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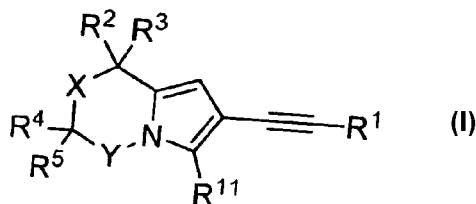
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(54) Title: DIHYDROINDOLIZINE DERIVATE AS METABOTROPIC GLUTAMATE RECEPTOR MODULATORS



(57) Abstract: The invention relates to heterocyclic derivatives of formula I, wherein the substituents R¹-R⁵ and R¹¹ are as defined in the claims, 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.



DIHYDROINDOLIZINE DERIVATE AS 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.

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[0004] In contrast to class A GPCRs (rhodopsin like receptors) where orthosteric ligands bind to a site within the transmembrane helix bundle, for class C GPCRs (the class to which mGluR5 belongs) the orthosteric ligand (e.g. glutamate) binds to a distinct module at the N-terminus of the receptor, the venus fly trap module (Bockaert, et al., *The EMBO Journal*, **1999**, 18, 1723-1729). Moreover, within the helix bundle of mGluR5 a binding site for allosteric ligands, exemplified by MPEP, exists.

[0005] In analogy to ligands to the orthosteric site of class A receptors, where full agonists, partial agonists, neutral antagonists, and inverse agonists can be described (Seifert, et al., *Naunyn Schmiedebergs Arch Pharmacol.*, **2002**, 366, 381-416), a spectrum of ligands to the allosteric site (i.e., negative allosteric modulators, positive allosteric modulators, and silent allosteric modulators) may be observed. The first example of a silent allosteric modulator for mGluR5 (5-MPEP) was reported by Rodriguez, et al. (*Molecular Pharmacology*, **2005**, 68, 1793-1802).

[0006] 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.

[0007] 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.

[0008] 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

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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, synucleinopathies, alpha-synucleinopathies, Lewy body dementia, neurodegeneration with Brain Iron Accumulation, Parkinson-plus syndrome, Pick's disease, progressive supranuclear palsy (PSP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), neurodegenerative diseases, 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 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 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

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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 negative symptoms of schizophrenia, cognitive deficits 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, diabetes, hyperammonemia and liver failure and sleep disturbances.

[0009] 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

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skin cells, melanoma, malignant melanoma, epithelial neoplasm, lymphoma, myeloma, Hodgkin's disease, Burkitt's lymphoma, leukemia, thymoma, and other tumours.

[0010] 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.

[0011] 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.

[0012] Positive modulators may be particularly useful in the treatment of positive and negative symptoms and cognitive deficits in schizophrenia as well as cognitive deficits in various forms of dementia and mild cognitive impairment.

[0013] Silent modulators may be useful for attenuation of disease states emerging from dysregulation of a natural ligand for the allosteric site.

[0014] Moreover, mGluR modulators may have activity when administered in combination with other substances exhibiting neurological effects via different mechanisms.

[0015] Simultaneous administration of Group I mGluR modulators and NMDA receptor antagonists has also been shown to provide neuroprotection in animal models (Ziemska et al. *Acta Neurobiol. Exp.*, **2006**, 66, 301-309; Ziemska et al. *Neurochemistry International*, **2003**, 43, 481-492; and Ziemska et al. *Neurochemistry International*, **2006**, 48, 491-497).

[0016] Simultaneous administration of Group I mGluR modulators and compounds such as L-DOPA, dopaminomimetics, and/or neuroleptics may be useful in treating

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various conditions including drug induced dyskinesias, neuroleptic-induced dyskinesias, haloperidol-induced dyskinesias, dopaminomimetic-induced dyskinesias.

[0017] In the literature, several types of modulators of mGluR5 have already been described.

THE PRESENT INVENTION

[0018] 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

[0019] 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.

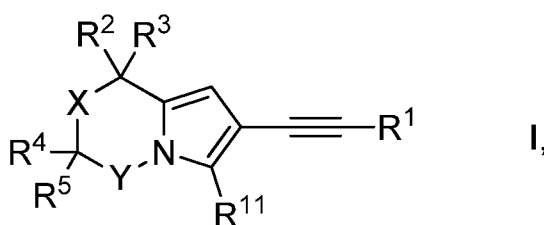
[0020] An additional object of the invention is the provision of processes for producing the heterocyclic derivatives.

SUMMARY OF THE INVENTION

[0021] 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

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wherein

R^1 represents aryl, heteroaryl, cycloC₃₋₇alkyl or heterocyclyl, wherein the cycloC₃₋₇alkyl and heterocyclyl groups may be optionally fused with an aryl or heteroaryl ring;

R^2 and R^3 , which may be the same or different, each independently represent H, C₁₋₆alkyl, F, OH, C₁₋₆alkoxy, or R^2 and R^3 together with the carbon atom to which they are attached form a carbonyl group, or R^2 and R^3 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R^4 and R^5 , which may be the same or different each independently represent H, C₁₋₆alkyl or F or R^4 and R^5 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

X represents CR⁶R⁷ or NR⁸;

R^6 and R^7 , which may be the same or different, each independently represent H, C₁₋₆alkyl, F, amino, C₁₋₆alkylamino or di-(C₁₋₆alkyl)amino or R^6 and R^7 , together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

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or R³ and R⁶, together with the carbon atoms to which they are attached, may form a 4 to 7 membered ring wherein the ring may optionally contain one or two heteroatoms selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R⁸ represents H, C₁₋₆alkyl, acyl, aryl, heteroaryl, aryl-C₁₋₆alkyl, heteroaryl-C₁₋₆alkyl, or di-(C₁₋₆ alkyl)aminosulfonyl;

or R² and R⁸ together with the atoms to which they are attached, may form a 4 to 7 membered ring wherein the ring may optionally contain one or two additional heteroatoms selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl which is optionally substituted by one or more halogen atoms, F, oxo, and acyl;

Y represents a bond, CR⁹R¹⁰ or -CR⁹R¹⁰-CH₂-;

R⁹ and R¹⁰, which may be the same or different, each independently represent H, C₁₋₆alkyl or F or R⁹ and R¹⁰, together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆alkyl, F, oxo, and acyl;

R¹¹ represents H, halogen, C₁₋₆alkyl, aryl, heteroaryl, cycloC₃₋₇alkyl or heterocyclyl; and optical isomers, prodrugs, pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0022] A further aspect of the invention relates to a compound of Formula I, wherein R¹ represents aryl or heteroaryl.

[0023] Such a compound of Formula I, wherein R² represents H or OH, and R³ represents H.

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[0024] Such a compound of Formula I, wherein R^2 and R^3 together with the carbon atom to which they are attached form a carbonyl group.

[0025] Such a compound of Formula I, wherein R^4 and R^5 each independently represent H or C_{1-6} alkyl.

[0026] Such a compound of Formula I, wherein R^4 and R^5 each independently represent H or methyl.

[0027] Such a compound of Formula I, wherein X represents CR^6R^7 and Y represents a bond, CR^9R^{10} , or $-CR^9R^{10}-CH_2-$.

[0028] Such a compound of Formula I, wherein R^6 and R^7 each independently represent H or C_{1-6} alkyl, and Y represents CR^9R^{10} or $-CR^9R^{10}-CH_2-$, wherein R^9 and R^{10} each represent H.

[0029] Such a compound of Formula I, wherein R^6 and R^7 each independently represent H or methyl, and R^9 and R^{10} each represent H.

[0030] Such a compound of Formula I, wherein X represents NR^8 and Y represents CR^9R^{10} or $-CR^9R^{10}-CH_2-$.

[0031] Such a compound of Formula I, wherein R^8 represents H, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, di- $(C_{1-6}$ alkyl)aminocarbonyl, arylcarbonyl, heterocyclylcarbonyl, aryl or aryl- C_{1-6} alkyl and R^9 and R^{10} each represent H.

[0032] Such a compound of Formula I, wherein R^8 represents H, methyl, ethyl, propyl, butyl, *tert*-butylcarbonyl, dimethylaminocarbonyl, pyrrolidinocarbonyl, phenyl, benzyl, wherein the phenyl moiety may be optionally substituted by one or more substituents selected from F and C_{1-6} alkyl (e.g., methyl) and wherein the methylene moiety may be optionally substituted by C_{1-6} alkyl (e.g., methyl), or phenethyl.

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[0033] Such a compound of Formula I, wherein R¹¹ represents H, halogen, or cycloC₃₋₇alkyl.

[0034] Such a compound of Formula I, wherein R¹¹ represents H, bromo, or cyclopropyl.

[0035] Such a compound of Formula I, wherein R¹¹ represents H.

[0036] Such a compound of Formula I, wherein R¹ represents phenyl optionally substituted by one or more substituents selected from F, C₁₋₆alkyl, cyano, and fluoromethyl; pyridyl optionally substituted by one or more substituents selected from amino and C₁₋₆alkylamino; thienyl optionally substituted by one or more chlorine atoms; or dihydroindoliziny.

[0037] Such a compound of Formula I, wherein R¹ represents phenyl substituted by one or more fluorine atoms.

[0038] Such a compound of Formula I, wherein R¹ represents phenyl substituted by one or more C₁₋₆alkyl (e.g., methyl) groups.

[0039] Such a compound of Formula I, wherein R¹ represents phenyl substituted by one or more cyano groups.

[0040] Such a compound of Formula I, wherein R¹ represents phenyl substituted by one or more fluoromethyl groups.

[0041] Such a compound of Formula I, wherein represents phenyl substituted by one or more fluorine atoms and one or more C₁₋₆alkyl (e.g., methyl) groups.

[0042] Such a compound of Formula I, wherein R¹ represents pyridyl substituted by one or more amino groups.

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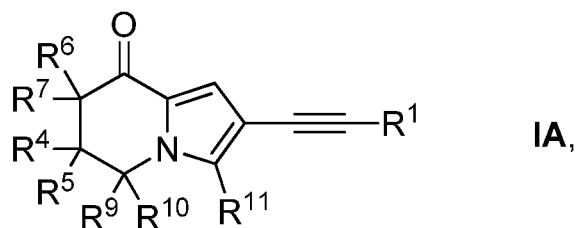
[0043] Such a compound of Formula I, wherein R¹ represents pyridyl substituted by one or more C₁₋₆alkylamino (e.g., methylamino) groups.

[0044] Such a compound of Formula I, wherein R¹ represents thienyl.

[0045] Such a compound of Formula I, wherein R¹ represents thienyl substituted by chloro.

[0046] Such a compound of Formula I, wherein R¹ represents dihydroindoliziny.

[0047] A further aspect of the invention relates to a compound of Formula I, which is selected from those of Formula **IA**



wherein

R¹ represents aryl, heteroaryl, cycloC₃₋₇alkyl or heterocyclyl, wherein the cycloC₃₋₇alkyl or heterocyclyl group may be optionally fused with an aryl or heteroaryl ring;

R⁴ and R⁵, which may be the same or different each independently represent H, C₁₋₆alkyl or F or R⁴ and R⁵ together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R⁶ and R⁷, which may be the same or different, each independently represent H, C₁₋₆alkyl, F, amino, C₁₋₆alkylamino or di-(C₁₋₆alkyl)amino or R⁶ and R⁷, together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R⁹ and R¹⁰, which may be the same or different, each independently represent H, C₁₋₆alkyl or F or R⁹ and R¹⁰, together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆alkyl, F, oxo, and acyl;

R¹¹ represents H, halogen, C₁₋₆alkyl, aryl, heteroaryl, cycloC₃₋₇alkyl or heterocyclyl;

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

[0048] A further aspect of the invention relates to a compound of Formula **IA**, wherein

R¹ represents aryl or heteroaryl;

R⁴ and R⁵, which may be the same or different, each independently represent H, C₁₋₆alkyl or F; or R⁴ and R⁵ together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R⁶ and R⁷, which may be the same or different, each independently represent H, C₁₋₆alkyl or F; or R⁶ and R⁷ together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R⁹ and R¹⁰, which may be the same or different, each independently represent H, C₁₋₆alkyl or F or R⁹ and R¹⁰, together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆alkyl, F, oxo, and acyl.

[0049] Such a compound of Formula **IA**, wherein R^4 and R^5 each independently represent H or C_{1-6} alkyl.

[0050] Such a compound of Formula **IA**, wherein R^4 and R^5 each independently represent H or methyl.

[0051] Such a compound of Formula **IA**, wherein R^6 and R^7 each independently represent H or C_{1-6} alkyl.

[0052] Such a compound of Formula **IA**, wherein R^6 and R^7 each independently represent H or methyl.

[0053] Such a compound of Formula **IA**, wherein R^9 and R^{10} each represent H.

[0054] Such a compound of Formula **IA**, wherein R^{11} represents H, halogen, or cyclo C_{3-7} alkyl.

[0055] Such a compound of Formula **IA**, wherein R^{11} represents H, bromo, or cyclopropyl.

[0056] Such a compound of Formula **IA**, wherein R^{11} represents H.

[0057] Such a compound of Formula **IA**, wherein R^1 represents phenyl optionally substituted by one or more substituents selected from F, C_{1-6} alkyl, cyano, and fluoromethyl; pyridyl optionally substituted by one or more substituents selected from amino and C_{1-6} alkylamino; thienyl optionally substituted by one or more chlorine atoms; or dihydroindoliziny.

[0058] Such a compound of Formula **IA**, wherein R^1 represents phenyl substituted by one or more fluorine atoms.

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[0059] Such a compound of Formula **IA**, wherein R¹ represents phenyl substituted by one or more C₁₋₆alkyl (e.g., methyl) groups.

[0060] Such a compound of Formula **IA**, wherein R¹ represents phenyl substituted by one or more cyano groups.

[0061] Such a compound of Formula **IA**, wherein R¹ represents phenyl substituted by one or more fluoromethyl groups.

[0062] Such a compound of Formula **IA**, wherein represents phenyl substituted by one or more fluorine atoms and one or more C₁₋₆alkyl (e.g., methyl) groups.

[0063] Such a compound of Formula **IA**, wherein R¹ represents pyridyl substituted by one or more amino groups.

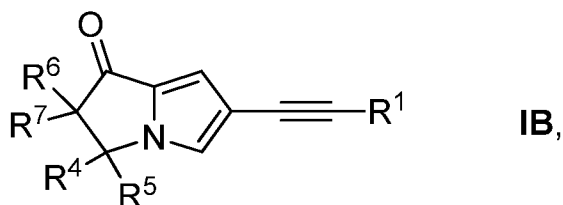
[0064] Such a compound of Formula **IA**, wherein R¹ represents pyridyl substituted by one or more C₁₋₆alkylamino (e.g., methylamino) groups.

[0065] Such a compound of Formula **IA**, wherein R¹ represents thienyl.

[0066] Such a compound of Formula **IA**, wherein R¹ represents thienyl substituted by chloro.

[0067] Such a compound of Formula **IA**, wherein R¹ represents dihydroindoliziny.

[0068] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IB**



wherein

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R¹ represents aryl, heteroaryl, cycloC₃₋₇alkyl or heterocyclyl, wherein the cycloC₃₋₇alkyl or heterocyclyl group may be optionally fused with an aryl or heteroaryl ring;

R⁴ and R⁵, which may be the same or different each independently represent H, C₁₋₆alkyl or F or R⁴ and R⁵ together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R⁶ and R⁷, which may be the same or different, each independently represent H, C₁₋₆alkyl, F, amino, C₁₋₆alkylamino or di-(C₁₋₆alkyl)amino or R⁶ and R⁷, together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

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

[0069] Such a compound of Formula **IB**, wherein R⁴ and R⁵ each independently represent H or C₁₋₆alkyl.

[0070] Such a compound of Formula **IB**, wherein R⁴ and R⁵ each independently represent H or methyl.

[0071] Such a compound of Formula **IB**, wherein R⁶ and R⁷ each independently represent H or C₁₋₆alkyl.

[0072] Such a compound of Formula **IB**, wherein R⁶ and R⁷ each independently represent H or methyl.

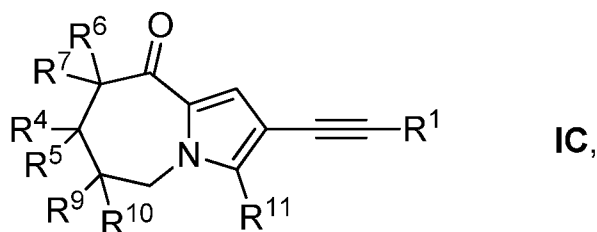
[0073] Such a compound of Formula **IB**, wherein R¹¹ represents H.

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[0074] Such a compound of Formula **IB**, wherein R^1 represents phenyl optionally substituted by one or more substituents selected from fluoro and cyano or pyridyl optionally substituted by one or more amino groups,

[0075] Such a compound Formula **IB**, wherein R^1 represents phenyl substituted by one or more fluorine atoms.

[0076] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IC**



wherein

R^1 represents aryl, heteroaryl, cycloC₃₋₇alkyl or heterocyclyl, wherein the cycloC₃₋₇alkyl or heterocyclyl group may be optionally fused with an aryl or heteroaryl ring;

R^4 and R^5 , which may be the same or different each independently represent H, C₁₋₆alkyl or F or R^4 and R^5 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R^6 and R^7 , which may be the same or different, each independently represent H, C₁₋₆alkyl, F, amino, C₁₋₆alkylamino or di-(C₁₋₆alkyl)amino or R^6 and R^7 , together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆ alkyl, F, oxo, and acyl;

R^9 and R^{10} , which may be the same or different, each independently represent H, C₁₋₆alkyl or F or R^9 and R^{10} , together with the carbon atom to which they are attached,

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form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C₁₋₆alkyl, F, oxo, and acyl;

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

[0077] Such a compound of Formula **IC**, wherein R⁴ and R⁵ each independently represent H or C₁₋₆alkyl.

[0078] Such a compound of Formula **IC**, wherein R⁴ and R⁵ each independently represent H or methyl.

[0079] Such a compound of Formula **IC**, wherein R⁶ and R⁷ each independently represent H or C₁₋₆alkyl.

[0080] Such a compound of Formula **IC**, wherein R⁶ and R⁷ each independently represent H or methyl.

[0081] Such a compound of Formula **IC**, wherein R⁸ and R⁹ each independently represent H or C₁₋₆alkyl.

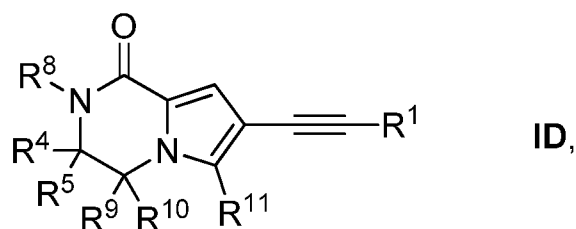
[0082] Such a compound of Formula **IC**, wherein R⁸ and R⁹ each independently represent H or methyl.

[0083] Such a compound of Formula **IC**, wherein R¹¹ represents H.

[0084] Such a compound of Formula **IC**, wherein R¹ represents phenyl optionally substituted by one or more fluorine atoms or pyridyl optionally substituted by one or more amino groups.

[0085] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **ID**

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wherein R^1 , R^4 , R^5 , and R^9 - R^{11} are as defined above for Formula I,

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

[0086] Such a compound of Formula **ID**, wherein R^4 and R^5 each independently represent H or C_{1-6} alkyl.

[0087] Such a compound of Formula **ID**, wherein R^4 and R^5 each independently represent H or methyl.

[0088] Such a compound of Formula **ID**, wherein R^8 represents H, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, di- $(C_{1-6}$ alkyl)aminocarbonyl, arylcarbonyl, heterocyclylcarbonyl, aryl or aryl- C_{1-6} alkyl.

[0089] Such a compound of Formula **ID**, wherein R^8 represents H, methyl, ethyl, propyl, butyl, *tert*-butylcarbonyl, dimethylaminocarbonyl, pyrrolidinocarbonyl, phenyl, or benzyl, wherein the phenyl moiety may be optionally substituted by one or more substituents selected from F and C_{1-6} alkyl (e.g., methyl) and wherein the methylene moiety may be optionally substituted by C_{1-6} alkyl (e.g., methyl), or phenethyl.

[0090] Such a compound of Formula **ID**, wherein R^9 and R^{10} each represent H.

[0091] Such a compound of Formula **ID**, wherein R^{11} represents H.

[0092] Such a compound of Formula **ID**, wherein R^1 represents phenyl optionally substituted by one or more substituents selected from F, C_{1-6} alkyl, cyano, and

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fluoromethyl or pyridyl optionally substituted by one or more substituents selected from amino and C₁₋₆alkylamino.

[0093] Such a compound of Formula **ID**, wherein R¹ represents phenyl substituted by one or more fluorine atoms.

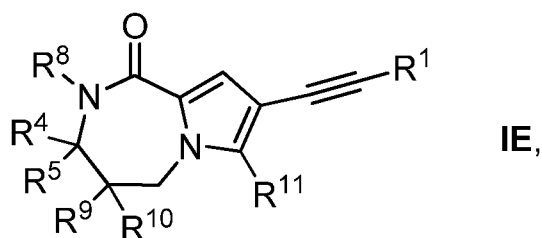
[0094] Such a compound of Formula **ID**, wherein R¹ represents phenyl substituted by one or more C₁₋₆alkyl (e.g., methyl) groups.

[0095] Such a compound of Formula **ID**, wherein R¹ represents phenyl substituted by one or more cyano groups.

[0096] Such a compound of Formula **ID**, wherein R¹ represents pyridyl substituted by one or more amino groups.

[0097] Such a compound of Formula **ID**, wherein R¹ represents pyridyl substituted by one or more C₁₋₆alkylamino (e.g., methylamino) groups.

[0098] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IE**



wherein R¹, R⁴, R⁵, and R⁹-R¹¹ are as defined above for Formula **I**,

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

[0099] Such a compound of Formula **IE**, wherein R⁴ and R⁵ each independently represent H or C₁₋₆alkyl.

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[00100]Such a compound of Formula **IE**, wherein R^4 and R^5 each independently represent H or methyl.

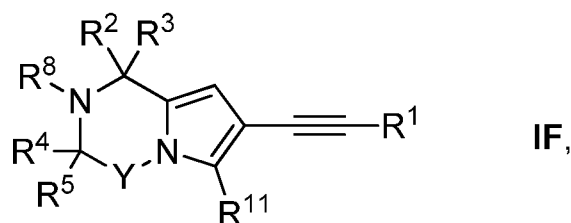
[00101]Such a compound of Formula **IE**, wherein R^8 represents H or C_{1-6} alkyl (e.g., methyl).

[00102]Such a compound of Formula **IE**, wherein R^9 and R^{10} each represent H.

[00103]Such a compound of Formula **IE**, wherein R^{11} represents H.

[00104]Such a compound of Formula **IE**, wherein R^1 represents phenyl optionally substituted by one or more substituents selected from F, C_{1-6} alkyl, cyano, and fluoromethyl or pyridyl optionally substituted by one or more substituents selected from amino and C_{1-6} alkylamino.

[00105]A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IF**



wherein R^1 , R^4 , R^5 , Y, and R^{11} are as defined above for Formula **I**;

R^3 represents H, C_{1-6} alkyl, F, OH, C_{1-6} alkoxy;

R^2 and R^8 together with the atoms to which they are attached, form a 4 to 7 membered ring wherein the ring may optionally contain one or two additional heteroatoms selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl which is optionally substituted by one or more halogen atoms, F, oxo, and acyl;

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

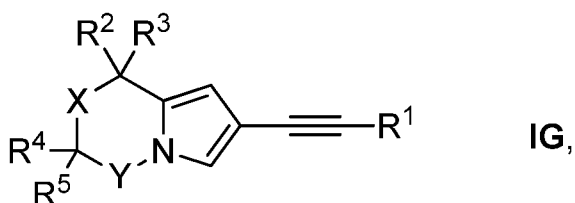
[00106] Such a compound of Formula **IF**, wherein R^2 and R^8 together with the atoms to which they are attached form an oxazine ring which is substituted by one or more substituents selected from C_{1-6} alkyl which is optionally substituted by one or more fluorine atoms, C_{1-6} alkoxycarbonyl, di- $(C_{1-6}$ alkyl)aminocarbonyl, and heterocyclylcarbonyl.

[00107] Such a compound of Formula **IF**, wherein R^3 , R^4 , R^5 , and R^{11} each represent H.

[00108] Such a compound of Formula **IF**, wherein Y represents CH_2 .

[00109] Such a compound of Formula **IF**, wherein R^1 represents phenyl.

[00110] A further aspect of the invention relates to a compound of Formula **I**, which is selected from those of Formula **IG**



wherein

R^1 represents aryl, heteroaryl, cyclo C_{3-7} alkyl or heterocyclyl, wherein the cyclo C_{3-7} alkyl and heterocyclyl groups may be optionally fused with an aryl or heteroaryl ring;

R^2 and R^3 , which may be the same or different, each independently represent H, C_{1-6} alkyl, F, OH, C_{1-6} alkoxy, or R^2 and R^3 together with the carbon atom to which they are attached form a carbonyl group, or R^2 and R^3 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

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R^4 and R^5 , which may be the same or different each independently represent H, C_{1-6} alkyl or F or R^4 and R^5 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

X represents CR^6R^7 or NR^8 ;

R^6 and R^7 , which may be the same or different, each independently represent H, C_{1-6} alkyl, F, amino, C_{1-6} alkylamino or di- $(C_{1-6}$ alkyl)amino or R^6 and R^7 , together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

or R^3 and R^6 , together with the carbon atoms to which they are attached, may form a 4 to 7 membered ring wherein the ring may optionally contain one or two heteroatoms selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

R^8 represents H, C_{1-6} alkyl, acyl, aryl, or heteroaryl;

Y represents a bond, CR^9R^{10} or $-CR^9R^{10}-CH_2-$;

R^9 and R^{10} , which may be the same or different, each independently represent H, C_{1-6} alkyl or F or R^9 and R^{10} , together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

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

[00111] A further aspect of the invention relates to a compound of Formula **IG**, wherein R^1 represents aryl or heteroaryl.

[00112] Such a compound of Formula **IG**, wherein R^2 and R^3 together with the carbon atom to which they are attached form a carbonyl group.

[00113] Such a compound of Formula **IG**, wherein R^4 and R^5 each independently represent H or C_{1-6} alkyl.

[00114] Such a compound of Formula **IG**, wherein R^4 and R^5 each independently represent H or methyl.

[00115] Such a compound of Formula **IG**, wherein X represents CR^6R^7 and Y represents a bond or CR^9R^{10} .

[00116] Such a compound of Formula **IG**, wherein R^6 and R^7 each independently represent H or C_{1-6} alkyl, and Y represents CR^9R^{10} , wherein R^9 and R^{10} each represent H

[00117] Such a compound of Formula **IG**, wherein R^6 and R^7 each independently represent H or methyl, and R^9 and R^{10} each represent H.

[00118] Such a compound of Formula **IG**, wherein R^1 represents phenyl optionally substituted by one or more substituents selected from F, C_{1-6} alkyl, cyano, and fluoromethyl; pyridyl optionally substituted by one or more substituents selected from amino and C_{1-6} alkylamino; or thienyl.

[00119] Such a compound of Formula **IG**, wherein R^1 represents phenyl substituted by one or more fluorine atoms.

[00120] Such a compound of Formula **IG**, wherein R^1 represents phenyl substituted by one or more C_{1-6} alkyl (e.g., methyl) groups.

[00121]Such a compound of Formula **IG**, wherein R¹ represents phenyl substituted by one or more cyano groups.

[00122]Such a compound of Formula **IG**, wherein R¹ represents phenyl substituted by one or more fluoromethyl groups.

[00123]Such a compound of Formula **IG**, wherein R¹ represents pyridyl substituted by one or more amino groups.

[00124]Such a compound of Formula **IG**, wherein R¹ represents pyridyl substituted by one or more C₁₋₆alkylamino (e.g., methylamino) groups.

[00125]Such a compound of Formula **IG**, wherein R¹ represents thienyl.

[00126]Specific compounds of Formula **I** within the present invention include, but are not limited to, the following compounds:

2-(Phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,6-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,3-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(*m*-Tolylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
3-((8-Oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
2-((6-Aminopyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Thiophen-3-ylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Thiophen-2-ylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-(Fluoromethyl)phenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,3,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,4,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,3,4,5-Tetrafluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,

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7-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
7-Methyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((4-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
7,7-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
7,7-Dimethyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one,
7,7-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
6-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((4-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((2-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
3-((6-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
6-Methyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
6,6-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
6,6-Dimethyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
6,6-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((4-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((2-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((2,3,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,3,4-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(*p*-Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(*o*-Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-(Fluoromethyl)phenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,

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6-(Phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((3-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
3-((6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
3-((7-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
2-((6-Aminopyridin-2-yl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5*H*)-one,
7-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((6-(Methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
6-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7-methyl-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6-methyl-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one,
6-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
2,2-Dimethyl-6-(phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-Methyl-6-(phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
3-((2-Methyl-1-oxo-2,3-dihydro-1*H*-pyrrolizin-6-yl)ethynyl)benzonitrile,
3-((2,2-Dimethyl-1-oxo-2,3-dihydro-1*H*-pyrrolizin-6-yl)ethynyl)benzonitrile,
3-((1-Oxo-2,3-dihydro-1*H*-pyrrolizin-6-yl)ethynyl)benzonitrile,
6-((3-Fluorophenyl)ethynyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((3-Fluorophenyl)ethynyl)-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-Aminopyridin-2-yl)ethynyl)-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-Aminopyridin-2-yl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-((6-Aminopyridin-2-yl)ethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-(Phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
8,8-Dimethyl-2-(phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
8-((6-Aminopyridin-2-yl)ethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,

8-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
2-Methyl-8-(phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
8-(Phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Methyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((6-Aminopyridin-2-yl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
1-(7-((6-Aminopyridin-2-yl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-2,2-dimethylpropan-1-one,
7-((6-Aminopyridin-2-yl)ethynyl)-*N,N*-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide,
N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide,
2,2-Dimethyl-1-(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)propan-1-one,
2-(Phenylethynyl)-5,6,7,8-tetrahydroindolizine,
6-(Phenylethynyl)-2,3-dihydro-1*H*-pyrrolizine,
2-(Phenylethynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine,
6-((2-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((4-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-(Methylamino)pyridin-2-yl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-Methyl-6-(*m*-tolylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-((2-Fluoro-3-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Fluoro-3-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2,2-Dimethyl-6-(phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2,2-Dimethyl-6-(*m*-tolylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-((3-Fluorophenyl)ethynyl)-5,6,7,8-tetrahydroindolizin-8-ol,
2-((2-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,

2-((5-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((2-Fluoro-6-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((5-Chlorothiophen-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one,
8-(Phenylethynyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one,
2-((3-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((4-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-Methyl-8-(phenylethynyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one,
2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
2-(Phenylethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one,
3-((1-Oxo-2-propyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile,
2-Methyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
3-((2-Methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile,
7-((3-Fluorophenyl)ethynyl)-2-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Methyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Benzyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Benzyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Benzyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
3-((2-Benzyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile,
7-(Phenylethynyl)-2-propyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Propyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
8-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one,
2-Ethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Butyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Butyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
7-((3-Fluorophenyl)ethynyl)-2-isopropyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
2-Isopropyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,
8,8-Dimethyl-2-(phenylethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one,
2-Phenyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,

7-((3-Fluorophenyl)ethynyl)-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Phenyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one,
2,2-Dimethyl-1-(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)propan-1-one,
3-Bromo-2-(phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
3-Cyclopropyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide,
2-(2-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Methylbenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Methylbenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(2-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(2-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(2-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
Phenyl(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)methanone,
(*R*)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*R*)-2-(1-Phenylethyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*R*)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,

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2-(3-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*S*)-2-(1-Phenylethyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*S*)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*S*)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone,
Methyl 7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate,
2'-(Phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione,
1,3-Dimethyl-2'-(phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione,
cis-9-(Phenylethynyl)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-9-(Phenylethynyl)-4-(3,3,3-trifluoropropyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-9-(Phenylethynyl)-4-(2,2,2-trifluoroethyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-4-(2,2-Difluoroethyl)-9-(phenylethynyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-4-(2-Fluoroethyl)-9-(phenylethynyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-Methyl 9-(phenylethynyl)-4a,5,6,10b-tetrahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine-4(3*H*)-carboxylate,
cis-*N,N*-Dimethyl-9-(phenylethynyl)-4a,5,6,10b-tetrahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine-4(3*H*)-carboxamide,
Azetidin-1-yl(*cis*-9-(phenylethynyl)-5,6-dihydro-2*H*-[1,4]oxazino[3,2-*g*]indolizin-4(3*H*,4a*H*,10b*H*)-yl)methanone,
N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-sulfonamide,

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7-(Phenylethynyl)-2-(pyrimidin-2-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine,
Morpholino(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)methanone,
7-((3-Fluorophenyl)ethynyl)-2-phenethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Phenethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Phenethyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

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

[00127]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.

[00128]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 conditions or diseases selected from those described earlier in the description.

[00129]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, 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.

[00130] 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 deficits 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

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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 deficits of schizophrenia, cognitive impairment, or for cognitive enhancement and/or neuroprotection.

[00131]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.

[00132]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.

[00133]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.

[00134]A further aspect of the invention relates to the use of isotopic derivatives of the compounds of Formula I as PET or SPECT ligands.

[00135]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

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isomer, pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients.

[00136]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.

[00137]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.

[00138]A further aspect of the invention 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 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 least two different active ingredients, selected from at 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 neuroprotection.

[00139]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.

[00140]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

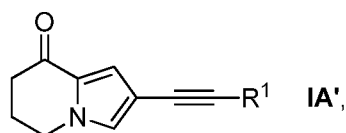
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bromocriptine, cabergolin, ropinirole, pramiperole, pergolide, rotigotine), and neuroleptics (such as classical neuroleptics, including haloperidol, perphenazin, chlorpromazine, metoclopramide or atypicals such as clozapine, risperidone or olanzapine).

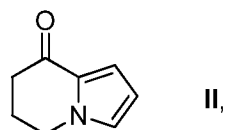
[00141]The invention also relates to a method of providing neuroprotection in a living animal, including a human, comprising the step of administering to a living animal, including a human, a therapeutically effective amount of a composition as described above.

[00142]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.

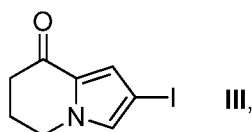
[00143]The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA'**



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



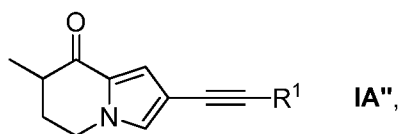
is iodinated to yield the compound of Formula **III**



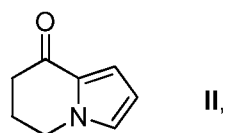
which compound of Formula **III** is reacted with an appropriately substituted acetylene in the presence of a suitable catalyst (e.g., $Pd[PPh_3]_2Cl_2$), to yield a compound of Formula **IA'**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

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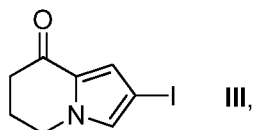
[00144]The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA''**



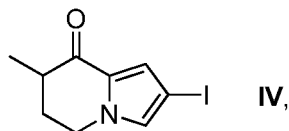
or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R¹ is as defined above for Formula **I**, wherein the compound of Formula **II**



is iodinated to yield the compound of Formula **III**

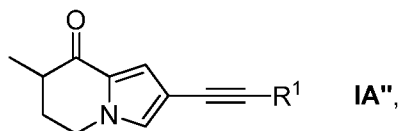


which compound of Formula **III** is treated with methyl iodide in the presence of a strong base (e.g., LDA) to yield the compound of Formula **IV**



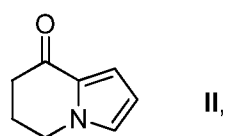
which compound of Formula **IV** is reacted with an appropriately substituted acetylene in the presence of a suitable catalyst (e.g., Pd[PPh₃]₂Cl₂), to yield a compound of Formula **IA''**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

[00145]The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA''**

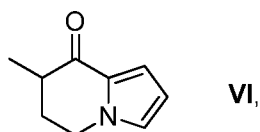


or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R¹ is as defined above for Formula **I**, wherein the compound of Formula **II**

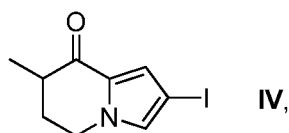
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is treated with methyl iodide in the presence of a strong base (e.g., LDA) to yield the compound of Formula **VI**

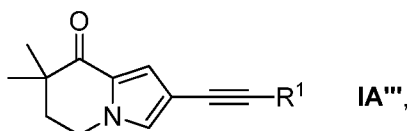


which compound of Formula **VI** is iodinated to yield the compound of Formula **IV**

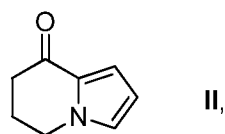


which compound of Formula **IV** is reacted with an appropriately substituted acetylene in the presence of a suitable catalyst (e.g., Pd[PPh₃]₂Cl₂), to yield a compound of Formula **IA''**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

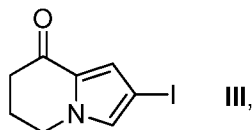
[00146]The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA'''**



or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R¹ is as defined above for Formula **I**, wherein the compound of Formula **II**

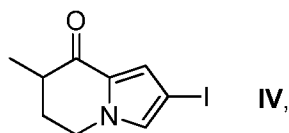


is iodinated to yield the compound of Formula **III**

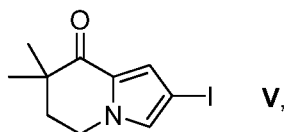


which compound of Formula **III** is treated with methyl iodide in the presence of a strong base (e.g., LDA) to yield the compound of Formula **IV**

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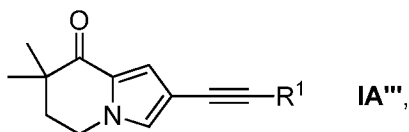


which compound of Formula **IV** is treated with methyl iodide in the presence of a strong base (e.g., LDA) to yield the compound of Formula **V**

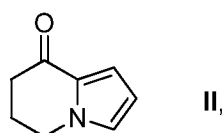


which compound of Formula **V** is reacted with an appropriately substituted acetylene in the presence of a suitable catalyst (e.g., Pd[PPh₃]₂Cl₂), to yield a compound of Formula **IA'''**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

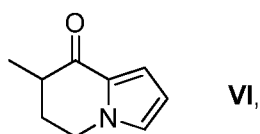
[00147]The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA'''**



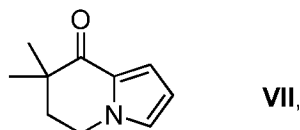
or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R¹ is as defined above for Formula **I**, wherein the compound of Formula **II**



is treated with methyl iodide in the presence of a strong base (e.g., LDA) to yield the compound of Formula **VI**

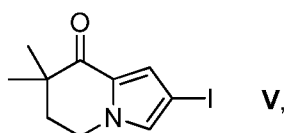


which compound of Formula **VI** is treated with methyl iodide in the presence of a strong base (e.g., LDA) to yield the compound of Formula **VII**



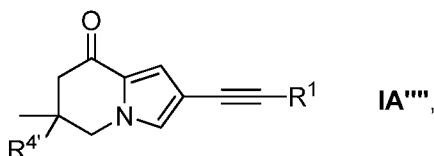
which compound of Formula **VII** is iodinated to yield the compound of Formula **V**

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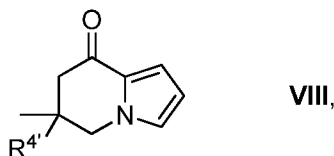


which compound of Formula **V** is reacted with an appropriately substituted acetylene in the presence of a suitable catalyst (e.g., Pd[PPh₃]₂Cl₂), to yield a compound of Formula **IA'''**, which may be converted, if desired, to an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph.

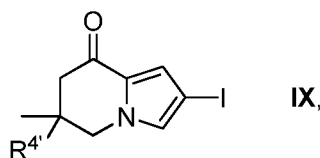
[00148]The invention also relates to a process for the synthesis or preparation of a compound of Formula **IA''''**



or an optical isomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein R¹ is as defined above for Formula **I** and R^{4'} represents H or methyl, wherein a compound of Formula **VIII**



is iodinated to yield the compound of Formula **IX**



which compound of Formula **IX** is reacted with an appropriately substituted acetylene in the presence of a suitable catalyst (e.g., Pd[PPh₃]₂Cl₂), 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.

DETAILED DESCRIPTION OF THE INVENTION

[00149]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.

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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 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).

[00150]As used herein, the following definitions are applicable unless otherwise described, the term "C₁₋₆alkyl" represents straight or branched chain alkyl groups. Examples of such alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

[00151]The term "C₂₋₆alkenyl" represents straight or branched chain alkenyl groups.

[00152]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.

[00153]The term "acyl" represents C₁₋₆alkylcarbonyl, trifluoroacetyl, hydroxy-C₁₋₆alkylcarbonyl, C₁₋₆alkoxycarbonyl, *N*-C₁₋₆alkylaminocarbonyl, *N,N*-di-(C₁₋₆alkyl)aminocarbonyl, C₁₋₆alkoxy-C₁₋₆alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, cyclo-C₃₋₁₂alkylcarbonyl, aryl-C₁₋₆alkylcarbonyl, heteroaryl-C₁₋₆alkylcarbonyl, arylamino-C₁₋₆alkylcarbonyl, heteroarylamino-C₁₋₆alkylcarbonyl, heterocyclylcarbonyl and heterocyclyl-C₁₋₆alkylcarbonyl.

[00154]The term "cycloC₃₋₁₂alkyl" represents monocyclic, 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, C₁₋₆alkylcarbonylamino, oxo, C₁₋₆alkoxyimino, *N*-C₁₋₆alkylaminocarbonyl, *N,N*-di-(C₁₋₆alkyl)aminocarbonyl, arylC₁₋₆alkoxycarbonyl, and C₁₋₆alkylenedioxy.

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[00155]The term "cycloC₃₋₇alkyl" 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.

[00156]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, piperazinyl, cycloC₃₋₁₂alkyl, pyridyl, and C₁₋₆alkylenedioxy.

[00157]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, cycloC₃₋₁₂alkyl,

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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.

[00158]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 oxetanyl, piperidinyl, morpholinyl, thiomorpholinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, 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.

[00159]The term "halogen" represents fluorine, chlorine, bromine and iodine.

[00160]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).

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[00161]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.

[00162]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. Geriatr. Psychiatry*, **1999**, 14:135-146; Rogawski, *Amino Acids*, **2000**, 19: 133-49; Danysz et al., *Curr. Pharm. Des.*, **2002**, 8:835-43; Jirgensons et. al. *Eur. J. Med. Chem.*, **2000**, 35: 555-565).

[00163]The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a reference 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 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.

[00164]In addition, using methods known to those skilled in the art, analogs and 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.

[00165]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

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functional group present in the compound of Formula I such that the chemically 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 been described in the art (see, for example, Stella V., et al., *Prodrugs: Challenges and Rewards*, AAPS Press/Springer, New York, **2007**).

[00166]The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such 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.

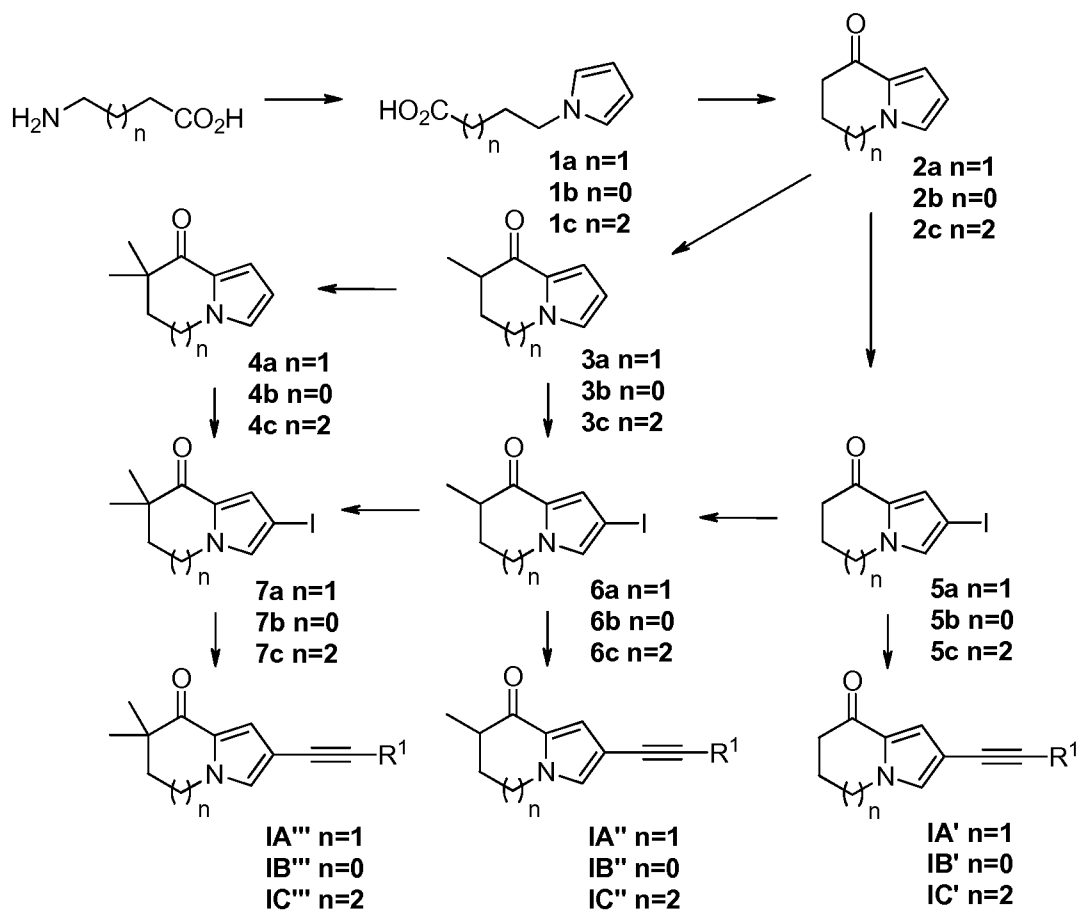
[00167]Compounds of the present invention may be in the form of pharmaceutically acceptable salts. "Pharmaceutically acceptable salts" refers to those salts which possess the biological effectiveness and properties of the parent compound and which are not biologically or otherwise undesirable. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

[00168]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. 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.

[00169]The following **Schemes 1-6** 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 procedures analogous thereto, which would be well known to one of ordinary skill in organic chemistry. All of the variables used in **Schemes 1-6** 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.

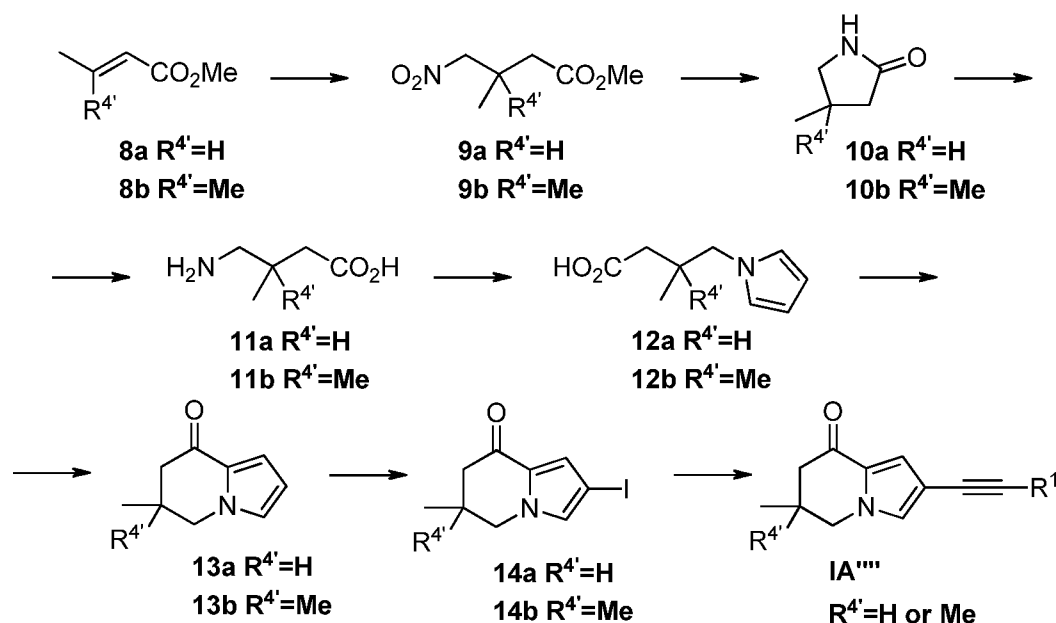
Scheme 1 – Synthesis of compounds of Formula IA-IC



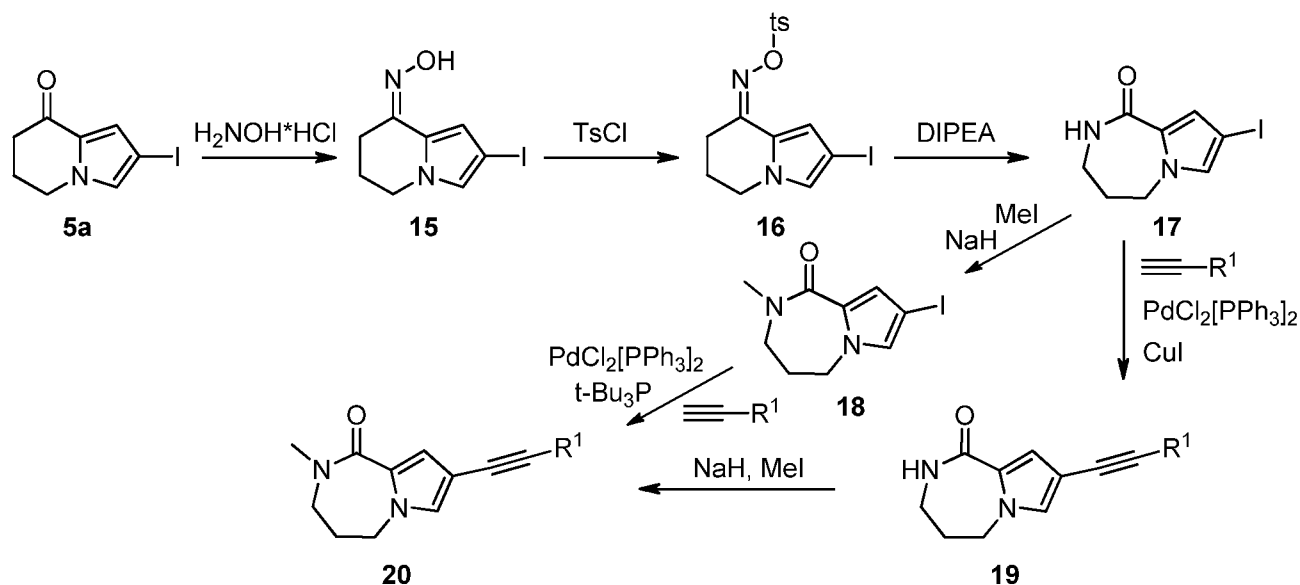
[00170] Compounds of general Formulas **IA'**, **IA''**, **IA'''**, **IB'**, **IB''**, **IB'''**, **IC'**, **IC''**, and **IC'''** are prepared by Sonogashira coupling of 2-iodo-6,7-dihydroindolizin-8(5H)-one (**5a**), 2-iodo-7-methyl-6,7-dihydroindolizin-8(5H)-one (**6a**), 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one (**7a**), 6-iodo-2,3-dihydro-1H-pyrrolizin-1-one (**5b**), 6-iodo-2-

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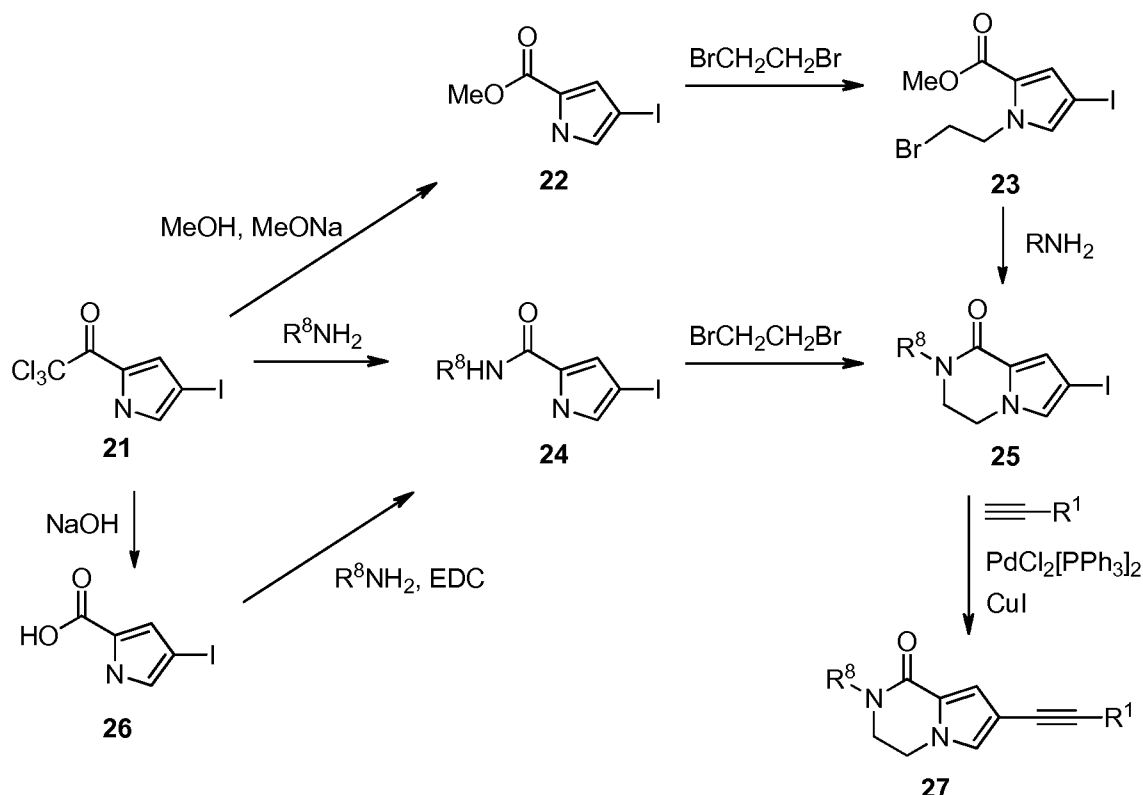
methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**6b**), 6-iodo-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**7b**), 2-iodo-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**5c**), 2-iodo-8-methyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**6c**), or 2-iodo-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**7c**) with substituted acetylenes in the presence of a suitable catalyst, such as Pd[PPh₃]₂Cl₂. 2-Iodo-6,7-dihydroindolizin-8(5*H*)-one (**5a**), 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one (**5b**), 2-iodo-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**5c**) and their methylated analogues **6a**, **6b**, **6c**, **7a**, **7b** and **7c** are prepared by iodination of 6,7-dihydroindolizin-8(5*H*)-one (**2a**), 2,3-dihydro-1*H*-pyrrolizin-1-one (**2b**), 7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**2c**) or corresponding analogues **3a**, **3b**, **3c**, **4a**, **4b** and **4c**. The synthesis of 6,7-dihydroindolizin-8(5*H*)-one (**2a**) from 4-aminobutanoic acid via 4-(1*H*-pyrrol-1-yl)butanoic acid (**1a**), is described in the literature (*J. Org. Chem.*, **2009**, 74 (8), 3160-63). In close analogy, 2,3-dihydro-1*H*-pyrrolizin-1-one (**2b**) is synthesized from 3-aminopropanoic acid via 4-(1*H*-pyrrol-1-yl)propanoic acid (**1b**) and 7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**2c**) is similarly synthesized via 5-(1*H*-pyrrol-1-yl)pentanoic acid. Methylation of 6,7-dihydroindolizin-8(5*H*)-one (**2a**), 2,3-dihydro-1*H*-pyrrolizin-1-one (**2b**) or 7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**2c**) with methyl iodide in the presence of a strong base, such as LDA, provides 7-methyl-6,7-dihydroindolizin-8(5*H*)-one, (**3a**) 2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**3b**) or 8-methyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**3c**), correspondingly. The second methylation of 7-methyl-6,7-dihydroindolizin-8(5*H*)-one (**3a**), 2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**3b**) or 8-methyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**3c**) under similar conditions provides 7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**4a**), 2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**4b**) or 8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**4c**), correspondingly. Alternatively, the methylation can be performed after the iodination step, thus converting 2-iodo-6,7-dihydroindolizin-8(5*H*)-one (**5a**), 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one (**5b**) or 2-iodo-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (**5c**), to their methylated analogues **6a**, **6b**, **6c** and further to **7a**, **7b** and **7c**.

Scheme 2 – Synthesis of 6-substituted dihydroindolizin-8(5*H*)-ones

[00171] Compounds of Formula **IA''''** are prepared by Sonogashira coupling of 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one (**14a**) or 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**14b**) with substituted acetylenes in the presence of a suitable catalyst, such as $Pd[PPh_3]_2Cl_2$. 2-Iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one (**14a**) and 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**14b**) are prepared by iodination of 6-methyl-6,7-dihydroindolizin-8(5*H*)-one (**13a**) or 6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**13b**) accordingly. Compounds **13a** and **13b** are synthesized from 4-amino-3-methylbutanoic acid (**11a**) or 4-amino-3,3-dimethylbutanoic acid (**11b**) via 3-methyl-4-(1*H*-pyrrol-1-yl)butanoic acid (**12a**) and 3,3-dimethyl-4-(1*H*-pyrrol-1-yl)butanoic acid (**12b**) in close analogy to the method described in the literature (*J. Org. Chem.*, **2009**, 74 (8), 3160-63) for 6,7-dihydroindolizin-8(5*H*)-one (**2**, **Scheme 1**). The synthesis of 4-amino-3,3-dimethylbutanoic acid (**11b**) from methyl 3-methylbut-2-enoate (**8b**) via methyl 3,3-dimethyl-4-nitrobutanoate (**9b**) and 4,4-dimethylpyrrolidin-2-one (**10b**) is performed according to procedures described in the literature (US Published Application No. 2008/0039456A1). A closely analogous sequence starting from methyl crotonate (**8a**) provides 4-amino-3-methylbutanoic acid (**11a**).

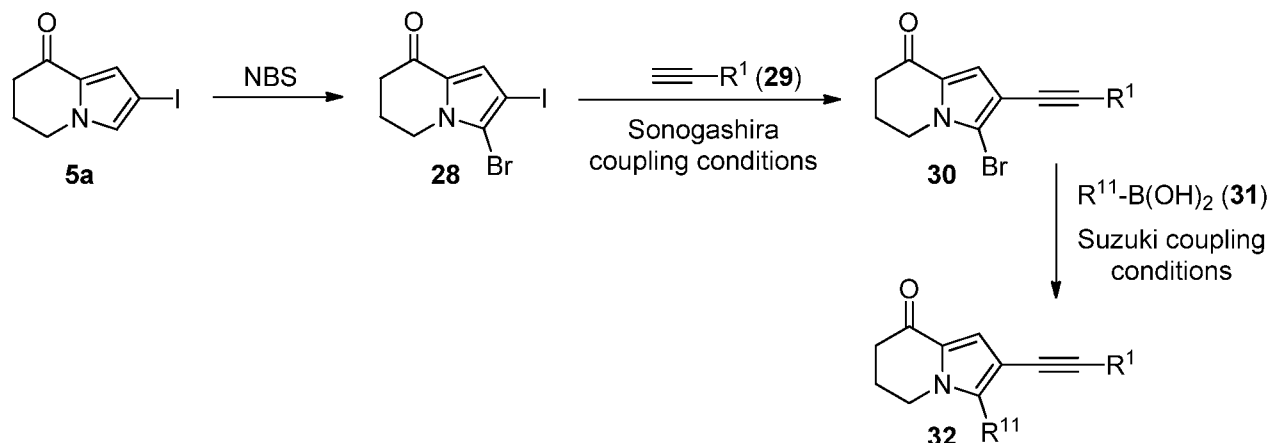
Scheme 3 – Synthesis of 2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-ones

[00172] Methods for the preparation of pyrrolo[1,2-*a*][1,4]diazepin-1-one derivatives **19** and **20** are shown in **Scheme 3**. Lactam **17** is prepared from ketone **5a** via three steps, i.e., oxime formation (**15**) using hydroxyl amine hydrochloride, tosylation (**16**), and subsequent rearrangement under basic conditions. Standard Sonogashira coupling reactions provide compounds of general formula **19**, which may be further derivatized by, e.g., *N*-methylation using methyl iodide to furnish target compounds **20**. Alternatively, lactam **17** may first be methylated and then coupled with an appropriate terminal acetylene under Sonogashira conditions to give compounds of general formula **20**.

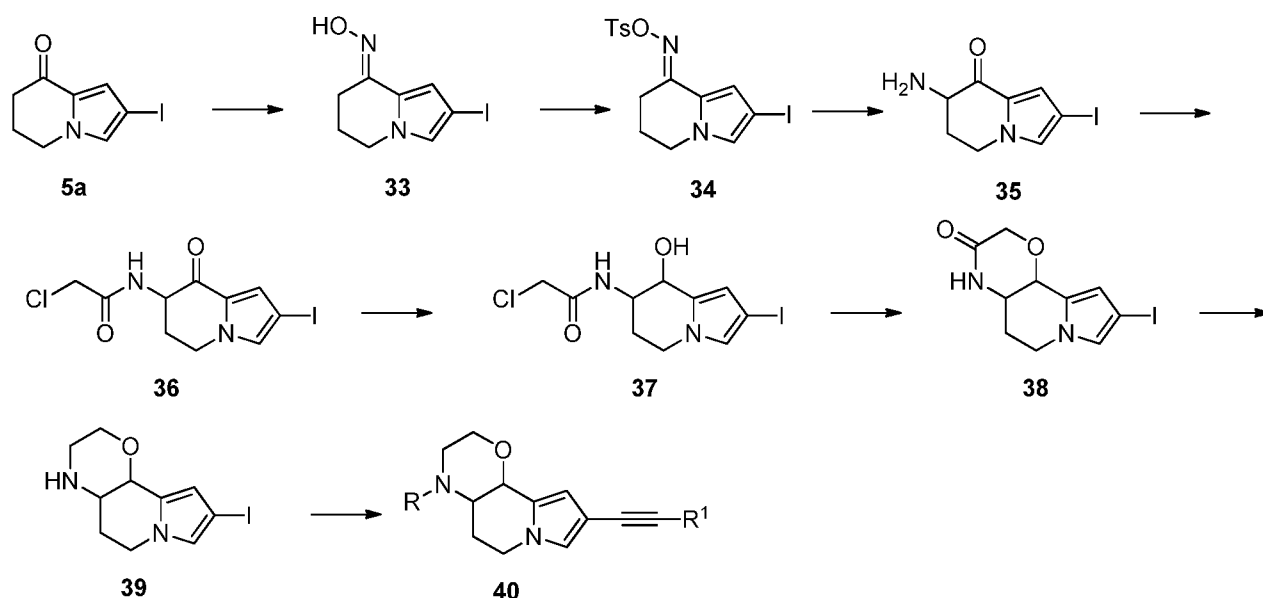
Scheme 4 – Synthesis of 3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-ones

[00173] Compounds of general formula of type **27** are synthesized according to **Scheme 4**. A known trichloroacetyl derivative **21** (WO2005/113541) is converted to ester **22** in methanol in the presence of subequimolar amount of sodium methoxide. In close analogy to published procedures (*Aust. J. Chem.* **1988**, 41, 1583), ester **22** is then alkylated with dibromoethane in DMSO using potassium hydroxide as a base. Lactam **25** is obtained in the reaction of compound **23** with 4 eq. of the desired amine. Alternatively, pyrrole **21** is directly converted into amide **24** in the reaction of 1.2 eq. of the amine in THF, followed by alkylation with dibromoethane under phase transfer catalysis conditions to furnish target lactam **25**. In the case of unreactive amines, pyrrole **21** is hydrolyzed with sodium hydroxide to give carboxylic acid, which is then converted to amide **24** using standard condensation conditions (EDC, HOBT) in DMF. Sonogashira coupling of lactams **25** with arylacetylenes provides the target compounds **27**.

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Scheme 5 – Synthesis of 3-substituted 6,7-dihydroindolizin-8(5H)-ones

[00174] 3-Substituted 6,7-dihydroindolizin-8(5H)-one derivatives are accessible via the synthesis route described in **Scheme 5**. First, ketone **5a** is brominated in 3-position by means of *N*-bromosuccinimide in DMF to give dihalogenated intermediate **28** followed by a Sonogashira coupling reaction with an appropriate acetylene **29** to furnish compounds of general structure **30**. The bromo substituent may be substituted by alkyl or aryl groups using boronic acids (**31**) in a Suzuki coupling reaction to provide compounds of general formula **32**.

Scheme 6 – Synthesis of 3,4,4a,5,6,10b-hexahydro-2H-[1,4]oxazino[3,2-g]indolizine derivativesR = H, C₁₋₆alkyl, acyl

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[00175]Ketone **5a** may be transformed into oxime **33** in the presence of sodium acetate and hydroxylamine hydrochloride. Oxime **33** is then converted into the corresponding tosylate **34** using a standard protocol. α -Amino group is introduced in Neber rearrangement reaction in the presence of potassium *t*-butoxide, which gives (in rather low yield) a mixture of aminoketone **35** and its dimethyl acetal, which is hydrolyzed during work up into aminoketone **35**. Acylation of aminoketone **35** with chloroacetyl chloride gives the corresponding amide **36**. The carbonyl group is reduced with DIBALH to give alcohol **37**, which cyclizes in the presence of sodium hydride to provide the morpholinone derivative **38**. Reduction of this lactam with LAH provides the key intermediate morpholine **39**.

[00176]Morpholine **39** may be *N*-alkylated under standard reaction conditions with an appropriate alkyl halide and then coupled with an arylacetylene to provide compound **40**.

[00177]Analogously, morpholine **39** may be acylated with acyl chlorides, chloroformates and carbomoyl chlorides to give the corresponding *N*-acyl derivatives, which may be coupled with an arylacetylene to provide the compound **40**.

[00178]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 order to avoid undesirable side reactions.

[00179]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 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.

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[00180]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.

[00181]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

[00182]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

[00183]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.

[00184]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, and the parenteral route, respectively. 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.

[00185]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

[00186] 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.

[00187] 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.

[00188] 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.

[00189] 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

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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.

[00190]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.

[00191]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.

[00192]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

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

[00193]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.

[00194]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.

[00195]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,

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polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

[00196]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, dichlorotetrafluoroethane, 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.

[00197]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.

[00198]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).

[00199]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

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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.

[00200]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.

[00201]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. Compositions that exhibit large therapeutic indices are preferred.

[00202]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 present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith.

[00203]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

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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.

[00204]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.

[00205]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.

[00206]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.

[00207]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.

[00208]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-

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treating, pharmaceutical compositions, and use of a compound of the present invention in the manufacture of a medicament.

[00209]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.

EXPERIMENTAL PART

[00210]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.

[00211]Hereinafter, "DCM" is defined as dichloromethane, "BuLi" as *n*-butyllithium, "DBU" as 1,8-diazabicyclo[5.4.0]undec-7-ene, "DIPEA" as *N,N*-diisopropylethylamine, "DMAP" as 4-dimethylaminopyridine, "DMF" as *N,N*-dimethylformamide, "EtOAc" as ethyl acetate, "LDA" as lithium diisopropylamide, "MeOH" as methanol, "Pd(dppf)Cl₂" as 1,1'-bis(diphenylphosphino)ferrocenepalladium(II)dichloride, "TBAF" as tetrabutylammonium fluoride, "TEA" as triethylamine, and "THF" as tetrahydrofuran.

Preparation 1

2-Iodo-6,7-dihydroindolizin-8(5*H*)-one (5a)

[00212]6,7-Dihydroindolizin-8(5*H*)-one (**2a**) (5170 mg, 38.25 mmol, 1 eq.) is dissolved in 130 mL of anhydrous DMF, and *N*-iodosuccinimide (8605 mg, 38.25 mmol, 1 eq.) is added in single portion. The resulting mixture is stirred for 24 h at room temperature. The mixture is diluted with water, and the formed precipitate is filtered off. The filtrate consists mainly of 2- and 3-monoiodides, whereas the precipitate is found to be mainly 2-iodide (**5a**) and 2,3-diiodide.

[00213]The precipitate is recrystallized from ethyl acetate to give 4800 mg of 2-iodide (**5**) and 1700 mg of 2,3-diiodide. The filtrate is extracted with EtOAc, dried over

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anhydrous sodium sulfate, and the solvent is evaporated *in vacuo*. The residue is purified by flash column chromatography, using hexanes/ethyl acetate mixture as an eluent, providing 1220 mg of 2-iodide (**5a**) and 1460 mg of 3-iodide. The combined yield of title compound **5a** is 6020 mg (60%).

[00214]The 2,3-diiodide by-product can be converted to 2-iodide (**5a**) by its treatment at low temperature with BuLi or isopropylmagnesium bromide and quenching the reaction mixture with water.

Preparation 2

7-Methyl-6,7-dihydroindolizin-8(5H)-one (**3a**)

[00215]To a solution of freshly distilled diisopropylamine (1152 mg, 11.39 mmol, 1.1 eq.) in 11 mL of THF at -78 °C is added a solution of BuLi (2.5 M in hexane, 4.6 mL, 11.39 mmol, 1.1 eq.) with stirring under argon. The solution is warmed to 0 °C over 15 min to provide a solution of LDA. The LDA solution is cooled to -78 °C and added via cannula to a stirred solution of 6,7-dihydroindolizin-8(5H)-one (**2a**) (1400 mg, 10.36 mmol, 1 eq.) in 12 mL of THF under argon. The mixture is stirred for 1 h at -78 °C, then methyl iodide (1617 mg, 11.39 mmol, 1.1 eq.) is added dropwise, and the mixture is stirred for 3 h at -78 °C and then allowed to warm to room temperature. A saturated solution of ammonium chloride is added, and the mixture is extracted with DCM. The organic phase is dried over anhydrous Na₂SO₄, and the solvent is evaporated. Purification of the residue by flash column chromatography provides 885 mg (57%) of the title compound along with 250 mg of the recovered starting material and 150 mg of 7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one (**4a**).

Preparation 3

7,7-Dimethyl-6,7-dihydroindolizin-8(5H)-one (**4a**)

[00216]To a solution of freshly distilled diisopropylamine (335 mg, 3.32 mmol, 1.1 eq.) in 4 mL of THF at -78 °C is added a solution of BuLi (2.5 M in hexane, 1.33 mL, 3.32 mmol, 1.1 eq.) with stirring under argon. The solution is warmed to 0 °C over 15 min to provide a 0.7 M solution of LDA. The LDA solution is cooled to -78 °C and added via

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cannula to a stirred solution of 7-methyl-6,7-dihydroindolizin-8(5*H*)-one (**3a**) in 4 mL of THF under argon. The mixture is stirred for 1 h at -78 °C. Methyl iodide (470 mg, 3.32 mmol, 1.1 eq.) is added dropwise, and the mixture is stirred for 3 h at -78 °C and then allowed to warm to room temperature. A saturated solution of ammonium chloride is added, and the mixture is extracted with DCM. The organic phase is dried over anhydrous Na₂SO₄, and the solvent is evaporated. Purification of the residue by flash column chromatography provides 428 mg (87%) of the title compound as yellow crystals.

Preparation 4

6,6-Dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**13b**)

[00217] 1 eq of NaOH is added to a stirred solution of 4-amino-3,3-dimethylbutanoic acid (**11b**) (2270 mg, 13.54 mmol, 1 eq.) and NaOAc (1116 mg, 13.61 mmol, 1 eq.) in 20 mL of water, then AcOH (7 mL) and dichloroethane (20 mL) are added. The mixture is heated to 90 °C, and 2,5-dimethoxytetrahydrofuran (1793 mg, 13.57 mmol, 1 eq.) is added. The reaction mixture is stirred for 20 h at 90 °C, then quenched by addition of 1M HCl. The pH is adjusted to 10 with saturated NaHCO₃, and the mixture is extracted with DCM. The aqueous phase is acidified with HCl (1M) and extracted with DCM. The organic phase is dried over anhydrous Na₂SO₄, and the solvent is evaporated to give sufficiently pure 3,3-dimethyl-4-(1*H*-pyrrol-1-yl)butanoic acid (**12b**). This intermediate (1916 mg, 10.57 mmol, 1 eq.) is dissolved in 8 mL of polyphosphoric acid, and the mixture is stirred for 24 h at 30 °C. Then water is added, and the resulting mixture is extracted with DCM. The organic phase is dried over anhydrous Na₂SO₄, and the solvent is evaporated. Purification of the residue by flash column chromatography provides 600 mg (35%) of the title compound as yellow oil.

Preparation 5

6-Methyl-6,7-dihydroindolizin-8(5*H*)-one (**13a**)

[00218] The title compound is synthesized from 4-amino-3-methylbutanoic acid (**11a**) using identical procedure to that described for 6,6-dimethyl-6,7-dihydro-5*H*-indolizin-8-one (**13b**, Preparation 4).

Preparation 6**2,3-Dihydro-1*H*-pyrrolizin-1-one (2b)**

[00219]The title compound is synthesized from 3-aminopropanoic acid (beta-alanine) using identical procedure to that described for 6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**13b**, Preparation 4).

Preparation 7**2-Iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one (14a)****2-Iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (14b)****2-Iodo-7-methyl-6,7-dihydroindolizin-8(5*H*)-one (6a)****2-Iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (7a)**

[00220]The title compounds are prepared by iodination of 6-methyl-6,7-dihydroindolizin-8(5*H*)-one (**13a**), 6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**13b**), 7-methyl-6,7-dihydroindolizin-8(5*H*)-one (**3a**), or 7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (**4a**) correspondingly, using identical procedures to that described for 2-iodo-6,7-dihydroindolizin-8(5*H*)-one (**5a**, Preparation 1).

Preparation 8**6-Iodo-2,3-dihydro-1*H*-pyrrolizin-1-one (5b)**

[00221]The title compound is prepared by iodination of 2,3-dihydro-1*H*-pyrrolizin-1-one (**2b**) using identical procedure to that described for 2-iodo-6,7-dihydroindolizin-8(5*H*)-one (**5a**, Preparation 1).

General Procedure 1 – Sonogashira coupling of 2-iodo-6,7-dihydroindolizin-8(5*H*)-ones and 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-ones with substituted acetylenes

[00222] 2-Iodo-6,7-dihydroindolizin-8(5*H*)-one or 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one (5.75 mmol, 1.0 eq.), substituted acetylene (8.62 mmol, 1.5 eq.), triphenylphosphine (45 mg, 0.17 mmol, 0.03 eq.) and copper(I)iodide (54 mg, 0.29 mmol, 0.05 eq.) are dissolved in 25 mL of anhydrous DMF. The mixture is flushed thoroughly with argon.

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$\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (121 mg, 0.17 mmol, 0.03 eq.) and TEA (3 mL) are added, and the reaction mixture is stirred at 60 °C for 4 h. The reaction mixture is then diluted with water and extracted with chloroform. The organic extracts are combined, dried over anhydrous Na_2SO_4 , and the solvent is evaporated. The residue is purified by flash column chromatography using hexanes/ethyl acetate mixture as an eluent to give the title compound.

Preparation 9

2-Ethynyl-6,7-dihydroindolizin-8(5H)-one

[00223] A solution of 2-iodo-6,7-dihydroindolizin-8(5H)-one (4.76 g, 18.23 mmol) in dry DMF (50 mL) is flushed with argon for 10 min. Trimethylsilylacetylene (5.19 mL, 36.5 mmol) is added, followed by TEA (10.14 mL, 72.9 mmol), copper(I)iodide (0.174 g, 0.912 mmol) and $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (0.640 g, 0.912 mmol). The mixture is stirred overnight at room temperature, then poured into cold water (300 mL) and extracted with EtOAc (200 mL). The organic layer is washed with brine (3x100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica, 33% EtOAc/heptane) affords the intermediate product 2-((trimethylsilyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one (3.58 g, 85%).

[00224] To a dark-brown solution of 2-((trimethylsilyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one (3.58 g, 15.47 mmol) in MeOH (40 mL) is added K_2CO_3 (4.28 g, 30.9 mmol). The mixture is stirred at room temperature for 1 h after which water (100 mL) is added. The mixture is extracted with EtOAc (2x100 mL). The combined organic layers are washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to yield the title compound (2.26 g, 92%).

General Procedure 2 – Sonogashira coupling of 2-ethynyl-6,7-dihydroindolizin-8(5H)-one with aryl bromides

[00225] A solution of 2-ethynyl-6,7-dihydroindolizin-8(5H)-one, an appropriate aryl bromide (1.1 eq.) and TEA (4 eq.) in dry DMF (2.5 mL) is flushed with argon for 10 min. $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (0.05 eq.) and copper(I)iodide (0.01 eq.) are added, and the reaction

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mixture is heated at 90 °C for 30 min under microwave conditions. After cooling down to room temperature the mixture is diluted with EtOAc (50 mL), washed with brine (3x50 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Purification by preparative TLC (silica, 50% EtOAc/heptane) and co-evaporation with Et₂O (2x2 mL) provides the final compound.

Preparation 10

2-Iodo-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one

[00226] A mixture of 5-aminovaleric acid (5.00 g, 42.74 mmol, 1.00 eq.), AcONa×3H₂O (5.81 g, 42.74 mmol, 1.00 eq.), water (50 mL), DCE (50 mL), acetic acid (22 mL), and 2,5-dimethoxytetrahydrofuran (5.923 g, 44.87 mmol, 1.05 eq.) is stirred at 110 °C for 20 h, cooled down to room temperature, washed with water (3x50 mL), dried over Na₂SO₄ and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/EtOH) to give 5-(1H-pyrrol-1-yl)pentanoic acid (5.156 g, 72%) as a gray solid.

[00227] P₂O₅ (2.10 g) is added to methanesulfonic acid (21.21 g, 15 mL), and the resulting mixture is stirred in a flask equipped with CaCl₂ tube at room temperature for 4 h to dissolve P₂O₅. Then 5-(1H-pyrrol-1-yl)pentanoic acid (1.70 g, 10.2 mmol) is added to the obtained solution. The reaction mixture is stirred at room temperature for 6 h and poured onto ice. The formed solid is filtered. The filtrate is neutralized with an aqueous K₂CO₃ solution (25%) and extracted with DCM (3x50 mL). The combined organic phases are dried over Na₂SO₄ and concentrated at reduced pressure. The obtained residue is dried at reduced pressure to yield 7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one (0.71 g, 47%) as a light brown oil.

[00228] N-Iodosuccinimide (560 mg, 2.48 mmol, 1.0 eq.) is added to a solution of 7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one (370 mg, 2.48 mmol, 1.0 eq.) in acetonitrile (15 mL). The mixture is stirred at room temperature for 5 h, concentrated at reduced pressure, diluted with DCM (30 mL), washed with an aqueous Na₂S₂O₃ solution (5%, 20 mL) and water (2x15 mL), dried over Na₂SO₄, and concentrated at reduced pressure.

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The obtained residue is purified by column chromatography (silica gel, DCM/EtOH) to provide the title compound (100 mg, 17%) as a brown solid.

Preparation 11

2-Iodo-8,8-dimethyl-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one

[00229] *t*-BuOK (1.172 g, 10.47 mmol, 4.0 eq.) is added to a solution of 7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one (390 mg, 2.62 mmol, 1.0 eq.) (see **Preparation 10**) in anhydrous THF (15 mL) at 0 °C. The mixture is stirred at 0 °C for 15 min. Then methyl iodide (3.55 mL, 10.47 mmol, 4.0 eq.) is added. The reaction mixture is stirred at room temperature for 6 h, filtered through a pad of Celite and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, hexane/ethyl acetate) followed by preparative TLC (silica gel, hexane/EtOAc, 4:1) to give 8,8-dimethyl-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one (110 mg, 24%) as a brown oil.

[00230] Iodination of 8,8-dimethyl-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one is accomplished according to the procedure described in **Preparation 10** using *N*-iodosuccinimide (yield: 29%).

Preparation 12

Methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate

[00231] Finely ground KOH (1.64 g, 29 mmol, 7 eq.) is added to a solution of methyl 4-iodo-1H-pyrrole-2-carboxylate (prepared according to WO2005/113541), (1.05 g, 4.2 mmol, 1 eq.) in 2 mL of anhydrous DMSO, and the resulting mixture is stirred at room temperature for 3 h. Dibromoethane (11.78 g, 62.7 mmol, 15 eq.) is added in a single portion, and the mixture is stirred for additional 3 h, then diluted with water and extracted with EtOAc. The organic phase is dried over anhydrous Na₂SO₄, and the solvent is evaporated to give sufficiently pure (ca. 94%) title compound (1.46 g, 88%) as a slightly yellow oil.

General Procedure 3 – Synthesis of *N*-substituted 7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate

[00232] 4-8 fold excess of an appropriate amine (or ammonia solution) is added to a solution of methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), (52 mg, 0.15 mmol) in 2 mL of EtOH. The reaction mixture is heated to 80 °C in a closed microwave vial for 1 to 12 h (TLC or LC-MS monitoring). The solvent is evaporated, and the residue is purified by flash column chromatography or preparative HPLC to give the target compound in good to moderate yield.

Example 1

2-(Phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00233] According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.12 (t, 2H), 7.07 (d, 1H), 7.12 (d, 1H), 7.30-7.34 (m, 3H), 7.46-7.49 (m, 2H).

LC/MS (M+H)⁺ = 236

Example 2

2-((4-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00234] According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-4-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.12 (t, 2H), 7.02 (t, 2H), 7.06 (d, 1H), 7.11 (d, 1H), 7.45 (dd, 2H).

LC/MS (M+H)⁺ = 254

Example 3

2-((3-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

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[00235]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.27 (m, 2H), 2.62 (t, 2H), 4.13 (t, 2H), 6.97-7.04 (m, 1H), 7.09 (d, 1H), 7.12 (d, 1H), 7.14-7.31 (m, 3H).

LC/MS (M+H)⁺ = 254

Example 4

2-((2-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00236]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-2-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.31 (m, 2H), 2.62 (t, 2H), 4.13 (t, 2H), 7.03-7.11 (m, 2H), 7.12 (d, 1H), 7.15 (d, 1H), 7.23-7.33 (m, 1H), 7.44-7.52 (m, 1H).

LC/MS (M+H)⁺ = 254

Example 5

2-((2,6-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00237]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 2-ethynyl-1,3-difluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.60 (t, 2H), 4.13 (t, 2H), 6.96-7.04 (m, 2H), 7.12 (d, 1H), 7.14 (d, 1H), 7.15-7.20 (m, 1H).

LC/MS (M+H)⁺ = 272

Example 6

2-((2,3-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00238]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-2,3-difluorobenzene to provide the title compound as a colorless solid.

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^1H NMR (CDCl_3), δ_{H} : 2.30 (m, 1H), 2.62 (t, 2H), 4.13 (t, 2H), 6.97-7.15 (m, 3H), 7.12 (d, 1H), 7.15 (d, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 272

Example 7

2-((2,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00239]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 2-ethynyl-1,4-difluorobenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 2.30 (m, 2H), 2.62 (t, 2H), 4.13 (t, 2H), 6.87-6.95 (m, 2H), 7.14 (d, 1H), 7.17 (d, 1H), 7.24 (m, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 272

Example 8

2-(*m*-Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one

[00240]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 2.30 (m, 2H), 2.34 (s, 3H), 2.62 (t, 2H), 4.12 (t, 2H), 7.06 (d, 1H), 7.12 (d, 1H), 7.17 (d, 1H), 7.21-7.32 (m, 3H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 250

Example 9

3-((8-Oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile

[00241]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 3-ethynylbenzonitrile to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 2.29 (m, 2H), 2.62 (t, 2H), 4.14 (t, 2H), 7.10 (d, 1H), 7.12 (d, 1H), 7.45 (t, 1H), 7.54-7.59 (m, 1H), 7.65-7.74 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 261

Example 10**2-((6-Aminopyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00242]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 6-ethynylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.28 (m, 2H), 2.60 (t, 2H), 4.11 (t, 2H), 6.45 (d, 1H), 6.82 (d, 1H), 7.13 (s, 2H), 7.41 (t, 1H).

LC/MS (M+H)⁺ = 252

Example 11**2-(Thiophen-3-ylethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00243]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 3-ethynylthiophene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.12 (t, 2H), 7.05 (d, 1H), 7.11 (d, 1H), 7.16 (dd, 1H), 7.28 (dd, 1H), 7.46 (dd, 2H).

LC/MS (M+H)⁺ = 242

Example 12**2-(Thiophen-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00244]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 2-ethynylthiophene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.12 (t, 2H), 6.98 (dd, 1H), 7.06 (d, 1H), 7.11 (d, 1H), 7.21-7.27 (m, 1H).

LC/MS (M+H)⁺ = 242

Example 13**2-(((3-(Fluoromethyl)phenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00245]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-3-(fluoromethyl)benzene to provide the title compound as a colorless solid.

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¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.13 (t, 2H), 5.36 (d, 2H), 7.07 (d, 1H), 7.12 (d, 1H), 7.32-7.49 (m, 4H).

LC/MS (M+H)⁺ = 268

Example 14

2-((2,3,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00246]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 2-ethynyl-1,3,4-trifluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.31 (m, 2H), 2.63 (t, 2H), 4.14 (t, 2H), 6.85 (m, 1H), 7.06 (m, 1H), 7.15 (d, 1H), 7.18 (d, 1H).

LC/MS (M+H)⁺ = 290

Example 15

2-((2,4,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00247]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 2-ethynyl-1,3,5-trifluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.63 (t, 2H), 4.13 (t, 2H), 6.70 (t, 2H), 7.13 (d, 1H), 7.16 (d, 1H).

LC/MS (M+H)⁺ = 290

Example 16

2-((2,3,4,5-Tetrafluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00248]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2,3,4,5-tetrafluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.32 (m, 2H), 2.63 (t, 2H), 4.14 (t, 2H), 7.02-7.15 (m, 3H).

LC/MS (M+H)⁺ = 308

Example 17**7-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00249]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.30 (d, 3H), 2.06 (m, 1H), 2.29 (m, 1H), 2.58 (m, 1H), 4.15 (AB m, 2H), 7.04 (d, 1H), 7.11 (d, 1H), 7.29-7.33 (m, 3H), 7.46-7.50 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 250

Example 18**7-Methyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00250]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.29 (d, 3H), 2.08 (m, 1H), 2.29 (m, 1H), 2.36 (s, 3H), 2.59 (m, 1H), 4.14 (AB m, 2H), 7.03 (d, 1H), 7.10 (d, 1H), 7.13-7.31 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 264

Example 19**2-((4-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one**

[00251]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-4-fluorobenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.29 (d, 3H), 2.09 (m, 1H), 2.29 (m, 1H), 2.59 (m, 1H), 4.15 (AB m, 2H), 6.97-7.10 (m, 4H), 7.45 (dd, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 20**2-((3-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one**

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[00252]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.30 (d, 3H), 2.10 (m, 1H), 2.29 (m, 1H), 2.60 (m, 1H), 4.15 (AB m, 2H), 6.99 (m, 1H), 7.04 (d, 1H), 7.10 (d, 1H), 7.14-7.30 (m, 3H).

LC/MS (M+H)⁺ = 268

Example 21

7,7-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00253]According to General Procedure 1, 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.25 (s, 6H), 2.11 (t, 2H), 4.13 (t, 2H), 7.02 (d, 1H), 7.10 (d, 1H), 7.29-7.33 (m, 3H), 7.45-7.48 (m, 2H).

LC/MS (M+H)⁺ = 264

Example 22

7,7-Dimethyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00254]According to General Procedure 1, 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.25 (s, 6H), 2.11 (t, 2H), 2.33 (s, 3H), 4.13 (t, 2H), 7.01 (d, 1H), 7.10 (d, 1H), 7.12-7.31 (m, 4H).

LC/MS (M+H)⁺ = 278

Example 23

2-((3-Fluorophenyl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one

[00255]According to General Procedure 1, 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as a colorless solid.

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^1H NMR (CDCl_3), δ_{H} : 1.25 (s, 6H), 2.12 (t, 2H), 4.14 (t, 2H), 6.97-7.04 (m, 1H), 7.02 (d, 1H), 7.10 (d, 1H), 7.13-7.30 (m, 3H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 282

Example 24

2-((6-Aminopyridin-2-yl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one

[00256]According to General Procedure 1, 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one is reacted with 6-ethynylpyridin-2-amine to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.25 (s, 6H), 2.12 (t, 2H), 4.14 (t, 2H), 6.46 (d, 1H), 6.83 (d, 1H), 7.10 (d, 1H), 7.13 (d, 1H), 7.43 (t, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 280

Example 25

7,7-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00257]According to General Procedure 1, 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one is reacted with 6-ethynyl-N-methylpyridin-2-amine to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.24 (s, 3H), 2.11 (t, 2H), 2.90 (s, 3H), 4.14 (t, 2H), 6.38 (d, 1H), 6.77 (d, 1H), 7.13 (s, 2H), 7.48 (t, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 294

Example 26

6-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one

[00258]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.16 (d, 3H), 2.30 (dd, 1H), 2.54 (m, 1H), 2.68 (dd, 1H), 3.73 (dd, 1H), 4.15 (dd, 1H), 7.06 (d, 1H), 7.11 (d, 1H), 7.30-7.33 (m, 3H), 7.46-7.49 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 250

Example 27**2-((3-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one**

[00259]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.16 (d, 3H), 2.30 (dd, 1H), 2.54 (m, 1H), 2.68 (dd, 1H), 3.73 (dd, 1H), 4.15 (dd, 1H), 7.00 (m, 1H), 7.05 (d, 1H), 7.10 (d, 1H), 7.13-7.30 (m, 3H).

LC/MS (M+H)⁺ = 268

Example 28**2-((4-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one**

[00260]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-4-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.16 (d, 3H), 2.30 (dd, 1H), 2.53 (m, 1H), 2.67 (dd, 1H), 3.73 (dd, 1H), 4.14 (dd, 1H), 6.97-7.09 (m, 4H), 7.45 (dd, 2H).

LC/MS (M+H)⁺ = 268

Example 29**2-((2-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one**

[00261]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.16 (d, 3H), 2.30 (dd, 1H), 2.53 (m, 1H), 2.67 (dd, 1H), 3.73 (dd, 1H), 4.14 (dd, 1H), 7.09-7.13 (m, 4H), 7.22-7.30 (m, 1H), 7.43-7.51 (m, 1H).

LC/MS (M+H)⁺ = 268

Example 30**3-((6-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile**

[00262]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 3-ethynylbenzonitrile to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.17 (d, 3H), 2.27 (dd, 1H), 2.55 (m, 1H), 2.69 (dd, 1H), 3.75 (dd, 1H), 4.17 (dd, 1H), 7.08 (d, 1H), 7.11 (d, 1H), 7.43 (t, 1H), 7.57 (d, 1H), 7.68 (d, 1H), 7.75 (s, 1H).

LC/MS (M+H)⁺ = 275

Example 31

6-Methyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00263]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.16 (d, 3H), 2.30 (dd, 1H), 2.34 (s, 3H), 2.53 (m, 1H), 2.68 (dd, 1H), 3.72 (dd, 1H), 4.14 (dd, 1H), 7.04 (d, 1H), 7.10 (d, 1H), 7.13-7.38 (m, 4H).

LC/MS (M+H)⁺ = 264

Example 32

2-((6-Aminopyridin-2-yl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5*H*)-one

[00264]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 6-ethynylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.16 (d, 3H), 2.29 (dd, 1H), 2.53 (m, 1H), 2.67 (dd, 1H), 3.73 (dd, 1H), 4.15 (dd, 1H), 6.46 (d, 1H), 6.82 (d, 1H), 7.14 (s, 2H), 7.43 (dd, 4H).

LC/MS (M+H)⁺ = 266

Example 33

6,6-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

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[00265] According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.12 (s, 6H), 2.45 (s, 2H), 3.85 (s, 2H), 7.05 (d, 1H), 7.13 (d, 1H), 7.30-7.33 (m, 3H), 7.46-7.51 (m, 2H).

LC/MS (M+H)⁺ = 264

Example 34

6,6-Dimethyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00266] According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.12 (s, 6H), 2.34 (s, 3H), 2.45 (s, 2H), 3.85 (s, 2H), 7.05 (d, 1H), 7.13 (d, 1H), 7.21-7.31 (m, 4H).

LC/MS (M+H)⁺ = 278

Example 35

2-((3-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one

[00267] According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.12 (s, 6H), 2.45 (s, 2H), 3.86 (s, 2H), 7.05 (d, 1H), 7.12 (d, 1H), 7.14-7.31 (m, 4H).

LC/MS (M+H)⁺ = 282

Example 36

2-((6-Aminopyridin-2-yl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one

[00268] According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 6-ethynylpyridin-2-amine to provide the title compound as a colorless solid.

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^1H NMR (CDCl_3), δ_{H} : 1.11 (s, 6H), 2.44 (s, 2H), 3.85 (s, 2H), 6.44 (d, 1H), 6.87 (d, 1H), 7.08 (d, 1H), 7.15 (d, 1H), 7.40 (t, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 280

Example 37

6,6-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00269]According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one is reacted with 6-ethynyl-*N*-methylpyridin-2-amine to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.10 (s, 6H), 2.43 (s, 2H), 2.91 (s, 3H), 3.84 (s, 2H), 6.37 (d, 1H), 6.78 (d, 1H), 7.14 (s, 2H), 7.46 (t, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 294

Example 38

2-((4-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one

[00270]According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-4-fluorobenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.11 (s, 6H), 2.44 (s, 2H), 3.84 (s, 2H), 7.02 (t, 2H), 7.06 (d, 1H), 7.11 (d, 1H), 7.45 (dd, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 282

Example 39

2-((2-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one

[00271]According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2-fluorobenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.10 (s, 6H), 2.43 (s, 2H), 3.84 (s, 2H), 7.02-7.14 (m, 2H), 7.06 (d, 1H), 7.11 (d, 1H), 7.22-7.29 (m, 1H), 7.42-7.51 (m, 1H).

LC/MS (M+H)⁺ = 282

Example 40

2-((2,3,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00272]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2,3,5-trifluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.31 (m, 2H), 2.66 (t, 2H), 4.14 (t, 2H), 6.85-7.01 (m, 2H), 7.14 (t, 2H).

LC/MS (M+H)⁺ = 290

Example 41

2-((3,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00273]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 5-ethynyl-1,2,3-trifluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.31 (m, 2H), 2.63 (t, 2H), 4.13 (t, 2H), 7.05-7.11 (m, 3H), 7.25 (d, 1H).

LC/MS (M+H)⁺ = 290

Example 42

2-((2,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00274]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2,4,5-trifluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.13 (t, 2H), 6.94 (m, 1H), 7.10 (d, 1H), 7.11 (d, 1H), 7.27 (m, 1H).

LC/MS (M+H)⁺ = 290

Example 43

2-((2,3,4-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00275] According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2,3,4-trifluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.31 (m, 2H), 2.63 (t, 2H), 4.14 (t, 2H), 6.95 (m, 1H), 7.12-7.21 (m, 3H).

LC/MS (M+H)⁺ = 290

Example 44**2-((3,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00276] According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 4-ethynyl-1,2-difluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.65 (t, 2H), 4.13 (t, 2H), 7.07-7.25 (m, 5H).

LC/MS (M+H)⁺ = 272

Example 45**2-((2,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one**

[00277] According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5H)-one is reacted with 1-ethynyl-2,4-difluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.13 (t, 2H), 6.85 (m, 2H), 7.10 (d, 1H), 7.13 (d, 1H), 7.44 (m, 1H).

LC/MS (M+H)⁺ = 272

Example 46**2-((3,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one**

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[00278]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3,5-difluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.31 (m, 2H), 2.65 (t, 2H), 4.13 (t, 2H), 6.76 (m, 1H), 6.98 (m, 2H), 7.09 (d, 1H), 7.11 (d, 1H).

LC/MS (M+H)⁺ = 272

Example 47

2-(*p*-Tolylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00279]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-4-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H : 2.29 (m, 2H), 2.35 (s, 3H), 2.62 (t, 2H), 4.12 (t, 2H), 7.06 (d, 1H), 7.11 (d, 1H), 7.13 (d, 2H), 7.38 (d, 2H).

LC/MS (M+H)⁺ = 250

Example 48

2-(*o*-Tolylethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00280]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-2-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H : 2.30 (m, 2H), 2.47 (s, 3H), 2.62 (t, 2H), 4.13 (t, 2H), 7.08 (d, 1H), 7.13 (d, 1H), 7.14-7.22 (m, 3H), 7.44 (d, 1H).

LC/MS (M+H)⁺ = 250

Example 49

2-((3-(Fluoromethyl)phenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5*H*)-one

[00281]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynyl-3-(fluoromethyl)benzene to provide the title compound as a colorless solid.

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^1H NMR (CDCl_3), δ_{H} : 1.17 (d, 3H), 2.31 (dd, 1H), 2.54 (m, 1H), 2.69 (dd, 1H), 3.74 (dd, 1H), 4.15 (dd, 1H), 5.36 (d, 2H), 7.06 (d, 1H), 7.11 (d, 1H), 7.32-7.49 (m, 4H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 282

Example 50**6-(Phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one**

[00282]According to General Procedure 1, 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 3.10 (t, 2H), 4.34 (t, 2H), 6.87 (s, 1H), 7.30-7.36 (m, 4H), 7.48-7.52 (m, 2H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 222

Example 51**6-((3-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one**

[00283]According to General Procedure 1, 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 3.11 (t, 2H), 4.34 (t, 2H), 6.86 (s, 1H), 6.98-7.07 (m, 1H), 7.15-7.34 (m, 4H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 240

Example 52**3-((6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile**

[00284]According to General Procedure 1, 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynylbenzonitrile to provide the title compound as a colorless solid.

^1H NMR (CDCl_3), δ_{H} : 1.12 (s, 6H), 2.45 (s, 2H), 3.87 (s, 2H), 7.07 (d, 1H), 7.12 (d, 1H), 7.44 (t, 1H), 7.57 (m, 1H), 7.67 (m, 1H), 7.74 (t, 1H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 289

Example 53**3-((7-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile**

[00285]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 1-ethynylbenzonitrile to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.29 (d, 3H), 2.09 (m, 1H), 2.29 (m, 1H), 2.60 (m, 1H), 4.17 (m, 2H), 7.07 (d, 1H), 7.11 (d, 1H), 7.43 (t, 1H), 7.56 (m, 1H), 7.67 (m, 1H), 7.74 (s, 1H).

LC/MS (M+H)⁺ = 275

Example 54**2-((6-Aminopyridin-2-yl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5*H*)-one**

[00286]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 6-ethynylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.28 (d, 3H), 2.09 (m, 1H), 2.29 (m, 1H), 2.59 (m, 1H), 4.17 (m, 2H), 6.47 (d, 1H), 6.82 (d, 1H), 7.13 (s, 2H), 7.43 (t, 1H).

LC/MS (M+H)⁺ = 266

Example 55**7-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one**

[00287]According to General Procedure 1, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 6-ethynylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.28 (d, 3H), 2.10 (m, 1H), 2.28 (m, 1H), 2.58 (m, 1H), 2.91 (s, 3H), 4.14 (m, 2H), 6.33 (d, 1H), 6.80 (d, 1H), 7.08 (d, 1H), 7.13 (d, 1H), 7.41 (t, 1H).

LC/MS (M+H)⁺ = 280

Example 56**2-((6-(Methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one**

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[00288]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 6-ethynyl-*N*-methylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.29 (m, 2H), 2.60 (t, 2H), 2.91 (s, 3H), 4.11 (t, 2H), 6.34 (d, 1H), 6.80 (d, 1H), 7.12 (d, 1H), 7.15 (d, 1H), 7.43 (t, 1H).

LC/MS (M+H)⁺ = 266

Example 57

6-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00289]According to General Procedure 1, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one is reacted with 6-ethynyl-*N*-methylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.15 (d, 3H), 2.29 (dd, 1H), 2.52 (m, 1H), 2.66 (dd, 1H), 2.91 (s, 3H), 3.72 (dd, 1H), 4.14 (dd, 1H), 6.34 (d, 1H), 6.80 (d, 1H), 7.10 (d, 1H), 7.13 (d, 1H), 7.41 (t, 1H).

LC/MS (M+H)⁺ = 280

Example 58

6-((2-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one

[00290]According to General Procedure 1, 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with 1-ethynyl-2-fluorobenzene to provide the title compound as a colorless solid .

¹H NMR (CDCl₃), δ_H: 3.10 (t, 2H), 4.33 (t, 2H), 6.88 (s, 1H), 7.04-7.14 (m, 2H), 7.21-7.31 (m, 2H), 7.44-7.52 (m, 1H).

LC/MS (M+H)⁺ = 240

Example 59

6-((4-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one

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[00291]According to General Procedure 1, 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with 1-ethynyl-4-fluorobenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.92 (d, 3H), 3.09 (t, 2H), 4.33 (t, 2H), 4.66 (br.s., 1H), 6.35 (d, 1H), 6.83 (d, 1H), 6.90 (s, 1H), 7.29-7.38 (m, 1H), 7.41-7.46 (dd, 1H).

LC/MS (M+H)⁺ = 240

Example 60

6-((6-(Methylamino)pyridin-2-yl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one

[00292]According to General Procedure 1, 6-iodo-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with 6-ethynyl-*N*-methylpyridin-2-amine to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 3.10 (t, 2H), 4.33 (t, 2H), 6.85 (s, 1H), 6.98-7.07 (m, 2H), 7.20-7.24 (m, 1H), 7.43-7.51 (m, 2H).

LC/MS (M+H)⁺ = 252

Example 61

2-Methyl-6-(*m*-tolylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one

[00293]According to General Procedure 1, 6-iodo-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.37 (d, 3H), 2.33 (s, 3H), 3.14 (m, 1H), 3.85 (dd, 1H), 4.50 (dd, 1H), 6.85 (s, 1H), 7.11 (d, 1H), 7.19-7.31 (m, 4H).

LC/MS (M+H)⁺ = 250

Example 62

2-((2-Fluoro-3-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00294]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5*H*)-one (150 mg, 0.942 mmol) is reacted with 1-bromo-2-fluoro-3-methylbenzene (129 μL, 1.04 mmol) to provide the title compound (45 mg, 18%) as a light yellow powder.

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^1H NMR (CDCl_3), δ_{H} : 2.28-2.34 (m, 5H), 2.62 (t, 2H), 4.13 (t, 2H), 6.96-7.31 (m, 5H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 63

2-((2-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00295]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5H)-one (150 mg, 0.942 mmol) is reacted with 2-bromo-1-fluoro-4-methylbenzene (130 μL , 1.04 mmol) to provide the title compound (87 mg, 35%) as a light yellow powder.

^1H NMR (CDCl_3), δ_{H} : 2.26-2.33 (m, 5H), 2.61 (t, 2H), 4.12 (t, 2H), 6.83-7.55 (m, 5H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 64

2-((3-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00296]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5H)-one (150 mg, 0.942 mmol) is reacted with 1-bromo-3-fluoro-2-methylbenzene (196 mg, 1.04 mmol) to provide the title compound (95 mg, 38%) as a light yellow powder.

^1H NMR (CDCl_3), δ_{H} : 2.28-2.39 (m, 5H), 2.63 (t, 2H), 4.13 (t, 2H), 6.95-7.47 (m, 5H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 65

2-((4-Fluoro-3-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00297]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5H)-one (150 mg, 0.942 mmol) is reacted with 4-bromo-1-fluoro-2-methylbenzene (131 μL , 1.04 mmol) to provide the title compound (32 mg, 13%) as a light yellow powder.

^1H NMR (CDCl_3), δ_{H} : 2.26-2.34 (m, 5H), 2.62 (t, 2H), 4.12 (t, 2H), 6.93-7.33 (m, 5H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 66

2,2-Dimethyl-6-(phenylethynyl)-2,3-dihydro-1H-pyrrolizin-1-one

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[00298]According to General Procedure 1, 6-iodo-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with ethynylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.34 (s, 6H), 4.09 (s, 2H), 6.87 (s, 1H), 7.20 (s, 1H), 7.30-7.38 (m, 3H), 7.47-7.52 (m, 2H).

LC/MS (M+H)⁺ = 250

Example 67

2,2-Dimethyl-6-(*m*-tolylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one

[00299]According to General Procedure 1, 6-iodo-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 1.33 (s, 6H), 2.34 (s, 3H), 4.08 (s, 2H), 6.87 (s, 1H), 7.10-7.32 (m, 5H).

LC/MS (M+H)⁺ = 264

Example 68

2-((3-Fluorophenyl)ethynyl)-5,6,7,8-tetrahydroindolizin-8-ol

[00300]2-((3-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one (**Example 3**) is reacted with DIBALH (1.2 eq.) in THF at -78 °C for 1.5 h. The reaction is quenched with EtOAc, and the mixture is then partitioned between EtOAc and water, the organic phase is separated, dried over anhydrous Na₂SO₄ and evaporated to dryness. Purification of the residue by preparative HPLC provides the title compound as an oil, decomposing over time.

¹H NMR (CDCl₃), δ_H: 1.93-1.95 (m, 1H), 2.28 (m, 1H), 3.83-3.88 (m, 1H), 3.90-3.99 (m, 1H), 4.86 (t, 1H), 6.31 (s, 1H), 6.84-7.01 (m, 1H), 7.12-7.28 (m, 3H)

LC/MS (M+H)⁺ = 256

Example 69

2-((2-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

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[00301]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5*H*)-one (150 mg, 0.942 mmol) is reacted with 1-bromo-2-fluoro-4-methylbenzene (132 μ L, 1.04 mmol) to provide the title compound (49 mg, 19%) as a beige solid.

^1H NMR (CDCl_3), δ_{H} : 2.27-2.35 (m, 5H), 2.62 (t, 2H), 4.12 (t, 2H), 6.88-7.37 (m, 5H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 70

2-((4-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00302]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5*H*)-one (150 mg, 0.942 mmol) is reacted with 1-bromo-4-fluoro-2-methylbenzene (131 μ L, 1.04 mmol) to provide the title compound (60 mg, 24%) as an off-white solid.

^1H NMR (CDCl_3), δ_{H} : 2.27-2.34 (m, 2H), 2.46 (s, 3H), 2.63 (t, 2H), 4.13 (t, 2H), 6.83-7.42 (m, 5H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 71

2-((3-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00303]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5*H*)-one (150 mg, 0.942 mmol) is reacted with 1-bromo-3-fluoro-4-methylbenzene (131 μ L, 1.04 mmol) to provide the title compound (54 mg, 21%) as an off-white solid.

^1H NMR (CDCl_3), δ_{H} : 2.27-2.33 (m, 5H), 2.62 (t, 2H), 4.13 (t, 2H), 7.07-7.17 (m, 5H).
LC/MS ($\text{M}+\text{H}$) $^+$ = 268

Example 72

2-((3-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00304]According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5*H*)-one (150 mg, 0.942 mmol) is reacted with 1-bromo-3-fluoro-5-methylbenzene (196 mg, 1.04 mmol) to provide the title compound (140 mg, 56%) as an off-white solid.

^1H NMR (CDCl_3), δ_{H} : 2.27-2.34 (m, 5H), 2.62 (t, 2H), 4.13 (t, 2H), 6.83 (t, 1H), 6.78 (d, 1H), 7.07-7.11 (m, 3H).

LC/MS (M+H)⁺ = 268

Example 73

2-((5-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00305] According to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5H)-one (150 mg, 0.942 mmol) is reacted with 2-bromo-4-fluoro-1-methylbenzene (131 μ L, 1.04 mmol) to provide the title compound (95 mg, 38%) as a light yellow solid.

¹H NMR (CDCl₃), δ _H: 2.25-2.30 (m, 2H), 2.42 (s, 3H), 2.63 (t, 2H), 4.13 (t, 2H), 6.89 (m, 1H), 6.99 (s, 1H), 7.08-7.16 (m, 3H).

LC/MS (M+H)⁺ = 268

Example 74

2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one

[00306] A mixture of 2-iodoimidazo[1,2-a]pyridine (2.00 g, 8.20 mmol), ethynyltrimethylsilane (1.21 g, 12.30 mmol), PdCl₂[PPh₃]₂ (190 mg, 0.27 mmol), CuI (150 mg, 0.80 mmol), and TEA (3.4 mL, 24.0 mmol) in benzene (15 mL) is stirred at 50 °C under argon atmosphere for 12 h, cooled down to room temperature and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, EtOAc/hexane) to give 2-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine (1.23 g, 70%) as light brown oil.

[00307] TBAF solution in THF (1M, 0.20 mL, 0.20 mmol) is added dropwise to a solution of 2-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine (636 mg, 2.90 mmol) in THF (10 mL) at 0 °C. The resulting mixture is stirred at 0 °C for 1 h, diluted with water and extracted with DCM (3x10 mL). The combined organic phases are dried over Na₂SO₄ and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, EtOAc/hexane) to give 2-ethynylimidazo[1,2-a]pyridine (230 mg, 55%) as brown oil.

[00308] A mixture of compound 2-iodo-6,7-dihydroindolizin-8(5H)-one (200 mg, 0.76 mmol), 2-ethynylimidazo[1,2-a]pyridine (119 mg, 0.84 mmol), PdCl₂[PPh₃]₂ (26 mg, 0.04

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mmol), *t*-Bu₃P (8 mg, 0.04 mmol), DBU (12 mg, 0.08 mmol), TEA (2 mL), and anhydrous acetonitrile (10 mL) is stirred at reflux for 6 h under argon atmosphere, cooled down to room temperature and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, EtOAc/hexane) to provide the title compound (48 mg, 23%) as a light yellow solid.

¹H NMR (CDCl₃), δ_H: 2.25-2.35 (m, 2H), 2.61 (t, 2H), 4.12 (t, 2H), 6.78 (dd, 1H), 7.09 (s, 1H), 7.13-7.21 (m, 2H), 7.54 (d, 1H), 7.71 (s, 1H), 8.05 (d, 1H).

LC/MS (M+H)⁺ = 276

Example 75

2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one

[00309]According to the procedure described in **Example 74**, 2-iodo-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (210 mg, 0.72 mmol) is reacted with 2-ethynylimidazo[1,2-*a*]pyridine (113 mg, 0.79 mmol) to provide the title compound (65 mg, 29%) as a light yellow solid.

¹H NMR (CDCl₃), δ_H: 1.26 (s, 6H), 2.13 (t, 2H), 4.14 (t, 2H), 6.78 (dd, 1H), 7.05 (s, 1H), 7.13 (s, 1H), 7.17 (dd, 1H), 7.55 (d, 1H), 7.71 (s, 1H), 8.05 (d, 1H).

LC/MS (M+H)⁺ = 304

Example 76

2-((2-Fluoro-6-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00310]In close analogy to General Procedure 2, 2-ethynyl-6,7-dihydroindolizin-8(5*H*)-one (150 mg, 0.942 mmol) is reacted with 2-bromo-1-fluoro-3-methylbenzene (196 mg, 1.04 mmol) under microwave conditions (90 °C, 30 min) to provide the title compound (42 mg, 17%) as a white powder.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.47 (s, 3H), 2.63 (t, 2H), 4.13 (t, 2H), 6.91 (t, 1H), 7.00 (d, 1H), 7.12-7.18 (m, 3H).

LC/MS (M+H)⁺ = 268

Example 77

2-((5-Chlorothiophen-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one

[00311]According to General Procedure 1, 2-iodo-6,7-dihydroindolizin-8(5*H*)-one is reacted with 2-chloro-5-ethynylthiophene to provide the title compound as a colorless solid.

¹H NMR (CDCl₃), δ_H: 2.30 (m, 2H), 2.62 (t, 2H), 4.12 (t, 2H), 6.79 (d, 1H), 6.78 (d, 1H), 6.98 (d, 1H), 7.06-7.09 (m, 2H).

LC/MS (M+H)⁺ = 276

Example 78

2-((Imidazo[1,2-*a*]pyridin-2-yl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5*H*)-one

[00312]According to the procedure described in **Example 74**, 2-iodo-6-methyl-6,7-dihydroindolizin-8(5*H*)-one (300 mg, 1.09 mmol) is reacted with 2-ethynylimidazo[1,2-*a*]pyridine (170 mg, 1.19 mmol) to provide the title compound (29 mg, 9%) as a brownish solid.

¹H NMR (CDCl₃), δ_H: 1.16 (d, 3H), 2.30 (dd, 1H), 2.48-2.61 (m, 1H), 2.67 (dd, 1H), 3.73 (dd, 1H), 4.14 (dd, 1H), 6.78 (dd, 1H), 7.07 (s, 1H), 7.14 (br s, 1H), 7.17 (dd, 1H), 7.54 (d, 1H), 7.71 (s, 1H), 8.05 (d, 1H).

LC/MS (M+H)⁺ = 290, 579

Example 79

2-((6-Aminopyridin-2-yl)ethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one

[00313]A mixture of 2-iodo-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (200 mg, 0.73 mmol) (see **Preparation 10**), TEA (2.5 mL), DMF (0.5 mL), PdCl₂[PPh₃]₂ (39 mg, 0.06 mmol) and 6-ethynylpyridin-2-amine (165 mg, 1.40 mmol) is stirred at 80 °C for 3 h under argon atmosphere, cooled down to room temperature, diluted with EtOAc (30 mL), washed with water (3x15 mL), dried over Na₂SO₄, and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/EtOH) and preparative TLC (silica gel, hexane/EtOAc, 1:1) to provide the title compound (51 mg, 26%) as a beige solid.

¹H NMR (DMSO-*d*₆), δ_H: 1.73-1.85 (m, 2H), 1.88-1.98 (m, 2H), 2.71 (dd, 2H), 4.32 (t, 2H), 5.95 (br s, 2H), 6.42 (d, 1H), 6.65 (d, 1H), 6.89 (d, 1H), 7.35 (dd, 1H), 7.45 (d, 1H).

LC/MS (M+H)⁺ = 266

Example 80

8-(Phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one

[00314] A mixture of 2-iodo-6,7-dihydroindolizin-8(5*H*)-one (2.40 g, 9.20 mmol), NH₂OH×HCl (1.98 g, 27.60 mmol), AcONa×3H₂O (3.754 g, 27.60 mmol), EtOH (33 mL), and water (11 mL) is stirred at reflux for 4 h. The formed white precipitate is collected by filtration, washed with water (20 mL) and dried at 50 °C to give 2-iodo-6,7-dihydroindolizin-8(5*H*)-one oxime (2.35 g, 93%) as white crystals.

[00315] *p*-Toluenesulfonyl chloride (1.81 g, 9.50 mmol) is added to a solution of 2-iodo-6,7-dihydroindolizin-8(5*H*)-one oxime (2.09 g, 7.60 mmol) in pyridine (25 mL) stirring at room temperature in one portion. The resulting mixture is stirred at room temperature for 48 h. Then pyridine is removed at reduced pressure. The obtained residue is dissolved in DCM (40 mL), washed with an aqueous NaOH solution (10%), an aqueous HCl solution (5%) and water, dried over MgSO₄ and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM) to afford 2-iodo-6,7-dihydroindolizin-8(5*H*)-one *O*-tosyl oxime (2.36 g, 72%) as an off-white solid.

[00316] A mixture of 2-iodo-6,7-dihydroindolizin-8(5*H*)-one *O*-tosyl oxime (2.36 g, 5.50 mmol), DIPEA (1.34 mL, 8.20 mmol) and aqueous EtOH (80%, 100 mL) is stirred at reflux for 4 h, allowed to stand overnight at room temperature and concentrated at reduced pressure. The residue is partitioned between water (10 mL) and DCM (25 mL). The organic phase is separated, and the aqueous one is additionally extracted with DCM (25 mL). The combined organic extracts are washed with an aqueous citric acid solution (10%), dried over MgSO₄, and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/MeOH, 15:1) to furnish 8-iodo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (980 mg, 65%) as beige crystalline solid.

[00317] A mixture of 8-iodo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (200 mg, 0.72 mmol), PdCl₂[PPh₃]₂ (48 mg, 0.07 mmol), CuI (20 mg, 0.11 mmol), TEA (0.40

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mL, 2.84 mmol), and THF (4 mL) is stirred for 15 min at room temperature under argon atmosphere. Then phenylacetylene (184 μ L, 1.68 mmol) is added. The reaction mixture is stirred at room temperature for 18 h, concentrated at reduced pressure, diluted with DCM (20 mL), washed with an aqueous citric acid solution (10%), dried over MgSO_4 , and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/MeOH, 30:1) and by preparative HPLC (C18, acetonitrile/water) to provide the title compound (84 mg, 47%) as a white powder.

^1H NMR (CDCl_3), δ_{H} : 2.10-2.21 (m, 2H), 3.34 (dd, 2H), 4.19 (t, 2H), 6.10 (s, 1H), 6.97 (s, 1H), 7.01 (d, 1H), 7.26-7.34 (m, 3H), 7.45-7.51 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 251

Example 81

2-((3-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00318] A mixture of 2-iodo-6,7-dihydroindolizin-8(5H)-one (200 mg, 0.766 mmol), 3-ethynylphenol (0.125 mL, 1.149 mmol), TEA (427 μ L, 3.06 mmol) and copper(I)iodide (7.30 mg, 0.038 mmol) in dry DMF (3 mL) is flushed with argon for 10 min. $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (16.13 mg, 0.023 mmol) is added, and the mixture is stirred at 60 $^\circ\text{C}$ for 1 h. The reaction mixture is cooled to room temperature, poured into saturated aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (2x20 mL). The combined organic layers are dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (silica, 50% EtOAc/heptane, isocratic), followed by recrystallization from *i*-PrOH (~ 4 mL) and air-drying provides the title compound (123 mg, 64%) as a beige powder.

^1H NMR ($\text{DMSO}-d_6$), δ_{H} : 2.14-2.20 (m, 2H), 2.53 (t, 2H), 4.15 (t, 2H), 6.76-6.91 (m, 4H), 7.18 (t, 1H), 7.50 (s, 1H), 9.63 (br s, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 252

Example 82

2-((4-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one

[00319] To a solution of 4-iodophenol (2.07 g, 9.42 mmol) in dry acetonitrile (100 mL) are added 2-ethynyl-6,7-dihydroindolizin-8(5H)-one (1.50 g, 9.42 mmol) and cesium carbonate (6.14 g, 18.85 mmol), and the mixture is flushed with N_2 for 10 min. The

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mixture is heated to reflux when $\text{Pd}(\text{PPh}_3)_4$ (544 mg, 0.471 mmol) is added, and the resulting mixture is stirred at reflux for 1 h. The mixture is filtered over kieselguhr, and the residue is extensively rinsed with acetonitrile (50 mL), DCM (50 mL) and EtOAc (50 mL). The filtrate is concentrated and partitioned between DCM (100 mL) and saturated aqueous NH_4Cl (100 mL). The organic layer is dried over Na_2SO_4 and concentrated. Purification by column chromatography (50% EtOAc/heptane to 100% EtOAc) and trituration from Et_2O (~ 10 mL) provides the title compound (530 mg, 22%) as a light yellow solid.

^1H NMR (DMSO-d_6), δ_{H} : 2.13-2.19 (m, 2H), 2.53 (t, 2H), 4.13 (t, 2H), 6.76 (d, 2H), 6.86 (d, 1H), 7.28 (d, 2H), 7.44 (d, 1H), 9.85 (br s, 1H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 252

[00320]Alternatively, the title compound can be prepared from the corresponding anisole derivative (synthesized from 2-iodo-6,7-dihydroindolizin-8(5*H*)-one and 4-methoxyphenylacetylene following General Procedure 1, yield: 84%) by means of a demethylation reaction using BBr_3 (yield: 21%).

Example 83

2-Methyl-8-(phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one

[00321]8-(Phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (**Example 80**, 52 mg, 0.21 mmol) is dissolved in dry THF (1.5 mL). To the formed solution sodium hydride (60% in oil, 14 mg, 0.35 mmol) is added, and the resulting mixture is stirred at room temperature for 15 min. Then methyl iodide (28 μL , 0.44 mmol) is added. The reaction mixture is stirred at 30 °C for 2 h, concentrated at reduced pressure, diluted with water (5 mL), and extracted with DCM (10 mL). The organic phase is separated, dried over MgSO_4 , and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, hexane, then DCM/MeOH, 10:1), washed with diethyl ether and dried to provide the title compound (46 mg, 84%) as grayish crystals.

^1H NMR (CDCl_3), δ_{H} : 2.10-2.22 (m, 2H), 3.12 (s, 3H), 3.37 (t, 2H), 4.09 (t, 2H), 6.90 (s, 2H), 7.26-7.37 (m, 3H), 7.47 (d, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 264, 306

Example 84**2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one**

[00322]According to the procedure described in **Example 74**, 2-iodo-7-methyl-6,7-dihydroindolizin-8(5H)-one (200 mg, 0.73 mmol) is reacted with 2-ethynylimidazo[1,2-a]pyridine (113 mg, 0.79 mmol) to provide the title compound (20 mg, 10%) as a yellowish solid.

¹H NMR (CDCl₃), δ_H: 1.30 (d, 3H), 2.01-2.14 (m, 1H), 2.22-2.36 (m, 1H), 2.53-2.64 (m, 1H), 4.05-4.23 (m, 2H), 6.78 (dd, 1H), 7.06 (s, 1H), 7.13 (s, 1H), 7.17 (dd, 1H), 7.54 (d, 1H), 7.71 (s, 1H), 8.04 (d, 1H).

LC/MS (M+H)⁺ = 290

Example 85**2-(Phenylethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one**

[00323]According to the procedure described in **Example 79**, 2-iodo-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one (370 mg, 1.35 mmol) (see **Preparation 10**) is reacted with ethynylbenzene (152 mg, 1.49 mmol) to provide the title compound (23 mg, 7%) as a sticky oil.

¹H NMR (CDCl₃), δ_H: 1.88-1.97 (m, 2H), 1.98-2.08 (m, 2H), 2.73-2.81 (m, 2H), 4.21 (t, 2H), 7.00 (br s, 1H), 7.13 (d, 1H), 7.26-7.35 (m, 3H), 7.44-7.50 (m, 2H).

LC/MS (M+H)⁺ = 250

Example 86**3-((1-Oxo-2-propyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile**

[00324]According to General Procedure 1, 7-iodo-2-propyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 3-ethynylbenzonitrile to provide the title compound as an oil.

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^1H NMR (CDCl_3), δ_{H} : 0.94 (t, 3H), 1.63 (m, 2H), 3.49 (t, 2H), 3.67 (t, 2H), 4.14 (t, 2H), 6.97 (s, 1H), 7.01 (s, 1H), 7.37-7.73 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 304

Example 87

2-Methyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00325]According to General Procedure 1, 7-iodo-2-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 3.10 (s, 3H), 3.66 (t, 2H), 4.14 (t, 2H), 6.93 (s, 1H), 7.02 (s, 1H), 7.29-7.32 (m, 3H), 7.45-7.50 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 251

Example 88

3-((2-Methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile

[00326]According to General Procedure 1, 7-iodo-2-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 3-ethynylbenzonitrile to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 3.11 (s, 3H), 3.68 (t, 2H), 4.17 (t, 2H), 6.96 (s, 1H), 7.02 (s, 1H), 7.42 (t, 1H), 7.55 (d, 1H), 7.65-7.73 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 276

Example 89

7-((3-Fluorophenyl)ethynyl)-2-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00327]According to General Procedure 1, 7-iodo-2-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-

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bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.11 (s, 3H), 3.67 (t, 2H), 4.15 (t, 2H), 6.94 (s, 1H), 7.00-7.04 (m, 2H), 7.13-7.28 (m, 3H).

LC/MS (M+H)⁺ = 269

Example 90

2-Methyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00328]According to General Procedure 1, 7-iodo-2-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.33 (s, 3H), 3.10 (s, 3H), 3.66 (t, 2H), 4.14 (t, 2H), 6.91 (s, 1H), 7.01 (s, 1H), 7.12-7.30 (m, 4H).

LC/MS (M+H)⁺ = 265

Example 91

2-Benzyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00329]According to General Procedure 1, 2-benzyl-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.57 (t, 2H), 4.07 (t, 2H), 4.75 (s, 2H), 6.94 (s, 1H), 6.99-7.04 (m, 2H), 7.09-7.32 (m, 8H).

LC/MS (M+H)⁺ = 345

Example 92

2-Benzyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00330]According to General Procedure 1, 2-benzyl-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-

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bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.55 (t, 2H), 4.05 (t, 2H), 4.74 (s, 2H), 6.92 (s, 1H), 7.09 (s, 1H), 7.29-7.32 (m, 8H), 7.46-7.51 (m, 2H).

LC/MS (M+H)⁺ = 327

Example 93

2-Benzyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00331]According to General Procedure 1, 2-benzyl-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.34 (s, 3H), 3.56 (t, 2H), 4.06 (t, 2H), 4.74 (s, 2H), 6.92 (s, 1H), 7.09 (s, 1H), 7.12-7.32 (m, 9H).

LC/MS (M+H)⁺ = 341

Example 94

3-((2-Benzyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl)ethynyl)benzonitrile

[00332]According to General Procedure 1, 2-benzyl-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 3-ethynylbenzonitrile to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.57 (t, 2H), 4.08 (t, 2H), 4.74 (s, 2H), 6.96(s, 1H), 7.08 (s, 1H), 7.32-7.73 (m, 9H).

LC/MS (M+H)⁺ = 352

Example 95

7-(Phenylethynyl)-2-propyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

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[00333]According to General Procedure 1, 7-iodo-2-propyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 0.95 (t, 3H), 1.63 (m, 2H), 3.49 (t, 2H), 3.65 (t, 2H), 4.11 (t, 2H), 6.93 (s, 1H), 7.02 (s, 1H), 7.28-7.34 (m, 3H), 7.46-7.49 (m, 2H).

LC/MS (M+H)⁺ = 279

Example 96

2-Propyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00334]According to General Procedure 1, 7-iodo-2-propyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 0.95 (t, 3H), 1.63 (m, 2H), 2.33 (s, 3H), 3.49 (t, 2H), 3.65 (t, 2H), 4.11 (t, 2H), 6.91 (s, 1H), 7.01 (s, 1H), 7.10 (d, 1H), 7.20 (t, 1H), 7.26-7.30 (m, 2H).

LC/MS (M+H)⁺ = 293

Example 97

8-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one

[00335]NaH (60% in oil, 84 mg, 2.1 mmol) is added to a solution of 8-iodo-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (505 mg, 1.83 mmol) in dry THF (10 mL). The mixture is stirred at room temperature for 15 min. The resulting suspension is treated with methyl iodide (148 μL, 2.38 mmol), and the formed reaction mixture is stirred at room temperature for 2 h, concentrated at reduced pressure, and diluted with water (20 mL) and DCM (20 mL). The organic phase is separated, dried over MgSO₄, and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, hexane, DCM/MeOH, 10:1), washed with diethyl ether (3 mL) and air-dried to furnish 8-iodo-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (458 mg, 86%) as off-white crystals.

[00336] A mixture of 8-iodo-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one (200 mg, 0.68 mmol), PdCl₂[PPh₃]₂ (24 mg, 0.04 mmol), *t*-Bu₃P (16 mg, 0.08 mmol), DBU (11 mg, 0.068 mL), and TEA (0.192 mL, 1.36 mmol) in acetonitrile (3 mL) is stirred under argon atmosphere at room temperature for 15 min. Then 6-ethynylpyridin-2-amine (140 mg, 1.19 mmol) is added. The mixture is stirred at 60 °C for 3 h, cooled down to room temperature, diluted with DCM (15 mL) and water, and filtered through a pad of Celite. The organic phase is separated, dried over MgSO₄ and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/MeOH, 25:1) and by preparative HPLC (C18, acetonitrile/water) to provide the title compound (32 mg, 17%) as off-white crystals. ¹H NMR (CDCl₃), δ_H: 2.11-2.20 (m, 2H), 3.11 (s, 3H), 3.36 (t, 2H), 4.08 (t, 2H), 4.46 (s, 2H), 6.41 (d, 1H), 6.85 (d, 1H), 6.93 (s, 1H), 6.94 (s, 1H), 7.37 (dd, 1H). LC/MS (M+H)⁺ = 281

Example 98

2-Ethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00337] According to General Procedure 1, 2-ethyl-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.20 (t, 3H), 3.53-3.69 (m, 4H), 4.13 (t, 2H), 6.94 (s, 1H), 7.02 (s, 1H), 7.30-7.32 (m, 3H), 7.46-7.50 (m, 2H).

LC/MS (M+H)⁺ = 279

Example 99

2-Butyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00338] According to General Procedure 1, 2-butyl-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

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^1H NMR (CDCl_3), δ_{H} : 0.94 (t, 3H), 1.36 (m, 2H), 1.58 (m, 2H), 3.52 (t, 2H), 3.66 (t, 2H), 4.11 (t, 2H), 6.92 (s, 1H), 7.02 (s, 1H), 7.28-7.34 (m, 3H), 7.45-7.50 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 293

Example 100

2-Butyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00339]According to General Procedure 1, 2-butyl-7-iodo-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 0.94 (t, 3H), 1.38 (m, 2H), 1.56 (m, 2H), 3.52 (t, 2H), 3.65 (t, 2H), 4.12 (t, 2H), 6.93 (s, 1H), 6.94-7.01 (m, 2H), 7.16 (d, 1H), 7.23-7.29 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 311

Example 101

7-((3-Fluorophenyl)ethynyl)-2-isopropyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00340]According to General Procedure 1, 7-iodo-2-isopropyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 1.19 (d, 6H), 3.57 (t, 2H), 4.10 (t, 2H), 5.02 (m, 1H), 6.95 (s, 1H), 7.02 (s, 1H), 7.15-7.29 (m, 4H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 297

Example 102

2-Isopropyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00341]According to General Procedure 1, 7-iodo-2-isopropyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-

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bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.19 (d, 6H), 2.31 (s, 3H), 3.56 (t, 2H), 4.10 (t, 2H), 5.02 (m, 1H), 6.93 (s, 1H), 7.02 (s, 1H), 7.08-7.31 (m, 4H).

LC/MS (M+H)⁺ = 293

Example 103

8,8-Dimethyl-2-(phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one

[00342] A mixture of 2-iodo-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (200 mg, 0.66 mmol) (see **Preparation 11**), TEA (2.5 mL), DMF (0.5 mL), PdCl₂[PPh₃]₂ (37 mg, 0.05 mmol), and ethynylbenzene (84 mg, 0.83 mmol) is stirred at 80 °C for 3 h under argon atmosphere, cooled down to room temperature, diluted with EtOAc (30 mL), washed with water (3x15 mL), dried over Na₂SO₄, and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/EtOH), preparative TLC (silica gel, hexane/EtOAc) followed by preparative HPLC (C18, acetonitrile/water) to provide the title compound (28 mg, 15%) as a white solid.

¹H NMR (CDCl₃), δ_H: 1.21 (s, 6H), 1.84 (t, 2H), 2.09-2.17 (m, 2H), 4.06 (t, 2H), 6.92 (s, 1H), 6.94 (s, 1H), 7.27-7.33 (m, 3H), 7.44-7.48 (m, 2H).

LC/MS (M+H)⁺ = 278

Example 104

2-Phenyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00343] According to General Procedure 1, 7-iodo-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 4.11 (t, 2H), 4.27 (t, 2H), 7.01 (s, 1H), 7.14 (s, 1H), 7.29-7.49 (m, 10H).

LC/MS (M+H)⁺ = 312

Example 105

7-((3-Fluorophenyl)ethynyl)-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00344]According to General Procedure 1, 7-iodo-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 4.06 (t, 2H), 4.21 (t, 2H), 6.91-6.96 (m, 1H), 7.01 (s, 1H), 7.12 (s, 1H), 7.17-7.36 (m, 8H).

LC/MS (M+H)⁺ = 331

Example 106**2-Phenyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one**

[00345]According to General Procedure 1, 7-iodo-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.33 (s, 3H), 4.11 (t, 2H), 4.26 (t, 2H), 7.00 (s, 1H), 7.10 (d, 1H), 7.12 (s, 1H), 7.18-7.42 (m, 8H).

LC/MS (M+H)⁺ = 327

Example 107**7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one**

[00346]According to General Procedure 1, 7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.17 (t, 2H), 4.13 (t, 2H), 6.73 (br.s., 1H), 7.01 (s, 1H), 7.06 (s, 1H), 7.30-7.33 (m, 3H), 7.47-7.51 (m, 2H).

LC/MS (M+H)⁺ = 237

Example 108

7-((3-Fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00347]According to General Procedure 1, 7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.72 (t, 2H), 4.14 (t, 2H), 7.01-7.14 (m, 3H), 7.19-7.30 (m, 3H).

LC/MS (M+H)⁺ = 255

Example 109**2-((6-Aminopyridin-2-yl)ethynyl)-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one**

[00348]According to the procedure described in **Example 103**, 2-iodo-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one (200 mg, 0.66 mmol) (see **Preparation 11**) is reacted with 6-ethynylpyridin-2-amine (97 mg, 0.83 mmol) to provide the title compound (18 mg, 9%) as a beige solid.

¹H NMR (CDCl₃), δ_H: 1.20 (s, 6H), 1.83 (t, 2H), 2.08-2.17 (m, 2H), 4.05 (t, 2H), 4.60 (br s, 2H), 6.42 (d, 1H), 6.84 (d, 1H), 6.96 (s, 1H), 6.97 (s, 1H), 7.39 (dd, 1H).

LC/MS (M+H)⁺ = 294

Example 110**2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one**

[00349]A mixture of 2-iodo-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one (290 mg, 1.0 mmol), PdCl₂[PPh₃]₂ (35 mg, 0.05 mmol), and TEA (0.68 mL, 5.0 mmol) in dry acetonitrile (5 mL) is stirred under argon atmosphere at room temperature for 10 min. Then 2-ethynylimidazo[1,2-*a*]pyridine (142 mg, 1.0 mmol) is added in one portion. The mixture is stirred at 50 °C for 5 h, cooled down to room temperature and concentrated at reduced pressure. The obtained residue is purified by preparative HPLC chromatography (C18, acetonitrile/water/TFA) to provide the title compound (37 mg, 9%) as a white powder.

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^1H NMR (CDCl_3), δ_{H} : 1.16 (s, 6H), 2.45 (s, 2H), 3.88 (s, 2H), 6.61 (br s, 1H+H₂O), 7.11 (s, 1H), 7.16-7.24 (m, 2H), 7.64 (dd, 1H), 7.77 (s 1H), 8.12 (d, 1H), 8.26 (d, 1H).

LC/MS ($\text{M}+\text{H}$)⁺ = 304

Example 111

2,2-Dimethyl-1-(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)propan-1-one

[00350] Pivaloyl chloride (3.27 g, 3.34 mL, 27.2 mmol) is added dropwise at 0 °C to a solution of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (3.01 g, 24.7 mmol) (WO 2009/90055) and TEA (4.60 mL, 32.6 mmol) in DCM (40 mL). The resulting mixture is stirred at 0 °C for 15 min and washed with an aqueous citric acid solution (10%). The organic phase is dried over MgSO_4 and concentrated at reduced pressure. The obtained residue is purified by column chromatography (silica gel, DCM/acetone, 10:1) to give 1-(3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (3.10 g, 61%) as a yellowish crystalline intermediate product.

[00351] *N*-Iodosuccinimide (1.64 g, 7.30 mmol) is added to a solution of 1-(3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (1.50 g, 7.28 mmol) in DMF (15 mL) at room temperature. The mixture is stirred for 16 h, diluted with brine (100 mL) and extracted with EtOAc (2x50 mL). The combined organic extracts are washed with brine (4x50 mL), dried over MgSO_4 and concentrated at reduced pressure. The obtained residue is dried affording a mixture of 1-(7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-2,2-dimethylpropan-1-one and 1-(6-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (2.39 g) as orange oil (ratio 1:3 according to NMR). The mixture is used on the next stage without separation as a solution in acetonitrile (0.45M).

[00352] A solution of this mixture in acetonitrile (0.45M, 7.0 mL, 3.1 mmol) is mixed with $\text{PdCl}_2[\text{PPh}_3]_2$ (112 mg, 0.16 mmol), CuI (42 mg, 0.22 mmol), and TEA (1.33 mL, 9.5 mmol) in acetonitrile (7 mL). The formed mixture is stirred under argon atmosphere at room temperature for 15 min. Then ethynylbenzene (0.45 mL, 4.1 mmol) is added, and the reaction mixture is stirred at 40 °C for 2 h, allowed to stand at room temperature for

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48 h, concentrated at reduced pressure, diluted with DCM (40 mL), washed with an aqueous citric acid solution (10%, 10 mL), dried over MgSO_4 , and concentrated at reduced pressure. Separation and purification is performed by column chromatography (silica gel, hexane/EtOAc, 4:1) followed by preparative HPLC (C18, acetonitrile/water) to provide the title compound (64 mg, 7% for two steps) as a light beige powder (regioisomeric by-product: 110 mg, 11% for two steps, red crystals).

^1H NMR (CDCl_3), δ_{H} : 1.35 (s, 9H), 3.96-4.01 (m, 4H), 4.92 (s, 2H), 6.32 (d, $J=2.8$ Hz, 1H), 6.52 (d, $J=2.8$ Hz, 1H), 7.27-7.35 (m, 3H), 7.43-7.49 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 307

Example 112

3-Bromo-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one

[00353] To a cooled solution (0°C) of 2-iodo-6,7-dihydroindolizin-8(5H)-one (7.97 g, 30.5 mmol) in DMF (120 mL) is added portionwise *N*-bromosuccinimide (5.43 g, 30.5 mmol). After complete addition, the mixture is stirred at room temperature for 2 h. A mixture of crushed ice and saturated aqueous NaHCO_3 solution (100 mL) is added, and the mixture is extracted with EtOAc (3x100 mL). The combined organic layers are washed with brine (2x100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue is triturated with EtOAc (100 mL), and the solids are isolated by filtration to give 3-bromo-2-iodo-6,7-dihydroindolizin-8(5H)-one (3.71 g, 36%).

[00354] A mixture of 3-bromo-2-iodo-6,7-dihydroindolizin-8(5H)-one (501 mg, 1.474 mmol), ethynylbenzene (163 μL , 1.484 mmol), copper(I)iodide (27 mg, 0.142 mmol) and TEA (0.70 mL, 5.04 mmol) in dry DMF (13 mL) is flushed with argon for ~ 5 min. $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (55 mg, 0.078 mmol) is added, and the reaction mixture is heated at 100°C for 10 min under microwave conditions. The reaction mixture is evaporated to dryness. Purification by column chromatography (silica, isocratic 33% EtOAc/heptane) provides the title compound (444 mg, 96%). A sample (~ 110 mg) is taken, which is purified further by recrystallisation from *i*- Pr_2O (~ 15 mL). The resulting solids are isolated by filtration, washed with *i*- Pr_2O (~ 15 mL) and air-dried to provide the title compound (40 mg, 35%).

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^1H NMR (CDCl_3), δ_{H} : 2.30-2.36 (m, 2H), 2.62 (t, 2H), 4.09 (t, 2H), 7.16 (s, 1H), 7.32-7.37 (m, 3H), 7.51-7.54 (m, 2H).

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

Example 113

3-Cyclopropyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one

[00355] A mixture of 1,2-dimethoxyethane (4 mL) and water (1 mL) is flushed with argon and added to a mixture of 3-bromo-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one (**Example 112**) (200 mg, 0.637 mmol), cyclopropylboronic acid (82 mg, 0.955 mmol) and K_3PO_4 (500 mg, 2.36 mmol). The mixture is flushed with argon for 10 min and then warmed to 90 °C. Next, $\text{Pd}(\text{dppf})\text{Cl}_2$ (52 mg, 0.064 mmol) is added, and the resulting mixture is stirred at 90 °C overnight. After cooling down to room temperature the mixture is diluted with EtOAc (30 mL) and water (30 mL). The mixture is filtered through kieselguhr, and the filtrate layers are separated. The organic layer is washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (silica, gradient 15% to 60% EtOAc/heptane) followed by recrystallisation from EtOAc/heptane provides the title compound (49 mg, 45%) as a slightly yellow solid.

^1H NMR ($\text{DMSO}-d_6$), δ_{H} : 1.01-1.09 (m, 4H), 1.90-1.99 (m, 1H), 2.17-2.24 (m, 2H), 2.50-2.52 (m, 2H), 4.15-4.18 (m, 2H), 6.85 (s, 1H), 7.35-7.39 (m, 3H), 7.38-7.40 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 276

Example 114

N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1H)-carboxamide

[00356] To a solution of 7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2H)-one (300 mg, 1.14 mmol), which is made according to General Procedure 3, in THF (6 mL) is added a solution of DIBALH (4.6 mmol, 3.25 mL of 1.2M solution in toluene), and the resulting mixture is heated to reflux for 4 days. The reaction mixture is cooled and partitioned between EtOAc and saturated sodium potassium tartrate solution. The organic phase is

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separated, dried over anhydrous Na_2SO_4 and evaporated to dryness to give sufficiently pure 7-iodo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine.

[00357] To a solution of 7-iodo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (96 mg, 0.39 mmol) in DCM (3 mL) are added dimethylcarbonyl chloride (50 mg, 0.46 mmol) and TEA (0.16 mL, 0.5 mmol), and the mixture is stirred at room temperature overnight. The reaction mixture is partitioned between EtOAc and saturated ammonium chloride solution. The organic phase is separated, dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification of the residue by flash column chromatography provides 7-iodo-*N,N*-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide (87 mg, 70%).

[00358] According to General Procedure 1, 7-iodo-*N,N*-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide is reacted with ethynylbenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 2.88 (s, 6H), 3.62 (t, 2H), 4.02 (t, 2H), 4.41 (s, 2H), 6.05 (s, 1H), 6.84 (s, 1H), 7.27-7.30 (m, 3H), 7.44-7.48 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 294

Example 115

2-(2-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00359] According to General Procedure 1, 7-iodo-2-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 2.32 (s, 3H), 3.50 (t, 2H), 4.02 (t, 2H), 4.75 (s, 2H), 6.91 (s, 1H), 7.08 (s, 1H), 7.18-7.31 (m, 7H), 7.47 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 341

Example 116

7-((3-Fluorophenyl)ethynyl)-2-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

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[00360]According to General Procedure 1, 7-iodo-2-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.31 (s, 3H), 3.50 (t, 2H), 4.02 (t, 2H), 4.74 (s, 2H), 6.92 (s, 1H), 6.97 (m, 1H), 7.08 (s, 1H), 7.14-7.27 (m, 7H).

LC/MS (M+H)⁺ = 359

Example 117

2-(3-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00361]According to General Procedure 1, 7-iodo-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.32 (s, 3H), 3.54 (t, 2H), 4.03 (t, 2H), 4.69 (s, 2H), 6.91 (s, 1H), 7.08-7.21 (m, 4H), 7.24-7.32 (m, 4H), 7.47 (m, 2H).

LC/MS (M+H)⁺ = 341

Example 118

2-(3-Methylbenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00362]According to General Procedure 1, 7-iodo-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.32 (s, 3H), 3.54 (t, 2H), 4.03 (t, 2H), 4.69 (s, 2H), 6.90 (s, 1H), 7.07-7.30 (m, 9H).

LC/MS (M+H)⁺ = 355

Example 119

7-((3-Fluorophenyl)ethynyl)-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00363]According to General Procedure 1, 7-iodo-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.28 (s, 3H), 3.51 (t, 2H), 4.01 (t, 2H), 4.65 (s, 2H), 6.89 (s, 1H), 6.94 (m, 1H), 7.04 (s, 1H), 7.06-7.21 (m, 7H).

LC/MS (M+H)⁺ = 359

Example 120

2-(4-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00364]According to General Procedure 1, 7-iodo-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.32 (s, 3H), 3.52 (t, 2H), 4.02 (t, 2H), 4.69 (s, 2H), 6.90 (s, 1H), 7.07 (s, 1H), 7.12-7.30 (m, 7H), 7.48 (m, 2H).

LC/MS (M+H)⁺ = 341

Example 121

2-(4-Methylbenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00365]According to General Procedure 1, 7-iodo-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.32 (s, 3H), 3.52 (t, 2H), 4.02 (t, 2H), 4.68 (s, 2H), 6.89 (s, 1H), 7.06-7.30 (m, 9H).

LC/MS (M+H)⁺ = 355

Example 122

7-((3-Fluorophenyl)ethynyl)-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00366]According to General Procedure 1, 7-iodo-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.32 (s, 3H), 3.53 (t, 2H), 4.02 (t, 2H), 4.68 (s, 2H), 6.91 (s, 1H), 7.07 (m, 1H), 7.12-7.20 (m, 8H).

LC/MS (M+H)⁺ = 359

Example 123**2-(2-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one**

[00367]According to General Procedure 1, 2-(2-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.59 (t, 2H), 4.01 (t, 2H), 4.71 (s, 2H), 6.85 (s, 1H), 6.98-7.05 (m, 3H), 7.20-7.24 (m, 4H), 7.40 (m, 3H).

LC/MS (M+H)⁺ = 345

Example 124**2-(2-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one**

[00368]According to General Procedure 1, 2-(2-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.31 (s, 3H), 3.65 (t, 2H), 4.06 (t, 2H), 4.77 (s, 2H), 6.89 (s, 1H), 7.02-7.29 (m, 8H), 7.42 (t, 1H).

LC/MS (M+H)⁺ = 359

Example 125**2-(2-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one**

[00369]According to General Procedure 1, 2-(2-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.59 (t, 2H), 4.02 (t, 2H), 4.71 (s, 2H), 6.86 (s, 1H), 6.91-7.20 (m, 8H), 7.37 (t, 1H).

LC/MS (M+H)⁺ = 363

Example 126**Phenyl(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)methanone**

[00370]In close analogy to the procedure given in **Example 114**, 7-iodo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine is acylated with benzoyl chloride to give (7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(phenyl)methanone, which – according to General Procedure 1 – is reacted with ethynylbenzene to provide the title compound as a crystalline solid.

¹H NMR (CDCl₃), δ_H: 4.06 (m, 4H), 4.70 (s, 2H), 6.04 (s, 1H), 6.87 (s, 1H), 7.27-7.31 (m, 4H), 7.44-7.49 (m, 6H).

LC/MS (M+H)⁺ = 327

Example 127**(*R*)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one**

[00371]According to General Procedure 1, (*R*)-7-iodo-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.58 (d, 3H), 3.12-3.24 (m, 1H), 3.46-3.59 (m, 1H), 3.82-4.03 (m, 2H), 6.16 (q, 1H), 6.91 (s, 1H), 7.08 (s, 1H), 7.21-7.51 (m, 9H).

LC/MS (M+H)⁺ = 341

Example 128

(R)-2-(1-Phenylethyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00372]According to General Procedure 1, (*R*)-7-iodo-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.57 (d, 3H), 2.33 (s, 3H), 3.11-3.23 (m, 1H), 3.45-3.58 (m, 1H), 3.84-4.02 (m, 2H), 6.15 (q, 1H), 6.89 (s, 1H), 7.08 (s, 1H), 7.11-7.36 (m, 9H).

LC/MS (M+H)⁺ = 355

Example 129

(R)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00373]According to General Procedure 1, (*R*)-7-iodo-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.58 (d, 3H), 3.12-3.24 (m, 1H), 3.45-3.59 (m, 1H), 3.82-4.03 (m, 2H), 6.15 (q, 1H), 6.91 (s, 1H), 6.93-7.07 (m, 1H), 7.08 (s, 1H), 7.15-7.35 (m, 8H).

LC/MS (M+H)⁺ = 359

Example 130

2-(3-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00374]According to General Procedure 1, 2-(3-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

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^1H NMR (CDCl_3), δ_{H} : 3.56 (t, 2H), 4.07 (t, 2H), 4.71 (s, 2H), 6.92 (s, 1H), 6.97-7.09 (m, 4H), 7.28-7.31 (m, 4H), 7.47 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 345

Example 131

2-(3-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00375]According to General Procedure 1, 2-(3-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 3.56 (t, 2H), 4.07 (t, 2H), 4.71 (s, 2H), 6.92 (s, 1H), 6.97-7.09 (m, 4H), 7.28-7.31 (m, 4H), 7.47 (m, 2H).

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

Example 132

2-(3-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00376]According to General Procedure 1, 2-(3-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as an oil.

^1H NMR (CDCl_3), δ_{H} : 3.56 (t, 2H), 4.07 (t, 2H), 4.71 (s, 2H), 6.93 (s, 1H), 6.97-7.08 (m, 4H), 7.13-7.30 (m, 5H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 363

Example 133

2-(4-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00377]According to General Procedure 1, 2-(4-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure

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3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.41 (t, 2H), 3.92 (t, 2H), 4.56 (s, 2H), 6.78 (s, 1H), 6.88 (t, 2H), 6.94 (s, 1H), 7.14-7.18 (m, 5H), 7.34 (m, 2H).

LC/MS (M+H)⁺ = 345

Example 134

2-(4-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00378]According to General Procedure 1, 2-(4-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 2.32 (s, 3H), 3.55 (t, 2H), 4.04 (t, 2H), 4.68 (s, 2H), 6.90 (s, 1H), 6.99-7.10 (m, 3H), 7.17-7.30 (m, 6H).

LC/MS (M+H)⁺ = 359

Example 135

2-(4-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00379]According to General Procedure 1, 2-(4-fluorobenzyl)-7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 3.55 (t, 2H), 4.06 (t, 2H), 4.69 (s, 2H), 6.93 (s, 1H), 6.99-7.07 (m, 3H), 7.14 (s, 1H), 7.16 (d, 1H), 7.26-7.35 (m, 4H).

LC/MS (M+H)⁺ = 363

Example 136

(*S*)-2-(1-Phenylethyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

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[00380]According to General Procedure 1, (S)-7-iodo-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-methylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.57 (d, 3H), 2.33 (s, 3H), 3.11-3.23 (m, 1H), 3.45-3.58 (m, 1H), 3.84-4.02 (m, 2H), 6.15 (q, 1H), 6.89 (s, 1H), 7.08 (s, 1H), 7.11-7.36 (m, 9H).

LC/MS (M+H)⁺ = 355

Example 137

(S)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00381]According to General Procedure 1, (S)-7-iodo-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.58 (d, 3H), 3.12-3.24 (m, 1H), 3.46-3.59 (m, 1H), 3.82-4.03 (m, 2H), 6.16 (q, 1H), 6.91 (s, 1H), 7.08 (s, 1H), 7.21-7.51 (m, 9H).

LC/MS (M+H)⁺ = 341

Example 138

(S)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one

[00382]According to General Procedure 1, (S)-7-iodo-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1H-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynyl-3-fluorobenzene to provide the title compound as an oil.

¹H NMR (CDCl₃), δ_H: 1.58 (d, 3H), 3.12-3.24 (m, 1H), 3.45-3.59 (m, 1H), 3.82-4.03 (m, 2H), 6.15 (q, 1H), 6.91 (s, 1H), 6.93-7.07 (m, 1H), 7.08 (s, 1H), 7.15-7.35 (m, 8H).

LC/MS (M+H)⁺ = 359

Example 139

(7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone

[00383] In close analogy to the procedure given in **Example 114**, 7-iodo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine is acylated with pyrrolidine-1-carbonyl chloride to give (7-iodo-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone, which – according to General Procedure 1 is reacted with ethynylbenzene to provide the title compound as a crystalline solid.

¹H NMR (CDCl₃), δ_H: 1.86 (t, 4H), 3.41 (t, 4H), 3.66 (t, 2H), 4.02 (t, 2H), 4.46 (s, 2H), 6.05 (s, 1H), 6.84 (s, 1H), 7.28-7.30 (m, 3H), 7.44-7.49 (m, 2H).

LC/MS (M+H)⁺ = 320

Example 140**Methyl 7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate**

[00384] In close analogy to the procedure given in **Example 114**, 7-iodo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine is acylated with methyl chloroformate to give methyl 7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate which – according to General Procedure 1 – is reacted with ethynylbenzene to provide the title compound as a crystalline solid.

¹H NMR (CDCl₃), δ_H: 3.76 (s, 3H), 3.85 (t, 2H), 3.95 (t, 2H), 4.63 (s, 2H), 6.08 (s, 1H), 6.85 (s, 1H), 7.27-7.31 (m, 3H), 7.44-7.49 (m, 2H).

LC/MS (M+H)⁺ = 281

Example 141**2'-(Phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione**

[00385] 2-(Phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one (**Example 1**) (180 mg, 0.77 mmol), potassium cyanide (75 mg, 1.15 mmol) and ammonium carbonate (515 mg, 5.36 mmol) are dissolved in a mixture of 3 mL of EtOH and 3 mL of water, and the mixture is heated in a closed vial to 80 °C overnight. The mixture is then cooled, diluted with water, and the formed precipitate is filtered off and dried to provide the title compound (190 mg, 81%) as a yellow solid.

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¹H NMR (CD₃OD), δ_H: 1.95-2.10 (m, 2H), 2.22-2.30 (m, 1H), 2.38-2.50 (m, 1H), 4.00 (m, 2H), 6.12 (s, 1H), 6.96 (s, 1H), 7.22-7.31 (m, 3H), 7.35-7.40 (m, 2H).

LC/MS (M+H)⁺ = 306

Example 142

1,3-Dimethyl-2'-(phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione

[00386]Potassium *t*-butoxide (99 mg, 0.88 mmol) is added to a solution of 2'-(phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione (**Example 141**) (90 mg, 0.29 mmol) in 2 mL of dry THF. After 1 h methyl iodide (125 mg, 0.88 mmol) is added, and the slurry is stirred overnight at room temperature. The mixture is then partitioned between water and DCM. The organic phase is separated, dried over anhydrous Na₂SO₄, filtered and evaporated. The residue is purified by flash column chromatography to provide the title compound (80 mg, 82%) of as a yellow solid.

¹H NMR (CDCl₃), δ_H: 1.99-2.15 (m, 4H), 2.22-2.30 (m, 1H), 2.83 (s, 3H), 3.05 (s, 1H), 3.89 (m, 1H), 4.10 (m, 1H), 6.09 (s, 1H), 6.93 (s, 1H), 7.27-7.31 (m, 3H), 7.42-7.45 (m, 2H).

LC/MS (M+H)⁺ = 334

Example 143

***cis*-9-(Phenylethynyl)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine**

[00387]9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is alkylated with an *n*-propyl halide under standard conditions to provide an *N*-propyl derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound .

Example 144

***cis*-9-(Phenylethynyl)-4-(3,3,3-trifluoropropyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine**

[00388] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is alkylated with a 3,3,3-trifluoropropyl halide under standard conditions to provide an *N*-3,3,3-trifluoropropyl derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound .

Example 145

***cis*-9-(Phenylethynyl)-4-(2,2,2-trifluoroethyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine**

[00389] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is alkylated with a 2,2,2-trifluoroethyl halide under standard conditions to provide an *N*-2,2,2-trifluoroethyl derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound .

Example 146

***cis*-4-(2,2-Difluoroethyl)-9-(phenylethynyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine**

[00390] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is alkylated with a 2,2-difluoroethyl halide under standard conditions to provide an *N*-2,2-difluoroethyl derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound .

Example 147

***cis*-4-(2-Fluoroethyl)-9-(phenylethynyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine**

[00391] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is alkylated with a 2-fluoroethyl halide under standard conditions to provide an *N*-2-difluoroethyl derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound .

Example 148

***cis*-Methyl 9-(phenylethynyl)-4a,5,6,10b-tetrahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine-4(3*H*)-carboxylate**

[00392] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is acylated with methyl chloroformate under standard conditions to provide a methyl carbamate derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound.

Example 149

***cis*-*N,N*-Dimethyl-9-(phenylethynyl)-4a,5,6,10b-tetrahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine-4(3*H*)-carboxamide**

[00393] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is acylated with dimethylcarbomoyl chloride under standard conditions to provide an *N,N*-dimethyl urea derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound.

Example 150

Azetidin-1-yl(*cis*-9-(phenylethynyl)-5,6-dihydro-2*H*-[1,4]oxazino[3,2-*g*]indolizin-4(3*H*,4a*H*,10b*H*)-yl)methanone

[00394] 9-Iodo-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine **39** is acylated with carbomoyl chloride under standard conditions to provide azetidinyll urea derivative, which is coupled with phenylacetylene according General Procedure 1 to provide the title compound.

Example 151

***N,N*-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-sulfonamide**

[00395] In close analogy to the procedure given in **Example 114**, 7-Iodo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine is acylated with dimethylsulfamoyl chloride to give 7-iodo-*N,N*-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-sulfonamide, which –

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according to General Procedure 1 – is reacted with ethynylbenzene to provide the title compound as a crystalline solid.

^1H NMR (CDCl_3), δ_{H} : 2.85 (s, 3H), 3.65 (t, 2H), 4.03 (t, 2H), 4.96 (s, 2H), 6.09 (s, 1H), 6.85 (s, 1H), 7.24-7.31 (m, 4H), 7.44-7.49 (m, 6H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 330

Example 152

7-((3-Fluorophenyl)ethynyl)-2-phenethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00396]According to General Procedure 1, 7-iodo-2-phenethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-fluorobenzene to provide the title compound as colorless solid.

^1H NMR (CDCl_3), δ_{H} : 2.88 (t, 2H), 3.37 (t, 2H), 3.69 (t, 2H), 3.85 (t, 2H), 6.83 (s, 1H), 7.00-7.04 (m, 4H), 7.13-7.28 (m, 6H).

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

Example 153

2-Phenethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00397]According to General Procedure 1, 7-iodo-2-phenethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with ethynylbenzene to provide the title compound as colorless solid.

^1H NMR (CDCl_3), δ_{H} : 2.94 (t, 2H), 3.41 (t, 2H), 3.75 (t, 2H), 3.91 (t, 2H), 6.88 (s, 1H), 7.02 (s, 1H), 7.22-7.30 (m, 8H), 7.45-7.47 (m, 2H).

LC/MS ($\text{M}+\text{H}$) $^+$ = 341

Example 154

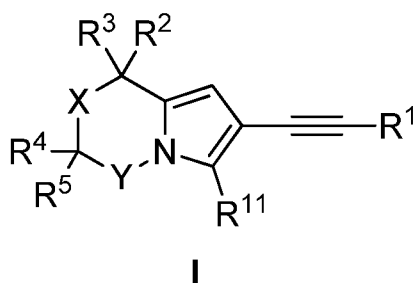
2-Phenethyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one

[00398]According to General Procedure 1, 7-iodo-2-phenethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one, which is made according to General Procedure 3 from methyl 1-(2-bromoethyl)-4-iodo-1*H*-pyrrole-2-carboxylate (**Preparation 12**), is reacted with 1-ethynyl-3-methylbenzene to provide the title compound as colorless solid.

¹H NMR (CDCl₃), δ_H: 2.88 (t, 2H), 3.35 (t, 2H), 3.69 (t, 2H), 3.84 (t, 2H), 6.81 (s, 1H), 6.96 (s, 1H), 7.02 (d, 1H), 7.11-7.28 (m, 8H).

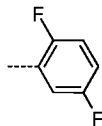
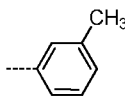
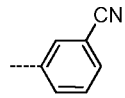
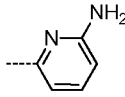
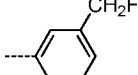
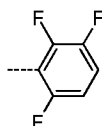
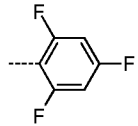
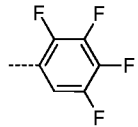
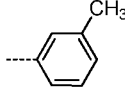
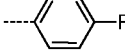
LC/MS (M+H)⁺ = 355

Table 1

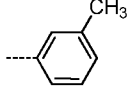
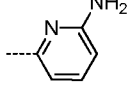
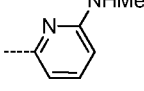
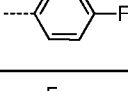
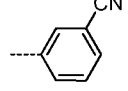
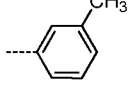
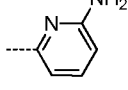


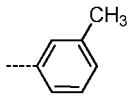
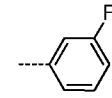
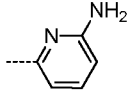
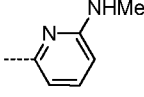
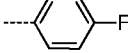
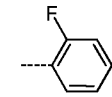
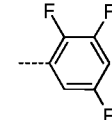
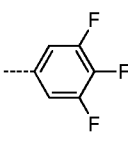
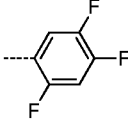
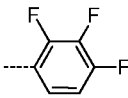
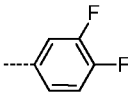
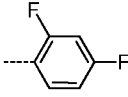
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
1	Ph	=O		H	H	CH ₂	CH ₂	H
2		=O		H	H	CH ₂	CH ₂	H
3		=O		H	H	CH ₂	CH ₂	H
4		=O		H	H	CH ₂	CH ₂	H
5		=O		H	H	CH ₂	CH ₂	H
6		=O		H	H	CH ₂	CH ₂	H

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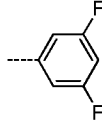
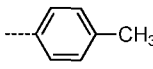
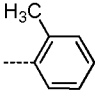
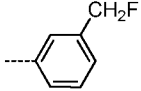
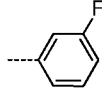
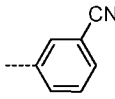
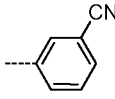
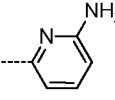
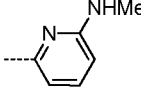
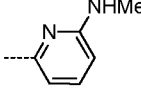
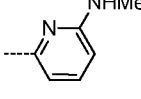
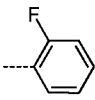
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
7		=O		H	H	CH ₂	CH ₂	H
8		=O		H	H	CH ₂	CH ₂	H
9		=O		H	H	CH ₂	CH ₂	H
10		=O		H	H	CH ₂	CH ₂	H
11		=O		H	H	CH ₂	CH ₂	H
12		=O		H	H	CH ₂	CH ₂	H
13		=O		H	H	CH ₂	CH ₂	H
14		=O		H	H	CH ₂	CH ₂	H
15		=O		H	H	CH ₂	CH ₂	H
16		=O		H	H	CH ₂	CH ₂	H
17	Ph	=O		H	H	CHMe	CH ₂	H
18		=O		H	H	CHMe	CH ₂	H
19		=O		H	H	CHMe	CH ₂	H

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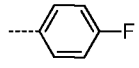
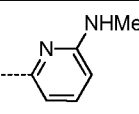
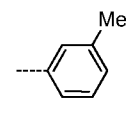
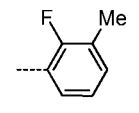
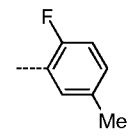
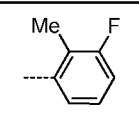
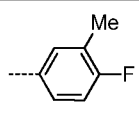
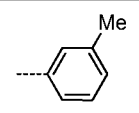
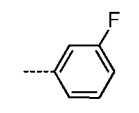
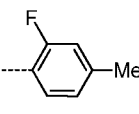
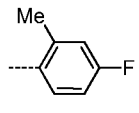
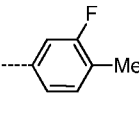
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
20		=O		H	H	CHMe	CH ₂	H
21	Ph	=O		H	H	CMe ₂	CH ₂	H
22		=O		H	H	CMe ₂	CH ₂	H
23		=O		H	H	CMe ₂	CH ₂	H
24		=O		H	H	CMe ₂	CH ₂	H
25		=O		H	H	CMe ₂	CH ₂	H
26	Ph	=O		Me	H	CH ₂	CH ₂	H
27		=O		Me	H	CH ₂	CH ₂	H
28		=O		Me	H	CH ₂	CH ₂	H
29		=O		Me	H	CH ₂	CH ₂	H
30		=O		Me	H	CH ₂	CH ₂	H
31		=O		Me	H	CH ₂	CH ₂	H
32		=O		Me	H	CH ₂	CH ₂	H
33	Ph	=O		Me	Me	CH ₂	CH ₂	H

Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
34		=O		Me	Me	CH ₂	CH ₂	H
35		=O		Me	Me	CH ₂	CH ₂	H
36		=O		Me	Me	CH ₂	CH ₂	H
37		=O		Me	Me	CH ₂	CH ₂	H
38		=O		Me	Me	CH ₂	CH ₂	H
39		=O		Me	Me	CH ₂	CH ₂	H
40		=O		H	H	CH ₂	CH ₂	H
41		=O		H	H	CH ₂	CH ₂	H
42		=O		H	H	CH ₂	CH ₂	H
43		=O		H	H	CH ₂	CH ₂	H
44		=O		H	H	CH ₂	CH ₂	H
45		=O		H	H	CH ₂	CH ₂	H

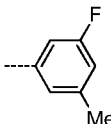
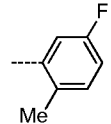
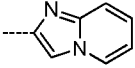
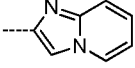
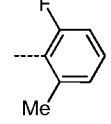
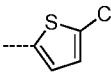
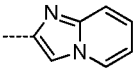
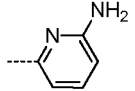
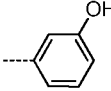
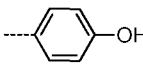
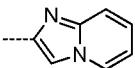
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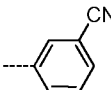
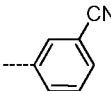
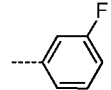
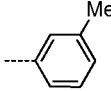
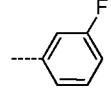
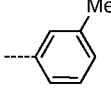
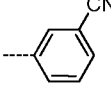
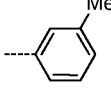
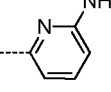
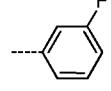
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
46		=O		H	H	CH ₂	CH ₂	H
47		=O		H	H	CH ₂	CH ₂	H
48		=O		H	H	CH ₂	CH ₂	H
49		=O		Me	H	CH ₂	CH ₂	H
50	Ph	=O		H	H	CH ₂	bond	H
51		=O		H	H	CH ₂	bond	H
52		=O		Me	Me	CH ₂	CH ₂	H
53		=O		H	H	CHMe	CH ₂	H
54		=O		H	H	CHMe	CH ₂	H
55		=O		H	H	CHMe	CH ₂	H
56		=O		H	H	CH ₂	CH ₂	H
57		=O		Me	H	CH ₂	CH ₂	H
58		=O		H	H	CH ₂	bond	H

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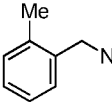
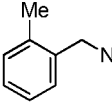
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
59		=O		H	H	CH ₂	bond	H
60		=O		H	H	CH ₂	bond	H
61		=O		H	H	CHMe	bond	H
62		=O		H	H	CH ₂	CH ₂	H
63		=O		H	H	CH ₂	CH ₂	H
64		=O		H	H	CH ₂	CH ₂	H
65		=O		H	H	CH ₂	CH ₂	H
66	Ph	=O		H	H	CMe ₂	bond	H
67		=O		H	H	CMe ₂	bond	H
68		OH	H	H	H	CH ₂	CH ₂	H
69		=O		H	H	CH ₂	CH ₂	H
70		=O		H	H	CH ₂	CH ₂	H
71		=O		H	H	CH ₂	CH ₂	H

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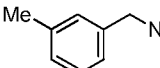
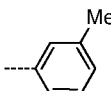
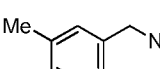
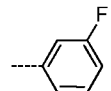
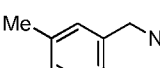
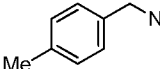
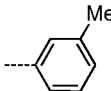
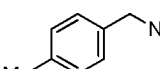
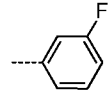
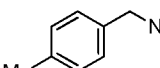
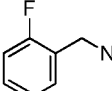
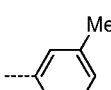
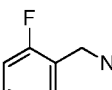
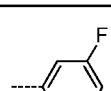
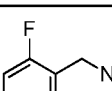
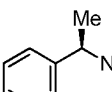
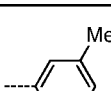
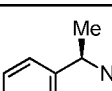
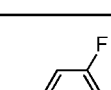
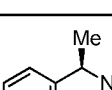
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
72		=O		H	H	CH ₂	CH ₂	H
73		=O		H	H	CH ₂	CH ₂	H
74		=O		H	H	CH ₂	CH ₂	H
75		=O		H	H	CMe ₂	CH ₂	H
76		=O		H	H	CH ₂	CH ₂	H
77		=O		H	H	CH ₂	CH ₂	H
78		=O		Me	H	CH ₂	CH ₂	H
79		=O		H	H	CH ₂	CH ₂ CH ₂	H
80	Ph	=O		H	H	NH	CH ₂ CH ₂	H
81		=O		H	H	CH ₂	CH ₂	H
82		=O		H	H	CH ₂	CH ₂	H
83	Ph	=O		H	H	NMe	CH ₂ CH ₂	H
84		=O		H	H	CHMe	CH ₂	H
85	Ph	=O		H	H	CH ₂	CH ₂ CH ₂	H

Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
86		=O		H	H	NPr- <i>n</i>	CH ₂	H
87	Ph	=O		H	H	NMe	CH ₂	H
88		=O		H	H	NMe	CH ₂	H
89		=O		H	H	NMe	CH ₂	H
90		=O		H	H	NMe	CH ₂	H
91		=O		H	H	NCH ₂ Ph	CH ₂	H
92	Ph	=O		H	H	NCH ₂ Ph	CH ₂	H
93		=O		H	H	NCH ₂ Ph	CH ₂	H
94		=O		H	H	NCH ₂ Ph	CH ₂	H
95	Ph	=O		H	H	NPr- <i>n</i>	CH ₂	H
96		=O		H	H	NPr- <i>n</i>	CH ₂	H
97		=O		H	H	NMe	CH ₂ CH ₂	H
98	Ph	=O		H	H	NEt	CH ₂	H
99	Ph	=O		H	H	NBu- <i>n</i>	CH ₂	H
100		=O		H	H	NBu- <i>n</i>	CH ₂	H

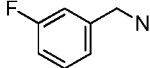
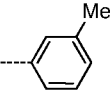
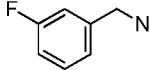
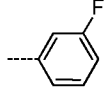
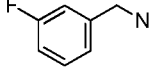
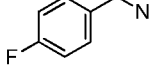
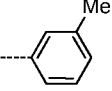
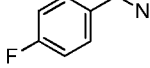
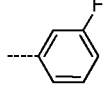
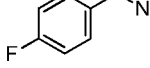
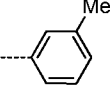
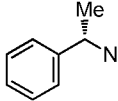
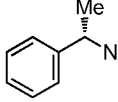
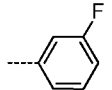
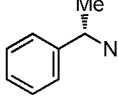
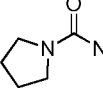
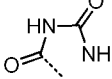
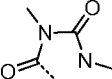
- 130 -

Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
101		=O		H	H	NPr- <i>i</i>	CH ₂	H
102		=O		H	H	NPr- <i>i</i>	CH ₂	H
103	Ph	=O		H	H	CMe ₂	CH ₂ CH ₂	H
104	Ph	=O		H	H	NPh	CH ₂	H
105		=O		H	H	NPh	CH ₂	H
106		=O		H	H	NPh	CH ₂	H
107	Ph	=O		H	H	NH	CH ₂	H
108		=O		H	H	NH	CH ₂	H
109		=O		H	H	CMe ₂	CH ₂ CH ₂	H
110		=O		Me	Me	CH ₂	CH ₂	H
111	Ph	H	H	H	H	NC(O)Bu- <i>t</i>	CH ₂	H
112	Ph	=O		H	H	CH ₂	CH ₂	Br
113	Ph	=O		H	H	CH ₂	CH ₂	
114	Ph	H	H	H	H	NC(O)NMe ₂	CH ₂	H
115	Ph	=O		H	H		CH ₂	H
116		=O		H	H		CH ₂	H

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Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
117	Ph	=O		H	H		CH ₂	H
118		=O		H	H		CH ₂	H
119		=O		H	H		CH ₂	H
120	Ph	=O		H	H		CH ₂	H
121		=O		H	H		CH ₂	H
122		=O		H	H		CH ₂	H
123	Ph	=O		H	H		CH ₂	H
124		=O		H	H		CH ₂	H
125		=O		H	H		CH ₂	H
126	Ph	H	H	H	H	NC(O)Ph	CH ₂	H
127	Ph	=O		H	H		CH ₂	H
128		=O		H	H		CH ₂	H
129		=O		H	H		CH ₂	H

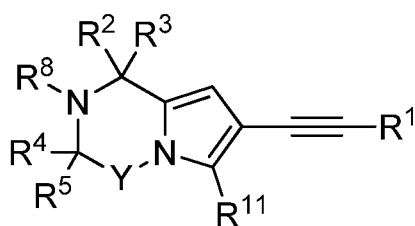
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Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
130	Ph	=O		H	H		CH ₂	H
131		=O		H	H		CH ₂	H
132		=O		H	H		CH ₂	H
133	Ph	=O		H	H		CH ₂	H
134		=O		H	H		CH ₂	H
135		=O		H	H		CH ₂	H
136		=O		H	H		CH ₂	H
137	Ph	=O		H	H		CH ₂	H
138		=O		H	H		CH ₂	H
139	Ph	H	H	H	H		CH ₂	H
140	Ph	H	H	H	H		CH ₂	H
141	Ph			H	H	CH ₂	CH ₂	H
142	Ph			H	H	CH ₂	CH ₂	H

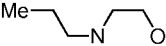
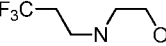
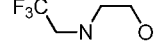
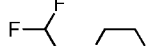
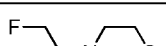
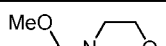
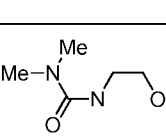
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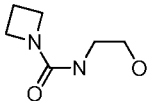
Example No.	R ¹	R ²	R ³	R ⁴	R ⁵	X	Y	R ¹¹
151	Ph	H	H	H	H	NSO ₂ NMe ₂	CH ₂	H
152		=O		H	H	NCH ₂ CH ₂ Ph	CH ₂	H
153	Ph	=O		H	H	NCH ₂ CH ₂ Ph	CH ₂	H
154		=O		H	H	NCH ₂ CH ₂ Ph	CH ₂	H

Table 2



IF

Example No.	R ¹	R ⁸	R ²	R ³	R ⁴	R ⁵	Y	R ¹¹
143	Ph			H	H	H	CH ₂	H
144	Ph			H	H	H	CH ₂	H
145	Ph			H	H	H	CH ₂	H
146	Ph			H	H	H	CH ₂	H
147	Ph			H	H	H	CH ₂	H
148	Ph			H	H	H	CH ₂	H
149	Ph			H	H	H	CH ₂	H

Example No.	R ¹	R ⁸	R ²	R ³	R ⁴	R ⁵	Y	R ¹¹
150	Ph			H	H	H	CH ₂	H

EXAMPLES OF REPRESENTATIVE PHARMACEUTICAL COMPOSITIONS

[00399] 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 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.

[00400] Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

FORMULATION EXAMPLES

[00401] The following examples are again given by way of illustration only and are not to be construed as limiting.

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EXAMPLE 1

Tablet Formulation

A suitable formulation for a tablet containing 10 mg 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

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

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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 mg 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.

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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

Liquid oral formulation

A suitable formulation for 1 L of a an oral solution containing 2 mg of active ingredient in one mL 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

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EXAMPLE 6

Liquid oral formulation

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

	g
Active Ingredient	2

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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.

EXAMPLE 9

TDS formulation

100 g solution contain:

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	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

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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:

	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.

EXAMPLE 12

Solution for Injection

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

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solution 1 is mixed with solution 2 by continuous stirring. The solution is sterilized by filtration of by autoclaving.

PHARMACOLOGY

[00402]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 exhibit, in standard accepted reliable test procedures, the following valuable properties and characteristics.

METHODS

BINDING ASSAYS FOR THE CHARACTERIZATION OF mGluR5 ANTAGONIST PROPERTIES

Preparation of rat cortical membranes:

[00403]Tissue preparation is performed according to Foster & Wong (*Br. J. Pharmacol.*, **1987**, 91, 403-409) with some modifications. Anaesthetised male Sprague-Dawley rats (200-250 g, Janvier, Le Genest-Isle, France) are decapitated and their brains are removed rapidly. The cortex is dissected out and processed as described by Parsons, et al. (*J. Pharmacol. Exp. Ther.*, **1997**, 283(3): 1264-1275). For isolation of the cell membranes, the cortices are homogenized in 20 volumes of ice-cold 0.32 M sucrose (Sigma-Aldrich, Taufkirchen, Germany) using a glass-Teflon homogenizer. The homogenate is centrifuged at 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. The supernatant and the buffy coat are then centrifuged six times (48,000 x g for 20 minutes) in the presence of 5 mM Tris-HCl, pH 7.5. All centrifugation steps are carried out at 4 °C. After resuspension in 5 volumes of 5 mM Tris-HCl, pH 7.5, the membrane suspension is frozen rapidly at -80 °C.

[00404]On the day of assay, the membrane suspensions are thawed, centrifuged (48,000 x g for 20 minutes) and then resuspended in 50 mM Tris-HCl, pH 7.5 (assay

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buffer). The amount of protein in the final membrane preparation is determined according to the method of Lowry, et al. (*J. Biol. Chem.*, **1951**, 193, 256-275). The final concentration used for our studies is 400 µg / ml.

[³H]-M-MPEP (2-(3-Methoxyphenylethynyl)-6-methylpyridine) Displacement Studies

[00405]The Tecan robotic system designed for binding assays is loaded with the membrane solution, a 96 well stock plate containing the solutions for bound control (buffer/DMSO 10%), unlabeled MPEP (10 µM) for evaluation of non-specific binding, all compounds to be tested (at 20-fold concentrations), various empty 96-well plates for dilutions and the final assay plates, as well as a 96-well plate filled with the radioligand.

[00406]Before performing displacement studies, saturation experiments are performed to determine the equilibrium dissociation constant (K_d , Cheng and Prussoff, *Biochem. Pharmacol.*, **1973**, 22: 3099-3108) of [³H]-M-MPEP, which is a parameter for the affinity of the radioligand to the binding site. On the basis of the saturation experiments, a final [³H]-M-MPEP concentration of 2 nM was selected.

[00407]Firstly, the assay plates are loaded with membrane solution and are shaken at 4 °C. The mother plates were then prepared by pipetting the compounds (n = 5) into assay buffer/10% DMSO to obtain the desired final concentrations. After transferring radioligand into the assay plates, the compounds are added (including the non-specific binding control containing MPEP). The final DMSO concentration is always 1%. The assay plates are incubated and shaken at 4 °C for 1 h, before the mixture is exhausted as rapidly as possible via a vacuum manifold using the Multiscreen HTS glass fibre (type B) high flow filter plates (Millipore, Schwalbach, Germany) under a constant vacuum of 450 mbar. The membranes are washed four times with cold assay buffer (100 µL). 50 µL of Ultima Gold scintillation cocktail (PerkinElmer) is added to the wet filter plates and incubated at room temperature overnight before counting the disintegration per minutes using a liquid scintillation counter (MicroBeta, PerkinElmer).

Characterization

[00408] For the evaluation of the test compound binding affinity to the mGluR5 binding site and its potency to displace [³H]-M-MPEP, the measured radioactivity of the radioligand alone was set as 100% bound control and the non-specific binding of the radioligand represented the 0% control. The residual radioactivity after displacement of the test compound was then corrected with respect to the set controls. Data are given as median IC₅₀ and K_i, respectively.

FUNCTIONAL ASSAY OF mGluR5 RECEPTORS

Cytosolic Calcium studies with stably transfected cells

[00409] Chinese hamster ovary cells (CHO-K1 cells), stably transfected for inducible expression of a human metabotropic glutamate receptor mGluR5 to form a cell line called h5CHO, are seeded into black clear bottom 96 well plates at a density of 35.000 cells per well. The standard growth 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 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 negatively 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). EC₅₀ values for positive allosteric modulators were determined by stimulating the cells which have been preincubated the modulators by an EC₂₀ concentration of L-glutamate.

Astrocyte culture

[00410] Primary astrocyte cultures are prepared from cortices of newborn rats as described by Booher and Sensenbrenner (*Neurobiology* **1972**, 2(3):97-105). Briefly,

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Sprague-Dawley rat pups (2 - 4 d old) are decapitated and neocortices are dissected, disintegrated with a nylon filter (pore size 80 μm) and carefully triturated. The cell suspension is plated on poly-D-lysine pre-coated flasks (Costar, Netherlands) and 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 $\mu\text{g/ml}$ gentamycin (both Biochrom, Germany) at 37 °C in a humidified atmosphere of 5% CO_2 / 95% air for 7 days with exchanging the medium at day 2 and 6.

[00411]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 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 $\mu\text{g/ml}$ heparan sulfate, and 1.5 $\mu\text{g/ml}$ fibronectin (both Sigma, Germany) (Miller et al., *Brain Res.* **1993**, 618(1):175-8). 3 days later the medium is exchanged and the cells incubated for another 2-3 days, so that at the time of experiments astrocytes are 14-15 DIV.

Immunocytochemistry

[00412]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 mGluR5 receptors.

Cytosolic Calcium studies with astrocytes

[00413]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-Kit (both Molecular Devices). Prior to addition of agonist or antagonist the medium is aspirated and cells are loaded for 2 h at room temperature with 150 μl 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

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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 room temperature before addition of the respective agonist.

[00414]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

[00415]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.

[00416]All responses (RFU-values) are determined as percentage of control (= maximum response). EC₅₀ and IC₅₀ are calculated according the logistic equation using XLFit (IDBS, UK) or Prism 4.0 (GraphPad Software, USA). The compounds of the present invention have a potency (EC₅₀ or IC₅₀) within a range of about 0.5 nM to about 100 μ M. The left shifts for positive or silent allosteric modulators (PAMs or SAMs, respectively) are determined by comparison of EC₅₀ values from agonist dose response curves run in the presence of 10 μ M modulator or vehicle (Vanejevs et al., *J. Med. Chem.*, **2008**, 51, 634-647).

[00417]The compounds of the present invention show an affinity to the allosteric site, i.e., the MPEP site, shown by the displacement of the radioligand [³H]-MMPEP.

[00418]Various functional consequences associated with this affinity are observed. Negative allosteric modulators (NAMs), which inhibit the calcium signals of mGluR5

orthostatic ligands, and positive allosteric modulators (PAMs), which modulate by amplification of small glutamate signals and thereby yield a left shift in agonist concentration response curves, (they might be classified into weak PAMs with a shift above 1.5-fold and strong PAMs with a shift above 3-fold) are observed. Moreover silent allosteric modulators (SAMs), which bind to the allosteric site (i.e., have the capacity to displace M-MPEP), but do not or only moderately influence the calcium signal of orthosteric agonists, are also observed.

[00419] Results for representative compounds of the invention are shown in Tables A1-A3.

Table A1

Compound	Chemical Name	Human mGluR5 (h5CHO) EC ₅₀ [μM]	h left shift (h5CHO) [fold]	Rat mGluR5 (rpA) EC ₅₀ [μM]	r left shift (rpA) [fold]	Rat cortex K _i [μM]
Example 1	2-(Phenylethynyl)- 6,7- dihydroindolizin- 8(5H)-one	0.00562	3.6	0.00222	3.9	0.0343
Example 2	2-((4- Fluorophenyl)ethyn yl)-6,7- dihydroindolizin- 8(5H)-one	0.0205	2.9	0.00876	3.2	0.212
Example 3	2-((3- Fluorophenyl)ethyn yl)-6,7- dihydroindolizin- 8(5H)-one	0.00545	3.0	0.00163	3.0	n.d.

Example 4	2-((2-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.00977	2.8	0.00400	3.4	0.0901
Example 5	2-((2,6-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0106	3.0	0.00262	2.5	n.d.
Example 6	2-((2,3-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0372	3.6	0.0321	4.7	n.d.
Example 7	2-((2,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0554	3.7	0.00851	3.8	n.d.
Example 8	2-(<i>m</i> -Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one	0.00705	1.5	n.d.	1.6	0.00693
Example 11	2-(Thiophen-3-ylethynyl)-6,7-dihydroindolizin-8(5H)-one	0.00807	2.8	0.0019	n.d.	n.d.
Example 12	2-(Thiophen-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0131	2.5	0.00414	2.7	n.d.
Example 14	2-((2,3,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.120	2.1	0.0539	3.4	1.95

Example 15	2-((2,4,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.125	2.7	0.0765	3.6	n.d.
Example 40	2-((2,3,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.637	2.1	1.26	2.6	n.d.
Example 42	2-((2,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.191	2.7	0.0599	2.1	n.d.
Example 43	2-((2,3,4-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.558	2.8	0.680	2.9	n.d.
Example 44	2-((3,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0551	2.4	0.0367	2.4	0.155
Example 45	2-((2,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.106	2.9	0.0459	3.0	n.d.
Example 46	2-((3,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.211	2.6	0.0591	4.2	n.d.

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Example 48	2-(<i>o</i> -Tolylethynyl)- 6,7- dihydroindolizin- 8(5 <i>H</i>)-one	0.417	2.5	0.867	2.1	n.d.
Example 58	6-((2- Fluorophenyl)ethyn yl)-2,3-dihydro-1 <i>H</i> - pyrrolizin-1-one	0.00835	1.8	0.0103	2.5	n.d.
Example 59	6-((4- Fluorophenyl)ethyn yl)-2,3-dihydro-1 <i>H</i> - pyrrolizin-1-one	0.0223	1.7	0.0271	2.3	n.d.
Example 62	2-((2-Fluoro-3- methylphenyl)ethyn yl)-6,7- dihydroindolizin- 8(5 <i>H</i>)-one	0.0234	2.8	0.0198	2.8	n.d.
Example 63	2-((2-Fluoro-5- methylphenyl)ethyn yl)-6,7- dihydroindolizin- 8(5 <i>H</i>)-one	0.00920	1.3	n.d.	1.2	n.d.
Example 64	2-((3-Fluoro-2- methylphenyl)ethyn yl)-6,7- dihydroindolizin- 8(5 <i>H</i>)-one	0.157	3.2	0.194	3.3	n.d.
Example 65	2-((4-Fluoro-3- methylphenyl)ethyn yl)-6,7- dihydroindolizin- 8(5 <i>H</i>)-one	0.0365	1.8	n.d.	n.d.	n.d.
Example 68	2-((3- Fluorophenyl)ethyn yl)-5,6,7,8- tetrahydroindolizin- 8-ol	0.229	2.6	0.129	2.5	n.d.

Example 69	2-((2-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.227	2.7	0.415	3.2	n.d.
Example 70	2-((4-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.270	n.d.	0.186	2.8	n.d.
Example 71	2-((3-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.336	1.6	0.179	3.3	n.d.
Example 72	2-((3-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.292	3.1	0.159	2.4	n.d.
Example 73	2-((5-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.377	2.3	0.295	2.8	n.d.
Example 76	2-((2-Fluoro-6-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	1.22	1.8	0.419	2.3	n.d.
Example 77	2-((5-Chlorothiophen-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0280	2.1	0.00717	1.8	n.d.

Example 80	8-(Phenylethynyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one	0.0531	1.3	n.d.	1.7	n.d.
Example 81	2-((3-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.132	2.2	0.0745	2.6	n.d.
Example 82	2-((4-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.206	2.1	0.202	3.8	n.d.
Example 85	2-(Phenylethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one	0.00330	2.1	0.00205	2.8	n.d.
Example 87	2-Methyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.0120	2.0	0.00925	3.5	n.d.
Example 89	7-((3-Fluorophenyl)ethynyl)-2-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.00739	2.3	0.00291	3.6	n.d.
Example 90	2-Methyl-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.00310	1.7	0.000939	1.8	0.0191
Example 91	2-Benzyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.0447	2.1	0.0332	5.9	n.d.

Example 93	2-Benzyl-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.146	2.4	0.0215	4.4	n.d.
Example 94	3-((2-Benzyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-<i>a</i>]pyrazin-7-yl)ethynyl)benzonitrile	0.0728	2.7	0.0344	5.6	n.d.
Example 95	7-(Phenylethynyl)-2-propyl-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0157	1.5	0.00148	1.6	n.d.
Example 98	2-Ethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0112	1.7	n.d.	1.3	n.d.
Example 99	2-Butyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0137	2.2	0.00801	3.2	n.d.
Example 100	2-Butyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0211	2.2	0.00227	1.7	n.d.
Example 104	2-Phenyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0155	2.2	0.0339	2.7	n.d.
Example 105	7-((3-Fluorophenyl)ethynyl)-2-phenyl-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0361	2.0	0.0222	2.2	n.d.

Example 106	2-Phenyl-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.00474	1.6	n.d.	1.8	n.d.
Example 107	7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0880	2.0	0.0683	2.9	n.d.
Example 108	7-((3-Fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	0.0657	2.1	0.0314	2.4	n.d.
Example 113	3-Cyclopropyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5<i>H</i>)-one	3.68	1.5	1.18	n.d.	n.d.
Example 115	2-(2-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	n.d.	3.8	0.0325	n.d.	n.d.
Example 116	7-((3-Fluorophenyl)ethynyl)-2-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	n.d.	2.3	0.0147	n.d.	n.d.
Example 117	2-(3-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	n.d.	n.d.	0.0714	n.d.	n.d.
Example 118	2-(3-Methylbenzyl)-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	n.d.	2.1	0.104	n.d.	n.d.

Example 120	2-(4-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	n.d.	4.1	0.0852	n.d.	n.d.
Example 121	2-(4-Methylbenzyl)-7-(<i>m</i> -tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	n.d.	3.0	0.0849	n.d.	n.d.
Example 122	7-((3-Fluorophenyl)ethynyl)-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	n.d.	2.3	0.0557	n.d.	n.d.
Example 123	2-(2-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	n.d.	n.d.	0.0274	n.d.	n.d.
Example 124	2-(2-Fluorobenzyl)-7-(<i>m</i> -tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	n.d.	2.3	0.0315	n.d.	n.d.
Example 125	2-(2-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	n.d.	n.d.	0.0425	n.d.	n.d.
Example 126	Phenyl(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methanone	0.168	1.9	0.864	n.d.	n.d.

Example 127	(<i>R</i>)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0160	n.d.	0.0290	n.d.	n.d.
Example 128	(<i>R</i>)-2-(1-Phenylethyl)-7-(<i>m</i> -tolylethynyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0693	3.4	0.0619	n.d.	n.d.
Example 129	(<i>R</i>)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0241	3.1	0.0259	n.d.	n.d.
Example 130	2-(3-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0031	n.d.	0.0332	5.4	n.d.
Example 131	2-(3-Fluorobenzyl)-7-(<i>m</i> -tolylethynyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0610	2.2	0.0398	2.7	n.d.
Example 132	2-(3-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.00951	n.d.	0.0497	5.1	n.d.
Example 133	2-(4-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.00639	n.d.	0.0184	5.7	n.d.

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Example 134	2-(4-Fluorobenzyl)- 7-(<i>m</i> -tolylethynyl)- 3,4- dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.103	2.7	0.0615	3.3	n.d.
Example 135	2-(4-Fluorobenzyl)- 7-((3- fluorophenyl)ethyn yl)-3,4- dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.00967	3.3	0.0413	n.d.	n.d.
Example 137	(<i>S</i>)-2-(1- Phenylethyl)-7- (phenylethynyl)-3,4- dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0739	1.7	0.0257	n.d.	n.d.
Example 138	(<i>S</i>)-7-((3- Fluorophenyl)ethyn yl)-2-(1- phenylethyl)-3,4- dihydropyrrolo[1,2- <i>a</i>]pyrazin-1(2 <i>H</i>)-one	0.0142	1.6	n.d.	n.d.	n.d.
Example 139	(7-(Phenylethynyl)- 3,4- dihydropyrrolo[1,2- <i>a</i>]pyrazin-2(1 <i>H</i>)- yl)(pyrrolidin-1- yl)methanone	n.d.	n.d.	0.382	3.1	n.d.
Example 141	2'-(Phenylethynyl)- 6',7'-dihydro-5' <i>H</i> - spiro[imidazolidine- 4,8'-indolizine]-2,5- dione	n.d.	n.d.	0.0417	n.d.	n.d.

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Example 142	1,3-Dimethyl-2'-(phenylethynyl)-6',7'-dihydro-5'<i>H</i>-spiro[imidazolidine-4,8'-indolizine]-2,5-dione	n.d.	n.d.	0.0723	n.d.	n.d.
Example 152	7-((3-Fluorophenyl)ethynyl)-2-phenethyl-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	n.d.	n.d.	0.0372	n.d.	n.d.
Example 153	2-Phenethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one,	n.d.	n.d.	0.0191	n.d.	n.d.
Example 154	2-Phenethyl-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-<i>a</i>]pyrazin-1(2<i>H</i>)-one	n.d.	n.d.	0.0229	n.d.	n.d.

Table A2

Compound	Chemical Name	Human mGluR5 (h5CHO) IC ₅₀ [μM]	Rat mGluR5 (rpA) IC ₅₀ [μM]	Rat cortex K _i [μM]
Example 18	7-Methyl-2-(<i>m</i>-tolylethynyl)-6,7-dihydro-5<i>H</i>-indolizin-8-one	0.0414	n.d.	0.00187
Example 22	7,7-Dimethyl-2-(<i>m</i>-tolylethynyl)-6,7-dihydroindolizin-8(5<i>H</i>)-one	0.206	n.d.	n.d.
Example 24	2-((6-Aminopyridin-2-yl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5<i>H</i>)-one	0.0690	0.0403	0.0404

Example 25	7,7-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0308	0.00981	n.d.
Example 30	3-((6-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile	0.0312	0.0115	0.00549
Example 31	6-Methyl-2-(<i>m</i>-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0187	0.00444	0.00778
Example 32	2-((6-Aminopyridin-2-yl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one	0.160	n.d.	0.0415
Example 34	6,6-Dimethyl-2-(<i>m</i>-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0257	n.d.	n.d.
Example 35	2-((3-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one	0.0622	0.00757	n.d.
Example 36	2-((6-Aminopyridin-2-yl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one	0.0932	n.d.	n.d.
Example 37	6,6-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0500	0.0249	n.d.
Example 38	2-((4-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one	0.248	0.0663	n.d.
Example 49	2-((3-(Fluoromethyl)phenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one	0.0156	n.d.	n.d.
Example 52	3-((6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile	0.0236	0.00745	n.d.

Example 53	3-((7-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile	0.0237	0.0406	0.00517
Example 54	2-((6-Aminopyridin-2-yl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one	0.140	n.d.	n.d.
Example 55	7-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0491	n.d.	n.d.
Example 56	2-((6-(Methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.809	n.d.	n.d.
Example 57	6-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	0.0372	n.d.	n.d.
Example 60	6-((6-(Methylamino)pyridin-2-yl)ethynyl)-2,3-dihydro-1H-pyrrolizin-1-one	0.878	n.d.	n.d.
Example 61	2-Methyl-6-(<i>m</i> -tolylethynyl)-2,3-dihydro-1H-pyrrolizin-1-one	0.0190	0.00463	n.d.
Example 67	2,2-Dimethyl-6-(<i>m</i> -tolylethynyl)-2,3-dihydro-1H-pyrrolizin-1-one	0.108	0.0650	n.d.
Example 74	2-(Imidazo[1,2- <i>a</i>]pyridin-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one	7.4 (est.)	n.d.	n.d.
Example 75	2-(Imidazo[1,2- <i>a</i>]pyridin-2-ylethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one	0.0702	0.0356	n.d.
Example 78	2-(Imidazo[1,2- <i>a</i>]pyridin-2-ylethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one	0.401	n.d.	n.d.

Example 79	2-((6-Aminopyridin-2-yl)ethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one	0.531	n.d.	n.d.
Example 83	2-Methyl-8-(phenylethynyl)-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one	0.172	n.d.	0.0137
Example 84	2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one	0.222	n.d.	n.d.
Example 86	3-((1-Oxo-2-propyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile	0.295	n.d.	0.0263
Example 92	2-Benzyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.323	n.d.	n.d.
Example 96	2-Propyl-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.098	n.d.	0.0163
Example 97	8-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3,4,5-tetrahydro-1H-pyrrolo[1,2-a][1,4]diazepin-1-one	0.187	n.d.	n.d.
Example 101	7-((3-Fluorophenyl)ethynyl)-2-isopropyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	9.0 (est.)	n.d.	n.d.
Example 102	2-Isopropyl-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	0.0147	n.d.	n.d.
Example 103	8,8-Dimethyl-2-(phenylethynyl)-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one	0.0283	n.d.	n.d.

Example 109	2-((6-Aminopyridin-2-yl)ethynyl)-8,8-dimethyl-7,8-dihydro-5H-pyrrolo[1,2-a]azepin-9(6H)-one	0.0157	n.d.	n.d.
Example 110	2-(Imidazo[1,2-a]pyridin-2-ylethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one	0.120	n.d.	n.d.
Example 111	2,2-Dimethyl-1-(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)propan-1-one	1.74	n.d.	n.d.
Example 112	3-Bromo-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one	9.5 (est.)	n.d.	n.d.
Example 114	N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxamide	< 1.0 (est.)	n.d.	n.d.
Example 119	7-((3-Fluorophenyl)ethynyl)-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	2.0 (est.)	n.d.	n.d.
Example 136	(S)-2-(1-Phenylethyl)-7-(<i>m</i>-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one	2.9 (est.)	n.d.	n.d.
Example 140	Methyl 7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate	0.164	n.d.	n.d.

Table A3

Compound	Chemical Name	h left shift (h5CHO) [fold]	Rat cortex K _i [μM]
Example 9	3-((8-Oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile	1.5	0.0112
Example 10	2-((6-Aminopyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	n.d.	0.180
Example 13	2-((3-(Fluoromethyl)phenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one	1.2	0.0111
Example 17	7-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one	1.6	0.0364
Example 19	2-((4-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one	1.6	0.0777
Example 20	2-((3-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one	1.2	0.0159
Example 21	7,7-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one	1.3	0.00581
Example 23	2-((3-Fluorophenyl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one	1.3	0.0237
Example 26	6-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one	1.3	0.0167
Example 27	2-((3-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one	1.1	0.0168

Example 28	2-((4-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one	1.5	0.117
Example 29	2-((2-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one	1.2	0.0280
Example 39	2-((2-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one	0.7	0.0758
Example 50	6-(Phenylethynyl)-2,3-dihydro-1H-pyrrolizin-1-one	1.6	0.00651
Example 51	6-((3-Fluorophenyl)ethynyl)-2,3-dihydro-1H-pyrrolizin-1-one	1.2	0.0117
Example 66	2,2-Dimethyl-6-(phenylethynyl)-2,3-dihydro-1H-pyrrolizin-1-one	1.1	0.0757
Example 88	3-((2-Methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-7-yl)ethynyl)benzonitrile	1.2	0.0462

[00420]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.

[00421]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

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

[00422]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.

[00423]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.

[00424]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.

[00425]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.

[00426]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.

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[00427]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.

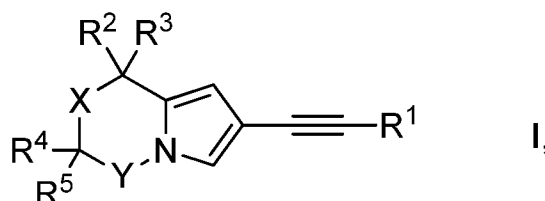
* * * * *

[00428]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.

[00429]All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

CLAIMS

1. A compound selected from those of Formula I



wherein

R^1 represents aryl, heteroaryl, cyclo C_{3-7} alkyl or heterocyclyl, wherein the cyclo C_{3-7} alkyl or heterocyclyl group may be optionally fused with an aryl or heteroaryl ring;

R^2 and R^3 , which may be the same or different, each independently represent H, C_{1-6} alkyl, F, OH, C_{1-6} alkoxy, or R^2 and R^3 together with the carbon atom to which they are attached form a carbonyl group, or R^2 and R^3 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

R^4 and R^5 , which may be the same or different each independently represent H, C_{1-6} alkyl or F or R^4 and R^5 together with the carbon atom to which they are attached form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

X represents CR^6R^7 or NR^8 ;

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R^6 and R^7 , which may be the same or different, each independently represent H, C_{1-6} alkyl, F, amino, C_{1-6} alkylamino or di- $(C_{1-6}$ alkyl)amino or R^6 and R^7 , together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

or R^3 and R^6 , together with the carbon atoms to which they are attached, may form a 4 to 7 membered ring wherein the ring may optionally contain one or two heteroatoms selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

R^8 represents H, C_{1-6} alkyl, acyl, aryl, heteroaryl, aryl- C_{1-6} alkyl, heteroaryl- C_{1-6} alkyl, or di- $(C_{1-6}$ alkyl)aminosulfonyl;

or R^2 and R^8 together with the atoms to which they are attached, may form a 4 to 7 membered ring wherein the ring may optionally contain one or two additional heteroatoms selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl which is optionally substituted by one or more halogen atoms, F, oxo, and acyl;

Y represents a bond, CR^9R^{10} or $-CR^9R^{10}-CH_2-$;

R^9 and R^{10} , which may be the same or different, each independently represent H, C_{1-6} alkyl or F or R^9 and R^{10} , together with the carbon atom to which they are attached, form a 3 to 6 membered ring, wherein the ring may optionally contain a heteroatom selected from O, S and N, and wherein the ring may be optionally substituted with one or more substituents selected from C_{1-6} alkyl, F, oxo, and acyl;

R^{11} represents H, halogen, C_{1-6} alkyl, aryl, heteroaryl, cyclo C_{3-7} alkyl or heterocyclyl;

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

2. The compound as claimed in Claim 1, wherein R^1 represents aryl or heteroaryl.
3. The compound as claimed in Claim 2, wherein R^1 represents phenyl optionally substituted by one or more substituents selected from F, C_{1-6} alkyl, cyano, and fluoromethyl; pyridyl optionally substituted by one or more substituents selected from amino and C_{1-6} alkylamino; or thienyl.
4. The compound as claimed in any preceding claim, wherein R^2 and R^3 together with the carbon atom to which they are attached form a carbonyl group.
5. The compound as claimed in any preceding claim, wherein R^4 and R^5 each independently represent H or C_{1-6} alkyl.
6. The compound as claimed in any preceding claim, wherein X represents CR^6R^7 and Y represents a bond, CR^9R^{10} , or $-CR^9R^{10}-CH_2-$.
7. The compound as claimed in any preceding claim, wherein X represents NR^8 and Y represents CR^9R^{10} or $-CR^9R^{10}-CH_2-$.
8. The compound as claimed in any preceding claim, wherein R^{11} represents hydrogen, halogen, or cyclo C_{3-7} alkyl.
9. The compound as claimed in Claim 1, which is selected from:
2-(Phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2-Fluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,6-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2,3-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,

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2-((2,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(*m*-Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
3-((8-Oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
2-((6-Aminopyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Thiophen-3-ylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Thiophen-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-(Fluoromethyl)phenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,3,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,4,6-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,3,4,5-Tetrafluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
7-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
7-Methyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((4-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
7,7-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
7,7-Dimethyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one,
7,7-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
6-Methyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((4-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
2-((2-Fluorophenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
3-((6-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
6-Methyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
6,6-Dimethyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5H)-one,
6,6-Dimethyl-2-(*m*-tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
6,6-Dimethyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,

2-((4-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((2-Fluorophenyl)ethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-((2,3,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,4,5-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,3,4-Trifluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((2,4-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3,5-Difluorophenyl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(*p*-Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(*o*-Tolylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((3-(Fluoromethyl)phenyl)ethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
6-(Phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((3-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
3-((6,6-Dimethyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
3-((7-Methyl-8-oxo-5,6,7,8-tetrahydroindolizin-2-yl)ethynyl)benzonitrile,
2-((6-Aminopyridin-2-yl)ethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
7-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-((6-(Methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
6-Methyl-2-((6-(methylamino)pyridin-2-yl)ethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7-methyl-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6-methyl-6,7-dihydroindolizin-8(5H)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5H)-one,
6-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
2,2-Dimethyl-6-(phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-Methyl-6-(phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
3-((2-Methyl-1-oxo-2,3-dihydro-1*H*-pyrrolizin-6-yl)ethynyl)benzonitrile,
3-((2,2-Dimethyl-1-oxo-2,3-dihydro-1*H*-pyrrolizin-6-yl)ethynyl)benzonitrile,
3-((1-Oxo-2,3-dihydro-1*H*-pyrrolizin-6-yl)ethynyl)benzonitrile,

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6-((3-Fluorophenyl)ethynyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((3-Fluorophenyl)ethynyl)-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-Aminopyridin-2-yl)ethynyl)-2,2-dimethyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-Aminopyridin-2-yl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-((6-Aminopyridin-2-yl)ethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-(Phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
8,8-Dimethyl-2-(phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
8-((6-Aminopyridin-2-yl)ethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
8-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
2-Methyl-8-(phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
8-(Phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Methyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((6-Aminopyridin-2-yl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
1-(7-((6-Aminopyridin-2-yl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)-2,2-dimethylpropan-1-one,
7-((6-Aminopyridin-2-yl)ethynyl)-*N,N*-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide,
N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide,
2,2-Dimethyl-1-(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)propan-1-one,
2-(Phenylethynyl)-5,6,7,8-tetrahydroindolizine,
6-(Phenylethynyl)-2,3-dihydro-1*H*-pyrrolizine,
2-(Phenylethynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine,

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6-((2-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((4-Fluorophenyl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
6-((6-(Methylamino)pyridin-2-yl)ethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-Methyl-6-(*m*-tolylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-((2-Fluoro-3-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((2-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Fluoro-3-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2,2-Dimethyl-6-(phenylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2,2-Dimethyl-6-(*m*-tolylethynyl)-2,3-dihydro-1*H*-pyrrolizin-1-one,
2-((3-Fluorophenyl)ethynyl)-5,6,7,8-tetrahydroindolizin-8-ol,
2-((2-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluoro-4-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((3-Fluoro-5-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((5-Fluoro-2-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7,7-dimethyl-6,7-dihydroindolizin-8(5*H*)-one,
2-((2-Fluoro-6-methylphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((5-Chlorothiophen-2-yl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6-methyl-6,7-dihydroindolizin-8(5*H*)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
8-(Phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
2-((3-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-((4-Hydroxyphenyl)ethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
2-Methyl-8-(phenylethynyl)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-7-methyl-6,7-dihydroindolizin-8(5*H*)-one,
2-(Phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
3-((1-Oxo-2-propyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl)ethynyl)benzonitrile,
2-Methyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,

3-((2-Methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl)ethynyl)benzonitrile,
7-((3-Fluorophenyl)ethynyl)-2-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Methyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Benzyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Benzyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Benzyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
3-((2-Benzyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-7-yl)ethynyl)benzonitrile,
7-(Phenylethynyl)-2-propyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Propyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
8-((6-Aminopyridin-2-yl)ethynyl)-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepin-1-one,
2-Ethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Butyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Butyl-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-isopropyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Isopropyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
8,8-Dimethyl-2-(phenylethynyl)-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-Phenyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-Phenyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-((6-Aminopyridin-2-yl)ethynyl)-8,8-dimethyl-7,8-dihydro-5*H*-pyrrolo[1,2-*a*]azepin-9(6*H*)-one,
2-(Imidazo[1,2-*a*]pyridin-2-ylethynyl)-6,6-dimethyl-6,7-dihydroindolizin-8(5*H*)-one,
2,2-Dimethyl-1-(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)propan-1-one,
3-Bromo-2-(phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,
3-Cyclopropyl-2-(phenylethynyl)-6,7-dihydroindolizin-8(5*H*)-one,

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N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxamide,
2-(2-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-(2-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Methylbenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-(3-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Methylbenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Methylbenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
7-((3-Fluorophenyl)ethynyl)-2-(4-methylbenzyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(2-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(2-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(2-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
Phenyl(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)methanone,
(*R*)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*R*)-2-(1-Phenylethyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(*R*)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(3-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Fluorobenzyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Fluorobenzyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
2-(4-Fluorobenzyl)-7-((3-fluorophenyl)ethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,

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(S)-2-(1-Phenylethyl)-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(S)-2-(1-Phenylethyl)-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(S)-7-((3-Fluorophenyl)ethynyl)-2-(1-phenylethyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one,
(7-(Phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone,
Methyl 7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate,
2'-(Phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione,
1,3-Dimethyl-2'-(phenylethynyl)-6',7'-dihydro-5'*H*-spiro[imidazolidine-4,8'-indolizine]-2,5-dione,
cis-9-(Phenylethynyl)-4-propyl-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-9-(Phenylethynyl)-4-(3,3,3-trifluoropropyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-9-(Phenylethynyl)-4-(2,2,2-trifluoroethyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-4-(2,2-Difluoroethyl)-9-(phenylethynyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-4-(2-Fluoroethyl)-9-(phenylethynyl)-3,4,4a,5,6,10b-hexahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine,
cis-Methyl 9-(phenylethynyl)-4a,5,6,10b-tetrahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine-4(3*H*)-carboxylate,
cis-*N,N*-Dimethyl-9-(phenylethynyl)-4a,5,6,10b-tetrahydro-2*H*-[1,4]oxazino[3,2-*g*]indolizine-4(3*H*)-carboxamide,
Azetidin-1-yl(*cis*-9-(phenylethynyl)-5,6-dihydro-2*H*-[1,4]oxazino[3,2-*g*]indolizin-4(3*H*,4a*H*,10b*H*)-yl)methanone,
N,N-Dimethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-sulfonamide,
7-(Phenylethynyl)-2-(pyrimidin-2-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine,
Morpholino(7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)methanone,

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7-((3-Fluorophenyl)ethynyl)-2-phenethyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,

2-Phenethyl-7-(phenylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,

2-Phenethyl-7-(*m*-tolylethynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one,

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, synucleinopathies, alpha-synucleinopathies, Lewy body dementia, neurodegeneration with Brain Iron Accumulation, Parkinson-plus syndrome, Pick's disease, progressive supranuclear palsy (PSP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), neurodegenerative diseases, 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,

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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 negative symptoms of schizophrenia, cognitive deficits of schizophrenia, spasticity, Tourette's syndrome, urinary incontinence, vomiting, pruritic conditions, pruritis, sleep disorders,

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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, synucleinopathies, alpha-synucleinopathies, Lewy body dementia, neurodegeneration with Brain Iron Accumulation, Parkinson-plus syndrome, Pick's disease, progressive supranuclear palsy (PSP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), neurodegenerative diseases,

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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,

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neuropathic pain, diabetic neuropathic pain (DNP), pain related to rheumatic arthritis, allodynia, hyperalgesia, nociceptive pain, cancer pain, posttraumatic stress disorder (PTSD), schizophrenia, positive or negative symptoms of schizophrenia, cognitive deficits 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.

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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, synucleinopathies, alpha-synucleinopathies, Lewy body dementia, neurodegeneration with Brain Iron Accumulation, Parkinson-plus syndrome, Pick's disease, progressive supranuclear palsy (PSP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), neurodegenerative diseases, 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,

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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 negative symptoms of schizophrenia, cognitive deficits 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,

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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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/061527

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61P25/00 A61K31/407 C07D487/14 C07D498/14
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

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

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A	WO 2011/015343 A1 (MERZ PHARMA GMBH & CO KGAA [DE]; HENRICH MARKUS [DE]; WEIL TANJA [SG];) 10 February 2011 (2011-02-10) page 88 - page 99; claims; examples -----	1-17
A	WO 2007/023242 A1 (MERZ PHARMA GMBH & CO KGAA [DE]; PARSONS CHRISTOPHER GRAHAM RAP [DE];) 1 March 2007 (2007-03-01) page 77 - page 83; claims; examples ----- -/-	1-17



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

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"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

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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A	WO 02/46166 A1 (HOFFMANN LA ROCHE [CH]) 13 June 2002 (2002-06-13) table-page 18; claims; examples 24, 25 -----	1-17

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