioligand. The
35 incubations are continued at room temperature for 60 minutes (equilibrium is achieved

under the conditions used). Non-specific binding is defined by the addition of unlabeled MPEP (10 μ M). Incubations are terminated using a Millipore filter system. The samples are rinsed twice with 4 ml of ice-cold assay buffer over glass fibre filters (Schleicher & Schuell, Germany) under a constant vacuum. Following separation and rinse, the filters
5 are placed into scintillation liquid (5 ml Ultima Gold, Perkin Elmer, Germany) and radioactivity retained on the filters is determined with a conventional liquid scintillation counter (Canberra Packard, Germany).

Characterization

10 [00186] Specific binding is extremely high i.e. normally > 85% and essentially independent of buffer (Tris or HEPES both 50 mM) and pH (6.8-8.9). There is a clear saturable protein dependence and the chosen protein concentration used for subsequent assays (500-700 μ g/ml) is within the linear portion of this dependence. Cold MPEP displaces hot ligand with an IC_{50} of 11.2 ± 0.64 nM. The K_d of [3H]-MPEP of 13.6 nM is
15 determined by Scatchard analysis and used according to the Cheng Prussoff relationship to calculate the affinity of displacers as K_d values (IC_{50} of cold MPEP equates to a K_i of 8.2 nM). B_{max} is 0.56 pm / mg protein.

FUNCTIONAL ASSAY OF mGluR5 RECEPTORS

Cytosolic Calcium studies with stably transfected cells

20 [00187] Chinese hamster ovary cells (CHO-K1 cells), stably transfected for inducible expression of a human metabotropic glutamate receptor mGluR5, are seeded into black clear bottom 96 well plates at a density of 35.000 cells per well. The standard growth
25 medium used (Dulbecco's modified Eagle Medium, DMEM plus L-proline) contains the appropriate inducer isopropyl- β -D-thiogalactopyranosid (IPTG) to achieve optimal receptor expression. One day after seeding the growth medium is exchanged for reconstituted Ca-Kit (Molecular Devices, USA) and incubated for one hour. Ca-Kit is reconstituted in an assay buffer containing 20 mM HEPES pH 7.4, glutamic-pyruvate
30 transaminase, pyridoxal phosphate and sodium pyruvate in Hank's balanced salt solution (HBBS). Agonistic compounds to the receptor elicit increases in cytosolic calcium which can be measured as increases in fluorescence signals by use of a fluorescence imaging plate reader (Molecular Devices). To analyze their potency to modulate the Ca-response test compounds, dissolved in a final DMSO concentration of

0.5%, are added on-line 5 minutes before the agonist to the receptor (L-quisqualic acid at a concentration giving ~80% of the maximal signal).

Astrocyte culture

- 5 [00188]Primary astrocyte cultures are prepared from cortices of newborn rats as described by Booher and Sensenbrenner (1972, Neurobiology 2(3):97-105). Briefly, Sprague-Dawley rat pups (2 - 4 d old) are decapitated and neocortices are dissected, disintegrated with a nylon filter (pore size 80 μ m) and carefully triturated. The cell suspension is plated on poly-D-lysine pre-coated flasks (Costar, Netherlands) and
- 10 cultivated in Dulbecco's Modified Eagle's Medium (DMEM, Invitrogen, Germany) supplemented with 10% foetal calf serum (FCS, Sigma, Germany), 4 mM glutamine and 50 μ g/ml gentamycin (both Biochrom, Germany) at 37°C in a humidified atmosphere of 5% CO₂/ 95% air for 7 days with exchanging the medium at day 2 and 6.
- 15 [00189]After 7 days in vitro (DIV), cells are shaken overnight at 250 rpm to remove oligodendrocytes and microglia. The next day, astrocytes are rinsed twice with CMF-PBS (calcium- and magnesium-free phosphate buffered saline, Biochrom, Germany), trypsinized and subplated on poly-D-lysine pre-coated 96-well plates (Greiner, Germany) at a density of 40,000 cells/well. 24 h after establishing the secondary culture
- 20 the astrocytes are rinsed with PBS⁺⁺ (phosphate buffered saline, Biochrom, Germany) and fed with astrocyte-defined medium (ADM) consisting of DMEM containing 1x G5-supplement (Invitrogen, Germany), 0.5 μ g/ml heparan sulfate, and 1.5 μ g/ml fibronectin (both Sigma, Germany) (Miller et al., (1993) Brain Res. 618(1):175-8). 3 days later the medium is exchanged and the cells incubated for another 2-3 days, so that
- 25 at the time of experiments astrocytes are 14-15 DIV.

Immunocytochemistry

- [00190]Immunostaining is performed to confirm the presence of astrocytic markers such as the glial fibrillary acidic protein (GFAP) as well as to monitor the expression of
- 30 mGluR5 receptors.

Cytosolic Calcium studies with astrocytes

- [00191]The increase of cytosolic calcium after stimulation with the mGluR5 agonist L-quisqualate is measured using a fluorometric imaging plate reader (FLIPR) and the Ca-
- 35 Kit (both Molecular Devices). Prior to addition of agonist or antagonist the medium is

aspirated and cells are loaded for 2 h at RT with 150 μ l of loading buffer consisting of Ca-sensitive dye reconstituted in sodium chloride (123 mM), potassium chloride (5.4 mM), magnesium chloride (0.8 mM), calcium chloride (1.8 mM), D-glucose (15 mM), and HEPES (20 mM), pH 7.3. Subsequently, plates are transferred to FLIPR to detect calcium increase with the addition of L-quisqualate (100 nM) measured as relative fluorescence units (RFU). If antagonists are tested, these compounds are pre-incubated for 10 minutes at RT before addition of the respective agonist.

[00192]For positive modulators, concentration-response curves for quisqualate are performed in the presence and absence of 10 μ M modulator to determine the extent of potentiation / agonist potency increase. Thereafter, concentration-response curves for the positive modulator are performed in the presence of a fixed concentration of quisqualate showing the biggest window for potentiation (normally 10-30 nM).

Data analysis

[00193]The fluorescence signal increase after addition of agonist reflects the increase of cytosolic calcium. Inconsistencies in the amount of cells per well are normalised by using the spatial uniformity correction of the FLIPR operating software Screenworks. The mean of replicated temporal data (n=3-5) is calculated and used for graphical representation. For the evaluation of the pharmacology, the calcium changes in response to different concentrations of agonist or antagonist are determined using a maximum minus minimum (MaxMin) calculation.

[00194]All responses (RFU-values) are determined as percentage of control (= maximum response). EC_{50} and IC_{50} are calculated according the logistic equation using GraFit 5.0 (Erithacus Software, GB) or Prism 4.0 (GraphPad Software, USA). The compounds of the present invention have a potency (IC_{50}) within a range of about 0.5 nM to about 100 μ M.

[00195]Results for representative compounds of the invention are shown in Table A1.

Table A1

Compound	Chemical Name	Human mGluR5 IC ₅₀ [μM]	Rat (rpA) mGluR5 IC ₅₀ [μM]
Example 1	(3 <i>r</i>)-Methyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0613	0.0678
Example 2	(3 <i>r</i>)-Methyl 3-((4-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	2.19	n.d.
Example 3	(3 <i>r</i>)-Methyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0274	0.0252
Example 4	(3 <i>r</i>)-Methyl 3-hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0507	0.0479
Example 5	(3 <i>r</i>)-Methyl 3-((3-cyanophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	0.187	n.d.
Example 6	(3 <i>r</i>)-Methyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0763	0.0740
Example 7	(3 <i>r</i>)-Methyl 3-((3-cyano-5-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]-octane-8-carboxylate	3.58	n.d.
Example 8	(3 <i>r</i>)-Methyl 3-hydroxy-3-((6-methylpyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.818	n.d.
Example 9	(3 <i>r</i>)-Methyl 3-((6-aminopyridin-2-yl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	5.19	n.d.
Example 10	(3 <i>r</i>)-Methyl 3-hydroxy-3-((6-methoxypyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	3.40	n.d.

Example 11	(3 <i>r</i>)-1-(3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone	0.543	n.d.
Example 12	(3 <i>r</i>)-1-(3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropan-1-one	0.266	n.d.
Example 13	(3 <i>r</i>)-1-(3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2,2-dimethylpropan-1-one	0.308	n.d.
Example 14	(3 <i>r</i>)-(3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(1-methylcyclopropyl)methanone	0.313	n.d.
Example 15	(3 <i>r</i>)-1-(3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylbutan-1-one	0.314	n.d.
Example 16	(3 <i>r</i>)-Ethyl 3-hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0478	0.0291
Example 17	(3 <i>r</i>)-3-Hydroxy- <i>N,N</i> -dimethyl-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide	0.132	0.113
Example 18	(3 <i>r</i>)- <i>N,N</i> -Diethyl-3-hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide	0.152	n.d.
Example 19	(3 <i>r</i>)-3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone	0.181	n.d.
Example 20	(3 <i>r</i>)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone	0.128	0.0925
Example 21	(3 <i>r</i>)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone	0.138	0.0663
Example 22	(3 <i>r</i>)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone	0.204	n.d.

Example 23	(3 <i>r</i>)-Ethyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0505	n.d.
Example 24	(3 <i>r</i>)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy- <i>N,N</i> -dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide	0.137	0.132
Example 25	(3 <i>r</i>)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy- <i>N,N</i> -dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide	0.0949	0.0545
Example 26	(3 <i>r</i>)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)- <i>N,N</i> -dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide	0.174	n.d.
Example 27	(3 <i>r</i>)-3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)nicotinonitrile	0.170	n.d.
Example 28	(3 <i>r</i>)-Methyl 3-((3-(difluoromethoxy)phenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0722	0.0907
Example 29	(3 <i>r</i>)-Methyl 3-hydroxy-3-(imidazo[1,2- <i>a</i>]pyridin-6-ylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	8.1 (est.)	n.d.
Example 30	(3 <i>r</i>)-8-(Methylsulfonyl)-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol	0.575	n.d.
Example 31	(3 <i>r</i>)-8-Isopropyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0904	0.0768
Example 32	(3 <i>r</i>)-Methyl 3-methoxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.137	n.d.
Example 33	(3 <i>r</i>)-Isopropyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0508	n.d.

Example 34	(3 <i>r</i>)-Isopropyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate	0.0840	n.d.
Example 35	(3 <i>r</i>)- <i>N</i> ¹ -Cyano-3-hydroxy- <i>N,N</i> -dimethyl-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboximidamide	0.168	n.d.
Example 36	(3 <i>r</i>)-8-(Isopropylsulfonyl)-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol	0.344	n.d.
Example 37	(3 <i>r</i>)-1,1,1-Trifluoro-2-methylpropan-2-yl 3-hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	1.62	n.d.
Example 38	(3 <i>r</i>)-Methyl 3-hydroxy-3-(phenylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.298	n.d.
Example 39	(3 <i>r</i>)-3-Hydroxy-3-(<i>m</i> -tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl(3-methyloxetan-3-yl)methanone	2.02	n.d.
Example 40	(3 <i>r</i>)-Methyl 3-hydroxy-3-((3-(trifluoromethoxy)phenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate	0.457	n.d.

[00196]In conclusion, from the foregoing, it is apparent that the present invention provides novel and valuable applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith.

[00197]The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior

approval by governmental agencies which are responsible for and authorized to pass judgment on such questions.

[00198]The instant compounds of Formula I represent a novel class of mGluR5 modulators. In view of their potency, they will be useful therapeutics in a wide range of disorders, in particular CNS disorders, which involve excessive glutamate induced excitation.

[00199]These compounds accordingly find application in the treatment of the disorders of a living animal body, especially a human, as listed earlier in the description.

[00200]These compounds also find application in the treatment of indications in a living animal body, especially a human, wherein a particular condition does not necessarily exist but wherein a particular physiological parameter may be improved through administration of the instant compounds, including cognitive enhancement.

[00201]Neuroprotection as well as cognitive enhancement may also be achieved by administration of the instant compounds in combination with a NMDA receptor antagonist like Memantine.

[00202]The method-of-treating a living animal body with a compound of the invention, for the inhibition of progression or alleviation of the selected ailment therein, is as previously stated by any normally-accepted pharmaceutical route, employing the selected dosage which is effective in the alleviation of the particular ailment desired to be alleviated. Use of the compounds of the present invention in the manufacture of a medicament for the treatment of a living animal for inhibition of progression or alleviation of selected ailments or conditions, particularly ailments or conditions susceptible to treatment with a Group I mGluR modulator is carried out in the usual manner comprising the step of admixing an effective amount of a compound of the invention with a pharmaceutically-acceptable diluent, excipient, or carrier, and the method-of-treating, pharmaceutical compositions, and use of a compound of the present invention in the manufacture of a medicament.

[00203]Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier,

include tablets, capsules, solutions for injection, liquid oral formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

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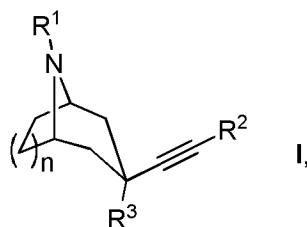
[00204]The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description.

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[00205]All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

PATENT CLAIMS

1. A compound selected from those of Formula I

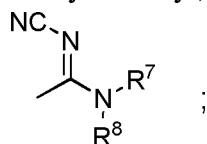


wherein

n represents 1 or 2;

R¹ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino,

C₃₋₆cycloalkyl, heterocyclyl, aryl, heteroaryl, C₁₋₆alkylsulfonyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino, C₃₋₆cycloalkylsulfonyl, -C(O)R⁴, or



R² represents aryl, heteroaryl, cycloC₃₋₁₂alkyl, or heterocyclyl;

R³ represents H, F, OH, C₁₋₆alkoxy;

R⁴ represents C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino,

C₃₋₆cycloalkyl, heterocyclyl, C₁₋₆alkoxy which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, and di-(C₁₋₆alkyl)amino,
5 or -NR⁵R⁶;

R⁵ and R⁶ which may be the same or different represent H or C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino,
10 and di-(C₁₋₆alkyl)amino, or

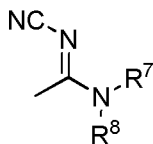
R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two additional heteroatoms selected from sulfur,
15 oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, and oxo;

R⁷ and R⁸ which may be the same or different represent H or C₁₋₆alkyl which may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino,
20 and di-(C₁₋₆alkyl)amino, or

R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 3-7 membered ring which may be saturated or unsaturated, wherein the ring may optionally contain one or two additional heteroatoms selected from sulfur,
25 oxygen, and nitrogen and wherein the ring may be optionally substituted by one or more substituents selected from halogen, trifluoromethyl, trifluoromethoxy, C₁₋₆alkoxy, amino, hydroxy, C₁₋₆alkylamino, di-(C₁₋₆alkyl)amino, and oxo;

30 and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

2. The compound as claimed in Claim 1, wherein R¹ represents heteroaryl, C₁₋₆alkylsulfonyl, -C(O)R⁴, or
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3. The compound as claimed in Claim 2, wherein R^1 represents $-C(O)R^4$ and R^4 represents C_{1-6} alkyl, C_{1-6} alkoxy, optionally substituted by one or more halogen atoms, C_{3-6} cycloalkyl optionally substituted by C_{1-6} alkyl, heterocyclyl, or $-NR^5R^6$.
4. The compound as claimed in Claim 3, wherein R^5 and R^6 each represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent pyrrolidino.
5. The compound as claimed in any preceding claim, wherein R^2 represents aryl or heteroaryl.
6. The compound as claimed in Claim 5, wherein R^2 represents phenyl which is optionally substituted by one or more substituents selected from halogen, C_{1-6} alkyl, cyano, C_{1-6} alkoxy, and trifluoromethoxy; pyridyl which is optionally substituted by one or more substituents selected from C_{1-6} alkyl, amino, and C_{1-6} alkoxy; or imidazopyridinyl.
7. The compound as claimed in any preceding claim, wherein R^3 represents OH or C_{1-6} alkoxy.
8. The compound as claimed in any preceding claim, wherein n represents 1.
9. The compound as claimed in Claim 1, which is selected from:
 - (3*r*)-Methyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
 - (3*r*)-Methyl 3-((4-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
 - (3*r*)-Methyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,
 - (3*r*)-Methyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-((3-cyanophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

5 (3*r*)-Methyl 3-((3-cyano-5-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-hydroxy-3-((6-methylpyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

10 (3*r*)-Methyl 3-((6-aminopyridin-2-yl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Methyl 3-hydroxy-3-((6-methoxypyridin-2-yl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)ethanone,

15 1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpropan-1-one,

1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2,2-dimethylpropan-1-one,

((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)(1-methylcyclopropyl)methanone,

20 1-((3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)-2-methylbutan-1-one,

(3*r*)-Ethyl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

25 (3*r*)-3-Hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide,

(3*r*)-*N,N*-Diethyl-3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxamide,

(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone,

30 (3*r*)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone,

(3*r*)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone,

35 (3*r*)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octan-8-yl(pyrrolidin-1-yl)methanone,

(3*r*)-Ethyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-3-((3-Fluorophenyl)ethynyl)-3-hydroxy-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide,

5 (3*r*)-3-((3-Chlorophenyl)ethynyl)-3-hydroxy-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide,

(3*r*)-3-Hydroxy-3-((3-methoxyphenyl)ethynyl)-*N,N*-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxamide,

10 (3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)nicotinonitrile, Azetidin-1-yl((3*r*)-3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl)methanone,

(3*r*)-Methyl 3-hydroxy-3-(imidazo[1,2-*a*]pyridin-6-ylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-8-(Methylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol,

15 (3*r*)-Isopropyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Isopropyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

20 (3*r*)-Isopropyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-*N*¹-Cyano-3-hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboximidamide,

(3*r*)-Methyl 3-methoxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

25 (3*r*)-Methyl 3-hydroxy-3-(imidazo[1,2-*a*]pyridin-6-ylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-8-(Methylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol,

(3*r*)-8-Isopropyl 3-hydroxy-3-((3-methoxyphenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

30 (3*r*)-Methyl 3-methoxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-Isopropyl 3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

35 (3*r*)-Isopropyl 3-((3-chlorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate,

(3*r*)-*N*-Cyano-3-hydroxy-*N,N*-dimethyl-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboximidamide,
(3*r*)-8-(Isopropylsulfonyl)-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-3-ol,
(3*r*)-1,1,1-Trifluoro-2-methylpropan-2-yl 3-hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-Methyl 3-hydroxy-3-(phenylethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,
(3*r*)-3-Hydroxy-3-(*m*-tolylethynyl)-8-azabicyclo[3.2.1]octan-8-yl(3-methyloxetan-3-yl)methanone,
(3*r*)-Methyl 3-hydroxy-3-((3-(trifluoromethoxy)phenyl)ethynyl)-8-azabicyclo[3.2.1]octane-8-carboxylate,

and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

10. A pharmaceutical composition comprising a compound as claimed in any preceding claim, together with one or more pharmaceutically acceptable excipients.

11. A compound as claimed in any of Claims 1 to 9 for use in therapy.

12. A compound as claimed in any of Claims 1 to 9 for use in the treatment and/or prevention of abnormal glutamate neurotransmission.

13. A compound as claimed in any of Claims 1 to 9, for use in the prevention and/or treatment of a condition or disease selected from Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis (ALS), multiple system atrophy, olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, cognitive deficits in various forms of mild cognitive

impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest or stroke or bypass operations or transplants, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, inner ear insult in tinnitus, tinnitus, sound- or drug-induced inner ear insult, sound- or drug-induced tinnitus, L-DOPA-induced dyskinesias, L-DOPA-induced dyskinesias in Parkinson's disease therapy, dyskinesias, dyskinesia in Huntington's disease, drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, HIV-1 encephalopathy, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, major depressive disorder, major depression, depression, depression resulting from Borna virus infection, major depression resulting from Borna virus infection, bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, fragile-X syndrome, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer pain, posttraumatic stress disorder (PTSD), schizophrenia, positive or cognitive or negative symptoms of schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition

disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), gastrointestinal dysfunction, lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity, obesity-related disorders, obesity abuse, food addiction, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, or delirium; inhibition of tumour cell growth, migration, invasion, adhesion and toxicity in the peripheral tissues, peripheral nervous system and CNS; neoplasia, hyperplasia, dysplasia, cancer, carcinoma, sarcoma, oral cancer, squamous cell carcinoma (SCC), oral squamous cell carcinoma (SCC), lung cancer, lung adenocarcinoma, breast cancer, prostate cancer, gastric cancer, liver cancer, colon cancer, colorectal carcinoma, rhabdomyosarcoma, brain tumour, tumour of a nerve tissue, glioma, malignant glioma, astroglioma, neuroglioma, neuroblastoma, glioblastoma, medulloblastoma, cancer of skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, tumours, diabetes, hyperammonemia and liver failure and sleep disturbances.

14. Use of a compound as claimed in any of Claims 1 to 9 for the manufacture of a medicament for treating or preventing a condition or disease selected from Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis (ALS), multiple system atrophy, olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, cognitive deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive

impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest or stroke or bypass operations or transplants, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, inner ear insult in tinnitus, tinnitus, sound- or drug-induced inner ear insult, sound- or drug-induced tinnitus, L-DOPA-induced dyskinesias, L-DOPA-induced dyskinesias in Parkinson's disease therapy, dyskinesias, dyskinesia in Huntington's disease, drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, HIV-1 encephalopathy, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, major depressive disorder, major depression, depression, depression resulting from Borna virus infection, major depression resulting from Borna virus infection, bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, fragile-X syndrome, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer pain, posttraumatic stress disorder (PTSD), schizophrenia, positive or cognitive or negative symptoms of schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), gastrointestinal dysfunction, lower esophageal sphincter

(LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity, obesity-related disorders, obesity abuse, food addiction, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, or delirium; inhibition of tumour cell growth, migration, invasion, adhesion and toxicity in the peripheral tissues, peripheral nervous system and CNS; neoplasia, hyperplasia, dysplasia, cancer, carcinoma, sarcoma, oral cancer, squamous cell carcinoma (SCC), oral squamous cell carcinoma (SCC), lung cancer, lung adenocarcinoma, breast cancer, prostate cancer, gastric cancer, liver cancer, colon cancer, colorectal carcinoma, rhabdomyosarcoma, brain tumour, tumour of a nerve tissue, glioma, malignant glioma, astroglioma, neuroglioma, neuroblastoma, glioblastoma, medulloblastoma, cancer of skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, tumours, diabetes, hyperammonemia and liver failure and sleep disturbances.

15. A method for treating or preventing a condition or disease associated with abnormal glutamate neurotransmission, or a method for modulating mGluR5 receptors to achieve therapeutic benefit, such method comprising the step of administering to a living animal, including a human, a therapeutically effective amount of a compound of as claimed in any of Claims 1 to 9.

16. The method as claimed in Claim 15, wherein the condition associated with abnormal glutamate transmission, or wherein modulation of mGluR5 receptors results in therapeutic benefit is selected from: Alzheimer's disease, Creutzfeld-Jakob's syndrome/disease, bovine spongiform encephalopathy (BSE), prion related infections, diseases involving mitochondrial dysfunction, diseases involving β -amyloid and/or tauopathy, Down's syndrome, hepatic encephalopathy, Huntington's disease, motor neuron diseases, amyotrophic lateral sclerosis (ALS), multiple system atrophy, olivoponto-cerebellar atrophy, post-operative cognitive deficit (POCD), systemic lupus erythematosus, systemic

sclerosis, Sjogren's syndrome, Neuronal Ceroid Lipofuscinosis, neurodegenerative cerebellar ataxias, Parkinson's disease, Parkinson's dementia, mild cognitive impairment, cognitive deficits in various forms of mild cognitive impairment, cognitive deficits in various forms of dementia, dementia pugilistica, vascular and frontal lobe dementia, cognitive impairment, learning impairment, eye injuries, eye diseases, eye disorders, glaucoma, retinopathy, macular degeneration, head or brain or spinal cord injuries, head or brain or spinal cord trauma, trauma, hypoglycaemia, hypoxia, perinatal hypoxia, ischaemia, ischaemia resulting from cardiac arrest or stroke or bypass operations or transplants, convulsions, epileptic convulsions, epilepsy, temporal lobe epilepsy, myoclonic epilepsy, inner ear insult, inner ear insult in tinnitus, tinnitus, sound- or drug-induced inner ear insult, sound- or drug-induced tinnitus, L-DOPA-induced dyskinesias, L-DOPA-induced dyskinesias in Parkinson's disease therapy, dyskinesias, dyskinesia in Huntington's disease, drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias, chorea, Huntington's chorea, athetosis, dystonia, stereotypy, ballism, tardive dyskinesias, tic disorder, torticollis spasmodicus, blepharospasm, focal and generalized dystonia, nystagmus, hereditary cerebellar ataxias, corticobasal degeneration, tremor, essential tremor, abuse, addiction, nicotine addiction, nicotine abuse, alcohol addiction, alcohol abuse, opiate addiction, opiate abuse, cocaine addiction, cocaine abuse, amphetamine addiction, amphetamine abuse, anxiety disorders, panic disorders, anxiety and panic disorders, social anxiety disorder (SAD), attention deficit hyperactivity disorder (ADHD), attention deficit syndrome (ADS), restless leg syndrome (RLS), hyperactivity in children, autism, dementia, dementia in Alzheimer's disease, dementia in Korsakoff syndrome, Korsakoff syndrome, vascular dementia, dementia related to HIV infections, HIV-1 encephalopathy, AIDS encephalopathy, AIDS dementia complex, AIDS-related dementia, major depressive disorder, major depression, depression, depression resulting from Borna virus infection, major depression resulting from Borna virus infection, bipolar manic-depressive disorder, drug tolerance, drug tolerance to opioids, movement disorders, fragile-X syndrome, irritable bowel syndrome (IBS), migraine, multiple sclerosis (MS), muscle spasms, pain, chronic pain, acute pain, inflammatory pain, neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer

pain, posttraumatic stress disorder (PTSD), schizophrenia, positive or cognitive or negative symptoms of schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders, micturition disorders, neuromuscular disorder in the lower urinary tract, gastroesophageal reflux disease (GERD), gastrointestinal dysfunction, lower esophageal sphincter (LES) disease, functional gastrointestinal disorders, dyspepsia, regurgitation, respiratory tract infection, bulimia nervosa, chronic laryngitis, asthma, reflux-related asthma, lung disease, eating disorders, obesity, obesity-related disorders, obesity abuse, food addiction, binge eating disorders, agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia, phobic disorders, substance-induced anxiety disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder, substance-induced psychotic disorder, or delirium; inhibition of tumour cell growth, migration, invasion, adhesion and toxicity in the peripheral tissues, peripheral nervous system and CNS; neoplasia, hyperplasia, dysplasia, cancer, carcinoma, sarcoma, oral cancer, squamous cell carcinoma (SCC), oral squamous cell carcinoma (SCC), lung cancer, lung adenocarcinoma, breast cancer, prostate cancer, gastric cancer, liver cancer, colon cancer, colorectal carcinoma, rhabdomyosarcoma, brain tumour, tumour of a nerve tissue, glioma, malignant glioma, astroglioma, neuroglioma, neuroblastoma, glioblastoma, medulloblastoma, cancer of skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, tumours, diabetes, hyperammonemia and liver failure and sleep disturbances.

17. A pharmaceutical composition comprising a combination of at least one compound as claimed in any of Claims 1 to 9 and at least one NMDA receptor antagonist, together with one or more pharmaceutically acceptable excipients.

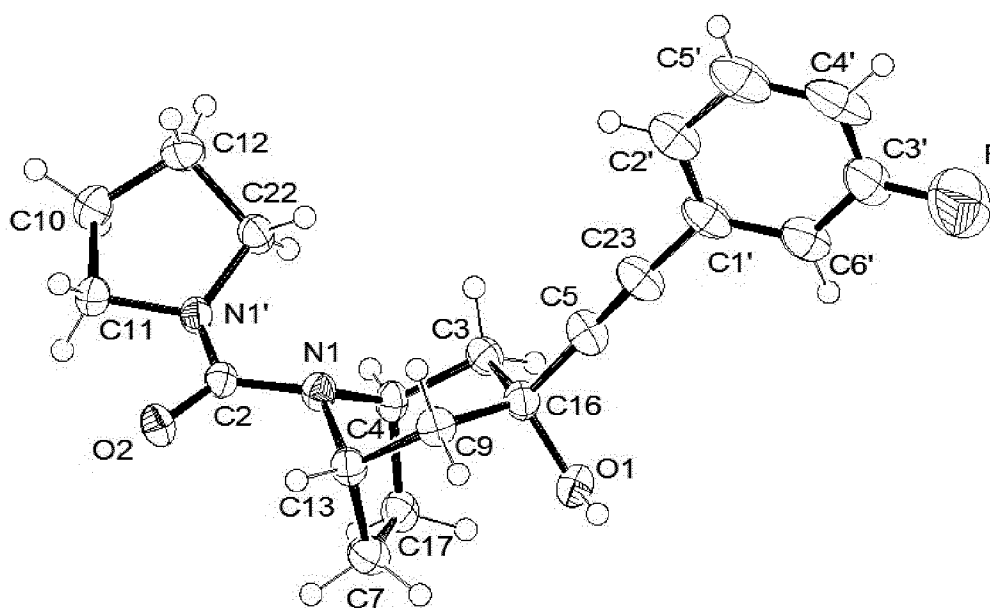


Figure 1 – Crystal Structure of (3*r*)-3-((3-fluorophenyl)ethynyl)-3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)(pyrrolidin-1-yl)methanone

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/058602

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D451/02 C07D451/06 A61K31/46 A61P25/00 ADD.		
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) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/015343 A1 (MERZ PHARMA GMBH & CO KGAA [DE]; HENRICH MARKUS [DE]; WEIL TANJA [SG];) 10 February 2011 (2011-02-10) the whole document -----	1-15
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
8 June 2012	26/06/2012	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Hacking, Michiel	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011015343 A1	10-02-2011	AR 077796 A1	21-09-2011
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