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(54) Title: METHODS AND COMPOSITIONS FOR IMPROVING COGNITIVE FUNCTION

(57) Abstract: The invention relates to compositions comprising a synaptic vesicle glycoprotein 2A (SV2A) inhibitor in an extended release and an acetylcholinesterase inhibitor (AChEIs). The invention also relates to using such compositions in treating cognitive impairment associated with central nervous system disorders in a subject in need or at risk thereof, including, without limitation, subjects having or at risk for age-related cognitive impairment, Mild Cognitive Impairment (MCI), dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, and substance addiction.

## METHODS AND COMPOSITIONS FOR IMPROVING COGNITIVE FUNCTION

### Related Application

5 [0001] This application claims the benefit of and priority from United States provisional patent application 61/800,191, filed March 15, 2013, the contents and disclosures of which are incorporated herein by reference in their entirety.

### Field of the Invention

10 [0002] The invention relates to methods and compositions for improving cognitive function by using a combination of a synaptic vesicle protein 2A (SV2A) inhibitor and an acetylcholinesterase inhibitor (AChEI). In particular, it relates to compositions comprising SV2A inhibitors in an extended release form in combination with AChEI and their use in treating cognitive impairment associated with central nervous system (CNS) disorders in a subject in need or at risk thereof, including, without limitation, subjects having or at risk for age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnestic MCI (aMCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD), dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, and substance addiction.

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### Background of the Invention

20 [0003] Cognitive ability may decline as a normal consequence of aging or as a consequence of a central nervous disorder.

25 [0004] For example, a significant population of elderly adults experiences a decline in cognitive ability that exceeds what is typical in normal aging. Such age-related loss of cognitive function is characterized clinically by progressive loss of memory, cognition, reasoning, and judgment. Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age-Related Cognitive Decline (ARCD) or similar clinical groupings are among those related to such age-related loss of cognitive function. According to some estimates, there are more than 16

million people with AAMI in the U.S. alone (Barker et al., 1995), and MCI is estimated to affect 5.5 - 7 million in the U.S. over the age of 65 (Plassman et al., 2008).

- 5 [0005] Cognitive impairment is also associated with other central nervous system (CNS) disorders, such as dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder (e.g., mania), amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, and substance addiction.
- 10 [0006] There is, therefore, a need for effective treatment for cognitive impairment associated with central nervous system (CNS) disorders and to improve cognitive function in patients diagnosed with, for example, age-related cognitive impairment, MCI, amnestic MCI, AAMI, ARCD, dementia, Alzheimer's Disease (AD), prodromal AD, post traumatic stress disorder (PTSD) PTSD, schizophrenia, bipolar, disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, substance addiction, and similar central nervous system (CNS) disorders with cognitive impairment or at risk of developing them.
- 15 [0007] Tacrine hydrochloride ("COGNEX™"), the first FDA approved drug for Alzheimer's disease ("AD") is an AChEI (Cutler et al, 1993). Other examples of clinically used AChEIs include galantamine ("REMINYL™") or rivastigmine ("EXELON™"). These drugs, however, have shown limited success in cognitive improvement in Alzheimer's disease patients and display a use-limiting side effect profile. Another AChEI, donepezil (also known as "ARICEPT™"), appears more effective than tacrine. With donepezil, Alzheimer's disease patients show slight cognitive improvements (Barner et al, 1998; Rogers et al, 1998), but the usefulness of donepezil is limited due to its moderate efficacy and side effects. The long-term therapeutic efficacy of donepezil has also been increasingly questioned (Maggini et al., 2006; Petersen et al., 2006). There is, therefore, a need for more effective treatment for disorders involving cognitive dysfunction and in particular cognitive impairment, in AD patients.

### Summary of the Invention

**[0008]** In accordance with a first aspect of this invention, there is provided a pharmaceutical composition for treating cognitive impairment or improving cognitive function in, a subject suffering from cognitive impairment associated with a CNS disorder, or at risk thereof, the composition comprising a synaptic vesicle protein 2A (SV2A) inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and an acetylcholinesterase inhibitor (AChEI) or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in an extended release form. In some embodiments, the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof are not in an extended release form. In some embodiments, the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof are in an immediate release form.

15 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 a suspension form. In some embodiments, the composition is in an aqueous solution. In some embodiments, the composition is for oral administration. In some embodiments, the composition is in a unit dosage form. In

20 some embodiments, the composition is administered once daily. 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 AChEI 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.

25 **[0009]** In some embodiments of this invention, the composition comprises levetiracetam or brivaracetam or seletracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in an extended release form and donepezil (or tacrine, rivatigmine, physostigmine,

galantamine, or metrifonate) or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof. In some embodiments of this invention, the composition comprises levetiracetam or brivaracetam or seletracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in an extended release form and donepezil (or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in a form that is not extended release. In some embodiments of this invention, the composition comprises 5 extended release levetiracetam and immediate release donepezil. In some embodiments, the extended release levetiracetam or brivaracetam or seletracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof present in the composition does not affect the pharmacokinetics or the half-life clearance of donepezil (or tacrine, rivatigmine, 10 physostigmine, galantamine, or metrifonate) or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof that are present in the same composition, or in the same unit dosage form, or in the 15 same single formulation.

**[0010]** In some embodiments of this invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in the composition is present in an amount of 0.07 - 350 mg, or 50 - 250 mg, or 20 3 - 50 mg. In some embodiments, the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate or 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 25 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 some embodiments, the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or 30 prodrug thereof in the composition is present in an amount of about 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.

[0011] In some embodiments of this invention, the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is present in an amount of 0.1 - 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg. In some embodiments, the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is present in an amount of less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg.

[0012] In accordance with another aspect of the present invention, there is provided a method for treating cognitive impairment or improving cognitive function, delaying or slowing the progression of cognitive impairment, or reducing the rate of decline of cognitive function, in a subject suffering from cognitive impairment associated with a central nervous system (CNS) disorder, or at risk thereof, the method comprising the step of administering to said subject a composition comprising a therapeutically effective amount of an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph, or prodrug thereof in combination with a therapeutically effective amount of an AChEI or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph, or prodrug thereof, wherein the SV2A inhibitor is in extended release form. In some embodiments, and the AChEI is in a form that is not extended release. In some 10 embodiments, the AChEI is in an immediate release form. In some embodiments of this invention, the methods of this invention prevent or slow the progression of said cognitive impairment associated with the CNS disorder in said subject. In other embodiments of this invention, the methods of this invention alleviate, ameliorate, or slow the progression, of one or more symptoms associated with said 15 cognitive impairment associated with the CNS disorder in said subject.

[0013] In one embodiment of the invention, the SV2A inhibitor and/or the AChEI are administered at doses that are subtherapeutic as compared to the doses at which they are therapeutically effective when administered in the absence of the other.

[0014] In some embodiments of the invention, the cognitive impairment associated with a CNS disorder is age-related cognitive impairment, such as Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age

Related Cognitive Decline (ARCD). In one embodiment of the invention, the MCI is amnestic MCI. In some embodiments of the invention, the CNS disorder is dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), 5 cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, or substance addiction. In one embodiment, the subject that suffers such CNS disorder or such cognitive impairment is a human patient.

[0015] The SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, 10 solvate or polymorph, or prodrug thereof that is useful in the methods and compositions of this 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 15 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. However, any 15 SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof may be used in the methods and compositions of the invention. In other embodiments, the SV2A inhibitor is selected from the group of SV2A inhibitors referred to in International Patent Application PCT/US2009/005647; International Patent Application Publications 20 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; 25 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 30 Patent Numbers 1,039,113; and 1,309,692; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof. 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, or polymorphs thereof. In other embodiments, the SV2A inhibitor is levetiracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph, or prodrug thereof.

5 [0016] AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof that is useful in the methods and compositions of this invention include those disclosed in, for example, International Patent Applications WO2010/057088; WO2009/008769; WO2008/097546; 10 WO2008/074896; WO2008/073452; WO2007/127474; WO2007/107846; WO2006/097588; WO2006/071274; WO2006/070394; WO2006/060082; WO2006/040688; WO2005/092009; WO2005/079789; WO2005/074535; WO2005/072713; WO 2005/042475; WO2005/039580; WO2005/027975; WO2004/084884; WO2004/080393; WO2004/052348; WO2004/037234; 15 WO2004/034963; WO2004/032929; WO2003/101458; WO2003/091220; WO2003/082820; WO2003/082794; WO2003/020289; WO2002/074293; WO2002/032412; WO2001/085145; WO2001/078728; WO2001/066114; WO2001/066096; WO2001/021590; WO2001/000215; WO2000/033840; WO2000/030446; WO2000/023057; WO2000/015205; WO2000/009483; 20 WO2000/007600; WO2000/002549; WO1999/047131; WO1999/008672; WO1999/007359; WO1998/039000; WO1998/030243; WO1997/138993; WO1997/119059; WO1997/038993; WO1997/029750; WO1997/021681; WO1997/013754; WO1997/008146; WO1996/040682; WO1994/029255; WO1994/020476; WO1994/019356; WO1993/116690; WO1993/113100; 25 WO1993/007140; WO1993/003041; WO1993/003034; WO1992/019238; WO1992/017475; WO1991/003467; and WO1988/008708; U.S. Patent No. 7,846,930; 7,732,162; 7,635,709; 7,378,425; 6,495,700; 6,479,523; 6,372,760; 6,245,911; 6,140,321; 5,985,864; 5,965,571; 5,965,569; 5,750,542; 5,744,476; 5,693,668; 5,668,117; 5,663,448; 5,622,976; 5,603,176; 5,602,176; 5,574,046; 30 5,455,245; 5,391,553; 5,389,629; 5,364,864; 5,338,548; 5,302,593; 5,300,517; 5,288,758; 5,246,947; 5,231,093; 5,187,165; 5,166,181; 5,106,856; 5,102,891; 5,100,901; 4,950,658; 4,948,807; 4,948,807; 4,948,807; 4,914,102; 4,895,841;

4,895,841; 4,816,456; 4,663,318; 4,663,318; 4,663,318; and 2,701,225; Japanese Patent Application Nos. 4-216704 and 4-187674, Canadian Patent No. 2,180,703, European Patent Application Publication Nos. 298202; 236684; 409676; 411534; 468187; 477903; 481429; 487071; 611769; 703901; 1050303; 2018874; and 5 2260839; U.S. Publication Nos. 20010036949; 20020119963; 20030078252; 2003069289; 20040082644; 20050245504; 20050124642; 20060052428; 20070275959; 20080103105; 20080261950; 20090124659; 20100152108; 20100227852; and 20100311697. However, any AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph may be used in the methods and 10 compositions of this invention.

[0017] In other embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or 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 15 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 other 20 embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or 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, 25 solvate or polymorph, or prodrug thereof is administered 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 30 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 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 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, or 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 is administered.

**[0018]** 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 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 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, 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. 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.

- [0019] 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 10 180 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.
- [0020] 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, 20 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, 25 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,

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.

- [0021]** 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.
- [0022]** In some embodiments, the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is administered at a daily dose of 0.1 - 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg. In some embodiments, a subtherapeutic amount of the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is administered. In some embodiments, the subtherapeutic amount of the AChEI administered is a daily dose of less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6

mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg. In the above embodiments, the AChEI inhibitor is donepezil.

**[0023]** In some embodiments of the invention, the combined treatment has a longer or improved therapeutic effect in the subject than is attained by 5 administering the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in the absence of the SV2A inhibitor or a pharmaceutically acceptable salt, solvate, hydrate, or 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 10 10x, or greater than about 10x.

**[0024]** In other 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 or polymorph, or prodrug thereof in the absence of the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or 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 20 provided a method of increasing the therapeutic index of an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in a method of treating cognitive impairment associated with a CNS disorder in a subject in need or at risk thereof, comprising administering a composition comprising an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof to said subject. In some embodiments of this aspect of the invention, the AChEI or the pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is not in an extended release 25 form. In other embodiments of this aspect of the invention, the AChEI or the pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is in an immediate release form.

- [0026] In some embodiments, the increase in the therapeutic index of the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is greater than the therapeutic index of the AChEI when administered in the absence of the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof or a pharmaceutically acceptable salt, hydrate, solvate or 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 the present invention, there is provided a method of increasing the therapeutic index of an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in a method of treating cognitive impairment associated with a CNS disorder in a subject in need or at risk thereof, comprising administering a composition comprising an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof to said subject. In some embodiments of this aspect of the invention, the AChEI or the pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is not in an extended release form. In other embodiments of this aspect of the invention, the AChEI or the pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is in an immediate release form.
- [0028] In some embodiments, the increase in the therapeutic index of the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof is greater than the therapeutic index of the SV2A inhibitor, hydrate, solvate or polymorph when administered in the absence of the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof or a pharmaceutically acceptable salt, hydrate, solvate or polymorph of the SV2A inhibitor when administered in the absence of the AChEI or a pharmaceutically acceptable salt, hydrate, solvate or 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.

[0029] In some embodiments, the methods of the invention improve or treat 5 cognitive function in said subject. In some embodiments of this aspect of the invention, the methods delay or slow the progression of cognitive impairment in said subject. In some embodiments of this aspect of the invention, the methods reduce the rate of decline of cognitive function in said subject. In some embodiments of this aspect of the invention, the methods prevent or slow the 10 progression of the cognitive impairment associated with said CNS disorder in said subject. In other embodiments of this aspect of the invention, the methods alleviate, ameliorate, or slow the progression, of one or more symptoms associated with the cognitive impairment aspects of said CNS disorder in said subject.

[0030] In some embodiments, the cognitive impairment is associated with 15 age-related cognitive impairment, such as Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD). In one embodiment of this aspect of the invention, the MCI is amnestic MCI. In some embodiments of this aspect of the invention, the cognitive impairment is associated with dementia, Alzheimer's Disease(AD), prodromal AD, 20 post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis, cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease, autism, compulsive behavior, or substance addiction. In one embodiment, the subject that suffers such cognitive impairment is a human patient.

25 [0031] In some embodiments, the effect of the treatment, the progression of cognitive impairment, or the rate of decline of cognitive function 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, the progression of 30 cognitive impairment, or the rate of decline of cognitive function is measured by detecting the difference between the levels of somatostatin in the subject prior to and after the administration step.

[0033] In some embodiments, there is provided a pharmaceutical composition for treating, or improving cognitive function in, a subject suffering from cognitive impairment associated with a CNS disorder, or at risk thereof, the composition comprising levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and donepezil or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof, wherein the levetiracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in an extended release form. In some embodiments, the donepezil or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is not in an extended release form. In some embodiments, the donepezil or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof are in an immediate release form. 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 for oral administration. In some embodiments, the composition is administered once daily. In some embodiments, the composition is in a suspension form. In some embodiments, the composition is in a unit dosage form. In some embodiments, the composition is in a tablet or capsule. In some embodiments, the extended release levetiracetam 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 donepezil or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the same composition or in the same formulation or in the same unit. In some embodiments, the extended release form may be 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 levetiracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is present in the composition in an amount of 7 - 350 mg, 70 - 350 mg, 100 - 300 mg, or 125 - 250 mg and the donepezil is present in the composition in an amount of 2 - 10 mg or 2 - 4 mg.

- [0034] In one embodiment of the invention, the SV2A inhibitor and/or the AChEI are administered at doses that are subtherapeutic as compared to the doses at which they are therapeutically effective when administered in the absence of the other.
- 5 [0035] In some embodiments of the invention, the cognitive impairment associated with a CNS disorder is age-related cognitive impairment, such as Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD). In one embodiment of the invention, the MCI is amnestic MCI. In some embodiments of the invention, the CNS disorder is 10 dementia, Alzheimer's Disease(AD), prodromal AD, post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, or substance addiction. In one embodiment, the subject that suffers such CNS disorder or such cognitive 15 impairment is a human patient.

#### Brief Description of the Drawings

- [0036] FIG. 1 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 20 (1.25 mg/kg/day), levetiracetam (2.5 mg/kg/day), levetiracetam (5 mg/kg/day), levetiracetam (10 mg/kg/day) and levetiracetam (20 mg/kg/day). 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 25 (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 during the retention phase 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 had already been visited. Paired t-tests are used to compare 30 the number of errors between different doses of levetiracetam and vehicle control.
- [0037] FIG. 2 depicts the effects of administering donepezil only and administering a combination of donepezil and levetiracetam on the spatial memory

retention of eight aged-impaired rats (AI) in an eight-arm Radial Arm Maze (RAM) test. Four treatment conditions are employed: vehicle control, donepezil only (1 mg/kg/day), donepezil (2 mg/kg/day), and a combination of donepezil (1 mg/kg/day) and levetiracetam (2.5 mg/kg/day). In the RAM task used, there is a  
5 two-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 during the retention phase is used as a measure of spatial memory retention. Errors are defined as  
10 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 have already been visited. Paired t-tests are used to compare the number of errors between different doses of drug treatment and vehicle control. Relative to vehicle control treatment, a combination of donepezil (1 mg/kg/day)  
15 and levetiracetam (2.5 mg/kg/day) significantly improves memory performance ( $t(7) = 2.16$ ,  $p = 0.034$ ).

**[0038]** **FIG. 3** depicts the experimental design of the human trials for levetiracetam treatment.

**[0039]** **FIG. 4A** depicts the average activity in the left CA3 of aMCI subjects  
20 with placebo treatment and age-matched control subjects with placebo treatment during the presentation of lure stimuli that the subject correctly identified as “similar.”

**[0040]** **FIG. 4B** depicts the average activity in the left CA3 of aMCI subjects  
25 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.”

**[0041]** **FIG. 4C** is a table of the data represent in **FIGS. 4A and 4B**.  
**[0042]** **FIG. 5A** depicts the average activity in the left entorhinal cortex of age-matched control subjects with placebo treatment and aMCI subjects with placebo  
30 treatment during the presentation of lure stimuli that the subject correctly identified as “similar.”

- [0043] **FIG. 5B** 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 identified as “similar.”
- 5 [0044] **FIG. 5C** is a table of the data represent in **FIGS. 5A and 5B**.
- [0045] **FIG. 6A** depicts an example of the sequence of images shown to subjects in the explicit 3-alternative forced choice task described in Example 2.
- [0046] **FIG. 6B** shows sample pairs of similar (“lure”) images.
- [0047] **FIG. 7** shows the difference between the aMCI (placebo) subjects and 10 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.
- [0048] **FIG. 8** shows the difference between the same aMCI subjects with 15 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.
- [0049] **FIG. 9** is a table of the data represent in **FIGS. 7 and 8**.
- 20 [0050] **FIG. 10A** 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 Bushke Selective reminding Test – Delayed Recall.
- [0051] **FIG. 10B** is a table of the data represent in **FIG. 10A**.
- 25 [0052] **FIG. 11A** 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.
- [0053] **FIG. 11B** is a table of the data represent in **FIG. 11A**.
- [0054] **FIG. 12A** shows the difference between the control (placebo) subjects 30 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.

- [0055] **FIG. 12B** is a table of the data represent in **FIG. 12A**.
- [0056] **FIG. 13A** 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 –  
5 Delayed Recall.
- [0057] **FIG. 13B** is a table of the data represent in **FIG. 13A**.
- [0058] **FIG. 14A** is a table showing the subject selection process for the human levetiracetam trial described in Example 2.
- [0059] **FIG. 14B** is a table showing the characteristics of the subjects selected for  
10 the human levetiracetam trial described in Example 2.
- [0060] **FIG. 15** 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  
15 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.
- [0061] **FIG. 16** 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 include 0.0625mg/kg,  
20 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. 17A and FIG. 17B** 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 ( $t(2) = 1.964$ ,  $p = 0.188$ ) showed a significant spatial bias for  
25 the target quadrant compared to the other controls quadrants. Brivaracetam-treated rats (2mg/kg/day) also spent 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) spent significantly more time in the target annulus (area surrounding the location of the escape platform) than the vehicle-treated rats,  $t(4) = 3.109$ ,  $p =$   
30  $0.036$ .

- [0063] **FIG. 18A and FIG. 18B** 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.
- 5 [0064] **FIG. 19A and FIG. 19B** 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.
- 10 [0065] **FIG. 20A and FIG. 20B** 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.
- 15 [0066] **FIG. 21** 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.
- 20 [0067] **FIG. 22** 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).
- [0068] **FIGS. 23A – 23C** 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**
- 25 [0069] 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,
- 30 pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

- [0070] 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).
- [0071] 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).
- [0072] 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.
- [0073] 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).
- [0074] The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates otherwise.
- [0075] The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.
- [0076] 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. The SV2A inhibitory activity or the AChEI activity of such agents may render them suitable as “therapeutic agents” in the methods and 5 compositions of this invention.

- [0077] 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).
- 10 [0078] “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, and expressing an interest in one’s surroundings and self-care, speed of processing, reasoning and problem solving and social cognition.
- 15 [0079] 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

20 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., Umbrecht, 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.

[0080] 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.

[0081] 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.

[0082] “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 a level of proficiency as close as possible to a normal, unimpaired subject or an age-matched normal, unimpaired subject.

[0083] In some cases, “promoting” cognitive function in a subject affected by age-related cognitive refers to affecting impaired cognitive function so that it more closely resembles the function of an aged-matched normal, unimpaired subject, or the function of a young adult subject. . Cognitive function of that subject 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 a level of proficiency as close as possible to a normal, unimpaired subject or a young adult subject or an age-matched 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 some cases, “cognitive impairment” in subjects affected by aged-related cognitive impairment refers to cognitive function in subjects that is not as robust as that expected in an aged-matched normal, unimpaired subject, or the function of a young adult subject (*i.e.* subjects with mean scores for a given age in a cognitive test).
- [0087] “Age-related cognitive impairment” refers to cognitive impairment in aged subjects, wherein their cognitive function is not as robust as that expected in an age-matched normal subject or as that expected in young adult subjects. In some cases, cognitive function is reduced by about 5%, about 10%, about 30%, or more, compared to cognitive function expected in an age-matched normal subject. In some cases, cognitive function is as expected in an age-matched normal subject, but reduced by about 5%, about 10%, about 30%, about 50% or more, compared to cognitive function expected in a young adult subject. Age-related impaired cognitive function may be associated with Mild Cognitive Impairment (MCI) (including amnestic MCI and non-amnestic MCI), Age-Associated Memory Impairment (AAMI), and Age-related Cognitive Decline (ARCD).
- [0088] “Cognitive impairment” associated with AD or related to AD or in AD refers to cognitive function in subjects that is not as robust as that expected in subjects who have not been diagnosed AD using conventional methodologies and standards.
- [0089] “Mild Cognitive Impairment” or “MCI” refers to a condition characterized by isolated memory impairment unaccompanied other cognitive abnormalities and relatively normal functional abilities. One set of criteria for a

clinical characterization of MCI specifies the following characteristics: (1) memory complaint (as reported by patient, informant, or physician), (2) normal activities of daily living (ADLs), (3) normal global cognitive function, (4) abnormal memory for age (defined as scoring more than 1.5 standard deviations below the mean for a given age), and (5) absence of indicators of dementia (as defined by DSM-IV guidelines). Petersen et al., *Srch. Neurol.* 56: 303-308 (1999); Petersen, "Mild cognitive impairment: Aging to Alzheimer's Disease." Oxford University Press, N.Y. (2003).

[0090] Diagnosis of MCI usually entails an objective assessment of cognitive impairment, which can be garnered through the use of well-established neuropsychological tests, including the Mini Mental State Examination (MMSE), the Cambridge Neuropsychological Test Automated Battery (CANTAB) and individual tests such as Rey Auditory Verbal Learning Test (AVLT), Logical Memory Subtest of the revised Wechsler Memory Scale (WMS-R) and the New York University (NYU) Paragraph Recall Test. See Folstein et al., *J Psychiatric Res* 12: 189-98 (1975); Robbins et al., *Dementia* 5: 266-81 (1994); Kluger et al., *J Geriatric Psychiatry Neurol* 12:168-79 (1999).

[0091] "Age-Associate Memory Impairment (AAMI)" refers to a decline in memory due to aging. A patient may be considered to have AAMI if he or she is at least 50 years old and meets all of the following criteria: a) The patient has noticed a decline in memory performance, b) The patient performs worse on a standard test of memory compared to young adults, c) All other obvious causes of memory decline, except normal aging, have been ruled out (in other words, the memory decline cannot be attributed to other causes such as a recent heart attack or head injury, depression, adverse reactions to medication, Alzheimer's disease, etc.).

[0092] "Age-Related Cognitive Decline (ARCD)" refers to declines in memory and cognitive abilities that are a normal consequence of aging in humans (e.g., Craik & Salthouse, 1992). This is also true in virtually all mammalian species. Age-Associated Memory Impairment refers to older persons with objective memory declines relative to their younger years, but cognitive functioning that is normal relative to their age peers (Crook et al., 1986). Age-Consistent Memory Decline is a less pejorative label which emphasizes that these are normal

developmental changes (Crook, 1993; Larrabee, 1996), are not pathophysiological (Smith et al., 1991), and rarely progress to overt dementia (Youngjohn & Crook, 1993). The DSM-IV (1994) has codified the diagnostic classification of ARCD.

5 [0093] Alzheimer's disease (AD) is characterized by memory deficits in its early phase. Later symptoms include impaired judgment, disorientation, confusion, behavior changes, trouble speaking, and motor deficits. Histologically, AD is characterized by beta-amyloid plaques and tangles of protein tau.

10 [0094] Vascular dementia is caused by strokes. Symptoms overlap with those of AD, but without the focus on memory impairment.

15 [0095] Dementia with Lewy bodies is characterized by abnormal deposits of alpha-synuclein that form inside neurons in the brain. Cognitive impairment may be similar to AD, including impairments in memory and judgment and behavior changes.

15 [0096] Frontotemporal dementia is characterized by gliosis, neuronal loss, superficial spongiform degeneration in the frontal cortex and/or anterior temporal lobes, and Pick's bodies. Symptoms include changes in personality and behavior, including a decline in social skills and language expression/comprehension.

20 [0097] "Post traumatic stress disorder (PTSD)" refers to an anxiety disorder characterized by an immediate or delayed response to a catastrophic event, characterized by re-experiencing the trauma, psychic numbing or avoidance of stimuli associated with the trauma, and increased arousal. Re-experiencing phenomena include intrusive memories, flashbacks, nightmares, and psychological or physiological distress in response to trauma reminders. Such responses produce anxiety and can have significant impact, both chronic and acute, on a patient's 25 quality of life and physical and emotional health. PTSD is also associated with impaired cognitive performance, and older individuals with PTSD have greater decline in cognitive performance relative to control patients.

30 [0098] "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.

- 5       **[0099]** “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.
- 10      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.
- 15      **[0100]** “Amyotrophic lateral sclerosis,” also known as ALS, refers to a progressive, fatal, neurodegenerative disease characterized by a degeneration of motor neurons, the nerve cells in the central nervous system that control voluntary muscle movement. ALS is also characterized by neuronal degeneration in the entorhinal cortex and hippocampus, memory deficits, and neuronal hyperexcitability in different brain areas such as the cortex.
- 20      **[0101]** “Cancer-therapy-related cognitive impairment” refers to cognitive impairment that develops in subjects that are treated with cancer therapies such as chemotherapy and radiation. Cytotoxicity and other adverse side-effects on the brain of cancer therapies result in cognitive impairment in such functions as memory, learning and attention.
- 25      **[0102]** Parkinson’s disease (PD) is a neurological disorder characterized by a decrease of voluntary movements. The afflicted patient has reduction of motor activity and slower voluntary movements compared to the normal individual. The patient has characteristic “mask” face, a tendency to hurry while walking, bent over posture and generalized weakness of the muscles. There is a typical “lead-pipe” rigidity of passive movements. Another important feature of the disease is the tremor of the extremities occurring at rest and decreasing during movements.

- [0103] “Autism”, as used herein, refers to an autism spectrum disorder characterized by a neural development disorder leading to impaired social interaction and communication by restricted and repetitive behavior. “Autism Spectrum Disorder” refers to a group of developmental disabilities that includes:
- 5 autism; Asperger syndrome; pervasive developmental disorder not otherwise specified (PDD-NOS or atypical autism); Rett syndrome; and childhood disintegrative disorder.
- [0104] Mental retardation is a generalized disorder characterized by significantly impaired cognitive function and deficits in adaptive behaviors. Mental retardation is often defined as an Intelligence Quotient (IQ) score of less than 70. Inborn causes are among many underlying causes for mental retardation. The dysfunction in neuronal communication is also considered one of the underlying causes for mental retardation (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* **2010**, 10, 207-214).
- 10 [0105] In some instances, mental retardation includes, but are not limited to, Down syndrome, velocardiofacial syndrome, fetal alcohol syndrome, Fragile X syndrome, Klinefelter’s syndrome, neurofibromatosis, congenital hypothyroidism, Williams syndrome, phenylketonuria (PKU), Smith-Lemli-Opitz syndrome, Prader-Willi syndrome, Phelan-McDermid syndrome, Mowat-Wilson syndrome, 15 ciliopathy, Lowe syndrome and siderium type X-linked mental retardation. Down syndrome is a disorder that includes a combination of birth defects, including some degree of mental retardation, characteristic facial features and, often, heart defects, increased infections, problems with vision and hearing, and other health problems. Fragile X syndrome is a prevalent form of inherited mental retardation, occurring 20 with a frequency of 1 in 4,000 males and 1 in 8,000 females. The syndrome is also characterized by developmental delay, hyperactivity, attention deficit disorder, and autistic-like behavior. There is no effective treatment for fragile X syndrome.
- 25 [0106] Obsessive compulsive disorder (“OCD”) is a mental condition that is most commonly characterized by intrusive, repetitive unwanted thoughts (obsessions) resulting in compulsive behaviors and mental acts that an individual feels driven to perform (compulsion). Current epidemiological data indicates that OCD is the fourth most common mental disorder in the United States. Some

studies suggest the prevalence of OCD is between one and three percent, although the prevalence of clinically recognized OCD is much lower, suggesting that many individuals with the disorder may not be diagnosed. Patients with OCD are often diagnosed by a psychologist, psychiatrist, or psychoanalyst according to the  
5 Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR) (2000) diagnostic criteria that include characteristics of obsessions and compulsions.

[0107] Substance addiction (e.g., drug addiction, alcohol addiction) is a mental disorder. The addiction is not triggered instantaneously upon exposure to substance  
10 of abuse. Rather, it involves multiple, complex neural adaptations that develop with different time courses ranging from hours to days to months (Kauer J. A. *Nat. Rev. Neurosci.* 2007, 8, 844-858). The path to addiction generally begins with the voluntary use of one or more controlled substances, such as narcotics, barbiturates, methamphetamines, alcohol, nicotine, and any of a variety of other such controlled  
15 substances. Over time, with extended use of the controlled substance(s), the voluntary ability to abstain from the controlled substance(s) is compromised due to the effects of prolonged use on brain function, and thus on behavior. As such, substance addiction generally is characterized by compulsive substance craving, seeking and use that persist even in the face of negative consequences. The  
20 cravings may represent changes in the underlying neurobiology of the patient which likely must be addressed in a meaningful way if recovery is to be obtained. Substance addiction is also characterized in many cases by withdrawal symptoms, which for some substances are life threatening (e.g., alcohol, barbiturates) and in others can result in substantial morbidity (which may include nausea, vomiting,  
25 fever, dizziness, and profuse sweating), distress, and decreased ability to obtain recovery. For example, alcoholism, also known as alcohol dependence, is one such substance addiction. Alcoholism is primarily characterized by four symptoms which include cravings, loss of control, physical dependence and tolerance. These symptoms also may characterize addictions to other controlled substances. The  
30 craving for alcohol, as well as other controlled substances, often is as strong as the need for food or water. Thus, an alcoholic may continue to drink despite serious family, health and/or legal ramifications.

[0108] “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, improving cognitive function, delaying or slowing the progression of cognitive impairment, reducing the rate of decline of cognitive function, preventing or slowing the progression of the disease or disorder, or alleviation, amelioration, or slowing the progression, of one or more symptoms associated cognitive impairment associated with CNS disorders, such as age-related cognitive impairment, Mild Cognitive Impairment (MCI), amnestic MCI, dementia, Alzheimer’s Disease (AD), prodromal AD, PTSD, schizophrenia or bipolar disorder (in particular, mania), amyotrophic lateral sclerosis (ALS), cancer therapy-related cognitive impairment, mental retardation, Parkinson’s disease (PD), autism, compulsive behavior, and substance addiction. Treating age-related cognitive impairment further comprises slowing the conversion of age-related cognitive impairment (including, but not limited to MCI, ARCD and AAMI) into dementia (e.g., AD).

[0109] “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 age-related cognitive impairment refers to taking 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 an age-matched normal, unimpaired subject, or the function of a young adult subject. In some cases, “treating cognitive impairment” in a subject refers to taking steps to delay or slow the progression of cognitive impairment in a subject with cognitive  
5 impairment. In some cases, “treating cognitive impairment” in a subject refers to taking steps to reduce the rate of decline of cognitive function in a subject with cognitive impairment.

[0110] “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  
10 those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, 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  
15 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  
20 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.

[0111] 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  
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administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

[0112] 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, or delaying or slowing the progression of cognitive impairment, or reducing the rate of decline of cognitive function in a subject, e.g., a patient having cognitive impairment associated with a CNS disorder. 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.

[0113] “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 involving cognitive dysfunction.

[0114] “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.

[0115] “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.

[0116] 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 AChEI. 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 an enzymatic activity of the host animal to an inhibitor of SV2A or 5 an AChEI.

[0117] “Pharmaceutically acceptable salts” 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 agents and compounds of the invention. The acid addition salt form of a compound that occurs in its free form as a base can be obtained by treating 10 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, 15 pamoic and the like. 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, hydrate, solvate, polymorph or prodrug thereof in combination with administration of an AChEI or a 20 pharmaceutically acceptable salt, hydrate, solvate, polymorph or prodrug thereof. The agents or compounds of the SV2A inhibitor or the AChEI 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 25 evaluating treatments for cognitive impairment associated with CNS disorders. 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 30 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 5 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 10 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 15 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 20 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 25 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 cognitive impairment associated with CNS disorders.

**[0121]** Another cognitive test that may be used to assess the effects of a test 30 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 5 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 10 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 15 conditions, can then be compared for efficacy of the test compound in treating cognitive impairment associated with CNS disorders.

**[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 20 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 25 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); 30 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, 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. 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  
5 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 present 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  
10 successful memory retrieval by the subject. By contrast, calling the lure stimulus “old” or “new” indicates that correct memory retrieval did not occur.

**[0123]** In addition to assessing cognitive performance, the progression of age-related cognitive impairment and dementia, as well as the conversion of age-related cognitive impairment into dementia, may be monitored by assessing  
15 surrogate changes in the brain of the subject. Surrogate changes include, without limitation, changes in regional brain volumes, perforant path degradation, and changes seen in brain function through resting state fMRI (R-fMRI) and fluorodeoxyglucose positron emission tomography (FDG-PET). Examples of regional brain volumes useful in monitoring the progression of age-related  
20 cognitive impairment and dementia include reduction of hippocampal volume and reduction in volume or thickness of entorhinal cortex. These volumes may be measured in a subject by, for example, MRI. Aisen et al., *Alzheimer's & Dementia* 6:239-246 (2010). Perforant path degradation has been shown to be linked to age, as well as reduced cognitive function. For example, older adults  
25 with more perforant path degradation tend to perform worse in hippocampus-dependent memory tests. Perforant path degradation may be monitored in subjects through ultrahigh-resolution diffusion tensor imaging (DTI). Yassa et al., *PNAS* 107:12687-12691 (2010). Resting-state fMRI (R-fMRI) involves imaging the brain during rest, and recording large-amplitude spontaneous low-frequency (<0.1  
30 Hz) fluctuations in the fMRI signal that are temporally correlated across functionally related areas. Seed-based functional connectivity, independent component analyses, and/or frequency-domain analyses of the signals are used to

reveal functional connectivity between brain areas, particularly those areas whose connectivity increase or decrease with age, as well as the extent of cognitive impairment and/or dementia. FDG-PET uses the uptake of FDG as a measure of regional metabolic activity in the brain. Decline of FDG uptake in regions such as 5 the posterior cingulated cortex, temporoparietal cortex, and prefrontal association cortex has been shown to relate to the extent of cognitive decline and dementia. Aisen et al., *Alzheimer's & Dementia* 6:239-246 (2010), Herholz et al., *NeuroImage* 17:302-316 (2002).

### **Age-Related Cognitive Impairment**

10 [0124] This invention provides methods and compositions for treating age-related cognitive impairment or the risk thereof using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in an extended release form in combination with an AChEI or a, hydrate, solvate, polymorph, or prodrug pharmaceutically acceptable salt thereof. In some 15 embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in an immediate release form. In certain embodiments, treatment comprises improving cognitive function in patients with age-related cognitive impairment. In certain embodiments, treatment 20 comprises slowing or delaying the progression of age-related cognitive impairment. In certain embodiments, treatment comprises reducing the rate of decline of cognitive function associated with dementia. In certain embodiments, treatment comprises preventing or slowing the progression, of age-related cognitive impairment. In certain embodiments, treatment comprises alleviation, 25 amelioration or slowing the progression, of one or more symptoms associated with age-related cognitive impairment. In certain embodiments, treatment of age-related cognitive impairment comprises slowing the conversion of age-related cognitive impairment (including, but not limited to MCI, ARCD and AAMI) into dementia (e.g., AD). The methods and compositions may be used for human 30 patients in clinical applications in the treating age-related cognitive impairment in conditions such as MCI, ARCD and AAMI or for the risk thereof. The dose of the

composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

[0125] In some embodiments, a subject to be treated by the methods and compositions of this invention exhibits age-related cognitive impairment or is at 5 risk of such impairment. In some embodiments, the age-related cognitive impairment includes, without limitation, Age-Associated Memory Impairment (AAMI), Mild Cognitive Impairment (MCI) and Age-related Cognitive Decline (ARCD).

[0126] Animal models serve as an important resource for developing and 10 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, expected to be predictive of efficacy in humans.

[0127] Various animal models of age-related cognitive impairment are known in 15 the art. For example, 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 20 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 25 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 30 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); Gallagher *et al.* *Behav. Neurosci.* 107:618-626, (1993); Rapp and Gallagher, *Proc. Natl. Acad. Sci.* 93: 9926-9930, (1996); Nicolle *et al.*, *Neuroscience* 74: 741-756, (1996); Nicolle *et al.*, *J. Neurosci.* 19: 9604-9610, (1999); International Patent Publication WO2007/019312 and International Patent 5 Publication WO 2004/048551. Such an animal model of age-related cognitive impairment may be used to assay the effectiveness of the methods and compositions this invention in treating age-related cognitive impairment.

[0128] The efficacy of the methods and compositions of this invention in treating age-related cognitive impairment may be assessed using a variety of cognitive 10 tests, including the Morris water maze and the radial arm maze, as discussed above.

### **Dementia**

[0129] This invention also provides methods and compositions for treating dementia using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, 15 solvate or polymorph thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In certain embodiments, treatment comprises improving cognitive function in patients with dementia. In certain embodiments, treatment comprises slowing or delaying the progression of dementia. In certain embodiments, 20 treatment comprises reducing the rate of decline of cognitive function associated with dementia. In certain embodiments, treatment comprises preventing or slowing the progression, of dementia. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with dementia. In certain embodiments, the symptom to be 25 treated is cognitive impairment. In certain embodiments, the dementia is Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, or frontotemporal dementia. The methods and compositions may be used for human patients in clinical applications in treating dementia. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and 30 efficacious in those applications.

[0130] Animal models serve as an important resource for developing and evaluating treatments for dementia. Features that characterize dementia in animal

- models typically extend to dementia in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of dementia are known in the art, such as the PDAPP, Tg2576, APP23, TgCRND8, J20, hPS2 Tg, and APP + PS1 transgenic mice. Sankaranarayanan, *Curr. Top. Medicinal Chem.* 6: 609-627, 2006; Kobayashi et al. *Genes Brain Behav.* 4: 173-196. 2005; Ashe and Zahns, *Neuron*. 66: 631-45, 2010. Such animal models of dementia may be used to assay the effectiveness of the methods and compositions of this invention of the invention in treating dementia.
- [0131] The efficacy of the methods and compositions of this invention in treating dementia, or cognitive impairment associated with dementia, may be assessed in animals models of dementia, as well as human subjects with dementia, using a variety of cognitive tests known in the art, as discussed above.
- Post Traumatic Stress Disorder**
- [0132] This invention also provides methods and compositions for treating post traumatic stress disorder (PTSD) using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In certain embodiments, treatment comprises improving cognitive function in patients with PTSD. In certain embodiments, treatment comprises slowing or delaying the progression of PTSD. In certain embodiments, treatment comprises reducing the rate of decline of cognitive function associated with PTSD. In certain embodiments, treatment comprises preventing or slowing the progression, of PTSD. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with PTSD. In certain embodiments, the symptom to be treated is cognitive impairment. The methods and compositions may be used for human patients in clinical applications in treating PTSD. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.
- [0133] Patients with PTSD (and, to a lesser degree trauma-exposed patients without PTSD) have smaller hippocampal volumes (Woon et al., *Prog. Neuropsychopharmac. & Biological Psych.* 34, 1181-1188; Wang et al., *Arch. Gen.*

*Psychiatry* 67:296-303, 2010). PTSD is also associated with impaired cognitive performance. Older individuals with PTSD have greater declines in cognitive performance relative to control patients (Yehuda *et al.*, *Bio. Psych.* 60: 714-721, 2006) and have a greater likelihood of developing dementia (Yaffe *et al.*, *Arch. 5 Gen. Psych.* 678: 608-613, 2010).

[0134] Animal models serve as an important resource for developing and evaluating treatments for PTSD. Features that characterize PTSD in animal models typically extend to PTSD in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans. Various animal models of 10 PTSD are known in the art.

[0135] One rat model of PTSD is Time-dependent sensitization (TDS). TDS involves exposure of the animal to a severely stressful event followed by a situational reminder of the prior stress. The following is an example of TDS. Rats are placed in a restrainer, then placed in a swim tank and made to swim for a 15 period of time, *e.g.*, 20 min. Following this, each rat is then immediately exposed to a gaseous anesthetic until loss of consciousness, and finally dried. The animals are left undisturbed for a number of days, *e.g.*, one week. The rats are then exposed to a “restress” session consisting of an initial stressor, *e.g.*, a swimming session in the swim tank (Liberzon *et al.*, *Psychoneuroendocrinology* 22: 443-453, 1997; 20 Harvery *et al.*, *Psychopharmacology* 175:494-502, 2004). TDS results in an enhancement of the acoustic startle response (ASR) in the rat, which is comparable to the exaggerated acoustic startle that is a prominent symptom of PTSD (Khan and Liberzon, *Psychopharmacology* 172: 225-229, 2004). Such animal models of PTSD may be used to assay the effectiveness of the methods and compositions of 25 this invention of the invention in treating PTSD.

[0136] The efficacy of the methods and compositions of this invention in treating PTSD, or cognitive impairment associated with PTSD, may also be assessed in animals models of PTSD, as well as human subjects with PTSD, using a variety of cognitive tests known in the art, as discussed above.

### 30 **Schizophrenia**

[0137] This invention provides methods and compositions for treating schizophrenia or bipolar disorder (in particular, mania) using an SV2A inhibitor or

a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In certain embodiments, treatment comprises improving cognitive function in patients with schizophrenia.

5    In certain embodiments, treatment comprises slowing or delaying the progression of schizophrenia. In certain embodiments, treatment comprises reducing the rate of decline of cognitive function associated with schizophrenia. In certain embodiments, treatment comprises preventing or slowing the progression of schizophrenia or bipolar disorder (in particular, mania). Schizophrenia is

10    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.

15    Further, there are a number of other psychiatric diseases such as schizotypal 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

20    composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

25    **[0138]**   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.,*

5 *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.

10 [0139] 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.

15 [0140] 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 20 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 25 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 30 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 5 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, 10 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 15 particular, mania).

**[0141]** 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 20 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 25 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 30 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.

[0142] In MAM-treated rats, hippocampal (HPC) dysfunction leads to dopamine system hyperactivity. A benzodiazepine-positive allosteric modulator (PAM), selective for the  $\alpha 5$  subunit of the GABA<sub>A</sub> receptor, SH-053-2'F-R-CH<sub>3</sub>, is tested for its effects on the output of the hippocampal (HPC). The effect of SH-053-2'F-R-CH<sub>3</sub> on the hyperactive locomotor response to amphetamine in MAM-treated animals is also examined. The  $\alpha 5$ GABAAR 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  $\alpha 5$ GABAAR PAM treatment. In addition, the increased locomotor response to amphetamine observed in MAM-treated rats is reduced following the  $\alpha 5$ GABA<sub>A</sub>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.

[0143] 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).

5 [0144] 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 10 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<sub>50</sub> 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 15 control values observed in vehicle 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) or cognitive impairment associated therewith.

20 [0145] The efficacy of the methods and compositions of this invention in treating schizophrenia or cognitive impairment associated with 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.

25 **Amyotrophic Lateral Sclerosis (ALS)**

[0146] This invention additionally provides methods and compositions for 30 treating ALS using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in

an immediate release form. In certain embodiments, treatment comprises improving cognitive function in patients with ALS. In certain embodiments, treatment comprises slowing or delaying the progression of ALS. In certain embodiments, treatment comprises reducing the rate of decline of cognitive function associated with ALS. In certain embodiments, treatment comprises preventing or slowing the progression, of ALS. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression, of one or more symptoms associated with ALS. In certain embodiments, the symptom to be treated is cognitive impairment. The methods and compositions may be used for 5 human patients in clinical applications in treating ALS. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

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**[0147]** In addition to the degeneration of motor neurons, ALS is characterized by neuronal degeneration in the entorhinal cortex and hippocampus, memory deficits, 15 and neuronal hyperexcitability in different brain areas such as the cortex.

**[0148]** The efficacy of the methods and compositions of this invention in treating ALS, or cognitive impairment associated with ALS, may also be assessed in animal models of ALS, as well as human subjects with ALS, using a variety of cognitive tests known in the art, as discussed above.

20 **Cancer therapy-related cognitive impairment**

**[0149]** This invention additionally provides methods and compositions for treating cancer therapy-related cognitive impairment using an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof in an 25 extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in an immediate release form. In certain 30 embodiments, treatment comprises preventing or slowing the progression, of cancer therapy-related cognitive impairment. In certain embodiments, treatment comprises improving cognitive function in patients with cancer therapy-related cognitive impairment. In certain embodiments, treatment comprises slowing or

delaying the progression of cancer therapy-related cognitive impairment. In certain embodiments, treatment comprises reducing the rate of decline of cognitive function associated with cancer therapy-related cognitive impairment. In certain embodiments, treatment comprises alleviation, amelioration or slowing the progression, of one or more symptoms associated with cancer therapy-related cognitive impairment. The methods and compositions may be used for human patients in clinical applications in treating cancer therapy-related cognitive impairment. The dose of the composition and dosage interval for the method is, as described herein, one that is safe and efficacious in those applications.

5 [0150] Therapies that are used in cancer treatment, including chemotherapy, radiation, or combinations thereof, can cause cognitive impairment in patients, in such functions as memory, learning and attention. Cytotoxicity and other adverse side-effects on the brain of cancer therapies are the basis for this form of cognitive impairment, which can persist for decades. (Dietrich *et al.*, Oncologist 13:1285-95, 2008; Soussain *et al.*, Lancet 374:1639-51, 2009).

10 [0151] Cognitive impairment following cancer therapies reflects dysfunction in frontal cortical and hippocampal circuits that are essential for normal cognition. In animal models, exposure to either chemotherapy or radiation adversely affects performance on tests of cognition specifically dependent on these brain systems, especially the hippocampus (Kim *et al.*, J. Radiat. Res. 49:517-526, 2008; Yang *et al.*, Neurobiol. Learning and Mem. 93:487-494, 2010). Thus, drugs targeting these cortical and hippocampal systems could be neuroprotective in patients receiving cancer therapies and efficacious in treating symptoms of cognitive impairment that may last beyond the interventions used as cancer therapies.

15 [0152] Animal models serve as an important resource for developing and evaluating treatments for cancer therapy-related cognitive impairment. Features that characterize cancer therapy-related cognitive impairment in animal models typically extend to cancer therapy-related cognitive impairment in humans. Thus, efficacy in such animal models is expected to be predictive of efficacy in humans.

20 [0153] Various animal models of cancer therapy-related cognitive impairment are known in the art.

[0153] Examples of animal models of cancer therapy-related cognitive impairment include treating animals with anti-neoplastic agents such as cyclophosphamide (CYP) or with radiation, *e.g.*,  $^{60}\text{Co}$  gamma-rays. (Kim *et al.*, *J. Radiat. Res.* 49:517-526, 2008; Yang *et al.*, *Neurobiol. Learning and Mem.* 93:487-494, 2010). The cognitive function of animal models of cancer therapy-related cognitive impairment may then be tested with cognitive tests to assay the effectiveness of the methods and compositions of the invention in treating cancer therapy-related cognitive impairment. The efficacy of the methods and compositions of this invention in treating cancer therapy-related cognitive impairment, as well as human subjects with cancer therapy-related cognitive impairment, using a variety of cognitive tests known in the art, as discussed above.

**Parkinson's disease (PD)**

[0154] Parkinson's disease (PD) is a neurological disorder characterized by a decrease of voluntary movements. The afflicted patient has reduction of motor activity and slower voluntary movements compared to the normal individual. The patient has characteristic "mask" face, a tendency to hurry while walking, bent over posture and generalized weakness of the muscles. There is a typical "lead-pipe" rigidity of passive movements. Another important feature of the disease is the tremor of the extremities occurring at rest and decreasing during movements.

[0155] Parkinson's disease, the etiology of which is unknown, belongs to a group of the most common movement disorders named parkinsonism, which affects approximately one person per one thousand. These other disorders grouped under the name of parkinsonism may result from viral infection, syphilis, arteriosclerosis and trauma and exposure to toxic chemicals and narcotics. Nonetheless, it is believed that the inappropriate loss of synaptic stability may lead to the disruption of neuronal circuits and to brain diseases. Whether as the result of genetics, drug use, the aging process, viral infections, or other various causes, dysfunction in neuronal communication is considered the underlying cause for many neurologic diseases, such as PD (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* 2010, 10, 207-214).

[0156] Regardless of the cause of the disease, the main pathologic feature is degeneration of dopaminergic cells in basal ganglia, especially in substantia nigra.

Due to premature death of the dopamine containing neurons in substantia nigra, the largest structure of the basal ganglia, the striatum, will have reduced input from substantia nigra resulting in decreased dopamine release. The understanding of the underlying pathology led to the introduction of the first successful treatment which 5 can alleviate Parkinson's disease. Virtually all approaches to the therapy of the disease are based on dopamine replacement. Drugs currently used in the treatment can be converted into dopamine after crossing the blood brain barrier, or they can boost the synthesis of dopamine and reduce its breakdown. Unfortunately, the main pathologic event, degeneration of the cells in substantia nigra, is not helped. The 10 disease continues to progress and frequently after a certain length of time, dopamine replacement treatment will lose its effectiveness.

**[0157]** This invention provides methods and compositions for treating PD using an SV2A inhibitor or a pharmaceutically acceptable salt thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt 15 thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in an immediate release form. In certain embodiments, treatment comprises preventing or slowing the progression of PD. In certain embodiments, treatment comprises alleviation, 20 amelioration, or slowing the progression of one or more symptoms associated with PD. In certain embodiments, the symptom to be treated is cognitive impairment. For example, methods and compositions of the disclosure can be used to improve the motor/cognitive impairments symptomatic of Parkinson's disease. Moreover, methods and compositions of the disclosure may be useful for treating the memory 25 impairment symptomatic of Parkinson's disease.

**[0120]** There are a number of animal models for PD. Exemplary animal models for PD include the reserpine model, the methamphetamine model, the 6-hydroxydopamine (6-OHDA) model, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model, the paraquat (PQ)-Maneb model, the rotenone 30 model, the 3-nitrotyrosine model and genetic models using transgenic mice. Transgenic models include mice that over express  $\alpha$ -synuclein, express human mutant forms of  $\alpha$ -synuclein, or mice that express LRKK2 mutations. See review

of these models by Ranjita B. et al. (Ranjita B. et al. *BioEssays* **2002**, 24, 308-318). Additional information regarding these animal models is readily available from Jackson Laboratories (see also <http://research.jax.org/grs/parkinsons.html>), as well as in numerous publications disclosing the use of these validated models.

- 5 [0158] The efficacy of the methods and compositions of this invention in treating PD, or cognitive impairment associated with PD, may be assessed in any of the above animal models of PD, as well as human subjects with PD, using a variety of cognitive tests known in the art, as discussed above.

### **Autism**

- 10 [0159] “Autism”, as used herein, refers to an autism spectrum disorder characterized by a neural development disorder leading to impaired social interaction and communication by restricted and repetitive behavior. “Autism Spectrum Disorder” refers to a group of developmental disabilities that includes: autism; Asperger syndrome; pervasive developmental disorder not otherwise specified (PDD-NOS or atypical autism); Rett syndrome; and childhood 15 disintegrative disorder.

- [0160] Autism is a neurodevelopmental disorder characterized by dysfunction in three core behavioral dimensions: repetitive behaviors, social deficits, and cognitive deficits. The repetitive behavior domain involves compulsive behaviors, unusual attachments to objects, rigid adherence to routines or rituals, and repetitive motor mannerisms such as stereotypies and self- stimulatory behaviors. The social deficit dimension involves deficits in reciprocal social interactions, lack of eye contact, diminished ability to carry on conversation, and impaired daily interaction skills. The cognitive deficits can include language abnormalities. Autism is a 20 disabling neurological disorder that affects thousands of Americans and encompasses a number of subtypes, with various putative causes and few documented ameliorative treatments. The disorders of the autistic spectrum may be present at birth, or may have later onset, for example, at ages two or three. There are no clear cut biological markers for autism. Diagnosis of the disorder is made by 25 considering the degree to which the child matches the behavioral syndrome, which is characterized by poor communicative abilities, peculiarities in social and cognitive capacities, and maladaptive behavioral patterns. The dysfunction in 30

neuronal communication is considered one of the underlying causes for autism (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* 2010, 10, 207-214).

[0161] This invention provides methods and compositions for treating autism 5 using an SV2A inhibitor or a pharmaceutically acceptable salt thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some 10 embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in an immediate release form. In certain embodiments, treatment comprises preventing or slowing the progression of autism. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with autism. In certain embodiments, the symptom to be treated is cognitive deficit. For example, methods and compositions of the 15 disclosure can be used to improve the motor/cognitive deficits symptomatic of autism.

[0162] The valproic acid (VPA) rat model of autism using in vitro electrophysiological techniques, established by Rodier et al. (Rodier, P. M. et al. *Reprod. Toxicol.* 1997, 11, 417-422) is one of the most exhaustively established 20 insult-based animal models of autism and is based on the observation that pregnant women treated with VPA in the 1960s, during a circumscribed time window of embryogenesis, had a much higher risk of giving birth to an autistic child than the normal population. Offspring of VPA-exposed pregnant rats show several anatomical and behavioral symptoms typical of autism, such as diminished number 25 of cerebellar Purkinje neurons, impaired social interaction, repetitive behaviors as well as other symptoms of autism, including enhanced fear memory processing. See, Rinaldi T. et al. *Frontiers in Neural Circuits*, 2008, 2, 1-7. The efficacy of the methods and compositions of this invention in treating autism, or cognitive deficits associated with autism, may be assessed in the VPA-treated rat model of autism, as 30 well as human subjects with autism, using a variety of cognitive tests known in the art, as discussed above.

**Mental retardation**

- [0163] Mental retardation is a generalized disorder characterized by significantly impaired cognitive function and deficits in adaptive behaviors. Mental retardation is often defined as an Intelligence Quotient (IQ) score of less than 70. Inborn causes are among many underlying causes for mental retardation. The dysfunction in neuronal communication is also considered one of the underlying causes for mental retardation (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* **2010**, 10, 207-214).
- [0164] In some instances, mental retardation includes, but are not limited to, Down syndrome, velocardiofacial syndrome, fetal alcohol syndrome, Fragile X syndrome, Klinefelter's syndrome, neurofibromatosis, congenital hypothyroidism, Williams syndrome, phenylketonuria (PKU), Smith-Lemli-Opitz syndrome, Prader-Willi syndrome, Phelan-McDermid syndrome, Mowat-Wilson syndrome, ciliopathy, Lowe syndrome and siderium type X-linked mental retardation. Down syndrome is a disorder that includes a combination of birth defects, including some degree of mental retardation, characteristic facial features and, often, heart defects, increased infections, problems with vision and hearing, and other health problems. Fragile X syndrome is a prevalent form of inherited mental retardation, occurring with a frequency of 1 in 4,000 males and 1 in 8,000 females. The syndrome is also characterized by developmental delay, hyperactivity, attention deficit disorder, and autistic-like behavior. There is no effective treatment for fragile X syndrome.
- [0165] The present invention contemplates the treatment of mild mental retardation, moderate mental retardation, severe mental retardation, profound mental retardation, and mental retardation severity unspecified. Such mental retardation may be, but is not required to be, associated with chromosomal changes, (for example Down Syndrome due to trisomy 21), heredity, pregnancy and perinatal problems, and other severe mental disorders. This invention provides methods and compositions for treating mental retardation using an SV2A inhibitor or a pharmaceutically acceptable salt thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the

pharmaceutically acceptable salt thereof is used in an immediate release form. In certain embodiments, treatment comprises preventing or slowing the progression of mental retardation. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with 5 mental retardation. In certain embodiments, the symptom to be treated is cognitive deficit/impairment. For example, methods and compositions of the disclosure can be used to improve the motor/cognitive impairments symptomatic of mental retardation.

[0166] Several animal models have been developed for mental retardation. For 10 example, a knockout mouse model has been developed for Fragile X syndrome. Fragile X syndrome is a common form of mental retardation caused by the absence of the FMR1 protein, FMRP. Two homologs of FMRP have been identified, FXR1P and FXR2P. FXR2P shows high expression in brain and testis, like FMRP. Both *Fxr2* and *Fmr1* knockout mice, and *Fmr1/Fxr2* double knockout 15 mice are believed to be useful models for mental retardation such as Fragile X syndrome. See, Bontekoe C. J. M. et al. *Hum. Mol. Genet.* 2002, 11 (5): 487-498. The efficacy of the methods and compositions of this invention in treating mental retardation, or cognitive deficit/impairment associated with mental retardation, may be assessed in the these mouse models and other animal models developed for 20 mental retardation, as well as human subjects with mental retardation, using a variety of cognitive tests known in the art, as discussed above.

#### **Compulsive behavior (obsessive compulsive disorder)**

[0167] Obsessive compulsive disorder (“OCD”) is a mental condition that is most commonly characterized by intrusive, repetitive unwanted thoughts 25 (obsessions) resulting in compulsive behaviors and mental acts that an individual feels driven to perform (compulsion). Current epidemiological data indicates that OCD is the fourth most common mental disorder in the United States. Some studies suggest the prevalence of OCD is between one and three percent, although the prevalence of clinically recognized OCD is much lower, suggesting that many 30 individuals with the disorder may not be diagnosed. Patients with OCD are often diagnosed by a psychologist, psychiatrist, or psychoanalyst according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision

(DSM-IV-TR) (2000) diagnostic criteria that include characteristics of obsessions and compulsions. Characteristics of obsession include: (1) recurrent and persistent thoughts, impulses, or images that are experienced as intrusive and that cause marked anxiety or distress; (2) the thoughts, impulses, or images are not simply 5 excessive worries about real-life problems; and (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind, and are not based in reality.

Characteristics of compulsion include: (1) repetitive behaviors or mental acts that 10 the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly; (2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not actually connected to the issue, or they are excessive.

15 [0168] Individuals with OCD typically perform tasks (or compulsion) to seek relief from obsession-related anxiety. Repetitive behaviors such as handwashing, counting, checking, or cleaning are often performed with the hope of preventing obsessive thoughts or making them go away. Performing these "rituals," however, only provides temporary relief. People with OCD may also be diagnosed with a 20 spectrum of other mental disorders, such as generalized anxiety disorder, anorexia nervosa, panic attack, or schizophrenia.

[0169] The dysfunction in neuronal communication is considered one of the underlying causes for obsession disorder (Myrrhe van Spronsen and Casper C. Hoogenraad, *Curr. Neurol. Neurosci. Rep.* 2010, 10, 207-214). Studies suggest 25 that OCD may be related to abnormal levels of a neurotransmitter called serotonin. The first-line treatment of OCD consists of behavioral therapy, cognitive therapy, and medications. Medications for treatment include serotonin reuptake inhibitors (SRIs) such as paroxetine (Seroxat™, Paxil®, Xetanor™, ParoMerck™, Rexetin™), sertraline (Zoloft®, Stimuloton™), fluoxetine (Prozac®, Bioxetin™), 30 escitalopram (Lexapro®), and fluvoxamine (Luvox®) as well as the tricyclic antidepressants, in particular clomipramine (Anafranil®). Benzodiazepines are also used in treatment. As much as 40 to 60% of the patients, however, fail to

adequately respond to the SRI therapy and an even greater proportion of patients fail to experience complete remission of their symptoms.

**[0170]** This invention provides methods and compositions for treating OCD using an SV2A inhibitor or a pharmaceutically acceptable salt thereof in an 5 extended release form in combination with an AChEI or a pharmaceutically acceptable salt thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in an immediate release form. In certain embodiments, treatment comprises 10 preventing or slowing the progression of OCD. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with OCD. In certain embodiments, the symptom to be treated is cognitive deficit. For example, methods and compositions of the disclosure can be used to treat the cognitive deficits in OCD, and/or to improve 15 cognitive function in patients with OCD. A quinpirole-sensitized rat model has been developed for OCD. The compulsive checking behavior of the quinpirole-sensitized rats is subject to interruption, which is an attribute characteristic of OCD compulsions. The efficacy of the methods and compositions of this invention in 20 treating OCD, or cognitive deficits associated with OCD, may be assessed in this rat model and other animal models developed for OCD, as well as human subjects with OCD, using a variety of cognitive tests known in the art, as discussed above.

#### **Substance addiction**

**[0171]** Substance addiction (e.g., drug addiction, alcohol addiction) is a mental disorder. The addiction is not triggered instantaneously upon exposure to substance 25 of abuse. Rather, it involves multiple, complex neural adaptations that develop with different time courses ranging from hours to days to months (Kauer J. A. *Nat. Rev. Neurosci.* 2007, 8, 844-858). The path to addiction generally begins with the voluntary use of one or more controlled substances, such as narcotics, barbiturates, methamphetamines, alcohol, nicotine, and any of a variety of other such controlled 30 substances. Over time, with extended use of the controlled substance(s), the voluntary ability to abstain from the controlled substance(s) is compromised due to the effects of prolonged use on brain function, and thus on behavior. As such,

substance addiction generally is characterized by compulsive substance craving, seeking and use that persist even in the face of negative consequences. The cravings may represent changes in the underlying neurobiology of the patient which likely must be addressed in a meaningful way if recovery is to be obtained.

5     Substance addiction is also characterized in many cases by withdrawal symptoms, which for some substances are life threatening (e.g., alcohol, barbiturates) and in others can result in substantial morbidity (which may include nausea, vomiting, fever, dizziness, and profuse sweating), distress, and decreased ability to obtain recovery. For example, alcoholism, also known as alcohol dependence, is one

10    such substance addiction. Alcoholism is primarily characterized by four symptoms, which include cravings, loss of control, physical dependence and tolerance. These symptoms also may characterize addictions to other controlled substances. The craving for alcohol, as well as other controlled substances, often is as strong as the need for food or water. Thus, an alcoholic may continue to drink despite serious

15    family, health and/or legal ramifications.

[0172]   Recent work exploring the effects of abusing alcohol, central stimulants, and opiates on the central nervous system (CNS) have demonstrated a variety of adverse effects related to mental health, including substance-induced impairments in cognition. See, Nyberg F. *Cognitive Impairments in Drug Addicts*, Chapter 9. In

20    several laboratories and clinics substantial damages of brain function are seen to result from these drugs. Among the harmful effects of the abusing drugs on brain are those contributing to accelerated obsolescence. An observation that has received special attention during recent years is that chronic drug users display pronounced impairment in brain areas associated with executive and memory

25    function. A remarked neuroadaptation caused by addictive drugs, such as alcohol, central stimulants and opiates involves diminished neurogenesis in the subgranular zone (SGZ) of the hippocampus. Indeed, it has been proposed that decreased adult neurogenesis in the SGZ could modify the hippocampal function in such a way that it contributes to relapse and a maintained addictive behavior. It also raises the

30    possibility that decreased neurogenesis may contribute to cognitive deficits elicited by these abusing drugs.

- [0173] This invention provides methods and compositions for treating substance addiction using an SV2A inhibitor or a pharmaceutically acceptable salt thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt thereof. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof is used in an immediate release form. In certain embodiments, treatment comprises preventing or slowing the progression of substance addiction. In certain embodiments, treatment comprises alleviation, amelioration, or slowing the progression of one or more symptoms associated with substance addiction. In certain embodiments, the symptom to be treated is cognitive impairment. For example, methods and compositions of the disclosure can be used to treat the cognitive impairment and/or to improve cognitive function in patients with addiction.
- [0174] Several animal models have been developed to study substance addiction. For example, a genetically selected Marchigian Sardinian alcohol-preferring (msP) rat models was developed to study the neurobiology of alcoholism. See, Ciccocioppo R. et al. *Addiction Biology* 2006, 11, 339-355. The efficacy of the methods and compositions of this invention in treating substance addiction, or cognitive impairment associated with substance addiction, may also be assessed in animal models of substance addiction, as well as human subjects with addiction, using a variety of cognitive tests known in the art, as discussed above.

### SV2A Inhibitor

- [0175] “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  $\text{Ca}^{2+}$ - 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).

[0176] “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, 10 “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 15 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.

[0177] Among the SV2A inhibitors or pharmaceutically acceptable salts, 20 hydrates, solvates and polymorphs 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, International Patent Application PCT/US2009/005647, U.S. Patent Application 61/105,847, U.S. Patent Application 61/152,631, and U.S. Patent Application 61/175,536. However, any 25 SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or 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; 30 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, or polymorphs. Other SV2A inhibitors may also be used in this invention. Applicants also refer to methods of preparing these compounds found 5 in the documents cited above. Other synthetic methods may also be used. These methods are well known to those skilled in the art.

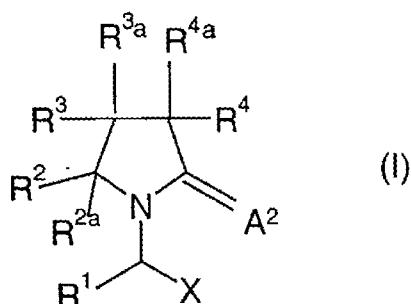
10 [0178] In some embodiments of this invention, the SV2A inhibitor is selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or prodrugs thereof.

15 [0179] 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).

20 [0180] 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,



25

wherein X is -CA<sup>1</sup>NR<sup>5</sup>R<sup>6</sup> or -CA<sup>1</sup>OR<sup>7</sup> or -CA<sup>1</sup>-R<sup>8</sup> or CN;

A<sup>1</sup> and A<sup>2</sup> are independently oxygen, sulfur or -NR<sup>9</sup>;

R<sup>1</sup> is hydrogen, alkyl, aryl or -CH<sub>2</sub>-R<sup>1a</sup> wherein R<sup>1a</sup> is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

5 R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> 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;

10 R<sup>2a</sup>, R<sup>3a</sup> and R<sup>4a</sup> are the same or different and each is independently hydrogen, halogen, alkyl, alkenyl, alkynyl or aryl;

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

20 R<sup>8</sup> is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

25 with the provisos that at least one of as R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>2a</sup>, R<sup>3a</sup> and R<sup>4a</sup> is other than hydrogen; and that when the compound is a mixture of all possible isomers, X is -CONR<sup>5</sup>R<sup>6</sup>, A<sup>2</sup> is oxygen and R<sup>1</sup> is hydrogen, methyl, ethyl or propyl then substitution on the pyrrolidine ring is other than mono-, di-, or trimethyl or mono-ethyl; and that when R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup>, R<sup>2a</sup>, R<sup>3a</sup> and R<sup>4a</sup> are each hydrogen, A<sup>2</sup> is oxygen and X is CONR<sup>5</sup>R<sup>6</sup> then R<sup>3</sup> 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.

30 In the definitions set forth below, unless otherwise stated, R<sup>11</sup> and R<sup>12</sup> 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.

35 The term “oxy derivative”, as used herein is defined as including -O-R<sup>11</sup> groups wherein R<sup>11</sup> is as defined above except for “oxy derivative”. Non-limiting examples are alkoxy, alkenyloxy, alkynyoxy, acyloxy, oxyester,

oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocycloxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyoxy, 2-pyridyloxy, methylenedioxy, carbonate.

5 The term “thio derivative” as used herein, is defined as including-S-R<sup>11</sup> groups wherein R<sup>11</sup> is as defined above except for “thio derivative”. Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

10 The term “amino derivative” as used herein, is defined as including-NHR<sup>11</sup> or -NR<sup>11</sup>R<sup>12</sup> groups wherein R<sup>11</sup> and R<sup>12</sup> are as defined above. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl- and arylamino or mixed amino.

15 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<sup>11</sup>-CO-, wherein R<sup>11</sup> 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, oxanyl, ethoxanyl, cysteinyl, oxamoyl.

20 The term “sulfonyl derivative” as used herein, is defined as including a group of the formula -SO<sub>2</sub>-R<sup>11</sup>, wherein R<sup>11</sup> is as defined above except for “sulfonyl derivative”. Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

25 The term “sulfinyl derivative” as used herein, is defined as including a group of the formula -SO-R<sup>11</sup>, wherein R<sup>11</sup> is as defined above except for “sulfinyl derivative”. Non-limiting examples are alkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl and arylsulfinyl.

30 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-  
5 aryloxy and C6-10-aryl.

Preferred alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, iso or terbutyl, 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-  
10 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-  
15 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  
20 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.  
25

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.  
30

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 5 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 10 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.
- 15 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<sub>2</sub>.
- The term “nitrooxy”, as used herein, represents a group of the formula -  
ONO<sub>2</sub>.
- 20 The term “amino”, as used herein, represents a group of the formula -NH<sub>2</sub>.
- The term “azido”, as used herein, represents a group of the formula -N<sub>3</sub>.
- The term “carboxy”, as used herein, represents a group of the formula -  
COOH.
- 25 The term “sulfonic acid”, as used herein, represents a group of the formula -  
-SO<sub>3</sub>H.
- The term “sulfonamide”, as used herein, represents a group of the formula -  
SO<sub>2</sub>NH<sub>2</sub>.
- 30 The term “ester”, as used herein is defined as including a group of formula -COO-R<sup>11</sup> wherein R<sup>11</sup> 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.

5 The term “amido” is defined as including a group of formula -CONH<sub>2</sub> or -CONHR<sup>11</sup> or -CONR<sup>11</sup>R<sup>12</sup> wherein R<sup>11</sup> and R<sup>12</sup> are as defined above.

10 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.

5 In the above definitions it is to be understood that when a substituent such as R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>2a</sup>, R<sup>3a</sup>, R<sup>4a</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> 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.

10 Preferred examples of X are -COO R<sup>7</sup> or -CONR<sup>5</sup>R<sup>6</sup>, wherein R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are preferably hydrogen, C1-4-alkyl, phenyl or alkylphenyl.

15 Preferably X is carboxy or -CONR<sup>5</sup>R<sup>6</sup>, wherein R<sup>5</sup> and R<sup>6</sup> are preferably hydrogen, C1-4-alkyl, phenyl or alkylphenyl, especially -CONH<sub>2</sub>.

Preferably A<sup>1</sup> and A<sup>2</sup> are each oxygen.

20 Preferably R<sup>1</sup> is hydrogen, alkyl, especially C1-12 alkyl, particularly lower alkyl or aryl especially phenyl.

25 Examples of preferred R<sup>1</sup> 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<sup>1</sup> as ethyl is especially preferred.

30 Preferably R<sup>2</sup> and R<sup>2a</sup> are independently hydrogen, halogen or alkyl, especially lower alkyl.

Examples of preferred R<sup>2</sup> and R<sup>2a</sup> 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<sup>2</sup> and R<sup>2a</sup> are hydrogen.

Preferably R<sup>3a</sup>, R<sup>4</sup> and R<sup>4a</sup> are independently hydrogen, alkyl, especially methyl or ethyl or aryl especially phenyl or aralkyl, especially benzyl.

5 Examples of preferred R<sup>3a</sup>, R<sup>4</sup> and R<sup>4a</sup> 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<sup>4</sup> and R<sup>4a</sup> are hydrogen.

10 R<sup>3a</sup> is particularly hydrogen or alkyl, especially lower alkyl and is most preferably hydrogen.

15 Preferably R<sup>3</sup> 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.

25 30 Also, preferably, R<sup>3</sup> 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

5 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.

10 Other examples of preferred R<sup>3</sup> 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, 1-dimethyl-2, 2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl.

15 R<sup>3</sup> 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<sup>3</sup> groups are C1-6 alkyl and C2-6 haloalkenyl.

20 Preferably R<sup>5</sup> and R<sup>6</sup> 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<sup>5</sup> and R<sup>6</sup> are hydrogen.

25 Preferably R<sup>7</sup> 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<sup>7</sup> is hydrogen, methyl or ethyl especially hydrogen.

30 Preferably R<sup>8</sup> 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<sup>8</sup> 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<sup>2</sup> is oxygen;

X is-CNR<sup>5</sup>R<sup>6</sup> or-COOR<sup>7</sup> or-CO-R<sup>8</sup> or CN ;

5 R<sup>1</sup> is hydrogen or alkyl, aryl, halogen, hydroxy, amino, nitro, cyano; R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, 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,,, alkoxy carbonyl,,, a thio derivative,, alkyl, alkoxy, oxyester, oxyamido, aryl,, an oxy derivative, heterocycle, vinyl and R<sup>3</sup> may additionally represent C2-5 alkenyl, C2-5 alkynyl or azido each optionally substituted by one or more halogen, cyano, thiocyanato, 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.

10 R<sup>2a</sup>, R<sup>3a</sup> and R<sup>4a</sup> are hydrogen;

15 R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or oxy derivative; and

20 R<sup>8</sup> is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle, alkylthio or thio derivative.

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

25 R<sup>2</sup> and R<sup>4</sup> are preferably independently hydrogen or halogen or methyl, ethyl, propyl, isopropyl, butyl, isobutyl ; and, most preferably, are each hydrogen.

30 R<sup>3</sup> is preferably C1-5 alkyl, C2-5 alkenyl, C2-C5 alkynyl, cyclopropyl, azido, each optionally substituted by one or more halogen, cyano, thiocyanato, 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<sub>2</sub> ; most preferably -CONH<sub>2</sub>.

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

X is -CA<sup>1</sup>NH<sub>2</sub>, -CA<sup>1</sup>NHCH<sub>3</sub> or -CA<sup>1</sup>N(CH<sub>3</sub>)<sub>2</sub> ;

R<sup>1</sup> is alkyl or phenyl ;

10 R<sup>3</sup> is alkyl, alkenyl, alkynyl, cyano, isothiocyanato, ether, carboxyl, amido, aryl, heterocycle ; or

R<sup>3</sup> is CH<sub>2</sub>R<sup>10</sup> wherein R<sup>10</sup> is hydrogen, cycloalkyl, oxyester, oxyalkylsulfonyl, oxyarylsulfonyl, aminoalkylsulfonyl, aminoarylsulfonyl, nitrooxy, cyano, isothiocyanato, azido, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, heterocycle, aryloxy, alkoxy or trifluoroethyl;

15 R<sup>3a</sup> is hydrogen, alkyl or aryl (especially with the proviso that when R<sup>3a</sup> is hydrogen, R<sup>3</sup> other than methyl);

or R<sup>3</sup>R<sup>3a</sup> form a cycloalkyl ;

and R<sup>2</sup>, R<sup>2a</sup>, R<sup>4</sup> and R<sup>4a</sup> are each hydrogen.

Within the compounds of formula I,

20 R<sup>1</sup> is preferably alkyl especially C1-12- more particularly C1-6-alkyl and is most preferably ethyl;

R<sup>2</sup>, R<sup>2a</sup>, R<sup>3a</sup> and R<sup>4a</sup> are preferably hydrogen;

25 R<sup>3</sup> 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 ;

30 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 ;

10  $R^{3a}$  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  $\text{CONR}^5\text{R}^6$  and  $\text{R}^1$  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<sup>5</sup>R<sup>6</sup> and R<sup>1</sup> 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,

25                    X is -CA<sup>1</sup>NH<sub>2</sub> ;  
                   R<sup>1</sup> is H ;  
                   R<sup>3</sup> 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<sup>3a</sup> is hydrogen or halogen, preferably fluorine ;  
                   and R<sup>2</sup>, R<sup>2a</sup>, R<sup>4</sup> and R<sup>4a</sup> 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<sup>1</sup>NH<sub>2</sub> ;

R<sup>1</sup> is H ;

5 R<sup>3</sup> is C1-6-alkyl, C2-6-alkenyl or C2-6-alkynyl optionally substituted by azido, oxynitro, 1 to 6 halogen atoms ;

R<sup>3a</sup> is hydrogen or halogen, preferably fluorine ;

and R<sup>2</sup>, R<sup>2a</sup>, R<sup>4</sup> and R<sup>4a</sup> are each hydrogen ; as their racemates or in enantiomerically enriched form, preferably the pure enantiomers.

10 In all the above mentioned scopes when the carbon atom to which R<sup>1</sup> 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;

15 (2S)-2-[(4R)-4-(iodomethyl)-2-oxopyrrolidinyl]butanamide;

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

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

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

20 {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;

25 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;

30 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;

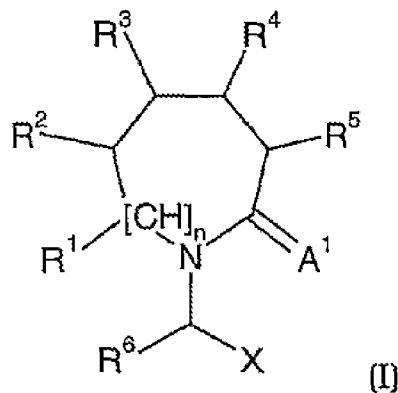
(2S)-2-[4-(3-methoxyphenyl)-2-oxo-1-pyrrolidinyl]butanamide;  
(2S)-2-[4-(4-azidophenyl)-2-oxo-1-pyrrolidinyl]butanamide;  
(2S)-2-[2-oxo-4-(3-thienyl)-1-pyrrolidinyl]butanamide;  
(2S)-2-[4-(3-azidophenyl)-2-oxo-1-pyrrolidinyl]butanamide;  
5 (2S)-2-[2-oxo-4-(3-thienyl)-1-pyrrolidinyl]butanamide;  
(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;  
10 (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;  
15 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;  
20 (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;  
25 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;  
30 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;  
5 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;  
10 (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;  
15 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;  
20 (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;  
25 (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;  
30 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;  
 5 (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 :

10 (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



15 wherein n represents 0 or 1 whereby R<sup>1</sup> is not existent when n=0 and R<sup>1</sup> is existent when n= 1 ;

A<sup>1</sup> represents an oxygen or a sulfur atom;

X is-CONR<sup>7</sup>R<sup>8</sup>,-COOR<sup>9</sup>,-CO-R<sup>10</sup> or CN;

20 R<sup>1</sup> when existent, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> 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<sup>1</sup> when existent, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> or R<sup>5</sup> is not hydrogen;

R<sup>6</sup> is hydrogen, alkyl, aryl or -CH<sub>2</sub>-R<sup>6a</sup> wherein R<sup>6a</sup> is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

5 R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are the same or different and each is independently hydrogen, hydroxy, alkyl, aryl, heterocycle or an oxy derivative; and

R<sup>10</sup> is hydrogen, hydroxy, thiol, halogen, alkyl, aryl, heterocycle or a thio derivative;

10 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<sup>1</sup> to R<sup>5</sup> 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.

25 In the definitions set forth below, unless otherwise stated, R<sup>11</sup> and R<sup>12</sup> 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<sup>11</sup> groups wherein R<sup>11</sup> is as defined above except for “oxy derivative”. Non-limiting examples are alkoxy, alkenyloxy, alkynyoxy, acyloxy, oxyester, oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, 5 arylsulfinyloxy, aryloxy, aralkoxy or heterocycloxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyoxy, 2-pyridyloxy, methylenedioxy, carbonate.

10 The term “thio derivative”, as used herein, is defined as including-S-R<sup>11</sup> groups wherein R<sup>11</sup> is as defined above except for “thio derivative”. Non-limiting examples are alkylthio, alkenylthio, alkynylthio and arylthio.

15 The term “amino derivative”, as used herein, is defined as including-NHR<sup>11</sup> or-NR<sup>11</sup>R<sup>12</sup> groups wherein R<sup>11</sup> and R<sup>12</sup> are as defined above. Non-limiting examples are mono- or di-alkyl-, alkenyl-, alkynyl-and arylamino or mixed amino.

20 15 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<sup>11</sup>-CO-, wherein R<sup>11</sup> is as defined above and may also be hydrogen. Preferred are acyl derivatives of formula -COR<sup>11</sup> wherein R<sup>11</sup> is selected from hydrogen, C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl, heterocyle and aryl. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxanyl, ethoxanyl, cysteinyl, oxamoyl.

25 25 The term “sulfonyl derivative”, as used herein, is defined as including a group of the formula -SO<sub>2</sub>-R<sup>11</sup>, wherein R<sup>11</sup> is as defined above except for “sulfonyl derivative”. Non-limiting examples are alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl and arylsulfonyl.

30 30 The term “sulfinyl derivative”, as used herein, is defined as including a group of the formula -SO-R<sup>11</sup>, wherein R<sup>11</sup> 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<sub>1</sub> to C<sub>7</sub> 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-methylpentyl, 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, 1-5 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.  
10

15 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.

20 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.

25 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.

30 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, 5 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.

10 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.

15 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<sub>2</sub>.

The term “nitrooxy”, as used herein, represents a group of the formula -  
ONO<sub>2</sub>.

20 The term “amino”, as used herein, represents a group of the formula -NH<sub>2</sub>.

The term “azido”, as used herein, represents a group of the formula -N<sub>3</sub>.

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

25 The term “sulfonic acid”, as used herein, represents a group of the formula -  
-SO<sub>3</sub>H.

The term “sulfonamide”, as used herein, represents a group of the formula -  
SO<sub>2</sub>NH<sub>2</sub>.

30 The term “ester”, as used herein, is defined as including a group of formula -COO-R<sup>11</sup> wherein R<sup>11</sup> is as defined above except oxy derivative, thio derivative or amino derivative. Preferred are esters of formula -COOR<sup>11</sup> wherein R<sup>11</sup> is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl and aryl. Most preferred are esters where R<sup>11</sup> 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.

5 The term “amido” is defined as including a group of formula -CONH<sub>2</sub> or -CONHR<sup>11</sup> or -CONR<sup>11</sup>R<sup>12</sup> wherein R<sup>11</sup> and R<sup>12</sup> are as defined above.

10 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, 15 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, fuopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, 20 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, 25 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 30 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.

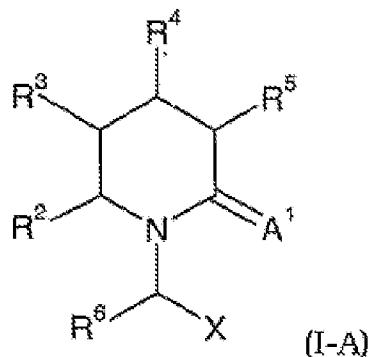
5 The heterocycle is preferably selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1- oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from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

10 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.

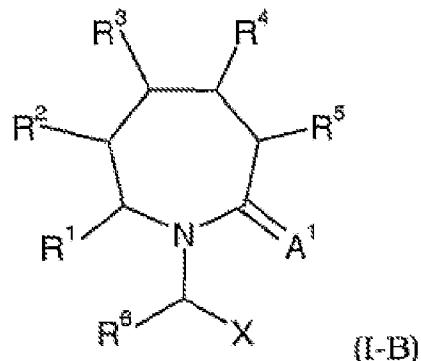
15 In the above definitions it is to be understood that when a substituent such as  $R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}$  is attached to the rest of the molecule *via* a heteroatom or a carbonyl, a straight- or branched chain, C1-12-, preferably C1-4-alkylene or C2-12, preferably C2-4-alkenylene or-alkynylene bridge may 20 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 25 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).



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<sup>1</sup> is existent since n=1 and depicted by the formula (I-B).



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

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

According to a yet more preferred embodiment, said compound is as defined above wherein only one R substituent chosen from R<sup>3</sup> or R<sup>4</sup> when n=0 or from R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup> 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<sup>1</sup> 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<sup>7</sup>R<sup>8</sup>, especially CONH<sub>2</sub>. 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<sup>6</sup> represents hydrogen, C1-4 alkyl, or a CH<sub>2</sub>-R<sup>6a</sup> group wherein R<sup>6a</sup> represents a heterocycle. Most preferably R<sup>6</sup> is a C1-4 alkyl, especially ethyl. When R<sup>6</sup> 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<sup>6</sup> is attached is of the S configuration. In case where R<sup>6</sup> is ethyl, A is oxygen and X is CONR<sup>7</sup>R<sup>8</sup> we refer then to (2S)-2-(2-oxo-1-piperidinyl) butanamide or (2S)-2- (2-oxo-1-azepanyl) butanamide derivatives.

According to a preferred embodiment, the compound is as defined above wherein R<sup>2</sup> when n=1, R<sup>3</sup> and R<sup>4</sup> 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<sup>1</sup> when existent, R<sup>2</sup> when n=0 and R<sup>5</sup> are hydrogen;  
R<sup>6</sup> is hydrogen, alkyl, aryl or-CH<sub>2</sub>-R<sup>6a</sup> wherein R<sup>6a</sup> is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

According to this preferred embodiment, the compound is generally such that when R<sup>6</sup> is benzyl, X is-COOCH<sub>3</sub> and n=1, R<sup>2</sup> is different from methyl when R<sup>3</sup> and R<sup>4</sup> are both hydrogen and R<sup>4</sup> is different from methyl when R<sup>2</sup> and R<sup>3</sup> are both hydrogen.

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

5 C1-12 alkyl, each optionally substituted by one or more substituents selected from hydroxy, halogen, cyano, thiocyanato, alkoxy, azido, alkylthio, 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;

10 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<sup>11</sup>, wherein R<sup>11</sup> is selected from C1-12 alkyl, C2-12 alkenyl, C2-12 alkynyl, heterocycle and aryl;

15 ester of formula -CO-O-R<sup>11</sup> wherein R<sup>11</sup> 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,

20 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 25 above, wherein R<sup>2</sup> when n= 1, R<sup>3</sup> and R<sup>4</sup> 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, alkylthio, cyclopropyl, acyl and phenyl;

30 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;

5 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;

10 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.

15 According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> when n=1 or from the group R<sup>3</sup> and R<sup>4</sup> when n=0, represents independently C1-4-alkyl or C3-7-cycloalkyl, optionally substituted by one or

15 independently C1-4-alkyl or C3-7-cycloalkyl, optionally substituted by one or more halogen, hydroxy, lower alkyl and/or azido.

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

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

30 According to another preferred embodiment, the compound is as defined above wherein at least one of the R substituents chosen from the group R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> when n=1 or from the group R<sup>3</sup> and R<sup>4</sup> 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<sup>2</sup>, R<sup>3</sup>

and R<sup>4</sup> when n=1 or from the group R<sup>3</sup> and R<sup>4</sup> 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<sup>3</sup>, R<sup>4</sup> and R<sup>2</sup> when n= 1 or from the group R<sup>3</sup> and R<sup>4</sup> 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 preferred embodiment, the compound is as defined above wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>4</sup> and R<sup>5</sup> are hydrogen.

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

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

In all the above-mentioned scopes when the carbon atom to which R<sup>6</sup> 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,  
5 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,  
10 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,  
15 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,  
20 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-trifluoropropyl)-1-piperidinyl]butanamide,  
2-[4-(cyclopropylmethyl)-2-oxo-1-piperidinyl]butanamide,  
25 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,  
30 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,  
5 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,  
10 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,  
15 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,  
20 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,  
25 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,  
30 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,  
5 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,  
10 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,  
15 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,  
20 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,  
25 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,  
30 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,  
5 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,  
10 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,  
15 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,  
20 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,  
25 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,  
30 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,

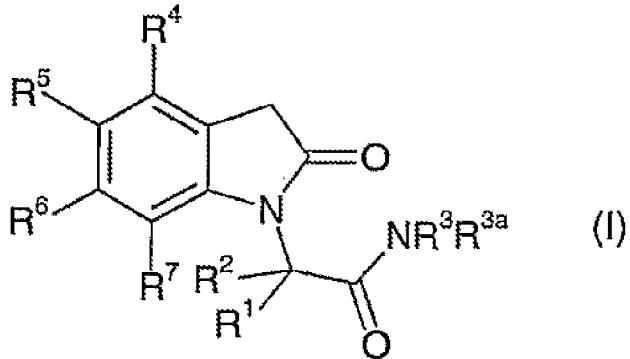
2-[2-oxo-4-(1-propynyl)-1-azepanyl]butanamide,  
 2-[4-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide,  
 2-[4-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide,  
 2-[4-(1-butynyl)-2-oxo-1-azepanyl]butanamide,  
 5 2-[4-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide,  
 2-[4-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,  
 2-[4-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide,  
 2-[4-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide.

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

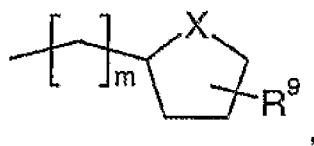
(2S)-2-[5-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,  
 (2S)-2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide,  
 2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,  
 (2S)-2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide,  
 15 2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide.

iii) International Patent Application WO 2004/087658:

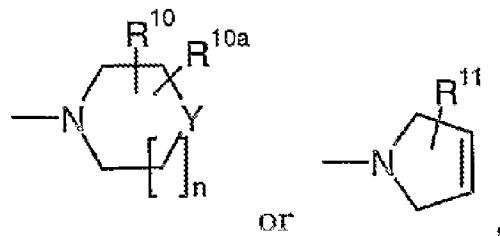
A compound having the formula I or a pharmaceutically acceptable salt  
 thereof or stereoisomeric forms thereof,



20 wherein  
 R<sup>1</sup> is hydrogen,  
 R<sup>2</sup> is hydrogen or C1-20-alkyl,  
 R<sup>3</sup> 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 -  
 25 W-R<sup>8</sup>, R<sup>3a</sup> is hydrogen, C1-20-alkyl or a group of formula :



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



$\text{R}^4$  is hydrogen,

5  $\text{R}^5$  is hydrogen; nitro; halogen; azido; cyano;  $-\text{S-C1-4-alkyl}$ ;  $-\text{SO-C1-4-alkyl}$ ;  $-\text{SO}_2\text{-C1-4-alkyl}$ ;  $-\text{SONH}_2$ ; C1-20-alkyl unsubstituted or substituted by halogen; or C1-20-alkoxy unsubstituted or substituted by halogen,

$\text{R}^6$  is hydrogen, C1-20-alkyl or halogen,

$\text{R}^7$  is hydrogen, C1-20-alkyl or halogen,

10  $\text{W}$  is C1-12-alkylene,  $-\text{NH-}$  or  $-\text{NHC(=O)-}$ ,

$\text{X}$  is O, S or NH,

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

$\text{R}^8$  is aryl or heterocycle,

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

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

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

$\text{R}^{13}$  is hydrogen,

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

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

$\text{V}$  is C<sub>1-12</sub>-alkylene,

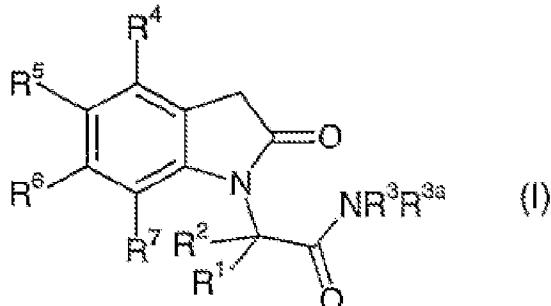
$\text{R}^{15}$  is aryl or heterocycle,

$\text{m}$  is 1 to 4,

$\text{n}$  is 0 or 1,

and at least one of R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is different from hydrogen when R<sup>2</sup> is hydrogen, R<sup>3</sup> is H or 2, 6-diisopropylphenyl, and R<sup>3a</sup> is H.

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



5

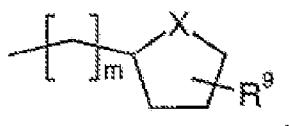
wherein

R<sup>1</sup> is hydrogen,

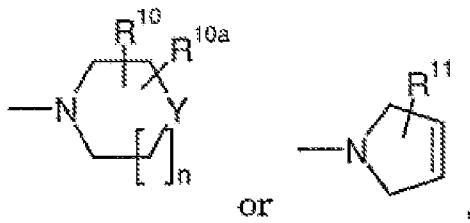
R<sup>2</sup> is hydrogen or C1-20-alkyl,

R<sup>3</sup> 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<sup>8</sup>,

R<sup>3a</sup> is hydrogen, C1-20-alkyl or a group of formula:



or NR<sup>3</sup>R<sup>3a</sup> is a group of formula



15

R<sup>4</sup> is hydrogen,

R<sup>5</sup> is hydrogen; nitro; halogen; C1-20-alkyl unsubstituted or substituted by halogen; or C1-20-alkoxy unsubstituted or substituted by halogen,

R<sup>6</sup> is hydrogen, C1-20-alkyl or halogen,

20

R<sup>7</sup> 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<sup>12</sup>R<sup>13</sup>-, -NR<sup>14</sup>- or -C(=O)-,  
R<sup>8</sup> is aryl or heterocycle,  
R<sup>9</sup>, R<sup>10</sup>, R<sup>10a</sup> and R<sup>11</sup> are independently selected from hydrogen, C1-4-alkyl,  
5 halogen, hydroxy or methoxycarbonyl,  
or R<sup>10</sup> and R<sup>10a</sup> together form a C3-6-alkylene,  
R<sup>12</sup> is hydrogen, C1-4-alkyl, halogen or hydroxy,  
R<sup>13</sup> is hydrogen,  
or CR<sup>12</sup>R<sup>13</sup> is dioxolanyl,  
10 R<sup>14</sup> is aryl, heterocycle or a group of formula -V-R<sup>15</sup>,  
V is C1-12-alkylene,  
R<sup>15</sup> is aryl or heterocycle,  
m is 1 to 4,  
n is 0 or 1,  
15 and at least one of R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is different from hydrogen when R<sup>2</sup> is  
hydrogen, R<sup>3</sup> is H or 2,6-diisopropylphenyl, and R<sup>3a</sup> 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  
20 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,  
25 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  
30 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.

5                   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.

10                  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.

15                  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.

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

25                  The term “nitro”, as used herein, represents a group of the formula -NO<sub>2</sub>.

                        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<sup>b</sup> wherein R<sup>b</sup> is an alkyl group, as defined above.

30                  The term “ester”, as used herein, represents a group of formula -COOR<sup>c</sup> wherein R<sup>c</sup> is an alkyl group or an aryl group, as defined above.

                        The term “alkoxycarbonyl”, as used herein, represents a group of formula -COOR<sup>d</sup> wherein R<sup>d</sup> is an alkyl group, as defined above.

The term “amino”, as used herein, represents a group of the formula -NH<sub>2</sub>.

The term “alkylamino”, as used herein, represents a group of formula -NHR<sup>e</sup> or -NR<sup>e</sup>R<sup>f</sup> wherein R<sup>e</sup> and R<sup>f</sup> are alkyl group as defined above.

5 The term alkylsulfonyl, as used herein is defined as representing a group of formula -SO<sub>2</sub>-R<sup>g</sup>, wherein R<sup>g</sup> is C1-4-alkyl.

10 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.

15 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.

20 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-1H-isochromen-1-yl, tetrahydropyranyl, oxooctahydroquinolinyl and dioxolanyl. The 5 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.

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

The term "azido" as used herein, represents a group of the formula -N<sub>3</sub>.

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

Generally, R<sup>2</sup> is hydrogen or C1-4-alkyl.

Preferably, R<sup>2</sup> is hydrogen, methyl or ethyl. More preferably, R<sup>2</sup> is hydrogen or methyl.

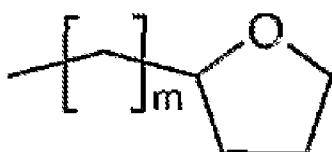
20 Generally, R<sup>3</sup> is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxy carbonyl or alkylamino; C5-7-cycloalkyl; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, 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<sup>8</sup> wherein:

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

R<sup>8</sup> 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; 30 pyridinyl; morpholinyl; tetrahydrobenzazocinyl; piperidinyl unsubstituted or substituted by methyl; dihydroisochromenyl or dihydroimidazolyl.

Preferably, R<sup>3</sup> 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-1H-isochromen-1-ylmethyl, methoxy, (4-pyridinylcarbonyl) amino or 4, 5-dihydro-1H-imidazol-2-ylamino. More preferably, R<sup>3</sup> is hydrogen.

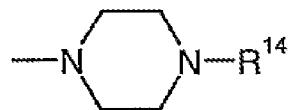
Generally, R<sup>3a</sup> is hydrogen, C1-4-alkyl or a group of formula



wherein m is 1 to 4.

Preferably, R<sup>3a</sup> is hydrogen, methyl or tetrahydrofuran-2-ylmethyl. More preferably, R<sup>3a</sup> is hydrogen.

In another embodiment, NR<sup>3</sup>R<sup>3a</sup> is piperidinyl unsubstituted or substituted by hydroxy; thiomorpholinyl; thiazolidinyl unsubstituted or substituted by C1-4- alkoxy carbonyl ; 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<sup>14</sup> is pyridinyl ; phenyl unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl ; or a group of formula -V-R<sup>15</sup> wherein V is unsubstituted C1-4- alkylene and R<sup>15</sup> is phenyl or morpholinyl.

5 In a preferred embodiment,  $\text{NR}^3\text{R}^{3a}$  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-1H-pyrrol-1-yl, 1,4-dioxa-8-azaspiro [4.5] dec-8-yl or 4-oxooctahydro-1(2H)-quinolinyl.

10 Generally,  $\text{R}^5$  is hydrogen, nitro, halogen, C1-4-alkyl, unsubstituted or substituted by halogen, or C1-4-alkoxy unsubstituted or substituted by halogen.

15 Preferably,  $\text{R}^5$  is hydrogen, methyl, ethyl, trifluoromethyl, trifluoromethoxy, n-propyl, isopropyl, nitro, or halogen. More preferably,  $\text{R}^5$  is halogen or trifluoromethyl.

Generally,  $\text{R}^6$  is hydrogen, C1-6-alkyl or halogen.

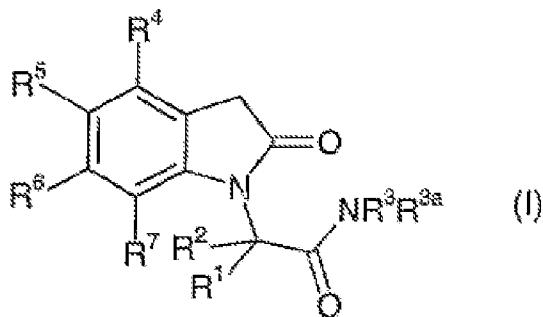
Preferably,  $\text{R}^6$  is hydrogen, methyl or Cl. More preferably,  $\text{R}^6$  is hydrogen.

Generally,  $\text{R}^7$  is hydrogen, methyl or halogen.

15 Preferably,  $\text{R}^7$  is hydrogen, methyl, Br, F or Cl. More preferably,  $\text{R}^7$  is hydrogen, Br or F.

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

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



wherein  $\text{R}^1$  is hydrogen,

$\text{R}^2$  is hydrogen or C1-4-alkyl,

25  $\text{R}^3$  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<sup>8</sup>,

R<sup>3a</sup> is hydrogen, C1-4-alkyl or a group of formula



5

or NR<sup>3</sup>R<sup>3a</sup> 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



10

R<sup>4</sup> is hydrogen,

R<sup>5</sup> 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,

15

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)-,

20

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<sup>14</sup> is pyridinyl; phenyl unsubstituted or substituted by halogen, hydroxy, C1-4-alkyl ; or a group of formula-V-R<sup>15</sup>,

25

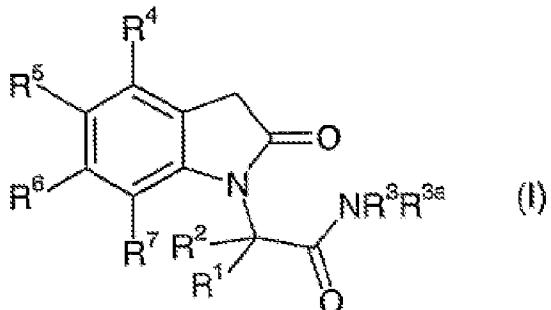
V is unsubstituted C1-4-alkylene,

R<sup>15</sup> is phenyl or morpholinyl,

m is 1 to 4,

and at least one of R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is different from hydrogen when R<sup>2</sup> is hydrogen, R<sup>3</sup> is H or 2,6-diisopropylphenyl, and R<sup>3a</sup> is H.

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



5

wherein

R<sup>1</sup> is hydrogen,

R<sup>2</sup> is hydrogen, methyl or ethyl,

R<sup>3</sup> 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-1H-isochromen-1-ylmethyl, methoxy, (4-pyridinylcarbonyl) amino or 4,5-dihydro-1H-imidazol-2-ylamino,

10

15

20

25

R<sup>3a</sup> is hydrogen, methyl or tetrahydrofuran-2-ylmethyl, or NR<sup>3</sup>R<sup>3a</sup> 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-1H-pyrrol-1-yl, 1,4-dioxa-8- azaspiro [4.5]dec-8-yl or 4-oxooctahydro-1(2H)-quinolinyl, R<sup>4</sup> is hydrogen, R<sup>5</sup> is hydrogen, methyl, ethyl, trifluoromethyl, trifluoromethoxy, n-propyl, isopropyl, nitro or halogen, R<sup>6</sup> is hydrogen, methyl or Cl, R<sup>7</sup> is hydrogen, methyl, Br, F or Cl, and at least one of R<sup>5</sup>, R<sup>6</sup> or R<sup>7</sup> is different from hydrogen when R<sup>2</sup> is hydrogen, R<sup>3</sup> is H or 2,6-diisopropylphenyl, and R<sup>3a</sup> is H.

More preferably, R<sup>2</sup> is hydrogen or methyl, R<sup>3</sup> is hydrogen, R<sup>3a</sup> is hydrogen, R<sup>5</sup> is halogen or trifluoromethyl, R<sup>6</sup> is hydrogen and R<sup>7</sup> is hydrogen, Br or F.

In all the above-mentioned scopes, when R<sup>2</sup> is C1-20-alkyl, the carbon atom to which R<sup>2</sup> 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-1H-indol-1-yl) acetamide ; 2- (5, 7-dibromo- 2-oxo-2, 3-dihydro-1H-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-1H-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-1H-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-1H-indol-1-yl) acetamide; 2- (5-bromo-2-oxo-2, 3- dihydro-1H-indol-1-yl) acetamide ; 2-(2-oxo-5-propyl-2, 3-dihydro-1H-indol-1- yl) acetamide ; 2-[2-oxo-5-(trifluoromethyl)-2, 3-dihydro-1H-indol-1-yl] acetamide ; 2- (5, 6-dimethyl-2-oxo-2, 3-dihydro-1H-indol-1-yl) acetamide; 2- (7-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl) acetamide; 2- (6-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl) acetamide; 2- (5- chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl)

butanamide ; (+)-2- (5-chloro-2-oxo-2, 3- dihydro-1H-indol-1-yl) butanamide;  
(-)2- (5-chloro-2-oxo-2, 3-dihydro-1H-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-1H-  
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-1H-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-1H-indol-1-yl)-N- (3- fluorophenyl) acetamide ; 2-  
10 (5-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl)-N- [3- (2-pyridin- 2-ylethyl)  
phenyllacetamide ; 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) ethyl]3-1, 3-dihydro-2H-indol-2-one ; 5-chloro-1-  
15 {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-1H-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-  
20 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-1H-indol-1-yl)-N- [4-  
25 (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-1H-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-  
30 oxo-2,3-dihydro-1H-indol-1-yl)-N- [3- (dimethylamino) propyl] acetamide ; 5-  
chloro-1-{2-oxo-2[4-(2-phenylethyl)piperazin-1- yl] ethyl}-1, 3-dihydro-2H-  
indol-2-one; ethyl {[ (5-chloro-2-oxo-2, 3-dihydro-1H-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-1H-indol-1-yl)-N-(2- fluoroethyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-1H-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-1H- indol-1-yl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-1H-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-1H-indol-1-yl)-N- (3,3, 3-trifluoro-2- 5 hydroxypropyl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-1H-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-1H-indol-1-yl)-N- [3- (1H-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-1H-pyrrol-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, 5-dihydro-1H-imidazol-2- yl) acetohydrazide ; 2- (5-chloro-2-oxo-2, 3-dihydro-1H-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-1H-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-1H-indol-1-yl)-N-[2-(2-methylpiperidin-1-yl) ethyl] acetamide ; 2- (5-chloro-2- oxo-2, 3-dihydro-1H-indol-1-yl)-N-(2-nitrobenzyl) acetamide ; 2- (5-chloro-2-oxo-2, 3- dihydro-1H-indol-1-yl)-N- (3, 4-dihydro-1H-isochromen-1-ylinethyl) acetamide ; N- (2- chloro-6-fluorobenzyl)-2- (5-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl) acetamide ; N- benzyl-2- (5-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl)-N- methylacetamide ; 2- (5-chloro- 2-oxo-2, 3-dihydro-1H-indol-1-yl)-N- {2-

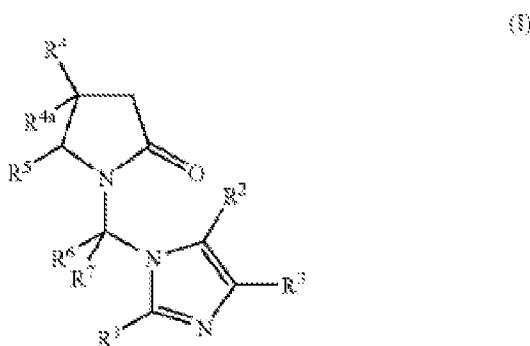
5 [ (trifluoromethyl) thio] benzyl} acetamide ; 5- chloro-1- [2- (1, 4-dioxa-8-azaspiro [4.5] dec-8-yl)-2-oxoethyl]-1, 3-dihydro-2H-indol-2- one; 2-(5-chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl)-N-cycloheptylacetamide ; 5-chloro-1- {2-[4- (2-morpholin-4-ylethyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one ; 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-1H-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-1H-indol-1- yl] acetamide and 2-(5-chloro-7-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl) acetamide.

15 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-1H-indol-1-yl) propanamide.

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

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

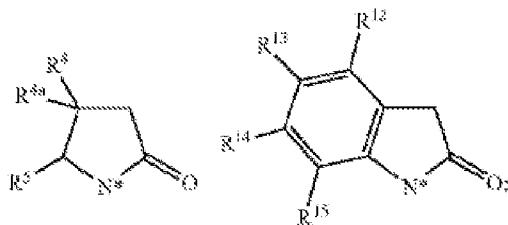


25 wherein R<sup>1</sup> is hydrogen, C<sub>1-20</sub> alkyl, C<sub>3-8</sub> cycloalkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, guanidine, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, aryl or heterocycle;

$R^2$  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;

5 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, alkoxy carbonylamino, arylsulfonyloxy or heterocycle;

10  $R^{4a}$  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

15  $R^6$  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;

20  $R^9$  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;

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

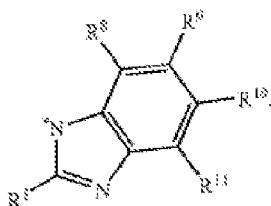
$R^{12}$  is hydrogen or halogen;

$R^{13}$  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;

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

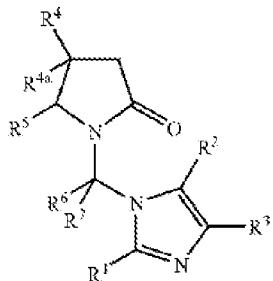
with the proviso that  $R^4$  is different from hydrogen when represents a group of formula



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

10 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)

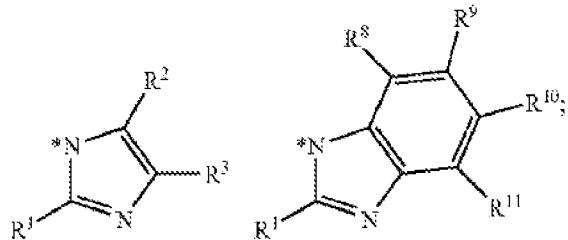


15 wherein  $R^1$  is hydrogen,  $C_{1-20}$  alkyl,  $C_{3-8}$  cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle;

$R^2$  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<sup>2</sup> and R<sup>3</sup> can form together with the imidazole ring the following 1H-benzimidazole cycle

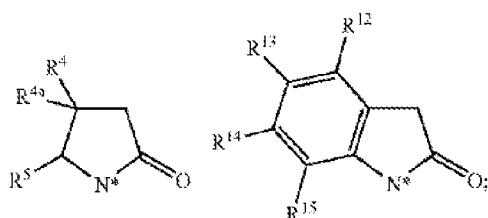


R<sup>4</sup> is hydrogen, C<sub>1-20</sub> alkyl, C<sub>2-12</sub> alkenyl or aryl;

5 R<sup>4a</sup> is hydrogen;

R<sup>5</sup> is hydrogen;

or R<sup>4</sup>, R<sup>4a</sup> and R<sup>5</sup> can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



10 R<sup>6</sup> is hydrogen or C<sub>1-20</sub> alkyl;

R<sup>7</sup> is hydrogen; or R<sup>6</sup> and R<sup>7</sup> are linked together to form a C<sub>3-6</sub> cycloalkyl;

R<sup>8</sup> is hydrogen;

R<sup>9</sup> is hydrogen, C<sub>1-20</sub> alkyl, halogen or alkoxy;

R<sup>10</sup> is hydrogen, C<sub>1-20</sub> alkyl, halogen or cyano;

15 R<sup>11</sup> is hydrogen;

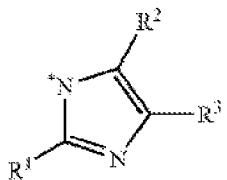
R<sup>12</sup> is hydrogen or halogen;

R<sup>13</sup> is hydrogen, halogen, heterocycle or C<sub>1-20</sub> alkyl;

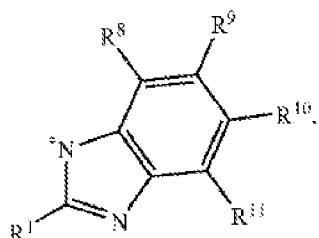
R<sup>14</sup> is hydrogen;

R<sup>15</sup> is hydrogen;

with the proviso that R<sup>4</sup> is different from hydrogen when



represents a group of formula



5        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 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-

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propyl, n-butyl, azidomethyl or trifluoromethyl. Most preferred alkyl groups are methyl or n-propyl.

5 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.

10 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 15 ethenyl (vinyl) optionally substituted by 1 to 3 halogens. Preferred alkenyl group, in the present case, is 2, 2-difluorovinyl.

20 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.

25 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<sub>1-3</sub> 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<sup>a</sup> wherein R<sup>a</sup> is an alkyl group, as defined above. Preferred alkoxy group is methoxy.

The term “aryloxy”, as used herein, represents a group of formula --OR<sup>b</sup> wherein R<sup>b</sup> is an aryl group, as defined above. Preferred aryloxy group is phenoxy.

The term “ester”, as used herein, represents a group of formula --COOR<sup>c</sup> wherein R<sup>c</sup> 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<sub>2</sub>.
- The term “amino”, as used herein, represents a group of formula --NH<sub>2</sub>.
- The term “aminoderivative”, as used herein, represents an alkylamino or an arylamino group, wherein the terms “alkyl” and “aryl” are defined as above.
- 5        The term “cyano”, as used herein, represents a group of formula --CN.
- The term “nitro”, as used herein, represents a group of formula --NO<sub>2</sub>.
- The term “azido”, as used herein, represents a group of formula --N<sub>3</sub>.
- The term “guanidine”, as used herein, represents a group of formula --NHC(=NH)NH<sub>2</sub>.
- 10      The term “alkylthio”, as used herein, represents a group of formula --SR<sup>d</sup> wherein R<sup>d</sup> 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)<sub>2</sub>R<sup>e</sup> wherein R<sup>e</sup> is an alkyl group, as defined above. Preferred alkylsulfonyl group is methylsulfonyl.
- 15      The term “alkylsulfinyl”, as used herein, represents a group of formula --S(=O)R<sup>f</sup> wherein R<sup>f</sup> is an alkyl group, as defined above. Preferred alkylsulfinyl group is methylsulfinyl.
- The term “arylthio”, as used herein, represents a group of formula --SR<sup>g</sup> wherein R<sup>g</sup> is an aryl group, as defined above.
- 20      The term “arylsulfonyl”, as used herein, represents a group of the formula --S(=O)<sub>2</sub>R<sup>h</sup> wherein R<sup>h</sup> is an aryl group, as defined above.
- The term “arylsulfinyl”, as used herein, represents a group of the formula --S(=O)R<sup>i</sup> wherein R<sup>i</sup> is an aryl group, as defined above.
- 25      The term “carbamate” as used herein, represents a group of formula --N(H)C(O)OR<sup>j</sup>, wherein R<sup>j</sup> is an alkyl or an aryl, as defined above. Usually carbamate groups are (propoxycarbonyl)amino or (benzyloaaxycarbonyl)amino. Preferred carbamate group is (benzyloaaxycarbonyl)amino.
- The term “alkanoylamino” as used herein, represents a group of the formula --NHC(=O)R<sup>k</sup> wherein R<sup>k</sup> is an alkyl group, as defined above.

The term “(arylcarbonyl)amino” as used herein, represents a group of the formula --NHC(=O)R<sup>m</sup> wherein R<sup>m</sup> is an aryl group, as defined above. Preferred (arylcarbonyl)amino is benzoylamino.

Usually, R<sup>1</sup> is hydrogen; C<sub>1-10</sub> alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy; hydroxy; C<sub>3-6</sub> cycloalkyl; halogen; ester; amido; nitro; cyano; amino; phenyl; alkylthio; alkylsulfonyl; alkylsulfinyl; heterocycle unsubstituted or substituted by alkyl groups; or guanidine. Preferably, R<sup>1</sup> 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<sup>1</sup> is hydrogen; methyl; ethyl; i-propyl; n-propyl; n-butyl; methylthio; nitro; cyano; amino; chloro or 1H-pyrrol-2-yl. Most preferably, R<sup>1</sup> is hydrogen; methyl; methylthio; nitro; cyano; amino or chloro.

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

Usually, R<sup>3</sup> is hydrogen; C<sub>1-4</sub> alkyl unsubstituted or substituted by hydroxy; halogen; ester or cyano. Preferably, R<sup>3</sup> is hydrogen; hydroxymethyl; chloro; cyano. More preferably, R<sup>3</sup> is hydrogen or cyano. Most preferred R<sup>3</sup> is hydrogen.

Usually, R<sup>4</sup> is hydrogen; C<sub>1-4</sub> alkyl unsubstituted or substituted by halogens; C<sub>2-4</sub> alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or/and halogens. Preferably, R<sup>4</sup> 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<sup>4</sup> 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<sup>4</sup> 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.

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Usually, R<sup>4a</sup> is hydrogen.

Usually, R<sup>5</sup> is hydrogen.

Usually, R<sup>6</sup> is hydrogen or C<sub>1-10</sub> alkyl unsubstituted or substituted by hydroxy or azido. Preferably, R<sup>6</sup> is hydrogen or azidomethyl. More preferably R<sup>6</sup> is hydrogen.

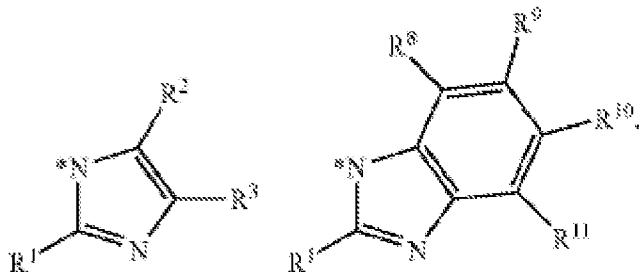
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Usually R<sup>7</sup> is hydrogen.

In other preferred embodiments, R<sup>6</sup> and R<sup>7</sup> are linked to form a cyclopropyl.

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



Usually, R<sup>8</sup> is hydrogen.

Usually, R<sup>9</sup> is hydrogen; halogen; C<sub>1-3</sub> alkyl or alkoxy. Preferably, R<sup>9</sup> is hydrogen; methyl; chloro or methoxy. More preferred R<sup>9</sup> is hydrogen.

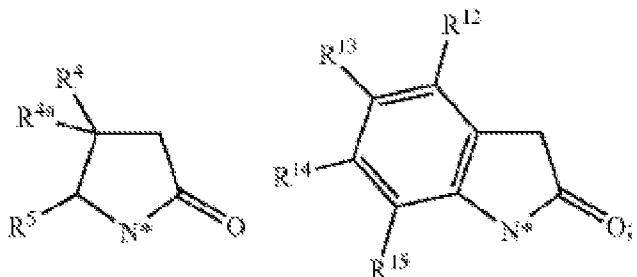
25

Usually, R<sup>10</sup> is hydrogen; halogen; cyano; C<sub>1-3</sub> alkyl unsubstituted or substituted by halogens; or alkoxy. Preferably, R<sup>10</sup> is methyl; hydrogen;

trifluoromethyl; fluoro; cyano or methoxy. More preferred R<sup>10</sup> is hydrogen; trifluoromethyl; fluoro or cyano.

Usually, R<sup>11</sup> is hydrogen.

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



Usually, R<sup>12</sup> is hydrogen or halogen. Preferably R<sup>12</sup> is hydrogen; chloro or fluoro. More preferred R<sup>12</sup> is hydrogen.

10 Usually, R<sup>13</sup> is hydrogen; C<sub>1-3</sub> alkyl; halogen or thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl. Preferably R<sup>13</sup> is hydrogen; chloro; bromo or methyl. Most preferred R<sup>13</sup> is chloro; bromo or methyl.

Usually R<sup>14</sup> is hydrogen.

Usually, R<sup>15</sup> is hydrogen.

15 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

20 R<sup>1</sup> is selected from hydrogen; C<sub>1-10</sub> alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy; C<sub>3-6</sub> cycloalkyl; halogen; ester; amido; nitro; cyano; amino; phenyl; alkylthio; alkylsulfonyl; alkylsulfinyl; heterocycle unsubstituted or substituted by alkyl group; or guanidine;

25 R<sup>2</sup> is selected from hydrogen; C<sub>1-4</sub> alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen; ester; cyano; alkyl carbamate or [(N-methoxy-N-methyl)amino]carbonyl.

R<sup>3</sup> is selected from hydrogen; C<sub>1-4</sub> alkyl unsubstituted or substituted by hydroxy; halogen; ester or cyano;

R<sup>4</sup> is selected from hydrogen; C<sub>1-4</sub> alkyl unsubstituted or substituted by halogens; C<sub>2-4</sub> alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or /and halogens;

5 R<sup>4a</sup> is hydrogen;

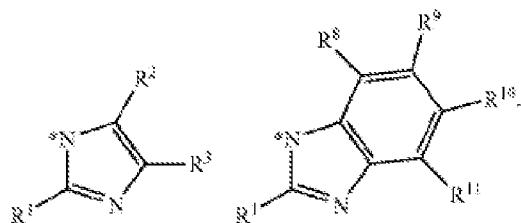
R<sup>5</sup> is hydrogen;

R<sup>6</sup> is selected from hydrogen or C<sub>1-10</sub> alkyl unsubstituted or substituted by hydroxy or azido;

10 R<sup>7</sup> is hydrogen;

or R<sup>6</sup> and R<sup>7</sup> can be linked to form a cyclopropyl;

or R<sup>2</sup> and R<sup>3</sup> can form together with the imidazole ring the following 1H-benzimidazole cycle



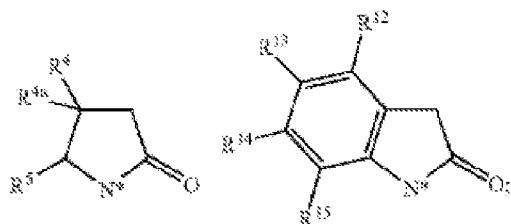
15 R<sup>8</sup> is hydrogen;

R<sup>9</sup> is selected from hydrogen; halogen; C<sub>1-3</sub> alkyl; alkoxy;

R<sup>10</sup> is selected from hydrogen; halogen; cyano or C<sub>1-3</sub> alkyl unsubstituted or substituted by halogens; or alkoxy;

R<sup>11</sup> is hydrogen;

20 or R<sup>4</sup>, R<sup>4a</sup> and R<sup>5</sup> can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



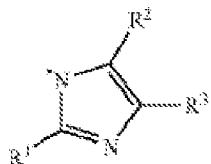
R<sup>12</sup> is selected from hydrogen or halogen;

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

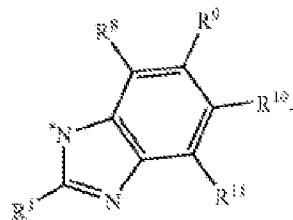
$R^{14}$  is hydrogen;

$R^{15}$  is hydrogen;

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

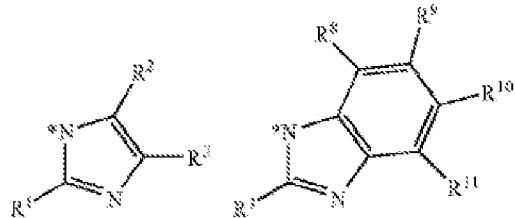


represents a group of formula



In a preferred embodiment, the compounds of formula I, or  
 10 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;  
 15  $R^2$  is selected from hydrogen; methyl; hydroxymethyl;  
 (acetylamino)methyl; (propionylamino)methyl; (benzoylamino)methyl;  
 (benzyloxycarbonyl)amino; chloro; or cyano;  
 20  $R^3$  is selected from hydrogen; hydroxymethyl; chloro; cyano;

or R<sup>2</sup> and R<sup>3</sup> can form together with the imidazole ring the following 1H-benzimidazole cycle



R<sup>8</sup> is hydrogen;

5 R<sup>9</sup> is selected from hydrogen; methyl; choro; methoxy;

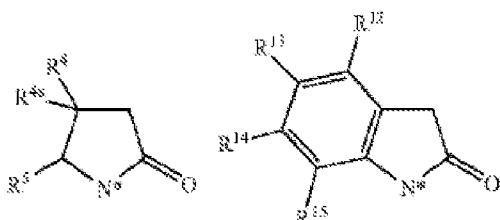
R<sup>10</sup> is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy;

R<sup>11</sup> is hydrogen;

10 R<sup>4</sup> 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<sup>4a</sup> is hydrogen; R<sup>5</sup> is hydrogen;

15 or R<sup>4</sup>, R<sup>4a</sup> and R<sup>5</sup> can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



R<sup>12</sup> is selected from hydrogen; choro; fluoro;

R<sup>13</sup> is selected from hydrogen; choro; bromo; methyl;

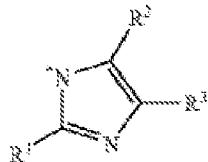
20 R<sup>14</sup> is hydrogen;

R<sup>15</sup> hydrogen;

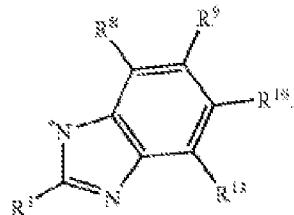
R<sup>6</sup> is selected from hydrogen; azidomethyl;

R<sup>7</sup> is hydrogen;

or R<sup>6</sup> and R<sup>7</sup> are linked to form a cyclopropyl;  
with the proviso that R<sup>4</sup> is different from hydrogen when



represents a group of formula



5

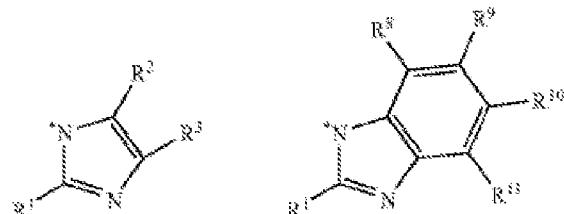
In a more preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

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

10 R<sup>2</sup> is selected from hydrogen; chloro; cyano;

R<sup>3</sup> is selected from hydrogen; cyano;

or R<sup>2</sup> and R<sup>3</sup> can form together with the imidazole ring the following 1H-benzimidazole cycle



15 R<sup>8</sup> is hydrogen;

R<sup>9</sup> is hydrogen;

R<sup>10</sup> is selected from hydrogen; trifluoromethyl; fluoro; cyano;

R<sup>11</sup> is hydrogen;

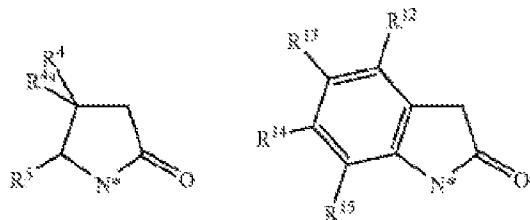
20 R<sup>4</sup> is selected from hydrogen; n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl; 3,5-difluorophenyl; 3,4-difluorophenyl; 3-chloro-4-fluorophenyl; 2,3,4-

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

5 R<sup>4a</sup> is hydrogen;

R<sup>5</sup> is hydrogen;

or R<sup>4</sup>, R<sup>4a</sup> and R<sup>5</sup> can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



wherein

R<sup>12</sup> is hydrogen;

10 R<sup>13</sup> is selected from methyl; chloro; bromo;

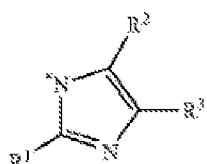
R<sup>14</sup> is hydrogen;

R<sup>15</sup> hydrogen;

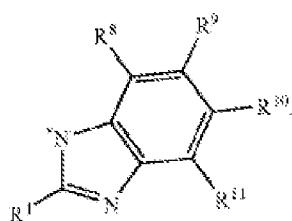
R<sup>6</sup> is hydrogen;

R<sup>7</sup> is hydrogen;

15 with the proviso that R<sup>4</sup> is different from hydrogen when



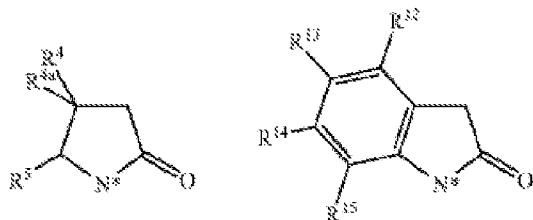
represents a group of formula



In a most preferred embodiment, the compounds of formula I, or 20 pharmaceutically acceptable salt thereof, are those wherein

R<sup>1</sup> is selected from hydrogen; methyl; methylthio; nitro; cyano; amino; chloro;

R<sup>2</sup> is selected from hydrogen; chloro; cyano;  
 R<sup>3</sup> is hydrogen;  
 R<sup>4</sup> is selected from n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 3,5-difluorophenyl; 2,3,4-trifluorophenyl; 2,4,5-trifluorophenyl;  
 5 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl; 3-azido-2,4-difluorophenyl;  
 R<sup>4a</sup> is hydrogen;  
 R<sup>5</sup> is hydrogen;  
 or R<sup>4</sup>, R<sup>4a</sup> and R<sup>5</sup> can form together with the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



10

R<sup>12</sup> is hydrogen;  
 R<sup>13</sup> is selected from chloro; bromo; methyl;  
 R<sup>14</sup> is hydrogen;  
 R<sup>15</sup> hydrogen;  
 15 R<sup>6</sup> is hydrogen;  
 R<sup>7</sup> 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-carboxylate; 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-  
5 {[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-  
10 {[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-  
15 {[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-  
20 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-  
25 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-  
30 [(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-one; {1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazol-2-yl}acetonitrile; 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-propylpyrrolidin-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-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-(1H-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]-1H-benzimidazole-5-carbonitrile; 1-{[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;

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-propylpyrrolidin-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-propylpyrrolidin-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-propylpyrrolidin-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-propylpyrrolidin-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-carbonitrile.

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-(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-{[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-car-

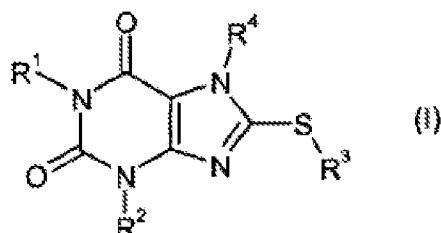
bonitrile; 1-{[2-ethyl-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4--propylpyrrolidin-2-one; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-1H-benzimidazol-1-yl]methyl}pyrrolidin-2-- one; 1-[(5-fluoro-2-propyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin- -2-one; 2-butyl-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole- -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:  
15 Compounds having formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



wherein

20 R<sup>1</sup> is hydrogen or C<sub>1-6</sub> alkyl;  
R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl;  
R<sup>3</sup> is a group of formula -CHR<sup>5</sup>R<sup>6</sup> or a benzyl group;  
R<sup>4</sup> is C<sub>1-8</sub> alkyl optionally substituted by alkoxy carbonyl, C<sub>3-6</sub> cycloalkyl, aryl or heterocycle;  
25 R<sup>5</sup> is C<sub>2-4</sub> alkyl;  
R<sup>6</sup> is C<sub>2-4</sub> alkyl, amido or -COOR<sup>7</sup>;  
R<sup>7</sup> is C<sub>1-4</sub> alkyl;

Usually when R<sup>3</sup> is a benzyl group, then R<sup>4</sup> is C<sub>1-8</sub> alkyl optionally substituted by alkoxycarbonyl.

Usually when R<sup>3</sup> is a group of formula –CHR<sup>5</sup>R<sup>6</sup> then R<sup>4</sup> is C<sub>1-8</sub> alkyl optionally substituted by C<sub>3-6</sub> cycloalkyl, aryl or heterocycle.

5 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, 10 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, 15 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.

20 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.

25 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  $-C_6H_5$ .

5 The term “benzyl group”, as used herein, represents a group of formula  $-CH_2\text{-aryl}$ . 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.

10 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  $-CN$ .

15 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.

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

The term “amido”, as used herein, represents a group of formula  $-C(=O)NH_2$ .

25 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.

30 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<sup>1</sup> is hydrogen or C<sub>1-6</sub> alkyl. Usually R<sup>1</sup> is hydrogen or C<sub>1-6</sub> alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl. Preferably R<sup>1</sup> 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<sup>1</sup> is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2- propynyl. Most preferably R<sup>1</sup> is hydrogen.

Generally R<sup>2</sup> is hydrogen or C<sub>1-4</sub> alkyl. Usually R<sup>2</sup> is hydrogen or unsubstituted C<sub>1-4</sub> alkyl. Preferably R<sup>2</sup> is hydrogen, methyl or n-butyl. More preferably, R<sup>2</sup> is methyl.

Generally R<sup>3</sup> is a group of formula –CHR<sup>5</sup>R<sup>6</sup> or a benzyl group. Preferably R<sup>3</sup> is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl. Most preferably R<sup>3</sup> is 1-(ethoxycarbonyl)propyl.

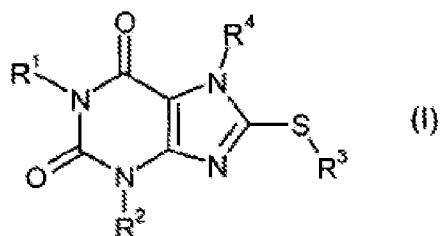
Generally R<sup>4</sup> is C<sub>1-8</sub> alkyl optionally substituted by alkoxycarbonyl, C<sub>3-6</sub> cycloalkyl, aryl or heterocycle. Usually R<sup>4</sup> is C<sub>1-8</sub> alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl. Preferably R<sup>4</sup> 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<sup>4</sup> 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<sup>4</sup> is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

Generally R<sup>5</sup> is C<sub>2-4</sub> alkyl. Usually R<sup>5</sup> is unsubstituted C<sub>2-4</sub> alkyl. Preferably R<sup>5</sup> 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.

5           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,



10           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;

15            $R^4$  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  $-COOR^7$ ;

20            $R^7$  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.

25           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,

5  $R^1$  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;

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

15  $R^4$  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.

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

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,

25  $R^1$  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;

30  $R^4$  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<sup>1</sup> is hydrogen, R<sup>2</sup> is methyl and R<sup>3</sup> is 1-(ethoxycarbonyl)propyl, then R<sup>4</sup> is different from 3-bromobenzyl.

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

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

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

A further embodiment consists in compounds wherein R<sup>2</sup> is methyl, R<sup>3</sup> is a group of formula -CHR<sup>5</sup>R<sup>6</sup> with R<sup>5</sup> being C<sub>2-4</sub> alkyl, R<sup>6</sup> being amido or -COOR<sup>7</sup> and R<sup>7</sup> being methyl or ethyl.

15 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-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-(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)-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-

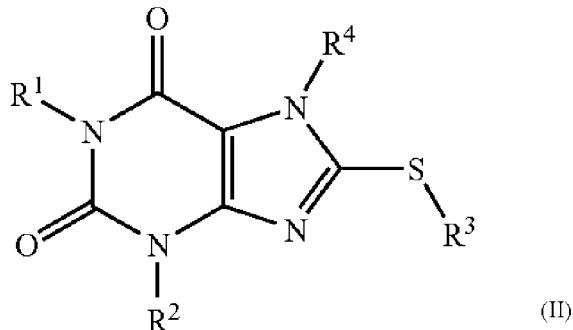
yl]thio}butanoate; ethyl 2-{{3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl}thio}butanoate; ethyl 2-{{7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl}thio}butanoate; ethyl 2-{{7-[4-(aminosulfonyl)benzyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl}thio}butanoate; 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-1 H-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-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-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-1 H-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-2,3,6,7-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; 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-1 H-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; 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-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.

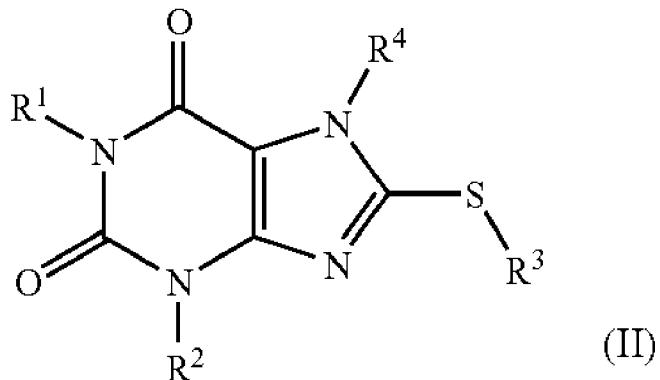
In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: ethyl 2- {[7-(3- methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl]thio}butanoate; ethyl 2- {[3-methyl-7-(3-nitrobenzyl)-2,6- dioxo-2,3,6,7- tetrahydro-1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



- wherein R.sup.1 is hydrogen or C.sub.1-6 alkyl;
- R.sup.2 is hydrogen or C.sub.1-4 alkyl;
- 5 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;
- 10 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;
- 15 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.
- 20 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.
- 25 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



5 wherein

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

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

10

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 alkoxy carbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

15

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;

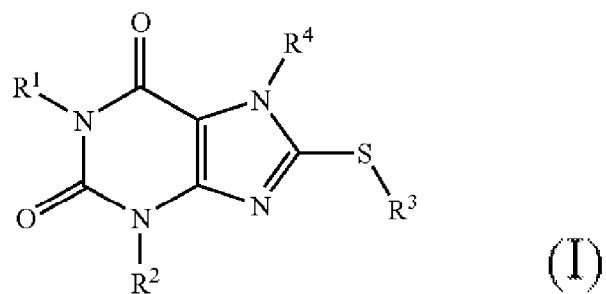
20

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]butanoate; 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]butanoate; 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



15        wherein

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

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

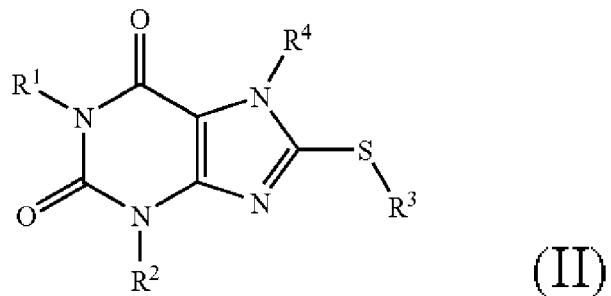
20        R.sup.3 is a group of formula --CHR.sup.5R.sup.6 or a benzyl group;

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

25        R.sup.5 is C.sub.2-4 alkyl;

25        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  
 5 mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



wherein

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

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

15 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 alkoxy carbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

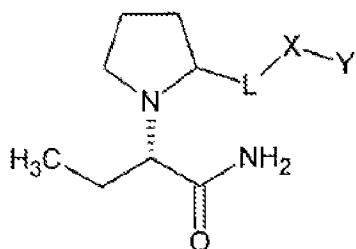
20 R.sup.5 is hydrogen or C.sub.1-4 alkyl;

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

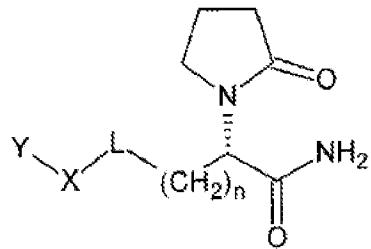
R.sup.7 is C.sub.1-4 alkyl;

25 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



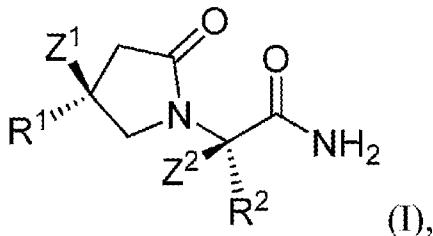
Formula 2

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 CH<sub>2</sub>, 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 Y<sub>i</sub>-Z where Y<sub>i</sub> 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:



or a pharmaceutically acceptable salt thereof, wherein: each Z is independently  
 5 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.

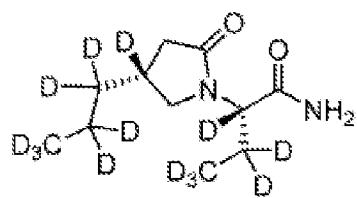
One embodiment of this invention provides compounds of Formula I wherein R1 is  
 selected from CD3CH2CH2-, CD3CD2CH2-, CD3CH2CD2-, CH3CH2CD2-,  
 10 CH3CD2CD2-, CD3CD2CD2- or CH3CH2CH2-. In a more specific embodiment,  
 R1 is CD3CD2CD2- or

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.

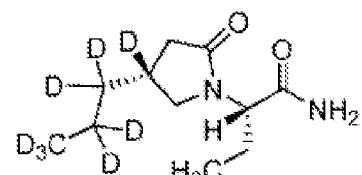
In another embodiment, R2 is selected from CH3CH2-, CD3CH2-, CH3CD2-, or  
 15 CD3CD2-. In a more specific embodiment, R2 is selected from CH3CH2- or  
 CD3CD2-. In one aspect of these embodiments, Z1 and Z2 are both hydrogen. In  
 another aspect of these embodiments, Z1 and Z2 are both deuterium.

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  
 20 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  
 25 CD3CD2CD2- or CD3CD2CH2-; and R2 is selected from CH3CH2-, CD3CH2-,  
 CH3CD2-, or CD3CD2-. In one aspect of this embodiment, R2 is CH3CH2- or  
 CD3CD2-.

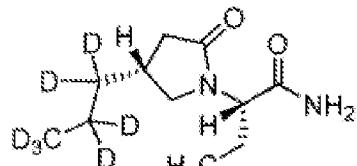
Examples of specific compounds of this invention include the following:



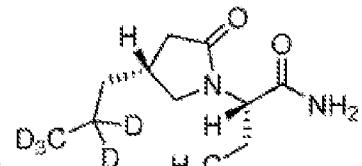
Compound 100;



Compound 101;



Compound 102; and

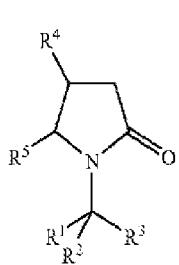


Compound 103

viii) 20090312333

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

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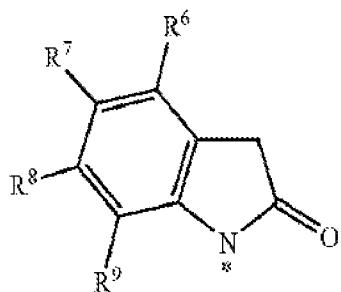


(I)

- 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.
- 10 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;
- 15 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-tetrahydromimidazo[1,2-b]pyridazin-3-yl;
- 20 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;  
5 1H-indol-3-yl;  
1H-indol-4-yl;  
1H-indol-7-yl;  
isoxazol-4-yl;  
1H-pyrazol-4-yl;  
10 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;  
15 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;  
20 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;  
25 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;  
30 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;  
5 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;  
10 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;  
15 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  
20 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;  
25 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  
30 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.

- 5 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, 10 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:

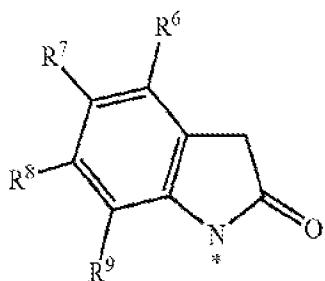
- 15 (a) a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms selected from the group consisting of:  
1H-benzimidazol-6-yl;  
1H-benzimidazol-7-yl;  
imidazo[1,2-a]pyridin-3-yl;
- 20 imidazo[1,2-a]pyrimidin-3-yl;  
imidazo[1,2-b][1,2,4]triazin-7-yl;  
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;
- 25 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;  
5 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;  
10 pyridazin-4-yl;  
pyridin-2-yl;  
pyridin-3-yl;  
pyridin-4-yl;  
1H-pyrrolo[2,3-b]pyridin-3-yl;  
15 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;  
20 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;  
25 [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:  
30 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;
- 5 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;
- 10 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;  
 15 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-  
 20 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



- 25 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:

5 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;

10 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;

15 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;

20 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;

25 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:

30 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;  
5 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;  
10 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, 15 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.
- 20 25 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.
- 30 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:

- 5 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;
- 10 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:

- 15 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.

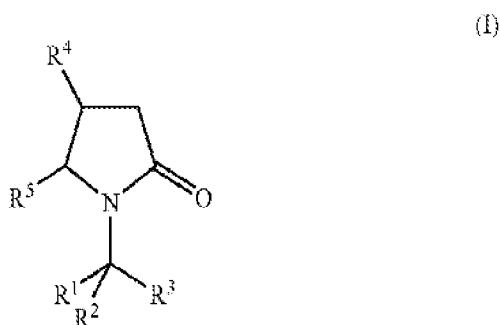
In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of 6-bromo-2-chloro-3H-imidazo[4,5-b]pyridin-3-yl, 6-bromo-2-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl, 1H-pyrrolo[3,2-b]pyridin-1-yl, 2,5-dichloro-1H-pyrrol-1-yl, 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;  
5 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;  
10 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, 15 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.  
20 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;  
25 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.

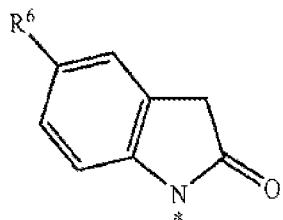


R1, R2 and R5 are hydrogen.

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:

- 5      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;
- 10     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;
- 15     1H-imidazol-4-yl;
- 1H-imidazol-5-yl;
- 1H-indol-2-yl;
- 1H-indol-3-yl;
- 1H-indol-4-yl;
- 20     1H-indol-7-yl;
- isoxazol-4-yl;
- 1H-pyrazol-4-yl;
- 1H-pyrazol-5-yl;
- 1H-pyrazolo[1,5-a]pyrimidin-3-yl;
- 25     1H-pyrazolo[3,4-b]pyridin-3-yl;
- pyridazin-4-yl;
- pyridin-2-yl;

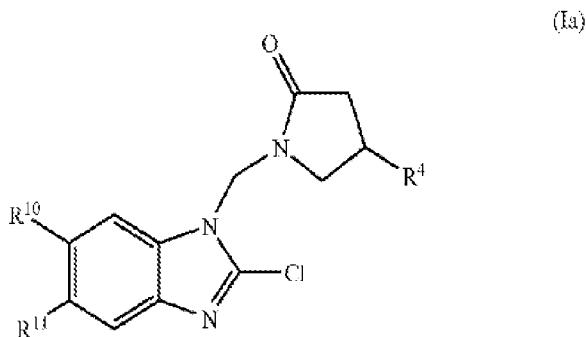
- pyridin-3-yl;  
 pyridin-4-yl;  
 1H-pyrrolo[2,3-b]pyridin-3-yl;  
 1H-pyrrolo[2,3-b]pyridin-4-yl;  
 5 1H-pyrrolo[2,3-b]pyridin-5-yl;  
 1H-pyrrolo[2,3-c]pyridin-2-yl;  
 1H-pyrrolo[2,3-c]pyridin-3-yl;  
 1H-pyrrolo[3,2-b]pyridin-3-yl;  
 1H-pyrrolo[3,2-c]pyridin-2-yl;  
 10 1H-pyrrolo[3,2-c]pyridin-3-yl;  
 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;  
 15 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  
 20 (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;  
 25 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. 5 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 10 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)-15 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.
- 20 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, 25 2,3,5-trifluorophenyl or phenyl.
- A further embodiment of the present invention consists in compounds having the specific formula (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.

- 5 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.
- 10 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.
- 15 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;
- 20 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;
- 25 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;
- 5 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}-4-10 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;
- 15 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}-4-20 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;
- 25 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}-4-30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 1-{{6-(cyclobutylmethoxy)-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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;
- 5 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-  
10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;  
5 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;  
10 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;  
15 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;  
20 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;  
25 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;  
30 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;  
5 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;  
10 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;  
15 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;  
20 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;  
25 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-  
30 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;
- 5 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-10 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-15 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-20 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;
- 25 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;
- 30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;

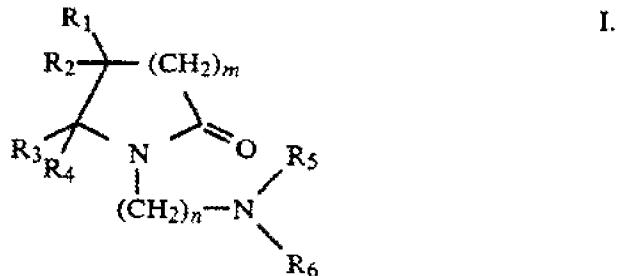
4-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)pyrrolidin-2-one;  
4-propyl-1-(1H-pyrrolo[3,2-c]pyridin-3-ylmethyl)pyrrolidin-2-one;  
4-propyl-1-(1,3,4-thiadiazol-2-ylmethyl)pyrrolidin-2-one;  
1-[(2-amino-1,3-thiazol-5-yl)methyl]pyrrolidin-2-one;  
5 1-(1,3-thiazol-5-ylmethyl)pyrrolidin-2-one;  
1-[(2-chloro-1,3-thiazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-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-  
10 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-  
15 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;  
20 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-  
25 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-  
30 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;
- 5 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;
- 10 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;
- 15 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;
- 20 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;
- 25 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;
- 30 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;  
5 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;  
10 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;  
15 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;  
20 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;  
25 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;  
30 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;
- 5 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
- 10 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
- 15 x) U.S. Patent 5,334,720

According to this invention we provide novel compounds of the formula 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;
- 20 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;
- 25 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 5 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- 10 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;

15 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;

20 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;

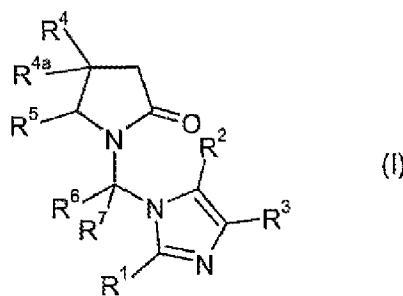
n represents an integer from 1-2, preferably 1.

25 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 30 a pharmaceutically acceptable salt thereof,

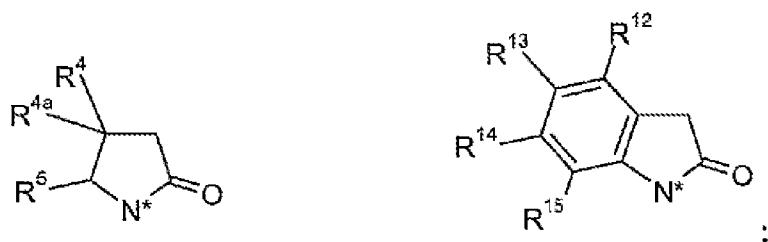


wherein

- RI is hydrogen, C1-20 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;
- 5 R3 is hydrogen, C1-20 alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;
- R10 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 ;

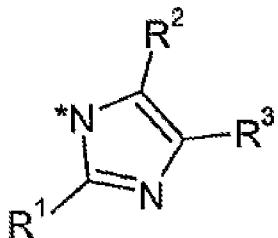
5 R10 is hydrogen, C1-20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

RI1 is hydrogen, halogen, nitro, cyano, C1-20 alkyl or alkoxy ; R12 is hydrogen or halogen;

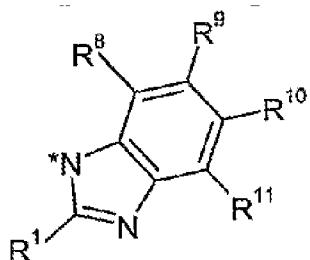
10 R13 is hydrogen, nitro, halogen, heterocycle, amino, aryl, C1-20 alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen; R14 is hydrogen, C1-20 alkyl or halogen;

R15 is hydrogen, C1-20 alkyl or halogen;

with the proviso that R4 is different from hydrogen when

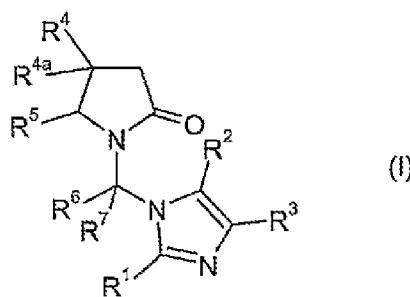


15 N represents a group of formula



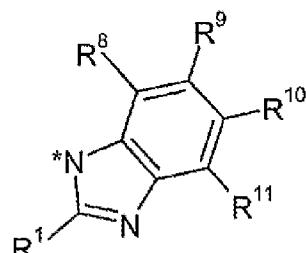
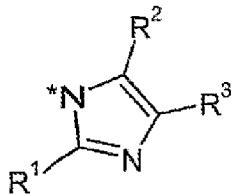
The asterisk \* indicates the point of attachment of the substituents.

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), 20 enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



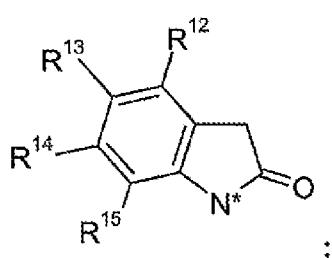
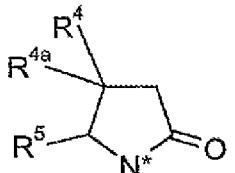
wherein

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, C1-20 alkyl, halogen or ester; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle

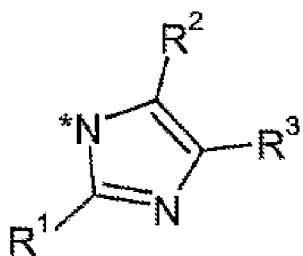


; R4 is

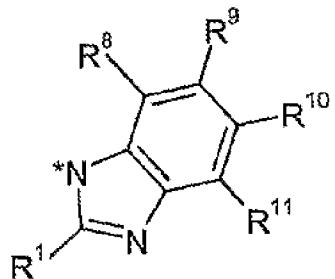
hydrogen, C1-20 alkyl, C2-12 alkenyl or aryl; R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle



R6 is hydrogen or C1-20 alkyl; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl; R8 is hydrogen; R9 is hydrogen, C1-20 alkyl, halogen or alkoxy; R10 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.

5 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.

10 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 moieties selected from groups as described above for the alkyl groups. Preferably an alkynyl group is a halogenoalkynyl group (haloalkynyl group).

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

20 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.

25 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-tetrahydrofuryl, 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.

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

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

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

25 The term "ester", as used herein, represents a group of formula-COOR<sub>c</sub> wherein R<sub>c</sub> 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<sub>2</sub>.

The term "amino", as used herein, represents a group of formula-NH<sub>2</sub>.

30 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.
- 5 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.
- 10 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.
- 15 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)
- 20 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.
- 25 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 to alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy ; hydroxy ; C3-6
- 30 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;

5 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, RI is hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl; methylthio; nitro ; cyano; amino; chloro or 1H-pyrrol-2-yl. Most preferably, RI is hydrogen; methyl;

10 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.

15 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.

20 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.

25 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-

30 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.

5 Usually, R4a is hydrogen.

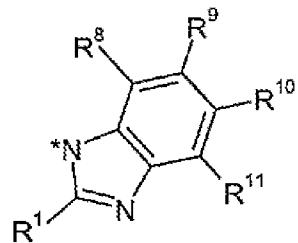
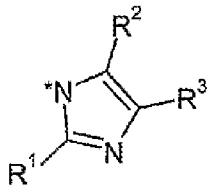
Usually, R5 is hydrogen.

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.

10 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-benzimidazole cycle



Usually, R8 is hydrogen.

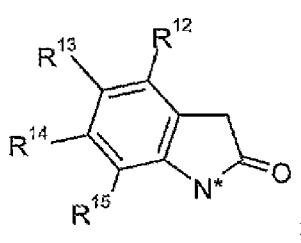
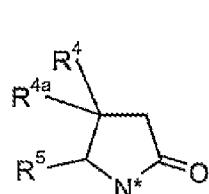
15 Usually, R9 is hydrogen; halogen ; 1-3 alkyl or alkoxy. In some embodiments, R9 is hydrogen; methyl; chloro or methoxy. In some embodiments R9 is hydrogen.

Usually, R10 is hydrogen; halogen; cyano; C1 3 alkyl unsubstituted or substituted by halogens; or alkoxy. In some embodiments, R10 is methyl; hydrogen; trifluoromethyl ; fluoro; cyano or methoxy. In some embodiments R10 is

20 hydrogen; trifluoromethyl ; fluoro or cyano.

Usually, R11 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

5       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

10      pharmaceutically acceptable salts thereof, are those wherein

RI is selected from hydrogen; C1-10 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

15      guanidine; R2 is selected from hydrogen; C1-4 alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen; ester; cyano; alkyl carbamate or [ (N-methoxy-N-methyl) amino] carbonyl.

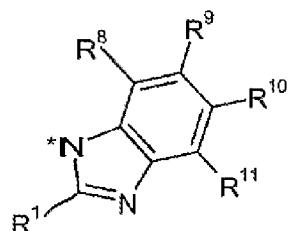
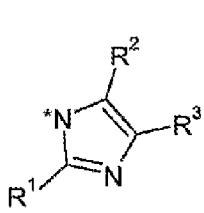
R3 is selected from hydrogen; C1-4 alkyl unsubstituted or substituted by hydroxy ; halogen; ester or cyano; R4 is selected from hydrogen; C1-4 alkyl unsubstituted or

20      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 C1-10 alkyl unsubstituted or substituted by hydroxy or azido;

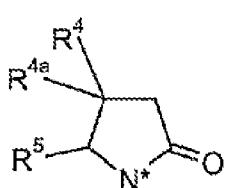
R7 is hydrogen; or R6 and R7 can be linked to form a cyclopropyl ; or R2 and R3

25      can form together with the imidazole ring the following 1H- benzimidazole cycle

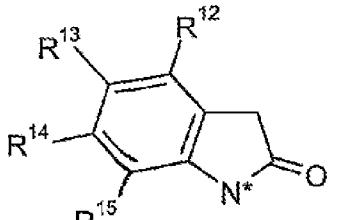


R8 is hydrogen; R9 is selected from hydrogen; halogen; C1-3 alkyl ; alkoxy ;

R10 is selected from hydrogen; halogen; cyano or C1-3 alkyl unsubstituted or substituted by halogens; or alkoxy ; R1 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

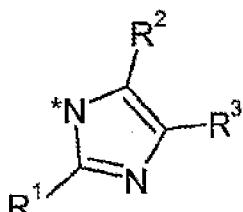


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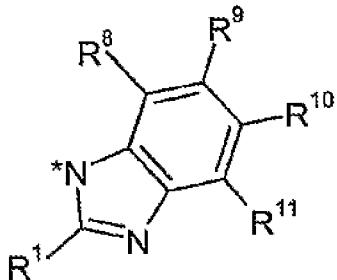
:

R12 is selected from hydrogen or halogen; R13 is selected from hydrogen; C1-3 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



10

represents a group of formula



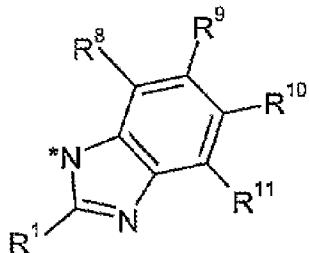
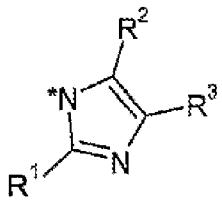
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In an embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

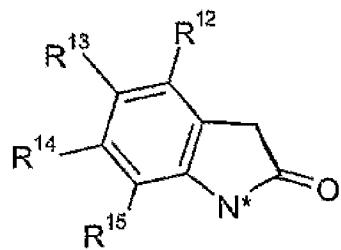
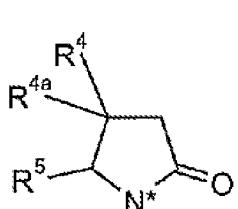
RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; cyclopropyl ; n-butyl; i-butyl; t-butyl; 1-ethylpropyl ; 2,4, 4-trimethylpentyl; trifluoromethyl; 2,2, 2-trifluoroethyl; hydroxymethyl; chloromethyl; cyanomethyl ; 2- (methylthio) ethyl; chloro; bromo; nitro; cyano ; amino; aminocarbonyl;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

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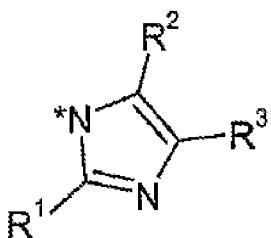
or 1H-imidazol-2-yl ; R2 is selected from hydrogen; methyl ; hydroxymethyl; (acetylamino) methyl; (propionylamino) methyl ; (benzoylamino) methyl; (benzyloxycarbonyl) amino; chloro; or cyano; R3 is selected from hydrogen; hydroxymethyl; chloro; cyano; or R2 and R3 can form together with the imidazole 5 ring the following 1H- benzimidazole cycle



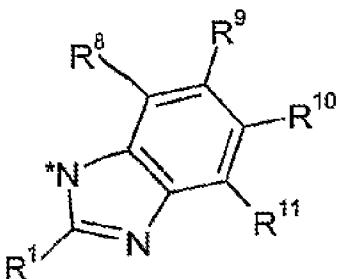
R8 is hydrogen; R9 is selected from hydrogen; methyl; chloro ; methoxy; R10 is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy; R is hydrogen; R4 is selected from hydrogen; n-propyl ; 2,2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 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. 10 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 20

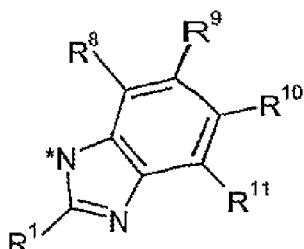
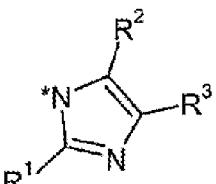


represents a group of formula



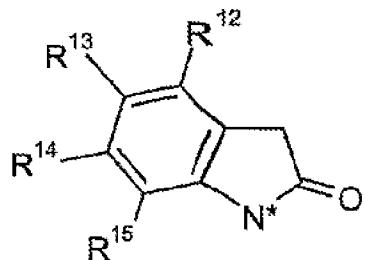
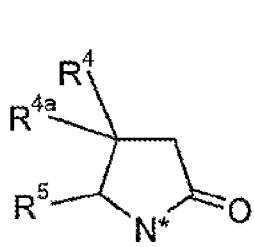
In one embodiment of the invention, the compounds of formula I, or  
5 pharmaceutically acceptable salt thereof, are those wherein  
RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl;  
methylthio; nitro; cyano ; amino; chloro ; or 1H-pyrrol-2-yl ; R2 is selected from  
hydrogen; chloro; cyano; R3 is selected from hydrogen; cyano; or R2 and R3 can  
form together with the imidazole ring the following 1H- benzimidazole cycle

10

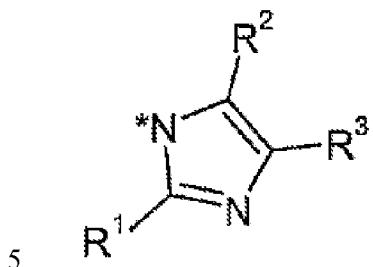


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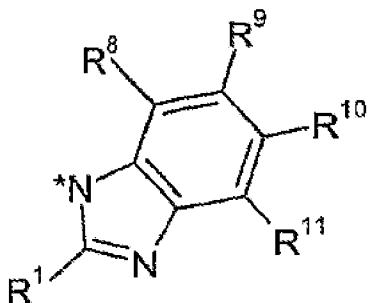
R8 is hydrogen; R9 is hydrogen;  
R10 is selected from hydrogen ; trifluoromethyl ; fluoro ; cyano;  
RI 1 is hydrogen; R4 is selected from hydrogen; n-propyl ; 2, 2-difluorovinyl ;  
phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3, 5-  
15 difluorophenyl ; 3,4- difluorophenyl ; 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  $R^{12}$  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

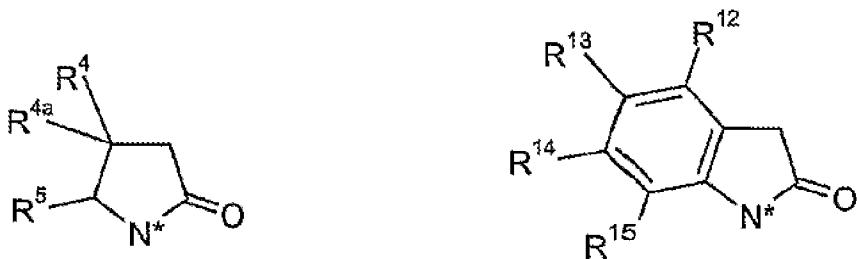


$R^{11}$  represents a group of formula



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

- 10  $R^1$  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;
- 15  $R^5$  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



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-(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]-4-propylpyrrolidin-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}-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- (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-carboxylate ; 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) pyrrolidin-1-yl] methyl}-1H-imidazole-4-carbonitrile ; (-)-1- {[2-oxo-4-(2, 3,4-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-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-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-(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-4-carbonitrile ; 1- {[2-oxo-4-(2, 3, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-1H-imidazole-4-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; (+)-1-1 [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-ylcarbamate ; 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 (1-1 [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-one ; 1- {[2-oxo-4-propylpyrrolidin-1-yl] methyl}-1 H-benzimidazol-2- yl} acetonitrile ; 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-propylpyrrolidin-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-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-(1H-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-  
5 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)-1 H-  
10 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-  
15 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-1H- benzimidazol-1-yl) methyl]-4- propylpyrrolidin-2-one; 1- [(2-isopropyl-6-  
20 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-  
25 benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1- {[2- (1- ethylpropyl)-6- methoxy-1H-benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1- {[6- methoxy-2- (1-methyl-1H-pyrrol-2-yl)-1H-benzimidazol-1-yl] methyl}-4-  
30 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] methyl}pyrrolidin-2-one ; 1- {[2- (3-furyl)-5- (trifluoromethyl)-1H-benzimidazol-1- yl] methyl}-4-propylpyrrolidin-2-one ; 1- {[2-cyclopropyl-5- (trifluoromethyl)-1H- benzimidazol-1-yl] methyl}-4-  
35 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-carbonitrile.

In some embodiments, compounds are: 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]-4-propylpyrrolidin-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-(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; 1-1 (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 ; (+)-1-1 [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-carbonitrile.

In some embodiments, compounds are: 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-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; 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-difluoromethyl)-1- (1H-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-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 ; (+)-1-1 [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- carbonitrile.

Some compounds are: (-)-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.

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.

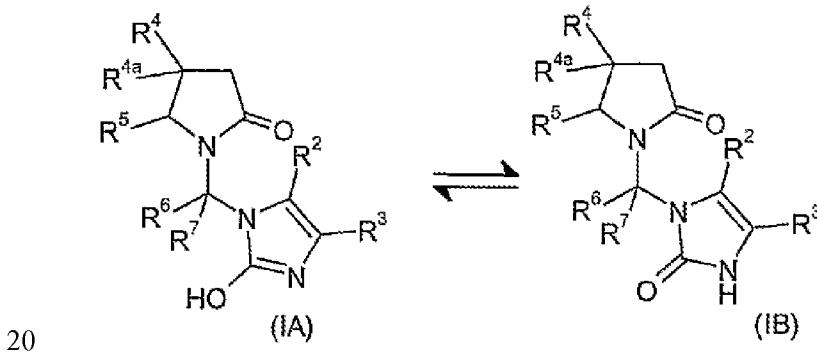
- 5 Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

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 10 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).

- 15 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



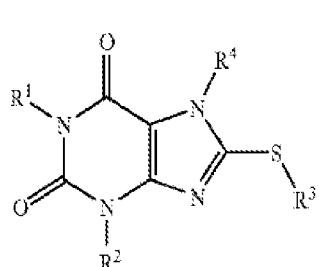
20 With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof, unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic 25 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 5 enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



wherein

- R1 is hydrogen or C1-6 alkyl;
- 10 R2 is hydrogen or C1-4 alkyl;
- R3 is a group of formula —CHR<sub>5</sub>R<sub>6</sub> or a benzyl group;
- R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle;
- R5 is C2-4 alkyl;
- 15 R6 is C2-4 alkyl, amido or —COOR<sub>7</sub>;
- R7 is C1-4 alkyl;

In one aspect, the invention provides compounds:

- When R1 is hydrogen, R2 is methyl, R3 is —CHR<sub>5</sub>R<sub>6</sub>, R6 is ethoxycarbonyl and R5 is ethyl, then R4 is different from methyl, n-propyl, i-propyl, n-pentyl, n-heptyl, 20 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;
- 25 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 5 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, alkoxy carbonyl, 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 10 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- 15 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 20 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 25 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, 30 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<sub>6</sub>H<sub>5</sub>.
- The term “benzyl group”, as used herein, represents a group of formula —CH<sub>2</sub>-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 —NH<sub>2</sub>.
- The term “ethynyl”, as used herein, represents a group of formula —C≡CH.
- The term “alkoxy”, as used herein, represents a group of formula —OR<sub>a</sub> wherein R<sub>a</sub> 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 —NO<sub>2</sub>.
- The term “amido”, as used herein, represents a group of formula —C(=O)NH<sub>2</sub>.
- The term “acyl”, as used herein, represents a group of formula —C(=O)R<sub>b</sub> wherein R<sub>b</sub> 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 —COOR<sub>c</sub> wherein R<sub>c</sub> is an alkyl group; with the proviso that R<sub>c</sub> does not represent an alkyl alpha-substituted by hydroxy. In some embodiments the alkoxy carbonyl 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<sub>1</sub>-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.

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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 10 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.

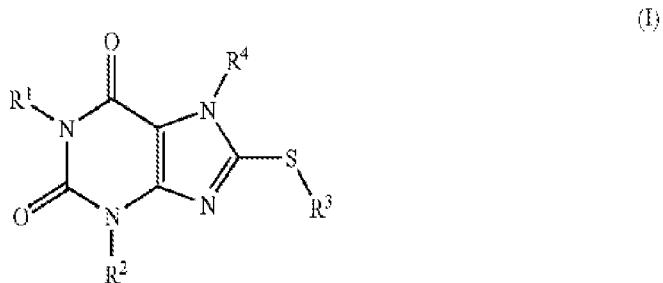
Generally R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 15 cycloalkyl, aryl or heterocycle. Usually R4 is C1-8 alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl. In some embodiments R4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3- 20 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- 25 (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 30 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 5 stereoisomers), or pharmaceutically acceptable salts thereof,



wherein

- R1 is hydrogen, C1-6 alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl;
- 10 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;
- 15 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.
- 20 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
- 25 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;
- 5 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 alkoxy carbonyl.
- 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.
- 10 In a more preferred embodiment, R1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl;
- R2 is methyl;
- 15 R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl;
- In a more preferred embodiment, R1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl;
- R2 is methyl;
- 20 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;
- 25 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;
- 30

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-(2-oxopropyl)-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-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; ethyl 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;

5 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.

10 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.

15 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,  
20 benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic  
and the like.

25 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.

30 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 5 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 10 (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 15 forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

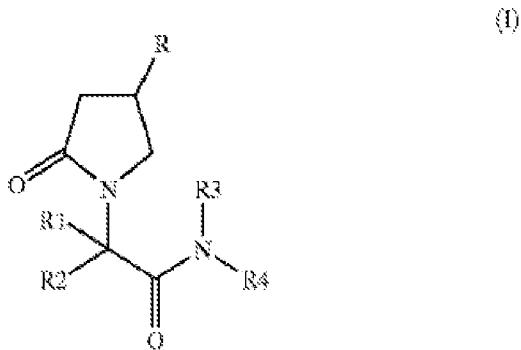
xiii) U.S. Patent 7,465,549

In some embodiments, the compound includes optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives. In some embodiments, those compounds are alkyl 20 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 30 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.

- 5 In some embodiments, the compounds include any acetam compound of formula I, in racemic or isomeric form, or a pharmaceutically acceptable salt thereof,

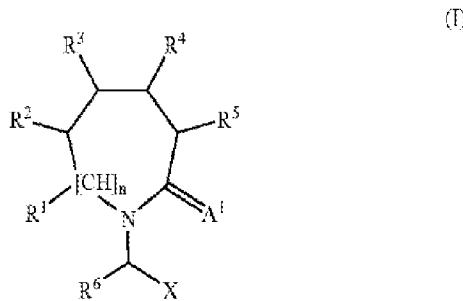


wherein

- R represents hydrogen or hydroxy;
- 10 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  $-(CH_2)_n-NR_5R_6$  wherein n is 1, 2 or 3 and R5 and R6 represent independently hydrogen or an alkyl group of 1-4 carbon atoms.
- 15 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.
- 20
- 25

xiv) U.S. Patent Application Publication No. 2006258704

This invention provides novel compounds of the formula I



wherein

- n represents 0 or 1 whereby R<1> is not existent when n=0 and R<1> is existent  
 5 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  
 10 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;
- 15 R<6> is hydrogen, alkyl, aryl or -CH<sub>2</sub>-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  
 20 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  
 25 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-1-pyrrolidinyl, 2-oxo-1-piperidinyl and azepanyl derivatives present at the N-terminus of 5 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.
- 10 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 15 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, alkynyoxy, acyloxy, oxyester, 20 oxyamido, alkylsulfonyloxy, alkylsulfinyloxy, arylsulfonyloxy, arylsulfinyloxy, aryloxy, aralkoxy or heterocycloxy such as pentyloxy, allyloxy, methoxy, ethoxy, phenoxy, benzyloxy, 2-naphthyoxy, 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. 25
- 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.
- 30 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, heterocycle and aryl. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, 5 nicotinoyl, 4-carboxybutanoyl, oxanyl, ethoxanyl, 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.
- 10 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 15 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 20 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).
- 25 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.
- 30 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 5 are methyl, ethyl, propyl, isopropyl, butyl, tertiobutyl, pentyl, cyclopropyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 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.
- 10 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.
- 15 In some embodiments are 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, 20 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 25 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, 30 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 5 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.
- 10 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, 15 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 20 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.
- 25 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<sub>2</sub>.
- The term "nitrooxy", as used herein, represents a group of the formula -ONO<sub>2</sub>.
- 30 The term "amino", as used herein, represents a group of the formula -NH<sub>2</sub>.
- The term "azido", as used herein, represents a group of the formula -N<sub>3</sub>.
- 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> 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)furan, 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, tetrahydrofuran, tetrahydropyran, 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 20 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 5 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.
- 10 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.
- 15 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 20 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.
- 25 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 30 included within the scope of the present invention.

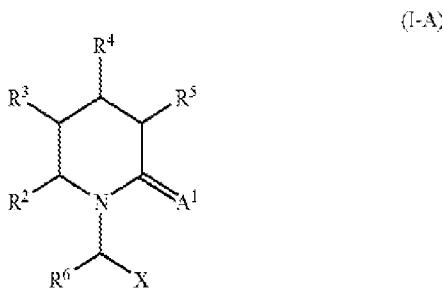
With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically. The invention also includes within its scope prodrug forms of 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.

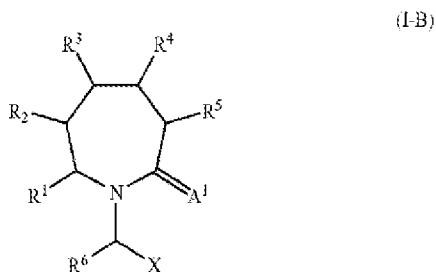
Such groups include moieties which are readily oxidised, cyclised or cleaved, which compound after biotransformation remains or becomes pharmacologically active. For example, metabolically cleavable groups form a class of groups well known to practitioners of the art. They include, but are not limited 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), alkoxy carbonyl (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).



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) 5 wherein R<1> is existent since n=1 and depicted by the formula (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. 10 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 15 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 20 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 CH<sub>2</sub>-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 -CH<sub>2</sub>-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 -COOCH<sub>3</sub> 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, alkylthio, cycloalkyl, acyl, aryl and heterocycle;

5 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;

10 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;

15 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.

20 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, alkylthio, cyclopropyl, acyl and phenyl;

25 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;

30 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 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 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.

10 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.

15 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-

20 [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-

25 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-

5 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-trifluoropropyl)-1-piperidinyl]butanamide, 2-14-(cyclopropylmethyl)-2-oxo-  
1-piperidinyl]butanamide, 2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide, 2-  
10 [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-  
15 [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-  
20 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-  
25 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-  
30 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-  
5 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-  
10 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-  
15 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-  
20 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-  
25 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-  
30 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-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-

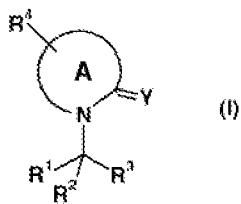
(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-4-propyl-1-azepanyl)butanamide, 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-[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-trifluoroethyl)-2-oxo-1-azepanyl]butanamide.

25 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,  
30 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:



wherein

Y is O or S. In some embodiments Y is O. R1 is hydrogen or C-<sub>1-6</sub> alkyl;

R2 is hydrogen;

- 5 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-<sub>1-6</sub> alkyl;
- R7 is C<<sub>1-6</sub> alkyl;
- A is a monocyclic or bicyclic heterocyclic moiety selected from the group
- 10 consisting of imidazolidin-1-yl, 1,3-oxazolidin-3-yl, 2,5-dihydro-1H-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-1H-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(1H)-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<sup>a</sup> or R<sup>b</sup> depending on whether A being is a monocyclic or a bicyclic heterocycle:
- where A is a monocyclic heterocyclic moiety, R<sup>a</sup> is R<sup>a</sup> which is selected from the group consisting of hydrogen; C-<sub>1-6</sub> alkyl optionally substituted by a substituent
- 15 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; alkoxycarbonyl amino; arylsulfonyloxy; a substituted or unsubstituted aryl; or a 3-8 membered substituted or unsubstituted heterocycle;
- where A is a bicyclic heterocyclic moiety R<sup>b</sup> is R<sup>b</sup> which is selected from the
- 20 group comprising or consisting of hydrogen; nitro; cyano; halogen; heterocycle; amino; aryl; C-<sub>1-6</sub> alkyl optionally substituted by at least one halogen; or C-<sub>1-6</sub> alkoxy optionally substituted by at least one halogen;
- In some embodiments the compounds are as follows:

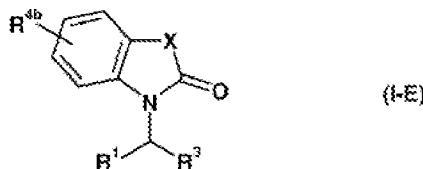
- For compounds where A=Y is selected from a 2-oxo-piperidin-1-yl, a 2-oxo-azepan-1-yl, a 2-oxo-1,3-benzothiazol-3(2H)-yl or a 2-oxo-1,3-benzoxazol-3(2H)-yl, R3 must be selected from an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl.
- 5 For compounds where A=Y is a 5-oxoimidazolidin-1-yl, R<sup>^</sup> and R<sup>^</sup> are hydrogen, R3 is -CONR5R6, R5 and R6 are as above defined, then R<sup>^a</sup> 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<sup>^</sup>, R<sup>^</sup> and R<sup>^a</sup> are all hydrogen, then R<sup>^</sup> could not be a 2-phenylimidazo[1,2-a]pyridin-3-yl.
- 10 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.
- 15 The asterisks in the above illustration indicate the attachment sites of the substituent R<sup>^a</sup>.
- In a specific embodiment, when R<sup>^</sup> is -CONR5R6 and R<sup>^</sup> is C- $\mu$ g alkyl, the carbon atom to which R-I and R<sup>^</sup> are attached is preferably in the "S"-configuration.

In a specific embodiment  $R^{\wedge}$  is hydrogen, methyl, ethyl and  $R^{\wedge}$  is hydrogen. In a specific embodiment  $R^3$  is -CONH<sub>2</sub>.

In a further specific embodiment  $R^{\wedge}$  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 5 specific embodiment  $R^{\wedge}a$  is a C- $\beta$ -alkyl which may optionally be substituted by a halogen; or a phenyl.

In another specific embodiment  $R^{\wedge}b$  is hydrogen, halogen, nitro, cyano or a C- $\mu$ g alkyl optionally substituted by a halogen.

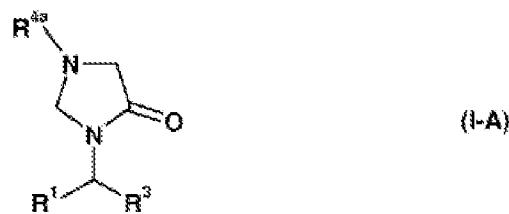
In still a further embodiment compounds may be used in the treatment of the above 10 mentioned disorders, in particular of epilepsy, having the formula (I-E), as well as its geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



wherein

15 X is O or S;  
 $R^1$  is hydrogen or C- $\beta$ -alkyl, in a more specific embodiment hydrogen;  
 $R^3$  is an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl;  $R^{\wedge}b$  is hydrogen; nitro; cyano; halogen; C- $\beta$ -alkyl optionally substituted by halogen; C- $\beta$ -alkoxy optionally substituted by halogen.

20 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,



wherein

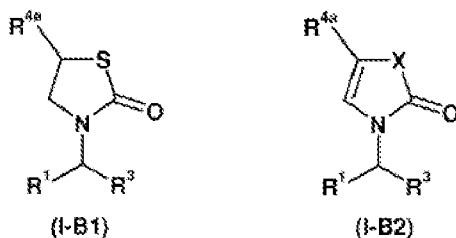
25  $R^1$  is hydrogen or C- $\beta$ -alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment  $R^{\wedge}$  is ethyl.

R<sup>3</sup> is -CONH<sub>2</sub>, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl, preferably R<sup>4</sup> is -CONH<sub>2</sub>.

R<sup>a</sup> is either hydrogen or an aryl; with the proviso that 2-(5-oxoimidazolidin-1-yl)acetamide is excluded. Preferably R<sup>a</sup> is an aryl, e.g. a phenyl which may be 5 substituted preferably by halogen, nitro, alkoxy, in particular by nitro.

In a particular embodiment, when R<sup>4</sup> is -CONH<sub>2</sub> and R<sup>4</sup> is C-<sub>1</sub>g alkyl, the carbon atom to which R<sup>1</sup> and R<sup>4</sup> 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 10 mixtures, or a pharmaceutically acceptable salt thereof,

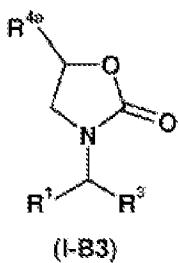


wherein X in formula (I-B2) is either S or O, in a more specific embodiment S; R<sup>1</sup> is hydrogen or C-<sub>1</sub>g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R<sup>4</sup> is ethyl.

15 R<sup>3</sup> is -CONH<sub>2</sub>, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; preferably R<sup>4</sup> is -CONH<sub>2</sub>  
R<sup>a</sup> is hydrogen; C-<sub>1</sub>g alkyl optionally substituted by halogen or C-1-4 alkoxy; an aryl; or C2-g alkenyl optionally substituted by halogen. Preferably, R<sup>a</sup> is C-<sub>1</sub>g 20 alkyl optionally substituted by halogen or C2-6 alkenyl optionally substituted by halogen or an aryl. In a more specific embodiment R<sup>a</sup> is C-<sub>1</sub>g alkyl optionally substituted by halogen or aryl.

In a particular embodiment, when R<sup>4</sup> is -CONH<sub>2</sub> and R<sup>4</sup> is C-<sub>1</sub>g alkyl, the carbon atom to which R<sup>1</sup> and R<sup>4</sup> are attached is preferably in the "S"-configuration.

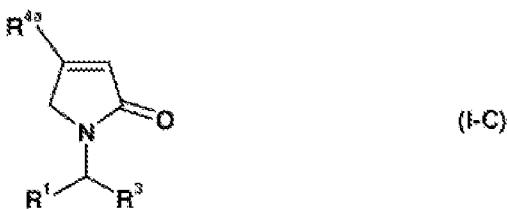
A further aspect of the present invention consists in novel compounds having the 25 formula (I-B3), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



wherein

R1 is either hydrogen or C- $\mu$ g alkyl, preferably hydrogen, methyl or ethyl; more preferably R1 is ethyl.

- 5 R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; preferably R $\wedge$  is -CONH2 R $\wedge$ a is C- $\mu$ 5 alkyl optionally substituted by halogen or C-1.4 alkoxy; an aryl; or C2-g alkenyl optionally substituted by halogen. Preferably, R $\wedge$ a is C- $\mu$ g alkyl optionally substituted by halogen or C2-g alkenyl optionally substituted by halogen.
- 10 In a particular embodiment, when R $\wedge$  is -CONH2 and R $\wedge$  is C- $\mu$ g alkyl, the carbon atom to which R-I and R $\wedge$  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,



15

wherein

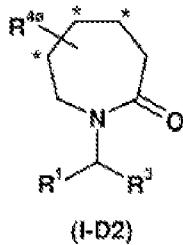
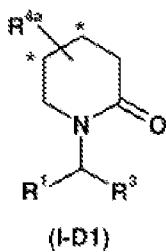
R1 is hydrogen or C- $\mu$ g alkyl, in particular hydrogen, methyl or ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in particular R $\wedge$  is -CONH2

- 20 R $\wedge$ 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- $\mu$ g alkyl optionally substituted by halogen or a C-1.4 alkoxy; or R $\wedge$ a is a C2-6 alkenyl optionally substituted by halogen. Preferably, R $\wedge$ a is methyl, optionally substituted by halogen, an unsubstituted phenyl or a phenyl substituted by halogen.

In a particular embodiment, when  $R^{\wedge}$  is  $-CONH_2$  and  $R^{\wedge}$  is C- $\beta$ -alkyl, the carbon atom to which  $R^1$  and  $R^{\beta}$  are attached is preferably in the "S"-configuration.

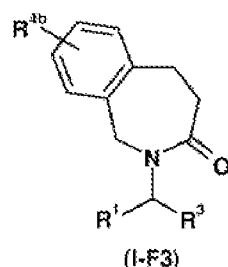
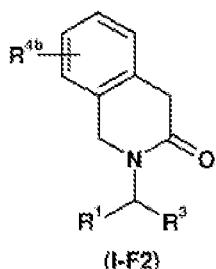
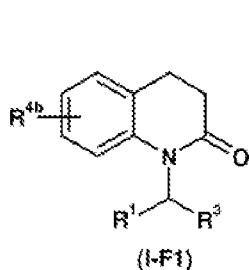
A further aspect of the present invention consists in compounds having the formula (I-D1 or I-D2), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



wherein

$R^1$  is hydrogen or C- $\beta$ -alkyl, in particular hydrogen;  $R^3$  is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl. In one embodiment,  $R^{\wedge}$  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,  $R^{\wedge}$  is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1,2-a]pyridin-3-yl;  $R^{\wedge}a$  is hydrogen, C- $\beta$ -alkyl optionally substituted by halogen or C-1,4 alkoxy; aryl; or C2- $\beta$  alkenyl optionally substituted by halogen. In a specific embodiment,  $R^{\wedge}a$  is C- $\beta$ -alkyl optionally substituted by halogen; aryl; or C2-6 alkenyl optionally substituted by halogen. In a more specific embodiment  $R^{\wedge}a$  is C- $\beta$ -alkyl optionally substituted by halogen; or aryl; e.g., propyl or phenyl; with the proviso that when  $R^{\wedge}$  and  $R^{\wedge}a$  are hydrogen,  $R^{\wedge}$  is not 2-phenylimidazo[1,2-a]pyridin-3-yl.

20 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,



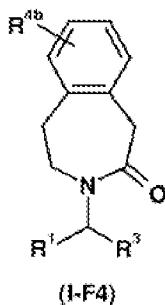
wherein

R-I is hydrogen or C-*l*.g alkyl, preferably hydrogen, methyl or ethyl; more preferably, R<sup>^</sup> 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<sup>^b</sup> 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<sup>^</sup> is hydrogen, halogen or cyano, more specifically halogen.

In a particular embodiment, when R<sup>^</sup> is -CONH2 and R<sup>^</sup> is C-*l*.g alkyl, the carbon atom to which R1 and R $\beta$  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,



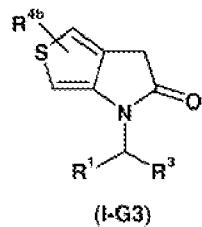
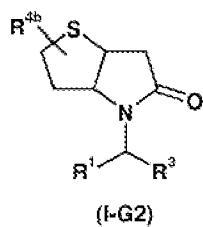
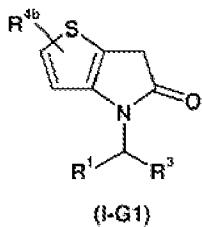
15 wherein

R-I is hydrogen or C-*l*.g alkyl, preferably hydrogen; R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl; more specifically R<sup>^</sup> 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<sup>^</sup> is 1 H-imidazol-4-yl or imidazo[1 ,2- a]pyridin-3-yl.

R<sup>^b</sup> is hydrogen; halogen; nitro; cyano; C-1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen; specifically R<sup>^</sup> is hydrogen, halogen or cyano.,

In a particular embodiment, when R<sup>^</sup> is -CONH2 and R<sup>^</sup> is C-*l*.g alkyl, the carbon atom to which R-I and R<sup>^</sup> 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,



5 wherein

R-I is hydrogen or C-1-4 alkyl; preferably hydrogen;

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in a more specific embodiment R<sup>3</sup> 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 10 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 15 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-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-OXO-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; 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; 1-5 (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.
- 15 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- $\beta$  alkyl” refers to alkyl groups having 1 to 6, or 1 to 4 carbon atoms. This 20 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.
- 25 “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 30 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-zoly1, 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, phthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-5]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=CH<sub>2</sub>), n-2-propenyl (allyl, -CH<sub>2</sub>CH=CH<sub>2</sub>) 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 (-CH<sub>2</sub>C≡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-1.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-1.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-<sub>1-5</sub> 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.

5 “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-<sub>1-5</sub> alkyl”, “C2-6 alkenyl”, “C2-6 alkynyl”, “C3.8 cycloalkyl”, “heterocycloalkyl”, “aryl” or “heteroaryl”.

10 “Sulfinyl” refers to the group -S(=O)R where R is “C-<sub>1-5</sub> 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-<sub>1-5</sub> alkyl”, “C2-6 alkenyl”, “C2-6 alkynyl”, “C3.8 cycloalkyl”, “heterocycloalkyl”, “aryl” or “heteroaryl”.

15 “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

20 “heteroaryl” etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of “C-<sub>1-5</sub> alkyl”, “C2-6 alkenyl”, “C2-6 alkynyl”, “cycloalkyl”, “heterocycloalkyl”, “amino”, “amido”, “acylamino”, “ureido”, “aryl”, “heteroaryl”, “alkoxy”, “halogen”, cyano, hydroxy, mercapto, nitro,

25 “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,

30 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.

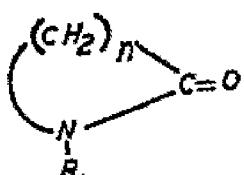
Some of the compounds of formula (I) may also exist in tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

The invention also includes within its scope pro-drug forms of the compounds of formula (I) and its various sub-scopes and sub-groups.

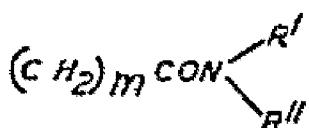
In a specific embodiment, the present invention concerns a compound selected from the group consisting of: (2S)-2-[3-(4-nitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-[3-(2,4-dinitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-(5-oxo-3- phenylimidazolidin-1 -yl)butanamide; 2-[5-(iodomethyl)-2-oxo-1,3-oxazolidin-3- 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-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- 5 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- 20 20 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  
25 of the general formula:



wherein N is a whole number of from 3 to 5 and R represents a

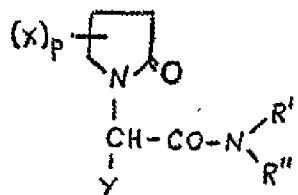


radical in which m is 0, 1 or 2 and R' is a hydrogen atom or an alkyl, cycloalkyl, alkenyl or alkynyl radical, which may contain 3 to 6 carbon atoms, or an aryl radical, and R'' is a hydrogen atom or an alkyl radical, or both R' and R'', together with the nitrogen atom to which they are attached, form a heterocyclic ring, such as

5 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:



10 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 15 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.

### Acetylcholinesterase Inhibitor

20 [0181] Among the AChEIs useful for the methods and compositions this invention are the following:  
 zanapezil, ganstigmine, phenethylnorcymserine (PENC), cymserine, thiacymserine, SPH 1371 (galantamine plus), ER 127528, RS 1259, F3796, tetrahydroaminoacridine, DFP (diisopropylfluorophosphate), Ladostigil, Memoquin, SP-004, BGC-20-1259, NP-0361, ZT-1, INM-176, pyridostigmine, ambenonium, demarcarium, edrophonium, pralidoxime, Amirine, SW-10888, MF-217, Ro 45-5934, HP-290, ENA 713, CP 118.954, ONO 1603, eptastigmine, extract of magnolia, for example, magnolol, honokiol, taspine and asimilobine,

alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, moexipril, moveltipril, omapatrilat, perindopril, quinapril, ramipril, sampatrilat, spirapril, temocapril, trandolapril, piperidinyl-alkanoyl heterocyclic compounds, N-benzyl-piperidine derivatives, 4-  
5 (1-benzylpiperidyl)-substituted fused quinoline derivatives, monoamine acridines and their derivatives, cyclic amide derivatives, carbonic acid derivatives, saliclate, obidoxime, trimedoxime, diacetyl monoxim, demecarium, icopezil (5,7-dihydro-3-(2-(1-(phenylmethyl)-4-piperidinyl)ethyl)-6H-pyrrolo(3,2-f)-1,2-benzisoxazol-6-one), heptylphysostigmine, E-2020, Citicoline, velnacrine maleate, sulfonyl  
10 fluorides such as methanesulfonyl fluoride (Moos and Hershenson, 1989) and phenylmethylsulfonyl fluoride (Ferris, 1990; Pope and Padilla, 1990), huperzine B, miotine, suronacrine and its maleate, 7-methoxytacrine, SM-10888 and its citrate, ENA-713, TAK-147, CP-118954, zifrosilone, (SR, 9R)-5-(r-chloro-2-hydroxy-3-methoxybenzylidene-amino)-11-ethlidene-7-methyl-1, 2,5, 6,9, 10-hexahydro-5,9-  
15 methanocycloocta [b] pyridin-2-one (ZT 1), stacofylline, SPH 1371, SPH 1373 and SPH 1375, tolserine, 1-(3-fluorobenzyl)-4-[(2-fluoro-5,6-dimethoxy-1- indanone-2-yl) methyl] piperidine hydrochloride (ER 127528), thiatolserine, (-)-12-amino-3-chloro-9-ethyl-6,7, 10, 11-tetrahydro-7, 11-methanocycloocta [b] quinoline hydrochloride (huperine X), N, N-dimethylcarbamic acid 4- [1 (S)- (methylamino)-  
20 3- (4- nitrophenoxy) propyl] phenyl ester hemifumarate (RS 1259), 2- [2- (1-benzylpiperidin-4-yl) ethyl] -2,3-dihydro-9- methoxy-1H-pyrrolo [3, 4-b] quinolin-1-one hemifumerate (T 82), 1,3-dichloro- 6,7, 8,9, 10,12-  
hexahydroazepino [2, 1-b]-quinazoline (CI 1002), N-heptylcarbamic acid, 2,4a, 9-trimethyl-2,3, 4,4a, 9, 9a-hexahydro-1, 2-oxazino [6, 5-b] indol-6-yl ester-  
25 L-tartrate (CHF 2060), 3-(2-[1-(1, 3-dioxolan-2-ylmethyl) piperidin-4-yl] ethyl)-3, 4-dihydro-2H-1, 3benzoxazine-2,4-dione hydrochloride (E 2030), N- [10-  
(diethylamino) decyl] carbamic acid (3aS, 8aR)-1, 3a, 8-trimethyl-1, 2,3, 3a, 8,8a-  
hexahydropsyrrolo [2,3-b] indol-5-yl ester (MF 247), 5-amino-6-chloro-4-hydroxy-  
3, 4-dihydro-1H-thiopyrano- [3, 4-b] quinoline (MF 8615), N- [8- (cis-2, 6-  
30 dimethylmorpholin-4-yl) octyl] carbamic acid (3aS, 8aR)-1, 3a, 8trimethyl-1, 2,3, 3a, 8, 8a-hexahydropsyrrolo [2,3-b] indol-5-yl ester L-bitartrate hydrate (MF 268),

(-) N- (3-piperidinopropyl)-N-demethylgalantamine (SPH 1286), N-propargyl-3Raminoidan-5-yl-ethyl methyl carbamate (TV 3326), cryptotanshinone, dihydrotanshinone I, and tanshinone I.

- 5 [0182] Among the acetylcholinesterase inhibitors useful for the methods and compositions of this invention are those compounds or agents as referred to in:
- i) U.S. Patent Application Publication No. 20080103105
- In one embodiment, an AChE is metrifonate, which is also known as metriphonate or trichlorfon or its active metabolite, 2,2-dimethyldichlorovinyl phosphate (or 10 dichlorvos or DDVP). Metrifonate is represented by the following formula:
- $$(\text{CH}_3\text{O})_2\text{—PO—CHOH—OCl}_3$$
.
- Echothiophate is also known as echothiopate, echothiophate iodide, phospholine iodide, (2-Mercaptoethyl)trimethylammonium S-ester with O,O'-diethylphosphorothioate, BRN 1794025, ecothiopatum, or phospholine.
- 15 Echothiophate is referenced by CAS Registry Number 6736-03-4.
- In other embodiments, an ACHE inhibitor is an aminoacridine such as tacrine or ipidacrine as non-limiting examples. Tacrine/COGNEX® (1,2,3,4-tetrahydro-9-aminoacridine hydrochloride) is also known as tetrahydroaminoacridine or THA. Tacrine is referenced by CAS Registry Number 321-64-2. Ipidacrine is also known 20 as Amiridin.
- In additional embodiments, an AChE inhibitor is a carbamate such as physostigmine, neostigmine, or rivastigmine as non-limiting examples.
- Physostigmine, also known as 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester) or (3aS,8aR)-pyrrolo[2,3-b]indol-5-ol, is referenced by 25 CAS number 57-47-6. It is a tertiary amine capable of crossing the blood-brain barrier.
- Neostigmine, or m-hydroxyphenyl)trimethyl-dimethylcarbamate(ester) ammonium, is referenced by CAS number 59-99-4.
- Rivastigmine is also known as rivastigmine tartrate or (S)—N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate or SDZ 30 ENA 713 or ENA 713. The reference for rivastigmine is CAS Registry Number 123441-03-2.

In further embodiments, an AChE inhibitor is a carbamate phenanthrine derivative such as galantamine or its hydrogen bromide form as non-limiting examples.

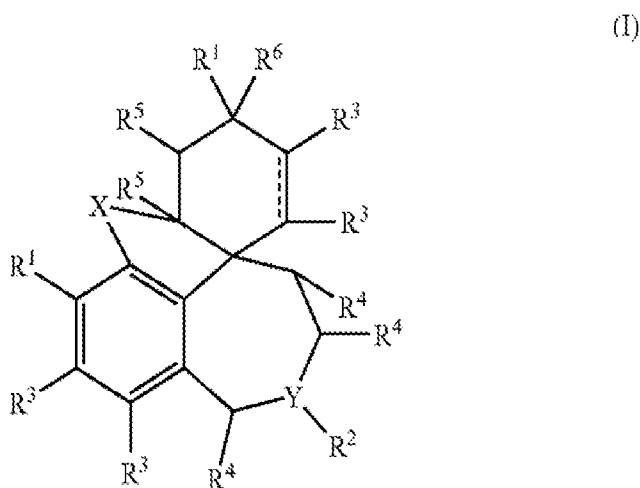
Galantamine is also known as (4aS,6R,8aS)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro(3a,3,2-ef)(2)benzazepin-6-ol and is often used 5 in its hydrogen bromide form. Galantamine is referenced by CAS number 357-70-0.

An AChE inhibitor may also be a piperidine derivative, such as donepezil as a non-limiting example. Donepezil is also known as 2,3-dihydro-5,6-dimethoxy-2-((1-(phenylmethyl)-4-piperidinyl)methyl)-1H-inden-1-one, and is referenced by CAS 10 number 120014-06-4.

15 Itopride may also be an AChE inhibitor for use in embodiments disclosed herein. Itopride HCl is referenced by CAS Registry Number 122898-67-3. In one embodiment, a total daily dose range for itopride HCl is from about 25 mg to about 1000 mg, or between about 100 mg to about 300 mg. In some embodiments, the AChE inhibitor, or neurogenic agent, is the N-oxide derivative of itopride, which is 15 the primary human metabolite of itopride HCl.

Another AChE inhibitor for use in the disclosed embodiments is (−)-huperzine A, which is also referred to as HupA and 1-amino-13-ethylidene-11-methyl-6-aza-tricyclo[7.3.1.02,7]trideca-2(7),3,10-trien-5-one. It is referenced by CAS number 20 102518-79-6.

A further embodiment of an ACHE inhibitor is phenserine, the structure and synthesis of which is described in U.S. Pat. No. 6,495,700. Although galantamine is only an example of an acetylcholinesterase inhibitor for use in the present invention, other acetylcholinesterase inhibitors may equally be 25 used. Examples of such compounds include galantamine derivatives, such as those compounds of formula (I):



in which:

the dotted line indicates that there is a single or double carbon-carbon bond;

the two symbols R1 are the same as or different from each other and each

5 represents a hydrogen atom, a hydroxy group, an alkyl group, an aryl group, an aralkyl group, a hydroxyalkyl group, a thioalkyl group, a carboxyalkyl group, a carboxyalkylamino group, an alkylamino group, an acyl group, a cyano group, a sulphhydryl group, a C1-C6 alkoxy group, an alkylthio group, an aryloxy group, an arylthio group, an aliphatic or aromatic carbamoyl group, an aralkoxy group, an

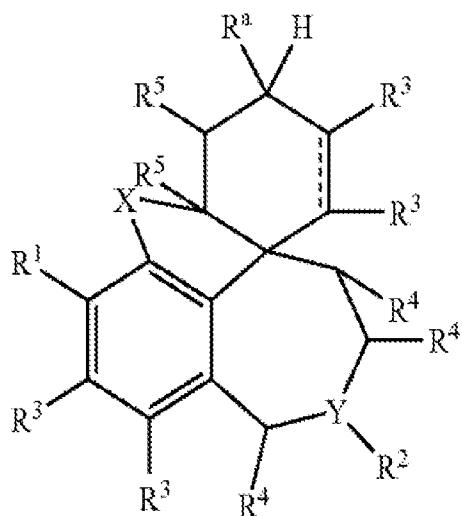
10 aralkylthio group, an aryloxymethyl group, an alkanoyloxy group, a hydroxyalkanoyloxy group, a benzoxyloxy group, a benzoxyloxy group substituted by one or more groups R3, as defined below, or an aryloxycarbonyl group;

R2 represents a hydrogen atom, a C1-C6 alkyl group, a C2-C6 alkenyl group (e.g. an allyl group), an aralkyl group, said alkyl, alkenyl and aralkyl groups being

15 unsubstituted or being substituted by at least one halogen atom, a cycloalkyl group, a hydroxy group, an alkoxy group, a nitro group, an amino group, an aminoalkyl group, an acylamino group, an aromatic or non-aromatic heterocyclic group (e.g. an  $\alpha$  - or  $\beta$ -furyl group, an  $\alpha$  - or  $\beta$ -thienyl group, an  $\alpha$  - or  $\beta$ -thenyl group, a pyridyl group, a pyrazinyl group, or a pyrimidyl group), an alkyl group substituted by an aromatic heterocyclic group, an aryl group (e.g. a phenyl group), an aralkyl group, a cyano group, an aroyl group, or a cycloalkylmethyl group;

20 the symbols R3 are the same as or different from each other and each represents a hydrogen atom, a hydroxy group, an alkyl group, an aryl group, an aralkyl group, a hydroxyalkyl group, a thioalkyl group, a sulphhydryl group, a C1-C6 alkoxy

group, an aryloxy group, an arylthio group, an aralkoxy group, an aralkylthio group, a nitro group, an amino group, an alkylamino group, an arylamino group, an aralkylamino group, a halogen atom or a trifluoromethyl group; the symbols R4 are the same as or different from each other and each represents a 5 hydrogen atom, a halogen atom, a trifluoromethyl group, or a C1-C4 alkyl group; the two symbols R5 are the same as or different from each other and each represents a hydrogen atom, or a hydroxymethyl group; R6 represents a hydrogen atom or a C1-C6 alkyl group, or, when the symbol R1 attached to the same carbon atom as R6 represents a hydrogen atom, R6 represents 10 a group of formula (Ia):



where Ra represents a linking bond, and R1, R2, R3, R4, R5, X and Y are as defined for formula (I); or R6 and the symbol R1 attached to the same carbon atom as R6 together 15 represent a semicarbazone; X represents an oxygen atom or a group of formula —NR3, where R3 is as defined above; Y represents a nitrogen atom or a phosphorus atom; and pharmaceutically acceptable salts thereof. 20 In the compounds of formula (I) above, except where otherwise indicated, alkyl groups may be straight or branched chain and preferably have from 1 to 10 carbon atoms, and examples of these include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl groups.

Alkoxy groups and other simple derivatives of the alkyl groups likewise preferably have from 1 to 10, more preferably from 1 to 6, carbon atoms.

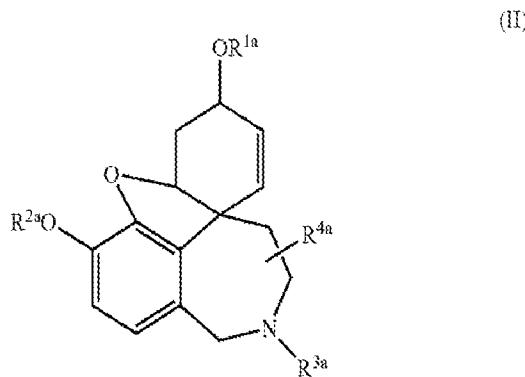
Aryl and heterocyclic groups may be unsubstituted or they may be substituted by one or more substituents selected from the groups and atoms defined for R3,

- 5 provided that any R3 substituent may not itself be further substituted by a substituted aryl or heterocyclic group.

Preferred halogen atoms are the fluorine, chlorine, bromine and iodine atoms.

- Preferred compounds of formula (I) are those in which the alkyl groups contain from 1 to 8, more preferably from 1 to 6, carbon atoms, halogen atoms are fluorine, 10 chlorine or bromine atoms, aryl groups are the phenyl group (which may be substituted or unsubstituted, preferably unsubstituted), cycloalkyl groups contain from 3 to 7 ring carbon atoms (preferably cyclopropyl or cyclobutyl), acyl groups are lower (e.g. C2-C6 alkanoyl groups) and heterocyclic groups are aromatic and contain from 5 to 8 ring atoms (e.g. the thienyl, furyl, pyridyl, pyrrolyl or pyrazinyl 15 groups).

Particularly preferred compounds for use in the present invention are those compounds of formula (II):



where:

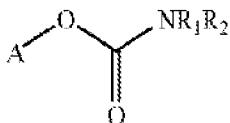
- 20 R1a and R2a are the same as or different from each other and each represents a hydrogen atom, an acyl group (preferably a lower alkanoyl group, such as an acetyl group) or a C1-C6 alkyl group (such as a methyl, ethyl, propyl or isopropyl group); R3a represents an alkyl, alkenyl or aralkyl group, any of which may be unsubstituted or substituted by one or more halogen atoms, or it represents a 25 cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, aromatic heterocyclic, aroyl, aroylalkyl or cyano group; and

R4a represents a hydrogen or halogen atom;  
 and pharmaceutically acceptable salts thereof, especially the hydrobromide,  
 hydrochloride, methylsulphonate or methiodide.  
 Of these compounds, we particularly prefer galantamine and its salts or donepezil  
 5 and its salts, especially the halides, such as galantamine hydrobromide or donepezil  
 hydrochloride.  
 Galantamine derivatives which may be used in the present invention include  
 norgalantamine, norgalantamine derivatives and epigalantamine.  
 Other compounds which may be used as the acetylcholinesterase inhibitor include:  
 10 physostigmine, tacrine and tacrine analogues, fasciculin, metrifonate, heptyl-  
 physostigmine, norpyridostigmine, norneostigmine, neostigmine, pyridostigmine,  
 huperzine or a prodrug therefor, rivastigmine or a prodrug therefor, gossypol or  
 phenserine, or a prodrug therefor.  
 Another particularly preferred acetylcholinesterase inhibitor is donepezil and its  
 15 salts, especially the halides, such as donepezil hydrochloride.

ii) U.S. Patent Application Publication No. 20070275959

In one embodiment, the invention is a carbamoyl ester having the following  
 structure:

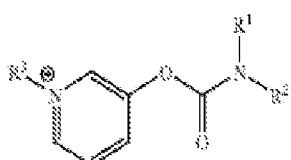
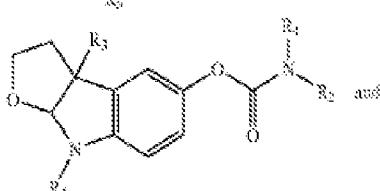
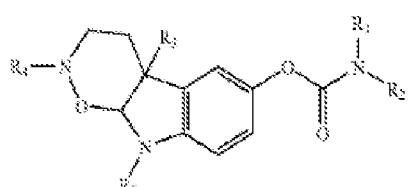
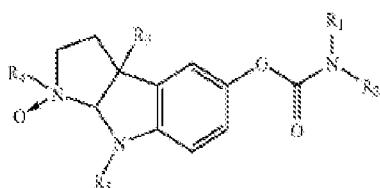
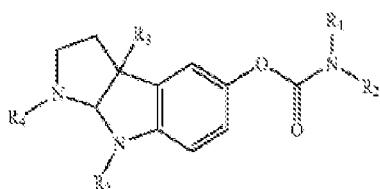
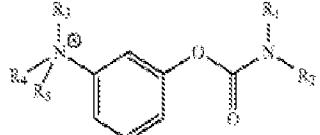
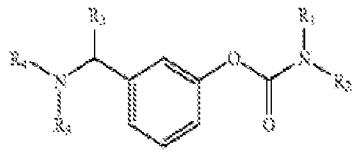
20



25

wherein A is selected from the group consisting of an unsubstituted aryl, a  
 substituted aryl, an unsubstituted heteroaryl and a substituted heteroaryl; and R1  
 and R2 are each, independently or in combination, selected from the group  
 consisting of a hydrogen, an unsubstituted alkyl, a substituted alkyl, an  
 unsubstituted aralkyl, a substituted aralkyl, an unsubstituted heteroalkyl, a  
 substituted heteroalkyl, an unsubstituted heteroaralkyl, a substituted heteroaralkyl,  
 an unsubstituted aryl, a substituted aryl, an unsubstituted heteroaryl, a substituted  
 heteroaryl, an unsubstituted cycloalkyl, a substituted cycloalkyl, an unsubstituted  
 heterocycloalkyl and a substituted heterocycloalkyl.

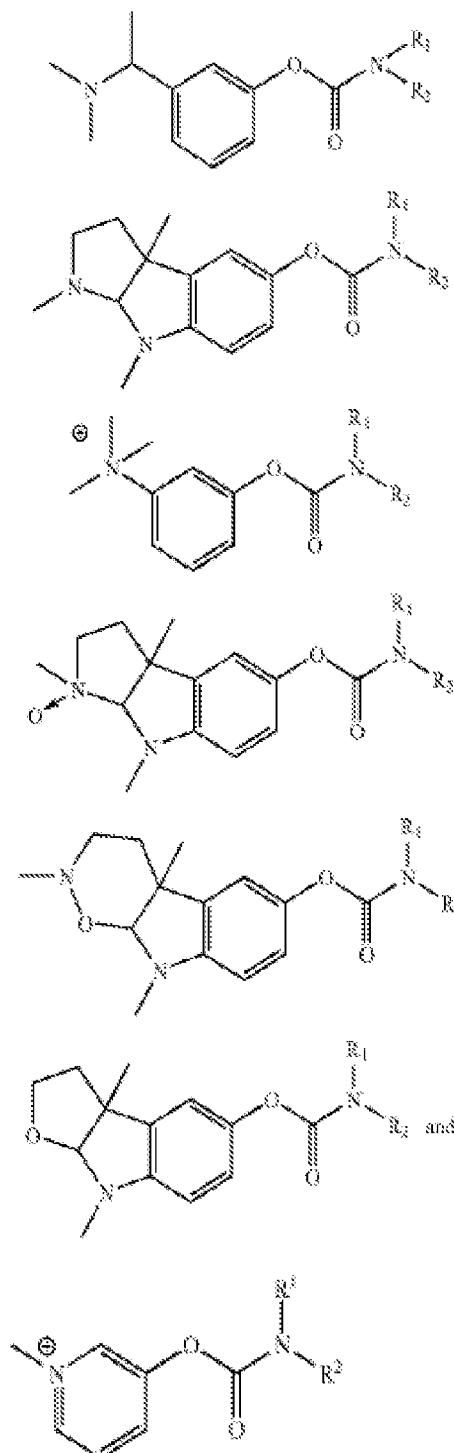
In an additional embodiment, the invention is a carbamoyl ester selected from the group consisting of:



- 5 wherein R3, R4 and R5 are each, independently or in combination, selected from the group consisting of a hydrogen, an unsubstituted alkyl, a substituted alkyl, an unsubstituted aralkyl, a substituted aralkyl, an unsubstituted heteroalkyl, a substituted heteroalkyl, an unsubstituted heteroaralkyl, a substituted heteroaralkyl,

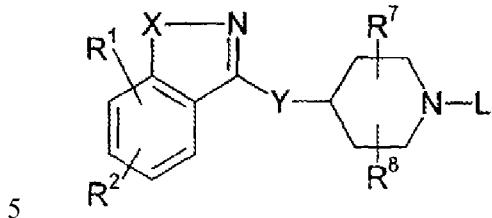
an unsubstituted aryl, a substituted aryl, an unsubstituted heteroaryl, a substituted heteroaryl, an unsubstituted cycloalkyl, a substituted cycloalkyl, an unsubstituted heterocycloalkyl and a substituted heterocycloalkyl.

In still another embodiment, the invention is a carbamoyl ester selected from the 5 group consisting of:



iii) European Patent Application No. EP1050303

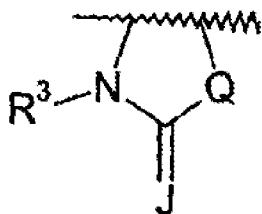
In some embodiments of the invention, the acetylcholinesterase inhibitor is a compound of Formula 1:



wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of hydrogen; (C1-C6) alkoxy; benzyloxy; phenoxy; hydroxy; phenyl; benzyl; halo; nitro; cyano; -COR<sup>5</sup>; -COOR<sup>5</sup>; -CONHR<sup>5</sup>; -NR<sup>5</sup>R<sup>6</sup>; -NR<sup>5</sup>COR<sup>6</sup>; -OCONR<sup>5</sup>R<sup>6</sup>; -NHCOOR<sup>5</sup>; (C1-C6) alkyl which may be substituted with from 1 to 3 fluorine atoms; SOpCH<sub>2</sub>-phenyl or SOp(C1-C6) alkyl, wherein p is 0, 1 or 2; pyridylmethoxy or thienylmethoxy; 2-oxazolyl; 2-thiazolyl; and benzenesulfonamide; wherein the phenyl moieties of said phenoxy, benzyloxy, phenyl, benzyl and benzenesulfonamide groups, the pyridyl and thienyl moieties of said pyridylmethoxy or thienylmethoxy groups, and the oxazolyl and thiazolyl moieties of said 2-oxazolyl and 2-thiazolyl groups may be substituted with 1 or 2 substituents independently selected from the group consisting of halo, (C1-C4) alkyl, trifluoromethyl, (C1-C4) alkoxy, cyano, nitro and hydroxy;

10 or R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms and form, together with the carbon atoms to which they are attached, a group of Formula 2:

20



wherein R<sup>3</sup> is hydrogen or (C1-C6) alkyl; J is oxygen, sulfur or NR<sup>4</sup>; R<sup>4</sup> is hydrogen or (C1-C4) alkyl; and Q is oxygen, sulfur, NH, CHCH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>, -CH=CH-, or (CH<sub>2</sub>)<sub>I</sub> wherein I is an integer from 1 to 3;

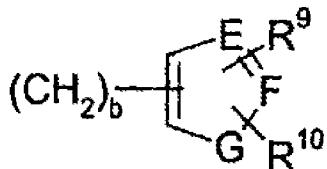
25 X is oxygen or sulfur;

Y is  $-(CH_2)m$ -,  $-CH=CH(CH_2)n$ -,  $-NR<4>CH_2m$ -, or  $-O(CH_2)m$ -, wherein n is an integer from 0 to 3, and m is an integer from 1 to 3;

5 R<sup>5</sup> and R<sup>6</sup> are each independently selected from the group consisting of hydrogen, (C1-C6) alkyl, phenyl, and benzyl, wherein the phenyl moieties of said phenyl and benzyl groups may be substituted with 1 or 2 substituents independently selected from the group consisting of fluoro, chloro, bromo, iodo, (C1-C4) alkyl, trifluoromethyl, (C1-C4) alkoxy, cyano, nitro and hydroxy; or NR<sup>5</sup>R<sup>6</sup> together form a 4 or 5 membered ring wherein one atom of the ring is nitrogen and the others are carbon, oxygen or nitrogen; or NR<sup>5</sup>COR<sup>6</sup> together form a 4 or 5

10 membered lactam ring;

L is phenyl, phenyl-(C1-C6) alkyl, cinnamyl or pyridylmethyl, wherein the phenyl moieties of said phenyl and phenyl-(C1-C6) alkyl may be substituted with 1 to 3 substituents independently selected from the group consisting of (C1-C6) alkyl, (C1-C6) alkoxy, (C1-C4) alkoxy carbonyl, (C1-C6) alkyl carbonyl, -OCONR<sup>5</sup>R<sup>6</sup>, -NHCOOR<sup>5</sup>, and halo; or L is a group of Formula 3:



wherein b is an integer from 1 to 4; R<sup>9</sup> and R<sup>10</sup> are independently selected from the group consisting of hydrogen, (C1-C4) alkyl, halo, and phenyl; E and F are independently -CH- or nitrogen; and G is oxygen, sulfur or NR<sup>4</sup>, with the proviso that when E and F are both nitrogen, one of R<sup>9</sup> and R<sup>10</sup> is absent; and

20 R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) alkoxy carbonyl, (C1-C6) alkyl carbonyl, and (C1-C6) alkoxy, with the proviso that said (C1-C6) alkoxy is not attached to a carbon that is adjacent to a nitrogen;

25 or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments of the invention, the compound of Formula 1 is selected from the group consisting of:

30 5,7-dihydro-7-methyl-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]1,2-benzisoxazol-6-one;

- 5,7-dihydro-7-ethyl-3-[2[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;
- 5,7-dihydro-3-[2-[1-(2-chloro-5-thiophenemethyl)-4-piperidinyl]ethyl]6H-pyrrolo[4,5-f]-1,2-benzisoxazal-6-one;
- 5 5,7-dihydro-3-[2-[1-(2-methyl-4-thiazolemethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;
- 3-[2-[1-(3-bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;
- 10 3-[2-[1-(4-bromophenylmethyl)-4-piperidinyl]ethyl]-5,7-dihydro-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;
- 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]propyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;
- 6,8-dihydro-3-[2-[1-(phenylmethyl)-4-piperidinyl]ethyl]-7H-pyrrolo[5,4-g]-1,2-benzisoxazal-7-one; and
- 15 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one;
- In some embodiments of the invention, the compound of Formula 1 is 5,7-dihydro-3-[3-[1-(phenylmethyl)-4-piperidinyl]ethyl]-6H-pyrrolo[4,5-f]-1,2-benzisoxazol-6-one.
- 20
- iv) International Patent Application Publication No. WO2000/030446
- a) An acetylcholinesterase inhibitor selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein the methoxy group thereof is replaced by another alkoxy group of from one to six carbon atoms,
- 25 a hydroxy group, hydrogen, an alkanoyloxy group, a benzyloxy or substituted benzyloxy group, a carbonate group or a carbamate group.
- b) An acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six
- 30 carbon atoms, hydrogen, an alkanoyloxy group, a benzyloxy or substituted benzyloxy group, a carbonate group or a carbamate group.

- c) An acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the N-methyl group of galanthamine or lycoramine is replaced by hydrogen, alkyl, benzyl or a cyclopropylmethyl group or a substituted or unsubstituted benzyloxy group.
- 5 d) An acetylcholinesterase inhibitor as in a) selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.
- e) An acetylcholinesterase inhibitor as in a) wherein said acetylcholinesterase
- 10 inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms
- f) An acetylcholinesterase inhibitor as in e) wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms
- 15 g) An acetylcholinesterase inhibitor as in a) wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.
- 20 h) An acetylcholinesterase inhibitor as in f) wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms.
- i) An acetylcholinesterase inhibitor as in a) wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.
- 25 j) An acetylcholinesterase inhibitor as in b) wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or

carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.

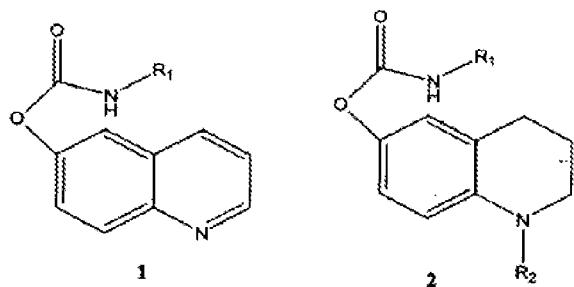
- 5 k) An acetylcholinesterase inhibitor as in b) wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.

10 l) An acetylcholinesterase inhibitor as in a) wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzyloxy or substituted benzyloxy group, a carbonate group or a carbamate group.

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v) International Patent Application Publication No. WO2006/070394

An AChEI that is a quinoline derivative represented by formula 1 and 2 below:



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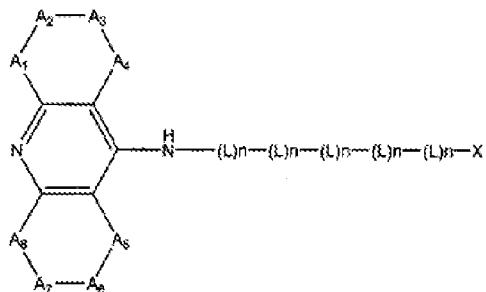
wherein  $R_1$  = alkyl, aryl;  $R_2$  = H, alkyl, aralkyl.

In one embodiment, substituted carbamic acid quinolinyl esters obtained are  
25 selected from the group consisting of: Ia. hexyl-carbamic acid quinolin-6-yl ester  
Ib. heptyl-carbamic acid quinolin-6-yl ester Ic. (2-chloro-phenyl)-carbamic acid  
quinolin-6-yl ester Id. (3-bromo-phenyl)-carbamic acid quinolin-6-yl ester 2a.  
hexyl-carbamic acid 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2b. heptyl-carbamic

- acid 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2c. (3-bromo-phenyl)-carbamic acid 1,2,3,4-tetrahydro-quinolin-6-yl ester 2d. (2-chloro-phenyl)-carbamic acid 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2e. (4-chloro-3-trifluoromethyl-phenyl)-carbamic acid 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester
- 5 2f. (4-bromo-phenyl)-carbamic acid 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester
- 2g. heptyl-carbamic acid 1 -benzyl- 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester
- 10 2h. hexyl-carbamic acid 1 -benzyl- 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester
- 2i. (2-chloro-phenyl)-carbamic acid 1-benzyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2j. (3-bromo-phenyl)-carbamic acid 1-benzyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester
- 15 2k. (4-chloro-3-trifluoromethyl-phenyl)-carbamic acid 1-benzyl-1, 2, 3, 4-tetrahydro- quinolin-6-yl ester
21. (4-bromo-phenyl)-carbamic acid 1-benzyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2m. hexyl-carbamic acid 1-methyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2n. heptyl-carbamic acid 1-methyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester
- 20 2o. (2-chloro-phenyl)-carbamic acid 1-methyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2p. (3-bromo-phenyl)-carbamic acid 1-methyl-1, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2q. (4-chloro-3-trifluoromethyl-phenyl)-carbamic acid 1-methyl-1, 2, 3, 4-tetrahydro- quinolin-6-yl ester 2r. (4-bromo-phenyl)-carbamic acid 1-methyl-1, 2, 3, 4-tetrahydro- quinolin-6-yl ester
- In one embodiment of the invention, when R1 is aryl it is selected from the group 30 consisting of 2- chloro, 3- bromo, 4-bromo and 4-chloro-3-trifluoromethyl-phenyl.

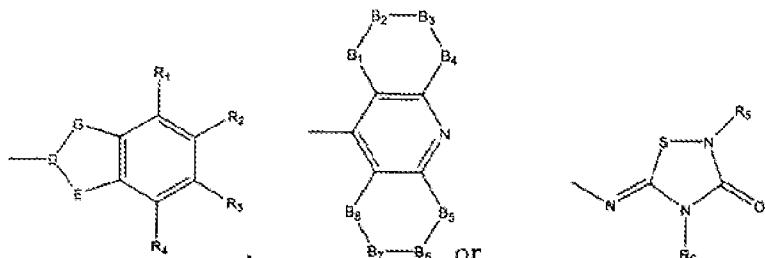
In another embodiment of the invention, R2 is selected from the group consisting of methyl and benzyl.

- vi) International Patent Application Publication No. WO2004/032929
- 5 An embodiment is directed to the compounds represented by the general formula I



Formula I

wherein: X is one of the following radicals:



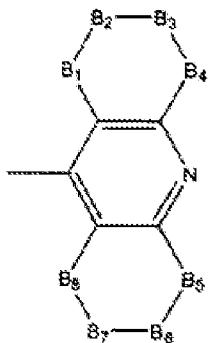
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- L is independently selected from -C (R) (R'')-, -CO-, -O- or -NR' - n is zero, one, two, three, four, five, six, seven, eight, nine or ten R and R'' are independently selected from hydrogen, alkyl, aryl, heteroaryl, halo, haloalkyl, alkoxy, hydroxyl, nitro and alkylthio D is independently selected from -C (R9)-, =C-, or -N- A1, A2, As, A4, As, A7, As, Bi, B2, Bs, B4, Bs, B6, B7, Bs, G and E are independently selected from -CO-, -C (R10) (Rn)-, =C (R10)-, -N (R12)-, =N-, -O-, -S (O) t- Ri, R2, R3, R4, R9, R10 and R11 are independently selected from hydrogen, alkyl, alkoxy, hydroxyl, alkylthio, cycloalkyl, haloalkyl, halo, aryl, -(Z) n-, aryl, heteroaryl, -O (R7), -C (O) R7, -C (O) OR7, -S (O) t, cyano, nitro and mercapto, aryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, nitro or alkylthio; and heteroaryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, nitro or alkylthio R5, R6, and R12 are independently selected from

hydrogen, alkyl, alkoxy, hydroxyl, cycloalkyl, haloalkyl, aryl, heteroaryl, aryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, or alkylthio; and heteroaryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, nitro or alkylthio Z is independently selected from -C (R7) (R8)-, -C (O)-, -O-, -C (=NR7)-, -S (O) t, N (R7)- R7 and R8 are independently selected from hydrogen, alkyl, alkoxy, alkylthio, cycloalkyl, haloalkyl, halo, aryl, heteroaryl, cyano, nitro, mercapto, aryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, nitro or alkylthio; and heteroaryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, nitro or alkylthio t is zero, one or two.

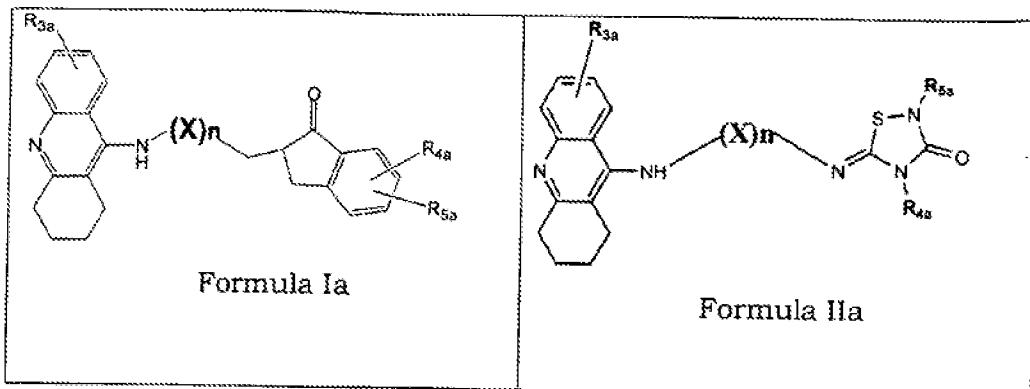
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In general, we have the proviso that when X is:



a) in no case each of the atoms in the groups Al-A4, As-As, Bi-B4, and Bs-Bs are at the same time =C (R10)-, and b) in no case each of the atoms in one of the two 15 groups Al-A4 and As-As, and each of the atoms in one of the two groups Bi-B4 and Bs-Bs are at the same time =C (R10)-.

In a related aspect, the invention is directed to the compounds within the formula 20 (I) and represented by the general formula Ia and IIa:



Where: X is -C (R1a) (R2a)-, -CO-, -O- or -NR1a-; n is zero, one, two, three, four, five, six, seven, eight, nine or ten;

R1a and R2a are independently selected from hydrogen, alkyl, aryl, halo, haloalkyl  
 5 ; R3a, R4a and R5a are independently selected from hydrogen, alkyl, cycloalkyl, haloalkyl, halo, aryl, -(Z) n-aryl, heteroaryl, OR3a,-C (O) R3a,-C (O) OR3a,-S (O) t- ; t is zero, one or two; Z is independently selected from C (R3a) (R4a)-,-C (O)-,-O-,-C (=NR3a)-, -S(O)t-, N (R3a)-.

10

#### Definitions

In vi), the following terms have the following meaning: ; “alkyl”refers to a straight-line or branched hydrocarbon chain comprising only atoms of carbon and  
 15 hydrogen and containing no unsaturated bonds, having from one to eight carbon atoms and bound to the remainder of the molecule by a single bond, e. g. methyl, ethyl, n-propyl, i-propyl, n- butyl, t-butyl, n-pentyl, etc. The alkyl radicals may optionally be substituted by one or more substituents chosen independently from the group comprising halogens, hydroxyl, alcoxides, carboxy, cyano, carbonyl,  
 20 acyl, alkoxycarbonyl, amino, nitro, mercapto and alkylthio.

Preferably, alkyl is Cl-C6 alkyl.

“alkoxy”refers to a radical of formula-ORa, where Ra is an alkyl radical as  
 25 described above, e. g. methoxy, ethoxy, propoxy, etc.

“alkoxycarbonyl” refers to a radical of formula-C (O) ORa, where Ra is an alkyl radical as described above, e. g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc. alkylthio” refers to a radical of formula-SRa, where Ra is an alkyl radical as described above, e. g. methylthio, ethylthio, propylthio, etc.

5 “amino” refers to a radical of formula-NH2 “aryl” refers to a phenyl or naphthyl radical. The aryl radical may optionally be substituted by one or more substituents selected from among the group comprising hydroxy, mercapto, halogens, alkyl, phenyl, alkoxy, haloalkyl, nitro, cyano, dialkylamino, aminoalkyl, acyl and alkoxy carbonyl as they are defined here.

10 “acyl” refers to a radical of formula-C (O)-Ra and-C (O)-Rb, where Ra is an alkyl radical as described above and Rb is an aryl radical as described above, e. g. acetyl, propionyl, benzoyl, and similar.

“carboxy” refers to a radical of formula-C (O) OH “cyano” refers to a radical of formula-CN “cycloalkyl” refers to stable cycles of 3 to 10 monocyclic or bicyclic members that are saturated or partially saturated and consist exclusively of carbon and hydrogen atoms. This term also includes cycloalkylo radicals, which may optionally be substituted by one or more substituents chosen independently from the group comprising alkyl, halogen, hydroxy, amino, cyano, nitro, alkoxy, carboxy and alkoxy carbonyl “halogens” refers to bromine, chlorine, iodine or fluorine “haloalkyl” refers to an alkyl radical, as defined above, which is substituted by one or more halogens, also as defined above, e. g. trifluoromethyl, trichloromethyl, 2,2, 2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and similar.

15 “heterocycle” refers to a heterocyclic radical. The heterocycle refers to a stable cycle of 3 to 15 members comprising carbon atoms and one to five heteroatoms chosen from the group comprising nitrogen, oxygen and sulphur. For the purposes of this invention, the heterocycle may be a monocyclic, bicyclic or tricyclic system that may include fused rings, and the nitrogen, carbon or sulphur atoms may optionally be oxidised, the nitrogen atom may optionally be quaternised, and the

20 heterocycle may be partly or totally saturated or aromatic. Examples of these heterocycles include, but are not limited to, azepines, benzimidazole, benzothiazole, furan, isothiazole, imidazole, indole, piperidine, piperazine, purine,

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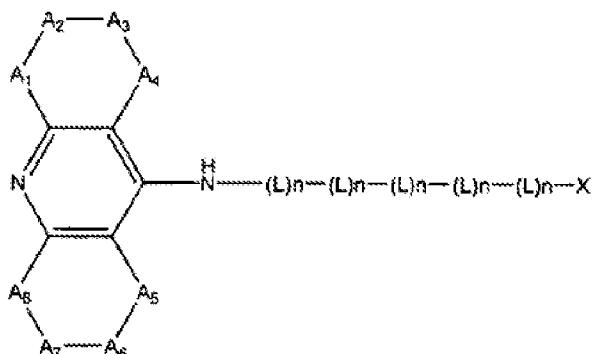
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quinoline, thiadiazole, tetrahydrofuran. The heterocycle may optionally be substituted by R3 and R4 as defined in the summary of the invention.

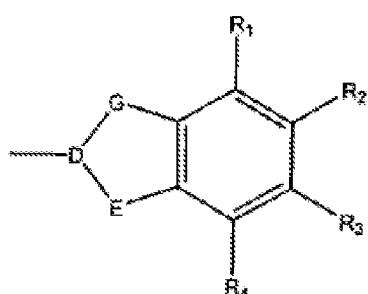
“mercapto” refers to a radical of formula-SH “nitro” refers to a radical of formula-N02.

- 5 In the chain- (L) n- (L) n- (L) n- (L) n- (L) n-, the or each group- (L) n- is preferably- (CH2) n- (where n is not zero),-CO--NH-or-NCH3-. Preferably there are at least one or two groups- (L) n- where n is not zero. Suitably the chain is of the formula- (CH2) n-,- (CH2) n-NRa- (CH2) n-,- (CH2) n-NRa-CO-,- (CH2) n-NRa-CO- (CH2) n-or-(CH2) n-NRa- (CH2) n-NRa-CO-, where the or each n is not zero, and the or each Ra is- NH-or-NCHs-, usually preferably-NH-. The total for the sum of the n integers is preferably in the range 2 to 15.
- 10 The total for the sum of the n integers is preferably in the range 2 to 15.

In the formula:



- each A group (that is, A1 to A8) is preferably =CH-or-CH2-, though one or both of 15 A2 and A7 can be halo, especially chloro, when the remaining A groups are =CH-. Some AChEIs are those in which X is represented by the following formula:



- Preferably D is-CH-, =C-or-N-. Preferably E is-CO-,-CH2-. 20 =CH-, =N-, =N--O-or-S-. Preferably G is-CO-,-CH2-. =CH-, or =N-.

Preferably R<sub>i</sub> to R<sub>4</sub> are hydrogen.

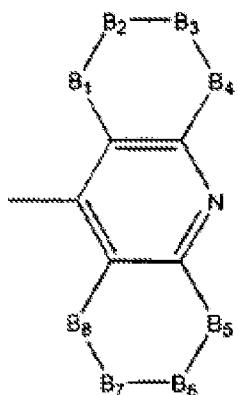
In some embodiments, within these compounds are those in which X is:

phthalimidyl (1, 3-dioxo-1, 3-dihydro-isoindol-2-yl), indol-2-yl, indanon-2-yl, benzimidazol-2-yl, indandion-2-yl, indazol-2-yl, benzofuran-2-yl, benzothiophen-5-2-yl or benzotriazol-2-yl.

In some embodiments are those in which X is phthalimide (1, 3-dioxo-1, 3-dihydro-isoindol-2-yl) and the cyclic part of formula I represents 9-acridinyl, 1, 2,3, 4-tetrahydro-acridin-9-yl or 6chloro, 1, 2,3, 4-tetrahydro-acridin-9-yl. Some compounds are: 2-[6-(acridin-9-ylamino)-hexyl]-isoindole-1, 3-dione (6), 2- [7-(acridin-9-ylamino)-heptyl]-isoindole-1, 3-dione (7), 2- [8- (acridin-9-ylamino)-octyl]-isoindole-1, 3-dione (8), 2- [9- (acridin-9-ylamino)-nonyl]-isoindole-1, 3-dione (9), N- [7- (6-Chloro-1, 2,3, 4-tetrahydro-acridin-9-ylamino)-heptyl]- 2- (1, 3-dioxo-1, 3-dihydro-isoindol-2-yl)-acetamide (10), N- (3- { [3- (6-Chloro-1, 2,3, 4-tetrahydro-acridin-9-ylamino) - propyl]-methyl-amino}-propyl)-2- (1, 3-dioxo-1, 15 3-dihydro- isoindol-2-yl) -acetamide (11), N-[6-(6-Chloro-1, 2,3, 4-tetrahydro-acridin-9-ylamino)-hexyl]-2- (1, 3-dioxo-1, 3-dihydro-isoindol-2-yl)-acetamide (12), 2- [6- (1, 2,3, 4-Tetrahydro-acridin-9-ylamino)-hexylamino]- indan-1, 3-dione (3), 2- [7- (1, 2,3, 4-Tetrahydro-acridin-9-ylamino)-heptyl]-isoindole-1,3-dione (4), and 2- [8- (1, 2,3, 4-Tetrahydro-acridin-9-ylamino)-octyl]-isoindole-1,3-dione (5).

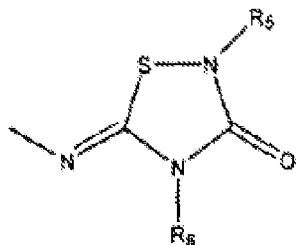
Some compounds are those in which X is 1-indanon-2-yl and the cyclic part of formula I represents 1, 2,3, 4-tetrahydro-acridin-9yl; within these compounds are included, among others, the following compounds: 5, 6-Dimethoxy-2- { [7- (1, 2,3, 4-tetrahydro-acridin-9-ylamino) - heptylamino]-methyl}-indan-1-one (1), and 5, 6-Dimethoxy-2- {[6-(1, 2,3, 4-tetrahydro-acridin-9-ylamino) - hexylamino]-methyl}-indan-1-one (2)

From those compounds in which X is represented by the following formula:



each B group (that is, Bi to Bs) is preferably =CH- or -CH<sub>2</sub>-, though one or both of B2 and B7 can be halo, especially chloro, when the remaining B groups are =CH-. Some compounds are those in which X is 9-acridinyl, 6-chloro-1, 2,3, 4-tetrahydro-acridin-9-yl and 1,2, 3,4-tetrahydro-acridin-9-yl. Within these compounds are those in which the cyclic part of formula I represents: 9-acridinyl, 6chloro-1,2, 3,4-tetrahydro-acridin-9-yl or 1,2, 3,4-tetrahydro-acridin-9-yl; within these compounds are included, among others, the following compounds: -N-[2-(6-Chloro-1, 2,3, 4,4a, 9a-hexahydro-acridin-9-ylamino) - ethyl]-N'-(6-chloro-1, 2,3, 4-tetrahydro-acridin-9-yl)-N-methyl- ethane-1, 2-diamine (19), -N-Acridin-9-yl-N'-(1, 2,3, 4-tetrahydro-acridin-9-yl)-nonane-1, 9-diamine (20) -N-Acridin-9-yl-N' [2-(1, 2,3, 4,4a, 9a-hexahydro-acridin-9-ylamino)-ethyl]-N'-methyl-ethane-1, 2-diamine (21), -N-[2-(Acridin-9-ylamino)-ethyl]-N'-(6-chloro-1, 2,3, 4-tetrahydro- acridin-9-yl)-N-methyl-ethane-1, 2-diamine (22), - N-Acridin-9-yl-N'-(6-chloro-1, 2,3, 4-tetrahydro-acridin-9-yl) - heptane-1, 7-diamine (23), and -N-Acridin-9-yl-N'-(6-chloro-1, 2,3, 4-tetrahydro-acridin-9-yl)- octane-1, 8-diamine (24).

From those compounds in which X is represented by the following formula:



the groups R<sub>s</sub> and R<sub>6</sub> are suitably alkyl or substituted alkyl, notably alkoxy carbonyl alkyl. The preferred compounds are those in which the cyclic part of formula I represents: 9-acridinyl, 6-chloro, 1, 2,3, 4- tetrahydro-acridin-9-yl or 1, 2,3, 4-tetrahydro-acridin-9-yl ; within these compounds are included, among 5 others, the following compounds: 2-Ethyl-4-isopropyl-5- [7- (1, 2,3, 4-tetrahydro-acridin-9- yl amino)-heptyl-imino]- [1, 2, 4] thiadiazolidin-3-one (13), - 2-Ethyl-4-isopropyl-5- [9- (1, 2,3, 4-tetrahydro-acridin-9- yl amino)-nonyl-imino]-[1, 2, 4] thiadiazolidin-3-one (14), 4-isopropyl-3-oxo-5- [9- (1, 2,3, 4-tetrahydro-acridin-9- yl amino) - nonyl-imino]- [1, 2,4] thiadiazolidine-2-carboxylic acid ethyl ester 10 (15), 4-Ethyl-2-propyl-5- [7- (1, 2,3, 4-tetrahydro-acridin-9-yl amino) - heptyl-imino]- [1, 2,4] thiadiazolidin-3-one (16), 4-Ethyl-2-isopropyl-5- [8- (1, 2,3, 4-tetrahydro-acridin-9- yl amino)-octylimino]- [1, 2,4] thiadiazolidin-3-one (17), and 4-Ethyl-2-isopropyl-5- [6- (1, 2,3, 4-tetrahydro-acridin-9- yl amino)-hexyl-imino]- [1, 2,4] thiadiazolidin-3-one (18).

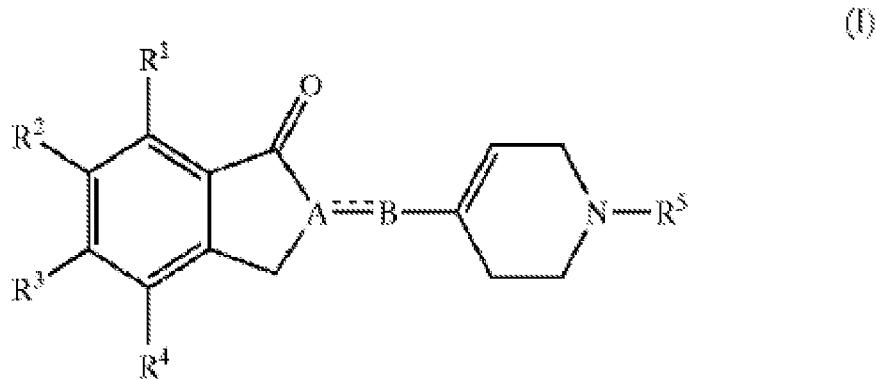
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vii) U.S. Patent Application Publication No. 20050124642

In some embodiments, an AChEI is:

1) an (1-indanone)-(1,2,3,6-tetrahydropyridine) compound represented by the formula:

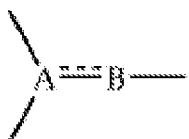
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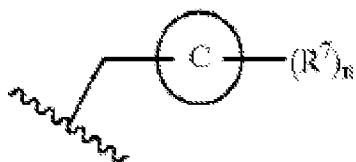
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(in the formula (I), R<1> , R<2> , R<3> and R<4> are the same as or different from each other and each represents a group selected from hydrogen atom, a halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an alkoxy group having one to six carbon

atoms which may be substituted, a cycloalkoxy group having three to eight carbon atoms which may be substituted, an acyl group having one to six carbon atoms which may be substituted, an C1-C6 alkoxy-carbonyl group which may be substituted, an C1-C6 alkyl-aminocarbonyloxy group which may be substituted, a 5 di-(C1-C6 alkyl)-aminocarbonyloxy group which may be substituted, nitro group, an amino group which may be substituted, an amide group which may be substituted, mercapto group and a thioalkoxy group having one to six carbon atoms which may be substituted, where R<1> and R<2>, or R<2> and R<3>, or R<3> and R<4> may together form an aliphatic ring, an aromatic ring, a heterocyclic 10 ring or an alkylenedioxy ring; the partial structure:



is a group represented by >C-CH-(CH<sub>2</sub>)<sub>m</sub>- or >C(R<6>)-CH(R<6>)-(CH<sub>2</sub>)<sub>m</sub>- (wherein m is 0 or an integer from 1 to 5; and R<6> is hydrogen atom, a halogen atom, hydroxyl group, an alkyl group having one to six carbon atoms, an alkoxy group having one to six carbon atoms, nitrile group, a haloalkyl group having one to six carbon atoms, a hydroxyalkyl group having one to six carbon atoms, a 15 cyano-C1-C6 alkyl group, an aminoalkyl group having one to six carbon atoms, nitro group, azide group, an amino group which may be substituted, carbamoyl group which may be substituted, carboxyl group which may be substituted, mercapto group or a thioalkoxy group having one to six carbon atoms); and R<5> is hydrogen atom, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group having two to six carbon atoms which may be substituted, an alkynyl group having two to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an 20 2,2-(alkylenedioxy)ethyl group or a group represented by the formula:

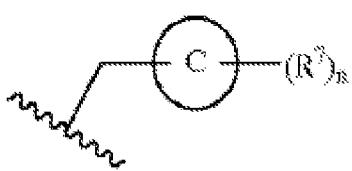


(wherein the ring C is benzene ring, an aliphatic ring or a heterocyclic ring; R<7> s are the same as or different from each other and each represents hydrogen atom, a halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group having two to six carbon atoms which may be substituted, an alkynyl group having two to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an alkoxy group having one to six carbon atoms which may be substituted, an C1-C6 alkoxy-alkoxy group which may be substituted, an aryloxy group which may be substituted, an aralkyloxy group which may be substituted or the like, where two of R<7> s may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring; and n is an integer from 1 to 5)), a pharmacologically acceptable salt thereof or a hydrate of them;

5 2) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 1), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<1> and R<4> are hydrogen atoms; and R<2> and R<3> are the same as or different from each other and each represents hydrogen atom, a halogen atom, an alkyl group having one to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an alkoxy group having one to six carbon atoms which may be substituted or a cycloalkoxy group having three to eight carbon atoms which may be substituted, or R<2> and R<3> may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring;

10 20 [0019] 3) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 1) or 2), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<6> is hydrogen atom, a halogen atom or an alkyl group having one to six carbon atoms;

15 25 [0020] 4) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in any one of 1) to 3), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<5> is a group represented by the formula:



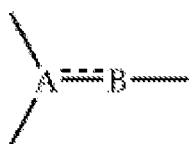
wherein the ring C, R<7> and n have the same meanings as defined above;

5) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the ring C is benzene ring or a cycloalkyl ring having three to eight carbon atoms;

5 6) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<7> s are the same as or different from each other and each represents hydrogen atom, a halogen atom, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group having two to six carbon atoms which may be substituted, an alkynyl group having two to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, or two of R<7> s may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring;

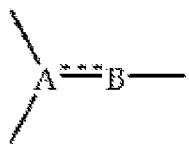
10 7) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein n is an integer of 1 or 2;

15 [0024] 8) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in any one of 1) to 7), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the partial structure:



20 is a group represented by >C(R<6>)-CH(R<6>)-(CH<sub>2</sub>)<sub>m</sub>- (wherein m is 0 or an integer from 1 to 5; and R<6> is hydrogen atom);

9) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in any one of 1) to 7), a pharmacologically acceptable salt thereof or a hydrate of them, wherein 25 the partial structure:



is a group represented by >C(R<6>)-CH(R<6>)-(CH<sub>2</sub>)<sub>m</sub>- (wherein m is 0 or an integer from 1 to 5; and R<6> is a halogen atom, hydroxyl group, an alkyl group

having one to six carbon atoms, an alkoxy group having one to six carbon atoms, a nitrile group, a haloalkyl group having one to six carbon atoms, a hydroxyalkyl group having one to six carbon atoms, a cyano-C1-C6 alkyl group, an aminoalkyl group having one to six carbon atoms, nitro group, azide group, an amino group which may be substituted, carbamoyl group which may be substituted, carboxyl group which may be substituted, mercapto group or a thioalkoxy group having one to six carbon atoms;

5 10) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 1), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound represented by the formula (I) is one selected from:

10 15 (1) 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine,

2) 1-benzyl-4-[(5,6-diethoxy-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine,

15 and

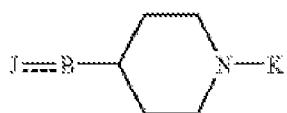
(3) 1-benzyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine;

See also, for example, those AChE inhibitors set forth in Brufani et al, Alzheimer Disease: From Molecular Biology to Therapy, eds. Becker et al., pp. 171-177 (1996); Schmidt et al., Alzheimer Disease: From Molecular Biology to Therapy, eds. Becker et al., pp. 217-221 (1996); Vargas et al., Alzheimer Disease: From Molecular Biology to Therapy, eds. Becker et al., pp. 261-255 (1996); Greig et al., Alzheimer Disease: From Molecular Biology to Therapy, eds. Becker et al., pp. 231-237 (1996); and Giacobini, Alzheimer Disease: From Molecular Biology to Therapy eds. Becker et al., pp. 187-204 (1996).

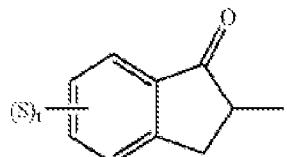
viii) U.S. Patent 7,378,425

In some embodiments, the following compounds ((1) to (4)) are compounds having 30 an acetylcholinesterase inhibitory action.

(1) A cyclic amine derivative represented by the following formula, a pharmacologically acceptable salt thereof or a hydrate of them.

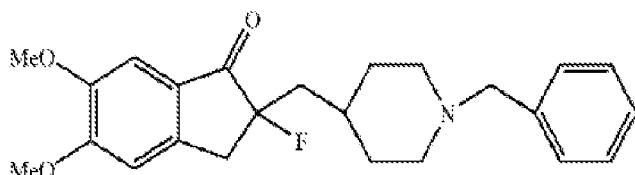


Wherein J is, for example, the formula:



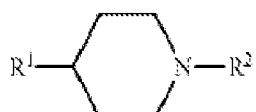
(wherein S is, for example, a lower alkoxy group having one to six carbon atoms; 5 and t is 0 or an integer of 1 to 4); B is, for example, methylene chain; K is, for example, a benzyl group which may be substituted; and the partial structure: - is a single bond or double bond, provided that a compound wherein J is 5,6-dimethoxy-1-indanon-2-yl group; B is -CH<sub>2</sub>- group; and K is unsubstituted benzyl group, a pharmacologically acceptable salt thereof or a hydrate of them are 10 excluded (JP-B2 2733203).

(2) A compound represented by the following formula:

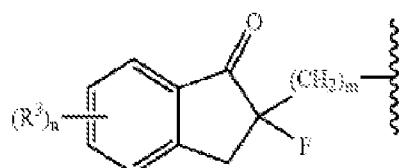


or a pharmacologically acceptable salt thereof (JP-A 2000-319257).

(3) A 4-substituted piperidine derivative fluoride represented by the following 15 formula:



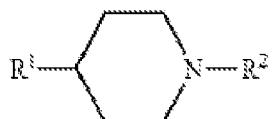
(wherein R<1> is, for example, a substituent represented by:



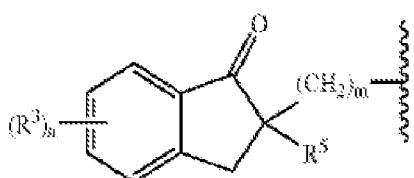
(wherein R<3> s are the same as or different from each other and each represents, 20 for example, an alkoxy group having one to six carbon atoms; m is 0 or an integer of 1 to 6; and n is an integer of 1 to 4); and R<2> is, for example, a benzyl group

which may be substituted, provided that 1-benzyl-4-[(5,6-dimethoxy-2-fluoro-1-indanon)-2-yl]methylpiperidine or a pharmacologically acceptable salt thereof is excluded), a pharmacologically acceptable salt thereof or a hydrate of them (JP-A 2000-319258).

- 5 (4) A 4-substituted piperidine derivative represented by the following formula:



(wherein R<1> is, for example, a group represented by the formula:

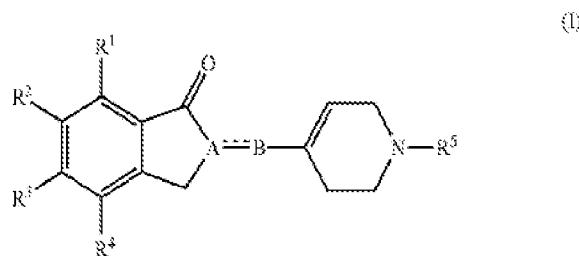


- 10 (wherein R<3> s are the same as or different from each other and each represents, for example, an alkoxy group having one to six carbon atoms; R<5> is, for example, a halogen atom except for fluorine atom; m is 0 or an integer of 1 to 6; and n is an integer of 1 to 4); and R<2> is, for example, benzyl group which may be substituted), a pharmacologically acceptable salt or a hydrate of them (JP-A 2001-139547).

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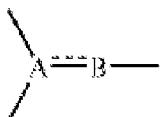
In some embodiments, the present invention relates to:

- 1) an (1-indanone)-(1,2,3,6-tetrahydropyridine) compound represented by the formula:



- 20 (in the formula (I), R<1> , R<2> , R<3> and R<4> are the same as or different from each other and each represents a group selected from hydrogen atom, a halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an alkoxy group having one to six carbon

atoms which may be substituted, a cycloalkoxy group having three to eight carbon atoms which may be substituted, an acyl group having one to six carbon atoms which may be substituted, an C1-C6 alkoxy-carbonyl group which may be substituted, an C1-C6 alkyl-aminocarbonyloxy group which may be substituted, a 5 di-(C1-C6 alkyl)-aminocarbonyloxy group which may be substituted, nitro group, an amino group which may be substituted, an amide group which may be substituted, mercapto group and a thioalkoxy group having one to six carbon atoms which may be substituted, where R<1> and R<2>, or R<2> and R<3>, or R<3> and R<4> may together form an aliphatic ring, an aromatic ring, a heterocyclic 10 ring or an alkylenedioxy ring; the partial structure:



is a group represented by >C-CH-(CH<sub>2</sub>)<sub>m</sub>- or >C(R<6>)-CH(R<6>)-(CH<sub>2</sub>)<sub>m</sub>- (wherein m is 0 or an integer from 1 to 5; and R<6> is hydrogen atom, a halogen atom, hydroxyl group, an alkyl group having one to six carbon atoms, an alkoxy group having one to six carbon atoms, nitrile group, a haloalkyl group having one to six carbon atoms, a hydroxyalkyl group having one to six carbon atoms, a cyano-C1-C6 alkyl group, an aminoalkyl group having one to six carbon atoms, nitro group, azide group, an amino group which may be substituted, carbamoyl group which may be substituted, carboxyl group which may be substituted, mercapto group or a thioalkoxy group having one to six carbon atoms); and R<5> 15 is hydrogen atom, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group having two to six carbon atoms which may be substituted, an alkynyl group having two to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an 2,2-(alkylenedioxy)ethyl group or a group represented by the 20 formula:



(wherein the ring C is benzene ring, an aliphatic ring or a heterocyclic ring; R<7> s 25 are the same as or different from each other and each represents hydrogen atom, a

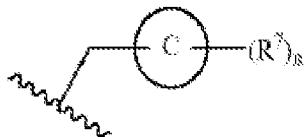
halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group having two to six carbon atoms which may be substituted, an alkynyl group having two to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an alkoxy group having one to six carbon atoms which may be substituted, an C1-C6 alkoxy-alkoxy group which may be substituted, an aryloxy group which may be substituted, an aralkyloxy group which may be substituted or the like, where two of R<7> s may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring; and n is an integer from 1 to 5)), a pharmacologically acceptable salt thereof or a hydrate of them;

5 2) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 1), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<1> and R<4> are hydrogen atoms; and R<2> and R<3> are the same as or different from each other and each represents hydrogen atom, a halogen atom, an alkyl group

10 15 having one to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, an alkoxy group having one to six carbon atoms which may be substituted or a cycloalkoxy group having three to eight carbon atoms which may be substituted, or R<2> and R<3> may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring;

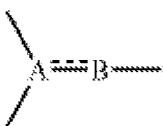
15 20 3) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 1) or 2), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<6> is hydrogen atom, a halogen atom or an alkyl group having one to six carbon atoms;

25 4) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in any one of 1) to 3), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<5> is a group represented by the formula:

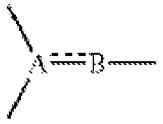


wherein the ring C, R<7> and n have the same meanings as defined above;

- 5) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the ring C is benzene ring or a cycloalkyl ring having three to eight carbon atoms;
- 6) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein R<7> s are the same as or different from each other and each represents hydrogen atom, a halogen atom, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group having two to six carbon atoms which may be substituted, an alkynyl group having two to six carbon atoms which may be substituted, a cycloalkyl group having three to eight carbon atoms which may be substituted, or two of R<7> s may together form an aliphatic ring, an aromatic ring, a heterocyclic ring or an alkylenedioxy ring;
- 10 7) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein n is an integer of 1 or 2;
- 15 8) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in any one of 1) to 7), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the partial structure:



- 20 is a group represented by >C(R<6>)-CH(R<6>)-(CH<sub>2</sub>)<sub>m</sub>- (wherein m is 0 or an integer from 1 to 5; and R<6> is hydrogen atom);
- 9) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in any one of 1) to 7), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the partial structure:



- 25 is a group represented by >C(R<6>)-CH(R<6>)-(CH<sub>2</sub>)<sub>m</sub>- (wherein m is 0 or an integer from 1 to 5; and R<6> is a halogen atom, hydroxyl group, an alkyl group having one to six carbon atoms, an alkoxy group having one to six carbon atoms, a nitrile group, a haloalkyl group having one to six carbon atoms, a hydroxyalkyl

group having one to six carbon atoms, a cyano-C1-C6 alkyl group, an aminoalkyl group having one to six carbon atoms, nitro group, azide group, an amino group which may be substituted, carbamoyl group which may be substituted, carboxyl group which may be substituted, mercapto group or a thioalkoxy group having one to six carbon atoms;

10) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 1), a pharmacologically acceptable salt thereof or a hydrate of them, wherein the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound represented by the formula (I) is one selected from:

10 (1) 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine,

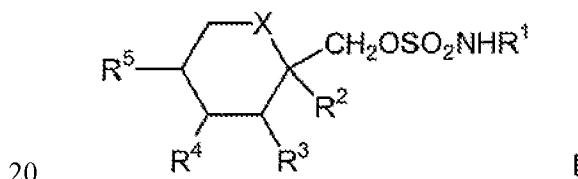
(2) 1-benzyl-4-[(5,6-diethoxy-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine, and

(3) 1-benzyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine.

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ix) International Patent Application Publication No. WO2003/020289

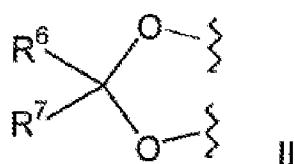
The compounds of formula I of the present invention are compounds of the following general formula 1 :



wherein

X is CH2 or oxygen;

RI is hydrogen or alkyl ; and R2, R3, R4 and R5 are independently hydrogen or lower alkyl and, when X is CH2, R4 and R5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R2 and R3 and/or R4 and R5 together may be a methylenedioxy group of the following formula II :



wherein

R6 and R7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

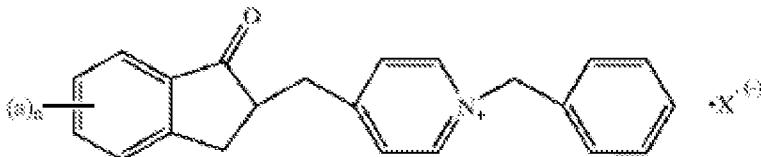
5 R<sup>1</sup> in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R2, R3, R4, R5, R6 and R7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl.

When X is CH<sub>2</sub>, R and R5 may combine to form a benzene ring fused to the 6-membered X-containing ring, i. e., R4 and R5 are defined by the alkatrienyl group 10 =C-CH=CH-CH=.

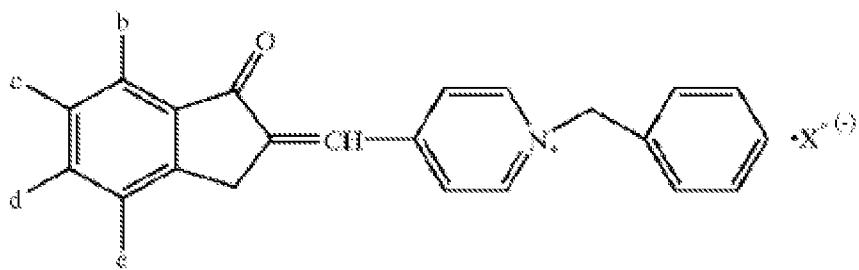
A particular group of compounds of formula I is that wherein X is oxygen and both R2 and R3 and R4 and R5 together are methylenedioxy groups of the formula il, 15 wherein R6 and R7 are both hydrogen, both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R6 and R7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH<sub>2</sub> and R4 and R5 are joined to form a benzene ring. A third group of compounds of formula I is that wherein both R2 and R3 are hydrogen.

x) U.S. Patent Application Publication No. 2003069289

20 In view of the circumstances described above, the present inventors made extensive study through which they found that both a compound represented by the formula:

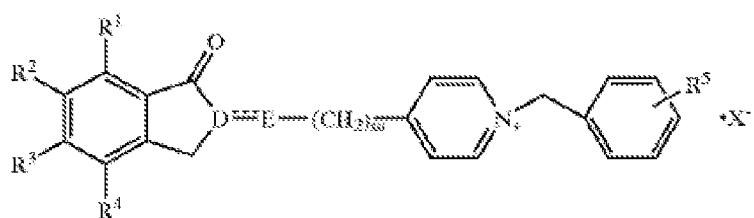


25 (wherein the “a” moieties are the same as or different from each other and each represents a hydrogen atom or a C1-6 alkoxy group; n is an integer from 1 to 4; and X<(-)>represents a halide ion) and a compound represented by the formula:

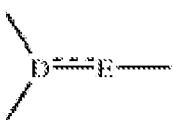


(wherein b, c, d and e are the same as or different from each other and each represents a hydrogen or a linear or branched C1-6 alkyl, C1-6alkoxy, C1-6alkoxy carbonyl, C1-6alkyl aminocarbonyloxy, di (C1-6alkyl)-aminocarbonyloxy or a halogen; and X''<(-)>represents an anion in the series of chloride, bromide, iodide and sulfate) exhibit an excellent inhibitory action on acetylcholinesterase. Further, on the basis of these findings, they found that a 1-benzylpyridinium salt represented by the formula:

(I)

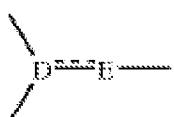


10 (wherein R<1>, R<2>, R<3> and R<4> are the same or different, and represent a hydrogen atom, a halogen atom, a hydroxyl group, a nitrile group, a C1-6 alkyl group, a C1-6 alkoxy group, a C1-6alkoxy carbonyl group, a C1-6 alkyl aminocarbonyloxy group or a di (C1-6 alkyl)-aminocarbonyloxy group; R<5> represents a hydrogen atom, a halogen atom, a C1-6alkyl group, a C2-6 alkenyl group or a C2-6 alkynyl group; the partial structure:

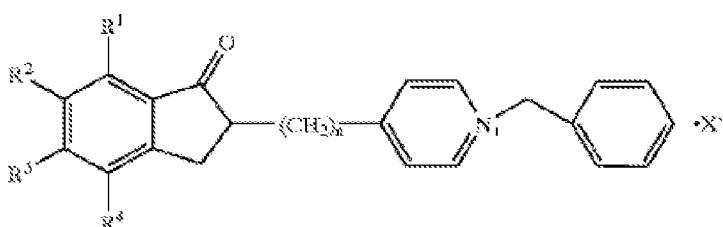


15 is a group represented by the formula >C(R<6>)-CH2- (wherein R<6> is a hydrogen atom or a halogen atom) or >C-CH-; X<-> represents a halide ion or organic sulfonic acid ion; and m is 0 or an integer from 1 to 5) exhibits an excellent inhibitory action on acetylcholinesterase, and accomplished the present invention. That is, the first aspect according to the present invention is (1) an acetylcholinesterase inhibitor comprising a 1-benzylpyridinium salt represented by

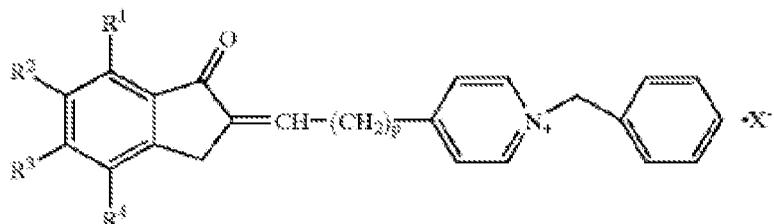
the above formula (I). Further, (2) in the above item (1), R<1>, R<2>, R<3> and R<4> may be the same as or different from each other and each represents a hydrogen atom or a C1-6 alkoxy group; (3) in the above item (1), R<1>, R<2> and R<3> and R<4> may be the same as or different from each other and each represents a hydrogen atom or a methoxy group; (4) in the above item (1), R<1> and R<4> may represent a hydrogen atom; and R<2> and R<3> may represent a methoxy group; (5) in the above item (1), R<5> may be a hydrogen atom; (6) in the above item (1), the partial structure:



10 may be a group represented by the formula >C (R<6>) -CH2- (wherein R<6> is a hydrogen atom or a halogen atom); (7) in the above item (1), m may be 0, 2 or 4; (8) in the above item (1), the halide ion represented by X<-> maybe a chloride ion, bromide ion or iodide ion, preferably a chloride ion or bromide ion; (9) in the above item (1), the organic sulfonic acid ion represented by X<-> may be a methanesulfonate ion, trifluoromethanesulfonate ion, ethanesulfonate ion, benzenesulfonate ion, toluenesulfonate ion or camphor sulfonate ion; (10) in the above item (1), the 1-benzylpyridinium salt may be a compound represented by the formula:



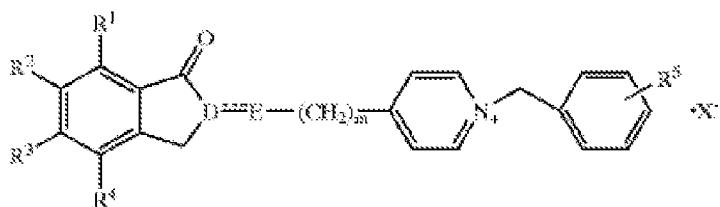
20 wherein R<1>, R<2>, R<3>, R<4> and X<-> have the same meanings as defined above; and n is an integer from 1 to 6; (11) in the above item (1), the 1-benzylpyridinium salt may be a compound represented by the formula:



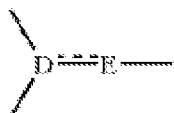
wherein R<1>, R<2>, R<3>, R<4> and X<-> have the same meanings as defined above; and p is 0 or an integer from 1 to 5; (12) in the above item (1), the preparation may be an agent for treating, preventing or improving senile dementia, cerebrovascular dementia or attention deficit hyperactivity disorder; and (13) in the 5 above item (12), the senile dementia may be Alzheimer type senile dementia.

The second aspect according to the present invention is (14) a pharmaceutical preparation comprising a 1-benzylpyridinium salt represented by the formula:

(1)



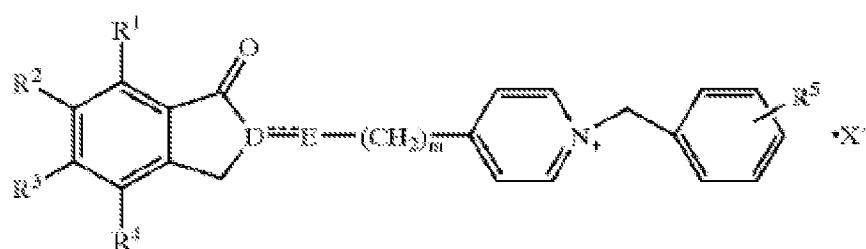
wherein R<1>, R<2>, R<3>, R<4>, R<5>, the partial structure:



10

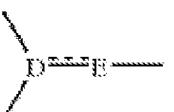
X<-> and m have the same meanings as defined above. Further, the third aspect according to the present invention is (15) use of a 1-benzylpyridinium salt represented by the formula:

(2)



15

(wherein R<1>, R<2>, R<3>, R<4>, R<5>, the partial structure:



X<-> and m have the same meanings as defined above) for producing an acetylcholinesterase inhibitor.

The present invention provides a method of preventing, treating or improving a 20 disease against which an inhibitory action on acetylcholinesterase is efficacious for

prevention, treatment or improvement, by administering a pharmacologically effective dose of the 1-benzylpyridinium salt represented by the above formula (I) to a patient.

- In the present invention, the disease against which an inhibitory action on
- 5 acetylcholinesterase is efficacious for prevention, treatment or improvement includes senile dementia such as Alzheimer type senile dementia, and cerebrovascular dementia and attention deficit hyperactivity disorder.
- Hereinafter, the meanings of symbols, terms etc. used in the specification are described, and the present invention is described in detail.
- 10 In the specification, the structural formulae of the compound may, for convenience' sake, indicate a certain isomer, but the present invention encompasses all possible isomers which can occur in the structures of the compound, for example geometric isomer, optical isomer based on asymmetrical carbon, stereoisomer and tautomer, and a mixture of such isomers, so the
- 15 compound according to the present invention may be any isomers or a mixture thereof without limitation to the formulae shown for convenience' sake. Accordingly, the compound according to the present invention can have an intramolecular asymmetrical carbon, thus occurring as optically active isomers or racemic modifications, and any of such compounds are included in the present
- 20 invention without limitation. When there is crystal polymorphism, the compound according to the present invention may be in a single crystal form or a mixed crystal form without limitation. Compound (I) or salts thereof may be anhydrides or hydrates, any of which fall under the embodiments in the specification. Further, metabolites formed by decomposition of Compound (I) in vivo, and prodrugs of
- 25 Compound (I) or salts thereof, also fall under the embodiments in the specification. The "halogen atom" used in the specification refers to an atom such as a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, preferably a fluorine atom, a chlorine atom or a bromine atom.
- The "C1-6 alkyl group" represented by R<1>, R<2>, R<3> and R<4> in the
- 30 specification refers to an alkyl group having 1 to 6 carbon atoms, and examples thereof include a methyl group, ethyl group, n-propyl group, iso-propyl group, n-butyl group, iso-butyl group, sec-butyl group, tert-butyl group, n-pentyl group, 1,1-

dimethylpropyl group, 1,2-dimethylpropyl group, 2,2-dimethylpropyl group, 1-ethylpropyl group, 2-ethylpropyl group, n-hexyl group, 1-methyl-2-ethylpropyl group, 1-ethyl-2-methylpropyl group, 1,1,2-trimethylpropyl group, 1-propylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,1-dimethylbutyl group, 1,2-  
5 dimethylbutyl group, 2,2-dimethylbutyl group, 1,3-dimethylbutyl group, 2,3-dimethylbutyl group, 2-ethylbutyl group, 2-methylpentyl group, 3-methylpentyl group etc., preferably a methyl group, ethyl group, n-propyl group, iso-propyl group, n-butyl group, iso-butyl group and tert-butyl group.

The “C1-6 alkoxy group” represented by R<1>, R<2>, R<3> and R<4> in the  
10 specification refers to an alkoxy group having 1 to 6 carbon atoms, and examples thereof include a methoxy group, ethoxy group, n-propoxy group, iso-propoxy group, sec-propoxy group, n-butoxy group, iso-butoxy group, sec-butoxy group, tert-butoxy group, n-pentyloxy group, iso-pentyloxy group, sec-pentyloxy group, n-hexoxy group, iso-hexoxy group, 1,1-dimethylpropyloxy group, 1,2-  
15 dimethylpropoxy group, 2,2-dimethylpropyloxy group, 2-ethylpropoxy group, 1-methyl-2-ethylpropoxy group, 1-ethyl-2-methylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1,2-trimethylpropoxy group, 1,1-dimethylbutoxy group, 1,2-dimethylbutoxy group, 2,2-dimethylbutoxy group, 2,3-dimethylbutyloxy group, 1,3-dimethylbutyloxy group, 2-ethylbutoxy group, 1,3-dimethylbutoxy group, 20 2-methylpentoxy group, 3-methylpentoxy group, hexyloxy group etc., preferably a methoxy group, ethoxy group, n-propoxy group and iso-propoxy group.

The “C1-6 aloxycarbonyl group” represented by R<1>, R<2>, R<3> and R<4> in the specification refers to a group in which a C1-6 alkoxy group having the same  
25 meaning as defined above is bound to a carbonyl group. For example, a methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, iso-propoxycarbonyl group, n-butoxycarbonyl group, iso-butoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group, hexyloxycarbonyl group etc., preferably a methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group and iso-propoxycarbonyl group.

The “C1-6alkyl aminocarbonyloxy group” represented by R<1>, R<2>, R<3> and R<4> in the specification refers to an aminocarbonyloxy group whose nitrogen

atom has been substituted with a C1-6alkyl group having the same meaning as defined above, and examples thereof include a methylaminocarbonyloxy group, ethylaminocarbonyloxy group, n-propylaminocarbonyloxy group, iso-propylaminocarbonyloxy group, n-butylaminocarbonyloxy group, iso-5 butylaminocarbonyloxy group, tert-butylaminocarbonyloxy group, n-pentylaminocarbonyloxy group, iso-pentylaminocarbonyloxy group, neopentylaminocarbonyloxy group, hexylaminocarbonyloxy group, 1-methylpropylaminocarbonyloxy group, 1-methyl butyl aminocarbonyloxy group, 2-methylbutylaminocarbonyloxy group etc.

10 The “di (C1-6 alkyl)-aminocarbonyloxy group” represented by R<1>, R<2>, R<3>and R<4>in the specification refers to an aminocarbonyloxy group whose nitrogen atom has been substituted with two C1-6 alkyl groups, and examples thereof include a dimethylaminocarbonyloxy group, diethylaminocarbonyloxy group, di(n-propyl)-aminocarbonyloxy group, di-(iso-propyl)-aminocarbonyloxy group, di(n-butyl)-aminocarbonyloxy group, di(iso-butyl)-aminocarbonyloxy group, di-(tert-butyl)-aminocarbonyloxy group, di(n-pentyl)-aminocarbonyloxy group, di-(iso-pentyl)-aminocarbonyloxy group, di-(neopentyl)-aminocarbonyloxy group, di-(n-hexyl)-aminocarbonyloxy group, di-(1-methylpropyl)-aminocarbonyloxy group, di-(1-methylbutyl)-aminocarbonyloxy group, di-(2-methylbutyl)-aminocarbonyloxy group etc.

15 As the preferable mode of R<1>, R<2>, R<3>and R<4>in the specification, R<1>, R<2>, R<3>and R<4>are the same as or different from each other and each represents a hydrogen atom, a halogen atom, a hydroxyl group, a nitrile group, a C1-6alkyl group or a C1-6 alkoxy group; more preferably, they are the same as or different from each other and each represents a hydrogen atom, a halogen atom, a hydroxyl group, a nitrile group or a C1-6alkoxy group; further preferably, they are the same as or different from each other and each represents a hydrogen atom or a C1-6alkoxy group; and the most preferably, R<1>and R<4>represent a hydrogen atom while R<2>and R<3>are the same as or different from each other and each represents a C1-6 alkoxy group (for example, a methoxy group, ethoxy group etc.).

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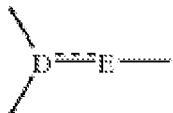
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The “halogen atom” and “C1-6 alkyl group” represented by R<5> in the specification refer to a halogen atom and C1-6alkyl group each having the same meaning as defined above.

- 5 The “C2-6 alkenyl group” represented by R<5> in the specification refers to an alkenyl group having 2 to 6 carbon atoms, and examples thereof include linear or branched C2-6 alkenyl groups such as a vinyl group, allyl group, 1-propenyl group, isopropenyl group, 1-buten-1-yl group, 1-buten-2-yl group, 1-buten-3-yl group, 2-buten-1-yl group and 2-buten-2-yl group, preferably a vinyl group, allyl group and isopropenyl group.
- 10 The “C2-6 alkynyl group” represented by R<5> in the specification refers to an alkynyl group having 2 to 6 carbon atoms, and examples thereof include linear or branched C2-6 alkynyl groups such as an ethynyl group, 1-propynyl group, 2-propynyl group, butynyl group, pentynyl group and hexynyl group.
- 15 Preferable examples of R<5> in the specification include a hydrogen atom and a halogen atom (for example, a fluorine atom, chlorine atom, bromine atom etc.).

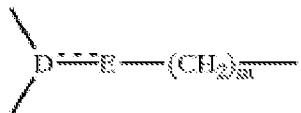
The partial structure:



- may be either a group represented by the formula >C(R<6>)-CH2- (wherein R<6> is a hydrogen atom or a halogen atom) or >C-CH-, preferably a group represented by the formula >C(R<6>)-CH2- wherein R<6> is a hydrogen atom or a halogen atom. Herein, the “halogen atom” represented by R<6> means an atom having the same meaning as the halogen atom in the above definition, and R<6> is preferably a hydrogen atom, fluorine atom, chlorine atom or bromine atom, more preferably a hydrogen atom or fluorine atom. That is, the group which can be represented by the partial structure is more preferably the formula >CH-CH2-, >C(F)-CH2-, >C(Cl)-CH2- or >C(Br)-CH2-, further preferably the formula >CH-CH2- or >C(F)-CH2-.

- The “halide ion” represented by X<-> in the specification refers to a fluoride ion, chloride ion, bromide ion, iodide ion etc., preferably a chloride ion, bromide ion and iodide ion, more preferably a chloride ion and bromide ion, most preferably a

chloride ion. The “organic sulfonic acid ion” represented by  $X<->$  refers to a methanesulfonate ion, trifluoromethanesulfonate ion, ethanesulfonate ion, benzenesulfonate ion, toluenesulfonate ion and camphor sulfonate ion etc. In the specification, m is 0 or an integer from 1 to 5, whereupon the partial structure:



represents (1) the formula  $>C(R<6>)-CH_2-$  or  $>C-CH-$  when m is 0, (2) the formula  $>C(R<6>)-(CH_2)_2-$  or  $>C=CH-(CH_2)-$  when m is 1, (3) the formula  $>C(R<6>)-(CH_2)_3-$  or  $>C-CH-(CH_2)_2-$  when m is 2, (4) the formula  $>C(R<6>)-(CH_2)_4-$  or  $>C-CH-(CH_2)_3-$  when m is 3, (5) the formula  $>C(R<6>)-(CH_2)_5-$  or  $>C-CH-(CH_2)_4-$  when m is 4, and (6) the formula  $>C(R<6>)-(CH_2)_6-$  or  $>C-CH-(CH_2)_5-$  when m is 5, respectively (in the formula,  $R<6>$  has the same meaning as defined above). m is preferably 0, 2 or 4, more preferably 0 or 2.

One embodiment of the acetylcholinesterase inhibitor in the present invention includes, for example, those acetylcholinesterase inhibitors comprising the following compounds. However, it goes without saying that the embodiments of the present invention are not limited to those acetylcholine esterase inhibitors comprising these compounds.

The acetylcholinesterase inhibitor comprises any one or two or more 1-benzylpyridinium salts selected from:

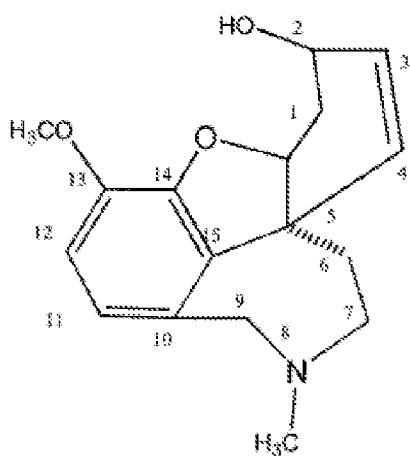
1-benzyl-4-(1-indanone-2-yl)methylpyridinium chloride;  
 1-benzyl-4-[(4-methoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(5-methoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(6-methoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(7-methoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(5,7-dimethoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(4,7-dimethoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(4,5-dimethoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(6,7-dimethoxy-1-indanone)-2-yl]methylpyridinium chloride;  
 1-benzyl-4-[(5,6,7-trimethoxy-1-indanone)-2-yl]methylpyridinium chloride;

- 1-benzyl-4-[(5,6-diethoxy-1-indanone)-2-yl]methylpyridinium chloride;  
1-benzyl-4-(1-indanone-2-yl)methylpyridinium bromide;  
1-benzyl-4-[(4-methoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(5-methoxy-1-indanone)-2-yl]methylpyridinium bromide;  
5 1-benzyl-4-[(6-methoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(7-methoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(5,6-dimethoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(5,7-dimethoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(4,7-dimethoxy-1-indanone)-2-yl]methylpyridinium bromide;  
10 1-benzyl-4-[(4,5-dimethoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(6,7-dimethoxy-1-indanone)-2-yl]methylpyridinium bromide;  
1-benzyl-4-[(5,6,7-trimethoxy-1-indanone)-2-yl]methylpyridinium bromide; and  
1-benzyl-4-[(5,6-diethoxy-1-indanone)-2-yl]methylpyridinium bromide.
- 15 xi) International Patent Application Publication No. WO2000/033840  
In some embodiments compounds include donepezil, rivastigmine, galantamine, lycoramine and the analogs of galantamine and lycoramine. Suitable compounds are galanthamine, lycoramine and their analogs wherein wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced  
20 as follows:  
the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzyloxy or substituted benzyloxy group, a carbonate group or a carbamate group or a trialkylsilyloxy group;  
25 the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzyloxy or substituted benzyloxy group, a carbonate group or a carbamate group;  
the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl group or a substituted or unsubstituted benzyloxy group.  
30 One or more of the methoxy, hydroxy and methyl groups of galanthamine or lycoramine may be replaced by the groups noted above.

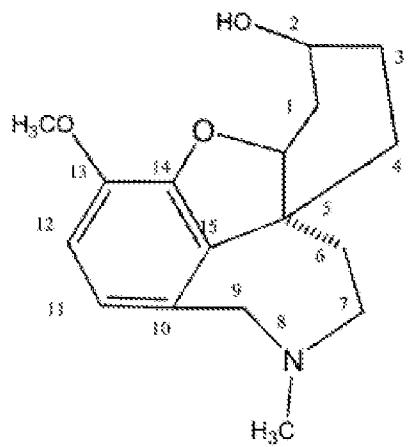
When reference is made to a substituent group, said group may be selected from alkyl or alkoxy groups of from 1 to 6 carbon atoms, halo groups, and haloalkyl groups such as trifluoromethyl. When reference is made to alkyl groups, where the context permits, the term also includes groups which are or contain cycloalkyl groups including adamantyl. Aryl groups are typically phenyl or naphthyl but may include heteroaryl such as morpholino.

Galanthamine and lycoramine have the following formulae:

## Galanthamine



## 10 Lycoramine



Suitable analogs are described for example in International Patent Publication W088/08708 and an article by Bores and Kosley in Drugs of the Future 21: 621-631 (1996).

15 Other useful pharmacologic agents for such preparations include rivastigmine, and other pharmacologic agents with half lives of 1-11 hours.

Particularly useful analogs of galanthamine and lycoramine that are of use in the present invention include analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group, for example an alkanoyloxy of from one to 5 seven carbon atoms or benzoyl group, or where the methoxy group is replaced by a mono or dialkyl carbamate or a mono or dialkyl carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 8 carbon atoms or wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl 10 and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Other useful analogs include compounds wherein, independently of whether or not the methoxy group has been replaced, the hydroxy group is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an acyloxy group, for example 15 an alkanoyloxy group, typically of from 1 to 7 carbon atoms, a benzoyloxy or substituted benzoyloxy group wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups, a carbonate group or a carbamate group which may be a mono or dialkyl or 20 an aryl carbamate or carbonate wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoromethyl groups and halo groups.

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xii) International Patent Application Publication No. WO1999/007359

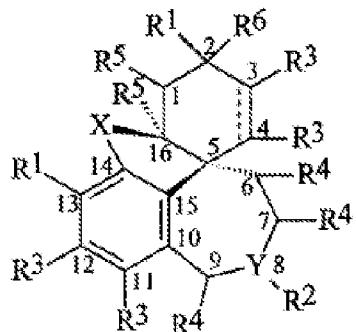
In some embodiments, cholinesterase inhibitors may include, but are not limited to, 30 physostigmine, tacrine and tacrine analogues, fasiculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these in which the inhibitor is modified in accordance with principles of pro-drug construction known in the art. Examples of such

modifications include the introduction of hydrophilic or lipophilic groups to enhance solubility, or penetration through cell membranes, respectively.

In some embodiments, cholinesterase inhibitors are acetylcholinesterase inhibitors, particularly those which are capable of crossing the blood brain barrier.

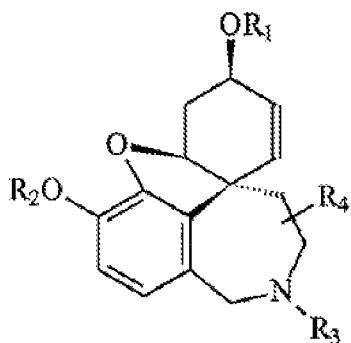
5      Particularly preferred cholinesterase inhibitors for use according to the invention include galantamine, epigalantamine and norgalantamine, and analogues, salts and derivatives of any of these. Galantamine was previously known as galanthamine. It is a tertiary alkaloid which can be extracted from various snowdrop bulbs e.g. the Caucasian snowdrop *galanthus woronowii*(Amaryllidaceae) and related species and daffodil bulbs or made by chemical synthesis. It has a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase. It is active substantially selectively at nicotinic receptor sites with substantially little effect on muscarinic receptor sites.

10     Particularly preferred cholinesterase inhibitors for use in the invention are 15     galantamine and its derivatives of formula (I):



wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each R1 is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, Cl6alkoxy, alkylthio, aryloxy, arylthio, R3substituted aryloxy, R3-substituted arylthio, aralkoxy, an optionally R3- 20     substituted aliphatic or aryl carbamyl group, aralkylthio, R3-substituted aralkoxy, R3substituted aralkylthio, aryloxymethyl, R3-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R3-substituted 25     benzoyloxy, aryloxycarbonyl and R3- substituted aryloxycarbonyl, R2 is selected from hydrogen, straight or branched chain Cl6alkyl, alkenyl or alkaryl group, optionally substituted by a halogen atom or a cycloalkyl, hydroxy,

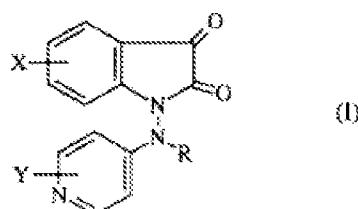
- alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroaryl-alkyl, aryl, arylalkyl, cyano, amyl, aroyl, cycloalkylmethyl, allyl, phenyl, R3-substituted phenyl, alkylphenyl, R3-substituted alkylphenyl, heterocycl selected from a- or ss-furyl, a- or ss-thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-  
5 heterocycl or R<sup>1</sup>-substituted heterocycl, where R<sup>1</sup> is alkyl or alkoxy, each R3 is independently selected from hydrogen, hydroxyl, sulfhydryl, alkyl, hydroxyalkyl, aryl, aralkyl, alkoxy, mercaptoalkyl, aryloxy, thiaryloxy, alkaryloxy, mercaptoalkaryl, nitro, amino, N-alkylamino, N-arylarnino, N-alkarylarnino, fluoro, chloro, bromo, iodo, and trifluoromethyl,  
10 each R4 is independently selected from hydrogen, halo, trifluoromethyl or Cl4-alkyl,  
each R5 is independently selected from hydrogen or hydroxymethyl,  
R6 is hydrogen or Cl6alkyl, or when R1 at carbon atom 2 is hydroxyl, R6 may be a moiety of formula I wherein R6 is hydrogen and R1 is a linking bond; or  
15 R1 at carbon atom 2 and R6 may jointly form semicarbazone,  
X is oxygen or NR3,  
Y is nitrogen or phosphorus,  
and methylenedioxy derivatives thereof and pharmaceutically acceptable acid addition salts thereof.  
20 Of the compounds of formula I which may be used in the method of the invention, some compounds are those in which the alkyl moieties contain 1 to 8 carbon atoms, halogen atoms are preferably fluorine, bromine, chlorine, aryl moieties are preferably phenyl, cycloalkyl groups are preferably 3- to 7-membered rings, especially cyclopropyl or cyclobutyl, acyl groups are preferably lower alkanoyl groups and heteroaryl moieties are preferably 5- to 8-membered rings, e.g., thienyl, furyl, pyridyl, pyrrolyl, or pyrizanyl.  
25 In some embodiments, compounds of formula I are the compounds of formula II



- wherein R1 and R2 which may be the same or different each represents a hydrogen atom or an acyl group, such as a lower alkanoyl group, e.g. an acetyl group or a straight-chained or branched alkyl group, e.g. methyl, ethyl, propyl, or isopropyl;
- 5 R3 is a straight or branched chain alkyl, alkenyl or alkaryl group which is optionally substituted by a halogen atom or a cycloalkyl, hydroxy, alkoxy, nitro, amino, aminoalkyl, acylamino, heteroaryl, heteroarylalkyl, aroyl, aroylalkyl or cyano group; and
- R4 represents a hydrogen or a halogen atom attached to at least one of the ring
- 10 carbons of the tetracyclic skeleton,
- and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.
- Formula II includes galantamine itself.
- In some embodiments, a compound is galantamine itself, and salts thereof such as
- 15 halides, for example galantamine hydrobromide.

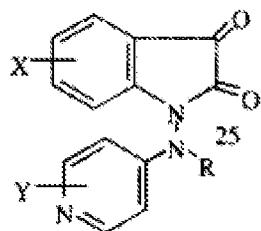
xiii) International Patent Application Publication No. WO1997/038993

This application relates to compounds of the formula



- 20 wherein
- R is hydrogen, (C1-C6)alkyl or hydroxy (C-C6)alkyl;
- X is hydrogen, hydroxy, (Ci-C6)alkoxy, phenyl(C1-C6)alkoxy, or -O(C=O)NRR ; and

- Y is hydrogen or halogen;
- where R is (C1-C6)alkyl, phenyl, or phenyl(Cl-C6)alkyl, where the phenyl group is optionally substituted by (C1-C6)alkyl, (C1-C6)alkoxy, halogen or trifluoromethyl;
- 5 R2 is hydrogen or (C1-C6)alkyl; or
- R and R2 taken together with the nitrogen to which they are attached form a tetrahydroisoquinoline group; and its pharmaceutically acceptable acid addition salts.
- The term “alkyl” shall mean a straight or branched alkyl group of the stated
- 10 number of carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, t-butyl, and straight and branched chain pentyl and hexyl.
- The term “halo” shall mean chloro, fluoro, bromo and iodo.
- The term “phenyl” shall mean phenyl having 0, 1, 2 or 3 substituents
- 15 independently selected from the group of (C1-C6)alkyl, (C1-C6)alkoxy, halo or trifluoromethyl.
- In a particular embodiment of the invention are compounds of the Formula (I)

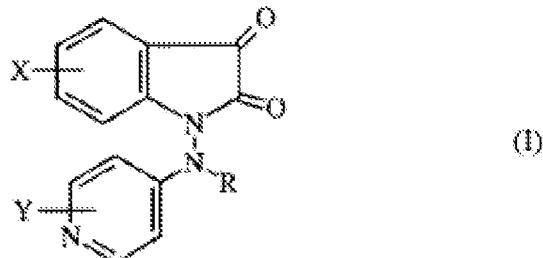


- wherein
- 20 R is hydrogen, (C1-C6)alkyl or hydroxy(C1-C6)alkyl;
- X is hydrogen, hydroxy, (C1-C6)alkoxy, benzyloxy, or -O(C=O)NR1R2 ; and
- Y is hydrogen or halogen;
- where R1 is (C1-C6)alkyl, phenethyl, or benzyl, where the phenyl group is
- 25 optionally substituted by (C1-C6)alkyl, (C1-C6)alkoxy, halogen or trifluoromethyl; and
- R2 is hydrogen or (C1-C6)alkyl; and its pharmaceutically acceptable acid addition salts.
- In one embodiment, when R1 is (C1-C6)alkyl, R2 is hydrogen.

In one embodiment are compounds of Formula I wherein R is (C1 -C6)alkyl.

In one embodiment X is hydrogen, Y is hydrogen and R is hydrogen, methyl, ethyl or propyl.

In another embodiment are compounds of Formula I



5

wherein

R is hydrogen, (Cs-C6)alkyl or hydroxy(C1-C6)alkyl;

X is hydrogen, hydroxy, (C1-C6)alkoxy, benzyloxy, or -O(C=O)NRIR2 ; and

10 Y is hydrogen or halogen; wherein

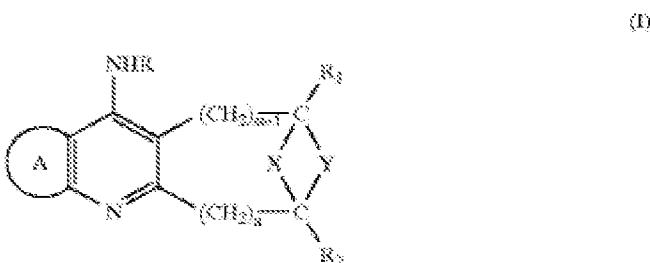
R and R2 taken together with the nitrogen to which they are attached form a tetrahydroisoquinoline group; and its pharmaceutically acceptable acid addition salts.

In one embodiment X is -O(C=O)NR'R2 and Y is hydrogen.

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xiv) U.S. Patent 5,965,569

The new aminopyridine compounds which are the subject of the present invention correspond to the general formula (I):

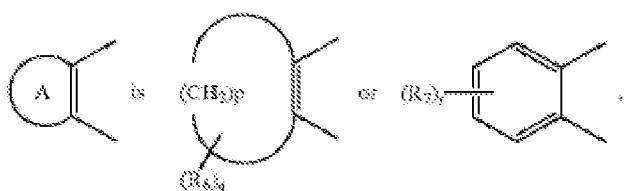


20 in which R can be hydrogen, alkyl, aralkyl or acyl;

R1 and R2 can be, independently, hydrogen, alkyl, aralkyl, alkoxy, alkoxycarbonyl, amino or amino substituted with one or two alkyl, aralkyl or acyl groups;

m and n can adopt the values 1, 2 or 3;

X and Y can be, independently, a bond between two carbons, an oxygen or sulphur atom, a group N--R3 or an alkylene or alkenylene bridge containing from 1 to 5 carbon atoms and which can contain one or more substituents R4. When X is an alkenylene group, the latter can be fused to a saturated or unsaturated carbocyclic or heterocyclic ring system, it being possible for the ring to be substituted with one or more groups R5 ; for example, X can be an ortho-phenylene group; and



p, q and r having a value equal to or greater than one and R6 and R7 being substituents which can individually be hydrogen, halogen, preferably fluorine or chlorine, lower alkoxy or lower alkyl.

In the above definitions:

The term "alkyl" represents a hydrocarbon residue having one to six carbon atoms with linear, branched, substituted cyclic or cycloalkyl chains, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, pentyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, and the like.

The term "aralkyl" means phenylalkyl or phenylalkyl substituted on the phenyl, containing from 7 to 12 carbon atoms. The term alkyl in "phenylalkyl" or "phenylalkyl substituted on the phenyl" means an alkylene group having a linear chain containing from one to four carbon atoms, for example methylene, ethylene, trimethylene or tetramethylene. The substituted phenyl in "phenylalkyl substituted on the phenyl" is a phenyl group containing one or more substituents selected from the group consisting of halogen, for example fluorine, chlorine, bromine and iodine, lower alkyl which includes alkyl groups containing from one to four carbon atoms with linear or branched chains, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl and tert-butyl, and lower alkoxy which includes an alkoxy group having a linear or branched chain containing from one to four carbon atoms, for example methoxy, ethoxy, propoxy, isopropoxy, butoxy and sec-butoxy.

Examples of such aralkyl groups include benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, 2-(4-methoxyphenyl)ethyl, 2-(2-methylphenyl)ethyl, 2-(4-fluorophenyl)ethyl and 4-(4-chlorophenyl)butyl.

5 The term “acyl” means an alkylcarbonyl or aralkylcarbonyl group in which the alkyl and aralkyl residues can adopt the meanings defined before.

In the context of R1 and R2, the terms alkyl and aralkyl have the meaning given above for R. The alkoxy substituent and the alkoxy group of the alkoxy carbonyl substituent can adopt the meanings given above for the lower alkoxy group. The alkyl, aralkyl and acyl substituents of the amino group can also adopt the meanings 10 given above in the context of R.

The group R3 of N--R3 can adopt the meanings defined above for R.

15 The groups R4 attached to the alkylene or alkenylene bridge can be, independently, hydrogen, lower alkyl, alkenyl or alkylidene having one to four carbon atoms with a linear or branched chain, phenyl, phenyl substituted with one or more lower alkyl groups having one to four carbon atoms, lower alkoxy groups having one to four carbon atoms or halogen (fluorine, chlorine, bromine or iodine) groups, aralkyl as defined above in the context of R, lower alkoxy containing from one to four carbons, and hydroxyl.

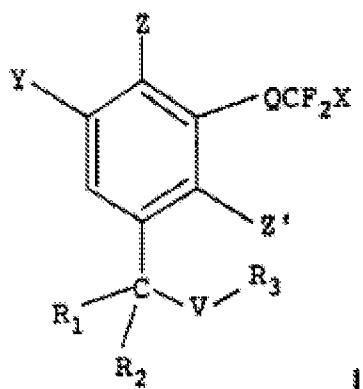
20 The groups R5 which are substituents of the ring fused to X or Y can be hydrogen, lower alkyl or lower alkoxy having one to four carbon atoms, or halogen (fluorine, chlorine, bromine and iodine).

25 Since the compounds of general formula (I) have at least two chiral centres, that is to say two asymmetric carbons, capable of generating optical isomerism, the present invention relates both to the racemic compounds and to all the possible enantiomers of these compounds or to the mixtures thereof in different proportions.

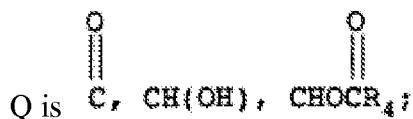
The pharmaceutically acceptable addition salts can be with organic or inorganic acids, such as hydrochloric, hydrobromic, sulphuric and nitric acids among inorganic acids and tartaric, succinic, maleic, fumaric and citric acids among organic acids.

30 xv) U.S. Patent 5,663,448

Compounds of the present invention have the following Formula I



stereoisomers and pharmaceutically acceptable salts thereof, wherein each of Z and Z' are independently H or F;



- 5 X is H, Br, Cl, F or CF3 ; Y is H, Br, Cl, F, OH, OR5, OC(O)R4, N3, CN, NO2, SO3 H, CO2 R4, NH2, NHR9, NR9 R'9, C(R6)(R7)(V'R8) or C(O)R7, provided that when both Z and Z' are F, then Y is H or F;
- V and V' are each independently CH2 or O;
- R1 is H or CH3 ;
- 10 R2, R9 and R'9 are each independently (C1-6)alkyl, or R2 and V--R3 taken together with the carbon atom to which they are attached form a 3-6 membered ring;
- R3, R6, R7 and R8 are each independently H, (C1-6)alkyl, or (C3-6)cycloalkyl;
- R4 is H, (C1-10)alkyl, (C0-4)alkylene aryl or (C3-8)cycloalkyl; and
- 15 R5 is (C1-10)alkyl, benzyl, phenethyl or (C3-6)cycloalkyl.
- The terms “(C1-6)alkyl” and “(C1-10)alkyl” mean straight or branched chain alkyl radicals containing respectively from 1 to 6 carbon atoms and from 1 to 10 carbon atoms, including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-
- 20 methylpentyl, 2,2-dimethylpropyl, n-hexyl and so on. Likewise, the term “(C0-4)alkylene aryl” can mean straight or branched chain alkylene groups up to 4 carbon atoms such as ethylethylene, 2-methyltrimethylene, and so on. C0 of course means no alkylene moiety attached to the aryl.

“Hydroxy(C1-6)alkyl” means a (C1-6)alkyl group having from 1 to 3 hydroxy substituents thereon. Preferably, there is only one hydroxy substituent at the alpha position (attached to the carbon atom which is directly attached to the phenyl).

“Ts” or “tosyl” means ##STR5## Tosyl derivatives mean ##STR6## wherein R is 5 C1-6 alkyl.

“Aryl” includes both carbocyclic and heterocyclic moieties of which phenyl, pyridyl, indolyl, indazolyl, furyl and thienyl are of primary interest; these moieties being inclusive of their position isomers such as, for example, 2-, 3-, or 4-pyridyl, 2- or 3-furyl and thienyl, 1-, 2-, or 3-indolyl or the 1- and 3-indazolyl, as well as 10 the dihydro and tetrahydro analogs of the furyl and thienyl moieties. Also included within the term “aryl” are such fused carbocyclic moieties as pentalenyl, indenyl, naphthalenyl, azulenyl, heptalenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl, anthracenyl, acephenanthrylenyl, aceanthrylenyl, triphenylenyl, pyrenyl, chrysenyl and naphthacenyl. Also included within the term “aryl” are such 15 other heterocyclic radicals as 2- or 3-benzo[b]thienyl, 2- or 3-naphtho[2,3-b]thienyl, 2- or 3-thianthrenyl, 2H-pyran-3-(or 4- or 5-)yl, 1-isobenzofuranyl, 2H-chromenyl-3-yl, 2- or 3-phenoxathiinyl, 2- or 3-pyrrolyl, 4- or 3-pyrazolyl, 2-pyrazinyl, 2-pyrimidinyl, 3-pyridazinyl, 2-indolizinyl, 1-isoindolyl, 4H-quinolizin-2-yl, 3-isoquinolyl, 2-quinolyl, 1-phthalazinyl, 1,8-naphthyridinyl, 2-quinoxalinyl, 20 2-quinazolinyl, 3-cinnolinyl, 2-pteridinyl, 4aH-carbazol-2-yl, 2-carbazolyl, .beta.-carbolin-3-yl, 3-phenanthridinyl, 2-acridinyl, 2-perimidinyl, 1-phenazinyl, 3-isothiazolyl, 2-phenothiazinyl, 3-isoxazolyl, 2-phenoxazinyl, 3-iso-chromanyl, 7-chromanyl, 2-pyrrolin-3-yl, 2-imidazolidinyl, 2-imidazolin-4-yl, 2-pyrazolidinyl, 3-pyrazolin-3-yl, 2-piperidyl, 2-piperazinyl, 1-indolinyl, 1-isoindolinyl, 3-morpholinyl, benzo[h]isoquinolinyl, and benzo[b]furanyl, including the position 25 isomers thereof except that the heterocyclic moieties cannot be attached directly through their nitrogen atoms. Aryl groups can be substituted or unsubstituted with one, two or three substituents independently selected from C1-6 alkyl, haloalkyl, alkoxy, thioalkoxy, aminoalkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, carboalkoxy and carboxamide.

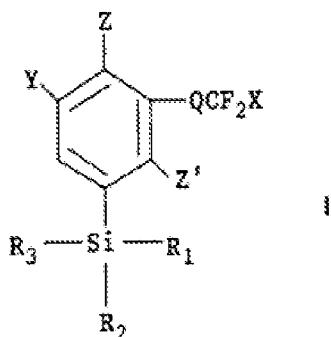
When R2 and V--R3 are taken together, they may form a 3 membered ring which includes the carbon atom to which R2 and V are attached (when R3 is H). Other

rings formed may have 4, 5 and 6 members to the ring. The term 3-6 membered ring refers to the number of carbon atoms, and oxygen atoms (when V is O) comprising the structure of the ring.

“Stereoisomers” for the compounds of Formula I is a general term for all isomers 5 of individual molecules that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric isomers (cis/trans), and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers), whichever forms are applicable to the compound.

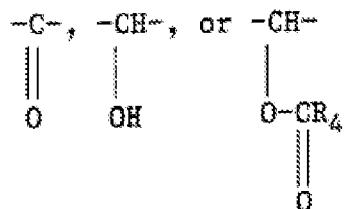
10 xvi) European Patent Application No. EP0611769

Compounds of the present invention have the following Formula I:



stereoisomers or mixtures thereof, and pharmaceutically acceptable salts thereof, wherein:

15 each of Z and Z' are independently H or F, provided that at least one of Z or Z' is F;



X is H, Br, Cl, F or CF<sub>3</sub>;

Y is H, OH, (C<sub>1</sub>-6) alkyl, -(CH<sub>2</sub>)<sub>m</sub>OR<sub>5</sub>, hydroxy (C<sub>1</sub>-6) alkyl, (CH<sub>2</sub>)<sub>n</sub>NR<sub>6</sub>R<sub>6</sub>', azido, CN, CO<sub>2</sub>R<sub>4</sub>, COR<sub>6</sub>, SO<sub>3</sub>H, Br, Cl, F, NO<sub>2</sub> or -(CH<sub>2</sub>)<sub>n</sub>SiR<sub>1</sub>'R<sub>2</sub>'R<sub>3</sub>', provided that when both Z and Z' are F then Y is H or F;

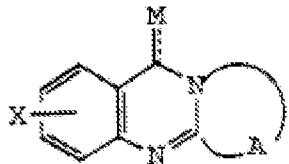
R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>1</sub>', R<sub>2</sub>' and R<sub>3</sub>' are each independently C<sub>1</sub>-10 alkyl or (CH<sub>2</sub>)<sub>n</sub> aryl; R<sub>4</sub> is H, (C<sub>1</sub>-10) alkyl, phenyl, benzyl or phenethyl;

- R5 is H, (C1-10) alkyl, benzyl or phenethyl;  
R6 and R6' are independently hydrogen or C1-10 alkyl;  
m is an integer of 0, 1, 2, 3 or 4; and  
n is an integer of 0, 1 or 2.
- 5 The terms “(C1-6) alkyl” and “(C1-10) alkyl” mean straight or branched chain alkyl radicals containing respectively from 1 to 6 carbon atoms and from 1 to 10 carbon atoms, including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and so on. Likewise, the terms  
10 “(CH<sub>2</sub>)<sub>n</sub>” or “(CH<sub>2</sub>)<sub>m</sub>” may represent alkylene chains which may be branched or straight-chained.
- “Hydroxy(C1-6) alkyl” means a (C1-6) alkyl group having from 1 to 3 hydroxy substituents thereon. Preferably, there is only one hydroxy substituent at the alpha  
15 position (attached to the carbon atom which is directly attached to the phenyl).  
“Ts” or “tosyl” means EMI3.1 Tosyl derivatives mean EMI3.2 wherein R is C1-6 alkylene.
- “Aryl” includes both carbocyclic and heterocyclic moieties of which phenyl, pyridyl, indolyl, indazolyl, furyl and thienyl are of primary interest; these moieties  
20 being inclusive of their position isomers such as, for example, 2-, 3-, or 4-pyridyl, 2- or 3-furyl and thienyl, 1-, 2-, or 3-indolyl or the 1- and 3-indazolyl, as well as the dihydro and tetrahydro analogs of the furyl and thienyl moieties. Also included within the term “aryl” are such fused carbocyclic moieties as pentalenyl, indenyl, naphthalenyl, azulenyl, heptalenyl, acenaphthylenyl, fluorenyl, phenalenyl,  
25 phenanthrenyl, anthracenyl, acephenanthrylenyl, aceanthrylenyl, triphenylenyl, pyrenyl, chrysenyl and naphthacenyl. Also included within the term “aryl” are such other heterocyclic radicals as 2- or 3-benzo[b]thienyl, 2- or 3-naphtho-[2,3-b]thienyl, 2- or 3-thianthrenyl, 2H-pyran-3-(or 4- or 5-)yl, 1-isobenofuranyl, 2H-chromenyl-3-yl, 2- or 3-phenoxathiinyl, 2- or 3-pyrrolyl, 4- or 3-pyrazolyl, 2-  
30 pyrazinyl, 2-pyrimidinyl, 3-pyridazinyl, 2-indolizinyl, 1-isoindolyl, 4H-quinolizin-2-yl, 3-isoquinolyl, 2-quinolyl, 1-phthalazinyl, 1,8-naphthyridinyl, 2-quinoxalinyl, 2-quinazolinyl, 3-cinnolinyl, 2-pteridinyl, 4aH-carbazol-2-yl, 2-carbazolyl, beta -

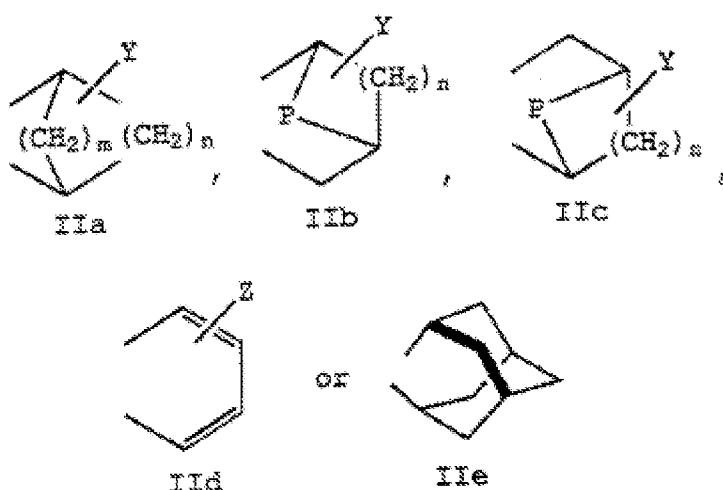
- carbolin-3-yl, 3-phenanthridinyl, 2-acridinyl, 2-perimidinyl, 1-phenazinyl, 3-isothiazolyl, 2-phenoxythiazinyl, 3-isoxasolyl, 2-phenoxyasolyl, 3-isochromanyl, 7-chromanyl, 2-pyrrolin-3-yl, 2-imidazolidinyl, 2-imidazolin-4-yl, 2-pyrazolidinyl, 3-pyrazolin-3-yl, 2-piperidyl, 2-piperazinyl, 1-indolinyl, 1-isoindolinyl, 3-morpholinyl, benzo[h]isoquinolinyl, and benzo[b]furanyl, including the position isomers thereof except that the heterocyclic moieties cannot be attached directly through their nitrogen atoms. Aryl groups can be substituted or unsubstituted with one, two or three substituents independently selected from C1-6 alkyl, haloalkyl, alkoxy, thioalkoxy, aminoalkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, carboalkoxy and carboxamide.
- R1, R2, R3, R1', R2', and R3' are each independently selected from C1-10 alkyl or (CH<sub>2</sub>)<sub>n</sub> aryl which means that, for example, R1 could be benzyl while R2 is methyl. In other words, none of R1, R2, R3, R1', R2', or R3' have to be the same moiety, although this may be the case.
- “Stereoisomers” for the compounds of Formula I is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric isomers (cis/trans), and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers), whichever forms are applicable to the compound.

xvii) International Patent Application Publication No. WO1993/03034

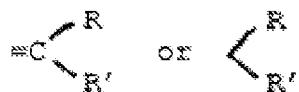
The present invention also includes novel compounds of the formula



wherein A represents



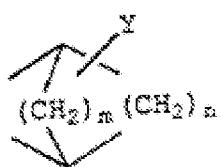
in which n is 1-10, P is a bond or  $(CH_2)_m$  in which m is 0-10, wherein a nitrogen, oxygen, or sulfur atom may replace a methylene group in ring A, which is not adjacent to the quinazoline moiety, and attached to a carbon atom in ring A is Y, in  
 5 which Y is hydrogen, hydroxy, halogen, carboxy, lower alkoxy, lower alkyl, aryl, heteroaryl, keto, lower alkoxy carbonyl or lower alkanoyl;  
 M is  $=S$ ,  $=NR$ ,



in which R and R' are independently hydrogen, hydroxy, lower alkyl,  
 10 lower alkoxy, lower alkenyl, lower alkynyl, aryl, aryloxy, aryl lower alkyl, heteroaryl or  
 heteroaryl lower alkyl and, when taken together, may form a three- to six-  
 membered ring optionally containing one to three heteroatoms selected from  
 nitrogen, oxygen, and sulfur; and  
 15 X is absent or one to four substituents selected from halogen, alkyl(C1~22),  
 straight or branched,  
 saturated or alkenyl or alkynyl, if alkyl of appropriate size can form a ring,  
 saturated or  
 unsaturated, containing (or not containing) one or more heteroatoms, such as O, S,  
 20 N, Se, P, and  
 the like, or an aromatic or heteroaromatic ring containing (or not containing) one  
 or more

heteroatoms, such as O, S, N, Se, and the like, primary, secondary, or tertiary amino nitro-lower alkylthio, or aryl (or heteroaryl)thio, mercapto, hydroxy, carboxy, lower alkoxy, or aryl (or heteroaryl)oxy, alkyl (C1-22) or aryl (or heteroaryl)sulfinyl, alkyl (C1-22), or aryl (or heteroaryl) sulfonyl, perfluoroalkyl (C1-22), such as trifluoromethyl, perfluoroalkoxy (C1-22) r such as trifluoromethoxy, perfluoroalkylthio (C122), such as trifluoromethylthio, perfluoroalkyl sulfinyl(C122), such as trifluoromethylsulfinyl, perfluoroalkylsulfonyl (C1-22) r such as trifluoromethylsulfonyl, alkyl (C1-22), or aryl (or heteroaryl)carbamoyl, or diacylamino, including cyclic imido, such as succinimido, alkyl(C1~22), or aryl (or heteroaryl)sulfinylamido, alkyl(C122), or aryl (or heteroaryl) sulfonylamido, perfluoroalkyl (C1-22) sulfinylamido, such as trifluoromethyl sulfinylamido, perfluoroalkyl (C1-22) sulfonylamido, such as trifluoromethyl sulfonylamido above, trialkylsilyl, such as trimethylsilyl, or triethylsilyl, acyl, such as acetyl, benzoyl, phenylacetyl, hydrocinnamoyl, and the like, perfluoroacyl, such as trifluoroacetyl, heptafluorobutyryl, and the like, acyl-lower alkyl, such as acetyl methyl, benzoylmethyl, phenylacetylmethyl, hydrocinnamoylmethyl, and the like, perfluoroacyl-lower alkyl, such as trifluoroacetylmethyl, heptafluorobutyrylmethyl, and the like, alkyl (C1-22), or aryl (or heteroaryl)carbamoyloxy, dialkyl(C122), or diaryl (or diheteroaryl) carbamoyloxy, alkyl(C1-22) or aryl (or heteroaryl) carbamoylthio, alkyl(C1-22) r or aryl (or heteroaryl)carbamoylalkyl, or diacylaminoalkyl, including cyclic imidoalkyl, such as acetamidomethyl, octanamidomethyl, or succinimidomethyl, aryl or aryl lower alkyl, including substituted aryl with groups such as halogen and groups described heteroaryl or heteroaryllower alkyl, such as furan, thiophene, pyrrole, pyridine and the like, including substituted derivatives with groups such as halogen and groups described above; Z is hydrogen, halogen, alkyl (C1-12)r straight or branched, saturated or alkenyl or alkynyl if alkyl of appropriate size can form a ring,

saturated or unsaturated, containing or not containing one or more heteroatoms, selected from O, S, and N, can also form an aromatic or heteroaromatic ring containing or not containing one or more heteroatoms, selected from O, S, and N, primary, secondary, or tertiary aminolower alkylthio-, aryl-, heteroarylthio, 5 mercapto, hydroxy, carboxy, carbalkoxy in which alkyl is C1-C22, lower alkoxy, aryl, or heteroaryloxy, perfluoroalkyl in which alkyl is C1-C22, perfluoroalkoxy in which alkyl portion is C1-C22), alkyl (C122), aryl or heteroarylcarbamoyl, diacylamino, cyclic imido, or acyl, or a pharmaceutically acceptable acid addition salt thereof; with the proviso that when A is

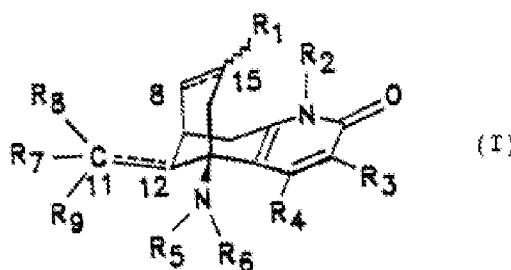
10 **IIIa**

in which n is 1-3, m is 0, Y is hydrogen, and M is RR' where R and R' are both hydrogen, X cannot be absent or a single hydroxy or methoxy group; and when A is of the Formula IIId, X is

15 1,3-dihalogeno or 2,4-dihalogeno.

xviii) International Patent Application Publication No. WO1992/019238

The present invention provides a number of compounds of general formula (I), which are formally derivatives of huperzine A:



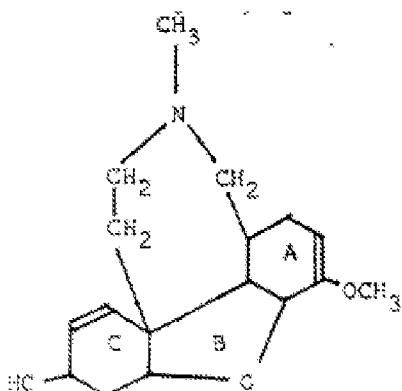
20 wherein R1 is H, (C1-C8)alkyl or halo; R2 is H or (C1-C8)alkyl; R3 and R4 are individually H, (C1-C8)alkyl, NO<sub>2</sub>, hydroxy or halo; R5 and R6 are individually H, (C1-C8)alkyl, aryl or aralkyl; R7 is H, halo or (C1-C8)alkyl, R8 is halo or (C1-C8)alkyl, R9 is absent or is H; and the bonds represented by -- are individually absent or, together with the adjacent bond, form the unit C.dbd.C, with the proviso

that if both of the bonds represented by--are present, R3 and R4 cannot both be H unless R7 or R8 is halo; and the pharmaceutically acceptable salts thereof. Therefore, the genus of compounds of formula I does not include huperzine A itself, or the simple N-alkylated derivatives thereof. Preferably, R1 is H, halo (Cl, 5 Br, I or F, most preferably F) or methyl. Preferably, R2 is H, preferably R3 is nitro or halo, preferably R4 is (C1 -C4)alkyl or OH, and preferably R5 .dbd.R6 .dbd.H. Preferably R7 and R9 are H and R8 is (C1 -C4)alkyl. Preferably, at least one of the bonds represented by--is absent. Therefore, the preferred compounds of formula I are dihydro or bis(di-hydro)analogs of huperzine A which can also comprise 10 substituents on the pyridone ring, or are pyridone ring-substituted analogs of huperzine A.

The compounds of the general formula I or II may exist in the form of optical isomers, and these isomers, as well as racemic (+-) mixtures are included within the invention. The present invention also includes both the 12R and 12S, and both 15 the 15R and 15S enantiomers of the present compounds, as well as unresolved or partially resolved mixtures thereof. The term "alkyl" includes linear or branched alkyl. The terms "aryl" and "aralkyl" are fully defined hereinbelow. In some embodiments aryl groups include phenyl, tolyl, xylyl, anisyl and the like. In some embodiments aralkyl groups include arlyoxy- and aryl-(C1 -C3)alkyl moieties.

20 The C15 --R1 bond is waved to indicate that the R1 substituent, when present may be equatorial or axial, or a mixture thereof. Although for convenience, the C11 - C12 bond is positioned equatorially, it may be either equatorial, axial or a mixture thereof.

25 xix) European Patent Application No. EP0236684  
Galanthamine is generally regarded as having the structure:



Compounds of a similar structure wherein the hydroxy is replaced by methoxy, ethoxy, lower alkanoyl oxy such as acetyloxy or oxy, the methoxy group is replaced by hydrogen, methoxy, ethoxy, or lower alkanoyloxy such as acetyloxy and the methyl group substituted on the nitrogen atom is replaced by other straight or branch chain lower alkyl groups such as ethyl, cyclopropylmethyl or cyclobutylmethyl, allyl, lower alkyl phenyl or substituted lower alkyl phenyl wherein the substituents are fluoro, chloro, bromo, lower alkoxy, hydroxy, nitro, amino lower alkyl or acylamino of from 1 to 5 carbon atoms, heteroaryl lower alkyl in which the heteroaryl group is thieryl, furyl, pyridyl, pyrrolyl, or pyrazinyl, or a cyano radical; or unsubstituted and halogen substituted benzoyl lower alkyl in which the substituents are on the phenyl ring, and compounds wherein hydrogen atoms in the “core” structure have been replaced by fluoro or chloro groups or the carbon to carbon single bond between the carbons common to the B and C rings is replaced by a double bond are likely to have similar properties to galanthamine.

and xx) U.S. Patent 4,895,841

The invention provides a cyclic amine compound having the following formula (XXV) and a pharmacologically acceptable salt thereof:



20

in which J is

(a) a group, substituted or unsubstituted, selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl and (7) furyl;

- (b) a monovalent or divalent group, in which the phenyl may have a substituent(s), selected from the group consisting of (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl and (9) C<sub>6</sub> H<sub>5</sub> --CO--CH(CH<sub>3</sub>)--;
- 5 (c) a monovalent group derived from a cyclic amide compound;
- (d) a lower alkyl or
- (e) a group of R<sub>21</sub> --CH.dbd.CH-- in which R<sub>21</sub> is hydrogen or a lower alkoxy carbonyl (dbd stands for a double bond);
- B is --(CHR<sub>22</sub>)<sub>r</sub>--, --CO--(CHR<sub>22</sub>)<sub>r</sub>--, --NR<sub>4</sub>--(CHR<sub>22</sub>)<sub>r</sub>--, R<sub>4</sub> being hydrogen, a lower alkyl, an acyl, a lower alkylsulfonyl, phenyl, a substituted phenyl, benzyl or a substituted benzyl, --CO--NR<sub>5</sub>--(CHR<sub>22</sub>)<sub>r</sub>--, R<sub>5</sub> being hydrogen, a lower alkyl or phenyl, --CH.dbd.CH--(CHR<sub>22</sub>)<sub>r</sub>--, --OCOO--(CHR<sub>22</sub>)<sub>r</sub>--, --OOC--NH--(CHR<sub>22</sub>)<sub>r</sub>--, --NH--CO--(CHR<sub>22</sub>)<sub>r</sub>--, --CH<sub>2</sub>--CO--NH--(CHR<sub>22</sub>)<sub>r</sub>--, --(CH<sub>2</sub>)<sub>2</sub>--NH--(CHR<sub>22</sub>)<sub>r</sub>--, --CH(OH)--(CHR<sub>22</sub>)<sub>r</sub>--, r being zero or an integer of 1 to 10,
- 10 15 R<sub>22</sub> being hydrogen or methyl so that one alkylene group may have no methyl branch or one or more methyl branch, .dbd.(CH--CH.dbd.CH)<sub>b</sub>--, b being an integer of 1 to 3, .dbd.CH--(CH<sub>2</sub>)<sub>c</sub>--, c being zero or an integer of 1 to 9, .dbd.(CH--CH)<sub>d</sub>.dbd., d being zero or an integer of 1 to 5; --CO--CH.dbd.CH--CH<sub>2</sub>--, --CO--CH<sub>2</sub>--CH(OH)--CH<sub>2</sub>--, --CH(CH<sub>3</sub>)--CO--NH--CH<sub>2</sub>--, --
- 20 25 CH.dbd.CH--CO--NH--(CH<sub>2</sub>)<sub>2</sub>--, --NH--, --O--, --S--, a dialkylaminoalkylcarbonyl or a lower alkoxy carbonyl;
- T is a nitrogen or carbon;
- Q is nitrogen, carbon or
- N → O;
- 25 and
- q is an integer of 1 to 3;
- K is hydrogen, phenyl, a substituted phenyl, an arylalkyl in which the phenyl may have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, a cycloalkylalkyl, adamantanemethyl, furylmenthyl, a cycloalkyl, a lower alkoxy carbonyl or an acyl;
- 30 and
-

shows a single bond or a double bond.

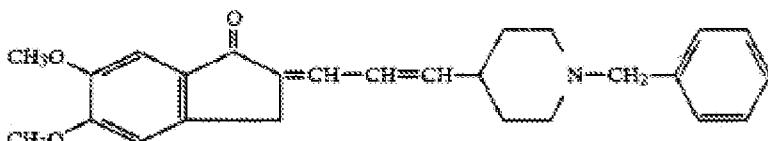
In the compounds having the formula (XXV), it is preferable that J is (a) or (b). In the definition (b), monovalent groups of (2), (3) and (5) and divalent groups of (2) are preferable. In the definition of B, --(CHR22) r--, .dbd.(CH--CH.dbd.CH)b--, 5 .dbd.CH--(CH2)c-- and .dbd.(CH--CH)d.dbd. are preferable. These preferable groups of (B) may be connected with (b) of J, in particular (2) of (b).

It is preferable in the formula (XXV) that Q is nitrogen, T is carbon and q is 1 or 3; and Q is carbon, T is nitrogen and q is 2. It is most preferable that Q is nitrogen, T is carbon and q is 2.

10 It is preferable that K is a phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

Preferable compounds of the invention include:

1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,  
 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methylpiperidine,  
 15 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine,  
 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine,  
 1-benzyl-4-((5,6-methylenedioxy-1-indanon)-2-yl)methylpiperidine,  
 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,  
 1-cyclohexymethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,  
 20 1-(m-florobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,  
 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine,  
 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine and  
 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine, having the  
 below shown formula.



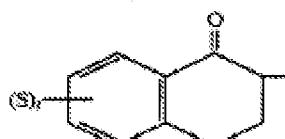
25 In addition, the invention provides a therapeutical composition which comprises a pharmacologically effective amount of the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier and then a method for preventing and treating 30 a disease due to the acetylcholinesterase activity by administering to a human

patient the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof.

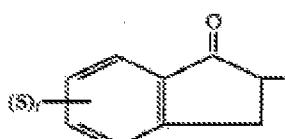
The preferable compound has the above shown formula in which J is (b). The group (b) includes ten groups having the respective formulae shown below. S is 5 hydrogen or a substituent such as a lower alkyl having 1 to 6 carbon atoms and a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferable. t is an integer of 1 to 4. The phenyl is most preferred to have 1 to 3 methoxy groups thereon. (S)<sub>t</sub> may form methylene dioxy group or ethylene dioxy group on two adjacent carbon atoms of the phenyl group.



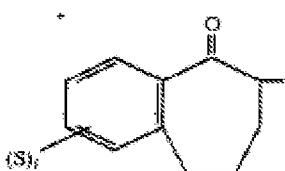
indanyl



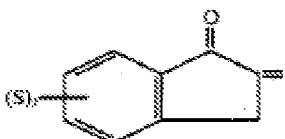
tetraisopropyl



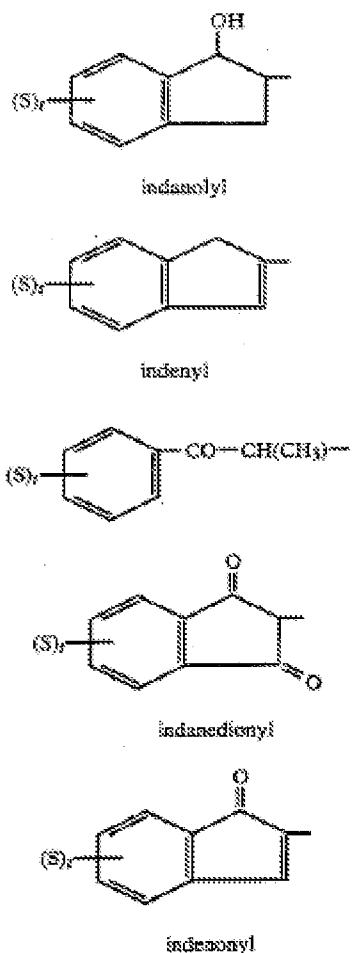
indenonyl



benzosuberoxy



indenoxylidienyl



A preferable definition of B includes --(CHR22)r --, --CO--(CHR22)r --, .dbd.(CH-CH.dbd.CH)b --, .dbd.CH--(CH<sub>2</sub>)c -- and .dbd.(CH--CH)d .dbd.. The group of --(CHR22)r -- in which R22 is hydrogen and r is an integer of 1 to 3 and then the group of .dbd.CH--(CH<sub>2</sub>)c --are most preferable.

In the above defined cyclic amine compound of the invention, it is preferable that J in the formula is (b) the monovalent or divalent group. In the definition (b), indanonyl, indanedionyl and indenyl are most preferable, optionally having a substituent(s) on the phenyl.

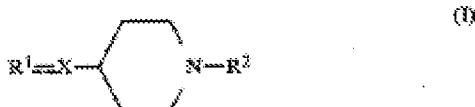
In the definition B, --(CHR22)r -- and .dbd.CH--(CH<sub>2</sub>)c -- are preferable. In the ring including T and Q, it may be a 5-, 6-or 7-membered ring. It is preferable that Q is nitrogen, T is carbon or nitrogen and n is 2; Q is nitrogen, T is carbon and n is 1 or 3; and Q is carbon, T is nitrogen and n is 2.

15 In the definition K, phenyl, an arylalkyl and cinnamyl are preferable, optionally having a substituent(s) on the phenyl.

The invention will be explained in detail in view of the piperidine compounds

which fall within the scope of the above defined cyclic amine compound. The explanation applies to the entire invention of the cyclic amine compound.

The piperidine compound is defined by the formula (I):

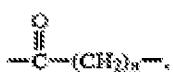


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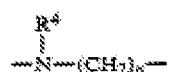
wherein R1 is the following substituted or unsubstituted group: .circle.1 a phenyl group, .circle.2 a pyridyl group, .circle.3 a pyrazyl group, .circle.4 a quinolyl group, .circle.5 an indanyl group, .circle.6 a cyclohexyl group, .circle.7 a quinoxalyl group, or 11 .circle.8 a furyl group; a monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl ring; a monovalent group derived from a cyclic amide compound; a lower alkyl group or a group represented by the formula R3 --CH.dbd.C-- (wherein R3 is a hydrogen atom or a lower alkoxy carbonyl group),

10 X is a group represented by the formula --(CH<sub>2</sub>)<sub>n</sub>--, a group represented by the formula

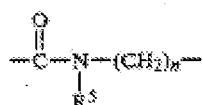
15



a group represented by the formula



(wherein R4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, or a substituted or unsubstituted phenyl or benzyl group), a group represented by the formula

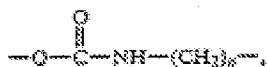


(wherein R5 is a hydrogen atom, a lower alkyl group, or a phenyl group), a group represented by the formula --CH.dbd.CH--(CH<sub>2</sub>)<sub>n</sub>--, a group represented by the formula

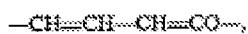
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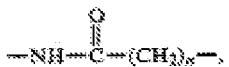
a group represented by the formula



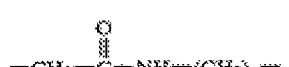
a group represented by the formula



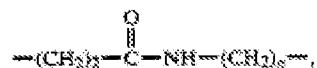
a group represented by the formula



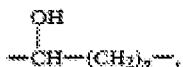
5 a group represented by the formula



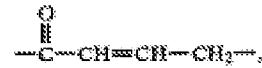
a group represented by the formula



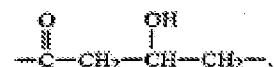
10 a group represented by the formula



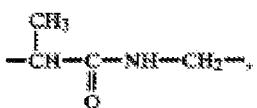
a group represented by the formula



a group represented by the formula



15 a group represented by the formula



a group represented by the formula



20 a dialkylaminoalkylcarbonyl group, or a lower alkoxy carbonyl group, provided that n's in the above definition of X are each independently an integer of 0 to 6, R2 is a substituted or unsubstituted phenyl group, a substituted or unsubstituted arylalkyl group, a cinnamyl group, a lower alkyl group, a pyridylmethyl group, a

cycloalkylalkyl group, an adamantanemethyl group, or a furoylmethyl group, and a symbol, ~~=====~~ in the above general formula, means a single bond or a double bond.

The term “lower alkyl group” used in the above definition of R1, R2, R4 and R5 with respect to the compound (I) of the present invention is intended to mean a straight-chain or branched alkyl group having 1 to 6 carbon atoms, and examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, and 1-ethyl-2-methylpropyl groups. Among them, methyl, ethyl, propyl, isopropyl groups etc, are preferable. A methyl group is the most preferable.

15 Examples of the substituent involved in the expression “the following substituted or unsubstituted group: (1) a phenyl group, (2) a pyridyl group, (3) a pyrazyl group, (4) a quinolyl group, (5) an indanyl group, (6) a cyclohexyl group, (7) a quinoxalyl group, or (8) a furyl group” in the definition of R1 include lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy group corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms such as chlorine, bromine, and fluorine; a carboxyl group; lower alkoxy carbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group, a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups,

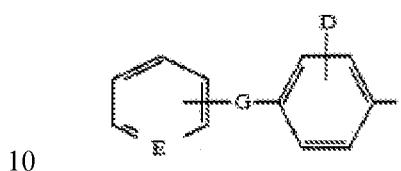
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such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups including a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy lower alkyl groups such as ethoxymethyl, methoxymethyl, and methoxyethyl groups. The “lower alkyl groups” and “lower alkoxy groups” in the above description of the substituent include all the groups derived from the above-mentioned groups. The substituent may be one to three of them which may be the same or different.

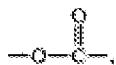
5 Further when the substituent is a phenyl group, the following group is within the scope of the substituted phenyl group:



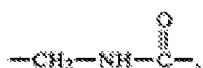
wherein G is a group represented by the formula



a group represented by the formula



15 a group represented by the formula --O--, a group represented by the formula



a group represented by the formula --CH2--O--, a group represented by the formula --CH2--SO2--, a group represented by the formula



20 and a group represented by the formula



and E is a carbon or nitrogen atom.

Preferable examples of the substituents for the phenyl group among them include lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxy carbonyl, 25 formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzoyl and benzylsulfonyl groups. The substituent may be two or more of them

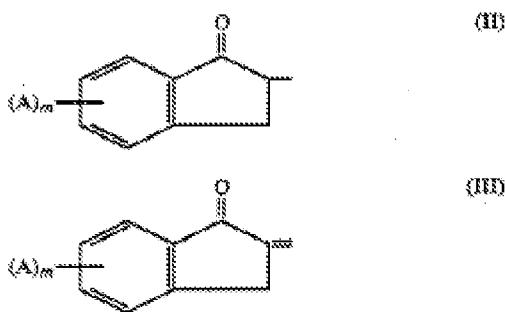
which may be the same or different.

Preferable examples of the substituent for the pyridyl group include loweralkyl and amino groups and halogen atoms.

Preferable examples of the substituent for the pyrazyl group include lower 5 alkoxycarbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxycarbonyl groups.

With respect to R1, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group is preferably a 2-quinolyl or 3-quinolyl group; the quinoxalinyl group is 10 preferable a 2-quinoxalinyl or 3-quinoxalinyl group; and the furyl group is preferably a 2-furyl group.

Specific examples of preferable monovalent or divalent group derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by the following formulae (II) and (III):

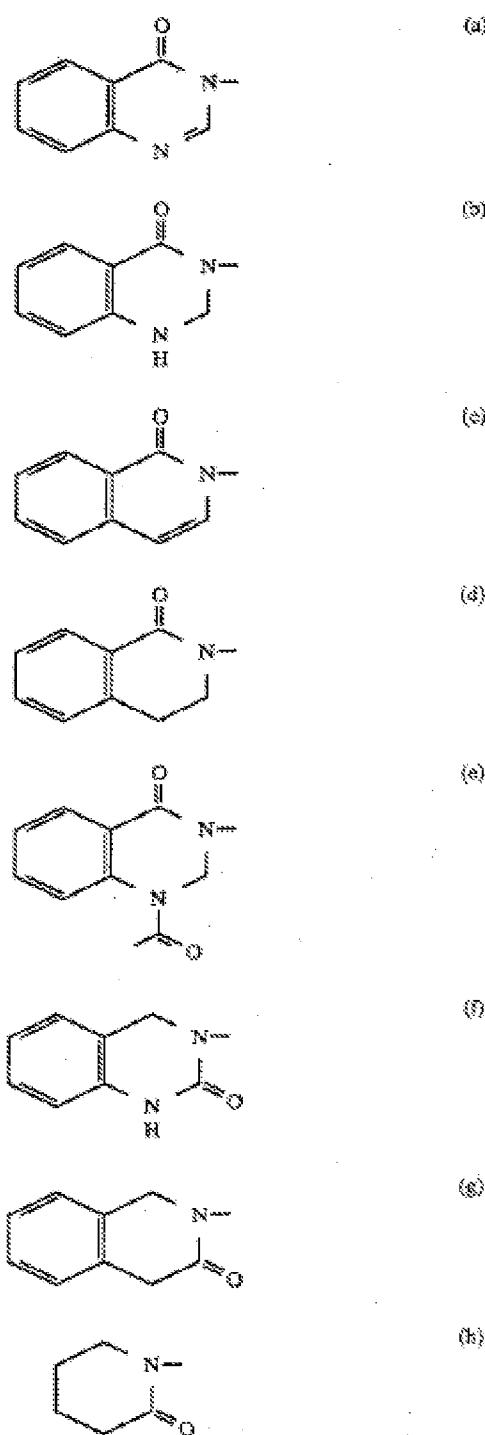


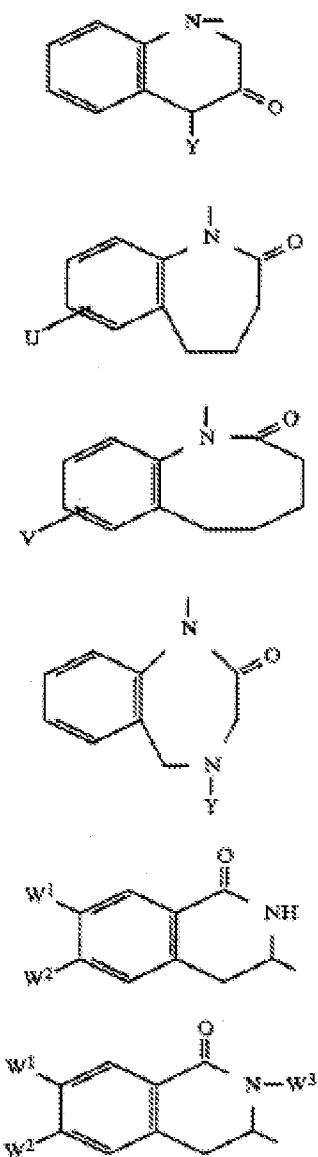
15 wherein m's are each an integer of 1 to 4 and A's which may be the same or different are each one of the substituents described in the above items (1) to (8) of the definition of R1 or a hydrogen atom, preferably a hydrogen atom (i.e. unsubstituted), a lower alkyl group, or a lower alkoxy group, and most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group may be any one having a cyclic amide group in the structural formula thereof and is not limited to the 20 above-described specific examples only. The cyclic amide group may be one derived from a monocyclic or condensed heterocyclic ring. The condensed 25 heterocyclic ring is preferably one formed by condensation with a phenyl ring. In

this case, the phenyl ring may be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferable examples of the monovalent group include the following groups:





In the above formulae, Y's in the formulae (i) and (l) are each a hydrogen atom or a lower alkyl group, V in the formula (k) is a hydrogen atom or a lower alkoxy group, W1 and W2 in the formulae (m) and (n) are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group and W3 is a hydrogen atom or a lower alkyl group.

The right-hand ring in each of the formulae (j) and (l) is a seven-membered ring, while the right-hand ring in the formula (k) is an eight-membered ring.

Certain examples of the above-defined R1 include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

Certain examples of the above-defined X include a group represented by the formula  $-(CH_2)_n-$ , a group having an amide group, and groups represented by the above formulae wherein n is 2. Therefore, it is most preferable that any portion of a group represented by the formula

5

~~R<sup>1</sup>— $\overset{\text{R}^2}{\text{C}}\text{—X—}$~~ 

have a carbonyl or amide group.

The substituents involved in the expressions “a substituted or unsubstituted phenyl group” and “a substituted or unsubstituted arylalkyl group” in the above definition of R<sub>2</sub> are the same as those described in the above items (1) to (8) in the above 10 definition of R<sub>1</sub>.

The term “arylalkyl group” is intended to mean an unsubstituted benzyl or phenethyl group, etc.

Specific examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

15 Preferable examples of R<sub>2</sub> include benzyl and phenethyl groups. The symbol

~~— $\overset{\text{R}^2}{\text{C}}\text{—}$~~ 

means either a single or a double bond. This bond is a double bond only when R<sub>1</sub> is the above-described divalent group (III) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

20 The compounds of the present invention may have an asymmetric carbon atom depending upon the kind of the substituent and, therefore, have stereoisomers.

They are, of course, within the scope of the present invention.

25 One specific example thereof will now be described. When R<sub>1</sub> has an indanone skeleton, the compound of the present invention has an asymmetric carbon atom and, therefore, may have stereoisomers, optical isomers, diastereomers, etc. All of these isomers are within the scope of the present invention.

**30 Method of Treating Cognitive Impairment Associated with CNS Disorders with the Administration of an SV2A Inhibitor and an AChEI or Pharmaceutically Acceptable Salts Thereof**

[0183] In one aspect, the invention provides methods and compositions for treating,

or improving cognitive function in, a subject suffering from cognitive impairment associated with a CNS disorder (e.g., age-related cognitive impairment, MCI, amnestic MCI, dementia, AD, prodromal AD, PTSD, schizophrenia, bipolar disorder, ALS, cancer therapy-related cognitive impairment, mental retardation, Parkinson's disease 5 (PD), autism, compulsive behavior, and substance addiction), or the risk thereof in a subject in need thereof by administering a composition comprising an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in an extended release form in combination with an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in an immediate 10 release form. 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. In other embodiments, the SV2A inhibitor is levetiracetam or a derivative or 15 an analog or a pharmaceutically acceptable salt, or a solvate, or a hydrate, or a polymorph, or a prodrug thereof. In some embodiments, the AChEI is donepezil, tacrine, rivatigmine, physostigmine, galantamine, or metrifonate or derivatives or analogs or pharmaceutically acceptable salts, or solvates, or hydrates, or polymorphs, or prodrugs thereof. In other embodiments, the AChEI is donepezil or a derivative or 20 an analog or a pharmaceutically acceptable salt or a solvate, or a hydrate, or a polymorph, or a prodrug thereof. In some embodiments, the cognitive impairment associated with a CNS disorder is age-related cognitive impairment, such as Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age Related Cognitive Decline (ARCD). In one embodiment of the invention, the MCI is amnestic MCI. In some embodiments of the invention, the CNS disorder is dementia, 25 post traumatic stress disorder (PTSD), schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, and substance addiction. In one embodiment, the subject that suffers such cognitive impairment 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. 30 [0184] When used clinically, donepezil shows a "cholinergic" side effect profile, and the dosage administered to patients is limited by such side effects. The use of the

SV2A inhibitors and pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof in combination with donepezil or other AChEIs and their pharmaceutically acceptable salts, hydrates, solvates and polymorphs reduces the amount of donepezil or other AChEIs necessary for the treatment of CNS disorders 5 involving cognitive dysfunction and other affective disorders, including MCI, amnestic MCI, AAMI, ARCE, dementia, AD, PTSD, schizophrenia, bipolar disorder, amyotrophic lateral sclerosis (ALS), cancer-therapy-related cognitive impairment, mental retardation, Parkinson's disease (PD), autism, compulsive behavior, and substance addiction. In one embodiment, the subject that suffers such cognitive 10 impairment is a human patient, and thus reduce the side effects caused by donepezil or other AChEIs without diminishing efficacy. Further, the efficacy of a combination of the SV2A inhibitor and donepezil or other AChEIs and pharmaceutically acceptable salts, solvates, hydrates, and polymorphs thereof exceeds the efficacy of either drug administered alone at its optimal dose and thus is an improved treatment for cognitive 15 impairment associated with a CNS disorder.

**[0185]** 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 20 system, e.g., by an intraventricular or other neuro-compatible route.

**[0186]** In accordance with this invention, the SV2A inhibitor and the AChEI, 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, 25 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 AChEI, 30 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 AChEI or its

salt, solvate, hydrate, or polymorph is administered orally.

**[0187]** 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, refers 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.

**[0188]** 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.

**[0189]** In certain embodiments of the present invention, the SV2A inhibitor is in an extended release form and the AChEI is in a form that is not extended release. In some embodiments, the AChEI is in an immediate release form.

**[0190]** 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.

[0191] 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 5 discretion of the attending physician. It will be understood that the amount of the SV2A inhibitor and the AChEI and their pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof administered will be amounts effective to produce a desired biological effect, such as beneficial results, including clinical results (e.g., an amount that increases GABAergic activity, reduces excitatory neurotransmission, and 10 blocks, suppresses, or reduces acetylcholinesterase activity, and/or amounts that in combination result in an improvement in cognitive function). It will be understood that an effective amount can be administered in more than one dose and over a course of treatment.

[0192] Desired duration of administration of the SV2A inhibitor and the AChEI and 15 their pharmaceutically acceptable salts, hydrates, solvates and polymorphs thereof can be determined by routine experimentation by one skilled in the art. For example, the SV2A inhibitor and the AChEI and their pharmaceutically acceptable salts, hydrates, solvates and polymorphs 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.

[0193] It is known in the art that normalization to body surface area is an 20 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,

25 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) = 30 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.

[0194] In certain embodiments of the invention, the SV2A inhibitor or a

pharmaceutically acceptable salt, hydrate, solvate and polymorph, or prodrug thereof can be administered at doses according to, for example, U.S. Patent Application 12/580,464, International Patent Application PCT/US2009/005647, U.S. Patent Application 61/105,847, U.S. Patent Application 61/152,631, and U.S. Patent Application 61/175,536. In certain embodiments of the invention, the SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate and polymorph, or prodrug thereof is administered 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 and polymorph, or prodrug thereof is administered 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. 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.

**[0195]** In certain embodiments of the invention, the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof can be administered at doses according to, for example, U.S. Patent Application 12/580,464, International Patent Application PCT/US2009/005647, 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 the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is administered 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 5 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.

**[0196]** In certain embodiments of the invention, the dose of the SV2A inhibitor is 10 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, 15 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, 20 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.

**[0197]** 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 30 also be used and may be determined by one skilled in the art following the methods of this invention.

**[0198]** 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, 5 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 10 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 15 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.

**[0199]** In certain embodiments of the invention, the dose of the SV2A inhibitor is 20 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 25 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, 25 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.

**[0200]** In certain embodiments of the invention, the interval of administration is 24 hours. Administration at less frequent intervals, such as once less than 24 hours, may also be used. In some embodiments, the SV2A inhibitor is 30 administered at a total daily dose of 0.1 to 5 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 at a daily dose of 0.01 to 2.5 mg/kg. In some embodiments, the SV2A inhibitor is administered at a daily dose of 0.1 to 2.5 mg/kg. In some embodiments, the SV2A inhibitor is administered at a daily dose of 0.4 to 2.5  
5 mg/kg. In some embodiments, the SV2A inhibitor is administered at a daily dose of 0.6 to 1.8 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered at a daily dose of 0.04 – 2.5 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered at a daily dose of 0.06 – 1.8 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered at a daily dose  
10 of 0.001 – 5 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered at a daily dose of 0.001 – 0.5 mg/kg. In some embodiments, the selective inhibitor of SV2A is administered at a daily dose of 0.01 – 0.5 mg/kg.

15 **[0201]** 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 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.

20 **[0202]** In other embodiments, the levetiracetam 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 1 or Table 2.

**Table 1 - Daily Doses of Levetiracetam**

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 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	+	+	+	+	+	+

5 [0203] 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 - 10 350 mg, about 70 - 350 mg, about 100 - 300 mg, or about 125 - 250 mg.

[0204] 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 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 15 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.

- [0205] 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, 0.5 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 5 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, 0.0075 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.
- 10 [0206] 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 3 or Table 4. For example, the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof may be administered at a daily dose of 0.1 - 35 mg, 15 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.
- 20

**Table 3 - Daily Doses of Brivaracetam**

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 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	+	+	+	+	+	+

[0207] 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.

[0208] 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 in a Human Subject of 70 KG (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	+	+	+	+	+	+	+	+	+

- 5 [0209] 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 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  
10 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 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.

5 [0210] 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 or polymorph may be administered 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, 10 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, 15 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**

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 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	+	+	+	+	+	+

5 [0211] 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,

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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  
5 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.

[0212] 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)**

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	+	+	+	+	+	+	+	+	+

5 **Table 10 - Daily Doses of Seletracetam in a Human Subject of 70 KG (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	+	+	+	+	+	+	+	+	+

[0213] The SV2A inhibitor or its pharmaceutically acceptable salt, hydrate, solvate and polymorph may be administered at a subtherapeutic dosage levels when provided in combination with an AChEI or its pharmaceutically acceptable salt, hydrate, solvate and polymorph, due to an AChEI-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 AChEI, is greater than the therapeutic index of the SV2A inhibitor administered in the absence of the AChEI 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 AChEI 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 AChEI 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.

15 [0214] The AChEI or its pharmaceutically acceptable salt, hydrate, solvate and polymorph may be administered at a dosage level up to conventional dosage levels. Suitable dosage levels will depend upon the specific AChEI that is chosen. The AChEI may be administered on a regimen of up to 2 times per day, 1 time per day, or it may be administered less often. For ARICEPT®, a typical daily dosage when administered alone is about 5 to 10 mg. In certain embodiments of the invention, the amount of ARICEPT® administered in combination with an SV2A inhibitor is about 0.1 to 10 mg. In some embodiments, the amount of ARICEPT® administered in combination with the SV2A inhibitor is a subtherapeutic amount. In some embodiments, the amount of ARICEPT® administered in combination with the SV2A inhibitor is less than 10 mg daily, less than 5 mg daily, less than 1 mg daily, less than 0.5 mg daily, or less than 0.1 mg daily.

20 [0215] The AChEI or a salt, hydrate, solvate or polymorph, or prodrug thereof may be administered at dosage levels distinct from conventional levels when provided in combination with an SV2A inhibitor, due to an SV2A inhibitor-dependent increase in the AChEI's therapeutic index. In some embodiments, the increase in the AChEI's therapeutic index due to the combination with an SV2A inhibitor thereof is greater than the therapeutic index of the AChEI 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, combinations of an AChEI with the SV2A inhibitor reduces the dosage of the AChEI required for its therapeutic effect. In some 5 embodiments, the amount of the AChEI administered in combination with the SV2A inhibitor thereof is about 0.1 to 10 mg. In some embodiments, the amount of the AChEI administered in combination with the SV2A inhibitor is a subtherapeutic amount. In some embodiments, the amount of the AChEI administered in combination with the SV2A inhibitor is less than 10 mg daily, less than 5 mg daily, less than 1 mg 10 daily, less than 0.5 mg daily, or less than 0.1 mg daily.

15 **[0216]** 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 AChEI and their salts, hydrates, solvates and polymorphs can be administered at different dosing frequencies or intervals. For example, an SV2A inhibitor can be administered daily (including multiple doses per day) or less frequently. An AChEI 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 AChEI may be desired. Various formulations and devices for achieving sustained release are known in the art.

20 **[0217]** As described above, some AChEIs (such as donepezil) and their salts, hydrates, solvates and polymorphs can cause cholinergic side effects. The use of a combination of an SV2A inhibitor and an AChEI may reduce the amount of the AChEI necessary for treatment of cognitive impairment associated with a CNS disorder, and may thus reduce the side effects caused by the AChEIs. In particular, the combination 25 of an SV2A inhibitor with a reduced amount of AChEI may reduce the cholinergic side effects without negatively impacting efficacy. Accordingly, in some embodiments, a subtherapeutic amount of AChEI is administered.

30 **[0218]** In some embodiments, a suitable amount of the SV2A inhibitor is administered so as to reduce the dose of the AChEI (e.g., a dose required to effect a degree of cognitive function improvement or treat age-associated cognitive impairment) 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 AChEI 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).

- 5 [0219] In certain embodiments of the invention, the combined administration of an SV2A inhibitor or a salt, hydrate, solvate and polymorph, or prodrug thereof and an AChEI or a salt, hydrate, solvate and polymorph, or prodrug thereof can attain a longer or improved therapeutic effect in the subject than that attained by administering only the AChEI or only the SV2A inhibitor, by at least about 1.5x, or 2.0x, or 2.5x, or 3.0x, 10 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**

- [0220] In one aspect, 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 AChEI and its salts, hydrates, solvates, polymorphs, or prodrugs. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof present in the composition of the invention is in a form that is not extended release. In some embodiments, the AChEI or the pharmaceutically acceptable salt thereof present in the composition of the invention is in an immediate release form. In some embodiments, the SV2A inhibitor and the AChEI may be present in a single dosage unit (e.g., combined together in one capsule, tablet, powder, or liquid, etc.). In some embodiments, the AChEI in the composition is donepezil. 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 donepezil or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph, or prodrug thereof as the AChEI. In some embodiments, the composition includes levetiracetam or a derivative or an analog or a pharmaceutically acceptable salt, hydrate, solvate and polymorph, or prodrug thereof and donepezil or a pharmaceutically acceptable salt, hydrate, solvate and polymorph, or prodrug thereof. The composition described herein can contain more than one SV2A inhibitor and/or more than one AChEI. 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 AChEI or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof present in the same 5 composition. For example, donepezil (an example of an AChEI) has a half life clearance of 70 hours and levetiracetam (an example of an SV2A inhibitor) has a half life clearance of  $7 \pm 1$  hour. In one embodiment, the present invention provides a composition comprising an extended release form of levetiracetam and a non-extended release form of donepezil and such composition is a once daily formulation. The once 10 daily formulation is for higher compliance among patients suffering from cognitive impairment.

15 **[0221]** 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 AChEI. The compositions may also contain additional agents known to be useful for treating cognitive function disorder.

20 **[0222]** The composition in the present invention may be in solid dosage forms such as capsules, tablets, dragees, 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 25 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”, 30 “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.

**[0223]** The compositions may be specifically formulated for administration by any suitable route as described herein and known in the art. Compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, 5 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 10 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 15 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.

**[0224]** The compositions may also contain adjuvants, such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of 20 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 25 absorption, such as aluminum monostearate and gelatin.

**[0225]** Therapeutic formulations can be prepared by methods well known in the art of 30 pharmacy, see, e.g., Goodman et al., 2001; Ansel, et al., 2004; Stoklosa et al., 2001; and Bustamante, et al., 1993.

**[0226]** In certain embodiments of the invention, a composition comprising an SV2A 35 inhibitor and an AChEI and their salts, hydrates, solvates, polymorphs, 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, the amount of the AChEI in the composition is about 0.1 - 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg. In some embodiments, the amount of the AChEI in the composition is less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg.

[0227] 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. In some of the above embodiments, the SV2A inhibitor is levetiracetam and the AChEI is donepezil. In some of the above embodiments, the SV2A inhibitor is brivaracetam and the AChEI is donepezil. In some of the above embodiments, the SV2A inhibitor is

seletracetam and the AChEI is donepezil. In the above embodiments, the donepezil may be substituted with tacrine, rivatigmine, physostigmine, galantamine, or metrifonate.

- [0228]** In certain embodiments of the invention, a composition comprising 5 levetiracetam and an AChEI (e.g., donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, prodrugs comprises an amount of the levetiracetam or its salts, hydrates, solvates, polymorphs, prodrugs in an extended release form between the ranges shown in Table 11 or less than any of the upper ranges shown in Table 11, and an amount of an AChEI (e.g., 10 donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, or prodrugs in an amount of 0.1 - 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg, or less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg. In some of the foregoing embodiments, the AChEI (e.g., donepezil or 15 tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, or prodrugs is not in an extended release form.
- [0229]** In certain embodiments of the invention, a composition comprising 20 brivaracetam and an AChEI (e.g., donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, prodrugs comprises an amount of the brivaracetam or its salts, hydrates, solvates, polymorphs, prodrugs in an extended release form between the ranges shown in Table 12 or less than any of the upper ranges shown in Table 12, and an amount of an AChEI (e.g., 25 donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, prodrugs in an amount of 0.1 - 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg, or less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg. In some of the foregoing embodiments, the AChEI (e.g., donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, or prodrugs is not in an extended release form.
- [0230]** In certain embodiments of the invention, a composition comprising 30 seletracetam and an AChEI (e.g., donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, prodrugs

comprises an amount of the seletracetam or its salts, hydrates, solvates, polymorphs, prodrugs in an extended release form between the ranges shown in Table 12 or less than any of the upper ranges shown in Table 12, and an amount of an AChEI (e.g., donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, solvates, polymorphs, prodrugs in an amount of 0.1 - 10 mg, 1 - 10 mg, 5 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg, or less than 10 mg, less than 9 mg, less than 8 mg, less than 7 mg, less than 6 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg. In some of the foregoing embodiments, the AChEI (e.g., donepezil or tacrine, rivatigmine, physostigmine, galantamine, or metrifonate) and their salts, hydrates, 10 solvates, polymorphs, or prodrugs is not in an extended release form.

**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	+	+	+	+	+	+	+	+	+

Lower range Upper range	0.1	0.7	1.8	3.0	3.5	5	7	15	35
280	+	+	+	+	+	+	+	+	+
300	+	+	+	+	+	+	+	+	+
350	+	+	+	+	+	+	+	+	+

- [0231] 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 5 methods described herein may be employed in other suitable applications, and that such other additions and modifications will not depart from the scope hereof.
- [0232] 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 10 described more fully in the embodiments which follow thereafter.

### **Examples**

#### **Introduction and Models of Cognitive Impairment**

[0233] A variety of conditions characterized by cognitive impairment, e.g., Age-Associated Memory Impairment (AAMI), Mild Cognitive Impairment (MCI) and 15 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.

20 Efficacy in such animal models is, thus, predictive of efficacy in humans.

[0234] 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 25 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

5 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  
10 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% falls outside the range of young performance. This variability among aged rats reflects reliable individual differences. Thus, within  
15 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).*

20 [0235] 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.

25 **Example 1: Behavioral Assessment of Levetiracetam, Donepezil, and Combined Treatments in a Radial Arm Maze Task**

30 [0236] Aged, male Long-Evans rats were obtained at 8 to 9 months of age from Charles River Laboratories (Raleigh, NC) and housed in a vivarium until 24 to 26 months of age. All rats were individually housed at 25°C and maintained on a 12 h light/dark cycle. Food and water were provided *ad libitum* unless noted otherwise. The rats were examined for health and pathogen-free status throughout the experiments, as well as necropsies at the time of killing.

[0237] All rats were screened in a standardized assessment of spatial cognition. This background assessment used the above-described well-established MWM protocol. Aged rats that demonstrated impaired memory performance in a standardized assessment of spatial cognition, i.e., AI rats, were selected for the drug intervention studies. The selected AI rats were tested for their memory of

- new spatial information in a Radial Arm Maze (RAM) task, under different drug/control treatment conditions: vehicle control, donepezil only, levetiracetam only, and a combination of donepezil and levetiracetam. The RAM task also extended the behavioral assessment to spatial memory using appetitive motivation.
- 5 We used a protocol that allowed within-subject assessment across drugs at different doses and in combinations (Koh et al., *Neuropsychopharmacology*, epub. 1-10, (2009)).
- Radial Arm Maze Task**
- [0238] The radial maze consisted of eight arms projecting from each side of an octagonal center platform, with food well located at the distal end of each arm. Plexiglas<sup>TM</sup> blocks could be positioned to prevent entry into any arm. Extra-maze cues were provided in the room surrounding the maze and illumination was provided by an overhead light. Pre-training, as described in detail in Chappell *et al.* *Neuropharmacology* 37: 481-487 (1998), consisted of habituation, standard 15 win-shift training, and win-shift training with delays interposed between information and memory test phases. Drug treatments began 2 days after the completion of pre-training. Three arms were blocked at the beginning of each trial (information phase). The identity and configuration of the blocked arms varied across trials. Food-deprived rats were allowed to retrieve food reward (Kellogg's Froot Loops<sup>TM</sup> cereal) from the five unblocked arms. The rat was then removed 20 from the maze for 60 min (retention interval), during which time the barriers on the blocked arms were removed allowing access to all eight arms. Rats were then placed back onto the center platform and allowed to retrieve the remaining food rewards (memory test phase).
- 25 [0239] The number of “errors” the AI rats made during the retention test phase was tracked. An error consisted of returning to an arm (all four paws on the arm) from which food had already been obtained. For example, an error occurs in the trials if the rats enter an arm from which food has already been retrieved in the pre-delay component of the trial or if it re-visits an arm in the post-delay session that 30 has already been visited.

#### **Levetiracetam Treatment**

[0240] An independent set of AI rats (n=10) are first tested with levetiracetam (Tecoland, Edison, NJ). The 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. 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.

[0241] Parametric statistics (paired t-tests) are 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. 1*). The average numbers of errors in the trials are significantly fewer with levetiracetam treatment of 5 mg/kg/day (average no. of errors  $\pm$  standard error of the mean (SEM) =  $0.75 \pm 0.32$ ) and 10 mg/kg/day (average no. of errors  $\pm$  SEM =  $0.80 \pm 0.27$ ) than using vehicle control (average no. of errors  $\pm$  SEM =  $2.00 \pm 0.42$ ). 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 ( $t(9) = 2.37$ ,  $p = 0.042$ ).

#### Donepezil Treatment

[0242] After the completion of levetiracetam assessment, a new set of AI rats (n=8) are tested with donepezil. The AI rats are pretreated 30-40 minutes before daily trials with a one-time shot of the following three conditions: 1) vehicle control (0.9% saline solution); 2) donepezil (1 mg/kg/day); 3) donepezil (2 mg/kg/day); through intraperitoneal (i.p.) injection. Injections are given every day. 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.

[0243] Parametric statistics (paired t-tests) are used to compare the retention test performance of the AI rats in a two-hour delay version of the RAM task in the

context of different doses of donepezil and vehicle control (*see FIG. 2*). The average numbers of errors that occur in the trials of using donepezil treatment of 1 mg/kg/day (average no. of errors  $\pm$  standard error of the mean (SEM) =  $2.88 \pm 0.46$ ) and 2 mg/kg/day (average no. of errors  $\pm$  SEM =  $2.81 \pm 0.43$ ) are not 5 significantly different from using vehicle control (average no. of errors  $\pm$  SEM =  $2.88 \pm 0.67$ ). Relative to vehicle control treatment, donepezil does not significantly improve memory performance at 1 mg/kg/day ( $t(7) = 0$ ,  $p = 1.00$ ) or 2 mg/kg/day ( $t(7) = 0.91$ ,  $p = 0.930$ ).

**Combination of Levetiracetam and Donepezil**  
10 [0244] We use the same AI rats (n=8) to test the memory improvement effects of the combination of levetiracetam and donepezil, when administered at subtherapeutic doses. In this experiment, the subtherapeutic doses are 2.5 mg/kg/day for levetiracetam and 1 mg/kg/day for donepezil. As described above, when levetiracetam is administered individually at a dose of 2.5 mg/kg/day in the 15 absence of donepezil, it does not significantly improve memory performance in AI rats (*See FIG. 1*). When donepezil is administered individually at a dose of 1 mg/kg/day in the absence of levetiracetam, it does not significantly improve memory performance in AI rats (*See FIG. 2*).

[0245] The AI rats are pretreated 30-40 minutes before daily trials with a one-time shot of the following two conditions: 1) vehicle control (0.9% saline 20 solution); 2) donepezil (1 mg/kg/day) and levetiracetam (2.5 mg/kg/day); through intraperitoneal (i.p.) injection. Injections are given every day. 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 25 descending order. Therefore, each dose has two determinations.

[0246] Parametric statistics (paired t-tests) are used to compare the retention test performance of the AI rats in a two-hour delay version of the RAM task in the context of a combination of levetiracetam and donepezil and vehicle control (*see FIG. 2*). The average numbers of errors that occur in the trials are significantly 30 fewer with the combined administration of donepezil (1 mg/kg/day) and levetiracetam (2.5 mg/kg/day) (average no. of errors  $\pm$  standard error of the mean (SEM) =  $1.69 \pm 0.53$ ) than using vehicle control (average no. of errors  $\pm$  SEM =

2.88 ± 0.67). Relative to vehicle control treatment, a combination of donepezil (1 mg/kg/day) and levetiracetam (2.5 mg/kg/day) significantly improves memory performance ( $t(7) = 2.16$ ,  $p = 0.034$ ).

5 [0247] Either donepezil or levetiracetam, when administered at the subtherapeutic doses as are tested in this experiment in the absence of the other drug, does not significantly improve the memory performance in AI rats (See **FIGS 1 and 2**). However, a combination of donepezil and levetiracetam administered at subtherapeutic doses significantly improves the memory performance in AI rats. Our results suggest super-additive or synergistic 10 interaction between donepezil and levetiracetam when administered together.

#### **Example 2: Levetiracetam Treatments in Human Subjects with aMCI**

15 [0248] 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 counterbalanced (see **FIG. 3**). Age-matched control subjects 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.

20 **Participants and clinical characterization**

25 [0249] 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-30 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, 5 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 10 informant) who can provide information about the subject's daily function and assure that medications are taken appropriately. See **FIGS. 14A and 14B**.

**[0250] Study Visits:** The study consists of 4 visits over the course of 8 weeks (see **FIG. 3**). The Baseline Visit is for the purpose of performing medical, neurological, psychiatric, and neurocognitive assessments. Visits 1 and 2 are 15 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.

**[0251] 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 20 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 25 exams are conducted (including vital signs). Blood is drawn in order to perform standard laboratory tests 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 30 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.

5 [0252] **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 dispensed at the Baseline Visit (drug or placebo) is 10 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.

15 [0253] **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 was assigned in the previous treatment period) for the final phase of the study with instructions about how it should be taken.

20 [0254] **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 were any changes related to drug 25 treatment; the subject's blood levetiracetam level is also obtained. All medication 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.

30 **Neuropsychological assessment**

[0255] 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 5 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 10 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**

15 [0256] 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 twice a day, which is approximately 3.6 mg/kg/day (assuming an average adult human weight of 70 kg).

20 [0257] All drug and placebo preparations are performed on a 1:1 allocation. The pharmacy randomizes patients top drug dose and condition as they enroll, and keep a list of drug assignment.

[0258] Levetiracetam is rapidly and almost completely absorbed after oral administration, and its bioavailability is not affected by food. Plasma half-life of 25 levetiracetam is approximately  $7 \pm 1$  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.

[0259] A typical starting dose of levetiracetam in treating epilepsy in humans is 30 500 mg twice a day, which is approximately 14.3 mg/kg/day. The dosage is then increased until optimal efficacy, up to 50 mg/kg/day. Thus, the dose used in this experiment is a quarter of the lowest human dose used for treating epilepsy.

[0260] Even lower dosages, e.g., of 25-60 mg twice a day, are contemplated, based on the results of previous animal studies that indicated 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 5 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**

[0261] Imaging data are obtained through high-resolution methods developed in the Stark laboratory. Data are collected on a Phillips 3 Tesla scanner (Eindhoven, 10 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 15 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**

[0262] 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 25 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.

[0263] The ROI-LDDMM (large deformation diffeomorphic metric mapping of 30 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, 5 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-LLDMM 3D vector field transformation for each subject using a customized template based on the mean of the entire sample tested as the target. 10 The ROI-LLDMM transformations for each individual subject's ROIs are then applied to the fit coefficient maps.

**[0264]** 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 15 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 allowed 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 20 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**

**[0265]** The activity of the subject's medial temporal lobe is measured by 25 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 30 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 present individually as a

series of images (see **FIG. 6A**). 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. 6B**). The correct identification by the subject of lure 5 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- 10 shown partner image. Identification of the lure stimulus as "new" indicates that the subject failed to recall the earlier-shown partner image altogether. Each run also contains a number of baseline trials that use a challenging perceptual discrimination task known to provide a lower and more-stable estimate of baseline activity in the medial temporal lobe (Stark & Squire, 2001 PNAS; Law et al, 15 2005).

**[0266]** A survey of the activity level of various subregions in the medial temporal lobe during the cognitive test, as measured by fMRI, shows that aMCI subjects have hyperactive DG/CA3 regions and a hypoactive entorhinal cortex during the performance of memory tasks, compared to age-matched control 20 subjects.

**[0267]** 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, as measured by fMRI, during the presentation of lure stimuli correctly identified by subject as "similar" that is calibrated for baseline activity. 25 **FIG. 4A** shows that aMCI patients exhibit DG/CA3 hyperactivity when making these judgments ( $p = 0.013$ ). **FIG. 4B**, 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 it is statistically indistinguishable from the activity of control 30 subjects treated with placebo. See **FIG. 4C** for the mean activity values shown in **FIGS. 4A and 4B**.

[0268] The activity level during successful memory judgments in EC is significantly lower in placebo-treated aMCI subjects compared to controls ( $p = 0.003$ ). See **FIG. 5A**. However, levetiracetam treatment normalizes activity in aMCI subjects in EC as well. Levetiracetam treatment increases EC activity 5 during memory judgments in aMCI subjects, such that it is statistically indistinguishable from placebo-treated control subjects. See **FIG. 5C** for the mean activity values shown in **FIGS. 5A and 5B**.

[0269] The normalization of DG/CA3 and EC activity during memory judgments by levetiracetam treatment is mirrored in the change seen in the aMCI subjects' 10 performance in the cognitive task. With placebo treatment, aMCI patients perform worse than control subjects, correctly identify lure items as "similar" less often and incorrectly identifying them as "old" more often ( $p = 0.009$ ). See **FIG. 7**. However, the performance of aMCI subjects improves significantly under 15 levetiracetam treatment. See **FIG. 8**. 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. 9** for a table of the data represent in **FIGS. 7 and 8**.

[0270] The performance of control-placebo subjects and aMCI subjects with 20 drug or placebo treatment is also compared in other common cognitive tests, such as the Buschke Selective Reminding Test – Delayed Recall (**FIGS. 10A and 10B**), the Benton Visual Rentention Test (**FIGS. 11A and 11B**), Verbal Paired 25 Associates Test – Recognition (**FIGS. 12A and 12B**) and Verbal Paired Associates Test – Delayed Recall (**FIGS. 13A and 13B**). In all of these tests, aMCI subjects treated with placebo perform worse than placebo-treated control subjects, and levetiracetam treatment fail to rescue performance in aMCI subjects.

[0271] There are a number of possible reasons why levetiracetam treatment does 30 not help aMCI subjects with performance in these other cognitive tests. The explicit 3-alternative forced choice task done in the fMRI study is a task that is especially sensitive to DG/CA3 function. As such, the performace 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 were 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, for the drug treatment will result in improved efficacy. Finally, comparative animal studies (see Example 1) indicate that an even lower dose would be more effective. The human dosage of 125 mg twice a day is 5 equivalent to a rat dosage of 22.3 mg/kg/day. As is shown in Example 1 and **FIG. 1**, 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 used in the animal model are 5-10 mg/kg. The human equivalent dose (HED) of the optimal rat dose is 0.8-1.6 mg/kg/day. Such a dosage would result in the 10 administration of 28-56 mg twice a day (which is substantially lower than the 125 mg twice a day 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 15 levetiracetam.

**[0272] Example 3: Effect of Levetiracetam in human subjects with aMCI**

**[0273]** 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 20 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 counterbalanced (see **FIG. 7**). Age-matched control subjects treated with placebo serve as a further control. Cognitive testing and fMRI imaging data are obtained from the subjects 25 after each two-week period of drug/placebo treatment.

**Participants and clinical characterization**

**[0274]** 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 30 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.

**[0275] 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.

**[0276] 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 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 5 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 10 advised about the potential for having suicidal thoughts and advised to stop taking the medication and immediately contact the study physician if this occurs.

[0277] **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. 15 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 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 20 immediately before or immediately after the clinical assessment. Subjects discontinue first period treatment at this visit.

[0278] **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 25 confirm washout). The subject is provided with new medication (drug or placebo, alternated from what was assigned in the previous treatment period) for the final phase of the study with instructions about how it should be taken.

[0279] **Visit 2:** At approximately 2 weeks after the Washout Visit (i.e., 2 weeks after starting the second treatment period), the medical, neurological and 30 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 were any changes related to drug

treatment; the subject's blood levetiracetam level is also obtained. All medication 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 5 clinical assessment.

### **Neuropsychological assessment**

**[0280]** 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 10 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., 15 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 20 specific practice effects. Breaks are provided to the subject as needed.

### **Drug administration**

**[0281]** 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 25 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 30 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.

- [0282] 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.
- [0283] 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  $7 \pm 1$  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.
- [0284] 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 increased until optimal efficacy, up to 50 mg/kg/day. Thus, the 250 mg BID dose (500 mg/day) 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**
- [0285] 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**
- [0286] 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 5 the same parameters are subsequently applied to the functional data. Behavioral vectors are produced to model different trial types.

[0287] 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 10 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 15 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 based 20 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.

[0288] 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 25 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 30 selection biases because any differences amongst the various conditions allowed 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 35 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**

[0289] 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.

5 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

10 image pairs are fully randomized throughout the run and present 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

15 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-

20 shown partner image. Identification of the lure stimulus as "new" indicates that the subject failed to recall the earlier-shown partner image altogether. Each run also contains a number of baseline trials that use a challenging perceptual discrimination task known to provide a lower and more-stable estimate of baseline activity in the medial temporal lobe (Stark & Squire, 2001 PNAS; Law et al,

25 2005).

[0290] A survey of the activity level of various subregions in the medial temporal lobe during the cognitive test, as measured by fMRI, shows that aMCI subjects have hyperactive DG/CA3 regions and a hypoactive entorhinal cortex during the performance of memory tasks, compared to age-matched control

30 subjects.

[0291] 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, as measured by fMRI, during the presentation of lure stimuli 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 5 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 or the 62.5 mg BID cohort.

[0292] The level of DG/CA3 activity during memory judgments by levetiracetam treatment is mirrored in the change seen in the aMCI subjects’ performance in the 10 cognitive task. With placebo treatment, aMCI patients perform worse than control subjects, correctly identify 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. 19A and 23B**. However, the performance of aMCI subjects improves significantly under 62.5 mg BID levetiracetam treatment. See 15 **FIG. 20A**. 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. 20B**.

20 **Example 4: Effect of Brivaracetam and Seletracetam in Aged-Impaired Rats**

[0293] Subjects

[0294] Aged, male Long-Evans rats were obtained at 8-9 month of age from 25 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 were housed in the same vivarium and tested at 6 month of age. All rats were individually housed at 25°C and maintained on a 12 hr light/dark cycle. Food and water were provided *ad libitum* unless noted otherwise. The rats were examined for health and pathogen-free status throughout the experiments, as well 30 as necropsies at the time of sacrifice. All procedures in the current investigations were approved by the Institutional Animal Care and Use Committee in accordance with the National Institutes of Health directive.

[0295] Background Characterization of Cognitive Status

[0296] All rats were screened in a standardized assessment of spatial cognition prior to the studies with experimental treatments. That background assessment used a well-established Morris Water Maze protocol. The MWM protocol was substantially the same as the one described in Example 1. See, also, Gallagher *et al.*, Behav. Neurosci. 107:618-626, (1993). Briefly, the rats were 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 consisted of a probe trial (free swim with no escape platform) that served to assess the development of a spatially localized search for the escape platform. During these probe trials, a learning index was generated from the proximity of the rat to the escape platform and was 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) occurred 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 were characterized as Aged-Impaired rats (i.e., AI rats). The AI rats were used for the studies as described below.

[0297] Treatments

[0298] The radial arm maze experiments used 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 were 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.

[0299] Behavioral Assessment in the Radial Arm Maze

[0300] A radial arm maze (RAM) task was used to assess effects of acute drug treatment with seletracetam and brivaracetam. This protocol allowed within-subject assessment across drugs at different doses. The radial maze consisted 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 could be positioned to prevent entry into any arm. Extra-maze cues were provided in the room surrounding the maze and illumination was provided by an overhead light.

5 [0301] Pre-training, as described in detail in Chappell et al. *Neuropharmacology* 37: 481-487, (1998), consisted of habituation, standard win-shift training, and win-shift training with delays interposed between information and memory test phases. Drug treatments began two days after the completion of pre-training. Three arms were blocked at the beginning of each trial (information phase). The identity and 10 configuration of the blocked arms were varied across trials. Food-deprived rats were allowed to retrieve food reward (Kellogg's Froot Loops cereal) from the five unblocked arms. The rat was then removed from the maze for 2 hr (retention interval), during which time the barriers on the blocked arms were removed allowing access to all eight arms. Rats were then placed back onto the center 15 platform and allowed to retrieve the remaining food rewards (memory test phase). An error consisted 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) were first tested with a series of drug doses in ascending/descending order; each dose was thus tested twice, with one 20 washout day in between each determination. The number of errors made in the retention phase after the 2-hr delay was used to assess memory performance. See FIG. 15 and FIG. 16. A series of different doses of brivaracetam was tested: 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. A series of different doses of seletracetam was tested: 0.0625mg/kg, 0.125 25 mg/kg, 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg and 4 mg/kg. As shown in FIG. 15, 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. 16, seletracetam also has a significant effect as a 30 function of dose in the range tested (repeated measures ANOVA for within-subject contrasts,  $F(1, 7) = 12.577$ ,  $p = 0.009$ ).

[0302] Behavioral Assessment in the Water Maze

[0303] Rats were trained and tested in a novel water maze environment to assess the effect of drug treatment. The water maze used here was housed in a different building and was surrounded by curtains with a novel set of patterns relative to the maze used for initial assessment of cognitive status. The training protocol 5 consisted of 6 trials per day for 2 days to locate a submerged escape platform. On each trial, a rat was released in the maze from one of four equally spaced starting positions around the perimeter of the pool. The starting position varied from trial to trial. If the rat did not locate the escape platform within 60 s on any trial, the experimenter guided and placed the rat on the platform, where it remained for 20 s. 10 The rat was then removed from the platform and placed in a holding cage for another 40 s before the next trial. Approximately 24 hr after the last training trial, a probe test in the absence of the escape platform was given to assess spatial memory. Results of the behavior assessment in the Water Maze task were shown in FIG. 17A and FIG. 17B. Rats treated with brivaracetam at 2 mg/kg/day ( $t(2) = 15 10.000, p = 0.010$ ) but not vehicle ( $t(2) = 1.964, p = 0.188$ ) showed a significant spatial bias for the target quadrant compared to the other controls quadrants. In addition, brivaracetam-treated rats (2mg/kg/day) spent 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) spent significantly more time in the target 20 annulus (area surrounding the location of the escape platform) than the vehicle-treated rats,  $t(4) = 3.109, p = 0.036$ .

#### **Example 5: Chronic Treatment with Levetiracetam in Aged-Impaired Rats**

##### **[0304] Subjects**

[0305] Aged, male Long-Evans rats were obtained at 8-9 month of age from 25 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 were housed in the same vivarium and tested at 6 month of age. All rats were individually housed at 25°C and maintained on a 12 hr light/dark cycle. Food and water were provided ad libitum unless noted otherwise. The rats were 30 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

were approved by the Institutional Animal Care and Use Committee in accordance with the National Institutes of Health directive.

**[0306] Background behavioral characterization**

[0307] All rats were screened in a standardized assessment of spatial cognition 5 prior to the studies with experimental treatments. That background assessment used a well-established Morris water maze protocol as described in Gallagher *et al*, 1993. Briefly, the rats were 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 consisted of a probe trial (free swim with 10 no escape platform) that served to assess the development of a spatially localized search for the escape platform. During these probe trials, a learning index was generated from the proximity of the rat to the escape platform and was 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 15 near the escape platform and high scores reflecting searches farther away from the platform (Gallagher *et al*, 1993). Cue training (visible escape platform) occurred on the last day of training to test for sensorimotor and motivational factors independent of spatial learning. Aged rats with impaired spatial memory 20 performance (i.e., those with learning index scores outside the young “normative” range) but successful cued training performance were used for the studies as described below.

**[0308] Surgery and treatments**

[0309] Under isoflurane anesthesia, memory-impaired aged rats were implanted 25 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, received either saline vehicle in mini-pumps or no implantation.

**[0310] Perfusion and tissue preparation**

[0311] At the end of the 4-week treatment period, rats were anesthetized with 30 isoflurane and perfused transcardiacally with 0.1 M phosphate buffer saline, followed by 4% paraformaldehyde in phosphate buffer. Brains were removed and post-fixed in paraformaldehyde overnight. The brains were then moved into 4%

paraformaldehyde in phosphate buffer containing 16% sucrose. The brains were then sectioned with a freezing microtome on the coronal plane at 40  $\mu$ m and stored in either 4% paraformaldehyde at 4°C for in situ hybridization or cryoprotectant at -20°C for immunohistochemistry.

5      **[0312] Probe synthesis**

[0313] Probe templates were synthesized as described in Haberman et al. (2008). Initial primer sequences for reelin were as follows: left, agtactcagacgtgcagtgg, right, ctcatgaagcaaagtccaa; PCR products were verified by restriction endonuclease digestion. Initial PCR products were amplified further with the same PCR primers 10 that had been modified by the addition of T7 or SP6 RNA polymerase binding sites. PCR products containing T7 and SP6 extensions were purified by SVgel and a PCR cleanup kit (Promega). 35S-UTP labeled riboprobe was then generated using the Maxiscript kit (Ambion). The probe was then phenol/choloroform extracted and precipitated in ethanol at -80°C. The final probe was resuspended in 15 RNase-free water and the specific activity was determined by scintillation counter.

**[0314] In situ hybridization**

[0315] In situ hybridization was carried out as described by Haberman et al., (2008). Free-floating tissue sections were washed in 0.75% glycine in 0.1M phosphate buffer two times, followed by a single wash in phosphate buffer. After 20 that, sections were reacted in Proteinase K buffer containing 1.0 $\mu$ g/ml proteinase K for 30 minutes at 37°C. Sections were 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 was followed by two 15-minute washes in 2x sodium chloride/citrate buffer (SSC buffer; 20x concentration, 3M NaCl, 0.3M 25 sodium citrate). Next, sections were transferred to 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 10<sup>7</sup> cpm/ml 35S-UTP-labeled probe for overnight reaction at 60°C. The following day, sections were washed at 60°C in 4xSSC/0.01M 30 DTT and 2x SSC/ 50% formamide. They were then incubated with RNase (20  $\mu$ g/ml) at 37°C for 30 min. Sections were washed with progressively decreasing concentrations of SSC before mounting on slides. Slides were dried overnight,

exposed to a phosphoimager screen, and quantified by using ImageQuant (GE Healthcare). Digital images were acquired of entorhinal cortical sections from the same levels for all animals and the subregion of interest was outlined and quantified. Sections were averaged to obtain a single score for each animal.

5      **[0316] Immunohistochemistry**

- [0317] Tissue was labeled with anti-SOM antiserum (Santa Cruz Biotechnology; cat. no. SC7819-P) using an established immunoperoxidase protocol and tissue sections were processed concurrently to minimize inter-replication variability (Haberman et al., 2009). The anti-SOM antiserum can detect somatostatin.
- 10     Briefly, sections were washed in 0.1M phosphate-buffered saline (PBS) to remove cryoprotectant, and endogenous peroxidases were quenched in 0.3% H2O2 in PBS. After additional PBS washes, sections were blocked in 5% normal horse serum in PBS with 0.3% Triton. Sections were then incubated with primary antibody at a dilution of 1:1600 in PBS containing 0.15% Triton and 3% normal serum for 72
- 15     hours at 4°C with agitation. Following primary antibody incubation, sections were 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 was detected with avidin-biotin complex (ABC Elite; Vector Laboratories Inc.,
- 20     Burlingame, CA) and the avidin-biotin complex was visualized with nickel-enhanced diaminobenzidine (Vector Laboratories Inc., Burlingame, CA). Tissue sections were mounted onto coated slides and dried, dehydrated with increasing concentrations of ethanol, cleared with xylene, and coverslipped using DPX mounting media.
- 25     [0318] Interneuron quantification was performed using a Zeiss Axioplan 2 microscope equipped with a motorized stage. All analyses were conducted blind with regards to animal age and cognitive status. The dentate hilar region was defined using the Paxinos and Watson rat brain atlas (1998). Dorsal hilar neuron counts were derived bilaterally from four matched tissue sections per animal with a
- 30     40x objective lens (Bregma -3.80mm to -4.16mm). Neuron counts were analyzed as the total number of hilar interneurons per hippocampal section for each rat.

**[0319] Results**

[0320] 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. 21. Aged-impaired rats that were 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<sub>2,20</sub> = 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).

[0321] 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. 22. 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 increased the expression of reelin, t(13) = 2.386, p = 0.033 (compared to AI-VEH).

**25 Example 6: Evaluation of Levetiracetam Blood Plasma Levels**

[0322] Human: in the human studies described in Examples 3 and 4, a subject's levetiracetam blood plasma level was assessed at each visit. The subject's blood was drawn by the Johns Hopkins Phlebotomy Service and analysis of levetiracetam blood plasma levels was 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. Upon completion of the levetiracetam treatment, subjects in the 62.5 mg BID cohort showed a mean levetiracetam blood

plasma level of 2.88 mcg/ml (SEM  $\pm$  0.288), while levels in the 125 mg BID had 4.4 mcg/ml (SEM  $\pm$  0.53) and subjects in the 250 mg BID cohort showed mean levetiracetam blood plasma level of 7.9 mcg/ml (SEM  $\pm$  0.92). See FIGS. 23A-23c.

- 5     **[0323]** Rats: Blood was drawn from aged-impaired rats by cardiac puncture during perfusion after a 28-day levetiracetam treatment period and sent for analysis of levetiracetam plasma levels by MedTox Laboratories in St. Paul, MN. Aged-impaired rats treated with 10 mg/kg/day of levetiracetam showed a mean levetiracetam blood plasma level of 3.8 mcg/ml (SEM  $\pm$  0.255), while those treated  
10 with 60 mg/kg/day showed a mean levetiracetam blood plasma level of 22.4 mcg/ml (SEM  $\pm$  3.371).

**WHAT IS CLAIMED IS:**

1. A composition comprising a synaptic vesicle protein 2A (SV2A) inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof and an acetylcholinesterase inhibitor (AChEI) or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof,

wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in an extended release form.

2. The composition of claim 1, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is not in an extended release form.

3. The composition of claim 2, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in a controlled release form, a prolonged release form, a sustained release form, a delayed release form, or a slow release form.

4. The composition of any one of claims 1-3, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is in an immediate release form.

5. The composition of any one of claims 1-4, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof and the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is in a unit dosage form.

6. The composition of any one of claims 1-5, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof and the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is in a tablet or capsule form.

7. The composition of any one of claims 1-6, wherein the composition is for oral administration.

8. The composition of any one of claims 1-4, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or

polymorph or prodrug thereof and the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is in separate units packaged together in a single formulation.

9. The composition of any one of claims 1-8, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof 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.

10. The composition of any one of claims 1-8, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is selected from the group consisting of levetiracetam, seletracetam, and brivaracetam and derivatives, analogs, pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

11. The composition of any one of claims 1-10, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof in the composition is present in an amount of about 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.

12. The composition of any one of claims 1-10, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or 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.

13. The composition of any one of claims 1-10, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is levetiracetam or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof.

14. The composition of claim 13, wherein the levetiracetam or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof in the composition is present in an amount of about 70 - 350 mg, 100 - 300 mg, or 125 - 250 mg.

15. The composition of any one of claims 1-10, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is brivaracetam or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof.

16. The composition of claim 15, wherein the brivaracetam or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof in the composition is present in an amount of about 0.1 - 350 mg, 0.7 - 350 mg, 3 - 300 mg, 3 - 150 mg, 3 - 110 mg, or 7 - 70 mg.

17. The composition of any one of claims 1-10, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is seletracetam or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof.

18. The composition of claim 17, wherein the seletracetam or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof in the composition is present in an amount of about 0.1 - 350 mg, 0.7 - 350 mg, 3 - 300 mg, 3 - 150 mg, 3 - 110 mg, or 7 - 70 mg.

19. The composition of any one of claims 1-18, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is selected from the group of AChEI referred to in International Patent Applications WO2010/057088; WO2009/008769; WO2008/097546; WO2008/074896; WO2008/073452; WO2007/127474; WO2007/107846;

WO2006/097588; WO2006/071274; WO2006/070394; WO2006/060082; WO2006/040688; WO2005/092009; WO2005/079789; WO2005/074535; WO2005/072713; WO 2005/042475; WO2005/039580; WO2005/027975; WO2004/084884; WO2004/080393; WO2004/052348; WO2004/037234; WO2004/034963; WO2004/032929; WO2003/101458; WO2003/091220; WO2003/082820; WO2003/082794; WO2003/020289; WO2002/074293; WO2002/032412; WO2001/085145; WO2001/078728; WO2001/066114; WO2001/066096; WO2001/021590; WO2001/000215; WO2000/033840; WO2000/030446; WO2000/023057; WO2000/015205; WO2000/009483; WO2000/007600; WO2000/002549; WO1999/047131; WO1999/008672; WO1999/007359; WO1998/039000; WO1998/030243; WO1997/138993; WO1997/119059; WO1997/038993; WO1997/029750; WO1997/021681; WO1997/013754; WO1997/008146; WO1996/040682; WO1994/029255; WO1994/020476; WO1994/019356; WO1993/116690; WO1993/113100; WO1993/007140; WO1993/003041; WO1993/003034; WO1992/019238; WO1992/017475; WO1991/003467; and WO1988/008708; U.S. Patent No. 7,846,930; 7,732,162; 7,635,709; 7,378,425; 6,495,700; 6,479,523; 6,372,760; 6,245,911; 6,140,321; 5,985,864; 5,965,571; 5,965,569; 5,750,542; 5,744,476; 5,693,668; 5,668,117; 5,663,448; 5,622,976; 5,603,176; 5,602,176; 5,574,046; 5,455,245; 5,391,553; 5,389,629; 5,364,864; 5,338,548; 5,302,593; 5,300,517; 5,288,758; 5,246,947; 5,231,093; 5,187,165; 5,166,181; 5,106,856; 5,102,891; 5,100,901; 4,950,658; 4,948,807; 4,948,807; 4,948,807; 4,914,102; 4,895,841; 4,895,841; 4,816,456; 4,663,318; 4,663,318; 4,663,318; and 2,701,225; Japanese Patent Application Nos. 4-216704 and 4-187674, Canadian Patent No. 2,180,703, European Patent Application Publication Nos. 298202; 236684; 409676; 411534; 468187; 477903; 481429; 487071; 611769; 703901; 1050303; 2018874; and 2260839; U.S. Publication Nos. 20010036949; 20020119963; 20030078252; 2003069289; 20040082644; 20050245504; 20050124642; 20060052428; 20070275959; 20080103105; 20080261950; 20090124659; 20100152108; 20100227852; and 20100311697; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

20. The composition of any one of claims 1-18, wherein the AChEI is donepezil, tacrine, rivatigmine, physostigmine, galantamine, or metrifonate or derivatives or analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

21. The composition of any one of claims 1-18, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is present in an amount of 0.1 - 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg.

22. The composition of any one of claims 1-18, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is present in an amount of less than 10 mg, less than 8 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg.

23. A method for treating cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need or at risk thereof, delaying or slowing the progression of cognitive impairment, or reducing the rate of decline of cognitive function in the subject, the method comprising the step of administering to said subject the composition of any one of claims 1-22.

24. A method for treating cognitive impairment associated with a central nervous system (CNS) disorder in a subject in need or at risk thereof, delaying or slowing the progression of cognitive impairment, or reducing the rate of decline of cognitive function in the subject, the method comprising the step of administering to the subject an SV2A inhibitor or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof in an extended release form and an AChEI or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof.

25. The method of claim 24, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is not in an extended release form.

26. The method of claim 24, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof is in a controlled release form, a prolonged release form, a sustained release form, a delayed release form, or a slow release form.

27. The method of claim 24, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is in an immediate release form.

28. The method of claim 24, wherein the SV2A inhibitor and the AChEI are in a unit dosage form.

29. The method of claim 24, wherein the SV2A inhibitor and/or the AChEI are administered at doses that are sub-therapeutic as compared to the doses at which they are therapeutically effective when administered in the absence of the other.

30. The method of claim 24, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, polymorph, or prodrug thereof 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.

31. The method of any one of claims 24, 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.

32. The method of any one of claims 24-31, wherein the SV2A inhibitor or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is administered 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.

33. The method of any one of claims 24-32, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or

prodrug thereof is selected from the group of AChEI referred to in International Patent Applications WO2010/057088; WO2009/008769; WO2008/097546; WO2008/074896; WO2008/073452; WO2007/127474; WO2007/107846; WO2006/097588; WO2006/071274; WO2006/070394; WO2006/060082; WO2006/040688; WO2005/092009; WO2005/079789; WO2005/074535; WO2005/072713; WO 2005/042475; WO2005/039580; WO2005/027975; WO2004/084884; WO2004/080393; WO2004/052348; WO2004/037234; WO2004/034963; WO2004/032929; WO2003/101458; WO2003/091220; WO2003/082820; WO2003/082794; WO2003/020289; WO2002/074293; WO2002/032412; WO2001/085145; WO2001/078728; WO2001/066114; WO2001/066096; WO2001/021590; WO2001/000215; WO2000/033840; WO2000/030446; WO2000/023057; WO2000/015205; WO2000/009483; WO2000/007600; WO2000/002549; WO1999/047131; WO1999/008672; WO1999/007359; WO1998/039000; WO1998/030243; WO1997/138993; WO1997/119059; WO1997/038993; WO1997/029750; WO1997/021681; WO1997/013754; WO1997/008146; WO1996/040682; WO1994/029255; WO1994/020476; WO1994/019356; WO1993/116690; WO1993/113100; WO1993/007140; WO1993/003041; WO1993/003034; WO1992/019238; WO1992/017475; WO1991/003467; and WO1988/008708; U.S. Patent No. 7,846,930; 7,732,162; 7,635,709; 7,378,425; 6,495,700; 6,479,523; 6,372,760; 6,245,911; 6,140,321; 5,985,864; 5,965,571; 5,965,569; 5,750,542; 5,744,476; 5,693,668; 5,668,117; 5,663,448; 5,622,976; 5,603,176; 5,602,176; 5,574,046; 5,455,245; 5,391,553; 5,389,629; 5,364,864; 5,338,548; 5,302,593; 5,300,517; 5,288,758; 5,246,947; 5,231,093; 5,187,165; 5,166,181; 5,106,856; 5,102,891; 5,100,901; 4,950,658; 4,948,807; 4,948,807; 4,948,807; 4,914,102; 4,895,841; 4,895,841; 4,816,456; 4,663,318; 4,663,318; 4,663,318; and 2,701,225; Japanese Patent Application Nos. 4-216704 and 4-187674, Canadian Patent No. 2,180,703, European Patent Application Publication Nos. 298202; 236684; 409676; 411534; 468187; 477903; 481429; 487071; 611769; 703901; 1050303; 2018874; and 2260839; U.S. Publication Nos. 20010036949; 20020119963; 20030078252; 2003069289; 20040082644; 20050245504; 20050124642; 20060052428; 20070275959; 20080103105; 20080261950; 20090124659;

20100152108; 20100227852; and 20100311697; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

34. The method of any one of claims 24-32, wherein the AChEI or the pharmaceutically acceptable salt, hydrate, solvate, or polymorph or prodrug thereof is donepezil, tacrine, rivatigmine, physostigmine, galantamine, or metrifonate or derivatives, analogs, pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

35. The method of any one of claims 24-34, wherein the AChEI is administered at a daily dose of 0.1 mg to 10 mg, 1 - 10 mg, 2 - 10 mg, 2 - 8 mg, or 2 - 5 mg.

36. The method of any one of claims 24-34, wherein the AChEI is administered at a daily dose of less than 10 mg, less than 8 mg, less than 5 mg, less than 2 mg, less than 1 mg, or less than 0.5 mg.

37. The method of any one of claims 24-36, wherein the SV2A inhibitor is administered at 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 3.6 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.

38. The method of any one of claims 1 to 37, wherein the treatment has a longer therapeutic effect in the subject than is attained by administering the AChEI 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.

39. The method of any one of claims 1 to 37, wherein the treatment has a longer therapeutic effect in the subject than is attained by administering the SV2A inhibitor in the absence of the AChEI 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.

40. A method of increasing the therapeutic index of an AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph, or prodrug thereof in a method of treating cognitive impairment associated with a CNS disorder in a subject in need or at risk thereof, comprising administering the composition of any one of claims 1-22.

41. The method of claim 40, wherein the increase in the therapeutic index of the AChEI is greater than the therapeutic index of the AChEI 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.

42. The method of claim 40, 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 method of claim 40, 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 method of claim 40, wherein the AChEI is selected from the group of AChEI referred to in International Patent Applications WO2010/057088; WO2009/008769; WO2008/097546; WO2008/074896; WO2008/073452; WO2007/127474; WO2007/107846; WO2006/097588; WO2006/071274; WO2006/070394; WO2006/060082; WO2006/040688; WO2005/092009; WO2005/079789; WO2005/074535; WO2005/072713; WO

2005/042475; WO2005/039580; WO2005/027975; WO2004/084884; WO2004/080393; WO2004/052348; WO2004/037234; WO2004/034963; WO2004/032929; WO2003/101458; WO2003/091220; WO2003/082820; WO2003/082794; WO2003/020289; WO2002/074293; WO2002/032412; WO2001/085145; WO2001/078728; WO2001/066114; WO2001/066096; WO2001/021590; WO2001/000215; WO2000/033840; WO2000/030446; WO2000/023057; WO2000/015205; WO2000/009483; WO2000/007600; WO2000/002549; WO1999/047131; WO1999/008672; WO1999/007359; WO1998/039000; WO1998/030243; WO1997/138993; WO1997/119059; WO1997/038993; WO1997/029750; WO1997/021681; WO1997/013754; WO1997/008146; WO1996/040682; WO1994/029255; WO1994/020476; WO1994/019356; WO1993/116690; WO1993/113100; WO1993/007140; WO1993/003041; WO1993/003034; WO1992/019238; WO1992/017475; WO1991/003467; and WO1988/008708; U.S. Patent No. 7,846,930; 7,732,162; 7,635,709; 7,378,425; 6,495,700; 6,479,523; 6,372,760; 6,245,911; 6,140,321; 5,985,864; 5,965,571; 5,965,569; 5,750,542; 5,744,476; 5,693,668; 5,668,117; 5,663,448; 5,622,976; 5,603,176; 5,602,176; 5,574,046; 5,455,245; 5,391,553; 5,389,629; 5,364,864; 5,338,548; 5,302,593; 5,300,517; 5,288,758; 5,246,947; 5,231,093; 5,187,165; 5,166,181; 5,106,856; 5,102,891; 5,100,901; 4,950,658; 4,948,807; 4,948,807; 4,948,807; 4,914,102; 4,895,841; 4,895,841; 4,816,456; 4,663,318; 4,663,318; 4,663,318; and 2,701,225; Japanese Patent Application Nos. 4-216704 and 4-187674, Canadian Patent No. 2,180,703, European Patent Application Publication Nos. 298202; 236684; 409676; 411534; 468187; 477903; 481429; 487071; 611769; 703901; 1050303; 2018874; and 2260839; U.S. Publication Nos. 20010036949; 20020119963; 20030078252; 2003069289; 20040082644; 20050245504; 20050124642; 20060052428; 20070275959; 20080103105; 20080261950; 20090124659; 20100152108; 20100227852; and 20100311697; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

45. The method of claim 40, wherein the AChEI is donepezil, tacrine, rivatigmine, physostigmine, galantamine, or metrifonate or derivatives or

analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

46. A method of increasing the therapeutic index of an SV2A inhibitor thereof in a method of treating cognitive impairment associated with a CNS disorder in a subject in need or at risk thereof, comprising administering the composition of any one of claims 1-22.

47. The method of claim 46, wherein the increase in the therapeutic index of the SV2A inhibitor is greater than the therapeutic index of the SV2A inhibitor when administered in the absence of the AChEI 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.

48. The method of claim 46, 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.

49. The method of claim 46, 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.

50. The method of claim 46, wherein the AChEI is selected from the group of AChEI referred to in International Patent Applications WO2010/057088; WO2009/008769; WO2008/097546; WO2008/074896; WO2008/073452; WO2007/127474; WO2007/107846; WO2006/097588; WO2006/071274; WO2006/070394; WO2006/060082; WO2006/040688;

WO2005/092009; WO2005/079789; WO2005/074535; WO2005/072713; WO2005/042475; WO2005/039580; WO2005/027975; WO2004/084884; WO2004/080393; WO2004/052348; WO2004/037234; WO2004/034963; WO2004/032929; WO2003/101458; WO2003/091220; WO2003/082820; WO2003/082794; WO2003/020289; WO2002/074293; WO2002/032412; WO2001/085145; WO2001/078728; WO2001/066114; WO2001/066096; WO2001/021590; WO2001/000215; WO2000/033840; WO2000/030446; WO2000/023057; WO2000/015205; WO2000/009483; WO2000/007600; WO2000/002549; WO1999/047131; WO1999/008672; WO1999/007359; WO1998/039000; WO1998/030243; WO1997/138993; WO1997/119059; WO1997/038993; WO1997/029750; WO1997/021681; WO1997/013754; WO1997/008146; WO1996/040682; WO1994/029255; WO1994/020476; WO1994/019356; WO1993/116690; WO1993/113100; WO1993/007140; WO1993/003041; WO1993/003034; WO1992/019238; WO1992/017475; WO1991/003467; and WO1988/008708; U.S. Patent No. 7,846,930; 7,732,162; 7,635,709; 7,378,425; 6,495,700; 6,479,523; 6,372,760; 6,245,911; 6,140,321; 5,985,864; 5,965,571; 5,965,569; 5,750,542; 5,744,476; 5,693,668; 5,668,117; 5,663,448; 5,622,976; 5,603,176; 5,602,176; 5,574,046; 5,455,245; 5,391,553; 5,389,629; 5,364,864; 5,338,548; 5,302,593; 5,300,517; 5,288,758; 5,246,947; 5,231,093; 5,187,165; 5,166,181; 5,106,856; 5,102,891; 5,100,901; 4,950,658; 4,948,807; 4,948,807; 4,948,807; 4,914,102; 4,895,841; 4,895,841; 4,816,456; 4,663,318; 4,663,318; 4,663,318; and 2,701,225; Japanese Patent Application Nos. 4-216704 and 4-187674, Canadian Patent No. 2,180,703, European Patent Application Publication Nos. 298202; 236684; 409676; 411534; 468187; 477903; 481429; 487071; 611769; 703901; 1050303; 2018874; and 2260839; U.S. Publication Nos. 20010036949; 20020119963; 20030078252; 2003069289; 20040082644; 20050245504; 20050124642; 20060052428; 20070275959; 20080103105; 20080261950; 20090124659; 20100152108; 20100227852; and 20100311697; or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

51. The method of claim 46, wherein the AChEI is donepezil, tacrine, rivatigmine, physostigmine, galantamine, or metrifonate or derivatives or

analogs or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, or prodrugs thereof.

52. The method of any one of claims 1-51, wherein the cognitive impairment is associated with age-related cognitive impairment.

53. The method of claim 52, wherein the age-related cognitive impairment is Mild Cognitive Impairment.

54. The method of claim 53, wherein the Mild Cognitive Impairment is amnestic Mild Cognitive Impairment.

55. The method of any one of claims 1-51, wherein the cognitive impairment is associated with dementia.

56. The method of claim 55, wherein the dementia is Alzheimer's disease.

57. The method of any one of claims 1-51, wherein the cognitive impairment is associated with schizophrenia.

58. The method of any one of claims 1-51, wherein the cognitive impairment is associated with amyotrophic lateral sclerosis.

59. The method of any one of claims 1-51, wherein the cognitive impairment is associated with post traumatic stress disorder.

60. The method of any one of claims 1-51, wherein the cognitive impairment is associated with cancer therapy.

61. The method of any one of claims 1-51, wherein the cognitive impairment is associated with bipolar disorder.

62. The method of any one of claims 1-51, wherein the cognitive impairment is associated with mental retardation.

63. The method of any one of claims 1-51, wherein the cognitive impairment is associated with Parkinson's disease.

64. The method of any one of claims 1-51, wherein the cognitive impairment is associated with autism.

65. The method of any one of claims 1-51, wherein the cognitive impairment is associated with compulsive behavior.

66. The method of any one of claims 1-51, wherein the cognitive impairment is associated with substance addiction.

67. The method of any one of claims 1-51, wherein the effect of the treatment, the progression of cognitive impairment, or the rate of decline of cognitive function is measured by the Clinical Dementia Rating Scale.

68. The method of any one of claims 1-51, wherein the effect of the treatment, the progression of cognitive impairment, or the rate of decline of cognitive function is measured by detecting the difference between the levels of reelin in the subject prior to and after the administration step.

69. The method of any one of claims 1-51, wherein the effect of the treatment, the progression of cognitive impairment, or the rate of decline of cognitive function is measured by detecting the difference between the levels of somatostatin in the subject prior to and after the administration step.

70. A composition comprising levetiracetam in an extended release form and donepezil ,

wherein levetiracetam is present in an amount of 7 - 350 mg, 70 - 350 mg, 100 - 300 mg, or 125 - 250 mg, and

wherein donepezil is present in an amount of 2 - 10 mg or 2 - 4 mg.

71. The composition of claim 70, wherein levetiracetam is present in an amount of 125 -250 mg.

72. The composition of claim 70, wherein donepezil is present in an amount of 2 - 4 mg.

73. The composition of any one of claims 70-72, wherein donepezil is in an immediate release form.

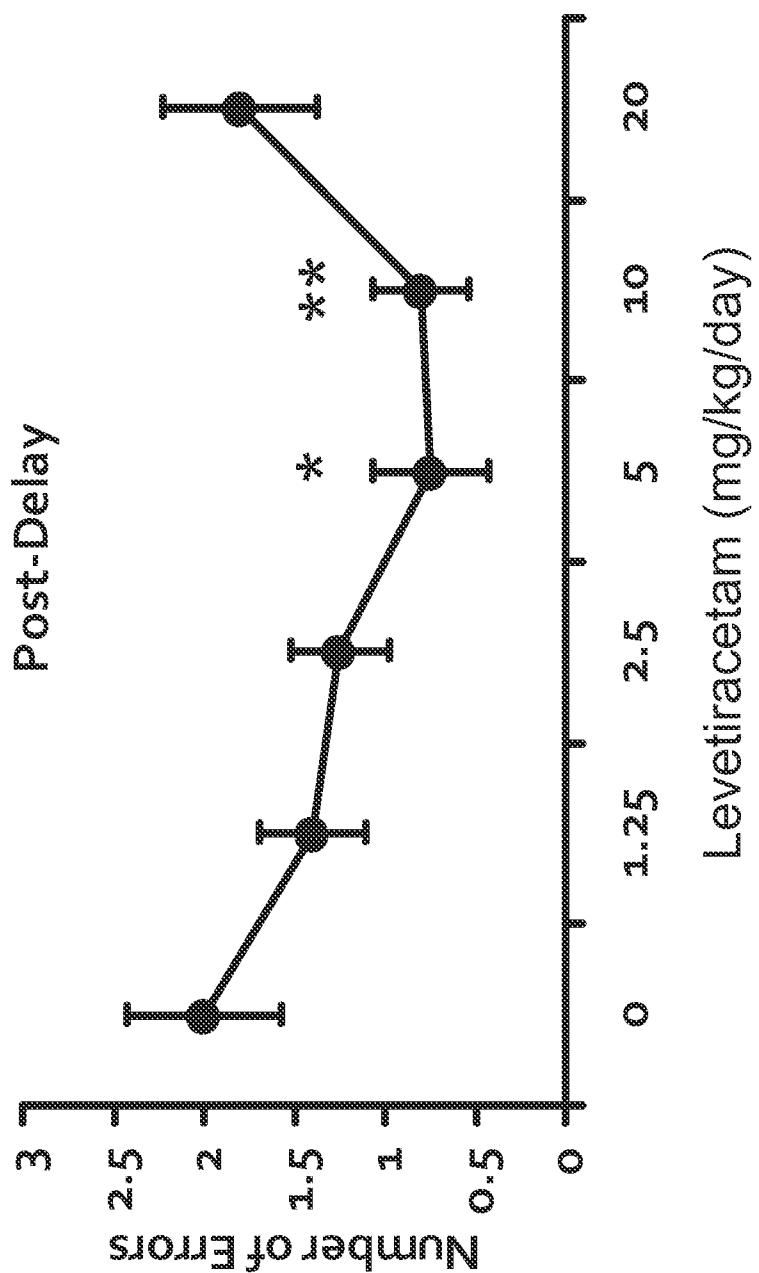


FIG. 1

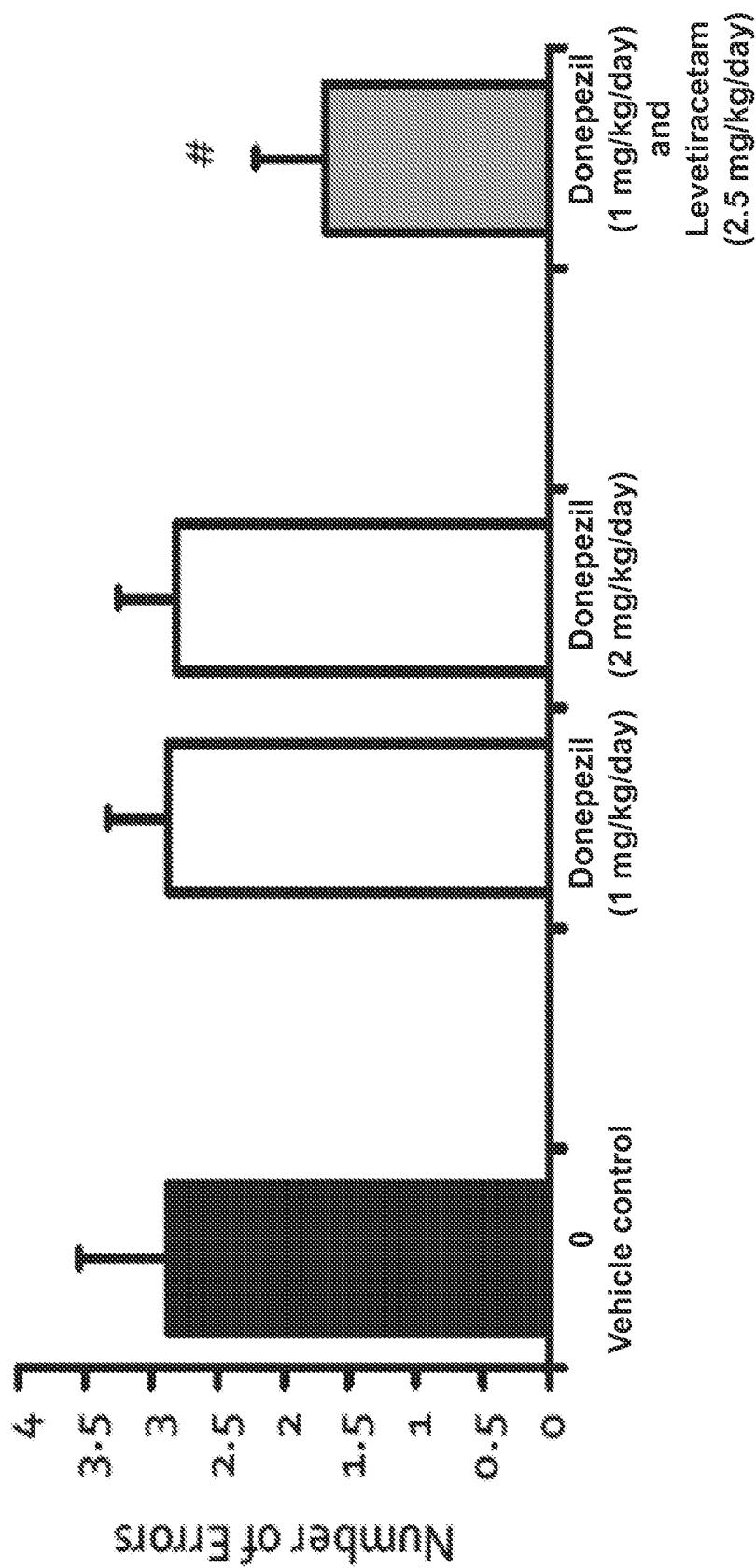
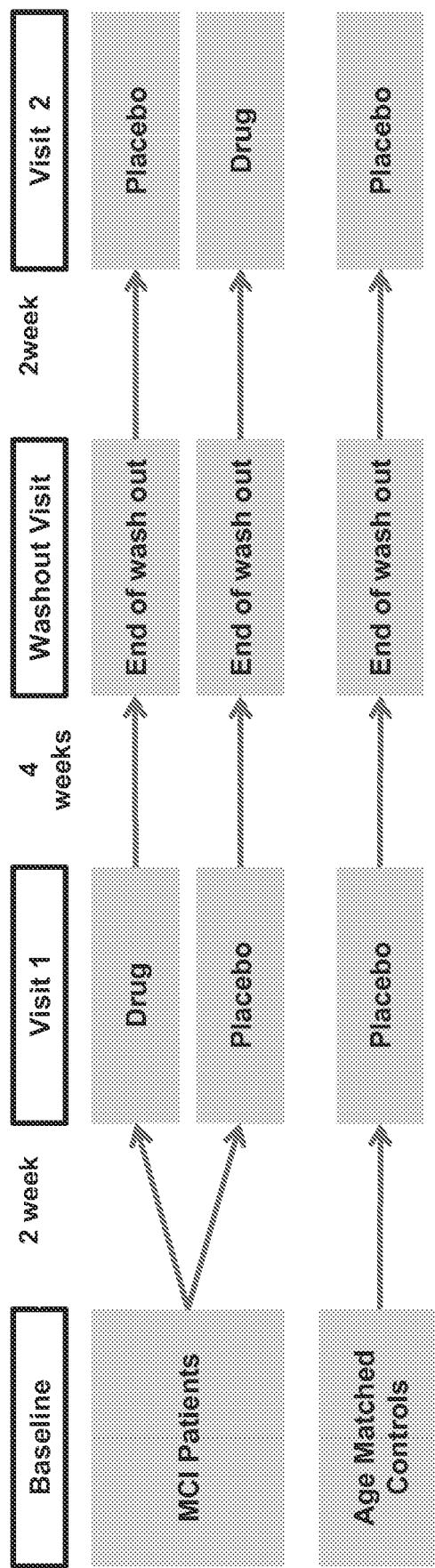


FIG. 2



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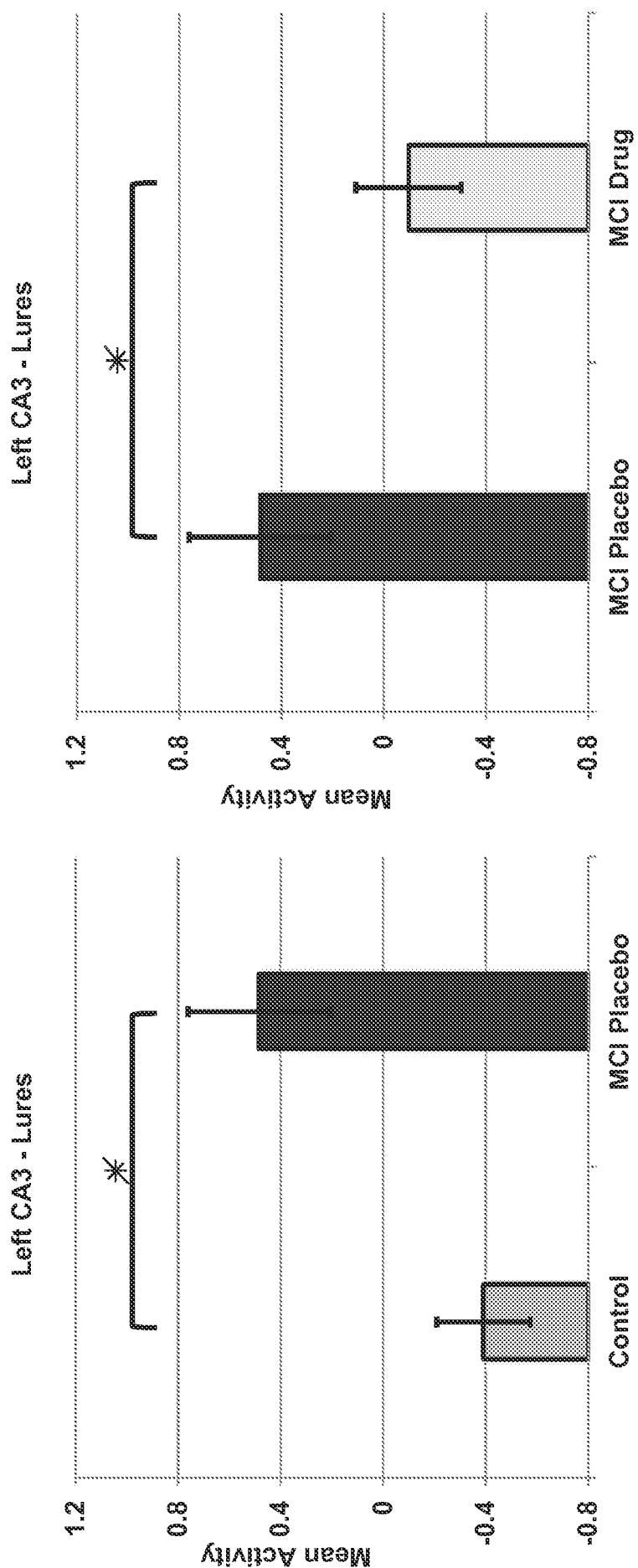


FIG. 4A

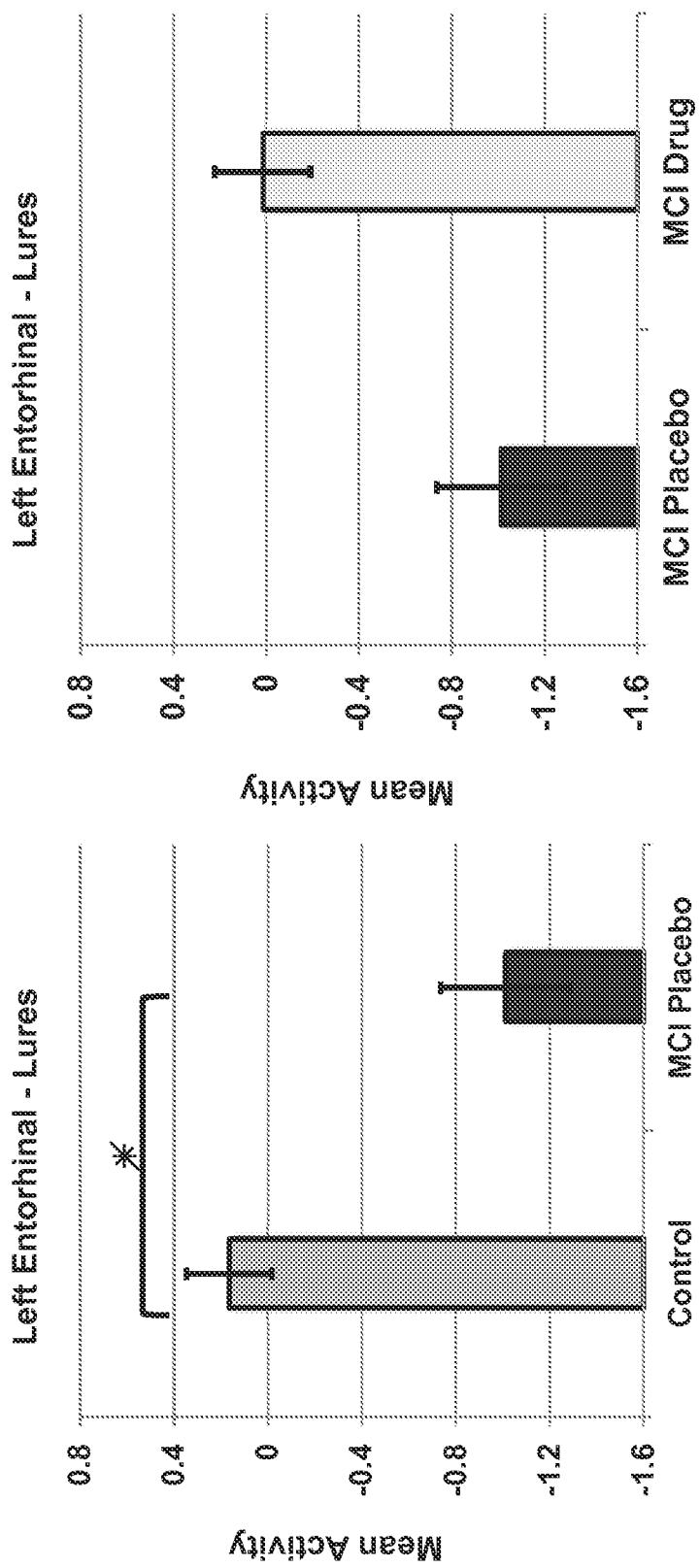
FIG. 4B

## 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. 4C

fMRI entorhinal activation in amnestic MCI is normalized by drug treatment



\*Independent samples t-test:  $t = 3.278$ ,  $p = 0.003$

Paired samples t-test:  $t = -1.600$ ,  $p = 0.129$

**FIG. 5A**

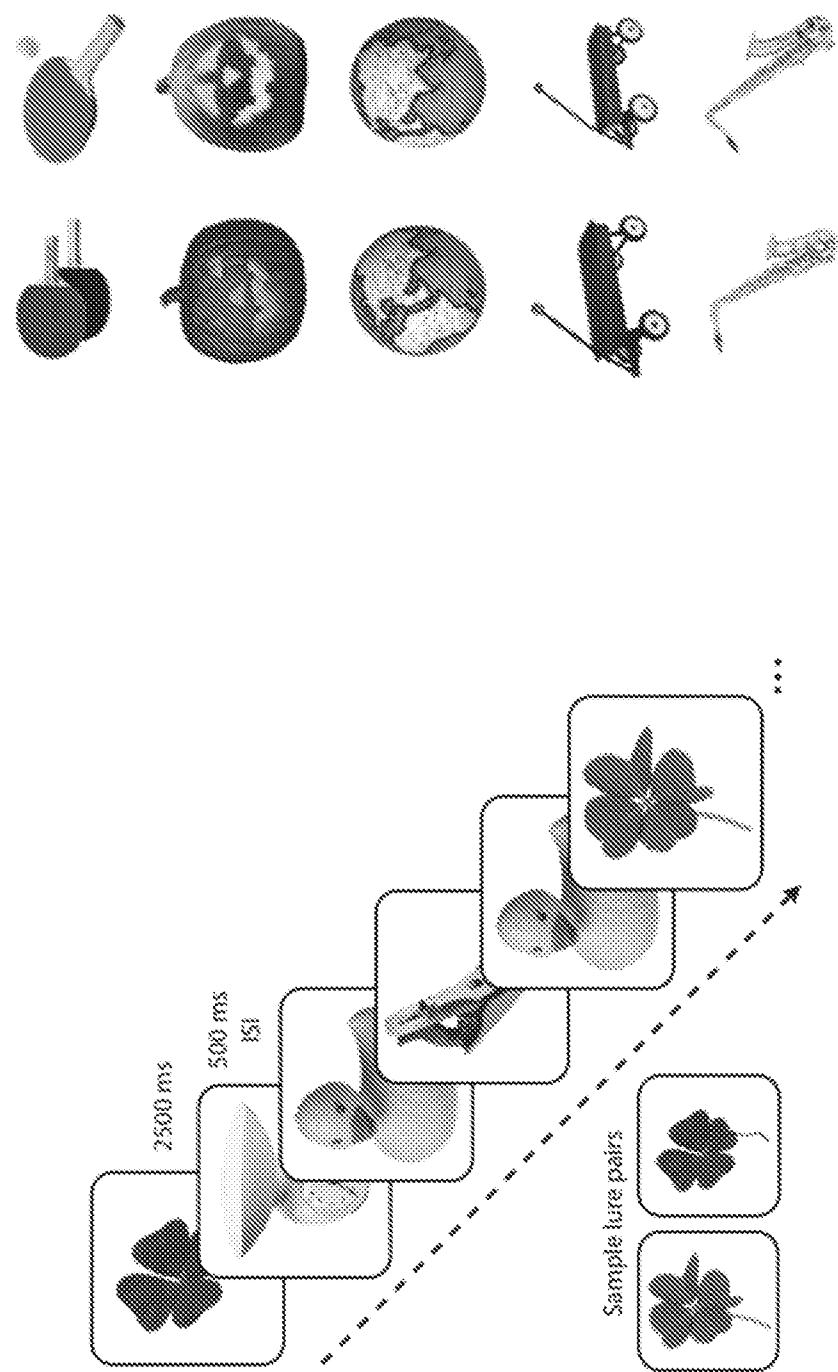
**FIG. 5B**

**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

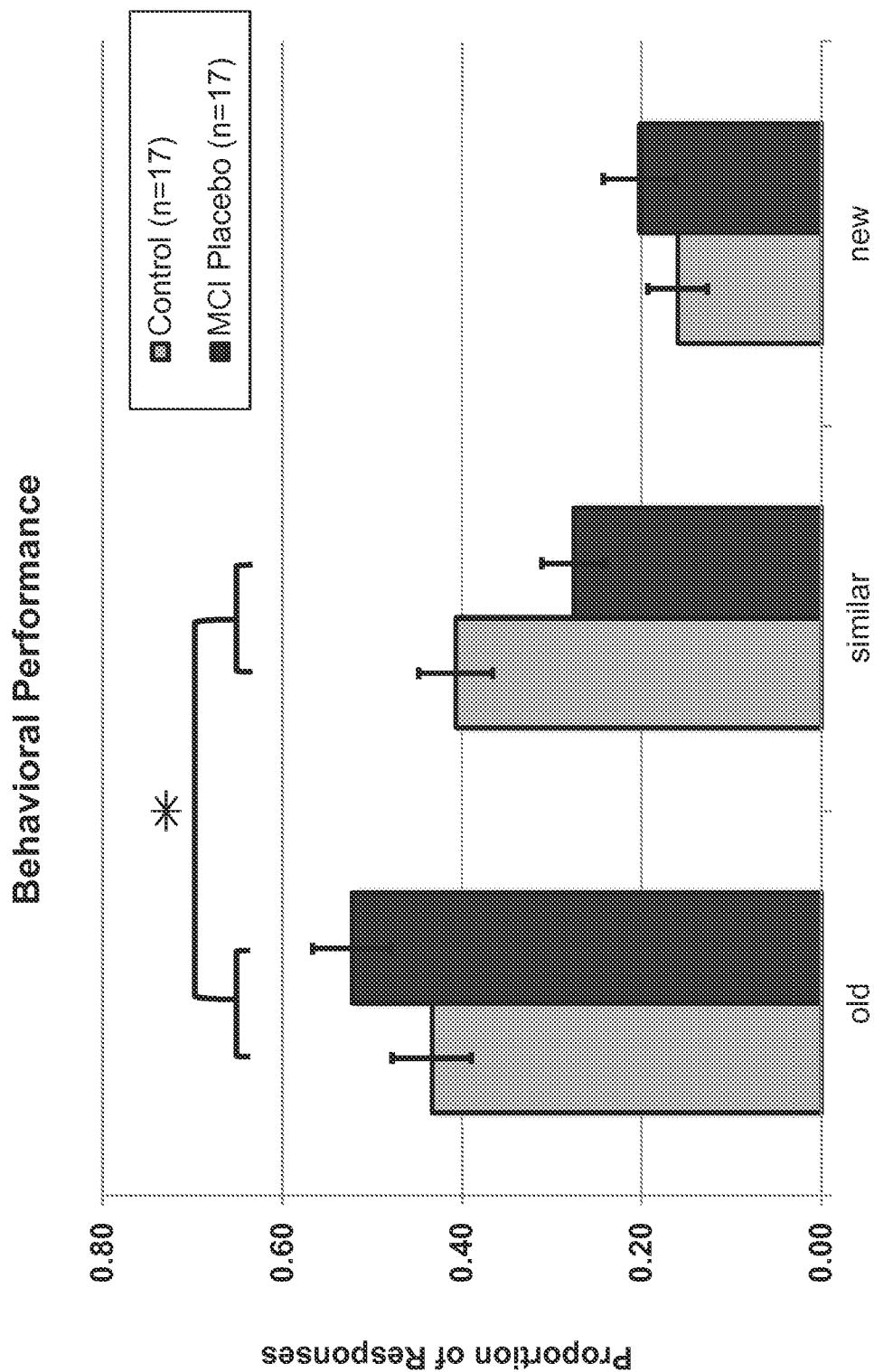
**FIG. 5C**

Reduced memory in task that taxes pattern separation



**FIG. 6A**

**FIG. 6B**



Control vs. MCI Placebo by Old vs. Similar:  $F = 7.687$ ,  $p = 0.009$

FIG. 7

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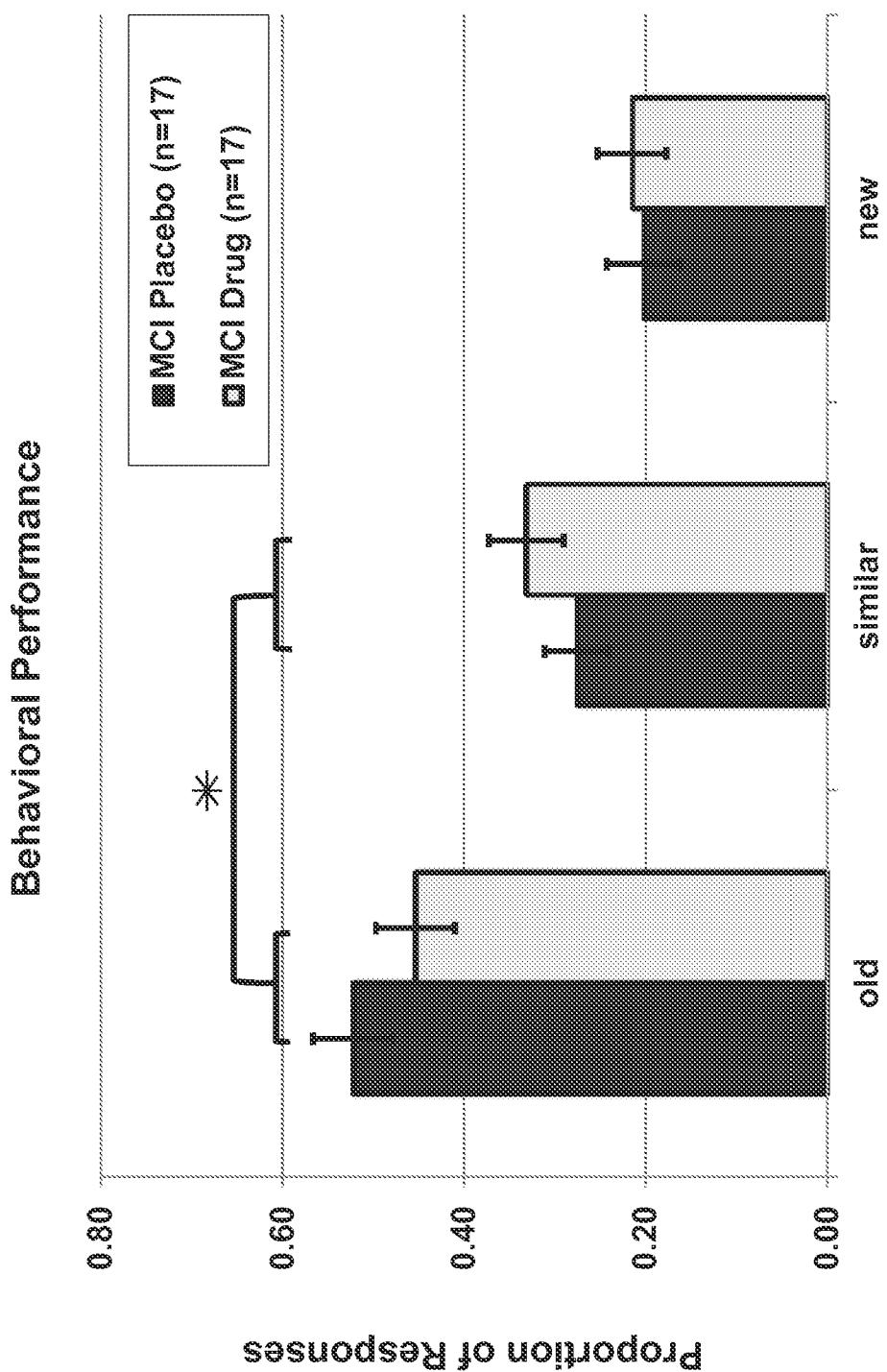
MCI Drug vs. MCI Placebo by Old vs. Similar:  $F = 5.028$ ,  $p = 0.039$ 

FIG. 8

## 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. 9

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## Buschke Selective Reminding Test - Delayed Recall

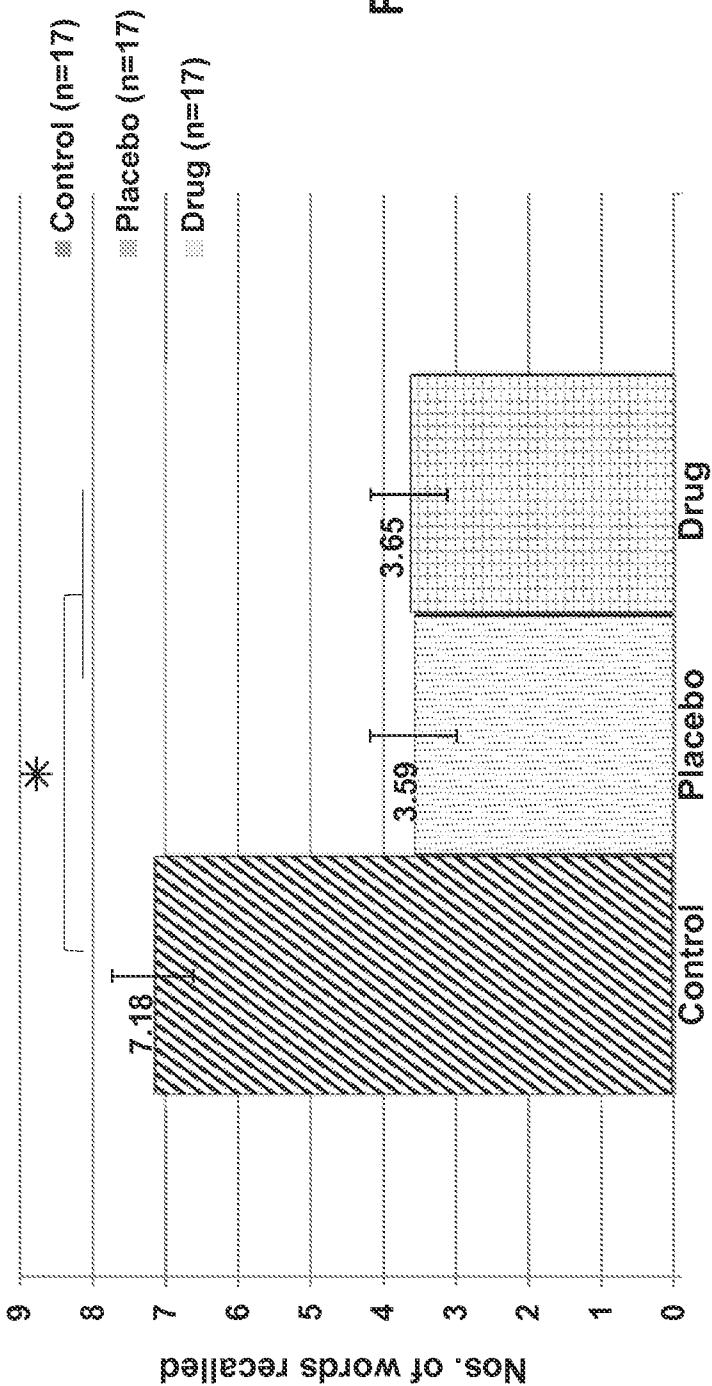


FIG. 10B

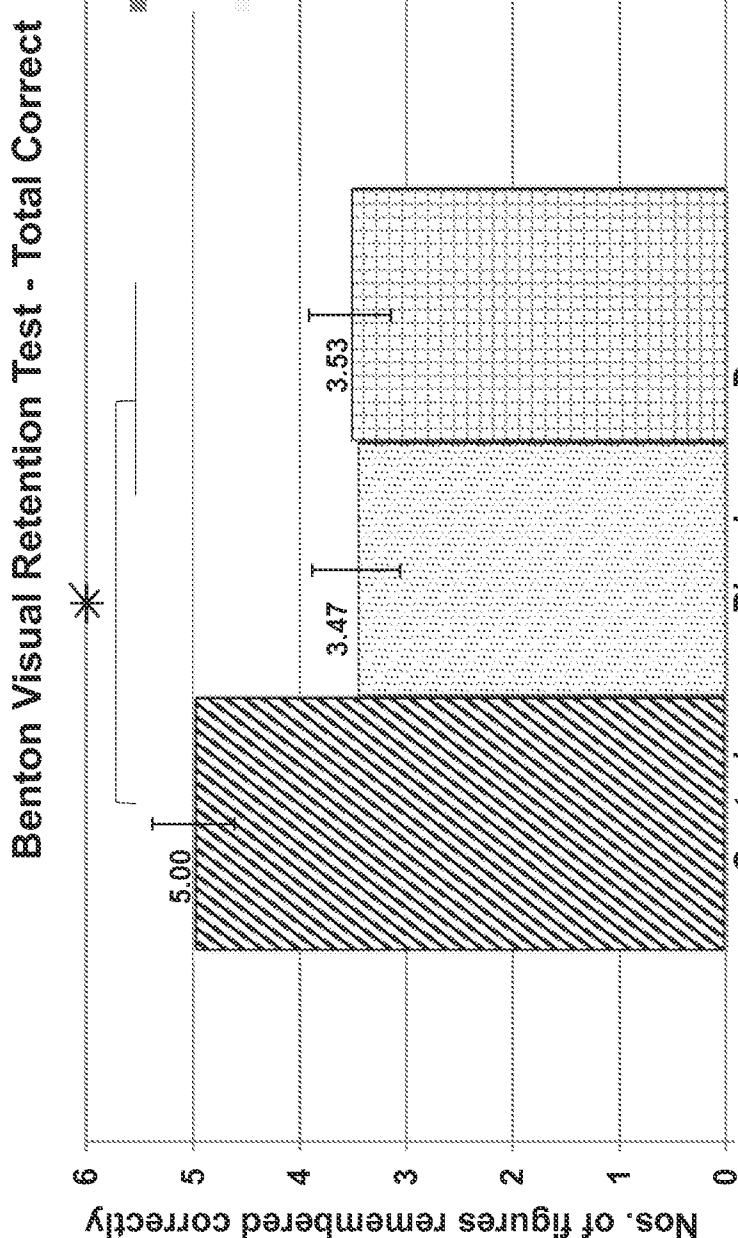


FIG. 11A

Group	Total Correct (p-value)		
	Mean	Standard Error	Control vs. Placebo: 0.011
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. 11B

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## Verbal Paired Associates - Recognition

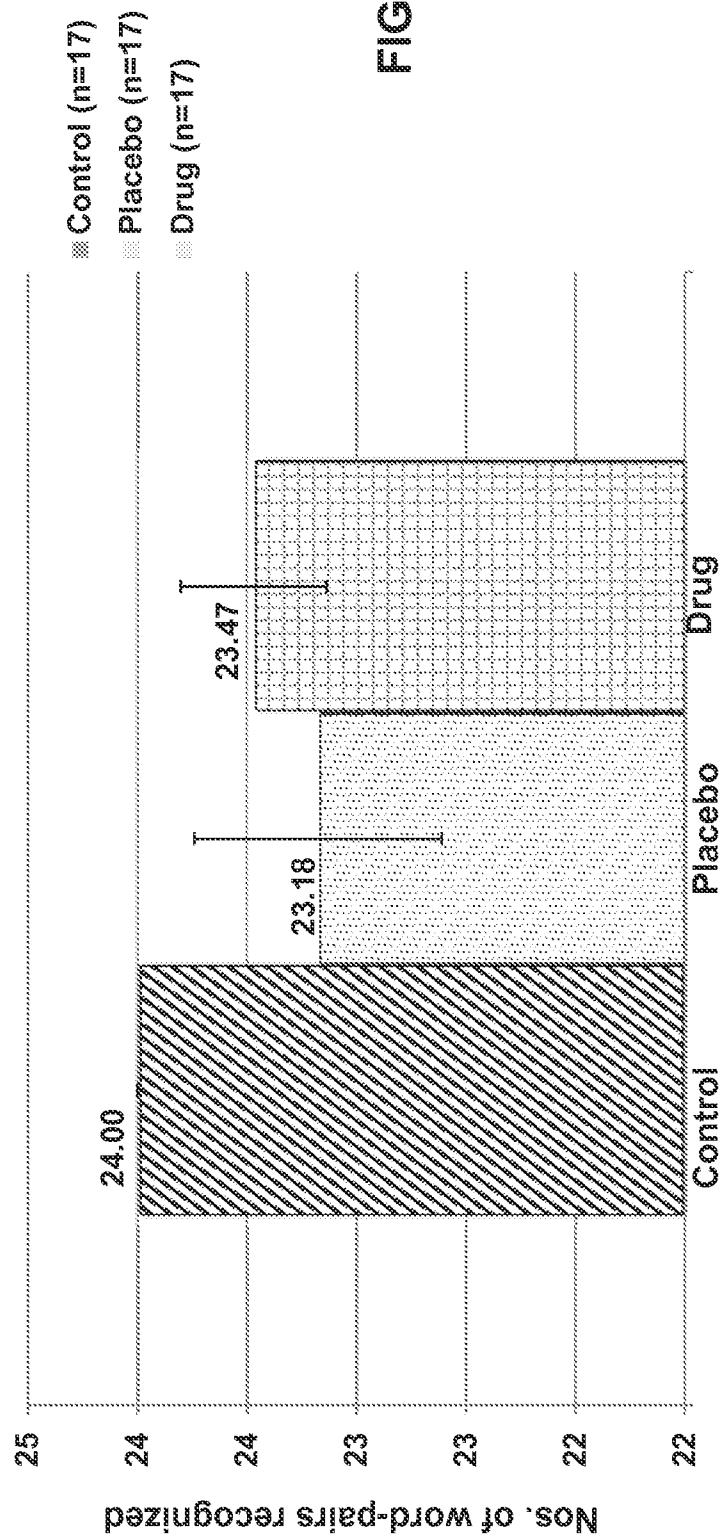


FIG. 12B

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

## Verbal Paired Associates - Delayed Recall

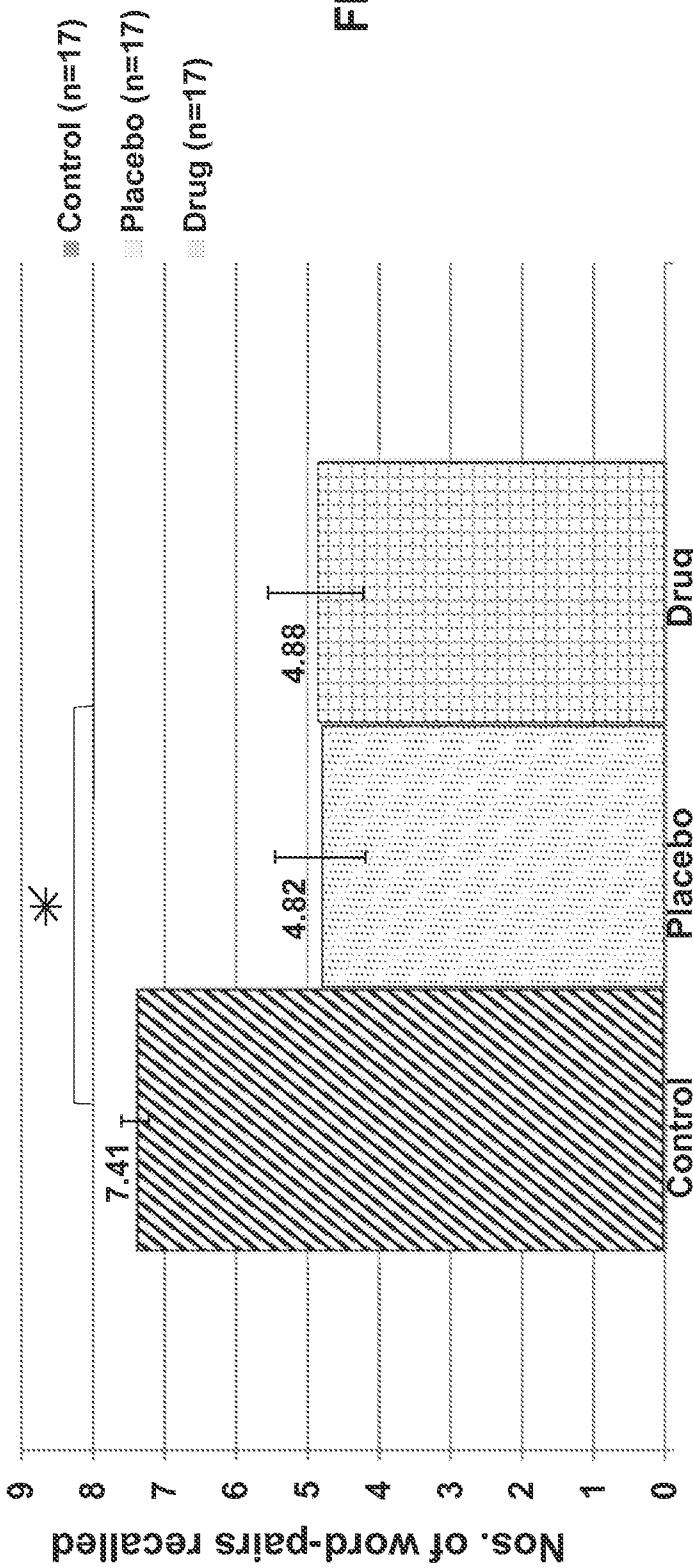


FIG. 13B

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## 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. 14A

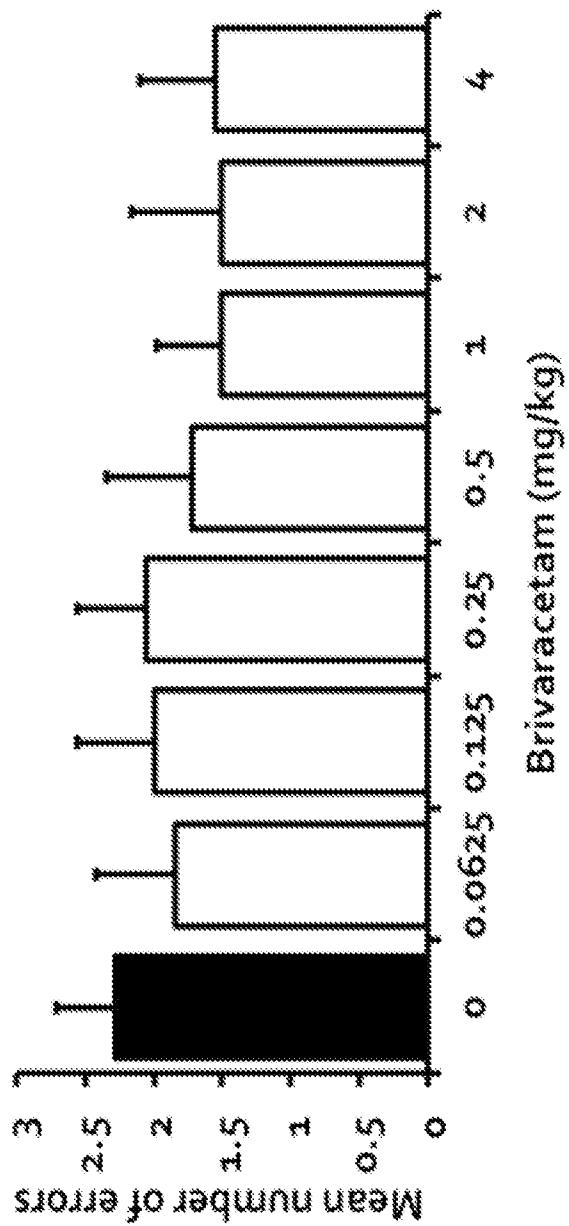
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## Characteristics of Study Samples

	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. 14B

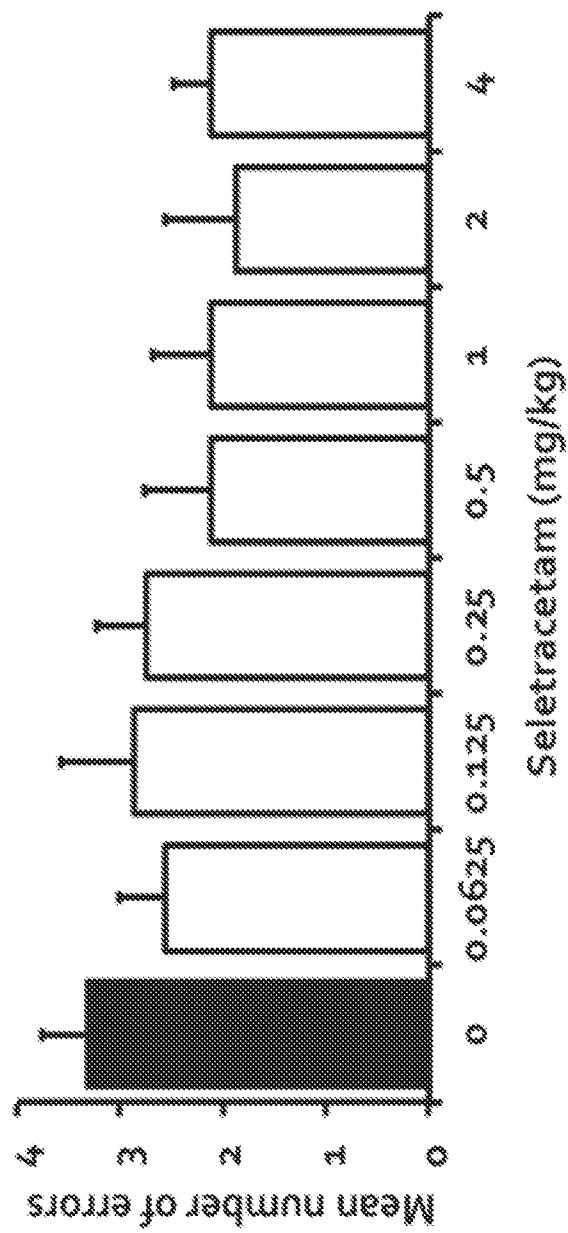
## Brivaracetam Treatment: Radial Arm Maze Task



Repeated measures ANOVA for within-subject contrasts,  $F(1, 8) = 6.046$ ,  $p = 0.039$   
Means and SEMs are shown

FIG. 15

## 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. 16

Performance of cognitively-impaired aged rats (n = 3/group) treated with brivaracetam (2 mg/kg/day after 14 days) in the water maze task

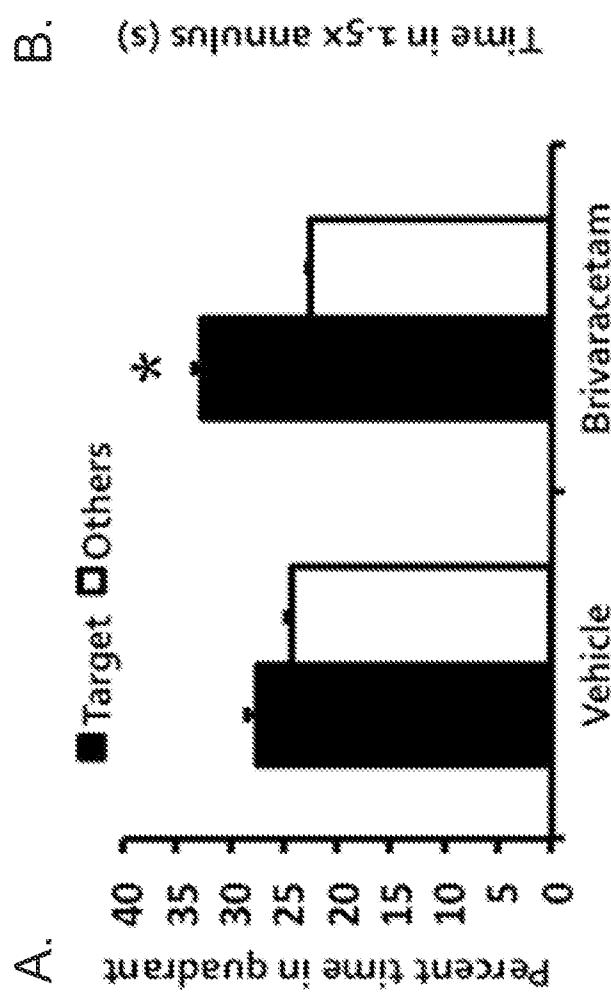


FIG. 17A

FIG. 17B

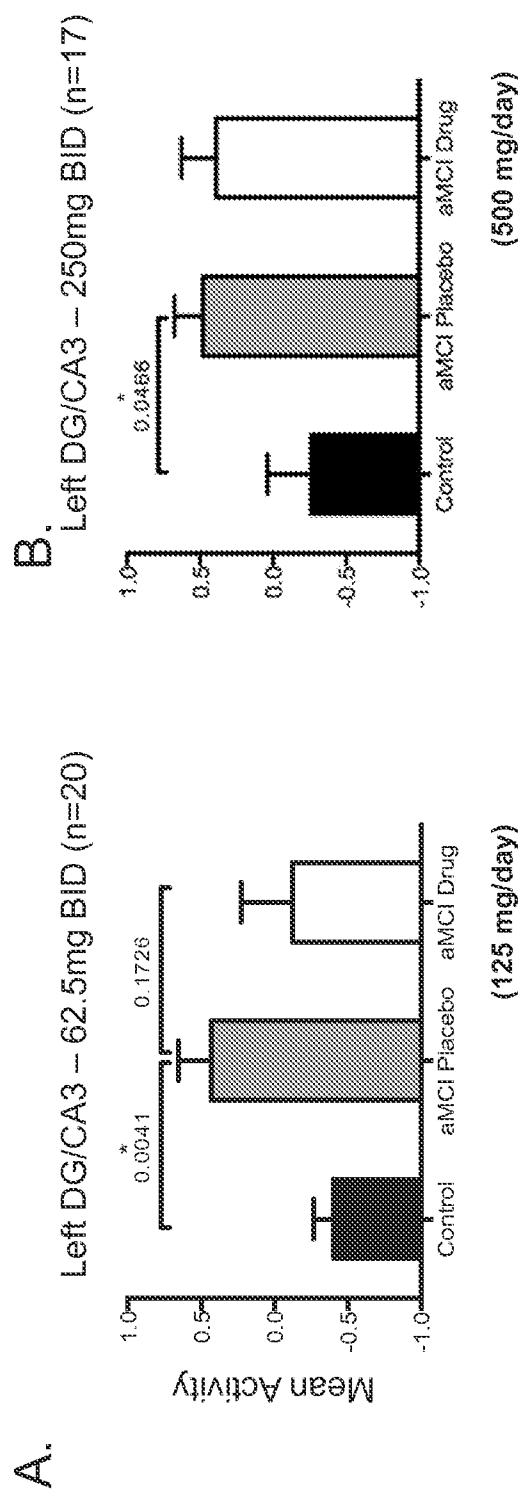


FIG. 18A

FIG. 18B

A. Behavior Performance - Lures (62.5 mg BID)



B. Behavior Performance - Lures (250 mg BID)

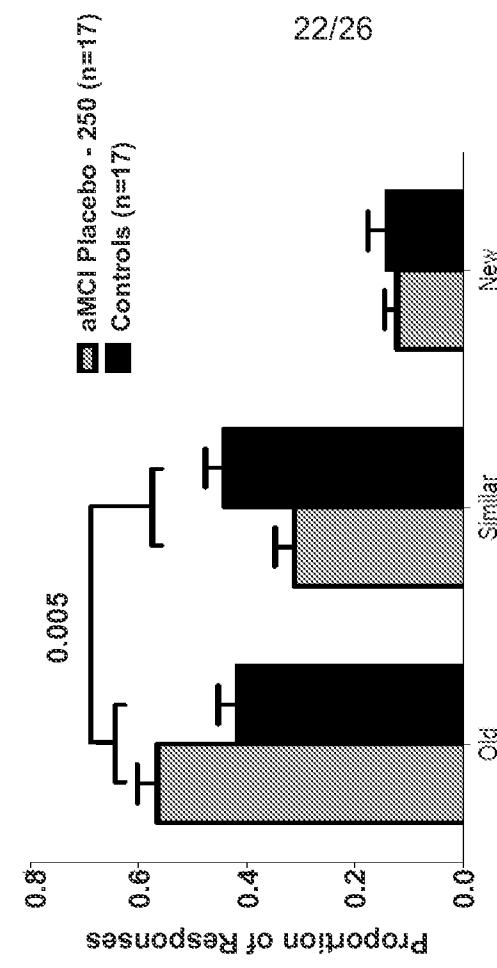
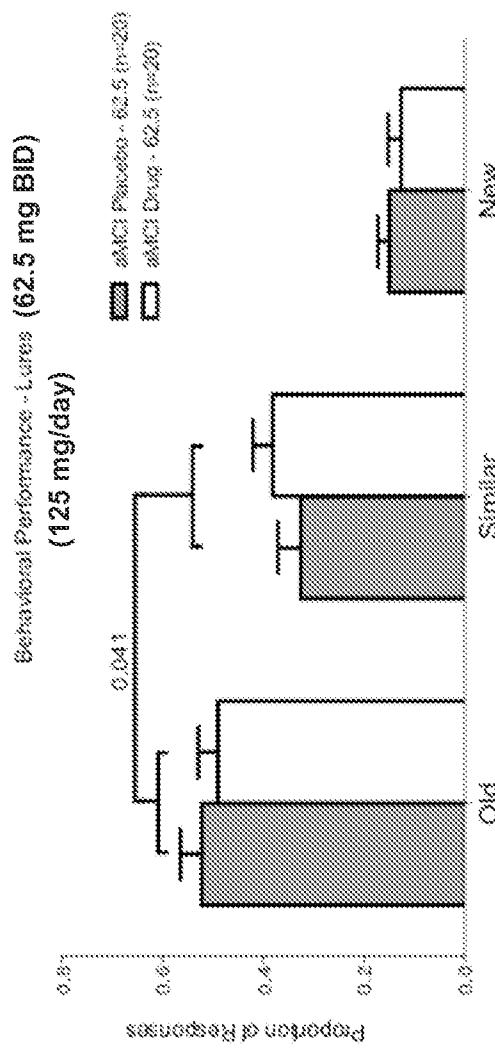
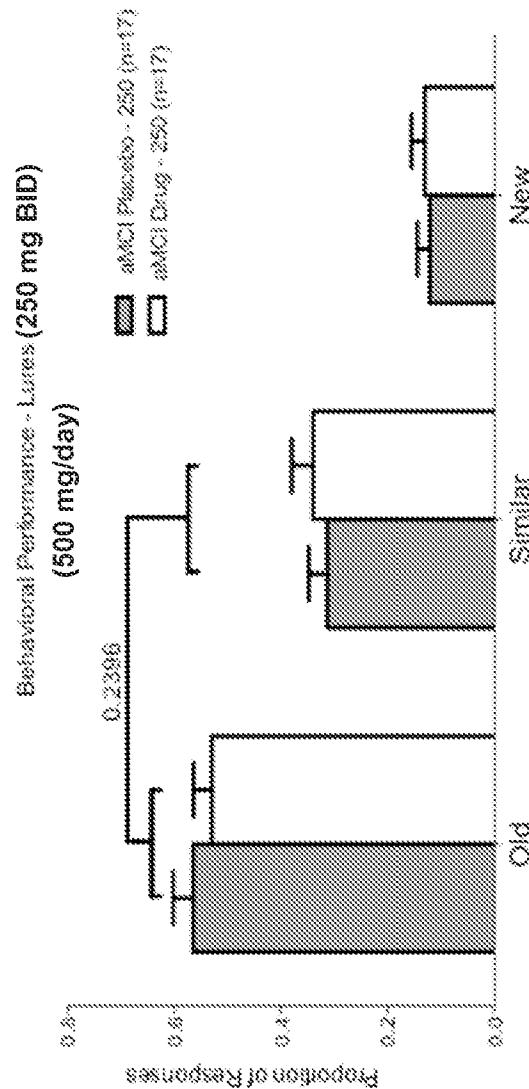


FIG. 19A

FIG. 19B

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**FIG. 20A****FIG. 20B**

Chronic Treatment with Levetiracetam (10 mg/kg/day) in  
Al Rats Restores Somatostatin in DG Hilus

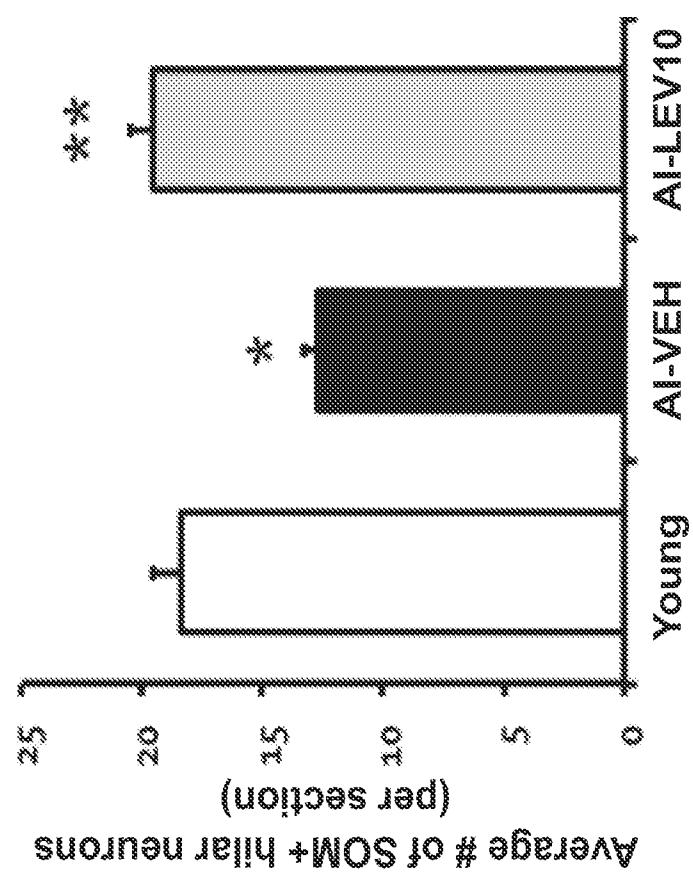


FIG. 21

Chronic Treatment with Levetiracetam (10 mg/kg/day) in  
Al Rats Restores Reelin in Entorhinal Cortex (EC2)

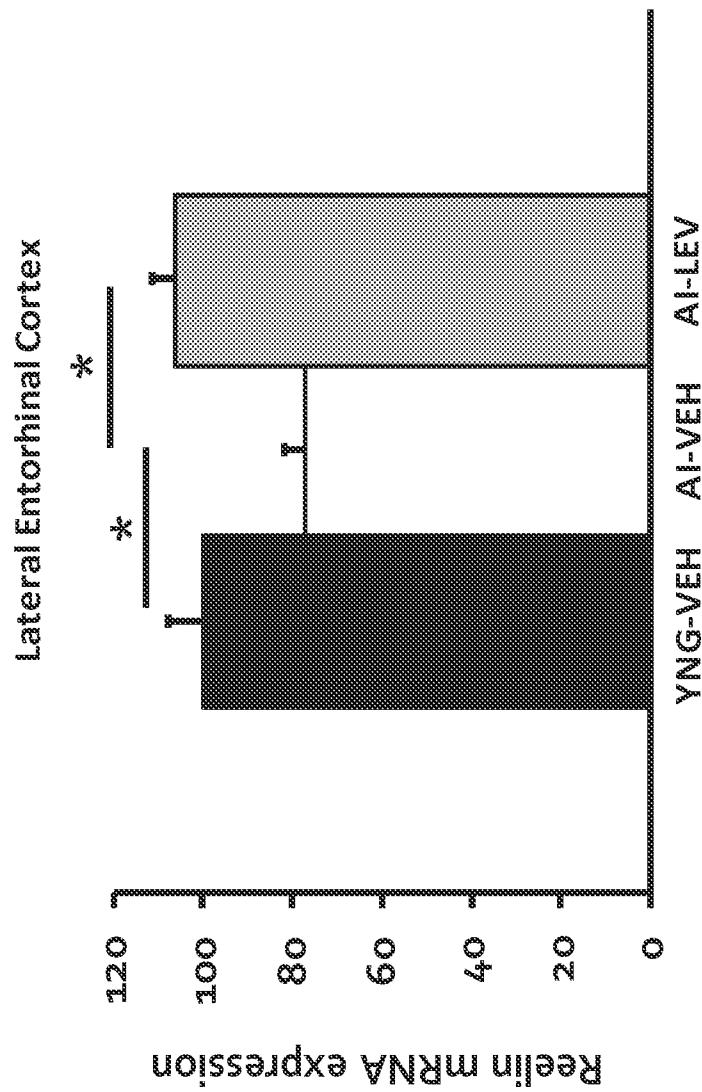


FIG. 22

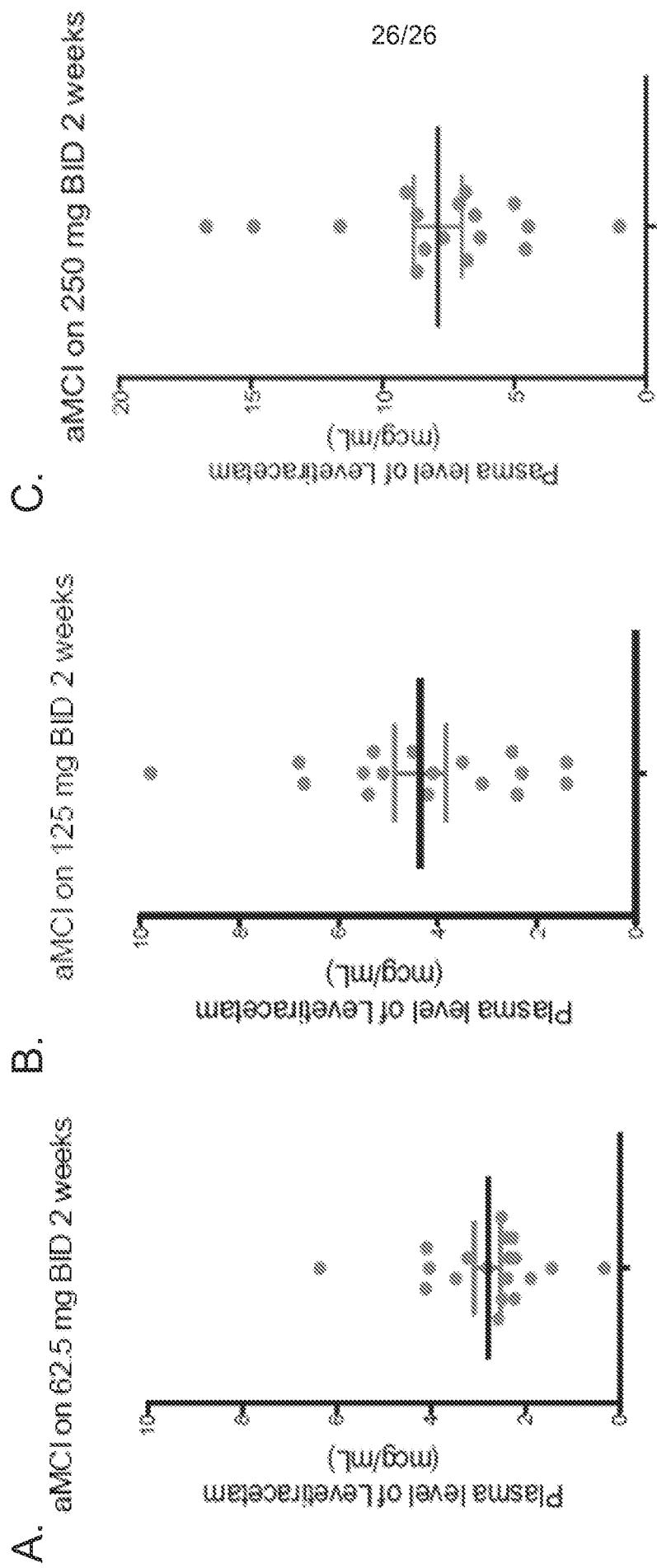


FIG. 23A

FIG. 23B

FIG. 23C