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(54) Title: METHODS AND COMPOSITIONS FOR TREATING SCHIZOPHRENIA

(57) Abstract: The invention relates to methods and compositions for treating schizophrenia or bipolar disorder (in particular, mania) by using a combination of a synaptic vesicle protein 2A (SV2A) inhibitor and an antipsychotic or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and prodrugs thereof. The methods and the compositions can be used for treating one or more positive and/or negative symptoms, as well as cognitive impairment, associated with schizophrenia or bipolar disorder (in particular, mania).

METHODS AND COMPOSITIONS FOR TREATING SCHIZOPHRENIA

[0001] This application claims priority and benefit from U.S. Provisional Patent Application 61/726,440, filed November 14, 2012, the contents and disclosures of which are incorporated herein by reference in their entirety.

Field of the Invention

[0002] The invention relates to methods and compositions for treating schizophrenia or bipolar disorder (in particular, mania). In particular, it relates to the use of a combination of a synaptic vesicle protein 2A (SV2A) inhibitor and an antipsychotic in treating a subject having or at risk for schizophrenia or bipolar disorder (in particular, mania).

Background of the Invention

[0003] Schizophrenia is a chronic psychiatric disorder, characterized by a wide spectrum of psychopathology, including positive symptoms such as aberrant or distorted mental representations (*e.g.*, hallucinations, delusions), negative symptoms characterized by diminution of motivation and adaptive goal-directed action (*e.g.*, anhedonia, affective flattening, avolition), and cognitive impairment. While abnormalities in the brain are proposed to underlie the full spectrum of psychopathology in schizophrenia, currently available antipsychotics are largely ineffective in treating cognitive impairments in schizophrenia patients.

[0004] Cognitive impairments in schizophrenia involve both frontal and temporal lobe functions that include memory, attention, processing speed, and executive control. Recent observations, drawn from preclinical animal models and human neuroimaging studies, indicate that altered brain activity/excitability in the medial temporal lobe memory system may contribute to cognitive impairment and may also play a role in augmenting psychotic symptoms due to disinhibition of dopaminergic neurons.

[0005] Cognitive deficits are increasingly recognized as a key clinical feature that can be detected in a prodromal phase and in remission, as well as during full expression of the illness but are not effectively treated by available antipsychotics. Because untreated features of schizophrenia, especially impaired cognition, predict long-term disability in patients (Green et al., *Schizophr. Res.* **2004**, 72, 41-45), it is critical to develop effective therapies for the spectrum of this illness.

Summary of the Invention

[0006] In accordance with a first aspect of the present invention, there is provided a method for treating a subject suffering from schizophrenia or bipolar disorder (in particular, mania), or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in combination with a therapeutically effective amount of an antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. In some embodiments, the methods of the present invention treat one or more positive and/or negative symptoms, as well as cognitive impairment, associated with schizophrenia. In some embodiments, the methods of the present invention treat one or more symptoms, as well as cognitive impairment, associated with bipolar disorder (in particular, mania). In some embodiments of this invention, the methods of this invention prevent or slow the progression of cognitive impairment or bipolar disorder (in particular, mania) of schizophrenia in said subject.

[0007] The SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof that is useful in the methods and compositions of this aspect of the invention include those disclosed in, for example, United States (U.S.) Patent Application 12/580,464 (Pub. No. US-2010-0099735), U.S. Patent Application 13/287,531 (Pub. No. US-2012-0046336), U.S. Patent Application 13/370,253 (Pub. No.US-2012-0214859), International Patent Application PCT/US2009/005647 (Pub. No. WO2010/044878), International Patent Application PCT/US12/24556 (Pub. No. WO2012/109491), U.S. Patent Provisional Application 61/105,847, 61/152,631, 61/175,536, and 61/441,251.. However, any SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be used in the methods and compositions of this aspect of the invention. In other embodiments, the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Applications WO2010/144712; WO2010/002869; WO2008/132139;

WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188; WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692 or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs. In other embodiments, the SV2A inhibitor is selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof. In other embodiments, the SV2A inhibitor is levetiracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. In other embodiments, the SV2A inhibitor is brivaracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. In other embodiments, the SV2A inhibitor is seletracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof.

[0008] The antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof that is useful in the methods and compositions of this invention include both typical and atypical antipsychotics.

[0009] In some embodiments, the antipsychotics suitable for use in the present invention are selected from atypical antipsychotics, including, but not limited to, those disclosed in, for example, U.S. Patents 4,734,416; 5,006,528; 4,145,434; 5,763,476; 3,539,573; 5,229,382; 5,532,372; 4,879,288; 4,804,663; 4,710,500; 4,831,031; and 5,312,925, and EP Patents EP402644 and EP368388, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0010] In some embodiments, atypical antipsychotics suitable for use in the present invention include, but are not limited to, aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof. In some embodiments, the antipsychotic of this invention is selected from aripiprazole (Bristol-Myers Squibb), olanzapine (Lilly) and ziprasidone (Pfizer), and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0011] In some embodiments, the antipsychotics suitable for use in the present invention are typical antipsychotics, including, but not limited to, acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

[0012] In some embodiments of the present invention, the antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be selected from compounds that are dopaminergic agents (such as dopamine D1 receptor antagonists or agonists, dopamine D_2 receptor antagonists or partial agonists, dopamine D3 receptor antagonists or partial agonists, dopamine D4 receptor antagonists), glutamatergic agents, N-methyl-D-aspartate (NMDA) receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs) (e.g., mGluR2/3 agonists or PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents (such as alpha-2 adrenergic receptor agonists or antagonists and catechol-O-methyl transferase (COMT) inhibitors), serotonin receptor modulators (such as 5-HT_{2A} receptor antagonists, 5-HT_{1A} receptor partial agonists, 5-HT_{2C} agonists, and 5-HT6 antagonists), cholinergic agents (such as alpha-7 nicotinic receptor agonists, alpha4-beta2 nicotinic receptor agonists, allosteric modulators of nicotinic receptors and acetylcholinesterase inhibitors, muscarinic receptor agonists and antagonists), cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, monoamine oxidase (MAO) B inhibitors, PDE10 inhibitors, neuronal nitric oxide synthase (nNOS) inhibitors, neurosteroids, and neurotrophic factors.

[0013] In some embodiments, the antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof that is useful in the methods and compositions of this invention include compounds that may be used to treat at least one sign or symptom of schizophrenia or bipolar disorder (in particular, mania).

[0014] In some embodiments of this aspect of the invention, the antipsychotic is administered at a dose that is subtherapeutic as compared to the dose at which it is therapeutically effective when administered in the absence of the SV2A inhibitor.

[0015] In some embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof can be administered at doses as disclosed, for example, in United States (U.S.) Patent Application 12/580,464 (Pub. No. US-2010-0099735), U.S. Patent Application 13/287,531 (Pub. No. US-2012-0046336), U.S. Patent Application 13/370,253 (Pub. No.US-2012-0214859), International Patent Application PCT/US2009/005647 (Pub. No. WO2010/044878), International Patent Application PCT/US12/24556 (Pub. No. WO2012/109491), U.S. Patent Provisional Application 61/105,847, 61/152,631, 61/175,536, and 61/441,251. In other embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered at a daily dose of about 0.001 mg/kg to 5 mg/kg. In other embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered every 12 or 24 hours at a daily dose of about 0.1 to 5 mg/kg, or about 1 to 2 mg/kg, or about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5 mg/kg, or about 0.6 to 1.8 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 0.01 to 1 mg/kg, or about 0.001 to 1 mg/kg, or about 0.5 mg/kg to 5 mg/kg, or about 0.05 mg/kg to 0.5 mg/kg; or at a daily dose of 0.0015 - 7 mg/kg, 0.0015 - 5 mg/kg, 0.01 - 5 mg/kg, 0.05 - 4.0 mg/kg, 0.05 - 2 mg/kg, 0.05 - 1.5 mg/kg, 0.1 - 1 mg/kg, 1 - 5 mg/kg, 1.5 - 4 mg/kg, or 1.8 - 3.6 mg/kg. In other embodiments of this aspect of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered every 12 or 24 hours at a daily dose of about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5 mg/kg, or about 0.6 to 1.8 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 2.0 to 4.0 mg/kg, or about 2.0 to 3.0 mg/kg, or about 3.0 to 4.0 mg/kg, or about 0.2 to 0.4 mg/kg, or about 0.2 to 0.3 mg/kg, or about 0.3 to 0.4 mg/kg, or about 0.001 - 5 mg/kg, or about 0.001 - 0.5 mg/kg, or about 0.01 - 0.5 mg/kg. In some embodiments, the SV2A inhibitor may be selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs, polymorphs, or prodrugs thereof, said SV2A inhibitor being administered every 12 or 24 hours at a daily dose selected from any of the above. In some embodiments, a subtherapeutic amount of the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is used. Such subtherapeutic amount, may be, for example, a daily dose of less than 7 mg/kg, less than 6 mg/kg, less than 5 mg/kg, less than 4 mg/kg, less than 3.8 mg/kg, less than 3.6 mg/kg, less than 3.4 mg/kg, less than 3.2 mg/kg, less than 3 mg/kg, less than 2.9 mg/kg, less than 2.8 mg/kg, less than 2.7 mg/kg, less than 2.6 mg/kg, less than 2.5 mg/kg, less than 2.4 mg/kg, less than 2.3 mg/kg, less than 2.2 mg/kg, less than 2.1 mg/kg, less than 2 mg/kg, less than 1.5 mg/kg, less than 1 mg/kg, less than 0.5 mg/kg, less than 0.1 mg/kg, less than 0.05 mg/kg, less than 0.01 mg/kg, or less than 0.0015 mg/kg; or less than 500 mg, less than 420 mg, less than 400 mg, less than 350 mg, less than 300 mg, less than 280 mg, less than 270 mg, less than 260 mg, less than 250 mg, less than 240 mg, less than 230 mg, less than 225 mg, less than 220 mg, less than 210 mg, less than 200 mg, less than 190 mg, less than 180 mg, less than 175 mg, less than 170 mg, less than 150 mg, less than 140 mg, less than 125 mg, less than 120 mg, less than 110 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 28 mg, less than 25 mg, less than 20 mg, less than 15 mg, less than 12 mg, less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5.5 mg, less than 5 mg, less than 4.2 mg, less than 3.5 mg, less than 3 mg, less than 2.8 mg, less than 2.5 mg, less than 2.0 mg, less than 1.5 mg, less than 0.7 mg, less than 0.35 mg, less than 0.18 mg, less than 0.15 mg, or less than 0.1 mg is administered. The SV2A inhibitors that can be used in the foregoing embodiments include, for example, levetiracetam, brivaracetam, and seletracetam or their pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof.

[0016] In some embodiments, the SV2A inhibitor present in the composition of this invention is administered at a daily dose of 0.0015 to 7 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.1 - 500 mg/day). Daily doses that may be used include, but are not limited to 0.0015 mg/kg, 0.002 mg/kg, 0.0025 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1 mg/kg, 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.8 mg/kg, 2.0 mg/kg, 2.2 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.8 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 6.0 mg/kg, or 7.0 mg/kg; or 0.1 mg, 0.15 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.8 mg, 3.0 mg, 3.5 mg, 4.2 mg, 5 mg, 5.5 mg, 6.0 mg, 7 mg, 8 mg, 9 mg, 10 mg, 12 mg, 15 mg, 20 mg, 25 mg, 28 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 125 mg, 140 mg, 150 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 225 mg, 250 mg, 280 mg, 300 mg, 350 mg, 400 mg, or 500 mg, or within the range of 0.0015 - 5 mg/kg, 0.01 - 0.8 mg/kg, 0.01 - 1 mg/kg, 0.01 - 1.5 mg/kg, 0.01 - 2 mg/kg, 0.01 - 2.5 mg/kg, 0.01 - 3 mg/kg, 0.01 - 3.5 mg/kg, 0.01 - 4 mg/kg, 0.01 - 5 mg/kg, 0.025 - 0.8 mg/kg, 0.025 - 1 mg/kg, 0.025 - 1.5 mg/kg, 0.025 - 2 mg/kg, 0.025 - 2.5 mg/kg, 0.025 - 3 mg/kg, 0.025 - 3.5 mg/kg, 0.025 - 4 mg/kg, 0.05 - 0.8 mg/kg, 0.05 - 1 mg/kg, 0.05 - 1.5 mg/kg, 0.05 - 2 mg/kg, 0.05 - 2.5 mg/kg, 0.05 - 3 mg/kg, 0.05 - 3.5 mg/kg, 0.05 - 4 mg/kg, 0.075 - 0.8 mg/kg, 0.075 - 1 mg/kg, 0.075 - 1.5 mg/kg, 0.075 - 2 mg/kg, 0.075 - 2.5 mg/kg, 0.075 - 3 mg/kg, 0.075 - 3.5 mg/kg, 0.075 - 4 mg/kg, 0.1

- 0.8 mg/kg, 0.1 - 1 mg/kg, 0.1 - 1.5 mg/kg, 0.1 - 2 mg/kg, 0.1 - 2.5 mg/kg, 0.1 - 3 mg/kg, 0.1 - 3.5 mg/kg, 0.1 - 4 mg/kg, 0.2 - 0.8 mg/kg, 0.2 - 1 mg/kg, 0.2 - 1.5 mg/kg, 0.2 - 2 mg/kg, 0.2 - 2.5 mg/kg, 0.2 - 3 mg/kg, 0.2 - 3.5 mg/kg, 0.2 - 4 mg/kg, 0.5 - 0.8 mg/kg, 0.5 - 1 mg/kg, 0.5 - 1.5 mg/kg, 0.5 - 2 mg/kg, 0.5 - 2.5 mg/kg, 0.5 - 3 mg/kg, 0.5 - 3.5 mg/kg, or 0.5 - 4 mg/kg; or within the range of 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg. In some embodiments, the levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is present in the composition of this invention in an amount of 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg; or 0.1 mg, 0.15 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.8 mg, 3.0 mg, 3.5 mg, 4.2 mg, 5 mg, 5.5 mg, 6.0 mg, 7 mg, 8 mg, 9 mg, 10 mg, 12 mg, 15 mg, 20 mg, 25 mg, 28 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 125 mg, 140 mg, 150 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 225 mg, 250 mg, 280 mg, 300 mg, 350 mg, 400 mg, or 500 mg. In some embodiments, a subtherapeutic amount of the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is used. The SV2A inhibitors that can be used in the foregoing embodiments include, for example, levetiracetam, brivaracetam, and seletracetam or their pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof.

[0017] In some embodiments, the SV2A inhibitor present in the composition of this invention is levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and is administered at according to one of the daily dose ranges indicated as "+" listed in Table 1 or Table 2. In some embodiments, the levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is present in the composition of this invention in an amount of about 70 to 140 mg, or about 7 to 180 mg, or about 25 to 180 mg, or about 40 to 130 mg, or about 140 to 300 mg, or about 200 to 300 mg, or about 140 to 200 mg, or about 7 to 350 mg, about 70 - 350 mg, about 100 - 300 mg, or about 125 -250 mg. In some embodiments, a subtherapeutic amount of levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is used.

[0018] In some embodiments, the SV2A inhibitor present in the composition of this invention is brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and is administered at according to one of the daily dose ranges indicated as "+" listed in Tables 3-6. In some embodiments, the brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is present in the composition of this invention in an amount of about 7 to 15 mg, or about 0.7 to 180 mg, or about 2.5 to 180 mg, or about 4.0 to 130 mg, or about 14 to 30 mg, or about 0.1 - 35 mg, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, or 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15

- 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg. In some embodiments, a subtherapeutic amount of brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is used.

[0019] In some embodiments, the SV2A inhibitor present in the composition of this invention is seletracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and is administered at according to one of the daily dose ranges indicated as "+" listed in Tables 7-10. In some embodiments, the seletracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is present in the composition of this invention in an amount of about 7 to 15 mg, or about 0.7 to 180 mg, or about 2.5 to 180 mg, or about 4.0 to 130 mg, or about 14 to 30 mg, or about 0.1 - 35 mg, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, or 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg. In some embodiments, a subtherapeutic amount of seletracetam or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is used.

[0020] In some embodiments of the invention, the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs are administered simultaneously, or sequentially, or in a single formulation, or in separate formulations packaged together. In other embodiments, the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs are administered via different routes. As used herein, “combination” includes administration by any of these formulations or routes of administration.

[0021] In some embodiments of the invention, the combined treatment has a longer or improved therapeutic effect in the subject than is attained by administering the antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in the absence of the SV2A inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or prodrug thereof by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

[0022] In some embodiments of the invention, the combined treatment has a longer or improved therapeutic effect in the subject than is attained by administering the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in the absence of the antipsychotic or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, or prodrug thereof by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

[0023] In accordance with another aspect of the present invention, there is provided a method of increasing the therapeutic index of an antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in a method of treating schizophrenia or bipolar disorder (in particular, mania) in a subject in need or at risk thereof, comprising administering an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in combination with the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof to said subject.

[0024] In some embodiments, the increase in the therapeutic index of the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is greater than the therapeutic index of the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof when administered in the absence of the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

[0025] In accordance with another aspect of the present invention, there is provided a method of increasing the therapeutic index of an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in a method of treating schizophrenia or bipolar disorder (in particular, mania) in a subject in need or at risk thereof, comprising administering the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in combination with an antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof to said subject.

[0026] In some embodiments, the increase in the therapeutic index of the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is greater than the therapeutic index of the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof when administered in the absence of the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

[0027] In accordance with another aspect of this invention, there is provided a pharmaceutical composition for treating a subject suffering from schizophrenia or bipolar disorder (in particular, mania), or at risk thereof, the composition comprising an SV2A inhibitor and an antipsychotic or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof. In some embodiments, the composition of this invention is for treating one or more positive and/or negative symptoms, as well as cognitive impairment, associated with schizophrenia. In some embodiments, the composition of this invention is for treating one or more symptoms, as well as cognitive impairment, associated with bipolar disorder (in particular, mania). In some embodiments, the composition is in a solid form (e.g., capsule or tablet). In some embodiments, the composition is in a liquid form. In some embodiments, the composition is in an aqueous solution. In some embodiments, the composition is in a suspension form. In some embodiments, the composition is in a sustained release form, or a controlled release form, or a delayed release form, or an extended release form. In some embodiments, the composition is in a unit dosage form. In other embodiments, the two components of the compositions are in separate delivery forms packaged together. In some embodiments, the composition is for oral administration. In some embodiments, the composition is in a unit dosage form. In some embodiments, the composition is administered once daily. In some embodiments, the composition is administered twice daily.

[0028] In some embodiments, both the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof are in an extended release form present in the composition. In some embodiments, both the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof are not in an extended release form present in the composition. In some embodiments, the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition is in an extended release form, while the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition is not in an extended release form. For example, the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in an immediate release form. In some embodiments, the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition is not in an extended release form, while the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition is in an extended release form. For example, the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in an immediate release form. In some embodiments, the extended release SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition does not affect the pharmacokinetics or the half-life clearance of the antipsychotics or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the same composition. In some embodiments, the extended release antipsychotics or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition does not affect the pharmacokinetics or the half-life clearance of SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the same composition. In some embodiments, the extended release form SV2A inhibitor includes without limitation a controlled release form, a prolonged release form, a sustained release form, a delayed release form, or a slow release form. In some embodiments, the extended release form antipsychotics includes without limitation a controlled release form, a prolonged release form, a sustained release form, a delayed release form, or a slow release form. The SV2A inhibitor that can be used in the composition according to the foregoing embodiments include, without limitation, levetiracetam, brivaracetam, seletracetam and their pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof.

[0029] In some embodiments of this invention, the composition comprises levetiracetam, brivaracetam, seletracetam, or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and an antipsychotic or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof.

[0030] In some embodiments of this invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in the composition is present in an amount of 0.07 - 350 mg, or 50 - 250 mg, 3 - 50 mg, 0.1 - 500 mg, 0.1 - 350 mg, 0.7 - 350 mg, 3 - 300 mg, 3 - 150 mg, 3 - 110 mg, 7 - 70 mg, 70 - 350 mg, 100 - 300 mg, or 125 - 250 mg. In some embodiments, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is present in an amount less than 500 mg, less than 350 mg, less than 300 mg, less than 250 mg, less than 200 mg, less than 150 mg, less than 110 mg, less than 100 mg, less than 70 mg, less than 50 mg, less than 35 mg, less than 10 mg, less than 7 mg, less than 5 mg, less than 3 mg, less than 1 mg, less than 0.7 mg, less than 0.5 mg, less than 0.1 mg, less than 0.07 mg, or less than 0.05 mg. In certain embodiments of this aspect of the invention, the SV2A inhibitor is present in an amount of 0.07 – 60 mg, 0.07 – 350 mg, 25 – 60 mg, 25 – 125 mg, 50 – 250 mg, 5 – 140 mg, 0.7 – 180 mg, 125 – 240 mg, 3 - 50 mg, or 3 – 60 mg . In other embodiments of this aspect of the invention, the SV2A inhibitor is present in an amount of 0.05 - 35 mg. In some embodiments of the composition of this invention, the SV2A inhibitor may be selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof, said SV2A inhibitor being present in an amount selected from any of the above.

[0031] In some embodiments, the effect of the treatment is measured by detecting the difference between the levels of reelin in the subject prior to and after the administration step.

[0032] In some embodiments, the effect of the treatment is measured by detecting the difference between the levels of somatostatin in the subject prior to and after the administration step.

Brief Description of the Drawings

[0033] **FIG. 1** depicts increased mRNA expression of the gene encoding SV2A in the dentate gyrus of the hippocampus of aged-impaired rats (AI) as compared to young rats (Y) and aged-unimpaired rats (AU). Normalized Affymetrix GeneChip probe set signal values (Y-axis), as a measure of mRNA expression, are plotted against learning indices of different rats, as a measure of cognitive impairment.

[0034] **FIG. 2** depicts the effects of administering levetiracetam on the spatial memory retention of six aged-impaired rats (AI) in a Morris Water Maze (MWM) test. Three treatment conditions are employed: vehicle control, levetiracetam (5 mg/kg/day) and levetiracetam (10 mg/kg/day). The AI rats are trained for two consecutive days, with a one-time treatment prior to the training trials per day. 24 hours later, the AI rats are tested. The time the AI rats, 24 hours after treatment with the different conditions and two days of training, spent swimming in the target quadrant or the target annulus in a memory retention trial is used as a measure of spatial memory retention. The target quadrant refers to the quadrant of the maze (which is a circular pool) where the escape platform is placed during the training trials. The target annulus refers to the exact location of the escape platform during the training trials.

[0035] **FIG. 3** depicts the effects of administering levetiracetam on the spatial memory retention of ten aged-impaired rats (AI) in an eight-arm Radial Arm Maze (RAM) test. Six treatment conditions are employed: vehicle control, levetiracetam (1.25 mg/kg), levetiracetam (2.5 mg/kg), levetiracetam (5 mg/kg), levetiracetam (10 mg/kg) and levetiracetam (20 mg/kg). In the RAM task used, there is a one-hour delay between presentation of a subset of arms (5 arms available and 3 arms blocked) and completion of the eight-arm win-shift task (eight arms available). Rats are pre-treated 30 – 40 minutes before daily trials with a one-time drug/control treatment. The number of errors made by the rats after the delay is used as a measure of spatial memory retention. Errors are defined as instances when rats enter an arm from which food has already been retrieved in the pre-delay component of the trial or when rats re-visit an arm in the post-delay session that has already been visited. Paired t-tests are used to compare the number of errors between different doses of levetiracetam and vehicle control.

[0036] **FIG. 4** depicts the effects of administering levetiracetam or valproate separately on the spatial memory retention of ten aged-impaired rats (AI) in an eight-arm Radial Arm Maze (RAM) test.

[0037] **FIG. 5** depicts the effects of administering levetiracetam or valproate in combination on the spatial memory retention of ten aged-impaired rats (AI) in an eight-arm Radial Arm Maze (RAM) test.

[0038] **FIG. 6** shows an isobologram plotting levetiracetam dose against valproate dose. The diagonal straight line is the line of additivity, anchored on each axis by the lowest effective doses of valproate and levetiracetam when assessed individually.

[0039] **FIG. 7** depicts the experimental design of the human trials for levetiracetam treatment.

[0040] **FIG. 8A** depicts the average activity in the left CA3 of aMCI subjects with placebo treatment and age-matched control subjects with placebo treatment during the presentation of lure stimuli that the subject correctly identified as "similar."

[0041] **FIG. 8B** depicts the average activity in the left CA3 of aMCI subjects with placebo treatment or levetiracetam treatment (125 mg twice a day for two weeks) during the presentation of lure stimuli that the subject correctly identified as "similar."

[0042] **FIG. 8C** is a table of the data represented in **FIGS. 8A** and **8B**.

[0043] **FIG. 9A** depicts the average activity in the left entorhinal cortex of age-matched control subjects with placebo treatment and aMCI subjects with placebo treatment during the presentation of lure stimuli that the subject correctly identify as "similar."

[0044] **FIG. 9B** depicts the average activity in the left entorhinal cortex of the same aMCI subjects with placebo treatment or levetiracetam treatment (125 mg twice a day for two weeks) during the presentation of lure stimuli that the subject correctly identify as "similar."

[0045] **FIG. 9C** is a table of the data represented in **FIGS. 9A** and **9B**.

[0046] **FIG. 10A** depicts an example of the sequence of images shown to subjects in the explicit 3-alternative forced choice task described in Example 2.

[0047] **FIG. 10B** shows sample pairs of similar ("lure") images.

[0048] **FIG. 11** shows the difference between the aMCI (placebo) subjects and age-matched control (placebo) subjects in their performance of the explicit 3-alternative forced choice task described in Example 2. Each bar represents the proportion of the subject responses (old, similar, or new) when presented with a lure image.

[0049] **FIG. 12** shows the difference between the same aMCI subjects with placebo treatment or with levetiracetam treatment (125 mg twice a day for two weeks) in their performance of the explicit 3-alternative forced choice task described in Example 2. Each bar represents the proportion of the subjects responses (old, similar, or new) when presented with a lure image.

[0050] **FIG. 13** is a table of the data represented in **FIGS. 11** and **12**.

[0051] **FIG. 14A** shows the difference between the age-matched control (placebo) subjects and the aMCI subjects treated with placebo or with levetiracetam (125 mg twice a day for two weeks) in their performance of the Buschke Selective reminding Test – Delayed Recall.

[0052] **FIG. 14B** is a table of the data represented in **FIG. 14A**.

[0053] **FIG. 15A** shows the difference between the control (placebo) subjects and the aMCI subjects treated with placebo or with levetiracetam (125 mg twice a day for two weeks) in their performance of the Benton Visual Retention Test.

[0054] **FIG. 15B** is a table of the data represented in **FIG. 15A**.

[0055] **FIG. 16A** shows the difference between the control (placebo) subjects and the aMCI subjects treated with placebo or with levetiracetam (125 mg twice a day for two weeks) in their performance of the Verbal Paired Associates Test - Recognition.

[0056] **FIG. 16B** is a table of the data represented in **FIG. 16A**.

[0057] **FIG. 17A** shows the difference between the control (placebo) subjects and the aMCI subjects treated with placebo or with levetiracetam (125 mg twice a day for two weeks) in their performance of the Verbal Paired Associates Test – Delayed Recall.

[0058] **FIG. 17B** is a table of the data represented in **FIG. 17A**.

[0059] **FIG. 18A** is a table showing the subject selection process for the human levetiracetam trial described in Example 2.

[0060] **FIG. 18B** is a table showing the characteristics of the subjects selected for the human levetiracetam trial described in Example 2.

0061] **FIG. 19** depicts the effects of administering brivaracetam on the memory performance of nine aged-impaired rats in an eight-arm Radial Arm Maze task. Doses of brivaracetam administered to the AI rats include 0.0625mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg. Means and SEMs for the number of errors are shown as the y-axis.

[0062] **FIG. 20** depicts the effects of administering seletracetam on the memory performance of nine aged-impaired rats in an eight-arm Radial Arm Maze test. Doses of seletracetam administered to the AI rats include 0.0625mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg. Means and SEMs for the number of errors are shown as the y-axis.

[0063] FIG. 21A and FIG. 21B depict the performance of aged-impaired rats (n = 3/group) treated with brivaracetam at a dose of 2 mg/kg/day after 14 days in the water maze task. Rats treated with brivaracetam at 2 mg/kg/day ($t(2) = 10.000$, $p = 0.010$) but not vehicle ($t(2) = 1.964$, $p = 0.188$) show a significant spatial bias for the target quadrant compared to the other controls quadrants. Brivaracetam-treated rats (2mg/kg/day) also spend significantly more time in the target quadrant than the vehicle-treated rats, $t(4) = 3.881$, $p = 0.018$. Brivaracetam-treated rats (2mg/kg/day) spend significantly more time in the target annulus (area surrounding the location of the escape platform) than the vehicle-treated rats, $t(4) = 3.109$, $p = 0.036$.

[0064] FIG. 22A and FIG. 22B depict the effects of levetiracetam on fMRI activities in Dentate Gyrus/CA3 region of aMCI patients at a dose of 62.5 mg BID and 250 mg BID.

[0065] FIG. 23A and FIG. 23B show the difference between the aMCI (placebo) subjects and age-matched control (placebo) subjects in their performance of the explicit 3-alternative forced choice task described in Example 4 at a dose of 62.5 mg BID placebo and 250 mg BID placebo. Each bar represents the proportion of the subject responses (old, similar, or new) when presented with a lure image.

[0066] FIG. 24A and FIG. 24B show the difference between the same aMCI subjects with placebo treatment or with levetiracetam treatment (62.5 mg BID and 250 mg BID) in their performance of the explicit 3-alternative forced choice task described in Example 4. Each bar represents the proportion of the subjects responses (old, similar, or new) when presented with a lure image.

[0067] FIG. 25 shows that administering levetiracetam at a dose of 10 mg/kg/day and vehicle in osmotic minipumps for four weeks in aged-impaired rats restores sematostatin in DG hilus.

[0068] FIG. 26 shows that administering levetiracetam at a dose of 10 mg/kg/day and vehicle in osmotic minipumps for four weeks in aged-impaired rats restores reelin in Entorhinal Cortex (EC2).

[0069] **FIGS. 27A – 27C** depict the levetiracetam blood plasma levels for the aMCI patients at a dose of 62.5 mg BID, 125 mg BID and 250 mg BID levetiracetam.

Detailed Description of the Invention

Definitions

[0070] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

[0071] The methods and techniques of the present invention are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

[0072] Chemistry terms used herein are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

[0073] All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

[0074] Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

[0075] The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates otherwise.

[0076] The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.

[0077] The term “agent” is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents which are known with respect to structure, and those which are not known with respect to structure.

[0078] A “patient”, “subject”, or “individual” are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

[0079] “Cognitive function” or “cognitive status” refers to any higher order intellectual brain process or brain state, respectively, involved in learning and/or memory including, but not limited to, attention, information acquisition, information processing, working memory, short-term memory, long-term memory, anterograde memory, retrograde memory, memory retrieval, discrimination learning, decision-making, inhibitory response control, attentional set-shifting, delayed reinforcement learning, reversal learning, the temporal integration of voluntary behavior, expressing an interest in one’s surroundings and self-care, speed of processing, reasoning and problem solving and social cognition.

[0080] In humans, cognitive function may be measured, for example and without limitation, by the clinical global impression of change scale (CIBIC-plus scale); the Mini Mental State Exam (MMSE); the Neuropsychiatric Inventory (NPI); the Clinical Dementia Rating Scale (CDR); the Cambridge Neuropsychological Test

Automated Battery (CANTAB); the Sandoz Clinical Assessment-Geriatric (SCAG), the Buschke Selective Reminding Test (Buschke and Fuld, 1974); the Verbal Paired Associates subtest; the Logical Memory subtest; the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997); the Benton Visual Retention Test, or the explicit 3-alternative forced choice task, or MATRICS consensus neuropsychological test battery. *See* Folstein et al., *J Psychiatric Res* 12: 189-98, (1975); Robbins et al., Dementia 5: 266-81, (1994); Rey, L'examen clinique en psychologie, (1964); Kluger et al., *J Geriatr Psychiatry Neurol* 12:168-79, (1999); Marquis et al., 2002 and Masur et al., 1994. Also see Buchanan, R.W., Keefe, R.S.E., Umbricht, D., Green, M.F., Laughren, T., and Marder, S.R. (2011), The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophr. Bull. *37*, 1209–1217.

[0081] In animal model systems, cognitive function may be measured in various conventional ways known in the art, including using a Morris Water Maze (MWM), Barnes circular maze, elevated radial arm maze, T maze or any other mazes in which the animals use spatial information. Cognitive function can be assessed by reversal learning, extradimensional set shifting, conditional discrimination learning and assessments of reward expectancy. Other tests known in the art may also be used to assess cognitive function, such as novel object recognition and odor recognition tasks.

[0082] Cognitive function may also be measured using imaging techniques such as Positron Emission Tomography (PET), functional magnetic resonance imaging (fMRI), Single Photon Emission Computed Tomography (SPECT), or any other imaging technique that allows one to measure brain function. In animals, cognitive function may also be measured with electrophysiological techniques.

[0083] “Promoting” cognitive function refers to affecting impaired cognitive function so that it more closely resembles the function of a normal, unimpaired subject. Cognitive function may be promoted to any detectable degree, but in humans preferably is promoted sufficiently to allow an impaired subject to carry out daily activities of normal life at the same level of proficiency as a normal, unimpaired subject.

[0084] “Preserving” cognitive function refers to affecting normal or impaired cognitive function such that it does not decline or does not fall below that observed in the subject upon first presentation or diagnosis, or delays such decline.

[0085] “Improving” cognitive function includes promoting cognitive function and/or preserving cognitive function in a subject.

[0086] “Cognitive impairment” refers to cognitive function in subjects that is not as robust as that expected in a normal, unimpaired subject. In some cases, cognitive function is reduced by about 5%, about 10%, about 30%, or more, compared to cognitive function expected in a normal, unimpaired subject. In other cases, “cognitive impairment” in subjects affected by schizophrenia or bipolar disorder (in particular, mania) refers to cognitive function in subjects that is not as robust as that expected in normal, unimpaired subject.

[0087] “Schizophrenia” refers to a chronic debilitating disorder, characterized by a spectrum of psychopathology, including positive symptoms such as aberrant or distorted mental representations (*e.g.*, hallucinations, delusions), negative symptoms characterized by diminution of motivation and adaptive goal-directed action (*e.g.*, anhedonia, affective flattening, avolition), and cognitive impairment. While abnormalities in the brain are proposed to underlie the full spectrum of psychopathology in schizophrenia, currently available antipsychotics are largely ineffective in treating cognitive impairments in patients.

[0088] "Bipolar disorder" or "BP" or "manic depressive disorder" or "manic depressive illness" refers to a chronic psychological/mood disorder which can be characterized by significant mood changes including periods of depression and euphoric manic periods. BP may be diagnosed by a skilled physician based on personal and medical history, interview consultation and physical examinations. The term "mania" or "manic periods" or other variants refers to periods where an individual exhibits some or all of the following characteristics: racing thoughts, rapid speech, elevated levels of activity and agitation as well as an inflated sense of self-esteem, euphoria, poor judgment, insomnia, impaired concentration and aggression.

[0089] “Treating” a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to, preventing or slowing the progression of the disease or disorder, or alleviation, amelioration, or slowing the progression, of one or more symptoms associated with CNS disorders with cognitive impairment, such as schizophrenia or bipolar disorder (in particular, mania).

[0090] “Treating cognitive impairment” refers to taking steps to improve cognitive function in a subject with cognitive impairment so that the subject’s performance in one or more cognitive tests is improved to any detectable degree, or is prevented from further decline. Preferably, that subject’s cognitive function, after treatment of cognitive impairment, more closely resembles the function of a normal, unimpaired subject. Treatment of cognitive impairment in humans may improve cognitive function to any detectable degree, but is preferably improved sufficiently to allow the impaired subject to carry out daily activities of normal life at the same level of proficiency as a normal, unimpaired subject. In some cases, “treating cognitive impairment” refers to taking steps to improve cognitive function in a subject with cognitive impairment so that the subject’s performance in one or more cognitive tests is improved to any detectable degree, or is prevented from further decline. Preferably, that subject’s cognitive function, after treatment of cognitive impairment, more closely resembles the function of a normal, unimpaired subject. In some cases, “treating cognitive impairment” in a subject affecting by schizophrenia or bipolar disorder (in particular, mania) refers to takings steps to improve cognitive function in the subject so that the subject’s cognitive function, after treatment of cognitive impairment, more closely resembles the function of a normal, unimpaired subject.

[0091] "Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitonealy, intravenously, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow, or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods. In some aspects, the administration includes both direct administration, including self-administration, and indirect administration, including the act of prescribing a drug. For example, as used herein, a physician who instructs a patient to self-administer a drug, or to have the drug administered by another and/or who provides a patient with a prescription for a drug is administering the drug to the patient.

[0092] Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age of the subject, whether the subject is active or inactive at the time of administering, whether the subject is cognitively impaired at the time of administering, the extent of the impairment, and the chemical and biological properties of the compound or agent (e.g. solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion, or intravenously, e.g., to a subject by injection. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

[0093] "SV2A inhibitor" refers to any agent, substance or compound that binds to SV2A and reduces synaptic function by reducing pre-synaptic vesicle release (See, e.g., Noyer et al. 1995; Fuks et al. 2003; Lynch et al. 2004; Gillard et al. 2006; Custer et al., 2006; Smedt et al., 2007; Yang et al., 2007; Meehan, “Levetiracetam has an activity-dependent effect on inhibitory transmission,” *Epilepsia*, 2012 Jan 31; and Example 8 of WO 2001/62726, all of which are specifically incorporated herein by reference.) A substance, or a compound or an agent is an SV2A inhibitor even if it does not itself bind to SV2A, as long as it causes, or affects the ability of, another compound or agent to bind SV2A or reduce synaptic function by reducing pre-synaptic vesicle release. SV2A inhibitors, as used herein, include pharmaceutically acceptable salts of the inhibitors thereof. They also include hydrates, polymorphs, prodrugs, salts, and solvates of these inhibitors.

[0094] “Antipsychotic”, “antipsychotic agent”, “antipsychotic drug”, or “antipsychotic compound” refers to (1) a typical or an atypical antipsychotic; (2) an agent that is selected from dopaminergic agents, glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs) (e.g., mGluR2/3 agonists or PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents, serotonin receptor modulators, cholinergic agents, cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, nNOS inhibits, neurosteroids, and neurotrophic factors; and/or (3) an agent that is useful in treating one or more signs or symptoms of schizophrenia or bipolar disorder (in particular, mania).

[0095] “Typical antipsychotics”, as used herein, refer to conventional antipsychotics, which produce antipsychotic effects as well as movement related adverse effects related to disturbances in the nigrostriatal dopamine system. These extrapyramidal side effects (EPS) include Parkinsonism, akathisia, tardive dyskinesia and dystonia. See Baldessarini and Tarazi in Goodman & Gilman's The Pharmacological Basis of Therapeutics 10 Edition, 2001, pp. 485-520.

[0096] "Atypical antipsychotics”, as used herein, refer to antipsychotic drugs that produce antipsychotic effects with little or no EPS and include, but are not limited to, aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone. "Atypical" antipsychotics differ from conventional antipsychotics in their pharmacological profiles. While conventional antipsychotics are characterized principally by D_2 dopamine receptor blockade, atypical antipsychotics show antagonist effects on multiple receptors including the $5HT_a$ and $5HT_c$ serotonin receptors and varying degrees of receptor affinities. Atypical antipsychotic drugs are commonly referred to as serotonin/dopamine antagonists, reflecting the influential hypothesis that greater affinity for the $5HT_2$ receptor than for the D_2 receptor underlies "atypical" antipsychotic drug action or "second generation" antipsychotic drugs. However, the atypical antipsychotics often display side effects, including, but not limited to, weight gain, diabetes (e.g., type II diabetes mellitus), hyperlipidemia, QTc interval prolongation, myocarditis, sexual side effects, extrapyramidal side effects and cataract. Thus, atypical antipsychotics do not represent a homogeneous class, given their differences in the context of both alleviation of clinical symptoms and their potential for inducing side effects such as the ones listed above. Further, the common side effects of the atypical antipsychotics as described above often limit the antipsychotic doses that can be used for these agents.

[0097] The term "simultaneous administration," as used herein, means that the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs, are administered with a time separation of no more than about 15 minutes, and in some embodiments no more than about 10 minutes. When the drugs are administered simultaneously, the SV2A inhibitor and the antipsychotic, or their salts, hydrates, solvates, polymorphs or prodrugs, may be contained in the same dosage (e.g., a unit dosage form comprising both the SV2A inhibitor and the antipsychotic) or in discrete dosages (e.g., the SV2A inhibitor or its salt, hydrate, solvate, polymorph, or prodrug is contained in one dosage form and the antipsychotic or its salt, hydrate, solvate, polymorph, or prodrug is contained in another dosage form).

[0098] The term "sequential administration" as used herein means that the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, are administered with a time separation of more than about 15 minutes, and in some embodiments more than about one hour, or up to 12-24 hours. Either the SV2A inhibitor or the antipsychotic may be administered first. The SV2A inhibitor and the antipsychotic, or their salts, hydrates, solvents, or polymorphs, for sequential administration may be contained in discrete dosage forms, optionally contained in the same container or package.

[0099] A "therapeutically effective amount" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect, e.g. improving cognitive function in a subject in a subject suffering from a disease or disorder (e.g., schizophrenia or bipolar disorder (in particular, mania)), preventing or slowing the progression of a disease or disorder (e.g., schizophrenia or bipolar disorder (in particular, mania)), and/or alleviating, ameliorating, or slowing the progression of one or more symptoms associated with the disease or disorder (e.g., schizophrenia or bipolar disorder (in particular, mania)). The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, the nature and extent of the cognitive impairment, and the therapeutics or combination of therapeutics selected for administration, and the mode of administration. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

[0100] "Subtherapeutic amount" refers to an amount administered of an agent or compound of the invention that is less than the therapeutic amount, that is, less than the amount normally used when said agent or compound is administered alone (i.e., individually and in the absence of other therapeutic agents or compounds) to treat disorders, such as schizophrenia or bipolar disorder (in particular, mania).

[0101] "Analog" is used herein to refer to a compound which functionally resembles another chemical entity, but does not share the identical chemical structure. For example, an analog is sufficiently similar to a base or parent compound such that it can substitute for the base compound in therapeutic applications, despite minor structural differences.

[0102] "Derivative" is used herein to refer to the chemical modification of a compound. Chemical modifications of a compound can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. Many other modifications are also possible.

[0103] The term "prodrug" is art-recognized and is intended to encompass compounds or agents which, under physiological conditions, are converted into an SV2A inhibitor or an antipsychotic. A common method for making a prodrug is to select moieties which are hydrolyzed or metabolized under physiological conditions to provide the desired compound or agent. In other embodiments, the prodrug is converted by, for example, an enzymatic activity of the host animal to an SV2A inhibitor or an antipsychotic.

[0104] The term "aliphatic" as used herein means a straight chained or branched alkyl, alkenyl or alkynyl. It is understood that alkenyl or alkynyl embodiments need at least two carbon atoms in the aliphatic chain. Aliphatic groups typically contains from 1 (or 2) to 12 carbons, such as from 1 (or 2) to 4 carbons.

[0105] The term "aryl" as used herein means a monocyclic or bicyclic carbocyclic aromatic ring system. For example, aryl as used herein can be a C5-C10 monocyclic or C8-C12 bicyclic carbocyclic aromatic ring system. Phenyl is an example of a monocyclic aromatic ring system. Bicyclic aromatic ring systems include systems wherein both rings are aromatic, e.g., naphthyl, and systems wherein only one of the two rings is aromatic, e.g., tetralin.

[0106] The term “heterocyclic” as used herein means a monocyclic or bicyclic non-aromatic ring system having 1 to 3 heteroatom or heteroatom groups in each ring selected from O, N, NH, S, SO, or SO_2 in a chemically stable arrangement. For example, heterocyclic as used herein can be a C5-C10 monocyclic or C8-C12 bicyclic non-aromatic ring system having 1 to 3 heteroatom or heteroatom groups in each ring selected from O, N, NH, S, SO, or SO_2 in a chemically stable arrangement. In a bicyclic non-aromatic ring system embodiment of "heterocyclyl", one or both rings may contain said heteroatom or heteroatom groups. In another bicyclic "heterocyclyl" embodiment, one of the two rings may be aromatic. In yet another heterocyclic ring system embodiment, a non-aromatic heterocyclic ring may optionally be fused to an aromatic carbocycle.

[0107] Examples of heterocyclic rings include 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, benzodithiane, and 1,3-dihydro-imidazol-2-one.

[0108] The term "heteroaryl" as used herein means a monocyclic or bicyclic aromatic ring system having 1 to 3 heteroatom or heteroatom groups in each ring selected from O, N, NH or S in a chemically stable arrangement. For example, heteroaryl as used herein can be a C5-C10 monocyclic or C8-C12 bicyclic aromatic ring system having 1 to 3 heteroatom or heteroatom groups in each ring selected from O, N, NH or S in a chemically stable arrangement. In such a bicyclic aromatic ring system embodiment of "heteroaryl":

- both rings are aromatic; and
- one or both rings may contain said heteroatom or heteroatom groups.

[0109] Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, benzimidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[0110] The term "cycloalkyl or cycloalkenyl" refers to a monocyclic or fused or bridged bicyclic carbocyclic ring system that is not aromatic. For example, cycloalkyl or cycloalkenyl as used herein can be a C5-C10 monocyclic or fused or bridged C8-C12 bicyclic carbocyclic ring system that is not aromatic. Cycloalkenyl rings have one or more units of unsaturation. Preferred cycloalkyl or cycloalkenyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, norbornyl, adamantyl and decalinyl.

[0111] As used herein, the carbon atom designations may have the indicated integer and any intervening integer. For example, the number of carbon atoms in a (C1-C4)-alkyl group is 1, 2, 3, or 4. It should be understood that these designation refer to the total number of atoms in the appropriate group. For example, in a (C3-

C10)-heterocyclyl the total number of carbon atoms and heteroatoms is 3 (as in aziridine), 4, 5, 6 (as in morpholine), 7, 8, 9, or 10.

[0112] "Pharmaceutically acceptable salt" is used herein to refer to an agent or a compound according to the invention that is a therapeutically active, non-toxic base and acid salt form of the compounds. The acid addition salt form of a compound that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p- aminosalicylic, pamoic and the like. See, e.g., WO 01/062726.

[0113] Compounds containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt form, e. g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e. g., lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e. g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely, said salt forms can be converted into the free forms by treatment with an appropriate base or acid. Compounds and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like. See, e.g., WO 01/062726.

[0114] As used herein, the term "hydrate" refers to a combination of water with a compound wherein the water retains its molecular state as water and is either absorbed, adsorbed or contained within a crystal lattice of the substrate compound.

[0115] As used herein, the term "polymorph" refers to different crystalline forms of the same compound and other solid state molecular forms including pseudo-polymorphs, such as hydrates (e.g., bound water present in the crystalline structure) and solvates (e.g., bound solvents other than water) of the same compound. Different crystalline polymorphs have different crystal structures due to a different packing of the molecules in the lattice. This results in a different crystal symmetry and/or unit cell parameters which directly influences its physical properties such the X-ray diffraction characteristics of crystals or powders. A different polymorph, for example, will in general diffract at a different set of angles and will give different values for the intensities. Therefore X-ray powder diffraction can be used to identify different polymorphs, or a solid form that comprises more than one polymorph, in a reproducible and reliable way. Crystalline polymorphic forms are of interest to the pharmaceutical industry and especially to those involved in the development of suitable dosage forms. If the polymorphic form is not held constant during clinical or stability studies, the exact dosage form used or studied may not be comparable from one lot to another. It is also desirable to have processes for producing a compound with the selected polymorphic form in high purity when the compound is used in clinical studies or commercial products since Impurities present may produce undesired toxicological effects. Certain polymorphic forms may exhibit enhanced thermodynamic stability or may be more readily manufactured in high purity in large quantities, and thus are more suitable for inclusion in pharmaceutical formulations. Certain polymorphs may display other advantageous physical properties such as lack of hygroscopic tendencies, improved solubility, and enhanced rates of dissolution due to different lattice energies.

[0116] Many of the compounds useful in the methods and compositions of this invention have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45,11-30. The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds or mixtures thereof (including all possible mixtures of stereoisomers). See, e.g., WO 01/062726.

[0117] Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the invention includes both mixture and separate individual isomers. Multiple substituents on a piperidinyl or the azepanyl ring can also stand in either cis or trans relationship to each other with respect to the plane of the piperidinyl or the azepanyl ring. Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present invention. With respect to the methods and compositions of the present invention, reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically. See, e.g., WO 01/062726.

Description of Methods of the Invention

[0118] The methods of this invention comprise administration of an SV2A inhibitor or a pharmaceutically acceptable salt thereof in combination with administration of an antipsychotic or a pharmaceutically acceptable salt thereof. The agents or compounds of the SV2A inhibitor or the antipsychotic and their pharmaceutically acceptable salts also include hydrates, solvates, polymorphs, and prodrugs of those agents, compounds, and salts.

Methods of Assessing Cognitive Impairment

[0119] Animal models serve as an important resource for developing and evaluating treatments for CNS disorders with cognitive impairment. Features that characterize cognitive impairment in animal models typically extend to cognitive impairment in humans. Efficacy in such animal models is, thus, expected to be predictive of efficacy in humans. The extent of cognitive impairment in an animal model for a CNS disorder, and the efficacy of a method of treatment for said CNS disorder may be tested and confirmed with the use of a variety of cognitive tests.

[0120] A Radial Arm Maze (RAM) behavioral task is one example of a cognitive test, specifically testing spacial memory (Chappell *et al. Neuropharmacology* 37: 481-487, 1998). The RAM apparatus consists of, *e.g.*, eight equidistantly spaced arms. A maze arm projects from each facet of a center platform. A food well is located at the distal end of each arm. Food is used as a reward. Blocks can be positioned to prevent entry to any arm. Numerous extra maze cues surrounding the apparatus may also be provided. After habituation and training phases, spatial memory of the subjects may be tested in the RAM under control or test compound-treated conditions. As a part of the test, subjects are pretreated before trials with a vehicle control or one of a range of dosages of the test compound. At the beginning of each trial, a subset of the arms of the eight-arm maze is blocked.

Subjects are allowed to obtain food on the unblocked arms to which access is permitted during this initial "information phase" of the trial. Subjects are then removed from the maze for a delay period, *e.g.*, a 60 second delay, a 15 minute delay, a one-hour delay, a two-hour delay, a six hour delay, a 24 hour delay, or longer) between the information phase and the subsequent "retention test," during which the barriers on the maze are removed, thus allowing access to all eight arms. After the delay period, subjects are placed back onto the center platform (with the barriers to the previously blocked arms removed) and allowed to obtain the remaining food rewards during this retention test phase of the trial. The identity and configuration of the blocked arms vary across trials. The number of "errors" the subjects make during the retention test phase is tracked. An error occurs in the trial if the subjects entered an arm from which food had already been retrieved in the pre-delay component of the trial, or if it re-visits an arm in the post-delay session that had already been visited. A fewer number of errors would indicate better spatial memory. The number of errors made by the test subject, under various test compound treatment regimes, can then be compared for efficacy of the test compound in treating CNS disorders with cognitive impairment.

[0121] Another cognitive test that may be used to assess the effects of a test compound on the cognitive impairment of a CNS disorder model animal is the Morris water maze. A water maze is a pool surrounded with a novel set of patterns relative to the maze. The training protocol for the water maze may be based on a modified water maze task that has been shown to be hippocampal-dependent (de Hoz *et al.*, *Eur. J. Neurosci.*, 22:745-54, 2005; Steele and Morris, *Hippocampus* 9:118-36, 1999). The subject is trained to locate a submerged escape platform hidden underneath the surface of the pool. During the training trial, a subject is released in the maze (pool) from random starting positions around the perimeter of the pool. The starting position varies from trial to trial. If the subject does not locate the escape platform within a set time, the experimenter guides and places the subject on the platform to "teach" the location of the platform. After a delay period following the last training trial, a retention test in the absence of the escape platform is given to assess spatial memory. The subject's level of preference for the location of the (now absent) escape platform, as measured by, *e.g.*, the time spent in that location or the number of crossings of that location made by the mouse, indicates better spatial memory, *i.e.*, treatment of cognitive impairment. The preference for the location of the escape platform under different treatment conditions, can then be compared for efficacy of the test compound in treating CNS disorders with cognitive impairment.

[0122] There are various tests known in the art for assessing cognitive function in humans, for example and without limitation, the clinical global impression of change scale (CIBIC-plus scale); the Mini Mental State Exam (MMSE); the Neuropsychiatric Inventory (NPI); the Clinical Dementia Rating Scale (CDR); the Cambridge Neuropsychological Test Automated Battery (CANTAB); the Sandoz Clinical Assessment-Geriatric (SCAG), the Buschke Selective Reminding Test (Buschke and Fuld, 1974); the Verbal Paired Associates subtest; the Logical Memory subtest; the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997); the Benton Visual Retention Test, or MATRICS consensus neuropsychological test battery which includes tests of working memory, speed of processing, attention, verbal learning, visual learning, reasoning and problem solving and social cognition. *See* Folstein et al., *J Psychiatric Res* 12: 189-98, (1975); Robbins et al., Dementia 5: 266-81, (1994); Rey, L'examen clinique en psychologie, (1964); Kluger et al., *J Geriatr Psychiatry Neurol* 12:168-79, (1999); Marquis et al., 2002 and Masur et al., 1994. Also see Buchanan, R.W., Keefe, R.S.E., Umbricht, D., Green, M.F., Laughren, T., and Marder, S.R. (2011) The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophr. Bull. *37*, 1209–1217. Another example of a cognitive test in humans is the explicit 3-alternative forced choice task. In this test, subjects are presented with color photographs of common objects consisting of a mix of three types of image pairs: similar pairs, identical pairs and unrelated foils. The second of the pair of similar objects is referred to as the "lure". These image pairs are fully randomized and presented individually as a series of images. Subjects are instructed to make a judgment as to whether the objects seen are new, old or similar. A “similar” response to the presentation of a lure stimulus indicates successful memory retrieval by the subject. By contrast, calling the lure stimulus “old” or “new” indicates that correct memory retrieval did not occur.

Schizophrenia

[0123] This invention provides methods and compositions for treating schizophrenia or bipolar disorder (in particular, mania) using an SV2A inhibitor or a pharmaceutically acceptable salt thereof in combination with an antipsychotic or a pharmaceutically acceptable salt thereof. In certain embodiments, treatment comprises preventing or slowing the progression of schizophrenia or bipolar disorder (in particular, mania). Schizophrenia is characterized by a wide spectrum of psychopathology, including positive symptoms such as aberrant or distorted mental representations (*e.g.*, hallucinations, delusions), negative symptoms characterized by diminution of motivation and adaptive goal-directed action (*e.g.*, anhedonia, affective flattening, avolition), and cognitive impairment. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression of one or more positive and/or negative symptoms, as well as cognitive impairment, associated with schizophrenia. Further, there are a number of other psychiatric diseases such as schizotypical and schizoaffective disorder, other acute- and chronic psychoses and bipolar disorder (in particular, mania), which have an overlapping symptomatology with schizophrenia. In some embodiments, treatment comprises alleviation, amelioration or slowing the progression of one or more symptoms, as well as cognitive impairment, associated with bipolar disorder (in particular, mania). The methods and compositions may be used for human patients in clinical applications in treating schizophrenia or bipolar disorder (in particular, mania). The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

[0124] Cognitive impairments are associated with schizophrenia. They precede the onset of psychosis and are present in non-affected relatives. The cognitive impairments associated with schizophrenia constitute a good predictor for functional outcome and are a core feature of the disorder. Cognitive features in schizophrenia reflect dysfunction in frontal cortical and hippocampal circuits. Patients with schizophrenia also present hippocampal pathologies such as reductions in hippocampal volume, reductions in neuronal size and dysfunctional hyperactivity. An imbalance in excitation and inhibition in these brain regions has also been documented in schizophrenic patients suggesting that drugs targeting inhibitory mechanisms could be therapeutic. *See*, *e.g.*, Guidotti *et al.*, *Psychopharmacology* 180: 191-205, 2005; Zierhut, *Psych. Res. Neuroimag.* 183:187-194, 2010; Wood *et al.*, *NeuroImage* 52:62-63, 2010; Vinkers *et al.*, *Expert Opin. Investig. Drugs* 19:1217-1233, 2009; Young *et al.*, *Pharmacol. Ther.* 122:150-202, 2009.

[0125] Animal models serve as an important resource for developing and evaluating treatments for schizophrenia. Features that characterize schizophrenia in animal models typically extend to schizophrenia in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of schizophrenia are known in the art.

[0126] One animal model of schizophrenia is protracted treatment with methionine. Methionine-treated mice exhibit deficient expression of GAD67 in frontal cortex and hippocampus, similar to those reported in the brain of postmortem schizophrenia patients. They also exhibit prepulse inhibition of startle and social interaction deficits (Tremonlizzo *et al.*, *PNAS*, 99: 17095–17100, 2002). Another animal model of schizophrenia is methylaoxymethanol acetate (MAM)-treatment in rats. Pregnant female rats are administered MAM (20 mg/kg, intraperitoneal) on gestational day 17. MAM-treatment recapitulate a pathodevelopmental process to schizophrenia-like phenotypes in the offspring, including anatomical changes, behavioral deficits and altered neuronal information processing. More specifically, MAM-treated rats display a decreased density of parvalbumin-positive GABAergic interneurons in portions of the prefrontal cortex and hippocampus. In behavioral tests, MAM-treated rats display reduced latent inhibition. Latent inhibition is a behavioral phenomenon where there is reduced learning about a stimulus to which there has been prior exposure with any consequence. This tendency to disregard previously benign stimuli, and reduce the formation of association with such stimuli is believed to prevent sensory overload. Low latent inhibition is indicative of psychosis. Latent inhibition may be tested in rats in the following manner. Rats are divided into two groups. One group is pre-exposed to a tone over multiple trials. The other group has no tone presentation.

Both groups are then exposed to an auditory fear conditioning procedure, in which the same tone is presented concurrently with a noxious stimulus, *e.g.* an electric shock to the foot. Subsequently, both groups are presented with the tone, and the rats' change in locomotor activity during tone presentation is monitored. After the fear conditioning the rats respond to the tone presentation by strongly reducing locomotor activity. However, the group that has been exposed to the tone before the conditioning period displays robust latent inhibition: the suppression of locomotor activity in response to tone presentation is reduced. MAM-treated rats, by contrast show impaired latent inhibition. That is, exposure to the tone previous to the fear conditioning procedure has no significant effect in suppressing the fear conditioning. (*see* Lodge *et al.*, J. Neurosci., 29:2344-2354, 2009) Such animal models of schizophrenia may be used to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania).

[0127] MAM-treated rats display a significantly enhanced locomotor response (or aberrant locomotor activity) to low dose D-amphetamine administration. The MAM-treated rats also display a significantly greater number of spontaneously firing ventral tegmental dopamine (DA) neurons. These results are believed to be a consequence of excessive hippocampal activity because in MAM-treated rats, the ventral hippocampus (vHipp) inactivation (e.g., by intra-vHipp administration of a sodium channel blocker, tetrodotoxin (TTX), to MAM rats) completely reversed the elevated DA neuron population activity and also normalized the augmented amphetamine-induced locomotor behavior. The correlation of hippocampal dysfunction and the hyper-responsivity of the DA system is believed to underlie the augmented response to amphetamine in MAM-treated animals and psychosis in schizophrenia patients. See Lodge D. J. et al. *Neurobiology of Disease* (2007), 27(42), 11424-11430. The use of MAM-treated rats in the above study may be suitable for use to assay the effectiveness of the methods and compositions of the present invention in treating schizophrenia or bipolar disorder (in particular, mania). For example, the methods and compositions of this invention maybe evaluated, using MAM-treated animals, for their effects on the central hippocampus (vHipp) regulation, on the elevated DA neuron population activity and on the hyperactive locomotor response to amphetamine in the MAM-treated animals.

[0128] In MAM-treated rats, hippocampal (HPC) dysfunction leads to dopamine system hyperactivity. A benzodiazepine-positive allosteric modulator (PAM), selective for the α5 subunit of the $GABA_A$ receptor, SH-053-2'F-R-CH_3, is tested for its effects on the output of the hippocampal (HPC). The effect of SH-053-2'F-R-CH_3 on the hyperactive locomotor response to amphetamine in MAM-treated animals is also examined. The α5GABAAR PAM reduces the number of spontaneously active DA neurons in the ventral tegmental area (VTA) of MAM rats to levels observed in saline-treated rats (control group), both when administered systemically and when directly infused into the ventral HPC. Moreover, HPC neurons in both saline-treated and MAM-treated animals show diminished cortical-evoked responses following the α5GABAAR PAM treatment. In addition, the increased locomotor response to amphetamine observed in MAM-treated rats is reduced following the α5$GABA_A$R PAM treatment. See Gill K. M et al. *Neuropsychopharmacology* (2011), 1-9. The use of MAM-treated rats in the above study may be suitable for use in the present invention to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania). For example, the methods and compositions of this invention maybe evaluated, using MAM-treated animals, for their effects on the output of the hippocampal (HPC) and on the hyperactive locomotor response to amphetamine in the MAM-treated animals.

[0129] Administration of MAM to pregnant rats on embryonic day 15 (E15) severely impairs spatial memory or the ability to learn the spatial location of four items on an eight-arm radial maze in the offspring. In addition, embryonic day 17 (E17) MAM-treated rats are able to reach the level of performance of control rats at the initial stages of training, but are unable to process and retrieve spatial information when a 30-min delay is interposed, indicating a significant impairment in working memory. See Gourevitch R. et al. (2004). *Behav. Pharmacol*, 15, 287-292. Such animal models of schizophrenia may be used to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania).

[0130] Apomorphine-induced climbing (AIC) and stereotype (AIS) in mice is another animal model useful in this invention. Agents are administered to mice at a desired dose level (e.g., via intraperitoneal administration). Subsequently, e.g., thirty minutes later, experimental mice are challenges with apomorphine (e.g., with 1 mg/kg sc). Five minutes after the apomorphine injection, the sniffing-licking-gnawing syndrome (stereotyped behavior) and climbing behavior induced by apomorphine are scored and recorded for each animal. Readings can be repeated every 5 min during a 30-min test session. Scores for each animal are totaled over the 30-min test session for each syndrome (stereotyped behavior and climbing). If an effect reached at least of 50% inhibition, and ID_{50} value (95% confidence interval) is calculated using a nonlinear least squares calculation with inverse prediction. Mean climbing and stereotype scores can be expressed as a percent of control values observed in vehible treated (e.g., saline-treated) mice that receive apomorphine. See Grauer S. M. et al. *Psychopharmacology* (2009) 204, 37-48. This mice model may be used to assay the effectiveness of the methods and compositions of the invention in treating schizophrenia or bipolar disorder (in particular, mania).

[0131] The efficacy of the methods and compositions of this invention in treating schizophrenia may also be assessed in animal models of schizophrenia or bipolar disorder (in particular, mania), as well as human subjects with schizophrenia, using a variety of cognitive tests known in the art, as discussed above.

SV2A inhibitors

[0132] "Synaptic vesicle protein-2 (SV2)" is a family of synaptic vesicle proteins, which consists of three members, designated SV2A, SV2B, and SV2C. SV2A is the most widely distributed family member, being expressed ubiquitously in the brain. The proteins are integral membrane proteins and have a low-level homology (20-30%) to the twelve transmembrane family of bacterial and fungal transporter proteins that transport sugar, citrate, and xenobiotics (Bajjalieh et al., Science. 257: 1271-1273. (1992)). SV2 family proteins are present in the brain and endocrine cells, and further are present in all synaptic and endocrine vesicles. SV2 proteins are reported to play a role in normal synaptic function, and functions in a maturation step of primed vesicles that converts the vesicles into a $Ca(^{2+})$- and synaptotagmin-responsive state (Sudhof et al., 2009). Functionally, SV2 proteins are reported to enhance synaptic currents and increase the probability of transmitter release by maintaining the size of the readily releasable pool of vesicles (Custer et al., 2006).

[0133] "SV2A inhibitor" refers to any agent, substance or compound that binds to SV2A and reduces synaptic function by reducing pre-synaptic vesicle release (See, e.g., Noyer et al. 1995; Fuks et al. 2003; Lynch et al. 2004; Gillard et al. 2006; Custer et al., 2006; Smedt et al., 2007; Yang et al., 2007; Meehan, "Levetiracetam has an activity-dependent effect on inhibitory transmission," *Epilepsia*, 2012 Jan 31; and Example 8 of WO 2001/62726, all of which are specifically incorporated herein by reference.) A substance, or a compound or an agent is an SV2A inhibitor even if it does not itself bind to SV2A, as long as it causes, or affects the ability of, another compound or agent to bind SV2A or reduce synaptic function by reducing pre-synaptic vesicle release. SV2A inhibitors, as used herein, include pharmaceutically acceptable salts of the inhibitors thereof. They also include hydrates, polymorphs, prodrugs, salts, and solvates of these inhibitors.

[0134] Among the SV2A inhibitors or pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof that are useful in the methods and compositions of this invention are those disclosed, for example, United States (U.S.) Patent Application 12/580,464 (Pub. No. US-2010-0099735), U.S. Patent Application 13/287,531 (Pub. No. US-2012-0046336), U.S. Patent Application 13/370,253 (Pub. No.US-2012-0214859), International Patent Application PCT/US2009/005647 (Pub. No. WO2010/044878), International Patent Application PCT/US12/24556 (Pub. No. WO2012/109491), U.S. Patent Provisional Application 61/105,847, 61/152,631, 61/175,536, and 61/441,251. . However, any SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be used in the methods and compositions of the invention. In some embodiments, the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Applications WO2010/144712; WO2010/002869; WO2008/132139; WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188;

WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692 or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs. Other SV2A inhibitors may also be used in this invention. Applicants also refer to methods of preparing these compounds found in the documents cited above. Other synthetic methods may also be used. These methods are well known to those skilled in the art.

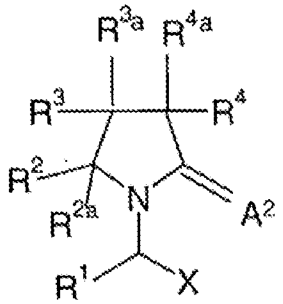
[0135] In some embodiments of this invention, the SV2A inhibitor is selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or prodrugs thereof.

[0136] In some embodiments of this invention, the SV2A inhibitor is levetiracetam or salts, solvates, hydrates, polymorphs or prodrugs thereof. Levetiracetam refers to the International Union of Pure and Applied Chemistry (IUPAC) name of the compound (2S)-2-(2-oxopyrrolidin-1-yl) butanamide). Levetiracetam is a widely used antiepileptic drug. Levetiracetam binds to a specific site in the CNS: the synaptic vesicle protein 2A (SV2A) (See. e.g., Noyer et al. 1995; Fuks et al. 2003; Lynch et al. 2004; Gillard et al. 2006) and has further been shown to directly inhibit synaptic activity and neurotransmission by inhibiting presynaptic neurotransmitter release (Yang et al., 2007).

[0137] Among the SV2A inhibitors useful for the methods and compositions of this invention are the following:

i) International Patent Application WO 2001/062726:

A compound having the formula I or a pharmaceutically acceptable salt thereof,



(I)

wherein X is-$CA^1NR^5R^6$ or-CA^1OR^7 or-CA^1-R^8 or CN ;

A^1 and A^2 are independently oxygen, sulfur or-NR^9;

R^1 is hydrogen, alkyl, aryl or-CH_2-R^{1a} wherein R^{1a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

R^2, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative;

R^{2a}, R^{3a} and R^{4a} are the same or different and each is independently hydrogen, halogen, alkyl, alkenyl, alkynyl or aryl;

R^5, R^6, R^7 and R^9 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

with the provisos that at least one of as R^2, R^3, R^4, R^{2a}, R^{3a} and R^{4a} is other than hydrogen; and that when the compound is a mixture of all possible isomers, X is-$CONR^5R^6$, A^2 is oxygen and R^1 is hydrogen, methyl, ethyl or propyl then substitution on the pyrollidine ring is other than mono-, di-, or tri-methyl or mono-ethyl; and that when R^1, R^2, R^4, R^{2a}, R^{3a} and R^{4a} are each hydrogen, A^2 is oxygen and X is $CONR^5R^6$ then R^3 is different from carboxy, ester, amido, substituted oxo-pyrrolidine, hydroxy, oxy derivative, amino, amino derivatives, methyl, naphthyl, phenyl optionally substituted by oxy derivatives or in the para position by an halogen atom.

In the definitions set forth below, unless otherwise stated, R^{11} and R^{12} are the same or different and each is independently amido, alkyl, alkenyl, alkynyl, acyl, ester, ether, aryl, aralkyl, heterocycle or an oxy derivative, thio derivative, acyl derivative, amino derivative, sulfonyl derivative, or sulfinyl derivative, each optionally substituted with any suitable group, including, but not limited to, one or more moieties selected from lower alkyl or other groups as described below as substituents for alkyl.

The term "oxy derivative", as used herein is defined as including -O-R^{11} groups wherein R^{11} is as defined above except for "oxy derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, oxyester, oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocyclooxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyloxy, 2-pyridyloxy, methylenedioxy, carbonate.

The term "thio derivative" as used herein, is defined as including-S-R^{11} groups wherein R^{11} is as defined above except for "thio derivative". Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

The term "amino derivative" as used herein, is defined as including-NHR^{11} or -$NR^{11}R^{12}$ groups wherein R^{11} and R^{12} are as defined above. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl- and arylamino or mixed amino.

The term "acyl derivative" as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula R^{11}-CO-, wherein R^{11} is as defined above and may also be hydrogen. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyl, oxamoyl.

The term "sulfonyl derivative" as used herein, is defined as including a group of the formula -SO_2-R^{11}, wherein R^{11} is as defined above except for "sulfonyl derivative". Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

The term "sulfinyl derivative" as used herein, is defined as including a group of the formula -SO-R^{11}, wherein R^{11} is as defined above except for "sulfinyl derivative". Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-6 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl"). Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, thiocyanato, acyl, acyloxy, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, oxyester, oxyamido, heterocycle, vinyl, C1-5-alkoxy, C6-10-aryloxy and C6-10-aryl.

Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, and 2,2,2-trimethylethyl each optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro and cyano, such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

The term "alkenyl" as used herein, is defined as including both branched and unbranched, unsaturated hydrocarbon radicals having at least one double bond such as ethenyl (= vinyl), 1- methyl-1-ethenyl, 2,2-dimethyl-1-ethenyl, 1-propenyl, 2-propenyl (= allyl), 1-butenyl, 2-butenyl, 3-butenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 1-hexenyl, 2-hexenyl, and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle such as mono- and di-halo vinyl where halo is fluoro, chloro or bromo.

The term "alkynyl" as used herein, is defined as including a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl (= propargyl), and the like and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl and heterocycle, such as haloethynyl.

When present as bridging groups, alkyl, alkenyl and alkynyl represent straight- or branched chains, C1-12, preferably C1-4-alkylene or C2-12-, preferably C2-4-alkenylene or -alkynylene moieties respectively.

Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e.g., "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.

The term "aryl" as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl, acyloxy, sulfonyl, sulfinyl, alkylamino, carboxy, ester, ether, amido, azido, sulfonic acid, sulfonamide, alkylsulfonyl, alkylsulfinyl, alkylthio, oxyester, oxyamido, aryl, C1-6-alkoxy, C6-10-aryloxy, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic containing 6-10 carbon atoms. Preferred aryl groups are phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6- alkylthio, C1-6-alkyl, C1-6-haloalkyl and phenyl.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "thiol", as used herein, represents a group of the formula -SH.

The term "cyano", as used herein, represents a group of the formula -CN.

The term "nitro", as used herein, represents a group of the formula $-NO_2$.

The term "nitrooxy", as used herein, represents a group of the formula $-ONO_2$.

The term "amino", as used herein, represents a group of the formula $-NH_2$.

The term "azido", as used herein, represents a group of the formula $-N_3$.

The term "carboxy", as used herein, represents a group of the formula -COOH.

The term "sulfonic acid", as used herein, represents a group of the formula $-SO_3H$.

The term "sulfonamide", as used herein, represents a group of the formula $-SO_2NH_2$.

The term "ester", as used herein is defined as including a group of formula -COO-R^{11} wherein R^{11} is as defined above except oxy derivative, thio derivative or amino derivative.

The term "ether" is defined as including a group selected from C1-50- straight or branched alkyl, or C2-50- straight or branched alkenyl or alkynyl groups or a combination of the same, interrupted by one or more oxygen atoms.

The term "amido" is defined as including a group of formula $-CONH_2$ or-$CONHR^{11}$ or $-CONR^{11}R^{12}$ wherein R^{11} and R^{12} are as defined above.

The term "heterocycle", as used herein is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Non-limiting examples of aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1, 2, 4-thiadiazolyl, thieno (2,3-b) furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro (4.5) dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i.e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) or the same which can optionally be substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, or other groups as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo (2.2.1)heptanyl, 7- oxabicyclo (2.2.1) heptanyl, 8-azabicyclo (3.2.1)octanyl.

In the above definitions it is to be understood that when a substituent such as R^2, R^3, R^4, R^{2a}, R^{3a}, R^{4a}, R^5, R^6, R^7, R^8 is attached to the rest of the molecule *via* a heteroatom or a carbonyl, a straight- or branched chain, C1-12-, preferably C1-4-alkylene or C2-12, preferably C2-4-alkenylene or-alkynylene bridge may optionally be interposed between the heteroatom or the carbonyl and the point of attachment to the rest of the molecule.

Preferred examples of X are -COO R^7 or -CONR^{5}R^6, wherein R^5, R^6 and R^7 are preferably hydrogen, C1-4-alkyl, phenyl or alkylphenyl.

Preferably X is carboxy or -CONR^{5}R^6, wherein R^5 and R^6 are preferably hydrogen, C1-4-alkyl, phenyl or alkylphenyl, especially -$CONH_2$.

Preferably A^1 and A^2 are each oxygen.

Preferably R^1 is hydrogen, alkyl, especially C1-12 alkyl, particularly lower alkyl or aryl especially phenyl.

Examples of preferred R^1 groups are methyl, ethyl, propyl, isopropyl, butyl, iso- or ter-butyl, 2,2,2-trimethylethyl each optionally attached *via* a methylene bridge or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

R^1 as ethyl is especially preferred.

Preferably R^2 and R^{2a} are independently hydrogen, halogen or alkyl, especially lower alkyl.

Examples of preferred R^2 and R^{2a} groups are independently hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

Especially at least one and most preferably both of R^2 and R^{2a} are hydrogen.

Preferably R^{3a}, R^4 and R^{4a} are independently hydrogen, alkyl, especially methyl or ethyl or aryl especially phenyl or aralkyl, especially benzyl.

Examples of preferred R^{3a}, R^4 and R^{4a} groups are independently hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1,1-dimethyl-2, 2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

Especially at least one and most preferably both of R^4 and R^{4a} are hydrogen.

R^{3a} is particularly hydrogen or alkyl, especially lower alkyl and is most preferably hydrogen.

Preferably R^3 is hydrogen, C1-12-alkyl, especially C1-6-alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato or alkoxy and attached to the ring either directly or *via* a thio, sulfinyl, sulfonyl, carbonyl or oxycarbonyl group and optionally, a C1-4-alkylene bridge, particularly methylene ; C2-6-alkenyl or -alkynyl, especially C2-3-alkenyl or-alkynyl each optionally substituted by one or more halogens ; azido ; cyano ; amido ; carboxy ; triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1- oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or piperazinyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl and phenyl and attached to the ring either directly or *via* a carbonyl group or a C1-4-alkylene bridge, particularly methylene ; naphthyl ; or phenyl, phenylalkyl or phenylalkenyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, C1-6-alkylthio, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* an oxy, sulfonyl, sulfonyloxy, carbonyl or carbonyloxy group and optionally additionally a C1-4-alkylene bridge, particularly methylene.

Also, preferably, R^3 is C1-6-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato, azido, alkoxy, alkylthio, phenylsulfonyl ; nitrooxy ; C2-3- alkenyl or-alkynyl each optionally substituted by one or more halogens or by acetyl ; tetrazolyl, pyridyl, furyl, pyrrolyl, thiazolyl or thienyl ; or phenyl or phenylalkyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* a sulfonyloxy and optionally additionally a C1-4-alkylene bridge, particularly methylene.

Other examples of preferred R^3 groups are hydrogen, halogen or methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl or the same substituted by at least one halogen atom such as trifluoromethyl, trichloromethyl, 2,2,2-trichloroethyl, 1, l-dimethyl-2, 2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

R^3 is especially C1-4-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato or azido; C2-5-alkenyl or-alkynyl, each optionally substituted by one or more halogens; thienyl; or phenyl optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl or azido.

Further examples of preferred R^3 groups are C1-6 alkyl and C2-6 haloalkenyl.

Preferably R^5 and R^6 are independently hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl, especially hydrogen or methyl.

Especially at least one and most preferably both of R^5 and R^6 are hydrogen.

Preferably R^7 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or tert-butyl, 2,2,2-trimethylethyl, methoxy, ethoxy, phenyl, benzyl or the same substituted by at least one halogen atom such as trifluoromethyl, chlorophenyl.

Preferably R^7 is hydrogen, methyl or ethyl especially hydrogen.

Preferably R^8 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, iso or ter-butyl, 2,2,2-trimethylethyl, phenyl, benzyl or the same substituted by at least one halogen atom such as trifluoromethyl, chlorobenzyl.

Preferably R^8 is hydrogen or methyl.

Combinations of one or more of these preferred compound groups are especially preferred.

A particular group of compounds of formula I (Compounds 1A) comprises those wherein,

A^2 is oxygen;

X is-CONR^{5}R^6 or-COOR^7 or-CO-R^8 or CN ;

R^1 is hydrogen or alkyl, aryl, halogen, hydroxy, amino, nitro, cyano;

R^2, R^3, R^4, are the same or different and each is independently hydrogen or halogen, hydroxy, amino, nitro, cyano, acyl, acyloxy, a sulfonyl derivative, a sulfinyl derivative, an amino derivative, carboxy, ester, ether, amido, sulfonic acid, sulfonamide,,, alkoxycarbonyl,,, a thio derivative,, alkyl, alkoxy, oxyester, oxyamido, aryl,, an oxy derivative, heterocycle, vinyl and R^3 may additionally represent C2-5 alkenyl, C2-5 alkynyl or azido each optionally substituted by one or more halogen, cyano, thiocyano, azido,, cyclopropyl, acyl and/or phenyl ; or phenylsulfonyloxy whereby any phenyl moiety may be substituted by one or more halogen, alkyl, haloalkyl, alkoxy, nitro, amino, and/or phenyl ; most preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl.

R^{2a}, R^{3a} and R^{4a} are hydrogen;

R^5, R^6, R^7 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or oxy derivative; and

R^8 is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle, alkylthio or thio derivative.

Within these Compounds 1A, R^1 is preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl ; most preferably methyl, ethyl or n-propyl.

R^2 and R^4 are preferably independently hydrogen or halogen or methyl, ethyl, propyl, isopropyl, butyl, isobutyl ; and, most preferably, are each hydrogen.

R^3 is preferably C1-5 alkyl, C2-5 alkenyl, C2-C5 alkynyl, cyclopropyl, azido, each optionally substituted by one or more halogen, cyano, thiocyano, azido, alkylthio, cyclopropyl, acyl and/or phenyl ; phenyl ; phenylsulfonyl ; phenylsulfonyloxy, tetrazole, thiazole, thienyl, furyl, pyrrole, pyridine, whereby any phenyl moiety may be substituted by one or more halogen, alkyl, haloalkyl, alkoxy, nitro, amino, and/or phenyl ; most preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl.

X is preferably -COOH or -COOMe or -COOEt or $-CONH_2$; most preferably $-CONH_2$.

A further particular group of compounds of formula I (Compounds 1B) comprises those wherein,

X is-CA^1NH_2,-CA^1NHCH_3 or-$CA^1N(CH_3)_2$;

R^1 is alkyl or phenyl ;

R^3 is alkyl, alkenyl, alkynyl, cyano, isothiocyanato, ether, carboxyl, amido, aryl, heterocycle ; or

R^3 is CH_2R^{10} wherein R^{10} is hydrogen, cycloalkyl, oxyester, oxyalkylsulfonyl, oxyarylsufonyl, aminoalkylsulfonyl, aminoarylsulfonyl, nitrooxy, cyano, isothiocyanato, azido, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, heterocycle, aryloxy, alkoxy or trifluoroethyl;

R^{3a} is hydrogen, alkyl or aryl (especially with the proviso that when R^{3a} is hydrogen, R^3 other than methyl);

or R^3R^{3a} form a cycloalkyl ;

and R^2, R^{2a}, R^4 and R^{4a} are each hydrogen.

Within the compounds of formula I,

R^1 is preferably alkyl especially C1-12- more particularly C1-6-alkyl and is most preferably ethyl;

R^2, R^{2a}, R^{3a} and R^{4a} are preferably hydrogen;

R^3 is preferably selected from hydrogen; C1-12-alkyl, especially C1-6-alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato or alkoxy and attached to the ring either directly or *via* a thio, sulfinyl, sulfonyl, carbonyl or oxycarbonyl group and optionally additionally a C1-4-alkylene bridge, particularly methylene; C2-6-

alkenyl or-alkynyl, especially C2-3-alkenyl or-alkynyl, each optionally substituted by one or more halogens ; azido ; cyano ; amido ; carboxy ; triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl or piperazinyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl and phenyl and attached to the ring either directly or *via* a carbonyl group or a C1-4-alkylene bridge, particularly methylene ; naphthyl ; or phenyl, phenylalkyl or phenylalkenyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, C1-6-alkylthio, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* an oxy, sulfonyl, sulfonyloxy, carbonyl or carbonyloxy group and optionally additionally a C1-4- alkylene bridge, particularly methylene ;

R^{3a} is preferably hydrogen or C1-4-alkyl ;

R^4 and R^{4a} are preferably, independently hydrogen, C1-4-alkyl, phenyl or benzyl.

A further group of compounds of formula I (Compounds 1C) comprises those in racemic form wherein, when X is-$CONR^5R^6$ and R^1 is hydrogen, methyl, ethyl or propyl, then substitution on the pyrrolidine ring is other than mono-, di-, or tri-methyl or mono-ethyl.

A further group of compound of formula I (Compounds 1D) comprises those in racemic form wherein, when X is-$CONR^5R^6$ and R^1 is hydrogen or C1-6-alkyl, C2-6-alkenyl or- alkynyl or cycloalkyl, each unsubstituted, then substitution in the ring is other than by alkyl, alkenyl or alkynyl, each unsubstituted.

A further particular group of compounds of formula I (Compounds IE) comprises those wherein,

X is-CA^1NH_2 ;

R^1 is H ;

R^3 is azidomethyl, iodomethyl, ethyl optionally substituted by 1 to 5 halogen atoms, n- propyl optionally substituted by 1 to 5 halogen atoms, vinyl optionally substituted by one or two methyl, and/or 1 to 3 halogen atoms, acetylene optionally substituted by C1-4-alkyl, phenyl or halogen ;

R^{3a} is hydrogen or halogen, preferably fluorine ;

and R^2, R^{2a}, R^4 and R^{4a} are each hydrogen ;

as their racemates or in enantiomerically enriched form, preferably the pure enantiomers.

A further particular group of compounds of formula I (Compounds 1F) comprises those wherein,

X is-CA^1NH_2 ;

R^1 is H ;

R^3 is C1-6-alkyl, C2-6-alkenyl or C2-6-alkynyl optionally substituted by azido, oxynitro, 1 to 6 halogen atoms ;

R^{3a} is hydrogen or halogen, preferably fluorine ;

and R^2, R^{2a}, R^4 and R^{4a} are each hydrogen ; as their racemates or in enantiomerically enriched form, preferably the pure enantiomers.

In all the above mentioned scopes when the carbon atom to which R^1 is attached is asymmetric it is preferably in the "S"-configuration.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of:

(2S)-2-[4-(bromomethyl)-2-oxo-1-pyrrolidinyl]butanamide;

(2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]butanamide;

(2S)-2-(2-oxo-4-phenyl-1-pyrrplidinyl)butanamide;

(2S)-2-[4-(iodomethyl)-2-oxo-1-pyrrolidinyl]butanamide;

(2S)-2-[4-(chloromethyl)-2-oxo-1-pyrrolidinyl]butanamide;

{1-[(1S)-1-(aminocarbonyl)propyl]-5-oxo-3-pyrrolidinyl}methyl 4-methylbenzenesulfonate;

(2S)-2-[(4R)-4-(azidomethyl)-2-oxopyrrolidinyl]butanamide;

2-[4-(2, 2-dibromovinyl)-2-oxo-1-pyrrolidinyl]butanamide;

{1 - [(1S) -1- (aminocarbonyl)propyl]-5-oxo-3-pyrrolidinyl}methyl nitrate;

(2S)-2-[2-oxo-4-(1H-tetraazol-1 -ylmethyl)-1-pyrrolidinyl]butanamide;

2-(2-oxo-4-vinyl-1-pyrrolidinyl)butanamide;

2-{2-oxo-4-[(phenylsulfonyl) methyl]-1-pyrrolidinyl]butanamide;

(2S)-2-[(4R)-4-(2, 2-dibromovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[(4S)-4-(2, 2-dibromovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[4-(isothiocyanatomethyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[2-oxo-4-(1,3-thiazol-2-yl)-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(2-thienyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(2-methoxyphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3-methoxyphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(4-azidophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(3-thienyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3-azidophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(3-thienyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[(4S)-2-oxo-4-vinylpyrrolidinyl]butanamide;
(2S)-2-[(4R)-2-oxo-4-vinylpyrrolidinyl]butanamide;
2-[4-(2-bromophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[2-oxo-4-(3-pyridinyl)-1-pyrrolidinyl]butanamide;
(2S)-2-(4-[1, 1'-biphenyl]-4-yl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-{4-[(methylsulfanyl) methyl]-2-oxo-1-pyrrolidinyl}butanamide;
2-[4-(iodomethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxo-1-pyrrolidinyl]pentanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]propanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)propanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)butanamide;
2-(2-oxo-4-pentyl-1-pyrrolidinyl)butanamide;
(2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]-N-methylbutanamide;
(2S)-2-(4-neopentyl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-(4-ethyl-2-oxo-1-pyrrolidinyl)butanamide;
2-[4-(2,2-difluorovinyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(2,2-difluoroethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide;
(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide;
2-{4-[(Z)-2-fluoroethenyl]-2-oxo-1-pyrrolidinyl}butanamide;
2-[4-(2-methyl-1-propenyl)-2-oxo-1-pyrrolidinyl]butanamide;

2-(4-butyl-2-oxo-1-pyrrolidinyl)butanamide;
2-[4-(cyclopropylmethyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-(4-isobutyl-2-oxo-1-pyrrolidinyl)butanamide;
2-[4-(4-chlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(3-chlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-{2-oxo-4-[2-(trifluoromethyl)phenyl]-1-pyrrolidinyl}butanamide;
2-[4-(2-fluorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(3-methylphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(2-phenylethyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3-bromophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-{4-[3,5-bis(trifluoromethyl)phenyl]-2-oxo-1-pyrrolidinyl}butanamide;
2-[4-(3,4-dichlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(2,4-dichlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(2-furyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(3-phenylpropyl)-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(3,5-dibromophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-[4-(3,4-dichlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-(2-oxo-4-propyl-1-pyrrolidinyl)butanamide;
2-[4-(3-chlorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
2-(4-ethynyl-2-oxo-1-pyrrolidinyl) butanamide;
2-[4-(2-fluorophenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(cyclopropylmethyl)-2-oxo-1-pyrrolidinyl}butanamide;
(2S)-2-[(4S)-4-(2, 2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(3, 3, 3-trifluoropropyl)-1-pyrrolidinyl]butanamide;
2-[4-(3-methylphenyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[4-(cyclopropylmethyl)-2-oxo-1-pyrrolidinyl]butanamide;
(2S)-2-[(4R)-4-(2, 2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;
(2S)-2-[2-oxo-4-(1H-pyrrol-1-yl)-1-pyrrolidinyl]butanamide;
(2S)-2-(4-allyl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[4-(2-iodopropyl)-2-oxo-1-pyrrolidinyl}butanamide;
(2S)-2-(4-allyl-2-oxo-1-pyrrolidinyl)butanamide;
(2S)-2-[2-oxo-4-(2-oxopropyl)-1-pyrrolidinyl]butanamide;

(2S)-2-[4-(2-bromo-1 H-pyrrol-1-yl)-2-oxo-1-pyrrolidinyl]butanamide;

(2S)-2-(4-methyl-2-oxo-4-propyl-1-pyrrolidinyl)butanamide;

(2R)-2-[4-(2, 2-dichlorovinyl)-2-oxo-1-pyrrolidinyl]butanamide;

2-[4-(bromoethynyl)-2-oxo-1-pyrrolidinyl]butanamide;

2-[(4S)-4-(2, 2-difluoropropyl)-2-oxopyrrolidinyl]butanamide;

(2S)-2-[4-(bromoethynyl)-2-oxo-1-pyrrolidinyl]butanamide;

2-(2-oxo-4-propyl-1-pyrrolidinyl)pentanamide;

3-cyclopropyl-2-(2-oxo-4-propyl-1-pyrrolidinyl)propanamide;

2-(2-oxo-4-propyl-1-pyrrolidinyl)-3-(1,3-thiazol-4-yl)propanamide;

2-(2-oxo-4-propyl-1-pyrrolidinyl)-4-pentenamide;

(2S)-2-[(4R)-2-oxo-4-vinylpyrrolidinyl]butanamide;

including all isomeric forms and mixtures thereof or a pharmaceutically acceptable salt thereof.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of :

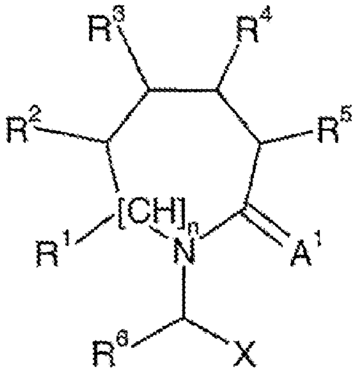
(2S)-2-[(4S)-4-(2, 2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;

(2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide;

(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide.

ii) International Patent Application WO 2002/094787:

Compounds of the formula I



(I)

wherein n represents 0 or 1 whereby R^1 is not existent when n=0 and R^1 is existent when n= 1 ;

A^1 represents an oxygen or a sulfur atom;

X is-$CONR^7R^8$,-$COOR^9$,-CO-R^{10} or CN;

R^1 when existent, R^2, R^3, R^4 and R^5 are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative,

provided that at least one of the substituents R chosen from R^1 when existent, R^2, R^3, R^4 or R^5 is not hydrogen;

R^6 is hydrogen, alkyl, aryl or-CH_2-R^{6a} wherein R^{6a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

R^7, R^8 and R^9 are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R^{10} is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

their pharmaceutically acceptable salts, geometrical isomers (including cis and trans, Z and E isomers), enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers).

In the above formula, at least one substituent R^1 to R^5 is different from hydrogen. Some non-substituted compounds are referred to in US Patent No. 5,468,733 and 5,516, 759. US Patent No. 5,468,733 refers to non-ring substituted 2-oxo-1-pyrrolidinyl and 2-oxo-1-piperidinyl derivatives as inhibitors of the oncogene Ras protein. In particular, these compounds block the ability of Ras to transform normal cells to cancer cells, and therefore can be included in several chemotherapeutic compositions for treating cancer.

US Patent No. 5,516,759 refers to non-ring substituted 2-oxo-1-pyrrolidinyl, 2-oxo-1- piperidinyl and azepanyl derivatives present at the N-terminus of dodecapeptides possessing LHRH (luteinizing hormone-releasing hormone) antagonistic activity. Such LHRH antagonists are useful in the treatment of a variety of conditions in which suppression of sex steroids plays a key role including contraception, delay of puberty, treatment of benign prostatic hyperplasia a. o.

In the definitions set forth below, unless otherwise stated, R^{11} and R^{12} are the same or different and each is independently amido, alkyl, alkenyl, alkynyl, acyl, ester, ether, aryl, aralkyl. heterocycle or an oxy derivative, thio derivative, acyl derivative, amino derivative, sulfonyl derivative, or sulfinyl derivative, each optionally substituted with any suitable group, including, but not limited to, one or more moieties selected from lower alkyl or other groups as described below as substituents for alkyl.

The term "oxy derivative", as used herein, is defined as including-O-R^{11} groups wherein R^{11} is as defined above except for "oxy derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, oxyester, oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocyclooxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyloxy, 2-pyridyloxy, methylenedioxy, carbonate.

The term "thio derivative", as used herein, is defined as including-S-R^{11} groups wherein R^{11} is as defined above except for "thio derivative". Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

The term "amino derivative", as used herein, is defined as including-NHR^{11} or-$NR^{11}R^{12}$ groups wherein R^{11} and R^{12} are as defined above. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl-and arylamino or mixed amino.

The term "acyl derivative", as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula R^{11}-CO-, wherein R^{11} is as defined above and may also be hydrogen. Preferred are acyl derivatives of formula -COR^{11} wherein R^{11} is selected from hydrogen, C1-12 alkyl, C2-12 alkenyl, C2-12 alkenyl, heterocyle and aryl. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyl, oxamoyl.

The term "sulfonyl derivative", as used herein, is defined as including a group of the formula -SO_2-R^{11}, wherein R^{11} is as defined above except for "sulfonyl derivative". Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

The term "sulfinyl derivative", as used herein, is defined as including a group of the formula -SO-R^{11}, wherein R^{11} is as defined above except for "sulfinyl derivative". Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and generally containing 1-20 carbon atoms, most often 1 to 12 carbon atoms, preferably 1-7 carbon atoms for non-cyclic alkyl and 3-7 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl"), each optionally substituted by, preferably 1 to 5, substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, thiocyanato, acyl, acyloxy, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, alkylthio, oxyester, oxyamido, heterocycle, vinyl, alkoxy (preferably C1-5), aryloxy (preferably C6-10) and aryl (preferably C6-10).

Preferred are alkyl groups containing 1 to 7 carbon atoms, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkylthio, cyclopropyl, acyl and phenyl. Most preferred are C1-4 alkyl and C3-7 cycloalkyl, each optionally substituted by one or more hydroxy, halogen, lower alkyl or/and azido.

Most preferred alkyl groups are hydroxymethyl, propyl, butyl, 2, 2,2-trifluoroethyl, 2- bromo-2,2-difluoroethyl, 2-chloro-2,2-difluoroethyl, 3,3,3-trifluoropropyl, cyclopropylmethyl, iodomethyl, azidomethyl, 2,2-difluoropropyl, 2-iodo-2,2-difluoroethyl.

The term "lower alkyl", as used herein, and unless otherwise specified, refers to C_1 to C_7 saturated straight, branched or cyclic hydrocarbon. Non limiting examples are methyl, ethyl, propyl, isopropyl, butyl, tertiobutyl, pentyl, cyclopropyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methypentyl, 2,2-dimethylbutyl, optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferably, lower alkyl is methyl.

The term "alkenyl", as used herein, is defined as including both branched and unbranched, unsaturated hydrocarbon radicals having at least one double bond, and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, thiocyanato, azido, alkylthio, cycloalkyl, acyl, nitro, cyano, aryl and heterocycle.

Preferred alkenyl groups are C2-C12 alkenyls, especially C2-6 alkenyls, such as ethenyl (= vinyl), 1-methyl-1-ethenyl, 2,2-dimethyl-1-ethenyl, 1-propenyl, 2-propenyl (= allyl), 1-butenyl, 2- butenyl, 3-butenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 1-hexenyl, 2-hexenyl and the like, optionally being substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, cycloalkyl, phenyl and acyl. Most preferred is vinyl, optionally substituted by one or more halogen or/and lower alkyl, and especially 2,2- difluorovinyl, 2,2-dibromovinyl and 2,2-dichlorovinyl.

The term "alkynyl" as used herein, is defined as including a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl (= propargyl), and the like, and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl, heterocycle, thiocyanato, azido, alkylthio, alkyl and acyl.

Preferred alkynyl groups are C2-12 alkynyl, especially C2-6 alkynyl, optionally being substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, acyl, aryl such as phenyl and alkyl, preferably cycloalkyl.

Most preferred are ethynyl, propynyl and butynyl, optionally substituted by lower alkyl or/and halogen, and especially 1-propynyl, cyclopropylethynyl, 3-methyl-1-butynyl and 3,3,3- trifluoro-1-propynyl.

When present as bridging groups, alkyl, alkenyl and alkynyl represent straight- or branched chains, C1-12, preferably C1-4-alkylene or C2-12-, preferably C2-4-alkenylene or- alkynylene moieties respectively.

Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e. g. "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.

The term "aryl", as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of at least one ring, most often 1 to 3 rings and generally containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl, each optionally substituted by one or more substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl, acyloxy, sulfonyl, sulfinyl, alkylamino, carboxy, ester, ether, amido, azido, sulfonic acid, sulfonamide, alkylsulfonyl, alkylsulfinyl, C1-6-alkylthio, oxyester, oxyamido, aryl, C1-6-alkoxy, C6-10-aryloxy, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic or bicyclic containing 6-10 carbon atoms. Preferred aryl groups are phenyl and naphthyl each optionally substituted by one or more substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkyl, C1-6-haloalkyl, sulfonyl and phenyl.

Preferred aryl is phenyl, optionally substituted by one or more halogen, lower alkyl, azido or nitro, such as 3-chlorophenyl and 3-azidophenyl.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "thiol", as used herein, represents a group of the formula -SH.

The term "cyano", as used herein, represents a group of the formula -CN.

The term "nitro", as used herein, represents a group of the formula $-NO_2$.

The term "nitrooxy", as used herein, represents a group of the formula $-ONO_2$.

The term "amino", as used herein, represents a group of the formula $-NH_2$.

The term "azido", as used herein, represents a group of the formula $-N_3$.

The term "carboxy", as used herein, represents a group of the formula -COOH.

The term "sulfonic acid", as used herein, represents a group of the formula $-SO_3H$.

The term "sulfonamide", as used herein, represents a group of the formula -SO_2NH_2.

The term "ester", as used herein, is defined as including a group of formula -COO-R^{11} wherein R^{11} is as defined above except oxy derivative, thio derivative or amino derivative. Preferred are esters of formula -COOR^{11} wherein R^{11} is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl and aryl. Most preferred are esters where R^{11} is a lower alkyl, especially methyl.

The term "ether" is defined as including a group selected from C1-50-straight or branched alkyl, or C2-50-straight or branched alkenyl or alkynyl groups or a combination of the same, interrupted by one or more oxygen atoms.

The term "amido" is defined as including a group of formula -$CONH_2$ or -CONHR^{11} or -CON$R^{11}R^{12}$ wherein R^{11} and R^{12} are as defined above.

The term "heterocycle", as used herein, is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl, and optionally being substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, or other groups as described above for the alkyl groups. Non-limiting examples of heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, triazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2,4-thiadiazolyl, thiomorpholinyl, thieno (2,3-b) furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, 1-oxidopyridyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, benzodioxolyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro

(4.5) dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i. e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) optionally substituted by alkyl or as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo (2.2.1) heptanyl, 7-oxabicyclo (2.2.1) heptanyl, 8-azabicyclo (3.2.1) octanyl.

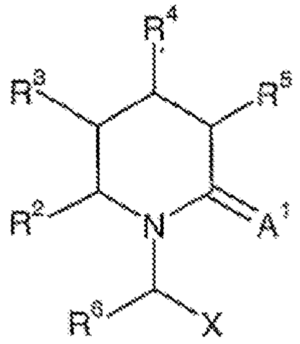
The heterocycle is preferably selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1- oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from halogen, alkyl, substituted alkyl, alkoxy, nitro, amino, acyl and phenyl.

More preferably the heterocycle is selected from tetrazolyl, pyrrolidinyl, pyridyl, furyl, pyrrolyl, thiazolyl and thienyl, each optionally substituted by one or more substituents selected from halogen, alkyl, halogen substituted alkyl, acyl, alkoxy, nitro, amino and phenyl, and especially from 2-and 3-thienyl, optionally substituted by one or more halogen, acyl such as formyl, cyano and/or lower alkyl, such as methyl.

In the above definitions it is to be understood that when a substituent such as R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10} is attached to the rest of the molecule *via* a heteroatom or a carbonyl, a straight- or branched chain, C1-12-, preferably C1-4-alkylene or C2-12, preferably C2-4-alkenylene or-alkynylene bridge may optionally be interposed between the heteroatom or the carbonyl and the point of attachment to the rest of the molecule.

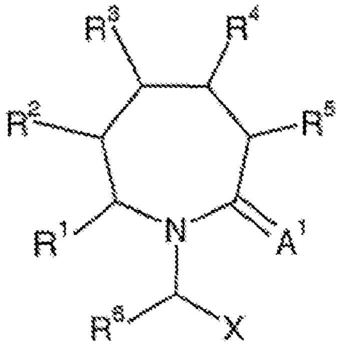
The term "R substituent" refers to R^1, R^2, R^3, R^4 or R^5, independently.

According to a preferred embodiment, a compound of formula I is as defined above wherein n represents 0. The compound is a 6-ring structure (2-thioxo- or 2-oxo-piperidinyl derivative) wherein R^1 is not existent since n=0, and is depicted by the formula (I-A).



(I-A)

According to a following embodiment, the compound of formula I is as defined above wherein n represents 1. The compound is a 7-ring structure (2-thioxo- or 2-oxo-azepanyl derivative) wherein R^1 is existent since n=1 and depicted by the formula (I-B).



(I-B)

According to a more preferred embodiment, said compound is as defined above wherein n=0, R^3 and/or R^4 are different from hydrogen and R^2 and R^5 represent hydrogen.

According to another more preferred embodiment, said compound is as defined above wherein n=1, R^2, R^3 and/or R^4 are different from hydrogen and wherein R^1 and R^5 represent hydrogen.

According to a yet more preferred embodiment, said compound is as defined above wherein only one R substituent chosen from R^3 or R^4 when n=0 or from R^2, R^3 or R^4 when n=1, is different from hydrogen and the remaining R substituent(s) is/are hydrogen. We hereby refer to a mono-substituted 2-thioxo- or 2-oxo-piperidinyl or 2-thioxo- or 2-oxo-azepanyl derivatives.

According to another preferred embodiment, compounds of formula I are as defined above wherein A^1 represents an oxygen atom. We hereby refer to 2-oxo-piperidinyl or 2-oxo-azepanyl derivatives.

According to another preferred embodiment, compounds of formula I are as defined above wherein X is $CONR^7R^8$, especially $CONH_2$. We hereby refer to amido derivatives of 2-oxo (or thioxo)-piperidinyl or 2-oxo (or thioxo) -azepanyl.

According to another preferred embodiment, compounds of formula I are as defined above wherein R^6 represents hydrogen, C1-4 alkyl, or a CH_2-R^{6a} group wherein R^{6a} represents a heterocycle. Most preferably R^6 is a C1-4 alkyl, especially ethyl. When R^6 is ethyl we refer to 2- (2-oxo (or thioxo)-1-piperidinyl) butanamide or 2- (2-oxo (or thioxo)-1-azepanyl) butanamide derivatives.

According to another preferred embodiment, compounds of formula I are as defined above wherein the carbon atom to which R^6 is attached is of the S configuration. In case where R^6 is ethyl, A is oxygen and X is $CONR^7R^8$ we refer then to (2S)-2-(2-oxo-1-piperidinyl) butanamide or (2S)-2- (2-oxo-1-azepanyl) butanamide derivatives.

According to a prefered embodiment, the compound is as defined above wherein R^2 when n=l, R^3 and R^4 are the same or different and each is independently hydrogen, halogen, nitro, nitrooxy, cyano, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, acyl derivative, sulfonyl derivative or sulfinyl derivative;

R^1 when existent, R^2 when n=0 and R^5 are hydrogen;

R^6 is hydrogen, alkyl, aryl or-CH_2-R^{6a} wherein R^{6a} is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

According to this preferred embodiment, the compound is generally such that when R^6 is benzyl, X is-$COOCH_3$ and n=1, R^2 is different from methyl when R^3 and R^4 are both hydrogen and R^4 is different from methyl when R^2 and R^3 are both hydrogen.

According to another preferred embodiment, the compound is as defined above wherein R^2 when n=1, R^3 and R^4 are the same or different and each is independently hydrogen; cyano; carboxy; amido ;

C1-12 alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkyltio, cycloalkyl, acyl, aryl and heterocycle;

C2-12 alkenyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, alkyl, aryl and acyl;

C2-12 alkynyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, alkyl, aryl and acyl ; acyl derivative of formula -CO-R^{11}, wherein R^{11} is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl, heterocycle and aryl;

ester of formula -CO-O-R^{11} wherein R^{11} is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl and aryl;

heterocycle selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from halogen, alkyl, substituted alkyl, alkoxy, nitro, amino, acyl and phenyl;

aryl, each optionally substituted by one or more substituents selected from C1-6 alkyl, C1-6 haloalkyl, C1-6 alkoxy, C1-6 alkylthio, amino, azido, sulfonyl, aryl and nitro.

According to another preferred embodiment, the compound is as defined above, wherein R^2 when n= 1, R^3 and R^4 are the same or different and each is independently hydrogen;

C1-7 alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkyltio, cyclopropyl, acyl and phenyl;

C2-6 alkenyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, cycloalkyl, phenyl and acyl ;

C2-6 alkynyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, cycloalkyl, phenyl and acyl;

heterocycle selected from tetrazolyl, pyrrolidinyl, pyridyl, furyl, pyrrolyl, thiazolyl and thienyl, each optionally substituted by one or more substituents selected from halogen, alkyl, halogen substituted alkyl, acyl, alkoxy, nitro, amino and phenyl;

phenyl, each optionally substituted by one or more substituents selected from C1-6 alkyl, halogen substituted alkyl, halogen, alkoxy, amino, azido, sulfonyl, phenyl and nitro.

According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R^2, R^3 and R^4 when n=l or from the group R^3 and R^4 when n=0, represents independently C1-4-alkyl or C3-7-cycloalkyl, optionally substituted by one or more halogen, hydroxy, lower alkyl and/or azido.

According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R^2, R^3 and R^4 when n=1 or from the group R^3 and R^4 when n=0, represents independently vinyl, optionally substituted by one or more halogen or/and lower alkyl.

According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R^2, R^3 and R^4 when n=1 or from the group R^3 and R^4 when n=0, represents independently ethynyl, propynyl or butynyl, optionally substituted by one or more halogen and/or lower alkyl.

According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R^2, R^3 and R^4 when n= 1 or from the group R^3 and R^4 when n=0, represents independently phenyl, optionally substituted by one or more halogen, lower alkyl, azido and/or nitro.

According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R^2, R^3

and R^4 when n=1 or from the group R^3 and R^4 when n=0, represents independently 2-or 3-thienyl, optionally substituted by one or more halogen, acyl, cyano or/and lower alkyl.

According to a particular preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R^3, R^4 and R^2 when n= 1 or from the group R^3 and R^4 when n=0, is hydroxymethyl, propyl, butyl, 3,3,3-trifluoropropyl, 2,2,2-trifluoroethyl, cyclopropylmethyl, iodomethyl, azidomethyl, 2- thienyl, 3-thienyl, phenyl, 3-chlorophenyl, 3-azidophenyl, 2,2-difluorovinyl, 2,2-dibromovinyl, 2, 2-dichlorovinyl, 2-ethynyl, 5-methyl-2-thienyl, 5-formyl-2-ethynyl, 5-cyano-2-thienyl, 3-bromo- 2-thienyl, 4-methyl-2-thienyl, 3,3,3-trifluoro-1-propynyl, l-propynyl, cyclopropylethynyl, 3- methyl-1-butynyl, 1-butynyl, 2,2-difluoropropyl, 2-chloro-2,2-difluoroethyl, 2-bromo-2,2- difluoroethyl and 2-iodo-2,2-difluoroethyl.

According to yet another preferred embodiment, the compound is as defined above wherein R^1, R^2, R^4 and R^5 are hydrogen.

According to even another preferred embodiment, the compound is as defined above wherein R^1, R^2, R^3 and R^5 are hydrogen.

According to even another preferred embodiment, the compound is as defined above wherein n=1 and R^1, R^3, R^4 and R^5 are hydrogen.

In all the above-mentioned scopes when the carbon atom to which R^6 is attached is asymmetric it is preferably in the "S"-configuration.

Representative compounds useful in the methods and compositions of this invention as defined above are selected from the group consisting of

2-[5-(hydroxymethyl)-2-oxo-1-piperidinyl]butanamide,

2-(2-oxo-5-propyl-1-piperidinyl)butanamide,

2-[2-oxo-5-(3,3,3-trifluoropropyl)-1-piperidinyl]butanamide,

2-[5-(cyclopropylmethyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(iodomethyl)-2-oxo-1-piperidinyl] butanamide,

2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide,

2-(2-oxo-5-phenyl-1-piperidinyl)butanamide,

2-[2-oxo-5-(2-thienyl)-1-piperidinyl]butanamide, 2-[2-oxo-5-(3-thienyl)-1-piperidinyl]butanamide,

2-[5-(3-chlorophenyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(3-azidophenyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(2, 2-difluorovinyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(2, 2-dibromovinyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(2, 2- dichlorovinyl)-2-oxo-1-piperidinyl]butanamide,

2-(5-ethynyl-2-oxo-1-piperidinyl)butanamide,

2[5-(5-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(5-formyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(5-cyano-2-thienyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(3-bromo-2-thienyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(4-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide,

2-[2-oxo-5-(3,3,3-trifluoro-1-propynyl)-1-piperidinyl]butanamide,

2-[2-oxo-5-(1-propynyl)-1-piperidinyl]butanamide,

2-[5-(cyclopropylethynyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(3-methyl-1-butynyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(1-butynyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(2,2-difluoropropyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(2-chloro-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(2-bromo-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide,

2-[4-(hydroxymethyl)-2-oxo-1-piperidinyl]butanamide,

2-(2-oxo-4-propyl-1-piperidinyl)butanamide,

2-[2-oxo-4-(3,3,3trifluoropropyl)-1-piperidinyl]butanamide,

2-[4-(cyclopropylrnethyl)-2-oxo-1-piperidinyl]butanamide,

2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,

2-[4-(azidomethyl)-2-oxo-1-piperidinyl]butanamide,

2-(2-oxo-4-phenyl-1-piperidinyl)butanamide,

2-[2-oxo-4-(2-thienyl)-1-piperidinyl]butanamide,

2-[2-oxo-4-(3-thienyl)-1-piperidinyl]butanamide,

2-[4-(3-chlorophenyl)-2-oxo-1-piperidinyl]butanamide,

2-[4-(3-azidophenyl)-2-oxo-1-piperidinyl]butanamide,

2-[4-(2,2-difluorovinyl)-2-oxo-1-piperidinyl]butanamide,

2-[4-(2,2-dibromovinyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(2,2-dichlorovinyl)-2-oxo-1-piperidinyl]butanamide,
2-(4-ethynyl-2-oxo-1-piperidinyl)butanamide,
2-[4-(5-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(5-formyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(5-cyano-2-thienyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(3-bromo-2-thienyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(4-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide,
2-[2-oxo-4-(3,3,3-trifluoro-1-propynyl)-1-piperidinyl]butanamide,
2-[2-oxo-4-(1-propynyl)-1-piperidinyl]butanamide,
2-[4-(cyclopropylethynyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(3-methyl-1-butynyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(1-butynyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(2, 2-difluoropropyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(2-chloro-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide,
2-[4-(2-bromo-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide,
2[4-(2,2,2-trifluoroethyl)-2-oxo-1-piperidinyl]butanamide,
2-[5-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide,
2-(2-oxo-5-propyl-1-azepanyl)butanamide,
2-[2-oxo-5-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide,
2-[5-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(azidomethyl)-2-oxo-1-azepanyl]butanamide,
2-(2-oxo-5-phenyl-1-azepanyl)butanamide,
2-[2-oxo-5-(2-thienyl)-1-azepanyl]butanamide,
2-[2-oxo-5-(3-thienyl)-1-azepanyl]butanamide,
2-[5-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide,
2-(5-ethynyl-2-oxo-1-azepanyl)butanamide,

2-[5-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[2-oxo-5-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide,
2-[2-oxo-5-(1-propynyl)-1-azepanyl]butanamide,
2-[5-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(l-butynyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,
2-[5-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide,
2-(2-oxo-6-propyl-1-azepanyl)butanamide,
2-[2-oxo-6-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide,
2-[6-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(iodomethyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(azidomethyl)-2-oxo-1-azepanyl]butanamide,
2-(2-oxo-6-phenyl-1-azepanyl)butanamide,
2-[2-oxo-6-(2-thienyl)-1-azepanyl]butanamide,
2-[2-oxo-6-(3-thienyl)-1-azepanyl]butanamide,
2-[6-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2, 2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide,
2-(6-ethynyl-2-oxo-1-azepanyl)butanamide,
2-[6-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(5-formyl-2-thienyl)-2-oxo-1-azepanyllbutanamide,
2-[6-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide,

2-[6-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[2-oxo-6-(3, 3, 3-trifluoro-1-propynyl)-1-azepanyl]butanamide,
2-[2-oxo-6-(1-propynyl)-1-azepanyl]butanamide,
2-[6-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(1-butynyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2, 2-difluoropropyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,
2-[6-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide,
2-(2-oxo-4-propyl-1-azepanyl)butanamide,
2-[2-oxo-4-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide,
2-[4-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(iodomethyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(azidomethyl)-2-oxo-1-azepanyl]butanamide,
2-(2-oxo-4-phenyl-1-azepanyl)butanamide,
2-[2-oxo-4-(2-thienyl)-1-azepanyl]butanamide,
2-[2-oxo-4-(3-thienyl)-1-azepanyl]butanamide,
2-[4-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(2, 2-difluorovinyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(2, 2-dibromovinyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide,
2-(4-ethynyl-2-oxo-1-azepanyl)butanamide,
2-[4-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[4-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide,
2-[2-oxo-4-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide,

2-[2-oxo-4-(1-propynyl)-1-azepanyl]butanamide,

2-[4-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide,

2-[4-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide,

2-[4-(1-butynyl)-2-oxo-1-azepanyl]butanamide,

2-[4-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide,

2-[4-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,

2-[4-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,

2-[4-(2,2,2-tritluoroethyl)-2-oxo-1-azepanyl]butanamide.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of:

(2S)-2-[5-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,

(2S)-2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide,

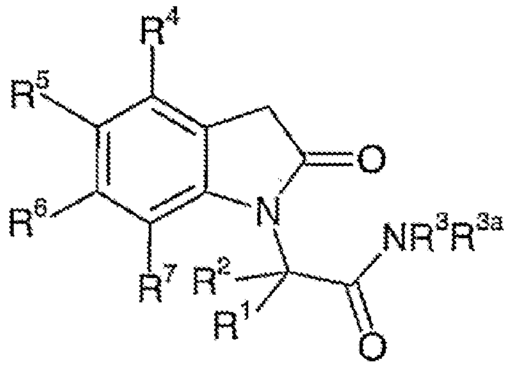
2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,

(2S)-2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,

2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide.

iii) International Patent Application WO 2004/087658:

A compound having the formula I or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof,



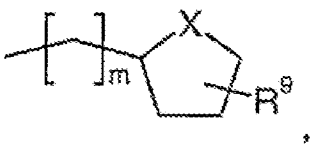
(I)

wherein

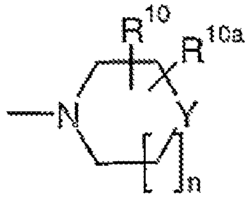
R^1 is hydrogen,

R^2 is hydrogen or C1-20-alkyl,

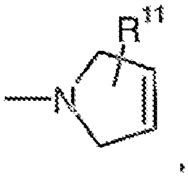
R^3 is hydrogen, C1-20-alkyl, C4-8-cycloalkyl, C5-8-cycloalkenyl, aryl, aromatic or non aromatic heterocycle, C1-20-alkoxy, or a group of formula -W-R^8, R^{3a} is hydrogen, C1-20-alkyl or a group of formula :



or NR^3R^{3a} is a group of formula



or



R^4 is hydrogen,

R^5 is hydrogen; nitro; halogen; azido; cyano; -S-C1-4-alkyl; -SO-C1-4-alkyl; -SO_2-C1-4-alkyl; -$SONH_2$; C1-20-alkyl unsubstituted or substituted by halogen; or C1-20-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, C1-20-alkyl or halogen,

R^7 is hydrogen, C1-20-alkyl or halogen,

W is C1-12-alkylene, -NH- or -NHC(=O)-,

X is O, S or NH,

Y is O, S, -$CR^{12}R^{13}$-, -NR^{14}- or -C(=O)-,

R^8 is aryl or heterocycle,

R^9, R^{10}, R^{10a} and R^{11} are independently selected from hydrogen, C1-4-alkyl, halogen, hydroxy or methoxycarbonyl,

or R^{10} and R^{10a} together form a C3-6-alkylene,

R^{12} is hydrogen, C1-4-alkyl, halogen or hydroxy,

R^{13} is hydrogen,

or $CR^{12}R^{13}$ is dioxolanyl,

R^{14} is aryl, heterocycle or a group of formula -V-R^{15},

V is C_{1-12}-alkylene,

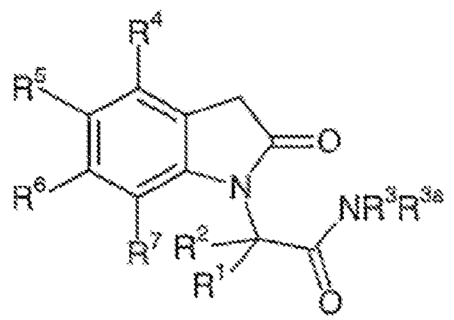
R^{15} is aryl or heterocycle,

m is 1 to 4,

n is 0 or 1,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen, R^3 is H or 2, 6-diisopropylphenyl, and R^{3a} is H.

In another aspect, the compound has the formula I or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof,



(I)

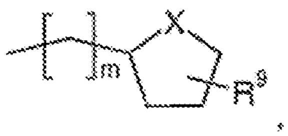
wherein

R^1 is hydrogen,

R^2 is hydrogen or C1-20-alkyl,

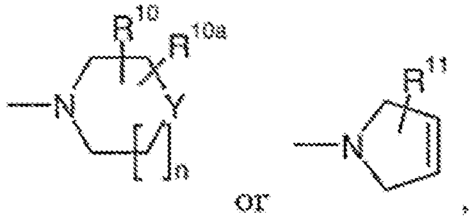
R^3 is hydrogen, C1-20-alkyl, C4-8-cycloalkyl, C5-8-cycloalkenyl, aryl, aromatic or non aromatic heterocycle, C1-20-alkoxy, or a group of formula -W-R^8,

R^{3a} is hydrogen, C1-20-alkyl or a group of formula:



,

or NR^3R^{3a} is a group of formula



,

R^4 is hydrogen,

R^5 is hydrogen; nitro; halogen; C1-20-alkyl unsubstituted or substituted by halogen; or C1-20-alkoxy unsubstituted or substituted by halogen,

R^6 is hydrogen, C1-20-alkyl or halogen,

R^7 is hydrogen, C1-20-alkyl or halogen,

W is C1-12-alkylene, -NH- or -NHC(=O)-,

X is O, S or NH,

Y is O, S, -CR^{12}R^{13}-, -NR^{14}- or -C(=O)-,

R^{8} is aryl or heterocycle,

R^{9}, R^{10}, R^{10a} and R^{11} are independently selected from hydrogen, C1-4-alkyl, halogen, hydroxy or methoxycarbonyl,

or R^{10} and R^{10a} together form a C3-6-alkylene,

R^{12} is hydrogen, C1-4-alkyl, halogen or hydroxy,

R^{13} is hydrogen,

or CR^{12}R^{13} is dioxolanyl,

R^{14} is aryl, heterocycle or a group of formula -V-R^{15},

V is C1-12-alkylene,

R^{15} is aryl or heterocycle,

m is 1 to 4,

n is 0 or 1,

and at least one of R^{5}, R^{6} or R^{7} is different from hydrogen when R^{2} is hydrogen, R^{3} is H or 2,6-diisopropylphenyl, and R^{3a} is H.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms and more preferably 1-4 carbon atoms for non-cyclic alkyl and 3-8 carbon atoms for cycloalkyl. Alliyl moieties may optionally be substituted by 1 to 5 substituents independently selected from halogen, hydroxy, alkoxy, alkoxycarbonyl, ester or alkylamino. Preferred alkyl groups are methyl, ethyl, n-propyl, isopropyl, trifluoromethyl, n-butyl, 2- fluoroethyl, 3-hydroxypropyl, 3-hydroxy-2, 2-dimethylpropyl, 1-(hydroxymethyl) propyl, 3,3, 3-trifluoro-2-hydroxypropyl, 3-ethoxypropyl, 2-ethoxy-2-oxoethyl and 3- (dimethylamino) propyl.

The term "cycloalkyl", as used herein, refers to a monovalent group of 3 to 18 carbon atoms, preferably 4-8 carbon atoms, derived from a saturated cyclic or polycyclic hydrocarbon which may be substituted by any suitable group including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkyl group is cycloheptyl.

The term "alkylene", as used herein, represents a divalent alkyl group, having straight or branched moieties, containing 1-12 carbon atoms, preferably 1-6 carbon atoms, and being optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred alkylene groups are methylene, ethylene, hydroxyethylene, trimethylene or propylene.

The term "cycloalkenyl", as used herein, is defined as a cyclic unsaturated hydrocarbon radical having at least one double bond, containing 4-20 carbon atoms, preferably 5-8 carbon atoms, and being optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkenyl group is 6- (hydroxymethyl) cyclohex-3-en-1-yl.

The term "aryl", as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, nitro, C1-6-alkyl, C1-6-alkoxy, C1-6-alkylsulfonyl, trifluoromethylthio or pyridinylalkyl. Aryl radicals are preferably phenyl radicals. Preferred aryl groups are phenyl, 3-hydroxyphenyl, 3-fluorophenyl, 3-methylphenyl, 4-methylphenyl, 4- hydroxyphenyl, 4-hydroxy-3-methoxyphenyl, 3-(2-pyridin-2-ylethyl) phenyl, 3,4- dimethylphenyl, 4-tert-butylphenyl, 4-methylsulfonylphenyl, 2-nitrophenyl, 2-chloro- 6-fluorophenyl, 2-[(trifluoromethyl) thio] phenyl, 2-chlorophenyl or 4-bromophenyl.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "nitro", as used herein, represents a group of the formula $-NO_2$.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "alkoxy", as used herein, represents a group of formula $-OR^b$ wherein R^b is an alkyl group, as defined above.

The term "ester", as used herein, represents a group of formula $-COOR^C$ wherein R^c is an alkyl group or an aryl group, as defined above.

The term "alkoxycarbonyl", as used herein, represents a group of formula -$COOR^d$ wherein R^d is an alkyl group, as defined above.

The term "amino", as used herein, represents a group of the formula $-NH_2$.

The term "alkylamino", as used herein, represents a group of formula -NHR^e or $-NR^eR^f$ wherein R^e and R^f are alkyl group as defined above.

The term alkylsulfonyl, as used herein is defined as representing a group of formula $-SO_2-R^g$, wherein R^g is C1-4-alkyl.

The term "heterocycle", as used herein is defined as including an aromatic or non aromatic cycloalkyl or cycloalkenyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl.

Non-limiting examples of aromatic heterocycles are pyrazolyl, furyl, imidazolyl, triazolyl, oxazolyl, pyridinyl, pyrrolyl, thienyl, isothiazolyl, benzimidazolyl, tetrazolyl, isooxazolyl, oxazolyl, thiazolyl, 1,2, 4-thiadiazolyl, oxadiazole, pyridazinyl, pyrimidinyl, pyrazinyl, isoindolyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, quinazolinyl, quinolizinyl, naphthyridinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, indolyl, indolizinyl, purinyl, carbazolyl, thieno (2,3- b) furanyl, thianthrenyl, benzothiazolyl, benzoxazolyl, cinnolinyl, quinoxalinyl, phenothiazinyl, isochromanyl and xanthenyl, optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl, formyl or ester. More preferred aromatic heterocycles are pyrazolyl, furyl, imidazolyl, triazolyl, oxazolyl and pyridinyl.

Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, thiazolidinyl, indolinyl, tetrahydrobenzazocinyl, dihydroisochromenyl, tetrahydropyranyl, oxooctahydroquinolinyl, dioxolanyl, 1-oxaspiro (4.5) dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, 8-thiabicyclo [3.2. 1] cyclooctanyl, 1,4-dithiepanyl, tetrahydro-2H-thiopyranyl, azepanyl and azocanyl, optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl, formyl or ester. More preferred non aromatic heterocycles are tetrahydrofuranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, thiazolidinyl, indolinyl, tetrahydro-1-benzazocin-1 (2H)-yl, 3, 4-dihydro-lH-isochromen-1-yl, tetrahydropyranyl, oxooctahydroquinolinyl and dioxolanyl. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cycloalkyl ring, a cycloalkenyl ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo (2.2.1)heptanyl, 7-oxabicyclo (2.2.1)heptanyl and 8- azabicyclo (3.2.1)octanyl.

The term "pyridinylalkyl", as used herein, represents a group of formula -R^h- pyridinyl in which R^h is C1-4-alkylene.

The term "azido" as used herein, represents a group of the formula $-N_3$.

The term "cyano" as used herein, represents a group of the formula -CN.

Generally, R^2 is hydrogen or C1-4-alkyl.

Preferably, R^2 is hydrogen, methyl or ethyl. More preferably, R^2 is hydrogen or methyl.

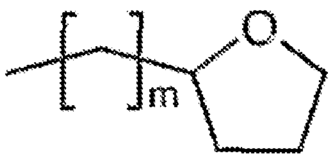
Generally, R^3 is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxycarbonyl or alkylamino; C5-7-cycloalkyl; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl, hydroxy, methoxy, nitro, methylsulfonyl, trifluoromethylthio or pyridinylalkyl ; pyridinyl unsubstituted or substituted by methoxy; triazolyl; C1-4-alkoxy ; or a group of formula -W-R^8 wherein:

Generally, W is C1-4-alkylene unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl or alkoxy ;-NH- ; or-NHC (=O)- ; and

R^8 is phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl, hydroxy, methoxy, nitro, methylsulfonyl or trifluoromethylthio; furyl unsubstituted or substituted by methyl; pyrazolyl; pyridinyl; morpholinyl ; tetrahydrobenzazocinyl; piperidinyl unsubstituted or substituted by methyl; dihydroisochromenyl or dihydroimidazolyl.

Preferably, R^3 is hydrogen, n-butyl, cycloheptyl, 2-fluoroethyl, 3-hydroxypropyl, 3-hydroxy-2, 2-dimethylpropyl, 1-(hydroxymethyl) propyl, 3,3, 3- trifluoro-2-hydroxypropyl, 3-ethoxypropyl, 2-ethoxy-2-oxoethyl, 3-(dimethylamino) propyl, 6-(hydroxymethyl) cyclohex-3-en-1-yl, 3-hydroxyphenyl, 3- fluorophenyl, 3- (2-pyridin-2-ylethyl) phenyl, 3, 4-dimethylphenyl, 4-tert-butylphenyl, benzyl, 4-hydroxy-3-methoxybenzyl, 4-methylsulfonylbenzyl, 2-nitrobenzyl, 2-chloro- 6-fluorobenzyl, 2-[(trifluoromethyl) thio] benzyl, 2-hydroxy-2-phenylethyl, 2- (3,4-dimethoxyphenyl) ethyl, 2- (2-chlorophenyl) ethyl, 2- (4-methylphenyl) ethyl, (4- bromophenyl) amino, pyridin-3-yl, 6-methoxypyridin-3-yl, 4H-1, 2, 4-triazol-3-yl, pyridin-4-ylmethyl, (5-methyl-2-furyl) methyl, 3-(1H-pyrazol-1-yl)propyl, 2-morpholin- 4-ylethyl, 2- ((3, 4,5, 6-tetrahydro-1-benzazocin-1 (2H)-yl) propyl, 2- (2-methylpiperidin-1- yl) ethyl, 3, 4-dihydro-lH-isochromen-1-ylmethyl, methoxy, (4-pyridinylcarbonyl) amino or 4, 5-dihydro-1H-imidazol-2-ylamino. More preferably, R^3 is hydrogen.

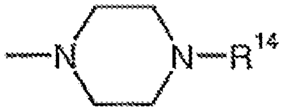
Generally, R^{3a} is hydrogen, C1-4-alkyl or a group of formula



wherein m is 1 to 4.

Preferably, R^{3a} is hydrogen, methyl or tetrahydrofuran-2-ylmethyl. More preferably, R^{3a} is hydrogen.

In another embodiment, NR^3R^{3a} is piperidinyl unsubstituted or substituted by hydroxy; thiomorpholinyl; thiazolidinyl unsubstituted or substituted by C1-4- alkoxycarbonyl ; 2, 5-dihydro-1H-pyrrol-1-yl ; 1, 4-dioxa-8-azaspiro [4.5] dec-8-yl; 4- oxooctahydro-1(2H)-quinolinyl; or a group of formula



wherein R^{14} is pyridinyl ; phenyl unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl ; or a group of formula -V-R^{15} wherein V is unsubstituted C1-4- alkylene and R^{15} is phenyl or morpholinyl.

In a preferred embodiment, NR^3R^{3a} is 4-pyridin-2-ylpiperazin-1-yl, 4-(3-methylphenyl) piperazin-1-yl, 4- (4-hydroxyphenyl) piperazin-1-yl, 4- (2-phenylethyl) piperazin-1-yl, 4- (2-morpholin-4-ylethyl) piperazin-1-yl, 3-hydroxypiperidin-1-yl, thiomorpholin-4-yl, 4-methoxycarbonyl-1,3-thiazolidin-3-yl, 2, 5-dihydro-lH-pyrrol-1-yl, 1, 4-dioxa-8-azaspiro [4.5] dec-8-yl or 4-oxooctahydro-1(2H)-quinolinyl.

Generally, R^5 is hydrogen, nitro, halogen, C1-4-alkyl, unsubstituted or substituted by halogen, or C1-4-alkoxy unsubstituted or substituted by halogen.

Preferably, R^5 is hydrogen, methyl, ethyl, trifluoromethyl, trifluoromethoxy, n- propyl, isopropyl, nitro, or halogen. More preferably, R^5 is halogen or trifluoromethyl.

Generally, R^6 is hydrogen, C1-6-alkyl or halogen.

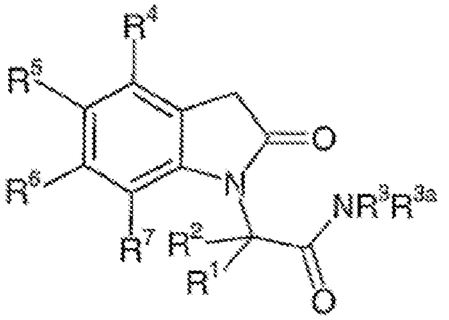
Preferably, R^6 is hydrogen, methyl or Cl. More preferably, R^6 is hydrogen.

Generally, R^7 is hydrogen, methyl or halogen.

Preferably, R^7 is hydrogen, methyl, Br, F or Cl. More preferably, R^7 is hydrogen, Br or F.

Combinations of one or more of these preferred compound groups are especially preferred.

In a preferred embodiment, the compound has the formula I or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof,


(I)

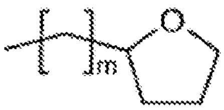
wherein R^1 is hydrogen,

R^2 is hydrogen or C1-4-alkyl,

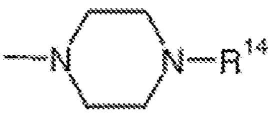
R^3 is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxycarbonyl or alkylamino ; C5-7-cycloalkyl ; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-

alkyl, hydroxy, methoxy, nitro, methylsulfonyl, trifluoromethylthio or pyridinylalkyl ; pyridinyl unsubstituted or substituted by methoxy; triazolyl; C1-4-alkoxy ; or a group of formula-W-R^8,

R^{3a} is hydrogen, C1-4-alkyl or a group of formula



or NR^3R^{3a} is piperidinyl unsubstituted or substituted by hydroxy; thiomorpholinyl ; thiazolidinyl unsubstituted or substituted by C1-4-alkoxycarbonyl ; 2,5-dihydro-lH-pyrrol-1-yl; 1,4-dioxa-8-azaspiro [4.5] dec-8-yl; 4-oxooctahydro-1(2H)-quinolinyl ; or a group of formula



R^4 is hydrogen,

R^5 is hydrogen; nitro; halogen; C1-4-alkyl, unsubstituted or substituted by halogen; or C1-4-alkoxy unsubstituted or substituted by halogen,

R6 is hydrogen, C1-6-allyl or halogen,

R7 is hydrogen, methyl or halogen,

W is C1-4-alkylene unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl or alkoxy ;-NH- ; or-NHC (=O)-,

R8 is phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl, hydroxy, methoxy, nitro, methylsulfonyl or trifluoromethylthio ; furyl unsubstituted or substituted by methyl; pyrazolyl; pyridinyl ; morpholinyl; tetrahydrobenzazocinyl ; piperidinyl unsubstituted or substituted by methyl ; dihydroisochromenyl or dihydroimidazolyl,

R^{14} is pyridinyl; phenyl unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl ; or a group of formula-V-R^{15},

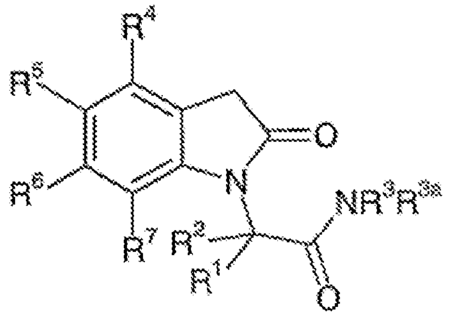
V is unsubstituted C1-4-alkylene,

R^{15} is phenyl or morpholinyl,

m is 1 to 4,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen, R^3 is H or 2,6-diisopropylphenyl, and R^{3a} is H.

In a more preferred embodiment, the compound has the formula I or a pharmaceutically acceptable salt thereof or stereoisomeric forms thereof,



(I)

wherein

R^1 is hydrogen,

R^2 is hydrogen, methyl or ethyl,

R^3 is hydrogen, n-butyl, cycloheptyl, 2-fluoroethyl, 3-hydroxypropyl, 3-hydroxy-2,2- dimethylpropyl, 1-(hydroxymethyl) propyl, 3,3, 3-trifluoro-2-hydroxypropyl, 3- ethoxypropyl, 2-ethoxy-2-oxoethyl, 3- (dimethylamino) propyl, 6- (hydroxymethyl) cyclohex-3-en-1-yl, 3-hydroxyphenyl, 3-fluorophenyl, 3- (2-pyridin-2-ylethyl) phenyl, 3,4-dimethylphenyl, 4-tert-butylphenyl, benzyl, 4-hydroxy-3- methoxybenzyl, 4-methylsulfonylbenzyl, 2-nitrobenzyl, 2-chloro-6-fluorobenzyl, 2- [(trifluoromethyl)thio] benzyl, 2-hydroxy-2-phenylethyl, 2- (3, 4-dimethoxyphenyl) ethyl, 2- (2-chlorophenyl) ethyl, 2- (4-methylphenyl) ethyl, (4-bromophenyl) amino, pyridin-3-yl, 6-methoxypyridin-3-yl, 4H-1,2,4-triazol-3-yl, pyridin-4-ylmethyl, (5-methyl-2-furyl) methyl, 3- (lH-pyrazol-1-yl) propyl, 2-morpholin-4-ylethyl, 2- ((3, 4,5, 6-tetrahydro- 1-benzazocin-1 (2H) -yl) propyl, 2- (2-methylpiperidin-1-yl) ethyl, 3, 4-dihydro-lH- isochromen-1-ylmethyl, methoxy, (4-pyridinylcarbonyl) amino or 4, 5-dihydro-lH- imidazol-2-ylamino,

R^{3a} is hydrogen, methyl or tetrahydrofuran-2-ylmethyl, or NR^3R^{3a} 4-pyridin-2-ylpiperazin-1-yl, 4-(3-methylphenyl) piperazin-1-yl, 4-(4-hydroxyphenyl) piperazin-1-yl, 4-(2-phenylethyl) piperazin-1-yl, 4-(2-morpholin-4- ylethyl) piperazin-1-yl, 3-hydroxypiperidin-1-yl, thiomorpholin-

4-yl, 4- methoxycarbonyl-l, 3-thiazolidin-3-yl, 2, 5-dihydro-1H-pyrrol-1-yl, 1,4-dioxa-8- azaspiro [4.5]dec-8-yl or 4-oxooctahydro-1(2H)-quinolinyl,

R^4 is hydrogen,

R5 is hydrogen, methyl, ethyl, trifluoromethyl, trifluoromethoxy, n-propyl, isopropyl, nitro or halogen,

R^6 is hydrogen, methyl or Cl,

R^7 is hydrogen, methyl, Br, F or Cl,

and at least one of R^5, R^6 or R^7 is different from hydrogen when R^2 is hydrogen, R^3 is H or 2,6-diisopropylphenyl, and R^{3a} is H.

More preferably, R^2 is hydrogen or methyl, R^3 is hydrogen, R^{3a} is hydrogen, R^5 is halogen or trifluoromethyl, R^6 is hydrogen and R^7 is hydrogen, Br or F.

In all the above-mentioned scopes, when R^2 is C1-20-alkyl, the carbon atom to which R^2 is attached is preferably in the "S"-configuration.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide ; 2- (5, 7-dibromo- 2-oxo-2, 3-dthydro-lH-indol-1-yl) acetamide ; 2-(5-nitro-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl) acetamide; 2- (5-chloro-2- oxo-2, 3-dihydro-lH-indol-1-yl) propanamide ; (2R)-2- (5-chloro-2-oxo-2, 3-dihydro-1H- indol-1-yl) propanamide ; (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl) propanamide; 2-[2-oxo-5-(trifluoromethoxy)-2, 3-dihydro-lH-indol-1-yl] acetamide ; 2- (5-isopropyl-2-oxo-2, 3-dihydro-1H-indol-1-yl)acetamide ; 2-(5-ethyl-2-oxo-2, 3-dihydro- 1H-indol-1-yl) acetamide ; 2-(5-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl) acetamide; 2- (5,7-dimethyl-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide; 2- (5-bromo-2-oxo-2, 3- dihydro-lH-indol-1-yl) acetamide ; 2-(2-oxo-5-propyl-2, 3-dihydro-lH-indol-1- yl) acetamide ; 2-[2-oxo-5-(trifluoromethyl)-2, 3-dihydro-lH-indol-1-yl] acetamide ; 2- (5, 6-dimethyl-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide; 2- (7-chloro-2-oxo-2, 3-dihydro- IH-indol-1-yl) acetamide; 2- (6-chloro-2-oxo-2, 3-dihydro-IH-indol-1-yl) acetamide; 2- (5- chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) butanamide ; (+)-2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl) butanamide; (-)-2- (5-chloro-2-oxo-2, 3-dihydro-IH-indol-1- yl) butanamide; 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide ; (+)-2- (5- methyl-2-oxo-2, 3-dihydro-1H-indol-1-yl) propanamide; (-)-2- (5-methyl-2-oxo-2, 3- dihydro-lH-indol-1-yl) propanamide ; 2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1- yl) propanamide ; (-)-2- (5-bromo-2-oxo-2, 3-dihydro-lH-indol-1-yl) propanamide ; (+)-2- (5-bromo-2-oxo-2, 3-dihydro-1H-indol-1-yl) propanamide; 2- (5-chloro-7-fluoro-2-oxo- 2, 3-dihydro-1H-indol-1-yl) acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N- (3-hydroxyphenyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- (3- fluorophenyl) acetamide ; 2-(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [3- (2-pyridin- 2-ylethyl) phenyllacetarnide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[6-(hydroxymethyl) cyclohex-3-en-1-yl]acetanuide ; 5-chloro-1-[2-oxo-2-(4-pyridin-2- ylpiperazin-1-yl) ethyl3-1, 3-dihydro-2H-indol-2-one ; 5-chloro-1-{2- [4- (3- methylphenyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one ; 2- (5-chloro-2- oxo-2, 3-dihydro-1H-indol-1-yl)-N-(4-hydroxy-3-methoxybenzyl)acetamide ; 2- (5-chloro- 2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-(pyridin-4-ylmethyl)-N- (tetrahydrofuran-2- ylmethyl) acetamide ; 5-chloro-1-[2-(3-hydroxypiperidin-1-yl)-2-oxoethyl]-1,3-dihydro- 2H-indol-2-one; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N'- isonicotinoylacetohydrazide ; 5-chloro-1-(2-oxo-2-thiomorpholin-4-ylethyl)-1,3-dihydro- 2H-indol-2-one; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(4H-1, 2, 4-triazol-3- yl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [4-(methylsulfonyl) benzyl] acetamide ; 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1- yl) acetyl] octahydroquinolin-4 (1H)-one ; N'- (4-bromophenyl)-2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl) acetohydrazide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N- (6-methoxypyridin-3-yl) acetamide; N-butyl-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(3- hydroxypropyl) acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N- [3- (dimethylamino) propyl] acetamide ; 5-chloro-1-{2-oxo-2[4-(2-phenylethyl)pperazin-1- yl] ethyl}-l, 3-dihydro-2H-indol-2-one; ethyl {[(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1- yl) acetyl]amino}acetate ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(3-ethoxypropyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-(2- fluoroethyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-methoxy-N- methylacetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(3, 4- dimethylphenyl) acetamide ; N- (4-tert-butylphenyl)-2- (5-chloro-2-oxo-2, 3-dihydro-lH- indol-1-yl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- (3-hydroxy-2, 2- dimethylpropyl) acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[1- (hydroxymethyl) propyl] acetamide ; 2-(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- (3,3, 3-trifluoro-2-hydroxypropyl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1- yl)-N-(2-hydroxy-2-phenylethyl) acetamide ; 5-chloro-1- {2- [4- (4- hydroxyphenyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one; 2- (5-chloro-2- oxo-2, 3-dihydro-1H-indol-1-yl)-N-(pyridin-4-ylmethyl)acetamide ; 2- (5-chloro-2-oxo- 2, 3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-furyl)methyl]acetamide ; 2-(5-chloro-2-oxo- 2, 3-dihydro-lH-indol-1-yl)-N- [3- (lH-pyrazol-1-yl) propyl] acetamide ; methyl 3- [(5- chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl] acetyl]-1, 3-thiazolidine-4-carboxylate ; 5- chloro-1-[2-(2, 5-dihydro-lH-pyrrol-1-yl)-2-oxoethyl]-1, 3-dihydro-2H-indol-2-one; 2- (5- chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N'- (4, 5-dihydro-lH-imidazol-2- yl) acetohydrazide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [2- (3, 4- dimethoxyphenyl) ethyl] acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[2- (2-chlorophenyl) etl-lyllacetaniide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[2-(4- methylphenyl) ethyl] acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(2- morpholin-4-ylethyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [2- (3,4, 5, 6-tetrahydro-1-benzazocin-1 (2H) -yl) propyl] acetamide ; 2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl)-N-[2-(2-methylpiperidin-1-yl) ethyl] acetamide ; 2- (5-chloro-2- oxo-2, 3-dihydro-lH-indol-1-yl)-N-(2-nitrobenzyl) acetamide ; 2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl)-N- (3, 4-dihydro-lH-isochromen-1-ylinethyl) acetamide ; N- (2-chloro-6-fluorobenzyl)-2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide ; N- benzyl-2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-methylacetamide ; 2- (5-chloro- 2-oxo-2, 3-dthydro-lH-indol-1-yl)-N-{2-

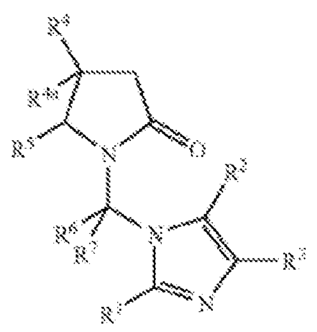
[(trifluoromethyl) thio] benzyl} acetamide ; 5- chloro-1- [2- (1, 4-dioxa-8-azaspiro [4.5] dec-8-yl)-2-oxoethyl]-1, 3-dihydro-2H-indol-2- one; 2-(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-cycloheptylacetamide ; 5-chloro-1- {2-[4- (2-morpholin-4-ylethyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one ; and 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-pyridin-3-ylacetamide.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide ; 2- (5, 7-dibromo- 2-oxo-2, 3-dihydro-1H-indol-1-yl)acetamide ; (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H- indol-1-yl) propanamide ; 2-[2-oxo-5-(trifluoromethyl)-2, 3-dihydro-lH-indol-1- yl] acetamide and 2-(5-chloro-7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl) acetamide.

In another embodiment, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 2- (5-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl) acetamide and (2S) -2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) propanamide.

iv) US Patent No. 7,244,747:

A compound having the formula I or a pharmaceutically acceptable salt thereof,



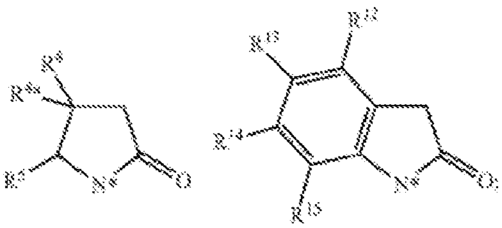
(I)

wherein R^1 is hydrogen, C_{1-20} alkyl, C_{3-8} cycloalkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, guanidine, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, aryl or heterocycle;

R^2 is hydrogen, C_{1-20} alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;

R^3 is hydrogen, C_{1-20} alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;

or R^2 and R^3 can form together with the imidazole ring the following 1H-benzimidazole cycle



R^4 is hydrogen, C_{1-20} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, aryl, azido, alkoxycarbonylamino, arylsulfonyloxy or heterocycle;

R^{4a} is hydrogen or C_{1-20} alkyl;

or R^4 and R^{4a} can form together a C_{3-8} cycloalkyl;

R^5 is hydrogen;

or R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle

R^6 is hydrogen or C_{1-20} alkyl;

R^7 is hydrogen;

or R^6 and R^7 are linked together to form a C_{3-6} cycloalkyl;

R^8 is hydrogen, halogen, nitro, cyano, C_{1-20} alkyl or alkoxy;

R^9 is hydrogen, C_{1-20} alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl;

R^{10} is hydrogen, C_{1-20} alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl;

R^{11} is hydrogen, halogen, nitro, cyano, C_{1-20} alkyl or alkoxy;

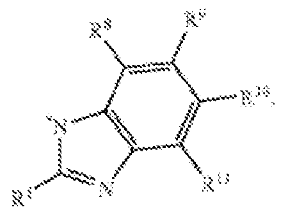
R^{12} is hydrogen or halogen;

R^{13} is hydrogen, nitro, halogen, heterocycle, amino, aryl, C_{1-20} alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen;

R^{14} is hydrogen, C_{1-20} alkyl or halogen;

R^{15} is hydrogen, C_{1-20} alkyl or halogen;

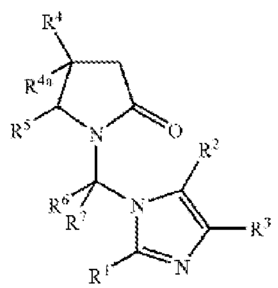
with the proviso that R^4 is different from hydrogen when represents a group of formula



The asterisk * indicates the point of attachment of the substituents.

In a preferred embodiment, the compounds have the formula I, their tautomers, geometrical isomers (including cis and trans, Z and E isomers), enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,

(I)

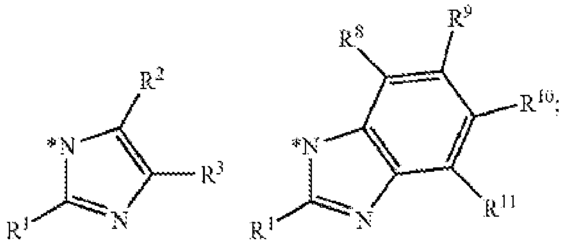


wherein R^1 is hydrogen, C_{1-20} alkyl, C_{3-8} cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle;

R^2 is hydrogen, C_{1-20} alkyl, halogen, cyano, ester, carbamate or amido;

R^3 is hydrogen, cyano, C_{1-20} alkyl, halogen or ester;

or R^2 and R^3 can form together with the imidazole ring the following 1H-benzimidazole cycle

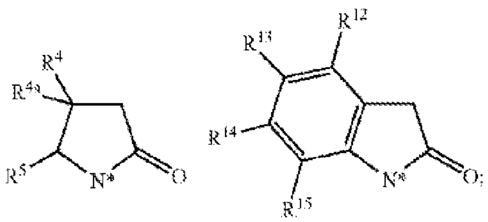


R^4 is hydrogen, C_{1-20} alkyl, C_{2-12} alkenyl or aryl;

R^{4a} is hydrogen;

R^5 is hydrogen;

or R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



R^6 is hydrogen or C_{1-20} alkyl;

R^7 is hydrogen; or R^6 and R^7 are linked together to form a C_{3-6} cycloalkyl;

R^8 is hydrogen;

R^9 is hydrogen, C_{1-20} alkyl, halogen or alkoxy;

R^{10} is hydrogen, C_{1-20} alkyl, halogen or cyano;

R^{11} is hydrogen;

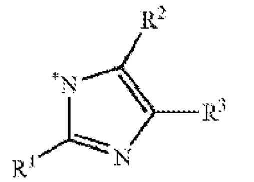
R^{12} is hydrogen or halogen;

R^{13} is hydrogen, halogen, heterocycle or C_{1-20} alkyl;

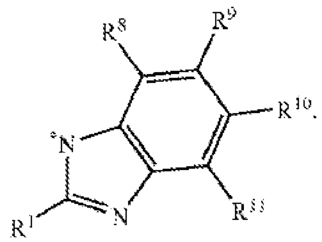
R^{14} is hydrogen;

R^{15} is hydrogen;

with the proviso that R^4 is different from hydrogen when



represents a group of formula



The term "alkyl", as used herein, represents saturated, monovalent hydrocarbon radicals having straight (unbranched) or branched or cyclic or combinations thereof and containing 1-20 carbon atoms, preferably 1-10 carbon atoms, more pre preferred alkyl groups have 1-3 carbon atoms. Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, cyano, azido, aryloxy, alkoxy, alkythio, alkanoylamino, arylcarbonylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl or aryl. Usually alkyl groups, in the present case, are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, 1-ethylpropyl, n-heptyl, 2,4,4-trimethylpentyl, n-decyl, chloromethyl, trifluoromethyl, 2-bromo-2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, hydroxymethyl, cyanomethyl, azidomethyl, (acetylamino)methyl, (propionylamino)methyl, (benzoylamino)methyl, (4-chlorophenoxy)methyl, benzyl, 2-phenylethyl or 2-(methylthio)ethyl. Preferred alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, 1-ethylpropyl, 2,4,4-trimethylpentyl, chloromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, hydroxymethyl, cyanomethyl, azidomethyl, (acetylamino)methyl, (propionylamino)methyl, (benzoylamino)methyl or 2-(methylthio)ethyl. More preferred alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, azidomethyl or trifluoromethyl. Most preferred alkyl groups are methyl or n-propyl.

The term "cycloalkyl", as used herein, represents a monovalent group of 3 to 8 carbon atoms, usually 3-6 carbon atoms derived from a saturated cyclic hydrocarbon, which may be substituted by any suitable group including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkyl groups are cyclopropyl and cyclohexyl.

The term "alkenyl" as used herein, represents straight, branched or cyclic unsaturated hydrocarbon radicals or combinations thereof having at least one carbon-carbon double bond, containing 2-12 carbon atoms, preferably usually 2-4 carbon atoms. Alkenyl groups are being optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Usually an alkenyl group is ethenyl (vinyl) optionally substituted by 1 to 3 halogens. Preferred alkenyl group, in the present case, is 2, 2-difluorovinyl.

The term a "alkynyl" as used herein, represents straight, branched or cyclic hydrocarbon radicals or combinations thereof containing at least one carbon-carbon triple bond, containing 2-12 carbon atoms, preferably 2-6 carbon atoms, and being optionally substituted by any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferably an alkynyl group is a halogenoalkynyl group (haloalkynyl group).

Groups qualified by prefixes such as "s", "i", "t" and the like (e.g. "i-propyl", "s-butyl") are branched derivatives.

The term "aryl" as used herein, is defined as phenyl optionally substituted by 1 to 4 substituents independently selected from halogen, cyano, alkoxy, alkylthio, C_{1-3} alkyl or azido, preferably halogen or azido. Usually aryl groups, in the present case are phenyl, 3-chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chloro-4-fluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,5-trifluorophenyl, 3,4,5-trifluorophenyl, 3-azido-2,4-difluorophenyl or 3-azido-2,4,6-trifluorophenyl. Preferably, aryl groups are phenyl, 3-chlorophenyl, 3-

fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chloro-4-fluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,5-trifluorophenyl, 3,4,5-trifluorophenyl or 3-azido-2,4-difluorophenyl. Most preferred aryl groups are phenyl, 3-chlorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl, 2,3,5-trifluorophenyl, 3,4,5-trifluorophenyl or 3-azido-2,4-difluorophenyl.

The term "heterocycle", as used herein, is defined as including an aromatic or non aromatic cycloalkyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure. Heterocyclic ring moieties can be optionally substituted by alkyl groups or halogens and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Usually heterocycles are 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-tetrahydrofuranyl, 1H-pyrrol-2-yl, 1-methyl-1H-pyrrol-2-yl, 1H-pyrazol-2-yl, 1H-pyrazol-3-yl, 4-chloro-1-methyl-1H-pyrazol-3-yl, 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl, 1,2,3-thiadiazol-4-yl, 3,5-dimethyl-4-isothiazyl, 1H-imidazol-2-yl, 1-methyl-1H-imidazol-2-yl, 4-methyl-1H-imidazol-5-yl, or 2-methyl-1,3-thiazol-4-yl. Preferred heterocycles are 1H-imidazol-2-yl, 1,2,3-thiadiazol-4-yl, 1H-pyrazol-3-yl, 2-furyl, 3-furyl, 2-thienyl, 1-methyl-1H-pyrrol-2-yl, 1H-pyrrol-2-yl.

The term "halogen", as used herein, includes an atom of chlorine, bromine, fluorine, iodine. Usually halogens are chlorine, bromine and fluorine. Preferred halogens are fluorine, bromine and chlorine.

The term "hydroxy", as used herein, represents a group of formula --OH.

The term "alkoxy", as used herein, represents a group of formula $-OR^a$ wherein R^a is an alkyl group, as defined above. Preferred alkoxy group is methoxy.

The term "aryloxy", as used herein, represents a group of formula $--OR^b$ wherein R^b is an aryl group, as defined above. Preferred aryloxy group is phenoxy.

The term "ester", as used herein, represents a group of formula $--COOR^c$ wherein R^c is an alkyl group or aryl group, as defined above. Preferred ester group is methoxycarbonyl.

The term "amido", as used herein, represents a group of formula $--CONH_2$.

The term "amino", as used herein, represents a group of formula $--NH_2$.

The term "aminoderivative", as used herein, represents an alkylamino or an arylamino group, wherein the terms "alkyl" and "aryl" are defined as above.

The term "cyano", as used herein, represents a group of formula --CN.

The term "nitro", as used herein, represents a group of formula $–NO_2$.

The term "azido", as used herein, represents a group of formula $--N_3$.

The term "guanidine", as used herein, represents a group of formula --NHC(=NH)NH_2.

The term "alkylthio", as used herein, represents a group of formula $--SR^d$ wherein R^d is an alkyl group, as defined above. Preferred alkylthio group is methylthio.

The term "alkylsulfonyl", as used herein, represents a group of formula --S(=O)$_2R^e$ wherein R^e is an alkyl group, as defined above. Preferred alkylsulfonyl group is methylsulfonyl.

The term "alkylsulfinyl", as used herein, represents a group of formula –S(=O)R^f wherein R^f is an alkyl group, as defined above. Preferred alkylsulfinyl group is methylsulfinyl.

The term "arylthio", as used herein, represents a group of formula $--SR^g$ wherein R^g is an aryl group, as defined above.

The term "arylsulfonyl", as used herein, represents a group of the formula --S(=O)$_2R^h$ wherein R^h is an aryl group, as defined above.

The term "arylsulfinyl", as used herein, represents a group of the formula --S(=O)R^i wherein R^i is an aryl group, as defined above.

The term "carbamate" as used herein, represents a group of formula --N(H)C(O)OR^j, wherein R^j is an alkyl or an aryl, as defined above. Usually carbamate groups are (propoxycarbonyl)amino or (benzyloaxycarbonyl)amino. Preferred carbamate group is (benzyloaxycarbonyl)amino.

The term "alkanoylamino" as used herein, represents a group of the formula --NHC(=O)R^k wherein R^k is an alkyl group, as defined above.

The term "(arylcarbonyl)amino" as used herein, represents a group of the formula --NHC(=O)R^m wherein R^m is an aryl group, as defined above. Preferred (arylcarbonyl)amino is benzoylamino.

Usually, R^1 is hydrogen; C_{1-10} alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy; hydroxy; C_{3-6} cycloalkyl; halogen; ester; amido; nitro; cyano; amino; phenyl; alkylthio; alkylsulfonyl; alkylsulfinyl; heterocycle unsubstituted or substituted by alkyl groups; or guanidine. Preferably, R^1 is hydrogen; methyl; ethyl; i-propyl; n-propyl; cyclopropyl; n-butyl; i-butyl; t-butyl; 1-ethylpropyl; 2,4,4-trimethylpentyl; hydroxymethyl; chloromethyl; trifluoromethyl; 2,2,2-trifluoroethyl; cyanomethyl; 2-(methylthio)ethyl; chloro; bromo; nitro; cyano; amino; aminocarbonyl; methoxycarbonyl; methylthio; methylsulfinyl; methylsulfonyl; phenyl; 2-furyl; 3-furyl; 1H-pyrrol-2-yl; 1-methyl-1H-pyrrol-2-yl; 2-thienyl; 1H-pyrazol-3-yl; 1,2,3-thiadiazol-4-yl or 1H-imidazol-2-yl. More preferably, R^1 is hydrogen; methyl; ethyl; i-propyl; n-propyl; n-butyl; methylthio; nitro; cyano; amino; chloro or 1H-pyrrol-2-yl. Most preferably, R^1 is hydrogen; methyl; methylthio; nitro; cyano; amino or chloro.

Usually, R^2 is hydrogen; C_{1-4} alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen; ester; cyano; alkyl carbamate; [(N-methoxy-N-methyl)amino]carbonyl. Preferably, R^2 is hydrogen; methyl; hydroxymethyl; (acetylamino)methyl; (propionylamino)methyl; (benzoylamino)methyl; [(benzyloxy)carbonyl]amino; chloro or cyano. More preferably, R^2 is hydrogen; chloro or cyano.

Usually, R^3 is hydrogen; C_{1-4} alkyl unsubstituted or substituted by hydroxy; halogen; ester or cyano. Preferably, R^3 is hydrogen; hydroxymethyl; chloro; cyano. More preferably, R^3 is hydrogen or cyano. Most preferred R^3 is hydrogen.

Usually, R^4 is hydrogen; C_{1-4} alkyl unsubstituted or substituted by halogens; C_{2-4} alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or/and halogens. Preferably, R^4 is hydrogen; n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl; 3,5-difluorophenyl; 3,4-difluorophenyl; 3-chloro-4-fluorophenyl;

2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl; 3-azido-2,4-difluorophenyl or 3-azido-2,4,6-trifluorophenyl. More preferably, R^4 is hydrogen; n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl; 3,5-difluorophenyl; 3,4-difluorophenyl; 3-chloro-4-fluorophenyl; 2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl or 3-azido-2,4-difluorophenyl. Most preferably, R^4 is n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 3,5-difluorophenyl; 2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl or 3-azido-2,4-difluorophenyl.

Usually, R^{4a} is hydrogen.

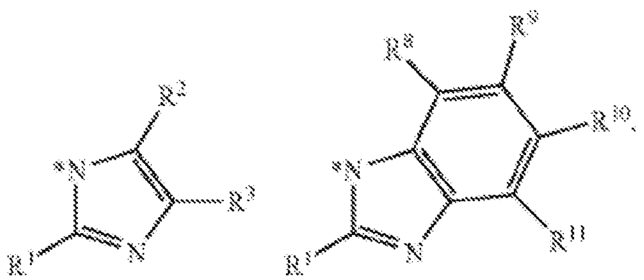
Usually, R^5 is hydrogen.

Usually, R^6 is hydrogen or C_{1-10} alkyl unsubstituted or substituted by hydroxy or azido. Preferably, R^6 is hydrogen or azidomethyl. More preferably R^6 is hydrogen.

Usually R^7 is hydrogen.

In other preferred embodiments, R^6 and R^7 are linked to form a cyclopropyl.

In other preferred embodiments, R^2 and R^3 can form together with the imidazole ring the following 1H-benzimidazole cycle



Usually, R^8 is hydrogen.

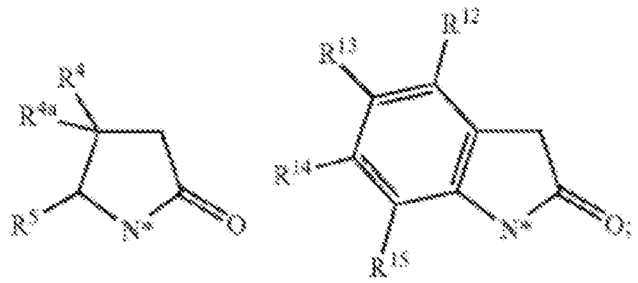
Usually, R^9 is hydrogen; halogen; C_{1-3} alkyl or alkoxy. Preferably, R^9 is hydrogen; methyl; chloro or methoxy. More preferred R^9 is hydrogen.

Usually, R^{10} is hydrogen; halogen; cyano; C_{1-3} alkyl unsubstituted or substituted by halogens; or alkoxy. Preferably, R^{10} is methyl; hydrogen;

trifluoromethyl; fluoro; cyano or methoxy. More preferred R^{10} is hydrogen; trifluoromethyl; fluoro or cyano.

Usually, R^{11} is hydrogen.

In other preferred embodiments, R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



Usually, R^{12} is hydrogen or halogen. Preferably R^{12} is hydrogen; chloro or fluoro. More preferred R^{12} is hydrogen.

Usually, R^{13} is hydrogen; C_{1-3} alkyl; halogen or thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl. Preferably R^{13} is hydrogen; chloro; bromo or methyl. Most preferred R^{13} is chloro; bromo or methyl.

Usually R^{14} is hydrogen.

Usually, R^{15} is hydrogen.

Combinations of one or more of these preferred compound groups are especially preferred.

Generally, among the embodiments, the compounds of formula I, or pharmaceutically acceptable salts thereof, are those wherein

R^1 is selected from hydrogen; C_{1-10} alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy; C_{3-6} cycloalkyl; halogen; ester; amido; nitro; cyano; amino; phenyl; alkylthio; alkylsulfonyl; alkylsulfinyl; heterocycle unsubstituted or substituted by alkyl group; or guanidine;

R^2 is selected from hydrogen; C_{1-4} alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen; ester; cyano; alkyl carbamate or [(N-methoxy-N-methyl)amino]carbonyl.

R^3 is selected from hydrogen; C_{1-4} alkyl unsubstituted or substituted by hydroxy; halogen; ester or cyano;

R^4 is selected from hydrogen; C_{1-4} alkyl unsubstituted or substituted by halogens; C_{2-4} alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or /and halogens;

R^{4a} is hydrogen;

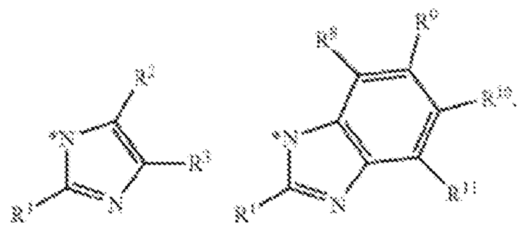
R^5 is hydrogen;

R^6 is selected from hydrogen or C_{1-10} alkyl unsubstituted or substituted by hydroxy or azido;

R^7 is hydrogen;

or R^6 and R^7 can be linked to form a cyclopropyl;

or R^2 and R^3 can form together with the imidazole ring the following 1H-benzimidazole cycle



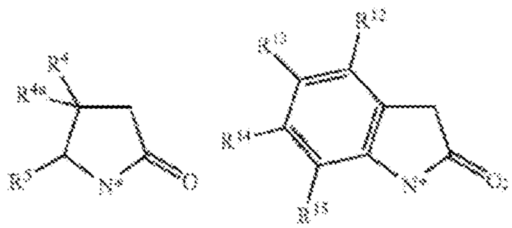
R^8 is hydrogen;

R^9 is selected from hydrogen; halogen; C_{1-3} alkyl; alkoxy;

R^{10} is selected from hydrogen; halogen; cyano or C_{1-3} alkyl unsubstituted or substituted by halogens; or alkoxy;

R^{11} is hydrogen;

or R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



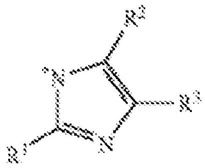
R^{12} is selected from hydrogen or halogen;

R^{13} is selected from hydrogen; C_{1-3} alkyl; halogen; thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl;

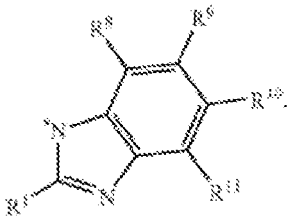
R^{14} is hydrogen;

R^{15} is hydrogen;

with the proviso that R^4 is different from hydrogen when



represents a group of formula



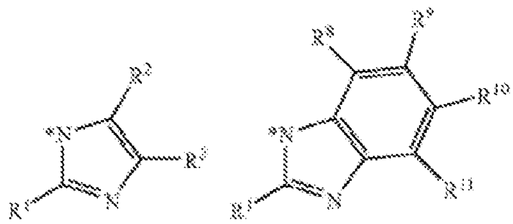
In a preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

R^1 is selected from hydrogen; methyl; ethyl; i-propyl; n-propyl; cyclopropyl; n-butyl; i-butyl; t-butyl; 1-ethylpropyl; 2,4,4-trimethylpentyl; trifluoromethyl; 2,2,2-trifluoroethyl; hydroxymethyl; chloromethyl; cyanomethyl; 2-(methylthio)ethyl; chloro; bromo; nitro; cyano; amino; aminocarbonyl; methoxycarbonyl; methylthio; methylsulfinyl; methylsulfonyl; phenyl; 2-furyl; 3-furyl; 1H-pyrrol-2-yl; 1-methyl-1H-pyrrol-2-yl; 2-thienyl; 1H-pyrazol-3-yl; 1,2,3-thiadiazol-4-yl; or 1H-imidazol-2-yl;

R^2 is selected from hydrogen; methyl; hydroxymethyl; (acetylamino)methyl; (propionylamino)methyl; (benzoylamino)methyl; (benzyloxycarbonyl)amino; chloro; or cyano;

R^3 is selected from hydrogen; hydroxymethyl; chloro; cyano;

or R^2 and R^3 can form together with the imidazole ring the following 1H-benzimidazole cycle



R^8 is hydrogen;

R^9 is selected from hydrogen; methyl; choro; methoxy;

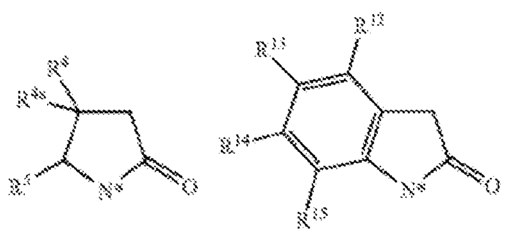
R^{10} is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy;

R^{11} is hydrogen;

R^4 is selected from hydrogen; n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl; 3,5-difluorophenyl; 3,4-difluorophenyl; 3-chloro-4-fluorophenyl; 2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl; 3-azido-2,4-difluorophenyl; or 3-azido-2,4,6-trifluorophenyl.

R^{4a} is hydrogen;R^5 is hydrogen;

or R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



R^{12} is selected from hydrogen; chloro; fluoro;

R^{13} is selected from hydrogen; chloro; bromo; methyl;

R^{14} is hydrogen;

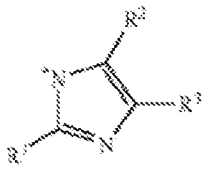
R^{15} hydrogen;

R^6 is selected from hydrogen; azidomethyl;

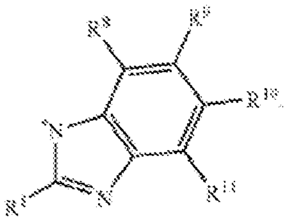
R^7 is hydrogen;

or R^6 and R^7 are linked to form a cyclopropyl;

with the proviso that R^4 is different from hydrogen when



represents a group of formula



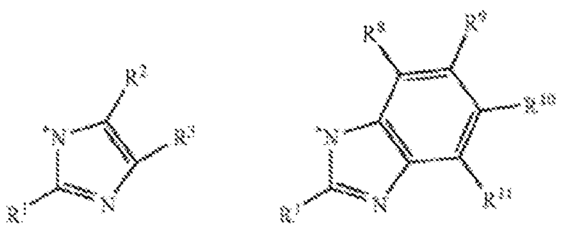
In a more preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

R^1 is selected from hydrogen; methyl; ethyl; i-propyl; n-propyl; n-butyl; methylthio; nitro; cyano; amino; chloro; or 1H-pyrrol-2-yl;

R^2 is selected from hydrogen; chloro; cyano;

R^3 is selected from hydrogen; cyano;

or R^2 and R^3 can form together with the imidazole ring the following 1H-benzimidazole cycle



R^8 is hydrogen;

R^9 is hydrogen;

R^{10} is selected from hydrogen; trifluoromethyl; fluoro; cyano;

R^{11} is hydrogen;

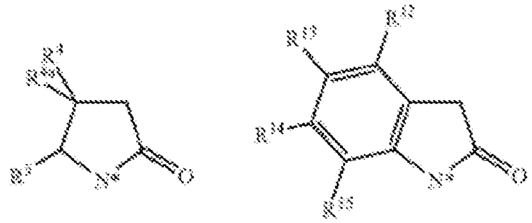
R^4 is selected from hydrogen; n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl; 3,5-

difluorophenyl; 3,4-difluorophenyl; 3-chloro-4-fluorophenyl; 2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl; or 3-azido-2,4-difluorophenyl;

R^{4a} is hydrogen;

R^5 is hydrogen;

or R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



wherein

R^{12} is hydrogen;

R^{13} is selected from methyl; chloro; bromo;

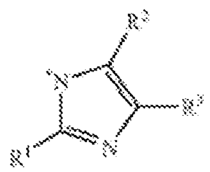
R^{14} is hydrogen;

R^{15} hydrogen;

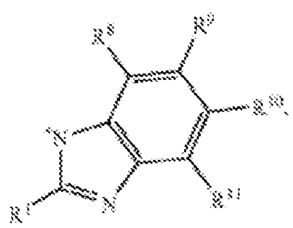
R^6 is hydrogen;

R^7 is hydrogen;

with the proviso that R^4 is different from hydrogen when



represents a group of formula



In a most preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

R^1 is selected from hydrogen; methyl; methylthio; nitro; cyano; amino; chloro;

R^2 is selected from hydrogen; chloro; cyano;

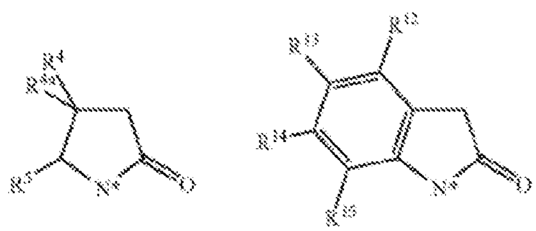
R^3 is hydrogen;

R^4 is selected from n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 3,5-difluorophenyl; 2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl; 3-azido-2,4-difluorophenyl;

R^{4a} is hydrogen;

R^5 is hydrogen;

or R^4, R^{4a} and R^5 can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



R^{12} is hydrogen;

R^{13} is selected from chloro; bromo; methyl;

R^{14} is hydrogen;

R^{15} hydrogen;

R^6 is hydrogen;

R^7 is hydrogen.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 4-(3-azido-2,4,6-trifluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-- one; 1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2- -one; (+)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-[(2-ethyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-isopropyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-phenyl-1H-imidazol-1-yl)methyl]-

4-propylpyrrolidin-2-one; 4-propyl-1-[(2-propyl-1H-imidazol-1-yl)methyl]pyrrolidin-2-one; (+)-1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; 4-(2,2-difluorovinyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3-chlorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-{[2-(methylthio)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-{[2-(methylsulfinyl)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-[(2-tert-butyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[1-(1H-imidazol-1-yl)cyclopropyl]pyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-phenylpyrrolidin-2-one; 1-{[2-(methylsulfonyl)-1H-imidazol-1-yl]methyl}-propylpyrrolidin-2-one; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-2-carboxamide, 4-(4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one; 4-(3-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3-chloro-4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(4-chlorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,4-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,4,5-trifluorophenyl)pyrrolidin-2-one; 1-{[2-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; methyl 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-2-carboxyla- te; 1-[(2-nitro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-2-carbonitrile; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2,4-dichloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one; 1-[(5-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; (+)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-

2-one; (-)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; (-)-1-{[2-oxo-4-(2,3,4-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; (+)-1-{[2-oxo-4-(2,3,4-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; (-)-1-{[2-oxo-4-(2,3,4-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (+)-1-{[2-oxo-4-(2,3,4-trifluorophenyl)-1- pyrrolidinyl]methyl}-1H-imidazole-4-carbonitrile; (-)-1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (+)-1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (+)-1-{[2-oxo-4-(2,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (-)-1-{[2-oxo-4-(2,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (-)-1-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (-)-1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; 1-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5- -carbonitrile; 1-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5- -carbonitrile; 1-[(5-methyl-2-phenyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5-methyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5-phenyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-ethyl-5-methyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2,5-dimethyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-[2-azido-1-(1H-imidazol-1-yl)ethyl]-4-propylpyrrolidin-2-one; 1-[(4-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-[(2-bromo-4,5-dichloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; (+)-1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; 1-{[5-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-{[4-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; benzyl 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-5-ylcarbamat- e; N-[(1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazol-5-

yl)methyl]acetamide; N-[(1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazol-5-yl)methyl]benzamide; N-[(1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazol-5-yl)methyl]propanamide; 1-(1H-benzimidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; 1-[(2-methyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 4-propyl-1-[(2-propyl-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one; 1-[(2-isopropyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 4-propyl-1-{[2-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}pyrrolidin-2- -one; 1-{[2-(methylthio)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2- -one; 1-[(2-amino-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-{[2-(chloromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-on- e; {1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazol-2-yl}acetoni- trile; 1-[(5-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one- ; 1-[(5-methyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5,6-dimethyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-{[2-isopropyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propyl-pyrrolidin-2-one; 1-[(6-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-2-propyl-1H-benzimidazole-5-car- bonitrile; 1-{[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-- propylpyrrolidin-2-one; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-1H-benzimidazol-1-yl]methyl}pyrrolidin-2-- one; 1-[(5-fluoro-2-propyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin- -2-one; 1-{[6-methyl-2-(1H-pyrrol-2-yl)-1H-benzimidazol-1-yl]methyl}-4-pro-pylpyrrolidin-2-one; 1-[(6-methoxy-2-propyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-- one ; 2-butyl-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-5- -carbonitrile; 1-{[2-[2-(methylthio)ethyl]-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-[(5-fluoro-2-isobutyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2- -one; 1-{[5-fluoro-2-(2,4,4-trimethylpentyl)-1H-benzimidazol-1-yl]methyl}-- 4-propylpyrrolidin-2-one; 2-cyclopropyl-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-- 5-carbonitrile; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-2-(1H-pyrazol-3-yl)-1H-benzimidazole-5-carbonitrile; 1-[(2-

cyclopropyl-5-fluoro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5-fluoro-2-isopropyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-{[2-(3-furyl)-6-methoxy-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin- -2-one; 1-[(2-cyclopropyl-6-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylp- yrrolidin-2-one; 1-[(2-isopropyl-6-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin- -2-one; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-2-(1,2,3-thiadiazol-4-yl-)-1H-benzimidazole-5-carbonitrile; 1-{[2-(1H-imidazol-2-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}- -4-propylpyrrolidin-2-one; 1-{[5-fluoro-2-(2,2,2-trifluoroethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-{[2-(1-ethylpropyl)-6-methoxy-1H-benzimidazol-1-yl]methyl}-4-propylpyrr- olidin-2-one; 1-{[6-methoxy-2-(1-methyl-1H-pyrrol-2-yl)-1H-benzimidazol-1-yl]methyl}-4-- propylpyrrolidin-2-one; 1-{[2-(2-furyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propyl- pyrrolidin-2-one; 4-propyl-1-{[2-thien-2-yl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl- }pyrrolidin-2-one; 1-{[2-(3-furyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propyl-pyrrolidin-2-one; 1-{[2-cyclopropyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]- methyl}pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 5-bromo-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 5-chloro-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 4-fluoro-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 4-chloro-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 1-(1H-imidazol-1-ylmethyl)-5-methyl-1,3-dihydro-2H-indol-2-one; 1-[(2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]-1H- imidazole-5-carbonitrile; and 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]-1H-imidazole-5-c- arbonitrile.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one, 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2- -one; (+)-4-(3-azido-

2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-[(2-ethyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-isopropyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 4-propyl-1-[(2-propyl-1H-imidazol-1-yl)methyl]pyrrolidin-2-one; (+)-1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; 4-(2,2-difluorovinyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3-chlorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-{[2-(methylthio)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-phenylpyrrolidin-2-one; 4-(4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one; 4-(3-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3-chloro-4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(4-chlorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,4-trifluorophenyl)pyrrolidin-2-one; 1-(l1H-imidazol-1-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,4,5-trifluorophenyl)pyrrolidin-2-one; 1-[(2-nitro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-- 2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-2-carbonitrile; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5- -carbonitrile; (+)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; (-)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; (+); 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4- -carbonitrile; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-[2-azido-1-(1H-imidazol-1-yl)ethyl]-4-propylpyrrolidin-2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; (+)-1-{[2-oxo-4-(3,4,5-

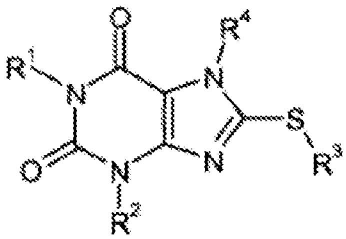
trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-2-propyl-1H-benzimidazole-5-carbonitrile; 1-{[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4--propylpyrrolidin-2-one; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-1H-benzimidazol-1-yl]methyl}pyrrolidin-2-- one; 1-[(5-fluoro-2-propyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin- -2-one; 2-butyl-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole- -5-carbonitrile; 1-[(5-fluoro-2-isopropyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-- 2-one; 1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 5-bromo-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 5-chloro-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 1-(1H-imidazol-1-ylmethyl)-5-methyl-1,3-dihydro-2H-indol-2-one; 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]-1H-imidazole-5-carbo- nitrile.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2- -one; (+)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(2,2-difluorovinyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-on- e; 4-(3-chlorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-{[2-(methylthio)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-phenylpyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-2-one; 4-(3-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,4-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2,4,5-trifluorophenyl)pyrrolidin-2-one; 1-[(2-nitro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin-- 2-one; 1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-2-carbonitrile; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; 1-[(5-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; (+)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; (-)-1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-(3,4,5-trifluorophenyl)pyrrolidin- -2-one; 1-[(2-chloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one; (+)-1-{[2-oxo-4-(3,4,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile; 5-bromo-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 5-chloro-1-(1H-imidazol-1-ylmethyl)-1,3-dihydro-2H-indol-2-one; 1-(1H-imidazol-1-ylmethyl)-5-methyl-1,3-dihydro-2H-indol-2-one; 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)methyl]-1H-imidazole-5-carbo- nitrile.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2- -one; (+)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one; 4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one.

v) International Patent Application WO 2007/065595:

Compounds having formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



(I)

wherein

R^1 is hydrogen or C_{1-6} alkyl;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is a group of formula $-CHR^5R^6$ or a benzyl group;

R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle;

R^5 is C2-4 alkyl;

R^6 is C2-4 alkyl, amido or $-COOR^7$;

R^7 is C1-4 alkyl;

Usually when R^3 is a benzyl group, then R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl.

Usually when R^3 is a group of formula $-CHR^5R^6$ then R^4 is C_{1-8} alkyl optionally substituted by C_{3-6} cycloalkyl, aryl or heterocycle.

The term "alkyl", as used herein, is a group which represents saturated, monovalent hydrocarbon radicals having straight (unbranched) or branched moieties, or combinations thereof, and containing 1-8 carbon atoms, preferably 1-6 carbon atoms; more preferably alkyl groups have 1-4 carbon atoms. Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl, acyl, aryl or heterocycle. Alkyl moieties may be optionally substituted by a cycloalkyl as defined hereafter. Preferred alkyl groups are methyl, cyanomethyl, ethyl, 2-ethoxy-2-oxoethyl, 2- methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-butyl, i-butyl, n-pentyl, 3-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1- phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl or (5-nitro-2-furyl)methyl. More preferred alkyl groups are methyl, ethyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3- hydroxypropyl, 2-propynyl, n-butyl, 3-pentyl, n-hexyl, benzyl, 3-bromobenzyl, 3- methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl or (5-nitro- 2-furyl)methyl. Most preferred alkyl groups are methyl, ethyl, 3-methoxybenzyl, 3- nitrobenzyl or (5-nitro-2-furyl)methyl.

The term "cycloalkyl", as used herein, represents a monovalent group of 3 to 8, preferably 3 to 6 carbon atoms derived from a saturated cyclic hydrocarbon, which may be substituted by any suitable group including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkyl group is cyclohexyl.

The term "aryl" as used herein, is defined as a phenyl group optionally substituted by 1 to 4 substituents independently selected from halogen, amino, nitro, alkoxy or aminosulfonyl. Preferred aryl groups are phenyl, 2-

bromophenyl, 3-bromophenyl, 4- bromophenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-aminophenyl or 4-(aminosulfonyl)phenyl.

The term "phenyl", as used herein, represents an aromatic hydrocarbon group of formula $–C_6H_5$.

The term "benzyl group", as used herein, represents a group of formula -CH_2-aryl. Preferred benzyl groups are benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3- methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl or 4-(aminosulfonyl)benzyl. More preferred benzyl groups are benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl or 3- aminobenzyl. Most preferred alkyl groups are 3-methoxybenzyl or 3-nitrobenzyl.

The term "halogen", as used herein, represents an atom of fluorine, chlorine, bromine, or iodine. Preferred halogen is bromine.

The term "hydroxy", as used herein, represents a group of formula -OH.

The term "cyano", as used herein, represents a group of formula -CN.

The term "amino", as used herein, represents a group of formula $-NH_2$.

The term "ethynyl", as used herein, represents a group of formula $-C\equiv CH$.

The term "alkoxy", as used herein, represents a group of formula $-OR^a$ wherein R^a is an alkyl group, as defined above. Preferred alkoxy group is methoxy.

The term "nitro", as used herein, represents a group of formula $-NO_2$.

The term "amido", as used herein, represents a group of formula -C(=O)NH2.

The term "acyl", as used herein, represents a group of formula $-C(=O)R^b$ wherein R^b is an alkyl group, as defined here above. Preferred acyl group is acetyl (-C(=O)Me).

The term "alkoxycarbonyl (or ester)", as used herein, represents a group of formula $–COOR^c$ wherein R^c is an alkyl group; with the proviso that R^c does not represent an alkyl alpha-substituted by hydroxy. Preferred alkoxycarbonyl group is ethoxycarbonyl.

The term "heterocycle", as used herein, represents a 5-membered ring containing one or two heteroatoms selected from O or N. The heterocycle may be substituted by one or two C_{1-4} alkyl or nitro. Preferred heterocycles are (3, 5-dimethylisoxazol-4-yl) or (5-nitro- 2-furyl). Most preferred heterocycle is (5-nitro-2-furyl).

Generally R^1 is hydrogen or C_{1-6} alkyl. Usually R^1 is hydrogen or C_{1-6} alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl. Preferably R^1 is hydrogen, methyl, cyanomethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n- propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-pentyl or n-hexyl. More preferably R^1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2- propynyl. Most preferably R^1 is hydrogen.

Generally R^2 is hydrogen or C_{1-4} alkyl. Usually R^2 is hydrogen or unsubstituted C_{1-4} alkyl. Preferably R^2 is hydrogen, methyl or n-butyl. More preferably, R^2 is methyl.

Generally R^3 is a group of formula $-CHR^5R^6$ or a benzyl group. Preferably R^3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl. Most preferably R^3 is 1-(ethoxycarbonyl)propyl.

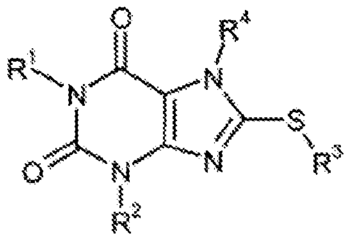
Generally R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl, C_{3-6} cycloalkyl, aryl or heterocycle. Usually R^4 is C_{1-8} alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl. Preferably R^4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2- bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3- aminobenzyl, 4-(aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl. More preferably R^4 is n- butyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1 -(ethoxycarbonyl)propyl. Most preferably R^4 is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

Generally R^5 is C_{2-4} alkyl. Usually R^5 is unsubstituted $C_{2-4}4$ alkyl. Preferably R^5 is ethyl.

Generally R^6 is C_{2-4} alkyl, amido or -$COOR^7$. Usually R^6 is unsubstituted C_{2-4} alkyl, amido or -$COOR^7$. Preferably R^6 is ethyl, amido or ethoxycarbonyl. Most preferably R^6 is ethoxycarbonyl.

Generally R^7 is C_{1-4} alkyl. Usually R^7 is unsubstituted C_{1-4} alkyl. Preferably, R^7 is ethyl.

In some embodiments, the compounds are those having formula I, and their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



(I)

wherein

R^1 is hydrogen, C_{1-6} alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl;

R^2 is hydrogen or unsubstituted C_{1-4} alkyl;

R^3 is a group of formula -$CHR^5 R^6$ or a benzyl group;

R^4 is C_{1-8} alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl;

R^5 is unsubstituted C_{2-4} alkyl;

R^6 is unsubstituted C_{2-4} alkyl, amido or -$COOR^7$;

R^7 is unsubstituted C_{1-4} alkyl;

with the proviso that when R^1 is hydrogen, R^2 is methyl, R^3 is -$CHR^5 R^6$, R^6 is ethoxycarbonyl and R^5 is ethyl, then R^4 is different from n-propyl, i-propyl, n-pentyl, n- heptyl, 3-bromobenzyl, 4-chlorobenzyl, 4-methylbenzyl or 2-phenylethyl.

In the above embodiment, preferably, when R^3 is a benzyl group, then R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, preferably, when R^3 is a group of formula -CHR^5R^6, then R^4 is C_{1-8} alkyl optionally substituted by C_{3-6} cycloalkyl, aryl or heterocycle.

In a preferred embodiment,

R^1 is hydrogen, methyl, cyanomethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n- propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-pentyl or n-hexyl;

R^2 is hydrogen, methyl or n-butyl;

R^3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1 -(ethoxycarbonyl)propyl or 3-bromobenzyl;

R^4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3- bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4- (aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl, (5- nitro-2-furyl)methyl or 1 -(ethoxycarbonyl)propyl;

with the proviso that when R^1 is hydrogen, R^2 is methyl and R^3 is 1-(ethoxycarbonyl)propyl, then R^4 is different from n-pentyl, 3-bromobenzyl or 2- phenylethyl.

In the above embodiment, preferably, when R^3 is 3-bromobenzyl, then R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, preferably, when R^3 is 3-pentyl, 1-(aminocarbonyl)propyl or 1-(ethoxycarbonyl)propyl, then R^4 is different from 1- (ethoxycarbonyl)propyl.

In a more preferred embodiment,

R^1 is hydrogen, methyl, cyanomethyl , 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl;

R^2 is methyl;

R^3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl;

R^4 is n-butyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3- aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1- (ethoxycarbonyl)propyl;

with the proviso that when R^1 is hydrogen, R^2 is methyl and R^3 is 1-(ethoxycarbonyl)propyl, then R^4 is different from 3-bromobenzyl.

In the above embodiment, preferably, when R^3 is 3-bromobenzyl, then R^4 is 1- (ethoxycarbonyl)propyl;

In the above embodiment, preferably, when R^3 is 3-pentyl, 1-(aminocarbonyl)propyl or 1-(ethoxycarbonyl)propyl, then R^4 is different from 1- (ethoxycarbonyl)propyl;

In a most preferred embodiment, R^1 is hydrogen; R^2 is methyl; R^3 is 1-(ethoxycarbonyl)propyl; and R^4 is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2- furyl)methyl.

A further embodiment consists in compounds wherein R^2 is methyl, R^3 is a group of formula $-CHR^5 R^6$ with R^5 being C_{2-4} alkyl, R^6 being amido or $-COOR^7$ and R^7 being methyl or ethyl.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: ethyl 2-[(7-benzyl-1 ,3-dimethyl-2,6-dioxo-2,3,6,7- tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-ethoxy-2- oxoethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7- (3-bromobenzyl)-1-(2-methoxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1 ,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro- 1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(2-bromobenzyl)-1 ,3-dimethyl-2,6-dioxo-2,3,6,7- tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(cyanomethyl)-3- methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-propyl-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-oxopropyl)-2,3,6,7-tetrahydro-1H- purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(3-hydroxypropyl)-3-methyl-2,6- dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3- methyl-2,6-dioxo-1-(2-propynyl)-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2- {[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-

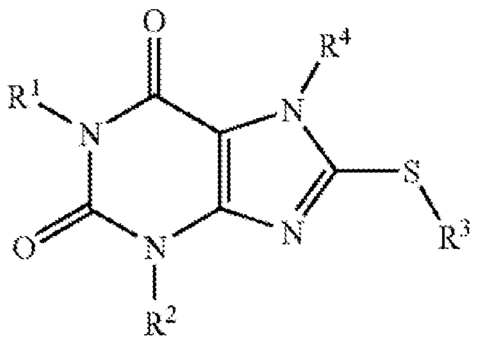
yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-({7-[4-(aminosulfonyl)benzyl]-3-methyl-2,6-dioxo-2, 3,6,7- tetrahydro-1 H-purin-8-yl}thio)butanoate; ethyl 2-{[7-(4-bromobenzyl)-1 ,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(cyclohexylmethyl)-1 ,3- dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[1 ,3-dimethyl- 2,6-dioxo-7-(1 -phenylethyl)-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[1 ,3- dimethyl-2,6-dioxo-7-(2-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-({7-[(3,5-dimethylisoxazol-4-yl)methyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl}thio)butanoate; ethyl 2-({3-methyl-7-[(5-nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro- 1 H-purin-8-yl}thio)butanoate; ethyl 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H- purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H- purin-8-yl]thio}butanoate; ethyl 2-[(1 ,7-dihexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H- purin-8-yl)thio]butanoate; ethyl 2-[(7-hexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin- 8-yl)thio]butanoate; ethyl 2-[(3-methyl-2,6-dioxo-1 ,7-dipentyl-2,3,6ı7-tetrahydro-1 H-purin-8-yl)thio]butanoate; 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8- yl]thio}butanamide; 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl)thio]butanamide; 7-(3-bromobenzyl)-8-[(1-ethylpropyl)thio]-3-methyl-3,7-dihydro-1 H- purine-2,6-dione; ethyl 2-{8-[(3-bromobenzyl)thio]-1 ,3-dimethyl-2,6-dioxo-1 ,2,3,6- tetrahydro-7H-purin-7-yl}butanoate; and ethyl 2-[(7-isobutyl-3-methyl-2,6-dioxo-2,3,6,7- tetrahydro-1H-purin-8-yl)thio]butanoate.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: ethyl 2-[(7-benzyl-1 ,3-dimethyl-2,6-dioxo-2,3,6,7- tetrahydro-1 H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-methoxyethyl)-3- methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3- bromobenzyl)-1 ,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-

{[7-(3-bromobenzyl)-1-(cyanomethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-propyl-2,3,6,7- tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(3-hydroxypropyl)-3- methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3- bromobenzyl)-3-methyl-2,6-dioxo-1-(2-propynyl)-2,3,6,7-tetrahydro-1 H-purin-8- yl]thio}butanoate; ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H- purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro- 1 H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7- tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-({7-[(3,5-dimethylisoxazol-4-yl)methyl]-3- methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyi 2-({3-methyi-7-[(5- nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl}thio)butanoate; ethyl 2-[(7- butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl)thio]butanoate; ethyl 2-[(7-hexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl)thio]butanoate; 2-{[7-(3-bromobenzyl)- 3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanamide; 7-(3-bromobenzyl)-8- [(1-ethylpropyl)thio]-3-methyl-3,7-dihydro-1 H-purine-2,6-dione; and ethyl 2-{8-[(3- bromobenzyl)thio]-1 ,3-dimethyl-2,6-dioxo-1 ,2,3,6-tetrahydro-7H-purin-7-yl}butanoate.

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6- dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; and ethyl 2-({3-methyl-7-[(5-nitro-2- furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl}thio)butanoate.

In some embodiments, the compounds are those having formula II, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts:



(II)

wherein R.sup.1 is hydrogen or C.sub.1-6 alkyl;

R.sup.2 is hydrogen or C.sub.1-4 alkyl;

R.sup.3 is a group of formula --CHR.sup.5R.sup.6 or a benzyl group;

R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

R.sup.5 is hydrogen or C.sub.1-4 alkyl;

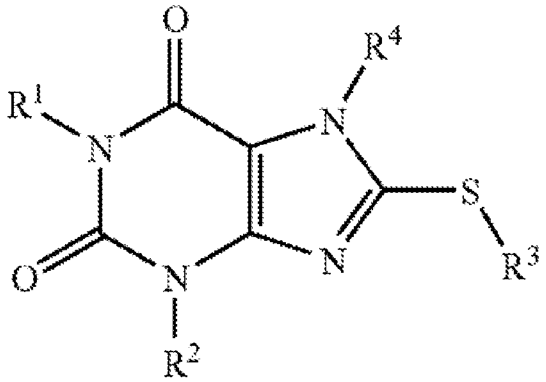
R.sup.6 is C.sub.1-4 alkyl, amido or --COOR.sup.7;

R.sup.7 is C.sub.1-4 alkyl;

In the above embodiment, in some cases, when R.sup.3 is a benzyl group, then R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, in some cases, when R.sup.3 is a group of formula --CHR.sup.5R.sup.6, then R.sup.4 is C.sub.1-8 alkyl optionally substituted by C.sub.3-6 cycloalkyl, aryl or heterocycle.

In some embodiments, the compounds are those compounds of formula II, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts



(II)

wherein

R.sup.1 is hydrogen or C.sub.1-6 alkyl;

R.sup.2 is hydrogen or C.sub.1-4 alkyl;

R.sup.3 is a group of formula --CHR.sup.5R.sup.6 or a benzyl group;

R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

R.sup.5 is hydrogen or C.sub.1-4 alkyl;

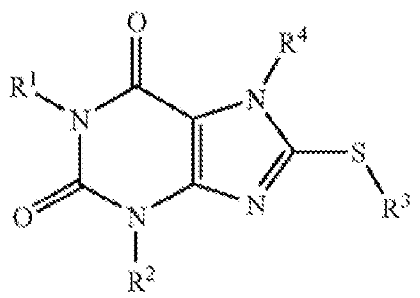
R.sup.6 is C.sub.1-4 alkyl, amido or --COOR.sup.7;

R.sup.7 is C.sub.1-4 alkyl.

In some embodiments, the compounds are compounds of formula II selected from ethyl 2-[(7-heptyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; 7-(3-bromobenzyl)-3-methyl-8-(propylthio)-3,7-dihydro-1H-purine-2,- 6-dione; ethyl 2-[(3-methyl-2,6-dioxo-7-pentyl-2,3,6,7-tetrahydro-1H-purin-8-

yl)thio]but- anoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl-]thio}butanoate; ethyl 2-[(3-methyl-2,6-dioxo-7-propyl-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]but- anoate; 7-(3-bromobenzyl)-8-[(3-chloro-2-hydroxypropyl)thio]-3-methyl-3,7-- dihydro-1H-purine-2,6-dione; and ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl-]thio}propanoate.

In some embodiments, the compounds are compounds of formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts



(I)

wherein

R.sup.1 is hydrogen or C.sub.1-6 alkyl;

R.sup.2 is hydrogen or C.sub.1-4 alkyl;

R.sup.3 is a group of formula --CHR.sup.5R.sup.6 or a benzyl group;

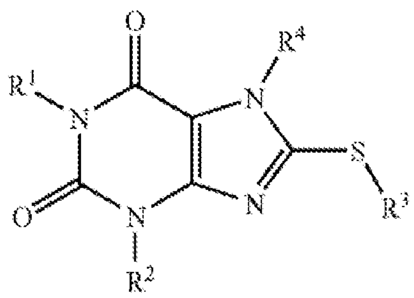
R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

R.sup.5 is C.sub.2-4 alkyl;

R.sup.6 is C.sub.2-4 alkyl, amido or --COOR.sup.7;

R.sup.7 is C.sub.1-4 alkyl;

In another embodiment, the compounds are compounds having formula II, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



(II)

wherein

R.sup.1 is hydrogen or C.sub.1-6 alkyl;

R.sup.2 is hydrogen or C.sub.1-4 alkyl;

R.sup.3 is a group of formula --CHR.sup.5R.sup.6 or a benzyl group;

R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

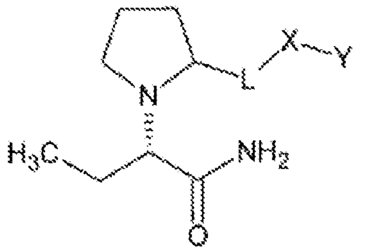
R.sup.5 is hydrogen or C.sub.1-4 alkyl;

R.sup.6 is C.sub.1-4 alkyl, amido or --COOR.sup.7;

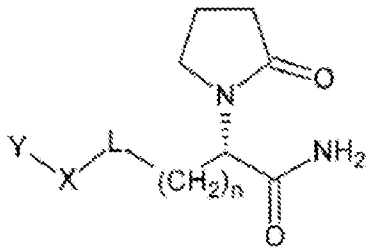
R.sup.7 is C.sub.1-4 alkyl;

vi) International Patent Application Publication No. WO2010/144712

In one embodiment, a chemical composition that includes a LEV derivative of Formula 1 or Formula 2 is disclosed.



Formula 1



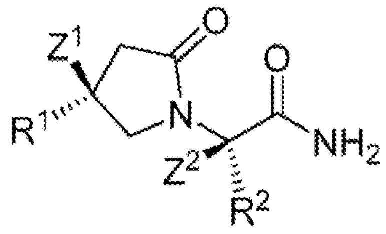
Formula 2

n of Formula 2 and L, X, and Y of Formulas 1 and 2 are defined as follows: a) n is an integer with a value of 0 to 8; b) L is one of the group consisting of CH2, CO, NHCO, NHCOO, CONH, NH, O, or S, and combinations thereof; c) X is an end group, an aromatic group, an aryl group, or a saturated, unsaturated, substituted, unsubstituted, straight chain, or branched chain aliphatic group having from 1 to 10 carbon and/or hetero chain atoms, the hetero chain atoms being selected from the group consisting of oxygen, nitrogen, sulfur, or phosphorus, and combinations thereof; and d) Y is optional and if present is one of a functional group selected from group consisting of alcohol amine, amide, carboxylic acid, aldehyde, ester, iminoester, isocyanate, isothiocyanate, anhydride, thiol, thiolacetone, diazonium, NHS, CO-NHS, O-NHS, maleimido; or e) Y is a Yi-Z where Yi is selected from the group consisting of COO, CO, O, CONH, NHCO, or NH and Z is an operative group.

In one embodiment of the method, the operative group of Z is selected from the group consisting of detectable labels, antigenic carriers, coupling agents, end groups, proteins, lipoproteins, glycoproteins, polypeptides, polysaccharides, nucleic acids, polynucleotides, teichoic acids, radioactive isotopes, enzymes, enzyme fragments, enzyme donor fragments, enzyme acceptor fragments, enzyme substrates, enzyme inhibitors, coenzymes, fluorescent moieties, phosphorescent moieties, anti-stokes up-regulating moieties, chemiluminescent moieties, luminescent moieties, dyes, sensitizers, particles, microparticles, magnetic particles, solid supports, liposomes, ligands, receptors, hapten radioactive isotopes, and combinations thereof.

vii) International Patent Application Publication No. WO2010/002869

The present invention provides a compound of Formula I:


(I),

or a pharmaceutically acceptable salt thereof, wherein: each Z is independently selected from hydrogen and deuterium; R1 is an n-propyl group having zero to seven deuterium atoms; R2 is an ethyl group having zero to five deuterium atoms, and when each R has zero deuterium atoms, at least one Z is deuterium.

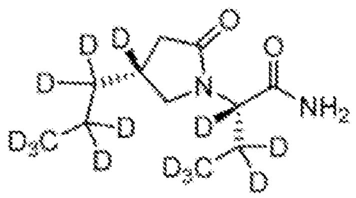
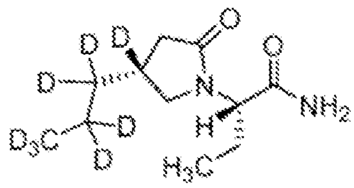
One embodiment of this invention provides compounds of Formula I wherein R1 is selected from CD3CH2CH2-, CD3CD2CH2-, CD3CH2CD2-, CH3CH2CD2-, CH3CD2CD2-, CD3CD2CD2- or CH3CH2CH2-. In a more specific embodiment, R1 is CD3CD2CD2- or

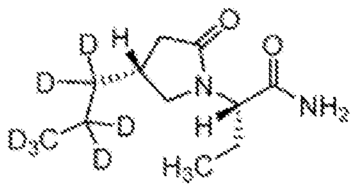
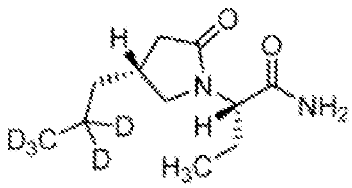
CD3CD2CH2-. In one aspect of these embodiments, Z1 and Z2 are both hydrogen. In another aspect of these embodiments, Z1 and Z2 are both deuterium.

In another embodiment, R2 is selected from CH3CH2-, CD3CH2-, CH3CD2-, or CD3CD2-. In a more specific embodiment, R2 is selected from CH3CH2- or CD3CD2-. In one aspect of these embodiments, Z1 and Z2 are both hydrogen. In another aspect of these embodiments, Z1 and Z2 are both deuterium.

The R and Z variables as described above may be selected and taken together to provide more specific embodiments of this invention. For example, in one embodiment, R1 is CD3CH2CH2-, CD3CD2CH2-, CD3CH2CD2-, CH3CH2CD2-, CH3CD2CD2-, CD3CD2CD2- or CH3CH2CH2-; and R2 is selected from CH3CH2-, CD3CH2-, CH3CD2-, or CD3CD2-. In one aspect of this embodiment, R2 is CH3CH2- or CD3CD2-. [0039] In another embodiment, R1 is CD3CD2CD2- or CD3CD2CH2-; and R2 is selected from CH3CH2-, CD3CH2-, CH3CD2-, or CD3CD2-. In one aspect of this embodiment, R2 is CH3CH2- or CD3CD2-.

Examples of specific compounds of this invention include the following:

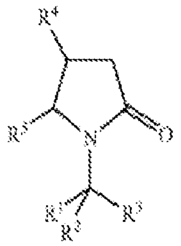
 Compound 100;  Compound 101;

 Compound 102; and  Compound 103.

viii) 20090312333

The compounds of the present invention are those covered by formula (I), their diastereomers and mixtures, or a pharmaceutically acceptable salt thereof.

(I)



R1 is hydrogen, substituted or unsubstituted C1-12 alkyl, substituted or unsubstituted aryl or substituted or unsubstituted 3-8 membered heterocycle.

R2 is hydrogen. Alternatively, R1 and R2 may be linked together in such a way to form a C3-6 cycloalkyl.

R3 is either

(a) a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms, said heterocycle is selected from the group consisting of:

1H-benzimidazol-6-yl;

1H-benzimidazol-7-yl;

imidazo[1,2-a]pyridin-3-yl;

imidazo[1,2-a]pyrimidin-3-yl;

imidazo[1,2-b][1,2,4]triazin-7-yl;

imidazo[1,2-b]pyridazin-3-yl;

5,6,7,8-tetrahydroimidazo[1,2-b]pyridazin-3-yl;

imidazo[2,1-b][1,3,4]thiadiazol-5-yl;

imidazo[2,1-b][1,3]thiazol-5-yl;

3H-imidazo[4,5-b]pyridin-7-yl;
1H-imidazol-4-yl;
1H-imidazol-5-yl;
1H-indol-2-yl;
1H-indol-3-yl;
1H-indol-4-yl;
1H-indol-7-yl;
isoxazol-4-yl;
1H-pyrazol-4-yl;
1H-pyrazol-5-yl;
1H-pyrazolo[1,5-a]pyrimidin-3-yl;
1H-pyrazolo[3,4-b]pyridin-3-yl;
pyridazin-4-yl;
pyridin-2-yl;
pyridin-3-yl;
pyridin-4-yl;
1H-pyrrolo[2,3-b]pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-4-yl;
1H-pyrrolo[2,3-b]pyridin-5-yl;
1H-pyrrolo[2,3-c]pyridin-2-yl;
1H-pyrrolo[2,3-c]pyridin-3-yl;
1H-pyrrolo[3,2-b]pyridin-3-yl;
1H-pyrrolo[3,2-c]pyridin-2-yl;
1H-pyrrolo[3,2-c]pyridin-3-yl;
1,3,4-thiadiazol-2-yl;
1,3-thiazol-5-yl;
[1,2,4]triazolo[4,3-b]pyridazin-7-yl;
[1,2,4]triazolo[4,3-b]pyridazin-8-yl;
indolizin-3-yl;
or R3 is
(b) a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its N atoms, said heterocycle is selected from the group consisting of:

1H-1,2,3-benzotriazol-1-yl;

1H-imidazo[4,5-b]pyridin-1-yl;

3H-imidazo[4,5-b]pyridin-3-yl;

7H-imidazo[4,5-c]pyridazin-7-yl;

1H-indol-1-yl;

2,3-dihydro-1H-indol-1-yl;

9H-purin-9-yl;

1H-pyrazolo[3,4-b]pyridin-1-yl;

2H-pyrazolo[3,4-b]pyridin-2-yl;

1H-pyrrolo[2,3-b]pyridin-1-yl;

1H-pyrrolo[3,2-b]pyridin-1-yl;

3,4-dihydroquinolin-1(2H)-yl;

8H-isothiazolo[5,4-b]indol-8-yl;

1H-1,2,4-triazol-1-yl;

1H-pyrrol-1-yl;

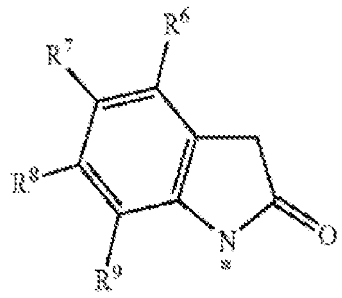
2-chloro-1H-benzimidazol-1-yl.

R4 in formula (I) is selected from the group comprising or consisting of hydrogen; C1-12 alkyl optionally substituted by halogen, C1-4 alkoxy, C1-4 alkylthio, azido, nitrooxy or an aryl; C2-12 alkenyl optionally substituted by halogen; C2-12 alkynyl optionally substituted by halogen; azido; alkoxycarbonylamino; arylsulfonyloxy; a substituted or unsubstituted aryl; or a 3-8 membered substituted or unsubstituted heterocycle;

In a specific embodiment R4 is hydrogen; or R4 is C1-12 alkyl or a C1-6 alkyl, optionally substituted by halogen, C1-4 alkoxy, C1-4 alkylthio, azido or nitrooxy; or R4 is C2-12 alkenyl or a C1-6 alkenyl optionally substituted by halogen; or R4 is C2-12 alkynyl or a C1-6 alkynyl optionally substituted by halogen; or R4 is alkoxycarbonylamino.

R5 is hydrogen;

Alternatively R4 may form together with R5 and the 2-oxo-1-pyrrolidine ring a 1,3-dihydro-2H-indol-2-one ring of the following structure:



The asterisk * indicates the point of attachment of the substituents;

R6 is hydrogen or halogen.

R7 in formula (I) is selected from the group comprising or consisting of hydrogen; nitro; halogen; heterocycle; amino; aryl; C1-12 alkyl optionally substituted by at least one halogen; or C1-12 alkoxy optionally substituted by at least one halogen.

R8 in formula (I) is selected from the group comprising or consisting of hydrogen, C1-12 alkyl optionally substituted by halogen, or halogen.

R9 in formula (I) is selected from the group comprising or consisting of hydrogen, C1-12 alkyl optionally substituted by halogen, or halogen.

A further aspect of the present invention consists in compounds of formula (I) wherein

R1 and R2 are both hydrogen.

R3 is:

(a) a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms selected from the group consisting of:

1H-benzimidazol-6-yl;

1H-benzimidazol-7-yl;

imidazo[1,2-a]pyridin-3-yl;

imidazo[1,2-a]pyrimidin-3-yl;

imidazo[1,2-b][1,2,4]triazin-7-yl;

imidazo[1,2-b]pyridazin-3-yl;

5,6,7,8-tetrahydroimidazo[1,2-b]pyridazin-3-yl;

imidazo[2,1-b][1,3,4]thiadiazol-5-yl;

imidazo[2,1-b][1,3]thiazol-5-yl;

3H-imidazo[4,5-b]pyridin-7-yl;

1H-imidazol-4-yl;

1H-imidazol-5-yl;

1H-indol-2-yl;
1H-indol-3-yl;
1H-indol-4-yl;
1H-indol-7-yl;
isoxazol-4-yl;
1H-pyrazol-4-yl;
1H-pyrazol-5-yl;
1H-pyrazolo[1,5-a]pyrimidin-3-yl;
1H-pyrazolo[3,4-b]pyridin-3-yl;
pyridazin-4-yl;
pyridin-2-yl;
pyridin-3-yl;
pyridin-4-yl;
1H-pyrrolo[2,3-b]pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-4-yl;
1H-pyrrolo[2,3-b]pyridin-5-yl;
1H-pyrrolo[2,3-c]pyridin-2-yl;
1H-pyrrolo[2,3-c]pyridin-3-yl;
1H-pyrrolo[3,2-b]pyridin-3-yl;
1H-pyrrolo[3,2-c]pyridin-2-yl;
1H-pyrrolo[3,2-c]pyridin-3-yl;
1,3,4-thiadiazol-2-yl;
1,3-thiazol-5-yl;
[1,2,4]triazolo[4,3-b]pyridazin-7-yl;
[1,2,4]triazolo[4,3-b]pyridazin-8-yl;
indolizin-3-yl.

Alternatively R3 is:

(b) a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its N atoms selected from the group consisting of:

1H-1,2,3-benzotriazol-1-yl;
1H-imidazo[4,5-b]pyridin-1-yl;
3H-imidazo[4,5-b]pyridin-3-yl;

7H-imidazo[4,5-c]pyridazin-7-yl;
1H-indol-1-yl;
2,3-dihydro-1H-indol-1-yl;
9H-purin-9-yl;
1H-pyrazolo[3,4-b]pyridin-1-yl;
2H-pyrazolo[3,4-b]pyridin-2-yl;
1H-pyrrolo[2,3-b]pyridin-1-yl;
1H-pyrrolo[3,2-b]pyridin-1-yl;
3,4-dihydroquinolin-1(2H)-yl;
8H-isothiazolo[5,4-b]indol-8-yl;
1H-1,2,4-triazol-1-yl;
1H-pyrrol-1-yl;
2-chloro-1H-benzimidazol-1-yl.

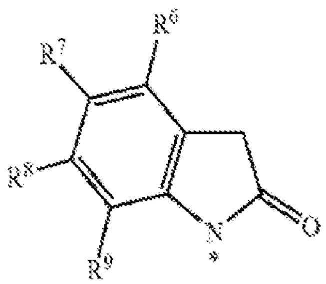
R4 in formula (I) is selected from the group comprising or consisting of hydrogen; C1-12 alkyl optionally substituted by halogen or C1-4 alkoxy; C2-12 alkenyl optionally substituted by halogen; C2-12 alkynyl optionally substituted by halogen.

In a further specific embodiment R4 is n-propyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2 bromo-2,2-difluoroethyl, 2,2-difluorovinyl.

In another specific embodiment R4 is phenyl, 2,3,5-trifluorophenyl or 3-chloro-4-fluorophenyl.

R5 is hydrogen;

A further embodiment of the present invention consists in compounds of formula (I) wherein R4 forms together with R5a 1,3-dihydro-2H-indol-2-one ring



The asterisk * indicates the point of attachment of the heteroaryl alkylene substituent, and wherein

R6 is hydrogen;

R7 is chlorine;

R8 is hydrogen;

R9 is hydrogen.

A further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of:

imidazo[1,2-a]pyrimidin-3-yl;

imidazo[1,2-b][1,2,4]triazin-7-yl;

imidazo[1,2-b]pyridazin-3-yl;

5,6,7,8-tetrahydroimidazo[1,2-b]pyridazin-3-yl;

imidazo[2,1-b][1,3,4]thiadiazol-5-yl;

imidazo[2,1-b][1,3]thiazol-5-yl;

3H-imidazo[4,5-b]pyridin-7-yl;

1H-imidazol-4-yl;

1H-imidazol-5-yl;

isoxazol-4-yl;

1H-pyrazol-4-yl;

1H-pyrazol-5-yl;

1H-pyrazolo[1,5-a]pyrimidin-3-yl;

1H-pyrazolo[3,4-b]pyridin-3-yl;

pyridin-3-yl;

1H-pyrrolo[2,3-b]pyridin-3-yl;

1H-pyrrolo[2,3-b]pyridin-4-yl;

1H-pyrrolo[2,3-b]pyridin-5-yl;

1H-pyrrolo[2,3-c]pyridin-2-yl;

1H-pyrrolo[2,3-c]pyridin-3-yl;

1,3-thiazol-5-yl;

[1,2,4]triazolo[4,3-b]pyridazin-8-yl;

indolizin-3-yl.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of:

imidazo[1,2-b]pyridazin-3-yl;

imidazo[2,1-b][1,3,4]thiadiazol-5-yl;

imidazo[2,1-b][1,3]thiazol-5-yl;

3H-imidazo[4,5-b]pyridin-7-yl;

1H-imidazol-4-yl;

1H-imidazol-5-yl;

1H-pyrazol-4-yl;

1H-pyrazolo[1,5-a]pyrimidin-3-yl;

pyridin-3-yl;

1H-pyrrolo[2,3-b]pyridin-3-yl;

1H-pyrrolo[2,3-b]pyridin-4-yl;

1,3-thiazol-5-yl;

Said heterocycles are optionally substituted by e.g. a methyl, n-propyl, trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, iodine, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclopropylmethoxy, cyclobutylmethoxy, amino, methylamino, cyclopropylamino, cyclobutylamino, 1-pyrrolidinyl, cyano, phenyl, benzyl or 3-thienyl.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of: 6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl, 6-(cyclopropyloxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl, 6-propoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl, 6-chloroimidazo[2,1-b][1,3]thiazol-5-yl, 2,6-dichloroimidazo[2,1-b][1,3]thiazol-5-yl, 5-chloro-1H-imidazol-4-yl, 5-bromo-1H-imidazol-4-yl, 4-bromo-1H-imidazol-5-yl, 4-chloro-1H-imidazol-5-yl, 1H-imidazol-5-yl, 1-methyl-1H-imidazol-5-yl, 4-chloro-1-methyl-1H-imidazol-5-yl, 1H-pyrazol-4-yl, 1H-pyrrolo[2,3-b]pyridin-3-yl.

A further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is a substituted or unsubstituted imidazo[1,2-a]pyridin-3-yl.

Said imidazo[1,2-a]pyridin-3-yl is optionally substituted by e.g. a methyl, cyclopropyl, bromine, chlorine, fluorine, iodine.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of:

imidazo[1,2-a]pyridin-3-yl, 6-methylimidazo[1,2-a]pyridin-3-yl, 2-chloroimidazo[1,2-a]pyridin-3-yl.

A further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its N atoms and is selected from the group consisting of:

3H-imidazo[4,5-b]pyridin-3-yl;

1H-indol-1-yl;

1H-pyrrolo[2,3-b]pyridin-1-yl;

1H-pyrrolo[3,2-b]pyridin-1-yl;

1H-pyrrol-1-yl;

2-chloro-1H-benzimidazol-1-yl.

A specific further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a heterocycle linked to the rest of the molecule via one of its N atoms and is selected from the group consisting of:

3H-imidazo[4,5-b]pyridin-3-yl;

1H-pyrrolo[3,2-b]pyridin-1-yl;

1H-pyrrol-1-yl;

2-chloro-1H-benzimidazol-1-yl;

Said heterocycles may optionally be substituted by trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, methoxy or cyano.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of 6-bromo-2-chloro-3H-imidazo[4,5-b]pyridin-3-yl, 6-bromo-2-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl, 1H-pyrrolo[3,2-b]pyridin-1-yl, 2,5-dichloro-1H-pyrrol-1-yl, 2-chloro-5-methoxy-1H-benzimidazol-1-yl, 5-bromo-2-chloro-1H-benzimidazol-1-yl or 2,5-dichloro-1H-benzimidazol-1-yl.

A further embodiment of the present invention consists in compounds of formula (I) wherein R1, R2 and R5 are hydrogen.

R4 is a C1-6 alkyl optionally substituted by halogen, a C2-6 alkenyl optionally substituted by halogen or C2-12 alkynyl optionally substituted by halogen.

R3 is selected from the group consisting of;

imidazo[1,2-b]pyridazin-3-yl;

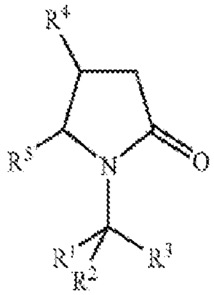
imidazo[2,1-b][1,3,4]thiadiazol-5-yl;
imidazo[2,1-b][1,3]thiazol-5-yl;
3H-imidazo[4,5-b]pyridin-7-yl;
1H-imidazol-4-yl;
1H-imidazol-5-yl;
1H-pyrazol-4-yl;
1H-pyrazolo[1,5-a]pyrimidin-3-yl;
pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-4-yl;
1,3-thiazol-5-yl;
and optionally substituted by methyl, n-propyl, trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, iodine, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclopropylmethoxy, cyclobutylmethoxy, amino, methylamino, cyclopropylamino, cyclobutylamino, 1-pyrrolidinyl, cyano, phenyl, benzyl or 3-thienyl.

A further embodiment of the present invention consists in compounds of formula (I) wherein R1, R2 and R5 are hydrogen.

R4 is a C1-6 alkyl optionally substituted by halogen, a C2-6 alkenyl optionally substituted by halogen or C2-12 alkynyl optionally substituted by halogen.

R3 is selected from the group consisting of
3H-imidazo[4,5-b]pyridin-3-yl;
1H pyrrolo[3,2-b]pyridin-1-yl;
1H-pyrrol-1-yl;
2-chloro-1H-benzimidazol-1-yl;
optionally substituted by trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, methoxy or cyano.

A further embodiment of the invention consists in compounds of formula (I), their diastereomers and mixtures, or a pharmaceutically acceptable salt thereof.



(I)

R1, R2 and R5 are hydrogen.

R3 is a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms, said heterocycle is selected from the group consisting of:

1H-benzimidazol-6-yl;

1H-benzimidazol-7-yl;

imidazo[1,2-a]pyridin-3-yl;

imidazo[1,2-a]pyrimidin-3-yl;

imidazo[1,2-b][1,2,4]triazin-7-yl;

imidazo[1,2-b]pyridazin-3-yl;

5,6,7,8-tetrahydroimidazo[1,2-b]pyridazin-3-yl;

imidazo[2,1-b][1,3,4]thiadiazol-5-yl;

imidazo[2,1-b][1,3]thiazol-5-yl;

3H-imidazo[4,5-b]pyridin-7-yl;

1H-imidazol-4-yl;

1H-imidazol-5-yl;

1H-indol-2-yl;

1H-indol-3-yl;

1H-indol-4-yl;

1H-indol-7-yl;

isoxazol-4-yl;

1H-pyrazol-4-yl;

1H-pyrazol-5-yl;

1H-pyrazolo[1,5-a]pyrimidin-3-yl;

1H-pyrazolo[3,4-b]pyridin-3-yl;

pyridazin-4-yl;

pyridin-2-yl;

pyridin-3-yl;
pyridin-4-yl;
1H-pyrrolo[2,3-b]pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-4-yl;
1H-pyrrolo[2,3-b]pyridin-5-yl;
1H-pyrrolo[2,3-c]pyridin-2-yl;
1H-pyrrolo[2,3-c]pyridin-3-yl;
1H-pyrrolo[3,2-b]pyridin-3-yl;
1H-pyrrolo[3,2-c]pyridin-2-yl;
1H-pyrrolo[3,2-c]pyridin-3-yl;
1,3,4-thiadiazol-2-yl;
1,3-thiazol-5-yl;
[1,2,4]triazolo[4,3-b]pyridazin-7-yl;
[1,2,4]triazolo[4,3-b]pyridazin-8-yl;
indolizin-3-yl;

Particularly preferred are imidazo[1,2-a]pyridin-3-yl; imidazo[1,2-a]pyrimidin-3-yl; imidazo[1,2-b]pyridazin-3-yl; 1H-imidazol-4-yl; 1H-imidazol-5-yl;

R4 is a substituted or unsubstituted phenyl moiety;

A further embodiment of the present invention consists in compounds of formula (I) wherein R1 is hydrogen or C1-12 alkyl;

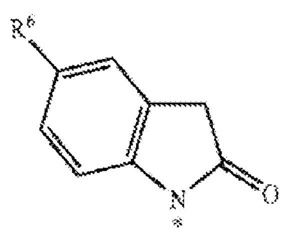
R2 is hydrogen;

R3 is an aromatic 5-membered heterocycle linked to the rest of the molecule via one of its C atoms;

R4 is hydrogen, C1-12 alkyl or aryl;

R5 is hydrogen;

Alternatively, R4 can form together with R5 and the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



wherein the asterisk * indicates the point of attachment of the substituents;

R6 is hydrogen or halogen;

In this embodiment R4 may not be hydrogen when R3 is substituted 1H-pyrazol-5-yl. Also this embodiment does not comprise 5-(2′-oxo-1′-pyrrolidinyl)methyl-1,3,4-tricarbomethoxy-pyrazole which is disclosed in A. Padwa et al J. Org. Chem. 2000, 65, 5223-5232 without any biological activity though.

In this embodiment wherein R3 is an aromatic 5-membered heterocycle linked to the rest of the molecule via one of its C atoms, specific moieties R3 may be selected from 1,3-thiazol-5-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 2-oxo-2,3-dihydro-1,3-thiazol-5-yl, each of them being optionally substituted by 1 to 3 substituents independently selected from methyl, chlorine, bromine, amino, methylamino, dimethylamino, (2-oxo-4-propyl-pyrrolidin-1-yl)methyl, 1-pyrrolidinyl, amido, cyano, methoxy, phenyl, 4-methylphenyl-sulfonyl, benzyl or 2-(benzylamino)-2-oxoethyl.

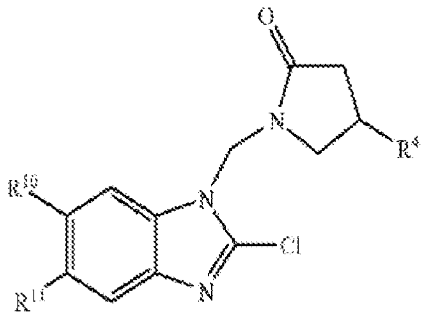
In this embodiment, more specific moieties R3 are selected from 2-(methylamino)-1,3-thiazol-5-yl; 2-pyrrolidin-1-yl-1,3-thiazol-5-yl; 5-bromo-1H-imidazol-4-yl; 5-chloro-1H-imidazol-4-yl; 1H-imidazol-5-yl; 1-methyl-1H-imidazol-5-yl; 4-bromo-1-methyl-1H-imidazol-5-yl; 4-chloro-1H-imidazol-5-yl; 4-chloro-1-methyl-1H-imidazol-5-yl; 4-cyano-1-methyl-1H-imidazol-5-yl; 1H-pyrazol-4-yl; 3,5-dimethyl-1H-pyrazol-4-yl; 3-methyl-1H-pyrazol-4-yl.

In this embodiment, most specific moieties R3 are selected from 5-bromo-1H-imidazol-4-yl; 5-chloro-1H-imidazol-4-yl; 1H-imidazol-5-yl; 4-bromo-1-methyl-1H-imidazol-5-yl; 4-chloro-1-methyl-1H-imidazol-5-yl; 1H-pyrazol-4-yl.

Still in this embodiment, a specific moiety R1 is selected from hydrogen or ethyl.

Still in this embodiment, a specific moiety R4 is selected from hydrogen, n-propyl, 2,3,5-trifluorophenyl or phenyl.

A further embodiment of the present invention consists in compounds having the specific formula (Ia).



(Ia)

In formula (Ia) the substituent R10 is hydrogen; halogen; C1-4 alkyl optionally substituted by at least one halogen; C1-4 alkoxy; methoxycarbonyl; nitro; amino; alkylamino; amido; or alkanoyl-amino. Preferably R10 is hydrogen.

R11 is hydrogen; halogen; C1-4 alkyl optionally substituted by at least one halogen; C1-4 alkoxy; methoxycarbonyl; nitro; amino; alkylamino; amido; or alkanoylamino. Preferably R11 is hydrogen.

R4 is C1-4 alkyl optionally substituted by at least one halogen; or C2-4 alkenyl optionally substituted by at least one halogen. Preferably R4 is n-propyl.

Still in this aspect of the invention a specific embodiment relates to an embodiment wherein R10 is selected from hydrogen; methyl; fluorine; chlorine; bromine; methoxy; methoxycarbonyl; nitro; or trifluoromethyl, while R11 is selected from hydrogen; methyl; fluorine; chlorine; bromine; methoxy; methoxycarbonyl; nitro; or trifluoromethyl; and R3 is n-propyl.

Specific compounds of the present invention are those selected from the group consisting of:

1-[(1-methyl-1H-benzimidazol-6-yl)methyl]-4-propylpyrrolidin-2-one;

1-(1H-benzimidazol-7-ylmethyl)-4-propylpyrrolidin-2-one;

1-(imidazo[1,2-a]pyridin-3-ylmethyl)-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[2-(4-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(5-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-phenylpyrrolidin-2-one;

1-(imidazo[1,2-a]pyridin-3-ylmethyl)-4-phenylpyrrolidin-2-one;

1-[(6-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromoimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(8-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-iodoimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[8-chloro-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(7-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6,8-dibromoimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6,8-dichloroimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-chloroimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloroimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-cyclopropyl-6-fluoroimidazo[1,2-a]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclopropylimidazo[1,2-a]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-(imidazo[1,2-a]pyrimidin-3-ylmethyl)-4-propylpyrrolidin-2-one;

1-{[2-(4-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl]methyl}-4-propyl pyrrolidin-2-one;

1-(imidazo[1,2-a]pyrimidin-3-ylmethyl)-4-phenylpyrrolidin-2-one;

1-[(6-chloroimidazo[1,2-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(6-phenylimidazo[1,2-b][1,2,4]triazin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(4-methylphenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(4-chlorophenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(6-chloroimidazo[1,2-b]pyridazin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-chloroimidazo[1,2-b]pyridazin-3-yl)methyl]-4-phenylpyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-phenylpyrrolidin-2-one;

5-chloro-1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-1,3-dihydro-2H-indol-2-one;

1-{[6-methoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-isopropoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(benzyloxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-cyclopropyl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(dimethylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-methoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2-chloro-2,2-difluoroethyl)-1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(methylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-hydroxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(methylthio)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

4-(2-bromo-2,2-difluoroethyl)-1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(methylsulfonyl)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(methylsulfinyl)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2,2-trifluoroethyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclobutylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(4-methylphenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-amino-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(ethylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

4-propyl-1-{[6-(propylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2-bromo-2,2-difluoroethyl)-1-{[6-(propylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-(propylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-methoxy-2-(4-methylphenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-propyl-1-{[6-pyrrolidin-1-yl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2-bromo-2,2-difluoroethyl)-1-{[6-methoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(cyclopropylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-(isopropylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[2-cyclopropyl-6-(propylamino)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-({2-cyclopropyl-6-[(2-fluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}methyl)-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-({2-cyclopropyl-6-[(2,2-difluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}methyl)-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-({2-cyclopropyl-6-[(2,2,2-trifluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}methyl)-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluoroethyl)-1-{[2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[2-cyclopropyl-6-(cyclopropylamino)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclobutylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(3-chloro-4-fluorophenyl)pyrrolidin-2-one;

1-{[6-(butylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-(cyclobutylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(2-cyclopropyl-6-methoxyimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-ethoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-isopropoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(cyclopropylmethoxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-(cyclobutylmethoxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-(cyclopropyloxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-{[6-propoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
3-{[4-(2,2-difluorovinyl)-2-oxopyrrolidin-1-yl]methyl}-2-(trifluoromethyl)imidazo[1,2-b]pyridazine-6-carbonitrile;
4-(2,2-difluorovinyl)-1-{[6-thien-3-yl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-{[6-phenyl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-{[6-methyl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-{[6-pyridin-3-yl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
4-propyl-1-{[2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
1-[(6-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[6-(4-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(2-cyclopropyl-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-methylimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-chloroimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2,6-dichloroimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-(3H-imidazo[4,5-b]pyridin-7-ylmethyl)-4-propylpyrrolidin-2-one;
1-(3H-imidazo[4,5-b]pyridin-7-ylmethyl)-4-phenylpyrrolidin-2-one;
4-phenyl-1-[(5-phenyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]pyrrolidin-2-one;
4-phenyl-1-{[5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl}pyrrolidin-2-one;
1-[(6-bromo-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-phenyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-methyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-methyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-{[5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl}pyrrolidin-2-one;

1-[(6-methyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-phenyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[1-(1H-imidazol-4-yl)propyl]pyrrolidin-2-one;

1-[(5-methyl-1H-imidazol-4-yl)methyl]pyrrolidin-2-one;

1-[(2-methyl-1H-imidazol-4-yl)methyl]pyrrolidin-2-one;

1-(1H-imidazol-4-ylmethyl)-4-propylpyrrolidin-2-one;

1-({1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-4-yl}methyl)-4-propylpyrrolidin-2-one;

1-[(5-chloro-1H-imidazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(5-bromo-1H-imidazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(5-bromo-1H-imidazol-4-yl)methyl]-5-chloro-1,3-dihydro-2H-indol-2-one;

1-(1H-imidazol-5-ylmethyl)pyrrolidin-2-one;

1-[(1-methyl-1H-imidazol-5-yl)methyl]pyrrolidin-2-one;

1-methyl-5-[(2-oxopyrrolidin-1-yl)methyl]-1H-imidazole-4-carbonitrile;

1-(1H-imidazol-5-ylmethyl)-4-phenylpyrrolidin-2-one;

1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-phenylpyrrolidin-2-one;

1-[(4-methoxy-1-methyl-1H-imidazol-5-yl)methyl]pyrrolidin-2-one;

1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-4-carbonitrile;

1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-4-carboxamide;

N-benzyl-2-{5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-1-yl}acetamide;

1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-2-carbonitrile;

1-[(4-chloro-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-methyl-5-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile;

1-[(4-bromo-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2,4-dichloro-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
benzyl 1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-2-ylcarbamate;
1-[(4-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
5-chloro-1-(1H-imidazol-5-ylmethyl)-1,3-dihydro-2H-indol-2-one;
1-[(2,4-dichloro-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(2,4-dichloro-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(2-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(4-bromo-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
5-chloro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-1,3-dihydro-2H-indol-2-one;
1-[(4-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-(1H-indol-2-ylmethyl)-4-propylpyrrolidin-2-one;
1-(1H-indol-3-ylmethyl)-4-propylpyrrolidin-2-one;
3-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-indole-5-carbonitrile;
1-[(2-methyl-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(7-methoxy-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-nitro-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-{[6-(trifluoromethyl)-1H-indol-3-yl]methyl}pyrrolidin-2-one;
1-[(5-nitro-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(7-fluoro-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-chloro-2-methyl-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[1H-indol-3-yl(phenyl)methyl]-4-propylpyrrolidin-2-one;
1-[1-(1H-indol-3-yl)propyl]-4-propylpyrrolidin-2-one;
1-[2-furyl(1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
3-[(2-oxo-4-propylpyrrolidin-1-yl)(phenyl)methyl]-1H-indole-5-carbonitrile;
1-(1H-indol-4-ylmethyl)-4-propylpyrrolidin-2-one;

1-(1H-indol-7-ylmethyl)-4-propylpyrrolidin-2-one;

1-(isoxazol-4-ylmethyl)-4-propylpyrrolidin-2-one;

1-[(1-phenyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(1-methyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(1-benzyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

4-(2,3,5-trifluorophenyl)-1-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]pyrrolidin-2-one;

4-phenyl-1-(1H-pyrazol-4-ylmethyl)pyrrolidin-2-one;

1-({1-[(4-methylphenyl)sulfonyl]-1H-pyrazol-4-yl}methyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-(1H-pyrazol-4-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(1-chloro-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(3-methyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(5-amino-1-methyl-1H-pyrazol-4-yl)methyl]-4-propylpyrrolidin-2-one;

(−)-1-(1H-pyrazol-4-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

(+)-1-(1H-pyrazol-4-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-(1H-pyrazol-4-ylmethyl)-1,3-dihydro-2H-indol-2-one;

5-chloro-1-(1H-pyrazol-4-ylmethyl)-1,3-dihydro-2H-indol-2-one;

5-chloro-1-({1-[(4-methylphenyl)sulfonyl]-1H-pyrazol-4-yl}methyl)-1,3-dihydro-2H-indol-2-one;

1-{[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(5-amino-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(1-benzyl-5-chloro-1H-pyrazol-4-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-(1H-pyrazol-5-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(4-bromo-1-methyl-1H-pyrazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(1-methyl-1H-pyrazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(6-bromo-2-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-[(2-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

1-[(6-bromo-2-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-tert-butylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-tert-butyl-6-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[2-(2-furyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(2-methyl-6-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-methyl-6-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[2-methyl-6-(1H-pyrrol-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-({6-[(1E)-hex-1-enyl]-2-methylpyrazolo[1,5-a]pyrimidin-3-yl}methyl)-4-propylpyrrolidin-2-one;

1-[(6-chloro-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[2-methyl-6-(phenylethynyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-hydroxy-2-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-[(2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

1-[(6-methoxy-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-chloropyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-[(5,6-dimethyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-[(6-fluoro-5-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

1-[(5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[2-(4-bromophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[2-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-[(6-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-[(5-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-[(2-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;

1-{[2-(4-chlorophenyl)-6-methylpyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[2-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-chloro-2-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(2-cyclopropyl-5-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(5-chloro-2-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(5-chloro-2,6-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(5-bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
4-propyl-1-(pyridin-3-ylmethyl)pyrrolidin-2-one;
(−)-1-(1-pyridin-3-ylpropyl)pyrrolidin-2-one;
5-chloro-1-[(2-fluoropyridin-3-yl)methyl]-1,3-dihydro-2H-indol-2-one;
1-[(6-chloropyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[6-(benzylamino)pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(2-aminopyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)pyrrolidin-2-one;
1-[(2-isopropyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-[(2-propyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyrrolidin-2-one;
1-[(6-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(1-benzoyl-6-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(7-oxido-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)pyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)pyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)pyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[2,3-c]pyridin-3-ylmethyl)pyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[3,2-b]pyridin-3-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[3,2-c]pyridin-3-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1,3,4-thiadiazol-2-ylmethyl)pyrrolidin-2-one;

1-[(2-amino-1,3-thiazol-5-yl)methyl]pyrrolidin-2-one;

1-(1,3-thiazol-5-ylmethyl)pyrrolidin-2-one;

1-[(2-chloro-1,3-thiazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-{[2-(dimethylamino)-1,3-thiazol-5-yl]methyl}-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-{[2-(methylamino)-1,3-thiazol-5-yl]methyl}-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-[(2-pyrrolidin-1-yl-1,3-thiazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

5-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1,3-thiazol-2(3H)-one;

4-phenyl-1-{[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-7-yl]methyl}pyrrolidin-2-one;

4-phenyl-1-[(3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-7-yl)methyl]pyrrolidin-2-one;

4-phenyl-1-{[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-8-yl]methyl}pyrrolidin-2-one;

4-propyl-1-{[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-8-yl]methyl}pyrrolidin-2-one;

4-phenyl-1-[(3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]pyrrolidin-2-one;

1-[(6-chloro-3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-chloro[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]-4-phenylpyrrolidin-2-one;

1-{[6-chloro-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-8-yl]methyl}-4-phenylpyrrolidin-2-one;

1-[(6-chloro-3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]-4-phenylpyrrolidin-2-one;

1-[(2-fluoroindolizin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-(1H-1,2,3-benzotriazol-1-ylmethyl)-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-chloro-1H-imidazo[4,5-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-phenyl-1H-imidazo[4,5-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-(3H-imidazo[4,5-b]pyridin-3-ylmethyl)-4-propylpyrrolidin-2-one;

1-[(6-bromo-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-chloro-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(3-chloro-7H-imidazo[4,5-c]pyridazin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-methyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-methyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-phenyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-fluoro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-bromo-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-chloro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-(2,3-dihydro-1H-indol-1-ylmethyl)-4-propylpyrrolidin-2-one;

1-[(5-fluoro-2-phenyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-indole-2-carbonitrile;

1-[(2-bromo-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2,5-dichloro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-amino-9H-purin-9-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-(9H-purin-9-ylmethyl)pyrrolidin-2-one;

1-{[6-(cyclopropylamino)-9H-purin-9-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(benzylamino)-9H-purin-9-yl]methyl}-4-propylpyrrolidin-2-one;

4-propyl-1-{[6-(propylamino)-9H-purin-9-yl]methyl}pyrrolidin-2-one;

1-({6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}methyl)-4-propylpyrrolidin-2-one;

4-propyl-1-[(6-pyrrolidin-1-yl-9H-purin-9-yl)methyl]pyrrolidin-2-one;

1-[(5-bromo-3-phenyl-1H-pyrazolo[3,4-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-bromo-2H-pyrazolo[3,4-b]pyridin-2-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-bromo-3-phenyl-2H-pyrazolo[3,4-b]pyridin-2-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[3,2-b]pyridin-1-ylmethyl)pyrrolidin-2-one;

1-(3,4-dihydroquinolin-1(2H)-ylmethyl)-4-propylpyrrolidin-2-one;

1-(8H-isothiazolo[5,4-b]indol-8-ylmethyl)-4-propylpyrrolidin-2-one;

1-(1H-1,2,4-triazol-1-ylmethyl)pyrrolidin-2-one;

1-[(2,5-dichloro-1H-pyrrol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-pyrrol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-benzimidazol-1-yl)methyl]-4-phenylpyrrolidin-2-one;

2-chloro-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile;

2-chloro-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-6-carbonitrile;

4-propyl-1-[(2,5,6-trichloro-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one;

1-[(2-chloro-6-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-5-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-6-nitro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-5-nitro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-6-methyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-benzimidazol-1-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-bromo-2-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-bromo-2-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-6-fluoro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-chloro-5-fluoro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2,6-dichloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2,5-dichloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[2-chloro-6-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[2-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one;

1-[(2-chloro-6-hydroxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-(pyridin-4-ylmethyl)pyrrolidin-2-one, and

1-[(2-chloro-5-hydroxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one.

viii) U.S. Patent 4,696,943

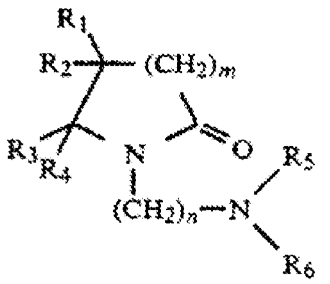
The present invention relates to the novel compound (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

ix) U.S. Patent 4,696,942

The present invention relates to the novel compound, (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

x) U.S. Patent 5,334,720

According to this invention we provide novel compounds of the formula I,



I.

wherein, R1, R2, R3 and R4, which may be the same or different independently represent hydrogen, C1-6 alkyl, phenyl or phenyl substituted by one or more halogen, hydroxyl, nitro, amino, C1-6 alkyl or C1 -C6 alkoxy groups;

R5 and R6 independently represent hydrogen, C1 -C6 alkyl or C3 -C6 cycloalkyl , or R5 and R6 together with the nitrogen form a C4-6 N heterocycle;

m represents an integer from 1-2; and

n represents an integer from 1-3;

provided that,

two of the substituents R1, R2, R3 and R4 independently represent phenyl or substituted phenyl and the other two independently represent hydrogen or C1-6 alkyl;

or a pharmaceutically acceptable acid addition salt thereof.

Pharmaceutically acceptable acid addition salts of the compounds of formula I include salts of mineral acids, for example, hydrohalic acids, e.g. hydrochloric or hydrobromic; or organic acids, e.g. formic, acetic or lactic acids. The acid may be polybasic, for example sulphuric, fumaric, maleic or citric acid.

This invention also relates to all stereoisomeric forms and optical enantiomeric forms of the compounds of formula I.

In the compounds of formula I: alkyl groups which R1, R2, R3, R4, R5 and R6 may represent include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl and s-butyl;

cycloalkyl groups which R5 and R6 may represent include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

C1-6 alkoxy groups include methoxy, ethoxy and propoxy;

halogen groups include fluorine, chlorine, bromine or iodine;

We prefer compounds of formula I or a pharmaceutically acceptable acid addition salt thereof, in which;

R1 is hydrogen, phenyl or substituted phenyl, preferably phenyl;

R2 is hydrogen, phenyl or substituted phenyl, preferably phenyl;

R3 is hydrogen , phenyl or substituted phenyl, preferably hydrogen;

R4 is hydrogen, phenyl or substituted phenyl, preferably hydrogen;

R5 is hydrogen , C1-3 alkyl or cyclopropyl , preferably hydrogen or methyl;

R6 is hydrogen , C1-3 alkyl or cyclopropyl , preferably hydrogen or methyl;

m represents an integer from 1-2 preferably 2;

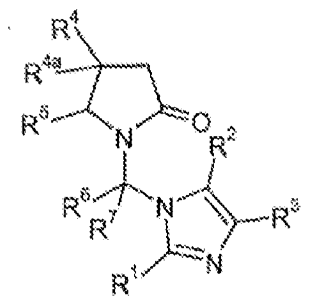
n represents an integer from 1-2, preferably 1.

We especially prefer compounds of formula I in which R1 and R2 are both phenyl.

We especially prefer compounds of formula I in which one of R5 and R6 is hydrogen and the other is hydrogen or methyl.

xi) International Patent Application Publication No. WO2005/054188

In one aspect the invention therefore provides a compound having the formula I or a pharmaceutically acceptable salt thereof,



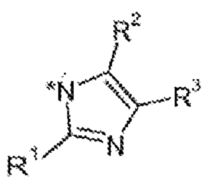
(I)

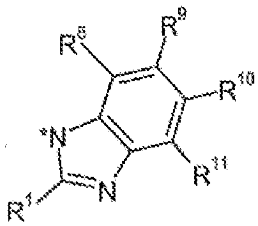
wherein

RI is hydrogen, CI-20 alkyl, C3 23 cycloalkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, guanidine, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, aryl or heterocycle; R2 is hydrogen, C1 20 alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;

R3 is hydrogen, C1 20 alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;

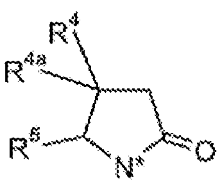
or R2 and R3 can form together with the imidazole ring the following 1H-benzimidazole cycle

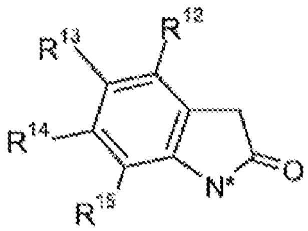




;

R4 is hydrogen, C1-20 alkyl, C2-12 alkenyl,C2-12 alkynyl, aryl, azido, alkoxycarbonylamino, arylsulfonyloxy or heterocycle; R4a is hydrogen or C1-20 alkyl; or R4 and R4a can form together a C3-8 cycloalkyl ; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





;

R6 is hydrogen or C1 20 alkyl ; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl ; R8 is hydrogen, halogen, nitro, cyano, C1 20 alkyl or alkoxy ; R9 is hydrogen, C1-20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

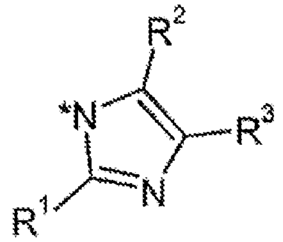
RIO is hydrogen, C1 20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

RI l is hydrogen, halogen, nitro, cyano, C1 20 alkyl or alkoxy ; R12 is hydrogen or halogen;

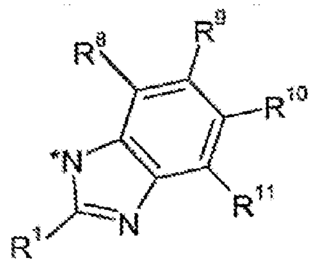
R13 is hydrogen, nitro, halogen, heterocycle, amino, aryl, C1-20 alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen; R14 is hydrogen, C1-20 alkyl or halogen;

R15 is hydrogen, C1 20 alkyl or halogen;

with the proviso that R4 is different from hydrogen when

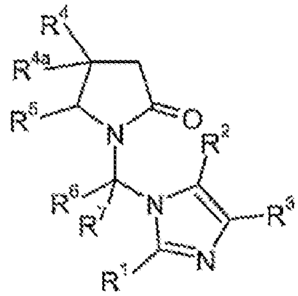


N represents a group of formula



The asterisk * indicates the point of attachment of the substituents.

In a preferred embodiment, the invention concerns a compound having the formula I, their tautomers, geometrical isomers (including cis and trans, Z and E isomers), enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,

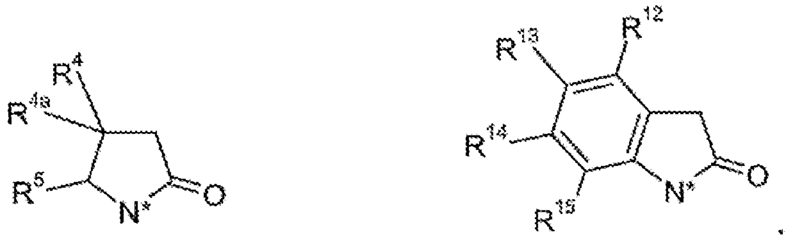


(I)

wherein

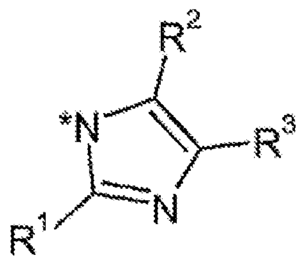
RI is hydrogen, C1-20 alkyl, C3-8 cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle; R2 is hydrogen, C1 20 alkyl, halogen, cyano, ester, carbamate or amido; R3 is hydrogen, cyano, C 1 20 alkyl, halogen or ester; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle

; R4 is hydrogen, C1 20 alkyl, C2 12 alkenyl or aryl; R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle

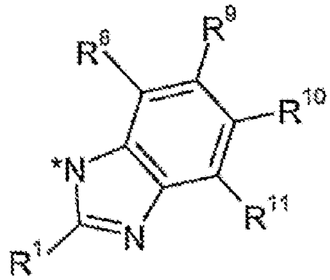


;

R6 is hydrogen or C 1 20 alkyl ; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl ; R8 is hydrogen; R9 is hydrogen, C 1-20 alkyl, halogen or alkoxy; RIO is hydrogen, C1 20 alkyl, halogen or cyano; R11 is hydrogen; R12 is hydrogen or halogen; R13 is hydrogen, halogen, heterocycle or C1 20 alkyl ; R14 is hydrogen; R15 is hydrogen; with the proviso that R4 is different from hydrogen when



represents a group of formula



The term "alkyl", as used herein, represents saturated, monovalent hydrocarbon radicals having straight (unbranched) or branched or cyclic or combinations thereof and containing 1-20 carbon atoms, preferably 1-10 carbon atoms, more preferably 1-4 carbon atoms; most preferred alkyl groups have 1-3 carbon atoms. Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, cyano, azido, aryloxy, alkoxy, alkylthio, alkanoylamino, arylcarbonylamino, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl or aryl. Usually alkyl groups, in the present case, are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, 1-ethylpropyl, n-heptyl, 2,4, 4-trimethylpentyl, n-decyl, chloromethyl, trifluoromethyl, 2-bromo-2,2-difluoroethyl, 2,2, 2-trifluoroethyl, 3,3, 3-trifluoropropyl, hydroxymethyl, cyanomethyl, azidomethyl, (acetylamino) methyl, (propionylamino) methyl, (benzoylamino) methyl, (4-chlorophenoxy) methyl, benzyl, 2-phenylethyl or 2- (methylthio) ethyl. Preferred alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, 1-ethylpropyl, 2,4, 4-trimethylpentyl, chloromethyl, trifluoromethyl, 2,2, 2-trifluoroethyl, hydroxymethyl, cyanomethyl, azidomethyl, (acetylamino) methyl, (propionylamino) methyl, (benzoylarnino) methyl or 2- (methylthio) ethyl. More preferred alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, azidomethyl or trifluoromethyl. Most preferred alkyl groups are methyl or n-propyl.

The term "cycloalkyl", as used herein, represents a monovalent group of 3 to 8 carbon atoms, usually 3-6 carbon atoms derived from a saturated cyclic hydrocarbon, which may be substituted by any suitable group including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkyl groups are cyclopropyl and cyclohexyl.
The term "alkenyl" as used herein, represents straight, branched or cyclic unsaturated hydrocarbon radicals or combinations thereof having at least one carbon- carbon double bond, containing 2-12 carbon atoms, preferably usually 2-4 carbon atoms. Alkenyl groups are being optionally substituted with any suitable group, including but not limited to one or more moities selected from groups as described above for the alkyl groups. Usually an alkenyl group is ethenyl (vinyl) optionally substituted by 1 to 3 halogens. Preferred alkenyl group, in the present case, is 2,2- difluorovinyl.
The term "alkynyl" as used herein, represents straight, branched or cyclic hydrocarbon radicals or combinations thereof containing at least one carbon-carbon triple bond, containing 2-12 carbon atoms, preferably 2-6 carbon atoms, and being optionally substituted by any suitable group, including but not limited to one or more moities selected from groups as described above for the alkyl groups. Preferably an alkynyl group is a halogenoalkynyl group (haloalkynyl group).
Groups qualified by prefixes such as "s", "i", "t" and the like (e. g. "i-propyl", "s-butyl") are branched derivatives.
The term "aryl" as used herein, is defined as phenyl optionally substituted by 1 to 4 substituents independently selected from halogen, cyano, alkoxy, alkylthio, C1 3 alkyl or azido, preferably halogen or azido. Usually aryl groups, in the present case are phenyl, 3-chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3, 5-difluorophenyl, 3-chloro-4-fluorophenyl, 2,3, 4-trifluorophenyl, 2,4, 5-trifluorophenyl, 2,3, 5-trifluorophenyl, 3,4, 5-trifluorophenyl, 3-azido-2,4- difluorophenyl or 3-azido-2,4, 6-trifluorophenyl. Preferably, aryl groups are phenyl, 3- chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3,5- difluorophenyl, 3-chloro-4-fluorophenyl, 2,3, 4-trifluorophenyl, 2,4, 5-trifluorophenyl, 2,3, 5-trifluorophenyl, 3,4, 5-trifluorophenyl or 3-azido-2, 4-difluorophenyl. Most preferred aryl groups

are phenyl, 3-chlorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, 2,3, 4-trifluorophenyl, 2,4, 5-trifluorophenyl, 2,3, 5-trifluorophenyl, 3, 4, 5-trifluorophenyl or 3-azido-2,4-difluorophenyl.

The term "heterocycle", as used herein, is defined as including an aromatic or non aromatic cycloalkyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure. Heterocyclic ring moities can be optionally substituted by alkyl groups or halogens and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Usually heterocycles are 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2- tetrahydrofuranyl, lH-pyrrol-2-yl, 1-methyl-lH-pyrrol-2-yl, 1H-pyrazol-2-yl, 1H- pyrazol-3-yl, 4-chloro-l-methyl-lH-pyrazol-3-yl, 5-chloro-1, 3-dimethyl-lH-pyrazol-4- yl, 1, 2,3-thiadiazol-4-yl, 3, 5-dimethyl-4-isothiazyl, 1H-imidazol-2-yl, 1-methyl-1H- imidazol-2-yl, 4-methyl-lH-imidazol-5-yl, or 2-methyl-1, 3-thiazol-4-yl. Preferred heterocycles are lH-imidazol-2-yl, 1, 2,3-thiadiazol-4-yl, lH-pyrazol-3-yl, 2-furyl, 3- furyl, 2-thienyl, 1-methyl-1H-pyrrol-2-yl, lH-pyrrol-2-yl.

The term "halogen", as used herein, includes an atom of chlorine, bromine, fluorine, iodine. Usually halogens are chlorine, bromine and fluorine. Preferred halogens are fluorine, bromine and chlorine.

The term "hydroxy", as used herein, represents a group of formula-OH.

The term "alkoxy", as used herein, represents a group of formula-ORa wherein Ra is an alkyl group, as defined above. Preferred alkoxy group is methoxy.

The term "aryloxy", as used herein, represents a group of formula-ORb wherein Rb is an aryl group, as defined above. Preferred aryloxy group is phenoxy.

The term "ester", as used herein, represents a group of formula-COORC wherein Rc is an alkyl group or aryl group, as defined above. Preferred ester group is methoxycarbonyl.

The term "amido", as used herein, represents a group of formula-CONH2.

The term "amino", as used herein, represents a group of formula-NH2.

The term "aminoderivative", as used herein, represents an alkylamino or an arylamino group, wherein the terms "alkyl" and "aryl" are defined as above.

The term "cyano", as used herein, represents a group of formula-CN.

The term "nitro", as used herein, represents a group of formula-N02.

The term "azido", as used herein, represents a group of formula-N3.

The term "guanidine", as used herein, represents a group of formula- NHC (=NH) NH2.

The term "alkylthio", as used herein, represents a group of formula-SRd wherein Rd is an alkyl group, as defined above. One alkylthio group is methylthio.

The term "alkylsulfonyl", as used herein, represents a group of formula- S (=O) 2Re wherein Re is an alkyl group, as defined above. One alkylsulfonyl group is methylsulfonyl.

The term "alkylsulfinyl", as used herein, represents a group of formula-S (=O) Rf wherein Rf is an alkyl group, as defined above. One alkylsulfinyl group is methylsulfinyl.

The term "arylthio", as used herein, represents a group of formula-SRg wherein Rg is an aryl group, as defined above.

The term "arylsulfonyl", as used herein, represents a group of the formula- S (=O) 2Rh wherein Rh is an aryl group, as defined above.

The term "arylsulfinyl", as used herein, represents a group of the formula- S (=O) Ri wherein Ri is an aryl group, as defined above.

The term "carbamate", as used herein, represents a group of formula- N (H) C (O) OR1, wherein Ri is an alkyl or an aryl, as defined above. Usually carbamate groups are (propoxycarbonyl) amino or (benzyloaxycarbonyl) amino. One carbamate group is (benzyloaxycarbonyl) amino.

The term "alkanoylamino", as used herein, represents a group of the formula- NHC (=O) Rk wherein Rk is an alkyl group, as defined above.

The term "(arylcarbonyl) amino", as used herein, represents a group of the formula-NHC (=O) Rm wherein Rm is an aryl group, as defined above. One (arylcarbonyl) amino is benzoylamino.

Usually, RI is hydrogen; Cl lo alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy ; hydroxy ; C3-6 cycloalkyl ; halogen; ester; amido; nitro ; cyano; amino ; phenyl; alkylthio; alkylsulfonyl ; alkylsulfinyl ; heterocycle unsubstituted or substituted by alkyl groups; or guanidine.

In some embodiments, RI is hydrogen; methyl; ethyl; i-propyl ; n-propyl ; cyclopropyl ; n-butyl; i- butyl; t-butyl; 1-ethylpropyl ; 2,4, 4-trimethylpentyl; hydroxymethyl ; chloromethyl; trifluoromethyl ; 2,2, 2-trifluoroethyl ; cyanomethyl; 2- (methylthio) ethyl; chloro; bromo; nitro ; cyano; amino; aminocarbonyl; methoxycarbonyl ; methylthio; methylsulfinyl ; methylsulfonyl; phenyl; 2-furyl ; 3-furyl; lH-pyrrol-2-yl ; 1-methyl-lH-pyrrol-2-yl ; 2- thienyl; lH-pyrazol-3-yl ; 1, 2,3-thiadiazol-4-yl or lH-imidazol-2-yl. More preferably, RI is hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl; methylthio; nitro ; cyano; amino; chloro or lH-pyrrol-2-yl. Most preferably, RI is hydrogen; methyl; methylthio ; nitro; cyano; amino or chloro.

Usually, R2 is hydrogen; C1 4 alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen ; ester; cyano ; alkyl carbamate; [(N-methoxy- N-methyl) amino] carbonyl. Preferably, R2 is hydrogen; methyl; hydroxymethyl ; (acetylamino) methyl; (propionylamino) methyl; (benzoylamino) methyl; [(benzyloxy) carbonyl] amino ; chloro or cyano. In some embodiments, R2 is hydrogen; chloro or cyano.

Usually, R3 is hydrogen; C1 4 alkyl unsubstituted or substituted by hydroxy; halogen; ester or cyano. In some embodiments, R3 is hydrogen; hydroxymethyl; chloro; cyano.

In some embodiments, R3 is hydrogen or cyano. In some embodiments R3 is hydrogen.

Usually, R4 is hydrogen; C1 4 alkyl tlnsubstituted or substituted by halogens; C2 4 alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or/and halogens. Preferably, R4 is hydrogen; n-propyl ; 2,2-difluorovinyl ; phenyl; 3-chlorophenyl ; 3-fluorophenyl ; 4-chlorophenyl; 4-fluorophenyl ; 3,5-difluorophenyl; 3,4-difluorophenyl ; 3-chloro-4-fluorophenyl ; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl ; 3,4, 5-trifluorophenyl ; 3-azido-2,4- difluorophenyl or 3-azido-2,4, 6-trifluorophenyl. More preferably, R4 is hydrogen; n- propyl ; 2,2-difluorovinyl ; phenyl; 3-chlorophenyl; 3-fluorophenyl ; 4-chlorophenyl; 4- fluorophenyl ; 3, 5-difluorophenyl ; 3,4-difluorophenyl ; 3-chloro-4-fluorophenyl; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl; 2,3, 5-trifluorophenyl; 3,4, 5-

trifluorophenyl or 3- azido-2,4-difluorophenyl. Most preferably, R4 is n-propyl ; 2,2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl ; 3,5-difluorophenyl ; 2,3, 4-trifluorophenyl ; 2,4, 5- trifluorophenyl ; 2,3, 5-trifluorophenyl ; 3,4, 5-trifluorophenyl or 3-azido-2,4- difluorophenyl.

Usually, R4a is hydrogen.

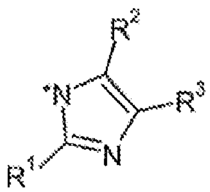
Usually, R5 is hydrogen.

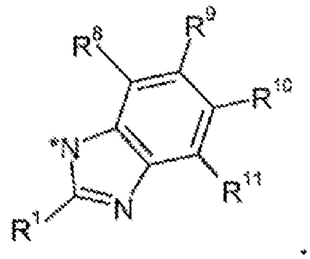
Usually, R6 is hydrogen or Cl-1~0 alkyl unsubstituted or substituted by hydroxy or azido. Preferably, R6 is hydrogen or azidomethyl. More preferably R6 is hydrogen.

Usually R7 is hydrogen.

In other embodiments, R6 and R7 are linked to form a cyclopropyl.

In other embodiments, R2 and R3 can form together with the imidazole ring the following 1H-benzimidaole cycle





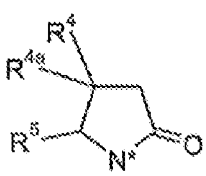
Usually, R8 is hydrogen.

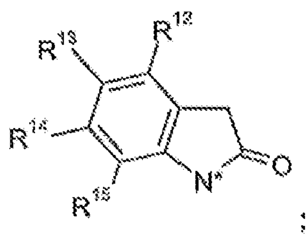
Usually, R9 is hydrogen; halogen ; 1-3 alkyl or alkoxy. In some embodiments, R9 is hydrogen; methyl; chloro or methoxy. In some embodiments R9 is hydrogen.

Usually, RIO is hydrogen; halogen; cyano; C1 3 alkyl unsubstituted or substituted by halogens; or alkoxy. In some embodiments, RIO is methyl; hydrogen; trifluoromethyl ; fluoro; cyano or methoxy. In some embodiments R10 is hydrogen; trifluoromethyl ; fluoro or cyano.

Usually, RI 1 is hydrogen.

In other embodiments, R4, R4a and R5 can form together with the 2- oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





Usually, R12 is hydrogen or halogen. In some embodiments R12 is hydrogen; chloro or fluoro. In some embodiments R12 is hydrogen.

Usually, R13 is hydrogen; C1 3 alkyl ; halogen or thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl. In some embodiments R13 is hydrogen; chloro; bromo or methyl. In some embodiments R13 is chloro; bromo or methyl.

Usually R14 is hydrogen.

Usually, R15 is hydrogen.

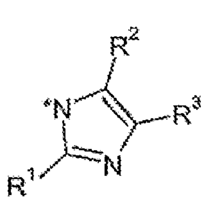
In a general embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salts thereof, are those wherein

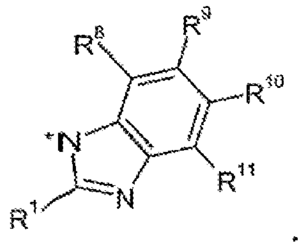
RI is selected from hydrogen; C1 lo alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy ; C3 6 cycloalkyl ; halogen; ester; amido; nitro; cyano; amino; phenyl; alkylthio ; alkylsulfonyl ; alkylsulfinyl ; heterocycle unsubstituted or substituted by alkyl group; or guanidine; R2 is selected from hydrogen; C 1-4 alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen; ester; cyano; alkyl carbamate or [(N-methoxy-N-methyl) amino] carbonyl.

R3 is selected from hydrogen; C1 4 alkyl unsubstituted or substituted by hydroxy ; halogen; ester or cyano; R4 is selected from hydrogen; C1 4 alkyl unsubstituted or substituted by halogens; C2 4 alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or/and halogens;

R4a is hydrogen; R5 is hydrogen; R6 is selected from hydrogen or C 1-10 alkyl unsubstituted or substituted by hydroxy or azido;

R7 is hydrogen; or R6 and R7 can be linked to form a cyclopropyl ; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle





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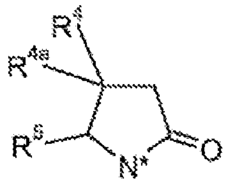
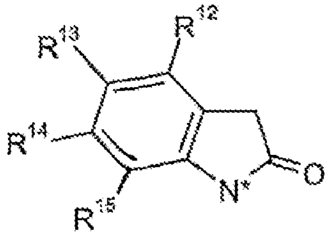
R8 is hydrogen; R9 is selected from hydrogen; halogen; C1-3 alkyl ; alkoxy ;

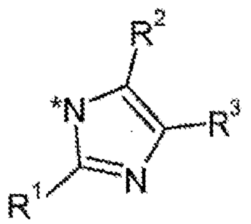
R10 is selected from hydrogen; halogen; cyano or Cil alkyl unsubstituted or substituted by halogens; or alkoxy ; R l is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle



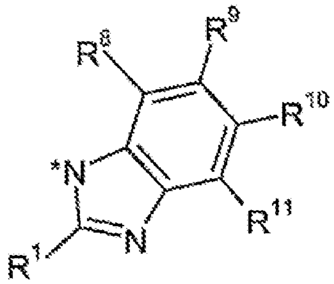


;

R12 is selected from hydrogen or halogen; R13 is selected from hydrogen; CI-3 alkyl ; halogen ; thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl; R14 is hydrogen; R15 is hydrogen; with the proviso that R4 is different from hydrogen when



represents a group of formula



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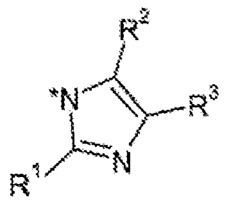
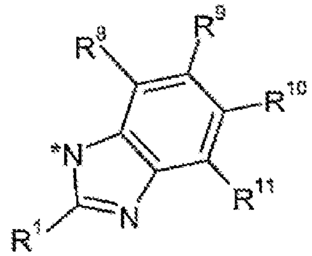
In an embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

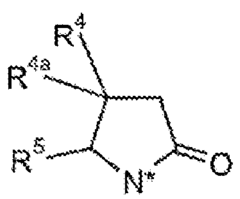
RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; cyclopropyl ; n-butyl; i-butyl; t-butyl; 1-ethylpropyl ; 2,4, 4-trimethylpentyl; trifluoromethyl; 2,2, 2- trifluoroethyl; hydroxymethyl; chloromethyl; cyanomethyl ; 2- (methylthio) ethyl; chloro; bromo; nitro; cyano ; amino; aminocarbonyl; methoxycarbonyl ; methylthio; methylsulfinyl; methylsulfonyl; phenyl; 2-furyl ; 3-furyl ; lH-pyrrol-2-yl ; 1-methyl-1H- pyrrol-2-yl ; 2-thienyl; lH-pyrazol-3-yl ; 1, 2, 3-thiadiazol-4-yl ;

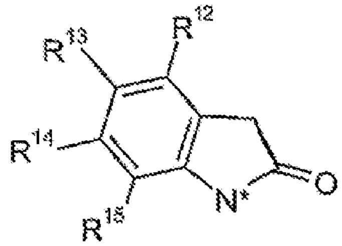
or lH-imidazol-2-yl ; R2 is selected from hydrogen; methyl ; hydroxymethyl; (acetylamino) methyl; (propionylamino) methyl ; (benzoylamino) methyl; (benzyloxycarbonyl) amino; chloro; or cyano; R3 is selected from hydrogen; hydroxymethyl; chloro; cyano; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle



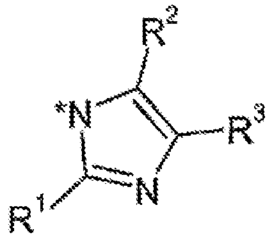


R8 is hydrogen; R9 is selected from hydrogen; methyl; choro ; methoxy; R10 is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy; R is hydrogen; R4 is selected from hydrogen; n-propyl ; 2,2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3,5-difluorophenyl ; 3,4- difluorophenyl; 3-chloro-4-fluorophenyl ; 2,3, 4-trifluorophenyl; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 5-trifluorophenyl ; 3-azido-2,4-difluorophenyl ; or 3-azido- 2,4, 6-trifluorophenyl. R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle

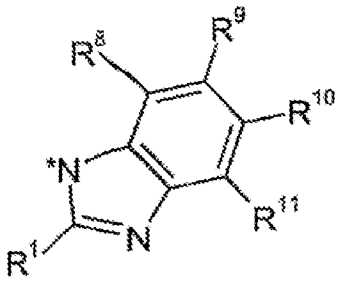




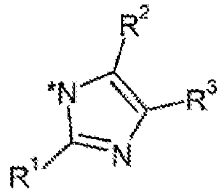
R12 is selected from hydrogen; chloro; fluoro; R13 is selected from hydrogen; chloro; bromo; methyl; R14 is hydrogen; R15 hydrogen; R6 is selected from hydrogen; azidomethyl; R7 is hydrogen; or R6 and R7 are linked to form a cyclopropyl ; with the proviso that R4 is different from hydrogen when

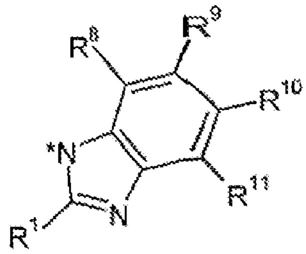


represents a group of formula

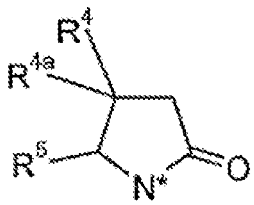


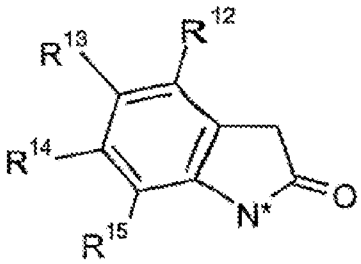
In one embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl; methylthio; nitro; cyano ; amino; chloro ; or lH-pyrrol-2-yl ; R2 is selected from hydrogen; chloro; cyano; R3 is selected from hydrogen; cyano; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle



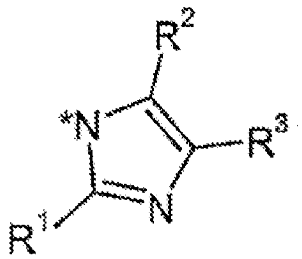


R8 is hydrogen; R9 is hydrogen;
R10 is selected from hydrogen ; trifluoromethyl ; fluoro ; cyano;
RI l is hydrogen; R4 is selected from hydrogen; n-propyl ; 2, 2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3, 5-difluorophenyl ; 3,4- difluorophenyl ; 3-chloro-4-fluorophenyl; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 5-trifluorophenyl; or 3-azido-2, 4-difluorophenyl ; R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle

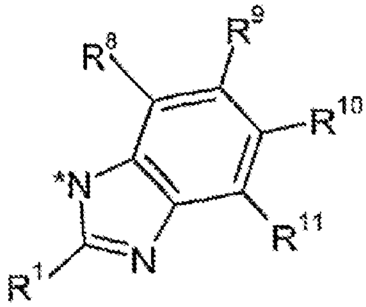




wherein R12 is hydrogen; R13 is selected from methyl; chloro; bromo; R14 is hydrogen; R15 hydrogen; R6 is hydrogen; R7 is hydrogen; with the proviso that R4 is different from hydrogen when



R11 represents a group of formula



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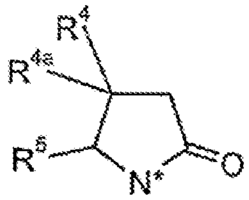
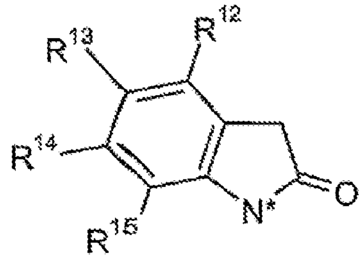
In one embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

RI is selected from hydrogen; methyl; methylthio; nitro ; cyano; amino; chloro; R2 is selected from hydrogen; chloro; cyano; R3 is hydrogen; R4 is selected from n-propyl ; 2, 2-difluorovinyl ; phenyl; 3-chlorophenyl; 3- fluorophenyl; 3,5-difluorophenyl ; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 5-trifluorophenyl; 3-azido-2,4-difluorophenyl ; R4a is hydrogen;

R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





R12 is hydrogen; R13 is selected from chloro; bromo; methyl ; R14 is hydrogen; R15 hydrogen; R6 is hydrogen; R7 is hydrogen.

In some embodiments, compounds are: 1-(lH-imidazol-l-ylmethyl) pyrrolidin-2-one ; 1- (1H- imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one ; 4- (3-azido-2, 4, 6-trifluorophenyl)-1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 1- (IH-imidazol-1-ylmethyl)-4- propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1- ylmethyl) pyrrolidin-2-one; (+)-4- (3-azido-2, 4-difluorophenyl)-l-(IH-imidazol-l- ylmethyl) pyrrolidin-2-one ; 1-[(2-ethyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2- one; 1-[(2-isopropyl-lH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-methyl- IH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-phenyl-1H-imidazol-1- yl) methyl]-4-propylpyrrolidin-2-one ; 4-propyl-1-[(2-propyl-lH-imidazol-1- yl) methyl] pyrrolidin-2-one ; (+)-1-(lH-imidazol-l-ylmethyl)-4-propylpyrrolidin-2-one ; (-)-1-(lH-imidazol-l-ylmethyl)-4-propylpyrrolidin-2-one ; 4- (2, 2-difluorovinyl)-1- (1H-imidazol-1-ylmethyl) pyrrolidin-2-one ; 4-(3-chlorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 1-{[2-(methylthio)-lH-imidazol-1-yl] methyl}-4-propylpyrrolidin-2-one; 1-{[2-(methylsulfinyl)-lH-imidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(2-tert-butyl-lH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2- one; 1- [1- (lH-imidazol-1-yl) cyclopropyl] pyrrolidin-2-one ; 1- [(2-methyl-1H-imidazol-1- yl) methyl]-4-phenylpyrrolidin-2-one ; 1-{[2-(methylsulfonyl)-lH-imidazol-l-yl] methyl}-4- propylpyrrolidin-2-one; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-2- carboxamide; 4-(4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one ; 1- (1H- imidazol-1-ylmethyl)-4-(3, 4, 5-trifluorophenyl) pyrrolidin-2-one; 4- (3-fluorophenyl)-1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin- 2-one; 4-(3-chloro-4-fluorophenyl)-1-(1H-imidazol-1-ylmelthyl) pyrrolidin-2-one; 4- (4- chlorophenyl)-1-(1H-imidazol-1-ylmelthyl) pyrrolidin-2-one; 1-(lH-imidazol-l-ylmethyl)- 4- (2, 3, 4-trifluorophenyl) pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2, 3,5-trifluorophenyl) pyrrolidin-2-one ; 1-(lH-imidazol-l-ylmethyl)-4-(2, 4,5- trifluorophenyl) pyrrolidin-2-one; 1-{[2-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4- propylpyrrolidin-2-one ; methyl 1-[(2-oxo-4-propylpyrrolidin-1-yl) methyl]-lH-imidazole- 2-carboxylate ; 1- [(2-nitro-IH-imidazol-1-yl) methyll-4- (3, 4,5-trifluorophenyl) pyrrolidin- 2-one; 1-{[2-oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-1H-imidazole-2-carbonitrile; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1- [(2, 4- dichloro-IH-imidazol-l-yl) methyl]-4- (3, 4, 5-trifluorophenyl) pyrrolidin-2-one ; 1- [(5- chloro-lH-imidazol-1-yl) methyl]-4- (3, 4, 5-trifluorophenyl) pyrrolidin-2-one ; 1-{[2-oxo-4- (3,4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-4-carbonitrile ; 1-{ [2-oxo-4- (3,4, 5-trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazole-5-carbonitrile ; (+)-1- (1H- imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one ; (-)-1-(1H-imidazol-1-ylmethyl)-4- phenylpyrrolidin-2-one ; 1- { [2-oxo-4- (2, 3, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-1H-imidazole-5-carbonitrile ; (-)-1-{[2-oxo-4-(2, 3, 4-trifluorophenyl) pyrrolidin-1-yl]methyl}- lH-imidazole-5-carbonitrile ; (+)-1-{[2-oxo-4-(2, 3,4-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-5-carbonitrile ; (-)-1-{[2-oxo-4-(2, 3,4-trifluorophenyl) pyrrolidin- l-yl] methyl}-lH-imidazole-4-carbonitrile ; (+)-1-{[2-oxo-4-(2, 3, 4-trifluorophenyl)-1- pyrrolidinyl] methyl}-lH-imidazole-4-carbonitrile ; (-)-1- { [2-oxo-4- (3, 4,5- trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (+)-1-{[2-oxo-4- (3,4, 5-trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazole-4-carbonitrile ; (+)-1-{[2-oxo- 4- (2, 4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-4-carbonitrile ; (-)-1-{[2-oxo-4- (2, 4,5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-4-carbonitrile ; (-)-1- {[2-oxo-4-(2, 3, 5-trifluorophenyl) pyrrolidin-1-ylmethyl}-1H-imidazole-4-carbonitrile ; (-)- 1-{[2-oxo-4-(3, 4, 5=trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-5-carbonitrile ; 1-{[2-oxo-4-(2, 3, 5-trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile ; 1-{[2-oxo-4-(2, 3,5-trifluorophenyl) pyrrolidin- methyl}-lH-imidazole-5-carbonitrile ; 1-[(5-methyl-2-phenyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1- [(5- methyl-IH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(5-phenyl-1H-imidazol- 1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-ethyl-5-methyl-1H-imidazol-1-yl)methyl]- 4-propylpyrrolidin-2-one; 1-[(2,5-dimethyl-1H-imidazol-1-yl)methyl]- 4- propylpyrrolidin-2-one; 1- [(2-chloro-IH-imidazol-1-yl) methyll-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 1-[2-azido-1-(lH-imidazol-1-yl) ethyl] -4-propylpyrrolidin-2-one ; 1- [(4-chloro-IH-imidazol-1-yl) methyll-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 1-[(2-bromo-4,5-dichloro-1H-imidazol-1-yl)methyl]-4- propylpyrrolidin-2-one; 1- [(2-chloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2- one; (+)-1-1 [2-oxo-4- (3, 4,5-trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-5- carbonitrile; 1-{[5-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one ; 1-{[4-(hydroxymethyl)-lH-imidazol-l-yl] methyl}-4-propylpyrrolidin-2-one ; benzyl 1- [(2- oxo-4-propylpyrrolidin-1-yl) methyl]-lH-imidazol-5-ylcarbamate ; N-[(1-{[2-oxo-4-(3, 4,5-trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazol-5-yl) methyl] acetamide ; N- [(1-{[2- oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazol-5- yl) methyl] benzamide; N-1 (1-1 [2-oxo-4- (3, 4, 5-trifluorophenyl) pyrroldin-1-yl]methyl}-1H- imidazol-5-yl) methyl] propanamide ; 1- (IH-benzimidazol-1-ylmethyl)-4-propylpyrrolidin- 2-one; 1-[(2-methyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 4-propyl- 1-[(2-propyl-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one ; 1-[(2-isopropyl-1H- benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(trifluoromethyl)- 1H-benzimidazol-1-yl] methyl} pyrrolidin-2-one; 1-{[2-(methylthio)-lH-benzimidazol-1- yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(2-amino-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1-{[2-(chloromethyl)-1H-benzimidazol-1-yl]melthyl}-4-propylpyrrolidin-2-one ; {1-[(2-oxo-4-propylpyrrolidin-1-yl) methyl]-1 H-benzimidazol-2- yl} acetonitrile ; 1- [(5-methoxy-lH-benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(5-methyl-lH-benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 1- [(5, 6-dimethyl- lH-benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-{[2-isopropyl-5- (trifluoromethyl)-lH-benzimidazol-l-yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(6-chloro- IH-benzimidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-oxo-4-propylpyrrolidin-1- yl) methyl]-2-propyl-1H-benzimidazole-5-carbonitrile ; 1-{[2-ethyl-5-(trifluoromethyl)- 1H-benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(1H-pyrrol-2-yl)- 1H-benzimidazol-1-yl] methyl} pyrrolidin-2-one ; 1- [(5-fluoro-2-propyl-1H-benzimidazol- 1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-{[6-methyl-2-(lH-pyrrol-2-yl)-1H- benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(6-methoxy-2-propyl-1H- benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 2-butyl-1- [(2-oxo-4- propylpyrrolidin-1-yl) methyl]-lH-benzimidazole-5-carbonitrile ; 1-{[2-[2- (methylthio) ethyl]-5-(trifluoromethyl)-lH-benzimidazol-1-yl] methyl}-4-propylpyrrolidin- 2-one; 1-[(5-fluoro-2-isobutyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1-{[5-fluoro-2-(2, 4, 4-trimethylpentyl)-1 H-benzimidazol-1-yl] methyl}-4-propylpyrrolidin- 2-one; 2-cyclopropyl-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-5- carbonitrile ; l- [(2-oxo-4-propylpyrrolidin-l-yl) methyl]-2- (lH-pyrazol-3-yl)-lH- benzimidazole-5-carbonitrile; 1-[(2-cyclopropyl-5-fluoro-1H-benzimidazol-1-yl)methyl]- 4-propylpyrrolidin-2-one ; 1-[(5-fluoro-2-isopropyl-1H-benzimidazol-1-yl)methyl]-4- propylpyrrolidin-2-one ; 1-{[2-(3-furyl)-6-methoxy-1H-benzimidazol-1-ylmethyl}-4- propylpyrrolidin-2-one; 1- [(2-cyclopropyl-6-methoxy-lH-benzimidazol-1-yl) methyl]-4- propylpyrrolidin-2-one; 1- [(2-isopropyl-6-methoxy-lH-benzimidazol-1-yl) methyl]-4- propylpyrrolidin-2-one ; 1- [(2-oxo-4-propylpyrrolidin-1-yl) methyl]-2-(1, 2,3-thiadiazol-4- yl)-lH-benzimidazole-5-carbonitrile ; 1-{[2-(lH-imidazol-2-yl)-5-(trifluoromethyl)-1H- benzimidazol-l-yl] methyl}-4-propylpyrrolidin-2-one ; 1-{[5-fluoro-2-(2, 2,2- trifluoroethyl)-lH-benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1- { [2- (1- ethylpropyl)-6-methoxy-IH-benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1-{[6-methoxy-2- (l-methyl-lH-pyrrol-2-yl)-IH-benzimidazol-l-yl] methyl}-4-propylpyrrolidin- 2-one; 1-{[2-(2-furyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4- propylpyrrolidin-2-one; 4-propyl-1-{[2-thien-2-yl-5-(trifluoromethyl)-1H-benzimidazol- 1-yl]melthyl}pyrrolidin-2-one ; 1-1 [2- (3-furyl)-5- (trifluoromethyl)-IH-benzimidazol-l- yl] methyl}-4-propylpyrrolidin-2-one ; 1- { [2-cyclopropyl-5- (trifluoromethyl)-lH- benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-5- (trifluoromethyl)-1H-benzimidazol-1-yl] methyl} pyrrolidin-2-one ; 1- (IH-imidazol-1- ylmethyl)-1, 3-dihydro-2H-indol-2-one ; 5-bromo-l-(lH-imidazol-l-ylmethyl)-1, 3- dihydro-2H-indol-2-one; 5-chloro-l- (lH-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2- one; 4-fluoro-l-(lH-imidazol-l-ylmethyl)-1, 3-dihydro-2H-indol-2-one; 4-chloro-1-(1H-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2-one ; 1-(lH-imidazol-l-ylmethyl)-5-methyl-1, 3-dihydro-2H-indol-2-one ; 1- [(2-oxo-2, 3-dihydro-lH-indol-1-yl) methyl]-1H- imidazole-5-carbonitrile; and 1- [(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) methyl]-1H- imidazole-5-carbonitrile.

In some embodiments, compounds are: 1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one, 1- (lH-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one ; l-(lH-imidazol-1-ylmethyl)-4- propylpyrrolidin-2-one; (-)-4- (3-azido-2, 4-difluorophenyl)-1- (lH-imidazol-1- ylmethyl) pyrrolidin-2-one; (+)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1- ylmethyl) pyrrolidin-2-one ; 1-[(2-ethyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2- one; 1-[(2-isopropyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1- [(2-methyl- 1H-imidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 4-propyl-1-[(2-propyl-1H-imidazol- 1-yl) methyl] pyrrolidin-2-one ; (+)-1- (lH-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one ; (-)-1-(lH-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one ; 4-(2, 2-difluorovinyl)-1-(1 H- imidazol-1-ylmethyl) pyrrolidin-2-one; 4- (3-chlorophenyl)-l- (lH-imidazol-l-ylmethyl) pyrrolidin-2-one ; 1-{[2-(methylthio)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one ; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-phenylpyrrolidin-2- one; 4-(4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 1-(lH-imidazol-1- ylmethyl)-4- (3, 4, 5-trifluorophenyl) pyrrolidin-2-one; 4-(3-fluorophenyl)-1-(1H-imidazol- 1-ylmethyl) pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1- ylmethyl) pyrrolidin-2-one ; 4-(3,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin- 2-one; 4-(3-chloro-4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4- (4- chlorophenyl)-1-(lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 1- (lH-imidazol-1-ylmethyl)- 4- (2, 3, 4-trifluorophenyl) pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2, 3,5-trifluorophenyl) pyrrolidin-2-one; 1- (1 H-imidazol-1-ylmethyl)-4- (2, 4,5-trifluorophenyl) pyrrolidin-2-one; 1-[(2-nitro-lH-imidazol-l-yl) methyl]-4-(3, 4,5-trifluorophenyl) pyrrolidin-2-one ; 1- { [2-oxo-4- (3, 4, 5-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-2-carbonitrile ; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4- propylpyrrolidin-2-one; 1-1 (5-chloro-IH-imidazol-1-yl) methyl]-

4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 1-{[2-oxo-4-(3, 4,5-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-4-carbonitrile ; 1-{[2-oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-5-carbonitrile ; (+)-1-(lH-imidazol-1-ylmethyl)-4- phenylpyrrolidin-2-one ; (-)-l-(lH-imidazol-l-ylmethyl)-4-phenylpyrrolidin-2-one ; (+); 1-{[2-oxo-4-(3, 4,5-trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile ; 1-[(2-chloro-lH-imidazol-l-yl) methyl]-4-(3, 4, 5-trifluorophenyl) pyrrolidin-2-one ; 1- [2- azido-l-(lH-imidazol-l-yl) ethyl]-4-propylpyrrolidin-2-one ; 1-[(2-chloro-lH-imidazol-1- yl) methyl]-4-propylpyrrolidin-2-one ; (+)-1-1 [2-oxo-4- (3, 4, 5-trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile ; 1-[(2-oxo-4-propylpyrrolidin-1-yl) methyl]-2- propyl-lH-benzimidazole-5-carbonitrile ; 1-{[2-ethyl-5-(trifluoromethyl)-1H- benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-1H- benzimidazol-1-yl]methyl}pyrrolidin-2-one ; 1-[(5-fluoro-2-propyl-1H-benzimidazol-1- yl) methyl]-4-propylpyrrolidin-2-one ; 2-butyl-1- [(2-oxo-4-propylpyrrolidin-1-yl) methyl]- lH-benzimidazole-5-carbonitrile ; 1- [(5-fluoro-2-isopropyl-lH-benzimidazol-1- yl) methyl]-4-propylpyrrolidin-2-one ; 1-(1H-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol- 2-one; 5-bromo-1- (lH-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2-one ; 5-chloro-1- (lH-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2-one ; 1-(1H-imidazol-1-ylmethyl)-5- methyl-1,3-dihydro-2H-indol-2-one ; 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1- yl) methyl]-lH-imidazole-5-carbonitrile.

In some embodiments, compounds are: 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin- 2-one; 1-(lH-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one ; (-)-4- (3-azido-2, 4- difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; (+)-4- (3-azido-2, 4- difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(2,2-difluorovinyl)-1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3-chlorophenyl)-1-(1H-imidazol-1- ylmethyl) pyrrolidin-2-one; 1-{[2-(methylthio)-lH-imidazol-1-yl] methyl}-4- propylpyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-phenylpyrrolidin-2- one; 1- (lH-imidazol-1-ylmethyl)-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 4- (3- fluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3,5-difluoromethyl)-1- (IH-imidazol-1-ylmetliyl) pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2, 3,4- trifluorophenyl) pyrrolidin-2-one; 1-

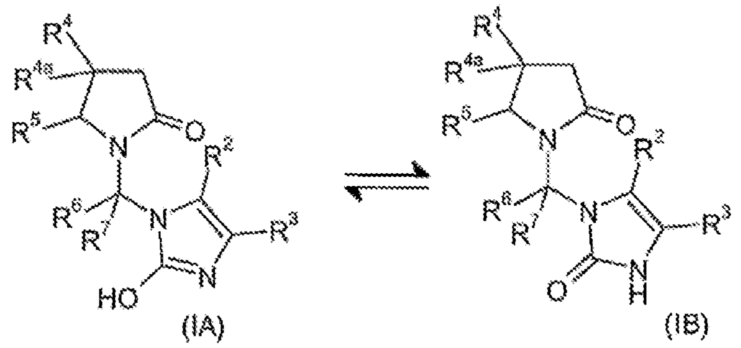
(1H-imidazol-1-ylmethyl)-4-(2, 3,5- trifluorophenyl) pyrrolidin-2-one; 1- H-imidazol-1-ylmethyl)-4-(2, 4,5- trifluorophenyl) pyrrolidin-2-one; 1-[(2-nitro-lH-imidazol-1-yl) methyl]-4-(3, 4,5- trifluorophenyl) pyrrolidin-2-one; 1-{[2-oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-2-carbonitrile ; 1-[(2-amino-lH-imidazol-1-yl) methyl]-4- propylpyrrolidin-2-one ; 1-[(5-chloro-1H-imidazol-1-yl)methyl]-4-(3, 4,5- trifluorophenyl) pyrrolidin-2-one; (+)-1-(lH-imidazol-l-ylmethyl)-4-phenylpyrrolidin-2- one; (-)-1-(lH-imidazol-l-ylmethyl)-4-phenylpyrrolidin-2-one ; 1-[(2-chloro-1H- imidazol-1-yl) methyl]-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one 1-[(2-chloro-1H-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; (+)-1-1 [2-oxo-4- (3, 4,5- trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazole-5-carbonitrile ; 5-bromo-1- (1H- imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2-one; 5-chloro-1-(lH-imidazol-l-ylmethyl)- 1, 3-dihydro-2H-indol-2-one; 1- (lH-imidazol-1-ylmethyl)-5-methyl-1, 3-dihydro-2H- indol-2-one; 1-[(5-chloro-2-oxo-2, 3-dihydro-lH-indol-l-yl) methyl]-lH-imidazole-5-carbonitrile.

Some compounds are: (-)-4- (3-azido-2, 4-difluorophenyl)-l- (lH-imidazol-l-ylmethyl) pyrrolidin-2-one ; (+)-4-(3-azido-2, 4-difluorophenyl)-1-(lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3-azido-2, 4-difluorophenyl)-1-(lH-imidazol-1-ylmethyl) pyrrolidin-2-one.

The acid addition salt form of a compound of formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, trifluoroacetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula I containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e. g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e. g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with

organic bases, e. g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.
Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.
Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.
Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. , 45 (1976) 11-30.
The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).
Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.
In another preferred embodiment, the present invention concerns also compounds of formula IA and their tautomeric form IB

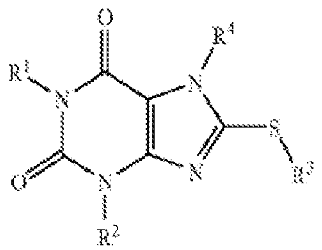


With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof, unless the particular isomeric form is referred to specifically.
Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

The invention also includes within its scope pro-drug forms of the compounds of formula I and its various sub-scopes and sub-groups.

xii) U.S. Patent Application Publication No. 20090018148

In one aspect the invention provides compounds having formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



(I)

wherein

R1 is hydrogen or C1-6 alkyl;

R2 is hydrogen or C1-4 alkyl;

R3 is a group of formula —CHR5R6 or a benzyl group;

R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle;

R5 is C2-4 alkyl;

R6 is C2-4 alkyl, amido or —COOR7;

R7 is C1-4 alkyl;

In one aspect, the invention provides compounds:

When R1 is hydrogen, R2 is methyl, R3 is —CHR5R6, R6 is ethoxycarbonyl and R5 is ethyl, then R4 is different from methyl, n-propyl, i-propyl, n-pentyl, n-heptyl, 3-bromobenzyl, 4-chlorobenzyl, 4-methylbenzyl or 2-phenylethyl;

When R1 is hydrogen, R2 is methyl, R3 is benzyl, then R4 is different from i-propyl, n-butyl, 3-methylbutyl, benzyl, phenylethyl-, or 3-phenylpropyl;

When R1 and R2 are methyl, R3 is benzyl, R4 is different from methyl, 3-methylbutyl, benzyl, 3-phenylpropyl or 4-chlorophenylmethyl;

Finally 8-(2-chloro-benzylsulfanyl)-3-methyl-7-octyl-3,7-dihydro-purine-2,6-dione is considered.

Usually when R3 is a benzyl group, then R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl.

Usually when R3 is a group of formula —CHR5R6, then R4 is C1-8 alkyl optionally substituted by C3-6 cycloalkyl, aryl or heterocycle.

The term “alkyl”, as used herein, is a group which represents saturated, monovalent hydrocarbon radicals having straight (unbranched) or branched moieties, or combinations thereof, and containing 1-8 carbon atoms, preferably 1-6 carbon atoms; more preferably alkyl groups have 1-4 carbon atoms. Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected from the group consisting of hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl, acyl, aryl or heterocycle. Alkyl moieties may be optionally substituted by a cycloalkyl as defined hereafter. Preferred alkyl groups according to the present invention are methyl, cyanomethyl, ethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-butyl, i-butyl, n-pentyl, 3-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl or (5-nitro-2-furyl)methyl. More preferred alkyl groups are methyl, ethyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl, 2-propynyl, n-butyl, 3-pentyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl or (5-nitro-2-furyl)methyl. Most preferred alkyl groups are methyl, ethyl, 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

The term “cycloalkyl”, as used herein, represents a monovalent group of 3 to 8, preferably 3 to 6 carbon atoms derived from a saturated cyclic hydrocarbon, which may be substituted by any suitable group including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferred cycloalkyl group according to the present invention is cyclohexyl.

The term “aryl” as used herein, is defined as a phenyl group optionally substituted by 1 to 4 substituents independently selected from halogen, amino, nitro, alkoxy or aminosulfonyl. Preferred aryl groups are phenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-aminophenyl or 4-(aminosulfonyl)phenyl.

The term “phenyl”, as used herein, represents an aromatic hydrocarbon group of formula —C6H5.

The term “benzyl group”, as used herein, represents a group of formula —CH2-aryl. Preferred benzyl groups are benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl or 4-(aminosulfonyl)benzyl. More preferred benzyl groups are benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl or 3-aminobenzyl. In some embodiments alkyl groups are 3-methoxybenzyl or 3-nitrobenzyl.

The term “halogen”, as used herein, represents an atom of fluorine, chlorine, bromine, or iodine. In some embodiments the halogen is bromine.

The term “hydroxy”, as used herein, represents a group of formula —OH.

The term “cyano”, as used herein, represents a group of formula —CN.

The term “amino”, as used herein, represents a group of formula —NH2.

The term “ethynyl”, as used herein, represents a group of formula —C≡CH.

The term “alkoxy”, as used herein, represents a group of formula —ORa wherein Ra is an alkyl group, as defined above. In some embodiments the alkoxy group is methoxy.

The term “nitro”, as used herein, represents a group of formula —NO2.

The term “amido”, as used herein, represents a group of formula —C(=O)NH2.

The term “acyl”, as used herein, represents a group of formula —C(=O)Rb wherein Rb is an alkyl group, as defined here above. In some embodiments the acyl group is acetyl (—C(=O)Me).

The term “alkoxycarbonyl (or ester)”, as used herein, represents a group of formula —COORc wherein Rc is an alkyl group; with the proviso that Rc does not represent an alkyl alpha-substituted by hydroxy. In some embodiments the alkoxycarbonyl group is ethoxycarbonyl.

The term “heterocycle”, as used herein, represents a 5-membered ring containing one or two heteroatoms selected from O or N. The heterocycle may be substituted by one or two C1-4 alkyl or nitro. In some embodiments the heterocycles are (3,5-dimethylisoxazol-4-yl) or (5-nitro-2-furyl). Most preferred heterocycle is (5-nitro-2-furyl).

Generally R1 is hydrogen or C1-6 alkyl. Usually R1 is hydrogen or C1-6 alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl. In some embodiments R1 is hydrogen, methyl, cyanomethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-pentyl or n-hexyl. In some embodiments R1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl. In some embodiments R1 is hydrogen.

Generally R2 is hydrogen or C1-4 alkyl. Usually R2 is hydrogen or unsubstituted C1-4 alkyl. In some embodiments R2 is hydrogen, methyl or n-butyl. In some embodiments, R2 is methyl.

Generally R3 is a group of formula —CHR5R6 or a benzyl group. In some embodiments R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl. In some embodiments R3 is 1-(ethoxycarbonyl)propyl.

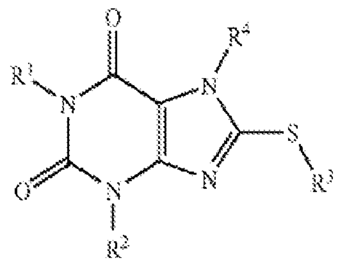
Generally R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle. Usually R4 is C1-8 alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl. In some embodiments R4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl. In some embodiments R4 is n-butyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl. In some embodiments R4 is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

Generally R5 is C2-4 alkyl. Usually R5 is unsubstituted C2-4 alkyl. In some embodiments R5 is ethyl.

Generally R6 is C2-4 alkyl, amido or —COOR7. Usually R6 is unsubstituted C2-4 alkyl, amido or —COOR7. In some embodiments R6 is ethyl, amido or ethoxycarbonyl. In some embodiments R6 is ethoxycarbonyl.

Generally R7 is C1-4 alkyl. Usually R7 is unsubstituted C1-4 alkyl. In some embodiments, R7 is ethyl.

Usually the invention provides compounds having formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



(I)

wherein

R1 is hydrogen, C1-6 alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl;

R2 is hydrogen or unsubstituted C1-4 alkyl;

R3 is a group of formula —CHR5R6 or a benzyl group;

R4 is C1-8 alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl;

R5 is unsubstituted C2-4 alkyl;

R6 is unsubstituted C2-4 alkyl, amido or —COOR7;

R7 is unsubstituted C1-4 alkyl;

with the proviso that when R1 is hydrogen, R2 is methyl, R3 is —CHR5R6, R6 is ethoxycarbonyl and R5 is ethyl, then R4 is different from n-propyl, i-propyl, n-pentyl, n-heptyl, 3-bromobenzyl, 4-chlorobenzyl, 4-methylbenzyl or 2-phenylethyl.

In the above embodiment, sometimes, when R3 is a benzyl group, then R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, sometimes, when R3 is a group of formula —CHR5R6, then R4 is C1-8 alkyl optionally substituted by C3-6 cycloalkyl, aryl or heterocycle.

In one embodiment,

R1 is hydrogen, methyl, cyanomethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-pentyl or n-hexyl;

R2 is hydrogen, methyl or n-butyl;

R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl;

R4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl;

with the proviso that when R1 is hydrogen, R2 is methyl and R3 is 1-(ethoxycarbonyl)propyl, then R4 is different from n-pentyl, 3-bromobenzyl or 2-phenylethyl.

In the above embodiment, sometimes, when R3 is 3-bromobenzyl, then R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, sometimes, when R3 is 3-pentyl, 1-(aminocarbonyl)propyl or 1-(ethoxycarbonyl)propyl, then R4 is different from 1-(ethoxycarbonyl)propyl.

In a more preferred embodiment, R1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl;

R2 is methyl;

R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl;

R4 is n-butyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl;

with the proviso that when R1 is hydrogen, R2 is methyl and R3 is 1-(ethoxycarbonyl)propyl, then R4 is different from 3-bromobenzyl.

In the above embodiment, sometimes, when R3 is 3-bromobenzyl, then R4 is 1-(ethoxycarbonyl)propyl;

In the above embodiment, sometimes, when R3 is 3-pentyl, 1-(aminocarbonyl)propyl or 1-(ethoxycarbonyl)propyl, then R4 is different from 1-(ethoxycarbonyl)propyl;

In one embodiment, R1 is hydrogen; R2 is methyl; R3 is 1-(ethoxycarbonyl)propyl; and R4 is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

A further embodiment consists in compounds wherein R2 is methyl, R3 is a group of formula —CHR5R6 with R5 being C2-4 alkyl, R6 being amido or —COOR7 and R7 being methyl or ethyl.

In some embodiments, compounds are ethyl 2-[(7-benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-ethoxy-2-oxoethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-methoxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(2-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(cyanomethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-propyl-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-oxopropyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(3-hydroxypropyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-propynyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-({7-[4-(aminosulfonyl)benzyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyl 2-{[7-(4-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(cyclohexylmethyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[1,3-dimethyl-2,6-dioxo-7-(1-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[1,3-dimethyl-2,6-dioxo-7-(2-

phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-({7-[(3,5-dimethylisoxazol-4-yl)methyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyl 2-({3-methyl-7-[(5-nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyl 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-[(1,7-dihexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-[(7-hexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-[(3-methyl-2,6-dioxo-1,7-dipentyl-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanamide; 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanamide; 7-(3-bromobenzyl)-8-[(1-ethylpropyl)thio]-3-methyl-3,7-dihydro-1H-purine-2,6-dione; ethyl 2-{8-[(3-bromobenzyl)thio]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl}butanoate; and ethyl 2-[(7-isobutyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate.

In some embodiments compounds are: ethyl 2-[(7-benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-methoxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(cyanomethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-propyl-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(3-hydroxypropyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-propynyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-({7-[(3,5-dimethylisoxazol-4-yl)methyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-

yl}thio)butanoate; ethyl 2-({3-methyl-7-[(5-nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyl 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-[(7-hexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanamide; 7-(3-bromobenzyl)-8-[(1-ethylpropyl)thio]-3-methyl-3,7-dihydro-1H-purine-2,6-dione; and ethyl 2-{8-[(3-bromobenzyl)thio]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl}butanoate.

In some embodiments compounds are: ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; and ethyl 2-({3-methyl-7-[(5-nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate.

The acid addition salt form of a compound of formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, trifluoroacetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula I containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof, unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

xiii) U.S. Patent 7,465,549

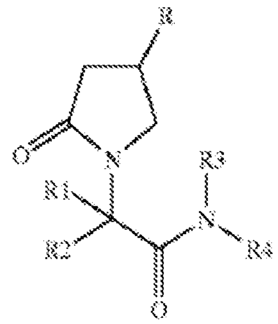
In some embodiments, the compound includes optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives. In some embodiments, those compounds are alkyl amides derivatives substituted on the positions 4 and/or 5 of the pyrrolidone ring. Examples of optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives include, but are not limited to, compounds such as (2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide, (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide, (2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide, and (2S)-2-[4-(3-azidophenyl)-2-oxopyrrolidin-1-yl]butanamide.

In some embodiments, the compounds further include optionally substituted N-alkylated 2-oxo-piperidinyl derivatives. In some embodiments, those compounds are alkyl amides derivatives substituted on the position 4 and/or 5 and/or 6 of the 2-oxo-piperidinyl ring. Examples of optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives include, but are not limited to, compounds such as those referred to in international patent application PCT/EP02/05503 such as (2S)-2-[5-

(iodomethyl)-2-oxo-1-piperidinyl]butanamide, (2S)-2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-5-phenyl-1-piperidinyl]butanamide, (2S)-2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide, and (2S)-2-[4-(2-fluoro-2-methylpropyl)-2-oxo-1-pyrrolidinyl]butanamide.

In some embodiments, the compounds include any acetam compound of formula I, in racemic or isomeric form, or a pharmaceutically acceptable salt thereof,

(I)



wherein

R represents hydrogen or hydroxy;

R1 and R2 represent independently hydrogen or an alkyl group of 1-4 carbon atoms; and

R3 and R4 represent independently hydrogen, an alkyl group of 1-4 carbon atoms or —(CH2)n—NR5R6 wherein n is 1, 2 or 3 and R5 and R6 represent independently hydrogen or an alkyl group of 1-4 carbon atoms.

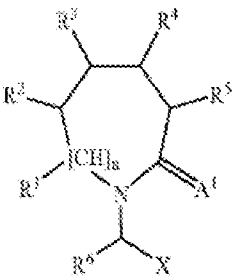
An example of such an acetam compound includes, but is not limited to, a compound of formula I wherein R, R1, R2, R3 and R4 are hydrogen, 2-oxo-pyrrolidineacetamide, known by the generic name piracetam as described in UK Patents Nos. 1,039,113 and 1,309,692.

In some embodiments, the compounds also include optionally substituted N-alkylated 2-oxo-azepanyl derivatives. Preferably, those compounds are alkyl amides derivatives substituted on the positions 4 and/or 5 and/or 6 and/or 7 of the 2-oxo-azepanyl ring. Examples of optionally substituted N-alkylated 2-oxo-azepanyl derivatives include, but are not limited to, compounds such as those referred to in international patent application PCT/EP02/05503 such as 2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide.

xiv) U.S. Patent Application Publication No. 2006258704

This invention provides novel compounds of the formula I

(I)



wherein

n represents 0 or 1 whereby R<1 > is not existent when n=0 and R<1 > is existent when n=1;

A<1 > represents an oxygen or a sulfur atom;

X is -CONR<7> R<8> , -COOR<9> , -CO-R<10 > or CN;

R<1 > when existent, R<2> , R<3> , R<4 > and R<5 > are the same or different and each is independently hydrogen, halogen, hydroxy, thiol, amino, nitro, nitrooxy, cyano, azido, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, or an oxy derivative, thio derivative, amino derivative, acyl derivative, sulfonyl derivative or sulfinyl derivative,

provided that at least one of the substituents R chosen from R<1 > when existent, R<2> , R<3> , R<4 > or R<5 > is not hydrogen;

R<6 > is hydrogen, alkyl, aryl or -CH2-R<6a > wherein R<6a > is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

R<7> , R<8 > and R<9 > are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R<10 > is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

their pharmaceutically acceptable salts, geometrical Isomers (including cis and trans, Z and E isomers), enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers).

In the above formula, at least one substituent R<1 > to R<5 > is different from hydrogen. Some non-substituted compounds are referred to in U.S. Pat. Nos. 5,468,733 and 5,516,759. U.S. Pat. No. 5,468,733 discloses non-ring substituted 2-oxo-1-pyrrolidinyl and 2-oxo-1-piperidinyl derivatives as inhibitors of the oncogene Ras protein. In particular, these compounds block the ability of Ras to transform normal cells to cancer cells, and therefore can be included in several chemotherapeutic compositions for treating cancer.

US Patent No. 5,516,759 discloses non-ring substituted 2-oxo-l-pyrrolidinyl, 2-oxo-1-piperidinyl and azepanyl derivatives present at the N-terminus of dodecapeptides possessing LHRH (luteinizing hormone-releasing hormone) antagonistic activity. Such LHRH antagonists are useful in the treatment of a variety of conditions in which suppression of sex steroids plays a key role including contraception, delay of puberty, treatment of benign prostatic hyperplasia a.o.

In the definitions set forth below, unless otherwise stated, R<11 > and R<12 > are the same or different and each is independently amido, alkyl, alkenyl, alkynyl, acyl, ester, ether, aryl, aralkyl, heterocycle or an oxy derivative, thio derivative, acyl derivative, amino derivative, sulfonyl derivative, or sulfinyl derivative, each optionally substituted with any suitable group, including, but not limited to, one or more moieties selected from lower alkyl or other groups as described below as substituents for alkyl.

The term "oxy derivative", as used herein, is defined as including -O-R<11 > groups wherein R<11 > is as defined above except for "oxy derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, oxyester, oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocyclooxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyloxy, 2-pyridyloxy, methylenedioxy, carbonate.

The term "thio derivative", as used herein, is defined as including -S-R<11 > groups wherein R<11 > is as defined above except for "thio derivative". Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

The term "amino derivative", as used herein, is defined as including -NHR<11 > or -NR<11> R<12 > groups wherein R<11 > and R<12 > are as defined above. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl- and arylamino or mixed amino.

The term "acyl derivative", as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula R<11> -CO-, wherein R<11 > is as defined above and may also be hydrogen. Preferred are acyl derivatives of formula -COR<11 > wherein R<11 > is selected from hydrogen, C1-12 alkyl, C2-12 alkenyl, C2-12 alkenyl, heterocyle and aryl. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyl, oxamoyl.

The term "sulfonyl derivative", as used herein, is defined as including a group of the formula -SO-R<11> , wherein R<11 > is as defined above except for "sulfonyl derivative". Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

The term "sulfinyl derivative", as used herein, is defined as including a group of the formula -SO-R<11> , wherein R<11 > is as defined above except for "sulfinyl derivative". Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and generally containing 1-20 carbon atoms, most often 1 to 12 carbon atoms, preferably 1-7 carbon atoms for non-cyclic alkyl and 3-7 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl"), each optionally substituted by, preferably 1 to 5, substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, thiocyanato, acyl, acyloxy, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, alkylthio, oxyester, oxyamido, heterocycle, vinyl, alkoxy (preferably C1-5), aryloxy (preferably C6-10) and aryl(preferably C6-10).

In some embodiments are alkyl groups containing 1 to 7 carbon atoms, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkylthio, cyclopropyl, acyl and phenyl. Most preferred are C1-4 alkyl and C3-7 cycloalkyl, each optionally substituted by one or more hydroxy, halogen, lower alkyl or/and azido.

In some embodiments are alkyl groups are hydroxymethyl, propyl, butyl, 2,2,2-trifluoroethyl, 2-bromo-2,2-difluoroethyl, 2-chloro-2,2-difluoroethyl, 3,3,3-

trifluoropropyl, cyclopropylmethyl, iodomethyl, azidomethyl, 2,2-difluoropropyl, 2-iodo-2,2-difluoroethyl.

The term "lower alkyl", as used herein, and unless otherwise specified, refers to C1 to C7 saturated straight, branched or cyclic hydrocarbon. Non limiting examples are methyl, ethyl, propyl, isopropyl, butyl, tertiobutyl, pentyl, cyclopropyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methypentyl, 2,2-dimethylbutyl, optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferably, lower alkyl is methyl.

The term "alkenyl", as used herein, is defined as including both branched and unbranched, unsaturated hydrocarbon radicals having at least one double bond, and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, thiocyanato, azido, alkylthio, cycloalkyl, acyl, nitro, cyano, aryl and heterocycle.

In some embodiments are alkenyl groups are C2-C12 alkenyls, especially C2-6alkenyls, such as ethenyl (=vinyl), 1-methyl-1-ethenyl, 2,2-dimethyl-1-ethenyl, 1-propenyl, 2-propenyl (=allyl), 1-butenyl, 2-butenyl, 3-butenyl, 4-pentenyl, 1-methyl-4-pentenyl, 3-methyl-1-pentenyl, 1-hexenyl, 2-hexenyl and the like, optionally being substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, cycloalkyl, phenyl and acyl. Most prefered is vinyl, optionally substituted by one or more halogen or/and lower alkyl, and especially 2,2-difluorovinyl, 2,2-dibromovinyl and 2,2-dichlorovinyl.

The term "alkynyl" as used herein, is defined as including a monovalent branched or unbranched hydrocarbon radical containing at least one carbon-carbon triple bond, for example ethynyl, 2-propynyl (=propargyl), and the like, and being optionally substituted by at least one substituent selected from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, aryl, heterocycle, thiocyanato, azido, alkylthio, alkyl and acyl.

In some embodiments are alkynyl groups are C2-12 alkynyl, especially C2-6 alkynyl, optionally being substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, acyl, aryl such as phenyl and alkyl, preferably cycloalkyl.

In some embodiments are ethynyl, propynyl and butynyl, optionally substituted by lower alkyl or/and halogen, and especially 1-propynyl, cyclopropylethynyl, 3-methyl-1-butynyl and 3,3,3-trifluoro-1-propynyl.

When present as bridging groups, alkyl, alkenyl and alkynyl represent straight- or branched chains, C1-12, preferably C1-4-alkylene or C2-12-, preferably C2-4-alkenylene or -alkynylene moieties respectively.

Groups where branched derivatives are conventionally qualified by prefixes such as "n", "sec", "iso" and the like (e.g. "n-propyl", "sec-butyl") are in the n-form unless otherwise stated.

The term "aryl", as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of at least one ring, most often 1 to 3 rings and generally containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl, each optionally substituted by one or more substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl, acyloxy, sulfonyl, sulfinyl, alkylamino, carboxy, ester, ether, amido, azido, sulfonic acid, sulfonamide, alkylsulfonyl, alkylsulfinyl, C1-6-alkylthio, oxyester, oxyamido, aryl, C1-6-alkoxy, C6-10-aryloxy, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic or bicyclic containing 6-10 carbon atoms. Preferred aryl groups are phenyl and naphthyl each optionally substituted by one or more substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkyl, C1-6-haloalkyl, sulfonyl and phenyl.

In some embodiments the aryl is phenyl, optionally substituted by one or more halogen, lower alkyl, azido or nitro, such as 3-chlorophenyl and 3-azidophenyl.

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "thiol", as used herein, represents a group of the formula -SH.

The term "cyano", as used herein, represents a group of the formula -CN.

The term "nitro", as used herein, represents a group of the formula -NO2.

The term "nitrooxy", as used herein, represents a group of the formula -ONO2.

The term "amino", as used herein, represents a group of the formula -NH2.

The term "azido", as used herein, represents a group of the formula -N3.

The term "carboxy", as used herein, represents a group of the formula -COOH.

The term "sulfonic acid", as used herein, represents a group of the formula -SO3H.
The term "sulfonamide", as used herein, represents a group of the formula -SO2NH2.
The term "ester", as used herein, is defined as including a group of formula -COO-R<11 > wherein R<11 > is as defined above except oxy derivative, thio derivative or amino derivative. Preferred are esters of formula -COOR<11 > wherein R<11 > is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl and aryl. Most preferred are esters where R<11 > is a lower alkyl, especially methyl.
The term "ether" is defined as including a group selected from C1-50-straight or branched alkyl, or C2-50-straight or branched alkenyl or alkynyl groups or a combination of the same, interrupted by one or more oxygen atoms.
The term "amido" is defined as including a group of formula -CONH2 or -CONHR<11 > or -CONR<11> R<12 > wherein R<11 > rand R<12 > are as defined above.
The term "heterocycle", as used herein, is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl, and optionally being substituted with any suitable group, including but not limited to one or more moieties selected from lower alkyl, or other groups as described above for the alkyl groups. Non-limiting examples of heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, triazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinolizinyl, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indolizinyl, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2,4-thiadiazolyl, thiomorpholinyl, thieno(2,3-b)furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, 1-oxidopyridyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, benzodioxolyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl,

imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i.e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) optionally substituted by alkyl or as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2. 1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

The heterocycle may be selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from halogen, alkyl, substituted alkyl, alkoxy, nitro, amino, acyl and phenyl. In some embodiments the heterocycle is selected from tetrazolyl, pyrrolidinyl, pyridyl, furyl, pyrrolyl, thiazolyl and thienyl, each optionally substituted by one or more substituents selected from halogen, alkyl, halogen substituted alkyl, acyl, alkoxy, nitro, amino and phenyl, and especially from 2-and 3-thienyl, optionally substituted by one or more halogen, acyl such as formyl, cyano and/or lower alkyl, such as methyl.

In the above definitions it is to be understood that when a substituent such as R<1> , R<2> , R<3> , R<4> , R<5> , R<7> , R<8> , R<9> , R<10 > is attached to the rest of the molecule via a heteroatom or a carbonyl, a straight- or branched chain, C1-12-, preferably C1-4-alkylene or C2-12, preferably C2-4-alkenylene or -alkynylene bridge may optionally be interposed between the heteroatom or the carbonyl and the point of attachment to the rest of the molecule.

The acid addition salt form of a compound of formula (I) that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt form, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

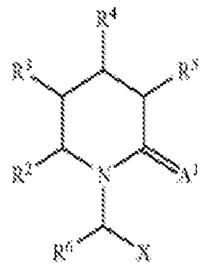
Furthermore, certain compounds of formula I which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the invention includes both mixture and separate individual isomers.

Multiple substituents on the piperidinyl or the azepanyl ring can also stand in either cis or trans relationship to each other with respect to the plane of the piperidinyl or the azepanyl ring.

Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

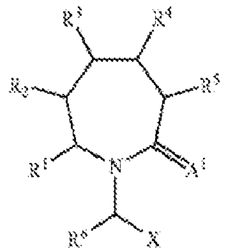
With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically. The invention also includes within its scope prodrug forms of the compounds of formula I and Its various sub-scopes and sub-groups.
The term "prodrug" as used herein includes compound forms which are rapidly transformed in vivo to the parent compound according to the invention, for example, by hydrolysis in blood. Prodrugs are compounds bearing groups which are modified by biotransformation prior to exhibiting their pharmacological action. Such groups include moieties which are readily oxidised, cyclised or cleaved, which compound after biotransformation remains or becomes pharmacologically active. For example, metabolically cleavable groups form a class of groups well known to practitioners of the art. They include, but are not limited to such groups as alkanoyl (i.e. acetyl, propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aroyl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate, sulfonyl, sulfinyl and the like. The compounds bearing the biotransformable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the biotransformable group. T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A.C.S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.
The term "R substituent" refers to R<1> , R<2> , R<3> , R<4 > or R<5 > , independently.
According to one embodiment, the present invention relates to a compound of formula I as defined above wherein n represents 0. The compound is a 6-ring structure (2-thioxo- or 2-oxo-piperidinyl derivative) wherein R<1 > is not existent since n=0, and is depicted by the formula (I-A).

(I-A)



According to a following embodiment, the present invention relates to a compound of formula I according to the invention as defined above wherein n represents 1. The compound is a 7-ring structure (2-thioxo- or 2-oxo-azepanyl derivative) wherein R<1 > is existent since n=1 and depicted by the formula (I-B).

(I-B)



According to one embodiment, the invention relates to said compound as defined above wherein n=0, R<3 > and/or R<4 > are different from hydrogen and R<2 > and R<5 > represent hydrogen.

According to another embodiment, the invention relates to said compound as defined above wherein n=1, R<2> , R<3 > and/or R<4 > are different from hydrogen and wherein R<1 > and R<5 > represent hydrogen.

According to another embodiment, the invention relates to said compound as defined above wherein only one R substituent chosen from R<3 > or R<4 > when n=0 or from R<2> , R<3 > or R<4 > when n=1, is different from hydrogen and the remaining R substituent(s) is/are hydrogen. We hereby refer to a mono-substituted 2-thioxo- or 2-oxo-piperidinyl or 2-thioxo- or 2-oxo-azepanyl derivatives.

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein A<1 > represents an oxygen atom. We hereby refer to 2-oxo-piperidinyl or 2-oxo-azepanyl derivatives.

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein X is CONR<7>

R<8> , especially CONH2. We hereby refer to amido derivatives of 2-oxo(or thioxo)-piperidinyl or 2-oxo(or thioxo)-azepanyl.

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein R<6 > represents hydrogen, C1-4 alkyl, or a CH2-R<6a > group wherein R<6a > represents a heterocycle. Most preferably R<6 > is a C1-4 alkyl, especially ethyl. When R<6 > is ethyl we refer to 2-(2-oxo(or thioxo)-1-piperidinyl)butanamide or 2-(2-oxo(or thioxo)-1-azepanyl)butanamide derivatives.

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein the carbon atom to which R<6 > is attached is of the S configuration. In case where R<6 > is ethyl, A is oxygen and X is CON R<7 > R<8> , we refer then to (2S)-2-(2-oxo-1-piperidinyl)butanamide or (2S)-2-(2-oxo-1-azepanyl)butanamide derivatives.

According to one embodiment, the present invention relates to a compound as defined above wherein R<2 > when n=1, R<3 > and R<4 > are the same or different and each is independently hydrogen, halogen, nitro, nitrooxy, cyano, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, acyl derivative, sulfonyl derivative or sulfinyl derivative:

R<1 > when existent, R<2 > when n=0 and R<5 > are hydrogen;

R<6 > is hydrogen, alkyl, aryl or -CH2-R<6a > wherein R<6a > is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

provided that, when R<6 > is hydrogen, X is -CONR<7> R<8 > and that the compound is

neither methyl (2R)-2-[(6R)-6-methyl-2-oxoazepanyl]-3-phenylpropanoate

nor methyl (2S)-2-[(4R)-4-methyl-2-oxoazepanyl]-3-phenylpropanoate.

According to this embodiment, the compound is generally such that when R<6 > is benzyl, X is -COOCH3 and n=1, R<2 > is different from methyl when R<3 > and R<4 > are both hydrogen and R<4 > is different from methyl when R<2 > and R<3 > are both hydrogen.

According to another embodiment, the present invention relates to a compound as defined above wherein R<2 > when n=1, R<3 > and R<4 > are the same or different and each is independently hydrogen; cyano; carboxy; amido;

C1-12 alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkyltio, cycloalkyl, acyl, aryl and heterocycle;

C2-12 alkenyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, alkyl, aryl and acyl;

C2-12 alkynyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, alkyl, aryl and acyl; acyl derivative of formula -CO-R<11> , wherein R<11 > is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl, heterocycle and aryl;

ester of formula -CO-O-R<11 > wherein R<11 > is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl and aryl;

heterocycle selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from halogen, alkyl, substituted alkyl, alkoxy, nitro, amino, acyl and phenyl;

aryl, each optionally substituted by one or more substituents selected from C1-6 alkyl, C1-6 haloalkyl, C1-6 alkoxy, C1-6 alkylthio, amino, azido, sulfonyl, aryl and nitro.

According to another embodiment, the present invention relates to a compound as defined above, wherein R<2 > when n=1, R<3 > and R<4 > are the same or different and each is independently hydrogen;

C1-7 alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkyltio, cyclopropyl, acyl and phenyl;

C2-6 alkenyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, cycloalkyl, phenyl and acyl:

C2-6 alkynyl, each optionally substituted by one or more substituents selected from halogen, cyano, thiocyanato, azido, alkylthio, cycloalkyl, phenyl and acyl:

heterocycle selected from tetrazolyl, pyrrolidinyl, pyridyl, furyl, pyrrolyl, thiazolyl and thienyl, each optionally substituted by one or more substituents selected from halogen, alkyl, halogen substituted alkyl, acyl, alkoxy, nitro, amino and phenyl;

phenyl, each optionally substituted by one or more substituents selected from C1-6 alkyl, halogen substituted alkyl, halogen, alkoxy, amino, azido, sulfonyl, phenyl and nitro.

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R<3 > and R<4 > when n=0, represents independently C1-4-alkyl or C3-7-cycloalkyl, optionally substituted by one or more halogen, hydroxy, lower alkyl and/or azido.

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R<3 > and R<4 > when n=0, represents independently vinyl, optionally substituted by one or more halogen or/and lower alkyl.

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R3 and R<4 > when n=0, represents independently ethynyl, propynyl or butynyl, optionally substituted by one or more halogen and/or lower alkyl.

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R<3 > and R<4 > when n=0, represents independently phenyl, optionally substituted by one or more halogen, lower alkyl, azido and/or nitro.

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R<3 > and R<4 > when n=0, represents independently 2- or 3-thienyl, optionally substituted by one or more halogen, acyl, cyano or/and lower alkyl.

According to a particular embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<3> , R<4 > and R<2 > when n=1 or from the group R<3 > and R<4 > when n=0, is hydroxymethyl, propyl, butyl, 3,3,3-trifluoropropyl, 2,2,2-trifluoroethyl, cyclopropylmethyl, iodomethyl, azidomethyl, 2-thienyl, 3-thienyl, phenyl, 3-chlorophenyl, 3-azidophenyl, 2,2-difluorovinyl, 2,2-dibromovinyl, 2,2-dichlorovinyl, 2-ethynyl, 5-methyl-2-thienyl, 5-formyl-2-ethynyl, 5-cyano-2-thienyl, 3-bromo-2-thienyl, 4-methyl-2-thienyl, 3,3,3-trifluoro-1-propynyl, 1-propynyl, cyclopropylethynyl, 3-methyl-1-butynyl, 1-butynyl, 2,2-difluoropropyl, 2-chloro-2,2-difluoroethyl, 2-bromo-2,2-difluoroethyl and 2-iodo-2,2-difluoroethyl.

According to yet another embodiment, the present invention relates to a compound as defined above wherein R<1> , R<2> , R<4 > and R<5 > are hydrogen.

According to another embodiment, the present invention relates to a compound as defined above wherein R<1> , R<2> , R<3 > and R<5 > are hydrogen.

According to another embodiment, the present invention relates to a compound as defined above wherein n=1 and R<1> , R<3> , R<4 > and R<5 > are hydrogen.

In all the above-mentioned scopes when the carbon atom to which R<6 > is attached is asymmetric it may be in the "S"-configuration.

Representative compounds of this invention as defined above are selected from the group consisting of 2-[5-(hydroxymethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-5-propyl-1-piperidinyl)butanamide, 2-12-oxo-5-(3,3,3-trifluoropropyl)-1-piperidinyl]butanamide, 2-[5-(cyclopropylmethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(iodomethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-5-phenyl-1-piperidinyl)butanamide, 2-[2-oxo-5-(2-thienyl)-1-piperidinyl]butanamide, 2-[2-oxo-5-(3-thienyl)-1-piperidinyl]butanamide, 2-[5-(3-chlorophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(3-azidophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-difluorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-dibromovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-dichlorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-(5-ethynyl-2-oxo-1-piperidinyl)butanamide, 2-[5-(5-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(5-formyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(5-cyano-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(3-bromo-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(4-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[2-oxo-5-(3,3,3-trifluoro-1-propynyl)-1-piperidinyl]butanamide, 2-[2-oxo-5-(1-propynyl)-1-

piperidinyl]butanamide, 2-[5-(cyclopropylethynyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(3-methyl-1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-difluoropropyl)-2-oxo 1-piperidinyl]butanamide, 2-[5-(2-chloro-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2-bromo-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(hydroxymethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-4-propyl-1-piperidinyl)butanamide, 2-[2-oxo-4-(3,3,3-trifluoroproyl)-1-piperidinyl]butanamide, 2-14-(cyclopropylmethyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(iodomethyl)-2-oxo-1-piperldinyl]butanamide, 2-[4-(azidomethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-4-phenyl-1-piperidinyl)butanamide, 2-12-oxo-4-(2-thienyl)-1-piperidinyl]butanamide, 2-[2-oxo-4-(3-thienyl)-1-piperidinyl]butanamide, 2-[4-(3-chlorophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(3-azidophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-difluorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-dibromovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-dichlorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-(4-ethynyl-2-oxo-1-piperidinyl)butanamide, 2-[4-(5-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(5-formyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(5-cyano-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(3-bromo-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(4-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[2-oxo-4-(3,3,3-trifluoro-1-propynyl)-1-piperidinyl]butanamide, 2-[2-oxo-4-(1-propynyl)-1-piperidinyl]butanamide, 2-[4-(cyclopropylethynyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(3-methyl-1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-difluoropropyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2-chloro-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-14-(2-bromo-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2,2-trifluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-5-propyl-1-azepanyl)butanamide, 2-[2-oxo-5-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide, 2-(5-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(azidomethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-5-phenyl-1-azepanyl)butanamide, 2-[2-oxo-5-(2-

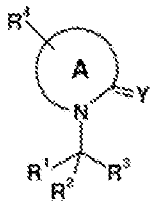
thienyl)-1-azepanyl]butanamide, 2-[2-oxo-5-(3-thienyl)-1-azepanyl]butanamide, 2-[5-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide, 2-(5-ethynyl-2-oxo-1-azepanyl)butanamide, 2-[5-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[2-oxo-5-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide, 2-[2-oxo-5-(1-propynyl)-1-azepanyl]butanamide, 2-[5-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-6-propyl-1-azepanyl)butanamide, 2-[2-oxo-6-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide, 2-[6-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(iodomethyl)-2-oxo-1-azepanyl]butanamide, 2-16-(azidomethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-6-phenyl-1-azepanyl)butanamide, 2-[2-oxo-6-(2-thienyl)-1-azepanyl]butanamide, 2-[2-oxo-6-(3-thienyl)-1-azepanyl]butanamide, 2-[6-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide, 2-(6-ethynyl-2-oxo-1-azepanyl)butanamide, 2-[6-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(4-methyl-2-thienyl]-2-oxo-1-azepanyl]butanamide, 2-[2-oxo-6-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide, 2-[2-oxo-6-(1-propynyl)-1-azepanyl]butanamide, 2-[6-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-

(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-4-propyl-1-azepanyl)butanamide, 2-[2-oxo-4-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide, 2-14-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(iodomethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(azidomethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-4-phenyl-1-azepanyl)butanamide, 2-[2-oxo-4-(2-thienyl)-1-azepanyl]butanamide, 2-[2-oxo-4-(3-thienyl)-1-azepanyl]butanamide, 2-f4-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide, 2-(4-ethynyl-2-oxo-1-azepanyl)butanamide, 2-[4-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[<4> -(5-cyano-<2> -thienyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[2-oxo-4-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide, 2-[2-oxo-4-(1-propynyl)-1-azepanyl]butanamide, 2-[4-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2-chloro-2,2-difluoroethyl]-2-oxo-1-azepanyl]butanamide, 2-[4-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide.

Results have been obtained with the following compounds:
(2S)-2-[5-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,
(2S)-2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide,
2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,
(2S)-2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,
2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide.

xv) International Patent Application Publication No. WO2008/132139

In some embodiments, the compounds are of formula (I) as follows:



(I)

wherein

Y is O or S. In some embodiments Y is O. R1 is hydrogen or C-|.g alkyl;

R2 is hydrogen;

R3 is -CONR5R6, -COR7, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; R5, R6 are the same or different and are independently selected from hydrogen and C-|_6 alkyl;

R7 is C<;|_6 alkyl;

A is a monocyclic or bicyclic heterocyclic moiety selected from the group consisting of imidazolidin-1-yl, 1 ,3-oxazolidin-3-yl, 2,5-dihydro-1 H-pyrrol-1-yl, 1 ,3-thiazol-3(2H)-yl, 1 ,3- thiazolidin-3-yl, piperidin-1-yl, azepan-1-yl, 5,6-dihydro-4H-thieno[3,2-b]pyrrol-4-yl, hexahydro-4H-thieno[3,2-b]pyrrol-4-yl, 2,3-dihydro-1 H-thieno[3,4-b]pyrrol-1-yl, 1 ,3- benzothiazol-3(2H)-yl, 1 ,3-benzoxazol-3(2H)-yl, pyrazolo[1 ,5-a]pyridin-1 (2H)-yl, 3,4- dihydroisoquinolin-2(1 H)-yl, 3,4-dihydroquinolin-1 (2H)-yl, 1 ,3,4,5-tetrahydro-2H-2- benzazepin-2-yl, 1 ,2,4,5-tetrahydro-3H-3-benzazepin-3-yl; R4 is either R^a or R^b depending on whether A being is a monocyclic or a bicyclic heterocycle:

where A is a monocyclic heterocyclic moiety, R^ is R^a which is selected from the group consisting of hydrogen; C-|.g alkyl optionally substituted by a substituent selected from halogen, C-1.4 alkoxy, C-1.4 alkylthio, azido, nitrooxy or an aryl; C2-6 alkenyl optionally substituted by halogen; C2-6 alkynyl optionally substituted by halogen; azido; alkoxycarbonylamino; arylsulfonyloxy; a substituted or unsubstituted aryl; or a 3-8 membered substituted or unsubstituted heterocycle;

where A is a bicyclic heterocyclic moiety R^ is R^ which is selected from the group comprising or consisting of hydrogen; nitro; cyano; halogen; heterocycle; amino; aryl; C-|.g alkyl optionally substituted by at least one halogen; or C-|.g alkoxy optionally substituted by at least one halogen;

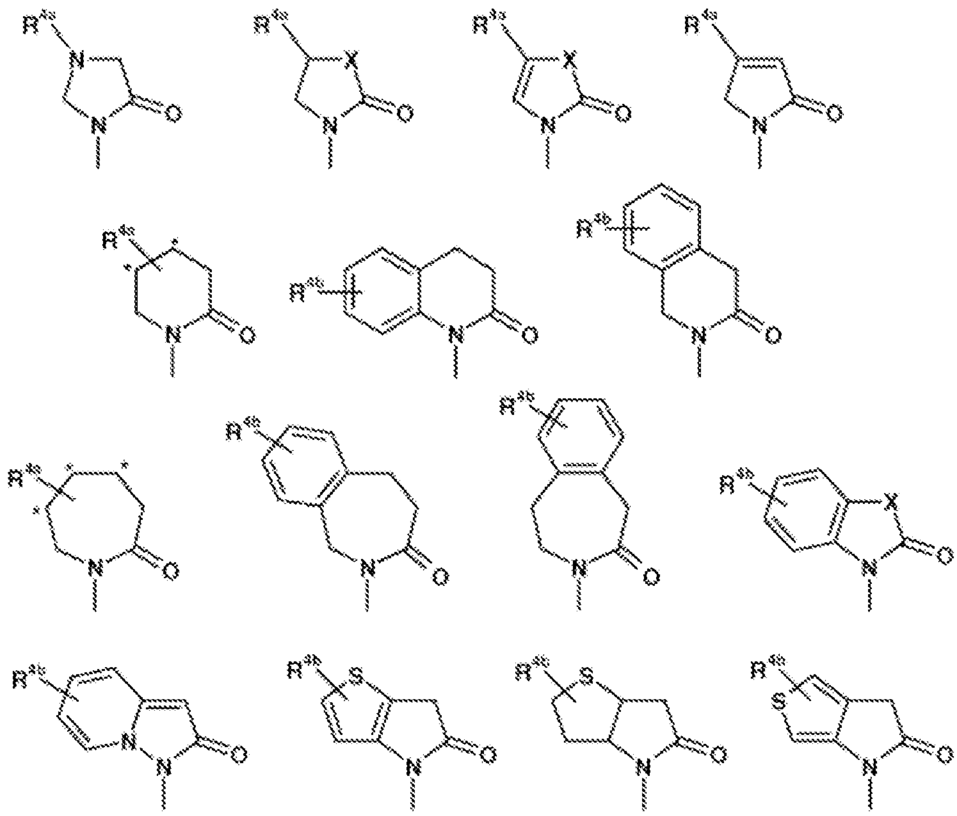
In some embodiments the compounds are as follows:

For compounds where A=Y is selected from a 2-oxo-piperidin-1-yl, a 2-oxo-azepan-1-yl, a 2-oxo-1 ,3-benzothiazol-3(2H)-yl or a 2-oxo-1 ,3-benzoxazol-3(2H)- yl, R3 must be selected from an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl.

For compounds where A=Y is a 5-oxoimidazolidin-1-yl, R^ and R^ are hydrogen, R3 is -CONR5R6, R5 and| R6 are as above defined, then R^a may not be an alkyl, aralkyl or substituted aralkyl.

Where A=Y is either of a 2-oxo-piperidin-1-yl and a 2-oxo-azepan-1-yl, R^ , R^ and R^a are all hydrogen, then R^ could not be a 2-phenylimidazo[1 ,2-a]pyridin-3-yl.

In a specific embodiment A=Y is selected from the list consisting of:



wherein X is O or S, in a more specific embodiment O; in another embodiment, X is S.

The asterisks in the above illustration indicate the attachment sites of the substituent R^a.

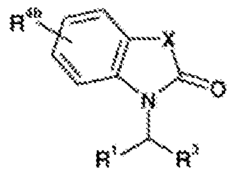
In a specific embodiment, when R^ is -CONR5R6 and R^ is C-µg alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

In a specific embodiment R^ is hydrogen, methyl, ethyl and R^ is hydrogen. In a specific embodiment R3 is -CONH2.

In a further specific embodiment R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5- yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a specific embodiment R^a is a C-|.g alkyl which may optionally be substituted by a halogen; or a phenyl.

In another specific embodiment R^b is hydrogen, halogen, nitro, cyano or a C-µg alkyl optionally substituted by a halogen.

In still a further embodiment compounds may be used in the treatment of the above mentioned disorders, in particular of epilepsy, having the formula (I-E), as wells as its geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-E)

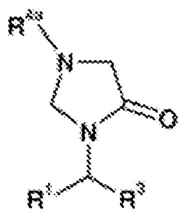
wherein

X is O or S;

R-I is hydrogen or C-|.g alkyl, in a more specific embodiment hydrogen;

R3 is an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; R^b is hydrogen; nitro; cyano; halogen; C-|.g alkyl optionally substituted by halogen; C-|.g alkoxy optionally substituted by halogen.

A further aspect of the present invention consists in novel compounds having the formula (I-A), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-A)

wherein

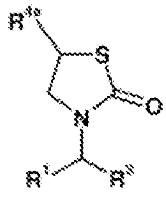
R1 is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R^ is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl, preferably R^ is -CONH2.

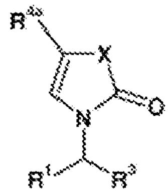
R^a is either hydrogen or an aryl; with the proviso that 2-(5-oxoimidazolidin-1-yl)acetamide is excluded. Preferably R^a is an aryl, e.g. a phenyl which may be substituted preferably by halogen, nitro, alkoxy, in particular by nitro.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R1 and R^ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in novel compounds having the formula (I-B1 or I-B2), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-B1)



(I-B2)

wherein X in formula (I-B2) is either S or O, in a more specific embodiment S;

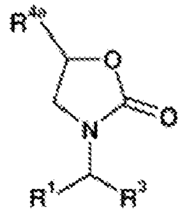
R1 is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R^ is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; preferably R^ is -CONH2

R^a is hydrogen; C-|.g alkyl optionally substituted by halogen or C-1.4 alkoxy; an aryl; or C2.g alkenyl optionally substituted by halogen. Preferably, R^a is C-|.g alkyl optionally substituted by halogen or C2-6 alkenyl optionally substituted by halogen or an aryl. In a more specific embodiment R^a is C-|.g alkyl optionally substituted by halogen or aryl.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in novel compounds having the formula (I-B3), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-B3)

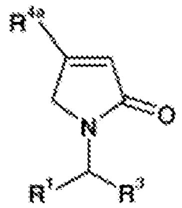
wherein

R1 is either hydrogen or C-μg alkyl, preferably hydrogen, methyl or ethyl; more preferably R1 is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; preferably R^ is -CONH2 R^a is C-|_5 alkyl optionally substituted by halogen or C-1.4 alkoxy; an aryl; or C2_g alkenyl optionally substituted by halogen. Preferably, R^a is C-|.g alkyl optionally substituted by halogen or C2_g alkenyl optionally substituted by halogen.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in novel compounds having the formula (I-C), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-C)

wherein

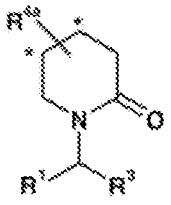
R1 is hydrogen or C-|.g alkyl, in particular hydrogen, methyl or ethyl.

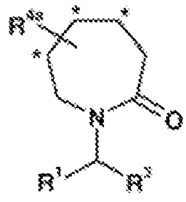
R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in particular R^ is -CONH2

R^a is methyl, ethyl, butyl optionally substituted by halogen or C-1.4 alkoxy, an unsubstituted phenyl or a phenyl substituted by halogen, a C-|.g alkyl optionally substituted by halogen or a C-1.4 alkoxy; or R^a is a C2-6 alkenyl optionally substituted by halogen. Preferably, R^a is methyl, optionally substituted by halogen, an unsubstituted phenyl or a phenyl substituted by halogen.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R1 and Rβ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in compounds having the formula (I-D1 or I-D2), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,


(I-D1)

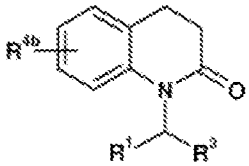

(I-D2)

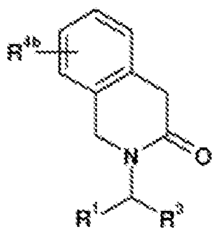
wherein

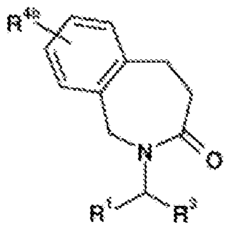
R-I is hydrogen or C-|.g alkyl, in particular hydrogen; R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl. In one embodiment, R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a more specific embodiment, R^ is 1 H-imidazol-1-yl, 1 H- imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl; R^a is hydrogen, C-|.g alkyl optionally substituted by halogen or C-1.4 alkoxy; aryl; or C2- g alkenyl optionally substituted by halogen. In a specific embodiment, R^a is C-|.g alkyl optionally substituted by halogen; aryl; or C2-6 alkenyl optionally substituted by halogen. In a more specific embodiment R^a is C-|.g alkyl optionally substituted by halogen; or aryl; e.g., propyl or phenyl;

with the proviso that when R^ and R^a are hydrogen, R^ is not 2-phenylimidazo[1 ,2- a]pyridin-3-yl.

A further aspect of the present invention consists in compounds having the formula (I-F1 , I-F2 or I-F3), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,


(I-F1)


(I-F2)


(I-F3)

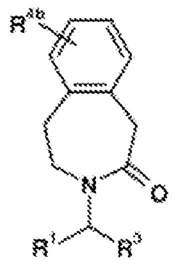
wherein

R-I is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; more preferably, R^ is hydrogen.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl; in a more specific embodiment R3 is -CONH2, 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. R^b is hydrogen; halogen; nitro; cyano; C1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen. In a more specific embodiment R^ is hydrogen, halogen or cyano, more specifically halogen.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R1 and Rβ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in compounds having the formula (I-F4), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-F4)

wherein

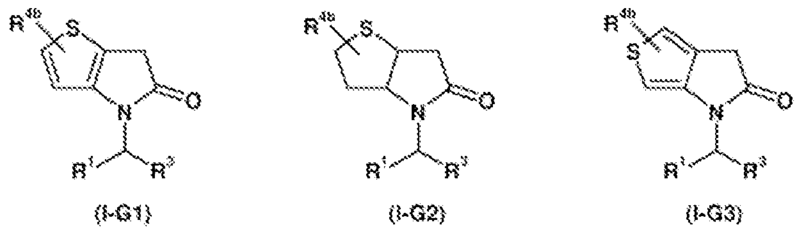
R-I is hydrogen or C-|.g alkyl, preferably hydrogen;

R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl; more specifically R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. More specifically R^ is 1 H-imidazol-4-yl or imidazo[1 ,2- a]pyridin-3-yl.

R^b is hydrogen; halogen; nitro; cyano; C-1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen; specifically R^ is hydrogen, halogen or cyano,.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in compounds having either of the formula (I-G1 , I-G2 or I-G3), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



wherein

R-I is hydrogen or C-|.g alkyl; preferably hydrogen;

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in a more specific embodiment R^ is -CONH2, 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a even more specific embodiment R3 is an 1 H-imidazol-4-yl or imidazo[1 ,2-a]pyridin-3-yl;

R4D is hydrogen; halogen; C-1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen.

Specific compounds of the present invention are those selected from the group consisting of: (2S)-2-[3-(4-nitrophenyl)-5-oxoimidazolidin-1 -yl]butanamide; (2S)-2-[3-(2,4- dinitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-(5-oxo-3-phenylimidazolidin-1- yl)butanamide; 2-[5-(iodomethyl)-2-oxo-1 ,3-oxazolidin-3-yl]butanamide; 2-(2-oxo-2,5- dihydro-1 H-pyrrol-1-yl)butanamide; 2-(2-oxo-4-phenyl-2,5-dihydro-1 H-pyrrol-1- yl)butanamide; 2-(4-methyl-2-oxo-2,5-dihydro-1 H-pyrrol-1-yl)butanamide; (2S)-2-(2-oxo-5- propyl-1 ,3-thiazol-3(2H)-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazol-3(2H)- yl)propanamide; 2-(5-butyl-2-oxo-1 ,3-thiazolidin-3-yl)butanamide; 2-(5-butyl-2-oxo-1 ,3- thiazolidin-3-yl)propanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)propanamide; 2-(2- oxo-5-propyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazolidin-3-yl)propanamide; (2S)-2-[2-oxo-5-(2,2,2- trifluoroethyl)-1 ,3-thiazolidin-3-yl]butanamide; 1-{[6-chloro-2-(trifluoromethyl)imidazo[1 ,2- b]pyridazin-3-yl]methyl}piperidin-2-one; 1 -(1 H-imidazol-4-ylmethyl)-5-propylpiperidin-2- one; 1-(1 H-imidazol-1-ylmethyl)-5-propylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3- ylmethyl)-5-propylpiperidin-

2-one; 1-(1 H-imidazol-1-ylmethyl)-5-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-5-phenylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-phenylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-5-ylmethyl)-4- propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-propylpiperidin-2-one; 1-{[6-chloro-2- (trifluoromethyl)imidazo[1 ,2-b]pyridazin-3-yl]methyl}azepan-2-one; 1 -(1 H-imidazol-5- ylmethyl)-5-propylazepan-2-one; 5-propyl-1-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}azepan-2-one; 5-phenyl-1-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3- yl]methyl}azepan-2-one; 1-(1 H-imidazol-5-ylmethyl)-6-propylazepan-2-one; 1-(1 H- imidazol-4-ylmethyl)-4-propylazepan-2-one; 4-(1 H-imidazol-4-ylmethyl)-4,6-dihydro-5H- thieno[3,2-b]pyrrol-5-one; 2-(5-oxo-5,6-dihydro-4H-thieno[3,2-b]pyrrol-4-yl)acetamide; 4- {[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5- one; 4-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}hexahydro-5H-thieno[3,2-b]pyrrol-5-one; 1-(1 H-imidazol-4-ylmethyl)-1 H-thieno[3,4-b]pyrrol-2(3H)-one; 2-(6-chloro- 2-0X0-1 ,3-benzothiazol-3(2H)-yl)acetamide; 6-bromo-3-(1 H-imidazol-1-ylmethyl)-1 ,3- benzothiazol-2(3H)-one; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6- bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6-fluoro-2-oxo-1 ,3-benzothiazol- 3(2H)-yl)acetamide; 2-(6-methyl-2-oxo-1 ,3-benzothiazol-3(2H)-yl)acetamide; 6-fluoro-3- (1 H-imidazol-1-ylmethyl)-1 ,3-benzoxazol-2(3H)-one; 1-(1 H-imidazol-4- ylmethyl)pyrazolo[1 ,5-a]pyridin-2(1 H)-one; 2-(6-chloro-3-oxo-3,4-dihydroisoquinolin- 2(1 H)-yl)propanamide; 5-chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,4-dihydroisoquinolin-3(2H)- one; 2-(6-chloro-2-oxo-3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-bromo-2-oxo-3,4- dihydroquinolin-1 (2H)-yl)acetamide; 1-(1 H-imidazol-4-ylmethyl)-3,4-dihydroquinolin-2(1 H)- one; 2-(6-iodo-2-oxo-3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-cyano-2-oxo-3,4- dihydroquinolin-1 (2H)-yl)acetamide; 7-chloro-2-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin- 3-yl]methyl}-1 ,2,4,5-tetrahydro-3H-2-benzazepin-3-one; 7-chloro-2-(1 H-imidazol-4- ylmethyl)-1 ,2,4,5-tetrahydro-3H-2-benzazepin-3-one; 7-chloro-3-(1 H-imidazol-4-ylmethyl)- 1 ,3,4,5-tetrahydro-2H-3-benzazepin-2-one; and 7-chloro-3-{[2-

(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}-1 ,3,4,5-tetrahydro-2H-3-benzazepin-2- one.

In some embodiments, compounds of the present invention are those selected from the group consisting of: 1-(1 H-imidazol-4-ylmethyl)-5-propylpiperidin-2-one; 1-(1 H-imidazol-1- ylmethyl)-5-propylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3-ylmethyl)-5-propylpiperidin-2- one; 1-(1 H-imidazol-1-ylmethyl)-5-phenylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3- ylmethyl)-4-phenylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-5-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol- 4-ylmethyl)-1 H-thieno[3,4-b]pyrrol-2(3H)-one; 6-bromo-3-(1 H-imidazol-1-ylmethyl)-1 ,3- benzothiazol-2(3H)-one; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; and 5-chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,4-dihydroisoquinolin-3(2H)-one.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly through- out the specification and embodiments unless an otherwise expressly set out definition provides a broader definition.

"C-|_β alkyl" refers to alkyl groups having 1 to 6, or 1 to 4 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert- butyl, n-pentyl, n-hexyl, trifluoromethyl and the like. "Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"Heterocycle" refers to a saturated or unsaturated ring system containing, in addition to carbon atoms, at least one hetero atom, such as nitrogen, oxygen and/or sulfur. "Heterocycle" includes both "heteroaryl" and "heterocycloalkyl".

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1 ,2,3-triazolyl, 1 ,2,4-triazolyl, 1 ,2,3-oxadiazolyl, 1 ,2,4-oxadia-zolyl, 1 ,2,5-oxadiazolyl, 1 ,3,4-oxadiazolyl,1 ,3,4-

triazinyl, 1 ,2,3-triazinyl, benzofuryl, [2,3- dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazopyridinyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8- tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl, benzoquinolyl, imidazopyrimidinyl, imidazopyridazinyl, imidazothiazolyl or imidazothiadiazolyl.

"C2-6 alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (vinyl, -CH=CH2), n-2-propenyl (allyl, -CH2CH=CH2) and the like.

"C2-6 alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH2C≡CH), and the like.

"C3.8 cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (e.g., cyclohexyl) or multiple condensed rings (e.g., norbornyl). Preferred cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl and the like.

"Heterocycloalkyl" refers to a C3.8 cycloalkyl group according to the definition above, in which 1 to 3 carbon atoms are replaced by hetero atoms chosen from the group consisting of O, S, NR, R being defined as hydrogen or C-|.g alkyl.

"Alkoxy" refers to the group -O-R where R includes " C-μg alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl".

"Amino" refers to the group -NRR' where each R, R' is independently hydrogen, "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3-8 cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"Amido" refers to the group -C(=O)NRR' where each R, R' is independently hydrogen, " C-|_5 alkyl", " C2-6 alkenyl", " C2-6 alkynyl", " C3.8 cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"Acylamino" refers to the group -NRC(O)R' wherein R and R' are as defined hereabove for the amino group.

"Ureido" refers to the group -NR"C(O)NRR' wherein R and R' are as defined hereabove for the amino group, and R" is as defined hereabove. "Sulfanyl" refers to the group -SR where R is "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

"Sulfinyl" refers to the group -S(=O)R where R is "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

"Sulfonyl" refers to the group -S(=O)2R where R is "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and

"heteroaryl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl",

"cycloalkyl", "heterocycloalkyl", "amino", "amido", "acylamino", "ureido", "aryl", "heteroaryl", "alkoxy", "halogen", cyano, hydroxy, mercapto, nitro, "amido", "sulfanyl", "sulfinyl", "sulfonyl" and the like.

The acid addition salt form of a compound of formula (I) that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, trifluoroacetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula (I) and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Many of the compounds of formula (I) and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula (I) or mixtures thereof (including all possible mixtures of stereoisomers). With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof, unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The invention also includes within its scope pro-drug forms of the compounds of formula (I) and its various sub-scopes and sub-groups.

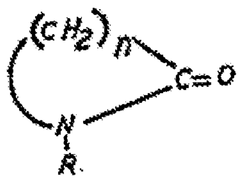
In a specific embodiment, the present invention concerns a compound selected from the group consisting of: (2S)-2-[3-(4-nitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-[3-(2,4-dinitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-(5-oxo-3- phenylimidazolidin-1 -yl)butanamide; 2-[5-(iodomethyl)-2-oxo-1

,3-oxazolidin-3- yl]butanamide; 2-(2-oxo-2,5-dihydro-1 H-pyrrol-1-yl)butanamide; 2-(2-oxo-4-phenyl-2,5- dihydro-1 H-pyrrol-1-yl)butanamide; 2-(4-methyl-2-oxo-2,5-dihydro-1 H-pyrrol-1- yl)butanamide; (+)-(2S)-2-(2-oxo-4-propyl-2,5-dihydro-1 H-pyrrol-1-yl)butanamide; (2S)-2- (2-oxo-5-propyl-1 ,3-thiazol-3(2H)-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazol-3(2H)- yl)propanamide; 2-(5-butyl-2-oxo-1 ,3-thiazolidin-3-yl)butanamide; 2-(5-butyl-2-oxo-1 ,3- thiazolidin-3-yl)propanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)propanamide; 2-(2- oxo-5-propyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazolidin-3-yl)propanamide; (2S)-2-[2-oxo-5-(2,2,2- trifluoroethyl)-1 ,3-thiazolidin-3-yl]butanamide; 1-{[6-chloro-2-(trifluoromethyl)imidazo[1 ,2- b]pyridazin-3-yl]methyl}piperidin-2-one; 1 -(1 H-imidazol-4-ylmethyl)-5-propylpiperidin-2- one; 1-(1 H-imidazol-1-ylmethyl)-5-propylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3- ylmethyl)-5-propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-5-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-5-phenylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-phenylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-5-ylmethyl)-4- propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-propylpiperidin-2-one; 1-{[6-chloro-2- (trifluoromethyl)imidazo[1 ,2-b]pyridazin-3-yl]methyl}azepan-2-one; 1 -(1 H-imidazol-5- ylmethyl)-5-propylazepan-2-one; 5-propyl-1-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}azepan-2-one; 1-(1 H-imidazol-5-ylmethyl)-5-phenylazepan-2-one; 5-phenyl-1- {[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}azepan-2-one; 1-(1 H-imidazol-5- ylmethyl)-6-propylazepan-2-one; 1-(1 H-imidazol-4-ylmethyl)-4-propylazepan-2-one; 4- (1 H-imidazol-4-ylmethyl)-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5-one; 2-(5-oxo-5,6-dihydro- 4H-thieno[3,2-b]pyrrol-4-yl)acetamide; 4-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3- yl]methyl}-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5-one; 4-{[2-(trifluoromethyl)imidazo[1 ,2- a]pyridin-3-yl]methyl}hexahydro-5H-thieno[3,2-b]pyrrol-5-one; 1 -(1 H-imidazol-4-ylmethyl)-1 H-thieno[3,4-b]pyrrol-2(3H)-one; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)acetamide; 2-(2-OXO- 1 ,3-benzothiazol-3(2H)-yl)acetamide; 2-(6-chloro-2-oxo-1 ,3-benzothiazol-3(2H)- yl)acetamide; 6-bromo-3-(1 H-imidazol-1-ylmethyl)-

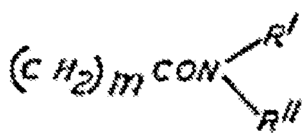
1 ,3-benzothiazol-2(3H)-one; 6-bromo- 3-(2-oxopropyl)-1 ,3-benzothiazol-2(3H)-one; 2-(6-nitro-2-oxo-1 ,3-benzothiazol-3(2H)- yl)acetamide; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6-bromo-2- oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6-fluoro-2-oxo-1 ,3-benzothiazol-3(2H)- yl)acetamide; 2-(6-methyl-2-oxo-1 ,3-benzothiazol-3(2H)-yl)acetamide; 6-fluoro-3-(1 H-imidazol-1-ylmethyl)-1 ,3-benzoxazol-2(3H)-one; 1-(1 H-imidazol-4-ylmethyl)pyrazolo[1 ,5- a]pyridin-2(1 H)-one; 2-(6-chloro-3-oxo-3,4-dihydroisoquinolin-2(1 H)-yl)propanamide; 5- chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,4-dihydroisoquinolin-3(2H)-one; 2-(6-chloro-2-oxo- 3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-bromo-2-oxo-3,4-dihydroquinolin-1 (2H)- yl)acetamide; 1-(1 H-imidazol-4-ylmethyl)-3,4-dihydroquinolin-2(1 H)-one; 2-(6-iodo-2-oxo- 3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-cyano-2-oxo-3,4-dihydroquinolin-1 (2H)- yl)acetamide; 7-chloro-2-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}-1 ,2,4,5- tetrahydro-3H-2-benzazepin-3-one; 7-chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,2,4,5- tetrahydro-3H-2-benzazepin-3-one; 7-chloro-3-(1 H-imidazol-4-ylmethyl)-1 ,3,4,5- tetrahydro-2H-3-benzazepin-2-one; and 7-chloro-3-{[2-(trifluoromethyl)imidazo[1 ,2- a]pyridin-3-yl]methyl}-1 ,3,4,5-tetrahydro-2H-3-benzazepin-2-one.

xvi) UK Patent 1,039,113

The new compounds according to the present invention are N-substituted lactams of the general formula:



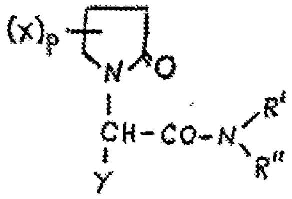
wherein N is a whole number of from 3 to 5 and R represents a



radical in which m is 0, 1 or 2 and R' is a hydrogen atom or an alkyl, cycloalkyl, alkenyl or alkynyl radical, which may contain 3 to 6 carbon atoms, or an aryl radical, and R" is a hydrogen atom or an alkyl radical, or both R' and R", together with the nitrogen atom to which they are attached, form a heterocyclic ring, such as 5 a pyrrolidine ring.

xvii) UK Patent 1,309,692

According to the present invention, there are provided new N-substituted lactams of the general formula:



wherein X is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, p is a whole number of from 1 to 6, Y is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms or a cycloalkyl radical and R' and R", which may be the same or different, are hydrogen atoms or alkyl, alkenyl, alkynyl, cycloalkyl or aryl radicals or R' and R", together with the nitrogen atom to which they are attached, form a heterocyclic radical which may contain further heteroatoms, with the proviso that at least one of the symbols X and Y is other than a hydrogen atom.

Antipsychotics

[0138] The antipsychotics suitable for use in the present invention may be any antipsychotic drugs or agents or pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof.

(1) "Typical" and "Atypical" Antipsychotics

[0139] Among the antipsychotics or pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof that are useful in the methods and compositions of this invention are atypical and typical antipsychotics.

[0140] In some embodiments, the antipsychotic is an atypical antipsychotic or pharmaceutically acceptable salts, hydrates, solvates, prodrugs and polymorphs thereof. Atypical antipsychotics offer several clinical benefits including, for example, superior side effect profiles, particularly with regard to extrapyramidal side effects (EPS). Atypical antipsychotics typically differ from typical antipsychotics in their "limbic-specific" dopamine type 2 (D2)-receptor binding. Atypical antipsychotics, also display a high ratio of serotonin type 2 (5-HT2)-

receptor binding to D2 binding. Atypical antipsychotics have high affinity for the 5-HT2-receptor and function as antagonists of serotonin for the 5-HT2-receptor.

[0141] Examples of atypical antipsychotics include, but are not limited to:

Aripiprazole, 7-[4-[4-(2,3-dichloropheny1)-1-piperazinyl]butoxy]-3,4-di-hydrocarbostyril (commercially available from Bristol-Meyers Squibb Co., Princeton, NJ under the trade name Ability®) is disclosed in U.S. Patents No. 4,734,416 and 5,006,528, which are incorporated herein by reference. Exemplary formulations and dosages of aripiprazole suitable for use in treating schizophrenia and bipolar disorder are described in U.S. Patents 6,977,257; 7,115,587; and 7,550445, which are herein incorporated by reference in their entirety.

Asenapine, trans-5- chloro-2-methyl-2,3,3a,12b-tetrahydro-1 H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole (under trade name Saphris® or Sycrest®) is disclosed in U.S. Patents 4,145,434 and 5,763,476, which are herein incorporated by reference in their entirety. An orthorhombic crystal form of asenapine is described in U.S. Patent 7,741,358, which is also incorporated herein by reference.

Clozapine, 8-chloro-11-(4-methyl-l-piperaziny1)-5H-dibenzo[b,e][1,4]-diazepine (commercially available from Mylan Pharmaceuticals, Morgantown, WV under the trade name Mylan®) is disclosed in U.S. Patent No. 3,539,573, which is herein incorporated by reference. Clinical efficacy of Clozapine in the treatment of schizophrenia has previously been disclosed. Hanes, et al., Psychopharmacol. Bull., 24, 62 (1988).

Iloperidone, 1-[4-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone (under trade name Fanapt®) is disclosed in EP Patent EP402644, which is incorporated herein by reference. The use of iloperidone in treating psychotic symptom and exemplary dosages of iloperidone suitable for such treatment are disclosed in U.S. Patent USRE39198, which is incorporated herein by reference.

Olanzapine, 2-methy1-4-(4-methyl-1-piperaziny1)-10H-thieno [2,3-b][1,5]benzodiazepine, disclosed in U.S. Patent No. 5,229,382 (commercially available from Eli Lilly, Indianapolis, IN under the trade name Zyprexa®) which is hereby incorporated by reference, as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. The use of olanzapine in treating schizophrenia and exemplary dosages of olanzapine for such use are disclosed in U.S. Patents 5,625897, 5627178, 5,817655, 5,919485 and 6960577. Olanzapine polymorphs are disclosed in U.S. Patent 5,736,541, incorporated herein by reference. Olanzapine hydrate forms are disclosed in U.S. Patent 6,251,895, incorporated herein by reference.

Lurasidone, (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)-piperazin-1-yl-methyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione (developed by Dainippon Sumitomo Pharma Co., Ltd. under trade name Latuda®) is disclosed in U.S. Patent 5,532,372, incorporated herein by reference.

Paliperidone, 3-[2-[4-(6-fluoro-l,2-benzisoxazol-3-yl)-l-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4Hpyrido[l,2-a]pyrimidin-4-one (developed by Janssen Pharmaceutica under the trade name Invega® or Invega sustenna®), is disclosed in EP Patent 368388. The use of paliperidone in treating psychosis and exemplary formulations for such use are disclosed in U.S. Patents 5,158,952, 5,254,556, 5,352459, 6,077,843 and 6,555,544, all of which are incorporated herein by reference.

Quetiapine, 5-[2-(4-dibenzo[b,f] [1,4] thiazepin-11-y1-1-piperaziny1)-eth-oxy]ethanol (commercially available from Astra Zeneca, Wilmington, DE under the tradename Seroquel®) its activity in assays which demonstrate utility in the treatment of schizophrenia are disclosed in U.S. Patent No. 4,879,288, which is herein incorporated by reference. Exemplary formulations of quetiapine for use in treating schizophrenia and bipolar disorder are disclosed in U.S. Patent 5,948,437, incorporated herein by reference.

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one (commercially available from Janssen under the trade name Risperdal®) and its use in the treatment of psychotic diseases are disclosed in U.S. Patent No. 4,804,663, which is herein incorporated by reference.

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluoropheny1)-1H-indol-3-y1]- 1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patents No. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety.

Ziprasidone, 5- [2-[4-(1,2-benzoisothiazol-3-y1)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, (commercially available from Pfizer Inc., New York, NY under the trade name Geodon®) is disclosed in U.S. Patents No. 4,831,031 and 5,312,925 and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031, all of which are herein incorporated by reference.

Surmontil (trimipramine maleate), 5-(3-dimethylamino-2-methylpropy1)-10,11-dihydro-5H-dibenz (b,f) azepine acid maleate (Commercially available from Odyssey Pharmaceuticals, Inc., North Hanover, NJ under the trade name Surmotil®).

[0142] In some embodiment, the antipsychotic for the methods and compositions of this invention is selected from aripiprazole, olanzapine and ziprasidone, or pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof.

[0143] In some embodiments of the invention, the antipsychotic is a typical antipsychotic. Such typical antipsychotics include, but are not limited to, acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol, and pharmaceutically acceptable salts, hydrates, solvates, prodrugs and polymorphs thereof.

(2) Antipsychotics Displaying Various Pharmacology/Mechanisms

[0144] Suitable antipsychotics or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof for the present invention may be selected from compounds/agents that are dopaminergic agents, glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs) (e.g., mGluR2/3 agonists or PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents, serotonin receptor modulators, cholinergic agents, cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, nNOS inhibits, neurosteroids, and neurotrophic factors.

[0145] In some embodiments, the antipsychotic is a dopaminergic agent selected from dopamine D1 receptor antagonists or agonists (for example, dihydrexidine, A77636 and SKF81297), dopamine D_2 receptor antagonists or partial agonists (e.g., some typical and atypical antipsychotics), dopamine D3 receptor antagonists or agonists (for example, S33084, SB-277011-A, AVE5997 and (±)-PD128907), dopamine D4 receptor antagonists (for examples, clozapine and sonepiprazole (U-101387 or PNU-101387G)).

[0146] In some embodiments, the antipsychotic is a glutamatergic agent selected from NMDA receptor positive allosteric modulators (e.g., glycine, D-cycloserine and D-serine), glycine reuptake inhibitors (e.g., N-(3-(4'-fluorophenyl)-3-(4'-phenylphenoxy)propyl) sarcosine and glycyldodecylamide) , glutamate reuptake inhibitor (e.g., excitatory amino-acid transporters EAAT3 antagonists), metabotropic glutamate receptors agonists (e.g., LY-354740), AMPA/kainate receptor antagonists (e.g., LY-293558, GYKI52466 and LY-326325), ampakines (CX-516), and glutathione prodrugs.

[0147] In some embodiments, the antipsychotic is a noradrenergic agent selected from alpha-2 adrenergic receptor agonists or antagonists (e.g., guanfacine, clozapine and risperidone) and COMT inhibitors (e.g., tolcapone).

[0148] In some embodiments, the antipsychotic is a serotonin receptor modulator selected from 5-HT_{2A} receptor antagonists, 5-HT_{1A} receptor partial agonists, 5-HT_{2C} agonists, and 5-HT6 antagonists (e.g., some atypical antipsychotics).

[0149] In some embodiments, the antipsychotic is a cholinergic agent selected from alpha-7 nicotinic receptor agonists (e.g., 3-2,4-dimethoxybenzylidene anabaseine (DMXB-A or GTS-21)), alpha4-beta2 nicotinic receptor agonists (e.g., SIB-1553A), allosteric modulators of nicotinic receptors and acetylcholinesterase inhibitors, muscarinic receptor agonists and antagonists (e.g., N-desmethylclozapine, xanomeline, PTAC, and BuTAC).

[0150] In some embodiments, the antipsychotic is selected from cannabinoid CB1 antagonists (e.g., SR141716) , neurokinin 3 antagonists (e.g., osanetant (SR-142801) and talnetant), neurotensin agonists (e.g., SR-48692), MAO B inhibitors (e.g., Selegiline (deprenyl) and rasagiline), PDE10 inhibitors (e.g., Papaverine), NNOS inhibits (e.g., methylene blue, LNOARG, L-NAME, and 7-nitroindazole), neurosteroids (e.g., dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S), pregnenolone (PREG) and pregnenolone sulfate (PREGS)), and neurotrophic factors (e.g., nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin (NT)-3/4/5)).

<u>(3) Antipsychotics Useful for Treating Symptoms of Schizophrenia or Bipolar Disorder (in particular, mania)</u>

[0151] In some embodiments, the antipsychotics or pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof that are useful in the methods and compositions of this invention include those that are useful in treating one or more signs or symptoms of schizophrenia or bipolar disorder (in particular, mania).

[0152] Schizophrenia is characterized by psychological symptoms such as perception (hallucinations), ideation, reality testing (delusions), thought processes (loose associations), feeling (flatness, inappropriate effect) , behavior (catatonia, disorganization), attention, concentration, motivation (avolition, impaired intentions and planning) and judgment (see for example Diagnostic and Statistical Manual of Mental Disorders IV, American Psychiatric Association). In general, the symptoms of schizophrenia are divided into positive and negative symptoms with hallucinations and delusions being positive features, and features such as flatness, poverty of speech and impaired executive functions representing negative symptoms. Clinical rating scales such as Positive and Negative Syndrome Scale and Scale for the Assessment of Negative Symptoms provide criteria to differentiate between, and rate, positive and negative symptoms. Frequently included in the description of negative symptoms are the cognitive deficits schizophrenic and schizotypical patients suffer from. These include impairment in attention, verbal fluency, executive functions such as planning, working memory and visual and verbal learning and memory. These types of cognitive dysfunction can be measured with a variety of tests, such as Visual Search, Verbal Fluency, Wisconsin Card Sorting, Trail Making - Part B, Symbol Digit, Hopkins Verbal Learning, Digit Span, Stroop-Color-Word and Attentional Capacity. MATRICS consensus neuropsychological test battery which includes tests of working memory, speed of processing, attention, verbal learning, visual learning, reasoning and problem solving and social cognition. Moreover, it has been found that cognitive measures predict work function and overall outcome as assessed by the Global Assessment Scale and Quality of Life Scale. Several studies have now demonstrated that neuropsychological functions, reflecting several negative and cognitive symptoms of the disease, may be more impaired in male schizophrenic patients when compared to female patients. Further, there are a number of other psychiatric diseases such as schizotypical and schizoaffective disorder, other acute- and chronic psychoses and bipolar disorder which have an overlapping symptomatology with schizophrenia. Any compounds or pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof that are useful in treating at least one of the signs or symptoms of schizophrenia or bipolar disorder (in particular, mania), including, for example, those recited above, are useful in the methods and compositions of this invention.

[0153] Among the antipsychotics or pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof that are useful in the methods and compositions of this invention are those disclosed, for example, in U.S. Patents 4,734,416; 5,006,528; 4,145,434; 5,763,476; 3,539,573; 5,229,382; 5,532,372; 4,879,288; 4,804,663; 4,710,500; 4,831,031; and 5,312,925, and EP Patents EP402644 and EP368388, and the pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof.

[0154] In some embodiments, the antipsychotics useful in this invention include those compounds/agents disclosed, for example, in U.S. Patents or Patent Publications US20020052401A1; US20020091118A1; US20020091119A1;

US20020094986A1; US20020123490A1; US20020147194A1; US20020156089A1; US20020165217A1; US20030008806A1; US20030008892A1; US20030013887A1; US20030018047A1; US20030027812A1; US20030032579A1; US20030130303A1; US20030158208A1; US20030162766A1; US20030181458A1; US20030191176A1; US20030208081A1; US20030232841A1; US20030235631A1; US20040001895A1; US20040006135A1; US20040029876A1; US20040039022A1; US20040048869A1; US20040049039A1; US20040082597A1; US20040106603A1; US20040110817A1; US20040116443A1; US20040132713A1; US20040138232A1; US20040162293A1; US20040162294A1; US20040167200A1; US20040204414A1; US20040204415A1; US20040204445A1; US20040204453A1; US20040209887A1; US20040220184A1; US20040220274A1; US20040229874A1; US20040229911A1; US20040242587A1; US20040254193A1; US20040259859A1; US20040266781A1; US20040266815A1; US20050004106A1; US20050004137A1; US20050009927A1; US20050014764A1; US20050014848A1; US20050026937A1; US20050026946A1; US20050032837A1; US20050038036A1; US20050043292A1; US20050070577A1; US20050080099A1; US20050080100A1; US20050101613A1; US20050107425A1; US20050113437A1; US20050143403A1; US20050171086A1; US20050171095A1; US20050182049A1; US20050203296A1; US20050209250A1; US20050215571A1; US20050227980A1; US20050227981A1; US20050234065A1; US20050245521A1; US20050245543A1; US20050250803A1; US20050256112A1; US20050256162A1; US20050282811A1; US20050282816A1; US20050288304A1; US20060014733A1; US20060019998A1; US20060025421A1; US20060047114A1; US20060052373A1; US20060058361A1; US20060069087A1; US20060084692A1; US20060094719A1; US20060148807A1; US20060166974A1; US20060166998A1; US20060173179A1; US20060183763A1;

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US5710168A; US5716965A; US5721255A; US5731307A; US5736541A; US5741797A; US5744480A; US5747501A; US5789423A; US5817656A; US5821248A; US5837711A; US5849739A; US5854232A; US5854239A; US5854256A; US5886008A; US5889010A; US5912256A; US5939433A; US5942524A; US5958921A; US5985322A; US5994352A; US6020335A; US6043258A; US6046193A; US6046213A; US6060479A; US6083943A; US6087392A; US6110918A; US6110919A; US6117890A; US6127373A; US6143767A; US6147072A; US6150366A; US6150388A; US6166020A; US6166064A; US6172073B1; US6174895B1; US6194454B1; US6197773B1; US6235734B1; US6235747B1; US6245765B1; US6245766B1; US6284771B1; US6312717B1; US6323208B1; US6326398B1; US6329396B1; US6358950B1; US6369074B1; US6380186B1; US6380233B1; US6395735B2; US6395784B1; US6399609B1; US6410739B1; US6429317B1; US6433009B1; US6436914B1; US6436938B1; US6441015B2; US6444665B1; US6448261B1; US6462048B2; US6465491B2; US6476051B2; US6506775B1; US6515005B2; US6518271B1; US6525048B1; US6525196B1; US6545018B2; US6545022B1; US6548493B1; US6548502B2; US6552017B1; US6596900B2; US6620830B2; US6627771B1; US6630469B2; US6630476B2; US6632831B2; US6635270B2; US6638934B2; US6673811B1; US6686361B2; US6710040B1; US6710071B2; US6713490B2; US6734185B2; US6777406B2; US6777437B2; US6784180B2; US6818648B2; US6821976B2; US6835733B2; US6844344B2; US6849619B2; US6875771B2; US6888004B2; US6894045B2; US6900210B2; US6924310B2; US6936601B2; US6958351B2; US6960577B2; US6992087B2; US7015229B2; US7030145B2; US7041672B2; US7045529B2; US7045551B2; US7049314B2; US7053122B2; US7067658B2; US7087609B2; US7098217B2; US7101881B2; US7101885B2; US7105516B2; US7109164B2; US7112585B2; US7115587B2; US7115600B2; US7135472B2; US7144881B2; US7144898B2; US7157488B2; US7238699B2; US7276526B2; US7319100B2; US7345038B2; US7384934B2; US7439236B2; US7485636B2; US7553836B2; US7662817B2; US7671072B2; US7678793B2; US7709522B2; US7851622B2; US7932249B2; US7956049B2; US7973159B2; US8022062B2; US8124639B2; USRE039679E; in EP Patents or Patent Publications EP1033364B1; EP104860B1; EP106486A2; EP106487A2;

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Method of Treating Schizophrenia or Bipolar Disorder (in particular, mania)with the Administration of an SV2A inhibitor and an Antipsychotic or Pharmaceutically Acceptable Salts Thereof

[0155] In one aspect, the invention provides methods for treating a subject suffering from schizophrenia or bipolar disorder (in particular, mania), or at risk thereof, by administering an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in combination with an antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. In some embodiments, the methods of this invention treat one or more positive and/or negative symptoms, as well as cognitive impairment, associated with schizophrenia In some embodiments, the methods of this invention treat one or more symptoms, as well as cognitive impairment, associated with bipolar disorder (in particular, mania)..

[0156] The SV2A inhibitor and the antipsychotic suitable for the method of this invention may be selected from any of those as described above. In some embodiments, the SV2A inhibitor is selected from any of those described above; and the antipsychotic is selected from (1) atypical and typical antipsychotics (such as those described above); (2) agents that are dopaminergic agents (such as dopamine D1 receptor antagonists or agonists, dopamine D_2 receptor antagonists or partial agonists, dopamine D3 receptor antagonists or partial agonists, dopamine D4 receptor antagonists), glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs) (e.g., mGluR2/3 agonists or PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents (such as alpha-2 adrenergic receptor agonists or antagonists and COMT inhibitors), serotonin receptor modulators (such as 5-HT_{2A} receptor antagonists, 5-HT_{1A} receptor partial agonists, 5-HT_{2C} agonists, and 5-HT6 antagonists), cholinergic agents (such as alpha-7 nicotinic receptor agonists, alpha4-beta2 nicotinic receptor agonists, allosteric modulators of nicotinic receptors and acetylcholinesterase inhibitors, muscarinic receptor agonists and antagonists), cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, nNOS inhibits, neurosteroids, and neurotrophic factors, including, e.g., those specific such agents as described above, and (3) any compounds that are useful in treating one or more sign or symptoms of schizophrenia or bipolar disorder (in particular, mania) (including, e.g., the agents disclosed in any of the above-listed patents or patent application publications), and pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof. In some embodiments, the SV2A inhibitor is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam or derivatives or analogs or pharmaceutically acceptable salts, or solvates, or hydrates, or polymorphs, or prodrugs thereof; and the antipsychotic is an atyptical antipsychotic selected from, e.g., aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof. In some embodiments, the SV2A inhibitor is selected from levetiracetam or derivatives or analogs or pharmaceutically acceptable salts, or solvates, or hydrates, or polymorphs, or prodrugs thereof; and the antipsychotic is an atyptical antipsychotic selected from, e.g., aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof.

[0157] In some embodiments, the subject that suffers schizophrenia or bipolar disorder (in particular, mania) is a human patient. The subject may be a human or other mammal such as a non-human primate, or rodent (e.g., rat). In some embodiments, the subject is a human patient.

[0158] In some embodiments, the use of the SV2A inhibitors and pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof in combination with antipsychotics and their pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs may reduce the amount of antipsychotics necessary for the treatment of schizophrenia or bipolar disorder (in particular, mania). In some embodiments, the subject that suffers schizophrenia or bipolar disorder (in particular, mania) is a human patient, and thus the use of the SV2A inhibitors reduce the side effects caused by antipsychotics without diminishing efficacy. Further, in some embodiments, the efficacy of a combination of the SV2A inhibitors and antipsychotics and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, and prodrugs thereof exceeds the efficacy of either drug administered alone at its optimal dose and thus, is an improved treatment for schizophrenia or bipolar disorder (in particular, mania).

[0159] It will be appreciated that compounds and agents used in the compositions and methods of this invention preferably should readily penetrate the blood-brain barrier when peripherally administered. Compounds which cannot penetrate the blood-brain barrier, however, can still be effectively administered directly into the central nervous system, e.g., by an intraventricular or other neuro-compatible routes.

[0160] As used herein, administration of SV2A inhibitor and an antipsychotic or pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof "in combination" includes simultaneous administration and/or administration at different times, such as sequential administration. Simultaneous administration of the SV2A inhibitor and the antipsychotic or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs can optionally be combined with supplemental doses of the SV2A inhibitor and/or the antipsychotic and their salts, hydrates, solvates, polymorphs and prodrugs. Simultaneous administration of drugs encompasses administration as co-formulation or, alternatively, as separate compositions.

[0161] In accordance with this invention, the SV2A inhibitor and the psychotic, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs thereof, can be administered to a subject via any suitable route or routes. In some embodiments, the drugs are administered orally; however, administration intravenously, subcutaneously, intra-arterially, intramuscularly, intraspinally, rectally, intrathoracically, intraperitoneally, intracentricularly, or transdermally, topically, or by inhalation is also contemplated. The agents can be administered orally, for example, in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, or the like, prepared by art recognized procedures. In certain embodiments, the SV2A inhibitor and the antipsychotic, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs thereof, can be administered to a subject via different routes. For example, the SV2A inhibitor or its salt, solvate, hydrate, or polymorph is administered intravenously and the antipsychotic or its salt, solvate, hydrate, or polymorph is administered orally.

[0162] In some embodiments, the administration is a slow or extended release. The term “extended release” is widely recognized in the art of pharmaceutical sciences and is used herein to refer to a controlled release of an active compound or agent from a dosage form to an environment over (throughout or during) an extended period of time, e.g. greater than or equal to one hour. An extended release dosage form will release drug at substantially constant rate over an extended period of time or a substantially constant amount of drug will be released incrementally over an extended period of time. The term “extended release” used herein includes the terms “controlled release,” “prolonged release,” “sustained release,” “delayed release,” or “slow release” as these terms are used in the pharmaceutical sciences. In some embodiments, the extended release dosage is administered in the form of a patch or a pump. The term “extended release form”, as used herein, may refer to a dosage form that contains one or more active ingredients, where the release of at least one of the active ingredient, when placed in water or other biological fluids or solvents, may occur over an extended period, such as a period of at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 10 days, at least about 20 days, at least about 30 days, at least about 60 days, at least about 90 days, or at least about 150 days.

[0163] As used herein, “immediate release formulation” refers to a formulation of an active pharmaceutical ingredient that releases greater than 80 percent of the active pharmaceutical ingredient in less than one hour in a USP dissolution method known in the art or by the manufacturer for a commercial product. Typically, the release of the active ingredient in an immediate release formulation is greater than 80 percent in less than 30 minutes.

[0164] When a solid carrier is used for administration, the preparation may be in a tablet, placed in a hard gelatin capsule in powder or pellet form, or it may be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the forms of a syrup, emulsion, soft gelatin capsule, or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

[0165] Dosage schedules of the agents and compositions according to the methods of the invention will vary according to the particular compound or compositions selected, the route of administration, the nature of the condition being treated, the age, and condition of the patient, the course, or stage of treatment, and will ultimately be at the discretion of the attending physician. It will be understood that the amount of the SV2A inhibitor and the antipsychotic and their pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof administered will be amounts effective to produce a desired biological effect, such as beneficial results, including clinical results. It will be understood that an effective amount can be administered in more than one dose and over a course of treatment.

[0166] Desired duration of administration of the SV2A inhibitor and the antipsychotic and their pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof can be determined by routine experimentation by one skilled in the art. For example, the SV2A inhibitor and the antipsychotic and their pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof may be administered for a period of 1-4 weeks, 1-3 months, 3-6 months, 6-12 months, 1-2 years, or more, up to the lifetime of the patient.

[0167] It is known in the art that normalization to body surface area is an appropriate method for extrapolating doses between species. The human equivalent dose (HED) for this dosage can be estimated using the following formula that accounts for differences in body surface area (see Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, December 2002, Center for Biologics Evaluation and Research):

HED = animal dose X (Km animal / Km human) where the Km factor is body weight divided by body surface area (Km rat has been determined as 6, and Km human is 37; see Reagan-Saw, Nihal, Ahmad, 2007). Thus, a dosage of 10 mg/kg in rats is equivalent to 1.6 mg/kg in humans (10 mg/kg X (6 / 37) = 1.6 mg/kg). For human subjects, to calculate a dose in mg from the dose in mg/kg, the dose in mg/kg is multiplied by a typical adult weight of 70 kg.

[0168] The HED calculation is based on body surface area. As a result, it is an estimate of what human dose corresponds to an animal (*e.g.*, rat) dose in the context of a maximum safe starting dose for clinical trials in humans. Calculating the HED is typically an initial step in carrying out the clinical trial of a drug in humans. It is not an indication of the ultimate human therapeutic dose. See, "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Health Volunteers, December 2002, Center for Biologics Evaluation and Research." Blood/plasma levels are a far better predictor of therapeutic dose correspondence between animals (*e.g.*, rats) and humans.

[0169] In certain embodiments of the invention, the dose of the SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is 0.1 to 5 mg/kg/day (which, given a typical human subject of 70 kg, is 7 to 350 mg/day).

[0170] In certain embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, and prodrugs thereof can be administered at doses according to, for example, United States (U.S.) Patent Application 12/580,464 (Pub. No. US-2010-0099735), U.S. Patent Application 13/287,531 (Pub. No. US-2012-0046336), U.S. Patent Application 13/370,253 (Pub. No.US-2012-0214859), International Patent Application PCT/US2009/005647 (Pub. No. WO2010/044878), International Patent Application PCT/US12/24556 (Pub. No. WO2012/109491), U.S. Patent Application 61/105,847, U.S. Patent Application 61/152,631, U.S. Patent Application 61/175,536, and U.S. Patent Application 61/441,251. In certain embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, and prodrugs thereof is administered every 12 or 24 hours at a daily dose of about 0.001 mg/kg to 5 mg/kg. In some embodiments, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, and prodrugs thereof is administered every 12 or 24 hours at a daily dose of about 0.1 to 5 mg/kg, or about 1 to 2 mg/kg, or about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5 mg/kg, or about

0.6 to 1.8 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 0.01 to 1 mg/kg, or about 0.001 to 1 mg/kg, or about 0.5 to 5 mg/kg, or about 0.05 to 0.5 mg/kg. In certain embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered every 12 or 24 hours at a daily dose of about 0.001 to 5 mg/kg, about 0.001 to 0.5 mg/kg, about 0.01 to 0.5 mg/kg, about 0.1 to 5 mg/kg, or about 1 to 2 mg/kg, or about 2 to 4 mg/kg, or about 2 to 3 mg/kg, or about 3 to 4 mg/kg, or about 0.2 to 0.4 mg/kg, or about 0.2 to 0.3 mg/kg, or about 0.3 to 0.4 mg/kg, or about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5 mg/kg, or about 0.6 to 1.8 mg/kg, or about 0.5 to 2 mg/kg, or about 0.8 to 1.6, or about 0.8 to 3.6, or about 0.5 to 4 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 0.05 to 3 mg/kg or about 0.08 to about 1.6 mg/kg, or about 0.08 to 3.6 or about 0.05 to 2 mg/kg, or about 0.01 to 1 mg/kg, or about 0.001 to 1 mg/kg, or about 0.5 to 5 mg/kg, or about 0.05 to 0.5 mg/kg, or about 0.8 mg/kg, or about 1.6 mg/kg, or about 3.6 mg/kg, or about 0.08 mg/kg, or about 0.16 mg/kg, or about 0.36 mg/kg. Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention. For repeated administrations over several days or weeks or longer, depending on the condition, the treatment is sustained until a sufficient level of cognitive function is achieved.

[0171] In certain embodiments of the invention, the dose of the SV2A inhibitor is 0.001 - 5 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.07 - 350 mg/day). Doses that may be used include, but are not limited to 0.001 mg/kg/day, 0.0015 mg/kg/day, 0.002 mg/kg/day, 0.005 mg/kg/day, 0.0075 mg/kg/day, 0.01 mg/kg/day, 0.015 mg/kg/day, 0.02 mg/kg/day, 0.03 mg/kg/day, 0.04 mg/kg/day, 0.05 mg/kg/day, 0.1 mg/kg/day, 0.2 mg/kg/day, 0.3 mg/kg/day, 0.4 mg/kg/day, 0.5 mg/kg/day, 0.75 mg/kg/day, 1.0 mg/kg/day, 1.5 mg/kg/day, 2.0 mg/kg/day, 2.5 mg/kg/day, 3.0 mg/kg/day, 4.0 mg/kg/day, or 5.0 mg/kg/day. In some embodiments, the dose of the SV2A inhibitor is 0.001 – 0.5 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.07 – 35 mg/day), or 0.01 – 0.5 mg/kg/day (which is about 0.7 – 35 mg/day). Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[0172] In certain embodiments of the invention, the dose of the SV2A inhibitor is 0.1 to 5 mg/kg/day (which, given a typical human subject of 70 kg, is 7 to 350 mg/day). Doses that may be used include, but are not limited to 0.1 mg/kg/day, 0.5 mg/kg/day, 1 mg/kg/day, 1.5 mg/kg/day, 2 mg/kg/day, 2.5 mg/kg/day, 3 mg/kg/day, 4 mg/kg/day, or 5 mg/kg/day. In certain embodiments, the dose is 1-2 mg/kg/day (which, given a typical human subject of 70 kg, is 70-140 mg/day). In other embodiments of the invention, the dose of the SV2A inhibitor is 0.1 to 0.2 mg/kg/day. Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[0173] In certain embodiments of the invention, the dose of the SV2A inhibitor is 0.01 to 2.5 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.7 - 180 mg/day). Doses that may be used include, but are not limited to 0.01 mg/kg/day, 0.02 mg/kg/day, 0.03 mg/kg/day, 0.04 mg/kg/day, 0.06 mg/kg/day, 0.08 mg/kg/day, 0.12 mg/kg/day, 0.14 mg/kg/day, 0.16 mg/kg/day, 0.18 mg/kg/day, 0.2 mg/kg/day, 0.4 mg/kg/day, 0.6 mg/kg/day, 0.8 mg/kg/day, 1.0 mg/kg/day, 1.2 mg/kg/day, 1.4 mg/kg/day, 1.6 mg/kg/day, 1.8 mg/kg/day, 2.0 mg/kg/day, 2.2 mg/kg/day, 2.4 mg/kg/day, or 2.5 mg/kg/day. In some embodiments, the dose of the SV2A inhibitor is 0.1 – 2.5 mg/kg/day (which, given a typical human subject of 70 kg, is about 7 – 180 mg/day), 0.1 – 0.2 mg/kg/day (which is about 7 – 15 mg/day), 0.2 – 0.4 mg/kg/day (about 14 – 30 mg/day), 0.4 – 2.5 mg/kg/day (about 25 – 180 mg/day), 0.6 – 1.8 mg/kg/day (about 40 – 130 mg/day), 0.04 – 2.5 mg/kg/day (about 2.5 – 180 mg/day) or 0.06 – 1.8 mg/kg/day (about 4 – 130 mg/day). In some embodiments of the invention, the dose of the SV2A inhibitor is 40 to 130 mg, 140 to 300 mg, 200 to 300 mg or 140 to 200 mg. Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[0174] In certain embodiments of the invention, the dose of the SV2A inhibitor is 0.0015 to 7 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.1 - 500 mg/day). Daily doses that may be used include, but are not limited to 0.0015 mg/kg, 0.002 mg/kg, 0.0025 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1 mg/kg, 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.8 mg/kg, 2.0 mg/kg, 2.2 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.8 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 6.0 mg/kg, or 7.0 mg/kg; or 0.1 mg, 0.15 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.8 mg, 3.0 mg, 3.5 mg, 4.2 mg, 5 mg, 5.5 mg, 6.0 mg, 7 mg, 8 mg, 9 mg, 10 mg, 12 mg, 15 mg, 20 mg, 25 mg, 28 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 125 mg, 140 mg, 150 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 225 mg, 250 mg, 280 mg, 300 mg, 350 mg, 400 mg, or 500 mg. In some embodiments, the daily dose of SV2A inhibitor that can be used in the methods of this invention include, without limitation, 0.0015 - 5 mg/kg (or 0.1 - 350 mg for a subject of 70kg), 0.01 - 0.8 mg/kg, 0.01 - 1 mg/kg, 0.01 - 1.5 mg/kg, 0.01 - 2 mg/kg, 0.01 - 2.5 mg/kg, 0.01 - 3 mg/kg, 0.01 - 3.5 mg/kg, 0.01 - 4 mg/kg, 0.01 - 5 mg/kg, 0.025 - 0.8 mg/kg, 0.025 - 1 mg/kg, 0.025 - 1.5 mg/kg, 0.025 - 2 mg/kg, 0.025 - 2.5 mg/kg, 0.025 - 3 mg/kg, 0.025 - 3.5 mg/kg, 0.025 - 4 mg/kg, 0.05 - 0.8 mg/kg, 0.05 - 1 mg/kg, 0.05 - 1.5 mg/kg, 0.05 - 2 mg/kg, 0.05 - 2.5 mg/kg, 0.05 - 3 mg/kg, 0.05 - 3.5 mg/kg, 0.05 - 4 mg/kg, 0.075 - 0.8 mg/kg, 0.075 - 1 mg/kg, 0.075 - 1.5 mg/kg, 0.075 - 2 mg/kg, 0.075 - 2.5 mg/kg, 0.075 - 3 mg/kg, 0.075 - 3.5 mg/kg, 0.075 - 4 mg/kg, 0.1 - 0.8 mg/kg, 0.1 - 1 mg/kg, 0.1 - 1.5 mg/kg, 0.1 - 2 mg/kg, 0.1 - 2.5 mg/kg, 0.1 - 3 mg/kg, 0.1 - 3.5 mg/kg, 0.1 - 4 mg/kg, 0.2 - 0.8 mg/kg, 0.2 - 1 mg/kg, 0.2 - 1.5 mg/kg, 0.2 - 2 mg/kg, 0.2 - 2.5 mg/kg, 0.2 - 3 mg/kg, 0.2 - 3.5 mg/kg, 0.2 - 4 mg/kg, 0.5 - 0.8 mg/kg, 0.5 - 1 mg/kg, 0.5 - 1.5 mg/kg, 0.5 - 2 mg/kg, 0.5 - 2.5 mg/kg, 0.5 - 3 mg/kg, 0.5 - 3.5 mg/kg, or 0.5 - 4 mg/kg; or 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg. Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[0175] In certain embodiments of the invention, the interval of administration is 12 or 24 hours. Administration at less frequent intervals, such as once every 6 hours, may also be used. In some embodiments, the SV2A inhibitor is administered every 12 or 24 hours at a total daily dose of 0.1 to 5 mg/kg (e.g., in the case of administration every 12 hours of a daily dose of 2 mg/kg, each administration is 1 mg/kg). In some embodiments, the SV2A inhibitor is administered every 24 hours at a daily dose of 1 to 2 mg/kg. In another embodiment, the SV2A inhibitor is administered every 24 hours at a daily dose of 0.1 – 0.2 mg/kg. In some embodiments, the SV2A inhibitor is administered every 12 or 24 hours at a daily dose of 0.01 to 2.5 mg/kg (e.g., in the case of administration every 12 hours of a daily dose of 0.8 mg/kg, each administration is 0.4 mg/kg). In some embodiments, the SV2A inhibitor is administered every 12 or 24 hours at a daily dose of 0.1 to 2.5 mg/kg. In some embodiments, the SV2A inhibitor is administered every 12 or 24 hours at a daily dose of 0.4 to 2.5 mg/kg. In some embodiments, the SV2A inhibitor is administered every 12 or 24 hours at a daily dose of 0.6 to 1.8 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered every 12 or 24 hours at a daily dose of 0.04 – 2.5 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered every 12 or 24 hours at a daily dose of 0.06 –1.8 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered every 12 or 24 hours at a daily dose of 0.001 –5 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered every 12 or 24 hours at a daily dose of 0.001 – 0.5 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered every 12 or 24 hours at a daily dose of 0.01 – 0.5 mg/kg.

[0176] In certain embodiments of the invention, the SV2A inhibitor is levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. The levetiracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered every 12 or 24 hours at a daily dose of about 1 to 2 mg/kg, or about 0.1 to 2.5 mg/kg, or about 0.4 to 2.5

mg/kg, or about 0.6 to 1.8 mg/kg, or about 2.0 to 3.0 mg/kg, or about 3.0 to 4.0 mg/kg, or about 2.0 to 4.0 mg/kg, or about 0.1 to 5 mg/kg, or about 70 to 140 mg, or about 7 to 180 mg, or about 25 to 180 mg, or about 40 to 130 mg, or about 140 to 300 mg, or about 200 to 300 mg, or about 140 to 200 mg, or about 7 to 350 mg.

[0177] In other embodiments, the levetiracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered every 12 or 24 hours according to one of the daily dose ranges indicated as "+" listed in Table 1 or Table 2.

Table 1 - Daily Doses of Levetiracetam (mg/kg)

Lower range / Upper range	0.1 mg/kg	0.4 mg/kg	0.6 mg/kg	1 mg/kg	2 mg/kg	3 mg/kg
1.8 mg/kg	+	+	+	+		
2 mg/kg	+	+	+	+		
2.5 mg/kg	+	+	+	+	+	
3 mg/kg	+	+	+	+	+	
4 mg/kg	+	+	+	+	+	+
5 mg/kg	+	+	+	+	+	+

Table 2 - Daily Doses of Levetiracetam (mg) in a Human Subject of 70 KG

Lower range / Upper range	7 mg	25 mg	40 mg	70 mg	140 mg	200 mg
130 mg	+	+	+	+		
140 mg	+	+	+	+		
180 mg	+	+	+	+	+	
200 mg	+	+	+	+	+	
300 mg	+	+	+	+	+	+
350 mg	+	+	+	+	+	+

[0178] In certain embodiments of the invention, the SV2A inhibitor is levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. The levetiracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered at a daily dose of about 0.1

- 5 mg/kg, about 1 - 5 mg/kg, about 1.5 - 4 mg/kg, about 1.8 - 3.6 mg/kg, about 7 - 350 mg, about 70 - 350 mg, about 100 - 300 mg, or about 125 -250 mg.

[0179] In certain embodiments of the invention, the SV2A inhibitor is brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. The brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered every 12 or 24 hours at a daily dose of about 0.1 to 0.2 mg/kg, or about 0.01 to 2.5 mg/kg, or about 0.04 to 2.5 mg/kg, or about 0.06 to 1.8 mg/kg, or about 0.2 to 0.4 mg/kg, or about 7 to 15 mg, or about 0.7 to 180 mg, or about 2.5 to 180 mg, or about 4.0 to 130 mg, or about 14 to 30 mg.

[0180] In other embodiments, the brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered every 12 or 24 hours at a daily dose of at least 0.1 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, or 2.0 mg, but no more than a daily dose of 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, or 35 mg. In other embodiments, the brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered every 12 or 24 hours at a daily dose of at least 0.0015 mg/kg, 0.0075 mg/kg, 0.01 mg/kg, 0.015 mg/kg, 0.02 mg/kg, or 0.03 mg/kg, but no more than a daily dose of 0.5 mg/kg, 0.4 mg/kg, 0.3 mg/kg, 0.2 mg/kg, 0.15 mg/kg, 0.1 mg/kg, 0.05 mg/kg, or 0.04 mg/kg.

[0181] In other embodiments, the brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered every 12 or 24 hours according to one of the daily dose ranges indicated as "+" listed in Table 3 or Table 4. For example, the brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be administered every 12 or 24 hours at a daily dose of 0.1 - 35 mg, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, 0.0015 - 0.5 mg/kg, 0.0075 - 0.5 mg/kg, 0.01 - 0.5 mg/kg, 0.015 - 0.5 mg/kg, 0.02 - 0.5 mg/kg, 0.03 - 0.5 mg/kg, 0.0015 - 0.4 mg/kg, 0.0015 - 0.3 mg/kg, 0.0015 - 0.2 mg/kg, 0.0015 - 0.15 mg/kg, 0.0015 - 0.1 mg/kg, 0.0015 - 0.05 mg/kg, or 0.0015 - 0.04 mg/kg.

Table 3 - Daily Doses of Brivaracetam (mg/kg)

Lower range / Upper range	0.0015 mg/kg	0.0075 mg/kg	0.01 mg/kg	0.015 mg/kg	0.02 mg/kg	0.03 mg/kg
0.04 mg/kg	+	+	+	+	+	+
0.05 mg/kg	+	+	+	+	+	+
0.1 mg/kg	+	+	+	+	+	+
0.15 mg/kg	+	+	+	+	+	+
0.2 mg/kg	+	+	+	+	+	+
0.3 mg/kg	+	+	+	+	+	+
0.4 mg/kg	+	+	+	+	+	+
0.5 mg/kg	+	+	+	+	+	+

Table 4 - Daily Doses of Brivaracetam (mg) in a Human Subject of 70 KG

Lower range / Upper range	0.1 mg	0.5 mg	0.75 mg	1.0 mg	1.5 mg	2.0 mg
2.5 mg	+	+	+	+	+	+
5 mg	+	+	+	+	+	+
10 mg	+	+	+	+	+	+
15 mg	+	+	+	+	+	+
20 mg	+	+	+	+	+	+
25 mg	+	+	+	+	+	+
30 mg	+	+	+	+	+	+
35 mg	+	+	+	+	+	+

[0182] In other embodiments, the brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered at a daily dose of at least 0.0015 mg/kg, 0.002 mg/kg, 0.0025 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, but no more than a daily dose of 1 mg/kg, 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.8 mg/kg, 2.0 mg/kg, 2.2 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.8 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, or 5.0 mg/kg. In other embodiments, the brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered at a daily dose of at least 0.1 mg, 0.15 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.8 mg, 3.0 mg, 3.5 mg, 4.2 mg, 5 mg, 5.5 mg, 6.0 mg, 7 mg, 10 mg, 15 mg, 20 mg, 25 mg, 28 mg, 30 mg, or 35 mg but no more than a daily dose of 70 mg, 80 mg, 85 mg, 100 mg, 110 mg, 125 mg, 140 mg, 150 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 225 mg, 250 mg, 280 mg, 300 mg, or 350 mg. In some embodiments, the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be administered at a daily dose of 0.0015 - 5 mg/kg, 0.1 - 350 mg, 0.01 - 5 mg/kg, 0.7 - 350 mg, 0.05 - 4 mg/kg, 3 - 300 mg, 0.05 - 2.0 mg/kg, 3 - 150 mg, 0.05 - 1.5 mg, 3 - 110 mg, 0.1 - 1.0 mg/kg, 7 -70 mg.

[0183] In other embodiments, the brivaracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered according to one of the daily dose ranges indicated as "+" listed in Table 5 or Table 6. For example, the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be administered at a daily dose of 0.01 - 0.8 mg/kg, 0.01 - 1 mg/kg, 0.01 - 1.5 mg/kg, 0.01 - 2 mg/kg, 0.01 - 2.5 mg/kg, 0.01 - 3 mg/kg, 0.01 - 3.5 mg/kg, 0.01 - 4 mg/kg, 0.01 - 5 mg/kg, 0.025 - 0.8 mg/kg, 0.025 - 1 mg/kg, 0.025 - 1.5 mg/kg, 0.025 - 2 mg/kg, 0.025 - 2.5 mg/kg, 0.025 - 3 mg/kg, 0.025 - 3.5 mg/kg, 0.025 - 4 mg/kg, 0.05 - 0.8 mg/kg, 0.05 - 1 mg/kg, 0.05 - 1.5 mg/kg, 0.05 - 2 mg/kg, 0.05 - 2.5 mg/kg, 0.05 - 3 mg/kg, 0.05 - 3.5 mg/kg, 0.05 - 4 mg/kg, 0.075 - 0.8 mg/kg, 0.075 - 1 mg/kg, 0.075 - 1.5 mg/kg, 0.075 - 2 mg/kg, 0.075 - 2.5 mg/kg, 0.075 - 3 mg/kg, 0.075 - 3.5 mg/kg, 0.075 - 4 mg/kg, 0.1 - 0.8 mg/kg, 0.1 - 1 mg/kg, 0.1 - 1.5 mg/kg, 0.1 - 2 mg/kg, 0.1 - 2.5 mg/kg, 0.1 - 3 mg/kg, 0.1 - 3.5 mg/kg, 0.1 - 4 mg/kg, 0.2 - 0.8 mg/kg, 0.2 - 1 mg/kg, 0.2 - 1.5 mg/kg, 0.2 - 2 mg/kg, 0.2 - 2.5 mg/kg, 0.2 - 3 mg/kg, 0.2 - 3.5 mg/kg, 0.2 - 4 mg/kg, 0.5 - 0.8 mg/kg, 0.5 - 1 mg/kg, 0.5 - 1.5 mg/kg, 0.5 - 2 mg/kg, 0.5 - 2.5 mg/kg, 0.5 - 3 mg/kg, 0.5 - 3.5 mg/kg, or 0.5 - 4 mg/kg; or 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg.

Table 5 - Daily Doses of Brivaracetam (mg/kg)

Lower range / Upper range	0.0015	0.01	0.025	0.04	0.05	0.075	0.1	0.2	0.5
0.8	+	+	+	+	+	+	+	+	+
1	+	+	+	+	+	+	+	+	+
1.5	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+
2.5	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+
3.5	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+

Table 6 - Daily Doses of Brivaracetam (mg) in a Human Subject of 70 KG

Lower range / Upper range	0.1	0.7	1.8	3.0	3.5	5	7	15	35
50	+	+	+	+	+	+	+	+	+
75	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	+	+
110	+	+	+	+	+	+	+	+	+
150	+	+	+	+	+	+	+	+	+
180	+	+	+	+	+	+	+	+	+
225	+	+	+	+	+	+	+	+	+
250	+	+	+	+	+	+	+	+	+
280	+	+	+	+	+	+	+	+	+
300	+	+	+	+	+	+	+	+	+
350	+	+	+	+	+	+	+	+	+

[0184] In certain embodiments of the invention, the SV2A inhibitor is seletracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof. In some embodiments, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered every 12 or 24 hours at a daily dose of at least 0.1 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, or 2.0 mg, but no more than a daily dose of 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, or 35 mg. In other embodiments, the seletracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered every 12 or 24 hours at a daily dose of at least 0.0015 mg/kg, 0.0075 mg/kg, 0.01 mg/kg, 0.015 mg/kg, 0.02 mg/kg, or 0.03 mg/kg, but no more than a daily dose of 0.5 mg/kg, 0.4 mg/kg, 0.3 mg/kg, 0.2 mg/kg, 0.15 mg/kg, 0.1 mg/kg, 0.05 mg/kg, or 0.04 mg/kg.

[0185] In certain embodiments of the invention, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered according to one of the daily dose ranges indicated as "+" listed in Table 7 or Table 8. For example, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug may be administered every 12 or 24 hours at a daily dose of 0.1 - 35 mg, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, 0.0015 - 0.5 mg/kg, 0.0075 - 0.5 mg/kg, 0.01 - 0.5 mg/kg, 0.015 - 0.5 mg/kg, 0.02 - 0.5 mg/kg, 0.03 - 0.5 mg/kg, 0.0015 - 0.4 mg/kg, 0.0015 - 0.3 mg/kg, 0.0015 - 0.2 mg/kg, 0.0015 - 0.15 mg/kg, 0.0015 - 0.1 mg/kg, 0.0015 - 0.05 mg/kg, or 0.0015 - 0.04 mg/kg.

Table 7 - Daily Doses of Seletracetam (mg/kg)

Lower range / Upper range	0.0015 mg/kg	0.0075 mg/kg	0.01 mg/kg	0.015 mg/kg	0.02 mg/kg	0.03 mg/kg
0.04 mg/kg	+	+	+	+	+	+
0.05 mg/kg	+	+	+	+	+	+
0.1 mg/kg	+	+	+	+	+	+
0.15 mg/kg	+	+	+	+	+	+
0.2 mg/kg	+	+	+	+	+	+
0.3 mg/kg	+	+	+	+	+	+

0.4 mg/kg	+	+	+	+	+	+
0.5 mg/kg	+	+	+	+	+	+

Table 8 - Daily Doses of Seletracetam (mg) in a Human Subject of 70 KG

Lower range / Upper range	0.1 mg	0.5 mg	0.75 mg	1.0 mg	1.5 mg	2.0 mg
2.5 mg	+	+	+	+	+	+
5 mg	+	+	+	+	+	+
10 mg	+	+	+	+	+	+
15 mg	+	+	+	+	+	+
20 mg	+	+	+	+	+	+
25 mg	+	+	+	+	+	+
30 mg	+	+	+	+	+	+
35 mg	+	+	+	+	+	+

[0186] In other embodiments, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered at a daily dose of at least 0.0015 mg/kg, 0.002 mg/kg, 0.0025 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, but no more than a daily dose of 1 mg/kg, 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.8 mg/kg, 2.0 mg/kg, 2.2 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.8 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, or 5.0 mg/kg. In other embodiments, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered at a daily dose of at least 0.1 mg, 0.15 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.8 mg, 3.0 mg, 3.5 mg, 4.2 mg, 5 mg, 5.5 mg, 6.0 mg, 7 mg, 10 mg, 15 mg, 20 mg, 25 mg, 28 mg, 30 mg, or 35 mg but no more than a daily dose of 70 mg, 80 mg, 85 mg, 100 mg, 110 mg, 125 mg, 140 mg, 150 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 225 mg, 250 mg, 280 mg, 300 mg, or 350 mg. In some embodiments, the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be administered at a daily dose of 0.0015 - 5 mg/kg, 0.1 - 350 mg, 0.01 - 5 mg/kg, 0.7 - 350 mg, 0.05 - 4 mg/kg, 3 - 300 mg, 0.05 - 2.0 mg/kg, 3 - 150 mg, 0.05 - 1.5 mg, 3 - 110 mg, 0.1 - 1.0 mg/kg, 7 -70 mg.

[0187] In other embodiments, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered according to one of the daily dose ranges indicated as "+" listed in Table 9 or Table 10. For example, the seletracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be administered at a daily dose of 0.01 - 0.8 mg/kg, 0.01 - 1 mg/kg, 0.01 - 1.5 mg/kg, 0.01 - 2 mg/kg, 0.01 - 2.5 mg/kg, 0.01 - 3 mg/kg, 0.01 - 3.5 mg/kg, 0.01 - 4 mg/kg, 0.01 - 5 mg/kg, 0.025 - 0.8 mg/kg, 0.025 - 1 mg/kg, 0.025 - 1.5 mg/kg, 0.025 - 2 mg/kg, 0.025 - 2.5 mg/kg, 0.025 - 3 mg/kg, 0.025 - 3.5 mg/kg, 0.025 - 4 mg/kg, 0.05 - 0.8 mg/kg, 0.05 - 1 mg/kg, 0.05 - 1.5 mg/kg, 0.05 - 2 mg/kg, 0.05 - 2.5 mg/kg, 0.05 - 3 mg/kg, 0.05 - 3.5 mg/kg, 0.05 - 4 mg/kg, 0.075 - 0.8 mg/kg, 0.075 - 1 mg/kg, 0.075 - 1.5 mg/kg, 0.075 - 2 mg/kg, 0.075 - 2.5 mg/kg, 0.075 - 3 mg/kg, 0.075 - 3.5 mg/kg, 0.075 - 4 mg/kg, 0.1 - 0.8 mg/kg, 0.1 - 1 mg/kg, 0.1 - 1.5 mg/kg, 0.1 - 2 mg/kg, 0.1 - 2.5 mg/kg, 0.1 - 3 mg/kg, 0.1 - 3.5 mg/kg, 0.1 - 4 mg/kg, 0.2 - 0.8 mg/kg, 0.2 - 1 mg/kg, 0.2 - 1.5 mg/kg, 0.2 - 2 mg/kg, 0.2 - 2.5 mg/kg, 0.2 - 3 mg/kg, 0.2 - 3.5 mg/kg, 0.2 - 4 mg/kg, 0.5 - 0.8 mg/kg, 0.5 - 1 mg/kg, 0.5 - 1.5 mg/kg, 0.5 - 2 mg/kg, 0.5 - 2.5 mg/kg, 0.5 - 3 mg/kg, 0.5 - 3.5 mg/kg, or 0.5 - 4 mg/kg; or 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg.

Table 9 - Daily Doses of Seletracetam (mg/kg)

Upper range \ Lower range	0.0015	0.01	0.025	0.04	0.05	0.075	0.1	0.2	0.5
0.8	+	+	+	+	+	+	+	+	+
1	+	+	+	+	+	+	+	+	+
1.5	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+
2.5	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+
3.5	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+

Table 10 - Daily Doses of Seletracetam (mg) in a Human Subject of 70 KG

Upper range \ Lower range	0.1	0.7	1.8	3.0	3.5	5	7	15	35
50	+	+	+	+	+	+	+	+	+
75	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	+	+
110	+	+	+	+	+	+	+	+	+
150	+	+	+	+	+	+	+	+	+
180	+	+	+	+	+	+	+	+	+
225	+	+	+	+	+	+	+	+	+
250	+	+	+	+	+	+	+	+	+
280	+	+	+	+	+	+	+	+	+
300	+	+	+	+	+	+	+	+	+
350	+	+	+	+	+	+	+	+	+

[0188] The SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, and prodrug may be administered at a subtherapeutic dosage levels when provided in combination with an antipsychotic or its pharmaceutically acceptable salt, hydrate, solvate, polymorph and prodrug, due to an antipsychotic-dependent increase in the therapeutic index of the SV2A inhibitor. In some embodiments, the increase in the therapeutic index of the SV2A inhibitor, due to the combination with an antipsychotic, is greater than the therapeutic index of the SV2A inhibitor administered in the absence of the antipsychotic by at least about 1.5x or 2.0x or 2.5x or 3.0x or 3.5x or 4.0x or 4.5x or 5.0x or 5.5x or 6.0x or 6.5x or 7.0x or 7.5x or 8.0x or 8.5x or 9.0x or 9.5x or 10x, or greater than about 10x. In some embodiments, combinations of an SV2A inhibitor with an antipsychotic reduces the dosage of the SV2A inhibitor required for its therapeutic effect. In some embodiments, the amount of the SV2A inhibitor administered in combination with the antipsychotic is a subtherapeutic amount. In some embodiments, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate and polymorph, or prodrug thereof is administered at a daily dose of less than 5 mg/kg, less than 2.5 mg/kg, less than 2 mg/kg, less than 1.5 mg/kg, less than 1 mg/kg, less than 0.5 mg/kg, less than 0.1 mg/kg, less than 0.05 mg/kg, less than 0.01 mg/kg, less than 0.005 mg/kg, or less than 0.001 mg/kg. In some embodiments, such subtherapeutic amount, may be, for example, a daily dose of less than 7 mg/kg, less than 6 mg/kg, less than 5 mg/kg, less than 4 mg/kg, less than 3.8 mg/kg, less than 3.6 mg/kg, less than 3.4 mg/kg, less than 3.2 mg/kg, less than 3 mg/kg, less than 2.9 mg/kg, less than 2.8 mg/kg, less than 2.7 mg/kg, less than 2.6 mg/kg, less than 2.5 mg/kg, less than 2.4 mg/kg, less than 2.3 mg/kg, less than 2.2 mg/kg, less than 2.1 mg/kg, less than 2 mg/kg, less than 1.5 mg/kg, less than 1 mg/kg, less than 0.5 mg/kg, less than 0.1 mg/kg, less than 0.05 mg/kg, less than 0.01 mg/kg, or less than 0.0015 mg/kg; or less than 500 mg, less than 420 mg, less than 400 mg, less than 350 mg, less than 300 mg, less than 280 mg, less than 270 mg, less than 260 mg, less than 250 mg, less than 240 mg, less than 230 mg, less than 225 mg, less than 220 mg, less than 210 mg, less than 200 mg, less than 190 mg, less than 180 mg, less than 175 mg, less than 170 mg, less than 150 mg, less than 140 mg, less than 125 mg, less than 120 mg, less than 110 mg, less than 100 mg, less than 95 mg, less than 90 mg, less than 85 mg, less than 80 mg, less than 75 mg, less than 70 mg, less than 65 mg, less than 60 mg, less than 55 mg, less than 50mg, less than 45 mg, less than 40 mg, less than 35 mg, less than 30 mg, less than 28 mg, less than 25 mg, less than 20 mg, less than 15 mg, less than 12 mg, less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5.5 mg, less than 5 mg, less than 4.2 mg, less than 3.5 mg, less than 3 mg, less than 2.8

mg, less than 2.5 mg, less than 2.0 mg, less than 1.5 mg, less than 0.7 mg, less than 0.35 mg, less than 0.18 mg, less than 0.15 mg, or less than 0.1 mg is administered. The SV2A inhibitors that can be used in the foregoing embodiments include, for example, levetiracetam, brivaracetam, and seletracetam or their pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof.

[0189] In certain embodiments of the invention, the seletracetam or its pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug is administered according to one of the daily dose ranges indicated above for levetiracetam.

[0190] In some embodiments, the antipsychotic useful in the present invention is a typical antipsychotic. Generally the amount of a typical antipsychotic administered to a patient is an amount sufficient to have a therapeutic effect. In a preferred embodiment the amount of a typical antipsychotic administered to a patient is an amount sufficient to treat at least one symptom or sign of schizophrenia or bipolar disorder (in particular, mania), wherein the one sign or symptom may include, but are not limited to, any of those described above, including, for example, delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior and negative symptoms (e.g., affective flattening, alogia, avolition). One skilled in the art will recognize that the amount of typical antipsychotic will vary with many factors including the potency of the typical antipsychotic, the age and weight of the patient, and the severity of the condition or disorder to be treated. The dosages of the drugs used in the present invention can, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as detem1ined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient.**[0191]** In some embodiments, the antipsychotic useful in the present invention is an atypical antipsychotic. Generally the amount of an atypical antipsychotic administered to a patient is an amount sufficient to have a therapeutic effect. In a preferred embodiment the amount of an atypical antipsychotic administered to a patient is an amount sufficient to treat at least one symptom or sign of schizophrenia or bipolar disorder (in particular, mania), wherein the one sign or symptom may include, but are not limited to, any of those described above, including, for example, delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior and negative symptoms (e.g., affective flattening, alogia, avolition). One skilled in the art will recognize that the amount of atypical antipsychotic will vary with many factors including the potency of the atypical antipsychotic, the age and weight of the patient, and the severity of the condition or disorder to be treated. The dosages of the drugs used in the present invention can, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as detem1ined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient.

[0192] Non-limiting daily dosage amounts for several atypical antipsychotics are provided herein:

Aripiprazole, about 0.1-150 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 1-80 mg/day, about 1-50 mg/day, or about 5-50 mg/day, and in some embodiments, up to about 30 mg/day or about 10-15 mg/day;

Asenapine, about 0.1-150 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 1-80 mg/day, about 1-50 mg/day, or about 5-50 mg/day, and in some embodiments, about 10 mg/day;

Clozapine, about 0.1-1000 mg/day, about 1-900 mg/day, about 5-900 mg/day, about 10-900 mg/day, about 100-900 mg/day, about 100-800 mg/day or about 100-750 mg/day, and in some embodiments, about 150-450 mg/day or about 300-450 mg/day;

Iloperidone, about 0.1-150 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 1-80 mg/day, about 1-50 mg/day, or about 5-50 mg/day, and in some embodiments, about 12-24 mg/day;

Olanzapine, about 0.1-150 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 1-80 mg/day, about 1-50 mg/day, or about 5-50 mg/day, and in some embodiments, about 10-15 mg/day;

Lurasidone, about 0.1-500 mg/day, about 1-500 mg/day, about 1-250 mg/day, about 10-250 mg/day, about 10-100 mg/day, or about 20-100 mg/day, and in some embodiments, about 40-80 mg/day;

Paliperidone, about 0.1-150 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 1-80 mg/day, about 1-50 mg/day, or about 5-50 mg/day, and in some embodiments, about 6 mg/day;

Quetiapine, about 0.1-1000 mg/day, about 1-900 mg/day, about 1-800 mg/day, about 50-800, about 100-800, or about 200-800 mg/day, and in some embodiments, about 150-750 mg/day, about 300 mg/day or about 400-800 mg/day;

Risperidone, about 0.1-150 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 1-80 mg/day, about 1-50 mg/day, or about 5-50 mg/day, and in some embodiments, about 4-8 mg/day or 1-6 mg/day;

Ziprasidone, about 0.1-250 mg/day, about 1-150 mg/day, about 1-100 mg/day, about 20-100, or about 20-80 mg/day, and in some embodiments, up to about 40 mg/day, or up to about 80 mg/day or about 40-80 mg/day.

[0193] For repeated administrations over several days or weeks or longer, depending on the condition, the treatment is sustained until a sufficient level of cognitive function is achieved.

[0194] The antipsychotic or a salt, hydrate, solvate, polymorph, or prodrug thereof may be administered at dosage levels distinct from conventional levels (e.g., at subtherapeutic doses) when provided in combination with SV2A inhibitor, due to an SV2A inhibitor-dependent increase in the antipsychotic's therapeutic index. In some embodiments, the increase in the antipsychotic's therapeutic index due to the combination with SV2A inhibitor is greater than the therapeutic index of the antipsychotic administered in the absence of an SV2A inhibitor by at least about 1.5x or 2.0x or 2.5x or 3.0x or 3.5x or 4.0x or 4.5x or 5.0x or 5.5x or 6.0x or 6.5x or 7.0x or 7.5x or 8.0x or 8.5x or 9.0x or 9.5x or 10x, or greater than about 10x. In some embodiments, combination of an antipsychotic with the SV2A inhibitor reduces the dosage of the antipsychotic required for its therapeutic effect. In some embodiments, the antipsychotic is an atypical antipsychotic. When used in combination with SV2A inhibitor, such atypical antipsychotic is administered at a dose lower than required for its therapeutic effect when administered in the absence of SV2A inhibitor.

[0195] The frequency of administration of the composition of this invention may be adjusted over the course of the treatment, based on the judgment of the administering physician. It will be clear that the SV2A inhibitor and the antipsychotic and their salts, hydrates, solvates, polymorphs and prodrugs can be administered at different dosing frequencies or intervals. For example, SV2A inhibitor can be administered daily (including multiple doses per day) or less frequently. An antipsychotic can be administered daily (including multiple doses per day) or less frequently. In some embodiments, sustained continuous release formulations of an SV2A inhibitor and an antipsychotic may be desired. Various formulations and devices for achieving sustained release are known in the art.

[0196] The use of a combination of an SV2A inhibitor and an antipsychotic may reduce the amount of the antipsychotic necessary for treatment of schizophrenia or bipolar disorder (in particular, mania), and may thus reduce the side effects caused by the antipsychotics. In particular, the combination of an SV2A inhibitor with a reduced amount of antipsychotic may reduce the side effects without negatively impacting efficacy. Accordingly, in some embodiments, a subtherapeutic amount of antipsychotic is administered.

[0197] In some embodiments, a suitable amount of the SV2A inhibitor is administered so as to reduce the dose of the antipsychotic by at least about 20%, at least about 30%, at least about 40%, or at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90% or more from to the dose of the antipsychotic normally used when administered alone (i.e., individually and not in combination with other therapeutic agents or compounds). The reduction may be reflected in terms of amount administered at a given administration and/or amount administered over a given period of time (reduced frequency).

[0198] In certain embodiments of the invention, the combined administration of SV2A inhibitor or a salt, hydrate, solvate, polymorph, and prodrug thereof and an antipsychotic or a salt, hydrate, solvate, polymorph, and prodrug thereof can attain a longer or improved therapeutic effect in the subject than that attained by administering only the SV2A inhibitor or only the antipsychotic, by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

Compositions of this Invention

[0199] In one aspect, the invention provides compositions comprising an SV2A inhibitor and at least one antipsychotic and their salts, hydrates, solvates, polymorphs and prodrugs. In some embodiments, the SV2A inhibitor and the antipsychotic may be present in a single dosage unit (e.g., combined together in one capsule, tablet, powder, or liquid, etc.). In some embodiments of this aspect of the invention, the invention provides compositions comprising an SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in an extended release form and an antipsychotic and its salts, hydrates, solvates, polymorphs, or prodrugs in an extended release form. In some embodiments of this aspect of the invention, the invention provides compositions comprising an SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in a form that is not extended release and an antipsychotic and its salts, hydrates, solvates, polymorphs, or prodrugs in a form that is not extended release. In some embodiments of this aspect of the invention, the invention provides compositions comprising an SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in an extended release form and an antipsychotic and its salts, hydrates, solvates, polymorphs, or prodrugs in a form that is not extended release. In some embodiments of this aspect of the invention, the invention provides compositions comprising an SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in a form that is not extended release and an antipsychotic and its salts, hydrates, solvates, polymorphs, or prodrugs in an extended release form. In some embodiments, the extended release SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition does not affect the pharmacokinetics or the half-life clearance of the antipsychotic or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the same composition. In some embodiments, the extended release antipsychotics or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition does not affect the pharmacokinetics or the half-life clearance of SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the same composition. In some embodiments, the extended release form includes without limitation a controlled release form, a prolonged release form, a sustained release form, a delayed release form, or a slow release form. In some embodiments, the form that is not extended release includes, without limitation, an immediate release. In some embodiments, the composition includes levetiracetam, or seletracetam, or brivaracetam, or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph, or prodrug thereof as the SV2A inhibitor, and includes at least one antipsychotic and their salts, hydrates, solvates, polymorphs and prodrugs. The composition described herein can contain more than one SV2A inhibitor and/or more than one antipsychotic.

[0200] The compositions described herein can further contain pharmaceutically acceptable excipient(s) and may contain other agents that serve to enhance and/or complement the effectiveness of the SV2A inhibitor and/or the antipsychotic. The compositions may also contain additional agents known to be useful for treating schizophrenia or bipolar disorder (in particular, mania).

[0201] The SV2A inhibitor and the antipsychotic suitable for the compositions of this invention may be selected from any of those as described above. In some embodiments, the SV2A inhibitor is selected from any of those described above; and the antipsychotic is selected from (1) atypical and typical antipsychotics (such as those described above); (2) agents that are dopaminergic agents (such as dopamine D1 receptor antagonists or agonists, dopamine D_2 receptor antagonists or partial agonists, dopamine D3 receptor antagonists or partial agonists, dopamine D4 receptor antagonists), glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs)agonists or positive allosteric modulators (PAMs) (e.g., mGluR2/3 agonists or PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents (such as alpha-2 adrenergic receptor agonists or antagonists and COMT inhibitors), serotonin receptor modulators (such as 5-HT_{2A} receptor antagonists, 5-HT_{1A} receptor partial agonists, 5-HT_{2C} agonists, and 5-HT6 antagonists), cholinergic agents (such as alpha-7 nicotinic receptor agonists, alpha4-beta2 nicotinic receptor agonists, allosteric modulators of nicotinic receptors and acetylcholinesterase inhibitors, muscarinic receptor agonists and antagonists), cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, nNOS inhibits, neurosteroids, and neurotrophic factors, including, e.g., those specific such agents described above, and (3) any compounds that are useful in treating one or more sign or symptoms of schizophrenia or bipolar disorder (in particular, mania) (including, e.g., the agents disclosed in any of the above-listed patents or patent application publications), and pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof. In some embodiments, the SV2A inhibitor is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam or derivatives or analogs or pharmaceutically acceptable salts, or solvates, or hydrates, or polymorphs, or prodrugs thereof; and the antipsychotic is an atyptical antipsychotic selected from, e.g., aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof. In some embodiments, the SV2A inhibitor is selected from levetiracetam or derivatives or analogs or pharmaceutically acceptable salts, or solvates, or hydrates, or polymorphs, or prodrugs thereof; and the antipsychotic is an atyptical antipsychotic selected from, e.g., aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof.

[0202] The composition described herein can contain more than one SV2A inhibitor and/or more than one antipsychotic. In some embodiments, the SV2A inhibitor and the antipsychotic are in a single dosage form, in a unit dosage form, in separate dosage forms, or in separate dosage forms packaged together.

[0203] The compositions described herein can further contain pharmaceutically acceptable excipient(s) and may contain other agents that serve to enhance and/or complement the effectiveness of the SV2A inhibitor and/or the antipsychotic. The compositions may also contain additional agents known to be useful for treating cognitive function disorder.

[0204] The composition in the present invention may be in solid dosage forms such as capsules, tablets, dragrees, pills, lozenges, powders and granule. Where appropriate, they may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled releases of one or more active ingredient such as sustained or prolonged release according to methods well known in the art. In certain embodiments, the composition is in form of a slow, controlled, or extended release. The term "extended release" is widely recognized in the art of pharmaceutical sciences and is used herein to refer to a controlled release of an active compound or agent from a dosage form to an environment over (throughout or during) an extended period of time, e.g. greater than or equal to one hour. An extended release dosage form will release drug at substantially constant rate over an extended period of time or a substantially constant amount of drug will be released incrementally over an extended period of time. The term "extended release" used herein includes the terms "controlled release", "prolonged release", "sustained release", or "slow release", as these terms are used in the pharmaceutical sciences. In some embodiments, the extended release dosage is administered in the form of a patch or a pump. The composition may also be in liquid dosage forms including solutions, emulsions, suspensions, syrups, and elixirs.

[0205] The compositions may be specifically formulated for administration by any suitable route as described herein and known in the art. Compositions for parental administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Compositions for intraoral and oral delivery (including sublingual and buccal administration, e.g. Danckwerts et al, and oral) include but are not limited to bioadhesive polymers, tablets, patches, liquids and semisolids (see e.g., Smart et al). Compositions for respiratory delivery (pulmonary and nasal delivery) include but are not limited to a variety of pressurized metered dose inhalers, dry powder inhalers, nebulizers, aqueous mist inhalers, drops, solutions, suspensions, sprays, powders, gels, ointments, and specialized systems such as liposomes and microspheres (see e.g. Owens et al, “Alternative Routes of Insulin Delivery” and Martini et al). Compositions for transdermal delivery include but are not limited to colloids, patches, and microemulsions. Other suitable administration forms for the above and other include depot injectable formulations, suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

[0206] The compositions may also contain adjuvants, such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[0207] Therapeutic formulations can be prepared by methods well known in the art of pharmacy, see, e.g., Goodman et al., 2001; Ansel, et al., 2004; Stoklosa et al., 2001; and Bustamante, et al., 1993.

[0208] In certain embodiments of the invention, a composition containing an SV2A inhibitor and an antipsychotic and their salts, hydrates, solvates, polymorphs and prodrugs comprises an amount of the SV2A inhibitor between 0.07 and 350 mg, or between 50 and 200 mg, or between 3 and 50 mg. In some embodiments, the amount of the SV2A inhibitor is less than 350 mg, less than 250 mg, less than 200 mg, less than 150 mg, less than 100 mg, less than 50 mg, less than 10 mg, less than 5 mg, less than 1 mg, less than 0.5 mg, less than 0.1 mg, or less than 0.07 mg. In certain embodiments of the invention, a composition containing an SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate or polymorph comprises the SV2A inhibitor in an amount of 0.07 – 60 mg, 0.07 – 350 mg, 25 – 60 mg, 25 – 125 mg, 50 – 250 mg, 5 – 140 mg, 0.7 – 180 mg, 125 – 240 mg, 3 - 50 mg, or 3 – 60 mg. In some embodiments, a composition containing an SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate polymorph, or prodrugs comprises the SV2A inhibitor in an amount of 0.05 - 35 mg. In some embodiments of the composition of the present invention, the SV2A inhibitor may be selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs thereof, said SV2A inhibitor being present in an amount selected from any of the above.

[0209] In some embodiments, the amount of the SV2A inhibitor present in the composition is 0.07 – 60 mg, 0.07 – 350 mg, 25 – 60 mg, 25 – 125 mg, 50 – 250 mg, 5 – 140 mg, 0.7 – 180 mg, 125 – 240 mg, 3 - 50 mg, 3 – 60 mg, 0.05 - 35 mg, 0.07 – 60 mg, 0.07 – 350 mg, 25 – 60 mg, 25 – 125 mg, 50 – 250 mg, 5 – 15 mg, 5 – 30 mg, 5 – 140 mg, 0.7 – 180 mg, 125 – 240 mg, 3 -50 mg, or 0.07 - 50 mg, or 3 – 60 mg. In some embodiments, the amount of the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition is less than 350 mg, less than 250 mg, less than 200 mg, less than 150 mg, less than 100 mg, less than 50 mg, less than 35 mg, less than 10 mg, less than 5 mg, less than 1 mg, less than 0.5 mg, less than 0.1 mg, less than 0.07 mg, or less than 0.05 mg. In some embodiments, the amount of the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the composition is about 0.1 - 500 mg, 0.1 - 300 mg, 0.7 - 300 mg, 3 - 300 mg, 3 - 150 mg, 3 - 110 mg, 7 - 70 mg, 7 - 300 mg, 70 - 300 mg, 100 - 300 mg, 125 - 250 mg, 0.5 - 50 mg, 0.5 - 75 mg, 0.5 - 100 mg, 0.5 - 150 mg, 0.5 - 200 mg, 0.5 - 225 mg, 0.5 - 250 mg, 0.5 - 300 mg, 1.5 - 50 mg, 1.5 - 75 mg, 1.5 - 100 mg, 1.5 - 150 mg, 1.5 - 200 mg, 1.5 - 225 mg, 1.5 - 250 mg, 1.5 - 300 mg, 3 - 50 mg, 3 - 75 mg, 3 - 100 mg, 3 - 150 mg, 3 - 200 mg, 3 - 225 mg, 3 - 250 mg, 3 - 300 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 200 mg, 5 - 225 mg, 5 - 250 mg, 5 - 300 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 200 mg, 7 - 225 mg, 7 - 250 mg, 7 - 300 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 200 mg, 15 - 225 mg, 15 - 250 mg, 15 - 300 mg, 30 - 50 mg, 30 - 75 mg, 30 - 100 mg, 30 - 150 mg, 30 - 200 mg, 30 - 225 mg, 30 - 250 mg, or 30 - 300 mg.

[0210] It will be understood by one of ordinary skill in the art that the compositions and methods described herein may be adapted and modified as is appropriate for the application being addressed and that the compositions and methods described herein may be employed in other suitable applications, and that such other additions and modifications will not depart from the scope hereof.

[0211] This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the embodiments which follow thereafter.

[0212] In certain embodiments of the invention, a composition comprising levetiracetam and an antipsychotic and their salts, hydrates, solvates, polymorphs, prodrugs comprises an amount of the levetiracetam or its salts, hydrates, solvates, polymorphs, prodrugs between the ranges shown in Table 11 or less than any of the upper ranges shown in Table 11. In certain embodiments of the invention, a composition comprising brivaracetam and an antipsychotic and their salts, hydrates, solvates, polymorphs, prodrugs comprises an amount of the brivaracetam or its salts, hydrates, solvates, polymorphs, prodrugs between the ranges shown in

Table 12 or less than any of the upper ranges shown in Table 12. In certain embodiments of the invention, a composition comprising seletracetam and an antipsychotic and their salts, hydrates, solvates, polymorphs, prodrugs comprises an amount of the seletracetam or its salts, hydrates, solvates, polymorphs, prodrugs between the ranges shown in Table 12 or less than any of the upper ranges shown in Table 12.

Table 11 - Amount of Levetiracetam Present in the Composition (mg)

Lower range / Upper range	7 mg	25 mg	40 mg	70 mg	125 mg	140 mg	200 mg
130 mg	+	+	+	+			
140 mg	+	+	+	+	+		
180 mg	+	+	+	+	+	+	
200 mg	+	+	+	+	+	+	
250 mg	+	+	+	+	+	+	+
300 mg	+	+	+	+	+	+	+
350 mg	+	+	+	+	+	+	+

Table 12 - Amount of Seletracetam or Brivaracetam Present in the Composition (mg)

Lower range / Upper range	0.1	0.7	1.8	3.0	3.5	5	7	15	35
50	+	+	+	+	+	+	+	+	+
75	+	+	+	+	+	+	+	+	+
100	+	+	+	+	+	+	+	+	+
110	+	+	+	+	+	+	+	+	+
150	+	+	+	+	+	+	+	+	+
180	+	+	+	+	+	+	+	+	+
225	+	+	+	+	+	+	+	+	+
250	+	+	+	+	+	+	+	+	+
280	+	+	+	+	+	+	+	+	+
300	+	+	+	+	+	+	+	+	+
350	+	+	+	+	+	+	+	+	+

Examples

[0213] Introduction and Models of Cognitive Impairment

[0214] A variety of conditions characterized by cognitive impairment, e.g., Age-Associated Memory Impairment (AAMI), Mild Cognitive Impairment (MCI) and Age-related Cognitive Decline (ARCD) are believed to be related to aging. Others are related to disease, for example, AD. Animal models serve as an important resource for developing and evaluating treatments for such age-related cognitive impairments. Features that characterize age-related cognitive impairment in animal models typically extend to age-related cognitive impairment in humans. Efficacy in such animal models is, thus, predictive of efficacy in humans.

[0215] Of available models, a Long-Evans rat model of cognitive impairment is particularly well suited for distinguishing the difference between cognitive impairment related to illness and that related to aging. Indeed, extensive behavioral characterization has identified a naturally occurring form of cognitive impairment in an outbred strain of aged Long-Evans rats (Charles River Laboratories; Gallagher et al., *Behav. Neurosci.* 107:618-626, (1993)). In a behavioral assessment with the Morris Water Maze (MWM), rats learn and remember the location of an escape platform guided by a configuration of spatial cues surrounding the maze. The cognitive basis of performance is tested in probe trials using measures of the animal's spatial bias in searching for the location of the escape platform. Aged rats in the study population have no difficulty swimming to a visible platform, but an age-dependent impairment is detected when the platform is camouflaged, requiring the use of spatial information. Performance for individual aged rats in the outbred Long-Evans strain varies greatly. For example, a proportion of those rats perform on a par with young adults. However, approximately 40-50% fall outside the range of young performance. This variability among aged rats reflects reliable individual differences. Thus, within the aged population some animals are cognitively impaired and designated aged-impaired (AI) and other animals are not impaired and are designated aged-unimpaired (AU). *See*, e.g., Colombo et al., *Proc. Natl. Acad. Sci.* 94: 14195-14199, (1997); Gallagher and Burwell, *Neurobiol. Aging* 10: 691-708, (1989); Rapp and Gallagher, *Proc. Natl. Acad. Sci.* 93: 9926-9930, (1996); Nicolle et al., *Neuroscience* 74: 741-756, (1996); and Nicolle et al., *J. Neurosci.* 19: 9604-9610, (1999).

[0216] We used the above-described rat model to identify individual AI and AU rats. We then conducted behavioral assessment on AI rats while administering various pharmacological treatments.

[0217] Example 1: Increased Gene Expression of SV2A in Aged-Impaired Rats

Behavioral Characterization of Young, Aged-Impaired and Aged-Unimpaired Rats in Morris Water Maze (MWM)

[0218] Behavioral tests are performed on young (4 months old) and aged (24 months old) pathogen-free male Long-Evans rats.

[0219] The MWM apparatus consists of a large, circular pool (diameter 1.83 m; height, 0.58 m) filled with water (27°C) that is made opaque through the addition of non-toxic pigment or some other substance. In the typical "hidden platform" version of the test, rats are trained to find a camouflaged white escape platform (height, 34.5 cm) that is positioned in the center of one quadrant of the maze about 1.0 cm below the water surface. This platform can be retracted to the bottom of the tank or raised to its normal position from outside the maze during behavioral testing. The location of the platform remains constant from trial to trial. Because there are no local cues that mark the position of the platform, the rat's ability to locate it efficiently from any starting position at the perimeter of the pool depends on using information surrounding the maze. The maze is surrounded by black curtains to which white patterns are affixed to provide a configuration of spatial cues. A second platform (height 37.5 cm), with its surface painted black is elevated 2 cm above the water surface during cue training to control for factors unrelated to cognition. The behavior of a rat in the pool is recorded by a camera that is suspended 2.5 m above the center of the pool. The camera is connected to a video tracking system (HVS Image Advanced Tracker VP200) and a PC computer running HVS software developed by Richard Baker of HVS Image, Hampton, UK.

[0220] The MWM protocol is optimized for sensitivity to the effects of aging on cognition and for measures of reliable individual differences within the aged population of out-bred Long-Evans rats (Gallagher et al. *Behav. Neurosci.*

107:618-626, (1993)). Rats receive three trials per day for 8 consecutive days, using a 60 sec inter-trial interval. On each training trial, the rat is released into the maze from one of four equally spaced starting positions around the perimeter of the pool. The starting position varies from trial to trial, thus preventing the use of a response strategy (e.g., always turning left from the start location to locate the escape platform). If a rat does not locate the escape platform within 90 sec on any trial, the experimenter guides the rat to the platform, where it remains for 30 sec. Every sixth trial consists of a probe trial to assess the development of spatial bias in the maze. During these trials, the rat swims with the platform being retracted to the bottom of the pool for 30 sec, at which time the platform is raised to its normal position for completion of the escape trial. At the completion of the protocol using the hidden platform, rats are assessed for cue learning using the visible platform. The location of this platform varies from trial to trial in a single session of 6 training trials.

[0221] The proximity of the animal's position with respect to the goal is used to analyze the training trial and probe trial performance. The proximity measure is obtained by sampling the position of the animal in the maze (10times/sec) to provide a record of distance from the escape platform in 1 sec averages. For both probe trials and training trials, a correction procedure is implemented so that trial performance is relatively unbiased by differences in distance to the goal from the various start locations at the perimeter of the pool. In making this correction, the average swimming speed is calculated for each trial (path length/latency). Then, the amount of time required to swim to the goal at that speed from the start location used for the trial is removed from the record prior to computing trial performance, i.e., cumulative distance on training trials and average distance from the goal on probe trials. Thus, the scores that are obtained using the proximity measure are designed to reflect search error, representing deviations from an optimal search, i.e. direct path to the goal and search in the immediate vicinity of that location during probe trials.

[0222] Computer records of video-tracking are compiled to provide data on each rat's performance in the maze. Measures on training trials and probe trials are analyzed by Analysis of Variance (ANOVA).

[0223] In one set of trials, the performance during training with the hidden, camouflaged platform differs between the groups of young and aged rats [F (1, 23) =12.69, p<0.002]. In this set of trials, no difference between the groups is observed for the cue training trials with a visible platform. In this set of trials, latencies to escape during cue training averaged 9.36 seconds for young and 10.60 seconds for the aged rats.

[0224] An average proximity measure on interpolated probe trials is used to calculate a spatial learning index for each individual subject as described in detail in Gallagher et al., *Behav. Neurosci.* 107:618-26, (1993). When a rat rapidly learns to search for the platform close to its position, its spatial learning index is low. Overall, in one set of trials aged rats differed from young rats [F (1, 23) =15.18, p<0.001]. Aged rats are classified as either unimpaired or impaired relative to the learning index profile of the young study population. Aged rats that fall within the normative range of young rats (index scores <241) are designated aged-unimpaired (AU). The remaining aged subjects that have index scores outside the range of young performance are designated aged-impaired (AI).

Preparation of RNA from Behaviorally Characterized Rats

[0225] Twenty-four outbred Long-Evans rats, that are behaviorally characterized as is described above, are killed by live decapitation to obtain fresh brain tissue. The brain is removed, and the dentate gyrus hippocampal region is microdissected from 500 micron sections taken through the transverse axis of the entire hippocampal formation (both left and right hippocampi) of 24 characterized rats. There are 8 animals in each group (AI, AU, and Y).

[0226] Total RNA is isolated using Trizol reagent (Invitrogen, Carlsbad, CA) according to the standard protocol (homogenization in Trizol reagent followed by chloroform extraction and isopropanol precipitation). Total RNA is further purified using the RNeasy mini kit (Qiagen, Valencia, CA). cRNA probes are then generated from the RNA samples at the Johns Hopkins Microarray Core Facility, generally according to Affymetrix specifications.

[0227] Briefly, 5 μg of total RNA is used to synthesize first strand cDNA using oligonucleotide probes with 24 oligo-dT plus T7 promoter as primer (Proligo LLC, Boulder, CA), and the SuperScript Choice System (Invitrogen). Following the double stranded cDNA synthesis, the product is purified by phenol-chloroform extraction, and biotinilated anti-sense cRNA is generated through in vitro transcription using the BioArray RNA High Yield Transcript Labeling kit (ENZO Life Sciences Inc., Farmingdale, NY). 15 μg of the biotinilated cRNA is fragmented at 94°C for 35 min (100mM Trix-acetate, pH 8.2, 500mM KOAC, 150mM MgOAC). 10 μg of total fragmented cRNA is hybridized to the RAT genome 230-2 Affymetrix GeneChip array for 16 hours at 45°C with constant rotation (60 rpm).

[0228] Affymetrix Fluidics Station 450 is then used to wash and stain the chips, removing the non-hybridized target and incubating with a streptavidin-phycoerythrin conjugate to stain the biotinilated cRNA. The staining is then amplified using goat immunoglobulin-G (IgG) as blocking reagent and biotinilated anti-streptavidin antibody (goat), followed by a second staining step with a streptavidin-phycoerythrin conjugate.

[0229] For quality control of the total RNA from the samples, the Agilent Bioanalyzer, Lab on a Chip technology, is used to confirm that all the samples had optimal rRNA ratios (1:2, for 18S and 28S, respectively) and clean run patterns.

[0230] For quality control of the hybridization, chip image, and comparison between chips, the following parameters are considered: Scaling factor: related to the overall intensity of the chip, to confirm the similar signal intensity and staining through out the samples; Background: estimation of unspecific or cross-hybridization; Percentage of present calls: percentage of transcripts that are considered significantly hybridized to the chip (present) by the algorithm; Glyseraldehyde-3-phosphate dehydrogenase (GAPDH) (3'/5'): representation of the RNA integrity by measuring the ratio of 3' to 5' regions for the housekeeping gene GAPDH, its presence in the chip and a ratio close to 1 advocates for a good integrity of the target (sample); Spikes (BioB/BioC) to confirm the detection level and sensitivity after hybridization.

Data Analysis of Microarray

[0231] Fluorescence is detected using the Affymetrix G3000 GeneArray Scanner and image analysis of each GeneChip is done through the GeneChip Operating System 1.1.1 (GCOS) software from Affymetrix, using the standard default settings. All of the GeneChip arrays use short oligonucleotides for genes in an RNA sample.

[0232] For comparison between different chips, global scaling is used, scaling all probe sets to target intensity (TGT) of 150. Total number of present calls and scaling factors are similar across all chips. Further analysis for presence/absence and statistical difference is performed on a region by region basis in the following manner. Probe sets are determined to be present in a region if it had a present call in four of eight animals in a single group.

[0233] Probe sets are annotated using the Affymetrix annotation of June 20, 2005, and all probe sets representing a specific gene are identified.

[0234] An ANOVA is conducted on the probe set signal values for all present probe sets by combining two groups of animals and comparing them to the third group. An "AI ANOVA" is performed, where AU group are combined with Young group and compared to AI group.

[0235] Pearsons's correlations comparing probe set signal values to learning indices are calculated for the aged animals (excluding young) across all present probe sets. As shown in **FIG. 1**, expression of genes encoding SV2A is significantly increased in aged-impaired (AI) individuals relative to young individuals (Y) and aged-unimpaired individuals (AU) in a set of experiments performed as above. These results show that increased SV2A expression is correlated to the development of age-related cognitive impairment.

[0236] Example 2: Effect of Levetiracetam in Aged-Impaired Rats

Morris Water Maze Results

[0237] Six Age-Impaired (AI) Long-Evans rats (as characterized above) are tested for their memory of new spatial information in the MWM, under different drug/control treatment conditions (vehicle control and two different dosage levels of levetiracetam). The MWM protocol is substantially the same as the one described in Example 1. Specifically for this study, a retention trial is performed after the training trials, as described below.

[0238] AI rats are given six training trials per training day with a 60-sec inter-trial interval between each training trial for two consecutive days. On each training trial, the rat is released in the maze from one of four equally spaced starting positions around the perimeter of the pool. If the rat does not locate the escape platform within 90 sec on any trial, the experimenter guides the rat to the platform, where it remains for 30 sec. 30 minutes to 1 hour prior to all the training trials on each training day, AI rats are pretreated with one of three drug conditions: 1) vehicle control (0.9% saline solution); 2) levetiracetam (5m/kg/day); and 3) levetiracetam (10mg/kg/day); through intraperitoneal (i.p.) injection. The same six AI rats are used for the entire trials so that each treatment condition is tested on all six rats. Therefore, to counterbalance any potential bias, both the location of the escape platform and the spatial cues surrounding the water maze are different in the three treatment conditions. Therefore, using one set of locations and spatial cues, two rats are treated with saline control solution, two with levetiracetam (5m/kg/day) and two with levetiracetam (10mg/kg/day). Using the second set of locations and spatial cues, the two rats that are treated with saline control solution in the first test are treated with either levetiracetam (5m/kg/day) or levetiracetam (10mg/kg/day), and the two rats that are previously treated with levetiracetam (5m/kg/day) are treated with either saline control solution or levetiracetam (10mg/kg/day), and the two rats that are previously treated with levetiracetam (10mg/kg/day) are treated with either saline control solution or levetiracetam (5m/kg/day). Using the last set of locations and spatial cues, the rat groupings are again switched so that each group is treated with a different condition than they have been treated previously.

[0239] After the second training day and completion of the twelve training trials (over the two days), the rat is returned to its home cage and placed in the animal housing room. After a delay of 24 hours from the last training trial, the rat is given one testing trial (the "retention trial"), which is the same MWM task as the training trials, but with the escape platform removed.

[0240] For the retention trial, the MWM circular pool is divided into 4 quadrants. The particular quadrant where the escape platform is placed in the training trials is referred as "target quadrant". The particular region where the platform is located in the training trials is referred as "target annulus". In the retention trial, the time the AI rats spent swimming in the target quadrant is measured and further plotted as a percentage of total swimming time. **FIG. 2** displays the results of one such set of retention trials. The time the AI rats spend in the target annulus is also measured. **FIG. 2** displays the results of one such set of retention trials. Time data are collected for all three drug treatment conditions.

[0241] In the retention trial, whose results are depicted in **FIG. 2**, the time the AI rats spend in the target quadrant is approximately 25%, which is a performance equivalent to them having no memory of the platform location. This performance does not significantly improve in the group treated with levetiractam at 5mg/kg/day. However, the group treated with levetiractam at 10 mg/kg/day demonstrates significantly improved memory as compared to vehicle-treated controls, as indicated by a significant increase in the time spent in the target quadrant to approximately 35% of total swimming time (*see* **FIG. 2)**. That level of performance is equivalent to young and age-unimpaired rats, indicating that treatment with 10 mg/kg/day levetiractam results in a significant recovery of the AI rats' ability to navigate this MWM. The effectiveness of the 10 mg/kg/day levetiracetam treatment is also seen in the time spent in the target annulus (*see* **FIG. 2**).

Radial Arm Maze Results

[0242] The effects of levetiracetam on the spatial memory retention of aged-impaired (AI) rats are assessed in a Radial Arm Maze (RAM) behavioral task using vehicle control and five different dosage levels of levetiracetam (1.25 mg/kg/day, 2.5 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day and 20 mg/kg/day). RAM behavioral tasks are preformed on ten AI rats. All six treatment conditions are tested on all ten rats, as described above for the MWM test.

[0243] The RAM apparatus used consists of eight equidistantly-spaced arms. An elevated maze arm (7 cm width x 75 cm length) projects from each facet of an octagonal center platform (30 cm diameter, 51.5 cm height). Clear side walls on the arms are 10 cm high and are angled at 65° to form a trough. A food well (4 cm diameter, 2 cm deep) is located at the distal end of each arm. Froot Loops™ (Kellogg Company) are used as rewards. Blocks constructed of Plexiglas™ (30 cm height x 12 cm width) can be positioned to prevent entry to any arm. Numerous extra maze cues surrounding the apparatus are also provided.

[0244] The AI rats are initially subjected to a pre-training test (Chappell *et al.* Neuropharmacology 37: 481-487, 1998). The pre-training test consists of a habituation phase (4 days), a training phase on the standard win-shift task (18 days) and another training phase (14 days) in which a brief delay is imposed between presentation of a subset of arms designated by the experimenter (e.g., 5 arms available and 3 arms blocked) and completion of the eight-arm win-shift task (i.e., with all eight arms available).

[0245] In the habituation phase, rats are familiarized to the maze for an 8-minute session on four consecutive days. In each of these sessions food rewards are scattered on the RAM, initially on the center platform and arms and then progressively confined to the arms. After this habituation phase, a standard training protocol is used, in which a food pellet is located at the end of each arm. Rats receiv one trial each day for 18 days. Each daily trial terminates when all eight food pellets have been obtained or when either 16 choices are made or 15 minutes had elapsed. After completion of this training phase, a second training phase is carried out in which the memory demand is increased by imposing a brief delay during the trial. At the beginning of each trial, three arms of the eight-arm maze are blocked. Rats are allowed to obtain food on the five arms to which access is permitted during this initial 'information phase' of the trial. Rats are then removed from the maze for 60 seconds, during which time the barriers on the maze are removed, thus allowing access to all eight arms. Rats are then placed back onto the center platform and allowed to obtain the remaining food rewards during this 'retention test' phase of the trial. The identity and configuration of the blocked arms varies across trials.

[0246] The number of "errors" the AI rats make during the retention test phase is tracked. An error occurs in the trial if the rats enter an arm from which food had already been retrieved in the pre-delay component of the trial, or if it re-visits an arm in the post-delay session that has already been visited.

[0247] After completion of the pre-training test, rats are subjected to trials with more extended delay intervals, i.e., a one-hour delay, between the information phase (presentation with some blocked arms) and the retention test (presentation of all arms). During the delay interval, rats remain off to the side of the maze in the testing room, on carts in their individual home cages. AI rats are pretreated 30 – 40 minutes before daily trials with a one-time shot of the following six conditions: 1) vehicle control (0.9% saline solution); 2) levetiracetam (1.25 mg/kg/day); 3) levetiracetam (2.5 mg/kg/day); 4) levetiracetam (5 mg/kg/day); 5) levetiracetam (10 mg/kg/day); 6) levetiracetam (20 mg/kg/day); through intraperitoneal (i.p.) injection. Injections are given every other day with intervening washout days. Each AI rat is treated with all six conditions within 23 days of testing. To counterbalance any potential bias, drug effect is assessed using ascending-descending dose series, i.e., the dose series are given first in an ascending order and then repeated in a descending order. Therefore, each dose has two determinations.

[0248] Parametric statistics (paired t-tests) is used to compare the retention test performance of the AI rats in the one-hour delay version of the RAM task in the context of different doses of levetiracetam and vehicle control (*see* **FIG. 3**). The average numbers of errors that occur in the trials are also significantly fewer with levetiracetam treatment of 5 mg/kg/day (average no. of errors ± standard error of the mean (SEM) = 0.75 ± 0.32) and 10 mg/kg/day (average no. of errors ± SEM = 0.80 ± 0.27) than using vehicle control (average no. of errors ± SEM = 2.00 ± 0.42). Relative to vehicle control treatment, levetiracetam significantly improves memory performance at 5 mg/kg/day ($t(9) = 2.18$, $p = 0.057$) and 10 mg/kg/day ($t(9) = 2.37$, $p = 0.042$).

[0249] The radial arm maze task is also used to evaluate the effect of a combination therapy with Levetiracetam (i.p. administration) and valproate (subcutaneous administration). Levetiracetam, on its own, is effective in reducing the number of errors by AI rats in the radial arm maze at 5-10 mg/kg doses, but not at 1.25 mg/kg or 2.5 mg/kg. Valproate, on its own, is effective at 100 mg/kg but not at 25 mg/kg or 50 mg/kg. See **FIG. 4**. Combining the two drugs, however, has a synergistic effect. A combined administration of 50 mg/kg valproate with 2.5 mg/kg levetiracetam, neither being an effective dose when administered individually, results in a reduced number of errors in the radial arm maze task. This result is also obtained at an even lower dose of 1.25 mg/kg levetiracetam combined with 50 mg/kg valproate. See **FIG. 5**. An isobologram of levetiracetam and valproate dosages confirms that the effect of the combined 50 mg/kg valproate and 1.25 mg/kg levetiracetam (VPA 50 + LEV 1.25; empty circle) has a synergistic (super-additive) effect. The combined 50 mg/kg valproate and 2.5 mg/kg levetiracetam (VPA 50 + LEV 2.5; dark circle), on the other hand, has a simple additive effect, as indicated by its placement on the line. See **FIG. 6**.

[0250] To calculate the human equivalent dose (HED) for levetiracetam dosage for treatment of age-dependent cognitive impairment in humans, we employ the formula HED (mg/kg) = rat dose (mg/kg) x 0.16 (*see* Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, December 2002, Center for Biologics Evaluation and Research). Therefore, based on the HED calculation, the dosage of 5 mg/kg/day in rats is equivalent to 0.8 mg/kg/day in humans and the dosage of 10 mg/kg/day in rats is equivalent to 1.6 mg/kg/day in humans.

[0251] The HED calculation is based on body surface area. As a result, it is an estimate of what human dose corresponds to an animal (*e.g.*, rat) dose in the context of a maximum safe starting dose for clinical trials in humans. Calculating the HED is typically an initial step in carrying out the clinical trial of a drug in humans. It is not an indication of the ultimate human therapeutic dose. See, "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Health Volunteers, December 2002, Center for Biologics Evaluation and Research." Blood/plasma levels are a far better predictor of therapeutic dose correspondence between animals (*e.g.*, rats) and humans. As described below in Example 7, the actual levetiracetam blood levels of its daily doses in the aMCI patient human clinical studies (62.5 mg BID, 125 mg BID, and 250 mg BID levetiracetam doses) (see Figs. 27A, 27B and 27C) and the actual levetiracetam blood levels of its daily doses of 10 mg/kg and 60 mg/kg in the AI rat experiments are evaluated. Based on the blood levels, the therapeutically effective human doses that correspond to the effective rat doses (*i.e.*, 5-10 mg/kg/day) are estimated to be 1.6- 3.3 mg/kg/day. Such a dosage would result in the administration of 56 - 115 mg twice a day in human subjects.

[0252] Example 3: Effect of Levetiracetam in human subjects with aMCI

[0253] A within-subjects trial of 8 weeks duration, involving 17 amnestic MCI (aMCI) subjects and 17 age-matched controls with a low dose treatment of levetiracetam is conducted. During the course of the study, each aMCI subject receives both drug and placebo treatments separately in two periods of two weeks each, with the order of treatments among different aMCI subjects being counterbalanced (see **FIG. 7**). Age-matched control subjects that are treated with placebo serve as a further control. Cognitive testing and fMRI imaging data are obtained from the subjects after each two week period of drug/placebo treatment.

Participants and clinical characterization

[0254] 17 right-handed aMCI patients are recruited from the Alzheimer’s Disease Research Center (ADRC) at the Johns Hopkins Hospital and other referrals. An additional 17 right-handed healthy volunteers are recruited from the pool of control participants in the ADRC and other referrals. All participants are administered the Telephone Interview of Cognitive Status to determine if they are likely to pass the entry criteria of the study (including criteria for MRI scanning). All participants further undergo neurological, psychiatric, and neuropsychological examination using standardized instruments and methods. The psychiatric evaluation includes administration of the Structured Clinical Interview for DSM-IV Axis I Disorders and the Clinical Dementia Rating (CDR) scale. All aMCI patients have CDR scores of 0.5. Diagnosis of aMCI is based on the criteria proposed by Petersen et al. (e.g., “Mild cognitive impairment: Aging to Alzheimer's Disease,” Oxford University Press, N.Y. (2003), which include a memory complaint (corroborated by an informant), impaired memory function on testing (1.5 standard deviations below norm), otherwise preserved cognitive functioning (within 1 standard deviation of norm), no decline in functional ability, and no dementia. Final aMCI diagnoses are reached by clinical consensus. Exclusion criteria include major neurological or psychiatric disorders, head trauma with loss of consciousness, history of drug abuse or dependency, and general contraindications to an MRI examination (e.g. cardiac pacemaker, aneurysm coils, claustrophobia). Each aMCI subject is required to have a study partner (i.e., an informant) who can provide information about the subject’s daily function and assure that medications are taken appropriately. See **FIGS. 18A** and **18B**.

[0255] Study Visits: The study consists of 4 visits over the course of 8 weeks (see **FIG. 7**). The Baseline Visit is for the purpose of performing medical, neurological, psychiatric, and neurocognitive assessments. Visits 1 and 2 are identical to the Baseline Visit but include a fMRI session. The Washout Visit, at the end of a 4 week washout period, is for the purpose of a brief clinical assessment and initiation of the second drug/placebo phase.

[0256] Baseline Visit: At the screening visit, informed consent is obtained from the subject (and an informant in the case of MCI subjects). The subject and the informant participate in a standardized clinical interview that is used to determine the degree of the subject's functional impairment in daily life, based on the Clinical Dementia Rating (CDR) scale. The subject's medical, neurological, and psychiatric history is obtained (including a review of current medications), as well as the family history of dementia. Brief medical, neurological and psychiatric exams are conducted (including vital signs). Blood is drawn in order to perform standard laboratory tests that are needed to determine if the subject meets the entry criteria. The subject is re-screened for contraindications to MRI scanning, using the standard form employed at the Kirby Imaging Center. Brief cognitive testing is performed (described in section on neuropsychological assessment below). These assessments are used to determine if the subject meets the entry criteria. All of the foregoing are completed using standardized forms. If the subject meets entry criteria for the study, the subject is given the study medication (drug or placebo, randomly selected), and instructions about how it should be taken. The subject is advised about the potential for having suicidal thoughts and advised to stop taking the medication and immediately contact the study physician if this occurs.

[0257] Visit 1: At the end of the first drug/placebo period 2 weeks after the Baseline Visit, the medical, neurological and psychiatric evaluations and cognitive testing are repeated. The subject is also clinically evaluated for suicidal ideation. Blood is drawn again to repeat the standard tests and to determine whether there are any changes related to drug treatment; the subject's blood levetiracetam level is also obtained. All medication that is dispensed at the Baseline Visit (drug or placebo) is collected and subject compliance with the medication regimen is assessed. The first fMRI session (with cognitive tests) is conducted on the same day, either immediately before or immediately after the clinical assessment. Subjects discontinue first period treatment at this visit.

[0258] **Washout Visit**: At the end of a washout period (4 weeks) following Visit 1, the subject receives a brief medical screening, including a medical and psychiatric evaluation. Blood is drawn to obtain the blood levetiracetam level (to confirm washout). The subject is provided with new medication (drug or placebo, alternated from what is assigned in the previous treatment period) for the final phase of the study with instructions about how it should be taken.

[0259] **Visit 2**: At approximately 2 weeks after the Washout Visit (i.e., 2 weeks after starting the second treatment period), the medical, neurological and psychiatric evaluations and the cognitive testing are repeated. The subject is clinically evaluated for suicidal ideation. Blood is drawn again to repeat the standard tests and to determine whether there are any changes related to drug treatment; the subject's blood levetiracetam level is also obtained. All medication that is dispensed at the Washout Visit is collected and subject compliance with the medication regimen is assessed. The second fMRI session (with cognitive tests) is repeated on the same day, either immediately before or immediately after the clinical assessment.

Neuropsychological assessment

[0260] All participants undergo neuropsychological evaluation at the time of assessment for treatment efficacy (Visits 1 and 2), as well as at the Baseline Visit. The evaluation occurs outside of the scanner and includes the Buschke Selective Reminding Test (Buschke and Fuld, 1974) and the Verbal Paired Associates subtest, the Logical Memory subtest, the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997), and the Benton Visual Retention Test, as these tasks are particularly sensitive to medial temporal lobe function and early memory problems (Marquis et al., 2002 and Masur et al., 1994). Additionally, subjects are asked to complete tests of more general cognitive function such as tests to assess general mental status, executive function, attention and general naming ability. All neuropsychological tests are administered by a trained research assistant during a 60-minute session. As the three neuropsychological assessments in this study occur within a time period of 8 weeks, different versions of the neuropsychological tests are used to minimize test specific practice effects. Breaks are provided to the subject as needed.

Drug administration

[0261] As described above, the drug treatment period is the two weeks preceding Visit 1 or 2 (with the two week period preceding the other Visit being the placebo phase). For the subjects receiving the drug treatment, half a scored 250 mg tablet of levetiracetam is used to achieve a dose of 125 mg/kg twice a day, which is approximately 3.6 mg/kg/day (assuming an average adult human weight of 70 kg).

[0262] All drug and placebo preparations are performed on a 1:1 allocation. The pharmacy randomizes patients as they enroll, and keeps a list of drug assignment.

[0263] Levetiracetam is rapidly and almost completely absorbed after oral administration, and its bioavailability is not affected by food. Plasma half-life of levetiracetam is approximately 7 ± 1 hour (expected to be 9-10 hours in elderly due to decreased renal function). Absorption is rapid, with peak plasma concentrations occurring about 1 hour following oral administration. Steady state can be achieved after 2 days of multiple twice-daily dosing.

[0264] A typical starting dose of levetiracetam in treating epilepsy in humans is 500 mg twice a day, which is approximately 14.3 mg/kg/day. The dosage is then is increased until optimal efficacy, typically up to 50 mg/kg/day. Thus, the dose that is used in this experiment is a quarter of the lowest human dose used for treating epilepsy.

[0265] Even lower dosages, e.g., of 25-60 mg twice a day, are contemplated, based on the results of previous animal studies that indicate low-dose efficacy. The highest effective doses of levetiracetam used in the animal model are 5-10 mg/kg (given acutely). The human equivalent dose (HED), calculated as described above, of this dosage for treatment of age-dependent cognitive impairment in humans is equivalent to 0.8-1.6 mg/kg/day (or 28-56 mg twice a day).

MRI data acquisition

[0266] Imaging data are obtained through high-resolution methods developed in the Stark laboratory. Data are collected on a Phillips 3 Tesla scanner (Eindhoven, The Netherlands) equipped with an 8-channel SENSE (Sensitivity Encoding) head coil, located at the F.M. Kirby Research Center for Functional Brain Imaging at the

Kennedy Krieger Institute (Baltimore, MD). High-resolution echo-planar images are collected using an acquisition matrix of 64 x 64, a repetition time of 1500 milliseconds, an echo time of 30 milliseconds, a flip angle of 70 degrees, a SENSE factor of 2, and an isotropic resolution of 1.5 mm x 1.5 mm x 1.5 mm with no gap. Nineteen oblique slices are acquired parallel to the principal longitudinal axis of the hippocampus and covered the entire medial temporal lobe region bilaterally. In addition to the functional runs, a whole-brain MPRAGE structural scan (parameters: 150 oblique slices, 1mm isotropic resolution) is acquired.

Image analysis

[0267] Data analysis is carried out using the Analysis for Functional Neuroimages (AFNI, release 2008_07_18_1710) software. Images are first co-registered to correct for within- and across-scan head motion. Acquisitions in which a significant motion event occur (more than 3 degrees of rotation or 2 mm of translation in any direction relative to prior acquisition), plus and minus one time repetition for 1.5 seconds, are excluded from the analyses. Structural anatomical data are registered to standard stereotaxic space (Talairach & Tournoux, 1988), and the same parameters are subsequently applied to the functional data. Behavioral vectors are produced to model different trial types.

[0268] The ROI-LDDMM (large deformation diffeomorphic metric mapping of the region of interest) method, a technique for cross-subject alignment, increases the power of multisubject regional fMRI studies by focusing the alignment power specifically on the ROIs (regions of interest) and not elsewhere in the brain. First, all subjects' anatomical and functional scans are normalized to the Talairach atlas using AFNI. Sub-regions of the medial temporal lobe and the hippocampus (bilateral entorhinal cortex, perirhinal cortex, parahippocampal cortex, CA3/dentate region, CA1 region, and subiculum) are segmented in three dimensions on the MPRAGE scans. The labels for the CA3 region and dentate gyrus (DG) are combined. The anatomically defined ROIs are then used to calculate the ROI-LDDMM 3D vector field transformation for each subject using a customized template that is based on the mean of the entire sample is tested as the target. The ROI-LDDMM transformations for each individual subject's ROIs are then applied to the fit coefficient maps.

[0269] Group data are analyzed using a two-way Analysis of Variance (ANOVA) with trial types and group as fixed factors, and subject as a random factor nested within group. A liberal peak threshold of $p<0.05$, along with a spatial extent threshold of 10 voxels are used to define functional ROIs on the overall F statistic. This approach, rather than using a direct pair-wise contrast, reduces voxel selection biases because any differences amongst the various conditions allows for a voxel to be selected. This threshold is then combined with the anatomical segmentations to only include voxels inside the regions of interest. This serves to exclude voxels that do not change with any of the model's factors, effectively limiting the analysis to voxels showing any changes with task condition or group. Voxels within each functional ROI are collapsed for further analysis.

Cognitive tests during fMRI scans at Visits 1 and 2

[0270] The activity of the subject's medial temporal lobe is measured by functional MRI during the subject's participation in an explicit 3-alternative forced choice task, where participants view novel, repeated and similar ("lure") stimuli. The Psychophysics Toolbox extensions in Matlab 7.0 (The MathWorks, Natick, MA) is used for stimulus presentation and behavioral data collection. Stimuli are color photographs of common objects. Each participant undergoes a series of testing runs during the functional imaging sessions, each run consisting of a mix of three types of image pairs: similar pairs, identical pairs and unrelated foils. These image pairs are fully randomized throughout the run and presented individually as a series of images (see **FIG. 10A**). Participants are instructed to make a judgment as to whether each object seen is new, old or similar. Of critical interest are the participants' responses when presented with the second of the pair of similar objects (the "lure"; see **FIG. 10B**). The correct identification by the subject of lure stimuli as "similar," provides behavioral evidence of pattern separation, i.e., the separation of similar experiences into distinct non-overlapping representations. However, an incorrect identification of lure stimuli as "old" or "new," indicates a failure of pattern separation. Identification of lure stimuli as "old" indicates that the subject is focused on the similarities between the lure stimulus and the earlier-shown partner image. Identification of the lure stimulus as "new" indicates that the subject fails to recall the earlier-shown partner image altogether. Each run also contains a number of baseline trials that use a challenging perceptual discrimination task which is known to provide a lower and more-stable estimate of baseline activity in the medial temporal lobe (Stark & Squire, 2001 PNAS; Law et al, 2005).

[0271] A survey of the activity level of various subregions in the medial temporal lobe during the cognitive test, which is measured by fMRI, shows that aMCI subjects have hyperactive DG/CA3 regions and a hypoactive entorhinal cortex during the performance of memory tasks, in comparison to age-matched control subjects.

[0272] We assess the level of activity in DG/CA3 during successful memory judgments in control and aMCI subjects. The mean activity is calculated from the average activity, which is measured by fMRI, during the presentation of lure stimuli correctly identified by subject as "similar" that is calibrated for baseline activity. **FIG. 8A** shows that aMCI patients exhibit DG/CA3 hyperactivity when making these judgments ($p = 0.013$). **FIG. 8B**, however, shows that treatment with levetiracetam reduces DG/CA3 hyper-activity in aMCI subjects ($p = 0.037$). The activity level in the aMCI subject treated with the drug, in fact, is normalized to the extent that that it is statistically indistinguishable from the activity of control subjects treated with placebo. See **FIG. 8C** for the mean activity values shown in **FIGS. 8A and 8B**.

[0273] The activity level during successful memory judgments in EC is significantly lower in placebo-treated aMCI subjects in comparison to controls ($p = 0.003$). See **FIG. 9A**. However, levetiracetam treatment normalizes activity in aMCI subjects in EC as well. See **FIG. 9B**. Levetiracetam treatment increases EC activity during memory judgments in aMCI subjects, such that it is statistically indistinguishable from placebo-treated control subjects. See **FIG. 9B**. See **FIG. 9C** for the mean activity values shown in **FIGS. 9A and 9B**.

[0274] The normalization of DG/CA3 and EC activity during memory judgments by levetiracetam treatment is mirrored in the change seen in the aMCI subjects' performance in the cognitive task. With placebo treatment, aMCI patients perform worse than control subjects, correctly identifying lure items as "similar" less often and incorrectly identifying them as "old" more often ($p = 0.009$). See **FIG. 11**.

However, the performance of aMCI subjects improves significantly under levetiracetam treatment. See **FIG. 12**. The interaction of more correct “similar” identifications with less incorrect “old” identifications under drug treatment results in a significant improvement in the performance of this memory task ($p = 0.039$). See **FIG. 13** for a table of the data represented in **FIGS. 11** and **12**.

[0275] The performance of control-placebo subjects and aMCI subjects with drug or placebo treatment is also compared in other common cognitive tests, such as the Buschke Selective Reminding Test – Delayed Recall (**FIGS. 14A** and **14B**), the Benton Visual Retention Test (**FIGS. 15A** and **15B**), Verbal Paired Associates Test – Recognition (**FIGS. 16A** and **16B**) and Verbal Paired Associates Test – Delayed Recall (**FIGS. 17A** and **17B**). In all of these tests, aMCI subjects who are treated with placebo perform worse than control subjects who are treated with placebo, and levetiracetam treatment fails to rescue performance in aMCI subjects.

[0276] There are a number of possible reasons why levetiracetam treatment does not help aMCI subjects with performance in these other cognitive tests. The explicit 3-alternative forced choice task that is done in the fMRI study is a task that is especially sensitive to DG/CA3 function. As such, the performance of the subjects in this task may be particularly attuned to the changes in DG/CA3 activity resulting from levetiracetam treatment. Further, the aMCI subjects are treated with levetiracetam for only two weeks prior to the administration of the cognitive tests. It is contemplated that a treatment duration of longer than two weeks, e.g., 16 weeks or 8 months, will result in improved efficacy. Finally, comparative animal studies (see Example 2) indicate that an even lower dose would be more effective. The human dosage of 125 mg twice a day is equivalent (HED) to a rat dosage of 22.3 mg/kg/day. As is shown in Example 2 and **FIG. 3**, 20 mg/kg levetiracetam is too high a dose in rats, and it fails to improve the performance of AI rats in the radial maze task. The effective doses of levetiracetam that are used in the animal model in Example 2 are 5-10 mg/kg. The human equivalent dose (HED) of the optimal rat dose in Example 2 is 0.8-1.6 mg/kg/day. Such a dosage would result in the administration of 28-56 mg twice a day (which is substantially lower than the 125 mg twice a day that is used in this study). Thus, it is contemplated that aMCI subjects will exhibit a further normalization of DG/CA3 and EC activity, as well as further improved performance in cognitive tests, if they are treated with lower doses equivalent to the effective doses in rat, e.g., 25 – 60 mg twice a day of levetiracetam.

[0277] The HED calculation is based on body surface area. As a result, it is an estimate of what human dose corresponds to an animal (*e.g.*, rat) dose in the context of a maximum safe starting dose for clinical trials in humans. Calculating the HED is typically an initial step in carrying out the clinical trial of a drug in humans. It is not an indication of the ultimate human therapeutic dose. See, "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Health Volunteers, December 2002, Center for Biologics Evaluation and Research." Blood/plasma levels are a far better predictor of therapeutic dose correspondence between animals (*e.g.*, rats) and humans. As described below in Example 7, the actual levetiracetam blood levels of its daily doses in the aMCI patient human clinical studies (62.5 mg BID, 125 mg BID, and 250 mg BID levetiracetam doses) (see Figs. 27A, 27B and 27C) and the actual levetiracetam blood levels of its daily doses of 10 mg/kg and 60 mg/kg in the AI rat experiments are evaluated. The levetiracetam blood level of its daily doses of 5 mg/kg and 20 mg/kg in the AI rats can be estimated by extrapolation. The therapeutically effective rat and human doses produce similar rat and human levetiracetam blood levels. Likewise, the non-therapeutically effective rat and human doses produce similar rat and human levetiracetam blood levels. Compare Humans: 7.9 mcg/ml (250 mg BID) with Rats: 7.6 mcg/ml (20 mg/kg). Based on the blood levels, the therapeutically effective human doses that correspond to the effective rat dose in Example 2 (*i.e.*, 5-10 mg/kg/day) are estimated to be 1.6- 3.3 mg/kg/day. Such a dosage would result in the administration of 56 - 115 mg twice a day. Example 4 confirms that aMCI subjects exhibit a further normalization of DG/CA3 and EC activity, as well as further improved performance in cognitive tests when they are treated with 62.5 mg BID levetiracetam (*i.e.*, a therapeutically effective dose that falls within 56 – 115 mg twice a day).

[0278] Example 4: Effect of Levetiracetam in human subjects with aMCI

[0279] A within-subjects trial of 8 weeks duration, involving 38 amnestic MCI (aMCI) subjects and 17 age-matched controls with a low dose treatment of levetiracetam is conducted. During the course of the study, each aMCI subject receives both drug and placebo treatments separately in two periods of two weeks each, with the order of treatments among different aMCI subjects being counterbalanced (see **FIG. 7**). Age-matched control subjects are treated with placebo to serve as a further control. Cognitive testing and fMRI imaging data are obtained from the subjects after each two-week period of drug/placebo treatment.

Participants and clinical characterization

[0280] 38 right-handed aMCI patients are recruited from the Alzheimer's Disease Research Center (ADRC) at the Johns Hopkins Hospital and other referrals. An additional 17 right-handed healthy volunteers are recruited from the pool of control participants in the ADRC and other referrals. All participants are administered the Telephone Interview of Cognitive Status to determine if they are likely to pass the entry criteria of the study (including criteria for MRI scanning). All participants further undergo neurological, psychiatric, and neuropsychological examination using standardized instruments and methods. The psychiatric evaluation includes administration of the Structured Clinical Interview for DSM-IV Axis I Disorders and the Clinical Dementia Rating (CDR) scale. All aMCI patients have CDR scores of 0.5. Diagnosis of aMCI is based on the criteria proposed by Petersen et al. (e.g., "Mild cognitive impairment: Aging to Alzheimer's Disease," Oxford University Press, N.Y. (2003), which include a memory complaint (corroborated by an informant), impaired memory function on testing (generally 1.5 standard deviations below the norm and at least 1 standard deviation below the norm), otherwise preserved cognitive functioning (within 1 standard deviation of norm), no decline in functional ability, and no dementia. Final aMCI diagnoses are reached by clinical consensus. Exclusion criteria include major neurological or psychiatric disorders, head trauma with loss of consciousness, history of drug abuse or dependency, and general contraindications to an MRI examination (e.g. cardiac pacemaker, aneurysm coils, claustrophobia). Each aMCI subject is required to have a study partner (i.e., an informant) who can provide information about the subject's daily function and assure that medications are taken appropriately.

[0281] Study Visits: The study consists of 4 visits over the course of 8 weeks (see **FIG. 7**). The Baseline Visit is for the purpose of performing medical, neurological, psychiatric, and neurocognitive assessments. Visits 1 and 2 are identical to the Baseline Visit but include an fMRI session. The Washout Visit, at the end of a 4 week washout period, is for the purpose of a brief clinical assessment and initiation of the second drug/placebo phase.

[0282] Baseline Visit: At the screening visit, informed consent is obtained from the subject (and an informant in the case of MCI subjects). The subject and the informant participate in a standardized clinical interview that is used to determine the degree of the subject's functional impairment in daily life, based on the Clinical Dementia Rating (CDR) scale. The subject's medical, neurological, and psychiatric history is obtained (including a review of current medications), as well as the family history of dementia. Brief medical, neurological and psychiatric exams are conducted (including vital signs). Blood is drawn in order to perform standard laboratory tests that are needed to determine if the subject meets the entry criteria. The subject is re-screened for contraindications to MRI scanning, using the standard form employed at the Kirby Imaging Center. Brief cognitive testing is performed (described in section on neuropsychological assessment below). These assessments are used to determine if the subject meets the entry criteria. All of the foregoing are completed using standardized forms. If the subject meets entry criteria for the study, the subject is randomly assigned to either the 62.5 mg BID or 250 mg BID study group and given the study medication (drug or placebo, randomly selected), and instructions about how it should be taken. The subject is advised about the potential for having suicidal thoughts and advised to stop taking the medication and immediately contact the study physician if this occurs.

[0283] Visit 1: At the end of the first drug/placebo period 2 weeks after the Baseline Visit, the medical, neurological and psychiatric evaluations and cognitive testing are repeated. The subject is also clinically evaluated for suicidal ideation. Blood is drawn again to repeat the standard tests and to determine whether there are any changes related to drug treatment; the subject's blood levetiracetam level is also obtained. All medication that is dispensed at the Baseline Visit (drug or placebo) is collected and subject compliance with the medication regimen is assessed. The first fMRI session (with cognitive tests) is conducted on the same day, either immediately before or immediately after the clinical assessment. Subjects discontinue first period treatment at this visit.

[0284] **Washout Visit**: At the end of a washout period (4 weeks) following Visit 1, the subject receives a brief medical screening, including a medical and psychiatric evaluation. Blood is drawn to obtain the blood levetiracetam level (to confirm washout). The subject is provided with new medication (drug or placebo, alternated from what is assigned in the previous treatment period) for the final phase of the study with instructions about how it should be taken.

[0285] **Visit 2**: At approximately 2 weeks after the Washout Visit (i.e., 2 weeks after starting the second treatment period), the medical, neurological and psychiatric evaluations and the cognitive testing are repeated. The subject is clinically evaluated for suicidal ideation. Blood is drawn again to repeat the standard tests and to determine whether there are any changes related to drug treatment; the subject's blood levetiracetam level is also obtained. All medication being dispensed at the Washout Visit is collected and subject compliance with the medication regimen is assessed. The second fMRI session (with cognitive tests) is repeated on the same day, either immediately before or immediately after the clinical assessment.

Neuropsychological assessment

[0286] All participants undergo neuropsychological evaluation at the time of assessment for treatment efficacy (Visits 1 and 2), as well as at the Baseline Visit. The evaluation occurs outside of the scanner and includes the Buschke Selective Reminding Test (Buschke and Fuld, 1974) and the Verbal Paired Associates subtest, the Logical Memory subtest, the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997), and the Benton Visual Retention Test, as these tasks are particularly sensitive to medial temporal lobe function and early memory problems (Marquis et al., 2002 and Masur et al., 1994). Additionally, subjects are asked to complete tests of more general cognitive function such as tests to assess general mental status, executive function, attention and general naming ability. All neuropsychological tests are administered by a trained research assistant during a 60-minute session. As the three neuropsychological assessments in this study occur within a time period of 8 weeks, different versions of the neuropsychological tests are used to minimize test specific practice effects. Breaks are provided to the subject as needed.

Drug administration

[0287] As described above, the drug treatment period is the two weeks preceding Visit 1 or 2 (with the two week period preceding the other Visit being the placebo phase). For the subjects receiving the 250 mg BID (BID stands for twice daily) drug treatment, two 250 mg tablets of levetiracetam are used to achieve a dose of 250 mg twice a day, i.e., 500 mg/day, which is approximately 7.1 mg/kg/day (assuming an average adult human weight of 70 kg). For the subjects receiving the 62.5 mg BID drug treatment, a quarter of a scored 250 mg tablet of levetiracetam is used to achieve a dose of 62.5 twice a day, i.e., 125 mg/day which is approximately 1.5 mg/kg/day.

[0288] All drug and placebo preparations are performed on a 1:1 allocation. The pharmacy randomizes patients to drug dose and condition as they enroll, and keep a list of drug assignment.

[0289] Levetiracetam is rapidly and almost completely absorbed after oral administration, and its bioavailability is not affected by food. Plasma half-life of levetiracetam is approximately 7 ± 1 hour (expected to be 9-10 hours in elderly due to decreased renal function). Absorption is rapid, with peak plasma concentrations occurring about 1 hour following oral administration. Steady state can be achieved after 2 days of multiple twice-daily dosing.

[0290] A typical starting dose of levetiracetam in treating epilepsy in humans is 500 mg twice a day, which is approximately 14.3 mg/kg/day. The dosage is then is increased until optimal efficacy, typically up to 50 mg/kg/day. Thus, the 250 mg BID dose (500 mg/day) that is used in this experiment is one-half of the lowest human dose used for treating epilepsy. The 62.5 mg BID dose (125 mg/day) is one eighth of the lowest human dose used for treating epilepsy.

MRI data acquisition

[0291] Imaging data are obtained through high-resolution methods developed in the Stark laboratory. Data are collected on a Phillips 3 Tesla scanner (Eindhoven, The Netherlands) equipped with an 8-channel SENSE (Sensitivity Encoding) head coil, located at the F.M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute (Baltimore, MD). High-resolution echo-planar images are collected using an acquisition matrix of 64 x 64, a repetition time of 1500 milliseconds, an echo time of 30 milliseconds, a flip angle of 70 degrees, a SENSE factor of 2, and an isotropic resolution of 1.5 mm x 1.5 mm x 1.5 mm with no gap. Nineteen oblique slices are acquired parallel to the principal longitudinal axis of the hippocampus and covered the entire medial temporal lobe region bilaterally. In addition to the functional runs, a whole-brain MPRAGE structural scan (parameters: 231 oblique slices, 0.65mm isotropic resolution) is acquired.

Image analysis

[0292] Data analysis is carried out using the Analysis for Functional Neuroimages (AFNI, release 2010_10_19_1028) software. Images are first co-registered to correct for within- and across-scan head motion. Acquisitions in which a significant motion event occur (more than 3 degrees of rotation or 2 mm of translation in any direction relative to prior acquisition), plus and minus one time repetition for 1.5 seconds, are excluded from the analyses. Structural anatomical data are registered to standard stereotaxic space (Talairach & Tournoux, 1988), and the same parameters are subsequently applied to the functional data. Behavioral vectors are produced to model different trial types.

[0293] The ROI-LDDMM (large deformation diffeomorphic metric mapping of the region of interest) method, a technique for cross-subject alignment, increases the power of multisubject regional fMRI studies by focusing the alignment power specifically on the ROIs (regions of interest) and not elsewhere in the brain. First, all subjects' anatomical and functional scans are normalized to the Talairach atlas using AFNI. Sub-regions of the medial temporal lobe and the hippocampus (bilateral entorhinal cortex, perirhinal cortex, parahippocampal cortex, CA3/dentate region, CA1 region, and subiculum) are segmented in three dimensions on the MPRAGE scans. The labels for the CA3 region and dentate gyrus (DG) are combined. The anatomically defined ROIs are then used to calculate the vector field transformation for each subject using the Advanced Normalization Tools (ANTs) software package and a customized template that is based on the mean of the entire sample tested as the target. The resulting vector transformations for each individual subject's ROIs are then applied to the fit coefficient maps.

[0294] Group data are analyzed using a two-way Analysis of Variance (ANOVA) with trial types and group as fixed factors, and subject as a random factor nested within group. A liberal peak threshold of $p<0.07$, along with a spatial extent threshold of 40 voxels are used to define functional ROIs on the overall F statistic. This approach, rather than using a direct pair-wise contrast, reduces voxel selection biases because any differences amongst the various conditions allows for a voxel to be selected. This threshold is then combined with the anatomical segmentations to only include voxels inside the regions of interest. This serves to exclude voxels that do not change with any of the model's factors, effectively limiting the analysis to voxels showing any changes with task condition or group. Voxels within each functional ROI are collapsed for further analysis.

Cognitive tests during fMRI scans at Visits 1 and 2

[0295] The activity of the subject's medial temporal lobe is measured by functional MRI during the subject's participation in an explicit 3-alternative forced choice task, where participants view novel, repeated and similar ("lure") stimuli. The Psychophysics Toolbox extensions in Matlab 7.0 (The MathWorks, Natick, MA) is used for stimulus presentation and behavioral data collection. Stimuli are color photographs of common objects. Each participant undergoes a series of testing runs during the functional imaging sessions, each run consisting of a mix of three types of image pairs: similar pairs, identical pairs and unrelated foils. These image pairs are fully randomized throughout the run and are presented individually as a series of images (see **FIG. 10A**). Participants are instructed to make a judgment as to whether each object seen is new, old or similar. Of critical interest are the participants' responses when they are presented with the second of the pair of similar objects (the "lure"; see **FIG. 10B**). The correct identification by the subject of lure stimuli as "similar," provides behavioral evidence of pattern separation, i.e., the separation of similar experiences into distinct non-overlapping representations. However, an incorrect identification of lure stimuli as "old" or "new," indicates a failure of pattern separation. Identification of lure stimuli as "old" indicates that the subject focused on the similarities between the lure stimulus and the earlier-shown partner image. Identification of the lure stimulus as “new” indicates that the subject fails to recall the earlier-shown partner image altogether. Each run also contains a number of baseline trials that use a challenging perceptual discrimination task is known to provide a lower and more-stable estimate of baseline activity in the medial temporal lobe (Stark & Squire, 2001 PNAS; Law et al, 2005).

[0296] A survey of the activity level of various subregions in the medial temporal lobe during the cognitive test, which is measured by fMRI, shows that aMCI subjects have hyperactive DG/CA3 regions and a hypoactive entorhinal cortex during the performance of memory tasks, in comparison to age-matched control subjects.

[0297] We assess the level of activity in DG/CA3 during successful memory judgments in control and aMCI subjects. The mean activity is calculated from the average activity, which is measured by fMRI, during the presentation of lure stimuli that are correctly identified by subject as “similar” that is calibrated for baseline activity. **FIGS. 22A and 22B** show that aMCI patients in both the 62.5 mg BID cohort (N=20) and 250 mg BID cohort (N=17) exhibit DG/CA3 hyperactivity when making these judgments ($p = 0.0041$ and $p = 0.0466$ respectively). Treatment with levetiracetam does not significantly reduce the DG/CA3 hyperactivity in aMCI subjects in the 250 mg BID cohort or the 62.5 mg BID cohort. However, treatment with levetiracetam in the 62.5 mg BID cohort reduces the DG/CA3 hyperactivity in aMCI subjects as compared to placebo control. No such improvement is observed in the 250 mg BID cohort.

[0298] We also assess the effect on cognition of levetiracetam using lure-based behavior performance. With placebo treatment, aMCI patients perform worse than control subjects, correctly identifying lure items as “similar” less often and incorrectly identifying them as “old” more often in both the 62.5 mg BID cohort and the 250 mg BID cohort. See **FIGS. 23A and 23B**. However, the performance of aMCI subjects improves significantly under 62.5 mg BID levetiracetam treatment. See **FIG. 24A**. The interaction of more correct “similar” identifications with less incorrect “old” identifications under drug treatment results in a significant improvement in the performance of this memory task ($p = 0.041$). The performance of aMCI subjects does not significantly improve under 250 mg BID levetiracetam treatment (p = 0.2396). See **FIG. 24B**.

Example 5: Effect of Brivaracetam and Seletractam in Aged-Impaired Rats

[0299] Subjects

[0300] Aged, male Long-Evans rats are obtained at 8-9 month of age from Charles River Laboratories (Raleigh, NC) and housed in a vivarium at Johns Hopkins University until 24-26 month of age. Young rats obtained from the same source are housed in the same vivarium and tested at 6 months of age. All rats are individually housed at 25°C and maintained on a 12 hr light/dark cycle. Food and water are provided *ad libitum* unless noted otherwise. The rats are examined for health and pathogen-free status throughout the experiments, as well as necropsies at the time of sacrifice. All procedures in the current investigations are approved by the Institutional Animal Care and Use Committee in accordance with the National Institutes of Health directive.

[0301] Background Characterization of Cognitive Status

[0302] All rats are screened in a standardized assessment of spatial cognition prior to the studies with experimental treatments. That background assessment uses a well-established Morris Water Maze ("MWM") protocol. The MWM protocol is substantially the same as the one described in Example 1. See, also, Gallagher *et al.*, Behav. Neurosci. 107:618-626, (1993). Briefly, the rats are trained for eight days (three trials per day) to locate a camouflaged escape platform that remained at the same location throughout training in a water maze. Every sixth trial consists of a probe trial (free swim with no escape platform) that serves to assess the development of a spatially localized search for the escape platform. During these probe trials, a learning index is generated from the proximity of the rat to the escape platform and is used to define impairment in the aged rats. The learning index is the sum of weighted proximity scores obtained during probe trials, with low scores reflecting a search near the escape platform and high scores reflecting searches farther away from the platform (Gallagher *et al*, 1993). Cue training (visible escape platform) occurs on the last day of training to test for sensorimotor and motivational factors independent of spatial learning. Aged rats with impaired spatial memory performance (i.e., those with learning index scores outside the young "normative" range) but successful cued training performance are characterized as Aged-Impaired rats (i.e., AI rats). The AI rats are used for the studies as described below.

[0303] Treatments

[0304] The radial arm maze experiments uses acute administration of seletracetam (0 – 4 mg/kg), brivaracetam (0 – 4 mg/kg), or saline vehicle given by intraperitoneal injection (in a volume of 1 ml/kg) 30-40 min prior to test sessions. In the chronic treatment experiment, memory-impaired aged rats are implanted subcutaneously in the intrascapular region with osmotic mini-pumps (ALZET, Durect Corporation, Cupertino, CA) with brivaracetam (2 mg/kg/day) or saline vehicle starting two weeks prior to assessment in the water maze.

[0305] Behavioral Assessment in the Radial Arm Maze

[0306] A radial arm maze (RAM) task is used to assess effects of acute drug treatment with seletracetam and brivaracetam. This protocol allows within-subject assessment across drugs at different doses. The radial maze consists of eight arms projecting from each side of an octagonal center platform, with a food well located at the distal end of each arm. Plexiglas blocks can be positioned to prevent entry into any arm. Extra-maze cues are provided in the room surrounding the maze and illumination is provided by an overhead light.

[0307] Pre-training, as described in detail in Chappell et al. Neuropharmacology 37: 481-487, (1998), consists of habituation, standard win-shift training, and win-shift training with delays interposed between information and memory test phases. Drug treatments begins two days after the completion of pre-training. Three arms are blocked at the beginning of each trial (information phase). The identity and configuration of the blocked arms are varied across trials. Food-deprived rats are allowed to retrieve food reward (Kellogg's Froot Loops cereal) from the five unblocked arms. The rat is then removed from the maze for 2 hrs (retention interval), during which time the barriers on the blocked arms re removed allowing access to all eight arms. Rats are then placed back onto the center platform and allowed to retrieve the remaining food rewards (memory test phase). An error consists of returning to an arm (all four paws on the arm) from which food had already been obtained. Memory-impaired aged rats (n = 8 for seletracetam, and n

= 9 for brivaracetam) are first tested with a series of drug doses in ascending/descending order; each dose is thus tested twice, with one washout day in between each determination. The number of errors made in the retention phase after the 2-hr delay is used to assess memory performance. See FIG. 19 and FIG. 20. A series of different doses of brivaracetam is tested: 0.0625 mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg. A series of different doses of seletracetam is tested: 0.0625 mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg. As shown in FIG. 19, brivaracetam has a significant effect as a function of dose in the range tested (repeated measures ANOVA for within-subject contrasts, $F(1, 8) = 6.046$, $p = 0.039$). As shown in FIG. 20, seletracetam also has a significant effect as a function of dose in the range tested (repeated measures ANOVA for within-subject contrasts, $F(1, 7) = 12.577$, $p = 0.009$).

[0308] Behavioral Assessment in the Water Maze

[0309] Rats are trained and tested in a novel water maze environment to assess the effect of drug treatment. The water maze used here is housed in a different building and is surrounded by curtains with a novel set of patterns relative to the maze used for initial assessment of cognitive status. The training protocol consists of 6 trials per day for 2 days to locate a submerged escape platform. On each trial, a rat is released in the maze from one of four equally spaced starting positions around the perimeter of the pool. The starting position varies from trial to trial. If the rat does not locate the escape platform within 60 s on any trial, the experimenter guides and places the rat on the platform, where it remains for 20 s. The rat is then removed from the platform and placed in a holding cage for another 40 s before the next trial. Approximately 24 hrs after the last training trial, a probe test in the absence of the escape platform is given to assess spatial memory. Results of the behavior assessment in the Water Maze task are shown in FIG. 21A and FIG. 21B. Rats treated with brivaracetam at 2 mg/kg/day ($t(2) = 10.000$, $p = 0.010$) but not vehicle ($t(2) = 1.964$, $p = 0.188$) show a significant spatial bias for the target quadrant compared to the other controls quadrants. In addition, brivaracetam-treated rats (2mg/kg/day) spend significantly more time in the target quadrant than the vehicle-treated rats, $t(4) = 3.881$, $p = 0.018$. Brivaracetam-treated rats (2mg/kg/day) spend significantly more time in the target annulus (area surrounding the location of the escape platform) than the vehicle-treated rats, $t(4) = 3.109$, $p = 0.036$.

Example 6: Chronic Treatment with Levetiracetam in Aged-Impaired Rats

[0310] Subjects

[0311] Aged, male Long-Evans rats are obtained at 8-9 month of age from Charles River Laboratories (Raleigh, NC) and housed in a vivarium at Johns Hopkins University until 24-26 month of age. Young rats obtained from the same source are housed in the same vivarium and tested at 6 month of age. All rats are individually housed at 25°C and maintained on a 12 hr light/dark cycle. Food and water are provided ad libitum unless noted otherwise. The rats are examined for health and pathogen-free status throughout the experiments, as well as necropsies at the time of sacrifice. All procedures in the current investigations are approved by the Institutional Animal Care and Use Committee in accordance with the National Institutes of Health directive.

[0312] Background behavioral characterization

[0313] All rats are screened in a standardized assessment of spatial cognition prior to the studies with experimental treatments. That background assessment uses a well-established Morris water maze protocol as described in Gallagher *et al*, 1993. Briefly, the rats are trained for eight days (three trials per day) to locate a camouflaged escape platform that remains at the same location throughout training in a water maze. Every sixth trial consists of a probe trial (free swim with no escape platform) that serves to assess the development of a spatially localized search for the escape platform. During these probe trials, a learning index is generated from the proximity of the rat to the escape platform and is used to define impairment in the aged rats. The learning index is the sum of weighted proximity scores obtained during probe trials, with low scores reflecting a search near the escape platform and high scores reflecting searches farther away from the platform (Gallagher *et al*, 1993). Cue training (visible escape platform) occurs on the last day of training to test for sensorimotor and motivational factors independent of spatial learning. Aged rats with impaired spatial memory performance (i.e., those with learning index scores outside the young "normative" range) but successful cued training performance are used for the studies as described below.

[0314] Surgery and treatments

[0315] Under isoflurane anesthesia, memory-impaired aged rats are implanted subcutaneously in the intrascapular region with osmotic mini-pumps (ALZET, Durect Corporation, Cupertino, CA) with levetiracetam (10 mg/kg/day) or saline vehicle for four weeks prior to perfusion. Young rats, which served as controls, receive either saline vehicle in mini-pumps or no implantation.

[0316] Perfusion and tissue preparation

[0317] At the end of the 4-week treatment period, rats are anesthetized with isoflurane and perfused transcardiacally with 0.1 M phosphate buffer saline, followed by 4% paraformaldehyde in phosphate buffer. Brains are removed and post-fixed in paraformaldehyde overnight. The brains are then moved into 4% paraformaldehyde in phosphate buffer containing 16% sucrose. The brains are then sectioned with a freezing microtome on the coronal plane at 40 μm and stored in either 4% paraformaldehyde at 4°C for in situ hybridization or cryoprotectant at -20°C for immunohistochemistry.

[0318] Probe synthesis

[0319] Probe templates are synthesized as described in Haberman et al. (2008). Initial primer sequences for reelin are as follows: left, agtactcagacgtgcagtgg, right, ctcatgaagcaaagtccaa; PCR products are verified by restriction endonuclease digestion. Initial PCR products are amplified further with the same PCR primers that had been modified by the addition of T7 or SP6 RNA polymerase binding sites. PCR products containing T7 and SP6 extensions are purified by SVgel and a PCR cleanup kit (Promega). 35S-UTP labeled riboprobe is then generated using the Maxiscript kit (Ambion). The probe is then phenol/choloroform extracted and precipitated in ethanol at -80°C. The final probe is resuspended in RNase-free water and the specific activity is determined by scintillation counter.

[0320] In situ hybridization

[0321] In situ hybridization is carried out as described by Haberman et al., (2008). Free-floating tissue sections are washed in 0.75% glycine in 0.1M phosphate buffer two times, followed by a single wash in phosphate buffer. After that, sections are reacted in Proteinase K buffer containing 1.0μg/ml proteinase K for 30 minutes at 37°C. Sections are then treated with acetic anhydride solution (11.3% triethanolamine, 0.25% acetic anhydride, 0.04 M acetic acid) for 10 minutes at room temperature. This is followed by two 15-minute washes in 2x sodium chloride/citrate buffer (SSC buffer; 20x concentration, 3M NaCl, 0.3M sodium citrate). Next, sections are transferred to a hybridization buffer containing 20% formamide, 0.4x Denhardt's solution, 4% dextran sulfate, and 1.6x SSC) supplemented with 0.25 mg/ml tRNA, 0.33 mg/ml sheared salmon sperm DNA, 100 mM DTT, and 1 x 107 cpm/ml 35S-UTP-labeled probe for overnight reaction at 60°C. The following day, sections are washed at 60°C in 4xSSC/0.01M DTTand 2x SSC/ 50% formamide. They are then incubated with RNase (20 μg/ml) at 37°C for 30 min. Sections are washed with progressively decreasing concentrations of SSC before mounting on slides. Slides are dried overnight, exposed to a phosphoimager screen, and quantified by using ImageQuant (GE Healthcare). Digital images are acquired of entorhinal cortical sections from the same levels for all animals and the subregion of interest is outlined and quantified. Sections are averaged to obtain a single score for each animal.

[0322] Immunohistochemistry

[0323] Tissue is labeled with anti-SOM antiserum (Santa Cruz Biotechnology; cat. no. SC7819-P) using an established immunoperoxidase protocol and tissue sections are processed concurrently to minimize inter-replication variability (Haberman et al., 2009). The anti-SOM antiserum can detect somatostatin. Briefly, sections are washed in 0.1M phosphate-buffered saline (PBS) to remove cryoprotectant, and endogenous peroxidases are quenched in 0.3% H202 in PBS. After additional PBS washes, sections are blocked in 5% normal horse serum in PBS with 0.3% Triton. Sections are then incubated with primary antibody at a dilution of 1:1600 in PBS containing 0.15% Triton and 3% normal serum for 72 hours at 4°C with agitation. Following primary antibody incubation, sections are washed in PBS and reacted with horse anti-goat IgG biotinylated secondary antibody (Vector Laboratories Inc., Burlingame, CA) diluted in PBS with 0.15% Triton and 5% normal horse serum for 45 minutes. The secondary antibody is detected with avidin-biotin complex (ABC Elite; Vector Laboratories Inc., Burlingame, CA) and the avidin-biotin complex is visualized with nickel-enhanced diaminobenzadine (Vector Laboratories Inc., Burlingame, CA). Tissue sections are mounted onto coated slides and dried, dehydrated with increasing concentrations of ethanol, cleared with xylene, and coverslipped using DPX mounting media.

[0324] Interneuron quantification is performed using a Zeiss Axioplan 2 microscope equipped with a motorized stage. All analyses are conducted blind with regards to animal age and cognitive status. The dentate hilar region is defined using the Paxinos and Watson rat brain atlas (1998). Dorsal hilar neuron counts are derived bilaterally from four matched tissue sections per animal with a 40x objective lens (Bregma -3.80mm to -4.16mm). Neuron counts are analyzed as the total number of hilar interneurons per hippocampal section for each rat.

[0325] Results

[0326] Somatostatin is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones. Somatostatin levels in the brain have been shown to drop as low as 10-20% in association with aging and Alzheimer's disease progression. A four-week treatment with levetiracetam at a dose of 10 mg/kg/day in aged-impaired rats restores the levels of somatostatin in DG hilus. See FIG. 25. Aged-impaired rats that are administered a saline vehicle rather than drug possessed significantly lower numbers of SOM-immunoreactive hilar neurons relative to both young and levetiracetam treated aged rats ($N=18$; $F_{2,20}= 15.739$, $p<0.001$; AI-LEV vs Y, $p=0.679$; AI-LEV vs AI-VEH, $p<0.01$; AI-VEH vs Y, $p<0.001$).

[0327] Reelin is a large secreted extracellular matrix glycoprotein that helps regulate processes of neuronal migration and positioning in the developing brain by controlling cell-cell interactions. Reduced reelin expression in EC2 neurons has been observed in aged rats with memory loss, in hAPPJ20 AD mice, as well as in human AD brains (Chin et al. 2007; Stranahan et al. 2010). A four-week treatment with levetiracetam at a dose of 10 mg/kg/day in aged-impaired rats restores the levels of reelin in Entorhinal Cortex (EC2). See FIG. 26. A one-way ANOVA shows a significant difference among the groups, $F(2, 20) = 5.035$, $p = 0.017$. Additional analysis shows that reelin mRNA expression in the lateral entorhinal cortex of AI rats treated with vehicle controls (AI-VEH) is significantly lower than that of young rats, $t(13) = 2.790$, $p = 0.015$. Treatment with levetiracetam in AI rats at a dose of 10 mg/kg/day for 28 days (AI-LEV) significantly increases the expression of reelin, $t(13) = 2.386$, $p = 0.033$ (compared to AI-VEH).

Example 7: Evaluation of Levetiracetam Blood Plasma Levels

[0328] Human: in the human studies described in Examples 3 and 4, a subject's levetiracetam blood plasma level is assessed at each visit. The subject's blood is drawn by the Johns Hopkins Phlebotomy Service and analysis of levetiracetam blood plasma levels is conducted either by the Johns Hopkins Core laboratory or by MedTox Laboratories in St. Paul, MN for the 62.5 mg BID cohort, the 125 mg BID cohort and the 250 mg BID cohort. When the levetiracetam treatment is completed, subjects in the 62.5 mg BID cohort shows a mean levetiracetam blood plasma level of 2.88 mcg/ml (SEM ± 0.288), while levels in the 125 mg BID had 4.4 mcg/ml (SEM ± 0.53) and subjects in the 250 mg BID cohort showed mean levetiracetam blood plasma level of 7.9 mcg/ml (SEM ± 0.92). See FIGS. 27A-27C.

[0329] Rats: Blood is drawn from aged-impaired rats by cardiac puncture during perfusion after a 28-day levetiracetam treatment period and is sent for analysis of levetiracetam plasma levels by MedTox Laboratories in St. Paul, MN. Aged-impaired rats that are treated with 10 mg/kg/day of levetiracetam shows a mean levetiracetam blood plasma level of 3.8 mcg/ml (SEM ± 0.255), while those that are treated with 60 mg/kg/day show a mean levetiracetam blood plasma level of 22.4 mcg/ml (SEM ± 3.371).

[0330] The levetiracetam blood levels in the aged-impaired rats treated with daily levetiracetam doses of 10 mg/kg and 60 mg/kg can be use to estimate the levetiracetam blood level of its daily dose of 20 mg/kg. This extrapolation gives an estimated levetiracetam blood level of 7.6 mcg/ml for the 20 mg/kg daily dose. These results, together with the levetiracetam blood levels in the three human cohorts (62.5 mg BID, 125 mg BID and 250 mg BID) show that the levetiracetam blood level (3.8 mcg/ml) in the aged-impaired rats treated with the 10 mg/kg therapeutically effective daily levetiracetam dose is consistent with the blood level of levetiracetam in the human patients who are treated with the therapeutically effective daily levetiracetam doses, *e.g.*, 2.88 mcg/ml (125mg levetiracetam) and 4.4 mcg/ml (250 mg levetiracetam). These results also show that the extrapolated levetiracetam blood level (7.6 mcg/ml) in the aged-impaired rats treated with the non-therapeutically effective 20 mg/kg daily dose is consistent with the levetiracetam blood level (7.9 mcg/ml) in our human patients treated with the non-therapeutically effective daily 500 mg levetiracetam dose.

WHAT IS CLAIMED IS:

1. A method for treating schizophrenia or bipolar disorder in a patient in need or at risk thereof, the method comprising the step of administering to said subject a therapeutically effective amount of a synaptic vesicle protein 2A (SV2A) inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and a therapeutically effective amount of an antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph or prodrug thereof.

2. The method of claim 1, wherein the antipsychotic is administered at a dose that is subtherapeutic as compared to the dose at which it is therapeutically effective when administered in the absence of the SV2A inhibitor.

3. The method of claim 1 or 2, wherein the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Application PCT/US2009/005647; International Patent Application Publications WO2010/144712; WO2010/002869; WO2008/132139; WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188; WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Applications 12/580,464; 61/105,847; 61/152,631; and 61/175,536; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

4. The method of claim 1 or 2, wherein the SV2A inhibitor is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam and derivatives, analogs, pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof.

5. The method of any one of claims 1-4, wherein the SV2A inhibitor is administered every 12 or 24 hours:

1) at a daily dose of 0.001 mg/kg to 5 mg/kg, 0.0015 - 7 mg/kg, 0.0015 - 5 mg/kg, 0.01 - 5 mg/kg, 0.05 - 4.0 mg/kg, 0.05 - 2 mg/kg, 0.05 - 1.5 mg/kg, 0.1 - 1 mg/kg, 1 - 5 mg/kg, 1.5 - 4 mg/kg, or 1.8 - 3.6 mg/kg; or

2) at a daily dose that is subtherapeutic as compared to the dose at which it is therapeutically effective when administered in the absence of the antipsychotic,

wherein the subtherapeutic daily doses are selected from the group consisting of less than 7 mg/kg, less than 6 mg/kg, less than 5 mg/kg, less than 4 mg/kg, less than 3.6 mg/kg, less than 3 mg/kg, less than 2 mg/kg, less than 1.5 mg/kg, less than 1.5 mg/kg, less than 1 mg/kg, less than 0.1 mg/kg, less than 0.05 mg/kg, less than 0.01 mg/kg, or less than 0.0015 mg/kg.

6. The method of claim 5, wherein the SV2A inhibitor is administered every 12 or 24 hours at a daily dose of 0.5 mg/kg to 5 mg/kg.

7. The method of claim 5, wherein the SV2A inhibitor is administered every 12 or 24 hours at a daily dose of 0.05 mg/kg to 0.5 mg/kg.

8 The method of any one of claims 1-7, wherein the antipsychotic is selected from atypical and typical antipsychotics.

9. The method of claim 8, wherein the antipsychotic is an atypical antipsychotic.

10. The method of claim 9, wherein the antipsychotic is selected from aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof.

11. The method of claim 10, wherein the antipsychotic is selected from aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and prodrugs thereof.

12. The method of claim 8, wherein the antipsychotic is a typical antipsychotic.

13. The method of claim 12, wherein the antipsychotic is selected from acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and prodrugs thereof.

14. The method of any one of claims 1-7, wherein the antipsychotic is a compound selected from dopaminergic agents, glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic agents, serotonin receptor modulators, cholinergic agents, cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, NNOS inhibits, neurosteroids, and neurotrophic factors.

15. The method of any one of claims 1-7, wherein the antipsychotic is useful in treating at least one sign or symptom of schizophrenia or bipolar disorder.

16. The method of any one of claims 1-7, wherein the antipsychotic is selected from the group of compounds referred to in U.S. Patents 4,734,416; 5,006,528; 4,145,434; 5,763,476; 3,539,573; 5,229,382; 5,532,372; 4,879,288; 4,804,663; 4,710,500; 4,831,031; and 5,312,925, and EP Patents EP402644 and EP368388, and the pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and prodrugs thereof.

17. The method of any one of claims 1-7, wherein the antipsychotic is selected from the group of compounds referred to in U.S. Patents or Patent Publications US20020052401A1; US20020091118A1; US20020091119A1; US20020094986A1; US20020123490A1; US20020147194A1; US20020156089A1; US20020165217A1; US20030008806A1; US20030008892A1; US20030013887A1; US20030018047A1; US20030027812A1; US20030032579A1; US20030130303A1; US20030158208A1; US20030162766A1; US20030181458A1; US20030191176A1; US20030208081A1; US20030232841A1; US20030235631A1; US20040001895A1; US20040006135A1; US20040029876A1; US20040039022A1; US20040048869A1; US20040049039A1; US20040082597A1; US20040106603A1; US20040110817A1; US20040116443A1; US20040132713A1;

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WO9961441A1, or pharmaceutically acceptable salts, hydrates, solvates polymorphs, and prodrugs thereof.

18. The method of any one of claims 1-17, wherein the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof are administered simultaneously.

19. The method of claim 18, wherein the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof are administered in a single formulation.

20. The method of any one of claims 1-17, wherein SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof are administered sequentially.

21. The method of claim 20, wherein the SV2A inhibitor and the antipsychotic, or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof are administered in separate formulations.

22. The method of any one of claims 1-21, a) wherein the SV2A inhibitor is levetiracetam or a derivative, analog, pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and the antipsychotic is selected from aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof, or b) wherein the SV2A inhibitor is brivaracetam or a derivative, analog, pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and the antipsychotic is selected from aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof; or c) wherein the SV2A inhibitor is seletraceatm or a derivative, analog, pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and the antipsychotic is selected from aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof .

23. The method of any one of claims 1 to 22, wherein the treatment has a longer therapeutic effect in the subject than is attained by administering the antipsychotic in the absence of the SV2A inhibitor by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

24. The method of any one of claims 1 to 22, wherein the treatment has a longer therapeutic effect in the subject than is attained by administering the SV2A inhibitor in the absence of the antipsychotic by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

25. A method of increasing the therapeutic index of an antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in a method of treating schizophrenia or bipolar disorder in a subject in need or at risk thereof, comprising administering an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in combination with the antipsychotic or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof to said subject.

26. The method of claim 25, wherein the increase in the therapeutic index of the antipsychotic is greater than the therapeutic index of the antipsychotic when administered in the absence of the SV2A inhibitor by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, or 3.5x, or 4.0x, or 4.5x, or 5.0x, or 5.5x, or 6.0x, or 6.5x, or 7.0x, or 7.5x, or 8.0x, or 8.5x, or 9.0x, or 9.5x, or 10x, or greater than about 10x.

27. The method of claim 25 or 26, wherein the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Application PCT/US2009/005647; International Patent Application Publications WO2010/144712; WO2010/002869; WO2008/132139; WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188; WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Applications 12/580,464; 61/105,847; 61/152,631; and 61/175,536; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

28. The method of claim 25 or 26, wherein the SV2A inhibitor is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam, and derivatives, analogs, pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof.

29. The method of any one of claims 25-28, wherein the antipsychotic is selected from atypical and typical antipsychotics.

30. The method of claim 29, wherein the antipsychotic is an atypical antipsychotic.

31. The method of claim 30, wherein the antipsychotic is selected from aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and prodrugs thereof.

32. The method of claim 31, wherein the antipsychotic is selected from aripiprazole, olanzapine and ziprasidone, and pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

33. The method of claim 29, wherein the antipsychotic is a typical antipsychotic.

34. The method of claim 33, wherein the antipsychotic is selected from acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol, and pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

35. The method of any one of claims 25-28, wherein the antipsychotic is a compound selected from dopaminergic agents, glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic

agents, serotonin receptor modulators, cholinergic agents, cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, NNOS inhibits, neurosteroids, and neurotrophic factors.

36. The method of any one of claims 25-28, wherein the antipsychotic is useful in treating at least one sign or symptom of schizophrenia or bipolar disorder.

37. The method of any one of claims 25-28, wherein the antipsychotic is selected from the group of compounds referred to in U.S. Patents 4,734,416; 5,006,528; 4,145,434; 5,763,476; 3,539,573; 5,229,382; 5,532,372; 4,879,288; 4,804,663; 4,710,500; 4,831,031; and 5,312,925, and EP Patents EP402644 and EP368388, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

38. The method of any one of claims 25-28, wherein the antipsychotic is selected from the group of compounds referred to in U.S. Patents or Patent Publications US20020052401A1; US20020091118A1; US20020091119A1; US20020094986A1; US20020123490A1; US20020147194A1; US20020156089A1; US20020165217A1; US20030008806A1; US20030008892A1; US20030013887A1; US20030018047A1; US20030027812A1; US20030032579A1; US20030130303A1; US20030158208A1; US20030162766A1; US20030181458A1; US20030191176A1; US20030208081A1; US20030232841A1; US20030235631A1; US20040001895A1; US20040006135A1; US20040029876A1; US20040039022A1; US20040048869A1; US20040049039A1; US20040082597A1; US20040106603A1; US20040110817A1; US20040116443A1; US20040132713A1; US20040138232A1; US20040162293A1; US20040162294A1; US20040167200A1; US20040204414A1; US20040204415A1; US20040204445A1; US20040204453A1; US20040209887A1; US20040220184A1; US20040220274A1; US20040229874A1; US20040229911A1; US20040242587A1; US20040254193A1; US20040259859A1; US20040266781A1; US20040266815A1; US20050004106A1; US20050004137A1; US20050009927A1; US20050014764A1; US20050014848A1; US20050026937A1;

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39. A pharmaceutical composition comprising an SV2A inhibitor and an antipsychotic or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs.

40. The pharmaceutical composition of claim 39, wherein the SV2A inhibitor and the antipsychotic or their pharmaceutically acceptable salts, hydrates, solvates, polymorphs or prodrugs are in separate dosage forms or in a unit dosage form.

41. The composition of claim 39 or 40, wherein the composition is in a solid form, a liquid form, a suspension form, a sustained release form, a delayed release form, or an extended release form.

42. The composition of any one of claims 39-41, wherein the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Application PCT/US2009/005647; International Patent Application Publications WO2010/144712; WO2010/002869; WO2008/132139; WO2007/065595; WO2006/128693; WO2006/128692; WO2005/054188; WO2004/087658; WO2002/094787; WO2001/062726; U.S. Patents 7,465,549; 7,244,747; 5,334,720; 4,696,943; 4,696,942; U.S. Patent Applications 12/580,464; 61/105,847; 61/152,631; and 61/175,536; U.S. Patent Application Publication Numbers 20090312333; 20090018148; 20080081832; 2006258704; and UK Patent Numbers 1,039,113; and 1,309,692; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

43. The composition of any one of claims 39-41, wherein the SV2A inhibitor is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam and derivatives, analogs, pharmaceutically acceptable salts, hydrates, solvates, polymorphs and prodrugs thereof.

44. The composition of any one of claims 39-41, wherein the SV2A inhibitor in the composition is present in an amount of 0.07 - 350 mg, or 0.1 - 500 mg, 0.1 - 350 mg, 0.7 - 350 mg, 3 - 300 mg, 3 - 150 mg, 3 - 110 mg, 7 - 70 mg, 70 - 350 mg, 100 - 300 mg, or 125 - 250 mg .

45. The composition of claim 44, wherein the SV2A inhibitor in the composition is present in an amount of 50 - 250 mg.

46. The composition of claim 44, wherein the SV2A inhibitor in the composition is present in an amount of 3 - 50 mg.

47. The composition of any one of claims 39-41, wherein the SV2A inhibitor is present in an amount less than 500 mg,less than 350 mg, less than 300 mg, less than 250 mg, less than 200 mg, less than 150 mg, less than 110 mg,less than 100 mg, less than 70 mg, less than 50 mg, less than 35 mg, less than 10 mg, less than 7 mg, less than 5 mg, less than 3 mg, less than 1 mg, less than 0.7 mg, less than 0.5 mg, less than 0.1 mg, less than 0.07 mg or less than 0.05 mg.

48. The composition of any one of claims 39-47, wherein the antipsychotic is selected from atypical and typical antipsychotics.

49. The composition of claim 48, wherein the antipsychotic is an atypical antipsychotic.

50. The composition of claim 49, wherein the antipsychotic is selected from aripiprazole, asenapine, clozapine, iloperidone, olanzapine, lurasidone, paliperidone, quetiapine, risperidone and ziprasidone, and the pharmaceutically acceptable salts, hydrates, solvates, polymorphs, and prodrugs thereof.

51. The composition of claim 50, wherein the antipsychotic is selected from aripiprazole, olanzapine and ziprasidone, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

52. The composition of claim 48, wherein the antipsychotic is a typical antipsychotic.

53. The composition of claim 52, wherein the antipsychotic is selected from acepromazine, benperidol, bromazepam, bromperidol, chlorpromazine, chlorprothixene, clotiapine, cyamemazine, diazepam, dixyrazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, heptaminol, isopropamide iodide, levomepromazine, levosulpiride, loxapine, melperone, mesoridazine, molindone, oxypertine, oxyprothepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, pyridoxine, sulpiride, sultopride, tetrabenazine, thioproperazine, thioridazine, tiapride, tiotixene, trifluoperazine, triflupromazine, trihexyphenidyl, and zuclopenthixol, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

54. The composition of any one of claims 39-47, wherein the antipsychotic is a compound selected from dopaminergic agents, glutamatergic agents, NMDA receptor positive allosteric modulators, glycine reuptake inhibitors, glutamate reuptake inhibitor, metabotropic glutamate receptors (mGluRs) agonists or positive allosteric modulators (PAMs), glutamate receptor glur5 positive allosteric modulators (PAMs), M1 muscarinic acetylcholine receptor (mAChR) positive allosteric modulators (PAMs), histamine H3 receptor antagonists, AMPA/kainate receptor antagonists, ampakines (CX-516), glutathione prodrugs, noradrenergic

agents, serotonin receptor modulators, cholinergic agents, cannabinoid CB1 antagonists, neurokinin 3 antagonists, neurotensin agonists, MAO B inhibitors, PDE10 inhibitors, NNOS inhibits, neurosteroids, and neurotrophic factors.

55. The composition of any one of claims 39-47, wherein the antipsychotic is useful in treating at least one sign or symptom of schizophrenia or bipolar disorder.

56. The composition of any one of claims 39-47, wherein the antipsychotic is selected from the group of compounds referred to in U.S. Patents 4,734,416; 5,006,528; 4,145,434; 5,763,476; 3,539,573; 5,229,382; 5,532,372; 4,879,288; 4,804,663; 4,710,500; 4,831,031; and 5,312,925, and EP Patents EP402644 and EP368388, and the pharmaceutically acceptable salts, hydrates, solvates, and polymorphs thereof.

57. The composition of any one of claims 39-47, wherein the antipsychotic is selected from the group of compounds referred to in U.S. Patents or Patent Publications US20020052401A1; US20020091118A1; US20020091119A1; US20020094986A1; US20020123490A1; US20020147194A1; US20020156089A1; US20020165217A1; US20030008806A1; US20030008892A1; US20030013887A1; US20030018047A1; US20030027812A1; US20030032579A1; US20030130303A1; US20030158208A1; US20030162766A1; US20030181458A1; US20030191176A1; US20030208081A1; US20030232841A1; US20030235631A1; US20040001895A1; US20040006135A1; US20040029876A1; US20040039022A1; US20040048869A1; US20040049039A1; US20040082597A1; US20040106603A1; US20040110817A1; US20040116443A1; US20040132713A1; US20040138232A1; US20040162293A1; US20040162294A1; US20040167200A1; US20040204414A1; US20040204415A1; US20040204445A1; US20040204453A1; US20040209887A1; US20040220184A1; US20040220274A1; US20040229874A1; US20040229911A1; US20040242587A1; US20040254193A1; US20040259859A1; US20040266781A1; US20040266815A1; US20050004106A1; US20050004137A1; US20050009927A1; US20050014764A1; US20050014848A1; US20050026937A1;

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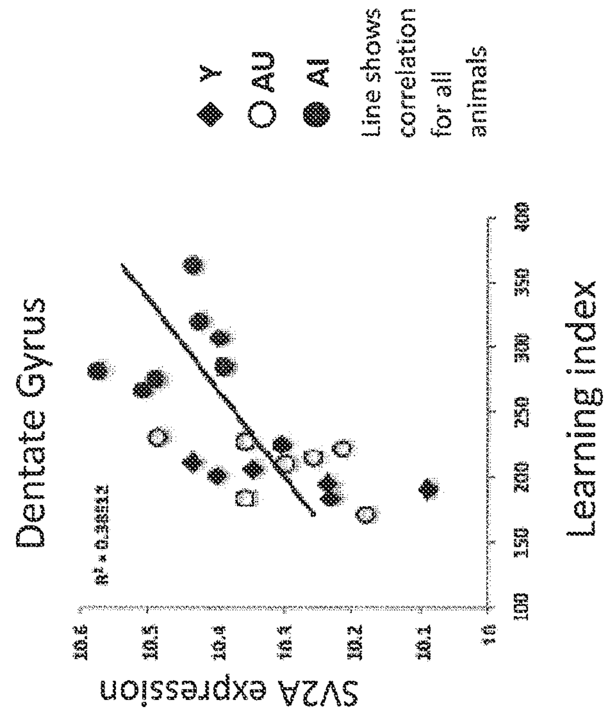


Correlations:
All r= 0.62
Aged: r = 0.61

FIG. 1

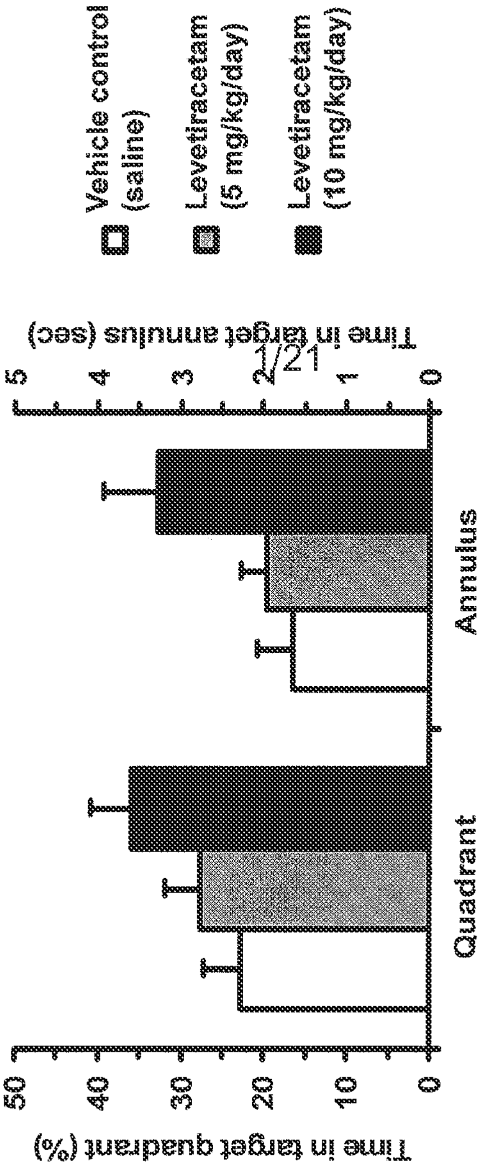
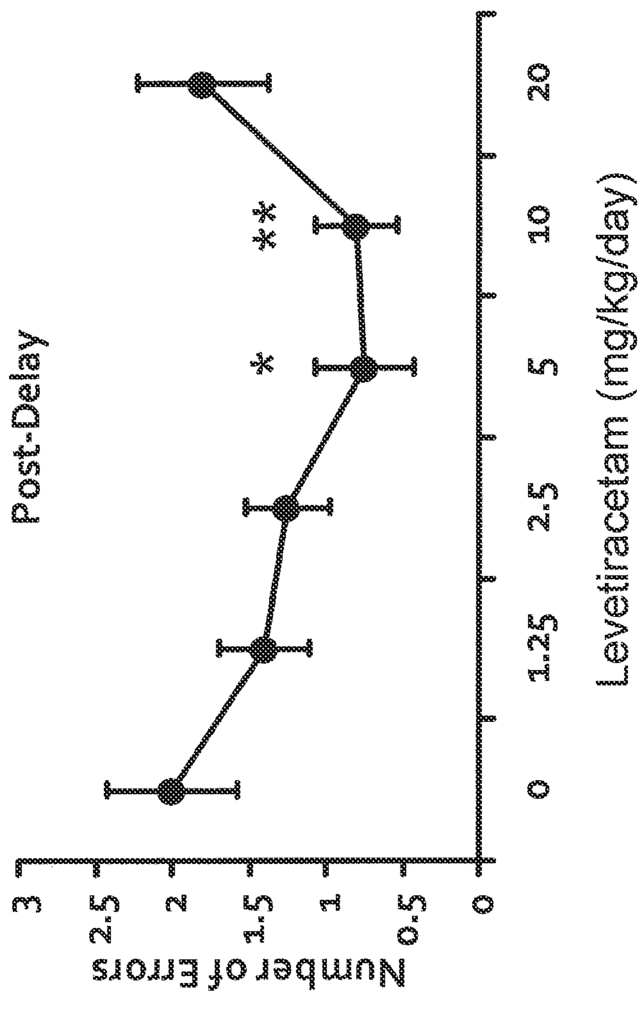

Vehicle control (saline)
Levetiracetam (5 mg/kg/day)
Levetiracetam (10 mg/kg/day)
Time in target quadrant (%)
0
10
20
30
40
50
Quadrant
Annulus
Time in target annulus (sec)
0
1
2
3
4
5

FIG. 2



* $t(9) = 2.18$, $p = 0.057$
** $t(9) = 2.37$, $p = 0.042$

FIG. 3

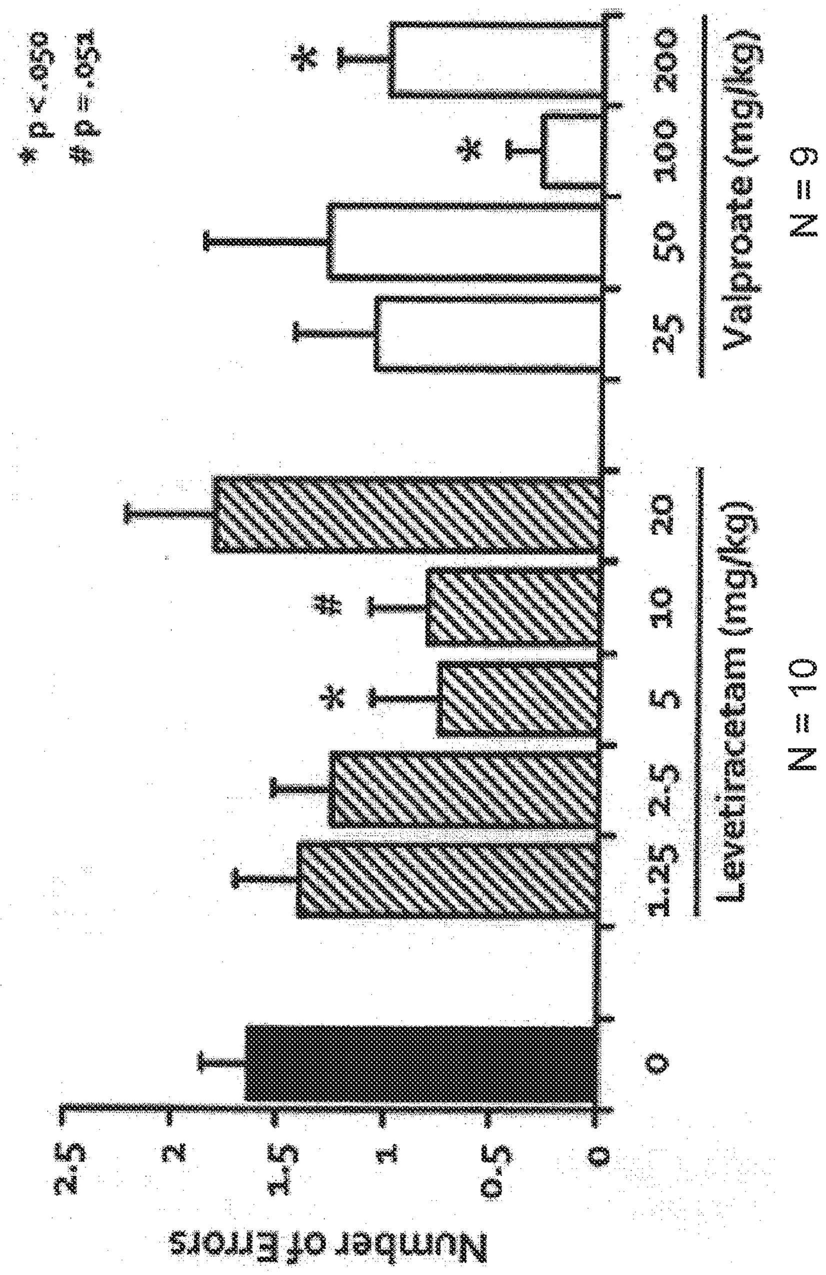

* p <.050
# p = .051
Number of Errors
2.5
2
1.5
1
0.5
0
0
1.25
2.5
5
10
20
Levetiracetam (mg/kg)
N = 10
25
50
100
200
Valproate (mg/kg)
N = 9

FIG. 4

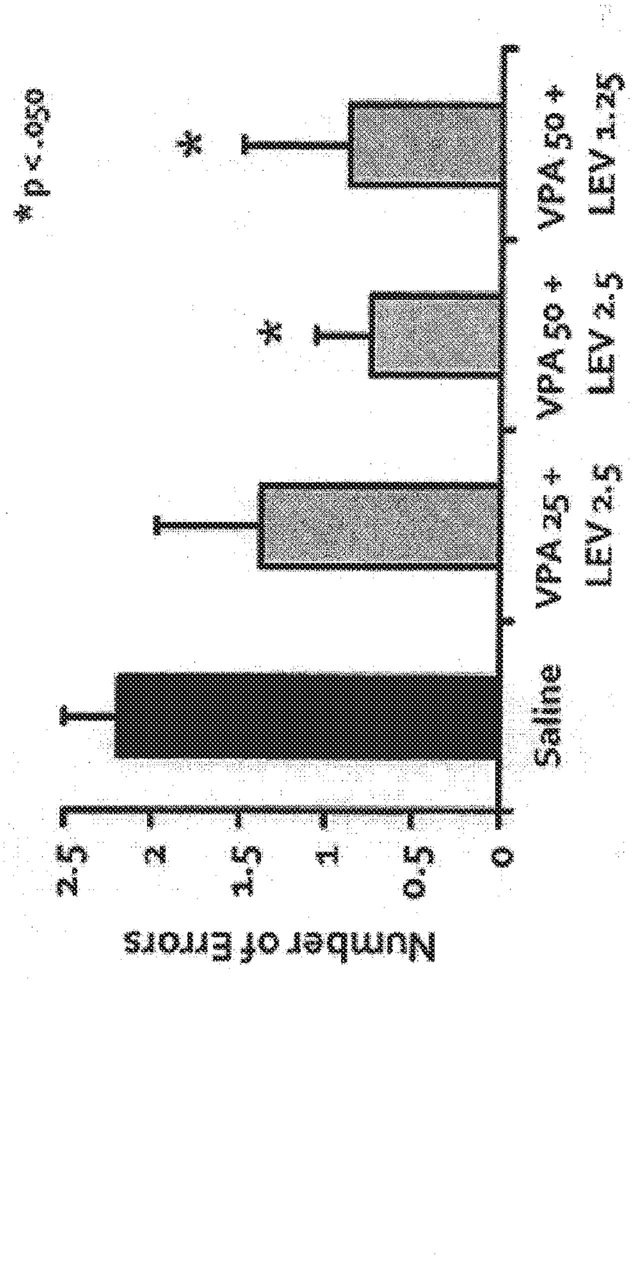

N = 8
* p < .050
Number of Errors
2.5
2
1.5
1
0.5
0
Saline
VPA 25 + LEV 2.5
VPA 50 + LEV 2.5
VPA 50 + LEV 1.25
*
*

FIG. 5

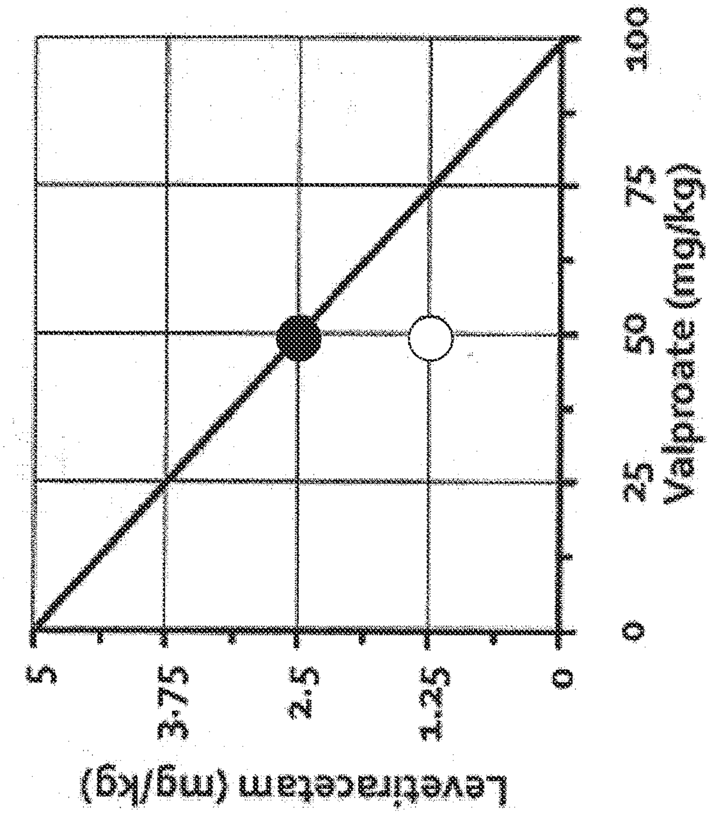

Levetiracetam (mg/kg)
5
3.75
2.5
1.25
0
Valproate (mg/kg)
0
25
50
75
100

FIG. 6

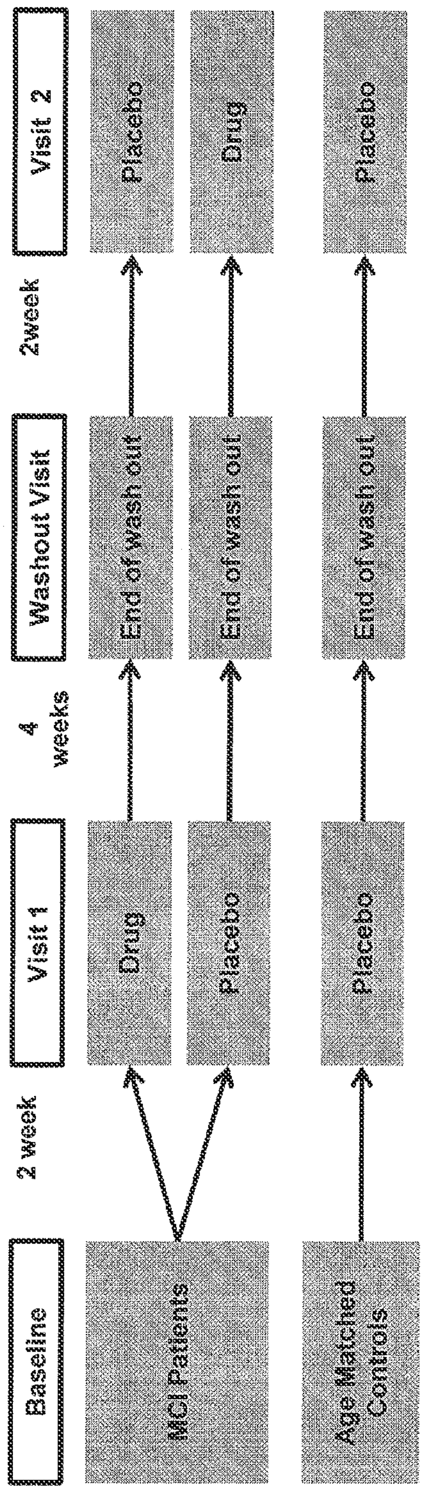
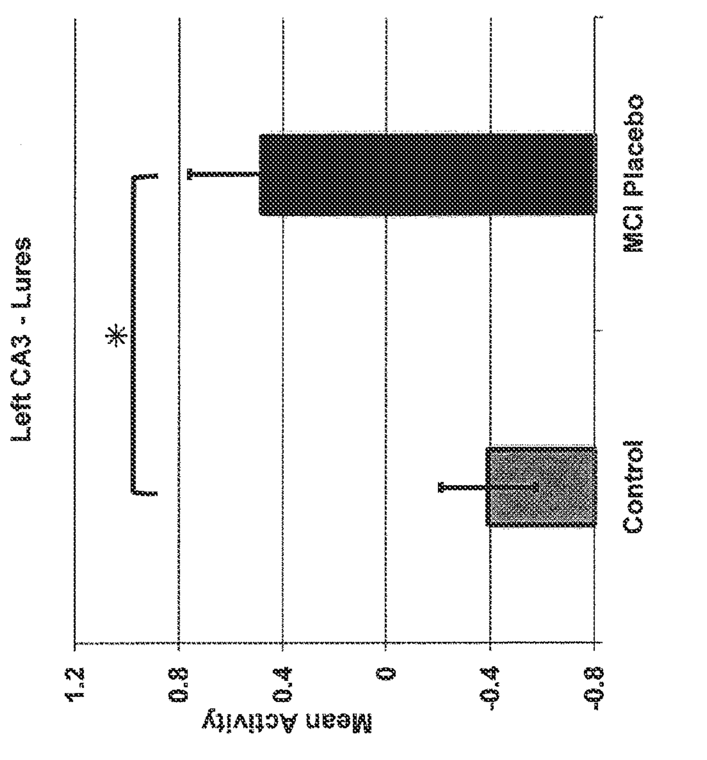
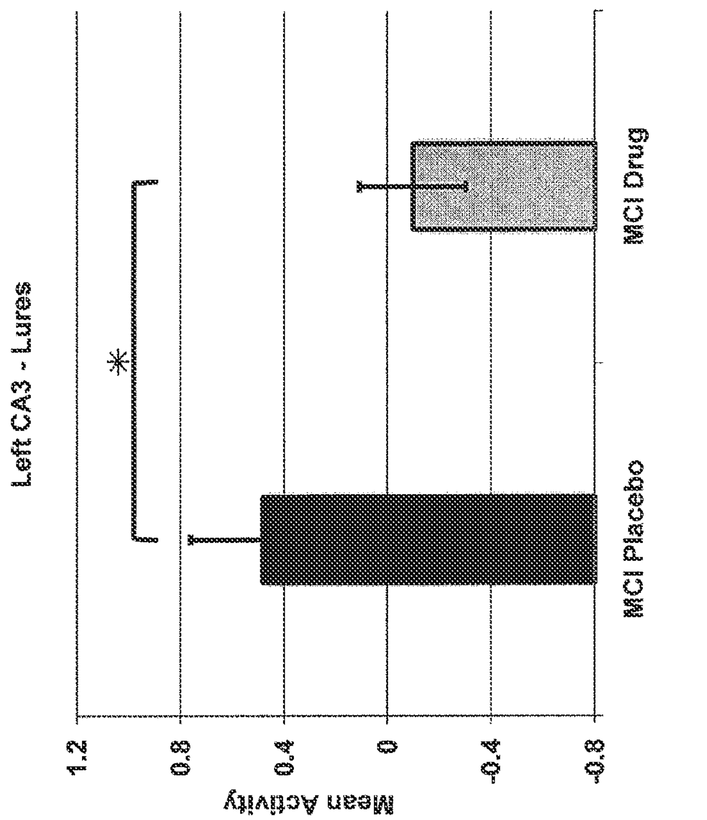

Baseline
MCI Patients
Age Matched Controls
2 week
Visit 1
Drug
Placebo
Placebo
4 weeks
Washout Visit
End of wash out
End of wash out
End of wash out
2week
Visit 2
Placebo
Drug
Placebo

FIG. 7



*Independent samples t-test: t = -2.636, p = 0.013

FIG. 8A



*Paired samples t-test: t = 2.276, p = 0.037

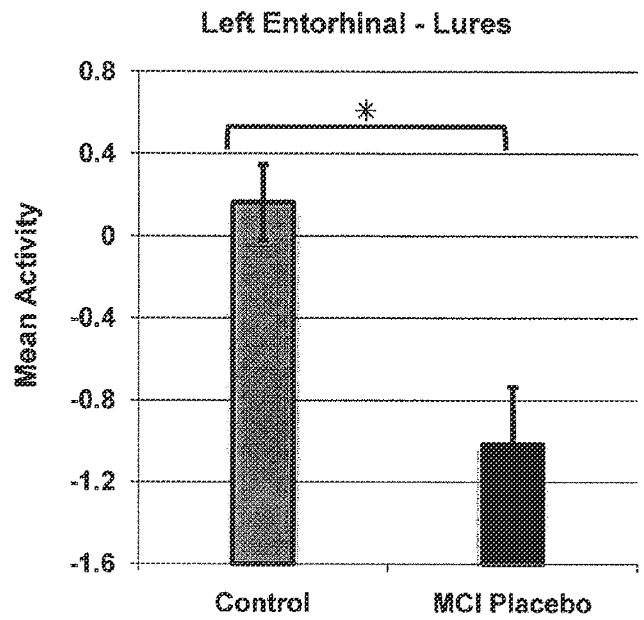
FIG. 8B

Left CA3 Lures

Group	Mean Activity	Standard Error
Control	-0.39129	0.182628
MCI Placebo	0.48440	0.277487
MCI Drug	-0.09653	0.205892

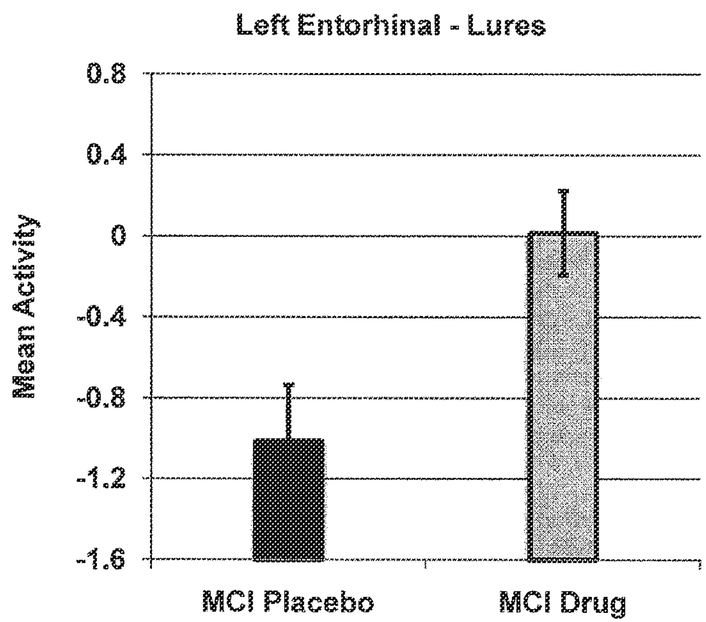
FIG. 8C

fMRI entorhinal activation in amnestic MCI is normalized by drug treatment



*Independent samples t-test: t = 3.278, p = 0.003

FIG. 9A



Paired samples t-test: t = -1.600, p= 0.129

FIG. 9B

Left Entorhinal Lures

Group	Mean Activity	Standard Error
Control	0.16444	0.143864
MCI Placebo	-1.01273	0.329062
MCI Drug	0.016291	0.411762

FIG. 9C

Reduced memory in task that taxes pattern separation

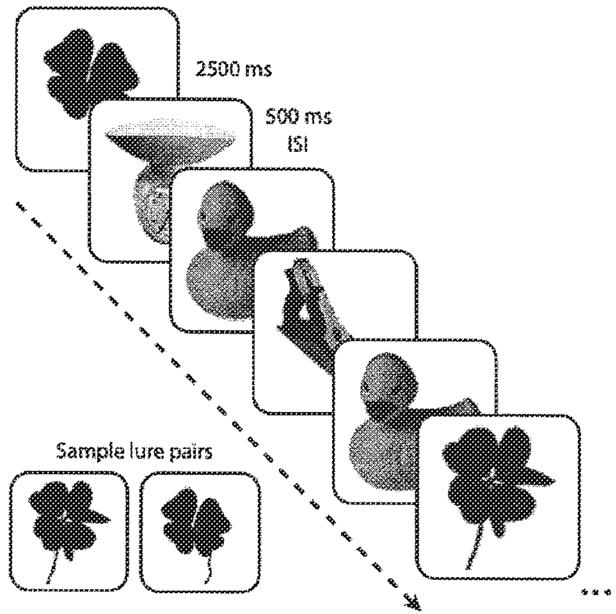


FIG. 10A

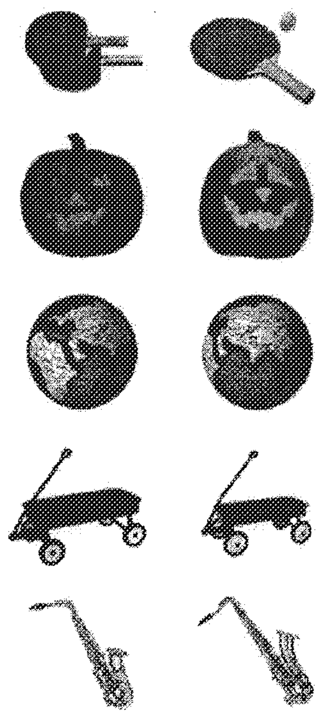
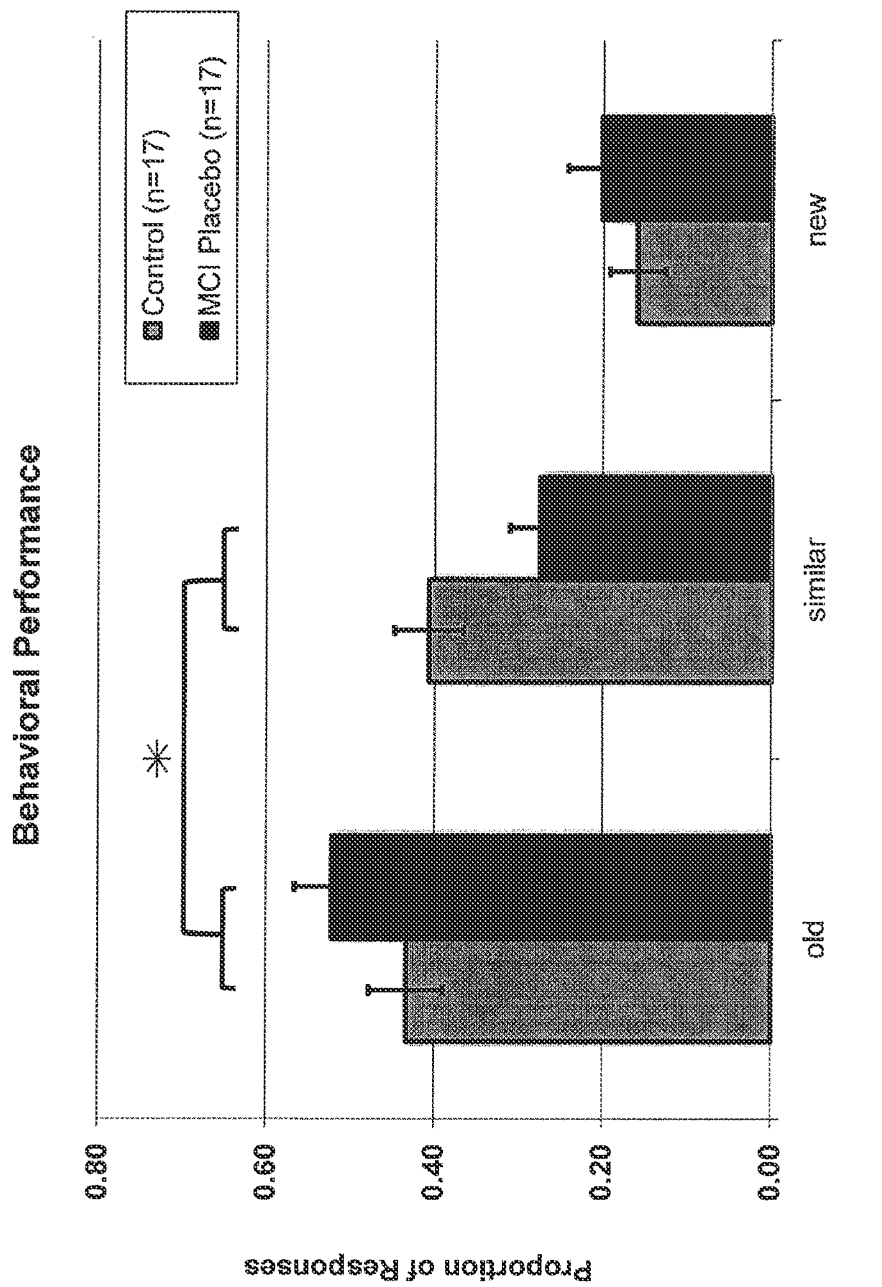
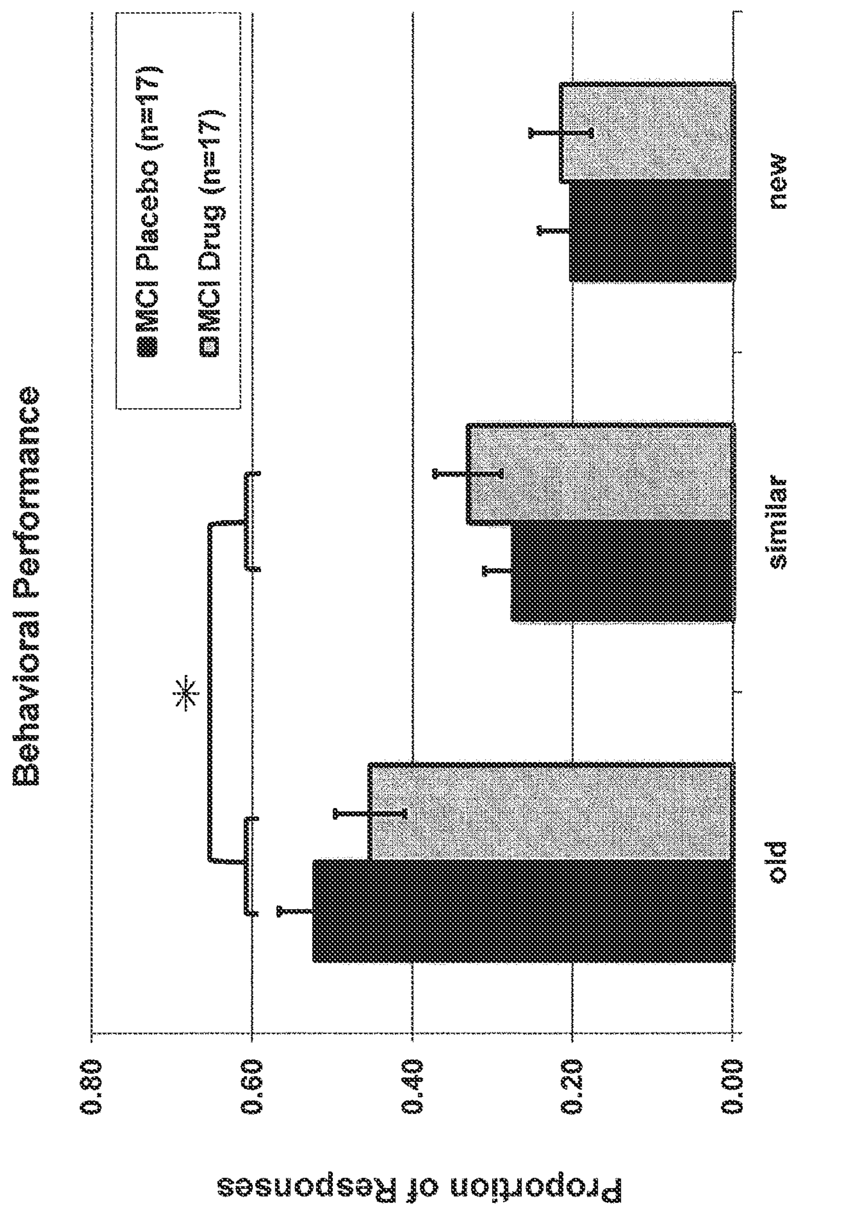


FIG. 10B



Control vs. MCI Placebo by Old vs. Similar: F= 7.687, p = 0.009

FIG. 11



MCI Drug vs. MCI Placebo by Old vs. Similar: F = 5.028, p = 0.039

FIG. 12

Behavioral Performance

Control Subjects	Proportion of Responses	Standard Error
Old	0.433676	0.04426
Similar	0.406771	0.04135
New	0.159553	0.03312
MCI Placebo Subjects	**Proportion of Responses**	**Standard Error**
Old	0.52262	0.04871
Similar	0.27549	0.03956
New	0.20188	0.04528
MCI Drug Subjects	**Proportion of Responses**	**Standard Error**
Old	0.45361	0.04825
Similar	0.33144	0.04592
New	0.21494	0.04202

FIG. 13

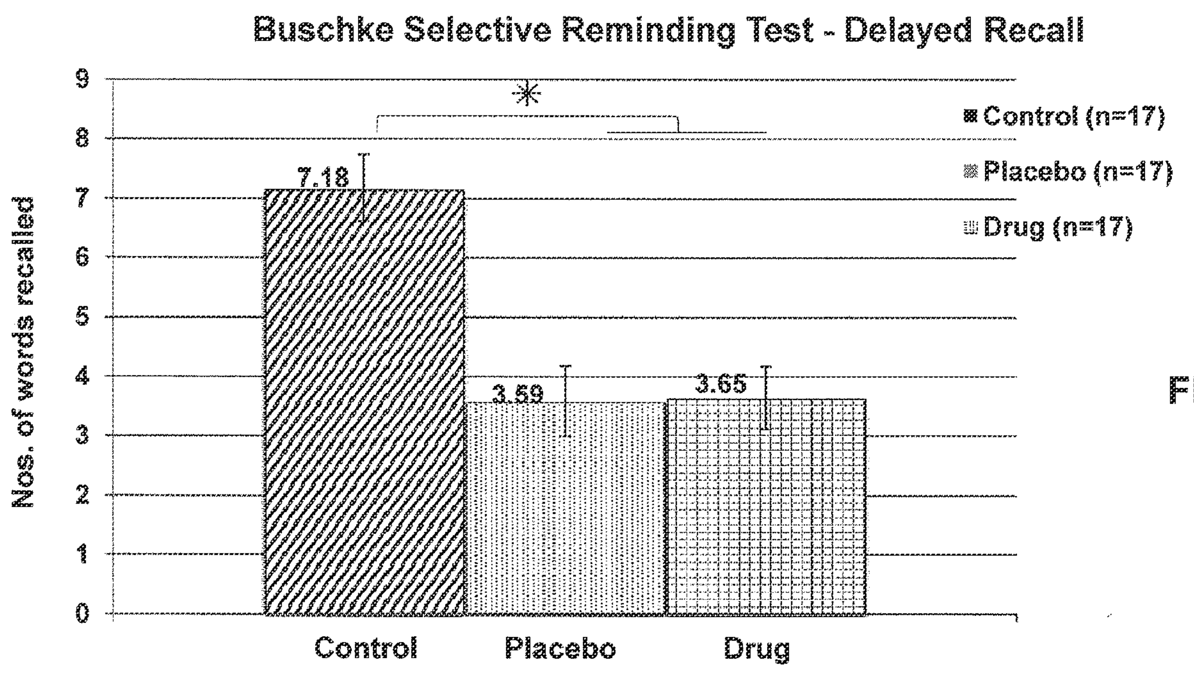


FIG. 14A

Group	Mean	Standard Error	Delayed (p-value)
Control	7.18	0.56	Control vs. Placebo: <0.001
MCI Placebo	3.59	0.59	Control vs. Drug: < 0.001
MCI Drug	3.65	0.53	Placebo vs. Drug: 0.887

FIG. 14B

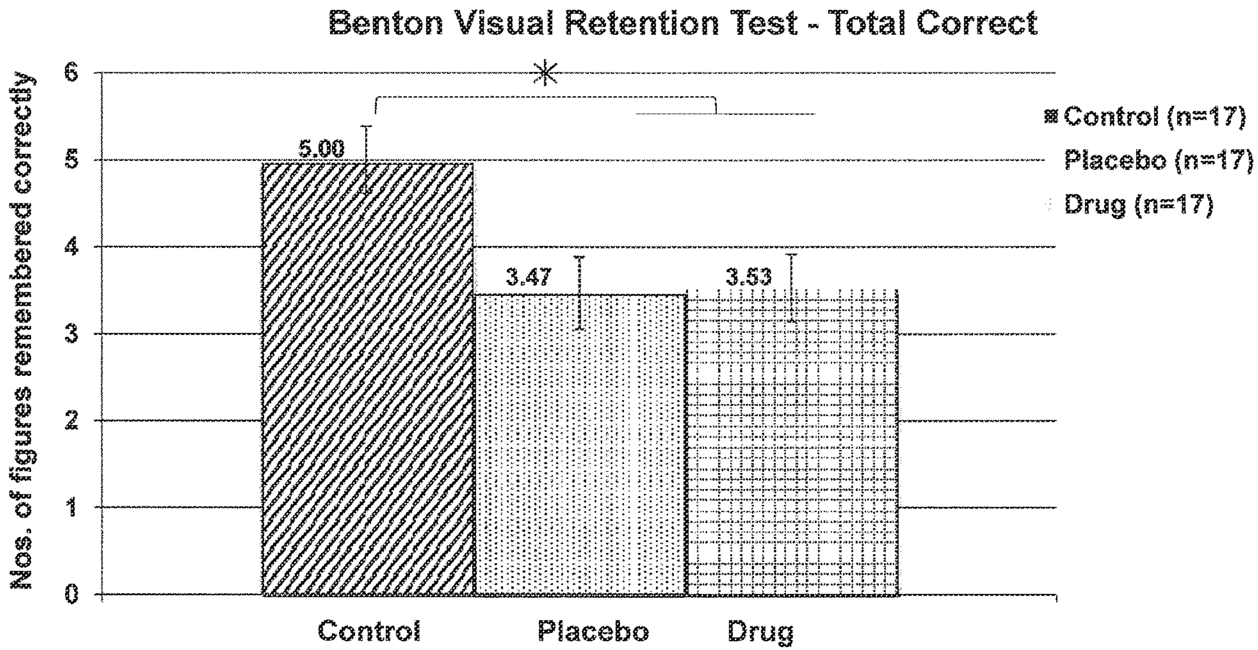


FIG. 15A

Group	Mean	Standard Error	Total Correct (p-value)
Control	5.00	0.38	Control vs. Placebo: 0.011
MCI Placebo	3.47	0.41	Control vs. Drug: 0.011
MCI Drug	3.53	0.38	Placebo vs. Drug: 0.805

FIG. 15B

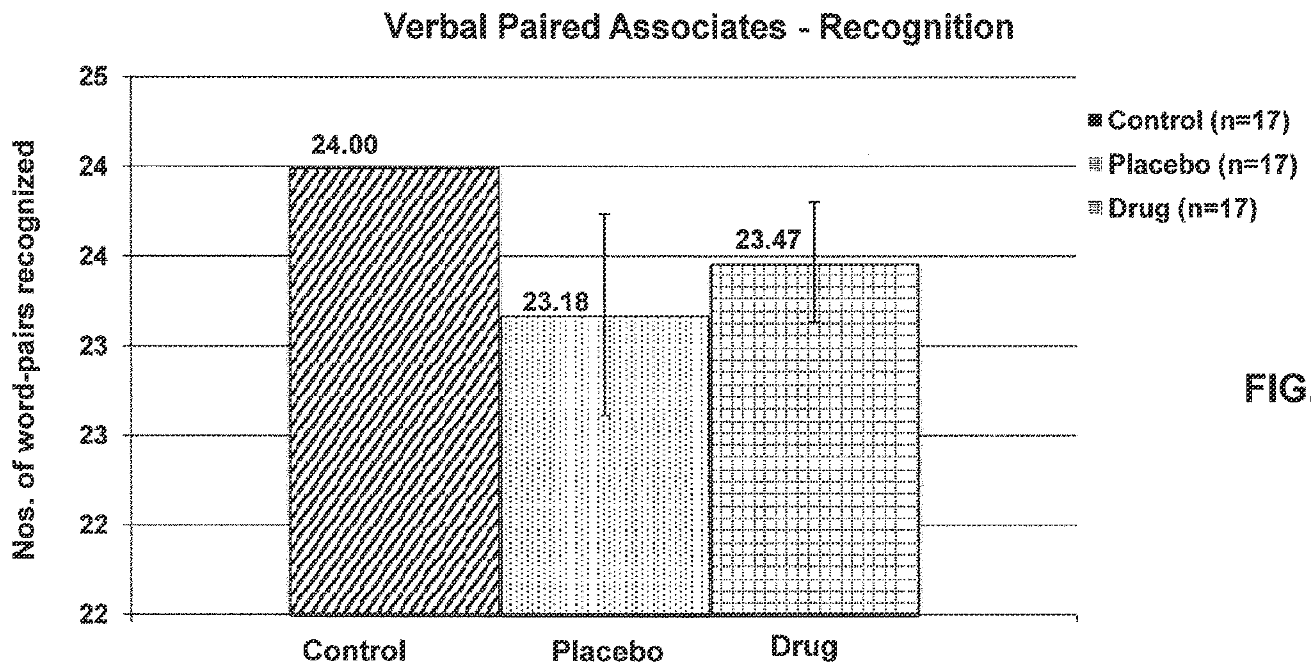


FIG. 16A

Group	Mean	Standard Error	Recognition (p-value)
Control	24.00	0.00	Control vs. Placebo: 0.154
MCI Placebo	23.18	0.56	Control vs. Drug: 0.122
MCI Drug	23.47	0.33	Placebo vs. Drug: 0.428

FIG. 16B

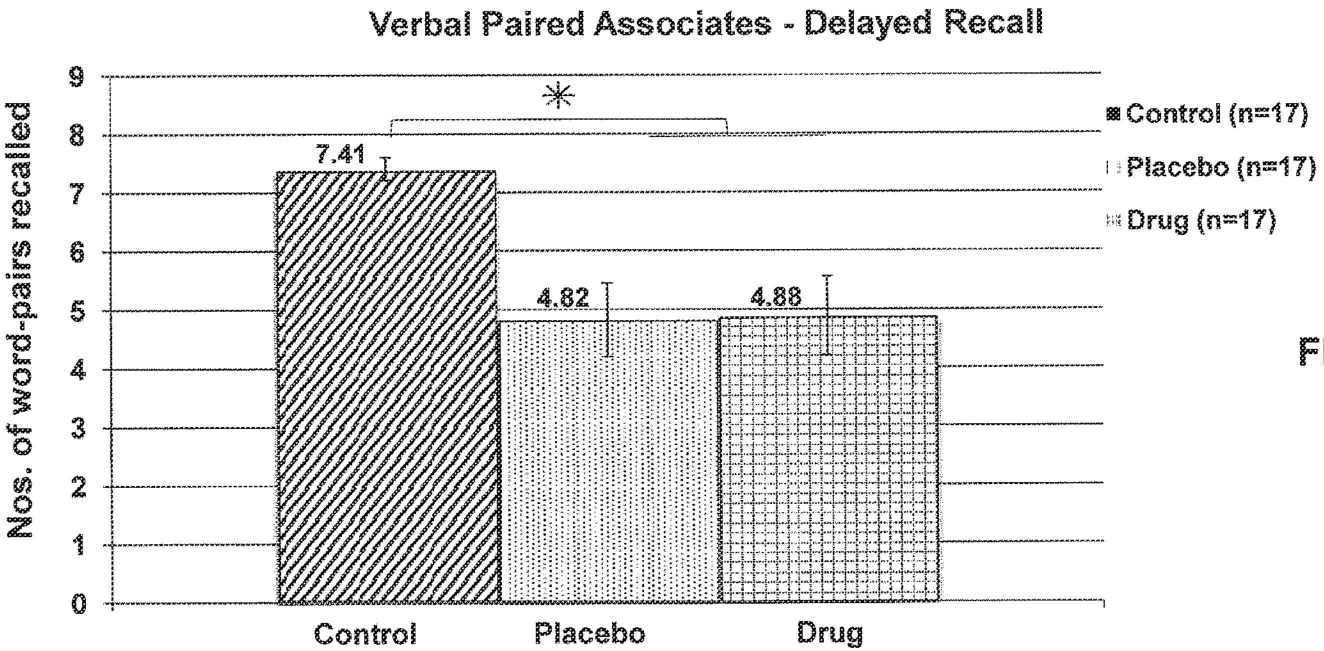


FIG. 17A

Group	Mean	Standard Error	Delayed Recall (p-value)
Control	7.41	0.19	Control vs. Placebo: <0.001
MCI Placebo	4.82	0.63	Control vs. Drug: 0.001
MCI Drug	4.88	0.67	Placebo vs. Drug: 0.848

FIG. 17B

Study Status

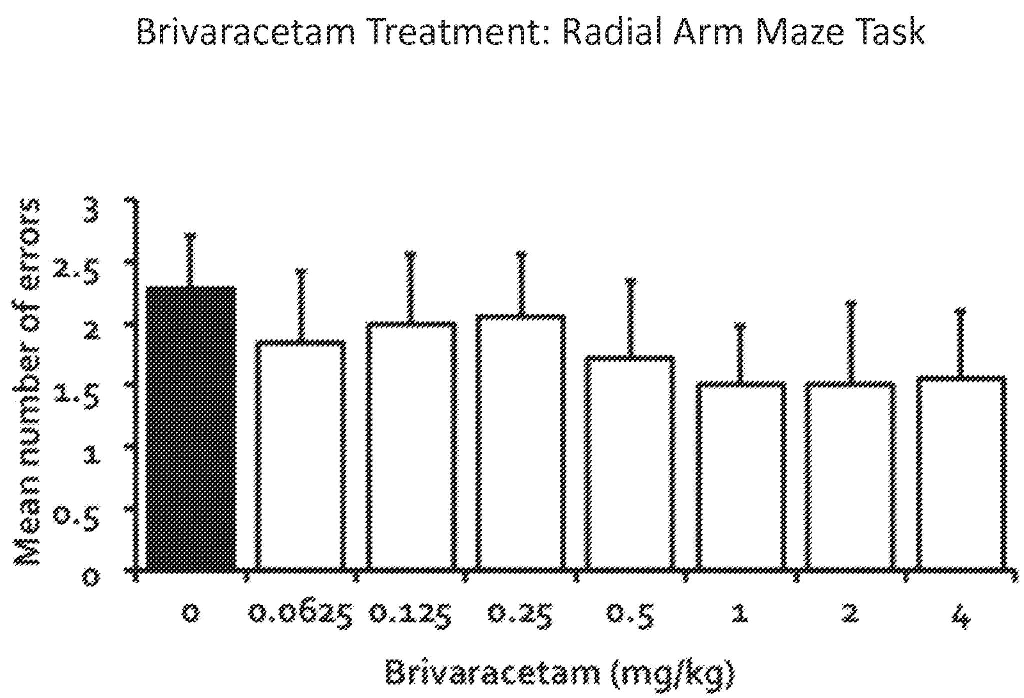
	Control subjects	MCI subjects	Total subjects
Participated in screening	26	32	58
Screening failures	4	9	13
Enrolled	22	23	45
Removed or withdrew from study	5	6	11
Total subjects used in analysis	17	17	34

FIG. 18A

Characteristics of Study Samples

	Control Subjects	MCI Subjects	p
N	17	17	
Sex (M/F)	9/8	6/11	0.307
Age (yrs)	69.3 (7.0)	72.9 (8.9)	0.201
Education (yrs)	15.9 (2.6)	15.8 (2.9)	0.951
Race (Caucasian/African American)	17/0	14/3	0.074
Hispanic or Latino (y/n)	0/17	1/16	0.317

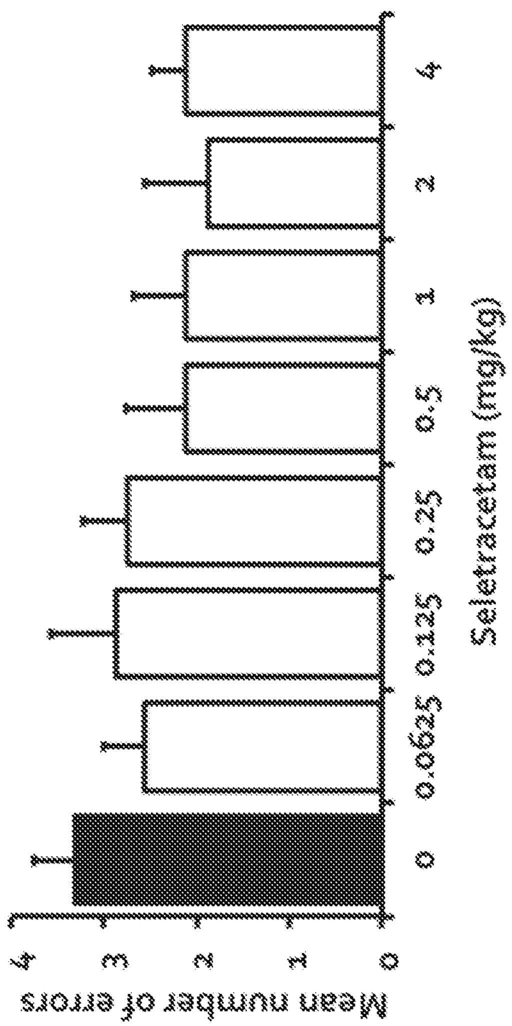
FIG. 18B



Repeated measures ANOVA for within-subject contrasts, $F(1, 8) = 6.046$, $p = 0.039$
Means and SEMs are shown

FIG. 19

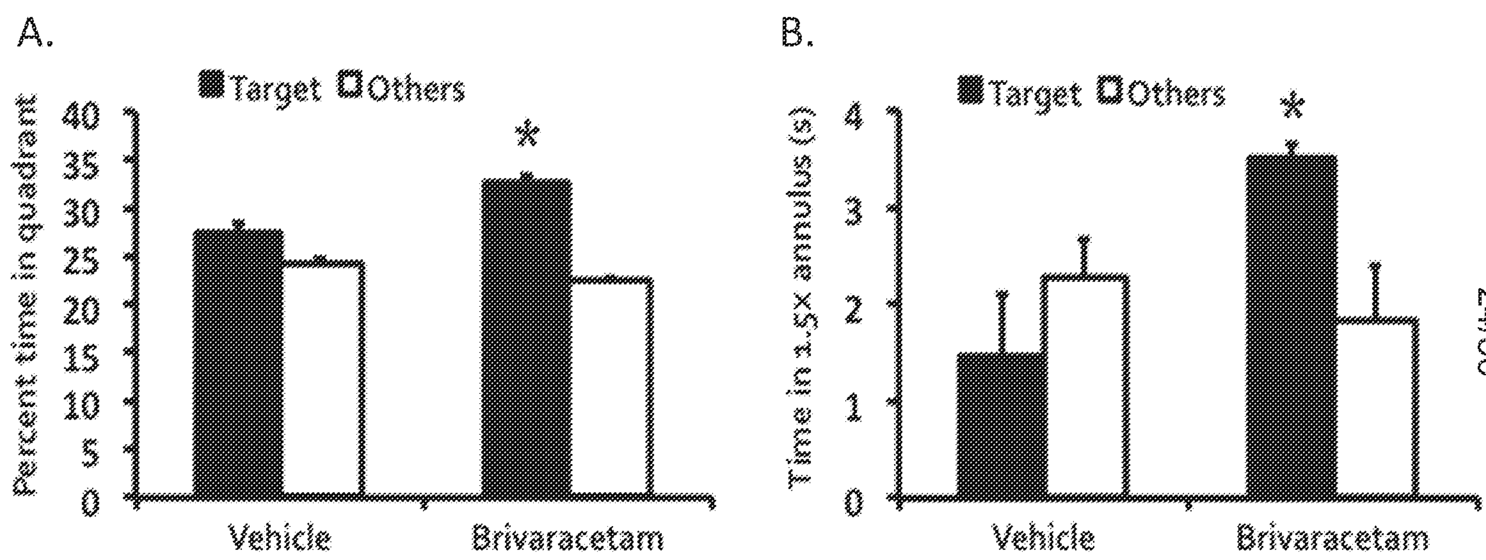
Seletracetam Treatment: Radial Arm Maze Task



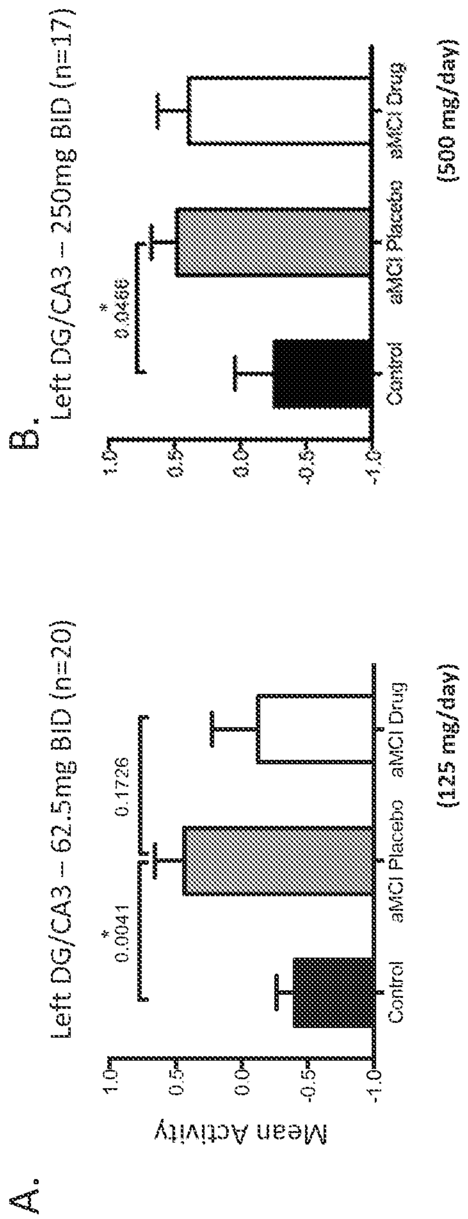
Repeated measures ANOVA for within-subject contrasts, $F(1, 7) = 12.577$, $p = 0.009$
Means and SEMs are shown

FIG. 20

Performance of cognitively-impaired aged rats (n = 3/group)
treated with brivaracetam (2 mg/kg/day after 14 days) in the water maze task

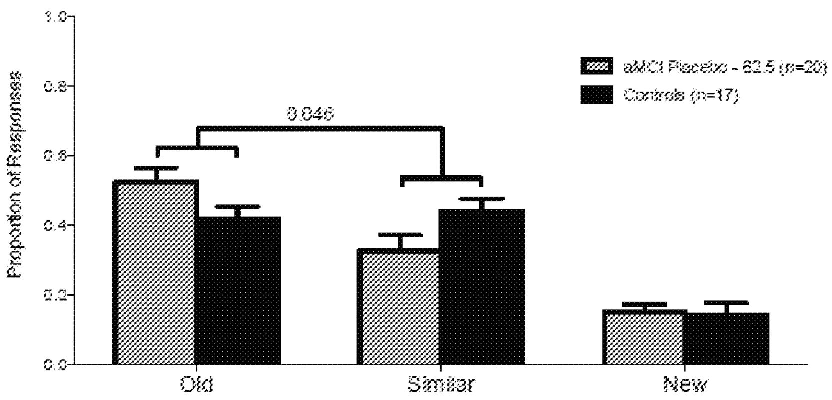


FIGS. 21A and 21B

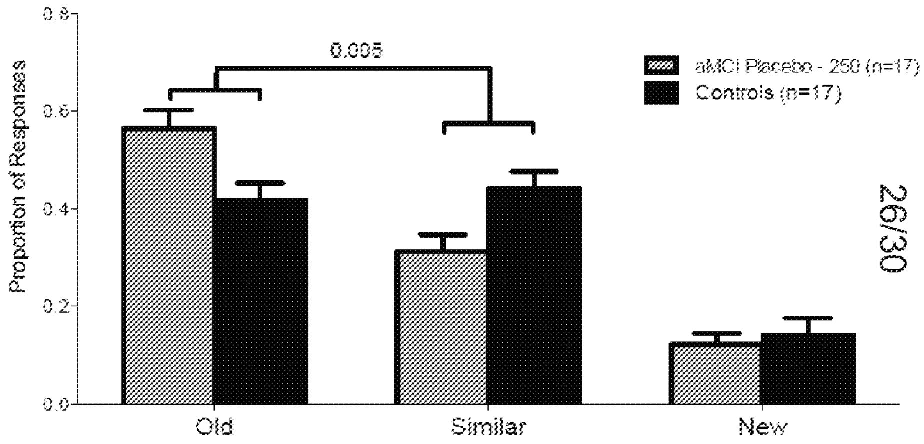


FIGS. 22A and 22B

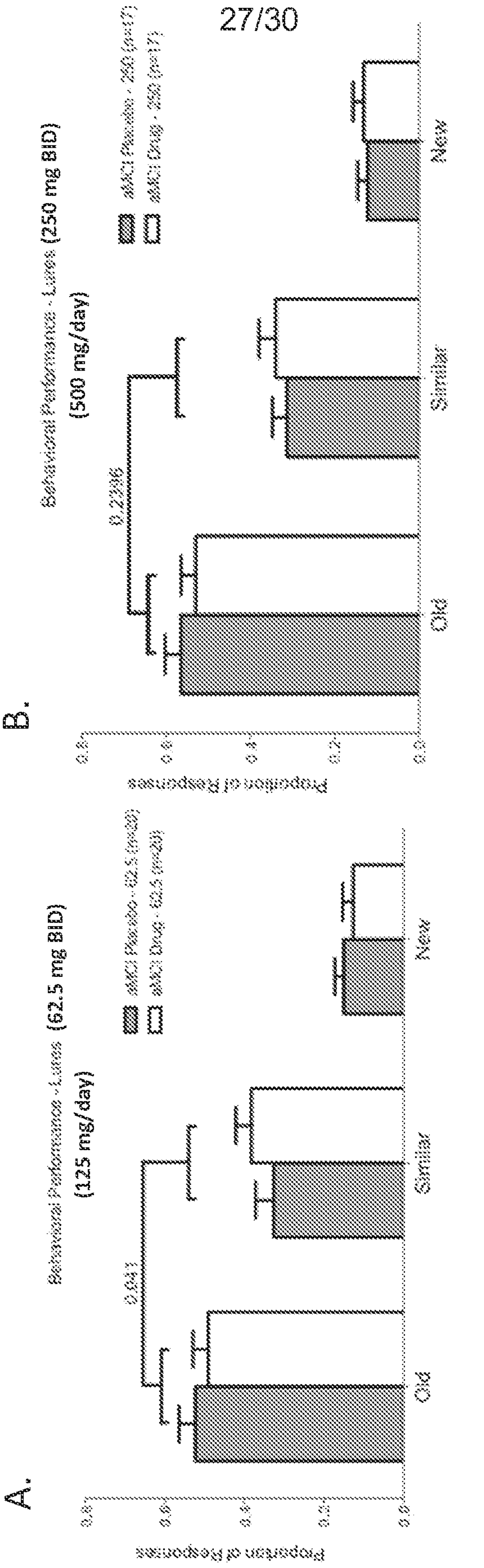
A. Behavior Performance – Lures (62.5 mg BID)



B. Behavior Performance – Lures (250 mg BID)



FIGS. 23A and 23B



FIGS. 24A and 24B

Chronic Treatment with Levetiracetam (10 mg/kg/day) in AI Rats Restores Somatostatin in DG Hilus

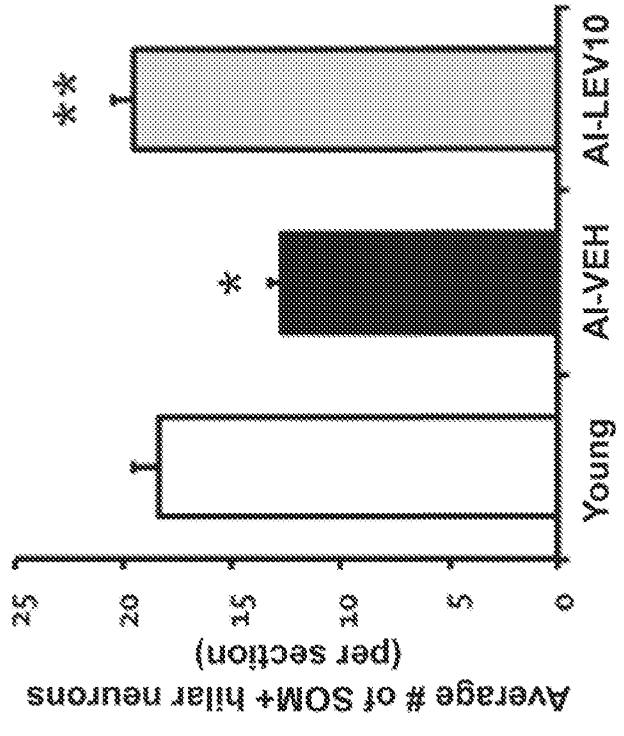


FIG. 25

Chronic Treatment with Levetiracetam (10 mg/kg/day) in AI Rats Restores Reelin in Entorhinal Cortex (EC2)

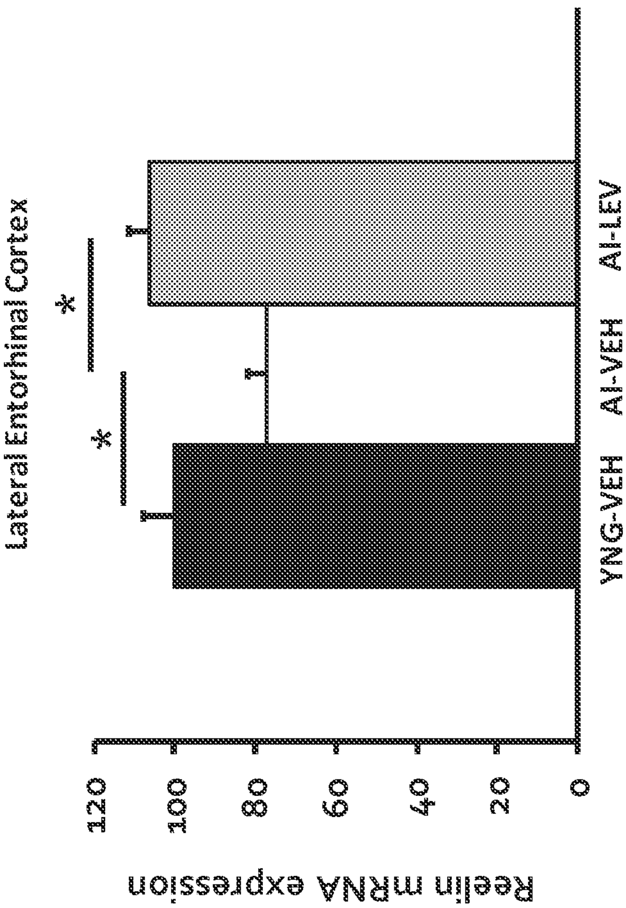
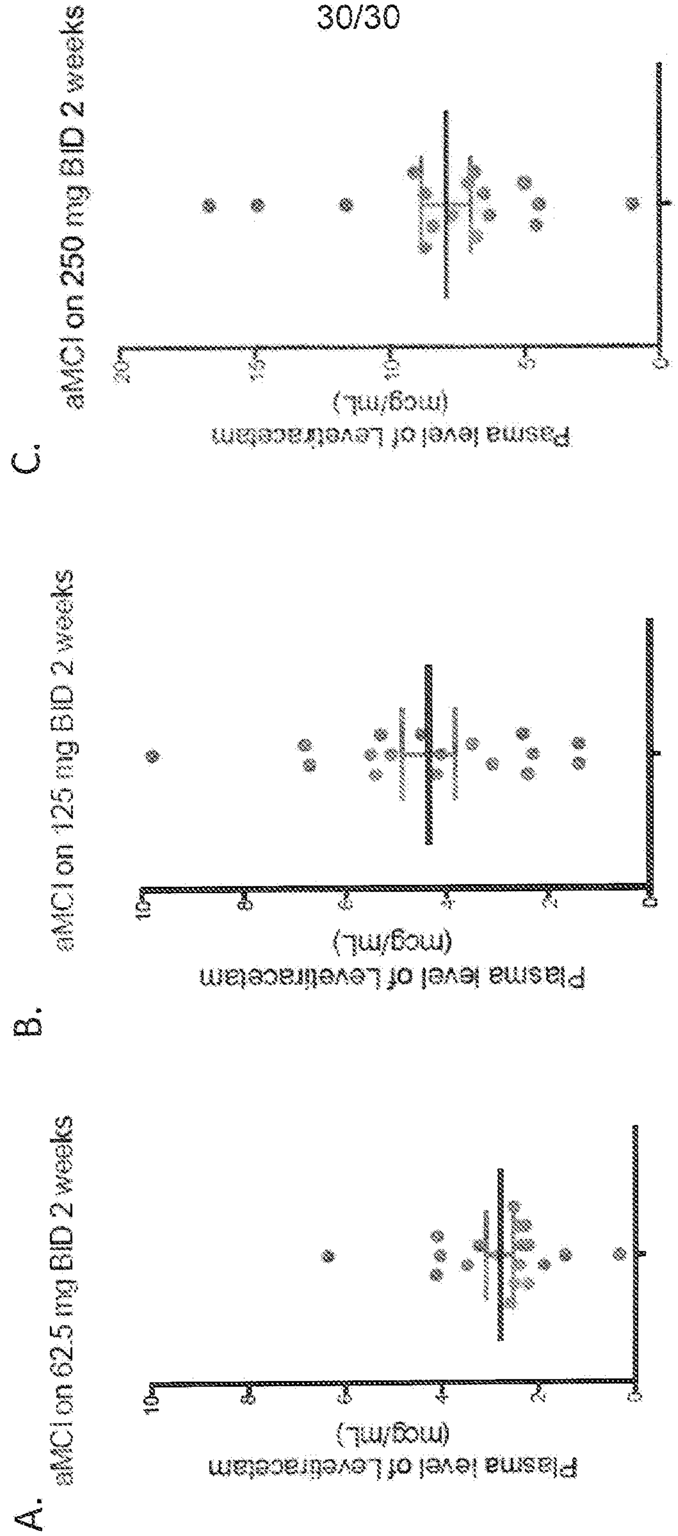


FIG. 26



FIGS. 27A, 27B, and 27C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/70144

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/55, 31/445, 31/662 (2014.01)
USPC - 514/129
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/55, 31/445, 31/662 (2014.01)
USPC: 514/129, 215, 297, 319, 411

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)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Scholar; ProQuest; IP.com; search terms: synaptic vesicle protein; SV2A; antipsychotic; schizophrenia; bipolar; therapeutic index; subterapeutic;

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0212928 A1 (GALLAGHER, M et al.) 01 September 2011; abstract; paragraphs [0002], [0007]-[0009], [0011], -[0020], [0023]	1-2, 4/1-2, 25-26, 28/25-26, 39-40, 41/39-40
A	US 7,563,808 B2 (PRATT, R) 21 July 2009; abstract	1-2, 4/1-2, 25-26, 28/25-26, 39-40, 41/39-40

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2014 (25.02.2014)	13 MAR 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/70144

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 3, 16-17, 27, 37-38, 42, 56-57
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 3, 16-17, 27, 37-38, 42, 56-57 are unsearchable for containing improper incorporation by reference to other patent publications.

3. ☒ Claims Nos.: 5-15, 18-24, 29-36, and 43-55
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.