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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

[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

[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.

Background of the Invention

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

[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).

[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.

[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.

[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. 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 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.

[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 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, 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 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 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 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 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 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 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), 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, 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 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 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 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. 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.

[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; 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. However, any AChEI or a pharmaceutically acceptable salt, hydrate, solvate or polymorph may be used in the methods and 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 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 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, 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 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, 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 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, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180

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

[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 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 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 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 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 of the AChEI when administered in the absence of the SV2A inhibitor 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 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 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 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, 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.

[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 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, t 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.

[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 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 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 (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 (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 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 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 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) 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 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 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 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."

[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 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 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**.

[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**.

[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 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 – 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 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 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, 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 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, $t(4) = 3.109$, $p = 0.036$.

[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.

[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.

[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.

[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.

[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

[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, 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 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).

[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.

[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 Verbal Paired Associates subtest; the Logical Memory subtest; the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997); the Benton Visual Retention Test, or the explicit 3-alternative forced choice task, or MATRICS consensus neuropsychological test battery. *See* Folstein et al., *J Psychiatric Res* 12: 189-98, (1975); Robbins et al., Dementia 5: 266-81, (1994); Rey, L'examen clinique en psychologie, (1964); Kluger et al., *J Geriatr Psychiatry Neurol* 12:168-79, (1999); Marquis et al., 2002 and Masur et al., 1994. Also see Buchanan, R.W., Keefe, R.S.E., Umbricht, D., Green, M.F.,

Laughren, T., and Marder, S.R. (2011), The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? Schizophr. Bull. *37*, 1209–1217.

[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.

[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.

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

[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.

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

[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 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.

[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.

[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. 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.

[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.

[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.

[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: 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).

[0105] In some instances, mental retardation includes, but are not limited to, Down syndrome, velocariofacial 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.

[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 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 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 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. 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 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 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 takings steps to improve cognitive function in the subject so that the subject's cognitive function, after

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

[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

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 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 said free base form with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p- aminosalicylic, pamoic and the like. See, e.g., WO 01/062726.

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 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 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 impairment in an animal model for a CNS disorder, and the efficacy of a method of treatment for said CNS disorder may be tested and confirmed with the use of a variety of cognitive tests.

[0120] A Radial Arm Maze (RAM) behavioral task is one example of a cognitive test, specifically testing spacial memory (Chappell *et al. Neuropharmacology* 37: 481-487, 1998). The RAM apparatus consists of, *e.g.*, eight equidistantly spaced arms. A maze arm projects from each facet of a center platform. A food well is located at the distal end of each arm. Food is used as a reward. Blocks can be positioned to prevent entry to any arm. Numerous extra maze cues surrounding the apparatus may also be provided. After habituation and training phases, spatial memory of the subjects may be tested in the RAM under control or test compound-treated conditions. As a part of the test, subjects are pretreated before trials with a vehicle control or one of a range of dosages of the test compound. At the beginning of each trial, a subset of the arms of the eight-arm maze is blocked. Subjects are allowed to obtain food on the unblocked arms to which access is permitted during this initial "information phase" of the trial. Subjects are then removed from the maze for a delay period, *e.g.*, a 60 second delay, a 15 minute delay, a one-hour delay, a two-hour delay, a six hour delay, a 24 hour delay, or longer) between the information phase and the subsequent "retention test," during which the barriers on the maze are removed, thus allowing access to all eight arms. After the delay period, subjects are placed back onto the center platform (with the barriers to the previously blocked arms removed) and allowed to obtain the remaining food rewards during this retention test phase of the trial. The identity and configuration of the blocked arms vary across trials. The number of "errors" the subjects make during the retention test phase is tracked. An error occurs in the trial if the subjects entered an arm from which food had already been retrieved in the pre-delay component of the trial, or if it re-visits an arm in the post-delay session that had already been visited. A fewer number of errors would indicate better spatial memory. The number of errors made by the test subject, under various test compound treatment regimes, can then be compared for efficacy of the test compound in treating cognitive impairment associated with CNS disorders.

[0121] Another cognitive test that may be used to assess the effects of a test compound on the cognitive impairment of a CNS disorder model animal is the Morris water maze. A water maze is a pool surrounded with a novel set of patterns relative to the maze. The training protocol for the water maze may be based on a

modified water maze task that has been shown to be hippocampal-dependent (de Hoz *et al.*, *Eur. J. Neurosci.*, 22:745-54, 2005; Steele and Morris, *Hippocampus* 9:118-36, 1999). The subject is trained to locate a submerged escape platform hidden underneath the surface of the pool. During the training trial, a subject is released in the maze (pool) from random starting positions around the perimeter of the pool. The starting position varies from trial to trial. If the subject does not locate the escape platform within a set time, the experimenter guides and places the subject on the platform to "teach" the location of the platform. After a delay period following the last training trial, a retention test in the absence of the escape platform is given to assess spatial memory. The subject's level of preference for the location of the (now absent) escape platform, as measured by, *e.g.*, the time spent in that location or the number of crossings of that location made by the mouse, indicates better spatial memory, *i.e.*, treatment of cognitive impairment. The preference for the location of the escape platform under different treatment conditions, can then be compared for efficacy of the test compound in treating 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 Neuropsychiatric Inventory (NPI); the Clinical Dementia Rating Scale (CDR); the Cambridge Neuropsychological Test Automated Battery (CANTAB); the Sandoz Clinical Assessment-Geriatric (SCAG), the Buschke Selective Reminding Test (Buschke and Fuld, 1974); the Verbal Paired Associates subtest; the Logical Memory subtest; the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997); the Benton Visual Retention Test, or MATRICS consensus neuropsychological test battery which includes tests of working memory, speed of processing, attention, verbal learning, visual learning, reasoning and problem solving and social cognition. *See* Folstein et al., *J Psychiatric Res* 12: 189-98, (1975); Robbins et al., Dementia 5: 266-81, (1994); Rey, L'examen clinique en psychologie, (1964); Kluger et al., *J Geriatr Psychiatry Neurol* 12:168-79, (1999); Marquis et al., 2002 and Masur et al., 1994, 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 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 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 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 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 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 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 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

[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 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 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, 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 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 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 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 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 configuration of spatial cues surrounding the maze. The cognitive basis of performance is tested in probe trials using measures of the animal's spatial bias in searching for the location of the escape platform. Aged rats in the study population have no difficulty swimming to a visible platform, but an age-dependent impairment is detected when the platform is camouflaged, requiring the use of spatial information. Performance for individual aged rats in the outbred Long-Evans strain varies greatly. For example, a proportion of those rats perform on a par with young adults. However, approximately 40-50% fall outside the range of young performance. This variability among aged rats reflects reliable individual differences. Thus, within the aged population some animals are cognitively impaired and designated aged-impaired (AI) and other animals are not impaired and are designated aged-unimpaired (AU). *See, e.g.*, Colombo *et al.*, *Proc. Natl. Acad. Sci.* 94: 14195-14199, (1997); Gallagher and Burwell, *Neurobiol. Aging* 10:

691-708, (1989); 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 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 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, 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, 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 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 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. Neuro-Psychopharm. & 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. 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 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 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; 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 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.

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

[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.*, *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.

[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.

[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 parvalbumin-positive GABAergic interneurons in portions of the prefrontal cortex and hippocampus. In behavioral tests, MAM-treated rats display reduced latent inhibition. Latent inhibition is a behavioral phenomenon where there is reduced learning about a stimulus to which there has been prior exposure with any consequence. This tendency to disregard previously benign stimuli, and reduce the formation of association with such stimuli is believed to prevent sensory overload. Low latent inhibition is indicative of psychosis. Latent inhibition may be tested in rats in the following manner. Rats are divided into two groups. One group is pre-

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

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

hippocampus (vHipp) regulation, on the elevated DA neuron population activity and on the hyperactive locomotor response to amphetamine in the MAM-treated animals.

[0142] In MAM-treated rats, hippocampal (HPC) dysfunction leads to dopamine system hyperactivity. A benzodiazepine-positive allosteric modulator (PAM), selective for the α5 subunit of the $GABA_A$ receptor, SH-053-2'F-R-CH_3, is tested for its effects on the output of the hippocampal (HPC). The effect of SH-053-2'F-R-CH_3 on the hyperactive locomotor response to amphetamine in MAM-treated animals is also examined. The α5GABAAR PAM reduces the number of spontaneously active DA neurons in the ventral tegmental area (VTA) of MAM rats to levels observed in saline-treated rats (control group), both when administered systemically and when directly infused into the ventral HPC. Moreover, HPC neurons in both saline-treated and MAM-treated animals show diminished cortical-evoked responses following the α5GABAAR PAM treatment. In addition, the increased locomotor response to amphetamine observed in MAM-treated rats is reduced following the α5$GABA_AR$ 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).

[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 every 5 min during a 30-min test session. Scores for each animal are totaled over the 30-min test session for each syndrome (stereotyped behavior and climbing). If an effect reached at least of 50% inhibition, and ID_{50} value (95% confidence interval) is calculated using a nonlinear least squares calculation with inverse prediction. Mean climbing and stereotype scores can be expressed as a percent of control values observed in 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.

[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.

Amyotropic Lateral Sclerosis (ALS)

[0146] This invention additionally provides methods and compositions for 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 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.

[0147] In addition to the degeneration of motor neurons, ALS is characterized by neuronal degeneration in the entorhinal cortex and hippocampus, memory deficits, 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.

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 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 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.

[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).

[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.

[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. 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}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 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 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 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, 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 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 model, the 3-nitrotyrosine model and genetic models using transgenic mice. Transgenic models include mice that over express α-synuclein, express human mutant forms of α -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.

[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

[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 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 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 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

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 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 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 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 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 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 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, velocariofacial 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 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 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 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 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 (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 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 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 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.

[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 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 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™), 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 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 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 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 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 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 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. 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 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 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 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 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 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 $Ca^{(2+)}$- 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, "Levetiracetam has an activity-dependent effect on inhibitory transmission," *Epilepsia*, 2012 Jan 31; and Example 8 of WO 2001/62726, all of which are specifically incorporated herein by reference.) A substance, or a compound or an agent is an SV2A inhibitor even if it does not itself bind to SV2A, as long as it causes, or affects the ability of, another compound or agent to bind SV2A or reduce synaptic function by reducing pre-synaptic vesicle release. SV2A inhibitors, as used herein, include pharmaceutically acceptable salts of the inhibitors thereof. They also include hydrates, polymorphs, prodrugs, salts, and solvates of these inhibitors.

[0177] Among the SV2A inhibitors or pharmaceutically acceptable salts, 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 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; 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 in the documents cited above. Other synthetic methods may also be used. These methods are well known to those skilled in the art.

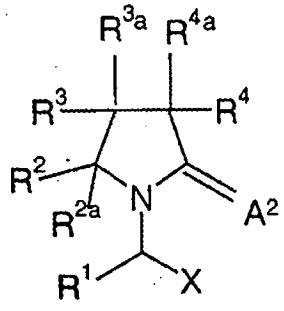
[0178] In some embodiments of this invention, the SV2A inhibitor is selected from the group consisting of levetiracetam, brivaracetam, and seletracetam or derivatives or analogs or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, or prodrugs thereof.

[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).

[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,



(I)

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

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

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

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

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

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

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

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

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

The term "oxy derivative", as used herein is defined as including -O-R^{11} groups wherein R^{11} is as defined above except for "oxy derivative". Non-limiting examples are alkoxy, alkenyloxy, alkynyloxy, acyloxy, oxyester,

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

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

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

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

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

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

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-6 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl"). Alkyl moieties may optionally be substituted by 1 to 5 substituents independently selected

from the group consisting of halogen, hydroxy, thiol, amino, nitro, cyano, thiocyanato, acyl, acyloxy, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, oxyester, oxyamido, heterocycle, vinyl, C1-5-alkoxy, C6-10-aryloxy and C6-10-aryl.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo (2.2.1)heptanyl, 7- oxabicyclo (2.2.1) heptanyl, 8-azabicyclo (3.2.1)octanyl.

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

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

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

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

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

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

R^1 as ethyl is especially preferred.

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

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

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

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

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

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

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

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

Also, preferably, R^3 is C1-6-alkyl optionally substituted by one or more substituents selected from halogen, thiocyanato, azido, alkoxy, alkylthio, phenylsulfonyl ; nitrooxy ; C2-3- alkenyl or-alkynyl each optionally substituted

by one or more halogens or by acetyl ; tetrazolyl, pyridyl, furyl, pyrrolyl, thiazolyl or thienyl ; or phenyl or phenylalkyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* a sulfonyloxy and optionally additionally a C1-4-alkylene bridge, particularly methylene.

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

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

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

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

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

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

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

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

Preferably R^8 is hydrogen or methyl.

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

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

A^2 is oxygen;

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

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

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

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

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

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

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

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

R^3 is preferably C1-5 alkyl, C2-5 alkenyl, C2-C5 alkynyl, cyclopropyl, azido, each optionally substituted by one or more halogen, cyano, thiocyano, azido, alkylthio, cyclopropyl, acyl and/or phenyl ; phenyl ; phenylsulfonyl ; phenylsulfonyloxy, tetrazole, thiazole, thienyl, furyl, pyrrole, pyridine, whereby any phenyl moiety may be substituted by one or more halogen, alkyl,

haloalkyl, alkoxy, nitro, amino, and/or phenyl ; most preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl.

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

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

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

R^1 is alkyl or phenyl ;

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

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

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

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

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

Within the compounds of formula I,

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

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

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

selected from halogen, C1-6-alkyl and phenyl and attached to the ring either directly or *via* a carbonyl group or a C1-4-alkylene bridge, particularly methylene ; naphthyl ; or phenyl, phenylalkyl or phenylalkenyl each optionally substituted by one or more substituents selected from halogen, C1-6-alkyl, C1-6 haloalkyl, C1-6-alkoxy, C1-6-alkylthio, amino, azido, phenyl and nitro and each attached to the ring either directly or *via* an oxy, sulfonyl, sulfonyloxy, carbonyl or carbonyloxy group and optionally additionally a C1-4- alkylene bridge, particularly methylene ;

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

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

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

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

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

X is-CA^1NH_2 ;

R^1 is H ;

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

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

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

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

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

X is-CA^1NH_2 ;

R^1 is H ;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2-[2-oxo-4-(1,3-thiazol-2-yl)-1-pyrrolidinyl]butanamide;

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

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

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

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

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

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

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

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

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

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

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

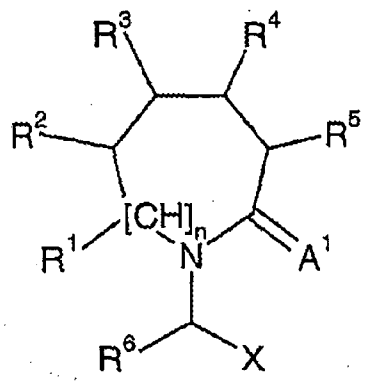
(2S)-2-[(4S)-4-(2, 2-difluorovinyl)-2-oxopyrrolidinyl]butanamide;

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

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

ii) International Patent Application WO 2002/094787:

Compounds of the formula I



(I)

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

A^1 represents an oxygen or a sulfur atom;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The term "alkenyl", as used herein, is defined as including both branched and unbranched, unsaturated hydrocarbon radicals having at least one double bond, and being optionally substituted by at least one substituent selected from

the group consisting of halogen, hydroxy, thiol, amino, thiocyanato, azido, alkylthio, cycloalkyl, acyl, nitro, cyano, aryl and heterocycle.

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

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

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

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

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

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

The term "aryl", as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of at least one ring, most often 1 to 3 rings and generally containing 6-30 carbon atoms by removal of

one hydrogen, such as phenyl and naphthyl, each optionally substituted by one or more substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, acyl, acyloxy, sulfonyl, sulfinyl, alkylamino, carboxy, ester, ether, amido, azido, sulfonic acid, sulfonamide, alkylsulfonyl, alkylsulfinyl, C1-6-alkylthio, oxyester, oxyamido, aryl, C1-6-alkoxy, C6-10-aryloxy, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic or bicyclic containing 6-10 carbon atoms. Preferred aryl groups are phenyl and naphthyl each optionally substituted by one or more substituents independently selected from halogen, nitro, amino, azido, C1-6-alkoxy, C1-6-alkyl, C1-6-haloalkyl, sulfonyl and phenyl.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The term "amido" is defined as including a group of formula $-CONH_2$ or $-CONHR^{11}$ or $-CONR^{11}R^{12}$ 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) furanyl, furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, 1-oxidopyridyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, benzodioxolyl, isochromanyl, indolinyl, xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro (4.5) dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i. e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) optionally substituted by alkyl or as described above for the alkyl groups. The term"heterocycle"also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic

heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo (2.2.1) heptanyl, 7-oxabicyclo (2.2.1) heptanyl, 8-azabicyclo (3.2.1) octanyl.

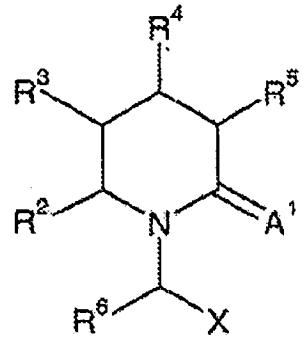
The heterocycle is preferably selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1- oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from halogen,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

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

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

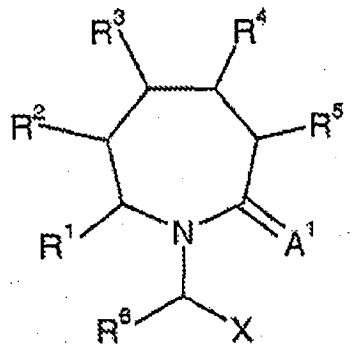
The term"R substituent"refers to R^1, R^2, R^3, R^4 or R^5, independently.

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



(I-A)

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



(I-B)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

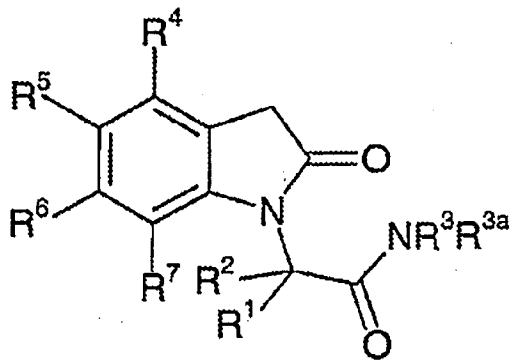
2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,

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

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

iii) International Patent Application WO 2004/087658:

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



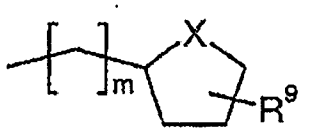
(I)

wherein

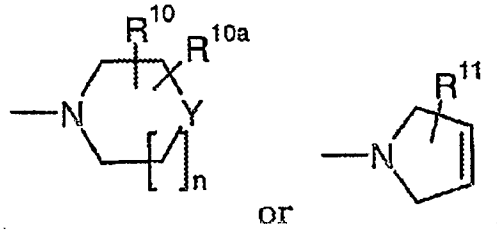
R^1 is hydrogen,

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

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



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



R^4 is hydrogen,

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

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

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

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

X is O, S or NH,

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

R^8 is aryl or heterocycle,

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

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

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

R^{13} is hydrogen,

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

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

V is C_{1-12}-alkylene,

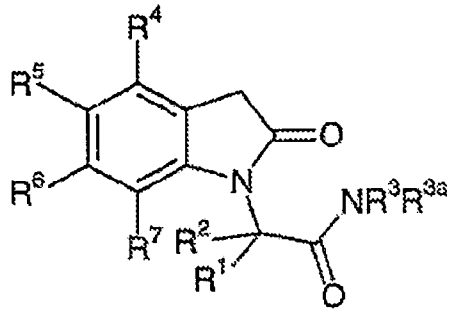
R^{15} is aryl or heterocycle,

m is 1 to 4,

n is 0 or 1,

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

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



(I)

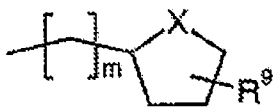
wherein

R^1 is hydrogen,

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

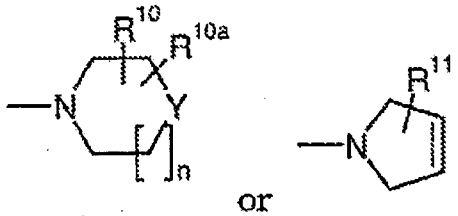
R^3 is hydrogen, C1-20-alkyl, C4-8-cycloalkyl, C5-8-cycloalkenyl, aryl, aromatic or non aromatic heterocycle, C1-20-alkoxy, or a group of formula -W-R^8,

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



,

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



or

,

R^4 is hydrogen,

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

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

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

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

X is O, S or NH,

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

R^8 is aryl or heterocycle,

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

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

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

R^{13} is hydrogen,

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

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

V is C1-12-alkylene,

R^{15} is aryl or heterocycle,

m is 1 to 4,

n is 0 or 1,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, thiazolidinyl, indolinyl, tetrahydrobenzazocinyl, dihydroisochromenyl, tetrahydropyranyl, oxooctahydroquinolinyl, dioxolanyl, 1-oxaspiro (4.5) dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, 8-thiabicyclo [3.2. 1] cyclooctanyl, 1,4-dithiepanyl, tetrahydro-2H-thiopyranyl, azepanyl and azocanyl, optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, azido, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl, formyl or ester. More preferred non

aromatic heterocycles are tetrahydrofuranyl, piperidinyl, piperidyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, thiazolidinyl, indolinyl, tetrahydro-1-benzazocin-1 (2H)-yl, 3, 4-dihydro-lH-isochromen-1-yl, tetrahydropyranyl, oxooctahydroquinolinyl and dioxolanyl. The term"heterocycle"also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cycloalkyl ring, a cycloalkenyl ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo (2.2.1)heptanyl, 7-oxabicyclo (2.2.1)heptanyl and 8- azabicyclo (3.2.1)octanyl.

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

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

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

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

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

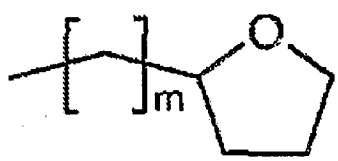
Generally, R^3 is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxycarbonyl or alkylamino; C5-7-cycloalkyl; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-alkyl,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

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

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

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

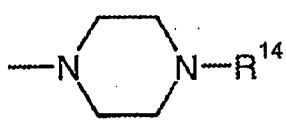
Generally, R^{3a} is hydrogen, C1-4-alkyl or a group of formula



wherein m is 1 to 4.

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

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



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

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

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

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

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

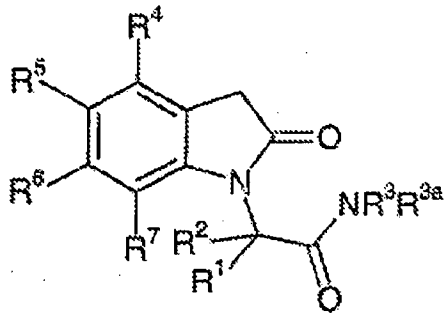
Preferably, R^6 is hydrogen, methyl or Cl. More preferably, R^6 is hydrogen.

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

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

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

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



(I)

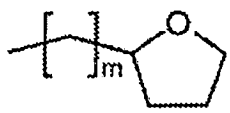
wherein R^1 is hydrogen,

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

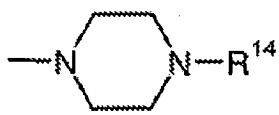
R^3 is hydrogen; C1-6-alkyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, hydroxy, alkoxy, alkoxycarbonyl or alkylamino ; C5-7-cycloalkyl ; (hydroxymethyl) cyclohexenyl; phenyl unsubstituted or substituted by 1 to 5 substituents selected from halogen, C1-4-

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

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



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



R^4 is hydrogen,

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

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

R7 is hydrogen, methyl or halogen,

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

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

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

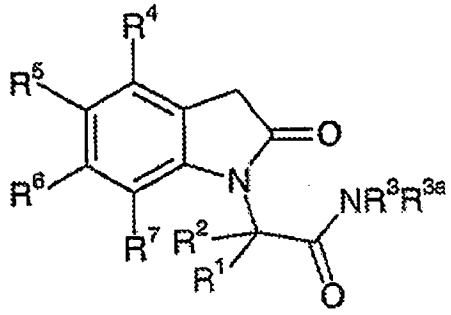
V is unsubstituted C1-4-alkylene,

R^{15} is phenyl or morpholinyl,

m is 1 to 4,

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

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



(I)

wherein

R^1 is hydrogen,

R^2 is hydrogen, methyl or ethyl,

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

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

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

R^4 is hydrogen,

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

R^6 is hydrogen, methyl or Cl,

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

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

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

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

In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 2-(5-iodo-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide ; 2- (5, 7-dibromo- 2-oxo-2, 3-dthydro-lH-indol-1-yl) acetamide ; 2-(5-nitro-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl) acetamide; 2- (5-chloro-2- oxo-2, 3-dihydro-lH-indol-1-yl) propanamide ; (2R)-2- (5-chloro-2-oxo-2, 3-dihydro-1H- indol-1-yl) propanamide ; (2S)-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl) propanamide; 2-[2-oxo-5-(trifluoromethoxy)-2, 3-dihydro-lH-indol-1-yl] acetamide ; 2- (5-isopropyl-2-oxo-2, 3-dihydro-1H-indol-1-yl)acetamide ; 2-(5-ethyl-2-oxo-2, 3-dihydro- 1H-indol-1-yl) acetamide ; 2-(5-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl) acetamide; 2- (5,7-dimethyl-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide; 2- (5-bromo-2-oxo-2, 3- dihydro-lH-indol-1-yl) acetamide ; 2-(2-oxo-5-propyl-2, 3-dihydro-lH-indol-1- yl) acetamide ; 2-[2-oxo-5-(trifluoromethyl)-2, 3-dihydro-lH-indol-1-yl] acetamide ; 2- (5, 6-dimethyl-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide; 2- (7-chloro-2-oxo-2, 3-dihydro- IH-indol-1-yl) acetamide; 2- (6-chloro-2-oxo-2, 3-dihydro-IH-indol-1-yl) acetamide; 2- (5- chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)

butanamide ; (+)-2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl) butanamide; (-)-2- (5-chloro-2-oxo-2, 3-dihydro-IH-indol-1- yl) butanamide; 2-(5-methyl-2-oxo-2,3-dihydro-1H-indol-1-yl)propanamide ; (+)-2- (5- methyl-2-oxo-2, 3-dihydro-1H-indol-1-yl) propanamide; (-)-2- (5-methyl-2-oxo-2, 3- dihydro-lH-indol-1-yl) propanamide ; 2-(5-bromo-2-oxo-2,3-dihydro-1H-indol-1- yl) propanamide ; (-)-2- (5-bromo-2-oxo-2, 3-dihydro-lH-indol-1-yl) propanamide ; (+)-2- (5-bromo-2-oxo-2, 3-dihydro-1H-indol-1-yl) propanamide; 2- (5-chloro-7-fluoro-2-oxo- 2, 3-dihydro-1H-indol-1-yl) acetamide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N- (3-hydroxyphenyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- (3- fluorophenyl) acetamide ; 2-(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [3- (2-pyridin- 2-ylethyl) phenyllacetarnide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[6-(hydroxymethyl) cyclohex-3-en-1-yl]acetanuide ; 5-chloro-1-[2-oxo-2-(4-pyridin-2- ylpiperazin-1-yl) ethyl3-1, 3-dihydro-2H-indol-2-one ; 5-chloro-1-{2- [4- (3- methylphenyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one ; 2- (5-chloro-2- oxo-2, 3-dihydro-1H-indol-1-yl)-N-(4-hydroxy-3-methoxybenzyl)acetamide ; 2- (5-chloro- 2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-(pyridin-4-ylmethyl)-N- (tetrahydrofuran-2- ylmethyl) acetamide ; 5-chloro-1-[2-(3-hydroxypiperidin-1-yl)-2-oxoethyl]-1,3-dihydro- 2H-indol-2-one; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N'- isonicotinoylacetohydrazide ; 5-chloro-1-(2-oxo-2-thiomorpholin-4-ylethyl)-1,3-dihydro- 2H-indol-2-one; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(4H-1, 2, 4-triazol-3- yl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [4-(methylsulfonyl) benzyl] acetamide ; 1-[(5-chloro-2-oxo-2,3-dihydro-1H-indol-1- yl) acetyl] octahydroquinolin-4 (1H)-one ; N'- (4-bromophenyl)-2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl) acetohydrazide; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N- (6-methoxypyridin-3-yl) acetamide; N-butyl-2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1- yl) acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(3- hydroxypropyl) acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N- [3- (dimethylamino) propyl] acetamide ; 5-chloro-1-{2-oxo-2[4-(2-phenylethyl)pperazin-1- yl] ethyl}-l, 3-dihydro-2H-indol-2-one; ethyl {[(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1- yl)

acetyl]amino}acetate ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(3-ethoxypropyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-(2- fluoroethyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-methoxy-N- methylacetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(3, 4- dimethylphenyl) acetamide ; N- (4-tert-butylphenyl)-2- (5-chloro-2-oxo-2, 3-dihydro-lH- indol-1-yl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- (3-hydroxy-2, 2- dimethylpropyl) acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[1- (hydroxymethyl) propyl] acetamide ; 2-(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- (3,3, 3-trifluoro-2-hydroxypropyl) acetamide; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1- yl)-N-(2-hydroxy-2-phenylethyl) acetamide ; 5-chloro-1- {2- [4- (4- hydroxyphenyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one; 2- (5-chloro-2- oxo-2, 3-dihydro-1H-indol-1-yl)-N-(pyridin-4-ylmethyl)acetamide ; 2- (5-chloro-2-oxo- 2, 3-dihydro-1H-indol-1-yl)-N-[(5-methyl-2-furyl)methyl]acetamide ; 2-(5-chloro-2-oxo- 2, 3-dihydro-lH-indol-1-yl)-N- [3- (lH-pyrazol-1-yl) propyl] acetamide ; methyl 3- [(5- chloro-2-oxo-2, 3-dihydro-1H-indol-1-yl] acetyl]-1, 3-thiazolidine-4-carboxylate ; 5- chloro-1-[2-(2, 5-dihydro-lH-pyrrol-1-yl)-2-oxoethyl]-1, 3-dihydro-2H-indol-2-one; 2- (5- chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N'- (4, 5-dihydro-lH-imidazol-2- yl) acetohydrazide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [2- (3, 4- dimethoxyphenyl) ethyl] acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[2- (2-chlorophenyl) etl-lyllacetaniide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-[2-(4- methylphenyl) ethyl] acetamide ; 2-(5-chloro-2-oxo-2,3-dihydro-1H-indol-1-yl)-N-(2- morpholin-4-ylethyl) acetamide ; 2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N- [2- (3,4, 5, 6-tetrahydro-1-benzazocin-1 (2H) -yl) propyl] acetamide ; 2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl)-N-[2-(2-methylpiperidin-1-yl) ethyl] acetamide ; 2- (5-chloro-2- oxo-2, 3-dihydro-lH-indol-1-yl)-N-(2-nitrobenzyl) acetamide ; 2- (5-chloro-2-oxo-2, 3- dihydro-lH-indol-1-yl)-N- (3, 4-dihydro-lH-isochromen-1-ylinethyl) acetamide ; N- (2-chloro-6-fluorobenzyl)-2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) acetamide ; N- benzyl-2- (5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-methylacetamide ; 2- (5-chloro- 2-oxo-2, 3-dthydro-lH-indol-1-yl)-N-{2-

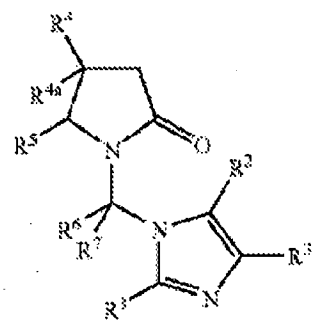
[(trifluoromethyl) thio] benzyl} acetamide ; 5- chloro-1- [2- (1, 4-dioxa-8-azaspiro [4.5] dec-8-yl)-2-oxoethyl]-1, 3-dihydro-2H-indol-2- one; 2-(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl)-N-cycloheptylacetamide ; 5-chloro-1- {2-[4- (2-morpholin-4-ylethyl) piperazin-1-yl]-2-oxoethyl}-1, 3-dihydro-2H-indol-2-one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

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

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

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

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



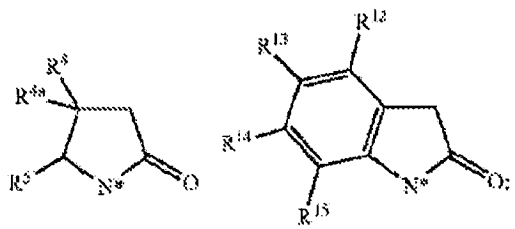
(I)

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

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

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

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



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

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

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

R^5 is hydrogen;

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

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

R^7 is hydrogen;

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

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

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

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

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

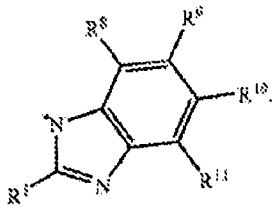
R^{12} is hydrogen or halogen;

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

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

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

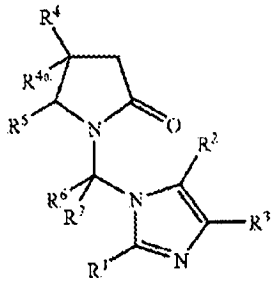
with the proviso that R^4 is different from hydrogen when represents a group of formula



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

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

(I)

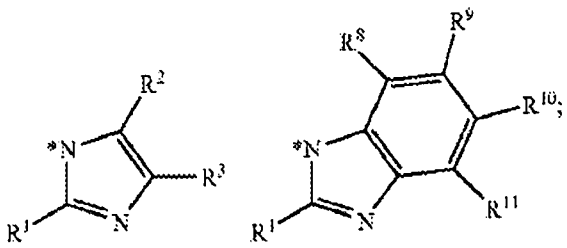


wherein R^1 is hydrogen, C_{1-20} alkyl, C_{3-8} cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle;

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

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

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

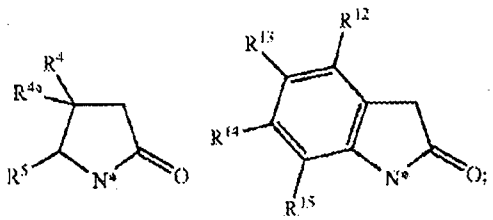


R^4 is hydrogen, C_{1-20} alkyl, C_{2-12} alkenyl or aryl;

R^{4a} is hydrogen;

R^5 is hydrogen;

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



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

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

R^8 is hydrogen;

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

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

R^{11} is hydrogen;

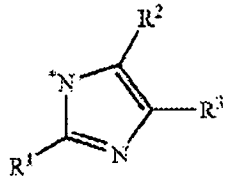
R^{12} is hydrogen or halogen;

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

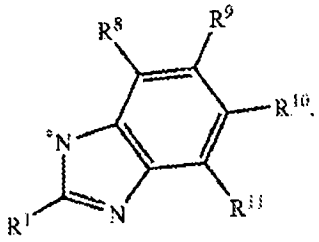
R^{14} is hydrogen;

R^{15} is hydrogen;

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



represents a group of formula



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Usually, R^{4a} is hydrogen.

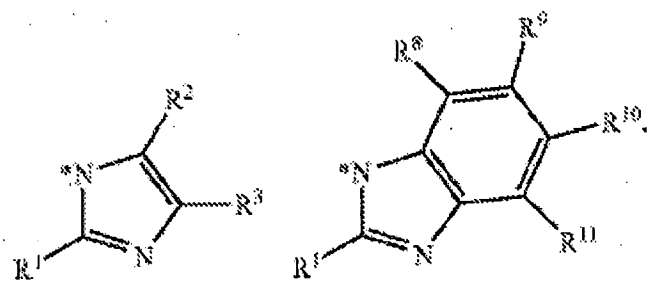
Usually, R^5 is hydrogen.

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

Usually R^7 is hydrogen.

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

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



Usually, R^8 is hydrogen.

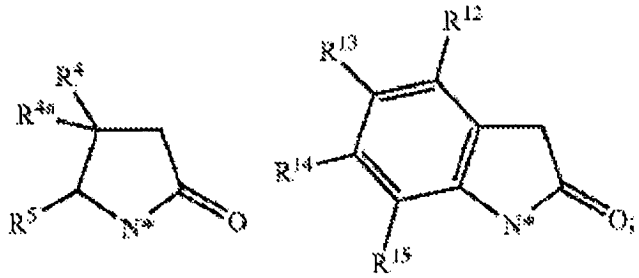
Usually, R^9 is hydrogen; halogen; C_{1-3} alkyl or alkoxy. Preferably, R^9 is hydrogen; methyl; chloro or methoxy. More preferred R^9 is hydrogen.

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

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

Usually, R^{11} is hydrogen.

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



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

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

Usually R^{14} is hydrogen.

Usually, R^{15} is hydrogen.

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

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

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

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

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

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

R^{4a} is hydrogen;

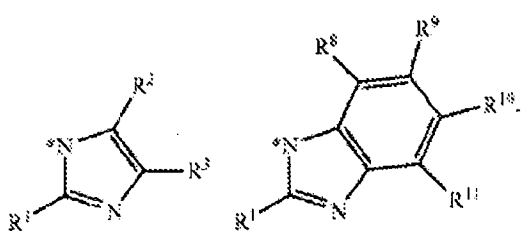
R^5 is hydrogen;

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

R^7 is hydrogen;

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

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



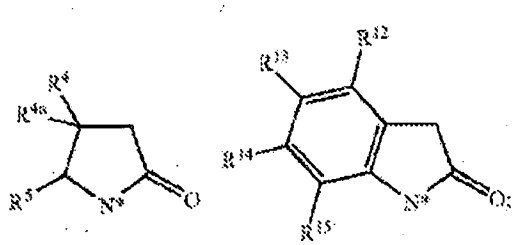
R^8 is hydrogen;

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

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

R^{11} is hydrogen;

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



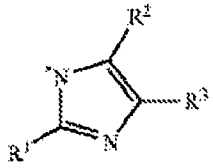
R^{12} is selected from hydrogen or halogen;

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

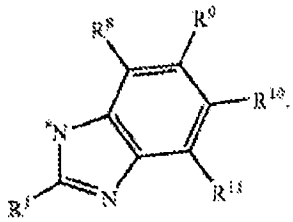
R^{14} is hydrogen;

R^{15} is hydrogen;

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



represents a group of formula



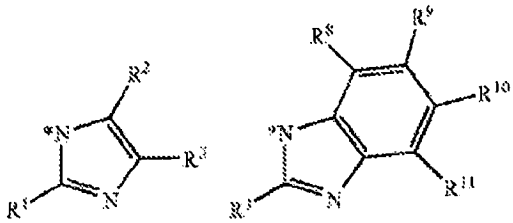
In a preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

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

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

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

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



R^8 is hydrogen;

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

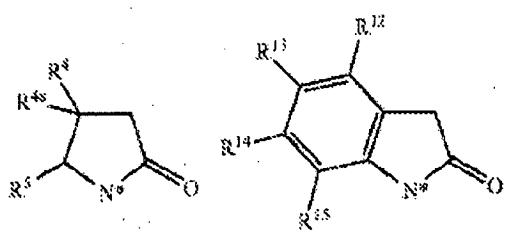
R^{10} is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy;

R^{11} is hydrogen;

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

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

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



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

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

R^{14} is hydrogen;

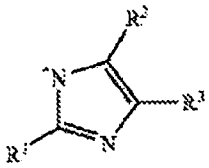
R^{15} hydrogen;

R^6 is selected from hydrogen; azidomethyl;

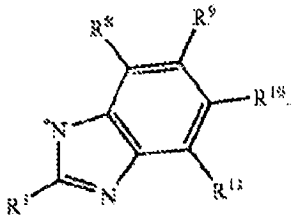
R^7 is hydrogen;

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

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



represents a group of formula



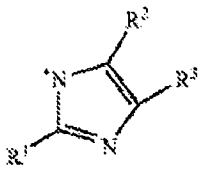
In a more preferred embodiment, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

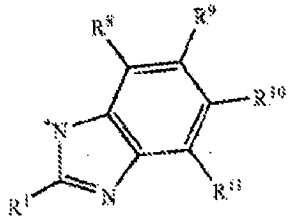
R^1 is selected from hydrogen; methyl; ethyl; i-propyl; n-propyl; n-butyl;methylthio; nitro; cyano; amino; chloro; or 1H-pyrrol-2-yl;

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

R^3 is selected from hydrogen; cyano;

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





R^8 is hydrogen;

R^9 is hydrogen;

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

R^{11} is hydrogen;

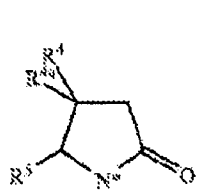
R^4 is selected from hydrogen; n-propyl; 2,2-difluorovinyl; phenyl; 3-chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl; 3,5-difluorophenyl; 3,4-difluorophenyl; 3-chloro-4-fluorophenyl; 2,3,4-

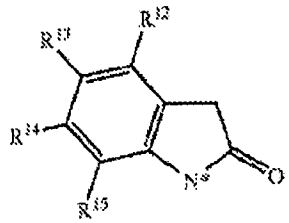
trifluorophenyl; 2,4,5-trifluorophenyl; 2,3,5-trifluorophenyl; 3,4,5-trifluorophenyl; or 3-azido-2,4-difluorophenyl;

R^{4a} is hydrogen;

R^5 is hydrogen;

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





wherein

R^{12} is hydrogen;

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

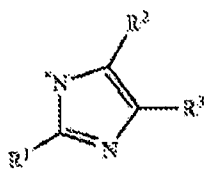
R^{14} is hydrogen;

R^{15} hydrogen;

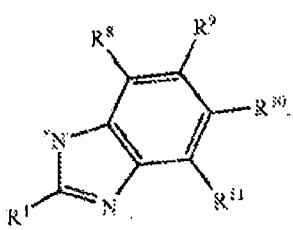
R^6 is hydrogen;

R^7 is hydrogen;

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



represents a group of formula



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

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

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

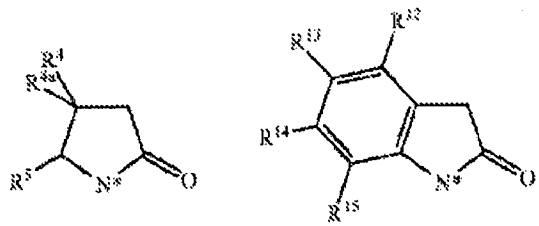
R^3 is hydrogen;

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

R^{4a} is hydrogen;

R^5 is hydrogen;

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



R^{12} is hydrogen;

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

R^{14} is hydrogen;

R^{15} hydrogen;

R^6 is hydrogen;

R^7 is hydrogen.

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

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

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

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

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

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

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

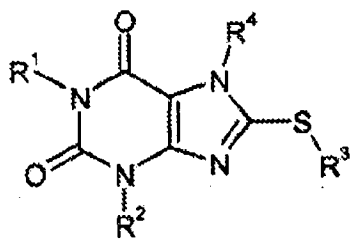
In some embodiments, compounds useful in the methods and compositions of this invention are selected from the group consisting of: 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-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

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



(I)

wherein

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

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

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

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

R^5 is C2-4 alkyl;

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

R^7 is C1-4 alkyl;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5-dimethylisoxazol-4-yl) or (5-nitro- 2-furyl). Most preferred heterocycle is (5-nitro-2-furyl).

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

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

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

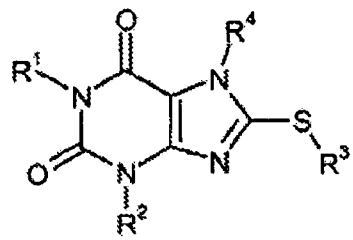
Generally R^4 is C_{1-8} alkyl optionally substituted by alkoxycarbonyl, C_{3-6} cycloalkyl, aryl or heterocycle. Usually R^4 is C_{1-8} alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl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

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

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

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

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



(I)

wherein

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

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

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

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

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

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

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

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

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

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

In a preferred embodiment,

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

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

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

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

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

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

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

In a more preferred embodiment,

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

R^2 is methyl;

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

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

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

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

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

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

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

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

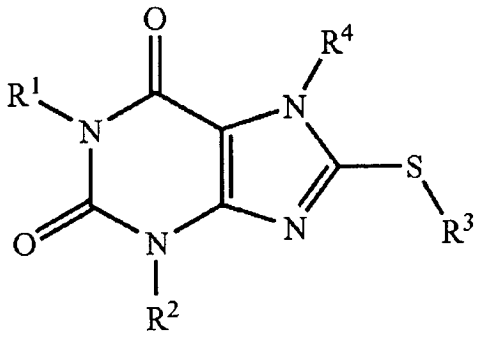
yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8- yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1 H-purin-8-yl]thio}butanoate; ethyl 2-({7-[4-(aminosulfonyl)benzyl]-3-methyl-2,6-dioxo-2, 3,6,7- tetrahydro-1 H-purin-8-yl}thio)butanoate;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

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

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

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

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



(II)

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

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

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

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

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

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

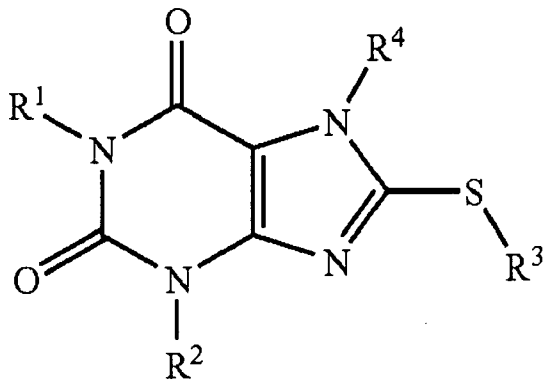
R.sup.7 is C.sub.1-4 alkyl;

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

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

In some embodiments, the compounds are those compounds of formula II, their enantiomers, diastereoisomers and mixtures thereof (including all possible

mixtures of stereoisomers), or pharmaceutically acceptable salts



(II)

wherein

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

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

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

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

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

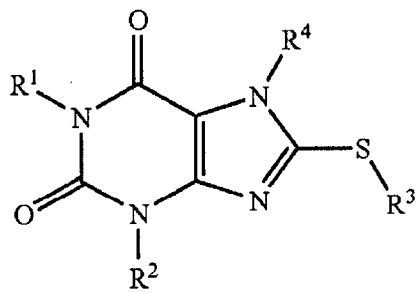
R.sup.6 is C.sub.1-4 alkyl, amido or --COOR.sup.7;

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

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

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

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



(I)

wherein

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

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

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

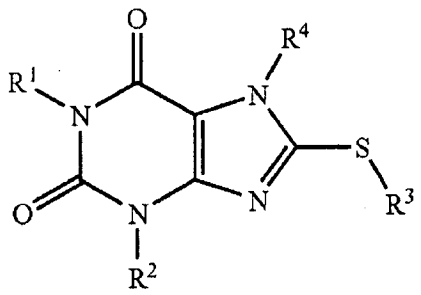
R.sup.4 is C.sub.1-8 alkyl optionally substituted by alkoxycarbonyl, C.sub.3-6 cycloalkyl, aryl or heterocycle;

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

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

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

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



(II)

wherein

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

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

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

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

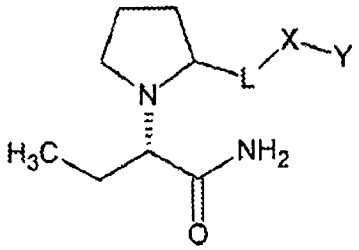
R.sup.5 is hydrogen or C.sub.1-4 alkyl;

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

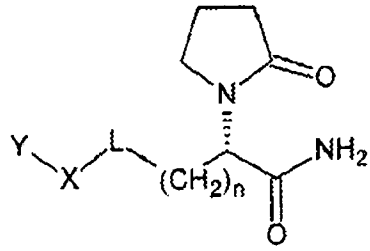
R.sup.7 is C.sub.1-4 alkyl;

vi) International Patent Application Publication No. WO2010/144712

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



Formula 1



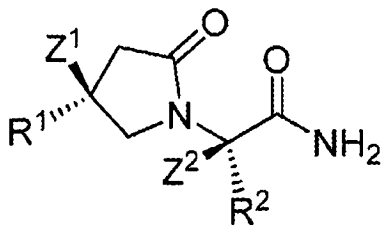
Formula 2

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

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

vii) International Patent Application Publication No. WO2010/002869

The present invention provides a compound of Formula I:



(I),

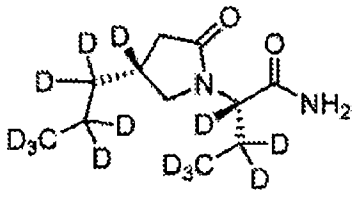
or a pharmaceutically acceptable salt thereof, wherein: each Z is independently selected from hydrogen and deuterium; R1 is an n-propyl group having zero to seven deuterium atoms; R2 is an ethyl group having zero to five deuterium atoms, and when each R has zero deuterium atoms, at least one Z is deuterium.

One embodiment of this invention provides compounds of Formula I wherein R1 is selected from CD3CH2CH2-, CD3CD2CH2-, CD3CH2CD2-, CH3CH2CD2-, CH3CD2CD2-, CD3CD2CD2- or CH3CH2CH2-. In a more specific embodiment, R1 is CD3CD2CD2- or CD3CD2CH2-. In one aspect of these embodiments, Z1 and Z2 are both hydrogen. In another aspect of these embodiments, Z1 and Z2 are both deuterium.

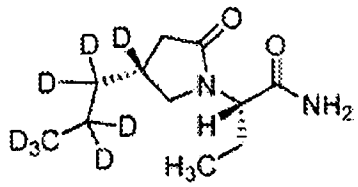
In another embodiment, R2 is selected from CH3CH2-, CD3CH2-, CH3CD2-, or CD3CD2-. In a more specific embodiment, R2 is selected from CH3CH2- or CD3CD2-. In one aspect of these embodiments, Z1 and Z2 are both hydrogen. In another aspect of these embodiments, Z1 and Z2 are both deuterium.

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

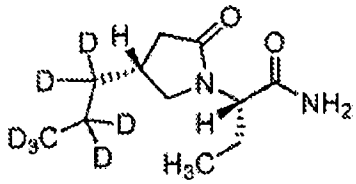
Examples of specific compounds of this invention include the following:



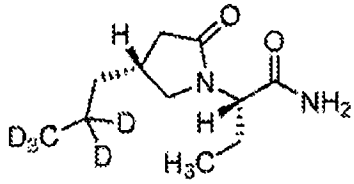
Compound 100;



Compound 101;



Compound 102; and

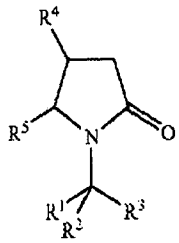


Compound 103

viii) 20090312333

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

(I)



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

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

R3 is either

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

1H-benzimidazol-6-yl;

1H-benzimidazol-7-yl;

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

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

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

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

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

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

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

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

or R3 is

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

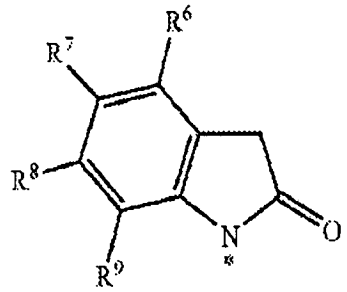
1H-1,2,3-benzotriazol-1-yl;
1H-imidazo[4,5-b]pyridin-1-yl;
3H-imidazo[4,5-b]pyridin-3-yl;
7H-imidazo[4,5-c]pyridazin-7-yl;
1H-indol-1-yl;
2,3-dihydro-1H-indol-1-yl;
9H-purin-9-yl;
1H-pyrazolo[3,4-b]pyridin-1-yl;
2H-pyrazolo[3,4-b]pyridin-2-yl;
1H-pyrrolo[2,3-b]pyridin-1-yl;
1H-pyrrolo[3,2-b]pyridin-1-yl;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

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

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

R5 is hydrogen;

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



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

R6 is hydrogen or halogen.

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

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

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

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

R1 and R2 are both hydrogen.

R3 is:

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

1H-benzimidazol-6-yl;

1H-benzimidazol-7-yl;

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

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

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

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

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

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

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

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

1H-imidazol-4-yl;

1H-imidazol-5-yl;

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

Alternatively R3 is:

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

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

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

1H-indol-1-yl;

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

9H-purin-9-yl;

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

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

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

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

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

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

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

1H-pyrrol-1-yl;

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

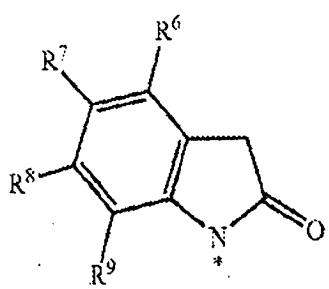
R4 in formula (I) is selected from the group comprising or consisting of hydrogen; C1-12 alkyl optionally substituted by halogen or C1-4 alkoxy; C2-12 alkenyl optionally substituted by halogen; C2-12 alkynyl optionally substituted by halogen.

In a further specific embodiment R4 is n-propyl, 2,2,2-trifluoroethyl, 2-chloro-2,2-difluoroethyl, 2 bromo-2,2-difluoroethyl, 2,2-difluorovinyl.

In another specific embodiment R4 is phenyl, 2,3,5-trifluorophenyl or 3-chloro-4-fluorophenyl.

R5 is hydrogen;

A further embodiment of the present invention consists in compounds of formula (I) wherein R4 forms together with R5a 1,3-dihydro-2H-indol-2-one ring



The asterisk * indicates the point of attachment of the heteroaryl alkylene substituent, and wherein

R6 is hydrogen;

R7 is chlorine;

R8 is hydrogen;

R9 is hydrogen.

A further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of:

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

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

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

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

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

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

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

1H-imidazol-4-yl;

1H-imidazol-5-yl;

isoxazol-4-yl;

1H-pyrazol-4-yl;

1H-pyrazol-5-yl;

1H-pyrazolo[1,5-a]pyrimidin-3-yl;

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

pyridin-3-yl;

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

1H-pyrrolo[2,3-b]pyridin-4-yl;

1H-pyrrolo[2,3-b]pyridin-5-yl;

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

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

1,3-thiazol-5-yl;

[1,2,4]triazolo[4,3-b]pyridazin-8-yl;

indolizin-3-yl.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of:

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

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

imidazo[2,1-b][1,3]thiazol-5-yl;
3H-imidazo[4,5-b]pyridin-7-yl;
1H-imidazol-4-yl;
1H-imidazol-5-yl;
1H-pyrazol-4-yl;
1H-pyrazolo[1,5-a]pyrimidin-3-yl;
pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-4-yl;
1,3-thiazol-5-yl;

Said heterocycles are optionally substituted by e.g. a methyl, n-propyl, trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, iodine, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclopropylmethoxy, cyclobutylmethoxy, amino, methylamino, cyclopropylamino, cyclobutylamino, 1-pyrrolidinyl, cyano, phenyl, benzyl or 3-thienyl.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of: 6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl, 6-(cyclopropyloxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl, 6-propoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl, 6-chloroimidazo[2,1-b][1,3]thiazol-5-yl, 2,6-dichloroimidazo[2,1-b][1,3]thiazol-5-yl, 5-chloro-1H-imidazol-4-yl, 5-bromo-1H-imidazol-4-yl, 4-bromo-1H-imidazol-5-yl, 4-chloro-1H-imidazol-5-yl, 1H-imidazol-5-yl, 1-methyl-1H-imidazol-5-yl, 4-chloro-1-methyl-1H-imidazol-5-yl, 1H-pyrazol-4-yl, 1H-pyrrolo[2,3-b]pyridin-3-yl.

A further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is a substituted or unsubstituted imidazo[1,2-a]pyridin-3-yl.

Said imidazo[1,2-a]pyridin-3-yl is optionally substituted by e.g. a methyl, cyclopropyl, bromine, chlorine, fluorine, iodine.

In a further specific embodiment R3 is a heterocycle linked to the rest of the molecule via one of its C atoms and is selected from the group consisting of:

imidazo[1,2-a]pyridin-3-yl, 6-methylimidazo[1,2-a]pyridin-3-yl, 2-chloroimidazo[1,2-a]pyridin-3-yl.

A further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its N atoms and is selected from the group consisting of:

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

1H-indol-1-yl;

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

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

1H-pyrrol-1-yl;

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

A specific further embodiment of the present invention consists in compounds of formula (I) wherein R3 is a heterocycle linked to the rest of the molecule via one of its N atoms and is selected from the group consisting of:

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

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

1H-pyrrol-1-yl;

2-chloro-1H-benzimidazol-1-yl;

Said heterocycles may optionally be substituted by trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, methoxy or cyano.

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

A further embodiment of the present invention consists in compounds of formula (I) wherein R1, R2 and R5 are hydrogen.

R4 is a C1-6 alkyl optionally substituted by halogen, a C2-6 alkenyl optionally substituted by halogen or C2-12 alkynyl optionally substituted by halogen.

R3 is selected from the group consisting of;

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

imidazo[2,1-b][1,3,4]thiadiazol-5-yl;
imidazo[2,1-b][1,3]thiazol-5-yl;
3H-imidazo[4,5-b]pyridin-7-yl;
1H-imidazol-4-yl;
1H-imidazol-5-yl;
1H-pyrazol-4-yl;
1H-pyrazolo[1,5-a]pyrimidin-3-yl;
pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-3-yl;
1H-pyrrolo[2,3-b]pyridin-4-yl;
1,3-thiazol-5-yl;
and optionally substituted by methyl, n-propyl, trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, iodine, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclopropylmethoxy, cyclobutylmethoxy, amino, methylamino, cyclopropylamino, cyclobutylamino, 1-pyrrolidinyl, cyano, phenyl, benzyl or 3-thienyl.

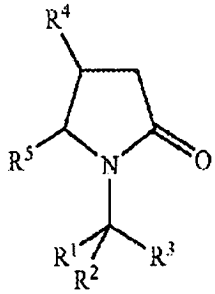
A further embodiment of the present invention consists in compounds of formula (I) wherein R1, R2 and R5 are hydrogen.

R4 is a C1-6 alkyl optionally substituted by halogen, a C2-6 alkenyl optionally substituted by halogen or C2-12 alkynyl optionally substituted by halogen.

R3 is selected from the group consisting of
3H-imidazo[4,5-b]pyridin-3-yl;
1H pyrrolo[3,2-b]pyridin-1-yl;
1H-pyrrol-1-yl;
2-chloro-1H-benzimidazol-1-yl;
optionally substituted by trifluoromethyl, cyclopropyl, bromine, chlorine, fluorine, methoxy or cyano.

A further embodiment of the invention consists in compounds of formula (I), their diastereomers and mixtures, or a pharmaceutically acceptable salt thereof.

(I)



R1, R2 and R5 are hydrogen.

R3 is a substituted or unsubstituted heterocycle linked to the rest of the molecule via one of its C atoms, said heterocycle is selected from the group consisting of:

1H-benzimidazol-6-yl;

1H-benzimidazol-7-yl;

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

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

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

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

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

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

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

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

1H-imidazol-4-yl;

1H-imidazol-5-yl;

1H-indol-2-yl;

1H-indol-3-yl;

1H-indol-4-yl;

1H-indol-7-yl;

isoxazol-4-yl;

1H-pyrazol-4-yl;

1H-pyrazol-5-yl;

1H-pyrazolo[1,5-a]pyrimidin-3-yl;

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

pyridazin-4-yl;

pyridin-2-yl;

pyridin-3-yl;

pyridin-4-yl;

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

1H-pyrrolo[2,3-b]pyridin-4-yl;

1H-pyrrolo[2,3-b]pyridin-5-yl;

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

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

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

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

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

1,3,4-thiadiazol-2-yl;

1,3-thiazol-5-yl;

[1,2,4]triazolo[4,3-b]pyridazin-7-yl;

[1,2,4]triazolo[4,3-b]pyridazin-8-yl;

indolizin-3-yl;

Particularly preferred are imidazo[1,2-a]pyridin-3-yl; imidazo[1,2-a]pyrimidin-3-yl; imidazo[1,2-b]pyridazin-3-yl; 1H-imidazol-4-yl; 1H-imidazol-5-yl;

R4 is a substituted or unsubstituted phenyl moiety;

A further embodiment of the present invention consists in compounds of formula (I) wherein R1 is hydrogen or C1-12 alkyl;

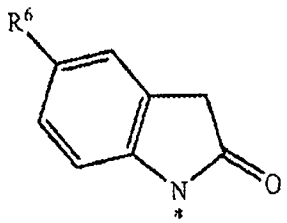
R2 is hydrogen;

R3 is an aromatic 5-membered heterocycle linked to the rest of the molecule via one of its C atoms;

R4 is hydrogen, C1-12 alkyl or aryl;

R5 is hydrogen;

Alternatively, R4 can form together with R5 and the 2-oxo-1-pyrrolidine ring the following 1,3-dihydro-2H-indol-2-one cycle



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

R6 is hydrogen or halogen;

In this embodiment R4 may not be hydrogen when R3 is substituted 1H-pyrazol-5-yl. Also this embodiment does not comprise 5-(2'-oxo-1'-pyrrolidinyl)methyl-1,3,4-tricarbomethoxy-pyrazole which is disclosed in A. Padwa et al J. Org. Chem. 2000, 65, 5223-5232 without any biological activity though.

In this embodiment wherein R3 is an aromatic 5-membered heterocycle linked to the rest of the molecule via one of its C atoms, specific moieties R3 may be selected from 1,3-thiazol-5-yl, 1H-imidazol-4-yl, 1H-imidazol-5-yl, 1H-pyrazol-4-yl, 1H-pyrazol-5-yl, 2-oxo-2,3-dihydro-1,3-thiazol-5-yl, each of them being optionally substituted by 1 to 3 substituents independently selected from methyl, chlorine, bromine, amino, methylamino, dimethylamino, (2-oxo-4-propyl-pyrrolidin-1-yl)methyl, 1-pyrrolidinyl, amido, cyano, methoxy, phenyl, 4-methylphenyl-sulfonyl, benzyl or 2-(benzylamino)-2-oxoethyl.

In this embodiment, more specific moieties R3 are selected from 2-(methylamino)-1,3-thiazol-5-yl; 2-pyrrolidin-1-yl-1,3-thiazol-5-yl; 5-bromo-1H-imidazol-4-yl; 5-chloro-1H-imidazol-4-yl; 1H-imidazol-5-yl; 1-methyl-1H-imidazol-5-yl; 4-bromo-1-methyl-1H-imidazol-5-yl; 4-chloro-1H-imidazol-5-yl; 4-chloro-1-methyl-1H-imidazol-5-yl; 4-cyano-1-methyl-1H-imidazol-5-yl; 1H-pyrazol-4-yl; 3,5-dimethyl-1H-pyrazol-4-yl; 3-methyl-1H-pyrazol-4-yl.

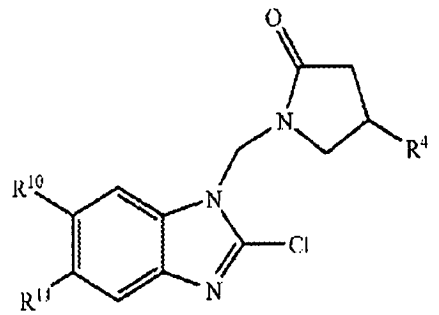
In this embodiment, most specific moieties R3 are selected from 5-bromo-1H-imidazol-4-yl; 5-chloro-1H-imidazol-4-yl; 1H-imidazol-5-yl; 4-bromo-1-methyl-1H-imidazol-5-yl; 4-chloro-1-methyl-1H-imidazol-5-yl; 1H-pyrazol-4-yl.

Still in this embodiment, a specific moiety R1 is selected from hydrogen or ethyl.

Still in this embodiment, a specific moiety R4 is selected from hydrogen, n-propyl, 2,3,5-trifluorophenyl or phenyl.

A further embodiment of the present invention consists in compounds having the specific formula (Ia).

(Ia)



In formula (Ia) the substituent R10 is hydrogen; halogen; C1-4 alkyl optionally substituted by at least one halogen; C1-4 alkoxy; methoxycarbonyl; nitro; amino; alkylamino; amido; or alkanoyl-amino. Preferably R10 is hydrogen.

R11 is hydrogen; halogen; C1-4 alkyl optionally substituted by at least one halogen; C1-4 alkoxy; methoxycarbonyl; nitro; amino; alkylamino; amido; or alkanoylamino. Preferably R11 is hydrogen.

R4 is C1-4 alkyl optionally substituted by at least one halogen; or C2-4 alkenyl optionally substituted by at least one halogen. Preferably R4 is n-propyl.

Still in this aspect of the invention a specific embodiment relates to an embodiment wherein R10 is selected from hydrogen; methyl; fluorine; chlorine; bromine; methoxy; methoxycarbonyl; nitro; or trifluoromethyl, while R11 is selected from hydrogen; methyl; fluorine; chlorine; bromine; methoxy; methoxycarbonyl; nitro; or trifluoromethyl; and R3 is n-propyl.

Specific compounds of the present invention are those selected from the group consisting of:

1-[(1-methyl-1H-benzimidazol-6-yl)methyl]-4-propylpyrrolidin-2-one;

1-(1H-benzimidazol-7-ylmethyl)-4-propylpyrrolidin-2-one;

1-(imidazo[1,2-a]pyridin-3-ylmethyl)-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[2-(4-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(5-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-phenylpyrrolidin-2-one;

1-(imidazo[1,2-a]pyridin-3-ylmethyl)-4-phenylpyrrolidin-2-one;

1-[(6-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-bromoimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(8-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-iodoimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[8-chloro-6-(trifluoromethyl)imidazo[1,2-a]pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(7-methylimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6,8-dibromoimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6,8-dichloroimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-chloroimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloroimidazo[1,2-a]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-cyclopropyl-6-fluoroimidazo[1,2-a]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(6-chloro-2-cyclopropylimidazo[1,2-a]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-(imidazo[1,2-a]pyrimidin-3-ylmethyl)-4-propylpyrrolidin-2-one;
1-{[2-(4-chlorophenyl)imidazo[1,2-a]pyrimidin-3-yl]methyl}-4-propyl pyrrolidin-2-one;
1-(imidazo[1,2-a]pyrimidin-3-ylmethyl)-4-phenylpyrrolidin-2-one;
1-[(6-chloroimidazo[1,2-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(6-phenylimidazo[1,2-b][1,2,4]triazin-7-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[6-chloro-2-(4-methylphenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-chloro-2-(4-chlorophenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(6-chloroimidazo[1,2-b]pyridazin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-chloroimidazo[1,2-b]pyridazin-3-yl)methyl]-4-phenylpyrrolidin-2-one;
1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-phenylpyrrolidin-2-one;
5-chloro-1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-1,3-dihydro-2H-indol-2-one;
1-{[6-methoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[6-isopropoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-(benzyloxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-cyclopropyl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-(dimethylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-{[6-methoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
4-(2-chloro-2,2-difluoroethyl)-1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;
1-{[6-(methylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-hydroxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-(methylthio)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;
4-(2-bromo-2,2-difluoroethyl)-1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(methylsulfonyl)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(methylsulfinyl)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2,2-trifluoroethyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclobutylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-chloro-2-(4-methylphenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-amino-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[6-(ethylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-propylpyrrolidin-2-one;

4-propyl-1-{[6-(propylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2-bromo-2,2-difluoroethyl)-1-{[6-(propylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-(propylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-methoxy-2-(4-methylphenyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-propyl-1-{[6-pyrrolidin-1-yl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2-bromo-2,2-difluoroethyl)-1-{[6-methoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(cyclopropylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-(isopropylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[2-cyclopropyl-6-(propylamino)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-({2-cyclopropyl-6-[(2-fluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}methyl)-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-({2-cyclopropyl-6-[(2,2-difluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}methyl)-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-({2-cyclopropyl-6-[(2,2,2-trifluoroethyl)amino]imidazo[1,2-b]pyridazin-3-yl}methyl)-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluoroethyl)-1-{[2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[2-cyclopropyl-6-(cyclopropylamino)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclobutylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(6-chloro-2-cyclopropylimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(3-chloro-4-fluorophenyl)pyrrolidin-2-one;

1-{[6-(butylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-(cyclobutylamino)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(2-cyclopropyl-6-methoxyimidazo[1,2-b]pyridazin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-ethoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-isopropoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-{[6-(cyclopropylmethoxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-(cyclobutylmethoxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-(cyclopropyloxy)-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-propoxy-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

3-{[4-(2,2-difluorovinyl)-2-oxopyrrolidin-1-yl]methyl}-2-(trifluoromethyl)imidazo[1,2-b]pyridazine-6-carbonitrile;

4-(2,2-difluorovinyl)-1-{[6-thien-3-yl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-phenyl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-methyl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-(2,2-difluorovinyl)-1-{[6-pyridin-3-yl-2-(trifluoromethyl)imidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

4-propyl-1-{[2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-b]pyridazin-3-yl]methyl}pyrrolidin-2-one;

1-[(6-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-(4-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(2-cyclopropyl-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-methylimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-chloroimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2,6-dichloroimidazo[2,1-b][1,3]thiazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-(3H-imidazo[4,5-b]pyridin-7-ylmethyl)-4-propylpyrrolidin-2-one;

1-(3H-imidazo[4,5-b]pyridin-7-ylmethyl)-4-phenylpyrrolidin-2-one;

4-phenyl-1-[(5-phenyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]pyrrolidin-2-one;

4-phenyl-1-{[5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl}pyrrolidin-2-one;

1-[(6-bromo-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-phenyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-methyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-methyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-{[5-(trifluoromethyl)-3H-imidazo[4,5-b]pyridin-7-yl]methyl}pyrrolidin-2-one;
1-[(6-methyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-phenyl-3H-imidazo[4,5-b]pyridin-7-yl)methyl]-4-propylpyrrolidin-2-one;
1-[1-(1H-imidazol-4-yl)propyl]pyrrolidin-2-one;
1-[(5-methyl-1H-imidazol-4-yl)methyl]pyrrolidin-2-one;
1-[(2-methyl-1H-imidazol-4-yl)methyl]pyrrolidin-2-one;
1-(1H-imidazol-4-ylmethyl)-4-propylpyrrolidin-2-one;
1-({1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-4-yl}methyl)-4-propylpyrrolidin-2-one;
1-[(5-chloro-1H-imidazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(5-bromo-1H-imidazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(5-bromo-1H-imidazol-4-yl)methyl]-5-chloro-1,3-dihydro-2H-indol-2-one;
1-(1H-imidazol-5-ylmethyl)pyrrolidin-2-one;
1-[(1-methyl-1H-imidazol-5-yl)methyl]pyrrolidin-2-one;
1-methyl-5-[(2-oxopyrrolidin-1-yl)methyl]-1H-imidazole-4-carbonitrile;
1-(1H-imidazol-5-ylmethyl)-4-phenylpyrrolidin-2-one;
1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-phenylpyrrolidin-2-one;
1-[(4-methoxy-1-methyl-1H-imidazol-5-yl)methyl]pyrrolidin-2-one;
1-[(1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-4-carbonitrile;
1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-4-carboxamide;
N-benzyl-2-{5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-1-yl}acetamide;
1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-2-carbonitrile;
1-[(4-chloro-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-methyl-5-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile;
1-[(4-bromo-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2,4-dichloro-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
benzyl 1-methyl-5-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazol-2-ylcarbamate;
1-[(4-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-propylpyrrolidin-2-one;
5-chloro-1-(1H-imidazol-5-ylmethyl)-1,3-dihydro-2H-indol-2-one;
1-[(2,4-dichloro-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(2,4-dichloro-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(2-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(4-bromo-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
5-chloro-1-[(1-methyl-1H-imidazol-5-yl)methyl]-1,3-dihydro-2H-indol-2-one;
1-[(4-chloro-1-methyl-1H-imidazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-(1H-indol-2-ylmethyl)-4-propylpyrrolidin-2-one;
1-(1H-indol-3-ylmethyl)-4-propylpyrrolidin-2-one;
3-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-indole-5-carbonitrile;
1-[(2-methyl-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(7-methoxy-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-nitro-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-{[6-(trifluoromethyl)-1H-indol-3-yl]methyl}pyrrolidin-2-one;
1-[(5-nitro-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(7-fluoro-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-chloro-2-methyl-1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[1H-indol-3-yl(phenyl)methyl]-4-propylpyrrolidin-2-one;
1-[1-(1H-indol-3-yl)propyl]-4-propylpyrrolidin-2-one;
1-[2-furyl(1H-indol-3-yl)methyl]-4-propylpyrrolidin-2-one;
3-[(2-oxo-4-propylpyrrolidin-1-yl)(phenyl)methyl]-1H-indole-5-carbonitrile;
1-(1H-indol-4-ylmethyl)-4-propylpyrrolidin-2-one;

1-(1H-indol-7-ylmethyl)-4-propylpyrrolidin-2-one;
1-(isoxazol-4-ylmethyl)-4-propylpyrrolidin-2-one;
1-[(1-phenyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(1-methyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(1-benzyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
4-(2,3,5-trifluorophenyl)-1-[(1,3,5-trimethyl-1H-pyrazol-4-yl)methyl]pyrrolidin-2-one;
4-phenyl-1-(1H-pyrazol-4-ylmethyl)pyrrolidin-2-one;
1-({1-[(4-methylphenyl)sulfonyl]-1H-pyrazol-4-yl}methyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-(1H-pyrazol-4-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(1-chloro-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(3,5-dimethyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(3-methyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(5-amino-1,3-dimethyl-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(5-amino-1-methyl-1H-pyrazol-4-yl)methyl]-4-propylpyrrolidin-2-one;
(−)-1-(1H-pyrazol-4-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
(+)-1-(1H-pyrazol-4-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-(1H-pyrazol-4-ylmethyl)-1,3-dihydro-2H-indol-2-one;
5-chloro-1-(1H-pyrazol-4-ylmethyl)-1,3-dihydro-2H-indol-2-one;
5-chloro-1-({1-[(4-methylphenyl)sulfonyl]-1H-pyrazol-4-yl}methyl)-1,3-dihydro-2H-indol-2-one;
1-{[5-chloro-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(5-amino-1H-pyrazol-4-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(1-benzyl-5-chloro-1H-pyrazol-4-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;

1-(1H-pyrazol-5-ylmethyl)-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(4-bromo-1-methyl-1H-pyrazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(1-methyl-1H-pyrazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(6-bromo-2-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-[(2-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
1-[(6-bromo-2-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-tert-butylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-tert-butyl-6-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[2-(2-furyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-[(2-methyl-6-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-methyl-6-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[2-methyl-6-(1H-pyrrol-2-yl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-({6-[(1E)-hex-1-enyl]-2-methylpyrazolo[1,5-a]pyrimidin-3-yl}methyl)-4-propylpyrrolidin-2-one;
1-[(6-chloro-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[2-methyl-6-(phenylethynyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(6-hydroxy-2-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-[(2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
1-[(6-methoxy-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-chloropyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-[(5,6-dimethyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-[(6-fluoro-5-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
1-[(5-methoxypyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-{[2-(4-bromophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-{[2-(4-fluorophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-[(6-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-[(5-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
4-(2,2-difluorovinyl)-1-[(2-thien-2-ylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]pyrrolidin-2-one;
1-{[2-(4-chlorophenyl)-6-methylpyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[2-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(6-chloro-2-phenylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-{[6-chloro-2-(4-chlorophenyl)pyrazolo[1,5-a]pyrimidin-3-yl]methyl}-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(2-cyclopropyl-5-methylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(5-chloro-2-cyclopropylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(5-chloro-2,6-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(5-bromo-1H-pyrazolo[3,4-b]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

4-propyl-1-(pyridin-3-ylmethyl)pyrrolidin-2-one;

(−)-1-(1-pyridin-3-ylpropyl)pyrrolidin-2-one;

5-chloro-1-[(2-fluoropyridin-3-yl)methyl]-1,3-dihydro-2H-indol-2-one;

1-[(6-chloropyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[6-(benzylamino)pyridin-3-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(2-aminopyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)pyrrolidin-2-one;

1-[(2-isopropyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(2-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-[(2-propyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]pyrrolidin-2-one;

1-[(6-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(1-benzoyl-6-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(6-phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

1-[(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;

1-[(7-oxido-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[2,3-b]pyridin-4-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[2,3-b]pyridin-5-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[2,3-c]pyridin-2-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[2,3-c]pyridin-3-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[3,2-b]pyridin-3-ylmethyl)pyrrolidin-2-one;

4-propyl-1-(1H-pyrrolo[3,2-c]pyridin-2-ylmethyl)pyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[3,2-c]pyridin-3-ylmethyl)pyrrolidin-2-one;
4-propyl-1-(1,3,4-thiadiazol-2-ylmethyl)pyrrolidin-2-one;
1-[(2-amino-1,3-thiazol-5-yl)methyl]pyrrolidin-2-one;
1-(1,3-thiazol-5-ylmethyl)pyrrolidin-2-one;
1-[(2-chloro-1,3-thiazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-{[2-(dimethylamino)-1,3-thiazol-5-yl]methyl}-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-{[2-(methylamino)-1,3-thiazol-5-yl]methyl}-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
1-[(2-pyrrolidin-1-yl-1,3-thiazol-5-yl)methyl]-4-(2,3,5-trifluorophenyl)pyrrolidin-2-one;
5-{[2-oxo-4-(2,3,5-trifluorophenyl)pyrrolidin-1-yl]methyl}-1,3-thiazol-2(3H)-one;
4-phenyl-1-{[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-7-yl]methyl}pyrrolidin-2-one;
4-phenyl-1-[(3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-7-yl)methyl]pyrrolidin-2-one;
4-phenyl-1-{[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-8-yl]methyl}pyrrolidin-2-one;
4-propyl-1-{[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-8-yl]methyl}pyrrolidin-2-one;
4-phenyl-1-[(3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]pyrrolidin-2-one;
1-[(6-chloro-3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-chloro[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]-4-phenylpyrrolidin-2-one;
1-{[6-chloro-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-8-yl]methyl}-4-phenylpyrrolidin-2-one;
1-[(6-chloro-3-phenyl[1,2,4]triazolo[4,3-b]pyridazin-8-yl)methyl]-4-phenylpyrrolidin-2-one;
1-[(2-fluoroindolizin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-(1H-1,2,3-benzotriazol-1-ylmethyl)-4-propylpyrrolidin-2-one;

1-[(6-bromo-2-chloro-1H-imidazo[4,5-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-phenyl-1H-imidazo[4,5-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-(3H-imidazo[4,5-b]pyridin-3-ylmethyl)-4-propylpyrrolidin-2-one;
1-[(6-bromo-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-chloro-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-phenyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-bromo-2-cyclopropyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(3-chloro-7H-imidazo[4,5-c]pyridazin-7-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-methyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-methyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-phenyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-fluoro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-bromo-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-chloro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-(2,3-dihydro-1H-indol-1-ylmethyl)-4-propylpyrrolidin-2-one;
1-[(5-fluoro-2-phenyl-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-indole-2-carbonitrile;
1-[(2-bromo-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2,5-dichloro-1H-indol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(6-amino-9H-purin-9-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-(9H-purin-9-ylmethyl)pyrrolidin-2-one;
1-{[6-(cyclopropylamino)-9H-purin-9-yl]methyl}-4-propylpyrrolidin-2-one;
1-{[6-(benzylamino)-9H-purin-9-yl]methyl}-4-propylpyrrolidin-2-one;
4-propyl-1-{[6-(propylamino)-9H-purin-9-yl]methyl}pyrrolidin-2-one;
1-({6-[(cyclopropylmethyl)amino]-9H-purin-9-yl}methyl)-4-propylpyrrolidin-2-one;

4-propyl-1-[(6-pyrrolidin-1-yl-9H-purin-9-yl)methyl]pyrrolidin-2-one;
1-[(5-bromo-3-phenyl-1H-pyrazolo[3,4-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-bromo-2H-pyrazolo[3,4-b]pyridin-2-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-bromo-3-phenyl-2H-pyrazolo[3,4-b]pyridin-2-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)methyl]-4-propylpyrrolidin-2-one;
4-propyl-1-(1H-pyrrolo[3,2-b]pyridin-1-ylmethyl)pyrrolidin-2-one;
1-(3,4-dihydroquinolin-1(2H)-ylmethyl)-4-propylpyrrolidin-2-one;
1-(8H-isothiazolo[5,4-b]indol-8-ylmethyl)-4-propylpyrrolidin-2-one;
1-(1H-1,2,4-triazol-1-ylmethyl)pyrrolidin-2-one;
1-[(2,5-dichloro-1H-pyrrol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1H-pyrrol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1H-benzimidazol-1-yl)methyl]-4-phenylpyrrolidin-2-one;
2-chloro-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile;
2-chloro-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-6-carbonitrile;
4-propyl-1-[(2,5,6-trichloro-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one;
1-[(2-chloro-6-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-5-methoxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-6-nitro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-5-nitro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-6-methyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-1H-benzimidazol-1-yl)methyl]-4-(2,2-difluorovinyl)pyrrolidin-2-one;
1-[(6-bromo-2-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(5-bromo-2-chloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-6-fluoro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2-chloro-5-fluoro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2,6-dichloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;
1-[(2,5-dichloro-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-{[2-chloro-6-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one;

1-{[2-chloro-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4-propylpyrrolidin-2-one;

1-[(2-chloro-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one;

1-[(2-chloro-6-hydroxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one;

1-(pyridin-4-ylmethyl)pyrrolidin-2-one, and

1-[(2-chloro-5-hydroxy-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one.

viii) U.S. Patent 4,696,943

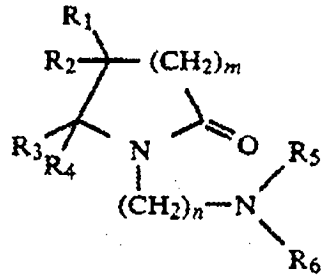
The present invention relates to the novel compound (S)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide.

ix) U.S. Patent 4,696,942

The present invention relates to the novel compound, (R)-alpha-ethyl-2-oxo-1-pyrrolidineacetamide

x) U.S. Patent 5,334,720

According to this invention we provide novel compounds of the formula I,



I.

wherein, R1, R2, R3 and R4, which may be the same or different independently represent hydrogen, C1-6 alkyl, phenyl or phenyl substituted by one or more halogen, hydroxyl, nitro, amino, C1-6 alkyl or C1 -C6 alkoxy groups;

R5 and R6 independently represent hydrogen, C1 -C6 alkyl or C3 -C6 cycloalkyl , or R5 and R6 together with the nitrogen form a C4-6 N heterocycle;

m represents an integer from 1-2; and

n represents an integer from 1-3;

provided that,

two of the substituents R1, R2, R3 and R4 independently represent phenyl or substituted phenyl and the other two independently represent hydrogen or C1-6 alkyl;

or a pharmaceutically acceptable acid addition salt thereof.

Pharmaceutically acceptable acid addition salts of the compounds of formula I include salts of mineral acids, for example, hydrohalic acids, e.g. hydrochloric or hydrobromic; or organic acids, e.g. formic, acetic or lactic acids. The acid may be polybasic, for example sulphuric, fumaric, maleic or citric acid.

This invention also relates to all stereoisomeric forms and optical enantiomeric forms of the compounds of formula I.

In the compounds of formula I: alkyl groups which R1, R2, R3, R4, R5 and R6 may represent include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl and s-butyl;

cycloalkyl groups which R5 and R6 may represent include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl;

C1-6 alkoxy groups include methoxy, ethoxy and propoxy;

halogen groups include fluorine, chlorine, bromine or iodine;

We prefer compounds of formula I or a pharmaceutically acceptable acidaddition salt thereof, in which;

R1 is hydrogen, phenyl or substituted phenyl, preferably phenyl;

R2 is hydrogen, phenyl or substituted phenyl, preferably phenyl;

R3 is hydrogen , phenyl or substituted phenyl, preferably hydrogen;

R4 is hydrogen, phenyl or substituted phenyl, preferably hydrogen;

R5 is hydrogen , C1-3 alkyl or cyclopropyl , preferably hydrogen or methyl;

R6 is hydrogen , C1-3 alkyl or cyclopropyl , preferably hydrogen or methyl;

m represents an integer from 1-2 preferably 2;

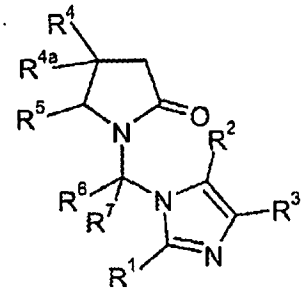
n represents an integer from 1-2, preferably 1.

We especially prefer compounds of formula I in which R1 and R2 are both phenyl.

We especially prefer compounds of formula I in which one of R5 and R6 is hydrogen and the other is hydrogen or methyl.

xi) International Patent Application Publication No. WO2005/054188

In one aspect the invention therefore provides a compound having the formula I or a pharmaceutically acceptable salt thereof,



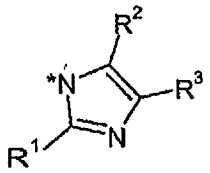
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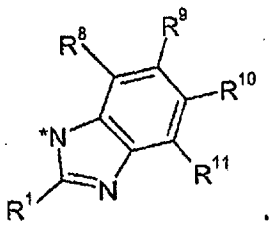
wherein

RI is hydrogen, CI-20 alkyl, C3 23 cycloalkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, guanidine, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, aryl or heterocycle; R2 is hydrogen, C1 20 alkyl, alkoxy, amino, halogen, hydroxy, ester, amido, nitro, cyano, carbamate, or aryl;

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

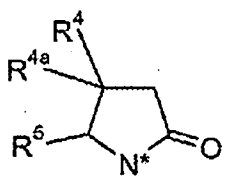
or R2 and R3 can form together with the imidazole ring the following 1H-benzimidazole cycle

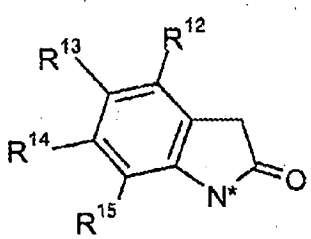




;

R4 is hydrogen, C1-20 alkyl, C2-12 alkenyl,C2-12 alkynyl, aryl, azido, alkoxycarbonylamino, arylsulfonyloxy or heterocycle; R4a is hydrogen or C1-20 alkyl; or R4 and R4a can form together a C3-8 cycloalkyl ; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





;

R6 is hydrogen or C1 20 alkyl ; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl ; R8 is hydrogen, halogen, nitro, cyano, C1 20 alkyl or

alkoxy ; R9 is hydrogen, C1-20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

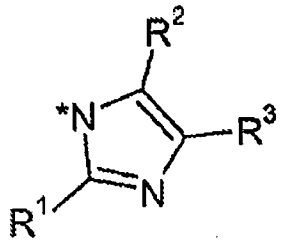
RIO is hydrogen, C1 20 alkyl, halogen, hydroxy, alkoxy, aryloxy, ester, amido, cyano, nitro, amino, amino derivative, alkylthio, arylthio, alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl ;

RI l is hydrogen, halogen, nitro, cyano, C1 20 alkyl or alkoxy ; R12 is hydrogen or halogen;

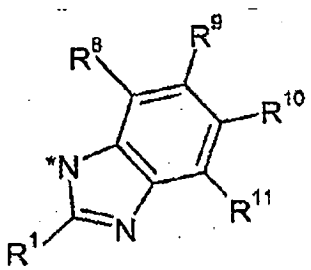
R13 is hydrogen, nitro, halogen, heterocycle, amino, aryl, C1-20 alkyl unsubstituted or substituted by halogen, or alkoxy unsubstituted or substituted by halogen; R14 is hydrogen, C1-20 alkyl or halogen;

R15 is hydrogen, C1 20 alkyl or halogen;

with the proviso that R4 is different from hydrogen when

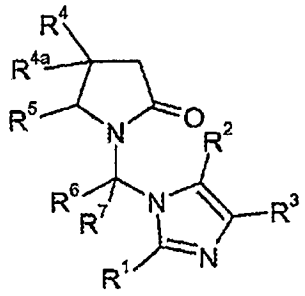


N represents a group of formula



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

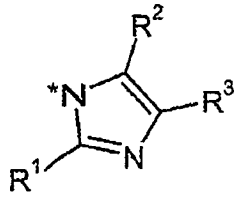
In a preferred embodiment, the invention concerns a compound having the formula I, their tautomers, geometrical isomers (including cis and trans, Z and E isomers), enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts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

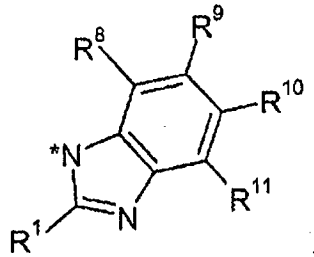


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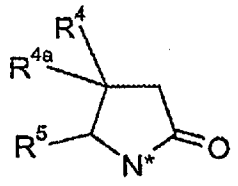
wherein

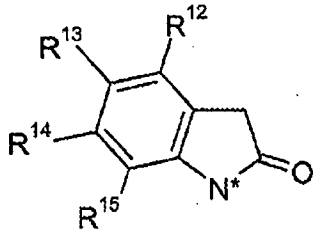
RI is hydrogen, C1-20 alkyl, C3-8 cycloalkyl, halogen, hydroxy, ester, amido, cyano, nitro, amino, guanidine, alkylthio, alkylsulfonyl, alkylsulfinyl, aryl or heterocycle; R2 is hydrogen, C1 20 alkyl, halogen, cyano, ester, carbamate or amido; R3 is hydrogen, cyano, C 1 20 alkyl, halogen or ester; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle





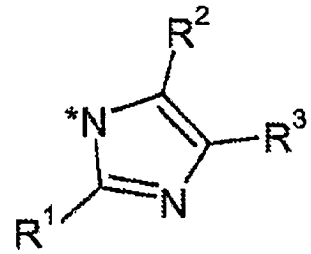
; R4 is hydrogen, C1 20 alkyl, C2 12 alkenyl or aryl; R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle



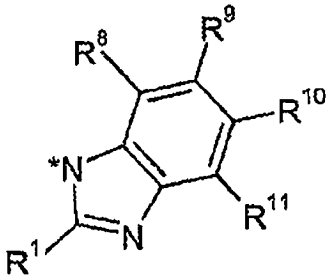


;

R6 is hydrogen or C 1 20 alkyl ; R7 is hydrogen; or R6 and R7 are linked together to form a C3-6 cycloalkyl ; R8 is hydrogen; R9 is hydrogen, C 1-20 alkyl, halogen or alkoxy; RIO is hydrogen, C1 20 alkyl, halogen or cyano; R11 is hydrogen; R12 is hydrogen or halogen; R13 is hydrogen, halogen, heterocycle or C1 20 alkyl ; R14 is hydrogen; R15 is hydrogen; with the proviso that R4 is different from hydrogen when



represents a group of formula



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

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

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

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

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

The term"aryl"as used herein, is defined as phenyl optionally substituted by 1 to 4 substituents independently selected from halogen, cyano, alkoxy, alkylthio, C1 3 alkyl or azido, preferably halogen or azido. Usually aryl groups, in the present case are phenyl, 3-chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3, 5-difluorophenyl, 3-chloro-4-fluorophenyl, 2,3, 4-trifluorophenyl, 2,4, 5-trifluorophenyl, 2,3, 5-trifluorophenyl, 3,4, 5-trifluorophenyl, 3-azido-2,4- difluorophenyl or 3-azido-2,4, 6-trifluorophenyl. Preferably, aryl groups are phenyl, 3- chlorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 3,4-difluorophenyl, 3,5- difluorophenyl, 3-chloro-4-fluorophenyl, 2,3, 4-trifluorophenyl, 2,4, 5-trifluorophenyl, 2,3, 5-trifluorophenyl, 3,4, 5-trifluorophenyl or 3-azido-2, 4-difluorophenyl. Most preferred aryl groups

are phenyl, 3-chlorophenyl, 3-fluorophenyl, 3,5-difluorophenyl, 2,3, 4-trifluorophenyl, 2,4, 5-trifluorophenyl, 2,3, 5-trifluorophenyl, 3, 4, 5-trifluorophenyl or 3-azido-2,4-difluorophenyl.

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

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

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

The term"alkoxy", as used herein, represents a group of formula-ORa wherein Ra is an alkyl group, as defined above. Preferred alkoxy group is methoxy.

The term"aryloxy", as used herein, represents a group of formula-ORb wherein Rb is an aryl group, as defined above. Preferred aryloxy group is phenoxy.

The term"ester", as used herein, represents a group of formula-COORC wherein Rc is an alkyl group or aryl group, as defined above. Preferred ester group is methoxycarbonyl.

The term"amido", as used herein, represents a group of formula-CONH2.

The term"amino", as used herein, represents a group of formula-NH2.

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

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

The term"nitro", as used herein, represents a group of formula-N02.

The term"azido", as used herein, represents a group of formula-N3.

The term"guanidine", as used herein, represents a group of formula- NHC (=NH) NH2.

The term"alkylthio", as used herein, represents a group of formula-SRd wherein Rd is an alkyl group, as defined above. One alkylthio group is methylthio.

The term"alkylsulfonyl", as used herein, represents a group of formula- S (=O) 2Re wherein Re is an alkyl group, as defined above. One alkylsulfonyl group is methylsulfonyl.

The term"alkylsulfinyl", as used herein, represents a group of formula-S (=O) Rf wherein Rf is an alkyl group, as defined above. One alkylsulfinyl group is methylsulfinyl.

The term"arylthio", as used herein, represents a group of formula-SRg wherein Rg is an aryl group, as defined above.

The term"arylsulfonyl", as used herein, represents a group of the formula- S (=O) 2Rh wherein Rh is an aryl group, as defined above.

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

The term"carbamate"as used herein, represents a group of formula- N (H) C (O) OR1, wherein Ri is an alkyl or an aryl, as defined above. Usually carbamate groups are (propoxycarbonyl) amino or (benzyloaxycarbonyl) amino. One carbamate group is (benzyloaxycarbonyl) amino.

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

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

Usually, RI is hydrogen; Cl lo alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy ; hydroxy ; C3-6 cycloalkyl ; halogen; ester; amido; nitro ; cyano; amino ; phenyl; alkylthio; alkylsulfonyl ; alkylsulfinyl ; heterocycle unsubstituted or substituted by alkyl groups; or guanidine.

In some embodiments, RI is hydrogen; methyl; ethyl; i-propyl ; n-propyl ; cyclopropyl ; n-butyl; i- butyl; t-butyl; 1-ethylpropyl ; 2,4, 4-trimethylpentyl; hydroxymethyl ; chloromethyl; trifluoromethyl ; 2,2, 2-trifluoroethyl ; cyanomethyl; 2- (methylthio) ethyl; chloro; bromo; nitro ; cyano; amino; aminocarbonyl; methoxycarbonyl ; methylthio; methylsulfinyl ; methylsulfonyl; phenyl; 2-furyl ; 3-furyl; lH-pyrrol-2-yl ; 1-methyl-lH-pyrrol-2-yl ; 2- thienyl; lH-pyrazol-3-yl ; 1, 2,3-thiadiazol-4-yl or lH-imidazol-2-yl. More preferably, RI is hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl; methylthio; nitro ; cyano; amino; chloro or lH-pyrrol-2-yl. Most preferably, RI is hydrogen; methyl; methylthio ; nitro; cyano; amino or chloro.

Usually, R2 is hydrogen; C1 4 alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen ; ester; cyano ; alkyl carbamate; [(N-methoxy- N-methyl) amino] carbonyl. Preferably, R2 is hydrogen; methyl; hydroxymethyl ; (acetylamino) methyl; (propionylamino) methyl; (benzoylamino) methyl; [(benzyloxy) carbonyl] amino ; chloro or cyano. In some embodiments, R2 is hydrogen; chloro or cyano.

Usually, R3 is hydrogen; C1 4 alkyl unsubstituted or substituted by hydroxy; halogen; ester or cyano. In some embodiments, R3 is hydrogen; hydroxymethyl; chloro; cyano.

In some embodiments, R3 is hydrogen or cyano. In some embodiments R3 is hydrogen.

Usually, R4 is hydrogen; C1 4 alkyl tlnsubstituted or substituted by halogens; C2 4 alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or/and halogens. Preferably, R4 is hydrogen; n-propyl ; 2,2-difluorovinyl ; phenyl; 3-chlorophenyl ; 3-fluorophenyl ; 4-chlorophenyl; 4-fluorophenyl ; 3,5-difluorophenyl; 3,4-difluorophenyl ; 3-chloro-4-fluorophenyl ; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl ; 3,4, 5-trifluorophenyl ; 3-azido-2,4- difluorophenyl or 3-azido-2,4, 6-trifluorophenyl. More preferably, R4 is hydrogen; n- propyl ; 2,2-difluorovinyl ; phenyl; 3-chlorophenyl; 3-fluorophenyl ; 4-chlorophenyl; 4- fluorophenyl ; 3, 5-difluorophenyl ; 3,4-difluorophenyl ; 3-chloro-4-fluorophenyl; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl; 2,3, 5-trifluorophenyl; 3,4, 5-

trifluorophenyl or 3- azido-2,4-difluorophenyl. Most preferably, R4 is n-propyl ; 2,2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl ; 3,5-difluorophenyl ; 2,3, 4-trifluorophenyl ; 2,4, 5- trifluorophenyl ; 2,3, 5-trifluorophenyl ; 3,4, 5-trifluorophenyl or 3-azido-2,4- difluorophenyl.

Usually, R4a is hydrogen.

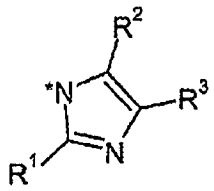
Usually, R5 is hydrogen.

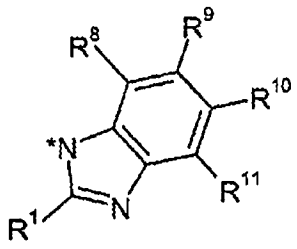
Usually, R6 is hydrogen or Cl-1~0 alkyl unsubstituted or substituted by hydroxy or azido. Preferably, R6 is hydrogen or azidomethyl. More preferably R6 is hydrogen.

Usually R7 is hydrogen.

In other embodiments, R6 and R7 are linked to form a cyclopropyl.

In other embodiments, R2 and R3 can form together with the imidazole ring the following 1H-benzimidaole cycle





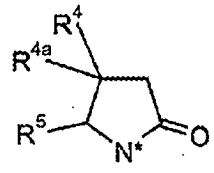
Usually, R8 is hydrogen.

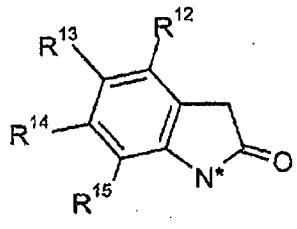
Usually, R9 is hydrogen; halogen ; 1-3 alkyl or alkoxy. In some embodiments, R9 is hydrogen; methyl; chloro or methoxy. In some embodiments R9 is hydrogen.

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

Usually, RI 1 is hydrogen.

In other embodiments, R4, R4a and R5 can form together with the 2- oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





;

Usually, R12 is hydrogen or halogen. In some embodiments R12 is hydrogen; chloro or fluoro. In some embodiments R12 is hydrogen.

Usually, R13 is hydrogen; C1 3 alkyl ; halogen or thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl. In some embodiments R13 is hydrogen; chloro; bromo or methyl. In some embodiments R13 is chloro; bromo or methyl.

Usually R14 is hydrogen.

Usually, R15 is hydrogen.

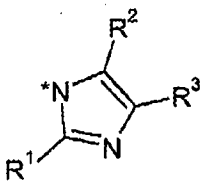
In a general embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salts thereof, are those wherein

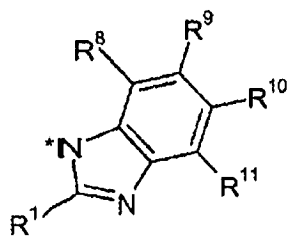
RI is selected from hydrogen; C1 lo alkyl unsubstituted or substituted by halogen, hydroxy, cyano, methylthio, phenyl or 4-chlorophenoxy ; C3 6 cycloalkyl ; halogen; ester; amido; nitro; cyano; amino; phenyl; alkylthio ; alkylsulfonyl ; alkylsulfinyl ; heterocycle unsubstituted or substituted by alkyl group; or guanidine; R2 is selected from hydrogen; C 1-4 alkyl unsubstituted or substituted by hydroxy, alkanoylamino or benzoylamino; halogen; ester; cyano; alkyl carbamate or [(N-methoxy-N-methyl) amino] carbonyl.

R3 is selected from hydrogen; C1 4 alkyl unsubstituted or substituted by hydroxy ; halogen; ester or cyano; R4 is selected from hydrogen; C1 4 alkyl unsubstituted or substituted by halogens; C2 4 alkenyl substituted by halogens or phenyl group unsubstituted or substituted by azido or/and halogens;

R4a is hydrogen; R5 is hydrogen; R6 is selected from hydrogen or C 1-10 alkyl unsubstituted or substituted by hydroxy or azido;

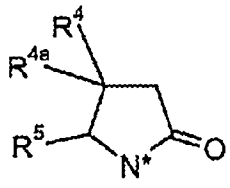
R7 is hydrogen; or R6 and R7 can be linked to form a cyclopropyl ; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle

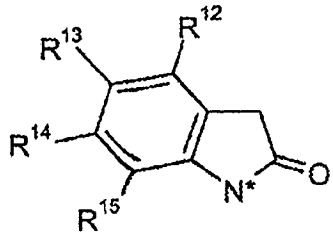




R8 is hydrogen; R9 is selected from hydrogen; halogen; C1-3 alkyl ; alkoxy ;

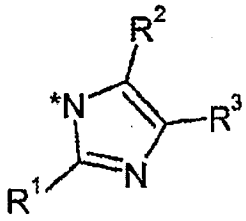
R10 is selected from hydrogen; halogen; cyano or Cil alkyl unsubstituted or substituted by halogens; or alkoxy ; R 1 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle



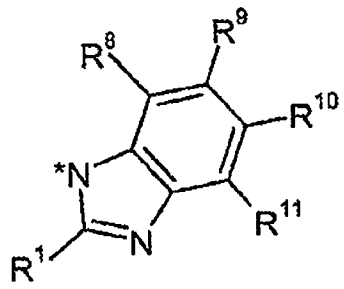


;

R12 is selected from hydrogen or halogen; R13 is selected from hydrogen; CI-3 alkyl ; halogen ; thiazolyl unsubstituted or substituted by alkyl groups, such as methylthiazolyl; R14 is hydrogen; R15 is hydrogen; with the proviso that R4 is different from hydrogen when



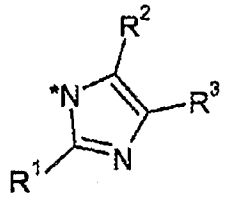
represents a group of formula

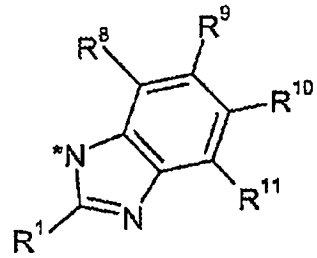


In an embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

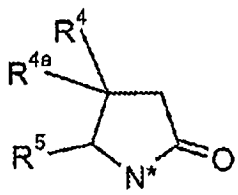
RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; cyclopropyl ; n-butyl; i-butyl; t-butyl; 1-ethylpropyl ; 2,4, 4-trimethylpentyl; trifluoromethyl; 2,2, 2- trifluoroethyl; hydroxymethyl; chloromethyl; cyanomethyl ; 2- (methylthio) ethyl; chloro; bromo; nitro; cyano ; amino; aminocarbonyl;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

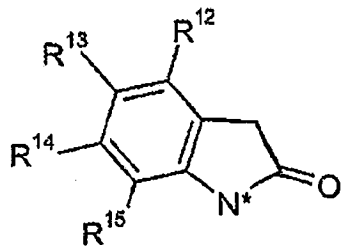
or lH-imidazol-2-yl ; R2 is selected from hydrogen; methyl ; hydroxymethyl; (acetylamino) methyl; (propionylamino) methyl ; (benzoylamino) methyl; (benzyloxycarbonyl) amino; chloro; or cyano; R3 is selected from hydrogen; hydroxymethyl; chloro; cyano; or R2 and R3 can form together with the imidazole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



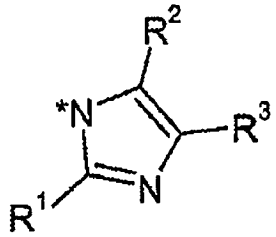


R8 is hydrogen; R9 is selected from hydrogen; methyl; choro ; methoxy; R10 is selected from methyl; hydrogen; trifluoromethyl; fluoro; cyano; or methoxy; R is hydrogen; R4 is selected from hydrogen; n-propyl ; 2,2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3,5-difluorophenyl ; 3,4- difluorophenyl; 3-chloro-4-fluorophenyl ; 2,3, 4-trifluorophenyl; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 5-trifluorophenyl ; 3-azido-2,4-difluorophenyl ; or 3-azido- 2,4, 6-trifluorophenyl. R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle

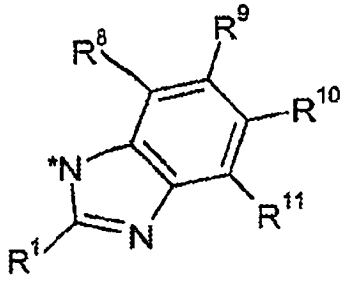




R12 is selected from hydrogen; chloro; fluoro; R13 is selected from hydrogen; chloro; bromo; methyl; R14 is hydrogen; R15 hydrogen; R6 is selected from hydrogen; azidomethyl; R7 is hydrogen; or R6 and R7 are linked to form a cyclopropyl ; with the proviso that R4 is different from hydrogen when

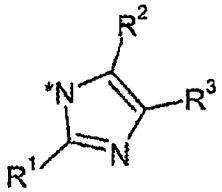


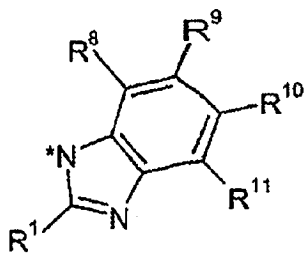
represents a group of formula



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

RI is selected from hydrogen; methyl; ethyl; i-propyl ; n-propyl ; n-butyl; methylthio; nitro; cyano ; amino; chloro ; or lH-pyrrol-2-yl ; R2 is selected from hydrogen; chloro; cyano; R3 is selected from hydrogen; cyano; or R2 and R3 can form together with the imidazole ring the following 1H- benzimidazole cycle

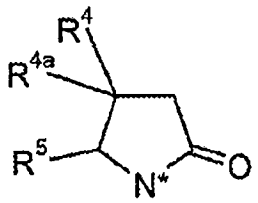
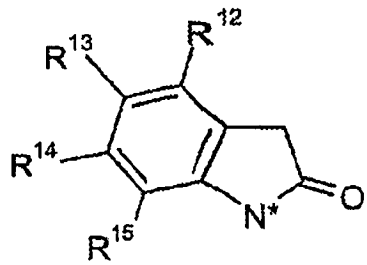




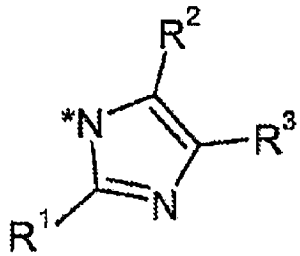
R8 is hydrogen; R9 is hydrogen;

R10 is selected from hydrogen ; trifluoromethyl ; fluoro ; cyano;

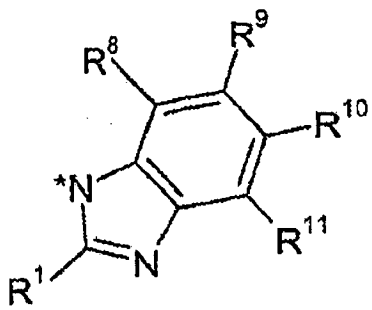
RI l is hydrogen; R4 is selected from hydrogen; n-propyl ; 2, 2-difluorovinyl ; phenyl; 3- chlorophenyl; 3-fluorophenyl; 4-chlorophenyl; 4-fluorophenyl ; 3, 5-difluorophenyl ; 3,4- difluorophenyl ; 3-chloro-4-fluorophenyl; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 5-trifluorophenyl; or 3-azido-2, 4-difluorophenyl ; R4a is hydrogen; R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle

wherein R12 is hydrogen; R13 is selected from methyl; chloro; bromo; R14 is hydrogen; R15 hydrogen; R6 is hydrogen; R7 is hydrogen; with the proviso that R4 is different from hydrogen when



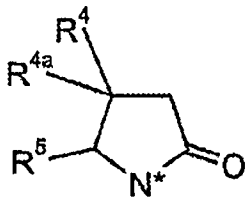
R11 represents a group of formula

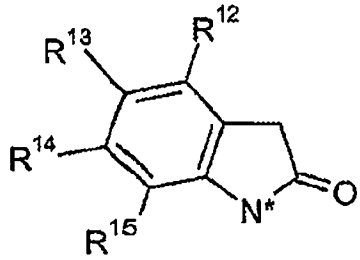


In one embodiment of the invention, the compounds of formula I, or pharmaceutically acceptable salt thereof, are those wherein

RI is selected from hydrogen; methyl; methylthio; nitro ; cyano; amino; chloro; R2 is selected from hydrogen; chloro; cyano; R3 is hydrogen; R4 is selected from n-propyl ; 2, 2-difluorovinyl ; phenyl; 3-chlorophenyl; 3- fluorophenyl; 3,5-difluorophenyl ; 2,3, 4-trifluorophenyl ; 2,4, 5-trifluorophenyl ; 2,3, 5-trifluorophenyl; 3,4, 5-trifluorophenyl; 3-azido-2,4-difluorophenyl ; R4a is hydrogen;

R5 is hydrogen; or R4, R4a and R5 can form together with the 2-oxo-1-pyrrolidine ring the following 1, 3-dihydro-2H-indol-2-one cycle





R12 is hydrogen; R13 is selected from chloro; bromo; methyl ; R14 is hydrogen; R15 hydrogen; R6 is hydrogen; R7 is hydrogen.

In some embodiments, compounds are: 1-(lH-imidazol-l-ylmethyl) pyrrolidin-2-one ; 1- (1H- imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one ; 4- (3-azido-2, 4, 6-trifluorophenyl)-1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 1- (IH-imidazol-1-ylmethyl)-4- propylpyrrolidin-2-one; (-)-4-(3-azido-2,4-difluorophenyl)-1-(1H-imidazol-1- ylmethyl) pyrrolidin-2-one; (+)-4- (3-azido-2, 4-difluorophenyl)-l-(IH-imidazol-l- ylmethyl) pyrrolidin-2-one ; 1-[(2-ethyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2- one; 1-[(2-isopropyl-lH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-methyl- IH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-phenyl-1H-imidazol-1- yl) methyl]-4-propylpyrrolidin-2-one ; 4-propyl-1-[(2-propyl-lH-imidazol-1- yl) methyl] pyrrolidin-2-one ; (+)-1-(lH-imidazol-l-ylmethyl)-4-propylpyrrolidin-2-one ; (-)-1-(lH-imidazol-l-ylmethyl)-4-propylpyrrolidin-2-one ; 4- (2, 2-difluorovinyl)-1- (1H-imidazol-1-ylmethyl) pyrrolidin-2-one ; 4-(3-chlorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 1-{[2-(methylthio)-lH-imidazol-1-yl] methyl}-4-propylpyrrolidin-2-one; 1-{[2-(methylsulfinyl)-lH-imidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(2-tert-butyl-lH-imidazol-l-yl) methyl]-4-propylpyrrolidin-2- one; 1- [1- (lH-imidazol-1-yl) cyclopropyl] pyrrolidin-2-one ; 1- [(2-methyl-1H-imidazol-1- yl) methyl]-4-phenylpyrrolidin-2-one ; 1-{[2-(methylsulfonyl)-lH-imidazol-l-yl] methyl}-4- propylpyrrolidin-2-one; 1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-imidazole-2- carboxamide; 4-(4-fluorophenyl)-1-(1H-imidazol-1-ylmethyl)pyrrolidin-2-one ; 1- (1H- imidazol-1-ylmethyl)-4-(3, 4, 5-trifluorophenyl) pyrrolidin-2-one; 4- (3-fluorophenyl)-1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3,5-difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3,4-difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin- 2-one; 4-(3-chloro-4-fluorophenyl)-1-(1H-imidazol-1-ylmelthyl)

pyrrolidin-2-one; 4- (4- chlorophenyl)-1-(1H-imidazol-1-ylmelthyl) pyrrolidin-2-one; 1-(lH-imidazol-l-ylmethyl)- 4- (2, 3, 4-trifluorophenyl) pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2, 3,5-trifluorophenyl) pyrrolidin-2-one ; 1-(lH-imidazol-l-ylmethyl)-4-(2, 4,5- trifluorophenyl) pyrrolidin-2-one; 1-{[2-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4- propylpyrrolidin-2-one ; methyl 1-[(2-oxo-4-propylpyrrolidin-1-yl) methyl]-lH-imidazole- 2-carboxylate ; 1- [(2-nitro-IH-imidazol-1-yl) methyll-4- (3, 4,5-trifluorophenyl) pyrrolidin- 2-one; 1-{[2-oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-1H-imidazole-2-carbonitrile; 1-[(2-amino-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1- [(2, 4- dichloro-IH-imidazol-l-yl) methyl]-4- (3, 4, 5-trifluorophenyl) pyrrolidin-2-one ; 1- [(5- chloro-lH-imidazol-1-yl) methyl]-4- (3, 4, 5-trifluorophenyl) pyrrolidin-2-one ; 1-{[2-oxo-4- (3,4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-4-carbonitrile ; 1-{ [2-oxo-4- (3,4, 5-trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazole-5-carbonitrile ; (+)-1- (1H- imidazol-1-ylmethyl)-4-phenylpyrrolidin-2-one ; (-)-1-(1H-imidazol-1-ylmethyl)-4- phenylpyrrolidin-2-one ; 1- { [2-oxo-4- (2, 3, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-1H-imidazole-5-carbonitrile ; (-)-1-{[2-oxo-4-(2, 3, 4-trifluorophenyl) pyrrolidin-1-yl]methyl}- lH-imidazole-5-carbonitrile ; (+)-1-{[2-oxo-4-(2, 3,4-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-5-carbonitrile ; (-)-1-{[2-oxo-4-(2, 3,4-trifluorophenyl) pyrrolidin- l-yl] methyl}-lH-imidazole-4-carbonitrile ; (+)-1-{[2-oxo-4-(2, 3, 4-trifluorophenyl)-1- pyrrolidinyl] methyl}-lH-imidazole-4-carbonitrile ; (-)-1- { [2-oxo-4- (3, 4,5- trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-4-carbonitrile; (+)-1-{[2-oxo-4- (3,4, 5-trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazole-4-carbonitrile ; (+)-1-{[2-oxo- 4- (2, 4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-4-carbonitrile ; (-)-1-{[2-oxo-4- (2, 4,5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-4-carbonitrile ; (-)-1- {[2-oxo-4-(2, 3, 5-trifluorophenyl) pyrrolidin-1-ylmethyl}-1H-imidazole-4-carbonitrile ; (-)- 1-{[2-oxo-4-(3, 4, 5=trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazole-5-carbonitrile ; 1-{[2-oxo-4-(2, 3, 5-trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-5-carbonitrile ; 1-{[2-oxo-4-(2, 3,5-trifluorophenyl) pyrrolidin- methyl}-lH-imidazole-5-carbonitrile ; 1-[(5-methyl-2-phenyl-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1- [(5- methyl-IH-

imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(5-phenyl-1H-imidazol- 1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-ethyl-5-methyl-1H-imidazol-1-yl)methyl]- 4-propylpyrrolidin-2-one; 1-[(2,5-dimethyl-1H-imidazol-1-yl)methyl]-4- propylpyrrolidin-2-one; 1- [(2-chloro-IH-imidazol-1-yl) methyll-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 1-[2-azido-1-(lH-imidazol-1-yl) ethyl] -4-propylpyrrolidin-2-one ; 1- [(4-chloro-IH-imidazol-1-yl) methyll-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 1-[(2-bromo-4,5-dichloro-1H-imidazol-1-yl)methyl]-4- propylpyrrolidin-2-one; 1- [(2-chloro-1H-imidazol-1-yl)methyl]-4-propylpyrrolidin-2- one; (+)-1-1 [2-oxo-4- (3, 4,5-trifluorophenyl) pyrrolidin-1-yl]methyl}-1H-imidazole-5- carbonitrile; 1-{[5-(hydroxymethyl)-1H-imidazol-1-yl]methyl}-4-propylpyrrolidin-2-one ; 1-{[4-(hydroxymethyl)-lH-imidazol-l-yl] methyl}-4-propylpyrrolidin-2-one ; benzyl 1- [(2- oxo-4-propylpyrrolidin-1-yl) methyl]-lH-imidazol-5-ylcarbamate ; N-[(1-{[2-oxo-4-(3, 4,5-trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazol-5-yl) methyl] acetamide ; N- [(1-{[2- oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1-yl] methyl}-lH-imidazol-5- yl) methyl] benzamide; N-1 (1-1 [2-oxo-4- (3, 4, 5-trifluorophenyl) pyrroldin-1-yl]methyl}-1H- imidazol-5-yl) methyl] propanamide ; 1- (IH-benzimidazol-1-ylmethyl)-4-propylpyrrolidin- 2-one; 1-[(2-methyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 4-propyl- 1-[(2-propyl-1H-benzimidazol-1-yl)methyl]pyrrolidin-2-one ; 1-[(2-isopropyl-1H- benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(trifluoromethyl)- 1H-benzimidazol-1-yl] methyl} pyrrolidin-2-one; 1-{[2-(methylthio)-lH-benzimidazol-1- yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(2-amino-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1-{[2-(chloromethyl)-1H-benzimidazol-1-yl]melthyl}-4-propylpyrrolidin-2-one ; {1-[(2-oxo-4-propylpyrrolidin-1-yl) methyl]-1 H-benzimidazol-2- yl} acetonitrile ; 1- [(5-methoxy-lH-benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(5-methyl-lH-benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 1- [(5, 6-dimethyl- lH-benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-{[2-isopropyl-5- (trifluoromethyl)-lH-benzimidazol-l-yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(6-chloro- IH-benzimidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; 1-[(2-oxo-4-propylpyrrolidin-1- yl) methyl]-2-propyl-1H-benzimidazole-5-carbonitrile ; 1-{[2-ethyl-5-(trifluoromethyl)- 1H-

benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(1H-pyrrol-2-yl)- 1H-benzimidazol-1-yl] methyl} pyrrolidin-2-one ; 1- [(5-fluoro-2-propyl-1H-benzimidazol- 1-yl) methyl]-4-propylpyrrolidin-2-one ; 1-{[6-methyl-2-(lH-pyrrol-2-yl)-1H- benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1-[(6-methoxy-2-propyl-1H- benzimidazol-1-yl) methyl]-4-propylpyrrolidin-2-one ; 2-butyl-1- [(2-oxo-4- propylpyrrolidin-1-yl) methyl]-lH-benzimidazole-5-carbonitrile ; 1-{[2-[2- (methylthio) ethyl]-5-(trifluoromethyl)-lH-benzimidazol-1-yl] methyl}-4-propylpyrrolidin- 2-one; 1-[(5-fluoro-2-isobutyl-1H-benzimidazol-1-yl)methyl]-4-propylpyrrolidin-2-one ; 1-{[5-fluoro-2-(2, 4, 4-trimethylpentyl)-1 H-benzimidazol-1-yl] methyl}-4-propylpyrrolidin- 2-one; 2-cyclopropyl-1-[(2-oxo-4-propylpyrrolidin-1-yl)methyl]-1H-benzimidazole-5- carbonitrile ; l- [(2-oxo-4-propylpyrrolidin-l-yl) methyl]-2- (lH-pyrazol-3-yl)-lH- benzimidazole-5-carbonitrile; 1-[(2-cyclopropyl-5-fluoro-1H-benzimidazol-1-yl)methyl]- 4-propylpyrrolidin-2-one ; 1-[(5-fluoro-2-isopropyl-1H-benzimidazol-1-yl)methyl]-4- propylpyrrolidin-2-one ; 1-{[2-(3-furyl)-6-methoxy-1H-benzimidazol-1-ylmethyl}-4- propylpyrrolidin-2-one; 1- [(2-cyclopropyl-6-methoxy-lH-benzimidazol-1-yl) methyl]-4- propylpyrrolidin-2-one; 1- [(2-isopropyl-6-methoxy-lH-benzimidazol-1-yl) methyl]-4- propylpyrrolidin-2-one ; 1- [(2-oxo-4-propylpyrrolidin-1-yl) methyl]-2-(1, 2,3-thiadiazol-4- yl)-lH-benzimidazole-5-carbonitrile ; 1-{[2-(lH-imidazol-2-yl)-5-(trifluoromethyl)-1H- benzimidazol-l-yl] methyl}-4-propylpyrrolidin-2-one ; 1-{[5-fluoro-2-(2, 2,2- trifluoroethyl)-lH-benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1- { [2- (1- ethylpropyl)-6-methoxy-IH-benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 1-{[6-methoxy-2- (l-methyl-lH-pyrrol-2-yl)-IH-benzimidazol-l-yl] methyl}-4-propylpyrrolidin- 2-one; 1-{[2-(2-furyl)-5-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl}-4- propylpyrrolidin-2-one; 4-propyl-1-{[2-thien-2-yl-5-(trifluoromethyl)-1H-benzimidazol- 1-yl]melthyl}pyrrolidin-2-one ; 1-1 [2- (3-furyl)-5- (trifluoromethyl)-IH-benzimidazol-l- yl] methyl}-4-propylpyrrolidin-2-one ; 1- { [2-cyclopropyl-5- (trifluoromethyl)-lH- benzimidazol-1-yl] methyl}-4-propylpyrrolidin-2-one ; 4-propyl-1-{[2-(1H-pyrrol-2-yl)-5- (trifluoromethyl)-1H-benzimidazol-1-yl] methyl} pyrrolidin-2-one ; 1- (IH-imidazol-1- ylmethyl)-1, 3-dihydro-2H-indol-2-one ; 5-bromo-l-(lH-imidazol-l-ylmethyl)-1, 3- dihydro-2H-

indol-2-one; 5-chloro-l- (lH-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2- one; 4-fluoro-l-(lH-imidazol-l-ylmethyl)-1, 3-dihydro-2H-indol-2-one; 4-chloro-1-(1H-imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2-one ; 1-(lH-imidazol-l-ylmethyl)-5-methyl-1, 3-dihydro-2H-indol-2-one ; 1- [(2-oxo-2, 3-dihydro-lH-indol-1-yl) methyl]-1H- imidazole-5-carbonitrile; and 1- [(5-chloro-2-oxo-2, 3-dihydro-lH-indol-1-yl) methyl]-1H- imidazole-5-carbonitrile.

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

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

In some embodiments, compounds are: 1-(1H-imidazol-1-ylmethyl)-4-phenylpyrrolidin- 2-one; 1-(lH-imidazol-1-ylmethyl)-4-propylpyrrolidin-2-one ; (-)-4- (3-azido-2, 4- difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; (+)-4- (3-azido-2, 4- difluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(2,2-difluorovinyl)-1- (lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3-chlorophenyl)-1-(1H-imidazol-1- ylmethyl) pyrrolidin-2-one; 1-{[2-(methylthio)-lH-imidazol-1-yl] methyl}-4- propylpyrrolidin-2-one; 1-[(2-methyl-1H-imidazol-1-yl)methyl]-4-phenylpyrrolidin-2- one; 1- (lH-imidazol-1-ylmethyl)-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one; 4- (3- fluorophenyl)-1-(1H-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3,5-difluoromethyl)-1- (IH-imidazol-1-ylmetliyl) pyrrolidin-2-one; 1-(1H-imidazol-1-ylmethyl)-4-(2, 3,4- trifluorophenyl) pyrrolidin-2-one; 1-

(1H-imidazol-1-ylmethyl)-4-(2, 3,5- trifluorophenyl) pyrrolidin-2-one; 1- H-imidazol-1-ylmethyl)-4-(2, 4,5- trifluorophenyl) pyrrolidin-2-one; 1-[(2-nitro-lH-imidazol-1-yl) methyl]-4-(3, 4,5- trifluorophenyl) pyrrolidin-2-one; 1-{[2-oxo-4-(3, 4, 5-trifluorophenyl) pyrrolidin-1- yl] methyl}-lH-imidazole-2-carbonitrile ; 1-[(2-amino-lH-imidazol-1-yl) methyl]-4- propylpyrrolidin-2-one ; 1-[(5-chloro-1H-imidazol-1-yl)methyl]-4-(3, 4,5- trifluorophenyl) pyrrolidin-2-one; (+)-1-(lH-imidazol-l-ylmethyl)-4-phenylpyrrolidin-2- one; (-)-1-(lH-imidazol-l-ylmethyl)-4-phenylpyrrolidin-2-one ; 1-[(2-chloro-1H- imidazol-1-yl) methyl]-4- (3, 4,5-trifluorophenyl) pyrrolidin-2-one 1-[(2-chloro-1H-imidazol-l-yl) methyl]-4-propylpyrrolidin-2-one ; (+)-1-1 [2-oxo-4- (3, 4,5- trifluorophenyl) pyrrolidin-l-yl] methyl}-lH-imidazole-5-carbonitrile ; 5-bromo-1- (1H- imidazol-1-ylmethyl)-1, 3-dihydro-2H-indol-2-one; 5-chloro-1-(lH-imidazol-l-ylmethyl)- 1, 3-dihydro-2H-indol-2-one; 1- (lH-imidazol-1-ylmethyl)-5-methyl-1, 3-dihydro-2H- indol-2-one; 1-[(5-chloro-2-oxo-2, 3-dihydro-lH-indol-l-yl) methyl]-lH-imidazole-5-carbonitrile.

Some compounds are: (-)-4- (3-azido-2, 4-difluorophenyl)-l- (lH-imidazol-l-ylmethyl) pyrrolidin-2-one ; (+)-4-(3-azido-2, 4-difluorophenyl)-1-(lH-imidazol-1-ylmethyl) pyrrolidin-2-one; 4-(3-azido-2, 4-difluorophenyl)-1-(lH-imidazol-1-ylmethyl) pyrrolidin-2-one.

The acid addition salt form of a compound of formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, trifluoroacetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula I containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e. g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e. g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with

organic bases, e. g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

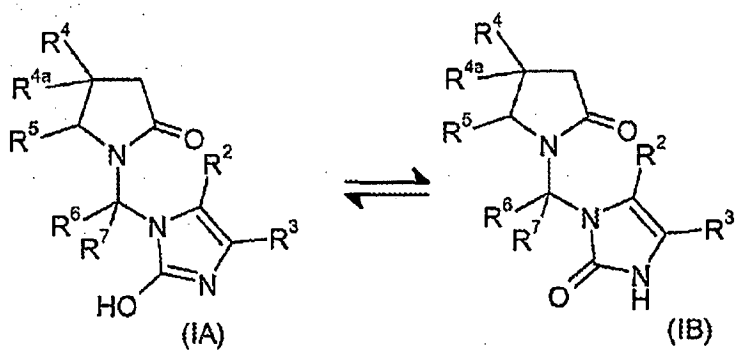
Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. , 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

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

In another preferred embodiment, the present invention concerns also compounds of formula IA and their tautomeric form IB



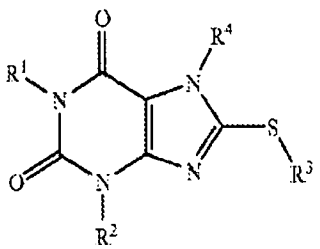
With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof, unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

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

xii) U.S. Patent Application Publication No. 20090018148

In one aspect the invention provides compounds having formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,



(I)

wherein

R1 is hydrogen or C1-6 alkyl;

R2 is hydrogen or C1-4 alkyl;

R3 is a group of formula —CHR5R6 or a benzyl group;

R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle;

R5 is C2-4 alkyl;

R6 is C2-4 alkyl, amido or —COOR7;

R7 is C1-4 alkyl;

In one aspect, the invention provides compounds:

When R1 is hydrogen, R2 is methyl, R3 is —CHR5R6, R6 is ethoxycarbonyl and R5 is ethyl, then R4 is different from methyl, n-propyl, i-propyl, n-pentyl, n-heptyl, 3-bromobenzyl, 4-chlorobenzyl, 4-methylbenzyl or 2-phenylethyl;

When R1 is hydrogen, R2 is methyl, R3 is benzyl, then R4 is different from i-propyl, n-butyl, 3-methylbutyl, benzyl, phenylethyl-, or 3-phenylpropyl;

When R1 and R2 are methyl, R3 is benzyl, R4 is different from methyl, 3-methylbutyl, benzyl, 3-phenylpropyl or 4-chlorophenylmethyl;

Finally 8-(2-chloro-benzylsulfanyl)-3-methyl-7-octyl-3,7-dihydro-purine-2,6-dione is considered.

Usually when R3 is a benzyl group, then R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl.

Usually when R3 is a group of formula —CHR5R6, then R4 is C1-8 alkyl optionally substituted by C3-6 cycloalkyl, aryl or heterocycle.

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

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

The term "aryl" as used herein, is defined as a phenyl group optionally substituted by 1 to 4 substituents independently selected from halogen, amino, nitro, alkoxy or aminosulfonyl. Preferred aryl groups are phenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 3-methoxyphenyl, 3-nitrophenyl, 3-aminophenyl or 4-(aminosulfonyl)phenyl.

The term "phenyl", as used herein, represents an aromatic hydrocarbon group of formula —C6H5.

The term "benzyl group", as used herein, represents a group of formula —CH2-aryl. Preferred benzyl groups are benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl or 4-(aminosulfonyl)benzyl. More preferred benzyl groups are benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl or 3-aminobenzyl. In some embodiments alkyl groups are 3-methoxybenzyl or 3-nitrobenzyl.

The term "halogen", as used herein, represents an atom of fluorine, chlorine, bromine, or iodine. In some embodiments the halogen is bromine.

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

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

The term "amino", as used herein, represents a group of formula —NH2.

The term "ethynyl", as used herein, represents a group of formula —C≡CH.

The term "alkoxy", as used herein, represents a group of formula —ORa wherein Ra is an alkyl group, as defined above. In some embodiments the alkoxy group is methoxy.

The term "nitro", as used herein, represents a group of formula —NO2.

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

The term "acyl", as used herein, represents a group of formula —C(=O)Rb wherein Rb is an alkyl group, as defined here above. In some embodiments the acyl group is acetyl (—C(=O)Me).

The term "alkoxycarbonyl (or ester)", as used herein, represents a group of formula —COORc wherein Rc is an alkyl group; with the proviso that Rc does not represent an alkyl alpha-substituted by hydroxy. In some embodiments the alkoxycarbonyl group is ethoxycarbonyl.

The term "heterocycle", as used herein, represents a 5-membered ring containing one or two heteroatoms selected from O or N. The heterocycle may be substituted by one or two C1-4 alkyl or nitro. In some embodiments the heterocycles are (3,5-dimethylisoxazol-4-yl) or (5-nitro-2-furyl). Most preferred heterocycle is (5-nitro-2-furyl).

Generally R1 is hydrogen or C1-6 alkyl. Usually R1 is hydrogen or C1-6 alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl. In some embodiments R1 is hydrogen, methyl, cyanomethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-pentyl or n-hexyl. In some embodiments R1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl. In some embodiments R1 is hydrogen.

Generally R2 is hydrogen or C1-4 alkyl. Usually R2 is hydrogen or unsubstituted C1-4 alkyl. In some embodiments R2 is hydrogen, methyl or n-butyl. In some embodiments, R2 is methyl.

Generally R3 is a group of formula —CHR5R6 or a benzyl group. In some embodiments R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl. In some embodiments R3 is 1-(ethoxycarbonyl)propyl.

Generally R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl, C3-6 cycloalkyl, aryl or heterocycle. Usually R4 is C1-8 alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl. In some embodiments R4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl. In some embodiments R4 is n-butyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl. In some embodiments R4 is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

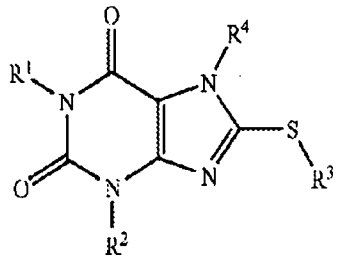
Generally R5 is C2-4 alkyl. Usually R5 is unsubstituted C2-4 alkyl. In some embodiments R5 is ethyl.

Generally R6 is C2-4 alkyl, amido or —COOR7. Usually R6 is unsubstituted C2-4 alkyl, amido or —COOR7. In some embodiments R6 is ethyl, amido or ethoxycarbonyl. In some embodiments R6 is ethoxycarbonyl.

Generally R7 is C1-4 alkyl. Usually R7 is unsubstituted C1-4 alkyl. In some embodiments, R7 is ethyl.

Usually the invention provides compounds having formula I, their enantiomers, diastereoisomers and mixtures thereof (including all possible mixtures of stereoisomers), or pharmaceutically acceptable salts thereof,

(I)



wherein

R1 is hydrogen, C1-6 alkyl optionally substituted by hydroxy, alkoxy, cyano, ethynyl, alkoxycarbonyl or acyl;

R2 is hydrogen or unsubstituted C1-4 alkyl;

R3 is a group of formula —CHR5R6 or a benzyl group;

R4 is C1-8 alkyl optionally substituted by cyclohexyl, phenyl, bromophenyl, aminophenyl, methoxyphenyl, nitrophenyl, aminosulfonylphenyl, 3,5-dimethylisoxazol-4-yl, 5-nitro-2-furyl or ethoxycarbonyl;

R5 is unsubstituted C2-4 alkyl;

R6 is unsubstituted C2-4 alkyl, amido or —COOR7;

R7 is unsubstituted C1-4 alkyl;

with the proviso that when R1 is hydrogen, R2 is methyl, R3 is —CHR5R6, R6 is ethoxycarbonyl and R5 is ethyl, then R4 is different from n-propyl, i-propyl, n-pentyl, n-heptyl, 3-bromobenzyl, 4-chlorobenzyl, 4-methylbenzyl or 2-phenylethyl.

In the above embodiment, sometimes, when R3 is a benzyl group, then R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, sometimes, when R3 is a group of formula —CHR5R6, then R4 is C1-8 alkyl optionally substituted by C3-6 cycloalkyl, aryl or heterocycle.

In one embodiment,

R1 is hydrogen, methyl, cyanomethyl, 2-ethoxy-2-oxoethyl, 2-methoxyethyl, n-propyl, 2-oxopropyl, 3-hydroxypropyl, 2-propynyl, n-pentyl or n-hexyl;

R2 is hydrogen, methyl or n-butyl;

R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl;

R4 is n-butyl, i-butyl, n-pentyl, n-hexyl, cyclohexylmethyl, benzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, 4-(aminosulfonyl)benzyl, 1-phenylethyl, 2-phenylethyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl;

with the proviso that when R1 is hydrogen, R2 is methyl and R3 is 1-(ethoxycarbonyl)propyl, then R4 is different from n-pentyl, 3-bromobenzyl or 2-phenylethyl.

In the above embodiment, sometimes, when R3 is 3-bromobenzyl, then R4 is C1-8 alkyl optionally substituted by alkoxycarbonyl.

In the above embodiment, sometimes, when R3 is 3-pentyl, 1-(aminocarbonyl)propyl or 1-(ethoxycarbonyl)propyl, then R4 is different from 1-(ethoxycarbonyl)propyl.

In a more preferred embodiment, R1 is hydrogen, methyl, cyanomethyl, 2-methoxyethyl, n-propyl, 3-hydroxypropyl or 2-propynyl;

R2 is methyl;

R3 is 3-pentyl, 1-(aminocarbonyl)propyl, 1-(ethoxycarbonyl)propyl or 3-bromobenzyl;

R4 is n-butyl, n-hexyl, benzyl, 3-bromobenzyl, 3-methoxybenzyl, 3-nitrobenzyl, 3-aminobenzyl, (3,5-dimethylisoxazol-4-yl)methyl, (5-nitro-2-furyl)methyl or 1-(ethoxycarbonyl)propyl;

with the proviso that when R1 is hydrogen, R2 is methyl and R3 is 1-(ethoxycarbonyl)propyl, then R4 is different from 3-bromobenzyl.

In the above embodiment, sometimes, when R3 is 3-bromobenzyl, then R4 is 1-(ethoxycarbonyl)propyl;

In the above embodiment, sometimes, when R3 is 3-pentyl, 1-(aminocarbonyl)propyl or 1-(ethoxycarbonyl)propyl, then R4 is different from 1-(ethoxycarbonyl)propyl;

In one embodiment, R1 is hydrogen; R2 is methyl; R3 is 1-(ethoxycarbonyl)propyl; and R4 is 3-methoxybenzyl, 3-nitrobenzyl or (5-nitro-2-furyl)methyl.

A further embodiment consists in compounds wherein R2 is methyl, R3 is a group of formula —CHR5R6 with R5 being C2-4 alkyl, R6 being amido or —COOR7 and R7 being methyl or ethyl.

In some embodiments, compounds are ethyl 2-[(7-benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-ethoxy-2-oxoethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-methoxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(2-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(cyanomethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-propyl-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-oxopropyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(3-hydroxypropyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-propynyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-({7-[4-(aminosulfonyl)benzyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyl 2-{[7-(4-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(cyclohexylmethyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[1,3-dimethyl-2,6-dioxo-7-(1-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[1,3-dimethyl-2,6-dioxo-7-(2-

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

In some embodiments compounds are: ethyl 2-[(7-benzyl-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(2-methoxyethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(cyanomethyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-propyl-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-1-(3-hydroxypropyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-1-(2-propynyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[7-(3-aminobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-({7-[(3,5-dimethylisoxazol-4-yl)methyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-

yl}thio)butanoate; ethyl 2-({3-methyl-7-[(5-nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate; ethyl 2-[(7-butyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; ethyl 2-[(7-hexyl-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)thio]butanoate; 2-{[7-(3-bromobenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanamide; 7-(3-bromobenzyl)-8-[(1-ethylpropyl)thio]-3-methyl-3,7-dihydro-1H-purine-2,6-dione; and ethyl 2-{8-[(3-bromobenzyl)thio]-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-7H-purin-7-yl}butanoate.

In some embodiments compounds are: ethyl 2-{[7-(3-methoxybenzyl)-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; ethyl 2-{[3-methyl-7-(3-nitrobenzyl)-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]thio}butanoate; and ethyl 2-({3-methyl-7-[(5-nitro-2-furyl)methyl]-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl}thio)butanoate.

The acid addition salt form of a compound of formula I that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, trifluoroacetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like.

The compounds of formula I containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

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

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

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

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

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

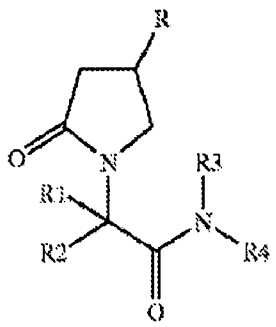
In some embodiments, the compound includes optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives. In some embodiments, those compounds are alkyl amides derivatives substituted on the positions 4 and/or 5 of the pyrrolidone ring. Examples of optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives include, but are not limited to, compounds such as (2S)-2-[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide, (2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]butanamide, (2S)-2-[(4S)-2-oxo-4-propylpyrrolidinyl]butanamide, and (2S)-2-[4-(3-azidophenyl)-2-oxopyrrolidin-1-yl]butanamide.

In some embodiments, the compounds further include optionally substituted N-alkylated 2-oxo-piperidinyl derivatives. In some embodiments, those compounds are alkyl amides derivatives substituted on the position 4 and/or 5 and/or 6 of the 2-oxo-piperidinyl ring. Examples of optionally substituted N-alkylated 2-oxo-pyrrolidine derivatives include, but are not limited to, compounds such as those referred to in international patent application PCT/EP02/05503 such as (2S)-2-[5-

(iodomethyl)-2-oxo-1-piperidinyl]butanamide, (2S)-2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-5-phenyl-1-piperidinyl]butanamide, (2S)-2-[4-(iodomethyl)-2-oxo-1-piperidinyl]butanamide, and (2S)-2-[4-(2-fluoro-2-methylpropyl)-2-oxo-1-pyrrolidinyl]butanamide.

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

(I)



wherein

R represents hydrogen or hydroxy;

R1 and R2 represent independently hydrogen or an alkyl group of 1-4 carbon atoms; and

R3 and R4 represent independently hydrogen, an alkyl group of 1-4 carbon atoms or —(CH2)n—NR5R6 wherein n is 1, 2 or 3 and R5 and R6 represent independently hydrogen or an alkyl group of 1-4 carbon atoms.

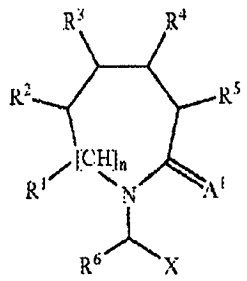
An example of such an acetam compound includes, but is not limited to, a compound of formula I wherein R, R1, R2, R3 and R4 are hydrogen, 2-oxo-pyrrolidineacetamide, known by the generic name piracetam as described in UK Patents Nos. 1,039,113 and 1,309,692.

In some embodiments, the compounds also include optionally substituted N-alkylated 2-oxo-azepanyl derivatives. Preferably, those compounds are alkyl amides derivatives substituted on the positions 4 and/or 5 and/or 6 and/or 7 of the 2-oxo-azepanyl ring. Examples of optionally substituted N-alkylated 2-oxo-azepanyl derivatives include, but are not limited to, compounds such as those referred to in international patent application PCT/EP02/05503 such as 2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide.

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

This invention provides novel compounds of the formula I

(I)



wherein

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

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

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

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

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

R<6 > is hydrogen, alkyl, aryl or -CH2-R<6a > wherein R<6a > is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

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

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

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

In the above formula, at least one substituent R<1 > to R<5 > is different from hydrogen. Some non-substituted compounds are referred to in U.S. Pat. Nos. 5,468,733 and 5,516,759. U.S. Pat. No. 5,468,733 discloses non-ring substituted 2-oxo-1-pyrrolidinyl and 2-oxo-1-piperidinyl derivatives as inhibitors of the oncogene Ras protein. In particular, these compounds block the ability of Ras to

transform normal cells to cancer cells, and therefore can be included in several chemotherapeutic compositions for treating cancer.

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

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

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

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

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

The term "acyl derivative", as used herein, represents a radical derived from carboxylic acid and thus is defined as including groups of the formula R<11> -CO-, wherein R<11 > is as defined above and may also be hydrogen. Preferred are acyl

derivatives of formula -COR<11 > wherein R<11 > is selected from hydrogen, C1-12 alkyl, C2-12 alkenyl, C2-12 alkenyl, heterocyle and aryl. Non-limiting examples are formyl, acetyl, propionyl, isobutyryl, valeryl, lauroyl, heptanedioyl, cyclohexanecarbonyl, crotonoyl, fumaroyl, acryloyl, benzoyl, naphthoyl, furoyl, nicotinoyl, 4-carboxybutanoyl, oxalyl, ethoxalyl, cysteinyl, oxamoyl.

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

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

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

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

In some embodiments are alkyl groups are hydroxymethyl, propyl, butyl, 2,2,2-trifluoroethyl, 2-bromo-2,2-difluoroethyl, 2-chloro-2,2-difluoroethyl, 3,3,3-

trifluoropropyl, cyclopropylmethyl, iodomethyl, azidomethyl, 2,2-difluoropropyl, 2-iodo-2,2-difluoroethyl.

The term "lower alkyl", as used herein, and unless otherwise specified, refers to C1 to C7 saturated straight, branched or cyclic hydrocarbon. Non limiting examples are methyl, ethyl, propyl, isopropyl, butyl, tertiobutyl, pentyl, cyclopropyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methypentyl, 2,2-dimethylbutyl, optionally substituted with any suitable group, including but not limited to one or more moieties selected from groups as described above for the alkyl groups. Preferably, lower alkyl is methyl.

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

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

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

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

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

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

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

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

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

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

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

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

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

The term "nitro", as used herein, represents a group of the formula -NO2.

The term "nitrooxy", as used herein, represents a group of the formula -ONO2.

The term "amino", as used herein, represents a group of the formula -NH2.

The term "azido", as used herein, represents a group of the formula -N3.

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

The term "sulfonic acid", as used herein, represents a group of the formula -SO3H.

The term "sulfonamide", as used herein, represents a group of the formula -SO2NH2.

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

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

The term "amido" is defined as including a group of formula -CONH2 or -CONHR<11 > or -CONR<11> R<12 > wherein R<11 > rand R<12 > are as defined above.

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

imidazolidinyl, morpholino, morpholinyl, 1-oxaspiro(4.5)dec-2-yl, pyrrolidinyl, 2-oxo-pyrrolidinyl, sugar moieties (i.e. glucose, pentose, hexose, ribose, fructose, which may also be substituted) optionally substituted by alkyl or as described above for the alkyl groups. The term "heterocycle" also includes bicyclic, tricyclic and tetracyclic, spiro groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring or where a monocyclic heterocyclic group is bridged by an alkylene group, such as quinuclidinyl, 7-azabicyclo(2.2.1)heptanyl, 7-oxabicyclo(2.2. 1)heptanyl, 8-azabicyclo(3.2.1)octanyl.

The heterocycle may be selected from triazolyl, tetrazolyl, pyrrolidinyl, pyridyl, 1-oxidopyridyl, thiomorpholinyl, benzodioxolyl, furyl, oxazolyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl and piperazinyl, each optionally substituted by one or more substituents selected from halogen, alkyl, substituted alkyl, alkoxy, nitro, amino, acyl and phenyl. In some embodiments the heterocycle is selected from tetrazolyl, pyrrolidinyl, pyridyl, furyl, pyrrolyl, thiazolyl and thienyl, each optionally substituted by one or more substituents selected from halogen, alkyl, halogen substituted alkyl, acyl, alkoxy, nitro, amino and phenyl, and especially from 2-and 3-thienyl, optionally substituted by one or more halogen, acyl such as formyl, cyano and/or lower alkyl, such as methyl.

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

The acid addition salt form of a compound of formula (I) that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic,

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

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt form, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

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

Many of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers).

Furthermore, certain compounds of formula I which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the invention includes both mixture and separate individual isomers.

Multiple substituents on the piperidinyl or the azepanyl ring can also stand in either cis or trans relationship to each other with respect to the plane of the piperidinyl or the azepanyl ring.

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

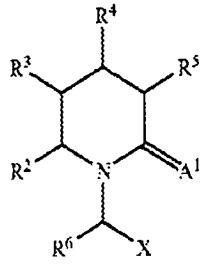
With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically. The invention also includes within its scope prodrug forms of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

The term "prodrug" as used herein includes compound forms which are rapidly transformed in vivo to the parent compound according to the invention, for example, by hydrolysis in blood. Prodrugs are compounds bearing groups which are modified by biotransformation prior to exhibiting their pharmacological action. Such groups include moieties which are readily oxidised, cyclised or cleaved, which compound after biotransformation remains or becomes pharmacologically active. For example, metabolically cleavable groups form a class of groups well known to practitioners of the art. They include, but are not limited to such groups as alkanoyl (i.e. acetyl, propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aroyl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate, sulfonyl, sulfinyl and the like. The compounds bearing the biotransformable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the biotransformable group. T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A.C.S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

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

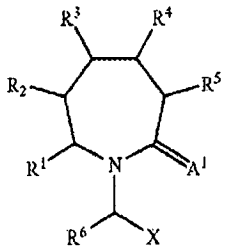
According to one embodiment, the present invention relates to a compound of formula I as defined above wherein n represents 0. The compound is a 6-ring structure (2-thioxo- or 2-oxo-piperidinyl derivative) wherein R<1 > is not existent since n=0, and is depicted by the formula (I-A).

(I-A)



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

(I-B)



According to one embodiment, the invention relates to said compound as defined above wherein n=0, R<3 > and/or R<4 > are different from hydrogen and R<2 > and R<5 > represent hydrogen.

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

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

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein A<1 > represents an oxygen atom. We hereby refer to 2-oxo-piperidinyl or 2-oxo-azepanyl derivatives.

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein X is CONR<7> R<8> , especially CONH2. We hereby refer to amido derivatives of 2-oxo(or thioxo)-piperidinyl or 2-oxo(or thioxo)-azepanyl.

According to another embodiment, the present invention relates to compounds of formula I according to the invention as defined above wherein R<6 > represents hydrogen, C1-4 alkyl, or a CH2-R<6a > group wherein R<6a > represents a heterocycle. Most preferably R<6 > is a C1-4 alkyl, especially ethyl. When R<6 > is ethyl we refer to 2-(2-oxo(or thioxo)-1-piperidinyl)butanamide or 2-(2-oxo(or thioxo)-1-azepanyl)butanamide derivatives.

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

According to one embodiment, the present invention relates to a compound as defined above wherein R<2 > when n=1, R<3 > and R<4 > are the same or different and each is independently hydrogen, halogen, nitro, nitrooxy, cyano, carboxy, amido, sulfonic acid, sulfonamide, alkyl, alkenyl, alkynyl, ester, ether, aryl, heterocycle, acyl derivative, sulfonyl derivative or sulfinyl derivative:

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

R<6 > is hydrogen, alkyl, aryl or -CH2-R<6a > wherein R<6a > is aryl, heterocycle, halogen, hydroxy, amino, nitro or cyano;

provided that, when R<6 > is hydrogen, X is -CONR<7> R<8 > and that the compound is

neither methyl (2R)-2-[(6R)-6-methyl-2-oxoazepanyl]-3-phenylpropanoate nor methyl (2S)-2-[(4R)-4-methyl-2-oxoazepanyl]-3-phenylpropanoate.

According to this embodiment, the compound is generally such that when R<6 > is benzyl, X is -COOCH3 and n=1, R<2 > is different from methyl when R<3 > and R<4 > are both hydrogen and R<4 > is different from methyl when R<2 > and R<3 > are both hydrogen.

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

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

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

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

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

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

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

According to another embodiment, the present invention relates to a compound as defined above, wherein R<2 > when n=1, R<3 > and R<4 > are the same or different and each is independently hydrogen;

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

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

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

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

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

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R<3 > and R<4 > when n=0, represents independently C1-4-alkyl or C3-7-cycloalkyl, optionally substituted by one or more halogen, hydroxy, lower alkyl and/or azido.

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

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R3 and R<4 > when n=0, represents independently ethynyl, propynyl or butynyl, optionally substituted by one or more halogen and/or lower alkyl.

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

According to another embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<2> , R<3 > and R<4 > when n=1 or from the group R<3 > and R<4 > when n=0, represents independently 2- or 3-thienyl, optionally substituted by one or more halogen, acyl, cyano or/and lower alkyl.

According to a particular embodiment, the present invention relates to a compound as defined above wherein at least one of the R substituents chosen from the group R<3> , R<4 > and R<2 > when n=1 or from the group R<3 > and R<4 > when n=0, is hydroxymethyl, propyl, butyl, 3,3,3-trifluoropropyl, 2,2,2-trifluoroethyl,

cyclopropylmethyl, iodomethyl, azidomethyl, 2-thienyl, 3-thienyl, phenyl, 3-chlorophenyl, 3-azidophenyl, 2,2-difluorovinyl, 2,2-dibromovinyl, 2,2-dichlorovinyl, 2-ethynyl, 5-methyl-2-thienyl, 5-formyl-2-ethynyl, 5-cyano-2-thienyl, 3-bromo-2-thienyl, 4-methyl-2-thienyl, 3,3,3-trifluoro-1-propynyl, 1-propynyl, cyclopropylethynyl, 3-methyl-1-butynyl, 1-butynyl, 2,2-difluoropropyl, 2-chloro-2,2-difluoroethyl, 2-bromo-2,2-difluoroethyl and 2-iodo-2,2-difluoroethyl.

According to yet another embodiment, the present invention relates to a compound as defined above wherein R<1> , R<2> , R<4 > and R<5 > are hydrogen.

According to another embodiment, the present invention relates to a compound as defined above wherein R<1> , R<2> , R<3 > and R<5 > are hydrogen.

According to another embodiment, the present invention relates to a compound as defined above wherein n=1 and R<1> , R<3> , R<4 > and R<5 > are hydrogen.

In all the above-mentioned scopes when the carbon atom to which R<6 > is attached is asymmetric it may be in the "S"-configuration.

Representative compounds of this invention as defined above are selected from the group consisting of 2-[5-(hydroxymethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-5-propyl-1-piperidinyl)butanamide, 2-12-oxo-5-(3,3,3-trifluoropropyl)-1-piperidinyl]butanamide, 2-[5-(cyclopropylmethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(iodomethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(azidomethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-5-phenyl-1-piperidinyl)butanamide, 2-[2-oxo-5-(2-thienyl)-1-piperidinyl]butanamide, 2-[2-oxo-5-(3-thienyl)-1-piperidinyl]butanamide, 2-[5-(3-chlorophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(3-azidophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-difluorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-dibromovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-dichlorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-(5-ethynyl-2-oxo-1-piperidinyl)butanamide, 2-[5-(5-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(5-formyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(5-cyano-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(3-bromo-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(4-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[2-oxo-5-(3,3,3-trifluoro-1-propynyl)-1-piperidinyl]butanamide, 2-[2-oxo-5-(1-propynyl)-1-

piperidinyl]butanamide, 2-[5-(cyclopropylethynyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(3-methyl-1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2,2-difluoropropyl)-2-oxo 1-piperidinyl]butanamide, 2-[5-(2-chloro-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(2-bromo-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(hydroxymethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-4-propyl-1-piperidinyl)butanamide, 2-[2-oxo-4-(3,3,3-trifluoroproyl)-1-piperidinyl]butanamide, 2-14-(cyclopropylmethyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(iodomethyl)-2-oxo-1-piperldinyl]butanamide, 2-[4-(azidomethyl)-2-oxo-1-piperidinyl]butanamide, 2-(2-oxo-4-phenyl-1-piperidinyl)butanamide, 2-12-oxo-4-(2-thienyl)-1-piperidinyl]butanamide, 2-[2-oxo-4-(3-thienyl)-1-piperidinyl]butanamide, 2-[4-(3-chlorophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(3-azidophenyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-difluorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-dibromovinyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-dichlorovinyl)-2-oxo-1-piperidinyl]butanamide, 2-(4-ethynyl-2-oxo-1-piperidinyl)butanamide, 2-[4-(5-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(5-formyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(5-cyano-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(3-bromo-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(4-methyl-2-thienyl)-2-oxo-1-piperidinyl]butanamide, 2-[2-oxo-4-(3,3,3-trifluoro-1-propynyl)-1-piperidinyl]butanamide, 2-[2-oxo-4-(1-propynyl)-1-piperidinyl]butanamide, 2-[4-(cyclopropylethynyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(3-methyl-1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(1-butynyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2-difluoropropyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2-chloro-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-14-(2-bromo-2,2-difluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[4-(2,2,2-trifluoroethyl)-2-oxo-1-piperidinyl]butanamide, 2-[5-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-5-propyl-1-azepanyl)butanamide, 2-[2-oxo-5-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide, 2-(5-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(iodomethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(azidomethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-5-phenyl-1-azepanyl)butanamide, 2-[2-oxo-5-(2-

thienyl)-1-azepanyl]butanamide, 2-[2-oxo-5-(3-thienyl)-1-azepanyl]butanamide, 2-[5-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide, 2-(5-ethynyl-2-oxo-1-azepanyl)butanamide, 2-[5-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[2-oxo-5-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide, 2-[2-oxo-5-(1-propynyl)-1-azepanyl]butanamide, 2-[5-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[5-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-6-propyl-1-azepanyl)butanamide, 2-[2-oxo-6-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide, 2-[6-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(iodomethyl)-2-oxo-1-azepanyl]butanamide, 2-16-(azidomethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-6-phenyl-1-azepanyl)butanamide, 2-[2-oxo-6-(2-thienyl)-1-azepanyl]butanamide, 2-[2-oxo-6-(3-thienyl)-1-azepanyl]butanamide, 2-[6-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide, 2-(6-ethynyl-2-oxo-1-azepanyl)butanamide, 2-[6-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(5-cyano-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(4-methyl-2-thienyl]-2-oxo-1-azepanyl]butanamide, 2-[2-oxo-6-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide, 2-[2-oxo-6-(1-propynyl)-1-azepanyl]butanamide, 2-[6-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[6-

(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2-chloro-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[6-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(hydroxymethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-4-propyl-1-azepanyl)butanamide, 2-[2-oxo-4-(3,3,3-trifluoropropyl)-1-azepanyl]butanamide, 2-14-(cyclopropylmethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(iodomethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(azidomethyl)-2-oxo-1-azepanyl]butanamide, 2-(2-oxo-4-phenyl-1-azepanyl)butanamide, 2-[2-oxo-4-(2-thienyl)-1-azepanyl]butanamide, 2-[2-oxo-4-(3-thienyl)-1-azepanyl]butanamide, 2-f4-(3-chlorophenyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(3-azidophenyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-difluorovinyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-dibromovinyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-dichlorovinyl)-2-oxo-1-azepanyl]butanamide, 2-(4-ethynyl-2-oxo-1-azepanyl)butanamide, 2-[4-(5-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(5-formyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[<4> -(5-cyano-<2> -thienyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(3-bromo-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(4-methyl-2-thienyl)-2-oxo-1-azepanyl]butanamide, 2-[2-oxo-4-(3,3,3-trifluoro-1-propynyl)-1-azepanyl]butanamide, 2-[2-oxo-4-(1-propynyl)-1-azepanyl]butanamide, 2-[4-(cyclopropylethynyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(3-methyl-1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(1-butynyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2-difluoropropyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2-chloro-2,2-difluoroethyl]-2-oxo-1-azepanyl]butanamide, 2-[4-(2-bromo-2,2-difluoroethyl)-2-oxo-1-azepanyl]butanamide, 2-[4-(2,2,2-trifluoroethyl)-2-oxo-1-azepanyl]butanamide.

Results have been obtained with the following compounds:

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

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

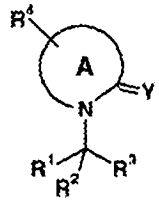
2-(2-oxo-5-phenyl-1-piperidinyl]butanamide,

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

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

xv) International Patent Application Publication No. WO2008/132139

In some embodiments, the compounds are of formula (I) as follows:



(I)

wherein

Y is O or S. In some embodiments Y is O. R1 is hydrogen or C-|.g alkyl;

R2 is hydrogen;

R3 is -CONR5R6, -COR7, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; R5, R6 are the same or different and are independently selected from hydrogen and C-|_6 alkyl;

R7 is C<;|_6 alkyl;

A is a monocyclic or bicyclic heterocyclic moiety selected from the group consisting of imidazolidin-1-yl, 1 ,3-oxazolidin-3-yl, 2,5-dihydro-1 H-pyrrol-1-yl, 1 ,3-thiazol-3(2H)-yl, 1 ,3- thiazolidin-3-yl, piperidin-1-yl, azepan-1-yl, 5,6-dihydro-4H-thieno[3,2-b]pyrrol-4-yl, hexahydro-4H-thieno[3,2-b]pyrrol-4-yl, 2,3-dihydro-1 H-thieno[3,4-b]pyrrol-1-yl, 1 ,3- benzothiazol-3(2H)-yl, 1 ,3-benzoxazol-3(2H)-yl, pyrazolo[1 ,5-a]pyridin-1 (2H)-yl, 3,4- dihydroisoquinolin-2(1 H)-yl, 3,4-dihydroquinolin-1 (2H)-yl, 1 ,3,4,5-tetrahydro-2H-2- benzazepin-2-yl, 1 ,2,4,5-tetrahydro-3H-3-benzazepin-3-yl; R4 is either R^a or R^b depending on whether A being is a monocyclic or a bicyclic heterocycle:

where A is a monocyclic heterocyclic moiety, R^ is R^a which is selected from the group consisting of hydrogen; C-|.g alkyl optionally substituted by a substituent selected from halogen, C-1.4 alkoxy, C-1.4 alkylthio, azido, nitrooxy or an aryl; C2-6 alkenyl optionally substituted by halogen; C2-6 alkynyl optionally substituted by halogen; azido; alkoxycarbonylamino; arylsulfonyloxy; a substituted or unsubstituted aryl; or a 3-8 membered substituted or unsubstituted heterocycle;

where A is a bicyclic heterocyclic moiety R^ is R^ which is selected from the group comprising or consisting of hydrogen; nitro; cyano; halogen; heterocycle; amino; aryl; C-|.g alkyl optionally substituted by at least one halogen; or C-|.g alkoxy optionally substituted by at least one halogen;

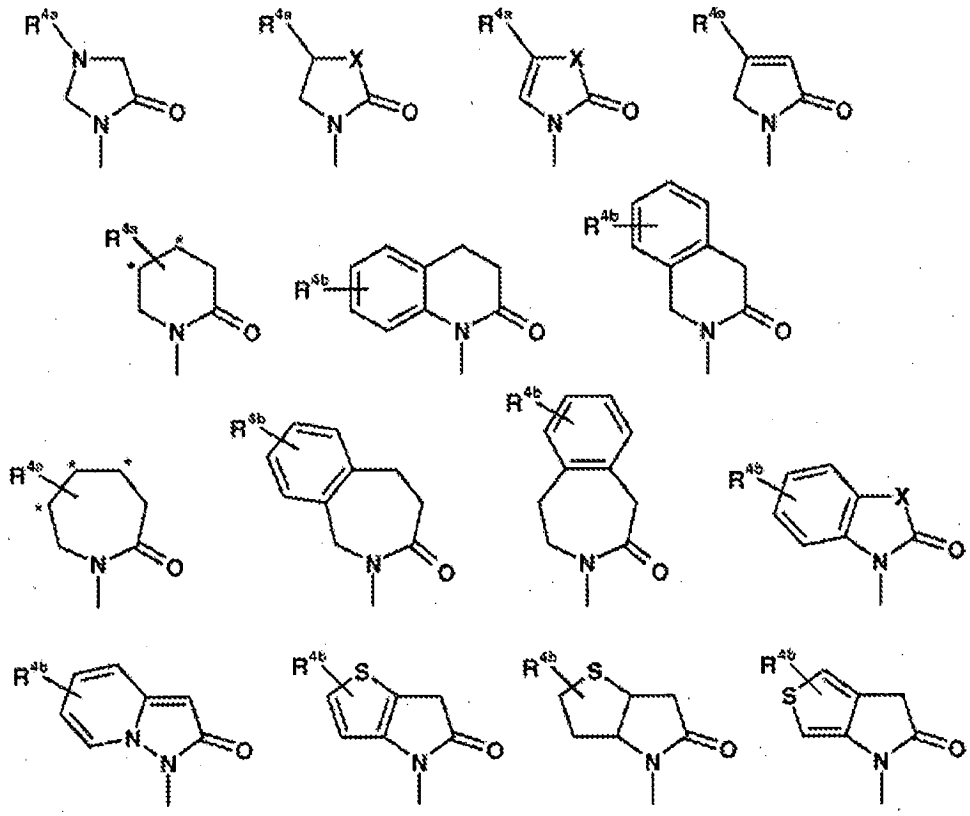
In some embodiments the compounds are as follows:

For compounds where A=Y is selected from a 2-oxo-piperidin-1-yl, a 2-oxo-azepan-1-yl, a 2-oxo-1 ,3-benzothiazol-3(2H)-yl or a 2-oxo-1 ,3-benzoxazol-3(2H)- yl, R3 must beselected from an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl.

For compounds where A=Y is a 5-oxoimidazolidin-1-yl, R^ and R^ are hydrogen, R3 is -CONR5R6, R5 anc| R6 are as above defined, then R^a may not be an alkyl, aralkyl or substituted aralkyl.

Where A=Y is either of a 2-oxo-piperidin-1-yl and a 2-oxo-azepan-1-yl, R^ , R^ and R^a are all hydrogen, then R^ could not be a 2-phenylimidazo[1 ,2-a]pyridin-3-yl.

In a specific embodiment A=Y is selected from the list consisting of:



wherein X is O or S, in a more specific embodiment O; in another embodiment, X is S.

The asterisks in the above illustration indicate the attachment sites of the substituent R^a.

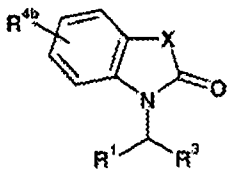
In a specific embodiment, when R^ is -CONR5R6 and R^ is C-µg alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

In a specific embodiment R^ is hydrogen, methyl, ethyl and R^ is hydrogen. In a specific embodiment R3 is -CONH2.

In a further specific embodiment R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5- yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a specific embodiment R^a is a C-|.g alkyl which may optionally be substituted by a halogen; or a phenyl.

In another specific embodiment R^b is hydrogen, halogen, nitro, cyano or a C-μg alkyl optionally substituted by a halogen.

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



(I-E)

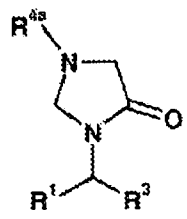
wherein

X is O or S;

R-I is hydrogen or C-|.g alkyl, in a more specific embodiment hydrogen;

R3 is an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; R^b is hydrogen; nitro; cyano; halogen; C-|.g alkyl optionally substituted by halogen; C-|.g alkoxy optionally substituted by halogen.

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



(I-A)

wherein

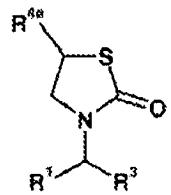
R1 is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R^ is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl, preferably R^ is -CONH2.

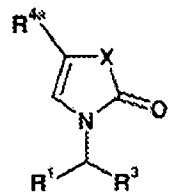
R^a is either hydrogen or an aryl; with the proviso that 2-(5-oxoimidazolidin-1-yl)acetamide is excluded. Preferably R^a is an aryl, e.g. a phenyl which may be substituted preferably by halogen, nitro, alkoxy, in particular by nitro.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R1 and R^ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in novel compounds having the formula (I-B1 or I-B2), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-B1)



(I-B2)

wherein X in formula (I-B2) is either S or O, in a more specific embodiment S;

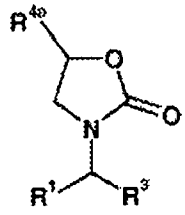
R1 is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; in a more specific embodiment R^ is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; preferably R^ is -CONH2

R^a is hydrogen; C-|.g alkyl optionally substituted by halogen or C-1.4 alkoxy; an aryl; or C2.g alkenyl optionally substituted by halogen. Preferably, R^a is C-|.g alkyl optionally substituted by halogen or C2-6 alkenyl optionally substituted by halogen or an aryl. In a more specific embodiment R^a is C-|.g alkyl optionally substituted by halogen or aryl.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

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



(I-B3)

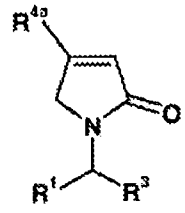
wherein

R1 is either hydrogen or C-μg alkyl, preferably hydrogen, methyl or ethyl; more preferably R1 is ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; preferably R^ is -CONH2 R^a is C-|_5 alkyl optionally substituted by halogen or C-1.4 alkoxy; an aryl; or C2_g alkenyl optionally substituted by halogen. Preferably, R^a is C-|.g alkyl optionally substituted by halogen or C2_g alkenyl optionally substituted by halogen.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

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



(I-C)

wherein

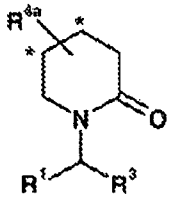
R1 is hydrogen or C-|.g alkyl, in particular hydrogen, methyl or ethyl.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in particular R^ is -CONH2

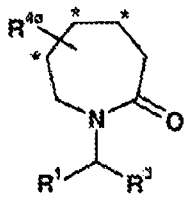
R^a is methyl, ethyl, butyl optionally substituted by halogen or C-1.4 alkoxy, an unsubstituted phenyl or a phenyl substituted by halogen, a C-|.g alkyl optionally substituted by halogen or a C-1.4 alkoxy; or R^a is a C2-6 alkenyl optionally substituted by halogen. Preferably, R^a is methyl, optionally substituted by halogen, an unsubstituted phenyl or a phenyl substituted by halogen.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R1 and Rβ are attached is preferably in the "S"-configuration.

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



(I-D1)



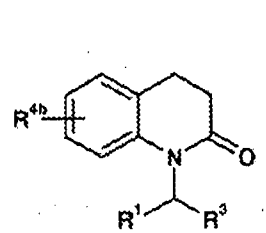
(I-D2)

wherein

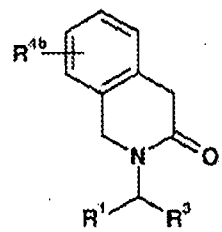
R-I is hydrogen or C-|.g alkyl, in particular hydrogen; R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl. In one embodiment, R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a more specific embodiment, R^ is 1 H-imidazol-1-yl, 1 H- imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl; R^a is hydrogen, C-|.g alkyl optionally substituted by halogen or C-1.4 alkoxy; aryl; or C2- g alkenyl optionally substituted by halogen. In a specific embodiment, R^a is C-|.g alkyl optionally substituted by halogen; aryl; or C2-6 alkenyl optionally substituted by halogen. In a more specific embodiment R^a is C-|.g alkyl optionally substituted by halogen; or aryl; e.g, propyl or phenyl;

with the proviso that when R^ and R^a are hydrogen, R^ is not 2-phenylimidazo[1 ,2- a]pyridin-3-yl.

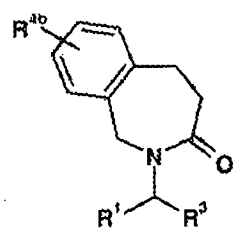
A further aspect of the present invention consists in compounds having the formula (I-F1 , I-F2 or I-F3), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-F1)



(I-F2)



(I-F3)

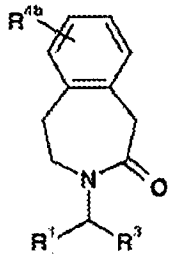
wherein

R-I is hydrogen or C-|.g alkyl, preferably hydrogen, methyl or ethyl; more preferably, R^ is hydrogen.

R3 is -CONH2, an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl; in a more specific embodiment R3 is -CONH2, 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. R^b is hydrogen; halogen; nitro; cyano; C1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen. In a more specific embodiment R^ is hydrogen, halogen or cyano, more specifically halogen.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R1 and Rβ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in compounds having the formula (I-F4), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,



(I-F4)

wherein

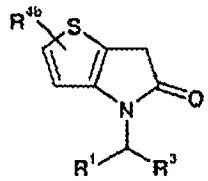
R-I is hydrogen or C-|.g alkyl, preferably hydrogen;

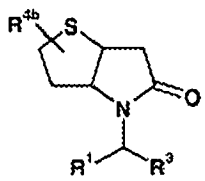
R3 is an imidazolyl, an imidazopyridinyl or an imidazopyridazinyl; more specifically R^ is 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. More specifically R^ is 1 H-imidazol-4-yl or imidazo[1 ,2- a]pyridin-3-yl.

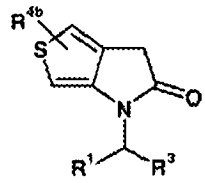
R^b is hydrogen; halogen; nitro; cyano; C-1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen; specifically R^ is hydrogen, halogen or cyano,.

In a particular embodiment, when R^ is -CONH2 and R^ is C-|.g alkyl, the carbon atom to which R-I and R^ are attached is preferably in the "S"-configuration.

A further aspect of the present invention consists in compounds having either of the formula (I-G1 , I-G2 or I-G3), their geometrical isomers, enantiomers, diastereomers and mixtures, or a pharmaceutically acceptable salt thereof,


(I-G1)


(I-G2)


(I-G3)

wherein

R-I is hydrogen or C-|.g alkyl; preferably hydrogen;

R3 is -CONH2, an imidazolyl, an imidazopyridinyl, an imidazopyridazinyl; in a more specific embodiment R^ is -CONH2, 1 H-imidazol-1-yl, 1 H-imidazol-4-yl, 1 H-imidazol-5-yl, imidazo[1 ,2-a]pyridin-3-yl or imidazo[1 ,2-b]pyridazin-3-yl. In a even more specific embodiment R3 is an 1 H-imidazol-4-yl or imidazo[1 ,2-a]pyridin-3-yl;

R4D js hydrogen; halogen; C-1.4 alkyl optionally substituted by halogen; C-1.4 alkoxy optionally substituted by halogen.

Specific compounds of the present invention are those selected from the group consisting of: (2S)-2-[3-(4-nitrophenyl)-5-oxoimidazolidin-1 -yl]butanamide; (2S)-2-[3-(2,4- dinitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-(5-oxo-3-phenylimidazolidin-1- yl)butanamide; 2-[5-(iodomethyl)-2-oxo-1 ,3-oxazolidin-3-yl]butanamide; 2-(2-oxo-2,5- dihydro-1 H-pyrrol-1-yl)butanamide; 2-(2-oxo-4-phenyl-2,5-dihydro-1 H-pyrrol-1- yl)butanamide; 2-(4-methyl-2-oxo-2,5-dihydro-1 H-pyrrol-1-yl)butanamide; (2S)-2-(2-oxo-5- propyl-1 ,3-thiazol-3(2H)-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazol-3(2H)- yl)propanamide; 2-(5-butyl-2-oxo-1 ,3-thiazolidin-3-yl)butanamide; 2-(5-butyl-2-oxo-1 ,3- thiazolidin-3-yl)propanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)propanamide; 2-(2- oxo-5-propyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazolidin-3-yl)propanamide; (2S)-2-[2-oxo-5-(2,2,2- trifluoroethyl)-1 ,3-thiazolidin-3-yl]butanamide; 1-{[6-chloro-2-(trifluoromethyl)imidazo[1 ,2- b]pyridazin-3-yl]methyl}piperidin-2-one; 1 -(1 H-imidazol-4-ylmethyl)-5-propylpiperidin-2- one; 1-(1 H-imidazol-1-ylmethyl)-5-propylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3- ylmethyl)-5-propylpiperidin-

2-one; 1-(1 H-imidazol-1-ylmethyl)-5-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-5-phenylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-phenylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-5-ylmethyl)-4- propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-propylpiperidin-2-one; 1-{[6-chloro-2- (trifluoromethyl)imidazo[1 ,2-b]pyridazin-3-yl]methyl}azepan-2-one; 1 -(1 H-imidazol-5- ylmethyl)-5-propylazepan-2-one; 5-propyl-1-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}azepan-2-one; 5-phenyl-1-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3- yl]methyl}azepan-2-one; 1-(1 H-imidazol-5-ylmethyl)-6-propylazepan-2-one; 1-(1 H- imidazol-4-ylmethyl)-4-propylazepan-2-one; 4-(1 H-imidazol-4-ylmethyl)-4,6-dihydro-5H- thieno[3,2-b]pyrrol-5-one; 2-(5-oxo-5,6-dihydro-4H-thieno[3,2-b]pyrrol-4-yl)acetamide; 4- {[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5- one; 4-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}hexahydro-5H-thieno[3,2-b]pyrrol-5-one; 1-(1 H-imidazol-4-ylmethyl)-1 H-thieno[3,4-b]pyrrol-2(3H)-one; 2-(6-chloro- 2-0X0-1 ,3-benzothiazol-3(2H)-yl)acetamide; 6-bromo-3-(1 H-imidazol-1-ylmethyl)-1 ,3- benzothiazol-2(3H)-one; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6- bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6-fluoro-2-oxo-1 ,3-benzothiazol- 3(2H)-yl)acetamide; 2-(6-methyl-2-oxo-1 ,3-benzothiazol-3(2H)-yl)acetamide; 6-fluoro-3- (1 H-imidazol-1-ylmethyl)-1 ,3-benzoxazol-2(3H)-one; 1-(1 H-imidazol-4- ylmethyl)pyrazolo[1 ,5-a]pyridin-2(1 H)-one; 2-(6-chloro-3-oxo-3,4-dihydroisoquinolin- 2(1 H)-yl)propanamide; 5-chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,4-dihydroisoquinolin-3(2H)- one; 2-(6-chloro-2-oxo-3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-bromo-2-oxo-3,4- dihydroquinolin-1 (2H)-yl)acetamide; 1-(1 H-imidazol-4-ylmethyl)-3,4-dihydroquinolin-2(1 H)- one; 2-(6-iodo-2-oxo-3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-cyano-2-oxo-3,4- dihydroquinolin-1 (2H)-yl)acetamide; 7-chloro-2-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin- 3-yl]methyl}-1 ,2,4,5-tetrahydro-3H-2-benzazepin-3-one; 7-chloro-2-(1 H-imidazol-4- ylmethyl)-1 ,2,4,5-tetrahydro-3H-2-benzazepin-3-one; 7-chloro-3-(1 H-imidazol-4-ylmethyl)- 1 ,3,4,5-tetrahydro-2H-3-benzazepin-2-one; and 7-chloro-3-{[2-

(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}-1 ,3,4,5-tetrahydro-2H-3-benzazepin-2- one.

In some embodiments, compounds of the present invention are those selected from the group consisting of: 1-(1 H-imidazol-4-ylmethyl)-5-propylpiperidin-2-one; 1-(1 H-imidazol-1- ylmethyl)-5-propylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3-ylmethyl)-5-propylpiperidin-2- one; 1-(1 H-imidazol-1-ylmethyl)-5-phenylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3- ylmethyl)-4-phenylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-5-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol- 4-ylmethyl)-1 H-thieno[3,4-b]pyrrol-2(3H)-one; 6-bromo-3-(1 H-imidazol-1-ylmethyl)-1 ,3- benzothiazol-2(3H)-one; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; and 5-chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,4-dihydroisoquinolin-3(2H)-one.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly through- out the specification and embodiments unless an otherwise expressly set out definition provides a broader definition.

"C-|_β alkyl" refers to alkyl groups having 1 to 6, or 1 to 4 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert- butyl, n-pentyl, n-hexyl, trifluoromethyl and the like. "Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl). Preferred aryl include phenyl, naphthyl, phenantrenyl and the like.

"Heterocycle" refers to a saturated or unsaturated ring system containing, in addition to carbon atoms, at least one hetero atom, such as nitrogen, oxygen and/or sulfur. "Heterocycle" includes both "heteroaryl" and "heterocycloalkyl".

"Heteroaryl" refers to a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1 ,2,3-triazolyl, 1 ,2,4-triazolyl, 1 ,2,3-oxadiazolyl, 1 ,2,4-oxadia-zolyl, 1 ,2,5-oxadiazolyl, 1 ,3,4-oxadiazolyl,1 ,3,4-

triazinyl, 1 ,2,3-triazinyl, benzofuryl, [2,3- dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazopyridinyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnolinyl, napthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8- tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl,benzoquinolyl, imidazopyrimidinyl, imidazopyridazinyl, imidazothiazolyl or imidazothiadiazolyl.

"C2-6 alkenyl" refers to alkenyl groups preferably having from 2 to 6 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (vinyl, -CH=CH2), n-2-propenyl (allyl, -CH2CH=CH2) and the like.

"C2-6 alkynyl" refers to alkynyl groups preferably having from 2 to 6 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH2C≡CH), and the like.

"C3.8 cycloalkyl" refers to a saturated carbocyclic group of from 3 to 8 carbon atoms having a single ring (e.g., cyclohexyl) or multiple condensed rings (e.g., norbornyl). Preferred cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl and the like.

"Heterocycloalkyl" refers to a C3.8 cycloalkyl group according to the definition above, in which 1 to 3 carbon atoms are replaced by hetero atoms chosen from the group consisting of O, S, NR, R being defined as hydrogen or C-|.g alkyl.

"Alkoxy" refers to the group -O-R where R includes " C-μg alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl".

"Amino" refers to the group -NRR' where each R, R' is independently hydrogen, "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3-8 cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"Amido" refers to the group -C(=O)NRR' where each R, R' is independently hydrogen, " C-|_5 alkyl", " C2-6 alkenyl", " C2-6 alkynyl", " C3.8 cycloalkyl", "heterocycloalkyl", "aryl", "heteroaryl", and where R and R', together with the nitrogen atom to which they are attached, can optionally form a 3-8-membered heterocycloalkyl ring.

"Acylamino" refers to the group -NRC(O)R' wherein R and R' are as defined hereabove for the amino group.

"Ureido" refers to the group -NR"C(O)NRR' wherein R and R' are as defined hereabove for the amino group, and R" is as defined hereabove. "Sulfanyl" refers to the group -SR where R is "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

"Sulfinyl" refers to the group -S(=O)R where R is "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

"Sulfonyl" refers to the group -S(=O)2R where R is "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "C3.8 cycloalkyl", "heterocycloalkyl", "aryl" or "heteroaryl".

"Halogen" refers to fluoro, chloro, bromo and iodo atoms.

"Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like "alkyl", "alkenyl", "alkynyl", "aryl" and "heteroaryl" etc. groups can optionally be substituted with from 1 to 5 substituents selected from the group consisting of "C-|.g alkyl", "C2-6 alkenyl", "C2-6 alkynyl", "cycloalkyl", "heterocycloalkyl", "amino", "amido", "acylamino", "ureido", "aryl", "heteroaryl", "alkoxy", "halogen", cyano, hydroxy, mercapto, nitro, "amido", "sulfanyl", "sulfinyl", "sulfonyl" and the like.

The acid addition salt form of a compound of formula (I) that occurs in its free form as a base can be obtained by treating the free base with an appropriate acid such as an inorganic acid, for example, a hydrohalic such as hydrochloric or hydrobromic, sulfuric, nitric, phosphoric and the like; or an organic acid, such as, for example, acetic, trifluoroacetic, hydroxyacetic, propanoic, lactic, pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic,

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

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active, non-toxic base addition salt forms, e.g. metal or amine salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e.g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

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

Many of the compounds of formula (I) and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem., 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds of formula (I) or mixtures thereof (including all possible mixtures of stereoisomers). With respect to the present invention reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof, unless the particular isomeric form is referred to specifically.

Compounds according to the present invention may exist in different polymorphic forms. Although not explicitly indicated in the above formula, such forms are intended to be included within the scope of the present invention.

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

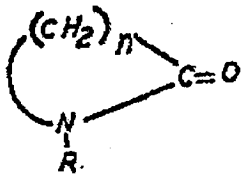
The invention also includes within its scope pro-drug forms of the compounds of formula (I) and its various sub-scopes and sub-groups.

In a specific embodiment, the present invention concerns a compound selected from the group consisting of: (2S)-2-[3-(4-nitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-[3-(2,4-dinitrophenyl)-5-oxoimidazolidin-1-yl]butanamide; (2S)-2-(5-oxo-3- phenylimidazolidin-1 -yl)butanamide; 2-[5-(iodomethyl)-2-oxo-1 ,3-oxazolidin-3- yl]butanamide; 2-(2-oxo-2,5-dihydro-1 H-pyrrol-1-yl)butanamide; 2-(2-oxo-4-phenyl-2,5- dihydro-1 H-pyrrol-1-yl)butanamide; 2-(4-methyl-2-oxo-2,5-dihydro-1 H-pyrrol-1- yl)butanamide; (+)-(2S)-2-(2-oxo-4-propyl-2,5-dihydro-1 H-pyrrol-1-yl)butanamide; (2S)-2- (2-oxo-5-propyl-1 ,3-thiazol-3(2H)-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazol-3(2H)- yl)propanamide; 2-(5-butyl-2-oxo-1 ,3-thiazolidin-3-yl)butanamide; 2-(5-butyl-2-oxo-1 ,3- thiazolidin-3-yl)propanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)propanamide; 2-(2- oxo-5-propyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-phenyl-1 ,3-thiazolidin-3-yl)butanamide; 2-(2-oxo-5-propyl-1 ,3-thiazolidin-3-yl)propanamide; (2S)-2-[2-oxo-5-(2,2,2- trifluoroethyl)-1 ,3-thiazolidin-3-yl]butanamide; 1-{[6-chloro-2-(trifluoromethyl)imidazo[1 ,2- b]pyridazin-3-yl]methyl}piperidin-2-one; 1 -(1 H-imidazol-4-ylmethyl)-5-propylpiperidin-2- one; 1-(1 H-imidazol-1-ylmethyl)-5-propylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3- ylmethyl)-5-propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-5-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-5-phenylpiperidin-2-one; 1-(imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-phenylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-phenylpiperidin-2-one; 1- (imidazo[1 ,2-a]pyridin-3-ylmethyl)-4-propylpiperidin-2-one; 1-(1 H-imidazol-5-ylmethyl)-4- propylpiperidin-2-one; 1-(1 H-imidazol-1-ylmethyl)-4-propylpiperidin-2-one; 1-{[6-chloro-2- (trifluoromethyl)imidazo[1 ,2-b]pyridazin-3-yl]methyl}azepan-2-one; 1 -(1 H-imidazol-5- ylmethyl)-5-propylazepan-2-one; 5-propyl-1-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}azepan-2-one; 1-(1 H-imidazol-5-ylmethyl)-5-phenylazepan-2-one; 5-phenyl-1- {[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}azepan-2-one; 1-(1 H-imidazol-5- ylmethyl)-6-propylazepan-2-one; 1-(1 H-imidazol-4-ylmethyl)-4-propylazepan-2-one; 4- (1 H-imidazol-4-ylmethyl)-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5-one; 2-(5-oxo-5,6-dihydro- 4H-thieno[3,2-b]pyrrol-4-yl)acetamide; 4-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3- yl]methyl}-4,6-dihydro-5H-thieno[3,2-b]pyrrol-5-one; 4-{[2-(trifluoromethyl)imidazo[1 ,2- a]pyridin-3-

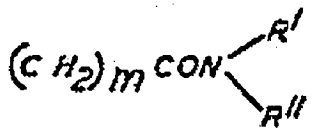
yl]methyl}hexahydro-5H-thieno[3,2-b]pyrrol-5-one; 1 -(1 H-imidazol-4-ylmethyl)- 1 H-thieno[3,4-b]pyrrol-2(3H)-one; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)acetamide; 2-(2-OXO- 1 ,3-benzothiazol-3(2H)-yl)acetamide; 2-(6-chloro-2-oxo-1 ,3-benzothiazol-3(2H)- yl)acetamide; 6-bromo-3-(1 H-imidazol-1-ylmethyl)-1 ,3-benzothiazol-2(3H)-one; 6-bromo- 3-(2-oxopropyl)-1 ,3-benzothiazol-2(3H)-one; 2-(6-nitro-2-oxo-1 ,3-benzothiazol-3(2H)- yl)acetamide; 2-(6-bromo-2-oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6-bromo-2- oxo-1 ,3-benzothiazol-3(2H)-yl)propanamide; 2-(6-fluoro-2-oxo-1 ,3-benzothiazol-3(2H)- yl)acetamide; 2-(6-methyl-2-oxo-1 ,3-benzothiazol-3(2H)-yl)acetamide; 6-fluoro-3-(1 H- imidazol-1-ylmethyl)-1 ,3-benzoxazol-2(3H)-one; 1-(1 H-imidazol-4-ylmethyl)pyrazolo[1 ,5- a]pyridin-2(1 H)-one; 2-(6-chloro-3-oxo-3,4-dihydroisoquinolin-2(1 H)-yl)propanamide; 5- chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,4-dihydroisoquinolin-3(2H)-one; 2-(6-chloro-2-oxo- 3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-bromo-2-oxo-3,4-dihydroquinolin-1 (2H)- yl)acetamide; 1-(1 H-imidazol-4-ylmethyl)-3,4-dihydroquinolin-2(1 H)-one; 2-(6-iodo-2-oxo- 3,4-dihydroquinolin-1 (2H)-yl)acetamide; 2-(6-cyano-2-oxo-3,4-dihydroquinolin-1 (2H)- yl)acetamide; 7-chloro-2-{[2-(trifluoromethyl)imidazo[1 ,2-a]pyridin-3-yl]methyl}-1 ,2,4,5- tetrahydro-3H-2-benzazepin-3-one; 7-chloro-2-(1 H-imidazol-4-ylmethyl)-1 ,2,4,5- tetrahydro-3H-2-benzazepin-3-one; 7-chloro-3-(1 H-imidazol-4-ylmethyl)-1 ,3,4,5- tetrahydro-2H-3-benzazepin-2-one; and 7-chloro-3-{[2-(trifluoromethyl)imidazo[1 ,2- a]pyridin-3-yl]methyl}-1 ,3,4,5-tetrahydro-2H-3-benzazepin-2-one.

xvi) UK Patent 1,039,113

The new compounds according to the present invention are N-substituted lactams of the general formula:



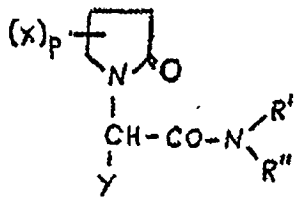
wherein N is a whole number of from 3 to 5 and R represents a



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

xvii) UK Patent 1,309,692

According to the present invention, there are provided new N-substituted lactams of the general formula:



wherein X is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms, p is a whole number of from 1 to 6, Y is a hydrogen atom or an alkyl, alkenyl or alkynyl radical containing 1 to 6 carbon atoms or a cycloalkyl radical and R' and R", which may be the same or different, are hydrogen atoms or alkyl, alkenyl, alkynyl, cycloalkyl or aryl radicals or R' and R", together with the nitrogen atom to which they are attached, form a heterocyclic radical which may contain further heteroatoms, with the proviso that at least one of the symbols X and Y is other than a hydrogen atom.

Acetylcholinesterase Inhibitor

[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, sprirapril, temocaptril, trandolapril, piperidinyl-alkanoyl heterocyclic compounds, N-benzyl-piperidine derivatives, 4-(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 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-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)-3- (4- nitrophenoxy) propyl] phenyl ester hemifumarate (RS 1259), 2- [2- (l-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-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-hexahydropyrrolo [2,3-b] indol-5-yl ester (MF 247), 5-amino-6-chloro-4-hydroxy-3, 4-dihydro-lH-thiopyrano- [3, 4-b] quinoline (MF 8615), N- [8- (cis-2, 6-dimethylmorpholin-4-yl) octyl] carbamic acid (3aS, 8aR)-1, 3a, 8trimethyl-1, 2,3, 3a, 8, 8a-hexahydropyrrolo [2,3-b] indol-5-yl ester L-bitartrate hydrate (MF 268),

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

[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 AChel is metrifonate, which is also known as metriphonate or trichlorfon or its active metabolite, 2,2-dimethyldichlorovinyl phosphate (or dichlorvos or DDVP). Metrifonate is represented by the following formula: (CH3O)2—PO—CHOH—OCl3.

Echothiophate is also known as ecothiopate, echothiophate iodide, phospholine iodide, (2-Mercaptoethyl)trimethylammonium S-ester with O,O'-diethylphosphorothioate, BRN 1794025, ecothiopatum, or phospholine. 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 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 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 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 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 number 120014-06-4.

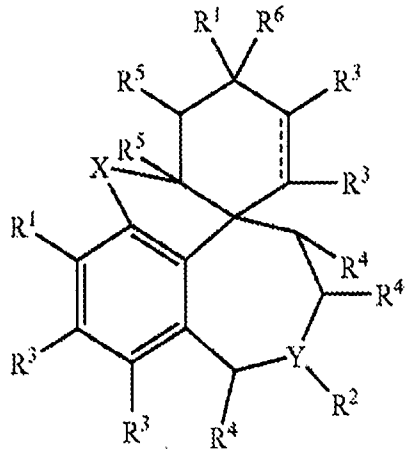
Itopride may also be an AChE inhibitor for use in embodiments disclosed herein. Itopride HCl is referenced by CAS Registry Number 122898-67-3. In one embodiment, a total daily dose range for itopride HCl is from about 25 mg to about 1000 mg, or between about 100 mg to about 300 mg. In some embodiments, the AChE inhibitor, or neurogenic agent, is the N-oxide derivative of itopride, which is 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 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 used. Examples of such compounds include galantamine derivatives, such as those compounds of formula (I):

(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 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 aralkylthio group, an aryloxymethyl group, an alkanoyloxy group, a hydroxyalkanoyloxy group, a benzoyloxy group, a benzoyloxy 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 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 α - or β-furyl group, an α - or β-thienyl group, an α - or β-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;

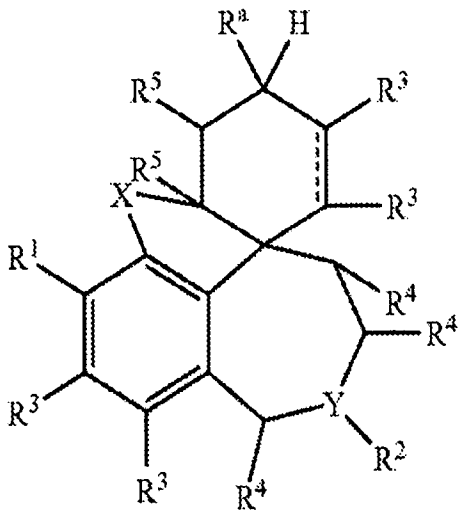
the symbols R3 are the same as or different from each other and each represents a hydrogen atom, a hydroxy group, an alkyl group, an aryl group, an aralkyl group, a hydroxyalkyl group, a thioalkyl group, a sulphhydryl group, a C1-C6 alkoxy

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 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 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 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.

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.

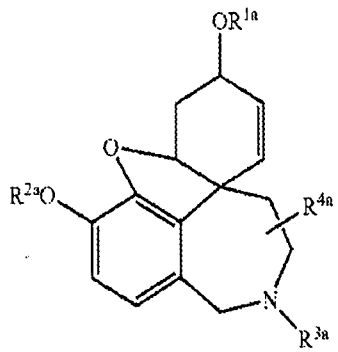
Aryl and heterocyclic groups may be unsubstituted or they may be substituted by one or more substituents selected from the groups and atoms defined for R3, provided that any R3 substituent may not itself be further substituted by a substituted aryl or heterocyclic group.

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, 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 groups).

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

(II)



where:

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 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 and its salts, especially the halides, such as galantamine hydrobromide or donepezil hydrochloride.

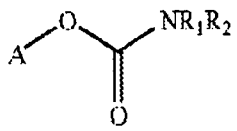
Galantamine derivatives which may be used in the present invention include norgalantamine, norgalantamine derivatives and epigalantamine.

Other compounds which may be used as the acetylcholinesterase inhibitor include: 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 salts, especially the halides, such as donepezil hydrochloride.

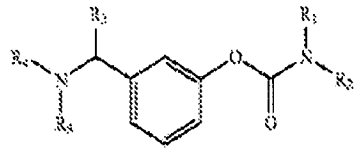
ii) U.S. Patent Application Publication No. 20070275959

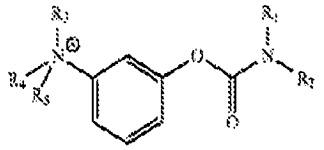
In one embodiment, the invention is a carbamoyl ester having the following structure:

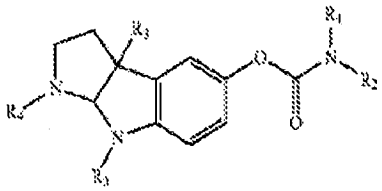


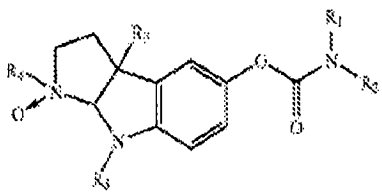
wherein A is selected from the group consisting of an unsubstituted aryl, a substituted aryl, an unsubstituted heteroaryl and a substituted heteroaryl; and R1 and R2 are each, independently or in combination, selected from the group consisting of a hydrogen, an unsubstituted alkyl, a substituted alkyl,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

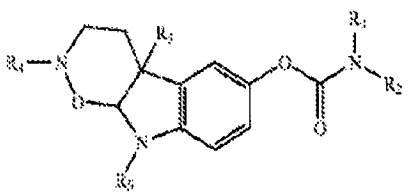
In an additional embodiment, the invention is a carbamoyl ester selected from the group consisting of:

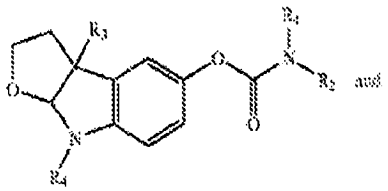




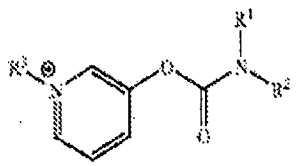








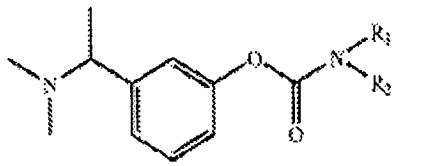
and

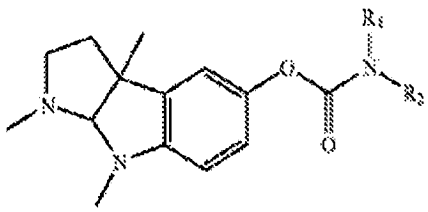


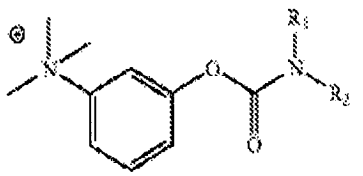
wherein R3, R4 and R5 are each, independently or in combination, selected from the group consisting of a hydrogen, an unsubstituted alkyl, a substituted alkyl, an unsubstituted aralkyl, a substituted aralkyl, an unsubstituted heteroalkyl, a substituted heteroalkyl, an unsubstituted heteroaralkyl, a substituted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

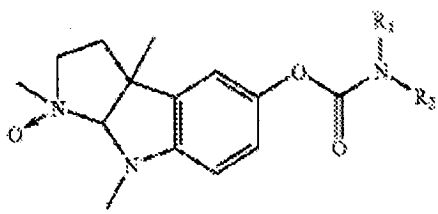
an unsubstituted aryl, a substituted aryl, an unsubstituted heteroaryl, a substituted heteroaryl, an unsubstituted cycloalkyl, a substituted cycloalkyl, an unsubstituted heterocycloalkyl and a substituted heterocycloalkyl.

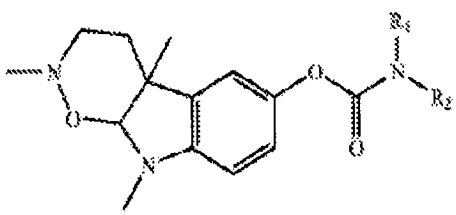
In still another embodiment, the invention is a carbamoyl ester selected from the group consisting of:

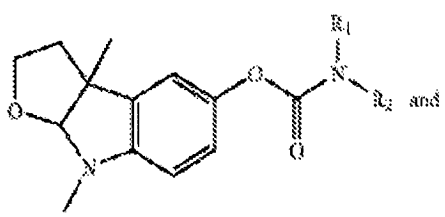




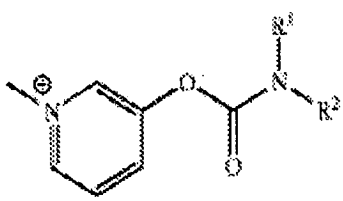






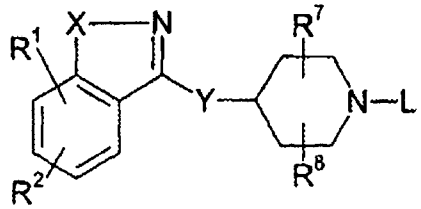


and



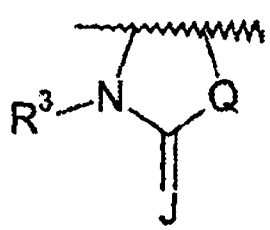
iii) European Patent Application No. EP1050303

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



wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen; (C1-C6) alkoxy; benzyloxy; phenoxy; hydroxy; phenyl; benzyl; halo; nitro; cyano; -COR^5; -$COOR^5$; -$CONHR^5$; -NR^5R^6; -NR^5COR^6; -$OCONR^5R^6$; -$NHCOOR^5$; (C1-C6) alkyl which may be substituted with from 1 to 3 fluorine atoms; SOpCH2-phenyl or SOp(C1-C6) alkyl, wherein p is 0, 1 or 2; pyridylmethyloxy or thienylmethyloxy; 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 pyridylmethyloxy or thienylmethyloxy 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;

or R^1 and R^2 are attached to adjacent carbon atoms and form, together with the carbon atoms to which they are attached, a group of Formula 2:



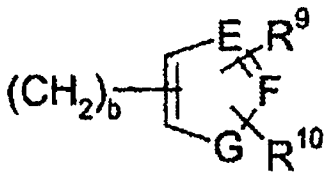
wherein R^3 is hydrogen or (C1-C6) alkyl; J is oxygen, sulfur or NR^4; R^4 is hydrogen or (C1-C4) alkyl; and Q is oxygen, sulfur, NH, CHCH3, C(CH3)2, -CH=CH-, or $(CH2)_I$ wherein $_I$ is an integer from 1 to 3;

X is oxygen or sulfur;

Y is -(CH2)m-, -CH=CH(CH2)n-, -NR<4)<CH2)m-, or -O(CH2)m-, wherein n is an integer from 0 to 3, and m is an integer from 1 to 3;

R^5 and R^6 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^5R^6 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^5COR^6 together form a 4 or 5 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) alkoxycarbonyl, (C1-C6) alkylcarbonyl, $-OCONR^5R^6$, $-NHCOOR^5$, and halo; or L is a group of Formula 3:



wherein b is an integer from 1 to 4; R^9 and R^{10} 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^4, with the proviso that when E and F are both nitrogen, one of R^9 and R^{10} is absent; and

R^7 and R^8 are independently selected from the group consisting of hydrogen, (C1-C6) alkyl, (C1-C6) alkoxycarbonyl, (C1-C6) alkylcarbonyl, and (C1-C6) alkoxy, with the proviso that said (C1-C6) alkoxy is not attached to a carbon that is adjacent to a nitrogen;

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:

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;

5,7-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;

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

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.

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, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy 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 carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy 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 benzoyloxy group.

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 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

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.

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, trifluoro methyl groups and halo groups.

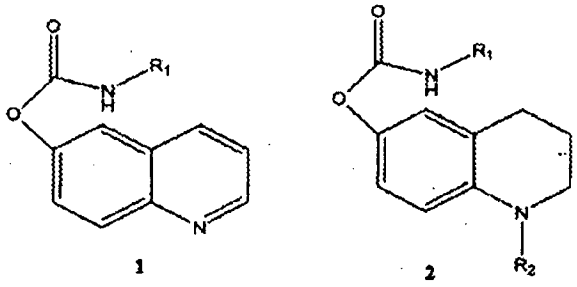
j) An acetylcholinesterase inhibitor as in b) wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or

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, trifluoro methyl groups and halo groups.

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.

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 benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

v) International Patent Application Publication No. WO2006/070394
An AChEI that is a quinoline derivative represented by formula 1 and 2 below:



1 2

wherein Ri= alkyl, aryl; R2= H, alkyl, aralkyl.

In one embodiment, substituted carbamic acid quinolinyl esters obtained are 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 l,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

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

2h. hexyl-carbamic acid 1 -benzyl- 1, 2, 3, 4-tetrahydro-quinolin-6-yl ester

2i. (2-chloro-phenyl)-carbamic acid 1-benzyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2j. (3-bromo-phenyl)-carbamic acid 1-benzyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester

2k. (4-chloro-3-trifluoromethyl-phenyl)-carbamic acid 1-benzyl-l, 2, 3, 4-tetrahydro- quinolin-6-yl ester

21. (4-bromo-phenyl)-carbamic acid 1-benzyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2m. hexyl-carbamic acid 1-methyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2n. heptyl-carbamic acid 1-methyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester

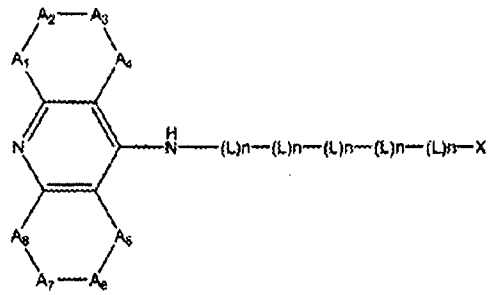
2o. (2-chloro-phenyl)-carbamic acid 1-methyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2p. (3-bromo-phenyl)-carbamic acid 1-methyl-l, 2, 3, 4-tetrahydro-quinolin-6-yl ester 2q. (4-chloro-3-trifluoromethyl-phenyl)-carbamic acid 1-methyl-l, 2, 3, 4-tetrahydro- quinolin-6-yl ester 2r. (4-bromo-phenyl)-carbamic acid 1-methyl-l, 2, 3, 4-tetrahydro- quinolin-6-yl ester

In one embodiment of the invention, when R1 is aryl it is selected from the group 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.

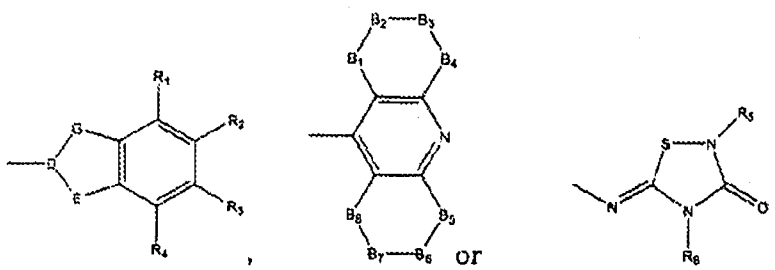
vi) International Patent Application Publication No. WO2004/032929

An embodiment is directed to the compounds represented by the general formula I



Formula I

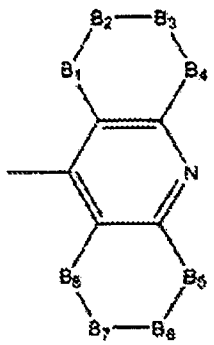
wherein: X is one of the following radicals:



L is independently selected from-C (R) (R")-,-CO-,-0-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- Al, A2, As, A4, As, A7, As, Bi, B2, Bs, B4, Bs, B6, B7, Bs, G and E are independently selected from-CO-,-C (Rio) (Rn)-, =C (Rio)-,-N (Rl2)-, =N-,-O-,-S (O) t- Ri, R2, R3, R4, R9, Rio and Ril 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

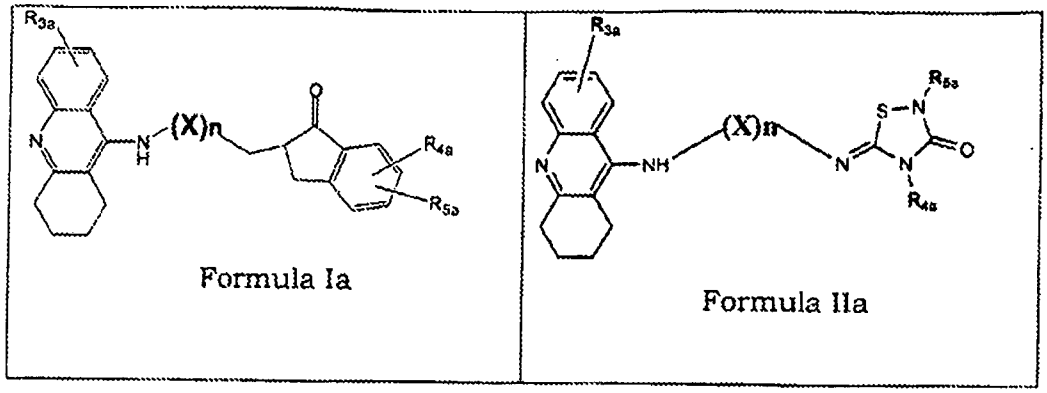
hydrogen, alkyl, alkoxy, hydroxyl, cycloalkyl, haloalkyl, aryl, heteroaryl, aryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, or alkylthio; and heteroaryl substituted by alkyl, alkoxy, hydroxy, halo, haloalkyl, nitro or alkylthio Z is independently selected from-C (R7) (R8)-,-C (O)-,-O-,-C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

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, Bl-B4, and Bs-Bs are at the same time =C (Rio)-, and b) in no case each of the atoms in one of the two groups Ai-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 (Rio)-.

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



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

Rla and R2a are independently selected from hydrogen, alkyl, aryl, halo, haloalkyl ; R3a, R4a and R5a are independently selected from hydrogen, alkyl, cycloaklyl, 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)-.

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 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, 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 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.

"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 alkoxycarbonyl as they are defined here.

"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 alkoxycarbonyl "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.

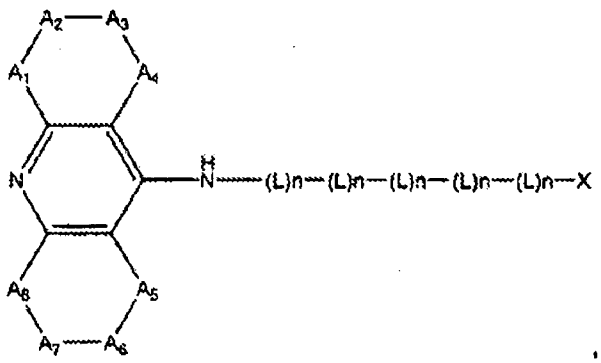
"heterocycle"refers to a heterocyclic radical. The heterocycle refers to a stable cycle of 3 to 15 members comprising carbon atoms and one to five heteroatoms chosen from the group comprising nitrogen, oxygen and sulphur. For the purposes of this invention, the heterocycle may be a monocyclic, bicyclic 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 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,

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.

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-.

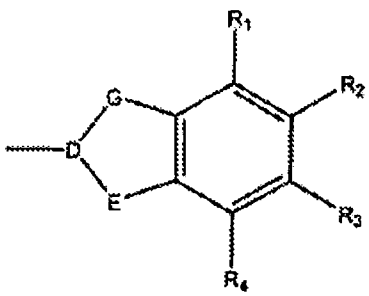
Preferably there are at least one or two groups- (L) n- where n is not zero. Suitably the chain is of the formula- (CH2) n-,- (CH2) n-NRa- (CH2) n-,- (CH2) n-NRa-CO-,- (CH2) n-NRa-CO- (CH2) n-or-(CH2) n-NRa- (CH2) n-NRa-CO-, where the or each n is not zero, and the or each Ra is- NH-or-NCHs-, usually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

In the formula:



each A group (that it, Al to As) is preferably =CH-or-CH2-, though one or both of 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-.

=CH-, =N--O-or-S-. Preferably G is-CO-,-CH2-. =CH-, or =N-.

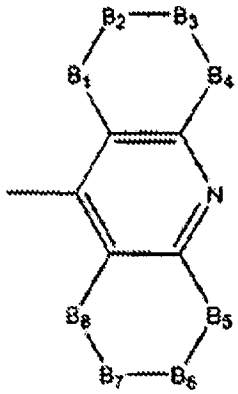
Preferably Ri to R4 are hydrogen.

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-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, 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).

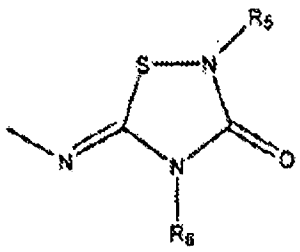
Some compounds are those in which X is 1-indanon-2-yl and the cyclic part of formula I represents 1, 2,3, 4-tetrahydro-acridin-9yl; within these compounds are included, among others, the following compounds: 5, 6-Dimethoxy-2- { [7- (l, 2,3, 4-tetrahydro-acridin-9-ylamino) - heptylamino]-methyl}-indan-1-one (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 it, Bi to Bs) is preferably =CH-or-CH2-, 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:



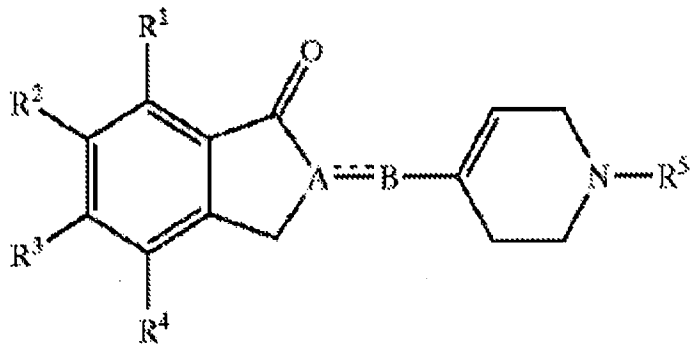
the groups Rs and R6 are suitably alkyl or substituted alkyl, notably alkoxycarbonylalkyl. The preferred compounds are those in which the cyclic part of formula I represents: 9-acridinyl, 6-chloro, 1, 2,3, 4- tetrahydro-acridin-9-yl or 1, 2,3, 4-tetrahydro-acridin-9-yl ; within these compounds are included, among others, the following compounds: 2-Ethyl-4-isopropyl-5- [7- (1, 2,3, 4-tetrahydro-acridin-9- ylamino)-heptyl-iminio]- [1, 2, 4] thiadiazolidin-3-one (13), - 2-Ethyl-4-isopropyl-5- [9- (1, 2,3, 4-tetrahydro-acridin-9- ylamino)-nonyl-iminio]-[1, 2, 4] thiadiazolidin-3-one (14), 4-isopropyl-3-oxo-5- [9- (1, 2,3, 4-tetrahydro-acridin-9-ylamino) - nonyl-iminio]- [1, 2,4] thiadiazolidine-2-carboxylic acid ethyl ester (15), 4-Ethyl-2-propyl-5- [7- (1, 2,3, 4-tetrahydro-acridin-9-ylamino) - heptyl-imino]- [1, 2,4] thiadiazolidin-3-one (16), 4-Ethyl-2-isopropyl-5- [8- (1, 2,3, 4-tetrahydro-acridin-9- ylamino)-octylimino]- [1, 2,4] thiadiazolidin-3-one (17), and 4-Ethyl-2-isopropyl-5- [6- (1, 2,3, 4-tetrahydro-acridin-9- ylamino)-hexyl-imino]- [1, 2,4] thiadiazolidin-3-one (18).

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

In some embodiments, an AChEI is:

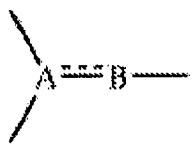
1) an (1-indanone)-(1,2,3,6-tetrahydropyridine) compound represented by the formula:

(I)

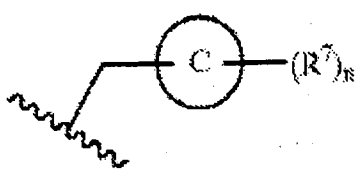


(in the formula (I), R<1> , R<2> , R<3 > and R<4 > are the same as or different from each other and each represents a group selected from hydrogen atom, a halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, a cycloalkyl group having three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



is a group represented by >C-CH-(CH2)m- or >C(R<6>)-CH(R<6>)-(CH2)m- (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 > 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 formula:

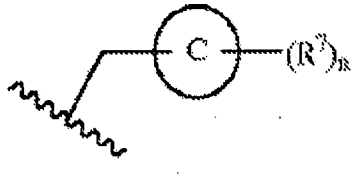


(wherein the ring C is benzene ring, an aliphatic ring or a heterocyclic ring; R<7> s are the same as or different from each other and each represents hydrogen atom, a halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, an alkenyl group 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;

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;

[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;

[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:



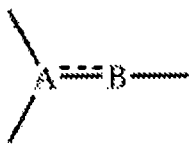
wherein the ring C, R<7 > and n have the same meanings as defined above;

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;

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;

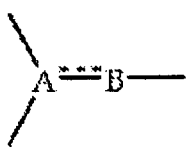
7) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein n is an integer of 1 or 2;

[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:



is a group represented by >C(R<6>)-CH(R<6>)-(CH2)m- (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:



is a group represented by >C(R<6>)-CH(R<6>)-(CH2)m- (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, 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:

(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

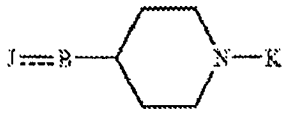
(3) 1-benzyl-4-[(5,6-diethoxy-2-fluoro-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine;

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).

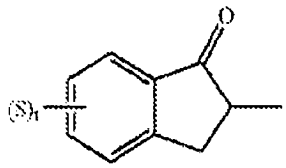
viii) U.S. Patent 7,378,425

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

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

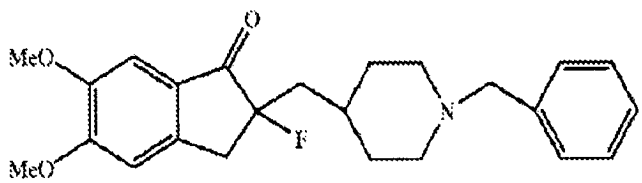


Wherein J is, for example, the formula:



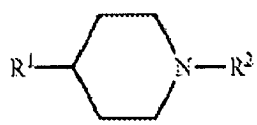
(wherein S is, for example, a lower alkoxy group having one to six carbon atoms; and t is 0 or an integer of 1 to 4); B is, for example, methylene chain; K is, for example, a benzyl group which may be substituted; and the partial structure: - is a single bond or double bond, provided that a compound wherein J is 5,6-dimethoxy-1-indanon-2-yl group; B is -CH2- group; and K is unsubstituted benzyl group, a pharmacologically acceptable salt thereof or a hydrate of them are excluded (JP-B2 2733203).

(2) A compound represented by the following formula:

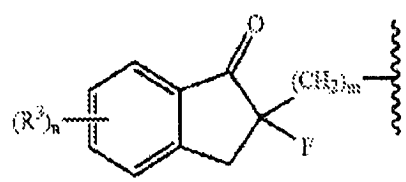


or a pharmacologically acceptable salt thereof (JP-A 2000-319257).

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



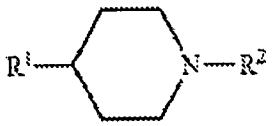
(wherein R<1 > is, for example, a substituent represented by:



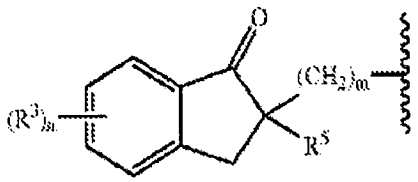
(wherein R<3> s are the same as or different from each other and each represents, for example, an alkoxy group having one to six carbon atoms; m is 0 or an integer of 1 to 6; and n is an integer of 1 to 4); and R<2 > is, for example, a benzyl group

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).

(4) A 4-substituted piperidine derivative represented by the following formula:



(wherein R<1 > is, for example, a group represented by the formula:

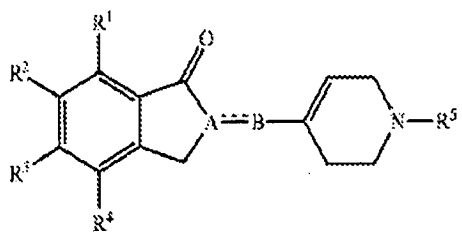


(wherein R<3> s are the same as or different from each other and each represents, for example, an alkoxy group having one to six carbon atoms; R<5 > is, for example, a halogen atom except for fluorine atom; m is 0 or an integer of 1 to 6; and n is an integer of 1 to 4); and R<2 > is, for example, benzyl group which may be substituted), a pharmacologically acceptable salt or a hydrate of them (JP-A 2001-139547).

In some embodiments, the present invention relates to:

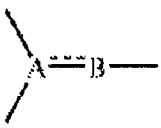
1) an (1-indanone)-(1,2,3,6-tetrahydropyridine) compound represented by the formula:

(I)

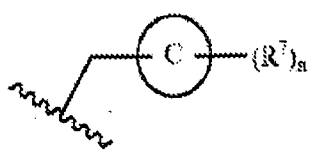


(in the formula (I), R<1> , R<2> , R<3 > and R<4 > are the same as or different from each other and each represents a group selected from hydrogen atom, a halogen atom, hydroxyl group, nitrile group, an alkyl group having one to six carbon atoms which may be substituted, a cycloalkyl group having three 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 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 ring or an alkylenedioxy ring; the partial structure:



is a group represented by >C-CH-(CH2)m- or >C(R<6>)-CH(R<6>)-(CH2)m- (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 > 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 formula:



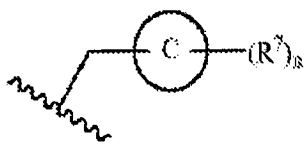
(wherein the ring C is benzene ring, an aliphatic ring or a heterocyclic ring; R<7> s are the same as or different from each other and each represents hydrogen atom, a

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;

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;

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;

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:



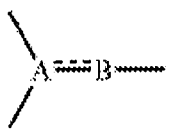
wherein the ring C, R<7 > and n have the same meanings as defined above;

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;

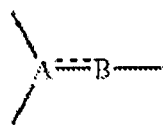
7) the (1-indanone)-(1,2,3,6-tetrahydropyridine) compound described in 4), a pharmacologically acceptable salt thereof or a hydrate of them, wherein n is an integer of 1 or 2;

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:



is a group represented by >C(R<6>)-CH(R<6>)-(CH2)m- (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:



is a group represented by >C(R<6>)-CH(R<6>)-(CH2)m- (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, 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:

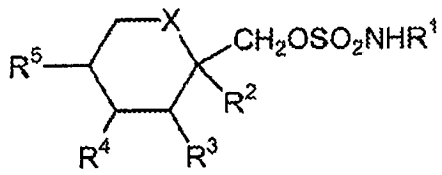
(1) 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methyl-1,2,3,6-tetrahydropyridine,

(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.

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 :

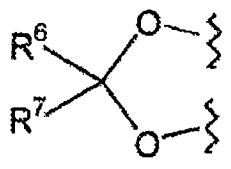


I

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 ll :



ll

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.

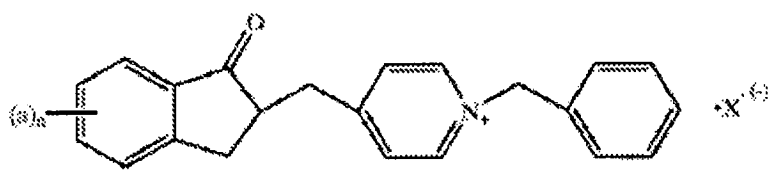
R^1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R2, R3, R4, R5, R6 and R7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl.

When X is CH2, 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 =C-CH=CH-CH=.

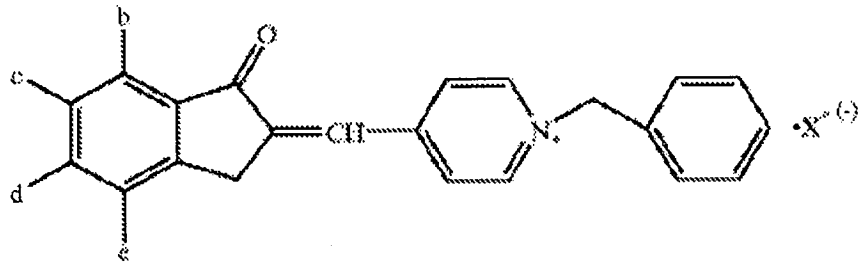
A particular group of compounds of formula I is that wherein X is oxygen and both R2 and R3 and R4 and R5 together are methylenedioxy groups of the formula il, wherein R6 and R7 are both hydrogen, both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R6 and R7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH2 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

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:

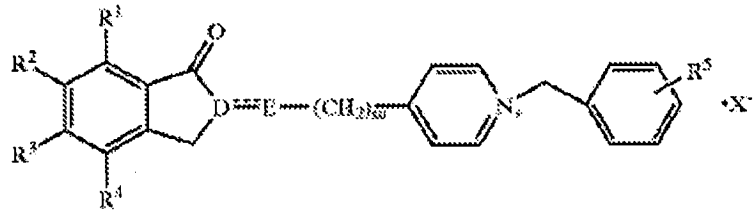


(wherein the "a" moieties are the same as or different from each other and each represents a hydrogen atom or a C1-6 alkoxy group; n is an integer from 1 to 4; and X<(-) >represents a halide ion) and a compound represented by the formula:

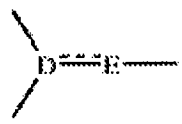


(wherein b, c, d and e are the same as or different from each other and each represents a hydrogen or a linear or branched C1-6 alkyl, C1-6alkoxy, C1-6alkoxy carbonyl, C1-6alkyl aminocarbonyloxy, di (C1-6alkyl)-aminocarbonyloxy or a halogen; and X''<(-) >represents an anion in the series of chloride, 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)

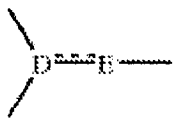


(wherein R<1>, R<2>, R<3 >and R<4 >are the same or different, and represent a hydrogen atom, a halogen atom, a hydroxyl group, a nitrile group, a C1-6 alkyl group, a C1-6 alkoxy group, a C1-6alkoxy carbonyl group, a C1-6 alkyl aminocarbonyloxy group or a di (C1-6 alkyl)-aminocarbonyloxy group; R<5 >represents a hydrogen atom, a halogen atom, a C1-6alkyl group, a C2-6 alkenyl group or a C2-6 alkynyl group; the partial structure:

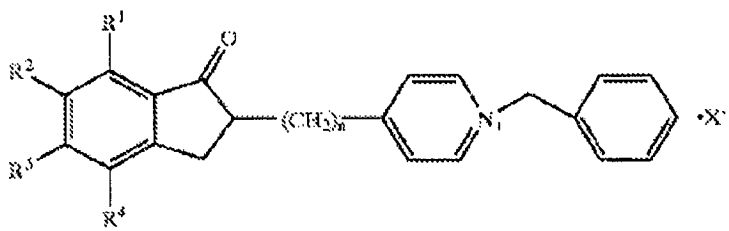


is a group represented by the formula >C(R<6>)-CH2- (wherein R<6 >is a hydrogen atom or a halogen atom) or >C-CH-; X<-> represents a halide ion or organic sulfonic acid ion; and m is 0 or an integer from 1 to 5) exhibits an excellent inhibitory action on acetylcholinesterase, and accomplished the present invention. That is, the first aspect according to the present invention is (1) an acetylcholinesterase inhibitor comprising a 1-benzylpyridinium salt represented by

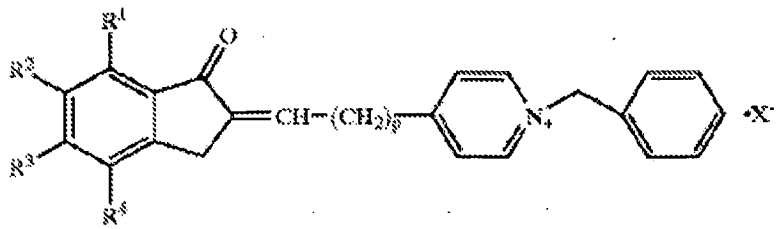
the above formula (I). Further, (2) in the above item (1), R<1>, R<2>, R<3 >and R<4 >may be the same as or different from each other and each represents a hydrogen atom or a C1-6 alkoxy group; (3) in the above item (1), R<1>, R<2 >R<3 >and R<4 >may be the same as or different from each other and each 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:



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:



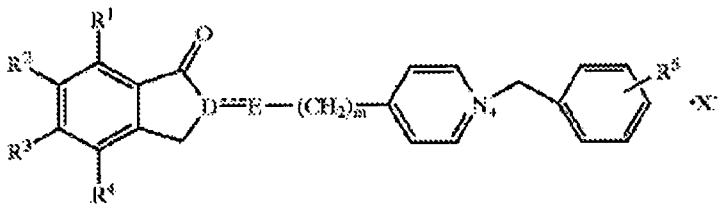
wherein R<1>, R<2>, R<3>, R<4 >and X<-> have the same meanings as defined above; and n is an integer from 1 to 6; (11) in the above item (1), the 1-benzylpyridinium salt may be a compound represented by the formula:



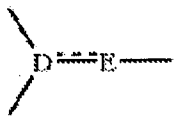
wherein R<1>, R<2>, R<3>, R<4 >and X<-> have the same meanings as defined above; and p is 0 or an integer from 1 to 5; (12) in the above item (1), the preparation may be an agent for treating, preventing or improving senile dementia, cerebrovascular dementia or attention deficit hyperactivity disorder; and (13) in the 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:

(I)

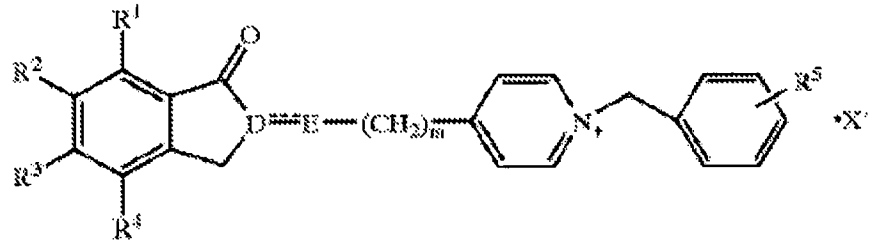


wherein R<1>, R<2>, R<3>, R<4>, R<5>, the partial structure:

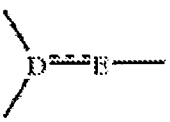


X<-> and m have the same meanings as defined above. Further, the third aspect according to the present invention is (15) use of a 1-benzylpyridinium salt represented by the formula:

(I)



(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 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 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.

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 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 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 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 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-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 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-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, 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 alkoxycarbonyl 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 meaning as defined above 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-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.

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.

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.).

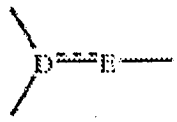
The "halogen atom" and "C1-6 alkyl group" represented by R<5 >in the specification refer to a halogen atom and C1-6alkyl group each having the same meaning as defined above.

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.

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.

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:

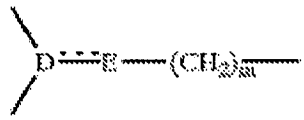


may be either a group represented by the formula >C(R<6>)-CH2- (wherein R<6 >is a hydrogen atom or a halogen atom) or >C-CH-, preferably a group represented by the formula >C(R<6>)-CH2- wherein R<6 >is a hydrogen atom or a halogen atom. Herein, the "halogen atom" represented by R<6 >means an atom having 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>)-CH2- or >C-CH- when m is 0, (2) the formula >C(R<6>)-(CH2)2- or >C=CH-(CH2)- when m is 1, (3) the formula >C(R<6>)-(CH2)3- or >C-CH-(CH2)2- when m is 2, (4) the formula >C(R<6>)-(CH2)4- or >C-CH-(CH2)3- when m is 3, (5) the formula >C(R<6>)-(CH2)5- or >C-CH-(CH2)4- when m is 4, and (6) the formula >C(R<6>)-(CH2)6- or >C-CH-(CH2)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 embodiments 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;

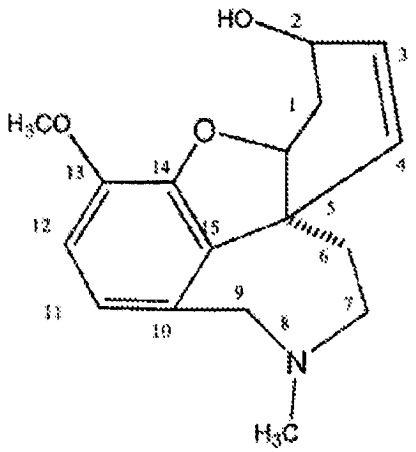
1-benzyl-4-[(5,6-diethoxy-1-indanone)-2-yl]methylpyridinium chloride;
1-benzyl-4-(1-indanone-2-yl)methylpyridinium bromide;
1-benzyl-4-[(4-methoxy-1-indanone)-2-yl]methylpyridinium bromide;
1-benzyl-4-[(5-methoxy-1-indanone)-2-yl]methylpyridinium bromide;
1-benzyl-4-[(6-methoxy-1-indanone)-2-yl]methylpyridinium 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;
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.

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 as follows:
the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate groupor a trialkylsilyloxy group;
the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;
the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.
One or more of the methoxy, hydroxy and methyl groups of galanthamine or lycoramine may be replaced by the groups noted above.

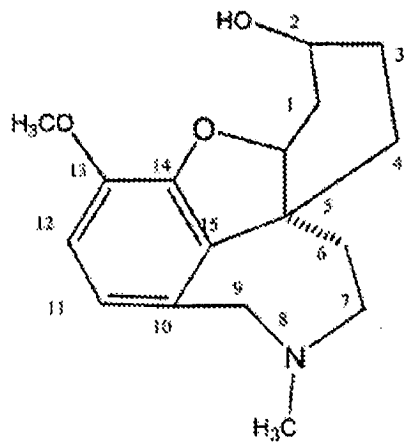
When reference is made to a substituent group, said group may be selected from alkyl or alkoxy groups of from 1 to 6 carbon atoms, halo groups, and haloalkyl groups such as trifluoromethyl. When reference is made to alkyl groups, where the context permits, the term also includes groups which are or contain cycloalkyl groups including adamantyl. Aryl groups are typically phenyl or naphthyl but may include heteroatyl such as morpholino.

Galanthamine and lycoramine have the following formulae:

Galanthamine



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).

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 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 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 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 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.

xii) International Patent Application Publication No. WO1999/007359

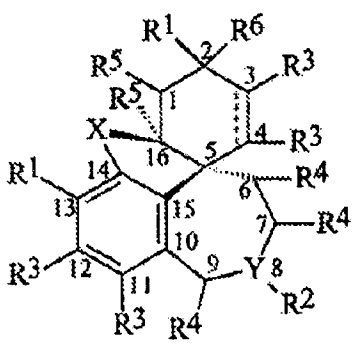
In some embodiments, cholinesterase inhibitors may include, but are not limited to, physostigmine, tacrine and tacrine analogues, fasiculin, metrifonate, heptyl-physostigmine, norpyridostigmine, norneostigmine, huperazine, donepezil and pro-drugs of any of these in which the inhibitor is modified in 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.

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.

Particularly preferred cholinesterase inhibitors for use in the invention are galantamine and its derivatives of formula (I):



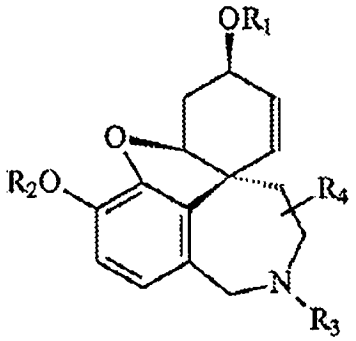
wherein the broken line represents an optionally present double bond between carbon atoms 3 and 4, each Rl is independently selected from hydrogen, hydroxyl, straight or branched chain alkyl, hydroxyalkyl, carboxyalkyl amino, alkylamino, acyl, lower alkanoyl, cyano, sulfhydryl, Cl6alkoxy, alkylthio, aryloxy, arylthio, R3substituted aryloxy, R3-substituted arylthio, aralkoxy, an optionally R3-substituted aliphatic or aryl carbamyl group, aralkylthio, R3-substituted aralkoxy, R3substituted aralkylthio, aryloxymethyl, R3-substituted aryloxymethyl, alkanoyloxy, hydroxy-substituted alkanoyloxy, benzoyloxy, R3-substituted 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, heterocyclyl selected from a- or ss-furyl, a- or ss-thienyl, thenyl, pyridyl, pyrazinyl, and pyrimidyl, alkyl-heterocyclyl or R^1-substituted heterocyclyl, where R^1 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-arylamino, N-alkarylamino, fluoro, chloro, bromo, iodo, and trifluoromethyl,
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
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.

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.

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;

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 carbons of the tetracyclic skeleton,

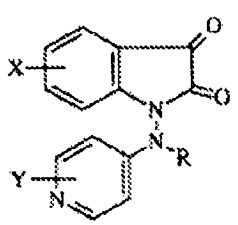
and pharmaceutically acceptable salts thereof, such as a hydrobromide, hydrochloride, methylsulphate or methiodide.

Formula II includes galantamine itself.

In some embodiments, a compound is galantamine itself, and salts thereof such as halides, for example galantamine hydrobromide.

xiii) International Patent Application Publication No. WO1997/038993

This application relates to compounds of the formula



(I)

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(CI-C6)alkyl, where the phenyl group is optionally substituted by (C1-C6)alkyl, (C,-C6)alkoxy, halogen or trifluoromethyl;

R2 is hydrogen or (C,-C6)alkyl; or

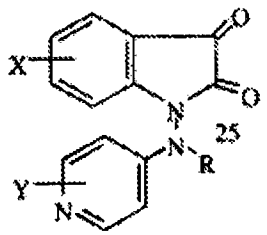
R and R2 taken together with the nitrogen to which they are attached form a tetrahydroisoquinoline group; and its pharmaceutically acceptable acid addition salts.

The term "alkyl" shall mean a straight or branched alkyl group of the stated 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 independently selected from the group of (Cl-C6)alkyl, (Cl-C6)alkoxy, halo or trifluoromethyl.

In a particular embodiment of the invention are compounds of the Formula (I)



wherein

R is hydrogen, (Cl-C6)alkyl or hydroxy(C1-C6)alkyl;

X is hydrogen, hydroxy, (C1-C6)alkoxy, benzyloxy, or

-O(C=O)NRlR2 ; and

Y is hydrogen or halogen;

where Rl is (Cl-C6)alkyl, phenethyl, or benzyl, where the phenyl group is optionally substituted by (C,-C6)alkyl, (Cl-C6)alkoxy, halogen or trifluoromethyl; and

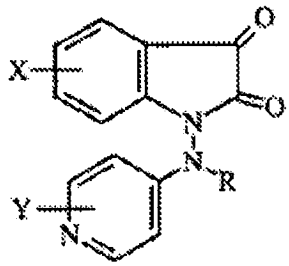
R2 is hydrogen or (C,-C6)alkyl; and its pharmaceutically acceptable acid addition salts.

In one embodiment, when Rl is (C-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



(I)

wherein

R is hydrogen, (Cs-C6)alkyl or hydroxy(CI-C6)alkyl;

X is hydrogen, hydroxy, (C1-C6)alkoxy, benzyloxy, or

-O(C=O)NRIR2 ; and

Y is hydrogen or halogen; wherein

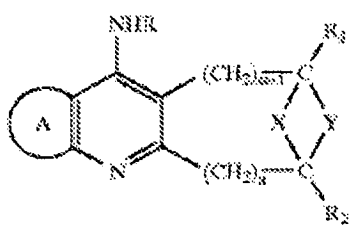
R and R2 taken together with the nitrogen to which they are attached form a tetrahydroisoquinoline group; and its pharmaceutically acceptable acid addition salts.

In one embodiment X is -O(C=O)NR'R2 and Y is hydrogen.

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):

(I)



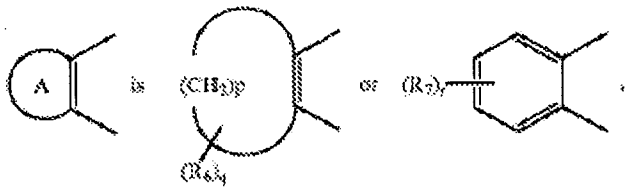
in which R can be hydrogen, alkyl, aralkyl or acyl;

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.

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 alkoxycarbonyl 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 given above in the context of R.

The group R3 of N--R3 can adopt the meanings defined above for R.

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.

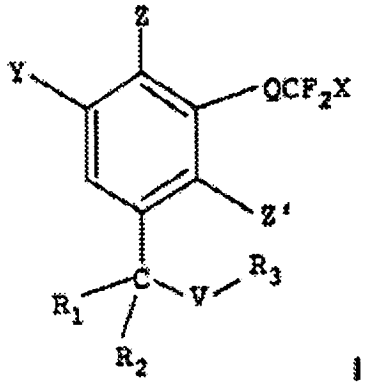
The groups R5 which are substituents of the ring fused to X or Y can be hydrogen, lower alkyl or lower alkoxy having one to four carbon atoms, or halogen (fluorine, chlorine, bromine and iodine).

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.

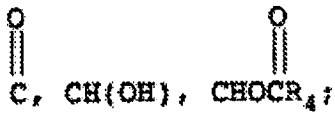
xv) U.S. Patent 5,663,448

Compounds of the present invention have the following Formula I



I

stereoisomers and pharmaceutically acceptable salts thereof, wherein each of Z and Z' are independently H or F;

Q is  ;

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 ;

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

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-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 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 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 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, 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 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.

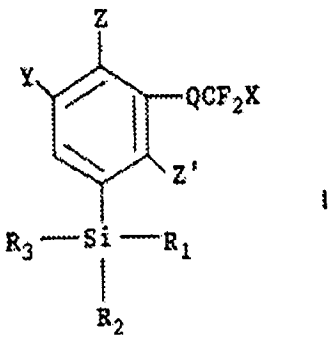
When R2 and V--R3 are taken together, they may form a 3 membered ring which includes the carbon atom to which R2 and V are attached (when R3 is H). Other

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 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.

xvi) European Patent Application No. EP0611769

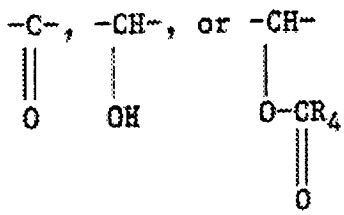
Compounds of the present invention have the following Formula I:



I

stereoisomers or mixtures thereof, and pharmaceutically acceptable salts thereof, wherein:

each of Z and Z' are independently H or F, provided that at least one of Z or Z' is F;



Q is

X is H, Br, Cl, F or CF3;

Y is H, OH, (C1-6) alkyl, -(CH2)mOR5, hydroxy (C1-6) alkyl, (CH2)nNR6R6', azido, CN, CO2R4, COR6, SO3H, Br, Cl, F, NO2 or -(CH2)n SiR1'R2'R3', provided that when both Z and Z' are F then Y is H or F;

R1, R2, R3, R1', R2'and R3' are each independently C1-10 alkyl or (CH2)n aryl;

R4 is H, (C1-10) 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.

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 "(CH2)n" or "(CH2)m" 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 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 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, 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-isobensofuranyl, 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, 2-quinazolinyl, 3-cinnolinyl, 2-pteridinyl, 4aH-carbazol-2-yl, 2-carbazolyl, beta -

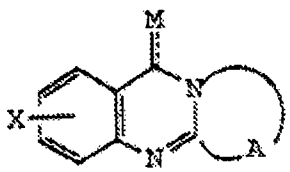
carbolin-3-yl, 3-phenanthridinyl, 2-acridinyl, 2-perimidinyl, 1-phenazinyl, 3-isothiazolyl, 2-phenothiazinyl, 3-isoxasolyl, 2-phenoxasinyl, 3-isochromanyl, 7-chromanyl, 2-pyrrolin-3-yl, 2-imidazolidinyl, 2-imidazolin-4-yl, 2-pyrazolidinyl, 3-pyrazolin-3-yl, 2-piperidyl, 2-piperazinyl, 1-indolinyl, 1-isoindolinyl, 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 (CH2)n 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.

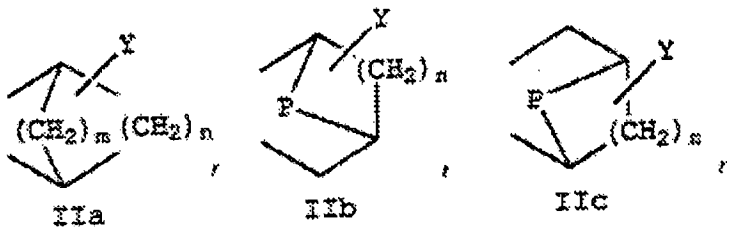
xvii) International Patent Application Publication No. WO1993/03034

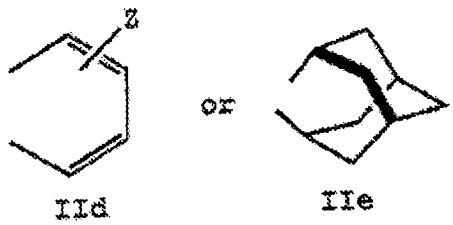
The present invention also includes novel compounds of the formula



I

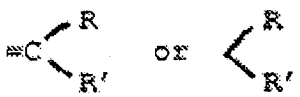
wherein A represents





in which n is 1-10, P is a bond or (CH2) 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 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, lower alkoxy, lower alkenyl, lower alkynyl, aryl, aryloxy, aryllower alkyl, heteroaryl or

heteroaryllower 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

X is absent or one to four substituents selected from halogen, alkyl(C1~22), straight or branched,

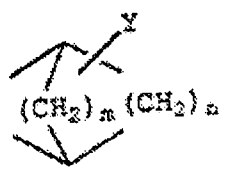
saturated or alkenyl or alkynyl, if alkyl of appropriate size can form a ring, saturated or

unsaturated, containing (or not containing) one or more heteroatoms, such as O, S, 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 acetylmethyl, 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 0, S, and N, primary, secondary, or tertiary aminolower alkylthio-, aryl-, heteroarylthio, 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

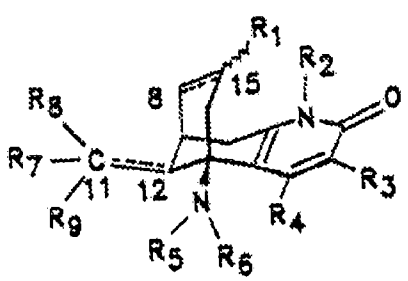


IIa

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 if of the Formula IId, X is 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:



(I)

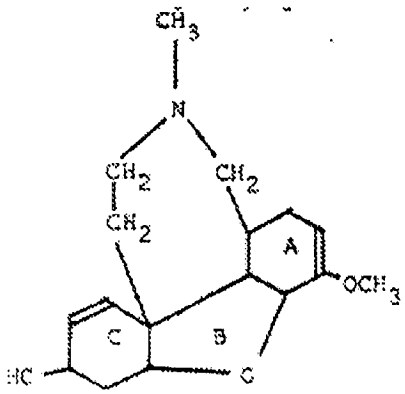
wherein R1 is H, (C1 -C8)alkyl or halo; R2 is H or (C1 -C8)alkyl; R3 and R4 are individually H, (C1 -C8)alkyl, NO2, hydroxy or halo; R5 and R6 are individually H, (C1 -C8)alkyl, aryl or aralkyl; R7 is H, halo or (C1 -C8)alkyl, R8 is halo or (C1 -C8)alkyl, R9 is absent or is H; and the bonds represented 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, 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 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 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. 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.

xix) European Patent Application No. EP0236684

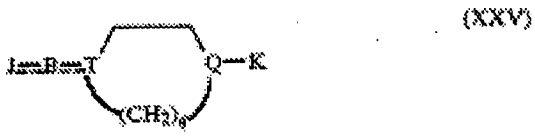
Galanthamine is generally regarded as having the structure:



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 thienyl, 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:



(XXV)

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) C6 H5 --CO--CH(CH3)--;

(c) a monovalent group derived from a cyclic amide compound;

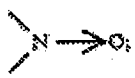
(d) a lower alkyl or

(e) a group of R21 --CH.dbd.CH-- in which R21 is hydrogen or a lower alkoxycarbonyl (dbd stands for a double bond);

B is --(CHR22)r --, --CO--(CHR22)r --, --NR4 --(CHR22)r --, R4 being hydrogen, a lower alkyl, an acyl, a lower alkylsulfonyl, phenyl, a substituted phenyl, benzyl or a substituted benzyl, --CO--NR5 --(CHR22)r --, R5 being hydrogen, a lower alkyl or phenyl, --CH.dbd.CH--(CHR22)r --, --OCOO--(CHR22)r --, --OOC--NH--(CHR22)r --, --NH--CO--(CHR22)r --, --CH2 --CO--NH--(CHR22)r --, --(CH2)2 --NH--(CHR22)r --, --CH(OH)--(CHR22)r --, r being zero or an integer of 1 to 10, R22 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)b--, b being an integer of 1 to 3, .dbd.CH--(CH2)c --, c being zero or an integer of 1 to 9, .dbd.(CH--CH)d .dbd., d being zero or an integer of 1 to 5; --CO--CH.dbd.CH--CH2 --, --CO--CH2 --CH(OH)--CH2 --, --CH(CH3)--CO--NH--CH2 --, --CH.dbd.CH--CO--NH--(CH2)2 --, --NH--, --O--, --S--, a dialkylaminoalkylcarbonyl or a lower alkoxycarbonyl;

T is a nitrogen or carbon;

Q is nitrogen, carbon or



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 alkoxycarbonyl or an acyl; 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--, .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.

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,

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-methnylenedioxy-1-indanon)-2-yl)methylpiperidine,

1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,

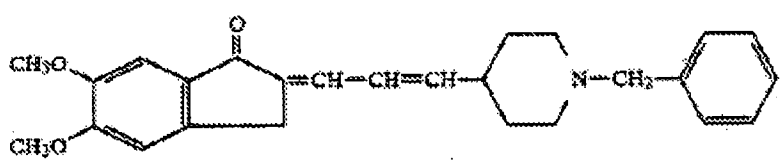
1-cyclohexymethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine,

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

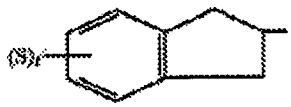
1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine, having the below shown formula.



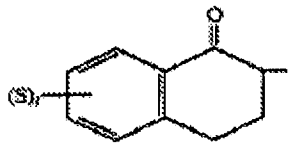
In addition, the invention provides a therapeutical composition which comprises a pharmacologically effective amount of the cyclic amine compound having the formula (XXV) or a pharmacologically acceptable salt thereof and a pharmacologically acceptable carrier and then a method for preventing and treating 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.

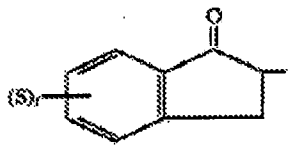
The preferable compound has the above shown formula in which J is (b). The group (b) includes ten groups having the respective formulae shown below. S is hydrogen or a substituent such as a lower alkyl having 1 to 6 carbon atoms and a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy 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)t may form methylene dioxy group or ethylene dioxy group on two adjacent carbon atoms of the phenyl group.



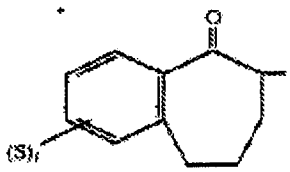
indanyl



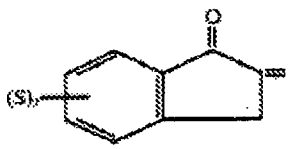
tetralonyl



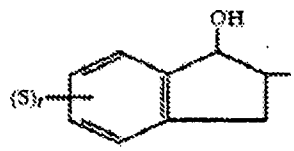
indanonyl



benzosuberonyl



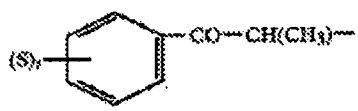
indanonylidenyl

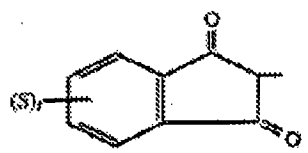


indanonyl

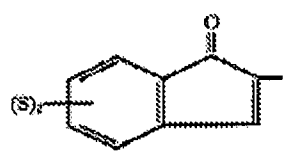


indenyl





indanedionyl



indenonyl

A preferable definition of B includes --(CHR22)r --, --CO--(CHR22)r --, .dbd.(CH--CH.dbd.CH)b --, .dbd.CH--(CH2)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--(CH2)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--(CH2)c -- are preferable.

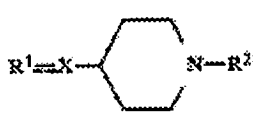
In the ring including T and Q, it may be a 5-, 6-or 7-membered ring. It is preferable that Q is nitrogen, T is carbon or nitrogen and n is 2; Q is nitrogen, T is carbon and n is 1 or 3; and Q is carbon, T is nitrogen and n is 2.

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):



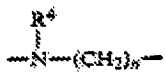
(I)

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 alkoxycarbonyl group),

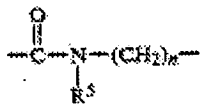
X is a group represented by the formula --(CH2)n --, a group represented by the formula



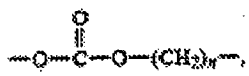
a group represented by the formula



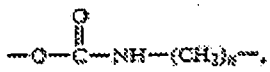
(wherein R4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, or a substituted or unsubstituted phenyl or benzyl group), a group represented by the formula



(wherein R5 is a hydrogen atom, a lower alkyl group, or a phenyl group), a group represented by the formula --CH.dbd.CH--(CH2)n --, a group represented by the formula



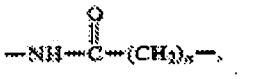
a group represented by the formula



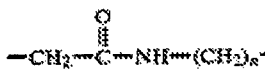
a group represented by the formula



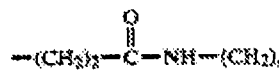
a group represented by the formula



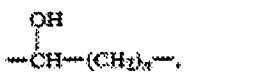
a group represented by the formula



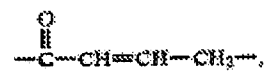
a group represented by the formula



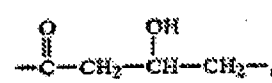
a group represented by the formula



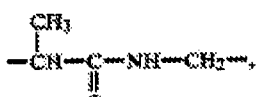
a group represented by the formula



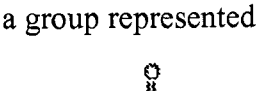
a group represented by the formula



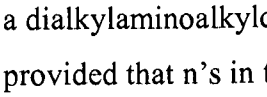
a group represented by the formula



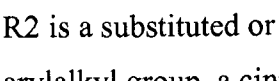
a group represented by the formula



a group represented by the formula



a group represented by the formula



a dialkylaminoalkylcarbonyl group, or a lower alkoxycarbonyl 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

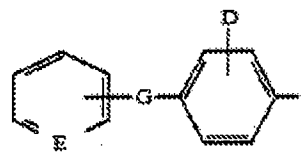
cycloalkylalkyl group, an adamantanemethyl group, or a furoylmethyl group, and a symbol, ⋯ in the above general formula, means a single bond or a double bond.

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), isopenthyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimenthylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimenthylbutyl, 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.

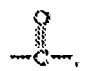
Examples of the substituent involved in the expression "the following substituted or unsubstituted group: (1) a phenyl group, (2) a pyridyl group, (3) a pyrazyl group, (4) a quinolyl group, (5) an indanyl group, (6) a cyclohexyl group, (7) a quinoxalyl group, or (8) a furyl group" in the definition of 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 alkoxycarbonyl 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,

such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogentated 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 alkoxyl groups" in the above description of the substituent include all the groups derived from the above-mentioned groups. The substitutent may be one to three of them which may be the same or different.

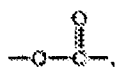
Further when the substitutent is a phenyl group, the following group is within the scope of the substituted phenyl group:



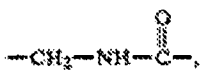
wherein G is a group represented by the formula



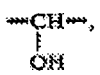
a group represented by the formula



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



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 alkoxycarbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzoyl and benzylsulfonyl groups. The substituent may be two or more of them

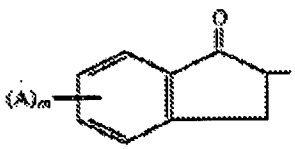
which may be the same or different.

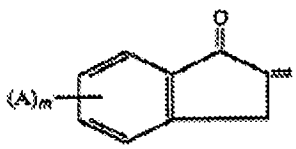
Preferable examples of the substituent for the pyridyl group include loweralkyl and amino groups and halogen atoms.

Preferable examples of the substituent for the pyrazyl group include lower 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 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):


(II)


(III)

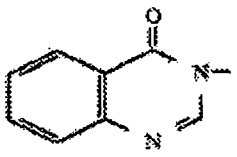
wherein m's are each an integer of 1 to 4 and A's which may be the same or different are each one of the substituents described in the above items (1) to (8) of the definition of R1 or a hydrogen atom, preferably a hydrogen atom (i.e. unsubstituted), a lower alkyl group, or a lower alkoxy group, and 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 above-described specific examples only. The cyclic amide group may be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocylcic ring is preferably one formed by condensation with a phenyl ring. In

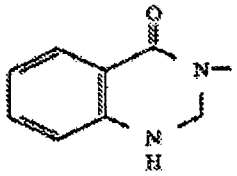
this case, the phenyl ring may be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferable examples of the monovalent group include the following groups:

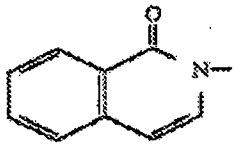
(a)



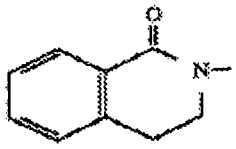
(b)



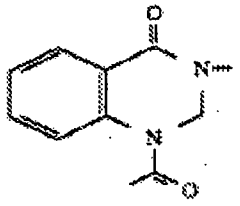
(c)



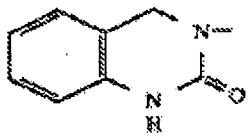
(d)



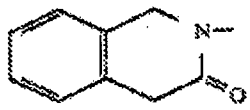
(e)



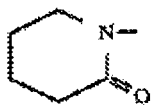
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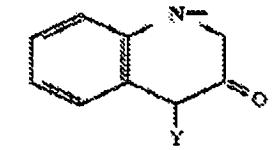


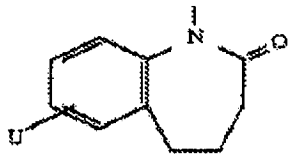
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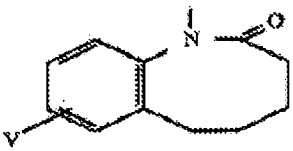


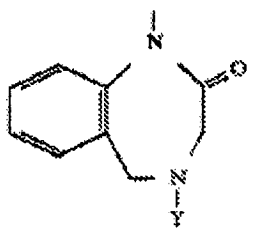
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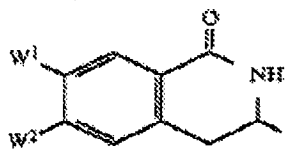


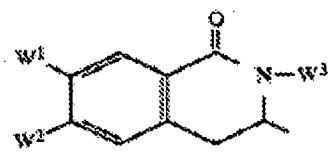










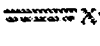


In the above formulae, Y's in the formulae (i) and (1) are each a hydrogen atom or a lower alkyl group, V in the formula (k) is a hydrogen atom or a lower alkoxy group, W1 and W2 in the formulae (m) and (n) are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group and W3 is a hydrogen atom or a lower alkyl group.

The right-hand ring in each of the formulae (j) and (1) 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 --(CH2)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



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 R2 are the same as those described in the above items (1) to (8) in the above definition of R1.

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.

Preferable examples of R2 include benzyl and phenethyl groups. The symbol

means either a single or a double bond. This bond is a double bond only when R1 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.

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.

One specific example thereof will now be described. When R1 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.

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 (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 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 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 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, 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.

[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 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 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 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 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, 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, 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 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 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 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 appropriate method for extrapolating doses between species. The human equivalent dose (HED) for this dosage can be estimated using the following formula that accounts for differences in body surface area (see Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers, December 2002, Center for Biologics Evaluation and Research):

HED = animal dose X (Km animal / Km human)

where the Km factor is body weight divided by body surface area (Km rat has been determined as 6, and Km human is 37; see Reagan-Saw, Nihal, Ahmad, 2007). Thus, a dosage of 10 mg/kg in rats is equivalent to 1.6 mg/kg in humans (10 mg/kg X (6 / 37) = 1.6 mg/kg). For human subjects, to calculate a dose in mg from the dose in mg/kg, the dose in mg/kg is multiplied bya 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 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 0.001 - 5 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.07 - 350 mg/day). Doses that may be used include, but are not limited to 0.001 mg/kg/day, 0.0015 mg/kg/day, 0.002 mg/kg/day, 0.005 mg/kg/day, 0.0075 mg/kg/day, 0.01 mg/kg/day, 0.015 mg/kg/day, 0.02 mg/kg/day, 0.03 mg/kg/day, 0.04 mg/kg/day, 0.05 mg/kg/day, 0.1 mg/kg/day, 0.2 mg/kg/day, 0.3 mg/kg/day, 0.4 mg/kg/day, 0.5 mg/kg/day, 0.75 mg/kg/day, 1.0 mg/kg/day, 1.5 mg/kg/day, 2.0 mg/kg/day, 2.5 mg/kg/day, 3.0 mg/kg/day, 4.0 mg/kg/day, or 5.0 mg/kg/day. In some embodiments, the dose of the SV2A inhibitor is 0.001 – 0.5 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.07 – 35 mg/day), or 0.01 – 0.5 mg/kg/day (which is about 0.7 – 35 mg/day). Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[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 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, 0.08 mg/kg/day, 0.12 mg/kg/day, 0.14 mg/kg/day, 0.16 mg/kg/day, 0.18 mg/kg/day, 0.2 mg/kg/day, 0.4 mg/kg/day, 0.6 mg/kg/day, 0.8 mg/kg/day, 1.0 mg/kg/day, 1.2 mg/kg/day, 1.4 mg/kg/day, 1.6 mg/kg/day, 1.8 mg/kg/day, 2.0 mg/kg/day, 2.2 mg/kg/day, 2.4 mg/kg/day, or 2.5 mg/kg/day. In some embodiments, the dose of the SV2A inhibitor is 0.1 – 2.5 mg/kg/day (which, given a typical human subject of 70 kg, is about 7 – 180 mg/day), 0.1 – 0.2 mg/kg/day (which is about 7 – 15 mg/day), 0.2 – 0.4 mg/kg/day (about 14 – 30 mg/day), 0.4 – 2.5 mg/kg/day (about 25 – 180 mg/day), 0.6 – 1.8 mg/kg/day (about 40 – 130 mg/day), 0.04 – 2.5 mg/kg/day (about 2.5 – 180 mg/day) or 0.06 – 1.8 mg/kg/day (about 4 – 130 mg/day). In some embodiments of the invention, the dose of the SV2A inhibitor is 40 to 130 mg, 140 to 300 mg, 200 to 300 mg or 140 to 200 mg. Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[0199] In certain embodiments of the invention, the dose of the SV2A inhibitor is 0.0015 to 7 mg/kg/day (which, given a typical human subject of 70 kg, is about 0.1 - 500 mg/day). Daily doses that may be used include, but are not limited to 0.0015 mg/kg, 0.002 mg/kg, 0.0025 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.02 mg/kg, 0.03 mg/kg, 0.04 mg/kg, 0.05 mg/kg, 0.06 mg/kg, 0.07 mg/kg, 0.08 mg/kg, 0.09 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1 mg/kg, 1.2 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.8 mg/kg, 2.0 mg/kg, 2.2 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.8 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, 4.5 mg/kg, 5.0 mg/kg, 6.0 mg/kg, or 7.0 mg/kg; or 0.1 mg, 0.15 mg, 0.18 mg, 0.35 mg, 0.7 mg, 1.5 mg, 2.0 mg, 2.5 mg, 2.8 mg, 3.0 mg, 3.5 mg, 4.2 mg, 5 mg, 5.5 mg, 6.0 mg, 7 mg, 8 mg, 9 mg, 10 mg, 12 mg, 15 mg, 20 mg, 25 mg, 28 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 125 mg, 140 mg, 150 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 225 mg, 250 mg,

280 mg, 300 mg, 350 mg, 400 mg, or 500 mg. In some embodiments, the daily dose of SV2A inhibitor that can be used in the methods of this invention include, without limitation, 0.0015 - 5 mg/kg (or 0.1 - 350 mg for a subject of 70kg), 0.01 - 0.8 mg/kg, 0.01 - 1 mg/kg, 0.01 - 1.5 mg/kg, 0.01 - 2 mg/kg, 0.01 - 2.5 mg/kg, 0.01 - 3 mg/kg, 0.01 - 3.5 mg/kg, 0.01 - 4 mg/kg, 0.01 - 5 mg/kg, 0.025 - 0.8 mg/kg, 0.025 - 1 mg/kg, 0.025 - 1.5 mg/kg, 0.025 - 2 mg/kg, 0.025 - 2.5 mg/kg, 0.025 - 3 mg/kg, 0.025 - 3.5 mg/kg, 0.025 - 4 mg/kg, 0.05 - 0.8 mg/kg, 0.05 - 1 mg/kg, 0.05 - 1.5 mg/kg, 0.05 - 2 mg/kg, 0.05 - 2.5 mg/kg, 0.05 - 3 mg/kg, 0.05 - 3.5 mg/kg, 0.05 - 4 mg/kg, 0.075 - 0.8 mg/kg, 0.075 - 1 mg/kg, 0.075 - 1.5 mg/kg, 0.075 - 2 mg/kg, 0.075 - 2.5 mg/kg, 0.075 - 3 mg/kg, 0.075 - 3.5 mg/kg, 0.075 - 4 mg/kg, 0.1 - 0.8 mg/kg, 0.1 - 1 mg/kg, 0.1 - 1.5 mg/kg, 0.1 - 2 mg/kg, 0.1 - 2.5 mg/kg, 0.1 - 3 mg/kg, 0.1 - 3.5 mg/kg, 0.1 - 4 mg/kg, 0.2 - 0.8 mg/kg, 0.2 - 1 mg/kg, 0.2 - 1.5 mg/kg, 0.2 - 2 mg/kg, 0.2 - 2.5 mg/kg, 0.2 - 3 mg/kg, 0.2 - 3.5 mg/kg, 0.2 - 4 mg/kg, 0.5 - 0.8 mg/kg, 0.5 - 1 mg/kg, 0.5 - 1.5 mg/kg, 0.5 - 2 mg/kg, 0.5 - 2.5 mg/kg, 0.5 - 3 mg/kg, 0.5 - 3.5 mg/kg, or 0.5 - 4 mg/kg; or 0.7 - 50 mg, 0.7 - 75 mg, 0.7 - 100 mg, 0.7 - 150 mg, 0.7 - 180 mg, 0.7 - 225 mg, 0.7 - 250 mg, 0.7 - 280 mg, 1.8 - 50 mg, 1.8 - 75 mg, 1.8 - 100 mg, 1.8 - 150 mg, 1.8 - 180 mg, 1.8 - 225 mg, 1.8 - 250 mg, 1.8 - 280 mg, 3.5 - 50 mg, 3.5 - 75 mg, 3.5 - 100 mg, 3.5 - 150 mg, 3.5 - 180 mg, 3.5 - 225 mg, 3.5 - 250 mg, 3.5 - 280 mg, 5 - 50 mg, 5 - 75 mg, 5 - 100 mg, 5 - 150 mg, 5 - 180 mg, 5 - 225 mg, 5 - 250 mg, 5 - 280 mg, 7 - 50 mg, 7 - 75 mg, 7 - 100 mg, 7 - 150 mg, 7 - 180 mg, 7 - 225 mg, 7 - 250 mg, 7 - 280 mg, 15 - 50 mg, 15 - 75 mg, 15 - 100 mg, 15 - 150 mg, 15 - 180 mg, 15 - 225 mg, 15 - 250 mg, 15 - 280 mg, 35 - 50 mg, 35 - 75 mg, 35 - 100 mg, 35 - 150 mg, 35 - 180 mg, 35 - 225 mg, 35 - 250 mg, or 35 - 280 mg. Other doses higher than, intermediate to, or less than these doses may also be used and may be determined by one skilled in the art following the methods of this invention.

[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 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 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 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.

[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.

[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	+	+	+	+	+	+

[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 - 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 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 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.

[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, 0.5 - 35 mg, 0.75 - 35 mg, 1.0 - 35 mg, 1.5 - 35 mg, 2.0 - 35 mg, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, 0.0015 - 0.5 mg/kg, 0.0075 - 0.5 mg/kg, 0.01 - 0.5 mg/kg, 0.015 - 0.5 mg/kg, 0.02 - 0.5 mg/kg, 0.03 - 0.5 mg/kg, 0.0015 - 0.4 mg/kg, 0.0015 - 0.3 mg/kg, 0.0015 - 0.2 mg/kg, 0.0015 - 0.15 mg/kg, 0.0015 - 0.1 mg/kg, 0.0015 - 0.05 mg/kg, or 0.0015 - 0.04 mg/kg.

Table 3 - Daily Doses of Brivaracetam

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	+	+	+	+	+	+	+	+	+

[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 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.

[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, 0.1 - 30 mg, 0.1 - 25 mg, 0.1 - 20 mg, 0.1 - 15 mg, 0.1 - 10 mg, 0.1 - 5 mg, 0.1 - 2.5 mg, 0.0015 - 0.5 mg/kg, 0.0075 - 0.5 mg/kg, 0.01 - 0.5 mg/kg, 0.015 - 0.5 mg/kg, 0.02 - 0.5 mg/kg, 0.03 - 0.5 mg/kg, 0.0015 - 0.4 mg/kg, 0.0015 - 0.3 mg/kg, 0.0015 - 0.2 mg/kg, 0.0015 - 0.15 mg/kg, 0.0015 - 0.1 mg/kg, 0.0015 - 0.05 mg/kg, or 0.0015 - 0.04 mg/kg.

Table 7 - Daily Doses of Seletracetam

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	+	+	+	+	+	+

[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,

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.

[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	+	+	+	+	+	+	+	+	+

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.

[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.

[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 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 daily, less than 0.5 mg daily, or less that 0.1 mg daily.

[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.

[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 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.

[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).

[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, 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 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 ± 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 daily formulation is for higher compliance among patients suffering from cognitive impairment.

[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.

[0222] The composition in the present invention may be in solid dosage forms such as capsules, tablets, dragrees, pills, lozenges, powders and granule. Where appropriate, they may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled releases of one or more active ingredient such as sustained or prolonged release according to methods well known in the art. In certain embodiments, the composition is in form of a slow, controlled, or extended release. The term "extended release" is widely recognized in the art of pharmaceutical sciences and is used herein to refer to a controlled release of an active compound or agent from a dosage form to an environment over (throughout or during) an extended period of time, e.g. greater than or equal to one hour. An extended release dosage form will release drug at substantially constant rate over an extended period of time or a substantially constant amount of drug will be released incrementally over an extended period of time. The term "extended release" used herein includes the terms "controlled release", "prolonged release", "sustained release", or "slow release", as these terms are used in the pharmaceutical sciences. In some embodiments, the extended release dosage is administered in the form of a patch or a pump. The composition may also be in liquid

dosage forms including solutions, emulsions, suspensions, syrups, and elixirs.

[0223] The compositions may be specifically formulated for administration by any suitable route as described herein and known in the art. Compositions for parental administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Compositions for intraoral and oral delivery (including sublingual and buccal administration, e.g. Danckwerts et al, and oral) include but are not limited to bioadhesive polymers, tablets, patches, liquids and semisolids (see e.g., Smart et al). Compositions for respiratory delivery (pulmonary and nasal delivery) include but are not limited to a variety of pressurized metered dose inhalers, dry powder inhalers, nebulizers, aqueous mist inhalers, drops, solutions, suspensions, sprays, powders, gels, ointments, and specialized systems such as liposomes and microspheres (see e.g. Owens et al, "Alternative Routes of Insulin Delivery" and Martini et al). Compositions for transdermal delivery include but are not limited to colloids, patches, and microemulsions. Other suitable administration forms for the above and other include depot injectable formulations, suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

[0224] The compositions may also contain adjuvants, such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[0225] Therapeutic formulations can be prepared by methods well known in the art of pharmacy, see, e.g., Goodman et al., 2001; Ansel, et al., 2004; Stoklosa et al., 2001; and Bustamante, et al., 1993.

[0226] In certain embodiments of the invention, a composition comprising an SV2A 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 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., 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 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 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., 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 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, 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.

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 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 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 Age-related Cognitive Decline (ARCD) are believed to be related to aging. Others are related to disease, for example, AD. Animal models serve as an important resource for developing and evaluating treatments for such age-related cognitive impairments. Features that characterize age-related cognitive impairment in animal models typically extend to age-related cognitive impairment in humans. Efficacy in such animal models is, thus, predictive of efficacy in humans.

[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 impairment in an outbred strain of aged Long-Evans rats (Charles River Laboratories; Gallagher et al., *Behav. Neurosci.* 107:618-626, (1993)). In a behavioral assessment with the Morris Water Maze (MWM), rats learn and remember the location of an escape platform guided by a configuration of spatial

cues surrounding the maze. The cognitive basis of performance is tested in probe trials using measures of the animal's spatial bias in searching for the location of the escape platform. Aged rats in the study population have no difficulty swimming to a visible platform, but an age-dependent impairment is detected when the platform is camouflaged, requiring the use of spatial information. Performance for individual aged rats in the outbred Long-Evans strain varies greatly. For example, a proportion of those rats perform on a par with young adults. However, approximately 40-50% falls outside the range of young performance. This variability among aged rats reflects reliable individual differences. Thus, within the aged population some animals are cognitively impaired and designated aged-impaired (AI) and other animals are not impaired and are designated aged-unimpaired (AU). *See*, e.g., Colombo et al., *Proc. Natl. Acad. Sci.* 94: 14195-14199, (1997); Gallagher and Burwell, *Neurobiol. Aging* 10: 691-708, (1989); Rapp and Gallagher, *Proc. Natl. Acad. Sci.* 93: 9926-9930, (1996); Nicolle et al., *Neuroscience* 74: 741-756, (1996); and Nicolle et al., *J. Neurosci.* 19: 9604-9610, (1999).

[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.

Example 1: Behavioral Assessment of Levetiracetam, Donepezil, and Combined Treatments in a Radial Arm Maze Task

[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. 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™ 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 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™ cereal) from the five unblocked arms. The rat was then removed 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).

[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 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 ± standard error of the mean (SEM) = 0.75 ± 0.32) and 10 mg/kg/day (average no. of errors ± SEM = 0.80 ± 0.27) than using vehicle control (average no. of errors ± SEM = 2.00 ± 0.42). Relative to vehicle control treatment, levetiracetam significantly improves memory performance at 5 mg/kg/day ($t(9) = 2.18$, $p = 0.057$) and 10 mg/kg/day ($t(9) = 2.37$, $p = 0.042$).

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 ± standard error of the mean (SEM) = 2.88 ± 0.46) and 2 mg/kg/day (average no. of errors ± SEM = 2.81 ± 0.43) are not significantly different from using vehicle control (average no. of errors ± SEM = 2.88 ± 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

[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 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 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 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 fewer with the combined administration of donepezil (1 mg/kg/day) and levetiracetam (2.5 mg/kg/day) (average no. of errors ± standard error of the mean (SEM) = 1.69 ± 0.53) than using vehicle control (average no. of errors ± 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 ($t(7) = 2.16$, $p = 0.034$).

[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 interaction between donepezil and levetiracetam when administered together.

Example 2: Levetiracetam Treatments in Human Subjects with aMCI

[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.

Participants and clinical characterization

[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-IV Axis I Disorders and the Clinical Dementia Rating (CDR) scale. All aMCI patients have CDR scores of 0.5. Diagnosis of aMCI is based on the criteria proposed by Petersen et al. (e.g., "Mild cognitive impairment: Aging to

Alzheimer's Disease," Oxford University Press, N.Y. (2003), which include a memory complaint (corroborated by an informant), impaired memory function on testing (1.5 standard deviations below norm), otherwise preserved cognitive functioning (within 1 standard deviation of norm), no decline in functional ability, and no dementia. Final aMCI diagnoses are reached by clinical consensus. Exclusion criteria include major neurological or psychiatric disorders, head trauma with loss of consciousness, history of drug abuse or dependency, and general contraindications to an MRI examination (e.g. cardiac pacemaker, aneurysm coils, claustrophobia). Each aMCI subject is required to have a study partner (i.e., an informant) who can provide information about the subject's daily function and assure that medications are taken appropriately. See **FIGS. 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 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 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 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.

[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 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.

[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.

[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 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.

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 Visual Retention Test, as these tasks are particularly sensitive to medial temporal lobe function and early memory problems (Marquis et al., 2002 and Masur et al., 1994). Additionally, subjects are asked to complete tests of more general cognitive function such as tests to assess general mental status, executive function, attention and general naming ability. All neuropsychological tests are administered by a trained research assistant during a 60-minute session. As the three neuropsychological assessments in this study occur within a time period of 8 weeks, different versions of the neuropsychological tests are used to minimize test specific practice effects. Breaks are provided to the subject as needed.

Drug administration

[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).

[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 levetiracetam is approximately 7 ± 1 hour (expected to be 9-10 hours in elderly due to decreased renal function). Absorption is rapid, with peak plasma concentrations occurring about 1 hour following oral administration. Steady state can be achieved after 2 days of multiple twice-daily dosing.

[0259] A typical starting dose of levetiracetam in treating epilepsy in humans is 500 mg twice a day, which is approximately 14.3 mg/kg/day. The dosage is then is increased until optimal efficacy, 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 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, The Netherlands) equipped with an 8-channel SENSE (Sensitivity Encoding) head coil, located at the F.M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute (Baltimore, MD). High-resolution echo-planar images are collected using an acquisition matrix of 64 x 64, a repetition time of 1500 milliseconds, an echo time of 30 milliseconds, a flip angle of 70 degrees, a SENSE factor of 2, and an isotropic resolution of 1.5 mm x 1.5 mm x 1.5 mm with no gap. Nineteen oblique slices are acquired parallel to the principal longitudinal axis of the hippocampus and covered the entire medial temporal lobe region bilaterally. In addition to the functional runs, a whole-brain MPRAGE structural scan (parameters: 150 oblique slices, 1mm isotropic resolution) is acquired.

Image analysis

[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 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 the region of interest) method, a technique for cross-subject alignment, increases the power of multisubject regional fMRI studies by focusing the alignment power

specifically on the ROIs (regions of interest) and not elsewhere in the brain. First, all subjects' anatomical and functional scans are normalized to the Talairach atlas using AFNI. Sub-regions of the medial temporal lobe and the hippocampus (bilateral entorhinal cortex, perirhinal cortex, parahippocampal cortex, CA3/dentate region, CA1 region, and subiculum) are segmented in three dimensions on the MPRAGE scans. The labels for the CA3 region and dentate gyrus (DG) are combined. The anatomically defined ROIs are then used to calculate the ROI-LDDMM 3D vector field transformation for each subject using a customized template based on the mean of the entire sample tested as the target. The ROI-LDDMM 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 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 exclude voxels that does 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 functional MRI during the subject's participation in an explicit 3-alternative forced choice task, where participants view novel, repeated and similar ("lure") stimuli. The Psychophysics Toolbox extensions in Matlab 7.0 (The MathWorks, Natick, MA) is used for stimulus presentation and behavioral data collection. Stimuli are color photographs of common objects. Each participant undergoes a series of testing runs duing 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 stimuli as "similar," provides behavioral evidence of pattern separation, i.e., the separation of similar experiences into distinct non-overlapping representations. However, an incorrect indentification of lure stimuli as "old" or "new," indicates a failure of pattern separation. Identification of lure stimuli as "old" indicates that the subject focused on the similarities between the lure stimulus and the earlier-shown partner image. Identification of the lure stimulus as "new" indicates that the subject 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, 2005).

[0266] A survery of the activity level of various subregions in the medial temporal lobe during the cogitive 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 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 idenfied by subject as "similar" that is calibrated for baseline activity. **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 that it is statistically indistinguishable from the activity of control 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 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' performace in the cognitive task. With placebo treatment, aMCI patients perform worse that 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 levetiracetam treatment. See **FIG. 8**. The interaction of more correct "similar" indenficiations 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 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 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 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 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 performace 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 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 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 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 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 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 assessments are used to determine if the subject meets the entry criteria. All of the foregoing are completed using standardized forms. If the subject meets entry criteria for the study, the subject is randomly assigned to either the 62.5 mg BID or 250 mg BID study group and given the study medication (drug or placebo, randomly selected), and instructions about how it should be taken. The subject is advised about the potential for having suicidal thoughts and advised to stop taking the medication and immediately contact the study physician if this occurs.

[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. 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 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 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 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 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 Reminding Test (Buschke and Fuld, 1974) and the Verbal Paired Associates subtest, the Logical Memory subtest, the Visual Reproduction subtest of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1997), and the Benton Visual Retention Test, as these tasks are particularly sensitive to medial temporal lobe function and early memory problems (Marquis et al., 2002 and Masur et al., 1994). Additionally, subjects are asked to complete tests of more general cognitive function such as tests to assess general mental status, executive function, attention and general naming ability. All neuropsychological tests are administered by a trained research assistant during a 60-minute session. As the three neuropsychological assessments in this study occur within a time period of 8 weeks, different versions of the neuropsychological tests are used to minimize test specific practice effects. Breaks are provided to the subject as needed.

Drug administration

[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 phase). For the subjects receiving the 250 mg BID (BID stands for twice daily) drug treatment, two 250 mg tablets of levetiracetam are used to achieve a dose of 250 mg twice a day, i.e., 500 mg/day, which is approximately 7.1 mg/kg/day (assuming an average adult human weight of 70 kg). For the subjects receiving the 62.5 mg BID drug treatment, a quarter of a scored 250 mg tablet of levetiracetam is used to achieve a dose of 62.5 twice a day, i.e., 125 mg/day which is approximately 1.5 mg/kg/day.

[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 ± 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 is 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 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 specifically on the ROIs (regions of interest) and not elsewhere in the brain. First, all subjects' anatomical and functional scans are normalized to the Talairach atlas using AFNI. Sub-regions of the medial temporal lobe and the hippocampus (bilateral entorhinal cortex, perirhinal cortex, parahippocampal cortex, CA3/dentate region, CA1 region, and subiculum) are segmented in three dimensions on the MPRAGE scans. The labels for the CA3 region and dentate gyrus (DG) are combined. The anatomically defined ROIs are then used to calculate the vector field transformation for each subject using the Advanced Normalization Tools (ANTs) software package and a customized template based on the mean of the entire sample tested as the target. The resulting vector transformations for each individual subject's ROIs are then applied to the fit coefficient maps.

[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 factor nested within group. A liberal peak threshold of $p<0.07$, along with a spatial extent threshold of 40 voxels are used to define functional ROIs on the overall F statistic. This approach, rather than using a direct pair-wise contrast, reduces voxel selection biases because any differences amongst the various conditions 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 does 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

[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. 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 duing 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. 10A**). Participants are instructed to make a judgment as to whether each object seen is new, old or similar. Of critical interest are the participants' responses when presented with the second of the pair of similar objects (the "lure"; see **FIG. 10B**). The correct identification by the subject of lure stimuli as "similar," provides behavioral evidence of pattern separation, i.e., the separation of similar experiences into distinct non-overlapping representations. However, an incorrect identification of lure stimuli as "old" or "new," indicates a failure of pattern separation. Identification of lure stimuli as "old" indicates that the subject focused on the similarities between the lure stimulus and the earlier-shown partner image. Identification of the lure stimulus as "new" indicates that the subject 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, 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 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 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 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 **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**.

Example 4: Effect of Brivaracetam and Seletractam in Aged-Impaired Rats

[0293] Subjects

[0294] Aged, male Long-Evans rats were obtained at 8-9 month of age from Charles River Laboratories (Raleigh, NC) and housed in a vivarium at Johns Hopkins University until 24-26 month of age. Young rats obtained from the same source 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 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.

[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 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 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 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 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 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 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. 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 ($t(2) = 10.000$, $p = 0.010$) 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 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 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 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 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 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 used for the studies as described below.

[0308] Surgery and treatments

[0309] Under isoflurane anesthesia, memory-impaired aged rats were implanted subcutaneously in the intrascapular region with osmotic mini-pumps (ALZET, Durect Corporation, Cupertino, CA) with levetiracetam (10 mg/kg/day) or saline vehicle for four weeks prior to perfusion. Young rats, which served as controls, 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 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 μm and stored in either 4% paraformaldehyde at 4°C for in situ hybridization or cryoprotectant at -20°C for immunohistochemistry.

[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 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 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 that, sections were reacted in Proteinase K buffer containing 1.0μg/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 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 107 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 DTTand 2x SSC/ 50% formamide. They were then incubated with RNase (20 μg/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.

[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. Briefly, sections were washed in 0.1M phosphate-buffered saline (PBS) to remove cryoprotectant, and endogenous peroxidases were quenched in 0.3% H202 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 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., Burlingame, CA) and the avidin-biotin complex was visualized with nickel-enhanced diaminobenzadine (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.

[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 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 ($N=18$; $F_{2,20}= 15.739$, $p<0.001$; AI-LEV vs Y, $p=0.679$; AI-LEV vs AI-VEH, $p<0.01$; AI-VEH vs Y, $p<0.001$).

[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).

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 ± 0.288), while levels in the 125 mg BID had 4.4 mcg/ml (SEM ± 0.53) and subjects in the 250 mg BID cohort showed mean levetiracetam blood plasma level of 7.9 mcg/ml (SEM ± 0.92). See FIGS. 23A-23c.

[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 ± 0.255), while those treated with 60 mg/kg/day showed a mean levetiracetam blood plasma level of 22.4 mcg/ml (SEM ± 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; 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.

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 ,

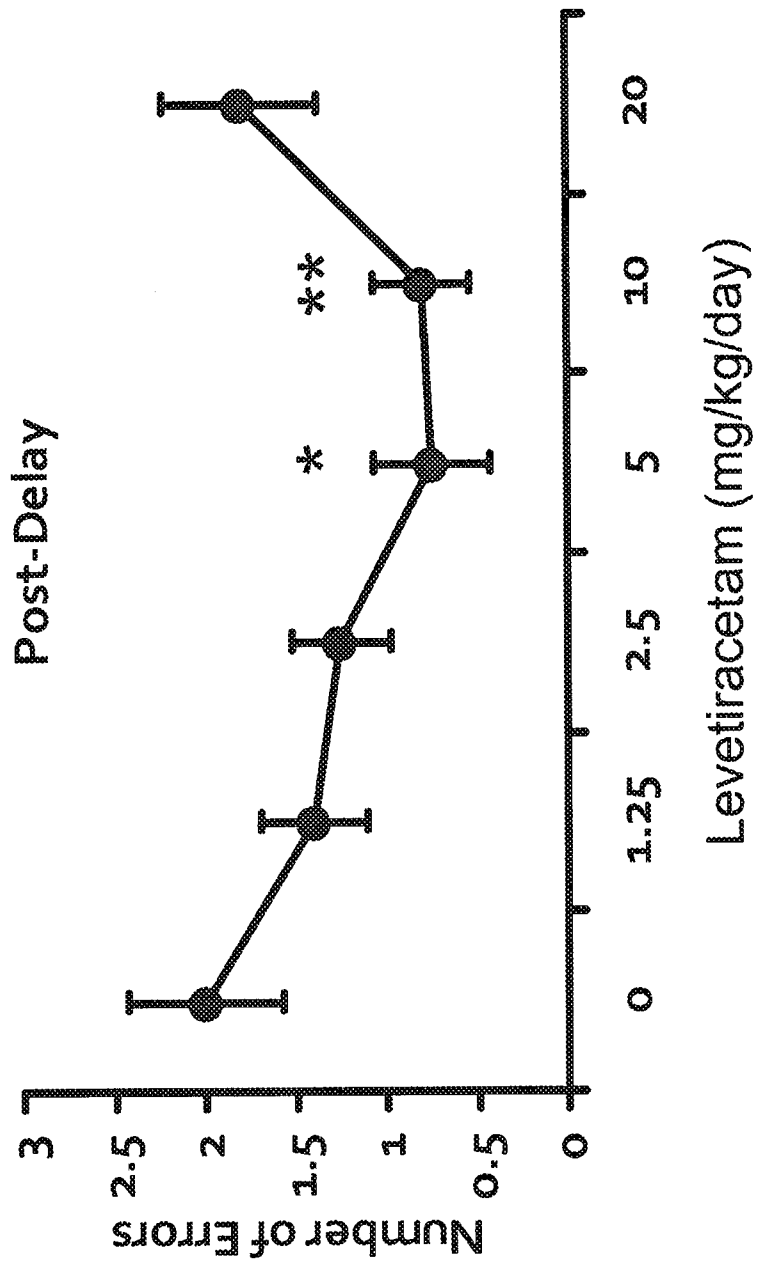
wherein levetiracetam is present in an amount of 7 - 350 mg, 70 - 350 mg, 100 - 300 mg, or 125 - 250 mg, and

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.

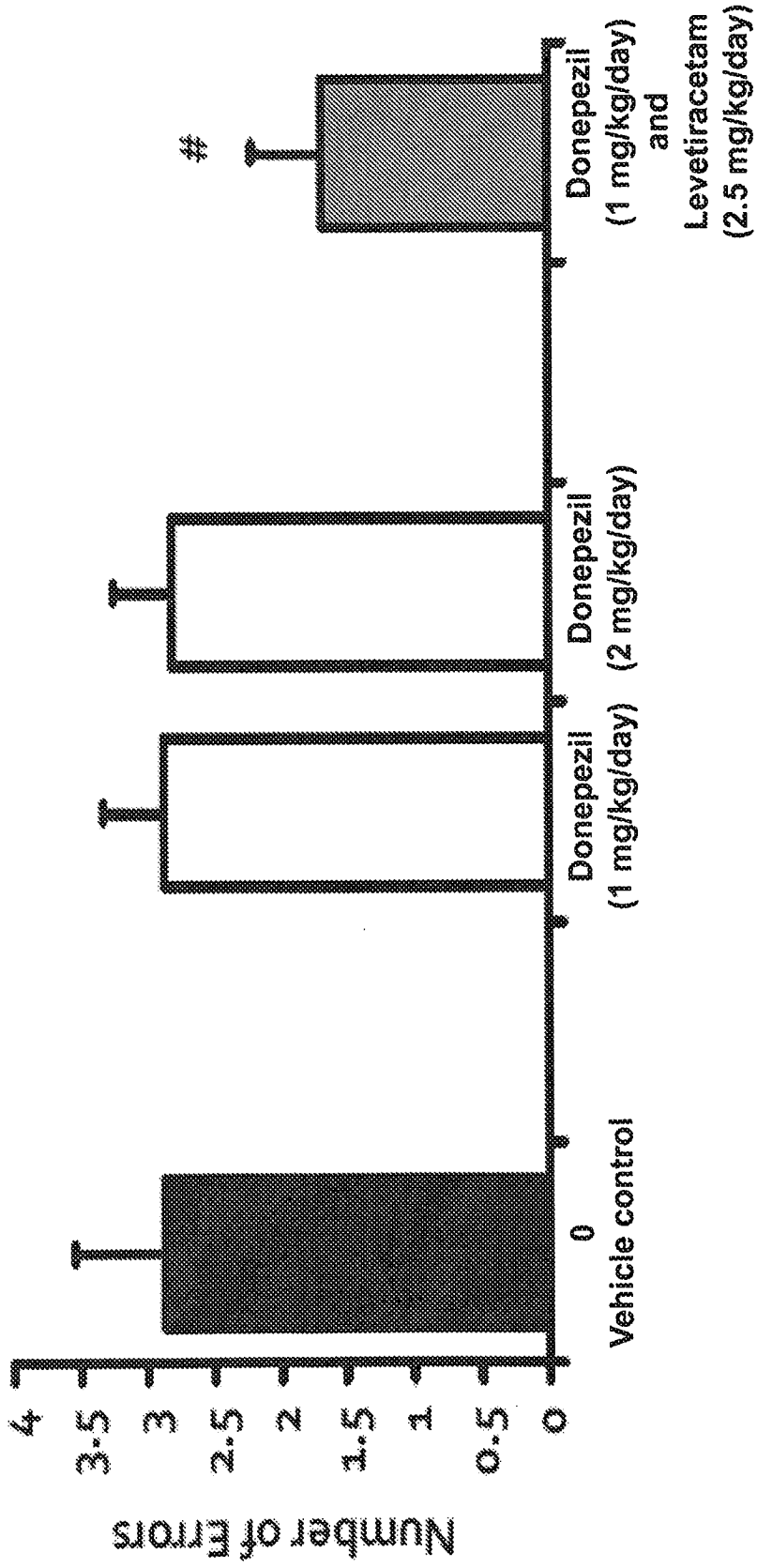
72. The composition of claim 70, wherein donepezil is present in an amount of 2 - 4 mg.

73. The composition of any one of claims 70-72, wherein donepezil is in an immediate release form.



* t(9) = 2.18, p = 0.057
** t(9) = 2.37, p = 0.042

FIG. 1



t(7) = 2.16, p = 0.034

FIG. 2

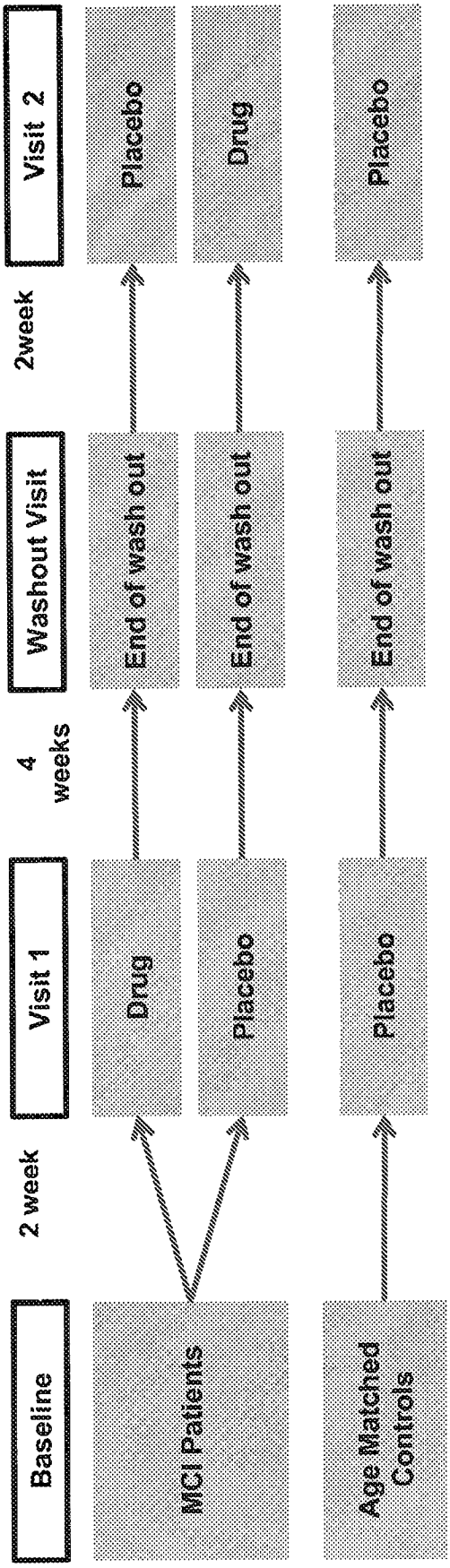

Baseline
2 week
Visit 1
4 weeks
Washout Visit
2week
Visit 2
MCI Patients
Drug
Placebo
End of wash out
Placebo
Drug
Age Matched Controls
Placebo
End of wash out
Placebo

FIG. 3

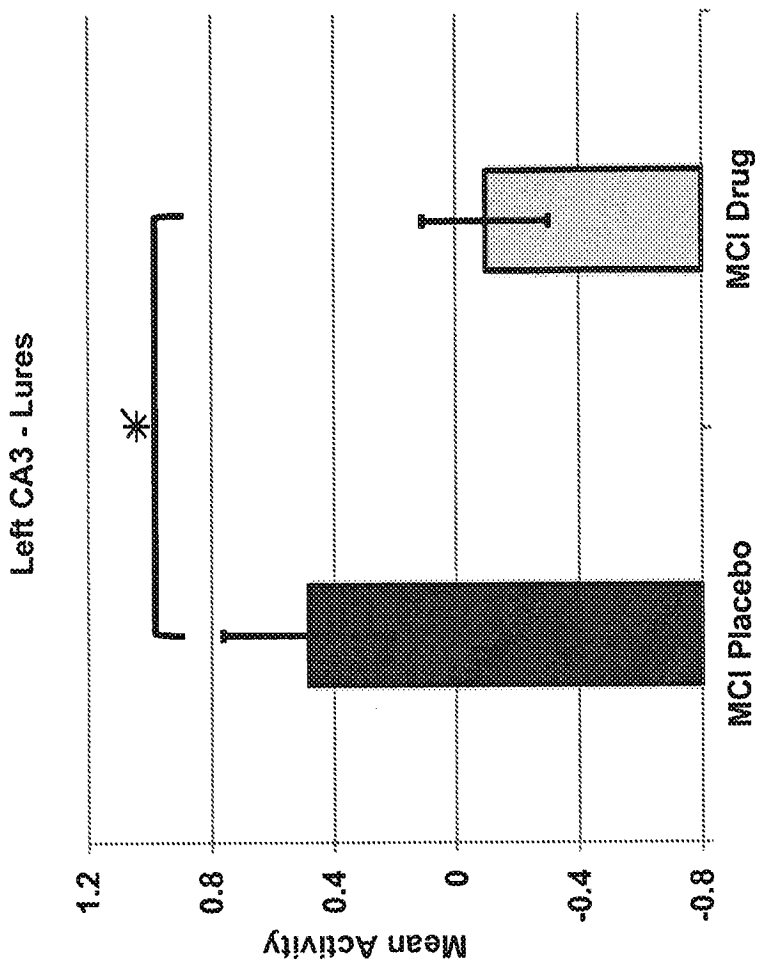

Left CA3 - Lures
Mean Activity
1.2
0.8
0.4
0
-0.4
-0.8
MCI Placebo
MCI Drug
*Paired samples t-test: t = 2.276, p = 0.037

FIG. 4B

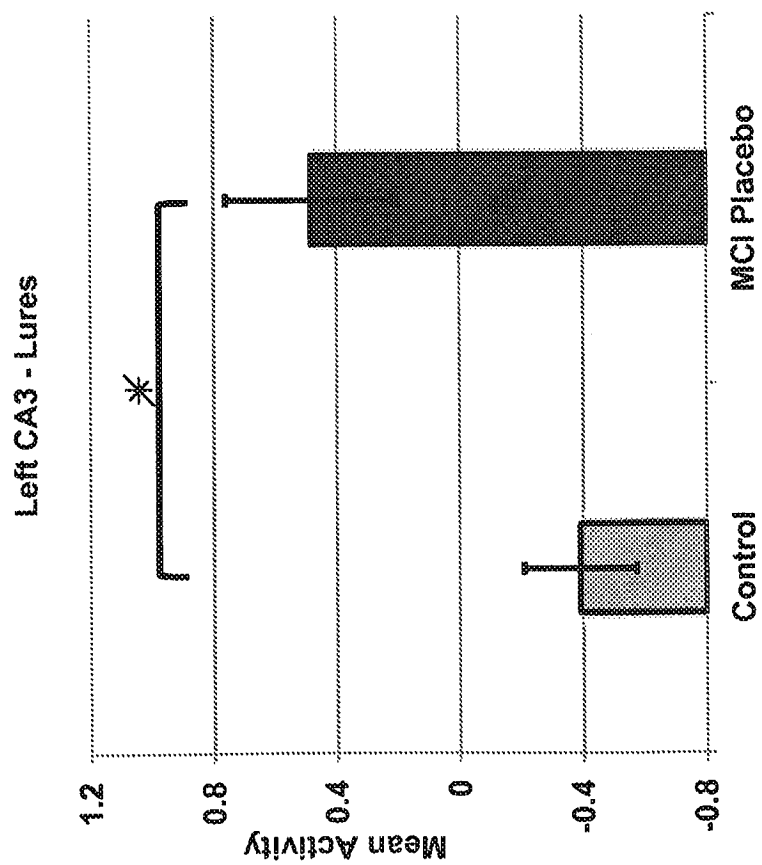

Left CA3 - Lures
Mean Activity
1.2
0.8
0.4
0
-0.4
-0.8
Control
MCI Placebo
*Independent samples t-test: t = -2.636, p = 0.013

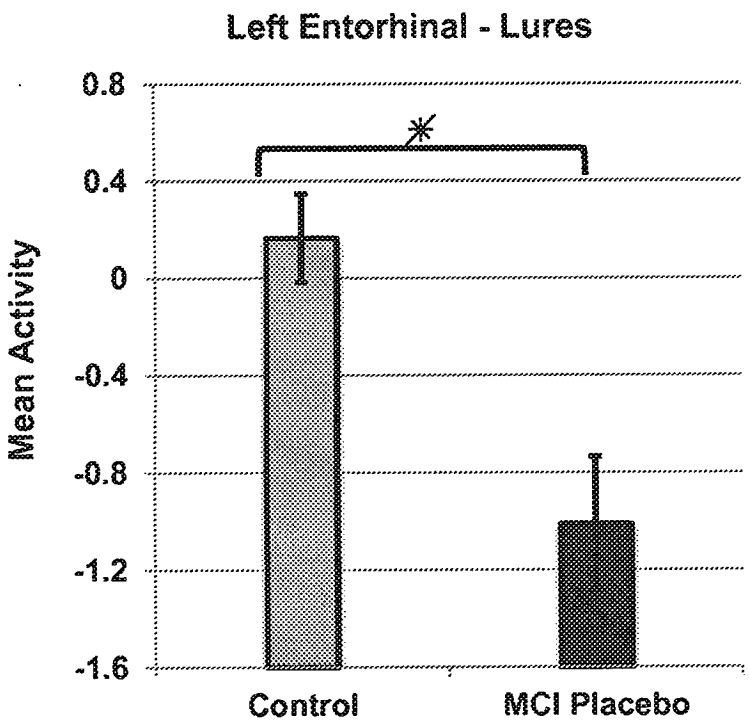
FIG. 4A

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

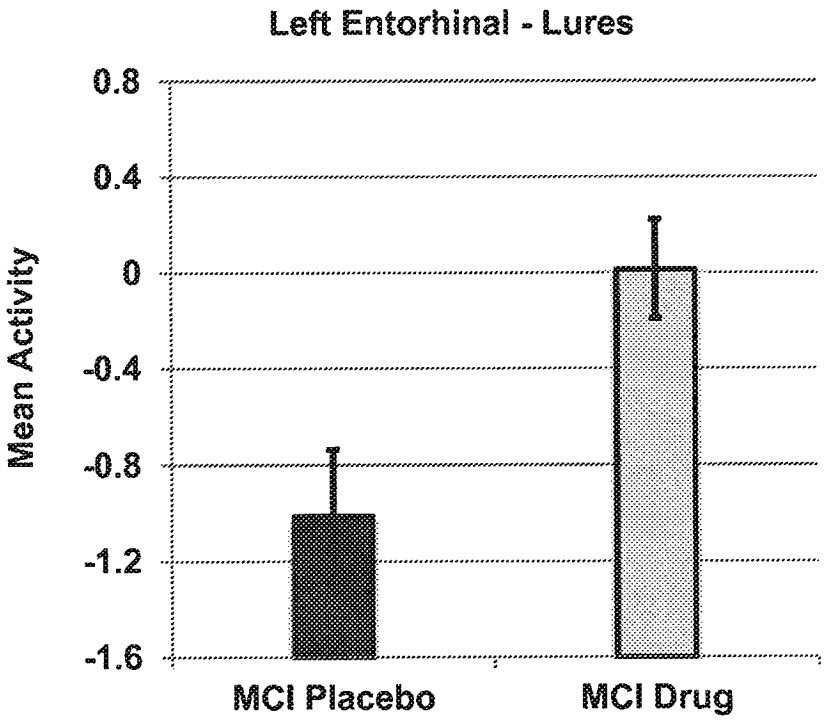
FIG. 4C

fMRI entorhinal activation in amnestic MCI is normalized by drug treatment



*Independent samples t-test: t = 3.278, p = 0.003

FIG. 5A



Paired samples t-test: t = -1.600, p= 0.129

FIG. 5B

Left Entorhinal Lures

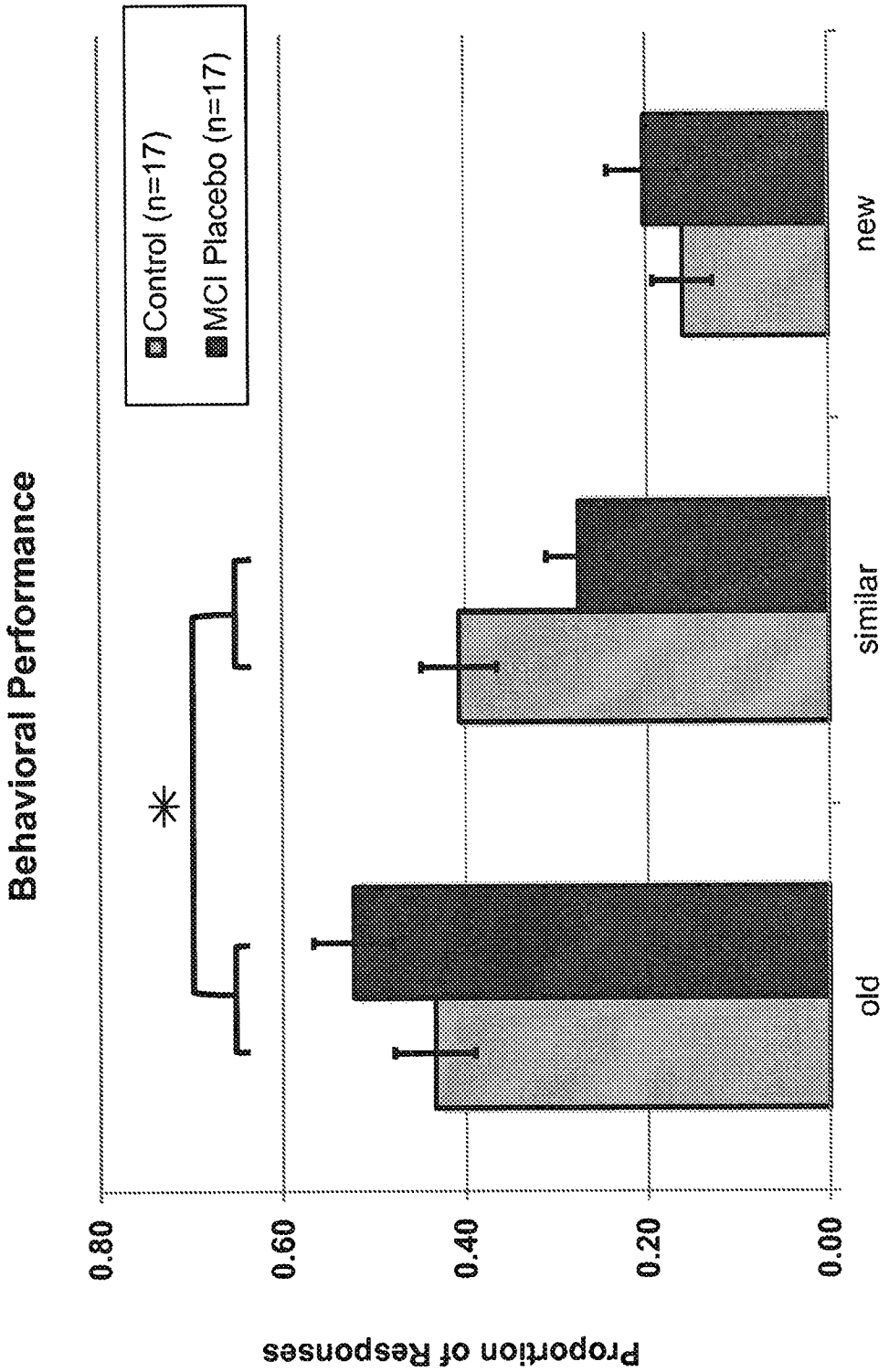
Group	Mean Activity	Standard Error
Control	0.16444	0.143864
MCI Placebo	-1.01273	0.329062
MCI Drug	0.016291	0.411762

FIG. 5C

Reduced memory in task that taxes pattern separation
2500 ms
500 ms
ISI
Sample lure pairs

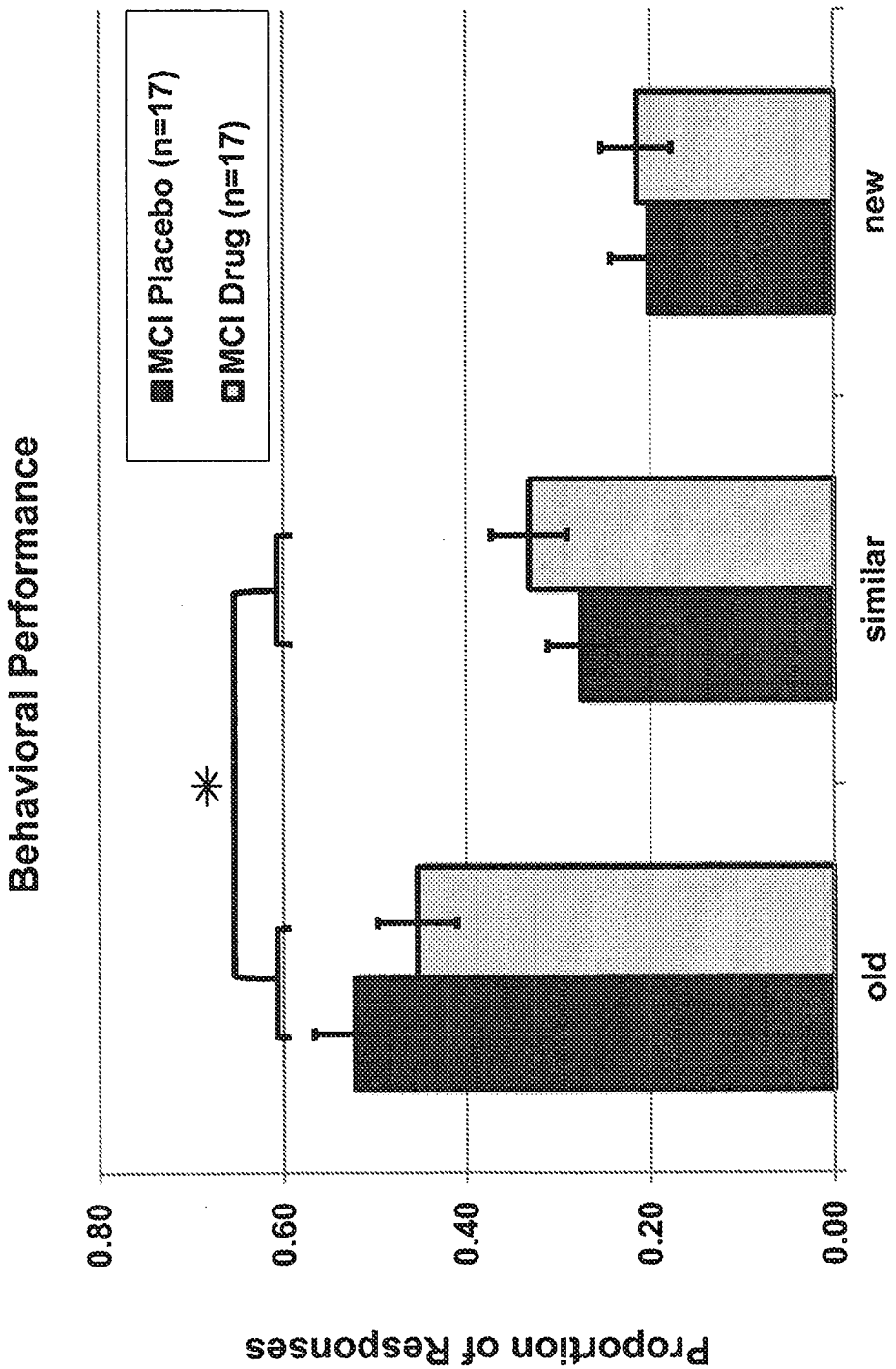
FIG. 6A

FIG. 6B



Control vs. MCI Placebo by Old vs. Similar: F= 7.687, p = 0.009

FIG. 7



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

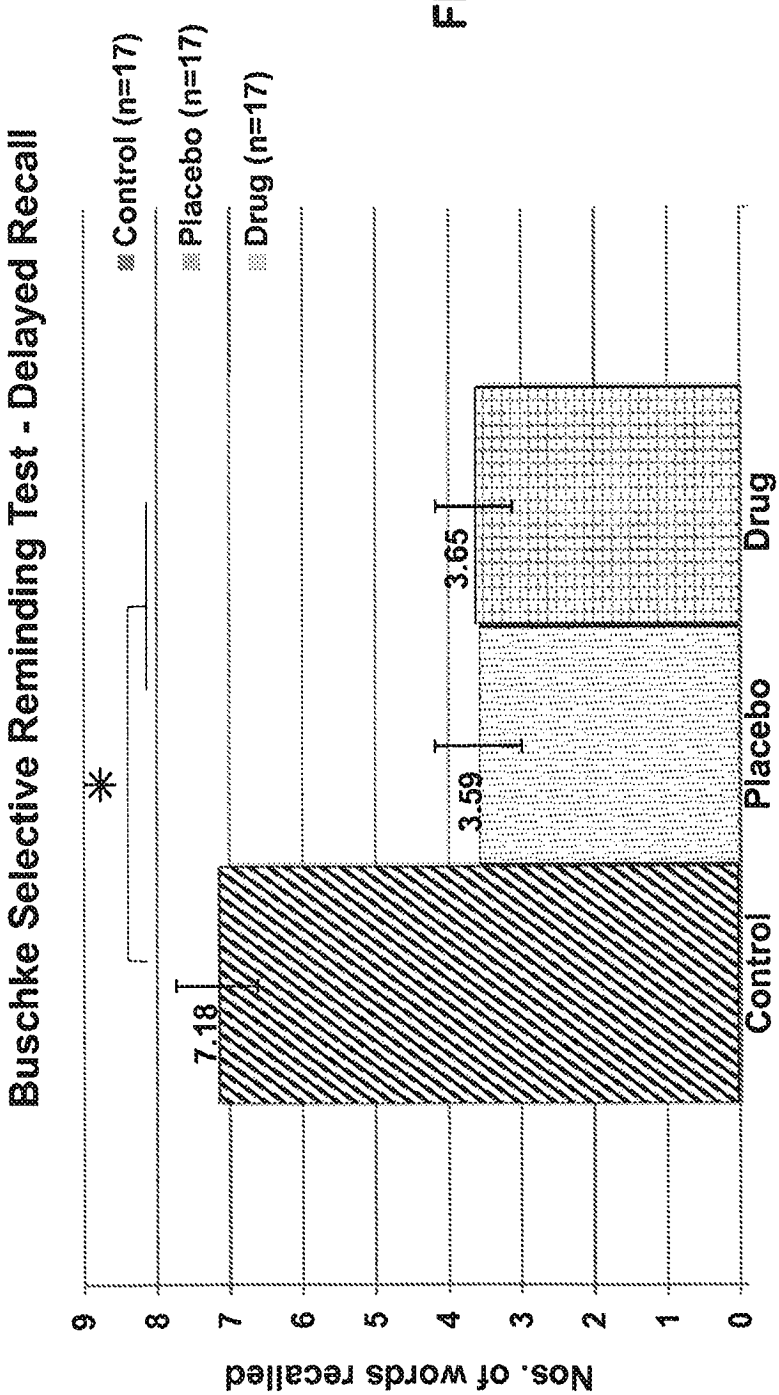


FIG. 10A

Group	Mean	Standard Error	Delayed (p-value)
Control	7.18	0.56	Control vs. Placebo: <0.001
MCI Placebo	3.59	0.59	Control vs. Drug: < 0.001
MCI Drug	3.65	0.53	Placebo vs. Drug: 0.887

FIG. 10B

FIG. 11A

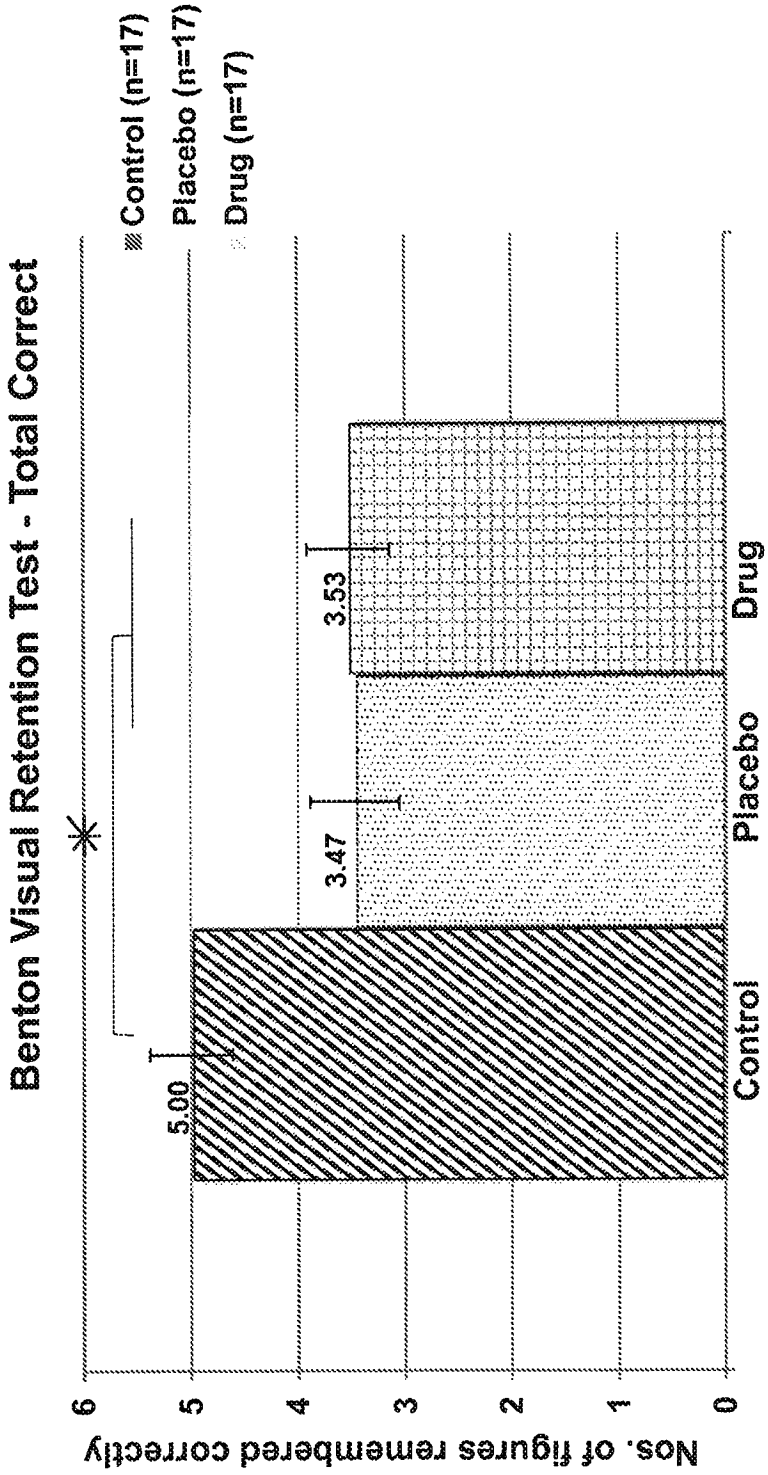


FIG. 11B

Group	Mean	Standard Error	Total Correct (p-value)
Control	5.00	0.38	Control vs. Placebo: 0.011
MCI Placebo	3.47	0.41	Control vs. Drug: 0.011
MCI Drug	3.53	0.38	Placebo vs. Drug: 0.805

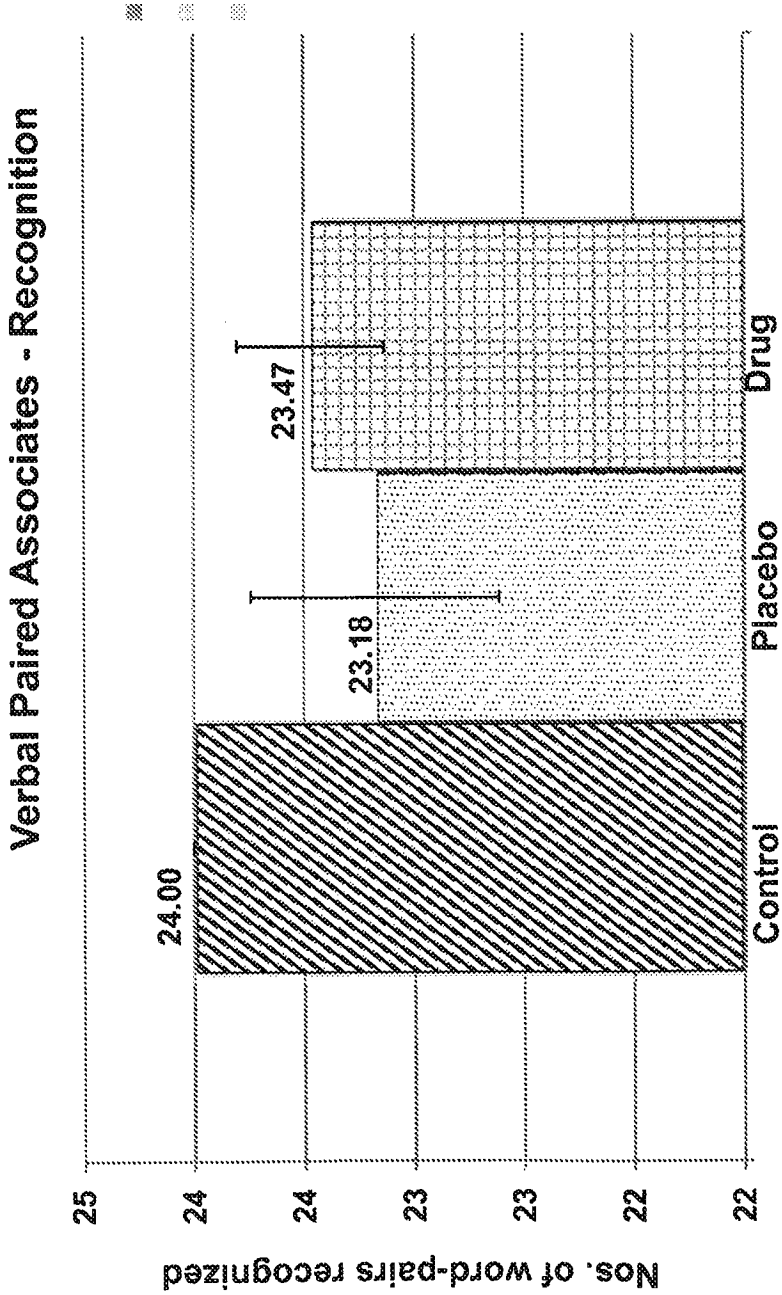


FIG. 12A

Group	Mean	Standard Error	Recognition (p-value)
Control	24.00	0.00	Control vs. Placebo: 0.154
MCI Placebo	23.18	0.56	Control vs. Drug: 0.122
MCI Drug	23.47	0.33	Placebo vs. Drug: 0.428

FIG. 12B

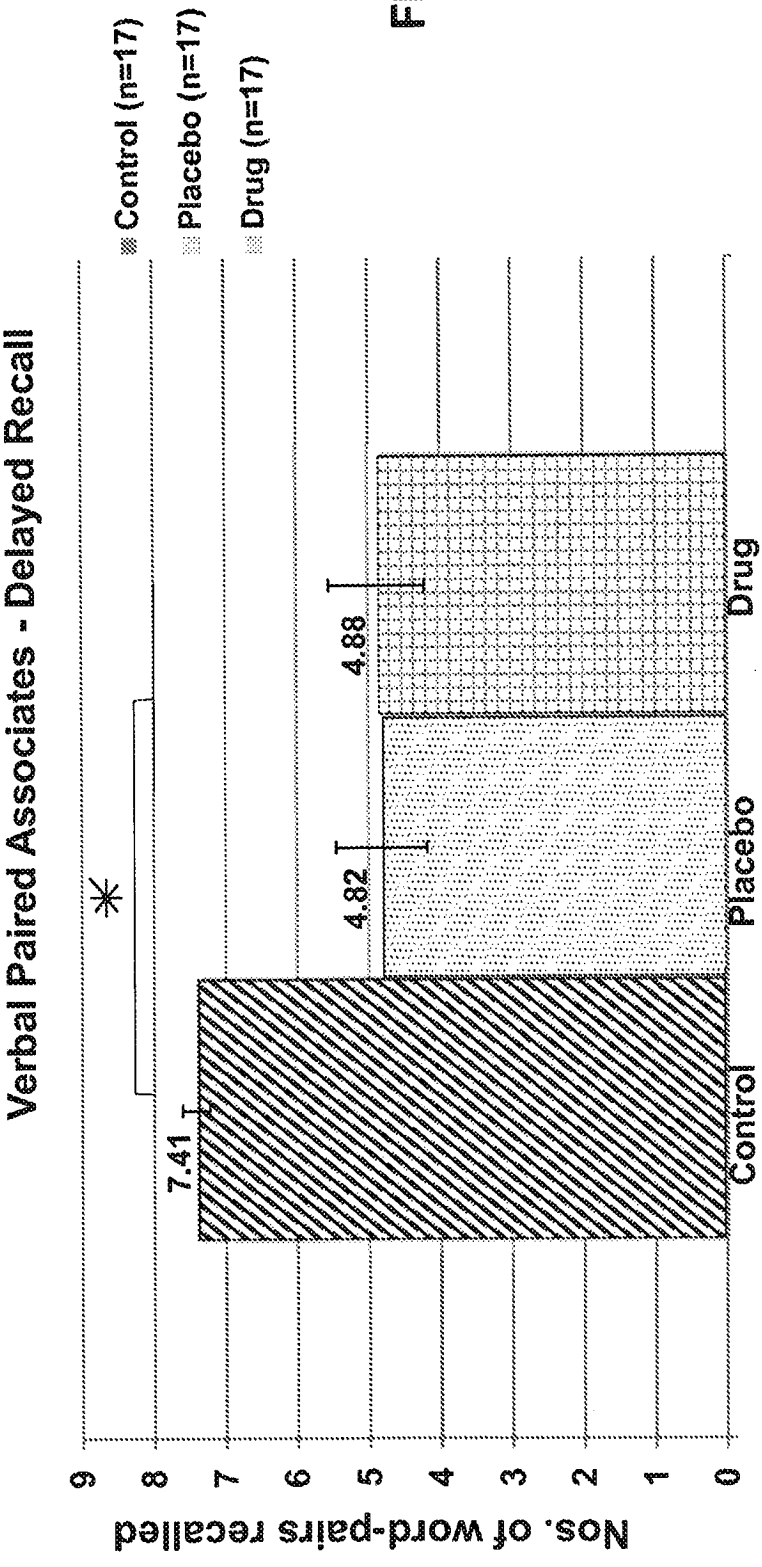


FIG. 13A

Group	Mean	Standard Error	Delayed Recall (p-value)
Control	7.41	0.19	Control vs. Placebo: <0.001
MCI Placebo	4.82	0.63	Control vs. Drug: 0.001
MCI Drug	4.88	0.67	Placebo vs. Drug: 0.848

FIG. 13B

Study Status

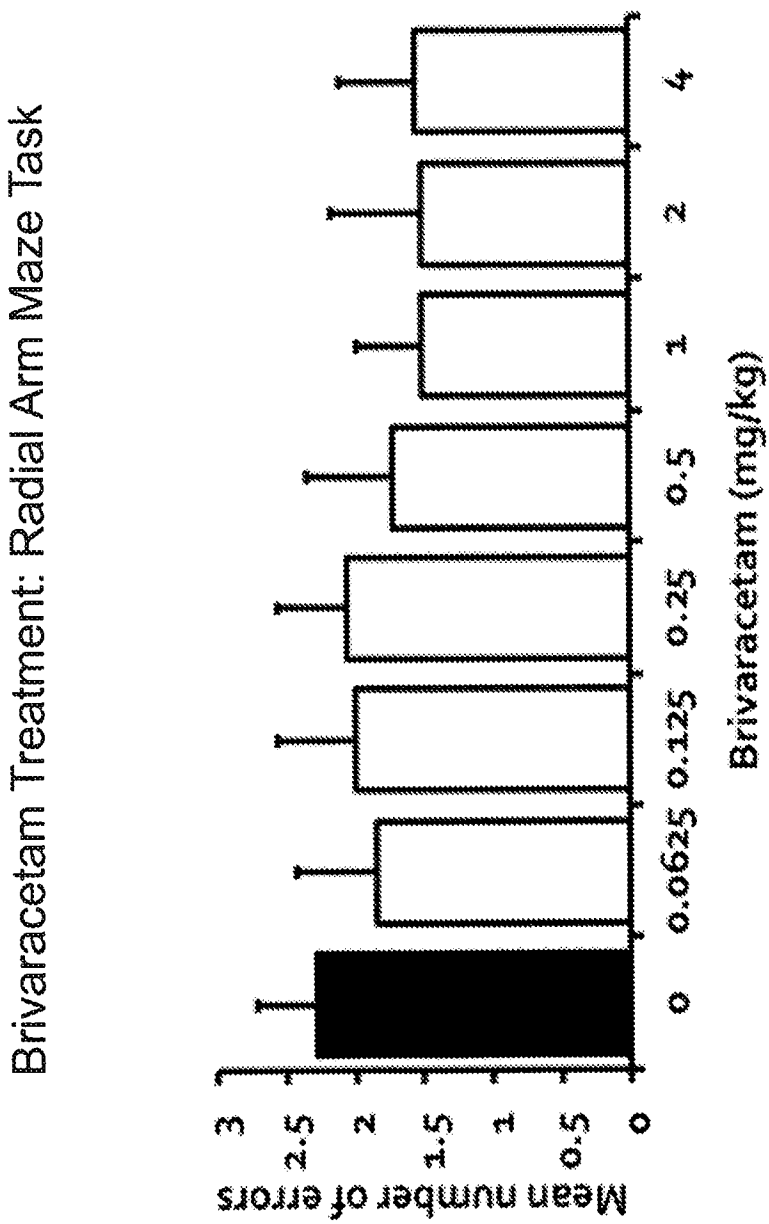
	Control subjects	MCI subjects	Total subjects
Participated in screening	26	32	58
Screening failures	4	9	13
Enrolled	22	23	45
Removed or withdrew from study	5	6	11
Total subjects used in analysis	17	17	34

FIG. 14A

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

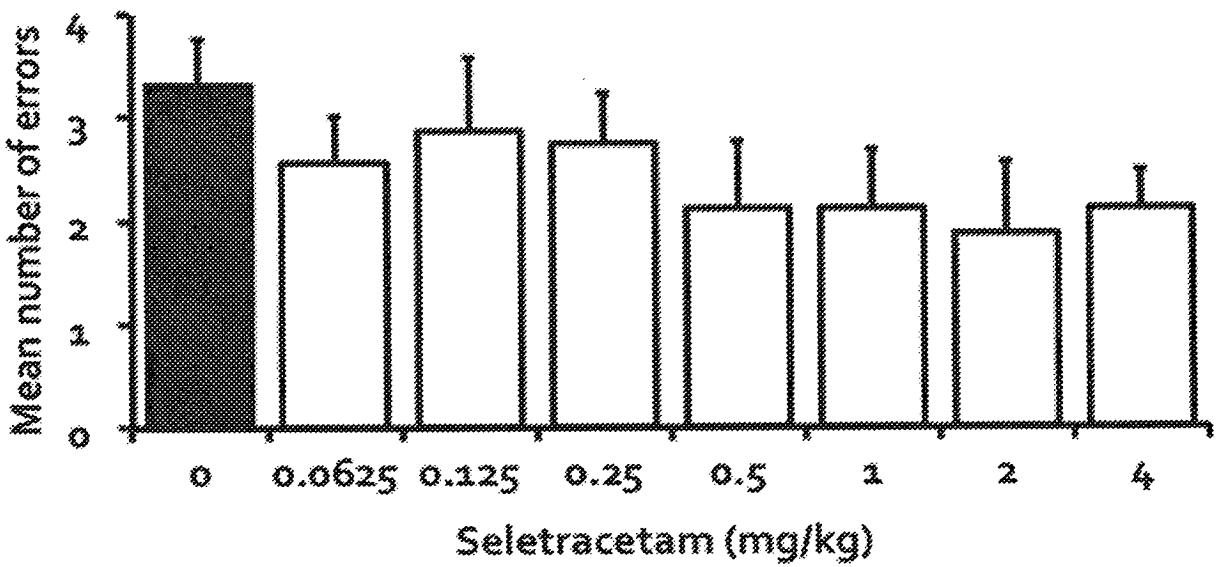
FIG. 14B



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

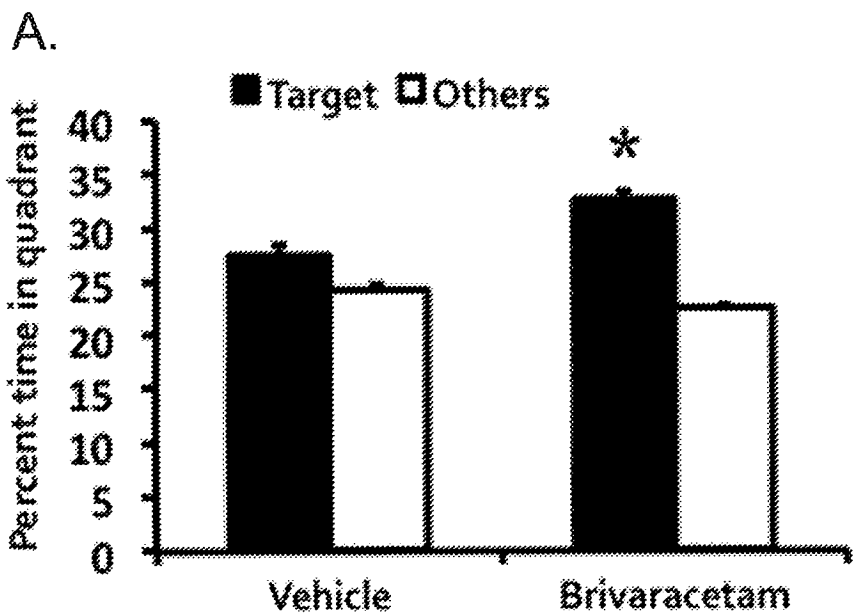


FIG. 17A

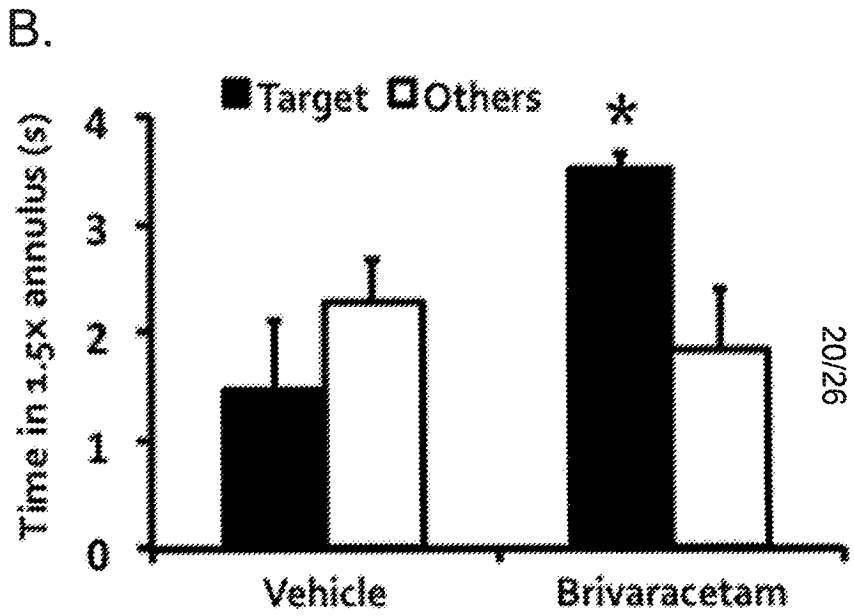


FIG. 17B

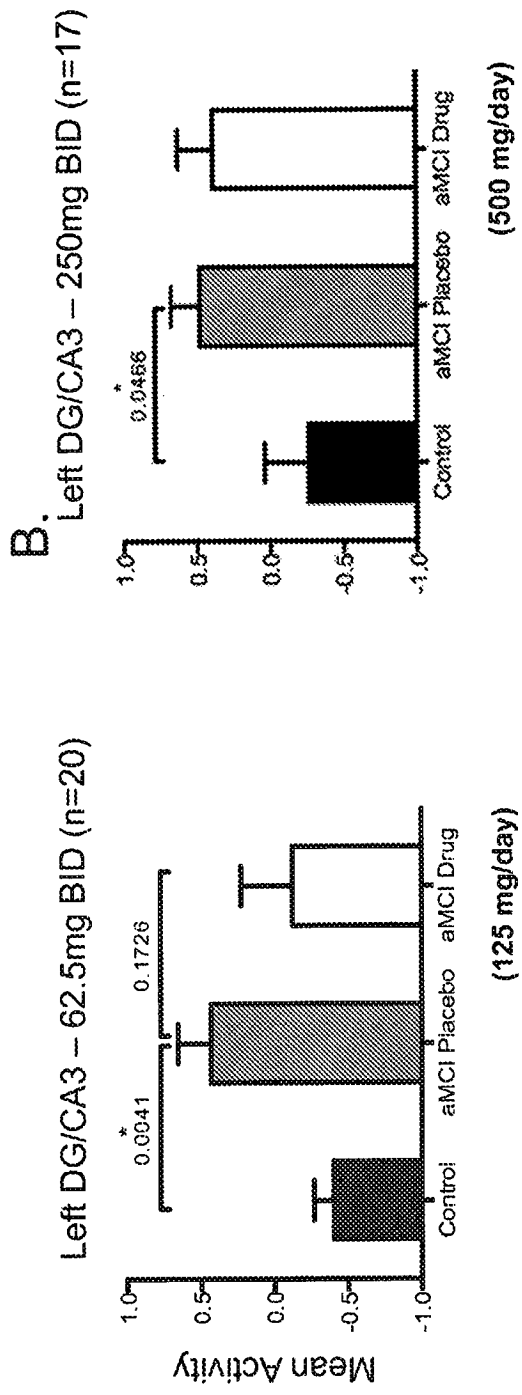


FIG. 18A

FIG. 18B

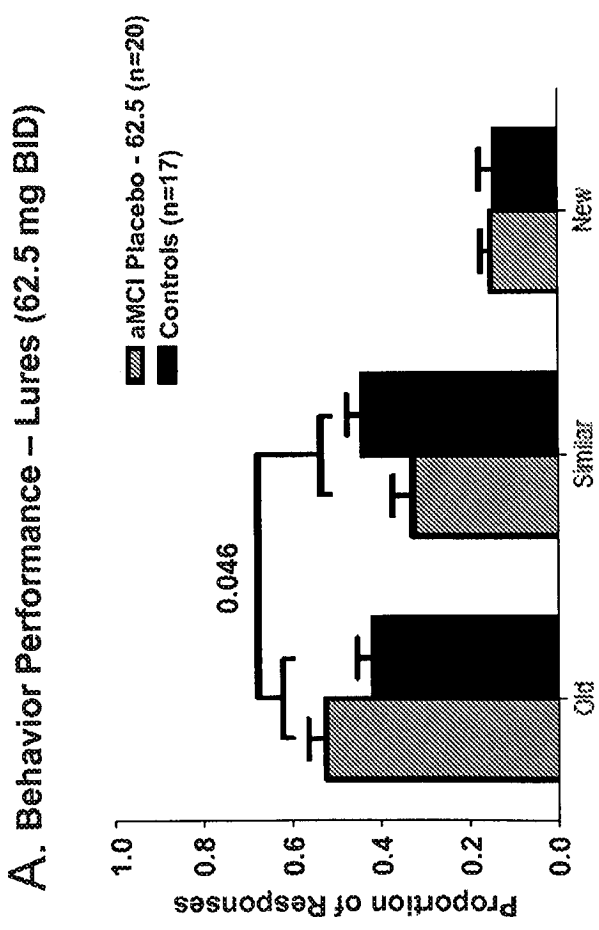


FIG. 19A

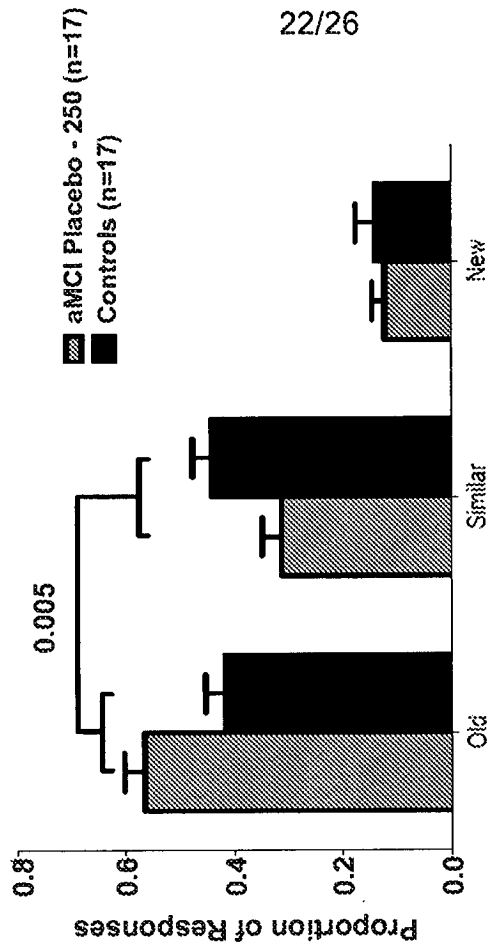


FIG. 19B

FIG. 20A

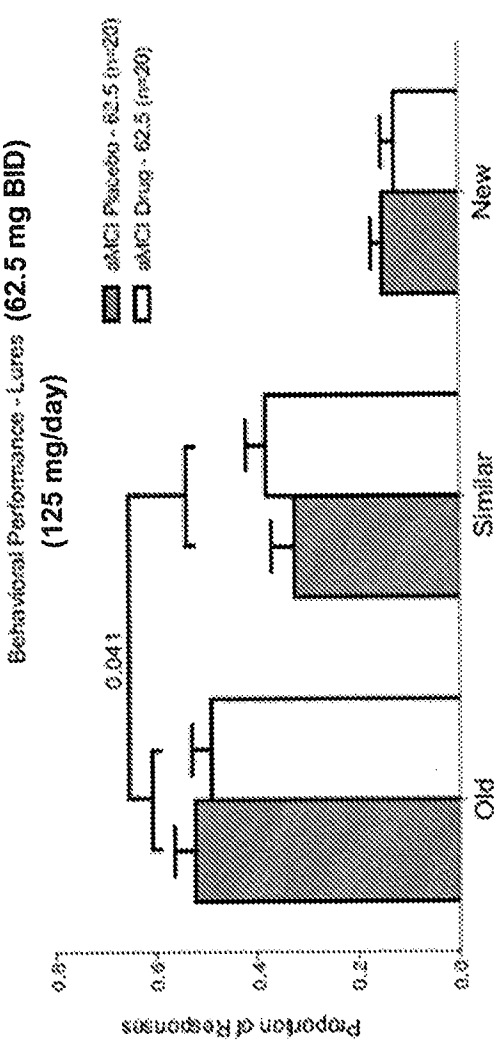
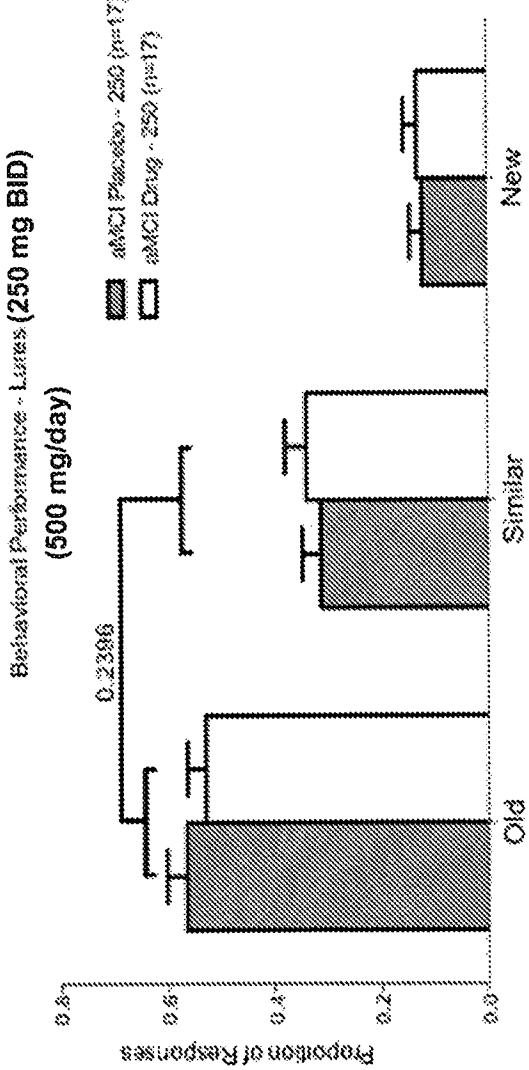


FIG. 20B



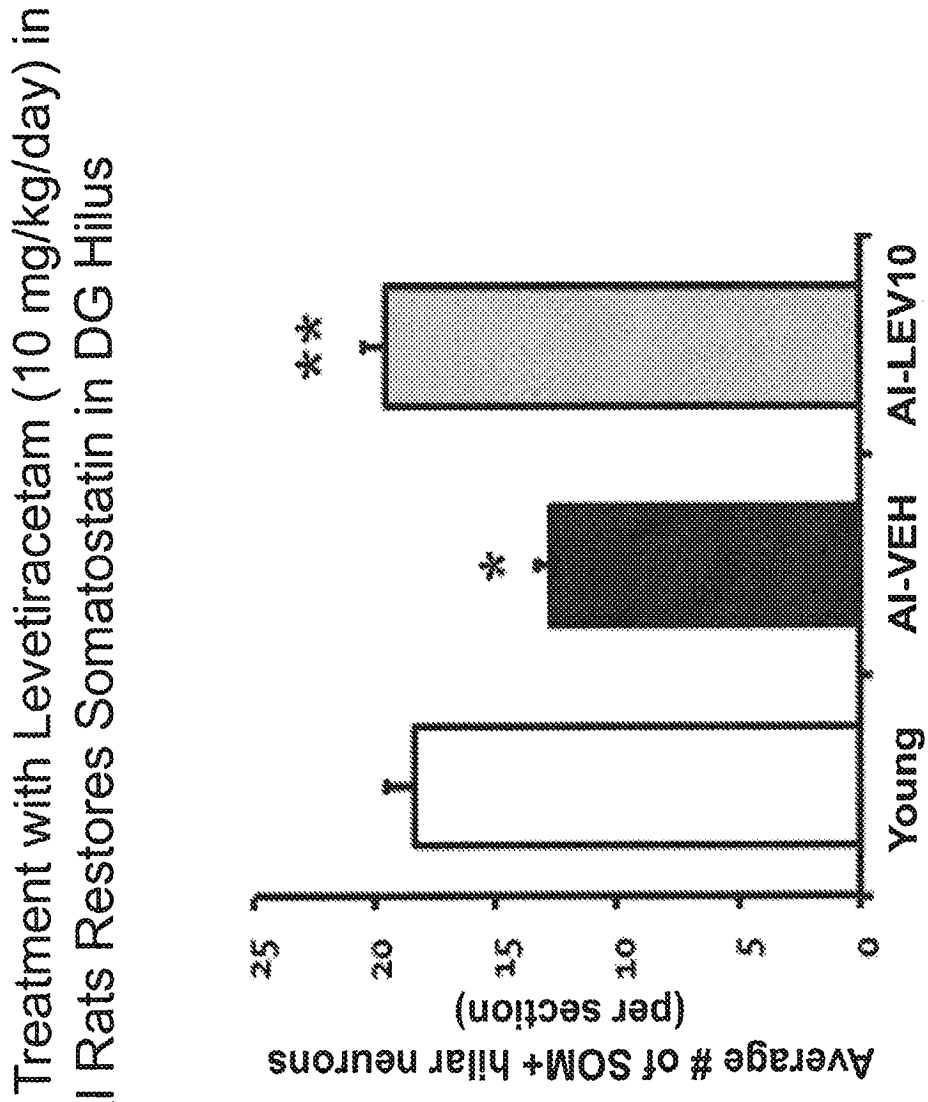

Chronic Treatment with Levetiracetam (10 mg/kg/day) in
AI Rats Restores Somatostatin in DG Hilus
Average # of SOM+ hilar neurons
(per section)
25
20
15
10
5
0
**
*
Young
AI-VEH
AI-LEV10

FIG. 21

Chronic Treatment with Levetiracetam (10 mg/kg/day) in AI Rats Restores Reelin in Entorhinal Cortex (EC2)

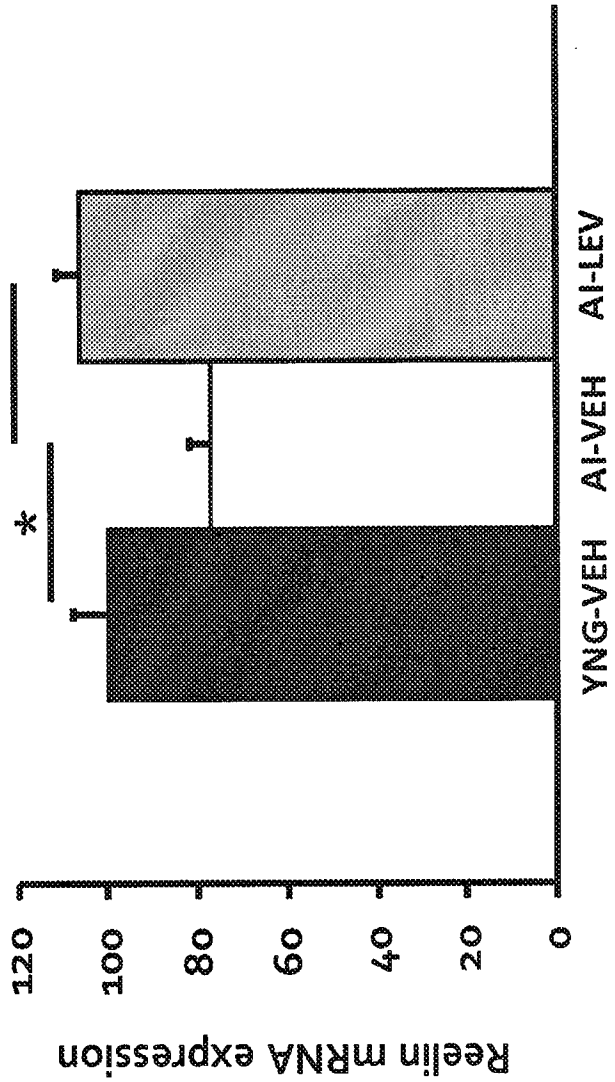


FIG. 22

FIG. 23A

FIG. 23B

FIG. 23C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/29362

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/13 (2014.01)
USPC - 514/661, 252.03, 247; 544/224, 238
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/661, 252.03

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/247; 544/224, 238 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, PubWest, ProQuest Dialog, Google Scholar, Google
Search Terms: acetylcholinesterase inhibitor, synaptic vesicle protein 2A, levetiracetam , seletracetam, brivaracetam, SV2A , SV2, donepezil, cognitive, acetylcholinesterase, AchEI, release

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2011/0212928 A1 (Gallagher et al.) 1 Septmber 2011 (01.09.2011) abstract, para [0008], [0011], [0013], [0023], [0025]-[0026], [2159]	1, 24, 26, 28-29, 31-32, 70-72 ---------- 2-4, 25, 27 and 73
Y	US 2007/0213337 A1 (Wacker et al.) 13 Septmber 2007 (13.09.2007) para [0056], [0085], [0092]	2-4, 25, 27 and 73
Y	US 2012/0171125 A1 (Kenda et al.) 5 July 2012 (05.07.2012) para [0025], [0054], [0057]	1, 24

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2014 (25.07.2014)	21 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/29362

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 30
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
because they are dependent claim is not drafted in accordance with PCT rule 6.2 and 6.3

3. ☒ Claims Nos.: 5-23, 33-69
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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(71)申请人 艾吉因生物股份有限公司
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代理人 王贵杰
(51)Int.Cl.
A61K 31/13(2006.01)

权利要求书8页 说明书245页 附图27页

(54)发明名称

用于改善认知功能的方法和组合物

(57)摘要

本发明涉及包含突触小泡糖蛋白2A(SV2A)抑制剂和乙酰胆碱酯酶抑制剂(AChEI)的组合物,所述突触小泡糖蛋白2A抑制剂是缓释形式。本发明还涉及通过使用这种组合物用于治疗受试者中与中枢神经系统障碍相关的认知缺损,所述受试者是有需要的或处于患有所述障碍风险中,包括但不限于,患有或处于患有与年龄相关的认知缺损、轻度认知缺损(MCI)、痴呆、阿尔茨海默病(AD)、前驱AD、创伤后应激障碍(PTSD)、精神分裂症、双向情感障碍、肌萎缩性侧索硬化(ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病(PD)、孤独症、强迫行为和物质成瘾风险中的受试者。

CN 105142623 A

1. 组合物，包含突触小泡蛋白 2A(SV2A) 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药和乙酰胆碱酯酶抑制剂 (AChEI) 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药，

其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是缓释形式。

2. 权利要求 1 的组合物，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药不是缓释形式。

3. 权利要求 2 的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是控制释放形式、延长释放形式、持续释放形式、延迟释放形式或缓慢释放形式。

4. 权利要求 1-3 任一项的组合物，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是立即释放形式。

5. 权利要求 1-4 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药和所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是单位剂型。

6. 权利要求 1-5 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药和所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是片剂或胶囊形式。

7. 权利要求 1-6 任一项的组合物，其中该组合物用于口服施用。

8. 权利要求 1-4 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药和所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药一起在单一制剂中的分开的单元包装中。

9. 权利要求 1-8 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药选自如下文献中涉及的 SV2A 抑制剂：国际专利申请 PCT/US2009/005647；国际专利申请公开号 WO2010/144712；WO2010/002869；WO2008/132139；WO2007/065595；WO2006/128693；WO2006/128692；WO2005/054188；WO2004/087658；WO2002/094787；WO2001/062726；美国专利 7,465,549；7,244,747；5,334,720；4,696,943；4,696,942；美国专利申请号 12/580,464；61/105,847；61/152,631；和 61/175,536；美国专利申请公开号 20090312333；20090018148；20080081832；2006258704；和英国专利号 1,039,113；和 1,309,692；或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

10. 权利要求 1-8 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药选自左乙拉西坦、塞曲西坦和布立西坦及其衍生物、类似物、药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

11. 权利要求 1-10 任一项的组合物，其中该组合物中的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 0.1-500mg、0.1-350mg、0.7-350mg、3-300mg、3-150mg、3-110mg、7-70mg、70-350mg、100-300mg 或 125-250mg 的量存在。

12. 权利要求 1-10 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以小于 500mg、小于 350mg、小于 300mg、小于 250mg、小于 200mg、小于 150mg、小于 110mg、小于 100mg、小于 70mg、小于 50mg、小于 35mg、小于 10mg、小

于 7mg、小于 5mg、小于 3mg、小于 1mg、小于 0.7mg、小于 0.5mg、小于 0.1mg、小于 0.07mg 或小于 0.05mg 的量存在。

13. 权利要求 1-10 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。

14. 权利要求 13 的组合物，其中该组合物中左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 70-350mg、100-300mg 或 125-250mg 的量存在。

15. 权利要求 1-10 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是布立西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。

16. 权利要求 15 的组合物，其中该组合物中布立西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 0.1-350mg、0.7-350mg、3-300mg、3-150mg、3-110mg 或 7-70mg 的量存在。

17. 权利要求 1-10 任一项的组合物，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是塞曲西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。

18. 权利要求 17 的组合物，其中该组合物中塞曲西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 0.1-350mg、0.7-350mg、3-300mg、3-150mg、3-110mg 或 7-70mg 的量存在。

19. 权利要求 1-18 任一项的组合物，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药选自如下文献中涉及的 AChEI：国际专利申请 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；和 WO1988/008708；美国专利号 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 ;和 2,701,225 ;日本专利申请号 4-216704 和 4-187674 ;加拿大专利号 2,180,703 ;欧洲专利申请公开号 298202 ;236684 ;409676 ;411534 ;468187 ;477903 ;481429 ;487071 ;611769 ;703901 ;1050303 ;2018874 ;和 2260839 ;美国公开号 20010036949 ;20020119963 ;20030078252 ;2003069289 ;20040082644 ;20050245504 ;20050124642 ;20060052428 ;20070275959 ;20080103105 ;20080261950 ;20090124659 ;20100152108 ;20100227852 ;和 20100311697 ;或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

20. 权利要求 1-18 任一项的组合物，其中所述 AChEI 是多奈哌齐、他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

21. 权利要求 1-18 任一项的组合物，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 的量存在。

22. 权利要求 1-18 任一项的组合物，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以小于 10mg、小于 8mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的量存在。

23. 用于治疗有需要的或处于患有所述障碍风险中的受试者中的与中枢神经系统 (CNS) 障碍相关的认知缺损、延缓或减缓受试者中的认知缺损进展或降低其认知功能减退速率的方法，该方法包括对所述受试者施用权利要求 1-22 任一项的组合物的步骤。

24. 用于治疗有需要的或处于患有所述障碍风险中的受试者中的与中枢神经系统 (CNS) 障碍相关的认知缺损、延缓或减缓受试者中的认知缺损进展或降低其认知功能减退速率的方法，该方法包括对所述受试者施用 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药和 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是缓释形式。

25. 权利要求 24 的方法，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药不是缓释形式。

26. 权利要求 24 的方法，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是控制释放形式、延长释放形式、持续释放形式、延迟释放形式或缓慢释放形式。

27. 权利要求 24 的方法，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是立即释放形式。

28. 权利要求 24 的方法，其中所述 SV2A 抑制剂和所述 AChEI 是单位剂型。

29. 权利要求 24 的方法，其中与没有另一种物质存在下施用时它们是治疗有效的剂量相比，以亚治疗剂量施用所述 SV2A 抑制剂和 / 或所述 AChEI。

30. 权利要求 24 的方法，其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药选自如下文献中涉及的 SV2A 抑制剂 :国际专利申请 PCT/US2009/005647 ;国际专利申请公开号 WO2010/144712 ;WO2010/002869 ;WO2008/132139 ;

WO2007/065595 ;WO2006/128693 ;WO2006/128692 ;WO2005/054188 ;WO2004/087658 ; WO2002/094787 ;WO2001/062726 ;美国专利7,465,549 ;7,244,747 ;5,334,720 ;4,696,943 ; 4,696,942 ;美国专利申请号 12/580,464 ;61/105,847 ;61/152,631 ;和 61/175,536 ;美国专利申请公开号 20090312333 ;20090018148 ;20080081832 ;2006258704 ;和英国专利号 1,039,113 ;和 1,309,692 ;或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

31. 权利要求 24 任一项的方法，其中所述 SV2A 抑制剂选自左乙拉西坦、塞曲西坦和布立西坦及其衍生物、类似物、药学上可接受的盐、水合物、溶剂合物、多晶型物和前药。

32. 权利要求 24-31 任一项的方法，其中以 0.0015-7mg/kg、0.0015-5mg/kg、0.01-5mg/kg、0.05-4.0mg/kg、0.05-2mg/kg、0.05-1.5mg/kg、0.1-1mg/kg、1-5mg/kg、1.5-4mg/kg 或 1.8-3.6mg/kg 的每日剂量施用所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。

33. 权利要求 24-32 任一项的方法，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药选自如下文献中涉及的 AChEI ：国际专利申请 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 ; 和 WO1988/008708 ; 美国专利号 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 ; 和 2,701,225 ; 日本专利申请号 4-216704 和 4-187674 ;加拿大专利号 2,180,703 ;欧洲专利申请公开号 298202 ; 236684 ;409676 ;411534 ;468187 ;477903 ;481429 ;487071 ;611769 ;703901 ;1050303 ; 2018874 ;和 2260839 ;美国公开号 20010036949 ;20020119963 ;20030078252 ;2003069289 ; 20040082644 ;20050245504 ;20050124642 ;20060052428 ;20070275959 ;20080103105 ; 20080261950 ;20090124659 ;20100152108 ;20100227852 ;和 20100311697 ;或其药学上可

接受的盐、水合物、溶剂合物、多晶型物或前药。

34. 权利要求 24-32 任一项的方法，其中所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是多奈哌齐、他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯或其衍生物、类似物、药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

35. 权利要求 24-34 任一项的方法，其中以 0.1mg-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 的每日剂量施用所述 AChEI。

36. 权利要求 24-34 任一项的方法，其中以小于 10mg、小于 8mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的每日剂量施用所述 AChEI。

37. 权利要求 24-36 任一项的方法，其中以小于 7mg/kg、小于 6mg/kg、小于 5mg/kg、小于 4mg/kg、小于 3.6mg/kg、小于 3mg/kg、小于 2mg/kg、小于 1.5mg/kg、小于 1.5mg/kg、小于 1mg/kg、小于 0.1mg/kg、小于 0.05mg/kg、小于 0.01mg/kg 或小于 0.0015mg/kg 的每日剂量施用所述 SV2A 抑制剂。

38. 权利要求 1-37 任一项的方法，其中所述治疗在所述受试者中具有更长的治疗作用，所述治疗作用比通过在不存在所述 SV2A 抑制剂的情况下施用所述 AChEI 获得的治疗作用长至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

39. 权利要求 1-37 任一项的方法，其中所述治疗在所述受试者中具有更长的治疗作用，所述治疗作用比通过在不存在所述 AChEI 的情况下施用所述 SV2A 抑制剂获得的治疗作用长至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

40. 增加 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药在治疗受试者的与 CNS 障碍相关的认知缺损的方法中的治疗指数的方法，所述受试者是有需要的或处于患有所述障碍风险中，该方法包括施用权利要求 1-22 任一项的组合物。

41. 权利要求 40 的方法，其中所述 AChEI 的所述治疗指数的所述增加比当在不存在所述 SV2A 抑制剂的情况下施用所述 AChEI 时所述 AChEI 的所述治疗指数大至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

42. 权利要求 40 的方法，其中所述 SV2A 抑制剂选自如下文献中涉及的 SV2A 抑制剂：国际专利申请 PCT/US2009/005647；国际专利申请公开号 WO2010/144712；WO2010/002869；WO2008/132139；WO2007/065595；WO2006/128693；WO2006/128692；WO2005/054188；WO2004/087658；WO2002/094787；WO2001/062726；美国专利 7,465,549；7,244,747；5,334,720；4,696,943；4,696,942；美国专利申请号 12/580,464；61/105,847；61/152,631；和 61/175,536；美国专利申请公开号 20090312333；20090018148；20080081832；2006258704；和英国专利号 1,039,113；和 1,309,692；或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

43. 权利要求 40 的方法，其中所述 SV2A 抑制剂选自左乙拉西坦、塞曲西坦和布立西坦及其衍生物、类似物、药学上可接受的盐、水合物、溶剂合物、多晶型物和前药。

44. 权利要求 40 的方法，其中所述 AChEI 选自如下文献中涉及的 AChEI：国际专利申请 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 ; 和 WO1988/008708 ; 美国专利号 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 ; 和 2,701,225 ; 日本专利申请号 4-216704 和 4-187674 ;加拿大专利号 2,180,703 ;欧洲专利申请公开号 298202 ;236684 ;409676 ;411534 ;468187 ;477903 ;481429 ;487071 ;611769 ;703901 ; 1050303 ;2018874 ; 和 2260839 ; 美国公开号 20010036949 ;20020119963 ;20030078252 ; 2003069289 ;20040082644 ;20050245504 ;20050124642 ;20060052428 ;20070275959 ; 20080103105 ;20080261950 ;20090124659 ;20100152108 ;20100227852 ; 和 20100311697 ; 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

45. 权利要求 40 的方法，其中所述 AChEI 是多奈哌齐、他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

46. 增加 SV2A 抑制剂在治疗受试者的与 CNS 障碍相关的认知缺损的方法中的治疗指数的方法，所述受试者是有需要的或处于患有所述障碍风险中，该方法包括施用权利要求 1-22 任一项的组合物。

47. 权利要求 46 的方法，其中所述 SV2A 抑制剂的所述治疗指数的所述增加比当在不存在所述 AChEI 的情况下施用所述 SV2A 抑制剂时所述 SV2A 抑制剂的所述治疗指数大至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

48. 权利要求 46 的方法，其中所述 SV2A 抑制剂选自如下文献中涉及的 SV2A 抑制剂：国际专利申请 PCT/US2009/005647 ;国际专利申请公开号 WO2010/144712 ;WO2010/002869 ; WO2008/132139 ;WO2007/065595 ;WO2006/128693 ;WO2006/128692 ;WO2005/054188 ;

WO2004/087658 ;WO2002/094787 ;WO2001/062726 ; 美 国 专 利 7,465,549 ;7,244,747 ; 5,334,720 ;4,696,943 ;4,696,942 ; 美 国 专 利 申 请 号 12/580,464 ;61/105,847 ; 61/152,631 ; 和 61/175,536 ; 美 国 专 利 申 请 公 开 号 20090312333 ;20090018148 ; 20080081832 ;2006258704 ;和英国专利号 1,039,113 ;和 1,309,692 ;或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

49. 权利要求 46 的方法，其中所述 SV2A 抑制剂选自左乙拉西坦、塞曲西坦和布立西坦及其衍生物、类似物、药学上可接受的盐、水合物、溶剂合物、多晶型物和前药。

50. 权利要求 46 的方法，其中所述 AChEI 选自如下文献中涉及的 AChEI ：国际专利申 请 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 ； 和 WO1988/008708 ; 美 国 专 利 号 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 ； 和 2,701,225 ; 日本专利申请号 4-216704 和 4-187674 ;加拿大专利号 2,180,703 ;欧洲专利申请公开号 298202 ;236684 ;409676 ;411534 ;468187 ;477903 ;481429 ;487071 ;611769 ;703901 ; 1050303 ;2018874 ; 和 2260839 ; 美 国 公 开 号 20010036949 ;20020119963 ;20030078252 ; 2003069289 ;20040082644 ;20050245504 ;20050124642 ;20060052428 ;20070275959 ; 20080103105 ;20080261950 ;20090124659 ;20100152108 ;20100227852 ； 和 20100311697 ; 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。

51. 权利要求 46 的方法，其中所述 AChEI 为多奈哌齐、他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物、多晶型物或其前药。

52. 权利要求 1-51 任一项的方法，其中所述认知缺损和与年龄相关的认知缺损相关。

53. 权利要求 52 的方法，其中所述与年龄相关的认知缺损是轻度认知缺损。

54. 权利要求 53 的方法，其中所述轻度认知缺损是遗忘性轻度认知缺损。

55. 权利要求 1-51 任一项的方法，其中所述认知缺损与痴呆相关。

56. 权利要求 55 的方法，其中所述痴呆是阿尔茨海默病。

57. 权利要求 1-51 任一项的方法，其中所述认知缺损与精神分裂症相关。

58. 权利要求 1-51 任一项的方法，其中所述认知缺损与肌萎缩性侧索硬化相关。

59. 权利要求 1-51 任一项的方法，其中所述认知缺损与创伤后应激障碍相关。

60. 权利要求 1-51 任一项的方法，其中所述认知缺损与癌症治疗相关。

61. 权利要求 1-51 任一项的方法，其中所述认知缺损与双相情感障碍相关。

62. 权利要求 1-51 任一项的方法，其中所述认知缺损与精神发育迟滞相关。

63. 权利要求 1-51 任一项的方法，其中所述认知缺损与帕金森病相关。

64. 权利要求 1-51 任一项的方法，其中所述认知缺损与孤独症相关。

65. 权利要求 1-51 任一项的方法，其中所述认知缺损与强迫行为相关。

66. 权利要求 1-51 任一项的方法，其中所述认知缺损与物质成瘾相关。

67. 权利要求 1-51 任一项的方法，其中通过临床痴呆等级量表测定治疗作用、认知缺损进展或认知功能减退速率。

68. 权利要求 1-51 任一项的方法，其中通过在施用步骤之前和之后检测受试者的颤蛋白水平之间的差异来测定治疗作用、认知缺损进展或认知功能减退速率。

69. 权利要求 1-51 任一项的方法，其中通过在施用步骤之前和之后检测受试者的生长抑素水平之间的差异来测定治疗作用、认知缺损进展或认知功能减退速率。

70. 组合物，包含左乙拉西坦和多奈哌齐，其中左乙拉西坦是缓释形式，

其中左乙拉西坦以 7-350mg、70-350mg、100-300mg 或 125-250mg 的量存在；且

其中多奈哌齐以 2-10mg 或 2-4mg 的量存在。

71. 权利要求 70 的组合物，其中左乙拉西坦以 125-250mg 的量存在。

72. 权利要求 70 的组合物，其中多奈哌齐以 2-4mg 的量存在。

73. 权利要求 70-72 任一项的组合物，其中多奈哌齐是立即释放形式。

用于改善认知功能的方法和组合物

[0001] 相关申请

[0002] 本申请要求享有来自美国临时专利申请61/800,191(提交于2013年3月15日)的优先权和权益,其的内容物和公开内容通过引用完整地并入本文。

发明领域

[0003] 本发明涉及通过使用突触小泡蛋白2A(SV2A)抑制剂和乙酰胆碱酯酶抑制剂(AChEI)的组合用于改善认知功能的方法和组合物。具体的是,它涉及包含SV2A抑制剂和AChEI的组合的缓释形式的组合物及其在受试者中治疗与中枢神经系统(CNS)障碍相关的认知缺损中的用途,所述受试者是有需要的或处于患有所述障碍风险中,包括,不限于,患有或处于患有与年龄相关的认知缺损、轻度认知缺损(MCI)、遗忘性MCI(aMCI)、与年龄相关的记忆缺损(AAMI)、与年龄相关的认知减退(ARCD)、痴呆、阿尔茨海默病(AD)、前驱AD、创伤后应激障碍(PTSD)、精神分裂症、双相情感障碍、肌萎缩性侧索硬化(ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病(PD)、孤独症、强迫行为和物质成瘾风险中的受试者。

[0004] 发明背景

[0005] 作为衰老的正常后果或作为中枢神经障碍的后果,认知能力可以减退。

[0006] 例如,大部分中老年人经历了超过在正常衰老中典型的认知能力的减退。认知功能的这类与年龄相关的丧失临床表征为进行性的记忆、认知、推理和判断的丧失。轻度认知缺损(MCI)、与年龄相关的记忆缺损(AAMI)、与年龄相关的认知减退(ARCD)或类似的临床分组是与这类与年龄相关的认知功能丧失相关的病症之一。根据一些估计,仅美国就有多于1,600万人患有AAMI(Barker等人,1995),而MCI估计会影响到美国550-700万65岁以上的人(Plassman等人,2008)。

[0007] 认知缺损也与例如痴呆、阿尔茨海默病(AD)、前驱AD、创伤后应激障碍(PTSD)、精神分裂症、双相情感障碍(例如躁狂)、肌萎缩性侧索硬化(ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病(PD)、孤独症、强迫行为和物质成瘾这样的其它中枢神经系统(CNS)障碍相关。

[0008] 因此,存在对有效治疗与中枢神经系统(CNS)障碍相关的认知缺损和改善诊断为患有例如与年龄相关的认知缺损、MCI、遗忘性MCI、AAMI、ARCD、痴呆、阿尔茨海默病(AD)、前驱AD、创伤后应激障碍(PTSD)PTSD、精神分裂症、双相情感障碍、肌萎缩性侧索硬化(ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病(PD)、孤独症、强迫行为、物质成瘾伴认知缺损的类似中枢神经系统(CNS)障碍或处于它们发展的风险中的患者的认知功能的需要。

[0009] 盐酸他克林("COGNEX™"),第一个FDA批准的用于阿尔茨海默病("AD")的药物是AChEI(Cutler等人,1993)。临床使用的AChEI的其它实例包括加兰他敏("REMINYL™")或利凡斯的明("EXELON™")。但是,已显示这些药物在阿尔茨海默病患者的认知改善中获得的成功有限,并显示了限制使用的副作用特征。另一个AChEI,多奈哌齐(也称为

"ARICEPT™"),显示比他克林更有效。用多奈哌齐的阿尔茨海默病患者显示轻度认知改善(Barner 等人,1998 ;Rogers 等人,1998),但是多奈哌齐的有用性却由于它的中度功效和副作用而受到限制。多奈哌齐长期治疗的功效也已经逐渐受到质疑 (Maggini 等人,2006 ; Petersen 等人,2006)。因此,存在对更有效治疗 AD 患者中涉及认知功能的障碍、具体的是认知缺损的障碍的需要他克林。

[0010] 发明概述

[0011] 依照本发明的第一个方面,提供了用于在患有与 (CNS) 障碍相关的认知缺损或处于患有其风险中的受试者中治疗或改善认知功能的药物组合物,该组合物包含突触小泡蛋白 2A(SV2A) 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药和乙酰胆碱酯酶抑制剂 (AChEI) 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药,其中所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是缓释形式 (extended release form)。在一些实施方案中,所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药不是缓释形式。在一些实施方案中,所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是立即释放形式 (immediate release form)。在一些实施方案中,该组合物是固体形式 (例如胶囊或片剂)。在一些实施方案中,该组合物是液体形式。在一些实施方案中,该组合物是混悬液形式。在一些实施方案中,该组合物是水溶液形式。在一些实施方案中,该组合物用于口服施用。在一些实施方案中,该组合物是单位剂型形式。在一些实施方案中,将该组合物每日施用 1 次。在一些实施方案中,组合物中存在的缓释的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药不影响存在于同一组合物中的所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的药代动力学或半衰期清除率。在一些实施方案中,缓释形式的 SV2A 抑制剂包括、但不限于控制释放形式 (controlled release form)、延长释放形式 (prolonged release form)、持续释放形式 (sustained release form)、延迟释放形式 (delayed release form) 或缓慢释放形式 (slow release form)。

[0012] 在本发明的一些实施方案中,所述组合物包含缓释形式的左乙拉西坦或布立西坦或塞曲西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药,和多奈哌齐 (或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯) 或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。在本发明的一些实施方案中,所述组合物包含缓释形式的左乙拉西坦或布立西坦或塞曲西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药和非缓释形式的多奈哌齐 (或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯) 或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。在本发明的一些实施方案中,所述组合物包含缓释的左乙拉西坦和立即释放的多奈哌齐。在一些实施方案中,组合物中存在的缓释的左乙拉西坦或布立西坦或塞曲西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药不影响存在于同一组合物或同一单位剂型或同一单一制剂中的多奈哌齐 (或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯) 或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的药代动力学或半衰期清除率。

[0013] 在本发明的一些实施方案中, SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以 0.07-350mg 或 50-250mg 或 3-50mg 的量存在。在一些实施方

案中，所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以小于 500mg、小于 350mg、小于 300mg、小于 250mg、小于 200mg、小于 150mg、小于 110mg、小于 100mg、小于 70mg、小于 50mg、小于 35mg、小于 10mg、小于 7mg、小于 5mg、小于 3mg、小于 1mg、小于 0.7mg、小于 0.5mg、小于 0.1mg、小于 0.07mg 或小于 0.05mg 的量存在。在一些实施方案中，组合物中存在的所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 0.1-500mg、0.1-350mg、0.7-350mg、3-300mg、3-150mg、3-110mg、7-70mg、70-350mg、100-300mg 或 125-250mg 的量存在。

[0014] 在本发明的一些实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 的量存在。在一些实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以小于 10mg、小于 9mg、小于 8mg、小于 7mg、小于 6mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的量存在。

[0015] 本发明的另一个方面提供用于在患有与中枢神经系统 (CNS) 障碍相关的认知缺损或处于患有其风险中的受试者中治疗或改善认知功能、延迟或减缓认知缺损进展或降低认知功能减退速率的方法，该方法包括将包含治疗有效量的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药与治疗有效量的 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的组合施用于所述受试者的步骤，其中所述 SV2A 抑制剂是缓释形式。在一些实施方案中，且所述 AChEI 不是缓释形式。在一些实施方案中，所述 AChEI 是立即释放形式。在本发明的一些实施方案中，本发明的方法预防或减缓在所述受试者中与 CNS 障碍相关的认知缺损的发展。在本发明的其它实施方案中，本发明的方法减轻、改善或减缓在所述受试者中与 CNS 障碍相关的所述认知缺损的一个或多个症状的发展。

[0016] 在本发明的一个实施方案中，所述 SV2A 抑制剂和 / 或所述 AChEI 以与在没有其中另一种成分存在下施用时它们是治疗有效的剂量相比以亚治疗剂量施用。

[0017] 在本发明的一些实施方案中，与 CNS 障碍相关的认知缺损是与年龄相关的认知缺损，例如轻度认知缺损 (MCI)、与年龄相关的记忆缺损 (AAMI)、与年龄相关的认知减退 (ARCD)。在本发明的一个实施方案中，所述 MCI 是遗忘性 MCI。在本发明的一些实施方案中，所述 CNS 障碍是痴呆、阿尔茨海默病 (AD)、前驱 AD、创伤后应激障碍 (PTSD)、精神分裂症、双相情感障碍、肌萎缩性侧索硬化 (ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病 (PD)、孤独症、强迫行为或物质成瘾。在一个实施方案中，患有这类 CNS 障碍或这类认知缺损的受试者是人患者。

[0018] 用于本发明方法和组合物的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药包括在下列文献中的那些，例如：美国 (U.S.) 专利申请 12/580,464（公开号 US-2010-0099735）；美国专利申请 13/287,531（公开号 US-2012-0046336）；美国专利申请 13/370,253（公开号 US-2012-0214859）；国际专利申请 PCT/US2009/005647（公开号 WO2010/044878）；国际专利申请 PCT/US12/24556（公开号 WO2012/109491）；美国专利申请 61/105,847；美国专利申请 61/152,631；美国专利申请 61/175,536 和美国专利申请 61/441,251。然而，任意 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药可以用于本发明的方法和组合物中。在其它

实施方案中，所述 SV2A 抑制剂选自如下文献中涉及的 SV2A 抑制剂：国际专利申请 PCT/US2009/005647；国际专利申请公开号 WO2010/144712；WO2010/002869；WO2008/132139；WO2007/065595；WO2006/128693；WO2006/128692；WO2005/054188；WO2004/087658；WO2002/094787；WO2001/062726；美国专利 7,465,549；7,244,747；5,334,720；4,696,943；4,696,942；美国专利申请号 12/580,464；61/105,847；61/152,631；和 61/175,536；美国专利申请公开号 20090312333；20090018148；20080081832；2006258704；和英国专利号 1,039,113；和 1,309,692；或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。在其它实施方案中，所述 SV2A 抑制剂选自左乙拉西坦、布立西坦和塞曲西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物。在其它实施方案中，所述 SV2A 抑制剂是左乙拉西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药。

[0019] 用于本发明方法和组合物中的 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药包括在下列文献中的那些，例如：国际专利申请 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；和 WO1988/008708；美国专利号 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；和 2,701,225；日本专利申请号 4-216704 和 4-187674；加拿大专利号 2,180,703；欧洲专利申请公开号 298202；236684；409676；411534；468187；477903；481429；487071；611769；703901；1050303；2018874；和 2260839；美国公开号 20010036949；20020119963；20030078252；2003069289；20040082644；20050245504；20050124642；20060052428；20070275959；20080103105；20080261950；20090124659；20100152108；20100227852；和 20100311697。然而，任意

AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物可以用于本发明的方法和组合物中。

[0020] 在本发明的其它实施方案中，SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药可以以下列文献中公开的剂量施用，例如：美国 (U.S.) 专利申请 12/580,464（公开号 US-2010-0099735）；美国专利申请 13/287,531（公开号 US-2012-0046336）；美国专利申请 13/370,253（公开号 US-2012-0214859）；国际专利申请 PCT/US2009/005647（公开号 WO2010/044878）；国际专利申请 PCT/US12/24556（公开号 WO2012/109491）；美国专利申请 61/105,847；美国专利申请 61/152,631；美国专利申请 61/175,536 和美国专利申请 61/441,251。在本发明的其它实施方案中，SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 0.001mg/kg-5mg/kg 的每日剂量施用。在本发明的其它实施方案中，SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以约 0.1-5mg/kg 或约 1-2mg/kg 或约 0.1-0.2mg/kg 或约 0.01-2.5mg/kg 或约 0.1-2.5mg/kg 或约 0.4-2.5mg/kg 或约 0.6-1.8mg/kg 或约 0.04-2.5mg/kg 或约 0.06-1.8mg/kg 或约 0.01-1mg/kg 或约 0.001-1mg/kg 或约 0.5mg/kg-5mg/kg 或约 0.05mg/kg-0.5mg/kg 的每日剂量施用；或以 0.0015-7mg/kg、0.0015-5mg/kg、0.01-5mg/kg、0.05-4.0mg/kg、0.05-2mg/kg、0.05-1.5mg/kg、0.1-1mg/kg、1-5mg/kg、1.5-4mg/kg 或 1.8-3.6mg/kg 的每日剂量施用。在一些实施方案中，使用 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的亚治疗量。这类亚治疗量可以例如以小于 7mg/kg、小于 5mg/kg、小于 2.5mg/kg、小于 2mg/kg、小于 1.5mg/kg、小于 1mg/kg、小于 0.5mg/kg、小于 0.1mg/kg、小于 0.05mg/kg、小于 0.01mg/kg、小于 0.005mg/kg 或小于 0.001mg/kg 或小于 7mg/kg、小于 6mg/kg、小于 5mg/kg、小于 4mg/kg、小于 3.6mg/kg、小于 3mg/kg、小于 2mg/kg、小于 1.5mg/kg、小于 1.5mg/kg、小于 1mg/kg、小于 0.1mg/kg、小于 0.05mg/kg、小于 0.01mg/kg 或小于 0.0015mg/kg 的每日剂量施用。

[0021] 在一些实施方案中，存在于本发明组合物中的 SV2A 抑制剂以 0.0015-7mg/kg/ 天的每日剂量施用（给予 70kg 的典型人体受试者约 0.1-500mg/ 天）。可以使用的每日剂量包括、但不限于 0.0015mg/kg、0.002mg/kg、0.0025mg/kg、0.005mg/kg、0.01mg/kg、0.02mg/kg、0.03mg/kg、0.04mg/kg、0.05mg/kg、0.06mg/kg、0.07mg/kg、0.08mg/kg、0.09mg/kg、0.1mg/kg、0.2mg/kg、0.3mg/kg、0.4mg/kg、0.5mg/kg、0.6mg/kg、0.7mg/kg、0.8mg/kg、0.9mg/kg、1mg/kg、1.2mg/kg、1.4mg/kg、1.5mg/kg、1.6mg/kg、1.8mg/kg、2.0mg/kg、2.2mg/kg、2.4mg/kg、2.5mg/kg、2.6mg/kg、2.8mg/kg、3.0mg/kg、3.5mg/kg、4.0mg/kg、4.5mg/kg、5.0mg/kg、6.0mg/kg 或 7.0mg/kg；或 0.1mg、0.15mg、0.18mg、0.35mg、0.7mg、1.5mg、2.0mg、2.5mg、2.8mg、3.0mg、3.5mg、4.2mg、5mg、5.5mg、6.0mg、7mg、8mg、9mg、10mg、12mg、15mg、20mg、25mg、28mg、30mg、35mg、40mg、45mg、50mg、55mg、60mg、70mg、75mg、80mg、85mg、90mg、95mg、100mg、110mg、120mg、125mg、140mg、150mg、170mg、175mg、180mg、190mg、200mg、210mg、225mg、250mg、280mg、300mg、350mg、400mg 或 500mg 或 0.0015-5mg/kg、0.01-0.8mg/kg、0.01-1mg/kg、0.01-1.5mg/kg、0.01-2mg/kg、0.01-2.5mg/kg、0.01-3mg/kg、0.01-3.5mg/kg、0.01-4mg/kg、0.01-5mg/kg、0.025-0.8mg/kg、0.025-1mg/kg、0.025-1.5mg/kg、0.025-2mg/kg、0.025-2.5mg/kg、0.025-3mg/kg、0.025-3.5mg/kg、0.025-4mg/kg、0.05-0.8mg/kg、0.05-1mg/kg、0.05-1.5mg/kg、0.05-2mg/kg、0.05-2.5mg/kg、0.05-3mg/kg、0.05-3.5mg/

kg、0.05-4mg/kg、0.075-0.8mg/kg、0.075-1mg/kg、0.075-1.5mg/kg、0.075-2mg/kg、0.075-2.5mg/kg、0.075-3mg/kg、0.075-3.5mg/kg、0.075-4mg/kg、0.1-0.8mg/kg、0.1-1mg/kg、0.1-1.5mg/kg、0.1-2mg/kg、0.1-2.5mg/kg、0.1-3mg/kg、0.1-3.5mg/kg、0.1-4mg/kg、0.2-0.8mg/kg、0.2-1mg/kg、0.2-1.5mg/kg、0.2-2mg/kg、0.2-2.5mg/kg、0.2-3mg/kg、0.2-3.5mg/kg、0.2-4mg/kg、0.5-0.8mg/kg、0.5-1mg/kg、0.5-1.5mg/kg、0.5-2mg/kg、0.5-2.5mg/kg、0.5-3mg/kg、0.5-3.5mg/kg 或 0.5-4mg/kg；或 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg。在一些实施方案中，本发明组合物中存在的左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的量为 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg 或 0.1mg、0.15mg、0.18mg、0.35mg、0.7mg、1.5mg、2.0mg、2.5mg、2.8mg、3.0mg、3.5mg、4.2mg、5mg、5.5mg、6.0mg、7mg、8mg、9mg、10mg、12mg、15mg、20mg、25mg、28mg、30mg、35mg、40mg、45mg、50mg、55mg、60mg、70mg、75mg、80mg、85mg、90mg、95mg、100mg、110mg、120mg、125mg、140mg、150mg、170mg、175mg、180mg、190mg、200mg、210mg、225mg、250mg、280mg、300mg、350mg、400mg 或 500mg。在一些实施方案中，使用 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的亚治疗量。

[0022] 在一些实施方案中，存在于本发明组合物中的 SV2A 抑制剂是左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药并且以如表 1 或表 2 中所列的“+”所示的每日剂量范围之一施用。在一些实施方案中，本发明组合物中存在的左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的量约为 70-140mg 或约 7-180mg 或约 25-180mg 或约 40-130mg 或约 140-300mg 或约 200-300mg 或约 140-200mg 或约 7-350mg、约 70-350mg、约 100-300mg 或约 125-250mg。在一些实施方案中，使用左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的亚治疗量。

[0023] 在一些实施方案中，存在于本发明组合物中的 SV2A 抑制剂是布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药并且以如表 3-6 中所列的“+”所示的每日剂量范围之一施用。在一些实施方案中，本发明组合物中存在的布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的量约为 7-15mg 或约 0.7-180mg 或约 2.5-180mg 或约 4.0-130mg 或约 14-30mg 或约 0.1-35mg、0.5-35mg、0.75-35mg、1.0-35mg、

1.5-35mg、2.0-35mg、0.1-30mg、0.1-25mg、0.1-20mg、0.1-15mg、0.1-10mg、0.1-5mg、0.1-2.5mg 或 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg。在一些实施方案中，使用布立西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的亚治疗量。

[0024] 在一些实施方案中，存在于本发明组合物中的 SV2A 抑制剂是塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药并且以表 7-10 中所列的“+”所示的每日剂量范围之一施用。在一些实施方案中，本发明组合物中存在的塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的量约为 7-15mg 或约 0.7-180mg 或约 2.5-180mg 或约 4.0-130mg 或约 14-30mg 或约 0.1-35mg、0.5-35mg、0.75-35mg、1.0-35mg、1.5-35mg、2.0-35mg、0.1-30mg、0.1-25mg、0.1-20mg、0.1-15mg、0.1-10mg、0.1-5mg、0.1-2.5mg 或 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg。在一些实施方案中，使用塞曲西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的亚治疗量。

[0025] 在一些实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药以 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 的每日剂量施。在一些实施方案中，施用所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的亚治疗量。在一些实施方案中，以小于 10mg、小于 9mg、小于 8mg、小于 7mg、小于 6mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的每日剂量施用所述 AChEI 的亚治疗量。在上述实施方案中，所述 AChEI 抑制剂是多奈哌齐。

[0026] 在本发明的一些实施方案中，组合治疗在受试者中具有更长或改善的治疗作用，所述治疗作用比通过在不存在 SV2A 抑制剂或其药学上可接受的盐、溶剂合物、水合物或多晶型物或前药的情况下施用 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药获得的治疗作用长至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

[0027] 在本发明的其它实施方案中，组合治疗在受试者中具有更长或改善的治疗作用，所述治疗作用比通过在不存在 AChEI 或其药学上可接受的盐，水合物、溶剂合物或多晶型

物的情况下施用 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物获得的治疗作用长至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

[0028] 依照本发明的另一个方面，提供了在治疗受试者与 CNS 障碍相关的认知缺损的方法中增加 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的治疗指数的方法，所述受试者是有需要的或处于患有所述障碍风险中，所述方法包括将包含缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的组合物施用于所述受试者。在本发明该方面的一些实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药不是缓释形式。在本发明该方面的其它实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是立即释放形式。

[0029] 在一些实施方案中，AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的治疗指数的增加大于 AChEI 当在不存在 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的情况下施用时的治疗指数、或者大于 AChEI 的药学上可接受的盐、水合物、溶剂合物或多晶型物或前药当在不存在 SV2A 抑制剂或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的情况下施用时的治疗指数的至少约 1.5x，或 2.0x，或 2.5x，或 3.0x，或 3.5x，或 4.0x，或 4.5x，或 5.0x，或 5.5x，或 6.0x，或 6.5x，或 7.0x，或 7.5x，或 8.0x，或 8.5x，或 9.0x，或 9.5x，或 10x，或大于约 10x。

[0030] 依照本发明的另一个方面，提供了在治疗受试者与 CNS 障碍相关的认知缺损的方法中增加 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的治疗指数的方法，所述受试者是有需要的或处于患有所述障碍风险中，所述方法包括将包含缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的组合的组合物施用于所述受试者。在本发明该方面的一些实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药不是缓释形式。在本发明该方面的其它实施方案中，所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药是立即释放形式。

[0031] 在一些实施方案中，SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的治疗指数增加大于 SV2A 抑制剂、水合物、溶剂合物或多晶型物或前药当在不存在 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的情况下施用时的治疗指数、或者大于 SV2A 抑制剂的药学上可接受的盐、水合物、溶剂合物或多晶型物或前药当在不存在 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药的情况下施用时的治疗指数的至少约 1.5x，或 2.0x，或 2.5x，或 3.0x，或 3.5x，或 4.0x，或 4.5x，或 5.0x，或 5.5x，或 6.0x，或 6.5x，或 7.0x，或 7.5x，或 8.0x，或 8.5x，或 9.0x，或 9.5x，或 10x，或大于约 10x。

[0032] 在一些实施方案中，本发明的方法改善或治疗所述受试者的认知功能。在本发明该方面的一些实施方案中，所述方法延迟或减缓所述受试者的认知缺损发展。在本发明该方面的一些实施方案中，所述方法降低所述受试者的认知功能减退速率。在本发明该方面的一些实施方案中，所述方法预防或减缓所述受试者的与所述 CNS 障碍相关的所述认知缺

损发展。在本发明该方面的其它实施方案中，所述方法缓解、改善或减缓所述受试者的与所述 CNS 障碍的所述认知缺损相关的一个或多个症状发展。

[0033] 在一些实施方案中，所述认知缺损是与年龄相关的认知缺损，例如轻度认知缺损 (MCI)、与年龄相关的记忆缺损 (AAMI)、与年龄相关的认知减退 (ARCD)。在本发明该方面的一个实施方案中，所述 MCI 是遗忘性 MCI。在本发明的一些实施方案中，所述 CNS 障碍与痴呆、阿尔茨海默病 (AD)、前驱 AD、创伤后应激障碍 (PTSD)、精神分裂症、双相情感障碍、肌萎缩性侧索硬化、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病、孤独症、强迫行为或物质成瘾相关。在一个实施方案中，患有这类认知缺损的受试者是人患者。

[0034] 在一些实施方案中，通过在施用步骤之前和之后检测受试者的颤蛋白 (reelin) 水平之间的差异来测定治疗作用、认知缺损进展或认知功能减退速率。

[0035] 在一些实施方案中，通过在施用步骤之前和之后检测受试者的生长抑素水平之间的差异来测定治疗作用、认知缺损进展或认知功能减退速率。

[0036] 在一些实施方案中，提供用于治疗或改善患有与 CNS 障碍相关的认知缺损或处于其风险中的受试者的认知功能的药物组合物，该组合物包含左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药和多奈哌齐或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药，其中左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是缓释形式。在一些实施方案中，多奈哌齐或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药不是缓释形式。在一些实施方案中，多奈哌齐或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药是立即释放形式。在一些实施方案中，所述组合物是固体形式（例如胶囊或片剂）。在一些实施方案中，所述组合物是液体形式。在一些实施方案中，所述组合物是水溶液形式。在一些实施方案中，所述组合物用于口服施用。在一些实施方案中，所述组合物每日施用 1 次。在一些实施方案中，所述组合物是混悬液形式。在一些实施方案中，所述组合物是单位剂型形式。在一些实施方案中，所述组合物是片剂或胶囊形式。在一些实施方案中，组合物中存在的缓释的左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药不影响同一组合物或同一制剂或同一单元中存在的多奈哌齐或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的药代动力学或半衰期清除率。在一些实施方案中，缓释形式可以是控制释放形式、延长释放形式、持续释放形式、延迟释放形式或缓慢释放形式。在一些实施方案中，左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以 7-350mg、70-350mg、100-300mg 或 125-250mg 的量存在于组合物中，且多奈哌齐以 2-10mg 或 2-4mg 的量存在于组合物中。

[0037] 在本发明的一个实施方案中，以与当其中一种成分不存在下施用时它们为治疗有效的剂量相比为亚治疗的剂量施用所述 SV2A 抑制剂和 / 或 AChEI。

[0038] 在本发明的一些实施方案中，所述与 CNS 相关的认知缺损是与年龄相关的认知缺损，例如轻度认知缺损 (MCI)、与年龄相关的记忆缺损 (AAMI)、与年龄相关的认知减退 (ARCD)。在本发明该方面的一个实施方案中，所述 MCI 是遗忘性 MCI。在本发明的一些实施方案中，所述 CNS 障碍是痴呆、阿尔茨海默病 (AD)、前驱 AD、创伤后应激障碍 (PTSD)、精神分裂症、双相情感障碍、肌萎缩性侧索硬化 (ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病 (PD)、孤独症、强迫行为或物质成瘾相关。在一个实施方案中，患有这类 CNS 障碍或这类认知缺损的受试者是人患者。

[0039] 附图简述

[0040] 图 1 描述在八臂放射臂迷宫 (RAM) 测试中施用左乙拉西坦对 10 只老龄受损大鼠 (A1) 空间记忆保留的效果。使用六种处理条件 :媒介物对照、左乙拉西坦 (1.25mg/kg/ 天)、左乙拉西坦 (2.5mg/kg/ 天)、左乙拉西坦 (5mg/kg/ 天)、左乙拉西坦 (10mg/kg/ 天) 和左乙拉西坦 (20mg/kg/ 天)。在所用的 RAM 任务中,小组臂 (5 个可利用的臂和 3 个隔断的臂) 的呈现 (presentation) 与八 - 臂得到 - 转移 (win-shift) 任务 (8 个可利用的臂) 的完成之间存在 1 小时延迟。在每日试验之前 30-40 分钟,使用一次药物 / 对照品治疗对大鼠进行预治疗。在保留阶段期间大鼠形成的错误数用作空间记忆保留的量度。将错误定义为当大鼠进入已经在试验的延迟部分前从中取回食物的臂时或大鼠在延迟期后再探访已经探访过的臂时的情况。配对 t 检验用于比较左乙拉西坦与媒介物对照不同剂量之间的错误数。

[0041] 图 2 描述在八臂放射臂迷宫 (RAM) 测试中仅仅施用多奈哌齐和施用多奈哌齐和左乙拉西坦组合对 8 只老龄 - 受损大鼠 (AI) 的空间记忆保留的效果。使用四种处理条件 :媒介物对照、仅多奈哌齐 (1mg/kg/ 天)、多奈哌齐 (2mg/kg/ 天),以及多奈哌齐 (1mg/kg/ 天) 和左乙拉西坦 (2.5mg/kg/ 天) 的组合。在所用的 RAM 任务中,小组臂 (5 个可利用的臂和 3 个隔断的臂) 的呈现与八 - 臂得到 - 转移任务 (8 个可利用的臂) 的完成之间存在 2 小时延迟。在每日试验之前 30-40 分钟,使用一次药物 / 对照品治疗对大鼠进行预治疗。在保留阶段期间大鼠形成的错误数用作空间记忆保留的量度。将错误定义为当大鼠进入已经在试验的延迟部分前从中取回食物的臂时或大鼠在延迟期后再探访已经探访过的臂时的情况。配对 t 检验用于比较药物治疗与媒介物对照不同剂量之间的错误数。相对于媒介物对照治疗,多奈哌齐 (1mg/kg/ 天) 和左乙拉西坦 (2.5mg/kg/ 天) 的组合显著改善记忆表现 ($t(7) = 2.16, p = 0.034$)。

[0042] 图 3 描述对于左乙拉西坦治疗的人试验的实验设计。

[0043] 图 4A 描述在受试者正确识别为“类似”的诱饵刺激物呈现期间用安慰剂治疗的 aMCI 受试者和用安慰剂治疗的年龄匹配对照受试者的左侧 CA3 中的平均活动。

[0044] 图 4B 描述在受试者正确识别为“类似”的诱饵刺激物呈现期间用安慰剂治疗或左乙拉西坦治疗 (一天两次 125mg 持续两周) 的 aMCI 受试者的左侧 CA3 中的平均活动。

[0045] 图 4C 是图 4A 和 4B 中所示数据的表。

[0046] 图 5A 描述在受试者正确识别为“类似”的诱饵刺激物呈现期间用安慰剂治疗的年龄匹配对照受试者和用安慰剂治疗的 aMCI 受试者的左侧内嗅皮层中的平均活动。

[0047] 图 5B 描述在受试者正确识别为“类似”的诱饵刺激呈现期间用安慰剂治疗或左乙拉西坦治疗 (一天两次 125mg 持续两周) 的相同 aMCI 受试者的左侧内嗅皮层中的平均活动。

[0048] 图 5C 是图 5A 和 5B 中所示数据的表。

[0049] 图 6A 描述了在实施例 2 中所述的外显 3 选项强迫选择任务中对受试者所示图像序列的实例。

[0050] 图 6B 显示类似 (“诱饵”) 图像的样品对。

[0051] 图 7 显示在实施例 2 中所述的外显 3 选项强迫选择任务的表现上,aMCI(安慰剂) 受试者和年龄匹配对照 (安慰剂) 受试者之间的不同。每个柱表示当呈现诱饵图像时受试者反应 (旧的、类似的或新的) 的比率。

[0052] 图 8 显示在实施例 2 中所述的外显 3 选项强迫选择任务的表现上，用安慰剂治疗或用左乙拉西坦治疗（一天两次 125mg 持续两周）的相同 aMCI 受试者之间的不同。每个柱表示当呈现诱饵图像时受试者反应（旧的、类似的或新的）的比率。

[0053] 图 9 是图 7 和 8 中所示数据的表。

[0054] 图 10A 显示在 Buschke 选择联想测试 - 延迟回忆的表现上，年龄匹配对照（安慰剂）受试者和用安慰剂或用左乙拉西坦（一天两次 125mg 持续两周）治疗的 aMCI 受试者之间的不同。

[0055] 图 10B 是图 10A 中所示数据的表。

[0056] 图 11A 显示在 Benton 视觉保留测试的表现上，对照（安慰剂）受试者和用安慰剂或用左乙拉西坦（一天两次 125mg 持续两周）治疗的 aMCI 受试者之间的不同。

[0057] 图 11B 是图 11A 中所示数据的表。

[0058] 图 12A 显示在口头配对相关测试 - 识别的表现上，对照（安慰剂）受试者和用安慰剂或用左乙拉西坦（一天两次 125mg 持续两周）治疗的 aMCI 受试者之间的不同。

[0059] 图 12B 是图 12A 中所示数据的表。

[0060] 图 13A 显示在口头配对相关测试 - 延时回忆的表现上，对照（安慰剂）受试者和用安慰剂或用左乙拉西坦（一天两次 125mg 持续两周）治疗的 aMCI 受试者之间的不同。

[0061] 图 13B 是图 13A 中所示数据的表。

[0062] 图 14A 是显示用于实施例 2 中所示的人左乙拉西坦试验的受试者选择过程的表。

[0063] 图 14B 是显示用于实施例 2 中所示的人左乙拉西坦试验的所选受试者特征的表。

[0064] 图 15 描述在八臂放射臂迷宫任务中施用左乙拉西坦对 9 只老龄受损大鼠记忆行为的效果。施用于 AI 大鼠的布立西坦剂量包括 0.0625mg/kg、0.125mg/kg、0.25mg/kg、0.5mg/kg、1mg/kg、2mg/kg 和 4mg/kg。错误数的平均值和 SEM 显示为 y- 轴。

[0065] 图 16 描述在八臂放射臂迷宫测试中施用塞曲西坦对 9 只老龄受损大鼠记忆行为的效果。施用于 AI 大鼠的塞曲西坦剂量包括 0.0625mg/kg、0.125mg/kg、0.25mg/kg、0.5mg/kg、1mg/kg、2mg/kg 和 4mg/kg。错误数的平均值和 SEM 显示为 y- 轴。

[0066] 图 17A 和图 17B 描述水迷宫任务中 14 天后以 2mg/kg/ 天剂量的布立西坦治疗的老龄 - 受损大鼠 (n = 3/ 组）的行为。用 2mg/kg/ 天的布立西坦 ($t(2) = 10.000$, $p = 0.010$)、但未用媒介物 ($t(2) = 1.964$, $p = 0.188$) 治疗的大鼠显示与另外的对照四分圆相比对目标四分圆的显著空间偏好。布立西坦 - 治疗的大鼠 (2mg/kg/ 天）在目标四分圆上花费的时间明显多于媒介物 - 治疗的大鼠，$t(4) = 3.881$, $p = 0.018$。布立西坦 - 治疗的大鼠 (2mg/kg/ 天）在目标环形物（逃避平台位置周围的区域）上花费的时间明显多于媒介物 - 治疗的大鼠，$t(4) = 3.109$, $p = 0.036$。

[0067] 图 18A 和图 18B 描述左乙拉西坦以 62.5mg BID 和 250mg BID 的剂量对 aMCI 患者的锯齿状脑回 /CA3 区中的 fMRI 活动的效果。

[0068] 图 19A 和图 19B 显示在 62.5mg BID 安慰剂和 250mg BID 安慰剂的剂量下在实施例 4 中所述的外显 3 选项强迫选择任务的表现上，aMCI（安慰剂）受试者与年龄匹配的对照组（安慰剂）受试者之间的差异。每个柱表示当呈现诱饵图像时受试者反应（旧的、类似的或新的）的比率。

[0069] 图 20A 和图 20B 显示在实施例 4 中所述的外显 3 选项强迫选择任务的表现上，用

安慰剂治疗或用左乙拉西坦治疗 (62.5mg BID 和 250mg BID) 的相同 aMCI 受试者之间的不同。每个柱表示当呈现诱饵图像时受试者反应 (旧的、类似的或新的) 的比率。

[0070] 图 21 显示用小型渗透泵在老龄受损大鼠中施用 10mg/kg/ 天剂量的左乙拉西坦和媒介物 4 周恢复 DG 门中的生长抑素 (sematostatin)。

[0071] 图 22 显示用小型渗透泵在老龄受损大鼠中施用 10mg/kg/ 天剂量的左乙拉西坦和媒介物 4 周恢复内嗅皮质 (EC2) 中的颤蛋白。

[0072] 图 23A-23C 描述 62.5mg BID、125mg BID 和 250mg BID 左乙拉西坦剂量下 aMCI 患者的左乙拉西坦的血浆水平。

[0073] 发明详述

[0074] 除非本文另有定义，否则本申请中使用的科学和技术术语应具有本领域技术人员通常所理解的含义。一般而言，本文所述的用于与细胞和组织培养物、分子生物学、细胞和癌症生物学、神经生物学、神经化学、病毒学、免疫学、微生物学、药理学、遗传学和蛋白质和核酸化学的技术和与之关联的命名法是本领域众所周知和常用的。

[0075] 除非另外指明，否则本发明的方法和技术根据本领域众所周知的常规方法和如本说明书上下文中引述和讨论的各种一般和更具体的参考文献中所述进行。例如，参见“Principles of Neural Science”, McGraw-Hill Medical, New York, N.Y. (2000) ; Motulsky,“Intuitive Biostatistics”, Oxford University Press, Inc. (1995) ; Lodish 等人,“Molecular Cell Biology, 第 4 版”, W.H. Freeman&Co., New York (2000) ; Griffiths 等 人,“Introduction to Genetic Analysis, 第 7 版”, W.H. Freeman&Co., N.Y. (1999) ;Gilbert 等 人,“Developmental Biology, 第 6 版”, Sinauer Associates, Inc., Sunderland, MA (2000)。

[0076] 根据本领域的常规应用使用本文所用的化学术语，以“The McGraw-Hill Dictionary of Chemical Terms”, Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985) 中为典型。

[0077] 特别将本申请中涉及的所有上述和任意其它公开文献、专利和公布的专利申请引入本文参考。如果出现矛盾的情况，则以本说明书包括其具体定义为准。

[0078] 在本说明书上下文中，措词“包含”或变化形式例如“包括”或“含有”将被理解为意指包含所述整数 (或成分) 或整数 (或成分) 组，但不排除任何其它整数 (或成分) 或整数 (或成分) 组。

[0079] 除非上下文中另有明确指明，否则单数形式“一个”、“一种”和“该”包括复数形式。

[0080] 术语“包括”用于指“包括但不限于”。“包括”和“包括但不限于”可互换使用。

[0081] 本文所用的术语“活性剂”表示化学化合物 (例如有机或无机化合物、化合物混合物)、生物大分子 (例如核酸、抗体包括其部分和人源化、嵌合和人抗体和单克隆抗体、蛋白质或其部分、例如肽、脂质、碳水化合物) 或由生物材料、例如细菌、植物、真菌或动物 (特别是哺乳动物) 细胞或组织制备的提取物。活性剂包括，例如就结构而言已知和就结构而言未知的活性剂。这种活性剂的 SV2A 抑制活性或 AChEI 活性使它们适合于作为本发明方法和组合物中的“治疗剂”。

[0082] “患者”、“受试者”或“个体”可互换使用并且意指人或非人动物。这些术语包括哺乳动物，例如人、灵长类、家畜类动物 (包括牛、猪等)、陪伴动物 (例如犬、猫等) 和啮齿动

物（例如小鼠和大鼠）。

[0083] “认知功能”或“认知状态”意指相应地涉及学习和/或记忆的任何高级智力脑过程或脑状态，包括但不限于注意、信息采集、信息加工、工作记忆、短期记忆、长期记忆、顺应性记忆、逆行性记忆、记忆恢复、辨别学习、决策制定、抑制响应控制、注意设定-移位、延迟强化学习、逆向学习、自发行为的瞬时整合和对某环境和自我护理表示关注。

[0084] 在人中，可测定认知功能，例如、但不限于通过临床总体印象的变化量表(clinical global impression of change scale)(CIBIC-plus scale)；简短精神状态检查(the mini Mental State Exam)(MMSE)；神经精神调查(the Neuropsychiatric Inventory)(NPI)；临床痴呆等级量表(the Clinical Dementia Rating Scale)(CDR)；剑桥心理测试自动成套测试(the Cambridge Neuropsychological Test Automated Battery)(CANTAB)；老年医学的桑多临床评价(the Sandoz Clinical Assessment-Geriatric)(SCAG)，Buschke选择联想测试(the Buschke Selective Reminding Test)(Buschke和Fuld,1974)；口头配对相关分测试(the Verbal Paired Associates subtest)；逻辑记忆分测试(the Logical Memory subtes t)；修订的韦克斯勒记忆量表(the Wechsler Memory Scale-Revised)(WMS-R)的视觉复现分测试(the Visual Reproduction subtest)(Wechsler,1997)；Benton视觉保留测试(the Benton Visual Retention Test)，或外显3选项强迫选择任务(the explicit 3-alternative forced choice task)。参见Folstein等人，J Psychiatric Res 12:189-98,(1975)；Robbins等人，Dementia 5:266-81,(1994)；Rey，L'examen clinique en psychologie,(1964)；Kluger等人，J Geriatr Psychiatry Neurol 12:168-79,(1999)；Marquis等人，2002以及Masur等人,1994。另外参见Buchanan，R.W.，Keefe，R.S.E.，Umbricht，D.，Green，M.F.，Laughren，T.和Marder，S.R.(2011)，The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs:what do we know 5years later？ Schizophr.Bull.37,1209-1217。

[0085] 在动物模型系统中，可按照本领域已知的各种常规方式测定认知功能，包括使用其中动物使用空间信息的莫里斯水迷宫(MWM)、巴恩斯环形迷宫、高架放射臂迷宫、T形迷宫或任何其它迷宫。本领域已知的其它试验也可用于评价认知功能，例如新目标识别和气味识别任务。

[0086] 还可使用成像技术测定认知功能，例如正电子发射断层摄影术(PET)、功能性磁共振成像(fMRI)、单光子发射计算体层摄影(SPECT)或任何其它能够测定脑功能的成像技术。在动物中，还可使用电生理技术测定认知功能。

[0087] “促进”认知功能意指影响受损的认知功能，使得它更接近类似于正常、未受损的受试者的功能。可将认知功能促进至任何可检测的程度，但在人中，优选将其促进至足以允许受损受试者以与正常未受损的受试者或年龄匹配的正常未受损受试者尽可能接近的熟练水平(level of proficiency)进行每日正常生活的活动。

[0088] 在一些情况下，“促进”在受与年龄相关认知影响的受试者中的认知功能意指影响受损的认知功能，使得它更接近类似于老龄匹配的正常、未受损的受试者的功能或年轻成年受试者的功能。可将该受试者的认知功能促进至任何可检测的程度，但在人中，优选将其促进至足以允许受损受试者以与正常未受损受试者或年轻成年受试者或年龄匹配正常未

受损受试者尽可能接近的熟练水平进行每日正常生活的活动。

[0089] “保护”认知功能意指影响正常或受损认知功能，使得它不减退或不降至低于在首次呈现或诊断时在受试者中观察到的水平或延迟这种减退。

[0090] “改善”认知功能包括促进受试者认知功能和／或保护其认知功能。

[0091] “认知缺损”意指在受试者中的认知功能并不象在正常、未受损受试者中所预期的一样强。在一些情况下，认知功能与在正常、未受损受试者中所预期的认知功能相比减少约5%、约10%、约30%、或更多。在一些情况下，在受与年龄相关认知缺损影响的受试者中的“认知缺损”意指在受试者中的认知功能并不象在老龄匹配的正常、未受损受试者中所预期的或年轻成年受试者（即，在认知测定中对于给定年龄具有平均得分的受试者）中所预期的功能一样强。

[0092] “与年龄相关的认知缺损”意指在老龄受试者中的认知缺损，其中它们的认知功能并不像在年龄匹配的正常的受试者中所预期的或在年轻成年受试者中所预期的一样强。在一些情况下，认知功能与在年龄匹配的正常受试者中所预期的认知功能相比减少约5%、约10%、约30%、或更多。在一些情况下，认知功能是如在年龄匹配的正常受试者中所预期的，但与在年轻成年受试者中所预期的认知功能相比减少约5%、约10%、约30%、约50%、或更多。与年龄相关受损的认知功能可能与轻度认知缺损(MCI)(包括遗忘性MCI和非遗忘性MCI)、与年龄相关的记忆损伤(AAMI)和与年龄相关的认知减退(ARCD)相关。

[0093] 与AD相关的或涉及AD或在AD中的“认知缺损”意指在受试者中的认知功能并不像在使用常规方法和标准未诊断出AD的受试者中所预期的一样强。

[0094] “轻度认知缺损”或“MCI”意指特征在于未伴随其它认知异常和相对正常功能的能力的单独的记忆缺陷的病症。MCI的临床特征的一组标准指定了如下特征：(1)记忆抱怨（如患者、填报人或医师报道的）；(2)正常日常生活活动(ADL)；(3)正常总体认知功能；(4)年龄记忆异常（定义为低于指定年龄平均值多于1.5标准偏差的得分）；和(5)不存在痴呆指示（如根据DSM-IV指导原则定义）。Petersen等人，Srch.Neurol.56：303-308(1999)；Petersen，“Mild cognitive impairment：Aging to Alzheimer's Disease.”Oxford University Press，N.Y.(2003)。

[0095] MCI诊断通常要求客观评价认知缺损，可通过使用充分确立的神经心理学测验获取，包括简短精神状态检查(MMSE)、剑桥心理测试自动成套测试(CANTAB)和个体测试例如Rey听觉言语学习测试(AVLT)、修订的韦克斯勒记忆量表的逻辑记忆分测试(WMS-R)和纽约大学(NYU)段落回忆测试(Paragraph Recall Test)。参见Folstein等人，J Psychiatric Res 12：189-98(1975)；Robbins等人，Dementia 5：266-81(1994)；Kluger等人，J Geriatric Psychiatry Neurol 12：168-79(1999)。

[0096] “与年龄相关的记忆缺陷(AAMI)”意指因老龄化导致的记忆减退。如果他或她至少为50岁且满足如下全部标准，则可将患者视为具有AAMI：a)患者注意到记忆表现减退；b)与年轻成年人相比患者在记忆标准试验时表现更差；c)除正常老龄化以外的记忆减退的所有其它明显原因被排除（换句话说，记忆减退不能归因于其它原因，例如近期心脏病发作或头部损伤、抑郁症、对药物的不良反应、阿尔茨海默病等）。

[0097] “与年龄相关的认知减退(ARCD)”意指人老龄化正常结果的记忆和认知能力减退（例如Craik&Salthouse，1992）。这种情况实际上在所有哺乳动物种类中也是真实的。与

年龄相关的记忆缺陷意指相对于其年轻时代而言具有客观记忆减退，但认知功能相对于其同龄人而言是正常的的老年人 (Crook 等人，1986)。年龄一致性记忆减退是强调这些是正常发育改变的较轻的恶化标记 (Crook，1993 ；Larrabee，1996)、是非病理生理性的 (Smith 等人，1991) 和罕有发展成明显的痴呆 (Youngjohn&Crook，1993)。DSM-IV(1994) 已经整理成 ARCD 诊断分类。

[0098] 阿尔茨海默病 (AD) 特征为在其早期阶段中的记忆缺陷。迟发症状包括受损的判断、定向障碍、意识错乱、行为变化、说话困难和运动缺陷。组织学上，AD 特征为 β - 淀粉样斑块和缠结的 tau 蛋白。

[0099] 血管性痴呆由中风引起。症状与 AD 的那些症状重叠，但是并没有多见于记忆缺损。

[0100] 痴呆伴列维小体 (Dementia with Lewy bodies) 特征为在脑中神经元内形成的 α - 突触核蛋白的异常沉着物。认知缺损可能类似于 AD，包括记忆和判断以及行为变化的缺损。

[0101] 额颞痴呆特征为在额皮层和 / 或前颞叶和皮克小体中神经胶质增生、神经元丧失、浅表海绵状变性。症状包括性格和行为的变化，其包括社会技能和语言表达 / 理解力的减退。

[0102] “创伤后应激障碍 (PTSD)”意指特征为对突变事件立即或延迟反应的焦虑障碍、特征为再次经历创伤、心理麻痹或避免与创伤相关的刺激和增加的觉醒。再次经历现象包括对创伤提醒有侵入性记忆、幻觉重现、梦魇和心理或生理困扰的反应。这类反应产生焦虑，并可对患者的生活质量及身体和情感健康具有慢性和急性的显著影响。PTSD 也与受损的认知表现相关，并且患 PTSD 的老年个体相对于对照患者认知表现有更大的减退。

[0103] “精神分裂症”意指慢性虚弱障碍，特征为精神病理学谱，包括例如异常或歪曲的心理特征（例如，幻觉、妄想）的阳性症状，特征为动机和适当的有意动作减少（例如，兴趣缺失、情感冷淡、无动机）和认知缺损的阴性症状。尽管建议将脑的异常作为在精神分裂症中精神病理学的全谱基础，但目前可利用的抗精神病药大多对治疗患者认知缺损无效。

[0104] “双相情感障碍”或“BP”或“躁郁症”或“躁狂抑郁病”意指慢性心理 / 情感障碍，其可以表征为显著的情绪改变，包括抑郁期和陶醉性狂躁期。BP 可以由本领域技术人员基于个人和医学史、防视会诊和身体检查来诊断。术语“躁狂”或“躁狂期”或其它变化形式意指其中个体显示如下特征的一些或全部的期限 ：快速思维、快速语言、活动水平升高和激动以及自我尊重感膨胀、陶醉感、判断力弱、失眠症、注意力不集中和进攻行为。

[0105] “肌萎缩性侧索硬化”也称为 ALS，意指特征为运动神经元（该神经细胞在中枢神经系统中控制随意肌运动）变性的进行性、致死性、神经变性疾病。ALS 也特征为在内嗅皮层和海马中神经元变性、记忆缺陷以及在例如皮层的不同脑区中神经元兴奋性过高。

[0106] “与癌症治疗相关的认知缺损”意指在用例如化学治疗和辐射的癌症治疗治疗的受试者中发展的认知缺损。癌症治疗对脑的的细胞毒性和其它不良副作用导致如记忆、学习和注意力的这类功能的认知缺损。

[0107] 帕金森病 (PD) 是特征在于随意运动减少的神经障碍。患病的患者与正常个体相比具有运动活动减少和较为缓慢的随意运动。该患者具有特征性“面具”脸、行走同时的匆忙倾向、弯曲的体姿和肌肉泛发性虚弱。存在典型的“铅管样”强直的被动运动。该病的另

一个重要特征在于在休息时的四肢震颤和运动过程中的减少。

[0108] 本文所用的“孤独症”意指孤独性谱群疾病，其特征在于导致社会相互作用和沟通削弱的受限和重复行为的神经发育障碍。“孤独性谱群疾病”意指一组发育性残疾，其包括：孤独症；阿斯佩格综合征；未有特殊说明的全身性发育迟缓（PDD-NOS 或不典型孤独症）；Rett 综合征；和童年瓦解性障碍。

[0109] 精神发育迟滞是泛发性障碍，其特征在于显著受损的认知功能和适应行为缺陷。精神发育迟滞通常被定义为小于 70 的智力商数（IQ）得分。在许多潜在的原因中，精神发育迟滞是先天性原因。神经元沟通功能障碍也被视为精神发育迟滞的潜在原因之一（Myrrhe van Spronsen 和 Casper C. Hoogenraad, Curr. Neurol. Neurosci. Rep. 2010, 10, 207-214）。

[0110] 在一些情况中，精神发育迟滞包括、但不限于唐氏综合征、腭－心－面综合征（velocariofacial syndrome）、胎儿酒精综合征、脆性 X 染色体综合征、克兰费尔特综合征、神经纤维瘤病、先天性甲状腺功能减退症、威廉斯综合征、苯丙酮尿（PKU）、史－伦－奥三氏综合证、帕－魏二氏综合征、Phelan-McDermid 综合征、Mowat-Wilson 综合征、纤毛类疾病（ciliopathy）、Lowe 综合征和 siderium 型 X- 连锁智力障碍。唐氏综合征是一种障碍，其包括初生缺陷包括一定程度的精神发育迟滞、特征性面部特征和通常的心脏缺陷、感染增加、与视觉和听觉相关的问题和其它健康问题的组合。脆性 X 染色体综合征是遗传性精神发育迟滞的普遍形式，其发生频率为 4,000 个男性中有 1 个和 8,000 个女性中有 1 个。这种综合征的特征还在于发展迟滞、活动过度、注意缺陷障碍和孤独样行为。对于脆性 X 染色体综合征没有有效的治疗方法。

[0111] 强迫性障碍（“OCD”）是一种精神病症，其最常见的特征在于导致强迫行为的插入性的、反复性的不需要的思维（强迫观念）和精神作用为个体感觉驱动行为（强迫）。当前的流行病学数据表明 OCD 是美国第四位最常见的精神障碍。一些研究启示 OCD 的发病率在 1% -3%之间，不过，临床公认的 OCD 的发病率非常低，这启示许多具有该障碍的个体可能未被诊断。具有 OCD 的患者通常由心理学家、精神病专家或精神分析学家根据《精神病诊断与统计手册》(Diagnostic and Statistical Manual of Mental Disorders，第 4 版修订版 (DSM-IV-TR) (2000) 诊断标准（包括强迫观念行为和强迫的特征）来诊断。

[0112] 物质成瘾（例如药物成瘾、酒精成瘾）是一种精神障碍。这种成瘾并不在接触物质滥用时被即时地触发。而是它牵涉随数小时至数日至数个月范围的不同时间过程发生的多个复杂的神经改变 (Kauer J. A. Nat. Rev. Neurosci. 2007, 8, 844-858)。成瘾的路径一般从自愿应用一种或多种受控的物质开始，例如麻醉品、巴比妥酸盐类、甲基苯丙胺、酒精、烟碱和任意种类的其它这类管制物质。随时间的推移，延长使用管制物质，自愿避开管制物质的能力因对脑功能的作用和由此的行为而受损。照此，物质成瘾的特征一般在于强迫的物质渴求、寻找和使用，甚至在面对消极后果时仍然持续。渴求可以代表患者的潜在神经生物学改变，如果需要恢复，则必须能够以有意义的方式解决该患者的问题。在许多情况中，物质成瘾的特征还在于戒断症状，对于一些物质（例如酒精、巴比妥酸盐类），所述戒断症状是威胁生命的，而在其它情况中，可能导致显著的病态（可以包括恶心、呕吐、发热、眩晕和大量出汗）、痛苦和得到恢复的能力降低。例如，酒精中毒、也称作酒精依赖性是一种这样的物质成瘾。酒精中毒的特征主要在于 4 种症状，包括渴求、失控、身体依赖性和耐受性。这些症状还可以表征对其它管制物质成瘾。对酒精以及其它管制物质的渴求通常与对于食物

或水的需求一样强烈。因此，尽管存在严重的家庭、健康和/或法律分歧，但是酒精可以持续饮用。

[0113] “治疗”病症或患者意指采取措施以得到有益的或所需的结果，包括临床结果。有益的或所需的临床结果包括，但是不限于，改善认知功能，延迟或减缓认知缺损的发展，降低认知功能减退速率，预防或减缓疾病或障碍的发展，或减轻、改善或减缓与 CNS 障碍相关的认知缺损（例如与年龄相关的认知缺损、轻度认知缺损 (MCI)、遗忘性 MCI、痴呆、阿尔茨海默病 (AD)、前驱 AD、PTSD、精神分裂症或双相情感障碍（特别是躁狂）、肌萎缩性侧索硬化 (ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病 (PD)）、孤独症、强迫行为和物质成瘾）相关的一个或多个症状的发展。治疗与年龄相关的认知缺损还包括减缓与年龄相关的认知缺损（包括，但不限于 MCI、ARCD 和 AAMI）转化为痴呆（例如，AD）。

[0114] “治疗认知缺损”意指采取措施以改善在患认知缺损的受试者中的认知功能，以使一个或多个认知测试中受试者的表现改善至任何可检测的程度，或预防进一步减退。优选地，在治疗认知缺损之后，受试者的认知功能更接近类似于正常、未受损的受试者的功能。治疗在人中的认知缺损可将认知功能改善至任何可检测的程度，但是优选改善至足以允许受损受试者以与正常未受损的受试者相同的熟练水平进行每日正常生活的活动。在一些情况下，“治疗认知缺损”意指采取措施以改善在患认知缺损的受试者中的认知功能，以使一个或多个认知测试中受试者的表现改善至任何可检测的程度，或预防进一步减退。优选地，在治疗认知缺损之后，受试者的认知功能更接近类似于正常、未受损的受试者的功能。在一些情况下，在受到与年龄相关的认知缺损影响的受试者中“治疗认知缺损”意指采取措施以改善该受试者中的认知功能，以使在治疗认知缺损之后受试者的认知功能更接近类似于年龄匹配的正常、未受损受试者的功能，或年轻成年受试者的功能。在一些情况下，“治疗认知缺损”意指采取措施以延迟或减缓在具有认知缺损的受试者中的认知缺损的发展。在一些情况下，在受试者中“治疗认知缺损”意指采取措施以降低具有认知缺损的受试者的认知功能减退速率。

[0115] 物质、化合物或活性剂对受试者的“施用 (Administering)”或“施用 (administration)”可使用本领域技术人员已知的各种方法进行。例如，可通过静脉内、动脉、皮内、肌内、腹膜内、静脉内、皮下、眼部、舌下、口服（通过摄入）、鼻内（通过吸入）、脊柱内、脑内和透皮（通过吸收，例如通过皮肤输送管）施用化合物或活性剂。还可通过可再加入或可生物降解的聚合物装置或其它装置例如贴剂和泵或制剂适当导入化合物或活性剂，这提供延长、减缓或受控的化合物或活性剂释放。施用还可进行例如一次、多次和/或在一个或多个延长期限内进行。在一些方面中，施用包括直接施用，包括自身施用；和间接施用，包括为药物开处方行为。例如，作为本文使用的，指导患者自身施用或由另一个人施用药物和/或给患者提供药物处方的临床医师对患者施用药物。

[0116] 物质、化合物或活性剂对受试者的适合的施用方法还取决于例如受试者年龄，无论该受试者在施用时是活动的还是不活动的，无论受试者在施用时是否是认识受损的；缺损程度和化合物或活性剂的化学和生物特性（例如溶解性、可消化性、生物利用度、稳定性和毒性）。在一些实施方案中，通过口服（例如通过摄入）或静脉内（例如，通过注射）对受试者施用化合物或活性剂。在一些实施方案中，口服施用的化合物或活性剂是缓释或缓慢释放制剂的形式或使用用于这种缓慢释放或缓释的装置施用。

[0117] 药物或活性剂的“治疗有效量”是在对受试者施用时具有指定治疗效果（例如改善受试者认知功能或减缓其认知缺损发展或降低其认知功能减退速率）的药物或活性剂用量，所述受试者例如为患有与 CNS 障碍相关的认知缺损的患者。完全的治疗效果不一定通过施用一次剂量出现且可能在施用一系列剂量之后出现。因此，可以以一次或多次施用来施用治疗有效量。受试者所需的精确有效量将取决于例如受试者体型、健康状况和年龄、认知缺损的性质和程度以及为施用和施用方式选择的治疗剂或治疗剂组合。本领域技术人员易于通过常规实验确定用于指定情况的有效量。

[0118] “亚治疗量”意指本发明的活性剂或化合物施用的量小于治疗量，即，小于当所述活性剂或化合物单独施用时（即，单独和在不存在其它治疗剂或化合物的情况下）以治疗涉及认知功能障碍的障碍通常使用的量。

[0119] 本文将“类似物”用于意指功能上类似于另一个化学实体，但是并没有共有相同化学结构的化合物。例如，类似物十分类似于基础或母体化合物，以至于尽管结构上稍有不同，它也可在治疗应用中替代基础化合物。

[0120] 本文将“衍生物”用于意指化合物的化学修饰。化合物的化学修饰可包括，例如，用烷基、酰基或氨基替代氢。许多其它修饰也是可能的。

[0121] 术语“前药”是本领域公认的，并意欲包括在生理条件下转化为 SV2A 抑制剂或 AChEI 的化合物或活性剂。用于制备前药的常见方法是选择在生理条件下被水解或代谢的部分以提供所需的化合物或活性剂。在其它实施方案中，将该前药通过宿主动物的酶活性转化为 SV2A 的抑制剂或 AChEI。

[0122] 本文将“药学上可接受的盐”用于意指是本发明活性剂和化合物的治疗活性、非毒性碱和酸盐形式的根据本发明的活性剂或化合物。可以通过用适合的酸处理所述游离碱得到以其游离形式出现的作为碱的化合物的酸加成的盐形式，所述酸例如有：无机酸，例如氢卤酸，例如盐酸或氢溴酸、硫酸、硝酸、磷酸等；或有机酸，例如，乙酸、羟基乙酸、丙酸、乳酸、丙酮酸、丙二酸、琥珀酸、马来酸、富马酸、苹果酸、酒石酸、柠檬酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、环状酸（cyclic）、水杨酸、对氨基水杨酸、扑酸等。参见，例如 WO01/062726。

[0123] 本发明方法的说明

[0124] 本发明方法包括 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药与 AChEI 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的组合施用。所述 SV2A 抑制剂或所述 AChEI 和它们的药学上可接受的盐的活性剂或化合物还包括那些活性剂、化合物和盐的水合物、溶剂合物、多晶型物和前药。

[0125] 评价认知缺损的方法

[0126] 动物模型用作发展和评价与 CNS 障碍相关的认知缺损的治疗的重要资源。在动物模型中表征认知缺损的特征通常扩展至人中的认知缺损。因此，在这类动物模型中的功效期望预测在人中的功效。用于 CNS 障碍的动物模型中认知缺损的程度和用于所述 CNS 障碍治疗方法的功效可用多种认知试验进行测试并证实。

[0127] 放射臂迷宫（RAM）行为任务是认知测定（具体的是测试空间记忆）的一个实例（Chappell 等人，Neuropharmacology 37：481-487，1998）。RAM 设备由例如 8 个等距隔开的臂组成。迷宫臂从中心平台每个面伸出。食槽位于每个臂末端。食物用作奖赏。放置隔断以阻止进入任何臂中。也可提供环绕该设备的很多特别的迷宫线索。在熟习和训练阶段之

后，在对照或受试化合物治疗的条件下可在 RAM 中测试受试者的空间记忆。作为该测试的一部分，在试验之前将受试者用媒介物对照或一系列剂量之一的受试化合物进行预治疗。在每个试验开始时，将八臂迷宫的一小组臂隔断。在该试验的最初“信息阶段”期间，允许受试者在允许进入的未隔断的臂上得到食物。随后在信息阶段和接下来的“保留测试”之间的延迟期（例如，60 秒延迟、15 分钟延迟，1 小时延迟、2 小时延迟、6 小时延迟、24 小时延迟、或更长）将受试者从该迷宫移除，在此期间移除该迷宫上的屏障，因此允许进入所有八个臂。在延迟期之后，在该试验的保留测试阶段期间将受试者放回中心平台上（移除先前隔断臂的屏障）并允许得到剩下的食物奖赏。隔断臂的特性和配置在试验中变化。跟踪受试者在保留测试阶段形成的“错误”数。如果受试者进入已经在试验的延迟部分前从中取回食物的臂，或如果它在延迟期后再探访已经探访过的臂，那么错误就在试验中出现。错误数越少表明空间记忆越好。在各种受试化合物治疗方案下，可将由受试者形成的错误数随后用于比较受试化合物在治疗与 CNS 障碍相关的认知缺损中的功效。

[0128] 可用于评价受试化合物对 CNS 障碍模型动物的认知缺损效果的另一个认知测试是莫里斯水迷宫。水迷宫是环绕着相对于迷宫的一组新奇图案的水池。用于水迷宫的训练方案可基于已显示是海马 - 依赖性的改良水迷宫任务 (de Hoz 等人，Eur. J. Neurosci.，22 :745-54，2005 ；Steele 和 Morris，Hippocampus 9 :118-36，1999)。训练受试者找到隐藏在水池表面下在水中的逃避平台的位置。在训练试验期间，将受试者从该水池周界周围的随机起点放入迷宫（水池）中。起点在每次试验中都有所变化。如果受试者在规定的时间内未找到逃避平台的位置，那么试验者就将受试者引导至并放在平台上以“教导”它们找到平台的位置。在最后一次训练试验后的延迟期之后，不存在逃避平台的保留测试用于评价空间记忆。如通过例如由小鼠做出的在该位置花费的时间或穿过该位置的次数所测量的，受试者对（现在不存在的）逃避平台位置优选的水平表明空间记忆较好，即，认知缺损的治疗。然后可将在不同治疗条件下对逃避平台位置的优选用于比较受试化合物在治疗与 CNS 障碍相关的认知缺损中的功效。

[0129] 有用于评价在人中的认知功能的本领域已知的多种测试，例如但不限于，临床总体印象的变化量表 (CIBIC-+ 量表）；简短精神状态检查 (MMSE) ；神经精神调查 (NPI) ；临床痴呆等级量表 (CDR) ；剑桥心理测试自动成套测试 (CANTAB) ；老年医学的桑多临床评价 (SCAG)，Buschke 选择联想测试 (Buschke 和 Fuld，1974) ；口头配对相关分测试 ；逻辑记忆分测试 ；修订的韦克斯勒记忆量表的视觉复现分测试 (WMS-R) (Wechsler，1997) ；或 Benton 视觉保留测试 ；或 MATRICS 共有神经心理测验组，其包括工作记忆、加工处理速度、记忆力、语言学习、视觉学习、推理和解决问题和社会认知。参见 Folstein 等人，J Psychiatric Res 12 :189-98，(1975) ；Robbins 等人，Dementia5 :266-81，(1994) ；Rey，L'examen clinique en psychologie，(1964) ；Kluger 等 人，J Geriatr Psychiatry Neurol 12 :168-79，(1999) ；Marquis 等人，2002 以及 Masur 等人，1994 ；或 MATRICS 共有神经心理测验组，其包括工作记忆、加工处理速度、记忆力、语言学习、视觉学习、推理和解决问题和社会认知。在人中认知测试的另一个实例是外显 3 选项强迫选择任务。在该测试中，向受试者呈现常见物体的彩色照片，该照片由以下 3 种类型的图像对的混合物组成 ：类似对、相同对和无关衬托 (foils)。类似物体对的第二个称为“诱饵”。这些图像对是完全随机的，并作为系列图像单独呈现。受试者被指示做出关于所看到的物体是否是新的、旧的或类似的判断。对呈

现诱饵刺激物的“类似”反应表明受试者记忆提取成功。相比之下，称诱饵刺激物为“旧的”或“新的”则表明正确的记忆提取未出现。

[0130] 除了评价认知表现外，还可将与年龄相关的认知缺损和痴呆的发展以及与年龄相关的认知缺损向痴呆的转化通过评价替代物在受试者脑中的变化来监测。替代物变化包括但不限于，局部脑容量的变化、穿通通路退化和通过静息态 fMRI(R-fMRI) 和氟脱氧葡萄糖正电子发射断层摄影术 (FDG-PET) 所见的脑功能变化。局部脑容量适用于监测与年龄相关的认知缺损和痴呆的发展的实例包括海马体积的减少和内嗅皮层的体积或厚度的减少。这些体积可在受试者中通过例如 MRI 来测量。Aisen 等人，Alzheimer's&Dementia 6 :239-246(2010)。已经显示穿通通路退化与年龄和降低的认知功能相关。例如，穿通通路越退化的老年成人在海马 - 依赖性记忆测试中倾向于表现越差。可通过超高分辨率弥散张量成像 (DTI) 监测在受试者中穿通通路退化。Yassa 等人，PNAS 107 : 12687-12691(2010)。静息态 fMRI(R-fMRI) 涉及在静息期间成像脑，并记录在跨越功能上相关区域的暂时相关的 fMRI 信号中大振幅自发的低频率 (<0.1Hz) 波动。将基于种子 (Seed-based) 的功能连接性、独立成分分析和 / 或信号的频域分析用于揭示在脑区之间的功能连接性，具体的是其连接性随年龄以及认知缺损和 / 或痴呆的程度增加或减少的那些区域。FDG-PET 使用 FDG 的摄取作为在脑中局部代谢活性的测量值。在例如后扣带皮层、颞顶皮层和前额叶联络皮层的区域中 FDG 摄取的减退已经显示涉及认知减退和痴呆的程度。Aisen 等人，Alzheimer's&Dementia 6 :239-246(2010)，Herholz 等人，NeuroImage 17 : 302-316(2002)。

[0131] 与年龄相关的认知缺损

[0132] 用与 AChEI 或其水合物、溶剂合物、多晶型物或前药或药学上可接受的盐组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药，本发明提供了用于治疗与年龄相关的认知缺损或其风险的方法和组合物。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以不是缓释的形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包括改善具有与年龄相关的认知缺损的患者的认知功能。在一些实施方案中，治疗包括减缓或延迟与年龄相关的认知缺损的发展。在一些实施方案中，治疗包括降低与痴呆相关的认知功能减退的速率。在一些实施方案中，治疗包括预防或减缓与年龄相关的认知缺损的发展。在一些实施方案中，治疗包括减轻、改善或减缓与年龄相关的认知缺损相关的一个或多个症状的发展。在一些实施方案中，与年龄相关的认知缺损的治疗包括减缓与年龄相关的认知缺损 (包括，但不限于 MCI、ARCD 和 AAMI) 转化为痴呆 (例如，AD)。该方法和组合物可在临床应用中用于人患者以治疗在例如 MCI、ARCD 和 AAMI 的病症中的与年龄相关的认知缺损或用于处于患有所述疾病风险中的患者。如本文所述的用于所述方法的组合物的剂量和剂量间隔，在那些应用中是安全的和有效的。

[0133] 在一些实施方案中，待通过本发明的方法和组合物治疗的受试者显示与年龄相关的认知缺损或处于患有这类缺损的风险中。在一些实施方案中，所述与年龄相关的认知缺损包括但不限于，与年龄相关的记忆损伤 (AAMI)、轻度认知缺损 (MCI) 和与年龄相关的认知减退 (ARCD)。

[0134] 动物模型用作发展和评价这类与年龄相关的认知缺损的治疗的重要资源。在动物

模型中表征与年龄相关的认知缺损的特征通常扩展至人中的与年龄相关的认知缺损。因此，在这类动物模型中的功效期望预测在人中的功效。

[0135] 与年龄相关的认知缺损的多种动物模型为本领域已知。例如，大量的行为特征已鉴定了在远交系老龄 Long-Evans 大鼠中认知损害的自然发生形式 (Charles River Laboratories ;Gallagher 等人，Behav. Neurosci. 107 :618-626，(1993))。在用莫里斯水迷宫 (MWM) 进行的行为评价中，大鼠学习和记忆由该迷宫周围的空间线索配置引导的逃避平台的位置。使用动物在搜寻所述逃避平台的位置中空间偏好的测量值，在探查试验中测试表现的认知基础。在该研究群体中老龄大鼠游至可见的平台并无困难，但是当将该平台伪装，需要利用空间信息时，就检测到了年龄依赖性缺损。在远交 Long-Evans 系中的个别老龄大鼠的表现有很大不同。例如，部分那些大鼠与年轻成年大鼠有同样表现。但是，约 40-50％超出了年轻大鼠表现的范围。在老龄大鼠中的这种可变性反映了可靠的个体差异。因此，在老龄群体中一些动物是认知受损的，并称为老龄受损 (AI)，而其它动物是未受损的，并称为老龄未受损 (AU)。参见，例如，Colombo 等人，Proc. Natl. Acad. Sci. 94 : 14195-14199，(1997) ;Gallagher 和 Burwell，Neurobiol. Aging 10 :691-708，(1989) ; Gallagher 等人，Behav. Neurosci. 107 :618-626，(1993) ;Rapp 和 Gallagher，Proc. Natl. Acad. Sci. 93 :9926-9930，(1996) ;Nicolle 等 人，Neuroscience 74 :741-756，(1996) ; Nicolle 等人，J. Neurosci. 19 :9604-9610，(1999) ;国际专利公开文本 WO2007/019312 和国际专利公开文本 WO2004/048551。与年龄相关的认知缺损的这类动物模型可用于测试本发明的方法和组合物在治疗与年龄相关的认知缺损中的有效性。

[0136] 本发明的方法和组合物在治疗与年龄相关的认知缺损中的功效可使用多种认知测试，包括如上所讨论的莫里斯水迷宫和放射臂迷宫进行评价。

[0137] 痴呆

[0138] 使用与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物，本发明还提供了用于治疗痴呆的方法和组合物。在一些实施方案中，治疗包括改善具有痴呆的患者的认知功能。在一些实施方案中，治疗包括减缓或延迟痴呆的发展。在一些实施方案中，治疗包括降低与痴呆相关的认知功能减退的速率。在一些实施方案中，治疗包括预防或减缓痴呆的发展。在一些实施方案中，治疗包括减轻、改善或减缓与痴呆相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺损。在一些实施方案中，所述痴呆是阿尔茨海默病 (AD)、血管痴呆、痴呆伴列维小体或额颞痴呆。该方法和组合物可在临床应用中用于人患者以治疗痴呆。如本文所述的用于所述方法的组合物剂量和剂量间隔，在那些应用中是安全的和有效的。

[0139] 动物模型用作发展和评价痴呆的治疗的重要资源。在动物模型中表征痴呆的特征通常扩展至人中的痴呆。因此，在这类动物模型中的功效期望预测在人中的功效。痴呆的各种动物模型为本领域已知，例如 PDAPP、Tg2576、APP23、TgCRND8、J20、hPS2Tg 和 APP+PS1 转基因小鼠。Sankaranarayanan，Curr. Top. Medicinal Chem. 6 :609-627，2006 ;Kobayashi 等人，Genes Brain Behav. 4 :173-196. 2005 ;Ashe 和 Zahns，Neuron. 66 :631-45，2010。痴呆的这类动物模型可用于测试本发明的方法和组合物在治疗痴呆中的有效性。

[0140] 本发明的方法和组合物在治疗痴呆或与痴呆相关的认知缺损中的功效可使用如

上所讨论的本领域已知的多种认知测试，在痴呆的动物模型以及患痴呆的人受试者中进行评价。

[0141] 创伤后应激障碍

[0142] 使用与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物，本发明还提供了用于治疗创伤后应激障碍 (PTSD) 的方法和组合物。在一些实施方案中，治疗包括减缓或延迟 PTSD 的发展。在一些实施方案中，治疗包括降低与 PTSD 相关的认知功能功能减退的速率。在一些实施方案中，治疗包括改善具有 PTSD 的患者的认知功能。在一些实施方案中，治疗包括预防或减缓 PTSD 的发展。在一些实施方案中，治疗包括减轻、改善或减缓与 PTSD 相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺损。该方法和组合物可在临床应用中用于人患者以治疗 PTSD。如本文所述的用于所述方法的组合物剂量和剂量间隔，在那些应用中是安全的和有效的。

[0143] 患 PTSD 的患者（和暴露于较小程度创伤、未患 PTSD 的患者）有更小的海马体积 (Woon 等人，Prog. Neuro-Psychopharm. &Biological Psych. 34，1181-1188；Wang 等人，Arch. Gen. Psychiatry 67：296-303，2010)。PTSD 也是与受损认知表现相关的。患 PTSD 的老年个体相对于对照患者，认知表现有更大减退 (Yehuda 等人，Bio. Psych. 60：714-721，2006) 并具有发展痴呆的更大可能性 (Yaffe 等人，Arch. Gen. Psych. 678：608-613，2010)。

[0144] 动物模型用作发展和评价 PTSD 的治疗的重要资源。在动物模型中表征 PTSD 的特征通常扩展至人中的 PTSD。因此，在这类动物模型中的功效期望预测在人中的功效。PTSD 的各种动物模型为本领域已知。

[0145] PTSD 的一个大鼠模型是时间依赖性致敏作用 (time-dependent sensitization) (TDS) 模型。TDS 涉及使动物暴露于强烈应激事件，之后进行先前应激的处境提醒。下列是 TDS 的实例。将大鼠置于制动器中，然后置于泳池中并使其游泳一段时间，例如，20 分钟。随后，立即将每个大鼠暴露于气态麻醉剂中直到意识丧失，并最终干燥。使动物不受打扰持续许多天，例如，一周。然后将大鼠暴露于包括初始应激源的“再次应激”期，例如，在泳池中游泳期 (Liberzon 等人，Psychoneuroendocrinology 22：443-453，1997；Harvery 等人，Psychopharmacology 175：494-502，2004)。TDS 引起大鼠增强的听觉惊恐反应 (ASR)，其可与夸张的听觉惊恐（为 PTSD 的显著症状）相比 (Khan 和 Liberzon，Psychopharmacology 172：225-229，2004)。PTSD 的这类动物模型可用于测试本发明的方法和组合物在治疗 PTSD 中的有效性。

[0146] 本发明的方法和组合物在治疗 PTSD 或与 PTSD 相关的认知缺损中的功效也可使用如上所讨论的本领域已知的多种认知测试，在 PTSD 的动物模型以及患 PTSD 的人受试者中进行评价。

[0147] 精神分裂症

[0148] 使用与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物，本发明提供了用于治疗精神分裂症或双相情感障碍（特别是躁狂）的方法和组合物。在一些实施方案中，治疗包括改善具有精神分裂症的患者的认知功能。在一些实施方案中，治疗包括减缓或延迟精神分裂症的发展。在一些实施方案中，治疗包括降低与精神分裂症相关的认知功能减

退的速率。在一些实施方案中，治疗包括预防或减缓精神分裂症或双相情感障碍（特别是躁狂）的发展。在一些实施方案中，精神分裂症的特征在于广谱精神病理学情况，包括阳性症状，例如异常或扭曲的心理表征（例如幻觉、妄想），阴性症状，其特征在于动机减少和适应性目标定向作用（例如兴趣缺失、情感冷淡、缺乏情感反应）和认知缺损。在一些实施方案中，治疗包括减轻、改善或减缓与精神分裂症相关的一个或多个阳性和/或阴性症状的发展。此外，存在许多其它精神病，例如典型精神分裂症（schizotypical disorder）和情感性分裂症，其它急性和慢性精神病和双相情感障碍（特别是躁狂），它们具有与精神分裂症重叠的复合症状。在一些实施方案中，治疗包括减轻、改善或减缓与双相情感障碍（特别是躁狂）相关的一个或多个症状的发展以及认知缺损。该方法和组合物可在临床应用中用于人患者以治疗精神分裂症或双相情感障碍（特别是躁狂）。如本文所述的用于所述方法的组合物剂量和剂量间隔，在那些应用中是安全的和有效的。

[0149] 认知缺损也与精神分裂症相关。它们先于精神病的发作，并且在未受影响的亲属（relatives）中存在。与精神分裂症相关的认知缺损构成功能后果的良好预报器，并且是该障碍的核心特征。精神分裂症中的认知特征反映在额皮层和海马回路中的功能障碍。患精神分裂症的患者也存在例如海马体积减少、神经元尺寸减少和功能障碍性活动过强的海马病状。也已在精神分裂症的患者中记录到这些脑区中兴奋和抑制的失衡，其暗示药物靶向抑制的机制可能是有疗效的。参见，例如，Guidotti 等人，Psychopharmacology 180 :191-205,2005 ;Zierhut, Psych. Res. Neuroimag. 183 :187-194,2010 ;Wood 等人，NeuroImage 52 :62-63,2010 ;Vinkers 等 人，Expert Opin. Investig. Drugs 19 : 1217-1233,2009 ;Young 等人，Pharmacol. Ther. 122 :150-202,2009。

[0150] 动物模型用作发展和评价精神分裂症的治疗的重要资源。在动物模型中表征精神分裂症的特征通常扩展至人中的精神分裂症。因此，在这类动物模型中的功效期望预测在人中的功效。精神分裂症的各种动物模型为本领域已知。

[0151] 精神分裂症的一个动物模型是用蛋氨酸长久治疗。蛋氨酸治疗的小鼠显示在额皮层和海马中缺乏 GAD67 的表达，类似于在精神分裂症患者死后脑中所报道的情况。它们也显示惊恐和社交缺陷的前冲动抑制（Tremonlizzo 等人，PNAS,99 :17095-17100,2002）。精神分裂症的另一个动物模型为在大鼠中用甲基氧化偶氮甲醇乙酸盐（MAM）治疗。在妊娠第 17 天向怀孕雌性大鼠施用 MAM(20mg/kg，腹膜内）。MAM- 治疗概括了在后代中精神分裂症 - 样表型的病理发展过程，包括解剖学变化、行为缺陷和改变的神经元信息处理。更具体的是，MAM 治疗的大鼠显示小白蛋白 - 阳性 GABA 能中间神经元在前额皮层和海马部分中密度降低。在行为测试中，MAM 治疗的大鼠显示减小的潜伏抑制。潜伏抑制是一种行为现象，其中减少了对刺激物的学习，对于该刺激物存在具有任何结果的先前暴露。忽视先前良性刺激和减少与这类刺激相关的信息的倾向被认为防止了感觉超负荷。潜伏抑制低表明精神病。潜伏抑制可在大鼠中以下列方式测试。将大鼠分成两组。将一组在多次试验中预暴露于一个声调下。另一组不呈现声调。然后将两组暴露于听觉恐惧条件反射程序中，其中相同的声调与伤害性刺激，例如电击足同时呈现。随后，向两组呈现该声调，并在声调呈现期间监测大鼠运动行为的变化。在恐惧条件反射之后，大鼠通过极力减少运动行为对声调呈现做出反应。但是，在条件反射期之前已暴露于该声调中的组显示强烈的潜伏抑制 ：响应声调呈现的运动行为抑制减少了。MAM 治疗的大鼠，相比之下显示受损潜伏抑制。也就是，在

恐惧条件反射程序之前暴露于该声调，在抑制恐惧条件反射中并不具有显著作用。（参见 Lodge 等人，J. Neurosci.，29 :2344-2354，2009）。精神分裂症的这类动物模型可用于测试本发明的方法和组合物在治疗精神分裂症或双相情感障碍（特别是躁狂）中的有效性。

[0152] MAM- 治疗的大鼠对低剂量右苯丙胺施用展示出显著增强的运动响应（或异常运动行为）。MAM- 治疗的大鼠还展示出明显巨大数量的自发激发腹侧盖多巴胺 (DA) 神经元。认为这些结果是过度海马活动的结果，因为在 MAM- 治疗的大鼠中，腹侧海马回 (vHipp) 失活（例如因 vHipp 内施用钠通道阻滞剂河豚毒素 (TTX) 给 MAM 大鼠）完全逆转了升高的 DA 神经元群体活动并且还纠正了增强的苯丙胺诱导的运动行为。认为海马功能障碍与 DA 系统的过度响应率的相关性以对 MAM- 治疗的动物中的苯丙胺响应增强和精神分裂症患者中的精神病为基础。参见 Lodge D. J. 等人，Neurobiology of Disease(2007)，27(42)，11424-11430。MAM- 治疗的大鼠在上述研究中的应用可以适用于测定本发明的方法和组合物在治疗精神分裂症或双相情感障碍（特别是躁狂）中的有效性。例如，可以使用 MAM- 治疗的动物评价本发明的方法和组合物对中枢海马 (vHipp) 调节、升高的 DA 神经元群体活动和对 MAM- 治疗的动物中苯丙胺的活动过强响应的作用。

[0153] 在 MAM- 治疗的大鼠中，海马 (HPC) 功能障碍导致多巴胺系统活动过度。测试对 $GABA_A$受体 α 5 亚单位具有选择性的苯二氮杂 [illegible]阳性变构调节剂 (PAM) SH-053-2' F-R-CH_3 对海马 (HPC) 输出量的作用。还检查了 SH-053-2' F-R-CH_3对苯丙胺在 MAM- 治疗动物中的活动过强的运动响应的作用。当全身施用和直接输注入腹侧 HPC 时，α 5GABAAR PAM 将在 MAM 大鼠的腹侧盖区域 (VTA) 中的自发活动的 DA 神经元数量降至在盐水治疗的大鼠（对照组）中观察到的水平。此外，盐水治疗和 MAM- 治疗的动物中的 HPC 神经元在 α 5GABAAR PAM 治疗后显示减少的皮质诱发反应。此外，对在 MAM- 治疗大鼠中观察到的对苯丙胺的运动响应增加在 α 5$GABA_A$R PAM 治疗后减少。参见 Gill K. M 等人 Neuropsychopharmacology (2011)，1-9。MAM- 治疗的大鼠在上述研究中的应用可以适用于本发明测定本发明方法和组合物在治疗精神分裂症或双相情感障碍（特别是躁狂）中的有效性。例如，可以使用 MAM- 治疗的动物评价本发明的方法和组合物对海马 (HPC) 输出量和对苯丙胺在 MAM- 治疗的动物中的活动过强响应的作用。

[0154] 在胚胎第 15 天 (E15) 时施用 MAM 给妊娠大鼠严重地影响了子代中空间记忆或学习在八臂放射迷宫上对 4 个物品的空间定位的能力。此外，胚胎第 17 天 (E17) MAM- 治疗的大鼠能够在训练的起始阶段达到对照大鼠的行为水平，但在插入 30min 延迟时不能加工和恢复空间信息，表明工作记忆显著受损。参见，Gourevi tch R. 等人，(2004)，Behav. Pharmacol，15，287-292。这类精神分裂症的动物模型可以用于测定本发明方法和组合物在治疗精神分裂症或双相情感障碍（特别是躁狂）中的有效性。

[0155] 阿扑吗啡诱导的小鼠中的攀爬 (AIC) 和刻板 (AIS) 是用于本发明的另一种动物模型。以期望的剂量水平（例如通过腹膜内施用）给小鼠施用活性剂。随后，例如在 30 分钟后，用阿扑吗啡（例如 1mg/kg sc）攻击实验小鼠。阿扑吗啡注射后 5 分钟，对每只动物给由阿扑吗啡诱导的鼻吸气 - 舔 - 撕咬综合征（刻板行为）和攀爬行为评分并且记录。在 30min 测试期间每隔 5min 重复读取。将 30min 测试期间每只动物的每种综合征（刻板行为和攀爬）的得分汇总。条件是效果达到至少 50％抑制，且使用非线性最小二乘法计算与反向预测来计算 ID_{50}值 (95％置信区间）。可以将平均攀爬和刻板得分表示为在接受阿扑

吗啡的媒介物治疗（例如盐水治疗的）的小鼠中观察到的对照值的百分比。参见 Grauer S.M. 等人，Psychopharmacology(2009)204,37-48。这种小鼠模型可以用于测定本发明方法和组合物在治疗精神分裂症或双相情感障碍（特别是躁狂）或与之相关的认知缺损中的有效性。

[0156] 本发明的方法和组合物在治疗精神分裂症或与精神分裂症相关的认知缺损中的功效也可使用如上所讨论的本领域已知的多种认知测试，在精神分裂症或双相情感障碍（特别是躁狂）的动物模型以及患精神分裂症的人受试者中进行评价。

[0157] 肌萎缩性侧索硬化 (ALS)

[0158] 使用与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物，本发明又提供了用于治疗 ALS 的方法和组合物。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以非延迟释放的形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包括改善具有 ALS 的患者的认知功能。在一些实施方案中，治疗包括减缓或延迟 ALS 的发展。在一些实施方案中，治疗包括降低与 ALS 相关的认知功能减退的速率。在一些实施方案中，治疗包括预防或减缓 ALS 的发展。在一些实施方案中，治疗包括减轻、改善或减缓与 ALS 相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺损。该方法和组合物可在临床应用中用于人患者以治疗 ALS。如本文所述的用于所述方法的组合物剂量和剂量间隔，在那些应用中是安全的和有效的。

[0159] 除了运动神经元变性外，ALS 表征为在内嗅皮层和海马中神经元变性、记忆缺陷以及在例如皮层的不同脑区中神经元兴奋性过高。

[0160] 本发明的方法和组合物在治疗 ALS 或与 ALS 相关的认知缺损中的功效也可使用如上所讨论的本领域已知的多种认知测试，在 ALS 的动物模型以及患 ALS 的人受试者中进行评价。

[0161] 与癌症治疗相关的认知缺损

[0162] 使用与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物，本发明又提供了用于治疗与癌症治疗相关的认知缺损的方法和组合物。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以非缓释形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包含预防或减缓与癌症治疗相关的认知缺损的发展。在一些实施方案中，治疗包括改善具有与癌症治疗相关的认知缺损的患者的认知功能。在一些实施方案中，治疗包括减缓或延迟与癌症治疗相关的认知缺损的发展。在一些实施方案中，治疗包括降低与癌症治疗相关的认知缺损的认知功能减退的速率。在一些实施方案中，治疗包括减轻、改善或减缓与癌症治疗相关的认知缺损相关的一个或多个症状的发展。该方法和组合物可在临床应用中用于人患者以治疗与癌症治疗相关的认知缺损。如本文所述的用于所述方法的组合物剂量和剂量间隔，在那些应用中是安全的和有效的。

[0163] 用于癌症治疗（包括化学治疗、辐射或其组合）的治疗可引起患者在如记忆、学习和注意力的这类功能中的认知缺损。对癌症治疗的脑的细胞毒性和其它不良副作用以这种形式的认知缺损为基础，该认知缺损可持续十年。(Dietrich 等人，Oncologist 13：

1285-95,2008 ;Soussain 等人, Lancet 374 :1639-51,2009)。

[0164] 癌症治疗之后的认知缺损反映了正常认知所必需的额皮层和海马回路功能障碍。在动物模型中,暴露于化学治疗或辐射对认知特异性依赖于这些脑系统特别是海马的测试表现有不利的影响 (Kim 等人, J. Radiat. Res. 49 :517-526,2008 ;Yang 等人, Neurobiol. Learning and Mem. 93 :487-494,2010)。因此,靶向这些皮层和海马系统的药物在接受癌症治疗患者中可以是神经保护的,并且在治疗认知缺损的症状中是有效的,可持续超过用作癌症治疗的干预。

[0165] 动物模型用作发展和评价与癌症治疗相关的认知缺损的治疗的重要资源。在动物模型中表征与癌症治疗相关的认知缺损的特征通常扩展至人中的与癌症治疗相关的认知缺损。因此,在这类动物模型中的功效期望预测在人中的功效。与癌症治疗相关的认知缺损的各种动物模型为本领域已知。

[0166] 与癌症治疗相关的认知缺损的动物模型的实例包括用例如环磷酰胺 (CYP) 的抗肿瘤剂或用辐射,例如,^{60}Co γ 射线治疗动物。(Kim 等人, J. Radiat. Res. 49 :517-526, 2008 ;Yang 等人, Neurobiol. Learning and Mem. 93 :487-494,2010)。然后可用认知测试来测试与癌症治疗相关的认知缺损的动物模型的认知功能,以测试本发明的方法和组合物在治疗与癌症治疗相关的认知缺损中的有效性。本发明的方法和组合物在治疗与癌症治疗相关的认知缺损以及患与癌症治疗相关的认知缺损的人受试者中的功效,使用了如上所讨论的本领域已知的多种认知测试。

[0167] 帕金森病 (PD)

[0168] 帕金森病 (PD) 是特征在于随意运动减少的神经障碍。患病的患者与正常个体相比具有运动活动减少和较为缓慢的随意运动。该患者具有特征性"面具"脸、行走同时的匆忙倾向、弯曲的体姿和肌肉泛发性虚弱。存在典型的"铅管样"强直的被动运动。该病的另一个重要特征在于在休息时的四肢震颤和运动过程中的减少。

[0169] 帕金森病,其病因尚不了解,属于一组最常见的运动障碍,称作帕金森综合征,其影响每 1000 人中的约 1 个人。在帕金森综合征名称下分组的这些另外的障碍可以因病毒感染、梅毒、动脉硬化和创伤和暴露于毒性化学药品和麻醉品导致。但是,认为突触稳定性的不适当缺失可以导致神经元回路破坏和脑疾病。无论是遗传、药物使用、衰老过程、病毒感染、还是其它各种原因的结果,认为神经元沟通中的功能障碍是许多神经病的主要原因,例如 PD(Myrrhe van Spronsen 和 Casper C. Hoogenraad, Curr. Neurol. Neurosci. Rep. 2010, 10,207-214)。

[0170] 与疾病的原因无关,主要的病理性特征是基底神经节、尤其是黑质中的多巴胺能细胞变性。由于黑质中包含多巴胺的神经元过早死亡,所以基底神经节的最大结构纹状体已经减少了从黑质的输入,导致多巴胺释放减少。对主要病理学的理解导致引入了第一种成功的治疗方法,其可以缓解帕金森病。实际上,所有针对该病治疗的方法均基于多巴胺替代。用于治疗的药物可以在交叉通过血脑屏障后被转化成多巴胺,或它们可以加强多巴胺的合成并且减少其分解。令人遗憾地,主要的病理学情况黑质中细胞的变性未得以解除。该病持续进展并且在一定时间期限后频繁,多巴胺替代疗法失去其有效性。

[0171] 使用与 AChEI 或其药学上可接受的盐组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐,本发明提供了用于治疗 PD 的方法和组合物。在一些实施方案中,所述 AChEI

或其药学上可接受的盐以非缓释形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包括预防或减缓 PD 的进展。在一些实施方案中，治疗包括缓解、改善或减缓与 PD 相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺损。例如，本公开文本的方法和组合物可以用于改善帕金森病的活动 / 认知缺损症状。此外，本公开文本的方法和组合物可以用于治疗帕金森病的记忆缺陷症状。

[0172] 存在许多 PD 的动物模型。PD 的示例性的动物模型包括利血平模型、甲基苯丙胺模型、6- 羟基多巴胺 (6-OHDA) 模型、1- 甲基 -4- 苯基 -1, 2, 3, 6- 四氢吡啶 (MPTP) 模型、百草枯 (PQ)- 代森锰模型、鱼藤酮模型、3- 硝基酪氨酸模型和使用转基因小鼠的遗传学模型。转基因模型包括超表达 α - 突触核蛋白、表达 α - 突触核蛋白的人突变型的小鼠或表达 LRKK2 突变的小鼠。参见 Ranjita B. 等人的这些模型的综述 (Ranjita B. 等人，BioEssays 2002, 24, 308-318)。有关这些动物模型的另外的信息易于得自 Jackson Laboratories(还参见 http://research.jax.org/grs/parkinsons.html) 以及公开这些经验证的模型应用的大量出版物。

[0173] 在任意上述 PD 动物模型以及在具有 PD 的人受试者中，使用了如上所讨论的本领域已知的多种认知测试来评价本发明的方法和组合物在治疗 PD 或与 PD 相关的认知缺损的功效。

[0174] 孤独症

[0175] 本文所用的“孤独症”意指孤独性谱群疾病，其特征在于导致社会相互作用和沟通削弱的受限和重复行为的神经发育障碍。“孤独性谱群疾病”意指一组发育性残疾，其包括：孤独症；阿斯佩格综合征；未有特殊说明的全身性发育迟缓 (PDD-NOS 或不典型孤独症)；Rett 综合征；和童年瓦解性障碍。

[0176] 孤独症是特征在于三种核心行为等级功能障碍的神经发育障碍：重复行为、社交缺乏和认知缺陷。重复行为领域包括强迫行为、对目标罕见接触、顽固性的墨守成规或礼仪行为和反复性的活动作态，例如刻板和自我激动行为。社交缺陷等级包括社会交流缺陷、缺乏眼睛接触、从事会话的能力减弱和每日社交机能受损。认知缺陷可以包括语言异常。孤独性障碍是致残性神经障碍，其影响数以千计的美国人并且包括大量亚型，具有不同的推定原因且几乎没有文献记载改善性的治疗。孤独性谱群疾病可以在出生时存在或可能随后发作，例如在 2 或 3 岁时。没有明确的孤独症的生物学标记。该障碍的诊断由考虑儿童匹配行为综合征的程度进行，所述行为综合征的特征在于畅谈能力差、社交和认知能力怪癖和不适合的行为模式。神经元沟通功能障碍被视为孤独症的主要原因之一 (Myrrhe van Spronsen 和 Casper C. Hoogenraad, Curr. Neurol. Neurosci. Rep. 2010, 10, 207-214)。

[0177] 使用与 AChEI 或其药学上可接受的盐组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐，本发明提供了用于治疗孤独症的方法和组合物。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以非缓释形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包括预防或减缓孤独症。在一些实施方案中，治疗包括缓解、改善或减缓与孤独症相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺陷。例如，本公开文本的方法和组合物可以用于改善孤独症的活动 / 认知缺损症状。

[0178] 使用 Rodier 等人 (Rodier, P.M. 等人 Reprod. Toxicol. 1997,11,417-422) 建立的体外电生理技术的孤独症丙戊酸 (VPA) 的大鼠模型是基于最充分建立的创伤的孤独症动物模型之一,并且基于如下观察结果:在胚胎发育限制的时间窗期间,在上世纪 60 年代用 VPA 治疗的孕妇生育孤独症儿童的风险远高于正常人群。暴露于 VPA 的妊娠大鼠的子代显示几个典型孤独症的解剖和行为症状,例如小脑普肯耶神经元数量减少、社会相互作用削弱、重复行为和其它孤独症症状,包括恐惧记忆加工处理增强。参见 Rinaldi T. 等人 Frontiers in Neural Circuits,2008,2,1-7。可以使用如上文所讨论的本领域公知的各种认知测试在 VPA- 治疗的孤独症大鼠模型以及具有孤独症的人中评价本发明方法和组合物在治疗孤独症或与孤独症相关的认知缺陷中的功效。

[0179] 精神发育迟滞

[0180] 精神发育迟滞是泛发性障碍,其特征在于显著受损的认知功能和适应行为缺陷。精神发育迟滞通常被定义为小于 70 的智力商数 (IQ) 得分。在许多潜在的原因中,精神发育迟滞是先天性原因。神经元沟通功能障碍也被视为精神发育迟滞的潜在原因之一 (Myrrhe van Spronsen 和 Casper C. Hoogenraad, Curr. Neurol. Neurosci. Rep. 2010,10,207-214)。

[0181] 在一些情况中,精神发育迟滞包括、但不限于唐氏综合征、腭 - 心 - 面综合征、胎儿酒精综合征、脆性 X 染色体综合征、克兰费尔特综合征、神经纤维瘤病、先天性甲状腺功能减退症、威廉斯综合征、苯丙酮尿 (PKU)、史 - 伦 - 奥三氏综合证、帕 - 魏二氏综合征、Phelan-McDermid 综合征、Mowat-Wilson 综合征、纤毛类疾病、Lowe 综合征和 siderium 型 X- 连锁智力障碍。唐氏综合征是一种障碍,其包括初生缺陷包括一定程度的精神发育迟滞、特征性面部特征和通常的心脏缺陷、感染增加、与视觉和听觉相关的问题和其它健康问题的组合。脆性 X 染色体综合征是遗传性精神发育迟滞的普遍形式,其发生频率为 4,000 个男性中有 1 个和 8,000 个女性中有 1 个。这种综合征的特征还在于发展迟滞、活动过度、注意缺陷障碍和孤独样行为。对于脆性 X 染色体综合征没有有效的治疗方法。

[0182] 本发明关注轻度精神发育迟滞、中度精神发育迟滞和未详细说明的严重性精神发育迟滞的治疗方法。这类精神发育迟滞可以是、但不一定与染色体改变 (例如唐氏综合征归因于三体性 21)、遗传性、妊娠和围产期问题和其它严重性精神障碍相关。使用与 AChEI 或其药学上可接受的盐组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐,本发明提供了用于治疗精神发育迟滞的方法和组合物。在一些实施方案中,所述 AChEI 或其药学上可接受的盐以非缓释形式使用。在一些实施方案中,所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中,治疗包括预防或减缓精神发育迟滞的发展。在一些实施方案中,治疗包括缓解、改善或减缓与精神发育迟滞相关的一个或多个症状的发展。在一些实施方案中,待治疗的症状是认知缺陷 / 缺损。例如,本公开文本的方法和组合物可以用于改善精神发育迟滞的活动 / 认知缺损症状。

[0183] 已经为精神发育迟滞研发了几种动物模型。例如,已经为脆性 X 染色体综合征研发了敲除小鼠模型。脆性 X 染色体综合征是因不存在 FMR1 蛋白 FMRP 导致的精神发育迟滞的常见形式。已经鉴定了 FMRP 的两种同源物 FXR1P 和 FXR2P。FXR2P 显示在脑和睾丸中高度表达,如 FMRP。认为 Fxr2 和 Fmr1 敲除小鼠和 Fmr1/Fxr2 双敲除小鼠是精神发育迟滞例如脆性 X 染色体综合征的有用的模型。参见 Bontekoe C. J. M. 等人 Hum. Mol. Genet. 2002, 11(5):487-498。可以使用如上文所讨论的本领域公知的各种认知测试在这些小鼠模型和

其它为精神发育迟滞研发的动物模型中评价本发明方法和组合物在治疗精神发育迟滞或与精神发育迟滞相关的认知缺陷 / 缺损中的功效。

[0184] 强迫行为（强迫性障碍）

[0185] 强迫性障碍（“OCD”）是一种精神病症，其最常见的特征在于导致强迫行为的插入性的、反复性的不需要的思维（强迫观念）和精神作用为个体感觉驱动行为（强迫）。当前的流行病学数据表明 OCD 是美国第四位最常见的精神障碍。一些研究启示 OCD 的发病率在 1% -3%之间，不过，临床公认的 OCD 的发病率非常低，这启示许多具有该障碍的个体可能未被诊断。具有 OCD 的患者通常由心理学家、精神病专家或精神分析学家根据《精神病诊断与统计手册》(Diagnostic and Statistical Manual of Mental Disorders，第 4 版修订版 (DSM-IV-TR) (2000) 诊断标准（包括强迫观念行为和强迫的特征）来诊断。强迫观念的特征包括 :(1) 反复和持续性的思维、冲动或经历作为插入并且导致显著的焦虑或痛苦的图像 ;(2) 思维、冲动或图像并非对有关现时问题的简单的过度担忧 ;和 (3) 人尝试忽略或抑制这类思维、冲动或图像或用一些另外的思维或行动中和它们。人认为强迫观念思维、冲动或图像是他 / 她自身思想的产物且不基于现实性。强迫的特征包括 :(1) 人感觉被驱使对强迫观念做出反应或根据必须严格地适应规则的重复性的行为或精神作用 ;(2) 行为或精神作用的目的在于预防或减少痛苦或预防一些令人畏惧的事件或情况 ;然而，这些行为或精神作用实际上与问题无关或它们是过度的。

[0186] 具有 OCD 的个体典型地完成任务（或强迫）以寻求从与强迫观念相关的焦虑中解除。借助于强迫观念思维或脱离它们通常进行反复性的行为，例如洗手、计数、检查或清洁。然而，完成这些“仪式”仅提供短暂的解脱。具有 OCD 的人还可以使用其它精神障碍谱诊断，例如一般焦虑症、神经性厌食、惊恐发作或精神分裂症。

[0187] 神经元沟通中的功能障碍被视为强迫障碍的主要原因 (Myrrhe van Spronsen 和 Casper C. Hoogenraad, Curr. Neurol. Neurosci. Rep. 2010, 10, 207-214)。研究启示 OCD 与称作 5- 羟色胺的神经递质异常水平相关。OCD 的一线治疗由行为疗法、认知疗法和药物组成。治疗用药包括 5- 羟色胺再摄取抑制剂 (SRI)，例如帕罗西汀 (Seroxat™, Paxil®, Xetanor™, ParoMerck™, Rexetin™)、舍曲林（Zoloft®, Stimuloton™）、氟西汀（Prozac®, Bioxetin™）、艾司西酞普兰（Lexapro®）和氟伏沙明（Luvox®）以及三环抗抑郁药，特别是氯米帕明（Anafranil®）。苯二氮杂䓬类也原因治疗。然而，高达 40-60%的患者难以对 SRI 疗法做出足够的响应，且甚至更大比例的患者难以经历其症状的完全缓解。

[0188] 使用与 AChEI 或其药学上可接受的盐组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐，本发明提供了用于治疗 OCD 的方法和组合物。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以非缓释形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包括预防或减缓 OCD 的发展。在一些实施方案中，治疗包括缓解、改善或减缓与 OCD 相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺陷。例如，本公开文本的方法和组合物可以用于治疗 OCD 中的认知缺陷和 / 或改善具有 OCD 的患者的认知功能。已经为 OCD 研发了喹吡罗致敏的大鼠模型。将喹吡罗致敏的大鼠强迫检查行为进行进行中断，其为 OCD 强迫的属性特征。可

以使用如上文所讨论的本领域公知的各种认知测试在为 OCD 研发的这种大鼠模型和其它动物模型中以及具有 OCD 的人受试者中评价本发明方法和组合物在治疗 OCD 或与 OCD 相关的认知缺陷 / 缺损中的功效。

[0189] 物质成瘾

[0190] 物质成瘾（例如药物成瘾、酒精成瘾）是一种精神障碍。这种成瘾并不在接触物质滥用时被即时地触发。而是它牵涉随数小时至数日至数个月范围的不同时间过程发生的多个复杂的神经改变 (Kauer J. A. Nat. Rev. Neurosci. 2007, 8, 844-858)。成瘾的路径一般从自愿应用一种或多种受控的物质开始，例如麻醉品、巴比妥酸盐类、甲基苯丙胺、酒精、烟碱和任意种类的其它这类管制物质。随时间的推移，延长使用管制物质，自愿避开管制物质的能力因对脑功能的作用和由此的行为而受损。照此，物质成瘾的特征一般在于强迫的物质渴求、寻找和使用，甚至在面对消极后果时仍然持续。渴求可以代表患者的潜在神经生物学改变，如果需要恢复，则必须能够以有意义的方式解决该患者的问题。在许多情况中，物质成瘾的特征还在于戒断症状，对于一些物质（例如酒精、巴比妥酸盐类），所述戒断症状是威胁生命的，而在其它情况中，可能导致显著的病态（可以包括恶心、呕吐、发热、眩晕和大量出汗）、痛苦和得到恢复的能力降低。例如，酒精中毒、也称作酒精依赖性是一种这样的物质成瘾。酒精中毒的特征主要在于 4 种症状，包括渴求、失控、身体依赖性和耐受性。这些症状还可以表征对其它管制物质成瘾。对酒精以及其它管制物质的渴求通常与对于食物或水的需求一样强烈。因此，尽管存在严重的家庭、健康和 / 或法律分歧，但是酒精可以持续饮用。

[0191] 近期探察针对中枢神经系统 (CNS) 的滥用酒精、中枢兴奋药和阿片类物质的工作已经证实了与精神卫生相关的各种不良反应，包括物质诱导的认知缺损。参见 Nyberg F. Cognitive Impairments in Drug Addicts，第 9 章。在几个实验室和临床脑功能主要损害中观察到因这些药物导致。在滥用药物对脑的有害作用中有促成退化加速的那些。在近年期间接受特别关注的观察结果在于长期药物使用者展示出与执行和记忆功能相关的脑区域中的显著性缺损。因成瘾药物例如酒精、中枢兴奋药和阿片类物质导致的显著的神经适应牵涉海马的亚粒状区 (SGZ) 中的神经发生减少。实际上，已经提出在 SGZ 中减少的成年人神经发生可以改变海马功能，按照这种方式，它促成复发和维持性的成瘾行为。还提高减少的神经发生可以促成由这些滥用药物引起的认知缺陷的可能性。

[0192] 使用与 AChEI 或其药学上可接受的盐组合的缓释形式的 SV2A 抑制剂或其药学上可接受的盐，本发明提供了用于治疗物质成瘾的方法和组合物。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以非缓释形式使用。在一些实施方案中，所述 AChEI 或其药学上可接受的盐以立即释放形式使用。在一些实施方案中，治疗包括预防或减缓物质成瘾的发展。在一些实施方案中，治疗包括缓解、改善或减缓与物质成瘾相关的一个或多个症状的发展。在一些实施方案中，待治疗的症状是认知缺损。例如，本公开文本的方法和组合物可以用于治疗所述认知缺损和 / 或改善具有成瘾的患者的认知功能。

[0193] 已经研发了几种动物模型用于研究物质成瘾。例如，研发了一般选择的偏好 Marchigian Sardinian 酒精的 (msP) 大鼠模型用于研究酒精中毒的神经生物学。参见 Ciccocioppo R. 等人 Addiction Biology 2006, 11, 339-355。可以使用如上文所讨论的本领域公知的各种认知测试在物质成瘾动物模型和具有物质成瘾的人体受试者中评价本发

明方法和组合物在治疗物质成瘾或与物质成瘾相关的认知缺损中的功效。

[0194] SV2A 抑制剂

[0195] “突触小泡蛋白 -2(SV2)”是突触小泡蛋白家族，其由三个成员组成，命名为 SV2A、SV2B 和 SV2C。SV2A 是最广泛分布的家族成员，其在脑内泛表达。这些蛋白质是结合膜蛋白质类并且与转运糖、柠檬酸和异生物质的细菌和真菌转运蛋白的 12 个跨膜家族具有低水平同源性 (20-30％) (Bajjalieh 等人，Science，257 :1271-1273，(1992))。SV2 家族蛋白存在于脑和内分泌细胞中并且进一步存在于所有突触和内分泌小泡中。据报道 SV2 蛋白在正常突触功能中起作用并且在将小泡转化成 Ca(2+)- 和突触结合蛋白 - 响应状态的已接触抗原的小泡成熟步骤中起作用 (Sudhof 等人，2009)。在功能上，据报道 SV2 蛋白加强突触电流和通过维持易于释放的小泡群 (pool) 的大小增加递质释放的可能性 (Custer 等人，2006)。

[0196] “SV2A 抑制剂”意指结合 SV2A 和通过减少突触前小泡释放而降低突触功能的任何的活性剂、物质或化合物 (例如，参见 Noyer 等人，1995 ;Fuks 等人，2003 ;Lynch 等人，2004 ;Gillard 等人，2006 ;Custer 等人，2006 ;Smedt 等人，2007 ;Yang 等人，2007 ;Meehan，“Levetiracetam has an activity-dependent effect on inhibitory transmission”，Epilepsia，2012Jan 31 ;和 WO2001/62726 的实施例 8，特别将所有这些文献引入本文参考)。即使其自身不结合 SV2A，但是只要物质或化合物或活性剂产生或影响另一种化合物或活性剂结合 SV2A 或通过减少突触前小泡释放降低突触功能的能力，那么所述物质或化合物或活性剂就是 SV2A 抑制剂。本文所用的 SV2A 抑制剂包括其抑制剂的药学可接受的盐。它们也包括这些抑制剂的水合物、多晶型物、前药、盐和溶剂合物。

[0197] 适用于本发明的方法和组合物的所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物和多晶型物是例如美国 (U.S.) 专利申请 12/580,464、国际专利申请 PCT/US2009/005647、美国专利申请 61/105,847、美国专利申请 61/152,631 和美国专利申请 61/175,536 公开的那些。但是，任何 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物或前药都可用于本发明的方法和组合物。在一些实施方案中，所述 SV2A 抑制剂选自在如下文献中涉及的 SV2A 抑制剂 :国际专利申请 WO2010/144712 ;WO2010/002869 ;WO2008/132139 ;WO2007/065595 ;WO2006/128693 ;WO2006/128692 ;WO2005/054188 ;WO2004/087658 ;WO2002/094787 ;WO2001/062726 ; 美 国 专 利 7,465,549 ;7,244,747 ;5,334,720 ;4,696,943 ;4,696,942 ; 美国专利申请公开号 20090312333 ;20090018148 ;20080081832 ;2006258704 ;和英国专利号 1,039,113 ;和 1,309,692 或其药学上可接受的盐、水合物、溶剂合物或多晶型物。其它 SV2A 抑制剂也可以用于本发明。申请人还涉及制备上文引述的对比文件中发现的这些化合物的方法。也可以使用其它合成方法。这些方法是本领域技术人员众所周知的。

[0198] 在本发明的一些实施方案中，所述 SV2A 抑制剂选自左乙拉西坦、布立西坦和塞曲西坦或其衍生物或类似物或药学上可接受的盐、溶剂合物、水合物、多晶型物或前药。

[0199] 在本发明的一些实施方案中，所述 SV2A 抑制剂是左乙拉西坦或其盐、溶剂合物、水合物、多晶型物或前药。左乙拉西坦意指国际纯粹与应用化学联合会 (IUPAC) 的化合物名称 (2S)-2-(2- 氧代吡咯烷 -1- 基) 丁酰胺。左乙拉西坦为广泛使用的抗癫痫药。左乙拉西坦与 CNS 中特异位点 :突触小泡蛋白 2A(SV2A) 结合 (参见，例如，Noyer 等人，1995 ;Fuks

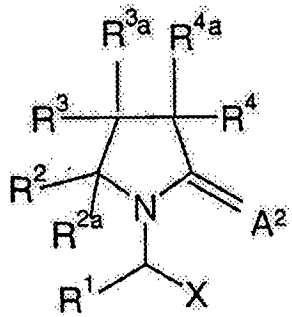
等人，2003；Lynch 等人，2004；Gillard 等人，2006）并进一步显示通过抑制突触前神经递质释放直接抑制突触活性和神经传递（Yang 等人，2007）。

[0200] 用于本发明方法和组合物的 SV2A 抑制剂包括如下：

[0201] i）国际专利申请 WO2001/062726：

[0202] 具有式 I 的化合物或其药学可接受的盐，

[0203]



(I)

[0204] 其中 X 是 $-CA^1NR^5R^6$ 或 $-CA^1OR^7$ 或 $-CA^1-R^8$ 或 CN；

[0205] A^1 和 A^2 独立地是氧、硫或 $-NR^9$；

[0206] R^1 是氢、烷基、芳基或 $-CH_2-R^{1a}$，其中 R^{1a} 是芳基、杂环、卤素、羟基、氨基、硝基或氰基；

[0207] R^2、R^3 和 R^4 相同或不同且各自独立地是氢、卤素、羟基、硫羟基、氨基、硝基、硝基氧基、氰基、叠氮基、羧基、酰氨基、磺酸、磺酰胺、烷基、烯基、炔基、酯、醚、芳基、杂环或氧基衍生物、硫基衍生物（thio derivative）、氨基衍生物、酰基衍生物、磺酰基衍生物或亚磺酰基衍生物；

[0208] R^{2a}、R^{3a} 和 R^{4a} 相同或不同且各自独立地是氢、卤素、烷基、烯基、炔基或芳基；

[0209] R^5、R^6、R^7 和 R^9 相同或不同且各自独立地是氢、羟基、烷基、芳基、杂环或氧基衍生物；且

[0210] R^8 是氢、羟基、硫羟基、卤素、烷基、芳基、杂环或硫基衍生物；

[0211] 条件是 R^2、R^3、R^4、R^{2a}、R^{3a} 和 R^{4a} 中的至少一个不是氢，且当化合物是所有可能异构体的混合物，X 是 $-CONR^5R^6$，A^2 是氧，R^1 是氢、甲基、乙基或丙基时，吡咯烷环上的取代不是一-、二-或三-甲基或一-乙基；且当 R^1、R^2、R^4、R^{2a}、R^{3a} 和 R^{4a} 各自是氢，A^2 是氧，X 是 $CONR^5R^6$ 时，R^3 不是羧基、酯、酰氨基、取代的氧代-吡咯烷、羟基、氧基衍生物、氨基、氨基衍生物、甲基、萘基、任选地被氧基衍生物或在对位被卤素原子取代的苯基。

[0212] 在如下举出的定义中，除非另作陈述，否则 R^{11} 和 R^{12} 相同或不同且各自独立地是酰氨基、烷基、烯基、炔基、酰基、酯、醚、芳基、芳烷基、杂环或氧基衍生物、硫基衍生物、酰基衍生物、氨基衍生物、磺酰基衍生物或亚磺酰基衍生物，其各自任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，所述部分选自低级烷基或如下对烷基取代基所述的其它基团。

[0213] 本文所用的术语“氧基衍生物”定义为包括 $-O-R^{11}$ 基团，其中 R^{11} 如上述所定义，除了“氧基衍生物”。非限制性实例是烷氧基、烯基氧基、炔基氧基、酰基氧基、氧基酯、氧基酰氨基、烷基磺酰基氧基、烷基亚磺酰基氧基、芳基磺酰基氧基、芳基亚磺酰基氧基、芳基氧基、芳烷氧基或杂环氧基，例如戊基氧基、烯丙基氧基、甲氧基、乙氧基、苯氧基、苄基氧基、

2- 萘基氧基、2- 吡啶基氧基、亚甲二氧基、碳酸酯。

[0214] 本文所用的术语“硫基衍生物”定义为包括 -S-R^{11}基团，其中 R^{11}如上述所定义，除了“硫基衍生物”。非限制性实例是烷硫基、烯硫基、炔硫基和芳硫基。

[0215] 本文所用的术语“氨基衍生物”定义为包括 -NHR^{11}或 -$NR^{11}R^{12}$基团，其中 R^{11}和 R^{12}如上述所定义。非限制性实例是一 - 或二 - 烷基 -、烯基 -、炔基 - 和芳基氨基或混合氨基。

[0216] 本文所用的术语“酰基衍生物”表示衍生自羧酸的基团且由此定义为包括式 R^{11}-CO- 的基团，其中，R^{11}如上述所定义且还可以是氢。非限制性实例是甲酰基、乙酰基、丙酰基、异丁酰基、戊酰基、月桂酰基、庚二酰基、环己烷羰基、巴豆酰基、富马酰基、丙烯酰基、苯甲酰基、萘甲酰基、糠酰基、烟酰基、4- 羧基丁酰基、草酰基、乙草酰基、半胱氨酰基、草氨酰基。

[0217] 本文所用的术语“磺酰基衍生物”定义为包括式 -SO_2-R^{11}的基团，其中 R^{11}如上述所定义，除了“磺酰基衍生物”。非限制性实例是烷基磺酰基、烯基磺酰基、炔基磺酰基和芳基磺酰基。

[0218] 本文所用的术语“亚磺酰基衍生物”定义为包括式 -SO-R^{11}的基团，其中 R^{11}如上述所定义，除了“亚磺酰基衍生物”。非限制性实例是烷基亚磺酰基、烯基亚磺酰基、炔基亚磺酰基和芳基亚磺酰基。

[0219] 本文所用的术语“烷基”定义为包括饱和一价烃基，其具有直链、支链或环状部分或其组合并且就非环烷基而言包含 1-20 个碳原子、优选 1-6 个碳原子且就环烷基而言包含 3-6 个碳原子（在这两种优选的情况中，除非另有指定，否则是“低级烷基”）。烷基部分可以任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、硫羟基、氨基、硝基、氰基、氰硫基、酰基、酰基氧基、磺酰基衍生物、亚磺酰基衍生物、烷基氨基、羧基、酯、醚、酰氨基、叠氮基、环烷基、磺酸、磺酰胺、硫基衍生物、氧基酯、氧基酰氨基、杂环、乙烯基、C1-5- 烷氧基、C6-10- 芳基氧基和 C6-10- 芳基。

[0220] 优选的烷基是甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基和 2,2,2- 三甲基乙基，其各自任选地被至少一个取代基取代，所述取代基选自卤素、羟基、硫羟基、氨基、硝基和氰基，例如三氟甲基、三氯甲基、2,2,2- 三氯乙基、1,1- 二甲基 -2,2- 二溴乙基、1,1- 二甲基 -2,2,2- 三氯乙基。

[0221] 本文所用的术语“烯基”定义为包括支链和无支链不饱和烃基，其具有至少一个双键例如乙烯基（＝乙烯基）、1- 甲基 -1- 乙烯基、2,2- 二甲基 -1- 乙烯基、1- 丙烯基、2- 丙烯基（＝烯丙基）、1- 丁烯基、2- 丁烯基、3- 丁烯基、4- 戊烯基、1- 甲基 -4- 戊烯基、3- 甲基 -1- 戊烯基、1- 己烯基、2- 己烯基等且任选地被至少一个取代基取代，所述取代基选自卤素、羟基、硫羟基、氨基、硝基、氰基、芳基和杂环，例如一 - 和二 - 卤代乙烯基，其中卤素是氟、氯或溴。

[0222] 本文所用的术语“炔基”定义为包括一价支链或无支链烃基，其包含至少一个碳 - 碳三键，例如乙炔基、2- 丙炔基（＝炔丙基）等且任选地被至少一个取代基取代，所述取代基选自卤素、羟基、硫羟基、氨基、硝基、氰基、芳基和杂环，例如卤代乙炔基。

[0223] 当作为桥连基团时，烷基、烯基和炔基分别表示直链 - 或支链 C1-12、优选 C1-4- 亚烷基或 C2-12-、优选 C2-4- 亚烯基或 - 亚炔基部分。

[0224] 除非另做陈述，否则其中支链衍生物通常被前缀例如“正”、“仲”、“异”等修饰的基

团（例如“正-丙基”、“仲-丁基”）是正-形式。

[0225] 本文所用的术语“芳基”定义为包括由 1-3 个环组成并且包含 6-30 个碳原子的芳香烃通过除去一个氢衍生的有机基团，例如苯基和萘基，其各自任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、硫羟基、氨基、硝基、氰基、酰基、酰基氧基、磺酰基、亚磺酰基、烷基氨基、羧基、酯、醚、酰氨基、叠氮基、磺酸、磺酰胺、烷基磺酰基、烷基亚磺酰基、烷硫基、氧基酯、氧基酰氨基、芳基、C1-6- 烷氧基、C6-10- 芳基氧基、C1-6- 烷基、C1-6- 卤代烷基。芳基优选为包含 6-10 个碳原子的单环。优选的芳基是苯基和萘基，其各自任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、硝基、氨基、叠氮基、C1-6- 烷氧基、C1-6- 烷硫基、C1-6- 烷基、C1-6- 卤代烷基和苯基。

[0226] 本文所用的术语“卤素”包括 Cl、Br、F、I 的原子。

[0227] 本文所用的术语“羟基”表示式 -OH 的基团。

[0228] 本文所用的术语“硫羟基”表示式 -SH 的基团。

[0229] 本文所用的术语“氰基”表示式 -CN 的基团。

[0230] 本文所用的术语“硝基”表示式 $-NO_2$ 的基团。

[0231] 本文所用的术语“硝基氧基”表示式 $-ONO_2$ 的基团。

[0232] 本文所用的术语“氨基”表示式 $-NH_2$ 的基团。

[0233] 本文所用的术语“叠氮基”表示式 $-N_3$ 的基团。

[0234] 本文所用的术语“羧基”表示式 -COOH 的基团。

[0235] 本文所用的术语“磺酸”表示式 $-SO_3H$ 的基团。

[0236] 本文所用的术语“磺酰胺”表示式 $-SO_2NH_2$ 的基团。

[0237] 本文所用的术语“酯”定义为包括式 $-COO-R^{11}$ 的基团，其中 R^{11} 如上述所定义，除了氧基衍生物、硫基衍生物或氨基衍生物。

[0238] 术语“醚”定义为包括选自 C1-50- 直链或支链烷基或 C2-50- 直链或支链烯基或炔基或其组合的基团，其被一个或多个氧原子间隔。

[0239] 术语“酰氨基”定义为包括式 $-CONH_2$ 或 $-CONHR^{11}$ 或 $-CONR^{11}R^{12}$ 的基团，其中 R^{11} 和 R^{12} 如上述所定义。

[0240] 本文所用的术语“杂环”定义为包括如上述所定义的芳族或非芳族环烷基、烯基或炔基部分，具有至少一个间隔碳环结构的 O、S 和 / 或 N 原子，且任选碳环结构的碳原子之一可以被羰基替代。芳族杂环的非限制性实例是吡啶基、呋喃基、吡咯基、噻吩基、异噻唑基、咪唑基、苯并咪唑基、四唑基、喹唑啉基、喹噁基、萘啶基、哒嗪基、嘧啶基、吡嗪基、喹啉基、异喹啉基、异苯并呋喃基、苯并噻吩基、吡唑基、吲哚基、吲噁基、嘌呤基、异吲哚基、咔唑基、噻唑基、1,2,4- 噻二唑基、噻吩并 (2,3-b) 呋喃基、呋喃并吡喃基、苯并呋喃基、苯并氧杂环庚三烯基、异噁唑基、噁唑基、噻蒽基、苯并噻唑基或苯并噁唑基、噌啉基、酞嗪基、喹喔啉基、菲啶基、吖啶基、萘嵌间二氮苯基、菲咯啉基、吩噻嗪基、呋咱基、异苯并二氢吡喃基、二氢吲哚基、呫吨基、次黄嘌呤基、蝶啶基、5- 氮杂胞苷基、5- 氮杂尿嘧啶基、三唑并吡啶基、咪唑并吡啶基、吡咯并嘧啶基和吡唑并嘧啶基，其任选地被烷基取代或如上述对烷基所述被取代。芳族杂环的非限制性实例是四氢呋喃基、四氢吡喃基、哌啶基、哌啶基、哌嗪基、咪唑烷基、吗啉代、吗啉基、1- 氧杂螺 (4.5) 癸 -2- 基、吡咯烷基、2- 氧代 - 吡咯烷基、糖部分（即葡萄糖、戊糖、己糖、核糖、果糖，其也可以被取代）或可以任选地被任意适合的基团取

代的相同部分，所述适合的基团包括、但不限于一个或多个部分，所述部分选自低级烷基或其它如上述对烷基所述的基团。术语“杂环”还包括双环、三环和四环、螺基团，其中任意上述杂环与一个或两个环稠合，所述环独立地选自芳基环、环己烷环、环己烯环、环戊烷环、环戊烯环或另一种单环杂环或其中单环杂环基通过亚烷基桥连，例如奎宁环基、7- 氮杂双环 (2.2.1) 庚烷基、7- 氧杂双环 (2.2.1) 庚烷基、8- 氮杂双环 (3.2.1) 辛烷基。

[0241] 在上述定义中，应理解当取代基、例如 R^2、R^3、R^4、R^{2a}、R^{3a}、R^{4a}、R^5、R^6、R^7、R^8通过杂原子或羰基与分子的其余部分连接时，直链 - 或支链 C1-12-、优选 C1-4- 亚烷基或 C2-12、优选 C2-4- 亚烯基或 - 亚炔基桥可以任选插于杂原子或羰基与分子其余部分连接点之间。

[0242] 优选的 X 实例是 $-COOR^7$ 或 $-CONR^5R^6$，其中 R^5、R^6 和 R^7 优选为氢、C1-4- 烷基、苯基或烷基苯基。

[0243] 优选 X 是羧基或 $-CONR^5R^6$，其中 R^5 和 R^6 优选为氢、C1-4- 烷基、苯基或烷基苯基、尤其是 $-CONH_2$。

[0244] 优选 A^1 和 A^2 各自是氧。

[0245] 优选 R^1 基团是氢、烷基，尤其是 C1-12 烷基，特别是低级烷基或芳基，尤其是苯基。

[0246] R^1 的优选实例是甲基、乙基、丙基、异丙基、丁基、异 - 或叔 - 丁基、2,2,2- 三甲基乙基，其各自任选通过亚甲基桥连接或被至少一个卤素原子取代的相同部分，例如三氟甲基、三氯甲基、2,2,2- 三氯乙基、1,1- 二甲基 -2,2- 二溴乙基、1,1- 二甲基 -2,2,2- 三氯乙基。

[0247] 尤其优选 R^1 为乙基。

[0248] 优选 R^2 和 R^{2a} 基团独立地是氢、卤素或烷基、尤其是低级烷基。

[0249] R^2 和 R^{2a} 的优选实例独立地是氢、卤素或甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基、2,2,2- 三甲基乙基或被至少一个卤素原子取代的相同部分，例如三氟甲基、三氯甲基、2,2,2- 三氯乙基、1,1- 二甲基 -2,2- 二溴乙基、1,1- 二甲基 -2,2,2- 三氯乙基。

[0250] 尤其是 R^2 和 R^{2a} 中的至少一个且最优选两个是氢。

[0251] 优选 R^{3a}、R^4 和 R^{4a} 基团独立地是氢、烷基，尤其是甲基或乙基或芳基，尤其是苯基或芳烷基，尤其是苄基。

[0252] 优选 R^{3a}、R^4 和 R^{4a} 的实例独立地是氢、卤素或甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基、2,2,2- 三甲基乙基或被至少一个卤素原子取代的相同基团，例如三氟甲基、三氯甲基、2,2,2- 三氯乙基、1,1- 二甲基 -2,2- 二溴乙基、1,1- 二甲基 -2,2,2- 三氯乙基。

[0253] 尤其是 R^4 和 R^{4a} 中的至少一个且最优选两个是氢。

[0254] R^{3a} 特别是氢或烷基，尤其是低级烷基且最优选是氢。

[0255] 优选 R^3 是氢、C1-12- 烷基、尤其是 C1-6- 烷基，其各自任选地被一个或多个取代基取代，所述取代基选自羟基、卤素、氰基、氰硫基或烷氧基且直接或通过硫代、亚磺酰基、磺酰基、羰基或氧基羰基和任选的 C1-4- 亚烷基桥（特别是亚甲基）与环连接；C2-6- 烯基或 - 炔基，尤其是 C2-3- 烯基或 - 炔基，其各自任选地被一个或多个卤素取代；叠氮基；氰基；酰氨基；羧基；三唑基，四唑基，吡咯烷基，吡啶基，1- 氧 (1-oxido) 吡啶基，硫吗啉基，苯并间二氧杂环戊烯基，呋喃基，噁唑基，嘧啶基，吡咯基，噻二唑基，噻唑基，噻吩基或哌嗪基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、C1-6- 烷基和苯基且直接或通过羰基或 C1-4- 亚烷基桥（特别是亚甲基）与环连接；萘基；或苯基、苯基烷基或苯基烯基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、C1-6- 烷基、C1-6

卤代烷基、C1-6- 烷氧基、C1-6- 烷硫基、氨基、叠氮基、苯基和硝基且各自直接或通过硫代、亚磺酰基、磺酰基、羰基或氧基羰基和任选附加的 C1-4- 亚烷基桥（特别是亚甲基）与环连接。

[0256] 此外，优选 R^3 是 C1-6- 烷基，其任选地被一个或多个取代基取代，所述取代基选自卤素、氰硫基、叠氮基、烷氧基、烷硫基、苯基磺酰基；硝基氧基；C2-3- 烯基或 - 炔基，其各自任选地被一个或多个卤素或乙酰基取代；四唑基、吡啶基、呋喃基、吡咯基、噻唑基或噻吩基；或苯基或苯基烷基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、C1-6- 烷基、C1-6 卤代烷基、C1-6- 烷氧基、氨基、叠氮基、苯基和硝基且各自直接或通过磺酰基氧基和任选附加的 C1-4- 亚烷基桥（特别是亚甲基）与环连接。

[0257] 优选的 R^3 基团的其它实例是氢、卤素或甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基、2,2,2- 三甲基乙基或被至少一个卤素原子取代的相同基团，例如三氟甲基、三氯甲基、2,2,2- 三氯乙基、1,1- 二甲基 -2,2- 二溴乙基、1,1- 二甲基 -2,2,2- 三氯乙基。

[0258] R^3 尤其是 C1-4- 烷基，其任选地被一个或多个取代基取代，所述取代基选自卤素、氰硫基或叠氮基；C2-5- 烯基或 - 炔基，其各自任选地被一个或多个卤素取代；噻吩基；或苯基，其任选地被一个或多个取代基取代，所述取代基选自卤素、C1-6- 烷基、C1-6 卤代烷基或叠氮基。

[0259] 优选的 R^3 的其它实例是 C1-6 烷基和 C2-6 卤代烯基。

[0260] 优选 R^5 和 R^6 独立地是氢、甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基、2,2,2- 三甲基乙基，尤其是氢或甲基。

[0261] 尤其是 R^5 和 R^6 中的至少一个且最优选两个是氢。

[0262] 优选 R^7 是氢、甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基、2,2,2- 三甲基乙基、甲氧基、乙氧基、苯基、苄基或被至少一个卤素原子取代的相同基团，例如三氟甲基、氯苯基。

[0263] 优选 R^7 是氢、甲基或乙基，尤其是氢。

[0264] 优选 R^8 是氢、甲基、乙基、丙基、异丙基、丁基、异或叔 - 丁基、2,2,2- 三甲基乙基、苯基、苄基或被至少一个卤素原子取代的相同基团，例如三氟甲基、氯苄基。

[0265] 优选 R^8 是氢或甲基。

[0266] 尤其优选这些优选的化合物基团的一个或多个组合。

[0267] 一组具体的式 I 化合物（化合物 1A）包含这样的化合物，其中

[0268] A^2 是氧；

[0269] X 是 $-CONR^5R^6$ 或 $-COOR^7$ 或 $-CO-R^8$ 或 CN；

[0270] R^1 是氢或烷基、芳基、卤素、羟基、氨基、硝基、氰基；

[0271] R^2、R^3、R^4 相同或不同且各自独立地是氢或卤素、羟基、氨基、硝基、氰基、酰基、酰基氧基、磺酰基衍生物、亚磺酰基衍生物、氨基衍生物、羧基、酯、醚、酰氨基、磺酸、磺酰胺、烷氧羰基、硫基衍生物、烷基、烷氧基、氧基酯、氧基酰氨基、芳基、氧基衍生物、杂环、乙烯基，R^3 还可以表示 C2-5 烯基、C2-5 炔基或叠氮基，其各自任选地被一个或多个卤素、氰基、氰硫基、叠氮基、环丙基、酰基和 / 或苯基取代；或苯基磺酰基氧基，其中任意的苯基部分可以被一个或多个卤素、烷基、卤代烷基、烷氧基、硝基、氨基和 / 或苯基取代；最优选甲基、乙基、丙基、异丙基、丁基或异丁基。

[0272] R^{2a}、R^{3a}和 R^{4a}是氢；

[0273] R^5、R^6、R^7相同或不同且各自独立地是氢、羟基、烷基、芳基、杂环或氧基衍生物；且

[0274] R^8是氢、羟基、硫羟基、卤素、烷基、芳基、杂环、烷硫基或硫基衍生物。

[0275] 在这些化合物 1A 中，R^1优选为甲基、乙基、丙基、异丙基、丁基或异丁基；最优选甲基、乙基或正 - 丙基。

[0276] R^2和 R^4优选独立地为氢或卤素或甲基、乙基、丙基、异丙基、丁基、异丁基；最优选各自是氢。

[0277] R^3优选是 C1-5 烷基、C2-5 烯基、C2-C5 炔基、环丙基、叠氮基，其各自任选地被一个或多个卤素、氰基、氰硫基、叠氮基、烷硫基、环丙基、酰基和 / 或苯基取代；苯基；苯基磺酰基；苯基磺酰基氧基、四唑、噻唑、噻吩基、呋喃基、吡咯、吡啶，其中任意苯基部分可以被一个或多个卤素、烷基、卤代烷基、烷氧基、硝基、氨基和 / 或苯基取代；最优选甲基、乙基、丙基、异丙基、丁基或异丁基。

[0278] X 优选是 -COOH 或 -COOMe 或 -COOEt 或 $-CONH_2$；最优选 $-CONH_2$。

[0279] 另一特定组的式 I 化合物（化合物 1B）包含这样的化合物，其中

[0280] X 是 $-CA^1NH_2$、$-CA^1NHCH_3$或 $-CA^1N(CH_3)_2$；

[0281] R^1是烷基或苯基；

[0282] R^3是烷基、烯基、炔基、氰基、氰硫基、醚、羧基、酰氨基、芳基、杂环；或

[0283] R^3是 CH_2R^{10}，其中 R^{10}是氢、环烷基、氧基酯、氧基烷基磺酰基、氧基芳基磺酰基、氨基烷基磺酰基、氨基芳基磺酰基、硝基氧基、氰基、氰硫基，叠氮基、烷硫基、芳硫基、烷基亚磺酰基、烷基磺酰基、杂环、芳基氧基、烷氧基或三氟乙基；

[0284] R^{3a}是氢、烷基或芳基（尤其是条件是当 R^{3a}是氢时，R^3不是甲基）；

[0285] 或 R^3R^{3a}形成环烷基；

[0286] 且 R^2、R^{2a}、R^4和 R^{4a}各自是氢。

[0287] 在式 I 化合物中，

[0288] R^1优选是烷基，尤其是 C1-12-、更具体地说是 C1-6- 烷基且最优选乙基；

[0289] R^2、R^{2a}、R^{3a}和 R^{4a}优选为氢；

[0290] R^3优选自氢；C1-12- 烷基、尤其是 C1-6- 烷基，其各自任选地被一个或多个取代基取代，所述取代基选自羟基、卤素、氰基、氰硫基或烷氧基且各自直接或通过硫代、亚磺酰基、磺酰基、羰基或氧基羰基和任选的 C1-4- 亚烷基桥（特别是亚甲基）与环连接；C2-6- 烯基或 - 炔基，尤其是 C2-3- 烯基或 - 炔基，其各自任选地被一个或多个卤素取代；叠氮基；氰基；酰氨基；羧基；三唑基，四唑基，吡咯烷基，吡啶基，1- 氧代吡啶基，硫吗啉基，苯并间二氧杂环戊烯基，呋喃基，噁唑基，嘧啶基，吡咯基，噻二唑基，噻唑基，噻吩基或哌嗪基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、C1-6- 烷基和苯基且直接或通过羰基或 C1-4- 亚烷基桥（特别是亚甲基）与环连接；萘基；或苯基、苯基烷基或苯基烯基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、C1-6- 烷基、C1-6 卤代烷基、C1-6- 烷氧基、C1-6- 烷硫基、氨基、叠氮基、苯基和硝基且各自直接或通过氧基、磺酰基、磺酰基氧基、羰基或氧基羰基和任选的 C1-4- 亚烷基桥（特别是亚甲基）与环连接；

[0291] R^{3a}基团优选是氢或 C1-4- 烷基；

[0292] R^4和 R^{4a}优选独立地为氢、C1-4- 烷基、苯基或苄基。

[0293] 另一组的式 I 化合物（化合物 1C）包含这样的外消旋形式的化合物，其中当 X 是 $-CONR^5R^6$，R^1是氢、甲基、乙基或丙基时，吡咯烷环上的取代不是一 -、二 - 或三 - 甲基或一 - 乙基。

[0294] 另一组的式 I 化合物（化合物 1D）包含这样的外消旋形式的化合物，其中当 X 是 $-CONR^5R^6$，R^1是氢或各自未被取代的 C1-6- 烷基、C2-6- 烯基或 - 炔基或环烷基时，环上的取代不采用各自未被取代的烷基、烯基或炔基。

[0295] 另一特定组的式 I 化合物（化合物 IE）包含这样的化合物，其中

[0296] X 是 $-CA^1NH_2$；

[0297] R^1是 H；

[0298] R^3是叠氮基甲基、碘甲基、任选地被 1-5 个卤素原子取代的乙基、任选地被 1-5 个卤素原子取代的正 - 丙基、任选地被 1 或 2 个甲基和 / 或 1-3 个卤素原子取代的乙烯基、任选地被 C1-4- 烷基、苯基或卤素取代的乙炔基；

[0299] R^{3a}是氢或卤素，优选氟；

[0300] R^2、R^{2a}、R^4和 R^{4a}各自是氢；

[0301] 其为其外消旋体或富含对映异构体的形式，优选纯对映异构体。

[0302] 另一特定组的式 I 化合物（化合物 1F）包含这样的化合物，其中

[0303] X 是 $-CA^1NH_2$；

[0304] R^1是 H；

[0305] R^3是 C1-6- 烷基、C2-6- 烯基或 C2-6- 炔基，其任选地被叠氮基、氧基硝基、1-6 个卤素原子取代；

[0306] R^{3a}是氢或卤素、优选氟；

[0307] R^2、R^{2a}、R^4和 R^{4a}各自是氢；其为其外消旋体或富含对映异构体的形式，优选纯对映异构体。

[0308] 在所有上述举出的范围中，当 R^1所连接的碳原子是不对称时，它优选是“S”- 构型形式。

[0309] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[0310] (2S)-2-[4-（溴甲基）-2- 氧代 -1- 吡咯烷基] 丁酰胺；

[0311] (2S)-2-[(4R)-4-（碘甲基）-2- 氧代吡咯烷基] 丁酰胺；

[0312] (2S)-2-(2- 氧代 -4- 苯基 -1- 吡咯烷基）丁酰胺；

[0313] (2S)-2-[4-（碘甲基）-2- 氧代 -1- 吡咯烷基] 丁酰胺；

[0314] (2S)-2-[4-（氯甲基）-2- 氧代 -1- 吡咯烷基] 丁酰胺；

[0315] {1-[(1S)-1-（氨基羰基）丙基]-5- 氧代 -3- 吡咯烷基 } 甲基 4- 甲基苯磺酸酯；

[0316] (2S)-2-[(4R)-4-（叠氮基甲基）-2- 氧代吡咯烷基] 丁酰胺；

[0317] 2-[4-(2,2- 二溴乙烯基）-2- 氧代 -1- 吡咯烷基] 丁酰胺；

[0318] 硝酸 {1-[(1S)-1-（氨基羰基）丙基]-5- 氧代 -3- 吡咯烷基 } 甲酯；

[0319] (2S)-2-[2- 氧代 -4-(1H- 四唑 -1- 基甲基）-1- 吡咯烷基] 丁酰胺；

[0320] 2-(2- 氧代 -4- 乙烯基 -1- 吡咯烷基）丁酰胺；

[0321] 2-{2- 氧代 -4-[（苯基磺酰基）甲基]-1- 吡咯烷基] 丁酰胺；

[0322] (2S)-2-[(4R)-4-(2,2- 二溴乙烯基）-2- 氧代吡咯烷基] 丁酰胺；

[0323] (2S)-2-[(4S)-4-(2,2-二溴乙烯基)-2-氧代吡咯烷基]丁酰胺；

[0324] (2S)-2-[4-(异氰硫基合甲基)-2-氧代-1-吡咯烷基]丁酰胺；

[0325] 2-[2-氧代-4-(1,3-噻唑-2-基)-1-吡咯烷基]丁酰胺；

[0326] (2S)-2-[2-氧代-4-(2-噻吩基)-1-吡咯烷基]丁酰胺；

[0327] (2S)-2-[4-(2-甲氧基苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0328] (2S)-2-[4-(3-甲氧基苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0329] (2S)-2-[4-(4-叠氮基苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0330] (2S)-2-[2-氧代-4-(3-噻吩基)-1-吡咯烷基]丁酰胺；

[0331] (2S)-2-[4-(3-叠氮基苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0332] (2S)-2-[2-氧代-4-(3-噻吩基)-1-吡咯烷基]丁酰胺；

[0333] (2S)-2-[(4S)-2-氧代-4-乙烯基吡咯烷基]丁酰胺；

[0334] (2S)-2-[(4R)-2-氧代-4-乙烯基吡咯烷基]丁酰胺；

[0335] 2-[4-(2-溴苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0336] 2-[2-氧代-4-(3-吡啶基)-1-吡咯烷基]丁酰胺；

[0337] (2S)-2-(4-[1,1'-联苯]-4-基-2-氧代-1-吡咯烷基)丁酰胺；

[0338] (2S)-2-{4-[(甲基硫烷基)甲基]-2-氧代-1-吡咯烷基}丁酰胺；

[0339] 2-[4-(碘甲基)-2-氧代-1-吡咯烷基]丁酰胺；

[0340] (2S)-2-[(4R)-4-(碘甲基)-2-氧代-1-吡咯烷基]戊酰胺；

[0341] (2S)-2-[(4R)-4-(碘甲基)-2-氧代吡咯烷基]丙酰胺；

[0342] 2-(2-氧代-4-丙基-1-吡咯烷基)丙酰胺；

[0343] 2-(2-氧代-4-丙基-1-吡咯烷基)丁酰胺；

[0344] 2-(2-氧代-4-戊基-1-吡咯烷基)丁酰胺；

[0345] (2S)-2-[(4R)-4-(碘甲基)-2-氧代吡咯烷基]-N-甲基丁酰胺；

[0346] (2S)-2-(4-新戊基-2-氧代-1-吡咯烷基)丁酰胺；

[0347] (2S)-2-(4-乙基-2-氧代-1-吡咯烷基)丁酰胺；

[0348] 2-[4-(2,2-二氟乙烯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0349] 2-[4-(2,2-二氟乙基)-2-氧代-1-吡咯烷基]丁酰胺；

[0350] (2S)-2-[(4S)-2-氧代-4-丙基吡咯烷基]丁酰胺；

[0351] (2S)-2-[(4R)-2-氧代-4-丙基吡咯烷基]丁酰胺；

[0352] 2-{4-[(Z)-2-氟乙烯基]-2-氧代-1-吡咯烷基}丁酰胺；

[0353] 2-[4-(2-甲基-1-丙烯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0354] 2-(4-丁基-2-氧代-1-吡咯烷基)丁酰胺；

[0355] 2-[4-(环丙基甲基)-2-氧代-1-吡咯烷基]丁酰胺；

[0356] 2-(4-异丁基-2-氧代-1-吡咯烷基)丁酰胺；

[0357] 2-[4-(4-氯苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0358] 2-[4-(3-氯苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0359] 2-{2-氧代-4-[2-(三氟甲基)苯基]-1-吡咯烷基}丁酰胺；

[0360] 2-[4-(2-氟苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0361] 2-[4-(3-甲基苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0362] (2S)-2-[2-氧代-4-(2-苯基乙基)-1-吡咯烷基]丁酰胺；

[0363] (2S)-2-[4-(3-溴苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0364] 2-{4-[3,5-双(三氟甲基)苯基]-2-氧代-1-吡咯烷基}丁酰胺；

[0365] 2-[4-(3,4-二氯苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0366] 2-[4-(2,4-二氯苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0367] 2-[4-(2-呋喃基)-2-氧代-1-吡咯烷基]丁酰胺；

[0368] (2S)-2-[2-氧代-4-(3-苯基丙基)-1-吡咯烷基]丁酰胺；

[0369] (2S)-2-[4-(3,5-二溴苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0370] 2-[4-(3,4-二氯苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0371] 2-(2-氧代-4-丙基-1-吡咯烷基)丁酰胺；

[0372] 2-[4-(3-氯苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0373] 2-(4-乙炔基-2-氧代-1-吡咯烷基)丁酰胺；

[0374] 2-[4-(2-氟苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0375] (2S)-2-[4-(环丙基甲基)-2-氧代-1-吡咯烷基}丁酰胺；

[0376] (2S)-2-[(4S)-4-(2,2-二氟乙烯基)-2-氧代吡咯烷基]丁酰胺；

[0377] (2S)-2-[2-氧代-4-(3,3,3-三氟丙基)-1-吡咯烷基]丁酰胺；

[0378] 2-[4-(3-甲基苯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0379] (2S)-2-[4-(环丙基甲基)-2-氧代-1-吡咯烷基]丁酰胺；

[0380] (2S)-2-[(4R)-4-(2,2-二氟乙烯基)-2-氧代吡咯烷基]丁酰胺；

[0381] (2S)-2-[2-氧代-4-(1H-吡咯-1-基)-1-吡咯烷基]丁酰胺；

[0382] (2S)-2-(4-烯丙基-2-氧代-1-吡咯烷基)丁酰胺；

[0383] (2S)-2-[4-(2-碘丙基)-2-氧代-1-吡咯烷基}丁酰胺；

[0384] (2S)-2-(4-烯丙基-2-氧代-1-吡咯烷基)丁酰胺；

[0385] (2S)-2-[2-氧代-4-(2-氧代丙基)-1-吡咯烷基]丁酰胺；

[0386] (2S)-2-[4-(2-溴-1H-吡咯-1-基)-2-氧代-1-吡咯烷基]丁酰胺；

[0387] (2S)-2-(4-甲基-2-氧代-4-丙基-1-吡咯烷基)丁酰胺；

[0388] (2R)-2-[4-(2,2-二氯乙烯基)-2-氧代-1-吡咯烷基]丁酰胺；

[0389] 2-[4-(溴乙炔基)-2-氧代-1-吡咯烷基]丁酰胺；

[0390] 2-[(4S)-4-(2,2-二氟丙基)-2-氧代吡咯烷基]丁酰胺；

[0391] (2S)-2-[4-(溴乙炔基)-2-氧代-1-吡咯烷基]丁酰胺；

[0392] 2-(2-氧代-4-丙基-1-吡咯烷基)戊酰胺；

[0393] 3-环丙基-2-(2-氧代-4-丙基-1-吡咯烷基)丙酰胺；

[0394] 2-(2-氧代-4-丙基-1-吡咯烷基)-3-(1,3-噻唑-4-基)丙酰胺；

[0395] 2-(2-氧代-4-丙基-1-吡咯烷基)-4-戊酰胺；

[0396] (2S)-2-[(4R)-2-氧代-4-乙烯基吡咯烷基]丁酰胺；

[0397] 包括所有的异构体形式和其混合物或其药学可接受的盐。

[0398] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[0399] (2S)-2-[(4S)-4-(2,2-二氟乙烯基)-2-氧代吡咯烷基]丁酰胺；

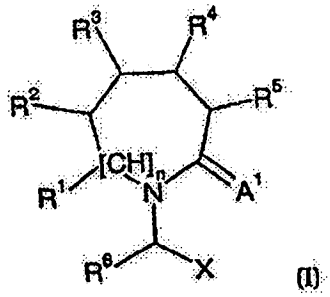
[0400] (2S)-2-[(4S)-2-氧代-4-丙基吡咯烷基]丁酰胺；

[0401] (2S)-2-[(4R)-2- 氧代 -4- 丙基吡咯烷基] 丁酰胺。

[0402] ii) 国际专利申请 WO2002/094787 :

[0403] 式 I 的化合物

[0404]



(I)

[0405] 其中 n 表示 0 或 1,其中当 n = 0 时,R^1不存在 ;当 n = 1 时,R^1存在 ;

[0406] A^1表示氧或硫原子 ;

[0407] X 是 $-CONR^7R^8$、$-COOR^9$、$-CO-R^{10}$或 CN ;

[0408] R^1(存在时)、R^2、R^3、R^4和 R^5相同或不同且各自独立地是氢、卤素、羟基、硫羟基、氨基、硝基、硝基氧基、氰基、叠氮基、羧基、酰氨基、磺酸、磺酰胺、烷基、烯基、炔基、酯、醚、芳基、杂环或氧基衍生物、硫基衍生物、氨基衍生物、酰基衍生物、磺酰基衍生物或亚磺酰基衍生物 ;

[0409] 条件是至少一个选自 R^1(存在时)、R^2、R^3、R^4或 R^5的取代基 R 不是氢 ;

[0410] R^6是氢、烷基、芳基或 $-CH_2-R^{6a}$,其中 R^{6a}是芳基、杂环、卤素、羟基、氨基、硝基或氰基 ;

[0411] R^7、R^8和 R^9相同或不同且各自独立地是氢、羟基、烷基、芳基、杂环或氧基衍生物 ; 且

[0412] R^{10}是氢、羟基、硫羟基、卤素、烷基、芳基、杂环或硫基衍生物 ;

[0413] 其药学可接受的盐、几何异构体 (包括顺式和反式、Z 和 E 异构体)、对映异构体、非对映异构体及其混合物 (包括所有可能的立体异构体混合物)。

[0414] 在上述式中,取代基 R^1-R^5中的至少一个不是氢。一些未取代的化合物是美国专利 US5,468,733 和 5,516,759 所涉及的。美国专利 US5,468,733 涉及无环取代的 2- 氧代 -1- 吡咯烷基和 2- 氧代 -1- 哌啶基衍生物作为癌基因 Ras 蛋白的抑制剂。特别地,这些化合物阻断 Ras 将正常细胞转化成癌细胞的能力且由此可以包括在治疗癌症的几种化疗组合物中。

[0415] 美国专利 US5,516,759 涉及无环取代的存在于具有 LHRH(促黄体激素 - 释放激素) 拮抗剂活性的十二肽 N 端上的 2- 氧代 -1- 吡咯烷基、2- 氧代 -1- 哌啶基和氮杂环庚烷基衍生物。这种 LHRH 拮抗剂用于治疗各种病症,其中性类固醇的抑制起关键作用,包括避孕、青春期延迟、良性前列腺增生症 a. o. 治疗。

[0416] 在如下举出的定义中,除非另做陈述,否则 R^{11}和 R^{12}相同或不同且各自独立地是酰氨基、烷基、烯基、炔基、酰基、酯、醚、芳基、芳烷基、杂环或氧基衍生物、硫基衍生物、酰基衍生物、氨基衍生物、磺酰基衍生物或亚磺酰基衍生物,其各自被任意适合的基团取代,所述基团包括、但不限于一个或多个部分,所述部分选自低级烷基或如下对烷基取代基所述的其它基团。

[0417] 本文所用的术语“氧基衍生物”定义为包括 -O-R^{11}基团，其中 R^{11}如上述所定义，除了“氧基衍生物”。非限制性实例是烷氧基、烯基氧基、炔基氧基、酰基氧基、氧基酯、氧基酰氨基、烷基磺酰基氧基、烷基亚磺酰基氧基、芳基磺酰基氧基、芳基亚磺酰基氧基、芳基氧基、芳烷氧基或杂环氧基，例如戊基氧基、烯丙基氧基、甲氧基、乙氧基、苯氧基、苄基氧基、2- 萘基氧基、2- 吡啶基氧基、亚甲二氧基、碳酸酯。

[0418] 本文所用的术语“硫基衍生物”定义为包括 -S-R^{11}基团，其中 R^{11}如上述所定义，除了“硫基衍生物”。非限制性实例是烷硫基、烯硫基、炔硫基和芳硫基。

[0419] 本文所用的术语“氨基衍生物”定义为包括 -NHR^{11}或 -$NR^{11}R^{12}$基团，其中 R^{11}和 R^{12}如上述所定义。非限制性实例是一 - 或二 - 烷基 -、烯基 -、炔基 - 和芳基氨基或混合氨基。

[0420] 本文所用的术语“酰基衍生物”表示衍生自羧酸的基团且由此定义为包括式 R^{11}-CO- 的基团，其中 R^{11}如上述所定义且还可以是氢。优选式 -COR^{11}的酰基衍生物，其中 R^{11}选自氢、C1-12 烷基、C2-12 烯基、C2-12 炔基、杂环和芳基。非限制性实例是甲酰基、乙酰基、丙酰基、异丁酰基、戊酰基、月桂酰基、庚二酰基、环己烷羰基、巴豆酰基、富马酰基、丙烯酰基、苯甲酰基、萘甲酰基、糠酰基、烟酰基、4- 羧基丁酰基、草酰基、乙草酰基、半胱氨酰基、草氨酰基。

[0421] 本文所用的术语“磺酰基衍生物”定义为包括式 -SO_2-R^{11}的基团，其中 R^{11}如上述所定义，除了“磺酰基衍生物”。非限制性实例是烷基磺酰基、烯基磺酰基、炔基磺酰基和芳基磺酰基。

[0422] 本文所用的术语“亚磺酰基衍生物”定义为包括式 -SO-R^{11}的基团，其中 R^{11}如上述所定义，除了“亚磺酰基衍生物”。非限制性实例是烷基亚磺酰基、烯基亚磺酰基、炔基亚磺酰基和芳基亚磺酰基。

[0423] 本文所用的术语“烷基”定义为包括饱和一价烃基，其具有直链、支链或环状部分或其组合并且就非环烷基而言包含 1-20 个碳原子、大部分通常 1-12 个碳原子、优选 1-7 个碳原子且就环烷基而言包含 3-7 个碳原子（在这两种优选的情况中，除非另做陈述，否则是“低级烷基”），其各自任选地被优选 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、硫羟基、氨基、硝基、氰基、氰硫基、酰基、酰基氧基、磺酰基衍生物、亚磺酰基衍生物、烷基氨基、羧基、酯、醚、酰氨基、叠氮基、环烷基、磺酸、磺酰胺、硫基衍生物、烷硫基、氧基酯、氧基酰氨基、杂环、乙烯基、烷氧基（优选 C1-5）、芳基氧基（优选 C6-10）和芳基（优选 C6-10）。

[0424] 优选包含 1-7 个碳原子的烷基，其各自任选地被一个或多个取代基取代，所述取代基选自羟基、卤素、氰基、氰硫基、烷氧基、叠氮基、烷硫基、环丙基、酰基和苯基。最优选 C1-4 烷基和 C3-7 环烷基，其各自任选地被一个或多个羟基、卤素、低级烷基或 / 和叠氮基取代。

[0425] 最优选的烷基是羟基甲基、丙基、丁基、2,2,2- 三氟乙基、2- 溴 -2,2- 二氟乙基、2- 氯 -2,2- 二氟乙基、3,3,3- 三氟丙基、环丙基甲基、碘甲基、叠氮基甲基、2,2- 二氟丙基、2- 碘 -2,2- 二氟乙基。

[0426] 本文所用的术语“低级烷基”，除非另作陈述，否则意指 C_1-C_7饱和直链、支链或环状烃。非限制性实例是甲基、乙基、丙基、异丙基、丁基、叔丁基、戊基、环丙基、环戊基、异戊基、新戊基、己基、异己基、环己基、3- 甲基戊基、2,2- 二甲基丁基，其任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，所述部分选自如上述对烷基所述的基

团。优选低级烷基是甲基。

[0427] 本文所用的术语“烯基”定义为包括支链和无支链不饱和烃基，其具有至少一个双键且任选地被至少一个取代基取代，所述取代基选自卤素、羟基、硫羟基、氨基、氰硫基、叠氮基、烷硫基、环烷基、酰基、硝基、氰基、芳基和杂环。

[0428] 优选的烯基是C2-C12烯基，尤其是C2-6烯基，例如乙烯基（＝乙烯基）、1-甲基-1-乙烯基、2,2-二甲基-1-乙烯基、1-丙烯基、2-丙烯基（＝烯丙基）、1-丁烯基、2-丁烯基、3-丁烯基、4-戊烯基、1-甲基-4-戊烯基、3-甲基-1-戊烯基、1-己烯基、2-己烯基等，其任选地被一个或多个取代基取代，所述取代基选自卤素、氰基、氰硫基、叠氮基、烷硫基、环烷基、苯基和酰基。最优选是乙烯基，其任选地被一个或多个卤素或/和低级烷基取代，尤其是2,2-二氟乙烯基、2,2-二溴乙烯基和2,2-二氯乙烯基。

[0429] 本文所用的术语“炔基”定义为包括包含至少一个碳-碳三键的一价支链或无支链烃基，例如乙炔基、2-丙炔基（＝炔丙基）等且任选地被至少一个取代基取代，所述取代基选自卤素、羟基、硫羟基、氨基、硝基、氰基、芳基、杂环、氰硫基、叠氮基、烷硫基、烷基和酰基。

[0430] 优选的炔基是C2-12炔基，尤其是C2-6炔基，其任选地被一个或多个取代基取代，所述取代基选自卤素、氰基、氰硫基、叠氮基、烷硫基、酰基、芳基，例如苯基和烷基，优选环烷基。

[0431] 最优选乙炔基、丙炔基和丁炔基，其任选地被低级烷基或/和卤素取代，尤其是1-丙炔基、环丙基乙炔基、3-甲基-1-丁炔基和3,3,3-三氟-1-丙炔基。

[0432] 当作为桥连基团存在时，烷基、烯基和炔基分别表示直链或支链C1-12、优选C1-4-亚烷基或C2-12-、优选C2-4-亚烯基或-亚炔基部分。

[0433] 除非另作陈述，否则其中支链衍生物通常被前缀例如“正”、“仲”、“异”等修饰的基团（例如“正-丙基”、“仲-丁基”）是正-形式。

[0434] 本文所用的术语“芳基”定义为包括通过除去一个氢衍生自由至少一个环、最通常1-3个环且一般包含6-30个碳原子的芳香烃的有机基团，例如苯基和萘基，其各自任选地被一个或多个取代基取代，所述取代基独立地选自卤素、羟基、硫羟基、氨基、硝基、氰基、酰基、酰基氧基、磺酰基、亚磺酰基、烷基氨基、羧基、酯、醚、酰氨基、叠氮基、磺酸、磺酰胺、烷基磺酰基、烷基亚磺酰基、C1-6-烷硫基、氧基酯、氧基酰氨基、芳基、C1-6-烷氧基、C6-10-芳基氧基、C1-6-烷基、C1-6-卤代烷基。芳基优选为包含6-10个碳原子的单环或双环。优选的芳基是苯基和萘基，其各自任选地被一个或多个取代基取代，所述取代基独立地选自卤素、硝基、氨基、叠氮基、C1-6-烷氧基、C1-6-烷基、C1-6-卤代烷基、磺酰基和苯基。

[0435] 优选的芳基是苯基，其任选地被一个或多个卤素、低级烷基、叠氮基或硝基取代，例如3-氯苯基和3-叠氮基苯基。

[0436] 本文所用的术语“卤素”包括Cl、Br、F、I的原子。

[0437] 本文所用的术语“羟基”表示式-OH的基团。

[0438] 本文所用的术语“硫羟基”表示式-SH的基团。

[0439] 本文所用的术语“氰基”表示式-CN的基团。

[0440] 本文所用的术语“硝基”表示式$-NO_2$的基团。

[0441] 本文所用的术语“硝基氧基”表示式$-ONO_2$的基团。

[0442] 本文所用的术语“氨基”表示式 $-NH_2$的基团。

[0443] 本文所用的术语“叠氮基”表示式 $-N_3$的基团。

[0444] 本文所用的术语“羧基”表示式 -COOH 的基团。

[0445] 本文所用的术语“磺酸”表示式 $-SO_3H$ 的基团。

[0446] 本文所用的术语“磺酰胺”表示式 $-SO_2NH_2$的基团。

[0447] 本文所用的术语“酯”定义为包括式 $-COO-R^{11}$的基团，其中 R^{11}如上述所定义，除了氧基衍生物、硫基衍生物或氨基衍生物。优选式 $-COOR^{11}$的酯类，其中 R^{11}选自 C1-12 烷基、C2-12 烯基、C2-12 炔基和芳基。最优选酯类，其中 R^{11}是低级烷基，尤其是甲基。

[0448] 术语“醚”定义为包括选自 C1-50- 直链或支链烷基或 C2-50- 直链或支链烯基或炔基或其组合的基团，其被一个或多个氧原子间隔。

[0449] 本文所用的术语“酰氨基”定义为包括式 $-CONH_2$或 $-CONHR^{11}$或 $-CONR^{11}R^{12}$的基团，其中 R^{11}和 R^{12}如上述所定义。

[0450] 本文所用的术语“杂环”定义为包括如上述所定义的芳族或非芳族环烷基、烯基或炔基部分，其具有至少一个间隔碳环结构的 O、S 和 / 或 N 原子且任选碳环结构的碳之一可以被羰基替代且任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，所述部分选自低级烷基或如上对烷基所述的其它基团。杂环的非限制性实例是吡啶基、呋喃基、吡咯基、噻吩基、异噻唑基、三唑基、咪唑基、苯并咪唑基、四唑基、喹唑啉基、喹噁基、萘啶基、哒噁基、嘧啶基、吡噁基、喹啉基、异喹啉基、异苯并呋喃基、苯并噻吩基、吡唑基、吲哚基、吲噁基、嘌呤基、异吲哚基、咔唑基、噻唑基、1,2,4- 噻二唑基、硫吗啉基、噻吩并(2,3-b) 呋喃基、呋喃并吡喃基、苯并呋喃基、苯并氧杂环庚三烯基、异噁唑基、噁唑基、噻蒽基、苯并噻唑基或苯并噁唑基、噌啉基、酞嗪基、喹喔啉基、1- 氧代吡啶基、菲啶基、吖啶基、萘嵌间二氮苯基、菲咯啉基、吩噻嗪基、呋咱基、苯并间二氧杂环戊烯基、异苯并二氢吡喃基、二氢吲哚基、呫吨基、次黄嘌呤基、蝶啶基、5- 氮杂胞苷基、5- 氮杂尿嘧啶基、三唑并吡啶基、咪唑并吡啶基、吡咯并嘧啶基、吡唑并嘧啶基、四氢呋喃基、四氢吡喃基、哌啶基、哌啶基、哌嗪基、咪唑烷基、吗啉代、吗啉基、1- 氧杂螺 (4.5) 癸 -2- 基、吡咯烷基、2- 氧代 - 吡咯烷基、糖部分 (即葡萄糖、戊糖、己糖、核糖、果糖，其也可以被取代)，其任选地被烷基或如上述对烷基所述取代。术语“杂环”还包括双环、三环和四环、螺基团，其中任意上述杂环与一个或两个环稠合，所述环独立地选自芳基环、环己烷环、环己烯环、环戊烷环、环戊烯环或另一种单环杂环或其中单环杂环基通过亚烷基桥连，例如奎宁环基、7- 氮杂双环 (2.2.1) 庚烷基、7- 氧杂双环 (2.2.1) 庚烷基、8- 氮杂双环 (3.2.1) 辛烷基。

[0451] 杂环优选自三唑基、四唑基、吡咯烷基、吡啶基、1- 氧代吡啶基、硫吗啉基、苯并间二氧杂环戊烯基、呋喃基、噁唑基、嘧啶基、吡咯基、噻二唑基、噻唑基、噻吩基和哌嗪基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、烷基、取代的烷基、烷氧基、硝基、氨基、酰基和苯基。

[0452] 更优选杂环选自四唑基、吡咯烷基、吡啶基、呋喃基、吡咯基、噻唑基和噻吩基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、烷基、卤代烷基、酰基、烷氧基、硝基、氨基和苯基，尤其选自 2- 和 3- 噻吩基，其任选地被一个或多个卤素、酰基 (例如甲酰基)、氰基和 / 或低级烷基 (例如甲基) 取代。

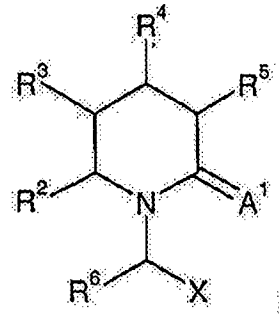
[0453] 在上述定义中，应理解当取代基例如 R^1、R^2、R^3、R^4、R^5、R^7、R^8、R^9、R^{10}通过杂原子或

羰基与分子的其余部分连接时，直链 - 或支链 C1-12-、优选 C1-4- 亚烷基或 C2-12、优选 C2-4- 亚烯基或 - 亚炔基桥可以任选插于杂原子或羰基与分子其余部分连接点之间。

[0454] 术语“R 取代基”独立地意指 R^1、R^2、R^3、R^4或 R^5。

[0455] 根据优选的实施方案，式 I 化合物如上述所定义，其中 n 表示 0。化合物是 6- 环结构 (2- 硫代 - 或 2- 氧代 - 哌啶基衍生物)，其中 R^1不存在，因为 n = 0，且描述为式 (I-A)。

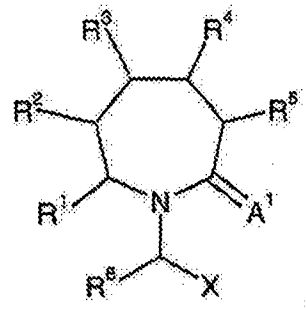
[0456]



(I-A)

[0457] 根据如下的实施方案，式 I 的化合物如上述所定义，其中 n 表示 1。化合物是 7- 环结构 (2- 硫代 - 或 2- 氧代 - 氮杂环庚烷基衍生物)，其中 R^1存在，因为 n = 1 且描述为式 (I-B)。

[0458]



(I-B)

[0459] 根据一个更优选的实施方案，所述化合物如上文所定义，其中 n = 0，R^3和 / 或 R^4不是氢，R^2和 R^5表示氢。

[0460] 根据另一个更优选的实施方案，所述化合物如上文所定义，其中 n = 1，R^2、R^3和 / 或 R^4不是氢，其中 R^1和 R^5表示氢。

[0461] 根据另一个更优选的实施方案，所述化合物如上文所定义，其中仅一个 R 取代基选自 R^3或 R^4，此时 n = 0，或选自 R^2、R^3或 R^4，此时 n = 1，该取代基不是氢，其余 R 取代基是氢。我们特此意指单 - 取代的 2- 硫代 - 或 2- 氧代 - 哌啶基或 2- 硫代 - 或 2- 氧代 - 氮杂环庚烷基衍生物。

[0462] 根据另一个优选的实施方案，式 I 的化合物如上文所定义，其中 A^1表示氧原子。我们在本文意指 2- 氧代 - 哌啶基或 2- 氧代 - 氮杂环庚烷基衍生物。

[0463] 根据另一个优选的实施方案，式 I 的化合物如上文所定义，其中 X 是 $CONR^7R^8$，尤其是 $CONH_2$。我们特此意指 2- 氧代 (或硫代)- 哌啶基或 2- 氧代 (或硫代)- 氮杂环庚烷基的酰氨基衍生物。

[0464] 根据另一个优选的实施方案，式 I 的化合物如上文所定义，其中 R^6表示氢、C1-4 烷基或 CH_2-R^{6a}基团，其中 R^{6a}表示杂环。最优选 R^6是 C1-4 烷基，尤其是乙基。当 R^6是乙基时，

我们意指 2-(2- 氧代（或硫代）-1- 哌啶基）丁酰胺或 2-(2- 氧代（或硫代）-1- 氮杂环庚烷基）丁酰胺衍生物。

[0465] 根据另一个优选的实施方案，式 I 的化合物如上文所定义，其中 R^6 所连接的碳原子是 S 构型。就 R^6 是乙基、A 是氧、X 是 $CONR^7R^8$ 的情况而言，我们意指 (2S)-2-(2- 氧代 -1- 哌啶基）丁酰胺或 (2S)-2-(2- 氧代 -1- 氮杂环庚烷基）丁酰胺衍生物。

[0466] 根据一个优选的实施方案，化合物如本上所定义，其中 R^2（当 n = 1 时），R^3 和 R^4 相同或不同且和各自独立地是氢、卤素、硝基、硝基氧基、氰基、羧基、酰氨基、磺酸、磺酰胺、烷基、烯基、炔基、酯、醚、芳基、杂环、酰基衍生物、磺酰基衍生物或亚磺酰基衍生物；

[0467] R^1（存在时）、R^2（当 n = 0 时）和 R^5 是氢；

[0468] R^6 是氢、烷基、芳基或 $-CH_2-R^{6a}$，其中 R^{6a} 是芳基、杂环、卤素、羟基、氨基、硝基或氰基；

[0469] 根据这种优选的实施方案，化合物一般使得在 R^6 是苄基，X 是 $-COOCH_3$ 和 n = 1 的情况下，当 R^3 和 R^4 均为氢时，R^2 不是甲基而当 R^2 和 R^3 均为氢时，R^4 不是甲基。

[0470] 根据另一个优选的实施方案，化合物如上文所定义，其中 R^2（当 n = 1 时）、R^3 和 R^4 相同或不同且各自独立地是氢；氰基；羧基；酰氨基；

[0471] C1-12 烷基，其各自任选地被一个或多个取代基取代，所述取代基选自羟基、卤素、氰基、氰硫基、烷氧基、叠氮基、烷硫基、环烷基、酰基、芳基和杂环；

[0472] C2-12 烯基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、氰基、氰硫基、叠氮基、烷硫基、烷基、芳基和酰基；

[0473] C2-12 炔基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、氰基、氰硫基、叠氮基、烷硫基、烷基、芳基和酰基；

[0474] 式 $-CO-R^{11}$ 的酰基衍生物，其中 R^{11} 选自 C1-12 烷基、C2-12 烯基、C2-12 炔基、杂环和芳基；

[0475] 式 $-CO-O-R^{11}$ 的酯，其中 R^{11} 选自 C1-12 烷基、C2-12 烯基、C2-12 炔基和芳基；

[0476] 杂环选自三唑基、四唑基、吡咯烷基、吡啶基、1- 氧代吡啶基、硫吗啉基、苯并间二氧杂环戊烯基、呋喃基、噁唑基、嘧啶基、吡咯基、噻二唑基、噻唑基、噻吩基和哌嗪基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、烷基、取代的烷基、烷氧基、硝基、氨基、酰基和苯基；

[0477] 芳基，其各自任选地被一个或多个取代基取代，所述取代基选自 C1-6 烷基、C1-6 卤代烷基、C1-6 烷氧基、C1-6 烷硫基、氨基、叠氮基、磺酰基、芳基和硝基。

[0478] 根据另一个优选的实施方案，化合物如上文所定义，其中 R^2（当 n = 1 时）、R^3 和 R^4 相同或不同且各自独立地是氢；

[0479] C1-7 烷基，其各自任选地被一个或多个取代基取代，所述取代基选自羟基、卤素、氰基、氰硫基、烷氧基、叠氮基、烷硫基、环丙基、酰基和苯基；

[0480] C2-6 烯基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、氰基、氰硫基、叠氮基、烷硫基、环烷基、苯基和酰基；

[0481] C2-6 炔基，其各自任选地被一个或多个取代基取代，所述取代基选自卤素、氰基、氰硫基、叠氮基、烷硫基、环烷基、苯基和酰基；

[0482] 选自四唑基、吡咯烷基、吡啶基、呋喃基、吡咯基、噻唑基和噻吩基的杂环，其各自

任选地被一个或多个取代基取代，所述取代基选自卤素、烷基、卤素取代的烷基、酰基、烷氧基、硝基、氨基和苯基；

[0483] 苯基，其各自任选地被一个或多个取代基取代，所述取代基选自 C1-6 烷基、卤素取代的烷基、卤素、烷氧基、氨基、叠氮基、磺酰基、苯基和硝基。

[0484] 根据另一个优选的实施方案，化合物如上文所定义，其中至少一个 R 取代基选自基团 R^2、R^3和 R^4，此时 n = 1，或选自基团 R^3和 R^4，此时 n = 0，该基团独立地表示 C1-4- 烷基或 C3-7- 环烷基，其任选地被一个或多个卤素、羟基、低级烷基和 / 或叠氮基取代。

[0485] 根据另一个优选的实施方案，化合物如上文所定义，其中至少一个 R 取代基选自基团 R^2、R^3和 R^4，此时 n = 1，或选自基团 R^3和 R^4，此时 n = 0，该基团独立地表示乙烯基，其任选地被一个或多个卤素或 / 和低级烷基取代。

[0486] 根据另一个优选的实施方案，化合物如上文所定义，其中至少一个 R 取代基选自基团 R^2、R^3和 R^4，此时 n = 1，或选自基团 R^3和 R^4，此时 n = 0，该基团独立地表示乙炔基、丙炔基或丁炔基，其任选地被一个或多个卤素和 / 或低级烷基取代。

[0487] 根据另一个优选的实施方案，化合物如上文所定义，其中至少一个 R 取代基选自基团 R^2、R^3和 R^4，此时 n = 1，或选自基团 R^3和 R^4，此时 n = 0，该基团独立地表示苯基，其任选地被一个或多个卤素、低级烷基、叠氮基和 / 或硝基取代。

[0488] 根据另一个优选的实施方案，化合物如上文所定义，其中至少一个 R 取代基选自基团 R^2、R^3和 R^4，此时 n = 1，或选自基团 R^3和 R^4，此时 n = 0，该基团独立地表示 2- 或 3- 噻吩基，其任选地被一个或多个卤素、酰基、氰基或 / 和低级烷基取代。

[0489] 根据一个具体的优选实施方案，化合物如上文所定义，其中至少一个 R 取代基选自基团 R^3、R^4和 R^2，此时 n = 1，或选自基团 R^3和 R^4，此时 n = 0，该基团是羟基甲基、丙基、丁基、3,3,3- 三氟丙基、2,2,2- 三氟乙基、环丙基甲基、碘甲基、叠氮基甲基、2- 噻吩基、3- 噻吩基、苯基、3- 氯苯基、3- 叠氮基苯基、2,2- 二氟乙烯基、2,2- 二溴乙烯基、2,2- 二氯乙烯基、2- 乙炔基、5- 甲基 -2- 噻吩基、5- 甲酰基 -2- 乙炔基、5- 氰基 -2- 噻吩基、3- 溴 -2- 噻吩基、4- 甲基 -2- 噻吩基、3,3,3- 三氟 -1- 丙炔基、1- 丙炔基、环丙基乙炔基、3- 甲基 -1- 丁炔基、1- 丁炔基、2,2- 二氟丙基、2- 氯 -2,2- 二氟乙基、2- 溴 -2,2- 二氟乙基和 2- 碘 -2,2- 二氟乙基。

[0490] 根据另一个优选的实施方案，化合物如上文所定义，其中 R^1、R^2、R^4和 R^5是氢。

[0491] 根据另一个优选的实施方案，化合物如上文所定义，其中 R^1、R^2、R^3和 R^5是氢。

[0492] 甚至根据另一个优选的实施方案，化合物如上文所定义，其中 n = 1 且 R^1、R^3、R^4和 R^5是氢。

[0493] 在所有上述举出的范围中，当 R^6所连接的碳原子是不对称时，它优选是“S”- 构型。

[0494] 如上述所定义的用于本发明方法和组合物的有代表性的化合物选自：

[0495] 2-[5-(羟基甲基)-2- 氧代 -1- 哌啶基] 丁酰胺；

[0496] 2-(2- 氧代 -5- 丙基 -1- 哌啶基) 丁酰胺；

[0497] 2-[2- 氧代 -5-(3,3,3- 三氟丙基)-1- 哌啶基] 丁酰胺；

[0498] 2-[5-(环丙基甲基)-2- 氧代 -1- 哌啶基] 丁酰胺；

[0499] 2-[5-(碘甲基)-2- 氧代 -1- 哌啶基] 丁酰胺；

[0500] 2-[5-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰胺；

[0501] 2-(2-氧代-5-苯基-1-哌啶基)丁酰胺；

[0502] 2-[2-氧代-5-(2-噻吩基)-1-哌啶基]丁酰胺；

[0503] 2-[2-氧代-5-(3-噻吩基)-1-哌啶基]丁酰胺；

[0504] 2-[5-(3-氯苯基)-2-氧代-1-哌啶基]丁酰胺；

[0505] 2-[5-(3-叠氮基苯基)-2-氧代-1-哌啶基]丁酰胺；

[0506] 2-[5-(2,2-二氟乙烯基)-2-氧代-1-哌啶基]丁酰胺；

[0507] 2-[5-(2,2-二溴乙烯基)-2-氧代-1-哌啶基]丁酰胺；

[0508] 2-[5-(2,2-二氯乙烯基)-2-氧代-1-哌啶基]丁酰胺；

[0509] 2-(5-乙炔基-2-氧代-1-哌啶基)丁酰胺；

[0510] 2[5-(5-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0511] 2-[5-(5-甲酰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0512] 2-[5-(5-氰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0513] 2-[5-(3-溴-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0514] 2-[5-(4-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0515] 2-[2-氧代-5-(3,3,3-三氟-1-丙炔基)-1-哌啶基]丁酰胺；

[0516] 2-[2-氧代-5-(1-丙炔基)-1-哌啶基]丁酰胺；

[0517] 2-[5-(环丙基乙炔基)-2-氧代-1-哌啶基]丁酰胺；

[0518] 2-[5-(3-甲基-1-丁炔基)-2-氧代-1-哌啶基]丁酰胺；

[0519] 2-[5-(1-丁炔基)-2-氧代-1-哌啶基]丁酰胺；

[0520] 2-[5-(2,2-二氟丙基)-2-氧代-1-哌啶基]丁酰胺；

[0521] 2-[5-(2-氯-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺；

[0522] 2-[5-(2-溴-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺；

[0523] 2-[4-(羟基甲基)-2-氧代-1-哌啶基]丁酰胺；

[0524] 2-(2-氧代-4-丙基-1-哌啶基)丁酰胺；

[0525] 2-[2-氧代-4-(3,3,3三氟丙基)-1-哌啶基]丁酰胺；

[0526] 2-[4-(环丙基甲基)-2-氧代-1-哌啶基]丁酰胺；

[0527] 2-[4-(碘甲基)-2-氧代-1-哌啶基]丁酰胺；

[0528] 2-[4-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰胺；

[0529] 2-(2-氧代-4-苯基-1-哌啶基)丁酰胺；

[0530] 2-[2-氧代-4-(2-噻吩基)-1-哌啶基]丁酰胺；

[0531] 2-[2-氧代-4-(3-噻吩基)-1-哌啶基]丁酰胺；

[0532] 2-[4-(3-氯苯基)-2-氧代-1-哌啶基]丁酰胺；

[0533] 2-[4-(3-叠氮基苯基)-2-氧代-1-哌啶基]丁酰胺；

[0534] 2-[4-(2,2-二氟乙烯基)-2-氧代-1-哌啶基]丁酰胺；

[0535] 2-[4-(2,2-二溴乙烯基)-2-氧代-1-哌啶基]丁酰胺；

[0536] 2-[4-(2,2-二氯乙烯基)-2-氧代-1-哌啶基]丁酰胺；

[0537] 2-(4-乙炔基-2-氧代-1-哌啶基)丁酰胺；

[0538] 2-[4-(5-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0539] 2-[4-(5-甲酰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0540] 2-[4-(5-氰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0541] 2-[4-(3-溴-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0542] 2-[4-(4-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺；

[0543] 2-[2-氧代-4-(3,3,3-三氟-1-丙炔基)-1-哌啶基]丁酰胺；

[0544] 2-[2-氧代-4-(1-丙炔基)-1-哌啶基]丁酰胺；

[0545] 2-[4-(环丙基乙炔基)-2-氧代-1-哌啶基]丁酰胺；

[0546] 2-[4-(3-甲基-1-丁炔基)-2-氧代-1-哌啶基]丁酰胺；

[0547] 2-[4-(1-丁炔基)-2-氧代-1-哌啶基]丁酰胺；

[0548] 2-[4-(2,2-二氟丙基)-2-氧代-1-哌啶基]丁酰胺；

[0549] 2-[4-(2-氯-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺；

[0550] 2-[4-(2-溴-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺；

[0551] 2[4-(2,2,2-三氟乙基)-2-氧代-1-哌啶基]丁酰胺；

[0552] 2-[5-(羟基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0553] 2-(2-氧代-5-丙基-1-氮杂环庚烷基)丁酰胺；

[0554] 2-[2-氧代-5-(3,3,3-三氟丙基)-1-氮杂环庚烷基]丁酰胺；

[0555] 2-[5-(环丙基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0556] 2-[5-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0557] 2-[5-(叠氮基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0558] 2-(2-氧代-5-苯基-1-氮杂环庚烷基)丁酰胺；

[0559] 2-[2-氧代-5-(2-噻吩基)-1-氮杂环庚烷基]丁酰胺；

[0560] 2-[2-氧代-5-(3-噻吩基)-1-氮杂环庚烷基]丁酰胺；

[0561] 2-[5-(3-氯苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0562] 2-[5-(3-叠氮基苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0563] 2-[5-(2,2-二氟乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0564] 2-[5-(2,2-二溴乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0565] 2-[5-(2,2-二氯乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0566] 2-(5-乙炔基-2-氧代-1-氮杂环庚烷基)丁酰胺；

[0567] 2-[5-(5-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0568] 2-[5-(5-甲酰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0569] 2-[5-(5-氰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0570] 2-[5-(3-溴-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0571] 2-[5-(4-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0572] 2-[2-氧代-5-(3,3,3-三氟-1-丙炔基)-1-氮杂环庚烷基]丁酰胺；

[0573] 2-[2-氧代-5-(1-丙炔基)-1-氮杂环庚烷基]丁酰胺；

[0574] 2-[5-(环丙基乙炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0575] 2-[5-(3-甲基-1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0576] 2-[5-(1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0577] 2-[5-(2,2-二氟丙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0578] 2-[5-(2-氯-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0579] 2-[5-(2-溴-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0580] 2-[5-(2,2,2-三氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0581] 2-[6-(羟基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0582] 2-(2-氧代-6-丙基-1-氮杂环庚烷基)丁酰胺；

[0583] 2-[2-氧代-6-(3,3,3-三氟丙基)-1-氮杂环庚烷基]丁酰胺；

[0584] 2-[6-(环丙基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0585] 2-[6-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0586] 2-[6-(叠氮基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0587] 2-(2-氧代-6-苯基-1-氮杂环庚烷基)丁酰胺；

[0588] 2-[2-氧代-6-(2-噻吩基)-1-氮杂环庚烷基]丁酰胺；

[0589] 2-[2-氧代-6-(3-噻吩基)-1-氮杂环庚烷基]丁酰胺；

[0590] 2-[6-(3-氯苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0591] 2-[6-(3-叠氮基苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0592] 2-[6-(2,2-二氟乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0593] 2-[6-(2,2-二溴乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0594] 2-[6-(2,2-二氯乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0595] 2-(6-乙炔基-2-氧代-1-氮杂环庚烷基)丁酰胺；

[0596] 2-[6-(5-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0597] 2-[6-(5-甲酰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基1丁酰胺；

[0598] 2-[6-(5-氰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0599] 2-[6-(3-溴-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0600] 2-[6-(4-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0601] 2-[2-氧代-6-(3,3,3-三氟-1-丙炔基)-1-氮杂环庚烷基]丁酰胺；

[0602] 2-[2-氧代-6-(1-丙炔基)-1-氮杂环庚烷基]丁酰胺；

[0603] 2-[6-(环丙基乙炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0604] 2-[6-(3-甲基-1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0605] 2-[6-(1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0606] 2-[6-(2,2-二氟丙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0607] 2-[6-(2-氯-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0608] 2-[6-(2-溴-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0609] 2-[6-(2,2,2-三氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0610] 2-[4-(羟基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0611] 2-(2-氧代-4-丙基-1-氮杂环庚烷基)丁酰胺；

[0612] 2-[2-氧代-4-(3,3,3-三氟丙基)-1-氮杂环庚烷基]丁酰胺；

[0613] 2-[4-(环丙基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0614] 2-[4-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0615] 2-[4-(叠氮基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0616] 2-(2-氧代-4-苯基-1-氮杂环庚烷基)丁酰胺；

[0617] 2-[2-氧代-4-(2-噻吩基)-1-氮杂环庚烷基]丁酰胺；

[0618] 2-[2-氧代-4-(3-噻吩基)-1-氮杂环庚烷基]丁酰胺；

[0619] 2-[4-(3-氯苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0620] 2-[4-(3-叠氮基苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0621] 2-[4-(2,2-二氟乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0622] 2-[4-(2,2-二溴乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0623] 2-[4-(2,2-二氯乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0624] 2-(4-乙炔基-2-氧代-1-氮杂环庚烷基)丁酰胺；

[0625] 2-[4-(5-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0626] 2-[4-(5-甲酰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0627] 2-[4-(5-氰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0628] 2-[4-(3-溴-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0629] 2-[4-(4-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0630] 2-[2-氧代-4-(3,3,3-三氟-1-丙炔基)-1-氮杂环庚烷基]丁酰胺；

[0631] 2-[2-氧代-4-(1-丙炔基)-1-氮杂环庚烷基]丁酰胺；

[0632] 2-[4-(环丙基乙炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0633] 2-[4-(3-甲基-1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0634] 2-[4-(1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0635] 2-[4-(2,2-二氟丙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0636] 2-[4-(2-氯-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0637] 2-[4-(2-溴-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺；

[0638] 2-[4-(2,2,2-三氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺。

[0639] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[0640] (2S)-2-[5-(碘甲基)-2-氧代-1-哌啶基]丁酰胺；

[0641] (2S)-2-[5-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰胺；

[0642] 2-(2-氧代-5-苯基-1-哌啶基]丁酰胺；

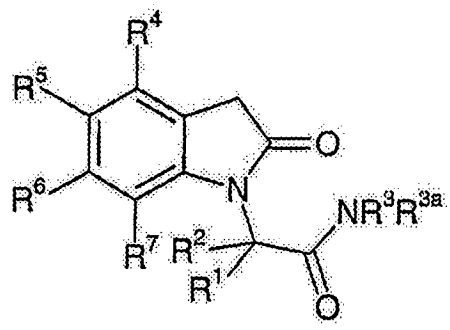
[0643] (2S)-2-[4-(碘甲基)-2-氧代-1-哌啶基]丁酰胺；

[0644] 2-[5-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺。

[0645] iii) 国际专利申请 WO2004/087658：

[0646] 具有式 I 的化合物或其药学可接受的盐或其立体异构体形式，

[0647]



(I)

[0648] 其中

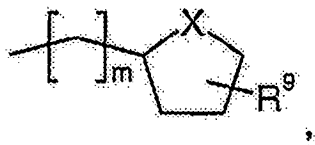
[0649] R^1是氢；

[0650] R^2是氢或C1-20-烷基；

[0651] R^3是氢、C1-20-烷基、C4-8-环烷基、C5-8-环烯基、芳基、芳族或非芳族杂环、C1-20-烷氧基或式-W-R^8的基团，

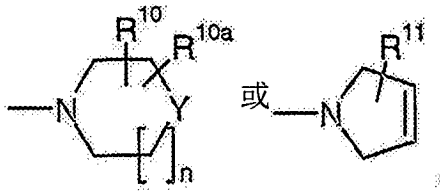
[0652] R^{3a}是氢、C1-20-烷基或下式的基团：

[0653]



[0654] 或NR^3R^{3a}是下式的基团：

[0655]



[0656] R^4是氢；

[0657] R^5是氢；硝基；卤素；叠氮基；氰基；-S-C1-4-烷基；-SO-C1-4-烷基；$-SO_2$-C1-4-烷基；$-SONH_2$；未取代的或被卤素取代的C1-20-烷基；或未取代的或被卤素取代的C1-20-烷氧基；

[0658] R^6是氢、C1-20-烷基或卤素；

[0659] R^7是氢、C1-20-烷基或卤素；

[0660] W是C1-12-亚烷基、-NH-或-NHC(=O)-；

[0661] X是O、S或NH；

[0662] Y是O、S、$-CR^{12}R^{13}-$、$-NR^{14}-$或-C(=O)-；

[0663] R^8是芳基或杂环；

[0664] R^9、R^{10}、R^{10a}和R^{11}独立地选自氢、C1-4-烷基、卤素、羟基或甲氧基羰基；

[0665] 或R^{10}和R^{10a}一起形成C3-6-亚烷基；

[0666] R^{12}是氢、C1-4-烷基、卤素或羟基；

[0667] R^{13}是氢；

[0668] 或$CR^{12}R^{13}$是二氧杂环戊烷基；

[0669] R^{14}是芳基、杂环或式-V-R^{15}的基团；

[0670] V是$C_{1\ 12}$-亚烷基；

[0671] R^{15}是芳基或杂环；

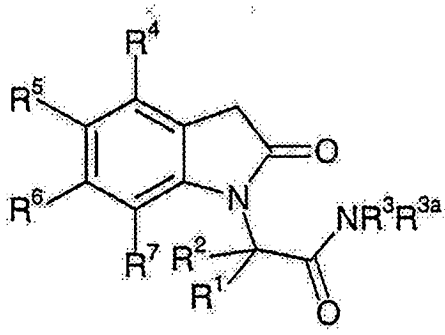
[0672] m是1-4；

[0673] n是0或1；

[0674] 且R^5、R^6或R^7中的至少一个不是氢，此时R^2是氢，R^3是H或2,6-二异丙基苯基，R^{3a}是H。

[0675] 在另一个方面中，化合物具有式I或其药学可接受的盐或其立体异构体形式，

[0676]



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[0677] 其中

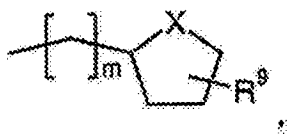
[0678] R^1是氢；

[0679] R^2是氢或C1-20-烷基；

[0680] R^3是氢、C1-20-烷基、C4-8-环烷基、C5-8-环烯基、芳基、芳族或非芳族杂环、C1-20-烷氧基或式-W-R^8的基团；

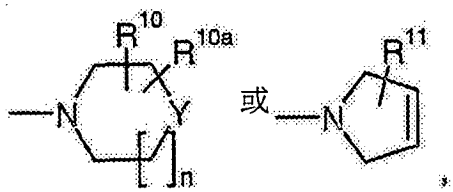
[0681] R^{3a}是氢、C1-20-烷基或下式的基团：

[0682]



[0683] 或NR^3R^{3a}是下式的基团：

[0684]



[0685] R^4是氢；

[0686] R^5是氢；硝基；卤素；未取代的或被卤素取代的C1-20-烷基；或未取代的或被卤素取代的C1-20-烷氧基；

[0687] R^6是氢、C1-20-烷基或卤素；

[0688] R^7是氢、C1-20-烷基或卤素；

[0689] W是C1-12-亚烷基、-NH-或-NHC(=O)-；

[0690] X是O、S或NH；

[0691] Y是O、S、-$CR^{12}R^{13}$-、-NR^{14}-或-C(=O)-；

[0692] R^8是芳基或杂环；

[0693] R^9、R^{10}、R^{10a}和R^{11}独立地选自氢、C1-4-烷基、卤素、羟基或甲氧基羰基；

[0694] 或R^{10}和R^{10a}一起形成C3-6-亚烷基；

[0695] R^{12}是氢、C1-4-烷基、卤素或羟基；

[0696] R^{13}是氢；

[0697] 或$CR^{12}R^{13}$是二氧杂环戊烷基；

[0698] R^{14}是芳基、杂环或式-V-R^{15}的基团；

[0699] V是C1-12-亚烷基；

[0700] R^{15}是芳基或杂环；

[0701] m 是 1-4；

[0702] n 是 0 或 1；

[0703] 且 R^5、R^6或 R^7中的至少一个不是氢，此时 R^2是氢，R^3是 H 或 2,6- 二异丙基苯基，R^{3a}是 H。

[0704] 本文所用的术语“烷基”定义为包括饱和一价烃基，其具有直链、支链或环状部分或其组合并且就非环烷基而言包含 1-20 个碳原子、优选 1-6 个碳原子且更优选 1-4 个碳原子且就环烷基而言包含 3-8 个碳原子。烯丙基部分可以任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、烷氧基、烷氧羰基、酯或烷基氨基。优选的烷基是甲基、乙基、正 - 丙基、异丙基、三氟甲基、正 - 丁基、2- 氟乙基、3- 羟基丙基、3- 羟基 -2,2- 二甲基丙基、1-(羟基甲基) 丙基、3,3,3- 三氟 -2- 羟基丙基、3- 乙氧基丙基、2- 乙氧基 -2- 氧代乙基和 3-(二甲氨基) 丙基。

[0705] 本文所用的术语“环烷基”意指 3-18 个碳原子、优选 4-8 个碳原子的一价基团，其衍生自饱和环状或多环烃，其可以被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。优选的环烷基是环庚基。

[0706] 本文所用的术语“亚烷基”表示二价烷基，其具有直链或支链部分，包含 1-12 个碳原子、优选 1-6 个碳原子且任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。优选的亚烷基是亚甲基、亚乙基、羟基亚乙基、三亚甲基或亚丙基。

[0707] 本文所用的术语“环烯基”定义为环状不饱和烃基，其具有至少一个双键，包含 4-20 个碳原子、优选 5-8 个碳原子且任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。优选的环烯基是 6-(羟基甲基) 环己 -3- 烯 -1- 基。

[0708] 本文所用的术语“芳基”定义为包括通过除去一个氢衍生自由 1-3 个环组成且包含 6-30 个碳原子的芳香烃的有机基团，例如苯基和萘基，其各自任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、硝基、C1-6- 烷基、C1-6- 烷氧基、C1-6- 烷基磺酰基、三氟甲硫基或吡啶基烷基。芳基优选为苯基。优选的芳基是苯基、3- 羟基苯基、3- 氟苯基、3- 甲基苯基、4- 甲基苯基、4- 羟基苯基、4- 羟基 -3- 甲氧基苯基、3-(2- 吡啶 -2- 基乙基) 苯基、3,4- 二甲基苯基、4- 叔 - 丁基苯基、4- 甲基磺酰基苯基、2- 硝基苯基、2- 氯 -6- 氟苯基、2-[(三氟甲基) 硫代] 苯基、2- 氯苯基或 4- 溴苯基。

[0709] 本文所用的术语“卤素”包括 Cl、Br、F、I 的原子。

[0710] 本文所用的术语“硝基”表示式 $-NO_2$的基团。

[0711] 本文所用的术语“羟基”表示式 -OH 的基团。

[0712] 本文所用的术语“烷氧基”表示式 $-OR^b$的基团，其中 R^b是如上文所定义的烷基。

[0713] 本文所用的术语“酯”表示式 $-COOR^c$的基团，其中 R^c是如上文所定义的烷基或芳基。

[0714] 本文所用的术语“烷氧羰基”表示式 $-COOR^d$的基团，其中 R^d是如上文所定义的烷基。

[0715] 本文所用的术语“氨基”表示式 $-NH_2$的基团。

[0716] 本文所用的术语“烷基氨基”表示式 -NHR^{e}或 -NR ^{e}R^{f}的基团，其中 R ^{e}和 R ^{f}是如上文所定义的烷基。

[0717] 本文所用的术语“烷基磺酰基”定义为表示式 -SO_2-R^{g}的基团，其中 R ^{g}是 C1-4- 烷基。

[0718] 本文所用的术语“杂环”定义为包括如上文所定义的芳族或非芳族环烷基或环烯基部分，其具有至少一个间隔碳环结构的 O、S 和 / 或 N 原子，且任选碳环结构的碳之一可以被羰基替代。

[0719] 芳族杂环的非限制性实例是吡唑基、呋喃基、咪唑基、三唑基、噁唑基、吡啶基、吡咯基、噻吩基、异噻唑基、苯并咪唑基、四唑基、异噁唑基、噁唑基、噻唑基、1,2,4- 噻二唑基、噁二唑、哒嗪基、嘧啶基、吡嗪基、异吲哚基、三唑并吡啶基、咪唑并吡啶基、吡咯并嘧啶基、吡唑并嘧啶基、喹唑啉基、喹喏基、萘啶基、喹啉基、异喹啉基、异苯并呋喃基、苯并噻吩基、吲哚基、吲嗪基、嘌呤基、咔唑基、噻吩并 (2,3-b) 呋喃基、噻蒽基、苯并噻唑基、苯并噁唑基、噌啉基、喹喔啉基、吩噻嗪基、异苯并二氢吡喃基和呫吨基，其任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、硫羟基、氨基、硝基、氰基、叠氮基、C1-6- 烷氧基、C1-6- 烷硫基、C1-6- 烷基、C1-6- 卤代烷基、甲酰基或酯。更优选的芳族杂环是吡唑基、呋喃基、咪唑基、三唑基、噁唑基和吡啶基。

[0720] 非芳族杂环的非限制性实例四氢呋喃基、哌啶基、哌啶基、哌嗪基、咪唑烷基、吗啉基、硫吗啉基、吡咯烷基、噻唑烷基、二氢吲哚基、四氢苯并𠰌辛因基、二氢异色烯基、四氢吡喃基、氧代八氢喹啉基、二氧杂环戊烷基、1- 氧杂螺 (4.5) 癸 -2- 基、吡咯烷基、2- 氧代 - 吡咯烷基、8- 硫杂双环 [3.2.1] 环辛烷基、1,4- 二噻庚环基、四氢 -2H- 硫代吡喃基、氮杂环庚烷基和氮杂环辛烷基，其任选地被 1-5 个取代基取代，所述取代基独立地选自卤素、羟基、硫羟基、氨基、硝基、氰基、叠氮基、C1-6- 烷氧基、C1-6- 烷硫基、C1-6- 烷基、C1-6- 卤代烷基、甲酰基或酯。更优选的非芳族杂环是四氢呋喃基、哌啶基、哌啶基、哌嗪基、咪唑烷基、吗啉基、硫吗啉基、吡咯烷基、噻唑烷基、二氢吲哚基、四氢 -1- 苯并𠰌辛因 -1(2H)- 基、3,4- 二氢 -1H- 异色烯 -1- 基、四氢吡喃基、氧代八氢喹啉基和二氧杂环戊烷基。术语“杂环”还包括双环、三环和四环、螺基团，其中任意上述杂环与一个或两个环稠合，所述环独立地选自芳基环、环烷基环、环烯基环或另一种单环杂环或其中单环杂环基通过亚烷基桥连，例如奎宁环基、7- 氮杂双环 (2.2.1) 庚烷基、7- 氧杂双环 (2.2.1) 庚烷基和 8- 氮杂双环 (3.2.1) 辛烷基。

[0721] 本文所用的术语“吡啶基烷基”表示式 -R^h- 吡啶基的基团，其中 R^{h}是 C1-4- 亚烷基。

[0722] 本文所用的术语“叠氮基”表示式 -N_3的基团。

[0723] 本文所用的术语“氰基”表示式 -CN 的基团。

[0724] 一般而言，R^2是氢或 C1-4- 烷基。

[0725] 优选 R^2是氢、甲基或乙基。更优选 R ^{2}是氢或甲基。

[0726] 一般而言，R^3是氢；C1-6- 烷基，其未取代或被 1-5 个取代基取代，所述取代基选自卤素、羟基、烷氧基、烷氧羰基或烷基氨基；C5-7- 环烷基；(羟基甲基) 环己烯基；苯基，其未取代或被 1-5 个取代基取代，所述取代基选自卤素、C1-4- 烷基、羟基、甲氧基、硝基、甲基磺酰基、三氟甲硫基或吡啶基烷基；吡啶基，其未取代或被甲氧基取代；三唑基；C1-4- 烷氧

基；或式 -W-R^8的基团，其中

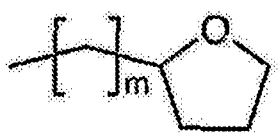
[0727] 一般而言，W 是未取代的或被卤素、羟基、C1-4- 烷基或烷氧基取代的 C1-4- 亚烷基；-NH- ；或 -NHC(= O)- ；且

[0728] R^8是未取代的或被 1-5 个选自卤素、C1-4- 烷基、羟基、甲氧基、硝基、甲基磺酰基或三氟甲硫基的取代基取代的苯基；未取代的或被甲基取代的呋喃基；吡唑基；吡啶基；吗啉基；四氢苯并吖辛因基；未取代的或被甲基取代的哌啶基；二氢异色烯基或二氢咪唑基。

[0729] 优选 R^3是氢、正 - 丁基、环庚基、2- 氟乙基、3- 羟基丙基、3- 羟基 -2,2- 二甲基丙基、1-(羟基甲基) 丙基、3,3,3- 三氟 -2- 羟基丙基、3- 乙氧基丙基、2- 乙氧基 -2- 氧代乙基、3-(二甲氨基) 丙基、6-(羟基甲基) 环己 -3- 烯 -1- 基、3- 羟基苯基、3- 氟苯基、3-(2- 吡啶 -2- 基乙基) 苯基、3,4- 二甲基苯基、4- 叔 - 丁基苯基、苄基、4- 羟基 -3- 甲氧基苄基、4- 甲基磺酰基苄基、2- 硝基苄基、2- 氯 -6- 氟苄基、2-[(三氟甲基) 硫代] 苄基、2- 羟基 -2- 苯基乙基、2-(3,4- 二甲氧基苯基) 乙基、2-(2- 氯苯基) 乙基、2-(4- 甲基苯基) 乙基、(4- 溴苯基) 氨基、吡啶 -3- 基、6- 甲氧基吡啶 -3- 基、4H-1,2,4- 三唑 -3- 基、吡啶 -4- 基甲基、(5- 甲基 -2- 呋喃基) 甲基、3-(1H- 吡唑 -1- 基) 丙基、2- 吗啉 -4- 基乙基、2-((3,4,5,6- 四氢 -1- 苯并吖辛因 -1(2H)- 基) 丙基、2-(2- 甲基哌啶 -1- 基) 乙基、3,4- 二氢 -1H- 异色烯 -1- 基甲基、甲氧基、(4- 吡啶基羰基) 氨基或 4,5- 二氢 -1H- 咪唑 -2- 基氨基。更优选 R^3是氢。

[0730] 一般而言，R^{3a}是氢、C1-4- 烷基或下式的基团：

[0731]

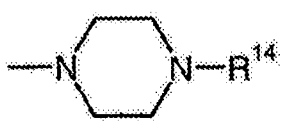


[0732] 其中 m 是 1-4。

[0733] 优选 R^{3a}是氢、甲基或四氢呋喃 -2- 基甲基。更优选 R^{3a}是氢。

[0734] 在另一个实施方案中，NR^3R^{3a}是未取代的或被羟基取代的哌啶基；硫吗啉基；未取代的或被 C1-4- 烷氧羰基取代的噻唑烷基；2,5- 二氢 -1H- 吡咯 -1- 基；1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸 -8- 基；4- 氧代八氢 -1(2H)- 喹啉基或下式的基团：

[0735]



[0736] 其中 R^{14}是吡啶基；未取代的或被卤素、羟基、C1-4- 烷基取代的苯基或式 -V-R^{15}的基团，其中 V 是未取代的 C1-4- 亚烷基，R^{15}是苯基或吗啉基。

[0737] 在一个优选的实施方案中，NR^3R^{3a}是 4- 吡啶 -2- 基哌嗪 -1- 基、4-(3- 甲基苯基) 哌嗪 -1- 基、4-(4- 羟基苯基) 哌嗪 -1- 基、4-(2- 苯基乙基) 哌嗪 -1- 基、4-(2- 吗啉 -4- 基乙基) 哌嗪 -1- 基、3- 羟基哌啶 -1- 基、硫吗啉 -4- 基、4- 甲氧基羰基 -1,3- 噻唑烷 -3- 基、2,5- 二氢 -1H- 吡咯 -1- 基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸 -8- 基或 4- 氧代八氢 -1(2H)- 喹啉基。

[0738] 一般而言，R^5是氢、硝基、卤素、未取代的或被卤素取代的 C1-4- 烷基或未取代的或

被卤素取代的 C1-4- 烷氧基。

[0739] 优选 R^5是氢、甲基、乙基、三氟甲基、三氟甲氧基、正 - 丙基、异丙基、硝基或卤素。更优选 R^5是卤素或三氟甲基。

[0740] 一般而言，R^6是氢、C1-6- 烷基或卤素。

[0741] 优选 R^6是氢、甲基或 Cl。更优选 R^6是氢。

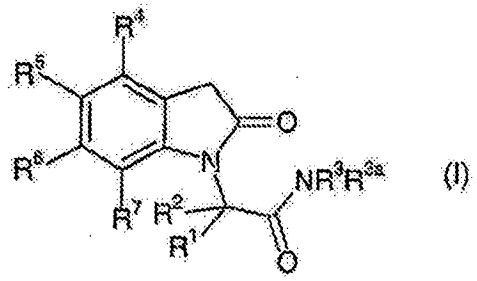
[0742] 一般而言，R^7是氢、甲基或卤素。

[0743] 优选 R^7是氢、甲基、Br、F 或 Cl。更优选 R^7是氢、Br 或 F。

[0744] 尤其优选这些优选化合物基团的一个或多个的组合。

[0745] 在一个优选的实施方案中，化合物具有式 I 或其药学可接受的盐或其立体异构体形式，

[0746]



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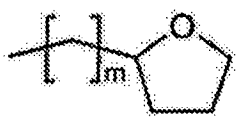
[0747] 其中 R^1是氢；

[0748] R^2是氢或 C1-4- 烷基；

[0749] R^3是氢；未取代的或被 1-5 个选自卤素、羟基、烷氧基、烷氧羰基或烷基氨基的取代基取代的 C1-6- 烷基；C5-7- 环烷基；(羟基甲基) 环己烯基；未取代的或被 1-5 个选自选自卤素、C1-4- 烷基、羟基、甲氧基、硝基、甲基磺酰基、三氟甲硫基或吡啶基烷基的取代基取代的苯基；未取代的或被甲氧基取代的吡啶基；三唑基；C1-4- 烷氧基；或式 $-W-R^8$的基团，

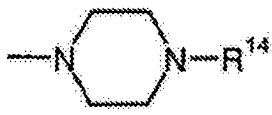
[0750] R^{3a}是氢、C1-4- 烷基或下式的基团

[0751]



[0752] 或 NR^3R^{3a}是未取代的或被羟基取代的哌啶基；硫吗啉基；未取代的或被 C1-4- 烷氧羰基取代的噻唑烷基；2,5- 二氢 -1H- 吡咯 -1- 基；1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸 -8- 基；4- 氧代八氢 -1(2H)- 喹啉基；或下式的基团：

[0753]



[0754] R^4是氢；

[0755] R^5是氢；硝基；卤素；未取代的或被卤素取代的 C1-4- 烷基；或未取代的或被卤素取代的 C1-4- 烷氧基；

[0756] R6 是氢、C1-6- 烯丙基或卤素；

[0757] R7 是氢、甲基或卤素；

[0758] W 是未取代的或被卤素、羟基、C1-4- 烷基或烷氧基取代的 C1-4- 亚烷基 ;-NH- ;或 -NHC(= O)- ;

[0759] R8 是未取代的或被 1-5 个选自卤素、C1-4- 烷基、羟基、甲氧基、硝基、甲基磺酰基或三氟甲硫基的取代基取代的苯基 ;未取代的或被甲基取代的呋喃基 ;吡唑基 ;吡啶基 ;吗啉基 ;四氢苯并吖辛因基 ;未取代的或被甲基取代的哌啶基 ;二氢异色烯基或二氢咪唑基 ;

[0760] R^{14}是吡啶基 ;未取代的或被卤素、羟基、C1-4- 烷基取代的苯基 ;或式 -V-R^{15}的基团 ;

[0761] V 是未取代的 C1-4- 亚烷基 ;

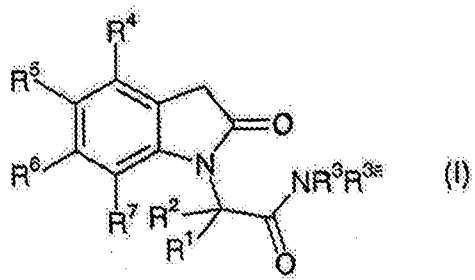
[0762] R^{15}是苯基或吗啉基 ;

[0763] m 是 1-4 ;

[0764] 且 R^5、R^6或 R^7中的至少一个不是氢,此时 R^2是氢,R^3是 H 或 2,6- 二异丙基苯基,R^{3a}是 H。

[0765] 在一个更优选的实施方案中,化合物具有式 I 或其药学可接受的盐或立体异构体形式,

[0766]



(I)

[0767] 其中

[0768] R^1是氢 ;

[0769] R^2是氢、甲基或乙基 ;

[0770] R^3是氢、正 - 丁基、环庚基、2- 氟乙基、3- 羟基丙基、3- 羟基 -2,2- 二甲基丙基、1-(羟基甲基) 丙基、3,3,3- 三氟 -2- 羟基丙基、3- 乙氧基丙基、2- 乙氧基 -2- 氧代乙基、3-(二甲氨基) 丙基、6-(羟基甲基) 环己 -3- 烯 -1- 基、3- 羟基苯基、3- 氟苯基、3-(2- 吡啶 -2- 基乙基) 苯基、3,4- 二甲基苯基、4- 叔 - 丁基苯基、苄基、4- 羟基 -3- 甲氧基苄基、4- 甲基磺酰基苄基、2- 硝基苄基、2- 氯 -6- 氟苄基、2-[(三氟甲基) 硫代] 苄基、2- 羟基 -2- 苯基乙基、2-(3,4- 二甲氧基苯基) 乙基、2-(2- 氯苯基) 乙基、2-(4- 甲基苯基) 乙基、(4- 溴苯基) 氨基、吡啶 -3- 基、6- 甲氧基吡啶 -3- 基、4H-1,2,4- 三唑 -3- 基、吡啶 -4- 基甲基、(5- 甲基 -2- 呋喃基) 甲基、3-(1H- 吡唑 -1- 基) 丙基、2- 吗啉 -4- 基乙基、2-((3,4,5,6- 四氢 -1- 苯并吖辛因 -1(2H)- 基) 丙基、2-(2- 甲基哌啶 -1- 基) 乙基、3,4- 二氢 -1H- 异色烯 -1- 基甲基、甲氧基、(4- 吡啶基羰基) 氨基或 4,5- 二氢 -1H- 咪唑 -2- 基氨基 ;

[0771] R^{3a}是氢、甲基或四氢呋喃 -2- 基甲基或 NR^3R^{3a}4- 吡啶 -2- 基哌嗪 -1- 基、4-(3- 甲基苯基) 哌嗪 -1- 基、4-(4- 羟基苯基) 哌嗪 -1- 基、4-(2- 苯基乙基) 哌嗪 -1- 基、4-(2- 吗啉 -4- 基乙基) 哌嗪 -1- 基、3- 羟基哌啶 -1- 基、硫吗啉 -4- 基、4- 甲氧基羰基 -1,3- 噻唑烷 -3- 基、2,5- 二氢 -1H- 吡咯 -1- 基、1,4- 二氧杂 -8- 氮杂螺 [4.5] 癸 -8- 基或 4- 氧代

八氢 -1(2H)- 喹啉基；

[0772] R^4是氢；

[0773] R5 是氢、甲基、乙基、三氟甲基、三氟甲氧基、正丙基、异丙基、硝基或卤素；

[0774] R^6是氢、甲基或 Cl；

[0775] R^7是氢、甲基、Br、F 或 Cl；

[0776] 且 R^5、R^6或 R^7中的至少一个不是氢，此时 R^2是氢，R^3是 H 或 2,6- 二异丙基苯基，R^{3a}是 H。

[0777] 更优选 R^2是氢或甲基、R^3是氢、R^{3a}是氢、R^5是卤素或三氟甲基、R^6是氢且 R^7是氢、Br 或 F。

[0778] 在所有上述举出的范围中，当 R^2是 C1-20- 烷基时，R^2所连接的碳原子优选是“S”- 构型。

[0779] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[0780] 2-(5- 碘 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0781] 2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0782] 2-(5,7- 二溴 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0783] 2-(5- 硝基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0784] 2-(5- 甲基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0785] 2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0786] (2R)-2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0787] (2S)-2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0788] 2-[2- 氧代 -5-（三氟甲氧基）-2,3- 二氢 -1H- 吲哚 -1- 基］乙酰胺；

[0789] 2-(5- 异丙基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0790] 2-(5- 乙基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0791] 2-(5- 氟 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0792] 2-(5,7- 二甲基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0793] 2-(5- 溴 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0794] 2-(2- 氧代 -5- 丙基 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0795] 2-[2- 氧代 -5-（三氟甲基）-2,3- 二氢 -1H- 吲哚 -1- 基］乙酰胺；

[0796] 2-(5,6- 二甲基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0797] 2-(7- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0798] 2-(6- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）乙酰胺；

[0799] 2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丁酰胺；

[0800] (+)-2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丁酰胺；

[0801] (-)-2-(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丁酰胺；

[0802] 2-(5- 甲基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0803] (+)-2-(5- 甲基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0804] (-)-2-(5- 甲基 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0805] 2-(5- 溴 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0806] (-)-2-(5- 溴 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基）丙酰胺；

[0807] (+)-2-(5-溴-2-氧代-2,3-二氢-1H-吲哚-1-基)丙酰胺；

[0808] 2-(5-氯-7-氟-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0809] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3-羟基苯基)乙酰胺；

[0810] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3-氟苯基)乙酰胺；

[0811] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[3-(2-吡啶-2-基乙基)苯基乙酰胺；

[0812] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[6-(羟基甲基)环己-3-烯-1-基]乙酰胺；

[0813] 5-氯-1-[2-氧代-2-(4-吡啶-2-基哌嗪-1-基)乙基]-1,3-二氢-2H-吲哚-2-酮；

[0814] 5-氯-1-{2-[4-(3-甲基苯基)哌嗪-1-基]-2-氧代乙基}-1,3-二氢-2H-吲哚-2-酮；

[0815] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(4-羟基-3-甲氧基苄基)乙酰胺；

[0816] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(吡啶-4-基甲基)-N-(四氢呋喃-2-基甲基)乙酰胺；

[0817] 5-氯-1-[2-(3-羟基哌啶-1-基)-2-氧代乙基]-1,3-二氢-2H-吲哚-2-酮；

[0818] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N'-异烟酰基乙酰肼；

[0819] 5-氯-1-(2-氧代-2-硫吗啉-4-基乙基)-1,3-二氢-2H-吲哚-2-酮；

[0820] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(4H-1,2,4-三唑-3-基)乙酰胺；

[0821] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[4-(甲基磺酰基)苄基]乙酰胺；

[0822] 1-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰基]八氢喹啉-4(1H)-酮；

[0823] N'-(4-溴苯基)-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰肼；

[0824] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(6-甲氧基吡啶-3-基)乙酰胺；

[0825] N-丁基-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0826] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3-羟基丙基)乙酰胺；

[0827] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[3-(二甲氨基)丙基]乙酰胺；

[0828] 5-氯-1-{2-氧代-2[4-(2-苯基乙基)哌嗪-1-基]乙基}-1,3-二氢-2H-吲哚-2-酮；

[0829] {[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰基]氨基}乙酸乙酯；

[0830] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3-乙氧基丙基)乙酰胺；

[0831] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(2-氟乙基)乙酰胺；

[0832] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-甲氧基-N-甲基乙酰胺；

[0833] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3,4-二甲基苯基)乙酰胺；

[0834] N-(4-叔-丁基苯基)-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0835] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3-羟基-2,2-二甲基丙基)乙酰胺；

[0836] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[1-(羟基甲基)丙基]乙酰胺；

[0837] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3,3,3-三氟-2-羟基丙基)乙酰胺；

[0838] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(2-羟基-2-苯基乙基)乙酰胺；

[0839] 5-氯-1-{2-[4-(4-羟基苯基)哌嗪-1-基]-2-氧代乙基}-1,3-二氢-2H-吲哚-2-酮；

[0840] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(吡啶-4-基甲基)乙酰胺；

[0841] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[(5-甲基-2-呋喃基)甲基]乙酰胺；

[0842] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[3-(1H-吡唑-1-基)丙基]乙酰胺；

[0843] 3-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰基]-1,3-噻唑烷-4-甲酸甲酯；

[0844] 5-氯-1-[2-(2,5-二氢-1H-吡咯-1-基)-2-氧代乙基]-1,3-二氢-2H-吲哚-2-酮；

[0845] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N'-(4,5-二氢-1H-咪唑-2-基)乙酰肼；

[0846] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[2-(3,4-二甲氧基苯基)乙基]乙酰胺；

[0847] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[2-(2-氯苯基)乙基]乙酰胺；

[0848] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[2-(4-甲基苯基)乙基]乙酰胺；

[0849] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(2-吗啉-4-基乙基)乙酰胺；

[0850] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[2-(3,4,5,6-四氢-1-苯并吖辛因-1(2H)-基)丙基]乙酰胺；

[0851] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-[2-(2-甲基哌啶-1-基)乙基]乙酰胺；

[0852] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(2-硝基苄基)乙酰胺；

[0853] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-(3,4-二氢-1H-异色烯-1-基甲基)乙酰胺；

[0854] N-(2-氯-6-氟苄基)-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0855] N-苄基-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-甲基乙酰胺；

[0856] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-{2-[(三氟甲基)硫代]苄

基｝乙酰胺；

[0857] 5-氯-1-[2-(1,4-二氧杂-8-氮杂螺[4.5]癸-8-基)-2-氧代乙基]-1,3-二氢-2H-吲哚-2-酮；

[0858] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-环庚基乙酰胺；

[0859] 5-氯-1-{2-[4-(2-吗啉-4-基乙基)哌嗪-1-基]-2-氧代乙基}-1,3-二氢-2H-吲哚-2-酮；和

[0860] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)-N-吡啶-3-基乙酰胺。

[0861] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[0862] 2-(5-碘-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0863] 2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0864] 2-(5,7-二溴-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺；

[0865] (2S)-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)丙酰胺；

[0866] 2-[2-氧代-5-(三氟甲基)-2,3-二氢-1H-吲哚-1-基]乙酰胺；和

[0867] 2-(5-氯-7-氟-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺。

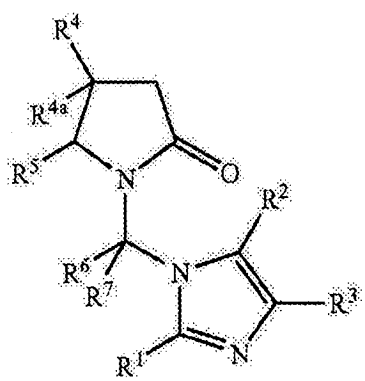
[0868] 在另一个实施方案中，用于本发明方法和组合物的化合物选自：2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)乙酰胺和(2S)-2-(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)丙酰胺。

[0869] iv)美国专利US7,244,747：

[0870] 具有式I的化合物或其药学可接受的盐，

[0871]

(I)



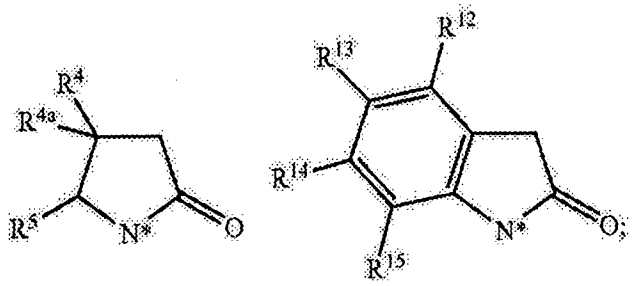
[0872] 其中R^1是氢、$C_{1\ 20}$烷基、$C_{3\ 8}$环烷基、卤素、羟基、烷氧基、芳基氧基、酯、酰氨基、氰基、硝基、氨基、胍、氨基衍生物、烷硫基、芳硫基、烷基磺酰基、芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、芳基或杂环；

[0873] R^2是氢、$C_{1\ 20}$烷基、烷氧基、氨基、卤素、羟基、酯、酰氨基、硝基、氰基、氨基甲酸酯或芳基；

[0874] R^3是氢、$C_{1\ 20}$烷基、烷氧基、氨基、卤素、羟基、酯、酰氨基、硝基、氰基、氨基甲酸酯或芳基；

[0875] 或R^2和R^3可以与咪唑环一起形成如下的1H-苯并咪唑环：

[0876]



[0877] R^4是氢、$C_{1\ 20}$烷基、$C_{2\ 12}$烯基、$C_{2\ 12}$炔基、芳基、叠氮基、烷氧羰基氨基、芳基磺酰基氧基或杂环；

[0878] R^{4a}是氢或$C_{1\ 20}$烷基；

[0879] 或R^4和R^{4a}可以一起形成$C_{3\ 8}$环烷基；

[0880] R^5是氢；

[0881] 或R^4、R^{4a}和R^5可以与2-氧代-1-吡咯烷环一起形成如下的1,3-二氢-2H-吲哚-2-酮环；

[0882] R^6是氢或$C_{1\ 20}$烷基；

[0883] R^7是氢；

[0884] 或R^6和R^7连接在一起形成$C_{3\ 6}$环烷基；

[0885] R^8是氢、卤素、硝基、氰基、$C_{1\ 20}$烷基或烷氧基；

[0886] R^9是氢、$C_{1\ 20}$烷基、卤素、羟基、烷氧基、芳基氧基、酯、酰氨基、氰基、硝基、氨基、氨基衍生物、烷硫基、芳硫基、烷基磺酰基、芳基磺酰基、烷基亚磺酰基或芳基亚磺酰基；

[0887] R^{10}是氢、$C_{1\ 20}$烷基、卤素、羟基、烷氧基、芳基氧基、酯、酰氨基、氰基、硝基、氨基、氨基衍生物、烷硫基、芳硫基、烷基磺酰基、芳基磺酰基、烷基亚磺酰基或芳基亚磺酰基；

[0888] R^{11}是氢、卤素、硝基、氰基、$C_{1\ 20}$烷基或烷氧基；

[0889] R^{12}是氢或卤素；

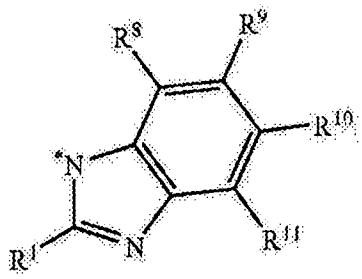
[0890] R^{13}是氢、硝基、卤素、杂环、氨基、芳基、未取代的或被卤素取代的$C_{1\ 20}$烷基或未取代的或被卤素取代的烷氧基；

[0891] R^{14}是氢、$C_{1\ 20}$烷基或卤素；

[0892] R^{15}是氢、$C_{1\ 20}$烷基或卤素；

[0893] 条件是R^4不是氢，此时表示下式的基团：

[0894]

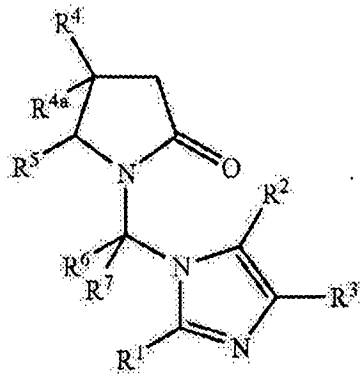


[0895] 星号*表示取代基的连接点。

[0896] 在一个优选实施方案中，化合物具有式I，其互变体、几何异构体（包括顺式和反式，Z和E异构体）、对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体混合物）或其药学可接受的盐，

[0897]

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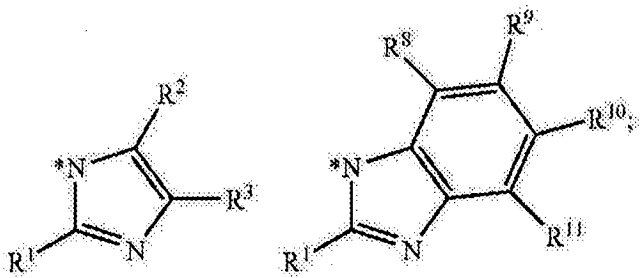
[0898] 其中 R^1是氢、$C_{1\ 20}$烷基、$C_{3\ 8}$环烷基、卤素、羟基、酯、酰氨基、氰基、硝基、氨基、胍、烷硫基、烷基磺酰基、烷基亚磺酰基、芳基或杂环；

[0899] R^2是氢、$C_{1\ 20}$烷基、卤素、氰基、酯、氨基甲酸酯或酰氨基；

[0900] R^3是氢、氰基、$C_{1\ 20}$烷基、卤素或酯；

[0901] 或 R^2和 R^3可以与咪唑环一起形成如下的 1H- 苯并咪唑环：

[0902]



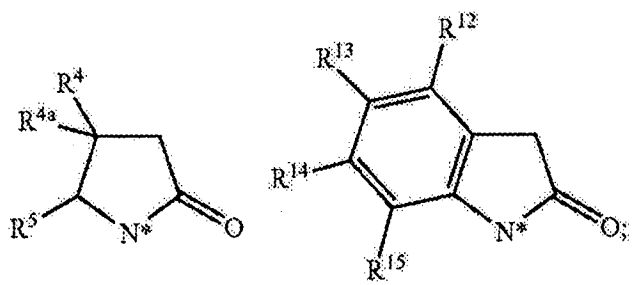
[0903] R^4是氢、$C_{1\ 20}$烷基、$C_{2\ 20}$烯基或芳基；

[0904] R^{4a}是氢；

[0905] R^5是氢；

[0906] 或 R^4、R^{4a}和 R^5可以与 2- 氧代 -1- 吡咯烷环一起形成 1,3- 二氢 -2H- 吲哚 -2- 酮环：

[0907]



[0908] R^6是氢或 $C_{1\ 20}$烷基；

[0909] R^7是氢；或 R^6和 R^7一起形成 $C_{3\ 6}$环烷基；

[0910] R^8是氢；

[0911] R^9是氢、$C_{1\ 20}$烷基、卤素或烷氧基；

[0912] R^{10}是氢、$C_{1\ 20}$烷基、卤素或氰基；

[0913] R^{11}是氢；

[0914] R^{12}是氢或卤素；

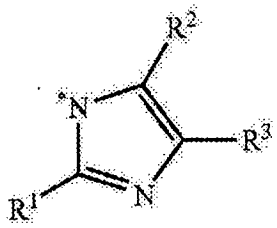
[0915] R^{13}是氢、卤素、杂环或C_{1-20}烷基；

[0916] R^{14}是氢；

[0917] R^{15}是氢；

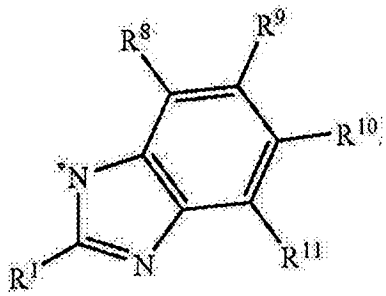
[0918] 条件是当

[0919]



[0920] 表示下式的基团时，R^4不是氢，

[0921]



[0922] 本文所用的术语“烷基”表示饱和一价烃基，其为直链（无支链）或支链或环状或其组合并且包含1-20个碳原子、优选1-10个碳原子，更优选具有1-3个碳原子的烷基。烷基部分可以任选地被1-5个取代基取代，所述取代基独立地选自卤素、羟基、氰基、叠氮基、芳基氧基、烷氧基、烷硫基、烷酰氨基、芳基羰基氨基、氨基羰基、甲氨基羰基、二甲氨基羰基或芳基。在目前的情况中，烷基通常是甲基、乙基、正-丙基、异-丙基、正-丁基、异-丁基、叔-丁基、1-乙基丙基、正-庚基、2,4,4-三甲基戊基、正-癸基、氯甲基、三氟甲基、2-溴-2,2-二氟乙基、2,2,2-三氟乙基、3,3,3-三氟丙基、羟基甲基、氰基甲基、叠氮基甲基、（乙酰基氨基）甲基、（丙酰基氨基）甲基、（苯甲酰基氨基）甲基、(4-氯苯氧基）甲基、苄基、2-苯基乙基或2-（甲硫基）乙基。优选的烷基是甲基、乙基、正-丙基、异-丙基、正-丁基、异-丁基、叔-丁基、1-乙基丙基、2,4,4-三甲基戊基、氯甲基、三氟甲基、2,2,2-三氟乙基、羟基甲基、氰基甲基、叠氮基甲基、（乙酰基氨基）甲基、（丙酰基氨基）甲基、（苯甲酰基氨基）甲基或2-（甲硫基）乙基。更优选的烷基是甲基、乙基、正-丙基、异-丙基、正-丁基、叠氮基甲基或三氟甲基。最优选的烷基是甲基或正-丙基。

[0923] 本文所用的术语“环烷基”表示3-8个碳原子、通常是3-6个碳原子的一价基团，其衍生自饱和环烃，可以被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。优选的环烷基是环丙基和环己基。

[0924] 本文所用的术语“烯基”表示直链、支链或环状不饱和烃基或其组合，其具有至少一个碳-碳双键、包含2-12个碳原子、优选通常包含2-4个碳原子。烯基任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。

烯基通常是任选地被 1-3 个卤素取代的乙烯基（乙烯基）。在目前的情况中，优选的烯基是 2,2- 二氟乙烯基。

[0925] 本文所用的术语“炔基”表示直链、支链或环状烃基或其组合，其具有至少一个碳 - 碳三键、包含 2-12 个碳原子、优选 2-6 个碳原子且任选地被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。优选炔基是卤代炔基（卤代炔基）。

[0926] 前缀例如“仲”、“异”、“叔”等修饰的基团（例如“异 - 丙基”、“仲 - 丁基”）是支链衍生物。

[0927] 本文所用的术语“芳基”定义为任选地被 1-4 个取代基取代的苯基，所述取代基独立地选自卤素、氰基、烷氧基、烷硫基、C_{1-3}烷基或叠氮基，优选卤素或叠氮基。在目前的情况中，芳基通常是苯基、3- 氯苯基、3- 氟苯基、4- 氯苯基、4- 氟苯基、3,4- 二氟苯基、3,5- 二氟苯基、3- 氯 -4- 氟苯基、2,3,4- 三氟苯基、2,4,5- 三氟苯基、2,3,5- 三氟苯基、3,4,5- 三氟苯基、3- 叠氮基 -2,4- 二氟苯基或 3- 叠氮基 -2,4,6- 三氟苯基。优选芳基是苯基、3- 氯苯基、3- 氟苯基、4- 氯苯基、4- 氟苯基、3,4- 二氟苯基、3,5- 二氟苯基、3- 氯 -4- 氟苯基、2,3,4- 三氟苯基、2,4,5- 三氟苯基、2,3,5- 三氟苯基、3,4,5- 三氟苯基或 3- 叠氮基 -2,4- 二氟苯基。最优选的芳基是苯基、3- 氯苯基、3- 氟苯基、3,5- 二氟苯基、2,3,4- 三氟苯基、2,4,5- 三氟苯基、2,3,5- 三氟苯基、3,4,5- 三氟苯基或 3- 叠氮基 -2,4- 二氟苯基。

[0928] 本文所用的术语“杂环”定义为包括如上述所定义的芳族或非芳族环烷基部分，其具有至少一个间隔碳环结构的 O、S 和 / 或 N 原子。杂环部分可以任选地被烷基或卤素取代，且任选碳环结构的碳之一可以被羰基替代。杂环通常是 2- 吡啶基、3- 吡啶基、4- 吡啶基、2- 呋喃基、3- 呋喃基、2- 噻吩基、3- 噻吩基、2- 四氢呋喃基、1H- 吡咯 -2- 基、1- 甲基 -1H- 吡咯 -2- 基、1H- 吡唑 -2- 基、1H- 吡唑 -3- 基、4- 氯 -1- 甲基 -1H- 吡唑 -3- 基、5- 氯 -1,3- 二甲基 -1H- 吡唑 -4- 基、1,2,3- 噻二唑 -4- 基、3,5- 二甲基 -4- 异噻唑基、1H- 咪唑 -2- 基、1- 甲基 -1H- 咪唑 -2- 基、4- 甲基 -1H- 咪唑 -5- 基或 2- 甲基 -1,3- 噻唑 -4- 基。优选的杂环是 1H- 咪唑 -2- 基、1,2,3- 噻二唑 -4- 基、1H- 吡唑 -3- 基、2- 呋喃基、3- 呋喃基、2- 噻吩基、1- 甲基 -1H- 吡咯 -2- 基、1H- 吡咯 -2- 基。

[0929] 本文所用的术语“卤素”包括氯、溴、氟、碘的原子。卤素通常是氯、溴和氟。优选的卤素是氟、溴和氯。

[0930] 本文所用的术语“羟基”表示式 -OH 的基团。

[0931] 本文所用的术语“烷氧基”表示式 $-OR^a$ 的基团，其中 R^a 是如上述所定义的烷基。优选的烷氧基是甲氧基。

[0932] 本文所用的术语“芳基氧基”表示式 $-OR^b$ 的基团，其中 R^b 是如上述所定义的芳基。优选的芳基氧基是苯氧基。

[0933] 本文所用的术语“酯”表示式 $-COOR^c$ 的基团，其中 R^c 是如上述所定义的烷基或芳基。优选的酯基团是甲氧基羰基。

[0934] 本文所用的术语“酰氨基”表示式 $-CONH_2$ 的基团。

[0935] 本文所用的术语“氨基”表示式 $-NH_2$ 的基团。

[0936] 本文所用的术语“氨基衍生物”表示烷基氨基或芳基氨基，其中术语“烷基”和“芳基”如上述所定义。

[0937] 本文所用的术语“氰基”表示式 -CN 的基团。

[0938] 本文所用的术语“硝基”表示式 $-NO_2$的基团。

[0939] 本文所用的术语“叠氮基”表示式 $-N_3$的基团。

[0940] 本文所用的术语“胍”表示式 $-NHC(=NH)NH_2$的基团。

[0941] 本文所用的术语“烷硫基”表示式 $-SR^d$的基团。其中 R^d是如上述所定义的烷基。优选的烷硫基是甲硫基。

[0942] 本文所用的术语“烷基磺酰基”表示式 $-S(=O)_2R^e$的基团，其中 R^e是如上述所定义的烷基。优选的烷基磺酰基是甲基磺酰基。

[0943] 本文所用的术语“烷基亚磺酰基”表示式 $-S(=O)R^f$的基团，其中 R^f是如上述所定义的烷基。优选的烷基亚磺酰基是甲基亚磺酰基。

[0944] 本文所用的术语“芳硫基”表示式 $-SR^g$的基团，其中 R^g是如上述所定义的芳基。

[0945] 本文所用的术语“芳基磺酰基”表示式 $-S(=O)_2R^h$的基团，其中 R^h是如上述所定义的芳基。

[0946] 本文所用的术语“芳基亚磺酰基”表示式 $-S(=O)R^i$的基团，其中 R^i是如上述所定义的芳基。

[0947] 本文所用的术语“氨基甲酸酯”表示式 $-N(H)C(O)OR^j$的基团，其中 R^j是如上述所定义的烷基或芳基。氨基甲酸酯基团通常是（丙氧羰基）氨基或（苄氧羰基）氨基。优选的氨基甲酸酯基团是（苄氧羰基）氨基。

[0948] 本文所用的术语“烷酰氨基”表示式 $-NHC(=O)R^k$的基团，其中 R^k是如上述所定义的烷基。

[0949] 本文所用的术语“（芳基羰基）氨基”表示式 $-NHC(=O)R^m$的基团，其中 R^m是如上述所定义的芳基。优选的（芳基羰基）氨基是苯甲酰基氨基。

[0950] R^1通常是氢；未取代的或被卤素、羟基、氰基、甲硫基、苯基或 4- 氯苯氧基取代的 $C_{1\ 10}$烷基；羟基；$C_{3\ 6}$环烷基；卤素；酯；酰氨基；硝基；氰基；氨基；苯基；烷硫基；烷基磺酰基；烷基亚磺酰基；未取代的或被烷基取代的杂环；或胍。优选 R^1是氢；甲基；乙基；异 - 丙基；正 - 丙基；环丙基；正 - 丁基；异 - 丁基；叔 - 丁基；1- 乙基丙基；2,4,4- 三甲基戊基；羟基甲基；氯甲基；三氟甲基；2,2,2- 三氟乙基；氰基甲基；2-（甲硫基）乙基；氯；溴；硝基；氰基；氨基；氨基羰基；甲氧基羰基；甲硫基；甲基亚磺酰基；甲基磺酰基；苯基；2- 呋喃基；3- 呋喃基；1H- 吡咯 -2- 基；1- 甲基 -1H- 吡咯 -2- 基；2- 噻吩基；1H- 吡唑 -3- 基；1,2,3- 噻二唑 -4- 基或 1H- 咪唑 -2- 基。更优选 R^1是氢；甲基；乙基；异 - 丙基；正 - 丙基；正 - 丁基；甲硫基；硝基；氰基；氨基；氯或 1H- 吡咯 -2- 基。最优选 R^1是氢；甲基；甲硫基；硝基；氰基；氨基或氯。

[0951] R^2通常是氢；未取代的或被羟基、烷酰氨基或苯甲酰基氨基取代的 $C_{1\ 4}$烷基；卤素；酯；氰基；烷基氨基甲酸酯；[(N- 甲氧基 -N- 甲基）氨基]羰基。优选 R^2是氢；甲基；羟基甲基；（乙酰基氨基）甲基；（丙酰基氨基）甲基；（苯甲酰基氨基）甲基；[（苄基氧基）羰基]氨基；氯或氰基。更优选 R^2是氢；氯或氰基。

[0952] R^3通常是氢；未取代的或被羟基取代的 $C_{1\ 4}$烷基；卤素；酯或氰基。优选 R^3是氢；羟基甲基；氯；氰基。更优选 R^3是氢或氰基。最优选的 R^3是氢。

[0953] R^4通常是氢；未取代的或被卤素取代的 $C_{1\ 4}$烷基；未取代的或被卤素取代的 $C_{2\ 4}$

烯基或未取代的或被叠氮基或 / 和卤素取代的苯基。优选 R^4是氢 ;正 - 丙基 ;2, 2- 二氟乙烯基 ;苯基 ;3- 氯苯基 ;3- 氟苯基 ;4- 氯苯基 ;4- 氟苯基 ;3, 5- 二氟苯基 ;3, 4- 二氟苯基 ;3- 氯 -4- 氟苯基 ;2, 3, 4- 三氟苯基 ;2, 4, 5- 三氟苯基 ;2, 3, 5- 三氟苯基 ;3, 4, 5- 三氟苯基 ;3- 叠氮基 -2, 4- 二氟苯基或 3- 叠氮基 -2, 4, 6- 三氟苯基。更优选 R^4是氢 ;正 - 丙基 ;2, 2- 二氟乙烯基 ;苯基 ;3- 氯苯基 ;3- 氟苯基 ;4- 氯苯基 ;4- 氟苯基 ;3, 5- 二氟苯基 ;3, 4- 二氟苯基 ;3- 氯 -4- 氟苯基 ;2, 3, 4- 三氟苯基 ;2, 4, 5- 三氟苯基 ;2, 3, 5- 三氟苯基 ;3, 4, 5- 三氟苯基或 3- 叠氮基 -2, 4- 二氟苯基。最优选 R^4是正 - 丙基 ;2, 2- 二氟乙烯基 ;苯基 ;3- 氯苯基 ;3- 氟苯基 ;3, 5- 二氟苯基 ;2, 3, 4- 三氟苯基 ;2, 4, 5- 三氟苯基 ;2, 3, 5- 三氟苯基 ;3, 4, 5- 三氟苯基或 3- 叠氮基 -2, 4- 二氟苯基。

[0954] R^{4a}通常是氢。

[0955] R^5通常是氢。

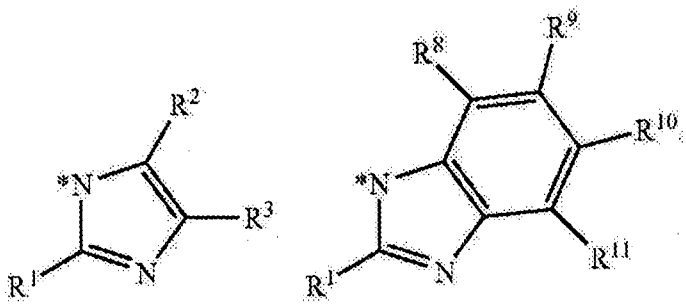
[0956] R^6通常是氢或未取代的或被羟基或叠氮基取代的 $C_{1\ 10}$烷基。优选 R^6是氢或叠氮基甲基。更优选 R^6是氢。

[0957] R^7通常是氢。

[0958] 在其它优选的实施方案中，R^6和 R^7连接形成环丙基。

[0959] 在其它优选的实施方案中，R^2和 R^3可以与咪唑环一起形成如下的 1H- 苯并咪唑环 :

[0960]



[0961] R^8通常是氢。

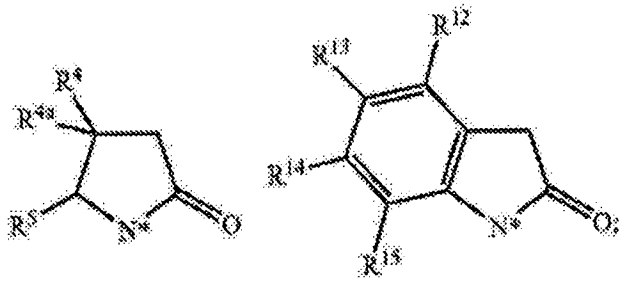
[0962] R^9通常是氢 ;卤素 ;$C_{1\ 3}$烷基或烷氧基。优选 R^9是氢 ;甲基 ;氯或甲氧基。更优选的 R^9是氢。

[0963] R^{10}通常是氢 ;卤素 ;氰基 ;未取代的或被卤素取代的 $C_{1\ 3}$烷基 ;或烷氧基。优选 R^{10}是甲基 ;氢 ;三氟甲基 ;氟 ;氰基或甲氧基。更优选的 R^{10}是氢 ;三氟甲基 ;氟或氰基。

[0964] R^{11}通常是氢。

[0965] 在其它优选的实施方案中，R^4、R^{4a}和 R^5可以与 2- 氧代 -1- 吡咯烷环一起形成如下的 1, 3- 二氢 -2H- 吲哚 -2- 酮环 :

[0966]



[0967] R^{12}通常是氢或卤素。优选 R^{12}是氢；氯或氟。更优选的 R^{12}是氢。

[0968] R^{13}通常是氢；C_{1-3}烷基；卤素或未取代的或被烷基取代的噻唑基，例如甲基噻唑基。优选 R^{13}是氢；氯；溴或甲基。最优选的 R^{13}是氯；溴或甲基。

[0969] R^{14}通常是氢。

[0970] R^{15}通常是氢。

[0971] 尤其优选这些优选化合物基团的一个或多个的组合。

[0972] 一般而言，在所述的实施方案中，式 I 的化合物或其药学可接受的盐是这样的化合物，其中：

[0973] R^{1}选自氢；未取代的或被卤素、羟基、氰基、甲硫基、苯基或 4- 氯苯氧基取代的 C_{1-10}烷基；C_{3-6}环烷基；卤素；酯；酰氨基；硝基；氰基；氨基；苯基；烷硫基；烷基磺酰基；烷基亚磺酰基；未取代的或被烷基取代的杂环；或胍；

[0974] R^{2}选自氢；未取代的或被羟基、烷酰氨基或苯甲酰基氨基取代的 C_{1-4}烷基；卤素；酯；氰基；烷基氨基甲酸酯或［(N- 甲氧基 -N- 甲基）氨基］羰基。

[0975] R^{3}选自氢；未取代的或被羟基取代的 C_{1-4}烷基；卤素；酯或氰基；

[0976] R^{4}选自氢；取未代的或被卤素取代的 C_{1-4}烷基；被卤素取代的 C_{2-4}烯基或未取代的或被叠氮基或 / 和卤素取代的苯基；

[0977] R^{4a}是氢；

[0978] R^{5}是氢；

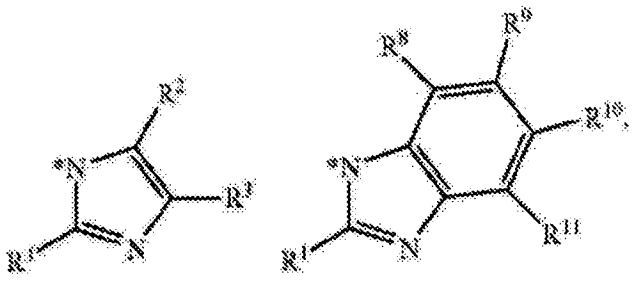
[0979] R^{6}选自氢或未取代的或被羟基或叠氮基取代的 C_{1-10}烷基；

[0980] R^{7}是氢；

[0981] 或 R^{6}和 R^{7}可以连接在一起形成环丙基；

[0982] 或 R^{2}和 R^{3}可以与咪唑环一起形成如下的 1H- 苯并咪唑环：

[0983]



[0984] R^{8}是氢；

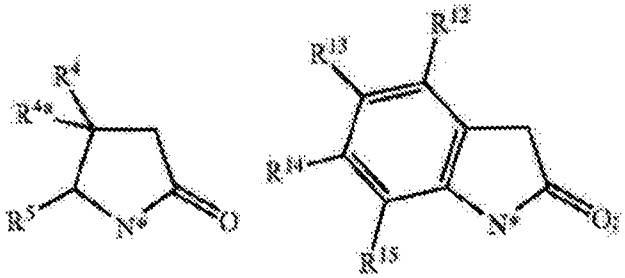
[0985] R^{9}选自氢；卤素；C_{1-3}烷基；烷氧基；

[0986] R^{10}选自氢；卤素；氰基或未取代的或被卤素取代的 C_{1-3}烷基；或烷氧基；

[0987] R^{11}是氢；

[0988] 或 R^4、R^{4a}和 R^5可以与 2- 氧代 -1- 吡咯烷环一起形成如下的 1,3- 二氢 -2H- 吲哚 -2- 酮环：

[0989]



[0990] R^{12}选自氢或卤素；

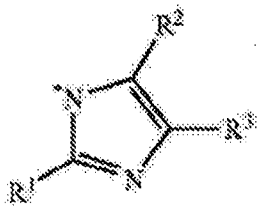
[0991] R^{13}选自氢；C_{1-3}烷基；卤素；未取代的或被烷基取代的噻唑基，例如甲基噻唑基；

[0992] R^{14}是氢；

[0993] R^{15}是氢；

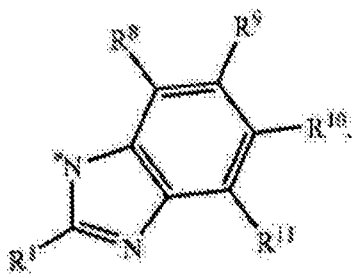
[0994] 条件是当

[0995]



[0996] 表示下式的基团时，R^4不是氢：

[0997]



[0998] 在一个优选的实施方案中，式 I 的化合物或其药学可接受的盐是这样的化合物，其中：

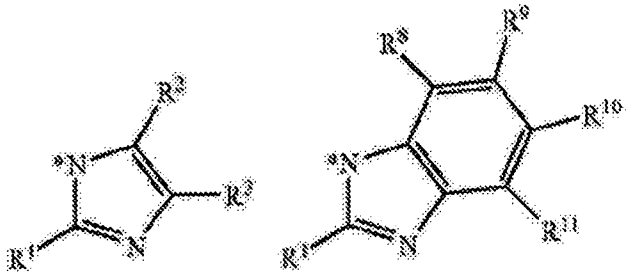
[0999] R^1选自氢；甲基；乙基；异 - 丙基；正 - 丙基；环丙基；正 - 丁基；异 - 丁基；叔 - 丁基；1- 乙基丙基；2,4,4- 三甲基戊基；三氟甲基；2,2,2- 三氟乙基；羟基甲基；氯甲基；氰基甲基；2-（甲硫基）乙基；氯；溴；硝基；氰基；氨基；氨基羰基；甲氧基羰基；甲硫基；甲基亚磺酰基；甲基磺酰基；苯基；2- 呋喃基；3- 呋喃基；1H- 吡咯 -2- 基；1- 甲基 -1H- 吡咯 -2- 基；2- 噻吩基；1H- 吡唑 -3- 基；1,2,3- 噻二唑 -4- 基；或 1H- 咪唑 -2- 基；

[1000] R^2选自氢；甲基；羟基甲基；（乙酰基氨基）甲基；（丙酰基氨基）甲基；（苯甲酰基氨基）甲基；（苄基氧基羰基）氨基；氯；或氰基；

[1001] R^3选自氢；羟基甲基；氯；氰基；

[1002] 或 R^2和 R^3可以与咪唑环一起形成如下的 1H- 苯并咪唑环：

[1003]



[1004] R^8是氢；

[1005] R^9选自氢；甲基；氯；甲氧基；

[1006] R^{10}选自甲基；氢；三氟甲基；氟；氰基；或甲氧基；

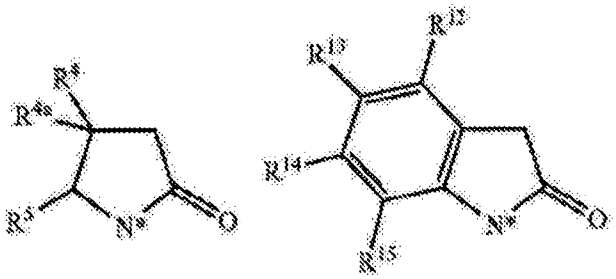
[1007] R^{11}是氢；

[1008] R^4选自氢；正-丙基；2,2-二氟乙烯基；苯基；3-氯苯基；3-氟苯基；4-氯苯基；4-氟苯基；3,5-二氟苯基；3,4-二氟苯基；3-氯-4-氟苯基；2,3,4-三氟苯基；2,4,5-三氟苯基；2,3,5-三氟苯基；3,4,5-三氟苯基；3-叠氮基-2,4-二氟苯基；或3-叠氮基-2,4,6-三氟苯基。

[1009] R^{4a}是氢；R^5是氢；

[1010] 或R^4、R^{4a}和R^5可以与2-氧代-1-吡咯烷环一起形成如下的1,3-二氢-2H-吲哚-2-酮环：

[1011]



[1012] R^{12}选自氢；氯；氟；

[1013] R^{13}选自氢；氯；溴；甲基；

[1014] R^{14}是氢；

[1015] R^{15}是氢；

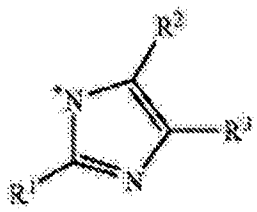
[1016] R^6选自氢；叠氮基甲基；

[1017] R^7是氢；

[1018] 或R^6和R^7可以连接在一起形成环丙基；

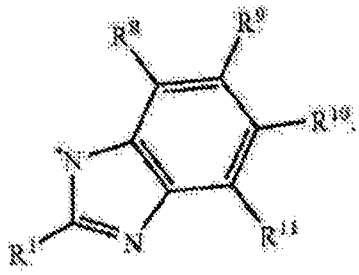
[1019] 条件是当

[1020]



[1021] 表示下式的基团时，R^4不是氢：

[1022]



[1023] 在一个更优选的实施方案中，式 I 的化合物或其药学可接受的盐是这样的化合物，其中

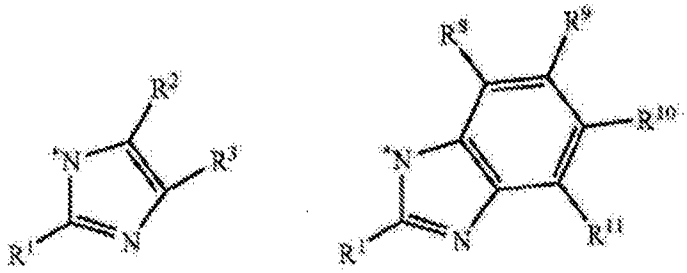
[1024] R^1选自氢；甲基；乙基；异 - 丙基；正 - 丙基；正 - 丁基；甲硫基；硝基；氰基；氨基；氯；或 1H- 吡咯 -2- 基；

[1025] R^2选自氢；氯；氰基；

[1026] R^3选自氢；氰基；

[1027] 或 R^2和 R^3可以与咪唑环一起形成如下的 1H- 苯并咪唑环：

[1028]



[1029] R^8是氢；

[1030] R^9是氢；

[1031] R^{10}选自氢；三氟甲基；氟；氰基；

[1032] R^{11}是氢；

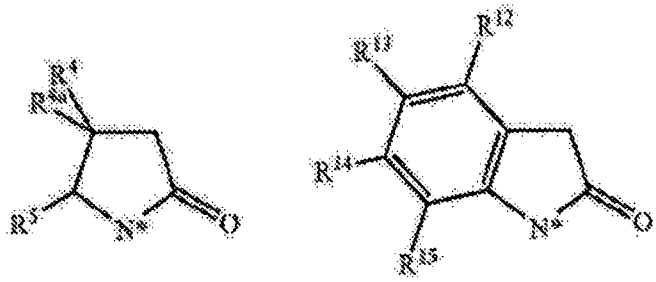
[1033] R^4选自氢；正 - 丙基；2, 2- 二氟乙烯基；苯基；3- 氯苯基；3- 氟苯基；4- 氯苯基；4- 氟苯基；3, 5- 二氟苯基；3, 4- 二氟苯基；3- 氯 -4- 氟苯基；2, 3, 4- 三氟苯基；2, 4, 5- 三氟苯基；2, 3, 5- 三氟苯基；3, 4, 5- 三氟苯基；或 3- 叠氮基 -2, 4- 二氟苯基；

[1034] R^{4a}是氢；

[1035] R^5是氢；

[1036] 或 R^4、R^{4a}和 R^5可以与 2- 氧代 -1- 吡咯烷环一起形成如下的 1, 3- 二氢 -2H- 吲哚 -2- 酮环：

[1037]



[1038] 其中

[1039] R^{12}是氢；

[1040] R^{13}选自甲基；氯；溴；

[1041] R^{14}是氢；

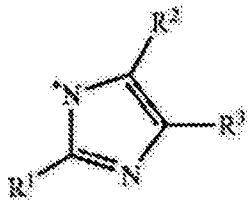
[1042] R^{15}是氢；

[1043] R^{6}是氢；

[1044] R^{7}是氢；

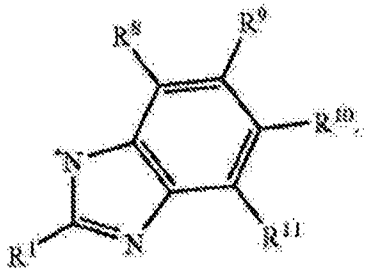
[1045] 条件是当

[1046]



[1047] 表示下式的基团时，R^{4}不是氢：

[1048]



[1049] 在一个最优选的实施方案中，式 I 的化合物或其药学可接受的盐是这样的化合物，其中：

[1050] R^{1}选自氢；甲基；甲硫基；硝基；氰基；氨基；氯；

[1051] R^{2}选自氢；氯；氰基；

[1052] R^{3}是氢；

[1053] R^{4}选自正-丙基；2,2-二氟乙烯基；苯基；3-氯苯基；3-氟苯基；3,5-二氟苯基；2,3,4-三氟苯基；2,4,5-三氟苯基；2,3,5-三氟苯基；3,4,5-三氟苯基；3-叠氮基-2,4-二氟苯基；

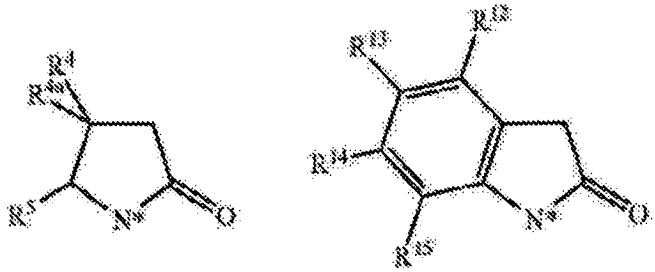
[1054] R^{4a}是氢；

[1055] R^{5}是氢；

[1056] 或 R^{4}、R^{4a}和 R^{5}可以与 2-氧代-1-吡咯烷环一起形成如下的 1,3-二氢-2H-吲

唑 -2- 酮环：

[1057]



[1058] R^{12}是氢；

[1059] R^{13}选自氯；溴；甲基；

[1060] R^{14}是氢；

[1061] R^{15}是氢；

[1062] R^{6}是氢；

[1063] R^{7}是氢。

[1064] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[1065] 1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1066] 1-(1H- 咪唑 -1- 基甲基）-4- 苯基吡咯烷 -2- 酮；

[1067] 4-(3- 叠氮基 -2,4,6- 三氟苯基）-1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1068] 1-(1H- 咪唑 -1- 基甲基）-4- 丙基吡咯烷 -2- 酮；

[1069] (-)-4-(3- 叠氮基 -2,4- 二氟苯基）-1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1070] (+)-4-(3- 叠氮基 -2,4- 二氟苯基）-1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1071] 1-[(2- 乙基 -1H- 咪唑 -1- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1072] 1-[(2- 异丙基 -1H- 咪唑 -1- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1073] 1-[(2- 甲基 -1H- 咪唑 -1- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1074] 1-[(2- 苯基 -1H- 咪唑 -1- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1075] 4- 丙基 -1-[(2- 丙基 -1H- 咪唑 -1- 基）甲基]吡咯烷 -2- 酮；

[1076] (+)-1-(1H- 咪唑 -1- 基甲基）-4- 丙基吡咯烷 -2- 酮；

[1077] (-)-1-(1H- 咪唑 -1- 基甲基）-4- 丙基吡咯烷 -2- 酮；

[1078] 4-(2,2- 二氟乙烯基）-1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1079] 4-(3- 氯苯基）-1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1080] 1-{[2-(甲硫基）-1H- 咪唑 -1- 基]甲基}-4- 丙基吡咯烷 -2- 酮；

[1081] 1-{[2-(甲基亚磺酰基）-1H- 咪唑 -1- 基]甲基}-4- 丙基吡咯烷 -2- 酮；

[1082] 1-[(2- 叔 - 丁基 -1H- 咪唑 -1- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1083] 1-[1-(1H- 咪唑 -1- 基）环丙基]吡咯烷 -2- 酮；

[1084] 1-[(2- 甲基 -1H- 咪唑 -1- 基）甲基]-4- 苯基吡咯烷 -2- 酮；

[1085] 1-{[2-(甲基磺酰基）-1H- 咪唑 -1- 基]甲基}- 丙基吡咯烷 -2- 酮；

[1086] 1-[(2- 氧代 -4- 丙基吡咯烷 -1- 基）甲基]-1H- 咪唑 -2- 甲酰胺；

[1087] 4-(4- 氟苯基）-1-(1H- 咪唑 -1- 基甲基）吡咯烷 -2- 酮；

[1088] 1-(1H- 咪唑 -1- 基甲基）-4-(3,4,5- 三氟苯基）吡咯烷 -2- 酮；

[1089] 4-(3-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1090] 4-(3,5-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1091] 4-(3,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1092] 4-(3-氯-4-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1093] 4-(4-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1094] 1-(1H-咪唑-1-基甲基)-4-(2,3,4-三氟苯基)吡咯烷-2-酮；

[1095] 1-(1H-咪唑-1-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1096] 1-(1H-咪唑-1-基甲基)-4-(2,4,5-三氟苯基)吡咯烷-2-酮；

[1097] 1-{[2-(羟基甲基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1098] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-2-甲酸甲酯；1-[(2-硝基-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1099] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-2-腈；

[1100] 1-[(2-氨基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1101] 1-[(2,4-二氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1102] 1-[(5-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1103] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1104] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1105] (+)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1106] (-)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1107] 1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1108] (-)-1-{[2-氧代-4-(2,3,4-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1109] (+)-1-{[2-氧代-4-(2,3,4-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1110] (-)-1-{[2-氧代-4-(2,3,4-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1111] (+)-1-{[2-氧代-4-(2,3,4-三氟苯基)-1-吡咯烷基]甲基}-1H-咪唑-4-腈；

[1112] (-)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1113] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1114] (+)-1-{[2-氧代-4-(2,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1115] (-)-1-{[2-氧代-4-(2,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1116] (-)-1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1117] (-)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1118] 1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1119] 1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1120] 1-[(5-甲基-2-苯基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；1-[(5-甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1121] 1-[(5-苯基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1122] 1-[(2-乙基-5-甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1123] 1-[(2,5-二甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1124] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1125] 1-[2-叠氮基-1-(1H-咪唑-1-基)乙基]-4-丙基吡咯烷-2-酮；

[1126] 1-[(4-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1127] 1-[(2-溴-4,5-二氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1128] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1129] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1130] 1-{[5-(羟基甲基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1131] 1-{[4-(羟基甲基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1132] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-5-基氨基甲酸苄酯；

[1133] N-[(1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-基)甲基]乙酰胺；

[1134] N-[(1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-基)甲基]苯甲酰胺；

[1135] N-[(1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-基)甲基]丙酰胺；

[1136] 1-(1H-苯并咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[1137] 1-[(2-甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1138] 4-丙基-1-[(2-丙基-1H-苯并咪唑-1-基)甲基]吡咯烷-2-酮；

[1139] 1-[(2-异丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1140] 4-丙基-1-{[2-(三氟甲基)-1H-苯并咪唑-1-基]甲基}吡咯烷-2-酮；

[1141] 1-{[2-(甲硫基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1142] 1-[(2-氨基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1143] 1-{[2-(氯甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1144] {1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-2-基}乙腈；

[1145] 1-[(5-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮-；

[1146] 1-[(5-甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1147] 1-[(5,6-二甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1148] 1-{[2-异丙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基-吡咯烷-2-酮；

[1149] 1-[(6-氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1150] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-丙基-1H-苯并咪唑-5-腈；

[1151] 1-{[2-乙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1152] 4-丙基-1-{[2-(1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}吡咯烷-2-酮；

[1153] 1-[(5-氟-2-丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1154] 1-{[6-甲基-2-(1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1155] 1-[(6-甲氧基-2-丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1156] 2-丁基-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[1157] 1-{[2-[2-(甲硫基)乙基]-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1158] 1-[(5-氟-2-异丁基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1159] 1-{[5-氟-2-(2,4,4-三甲基戊基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1160] 2-环丙基-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[1161] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-(1H-吡唑-3-基)-1H-苯并咪唑-5-腈；

[1162] 1-[(2-环丙基-5-氟-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1163] 1-[(5-氟-2-异丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1164] 1-{[2-(3-呋喃基)-6-甲氧基-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1165] 1-[(2-环丙基-6-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1166] 1-[(2-异丙基-6-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1167] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-(1,2,3-噻二唑-4-基-)-1H-苯并咪唑-5-腈；

[1168] 1-{[2-(1H-咪唑-2-基)-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1169] 1-{[5-氟-2-(2,2,2-三氟乙基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1170] 1-{[2-(1-乙基丙基)-6-甲氧基-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1171] 1-{[6-甲氧基-2-(1-甲基-1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1172] 1-{[2-(2-呋喃基)-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基-吡咯烷-2-酮；

[1173] 4-丙基-1-{[2-噻吩-2-基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基-}吡咯烷-2-酮；

[1174] 1-{[2-(3-呋喃基)-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基-吡咯烷-2-酮；

[1175] 1-{[2-环丙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1176] 4-丙基-1-{[2-(1H-吡咯-2-基)-5-(三氟甲基)-1H-苯并咪唑-1-基]-甲基}吡咯烷-2-酮；

[1177] 1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1178] 5-溴-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1179] 5-氯-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1180] 4-氟-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1181] 4-氯-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1182] 1-(1H-咪唑-1-基甲基)-5-甲基-1,3-二氢-2H-吲哚-2-酮；

[1183] 1-[(2-氧代-2,3-二氢-1H-吲哚-1-基)甲基]-1H-咪唑-5-腈；和

[1184] 1-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)甲基]-1H-咪唑-5-腈。

[1185] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[1186] 1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1187] 1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1188] 1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[1189] (-)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1190] (+)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1191] 1-[(2-乙基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1192] 1-[(2-异丙基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1193] 1-[(2-甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1194] 4-丙基-1-[(2-丙基-1H-咪唑-1-基)甲基]吡咯烷-2-酮；

[1195] (+)-1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[1196] (-)-1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[1197] 4-(2,2-二氟乙烯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1198] 4-(3-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1199] 1-{[2-(甲硫基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1200] 1-[(2-甲基-1H-咪唑-1-基)甲基]-4-苯基吡咯烷-2-酮；

[1201] 4-(4-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1202] 1-(1H-咪唑-1-基甲基)-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1203] 4-(3-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1204] 4-(3,5-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1205] 4-(3,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1206] 4-(3-氯-4-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1207] 4-(4-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1208] 1-(1H-咪唑-1-基甲基)-4-(2,3,4-三氟苯基)吡咯烷-2-酮；

[1209] 1-(11H-咪唑-1-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1210] 1-(1H-咪唑-1-基甲基)-4-(2,4,5-三氟苯基)吡咯烷-2-酮；

[1211] 1-[(2-硝基-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1212] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-2-腈；

[1213] 1-[(2-氨基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1214] 1-[(5-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1215] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1216] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1217] (+)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1218] (-)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1219] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1220] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1221] 1-[2-叠氮基-1-(1H-咪唑-1-基)乙基]-4-丙基吡咯烷-2-酮；

[1222] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1223] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1224] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-丙基-1H-苯并咪唑-5-腈；

[1225] 1-{[2-乙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1226] 4-丙基-1-{[2-(1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}吡咯烷-2-酮；

[1227] 1-[(5-氟-2-丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1228] 2-丁基-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[1229] 1-[(5-氟-2-异丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1230] 1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1231] 5-溴-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1232] 5-氯-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1233] 1-(1H-咪唑-1-基甲基)-5-甲基-1,3-二氢-2H-吲哚-2-酮；

[1234] 1-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)甲基]-1H-咪唑-5-腈。

[1235] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[1236] 1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1237] 1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[1238] (-)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1239] (+)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1240] 4-(2,2-二氟乙烯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1241] 4-(3-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1242] 1-{[2-(甲硫基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[1243] 1-[(2-甲基-1H-咪唑-1-基)甲基]-4-苯基吡咯烷-2-酮；

[1244] 1-(1H-咪唑-1-基甲基)-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1245] 4-(3-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1246] 4-(3,5-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1247] 1-(1H-咪唑-1-基甲基)-4-(2,3,4-三氟苯基)吡咯烷-2-酮；

[1248] 1-(1H-咪唑-1-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1249] 1-(1H-咪唑-1-基甲基)-4-(2,4,5-三氟苯基)吡咯烷-2-酮；

[1250] 1-[(2-硝基-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1251] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-2-腈；

[1252] 1-[(2-氨基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1253] 1-[(5-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1254] (+)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1255] (-)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[1256] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[1257] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[1258] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[1259] 5-溴-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1260] 5-氯-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1261] 1-(1H-咪唑-1-基甲基)-5-甲基-1,3-二氢-2H-吲哚-2-酮；

[1262] 1-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)甲基]-1H-咪唑-5-腈。

[1263] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[1264] (-)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

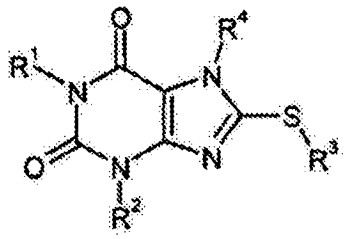
[1265] (+)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[1266] 4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮。

[1267] v) 国际专利申请 WO2007/065595：

[1268] 具有式 I 的化合物、其对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体混合物）或其药学可接受的盐，

[1269]



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[1270] 其中

[1271] R^1是氢或 C_{1-6}烷基；

[1272] R^2是氢或 C_{1-4}烷基；

[1273] R^3是式 $-CHR^5R^6$的基团或苄基基团；

[1274] R^4是 C_{1-8}烷基，其任选地被烷氧羰基、C3-6 环烷基、芳基或杂环取代；

[1275] R^5是 C2-4 烷基；

[1276] R^6是 C2-4 烷基、酰氨基或 $-COOR^7$；

[1277] R^7是 C1-4 烷基；

[1278] 通常当 R^3是苄基基团时，R^4是任选地被烷氧羰基取代的 C_{1-8}烷基。

[1279] 通常当 R^3是式 $-CHR^5R^6$的基团时，R^4是任选地被 C_{3-6}环烷基、芳基或杂环取代的 C_{1-8}烷基。

[1280] 本文所用的术语“烷基”是表示饱和一价烃基的基团，其具有直链（无支链）或支链部分或其组合并且包含 1-8 个碳原子、优选 1-6 个碳原子；更优选具有 1-4 个碳原子的烷基。烷基部分可以任选地被 1-5 个取代基取代，所述的取代基独立地选自羟基、烷氧基、氰基、乙炔基、烷氧羰基、酰基、芳基或杂环。烷基部分可以任选地被如下文所定义的环烷基取代。优选的烷基是甲基、氰基甲基、乙基、2-乙氧基-2-氧代乙基、2-甲氧基乙基、正-丙基、2-氧代丙基、3-羟基丙基、2-丙炔基、正-丁基、异-丁基、正-戊基、3-戊基、正-己基、环己基甲基、苄基、2-溴苄基、3-溴苄基、4-溴苄基、3-甲氧基苄基、3-硝基苄基、3-氨基苄基、4-(氨基磺酰基)苄基、1-苯基乙基、2-苯基乙基、(3,5-二甲基异噁唑-4-基)甲基或(5-硝基-2-呋喃基)甲基。更优选的烷基是甲基、乙基、氰基甲基、2-甲氧基乙基、正-丙基、3-羟基丙基、2-丙炔基、正-丁基、3-戊基、正-己基、苄基、3-溴苄基、3-甲氧基苄基、3-硝基苄基、3-氨基苄基、(3,5-二甲基异噁唑-4-基)甲基或(5-硝基-2-呋喃基)甲基。最优选的烷基是甲基、乙基、3-甲氧基苄基、3-硝基苄基或(5-硝基-2-呋喃基)甲基。

[1281] 本文所用的术语“环烷基”表示 3-8 个、优选 3-6 个碳原子的一价基团，其衍生自饱和环烃，可以被任意适合的基团取代，所述基团包括、但不限于一个或多个部分，其选自如上述对烷基所述的基团。优选的环烷基是环己基。

[1282] 本文所用的术语“芳基”定义为任选地被 1-4 个取代基取代的苯基，所述的取代基独立地选自卤素、氨基、硝基、烷氧基或氨基磺酰基。优选的芳基是苯基、2- 溴苯基、3- 溴苯基、4- 溴苯基、3- 甲氧基苯基、3- 硝基苯基、3- 氨基苯基或 4-（氨基磺酰基）苯基。

[1283] 本文所用的术语“苯基”表示式 $-C_6H_5$ 的芳香烃基。

[1284] 本文所用的术语“苄基基团”表示式 $-CH_2-$ 芳基的基团。优选的苄基基团是苄基、2- 溴苄基、3- 溴苄基、4- 溴苄基、3- 甲氧基苄基、3- 硝基苄基、3- 氨基苄基或 4-（氨基磺酰基）苄基。更优选的苄基基团是苄基、3- 溴苄基、3- 甲氧基苄基、3- 硝基苄基或 3- 氨基苄基。最优选的烷基基团是 3- 甲氧基苄基或 3- 硝基苄基。

[1285] 本文所用的术语“卤素”表示氟、氯、溴或碘的原子。优选的卤素是溴。

[1286] 本文所用的术语“羟基”表示式 -OH 的基团。

[1287] 本文所用的术语“氰基”表示式 -CN 的基团。

[1288] 本文所用的术语“氨基”表示式 $-NH_2$ 的基团。

[1289] 本文所用的术语“乙炔基”表示式 $-C\equiv CH$ 的基团。

[1290] 本文所用的术语“烷氧基”表示式 $-OR^a$ 的基团，其中 R^a 是如上述所定义的烷基。优选的烷氧基是甲氧基。

[1291] 本文所用的术语“硝基”表示式 $-NO_2$ 的基团。

[1292] 本文所用的术语“酰氨基”表示式 -C(=O)NH2 的基团。

[1293] 本文所用的术语“酰基”表示式 $-C(=O)R^b$ 的基团，其中 R^b 是如上述所定义的烷基。优选的酰基是乙酰基 (-C(=O)Me)。

[1294] 本文所用的术语“烷氧羰基（或酯）”表示式 $-COOR^c$ 的基团，其中 R^c 是烷基；条件是 R^c 不表示被羟基 α- 取代的烷基。优选的烷氧羰基是乙氧羰基。

[1295] 本文所用的术语“杂环”表示包含一个或两个选自 O 或 N 的杂原子的 5- 元环。该杂环可以被一个或两个 C_{1-4} 烷基或硝基取代。优选的杂环是 (3,5- 二甲基异噁唑 -4- 基）或 (5- 硝基 -2- 呋喃基）。最优选的杂环是 (5- 硝基 -2- 呋喃基）。

[1296] 一般而言，R^1 是氢或 C_{1-6} 烷基。R^1 通常是氢或任选地被羟基、烷氧基、氰基、乙炔基、烷氧羰基或酰基取代的 C_{1-6} 烷基。优选 R^1 是氢、甲基、氰基甲基、2- 乙氧基 -2- 氧代乙基、2- 甲氧基乙基、正 - 丙基、2- 氧代丙基、3- 羟基丙基、2- 丙炔基、正 - 戊基或正 - 己基。更优选 R^1 是氢、甲基、氰基甲基、2- 甲氧基乙基、正 - 丙基、3- 羟基丙基或 2- 丙炔基。最优选 R^1 是氢。

[1297] 一般而言，R^2 是氢或 C_{1-4} 烷基。R^2 通常是氢或未取代的 C_{1-4} 烷基。优选 R^2 是氢、甲基或正 - 丁基。更优选 R^2 是甲基。

[1298] 一般而言，R^3 是式 $-CHR^5R^6$ 的基团或苄基基团。优选 R^3 是 3- 戊基、1-（氨基羰基）丙基、1-（乙氧羰基）丙基或 3- 溴苄基。最优选 R^3 是 1-（乙氧羰基）丙基。

[1299] 一般而言，R^4 是任选地被烷氧羰基、C_{3-6} 环烷基、芳基或杂环取代的 C_{1-8} 烷基。R^4 通常是任选地被环己基、苯基、溴苯基、氨基苯基、甲氧基苯基、硝基苯基、氨基磺酰基苯基、3,5- 二甲基异噁唑 -4- 基、5- 硝基 -2- 呋喃基或乙氧羰基取代的 C_{1-8} 烷基。优选 R^4 是正 - 丁基、异 - 丁基、正 - 戊基、正 - 己基、环己基甲基、苄基、2- 溴苄基、3- 溴苄基、4- 溴苄基、3- 甲氧基苄基、3- 硝基苄基、3- 氨基苄基、4-（氨基磺酰基）苄基、1- 苯基乙基、2- 苯基乙基、(3,5- 二甲基异噁唑 -4- 基）甲基、(5- 硝基 -2- 呋喃基）甲基或 1-（乙氧羰基）丙

基。更优选 R^4是正－丁基、正－己基、苄基、3-溴苄基、3-甲氧基苄基、3-硝基苄基、3-氨基苄基、(3,5-二甲基异噁唑-4-基）甲基、(5-硝基-2-呋喃基）甲基或1-(乙氧羰基）丙基。最优选 R^4是3-甲氧基苄基、3-硝基苄基或(5-硝基-2-呋喃基）甲基。

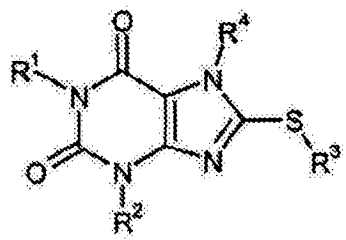
[1300] 一般而言，R^5是 C_{2-4}烷基。R^5通常是未取代的 C_{2-4}烷基。优选 R^5是乙基。

[1301] 一般而言，R^6是 C_{2-4}烷基、酰氨基或 $-COOR^7$。R^6通常是未取代的 C_{2-4}烷基、酰氨基或 $-COOR^7$。优选 R^6是乙基、酰氨基或乙氧羰基。最优选 R^6是乙氧羰基。

[1302] 一般而言，R^7是 C_{1-4}烷基。R^7通常是未取代的 C_{1-4}烷基。优选 R^7是乙基。

[1303] 在一些实施方案中，化合物是具有式I的那些化合物及其对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体混合物）或其药学可接受的盐，

[1304]



(I)

[1305] 其中

[1306] R^1是氢、任选地被羟基、烷氧基、氰基、乙炔基、烷氧羰基或酰基取代的 C_{1-6}烷基；

[1307] R^2是氢或未取代的 C_{1-4}烷基；

[1308] R^3是式 $-CHR^5R^6$的基团或苄基基团；

[1309] R^4是任选地被环己基、苯基、溴苯基、氨基苯基、甲氧基苯基、硝基苯基、氨基磺酰基苯基、3,5-二甲基异噁唑-4-基、5-硝基-2-呋喃基或乙氧羰基取代的 C_{1-8}烷基；

[1310] R^5是未取代的 C_{2-4}烷基；

[1311] R^6是未取代的 C_{2-4}烷基、酰氨基或 $-COOR^7$；

[1312] R^7是未取代的 C_{1-4}烷基；

[1313] 条件是当 R^1是氢、R^2是甲基、R^3是 $-CHR^5R^6$，R^6是乙氧羰基、R^5是乙基时，R^4不是正－丙基、异－丙基、正－戊基、正－庚基、3-溴苄基、4-氯苄基、4-甲基苄基或2-苯基乙基。

[1314] 在上述实施方案中，优选当 R^3是苄基基团时，R^4是任选地被烷氧羰基取代的 C_{1-8}烷基。

[1315] 在上述实施方案中，优选当 R^3是式 $-CHR^5R^6$的基团时，R^4是任选地被 C_{3-6}环烷基、芳基或杂环取代的 C_{1-8}烷基。

[1316] 在一个优选的实施方案中，

[1317] R^1是氢、甲基、氰基甲基、2-乙氧基-2-氧代乙基、2-甲氧基乙基、正－丙基、2-氧代丙基、3-羟基丙基、2-丙炔基、正－戊基或正－己基；

[1318] R^2是氢、甲基或正－丁基；

[1319] R^3是3-戊基、1-(氨基羰基）丙基、1-(乙氧羰基）丙基或3-溴苄基；

[1320] R^4是正－丁基、异－丁基、正－戊基、正－己基、环己基甲基、苄基、2-溴苄基、3-溴苄基、4-溴苄基、3-甲氧基苄基、3-硝基苄基、3-氨基苄基、4-(氨基磺酰基）苄基、1-苯基乙基、2-苯基乙基、(3,5-二甲基异噁唑-4-基）甲基、(5-硝基-2-呋喃基）甲基或1-(乙

氧羰基）丙基；

[1321] 条件是当R^1是氢、R^2是甲基、R^3是1-（乙氧羰基）丙基时，R^4不是正-戊基、3-溴苄基或2-苯基乙基。

[1322] 在上述实施方案中，优选当R^3是3-溴苄基时，R^4是任选地被烷氧羰基取代的C_{1-8}烷基。

[1323] 在上述实施方案中，优选当R^3是3-戊基、1-（氨基羰基）丙基或1-（乙氧羰基）丙基时，R^4不是1-（乙氧羰基）丙基。

[1324] 在一个更优选的实施方案中，

[1325] R^1是氢、甲基、氰基甲基、2-甲氧基乙基、正-丙基、3-羟基丙基或2-丙炔基；

[1326] R^2是甲基；

[1327] R^3是3-戊基、1-（氨基羰基）丙基、1-（乙氧羰基）丙基或3-溴苄基；

[1328] R^4是正-丁基、正-己基、苄基、3-溴苄基、3-甲氧基苄基、3-硝基苄基、3-氨基苄基、(3,5-二甲基异噁唑-4-基）甲基、(5-硝基-2-呋喃基）甲基或1-（乙氧羰基）丙基；

[1329] 条件是当R^1是氢、R^2是甲基、R^3是1-（乙氧羰基）丙基时，R^4不是3-溴苄基。

[1330] 在上述实施方案中，优选当R^3是3-溴苄基时，R^4是1-（乙氧羰基）丙基；

[1331] 在上述实施方案中，优选当R^3是3-戊基、1-（氨基羰基）丙基或1-（乙氧羰基）丙基时，R^4不是1-（乙氧羰基）丙基；

[1332] 在一个最优选的实施方案中，R^1是氢；R^2是甲基；R^3是1-（乙氧羰基）丙基；和R^4是3-甲氧基苄基、3-硝基苄基或（5-硝基-2-呋喃基）甲基。

[1333] 另一个实施方案在于化合物，其中R^2是甲基、R^3是式$-CHR^5R^6$的基团，其中R^5是C_{2-4}烷基，R^6是酰氨基或$-COOR^7$，R^7是甲基或乙基。

[1334] 在一些实施方案中，用于本发明方法和组合物的化合物选自：

[1335] 2-[(7-苄基-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基）硫代]丁酸乙酯；

[1336] 2-{[7-(3-溴苄基)-1-(2-乙氧基-2-氧代乙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1337] 2-{[7-(3-溴苄基)-1-(2-甲氧基乙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1338] 2-{[7-(3-溴苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1339] 2-{[7-(3-溴苄基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1340] 2-{[7-(2-溴苄基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1341] 2-{[7-(3-溴苄基)-1-(氰基甲基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1342] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-丙基-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1343] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-(2-氧代丙基)-2,3,6,7-四

氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1344] 2-{[7-(3-溴苄基)-1-(3-羟基丙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1345] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-(2-丙炔基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1346] 2-{[7-(3-甲氧基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1347] 2-{[3-甲基-7-(3-硝基苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1348] 2-{[7-(3-氨基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1349] 2-({7-[4-(氨基磺酰基)苄基]-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫代)丁酸乙酯；

[1350] 2-{[7-(4-溴苄基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1351] 2-{[7-(环己基甲基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1352] 2-{[1,3-二甲基-2,6-二氧代-7-(1-苯基乙基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1353] 2-{[1,3-二甲基-2,6-二氧代-7-(2-苯基乙基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1354] 2-({7-[(3,5-二甲基异噁唑-4-基)甲基]-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫代)丁酸乙酯；

[1355] 2-({3-甲基-7-[(5-硝基-2-呋喃基)甲基]-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫代)丁酸乙酯；

[1356] 2-[(7-丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯；

[1357] 2-{[7-(3-溴苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯；

[1358] 2-[(1,7-二己基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯；

[1359] 2-[(7-己基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯；

[1360] 2-[(3-甲基-2,6-二氧代-1,7-二戊基-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯；

[1361] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酰胺；

[1362] 2-[(7-丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酰胺；

[1363] 7-(3-溴苄基)-8-[(1-乙基丙基)硫代]-3-甲基-3,7-二氢-1H-嘌呤-2,6-二酮;

[1364] 2-{8-[(3-溴苄基)硫代]-1,3-二甲基-2,6-二氧代-1,2,3,6-四氢-7H-嘌呤-7-基}丁酸乙酯;和

[1365] 2-[(7-异丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯。

[1366] 在一些实施方案中,用于本发明方法和组合物的化合物选自:

[1367] 2-[(7-苄基-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯;

[1368] 2-{[7-(3-溴苄基)-1-(2-甲氧基乙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1369] 2-{[7-(3-溴苄基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1370] 2-{[7-(3-溴苄基)-1-(氰基甲基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1371] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-丙基-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1372] 2-{[7-(3-溴苄基)-1-(3-羟基丙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1373] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-(2-丙炔基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1374] 2-{[7-(3-甲氧基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1375] 2-{[3-甲基-7-(3-硝基苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1376] 2-{[7-(3-氨基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1377] 2-({7-[(3,5-二甲基异噁唑-4-基)甲基]-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫代)丁酸乙酯;

[1378] 2-({3-甲基-7-[(5-硝基-2-呋喃基)甲基]-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫代)丁酸乙酯;

[1379] 2-[(7-丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯;

[1380] 2-[(7-己基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫代]丁酸乙酯;

[1381] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酰胺;

[1382] 7-(3-溴苄基)-8-[(1-乙基丙基)硫代]-3-甲基-3,7-二氢-1H-嘌呤-2,6-二酮;和

[1383] 2-{8-[(3-溴苄基)硫代]-1,3-二甲基-2,6-二氧代-1,2,3,6-四氢-7H-嘌呤-7-基}丁酸乙酯。

[1384] 在一些实施方案中,用于本发明方法和组合物的化合物选自:

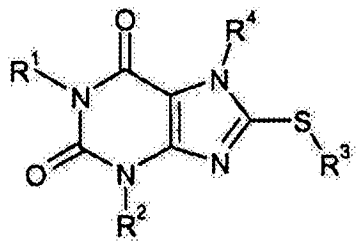
[1385] 2-{[7-(3-甲氧基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;

[1386] 2-{[3-甲基-7-(3-硝基苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫代}丁酸乙酯;和

[1387] 2-({3-甲基-7-[(5-硝基-2-呋喃基)甲基]-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫代)丁酸乙酯。

[1388] 在某些实施方案中,所述化合物为具有式I I的那些、它们的对映异构体、非对映异构体及其混合物(包括所有可能的立体异构体的混合物),或药学上可接受的盐:

[1389]



(II)

[1390] 其中R^1为氢或C_{1-6}烷基;

[1391] R^2为氢或C_{1-4}烷基;

[1392] R^3为式$-CHR^5R^6$基团或苄基;

[1393] R^4为被烷氧羰基、C_{3-6}环烷基、芳基或杂环任选地取代的C_{1-8}烷基;

[1394] R^5为氢或C_{1-4}烷基;

[1395] R^6为C_{1-4}烷基、酰氨基或$-COOR^7$;

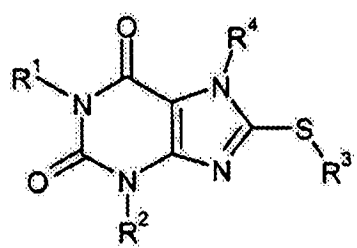
[1396] R^7为C_{1-4}烷基;

[1397] 在上述实施方案中,在某些情况下,当R^3为苄基时,那么R^4为被烷氧羰基任选地取代的C_{1-8}烷基。

[1398] 在上述实施方案中,在某些情况下,当R^3为式$-CHR^5R^6$基团时,那么R^4为被C_{3-6}环烷基、芳基或杂环任选地取代的C_{1-8}烷基。

[1399] 在某些实施方案中,所述化合物为式II的那些化合物、它们的对映异构体、非对映异构体及其混合物(包括所有可能的立体异构体的混合物),或药学上可接受的盐:

[1400]



(II)

[1401] 其中

[1402] R^1为氢或C_{1-6}烷基;

[1403] R^2为氢或C_{1-4}烷基；

[1404] R^3为式$-CHR^5R^6$基团或苄基；

[1405] R^4为被烷氧羰基、C_{3-6}环烷基、芳基或杂环任选地取代的C_{1-8}烷基；

[1406] R^5为氢或C_{1-4}烷基；

[1407] R^6为C_{1-4}烷基、酰氨基或$-COOR^7$；

[1408] R^7为C_{1-4}烷基。

[1409] 在某些实施方案中，所述化合物为选自以下的式II化合物：

[1410] 2-[(7-庚基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁-酸乙酯；

[1411] 7-(3-溴苄基)-3-甲基-8-(丙硫基)-3,7-二氢-1H-嘌呤-2,-6-二酮；

[1412] 2-[(3-甲基-2,6-二氧代-7-戊基-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁-酸乙酯；

[1413] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基-]硫基}丁酸乙酯；

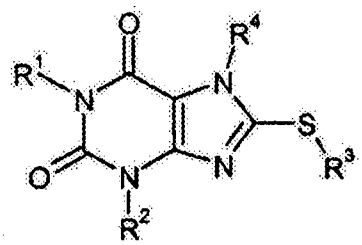
[1414] 2-[(3-甲基-2,6-二氧代-7-丙基-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁-酸乙酯；

[1415] 7-(3-溴苄基)-8-[(3-氯-2-羟丙基)硫基]-3-甲基-3,7-二氢-1H-嘌呤-2,6-二酮；和

[1416] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基-]硫基}丙酸乙酯。

[1417] 在某些实施方案中，所述化合物为式I化合物、它们的对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体的混合物）、或药学上可接受的盐

[1418]



(I)

[1419] 其中

[1420] R^1为氢或C_{1-6}烷基；

[1421] R^2为氢或C_{1-4}烷基；

[1422] R^3为式$-CHR^5R^6$基团或苄基；

[1423] R^4为被烷氧羰基、C_{3-6}环烷基、芳基或杂环任选地取代的C_{1-8}烷基；

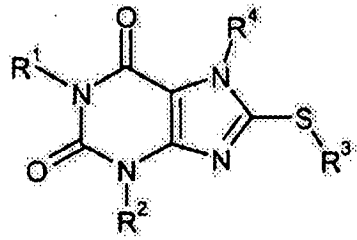
[1424] R^5为氢或C_{2-4}烷基；

[1425] R^6为C_{2-4}烷基、酰氨基或$-COOR^7$；

[1426] R^7为C_{1-4}烷基；

[1427] 在另一实施方案中，所述化合物为具有式II的化合物、它们的对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体的混合物）、或其药学上可接受的盐，

[1428]



(II)

[1429] 其中

[1430] R^1为氢或 C_{1-6}烷基；

[1431] R^2为氢或 C_{1-4}烷基；

[1432] R^3为式 $-CHR^5R^6$基团或苄基；

[1433] R^4为被烷氧羰基、C_{3-6}环烷基、芳基或杂环任选地取代的 C_{1-8}烷基；

[1434] R^5为氢或 C_{1-4}烷基；

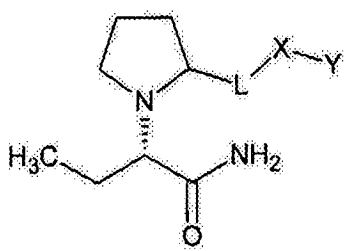
[1435] R^6为 C_{1-4}烷基、酰氨基或 $-COOR^7$；

[1436] R^7为 C_{1-4}烷基。

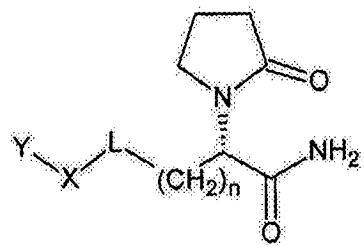
[1437] vi) 国际专利申请公开文本第 WO2010/144712 号

[1438] 在一个实施方案中，公开了包含式 1 或式 2 的 LEV 衍生物的化学组合物。

[1439]



式 1



式 2

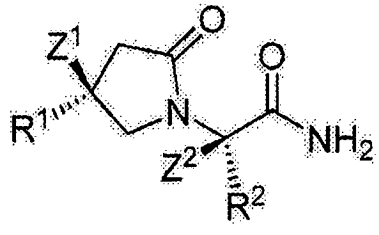
[1440] 将式 2 的 n 及式 1 和 2 的 L、X 和 Y 定义如下：a) n 是值为 0 至 8 的整数；b) L 为 CH2、CO、NHCO、NHCOO、CONH、NH、O 或 S 及其组合之一；c) X 为端基、芳族基团、芳基，或具有 1-10 个碳和 / 或杂链原子的饱和的、不饱和的、取代的、未取代的直链或支链脂族基，该杂链原子选自氧、氮、硫或磷，及其组合；和 d) Y 为任选的，且如果存在则为选自醇胺、酰胺、羧酸、醛、酯、亚氨酸酯、异氰酸酯、异硫氰酸酯、酐、巯基、硫内酯 (thiolacetone)、重氮正离子、NHS、CO-NHS、O-NHS、马来酰亚胺基团的官能团之一；或 e) Y 为 Yi-Z，其中 Yi 选自 COO、CO、O、CONH、NHCO，或 NH 且 Z 为操作基团 (operative group)。

[1441] 在所述方法的一个实施方案中，Z 的操作基团选自可检测标记、抗原载体、偶联剂、端基、蛋白质、脂蛋白、糖蛋白、多肽、多糖、核苷酸、聚核苷酸、磷壁酸、放射性同位素、酶、酶片段、酶供体片段、酶受体片段、酶底物、酶抑制剂、辅酶、荧光部分、磷光部分、抗 - 卒中 (stokes) 正调节部分、化学发光部分、发冷光部分、染料、感光剂、颗粒、微粒、磁性颗粒、固体载体、脂质体、配体、受体、半抗原放射性同位素及其组合。

[1442] vii) 国际专利申请公开文本第 WO2010/002869 号

[1443] 本发明提供了式 I 的化合物：

[1444]



(I),

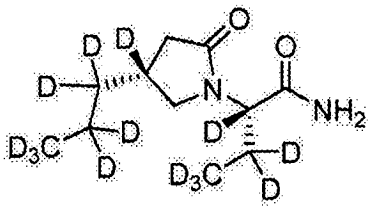
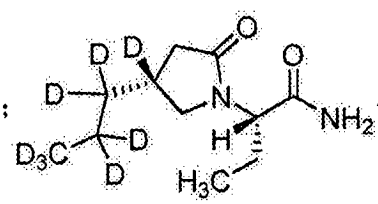
[1445] 或其药学上可接受的盐，其中：每个 Z 独立选自氢和氘；R1 为具有 0 至 7 个氘原子的正－丙基；R2 为具有 0 至 5 个氘原子的乙基，并且当每个 R 具有 0 个氘原子时，至少一个 Z 为氘。

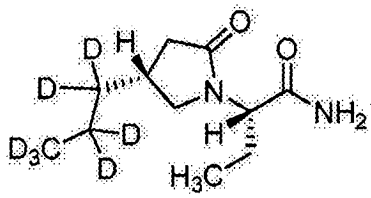
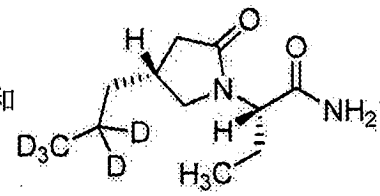
[1446] 本发明的一个实施方案提供了式 I 化合物，其中 R1 选自 CD3CH2CH2-、CD3CD2CH2-、CD3CH2CD2-、CH3CH2CD2-、CH3CD2CD2-、CD3CD2CD2- 或 CH3CH2CH2-。在更具体的实施方案中，R1 为 CD3CD2CD2- 或 CD3CD2CH2-。在这些实施方案的一个方面，Z1 和 Z2 都为氢。在这些实施方案的另一个方面，Z1 和 Z2 都为氘。

[1447] 在另一个实施方案中，R2 选自 CH3CH2-、CD3CH2-、CH3CD2-、或 CD3CD2-。在一个更具体的实施方案中，R2 选自 CH3CH2- 或 CD3CD2-。在这些实施方案的一个方面，Z1 和 Z2 都为氢。在这些实施方案的另一个方面，Z1 和 Z2 都为氘。

[1448] 可选择如上所述的 R 和 Z 变量，并将其合在一起以提供本发明更具体的实施方案。例如，在一个实施方案中，R1 为 CD3CH2CH2-、CD3CD2CH2-、CD3CH2CD2-、CH3CH2CD2-、CH3CD2CD2-、CD3CD2CD2- 或 CH3CH2CH2-；且 R2 选自 CH3CH2-、CD3CH2-、CH3CD2- 或 CD3CD2-。在该实施方案的一个方面，R2 为 CH3CH2- 或 CD3CD2-。在另一个实施方案中，R1 为 CD3CD2CD2- 或 CD3CD2CH2-；且 R2 选自 CH3CH2-、CD3CH2-、CH3CD2- 或 CD3CD2-。在该实施方案的一个方面，R2 为 CH3CH2- 或 CD3CD2-。

[1449] 本发明具体化合物的实例包括下列：

[1450]  化合物 100；  化合物 101：

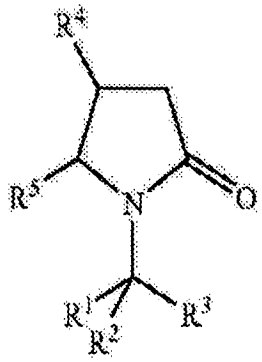
[1451]  化合物 102；和  化合物 103。

[1452] viii)20090312333

[1453] 本发明的化合物是式 (I) 涵盖的那些、它们的非对映异构体及混合物，或其药学上可接受的盐。

[1454]

(I)



[1455] R1 为氢、取代的或未取代的 C1-12 烷基、取代的或未取代的芳基或取代的或未取代的 3-8 元杂环。

[1456] R2 为氢。或者，可将 R1 和 R2 以这类方式连接在一起以形成 C3-6 环烷基。

[1457] R3 为下列任一：

[1458] (a) 经它的 C 原子之一连接分子其余部分的取代的或未取代的杂环，所述的杂环选自：

[1459] 1H- 苯并咪唑 -6- 基；

[1460] 1H- 苯并咪唑 -7- 基；

[1461] 咪唑并 [1,2-a] 吡啶 -3- 基；

[1462] 咪唑并 [1,2-a] 嘧啶 -3- 基；

[1463] 咪唑并 [1,2-b][1,2,4] 三嗪 -7- 基；

[1464] 咪唑并 [1,2-b] 哒嗪 -3- 基；

[1465] 5,6,7,8- 四氢咪唑并 [1,2-b] 哒嗪 -3- 基；

[1466] 咪唑并 [2,1-b][1,3,4] 噻二唑 -5- 基；

[1467] 咪唑并 [2,1-b][1,3] 噻唑 -5- 基；

[1468] 3H- 咪唑并 [4,5-b] 吡啶 -7- 基；

[1469] 1H- 咪唑 -4- 基；

[1470] 1H- 咪唑 -5- 基；

[1471] 1H- 吲哚 -2- 基；

[1472] 1H- 吲哚 -3- 基；

[1473] 1H- 吲哚 -4- 基；

[1474] 1H- 吲哚 -7- 基；

[1475] 异噁唑 -4- 基；

[1476] 1H- 吡唑 -4- 基；

[1477] 1H- 吡唑 -5- 基；

[1478] 1H- 吡唑并 [1,5-a] 嘧啶 -3- 基；

[1479] 1H- 吡唑并 [3,4-b] 吡啶 -3- 基；

[1480] 哒嗪 -4- 基；

[1481] 吡啶 -2- 基；

[1482] 吡啶 -3- 基；

[1483] 吡啶 -4- 基；

[1484] 1H- 吡咯并 [2,3-b] 吡啶 -3- 基；

[1485] 1H- 吡咯并 [2,3-b] 吡啶 -4- 基；

[1486] 1H- 吡咯并 [2,3-b] 吡啶 -5- 基；

[1487] 1H- 吡咯并 [2,3-c] 吡啶 -2- 基；

[1488] 1H- 吡咯并 [2,3-c] 吡啶 -3- 基；

[1489] 1H- 吡咯并 [3,2-b] 吡啶 -3- 基；

[1490] 1H- 吡咯并 [3,2-c] 吡啶 -2- 基；

[1491] 1H- 吡咯并 [3,2-c] 吡啶 -3- 基；

[1492] 1,3,4- 噻二唑 -2- 基；

[1493] 1,3- 噻唑 -5- 基；

[1494] [1,2,4] 三唑并 [4,3-b] 哒嗪 -7- 基；

[1495] [1,2,4] 三唑并 [4,3-b] 哒嗪 -8- 基；

[1496] 中氮茚 -3- 基；

[1497] 或 R3 为

[1498] (b) 经它的 N 原子之一连接分子其余部分的取代的或未取代的杂环，所述的杂环选自：

[1499] 1H-1,2,3- 苯并三唑 -1- 基；

[1500] 1H- 咪唑并 [4,5-b] 吡啶 -1- 基；

[1501] 3H- 咪唑并 [4,5-b] 吡啶 -3- 基；

[1502] 7H- 咪唑并 [4,5-c] 哒嗪 -7- 基；

[1503] 1H- 吲哚 -1- 基；

[1504] 2,3- 二氢 -1H- 吲哚 -1- 基；

[1505] 9H- 嘌呤 -9- 基；

[1506] 1H- 吡唑并 [3,4-b] 吡啶 -1- 基；

[1507] 2H- 吡唑并 [3,4-b] 吡啶 -2- 基；

[1508] 1H- 吡咯并 [2,3-b] 吡啶 -1- 基；

[1509] 1H- 吡咯并 [3,2-b] 吡啶 -1- 基；

[1510] 3,4- 二氢喹啉 -1(2H)- 基；

[1511] 8H- 异噻唑并 [5,4-b] 吲哚 -8- 基；

[1512] 1H-1,2,4- 三唑 -1- 基；

[1513] 1H- 吡咯 -1- 基；

[1514] 2- 氯 -1H- 苯并咪唑 -1- 基。

[1515] 在式 (I) 中的 R4 选自氢；被卤素、C1-4 烷氧基、C1-4 烷硫基、叠氮基、硝基氧基或芳基任选地取代的 C1-12 烷基；被卤素任选地取代的 C2-12 烯基；被卤素任选地取代的 C2-12 炔基；叠氮基；烷氧基羰基氨基；芳基磺酰基氧基；取代的或未取代的芳基；或 3-8 元取代的或未取代的杂环；

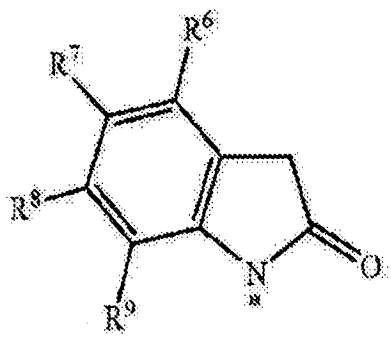
[1516] 在具体的实施方案中 R4 为氢；或 R4 为被卤素、C1-4 烷氧基、C1-4 烷硫基、叠氮基或硝基氧基任选地取代的 C1-12 烷基或 C1-6 烷基；或 R4 为被卤素任选地取代的 C2-12 烯

基或C1-6烯基；或R4为被卤素任选地取代的C2-12炔基或C1-6炔基；或R4为烷氧基羰基氨基。

[1517] R5为氢；

[1518] 或者R4可连同R5和2-氧代-1-吡咯烷环一起形成下列结构的1,3-二氢-2H-吲哚-2-酮环：

[1519]



[1520] 星号*表示取代基的连接点；

[1521] R6为氢或卤素。

[1522] 在式(I)中的R7选自氢；硝基；卤素；杂环；氨基；芳基；被至少一个卤素任选地取代的C1-12烷基；或被至少一个卤素任选地取代的C1-12烷氧基。

[1523] 在式(I)中的R8选自氢，被卤素任选地取代的C1-12烷基，或卤素。

[1524] 在式(I)中的R9选自氢，被卤素任选地取代的C1-12烷基，或卤素。

[1525] 本发明的另一个方面在于式(I)的化合物，其中

[1526] R1和R2都为氢。

[1527] R3为：

[1528] (a)经它的C原子之一连接分子其余部分的取代的或未取代的杂环，该杂环选自：

[1529] 1H-苯并咪唑-6-基；

[1530] 1H-苯并咪唑-7-基；

[1531] 咪唑并[1,2-a]吡啶-3-基；

[1532] 咪唑并[1,2-a]嘧啶-3-基；

[1533] 咪唑并[1,2-b][1,2,4]三嗪-7-基；

[1534] 咪唑并[1,2-b]哒嗪-3-基；

[1535] 5,6,7,8-四氢咪唑并[1,2-b]哒嗪-3-基；

[1536] 咪唑并[2,1-b][1,3,4]噻二唑-5-基；

[1537] 咪唑并[2,1-b][1,3]噻唑-5-基；

[1538] 3H-咪唑并[4,5-b]吡啶-7-基；

[1539] 1H-咪唑-4-基；

[1540] 1H-咪唑-5-基；

[1541] 1H-吲哚-2-基；

[1542] 1H-吲哚-3-基；

[1543] 1H-吲哚-4-基；

[1544] 1H-吲哚-7-基；

[1545] 异噁唑 -4- 基；

[1546] 1H- 吡唑 -4- 基；

[1547] 1H- 吡唑 -5- 基；

[1548] 1H- 吡唑并 [1,5-a] 嘧啶 -3- 基；

[1549] 1H- 吡唑并 [3,4-b] 吡啶 -3- 基；

[1550] 哒嗪 -4- 基；

[1551] 吡啶 -2- 基；

[1552] 吡啶 -3- 基；

[1553] 吡啶 -4- 基；

[1554] 1H- 吡咯并 [2,3-b] 吡啶 -3- 基；

[1555] 1H- 吡咯并 [2,3-b] 吡啶 -4- 基；

[1556] 1H- 吡咯并 [2,3-b] 吡啶 -5- 基；

[1557] 1H- 吡咯并 [2,3-c] 吡啶 -2- 基；

[1558] 1H- 吡咯并 [2,3-c] 吡啶 -3- 基；

[1559] 1H- 吡咯并 [3,2-b] 吡啶 -3- 基；

[1560] 1H- 吡咯并 [3,2-c] 吡啶 -2- 基；

[1561] 1H- 吡咯并 [3,2-c] 吡啶 -3- 基；

[1562] 1,3,4- 噻二唑 -2- 基；

[1563] 1,3- 噻唑 -5- 基；

[1564] [1,2,4] 三唑并 [4,3-b] 哒嗪 -7- 基；

[1565] [1,2,4] 三唑并 [4,3-b] 哒嗪 -8- 基；

[1566] 中氮茚 -3- 基。

[1567] 或者 R3 为：

[1568] (b) 经它的 N 原子之一连接分子其余部分的取代的或未取代的杂环，该杂环选自：

[1569] 1H-1,2,3- 苯并三唑 -1- 基；

[1570] 1H- 咪唑并 [4,5-b] 吡啶 -1- 基；

[1571] 3H- 咪唑并 [4,5-b] 吡啶 -3- 基；

[1572] 7H- 咪唑并 [4,5-c] 哒嗪 -7- 基；

[1573] 1H- 吲哚 -1- 基；

[1574] 2,3- 二氢 -1H- 吲哚 -1- 基；

[1575] 9H- 嘌呤 -9- 基；

[1576] 1H- 吡唑并 [3,4-b] 吡啶 -1- 基；

[1577] 2H- 吡唑并 [3,4-b] 吡啶 -2- 基；

[1578] 1H- 吡咯并 [2,3-b] 吡啶 -1- 基；

[1579] 1H- 吡咯并 [3,2-b] 吡啶 -1- 基；

[1580] 3,4- 二氢喹啉 -1(2H)- 基；

[1581] 8H- 异噻唑并 [5.4-b] 吲哚 -8- 基；

[1582] 1H-1,2,4- 三唑 -1- 基；

[1583] 1H- 吡咯 -1- 基；

[1584] 2- 氯 -1H- 苯并咪唑 -1- 基。

[1585] 在式 (I) 中的 R4 选自氢 ;被卤素或 C1-4 烷氧基任选地取代的 C1-12 烷基 ;被卤素任选地取代的 C2-12 烯基 ;被卤素任选地取代的 C2-12 炔基。

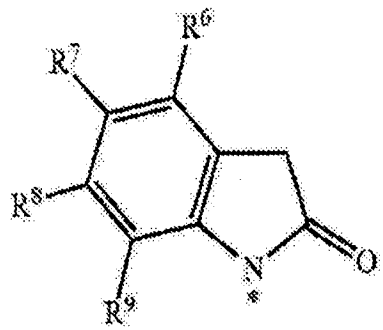
[1586] 在另一个具体实施方案中 R4 为正 - 丙基、2, 2, 2- 三氟乙基、2- 氯 -2, 2- 二氟乙基、2 溴 -2, 2- 二氟乙基、2, 2- 二氟乙烯基。

[1587] 在另一个具体实施方案中 R4 为苯基、2, 3, 5- 三氟苯基或 3- 氯 -4- 氟苯基。

[1588] R5 为氢 ;

[1589] 本发明的另一个实施方案在于式 (I) 的化合物,其中 R4 连同 R5 一起形成 1, 3- 二氢 -2H- 吲哚 -2- 酮环

[1590]



[1591] 星号 * 表示杂芳基亚烷基取代基的连接点,并且其中

[1592] R6 为氢 ;

[1593] R7 为氯 ;

[1594] R8 为氢 ;

[1595] R9 为氢。

[1596] 本发明的另一个实施方案在于式 (I) 的化合物,其中 R3 为经它的 C 原子之一连接分子其余部分的取代的或未取代的杂环,并且选自 :

[1597] 咪唑并 [1, 2-a] 嘧啶 -3- 基 ;

[1598] 咪唑并 [1, 2-b][1, 2, 4] 三嗪 -7- 基 ;

[1599] 咪唑并 [1, 2-b] 哒嗪 -3- 基 ;

[1600] 5, 6, 7, 8- 四氢咪唑并 [1, 2-b] 哒嗪 -3- 基 ;

[1601] 咪唑并 [2, 1-b][1, 3, 4] 噻二唑 -5- 基 ;

[1602] 咪唑并 [2, 1-b][1, 3] 噻唑 -5- 基 ;

[1603] 3H- 咪唑并 [4, 5-b] 吡啶 -7- 基 ;

[1604] 1H- 咪唑 -4- 基 ;

[1605] 1H- 咪唑 -5- 基 ;

[1606] 异噁唑 -4- 基 ;

[1607] 1H- 吡唑 -4- 基 ;

[1608] 1H- 吡唑 -5- 基 ;

[1609] 1H- 吡唑并 [1, 5-a] 嘧啶 -3- 基 ;

[1610] 1H- 吡唑并 [3, 4-b] 吡啶 -3- 基 ;

[1611] 吡啶 -3- 基 ;

[1612] 1H-吡咯并[2,3-b]吡啶-3-基；

[1613] 1H-吡咯并[2,3-b]吡啶-4-基；

[1614] 1H-吡咯并[2,3-b]吡啶-5-基；

[1615] 1H-吡咯并[2,3-c]吡啶-2-基；

[1616] 1H-吡咯并[2,3-c]吡啶-3-基；

[1617] 1,3-噻唑-5-基；

[1618] [1,2,4]三唑并[4,3-b]哒嗪-8-基；

[1619] 中氮茚-3-基。

[1620] 在另一个具体的实施方案中，R3为经它的C原子之一连接分子其余部分的取代的或未取代的杂环，并且选自：

[1621] 咪唑并[1,2-b]哒嗪-3-基；

[1622] 咪唑并[2,1-b][1,3,4]噻二唑-5-基；

[1623] 咪唑并[2,1-b][1,3]噻唑-5-基；

[1624] 3H-咪唑并[4,5-b]吡啶-7-基；

[1625] 1H-咪唑-4-基；

[1626] 1H-咪唑-5-基；

[1627] 1H-吡唑-4-基；

[1628] 1H-吡唑并[1,5-a]嘧啶-3-基；

[1629] 吡啶-3-基；

[1630] 1H-吡咯并[2,3-b]吡啶-3-基；

[1631] 1H-吡咯并[2,3-b]吡啶-4-基；

[1632] 1,3-噻唑-5-基；

[1633] 所述杂环被例如甲基、正-丙基、三氟甲基、环丙基、溴、氯、氟、碘、甲氧基、乙氧基、丙氧基、异丙氧基、环丙基氧基、环丙基甲氧基、环丁基甲氧基、氨基、甲氨基、环丙基氨基、环丁基氨基、1-吡咯烷基、氰基、苯基、苄基或3-噻吩基任选地取代。

[1634] 在另一个具体的实施方案中，R3为经它的C原子之一连接分子其余部分的取代的或未取代的杂环，并且选自：6-氯-2-环丙基咪唑并[1,2-b]哒嗪-3-基、6-(环丙基氧基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基、6-丙氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基、6-氯咪唑并[2,1-b][1,3]噻唑-5-基、2,6-二氯咪唑并[2,1-b][1,3]噻唑-5-基、5-氯-1H-咪唑-4-基、5-溴-1H-咪唑-4-基、4-溴-1H-咪唑-5-基、4-氯-1H-咪唑-5-基、1H-咪唑-5-基、1-甲基-1H-咪唑-5-基、4-氯-1-甲基-1H-咪唑-5-基、1H-吡唑-4-基、1H-吡咯并[2,3-b]吡啶-3-基。

[1635] 本发明的另一个实施方案在于式(I)的化合物，其中R3为经它的C原子之一连接分子其余部分的杂环，并且为取代的或未取代的咪唑并[1,2-a]吡啶-3-基。

[1636] 所述咪唑并[1,2-a]吡啶-3-基被例如甲基、环丙基、溴、氯、氟、碘任选地取代。

[1637] 在另一个具体的实施方案中，R3为经它的C原子之一连接分子其余部分的取代的或未取代的杂环，并且选自：咪唑并[1,2-a]吡啶-3-基、6-甲基咪唑并[1,2-a]吡啶-3-基、2-氯咪唑并[1,2-a]吡啶-3-基。

[1638] 本发明的另一个实施方案在于式(I)的化合物，其中R3为经它的N原子之一连接

分子其余部分的取代的或未取代的杂环，并且选自：

[1639] 3H- 咪唑并 [4,5-b] 吡啶 -3- 基；

[1640] 1H- 吲哚 -1- 基；

[1641] 1H- 吡咯并 [2,3-b] 吡啶 -1- 基；

[1642] 1H- 吡咯并 [3,2-b] 吡啶 -1- 基；

[1643] 1H- 吡咯 -1- 基；

[1644] 2- 氯 -1H- 苯并咪唑 -1- 基。

[1645] 本发明具体的另一个实施方案在于式 (I) 的化合物，其中 R3 为经它的 N 原子之一连接分子其余部分的杂环，并且选自：

[1646] 3H- 咪唑并 [4,5-b] 吡啶 -3- 基；

[1647] 1H- 吡咯并 [3,2-b] 吡啶 -1- 基；

[1648] 1H- 吡咯 -1- 基；

[1649] 2- 氯 -1H- 苯并咪唑 -1- 基；

[1650] 所述杂环可被三氟甲基、环丙基、溴、氯、氟、甲氧基或氰基任选地取代。

[1651] 在另一个具体的实施方案中，R3 为经它的 C 原子之一连接分子其余部分的杂环，并且选自 6- 溴 -2- 氯 -3H- 咪唑并 [4,5-b] 吡啶 -3- 基、6- 溴 -2- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -3- 基、1H- 吡咯并 [3,2-b] 吡啶 -1- 基、2,5- 二氯 -1H- 吡咯 -1- 基、2- 氯 -5- 甲氧基 -1H- 苯并咪唑 -1- 基、5- 溴 -2- 氯 -1H- 苯并咪唑 -1- 基或 2,5- 二氯 -1H- 苯并咪唑 -1- 基。

[1652] 本发明另一个实施方案在于式 (I) 的化合物，其中 R1、R2 和 R5 为氢。

[1653] R4 为被卤素任选地取代的 C1-6 烷基、被卤素任选地取代的 C2-6 烯基或被卤素任选地取代的 C2-12 炔基。

[1654] R3 选自：

[1655] 咪唑并 [1,2-b] 哒嗪 -3- 基；

[1656] 咪唑并 [2,1-b][1,3,4] 噻二唑 -5- 基；

[1657] 咪唑并 [2,1-b][1,3] 噻唑 -5- 基；

[1658] 3H- 咪唑并 [4,5-b] 吡啶 -7- 基；

[1659] 1H- 咪唑 -4- 基；

[1660] 1H- 咪唑 -5- 基；

[1661] 1H- 吡唑 -4- 基；

[1662] 1H- 吡唑并 [1,5-a] 嘧啶 -3- 基；

[1663] 吡啶 -3- 基；

[1664] 1H- 吡咯并 [2,3-b] 吡啶 -3- 基；

[1665] 1H- 吡咯并 [2,3-b] 吡啶 -4- 基；

[1666] 1,3- 噻唑 -5- 基；

[1667] 并且经下列基团任选地取代：甲基、正 - 丙基、三氟甲基、环丙基、溴、氯、氟、碘、甲氧基、乙氧基、丙氧基、异丙氧基、环丙基氧基、环丙基甲氧基、环丁基甲氧基、氨基、甲氨基、环丙基氨基、环丁基氨基、1- 吡咯烷基、氰基、苯基、苄基或 3- 噻吩基。

[1668] 本发明另一个实施方案在于式 (I) 的化合物，其中 R1、R2 和 R5 为氢。

[1669] R4 为被卤素任选地取代的 C1-6 烷基、被卤素任选地取代的 C2-6 烯基或被卤素任选地取代的 C2-12 炔基。

[1670] R3 选自

[1671] 3H- 咪唑并 [4,5-b] 吡啶 -3- 基；

[1672] 1H 吡咯并 [3,2-b] 吡啶 -1- 基；

[1673] 1H- 吡咯 -1- 基；

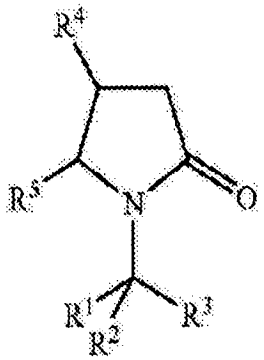
[1674] 2- 氯 -1H- 苯并咪唑 -1- 基；

[1675] 被三氟甲基、环丙基、溴、氯、氟、甲氧基或氰基任选地取代。

[1676] 本发明的另一个实施方案在于式 (I) 的化合物、它们的非对映异构体及混合物，或其药学上可接受的盐。

[1677]

(I)



[1678] R1、R2 和 R5 为氢；

[1679] R3 为经它的 C 原子之一连接分子其余部分的取代的或未取代的杂环，所述的杂环选自：

[1680] 1H- 苯并咪唑 -6- 基；

[1681] 1H- 苯并咪唑 -7- 基；

[1682] 咪唑并 [1,2-a] 吡啶 -3- 基；

[1683] 咪唑并 [1,2-a] 嘧啶 -3- 基；

[1684] 咪唑并 [1,2-b][1,2,4] 三嗪 -7- 基；

[1685] 咪唑并 [1,2-b] 哒嗪 -3- 基；

[1686] 5,6,7,8- 四氢咪唑并 [1,2-b] 哒嗪 -3- 基；

[1687] 咪唑并 [2,1-b][1,3,4] 噻二唑 -5- 基；

[1688] 咪唑并 [2,1-b][1,3] 噻唑 -5- 基；

[1689] 3H- 咪唑并 [4,5-b] 吡啶 -7- 基；

[1690] 1H- 咪唑 -4- 基；

[1691] 1H- 咪唑 -5- 基；

[1692] 1H- 吲哚 -2- 基；

[1693] 1H- 吲哚 -3- 基；

[1694] 1H- 吲哚 -4- 基；

[1695] 1H- 吲哚 -7- 基；

[1696] 异噁唑 -4- 基；

[1697] 1H- 吡唑 -4- 基；

[1698] 1H- 吡唑 -5- 基；

[1699] 1H- 吡唑并 [1,5-a] 嘧啶 -3- 基；

[1700] 1H- 吡唑并 [3,4-b] 吡啶 -3- 基；

[1701] 哒嗪 -4- 基；

[1702] 吡啶 -2- 基；

[1703] 吡啶 -3- 基；

[1704] 吡啶 -4- 基；

[1705] 1H- 吡咯并 [2,3-b] 吡啶 -3- 基；

[1706] 1H- 吡咯并 [2,3-b] 吡啶 -4- 基；

[1707] 1H- 吡咯并 [2,3-b] 吡啶 -5- 基；

[1708] 1H- 吡咯并 [2,3-c] 吡啶 -2- 基；

[1709] 1H- 吡咯并 [2,3-c] 吡啶 -3- 基；

[1710] 1H- 吡咯并 [3,2-b] 吡啶 -3- 基；

[1711] 1H- 吡咯并 [3,2-c] 吡啶 -2- 基；

[1712] 1H- 吡咯并 [3,2-c] 吡啶 -3- 基；

[1713] 1,3,4- 噻二唑 -2- 基；

[1714] 1,3- 噻唑 -5- 基；

[1715] [1,2,4] 三唑并 [4,3-b] 哒嗪 -7- 基；

[1716] [1,2,4] 三唑并 [4,3-b] 哒嗪 -8- 基；

[1717] 中氮茚 -3- 基；

[1718] 具体优选的是咪唑并 [1,2-a] 吡啶 -3- 基；咪唑并 [1,2-a] 嘧啶 -3- 基；咪唑并 [1,2-b] 哒嗪 -3- 基；1H- 咪唑 -4- 基；1H- 咪唑 -5- 基。

[1719] R4 为取代的或未取代的苯基部分；

[1720] 本发明另一个实施方案在于式 (I) 的化合物，其中 R1 为氢或 C1-12 烷基；

[1721] R2 为氢；

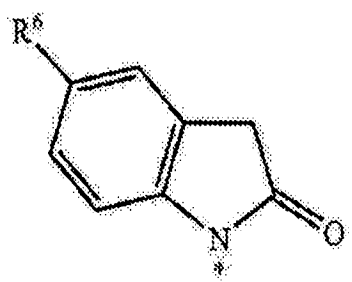
[1722] R3 为经它的 C 原子之一连接分子其余部分的芳族 5- 元杂环；

[1723] R4 为氢、C1-12 烷基或芳基；

[1724] R5 为氢；

[1725] 或者，R4 可连同 R5 和 2- 氧代 -1- 吡咯烷环一起形成下列 1,3- 二氢 -2H- 吲哚 -2- 酮环。

[1726]



[1727] 其中星号 * 表示取代基的连接点；

[1728] R6 为氢或卤素。

[1729] 在该实施方案中，当 R3 是取代的 1H- 吡唑 -5- 基时，R4 不可为氢。而且该实施方案并不包括公开于 A. Padwa 等人，J. Org. Chem. 2000，65，5223-5232 中但却没有任何生物活性的 5-(2'- 氧代 -1'- 吡咯烷基）甲基 -1，3，4- 三羰基甲氧基 - 吡唑。

[1730] 在其中 R3 为经它的 C 原子之一连接分子其余部分的芳族 5- 元杂环的实施方案中，具体部分 R3 可选自 1，3- 噻唑 -5- 基、1H- 咪唑 -4- 基、1H- 咪唑 -5- 基、1H- 吡唑 -4- 基、1H- 吡唑 -5- 基、2- 氧代 -2，3- 二氢 -1，3- 噻唑 -5- 基、它们中的每个被 1-3 个独立地选自下列基团的取代基任选地取代：甲基、氯、溴、氨基、甲氨基、二甲氨基、(2- 氧代 -4- 丙基 - 吡咯烷 -1- 基）甲基、1- 吡咯烷基、酰氨基、氰基、甲氧基、苯基、4- 甲基苯基 - 磺酰基、苄基或 2-(苄基氨基)-2- 氧代乙基。

[1731] 在该实施方案中，更具体部分 R3 选自 2-(甲氨基)-1，3- 噻唑 -5- 基；2- 吡咯烷 -1- 基 -1，3- 噻唑 -5- 基；5- 溴 -1H- 咪唑 -4- 基；5- 氯 -1H- 咪唑 -4- 基；1H- 咪唑 -5- 基；1- 甲基 -1H- 咪唑 -5- 基；4- 溴 -1- 甲基 -1H- 咪唑 -5- 基；4- 氯 -1H- 咪唑 -5- 基；4- 氯 -1- 甲基 -1H- 咪唑 -5- 基；4- 氰基 -1- 甲基 -1H- 咪唑 -5- 基；1H- 吡唑 -4- 基；3，5- 二甲基 -1H- 吡唑 -4- 基；3- 甲基 -1H- 吡唑 -4- 基。

[1732] 在该实施方案中，最具体部分 R3 选自 5- 溴 -1H- 咪唑 -4- 基；5- 氯 -1H- 咪唑 -4- 基；1H- 咪唑 -5- 基；4- 溴 -1- 甲基 -1H- 咪唑 -5- 基；4- 氯 -1- 甲基 -1H- 咪唑 -5- 基；1H- 吡唑 -4- 基。

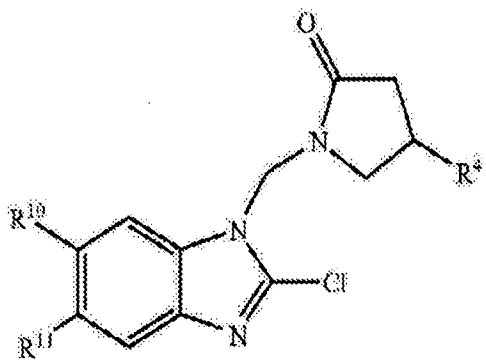
[1733] 仍然在该实施方案中，具体部分 R1 选自氢或乙基。

[1734] 仍然在该实施方案中，具体部分 R4 选自氢、正 - 丙基、2，3，5- 三氟苯基或苯基。

[1735] 本发明的另一个实施方案在于具有具体的式 (Ia) 的化合物。

[1736]

(Ia)



[1737] 在式 (Ia) 中，取代基 R10 为氢；卤素；被至少一个卤素任选地取代的 C1-4 烷基；C1-4 烷氧基；甲氧羰基；硝基；氨基；烷基氨基；酰氨基；或烷酰基 - 氨基。优选的是 R10 为氢。

[1738] R11 为氢；卤素；被至少一个卤素任选地取代的 C1-4 烷基；C1-4 烷氧基；甲氧羰基；硝基；氨基；烷基氨基；酰氨基；或烷酰氨基。优选的是 R11 为氢。

[1739] R4 为被至少一个卤素任选地取代的 C1-4 烷基；或被至少一个卤素任选地取代的 C2-4 烯基。优选的是 R4 为正 - 丙基。

[1740] 仍然在本发明的该方面，具体的实施方案涉及其中 R10 选自氢；甲基；氟；氯；溴；

甲氧基；甲氧羰基；硝基；或三氟甲基；而 R11 选自氢；甲基；氟；氯；溴；甲氧基；甲氧羰基；硝基；或三氟甲基；且 R3 为正 - 丙基的实施方案。

[1741] 本发明具体的化合物为选自下列的那些：

[1742] 1-[(1- 甲基 -1H- 苯并咪唑 -6- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1743] 1-(1H- 苯并咪唑 -7- 基甲基)-4- 丙基吡咯烷 -2- 酮；

[1744] 1-(咪唑并 [1,2-a] 吡啶 -3- 基甲基)-4- 丙基吡咯烷 -2- 酮；

[1745] 1-{[6- 氯 -2-(4- 甲基苯基) 咪唑并 [1,2-a] 吡啶 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1746] 1-{[2-(4- 氯苯基)-6- 甲基咪唑并 [1,2-a] 吡啶 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1747] 1-[(5- 甲基咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 苯基吡咯烷 -2- 酮；

[1748] 1-(咪唑并 [1,2-a] 吡啶 -3- 基甲基)-4- 苯基吡咯烷 -2- 酮；

[1749] 1-[(6- 甲基咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1750] 1-[(6- 溴咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1751] 1-[(8- 甲基咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1752] 1-[(6- 碘咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1753] 1-{[8- 氯 -6-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1754] 1-[(7- 甲基咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1755] 1-[(6,8- 二溴咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1756] 1-[(6,8- 二氯咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1757] 1-[(6- 氯咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1758] 1-[(2- 氯咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1759] 1-[(2- 环丙基 -6- 氟咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4-(2,2- 二氟乙烯基) 吡咯烷 -2- 酮；

[1760] 1-[(6- 氯 -2- 环丙基咪唑并 [1,2-a] 吡啶 -3- 基）甲基]-4-(2,2- 二氟乙烯基) 吡咯烷 -2- 酮；

[1761] 1-(咪唑并 [1,2-a] 嘧啶 -3- 基甲基)-4- 丙基吡咯烷 -2- 酮；

[1762] 1-{[2-(4- 氯苯基) 咪唑并 [1,2-a] 嘧啶 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1763] 1-(咪唑并 [1,2-a] 嘧啶 -3- 基甲基)-4- 苯基吡咯烷 -2- 酮；

[1764] 1-[(6- 氯咪唑并 [1,2-a] 嘧啶 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1765] 1-{[6- 氯 -2-(三氟甲基) 咪唑并 [1,2-a] 嘧啶 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1766] 1-[(6- 苯基咪唑并 [1,2-b][1,2,4] 三嗪 -7- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1767] 1-{[6- 氯 -2-(4- 甲基苯基) 咪唑并 [1,2-b] 哒嗪 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1768] 1-{[6- 氯 -2-(4- 氯苯基) 咪唑并 [1,2-b] 哒嗪 -3- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[1769] 1-[(6- 氯咪唑并 [1,2-b] 哒嗪 -3- 基）甲基]-4- 丙基吡咯烷 -2- 酮；

[1770] 1-[(6-氯咪唑并[1,2-b]哒嗪-3-基)甲基]-4-苯基吡咯烷-2-酮；

[1771] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1772] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1773] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1774] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1775] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-苯基吡咯烷-2-酮；

[1776] 5-氯-1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-1,3-二氢-2H-吲哚-2-酮；

[1777] 1-{[6-甲氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1778] 1-[(6-氯-2-环丙基咪唑并[1,2-b]哒嗪-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1779] 1-{[6-异丙氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1780] 1-{[6-(苄氧基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1781] 1-{[6-环丙基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1782] 1-{[6-(二甲氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1783] 4-(2,2-二氟乙烯基)-1-{[6-甲氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1784] 4-(2-氯-2,2-二氟乙基)-1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1785] 1-{[6-(甲氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1786] 1-{[6-羟基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1787] 1-{[6-(甲硫基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1788] 4-(2-溴-2,2-二氟乙基)-1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1789] 1-{[6-(甲基磺酰基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1790] 1-{[6-(甲基亚磺酰基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1791] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2,2-三氟乙基)吡咯烷-2-酮;

[1792] 1-[(6-氯-2-环丁基咪唑并[1,2-b]哒嗪-3-基)甲基]-4-丙基吡咯烷-2-酮;

[1793] 1-{[6-氯-2-(4-甲基苯基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1794] 1-{[6-氨基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮;

[1795] 1-{[6-(乙基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-丙基吡咯烷-2-酮;

[1796] 4-丙基-1-{[6-(丙基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1797] 4-(2-溴-2,2-二氟乙基)-1-{[6-(丙基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1798] 4-(2,2-二氟乙烯基)-1-{[6-(丙基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1799] 4-(2,2-二氟乙烯基)-1-{[6-甲氧基-2-(4-甲基苯基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1800] 4-丙基-1-{[6-吡咯烷-1-基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1801] 4-(2-溴-2,2-二氟乙基)-1-{[6-甲氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1802] 1-{[6-(环丙基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1803] 1-[(6-氯-2-环丙基咪唑并[1,2-b]哒嗪-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1804] 4-(2,2-二氟乙烯基)-1-{[6-(异丙基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1805] 4-(2,2-二氟乙烯基)-1-{[2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1806] 1-{[2-环丙基-6-(丙基氨基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1807] 1-({2-环丙基-6-[(2-氟乙基)氨基]咪唑并[1,2-b]哒嗪-3-基}甲基)-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1808] 1-({2-环丙基-6-[(2,2-二氟乙基)氨基]咪唑并[1,2-b]哒嗪-3-基}甲基)-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1809] 1-({2-环丙基-6-[(2,2,2-三氟乙基)氨基]咪唑并[1,2-b]哒嗪-3-基}甲基)-4-(2,2-二氟乙烯基)吡咯烷-2-酮;

[1810] 4-(2,2-二氟乙基)-1-{[2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮;

[1811] 1-{[2-环丙基-6-(环丙基氨基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1812] 1-[(6-氯-2-环丁基咪唑并[1,2-b]哒嗪-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1813] 1-[(6-氯-2-环丙基咪唑并[1,2-b]哒嗪-3-基)甲基]-4-(3-氯-4-氟苯基)吡咯烷-2-酮；

[1814] 1-{[6-(丁基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1815] 1-{[6-(环丁基氨基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1816] 1-[(2-环丙基-6-甲氧基咪唑并[1,2-b]哒嗪-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1817] 4-(2,2-二氟乙烯基)-1-{[6-乙氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1818] 4-(2,2-二氟乙烯基)-1-{[6-异丙氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1819] 1-{[6-(环丙基甲氧基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1820] 1-{[6-(环丁基甲氧基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1821] 1-{[6-(环丙氧基)-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1822] 4-(2,2-二氟乙烯基)-1-{[6-丙氧基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1823] 3-{[4-(2,2-二氟乙烯基)-2-氧代吡咯烷-1-基]甲基}-2-(三氟甲基)咪唑并[1,2-b]哒嗪-6-腈；

[1824] 4-(2,2-二氟乙烯基)-1-{[6-噻吩-3-基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1825] 4-(2,2-二氟乙烯基)-1-{[6-苯基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1826] 4-(2,2-二氟乙烯基)-1-{[6-甲基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1827] 4-(2,2-二氟乙烯基)-1-{[6-吡啶-3-基-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1828] 4-丙基-1-{[2-(三氟甲基)-5,6,7,8-四氢咪唑并[1,2-b]哒嗪-3-基]甲基}吡咯烷-2-酮；

[1829] 1-[(6-甲基咪唑并[2,1-b][1,3,4]噻二唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1830] 1-{[6-(4-甲基苯基)咪唑并[2,1-b][1,3,4]噻二唑-5-基]甲基}-4-丙基吡咯烷-2-酮；

[1831] 1-[(2-环丙基-6-苯基咪唑并[2,1-b][1,3,4]噻二唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1832] 1-[(6-甲基咪唑并[2,1-b][1,3]噻唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1833] 1-[(6-氯咪唑并[2,1-b][1,3]噻唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1834] 1-[(2,6-二氯咪唑并[2,1-b][1,3]噻唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1835] 1-(3H-咪唑并[4,5-b]吡啶-7-基甲基)-4-丙基吡咯烷-2-酮；

[1836] 1-(3H-咪唑并[4,5-b]吡啶-7-基甲基)-4-苯基吡咯烷-2-酮；

[1837] 4-苯基-1-[(5-苯基-3H-咪唑并[4,5-b]吡啶-7-基)甲基]吡咯烷-2-酮；

[1838] 4-苯基-1-{[5-(三氟甲基)-3H-咪唑并[4,5-b]吡啶-7-基]甲基}吡咯烷-2-酮；

[1839] 1-[(6-溴-3H-咪唑并[4,5-b]吡啶-7-基)甲基]-4-丙基吡咯烷-2-酮；

[1840] 1-[(2-苯基-3H-咪唑并[4,5-b]吡啶-7-基)甲基]-4-丙基吡咯烷-2-酮；

[1841] 1-[(5-甲基-3H-咪唑并[4,5-b]吡啶-7-基)甲基]-4-丙基吡咯烷-2-酮；

[1842] 1-[(2-甲基-3H-咪唑并[4,5-b]吡啶-7-基)甲基]-4-丙基吡咯烷-2-酮；

[1843] 4-丙基-1-{[5-(三氟甲基)-3H-咪唑并[4,5-b]吡啶-7-基]甲基}吡咯烷-2-酮；

[1844] 1-[(6-甲基-3H-咪唑并[4,5-b]吡啶-7-基)甲基]-4-丙基吡咯烷-2-酮；

[1845] 1-[(6-苯基-3H-咪唑并[4,5-b]吡啶-7-基)甲基]-4-丙基吡咯烷-2-酮；

[1846] 1-[1-(1H-咪唑-4-基)丙基]吡咯烷-2-酮；

[1847] 1-[(5-甲基-1H-咪唑-4-基)甲基]吡咯烷-2-酮；

[1848] 1-[(2-甲基-1H-咪唑-4-基)甲基]吡咯烷-2-酮；

[1849] 1-(1H-咪唑-4-基甲基)-4-丙基吡咯烷-2-酮；

[1850] 1-({1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-4-基}甲基)-4-丙基吡咯烷-2-酮；

[1851] 1-[(5-氯-1H-咪唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1852] 1-[(5-溴-1H-咪唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1853] 1-[(5-溴-1H-咪唑-4-基)甲基]-5-氯-1,3-二氢-2H-吲哚-2-酮；

[1854] 1-(1H-咪唑-5-基甲基)吡咯烷-2-酮；

[1855] 1-[(1-甲基-1H-咪唑-5-基)甲基]吡咯烷-2-酮；

[1856] 1-甲基-5-[(2-氧代吡咯烷-1-基)甲基]-1H-咪唑-4-腈；

[1857] 1-(1H-咪唑-5-基甲基)-4-苯基吡咯烷-2-酮；

[1858] 1-[(1-甲基-1H-咪唑-5-基)甲基]-4-苯基吡咯烷-2-酮；

[1859] 1-[(4-甲氧基-1-甲基-1H-咪唑-5-基)甲基]吡咯烷-2-酮；

[1860] 1-[(1-甲基-1H-咪唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1861] 1-甲基-5-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-4-腈；

[1862] 1-甲基-5-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-4-甲酰胺；

[1863] N-苄基-2-{5-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-1-基}乙酰胺；

[1864] 1-甲基-5-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-2-腈；

[1865] 1-[(4-氯-1H-咪唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1866] 1-甲基-5-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[1867] 1-[(4-溴-1-甲基-1H-咪唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1868] 1-[(2,4-二氯-1-甲基-1H-咪唑-5-基)甲基]-4-丙基吡咯烷-2-酮;1-甲基-5-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-2-基氨基甲酸苄酯；

[1869] 1-[(4-氯-1-甲基-1H-咪唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1870] 1-[(2-氯-1-甲基-1H-咪唑-5-基)甲基]-4-丙基吡咯烷-2-酮；

[1871] 5-氯-1-(1H-咪唑-5-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1872] 1-[(2,4-二氯-1H-咪唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1873] 1-[(2,4-二氯-1-甲基-1H-咪唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1874] 1-[(2-氯-1-甲基-1H-咪唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1875] 1-[(4-溴-1-甲基-1H-咪唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1876] 5-氯-1-[(1-甲基-1H-咪唑-5-基)甲基]-1,3-二氢-2H-吲哚-2-酮；

[1877] 1-[(4-氯-1-甲基-1H-咪唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1878] 1-(1H-吲哚-2-基甲基)-4-丙基吡咯烷-2-酮；

[1879] 1-(1H-吲哚-3-基甲基)-4-丙基吡咯烷-2-酮；

[1880] 3-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-吲哚-5-腈；

[1881] 1-[(2-甲基-1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1882] 1-[(7-甲氧基-1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1883] 1-[(6-硝基-1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1884] 4-丙基-1-{[6-(三氟甲基)-1H-吲哚-3-基]甲基}吡咯烷-2-酮；

[1885] 1-[(5-硝基-1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1886] 1-[(7-氟-1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1887] 1-[(5-氯-2-甲基-1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1888] 1-[1H-吲哚-3-基(苯基)甲基]-4-丙基吡咯烷-2-酮；

[1889] 1-[1-(1H-吲哚-3-基)丙基]-4-丙基吡咯烷-2-酮；

[1890] 1-[2-呋喃基(1H-吲哚-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1891] 3-[(2-氧代-4-丙基吡咯烷-1-基)(苯基)甲基]-1H-吲哚-5-腈；

[1892] 1-(1H-吲哚-4-基甲基)-4-丙基吡咯烷-2-酮；

[1893] 1-(1H-吲哚-7-基甲基)-4-丙基吡咯烷-2-酮；

[1894] 1-(异噁唑-4-基甲基)-4-丙基吡咯烷-2-酮；

[1895] 1-[(1-苯基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1896] 1-[(1-甲基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1897] 1-[(1-苄基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1898] 4-(2,3,5-三氟苯基)-1-[(1,3,5-三甲基-1H-吡唑-4-基)甲基]吡咯烷-2-酮；

[1899] 4-苯基-1-(1H-吡唑-4-基甲基)吡咯烷-2-酮；

[1900] 1-({1-[(4-甲基苯基)磺酰基]-1H-吡唑-4-基}甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1901] 1-(1H-吡唑-4-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1902] 1-[(5-氯-1,3-二甲基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1903] 1-[(1-氯-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1904] 1-[(3,5-二甲基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1905] 1-[(3-甲基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1906] 1-[(5-氨基-1,3-二甲基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1907] 1-[(5-氨基-1-甲基-1H-吡唑-4-基)甲基]-4-丙基吡咯烷-2-酮；

[1908] (-)-1-(1H-吡唑-4-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1909] (+)-1-(1H-吡唑-4-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1910] 1-(1H-吡唑-4-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1911] 5-氯-1-(1H-吡唑-4-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[1912] 5-氯-1-({1-[(4-甲基苯基)磺酰基]-1H-吡唑-4-基}甲基)-1,3-二氢-2H-吲哚-2-酮；

[1913] 1-{[5-氯-1-甲基-3-(三氟甲基)-1H-吡唑-4-基]甲基}-4-丙基吡咯烷-2-酮；

[1914] 1-[(5-氨基-1H-吡唑-4-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1915] 1-[(1-苄基-5-氯-1H-吡唑-4-基)甲基]-4-丙基吡咯烷-2-酮；

[1916] 1-[(1,3-二甲基-1H-吡唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1917] 1-(1H-吡唑-5-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1918] 1-[(4-溴-1-甲基-1H-吡唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1919] 1-[(1-甲基-1H-吡唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1920] 1-[(6-溴-2-甲基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1921] 1-[(2-甲基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1922] 1-[(6-溴-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1923] 1-[(6-溴-2-噻吩-2-基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1924] 4-丙基-1-[(2-噻吩-2-基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1925] 1-[(6-溴-2-环丙基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1926] 1-[(6-溴-2-叔丁基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1927] 1-[(2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1928] 1-[(2-叔丁基-6-环丙基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1929] 1-{[2-(2-呋喃基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1930] 1-[(2-甲基-6-噻吩-2-基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1931] 1-[(2-甲基-6-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1932] 1-{[2-甲基-6-(1H-吡咯-2-基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1933] 1-({6-[(1E)-己-1-烯基]-2-甲基吡唑并[1,5-a]嘧啶-3-基}甲基)-4-丙基吡咯烷-2-酮；

[1934] 1-[(6-氯-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1935] 1-{[2-甲基-6-(苯基乙炔基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1936] 1-[(6-溴-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1937] 1-[(6-羟基-2-甲基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1938] 1-[(6-甲基-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1939] 4-(2,2-二氟乙烯基)-1-[(2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1940] 1-[(6-甲氧基-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1941] 1-[(5-氯吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1942] 4-(2,2-二氟乙烯基)-1-[(5,6-二甲基-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1943] 4-(2,2-二氟乙烯基)-1-[(6-氟-5-甲基-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1944] 1-[(5-甲氧基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1945] 1-{[2-(4-溴苯基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1946] 1-{[2-(4-氟苯基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1947] 4-(2,2-二氟乙烯基)-1-[(6-甲基-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1948] 4-(2,2-二氟乙烯基)-1-[(5-甲基-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1949] 4-(2,2-二氟乙烯基)-1-[(2-噻吩-2-基吡唑并[1,5-a]嘧啶-3-基)甲基]吡咯烷-2-酮；

[1950] 1-{[2-(4-氯苯基)-6-甲基吡唑并[1,5-a]嘧啶-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1951] 1-{[2-(4-氯苯基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1952] 1-[(6-氯-2-苯基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1953] 1-{[6-氯-2-(4-氯苯基)吡唑并[1,5-a]嘧啶-3-基]甲基}-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1954] 1-[(2-环丙基-5-甲基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1955] 1-[(5-氯-2-环丙基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1956] 1-[(5-氯-2,6-二甲基吡唑并[1,5-a]嘧啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1957] 1-[(5-溴-1H-吡唑并[3,4-b]吡啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1958] 4-丙基-1-(吡啶-3-基甲基)吡咯烷-2-酮；

[1959] (-)-1-(1-吡啶-3-基丙基)吡咯烷-2-酮；

[1960] 5-氯-1-[(2-氟吡啶-3-基)甲基]-1,3-二氢-2H-吲哚-2-酮；

[1961] 1-[(6-氯吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1962] 1-{[6-(苄基氨基)吡啶-3-基]甲基}-4-丙基吡咯烷-2-酮；

[1963] 1-[(2-氨基吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1964] 4-丙基-1-(1H-吡咯并[2,3-b]吡啶-3-基甲基)吡咯烷-2-酮；

[1965] 1-[(2-异丙基-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1966] 1-[(2-苯基-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1967] 4-丙基-1-[(2-丙基-1H-吡咯并[2,3-b]吡啶-3-基)甲基]吡咯烷-2-酮；

[1968] 1-[(6-溴-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1969] 1-[(1-苯甲酰基-6-溴-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1970] 1-[(6-苯基-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1971] 1-[(5-溴-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[1972] 1-[(7-氧化-1H-吡咯并[2,3-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1973] 4-丙基-1-(1H-吡咯并[2,3-b]吡啶-4-基甲基)吡咯烷-2-酮；

[1974] 4-丙基-1-(1H-吡咯并[2,3-b]吡啶-5-基甲基)吡咯烷-2-酮；

[1975] 4-丙基-1-(1H-吡咯并[2,3-c]吡啶-2-基甲基)吡咯烷-2-酮；

[1976] 4-丙基-1-(1H-吡咯并[2,3-c]吡啶-3-基甲基)吡咯烷-2-酮；

[1977] 4-丙基-1-(1H-吡咯并[3,2-b]吡啶-3-基甲基)吡咯烷-2-酮；

[1978] 4-丙基-1-(1H-吡咯并[3,2-c]吡啶-2-基甲基)吡咯烷-2-酮；

[1979] 4-丙基-1-(1H-吡咯并[3,2-c]吡啶-3-基甲基)吡咯烷-2-酮；

[1980] 4-丙基-1-(1,3,4-噻二唑-2-基甲基)吡咯烷-2-酮；

[1981] 1-[(2-氨基-1,3-噻唑-5-基)甲基]吡咯烷-2-酮；

[1982] 1-(1,3-噻唑-5-基甲基)吡咯烷-2-酮；

[1983] 1-[(2-氯-1,3-噻唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1984] 1-{[2-(二甲氨基)-1,3-噻唑-5-基]甲基}-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1985] 1-{[2-(甲氨基)-1,3-噻唑-5-基]甲基}-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1986] 1-[(2-吡咯烷-1-基-1,3-噻唑-5-基)甲基]-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[1987] 5-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1,3-噻唑-2(3H)-酮；

[1988] 4-苯基-1-{[3-(三氟甲基)[1,2,4]三唑并[4,3-b]哒嗪-7-基]甲基}吡咯烷-2-酮；

[1989] 4-苯基-1-[(3-苯基[1,2,4]三唑并[4,3-b]哒嗪-7-基)甲基]吡咯烷-2-酮；

[1990] 4-苯基-1-{[3-(三氟甲基)[1,2,4]三唑并[4,3-b]哒嗪-8-基]甲基}吡咯烷-2-酮；

[1991] 4-丙基-1-{[3-(三氟甲基)[1,2,4]三唑并[4,3-b]哒嗪-8-基]甲基}吡咯烷-2-酮；

[1992] 4-苯基-1-[(3-苯基[1,2,4]三唑并[4,3-b]哒嗪-8-基)甲基]吡咯烷-2-酮；

[1993] 1-[(6-氯-3-苯基[1,2,4]三唑并[4,3-b]哒嗪-8-基)甲基]-4-丙基吡咯烷-2-酮；

[1994] 1-[(6-氯[1,2,4]三唑并[4,3-b]哒嗪-8-基)甲基]-4-苯基吡咯烷-2-酮；

[1995] 1-{[6-氯-3-(三氟甲基)[1,2,4]三唑并[4,3-b]哒嗪-8-基]甲基}-4-苯基吡咯烷-2-酮；

[1996] 1-[(6-氯-3-苯基[1,2,4]三唑并[4,3-b]哒嗪-8-基)甲基]-4-苯基吡咯烷-2-酮；

[1997] 1-[(2-氟吲嗪-3-基)甲基]-4-丙基吡咯烷-2-酮；

[1998] 1-(1H-1,2,3-苯并三唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[1999] 1-[(6-溴-2-氯-1H-咪唑并[4,5-b]吡啶-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2000] 1-[(6-溴-2-苯基-1H-咪唑并[4,5-b]吡啶-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2001] 1-(3H-咪唑并[4,5-b]吡啶-3-基甲基)-4-丙基吡咯烷-2-酮；

[2002] 1-[(6-溴-3H-咪唑并[4,5-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[2003] 1-[(6-溴-2-氯-3H-咪唑并[4,5-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[2004] 1-[(6-溴-2-苯基-3H-咪唑并[4,5-b]吡啶-3-基)甲基]-4-丙基吡咯烷-2-酮；

[2005] 1-[(6-溴-2-环丙基-3H-咪唑并[4,5-b]吡啶-3-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[2006] 1-[(3-氯-7H-咪唑并[4,5-c]哒嗪-7-基)甲基]-4-丙基吡咯烷-2-酮；

[2007] 1-[(2-氯-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2008] 1-[(5-甲基-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2009] 1-[(6-甲基-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2010] 1-[(2-苯基-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2011] 1-[(5-氟-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2012] 1-[(5-溴-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2013] 1-[(5-氯-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2014] 1-(2,3-二氢-1H-吲哚-1-基甲基)-4-丙基吡咯烷-2-酮；

[2015] 1-[(5-氟-2-苯基-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2016] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-吲哚-2-腈；

[2017] 1-[(2-溴-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2018] 1-[(2,5-二氯-1H-吲哚-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2019] 1-[(6-氨基-9H-嘌呤-9-基)甲基]-4-丙基吡咯烷-2-酮；

[2020] 4-丙基-1-(9H-嘌呤-9-基甲基)吡咯烷-2-酮；

[2021] 1-{[6-(环丙基氨基)-9H-嘌呤-9-基]甲基}-4-丙基吡咯烷-2-酮；

[2022] 1-{[6-(苄基氨基)-9H-嘌呤-9-基]甲基}-4-丙基吡咯烷-2-酮；

[2023] 4-丙基-1-{[6-(丙基氨基)-9H-嘌呤-9-基]甲基}吡咯烷-2-酮；

[2024] 1-({6-[(环丙基甲基)氨基]-9H-嘌呤-9-基}甲基)-4-丙基吡咯烷-2-酮；

[2025] 4-丙基-1-[(6-吡咯烷-1-基-9H-嘌呤-9-基)甲基]吡咯烷-2-酮；

[2026] 1-[(5-溴-3-苯基-1H-吡唑并[3,4-b]吡啶-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2027] 1-[(5-溴-2H-吡唑并[3,4-b]吡啶-2-基)甲基]-4-丙基吡咯烷-2-酮；

[2028] 1-[(5-溴-3-苯基-2H-吡唑并[3,4-b]吡啶-2-基)甲基]-4-丙基吡咯烷-2-酮；

[2029] 1-[(2-氯-1H-吡咯并[2,3-b]吡啶-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2030] 4-丙基-1-(1H-吡咯并[3,2-b]吡啶-1-基甲基)吡咯烷-2-酮；

[2031] 1-(3,4-二氢喹啉-1(2H)-基甲基)-4-丙基吡咯烷-2-酮；

[2032] 1-(8H-异噻唑并[5,4-b]吲哚-8-基甲基)-4-丙基吡咯烷-2-酮；

[2033] 1-(1H-1,2,4-三唑-1-基甲基)吡咯烷-2-酮；

[2034] 1-[(2,5-二氯-1H-吡咯-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2035] 1-[(2-氯-1H-吡咯-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2036] 1-[(2-氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2037] 1-[(2-氯-1H-苯并咪唑-1-基)甲基]-4-苯基吡咯烷-2-酮；

[2038] 2-氯-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[2039] 2-氯-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-6-腈；

[2040] 4-丙基-1-[(2,5,6-三氯-1H-苯并咪唑-1-基)甲基]吡咯烷-2-酮；

[2041] 1-[(2-氯-6-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2042] 1-[(2-氯-5-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2043] 1-[(2-氯-6-硝基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2044] 1-[(2-氯-5-硝基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2045] 1-[(2-氯-6-甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2046] 1-[(2-氯-1H-苯并咪唑-1-基)甲基]-4-(2,2-二氟乙烯基)吡咯烷-2-酮；

[2047] 1-[(6-溴-2-氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2048] 1-[(5-溴-2-氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2049] 1-[(2-氯-6-氟-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2050] 1-[(2-氯-5-氟-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2051] 1-[(2,6-二氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2052] 1-[(2,5-二氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2053] 1-{[2-氯-6-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2054] 1-{[2-氯-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2055] 1-[(2-氯-1H-苯并咪唑-1-基)甲基]吡咯烷-2-酮；

[2056] 1-[(2-氯-6-羟基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2057] 1-(吡啶-4-基甲基)吡咯烷-2-酮；和

[2058] 1-[(2-氯-5-羟基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮。

[2059] viii) 美国专利4,696,943

[2060] 本发明涉及新化合物(S)-α-乙基-2-氧代-1-吡咯烷乙酰胺。

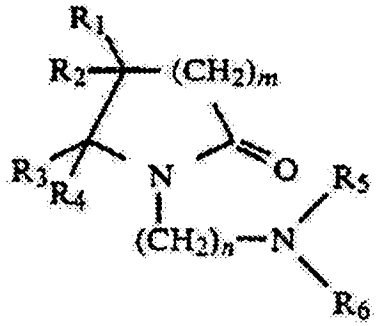
[2061] ix) 美国专利4,696,942

[2062] 本发明涉及新化合物(R)-α-乙基-2-氧代-1-吡咯烷乙酰胺。

[2063] x) 美国专利5,334,720

[2064] 根据本发明我们提供了式I的新化合物，

[2065]



I.

[2066] 其中，R1、R2、R3和R4，其可以相同或不同，独立地表示氢、C1-6烷基、苯基或经一个或多个卤素、羟基、硝基、氨基、C1-6烷基或C1-C6烷氧基取代的苯基；

[2067] R5和R6独立地表示氢、C1-C6烷基或C3-C6环烷基，或R5和R6连同氮一起形成C4-6N杂环；

[2068] m表示1-2的整数；且

[2069] n表示1-3的整数。

[2070] 条件是，

[2071] 取代基R1、R2、R3和R4中的两个独立地表示苯基或取代的苯基，并且其它的两个独立地表示氢或C1-6烷基；

[2072] 或其药学上可接受的酸加成盐。

[2073] 式I化合物的药学上可接受的酸加成盐包括无机酸，例如氢卤酸(例如盐酸或氢溴酸)；或有机酸(例如甲酸、乙酸或乳酸)的盐。所述酸可为多元的，例如硫酸、富马酸、马来酸或柠檬酸。

[2074] 本发明还涉及式I化合物的所有的立体异构体形式和光学对映异构形式。

[2075] 在式I化合物中：R1、R2、R3、R4、R5和R6可以表示的烷基包括甲基、乙基、丙基、异丙基、正-丁基、异-丁基和仲-丁基；

[2076] R5和R6可以表示的环烷基包括环丙基、环丁基、环戊基和环己基；

[2077] C1-6烷氧基包括甲氧基、乙氧基和丙氧基；

[2078] 卤素基团包括氟、氯、溴或碘；

[2079] 我们优选式 I 化合物或其药学上可接受的酸加成盐，其中：

[2080] R1 为氢、苯基或取代的苯基，优选的是苯基；

[2081] R2 为氢、苯基或取代的苯基，优选的是苯基；

[2082] R3 为氢、苯基或取代的苯基，优选的是氢；

[2083] R4 为氢、苯基或取代的苯基，优选的是氢；

[2084] R5 为氢，C1-3 烷基或环丙基，优选的是氢或甲基；

[2085] R6 为氢，C1-3 烷基或环丙基，优选的是氢或甲基；

[2086] m 表示 1-2 的整数，优选的是 2；

[2087] n 表示 1-2 的整数，优选的是 1；

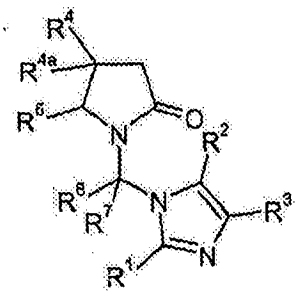
[2088] 我们特别优选式 I 化合物，其中 R1 和 R2 都为苯基。

[2089] 我们特别优选式 I 化合物，其中 R5 和 R6 之一为氢，而另外一个为氢或甲基。

[2090] xi) 国际专利申请公开文本第 WO2005/054188 号

[2091] 一个方面本发明因此提供了具有式 I 的化合物或其药学上可接受的盐，

[2092]



(I)

[2093] 其中

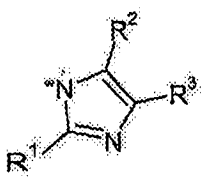
[2094] RI 为氢、CI-20 烷基、C323 环烷基、卤素、羟基、烷氧基、芳氧基、酯、酰氨基、氰基、硝基、氨基、胍、氨基衍生物、烷硫基、芳硫基、烷基磺酰基、芳基磺酰基、烷基亚磺酰基、芳基亚磺酰基、芳基或杂环；

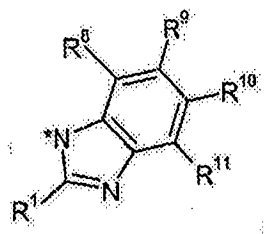
[2095] R2 为氢、C120 烷基、烷氧基、氨基、卤素、羟基、酯、酰氨基、硝基、氰基、氨基甲酸酯或芳基；

[2096] R3 为氢、C120 烷基、烷氧基、氨基、卤素、羟基、酯、酰氨基、硝基、氰基、氨基甲酸酯或芳基；

[2097] 或 R2 和 R3 可连同咪唑环一起形成下列 1H- 苯并咪唑环

[2098]





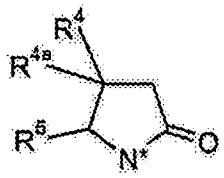
[2099] R4 为氢、C1-20 烷基、C2-12 烯基、C2-12 炔基、芳基、叠氮基、烷氧基羰基氨基、芳基磺酰基氧基或杂环；

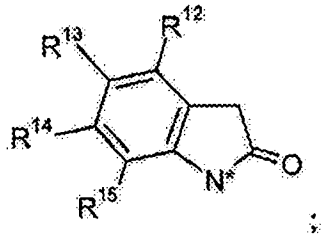
[2100] R4a 为氢或 C1-20 烷基 ;或 R4 和 R4a 可一起形成 C3-8 环烷基 ;

[2101] R5 为氢 ;或

[2102] R4、R4a 和 R5 可连同 2- 氧代 -1- 吡咯烷环一起形成下列 1,3- 二氢 -2H- 吲哚 -2- 酮环

[2103]





;

[2104] R6 为氢或 C120 烷基 ;

[2105] R7 为氢 ;或

[2106] 将 R6 和 R7 连接在一起以形成 C3-6 环烷基 ;

[2107] R8 为氢、卤素、硝基、氰基、C120 烷基或烷氧基 ;

[2108] R9 为氢、C1-20 烷基、卤素、羟基、烷氧基、芳氧基、酯、酰氨基、氰基、硝基、氨基、氨基衍生物、烷硫基、芳硫基、烷基磺酰基、芳基磺酰基、烷基亚磺酰基或芳基亚磺酰基 ;

[2109] RIO 为氢、C120 烷基、卤素、羟基、烷氧基、芳氧基、酯、酰氨基、氰基、硝基、氨基、氨基衍生物、烷硫基、芳硫基、烷基磺酰基、芳基磺酰基、烷基亚磺酰基或芳基亚磺酰基 ;

[2110] RI1 为氢、卤素、硝基、氰基、C120 烷基或烷氧基 ;

[2111] R12 为氢或卤素 ;

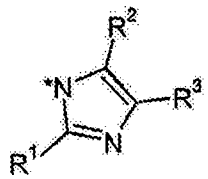
[2112] R13 为氢、硝基、卤素、杂环、氨基、芳基、未取代的或被卤素取代的 C1-20 烷基,或未取代的或被卤素取代的烷氧基 ;

[2113] R14 为氢、C1-20 烷基或卤素 ;

[2114] R15 为氢、C120 烷基或卤素 ;

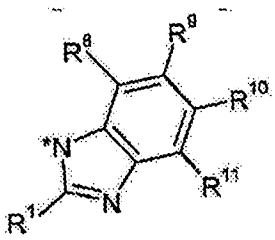
[2115] 条件是当

[2116]



[2117] 表示式

[2118]

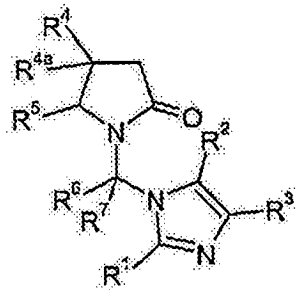


[2119] 的基团时,R4 不是氢。

[2120] 星号 * 表示取代基的连接点。

[2121] 在优选的实施方案中，本发明涉及具有式 I 的化合物、它们的互变异构体、几何异构体（包括顺式和反式、Z 和 E 异构体）、对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体的混合物），或其药学上可接受的盐，

[2122]



(I)

[2123] 其中

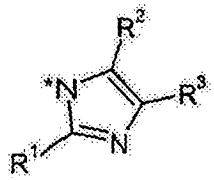
[2124] RI 为氢、C1-20 烷基、C3-8 环烷基、卤素、羟基、酯、酰氨基、氰基、硝基、氨基、胍、烷硫基、烷基磺酰基、烷基亚磺酰基、芳基或杂环；

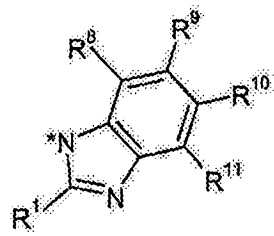
[2125] R2 为氢、C120 烷基、卤素、氰基、酯、氨基甲酸酯或酰氨基；

[2126] R3 为氢、氰基、C120 烷基、卤素或酯；或

[2127] R2 和 R3 可连同咪唑环一起形成下列 1H- 苯并咪唑环

[2128]





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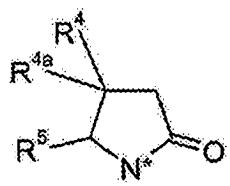
[2129] R4 为氢、C120 烷基、C212 烯基或芳基；

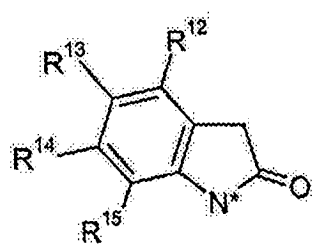
[2130] R4a 为氢；

[2131] R5 为氢；或

[2132] R4、R4a 和 R5 可连同 2- 氧代 -1- 吡咯烷环一起形成下列 1,3- 二氢 -2H- 吲哚 -2- 酮环

[2133]





；

[2134] R6 为氢或 C120 烷基；

[2135] R7 为氢；或将 R6 和 R7 连接在一起以形成 C3-6 环烷基；

[2136] R8 为氢；

[2137] R9 为氢、C120 烷基、卤素或烷氧基；

[2138] R10 为氢、C1-20 烷基、卤素或氰基；

[2139] R11 为氢；

[2140] R12 为氢或卤素；

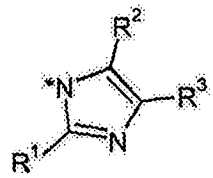
[2141] R13 为氢、卤素、杂环或 C120 烷基；

[2142] R14 为氢；

[2143] R15 为氢；

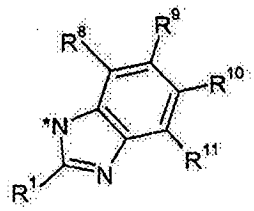
[2144] 条件是当

[2145]



[2146] 表示式

[2147]



[2148] 的基团时，R4 不是氢。

[2149] 如本文使用的术语“烷基”，表示饱和的、单价烃残基，该残基具有直链（非支链）或支链或环状或其组合，并含有 1-20 个碳原子，优选的是 1-10 个碳原子，更优选的是 1-4 个碳原子；最优选的烷基具有 1-3 个碳原子。烷基部分可被独立选自下列的 1-5 个取代基任选地取代：卤素、羟基、氰基、叠氮基、芳氧基、烷氧基、烷硫基、烷酰氨基、芳基羰基氨基、氨基羰基、甲氨基羰基、二甲氨基羰基或芳基。通常烷基，在存在的情况下，为甲基、乙基、正－丙基、异－丙基、正－丁基、异－丁基、叔－丁基、1-乙基丙基、正－庚基、2,4,4-三甲基戊基、正－癸基、氯甲基、三氟甲基、2-溴-2,2-二氟乙基、2,2,2-三氟乙基、3,3,3-三氟丙基、羟甲基、氰基甲基、叠氮基甲基、（乙酰氨基）甲基、（丙酰氨基）甲基、（苯甲酰氨基）甲基、(4-氯苯氧基）甲基、苄基、2-苯基乙基或 2-（甲硫基）乙基。优选的烷基为甲基、乙基、正－丙基、异－丙基、正－丁基、异－丁基、叔－丁基、1-乙基丙基、2,4,4-三甲基戊基、氯甲基、三氟甲基、2,2,2-三氟乙基、羟甲基、氰基甲基、叠氮基甲基、（乙酰氨基）甲基、（丙酰氨基）甲基、（苯甲酰氨基）甲基或 2-（甲硫基）乙基。更优选的烷基为甲基、乙基、正－丙基、异－丙基、正－丁基、叠氮基甲基或三氟甲基。最优选的烷基为甲基或正－丙基。

[2150] 如本文使用的术语“环烷基”，表示衍生自饱和环烃的 3-8 个碳原子，通常为 3-6 个碳原子的单价基团，其可被任何适合的基团（包括但不限于选自如上所述用于烷基的基团的一个或多个部分）取代。优选的环烷基为环丙基和环己基。

[2151] 如本文使用的术语“烯基”，表示具有至少一个碳－碳双键，含有 2-12 个碳原子，优选的是通常为 2-4 个碳原子的直链、支链或环状的不饱和的烃残基或其组合。将烯基用任何适合的基团任选地取代，该适合的基团包括但不限于选自如上所述用于烷基的基团一个

或多个部分。通常烯基为被 1-3 个卤素任选地取代的乙烯基 (ethenyl)(乙烯基 (vinyl))。优选的烯基，在现在的情况下，为 2,2- 二氟乙烯基。

[2152] 如本文使用的术语“炔基”，表示直链、支链或环状烃残基或其组合，该残基含有至少一个碳 - 碳三键，含有 2-12 个碳原子，优选的是 2-6 个碳原子，并且经任何适合的基团任选地取代，该适合的基团包括但不限于选自如上所述用于烷基的基团一个或多个部分。优选的是炔基为卤炔基 (卤代炔基)。

[2153] 通过例如“仲”、“异”、“叔”等的前缀限定的基团 (例如“异 - 丙基”、“仲 - 丁基”) 为支链衍生物。

[2154] 如本文使用的术语“芳基”，经定义为被独立地选自以下的 1-4 个取代基任选地取代的苯基 : 卤素、氰基、烷氧基、烷硫基、C1-3 烷基或叠氮基，优选的是卤素或叠氮基。通常芳基，在存在的情况下为苯基、3- 氯苯基、3- 氟苯基、4- 氯苯基、4- 氟苯基、3,4- 二氟苯基、3,5- 二氟苯基、3- 氯 -4- 氟苯基、2,3,4- 三氟苯基、2,4,5- 三氟苯基、2,3,5- 三氟苯基、3,4,5- 三氟苯基、3- 叠氮基 -2,4- 二氟苯基或 3- 叠氮基 -2,4,6- 三氟苯基。优选的是，芳基为苯基、3- 氯苯基、3- 氟苯基、4- 氯苯基、4- 氟苯基、3,4- 二氟苯基、3,5- 二氟苯基、3- 氯 -4- 氟苯基、2,3,4- 三氟苯基、2,4,5- 三氟苯基、2,3,5- 三氟苯基、3,4,5- 三氟苯基或 3- 叠氮基 -2,4- 二氟苯基。最优选的芳基为苯基、3- 氯苯基、3- 氟苯基、3,5- 二氟苯基、2,3,4- 三氟苯基、2,4,5- 三氟苯基、2,3,5- 三氟苯基、3,4,5- 三氟苯基或 3- 叠氮基 -2,4- 二氟苯基。

[2155] 如本文使用的术语“杂环”，被定义为包括如上文所定义的芳族的或非芳族的环烷基部分，其具有至少一个间隔碳环结构的 O、S 和 / 或 N 原子。杂环部分可被烷基或卤素任选地取代，并任选地，碳环结构的碳之一可被羰基替代。通常杂环为 2- 吡啶基、3- 吡啶基、4- 吡啶基、2- 呋喃基、3- 呋喃基、2- 噻吩基、3- 噻吩基、2- 四氢呋喃基、1H- 吡咯 -2- 基、1- 甲基 -1H- 吡咯 -2- 基、1H- 吡唑 -2- 基、1H- 吡唑 -3- 基、4- 氯 -1- 甲基 -1H- 吡唑 -3- 基、5- 氯 -1,3- 二甲基 -1H- 吡唑 -4- 基、1,2,3- 噻二唑 -4- 基、3,5- 二甲基 -4- 异噻唑基、1H- 咪唑 -2- 基、1- 甲基 -1H- 咪唑 -2- 基、4- 甲基 -1H- 咪唑 -5- 基或 2- 甲基 -1,3- 噻唑 -4- 基。优选的杂环为 1H- 咪唑 -2- 基、1,2,3- 噻二唑 -4- 基、1H- 吡唑 -3- 基、2- 呋喃基、3- 呋喃基、2- 噻吩基、1- 甲基 -1H- 吡咯 -2- 基、1H- 吡咯 -2- 基。

[2156] 如本文使用的术语“卤素”，包括氯、溴、氟、碘的原子。通常卤素为氯、溴和氟。优选的卤素为氟、溴和氯。

[2157] 如本文使用的术语“羟基”，表示式 -OH 的基团。

[2158] 如本文使用的术语“烷氧基”，表示式 -ORa 的基团，其中 Ra 为如上文所定义的烷基。优选的烷氧基为甲氧基。

[2159] 如本文使用的术语“芳氧基”，表示式 -ORb 基团，其中 Rb 为如上文所定义的芳基。优选的芳氧基为苯氧基。

[2160] 如本文使用的术语“酯”，表示式 -COORC 基团，其中 Rc 为如上文所定义的烷基或芳基。优选的酯基为甲氧羰基。

[2161] 如本文使用的术语“酰氨基”，表示式 -CONH2 的基团。

[2162] 如本文使用的术语“氨基”，表示式 -NH2 的基团。

[2163] 如本文使用的术语“氨基衍生物”，表示烷基氨基或芳基氨基，其中术语“烷基”和

“芳基”是如上文所定义的。

[2164] 如本文使用的术语“氰基”，表示式 -CN 的基团。

[2165] 如本文使用的术语“硝基”，表示式 -NO2 的基团。

[2166] 如本文使用的术语“叠氮基”，表示式 -N3 的基团。

[2167] 如本文使用的术语“胍”，表示式 -NHC(= NH)NH2 的基团。

[2168] 如本文使用的术语“烷硫基”，表示式 -SRd 的基团，其中 Rd 为如上文所定义的烷基。一个烷硫基为甲硫基。

[2169] 如本文使用的术语“烷基磺酰基”，表示式 -S(= 0)2Re 的基团，其中 Re 为如上文所定义的烷基。一个烷基磺酰基为甲磺酰基。

[2170] 如本文使用的术语“烷基亚磺酰基”，表示式 -S(= 0)Rf 基团，其中 Rf 为如上文所定义的烷基。一个烷基亚磺酰基为甲基亚磺酰基。

[2171] 如本文使用的术语“芳硫基”，表示式 -SRg 基团，其中 Rg 为如上文所定义的芳基。

[2172] 如本文使用的术语“芳基磺酰基”，表示式 -S(= 0)2Rh 基团，其中 Rh 为如上文所定义的芳基。

[2173] 如本文使用的术语“芳基亚磺酰基”，表示式 -S(= 0)Ri 基团，其中 Ri 为如上文所定义的芳基。

[2174] 术语“氨基甲酸酯”如本文使用的，表示式 -N(H)C(0)OR1 基团，其中 Ri 如上文所定义为烷基或芳基。通常氨基甲酸酯基为（丙氧基羰基）氨基或（苄氧基羰基）氨基。一个氨基甲酸酯基为（苄氧基羰基）氨基。

[2175] 如本文使用的术语“烷酰氨基”，表示式 -NHC(= 0)Rk 基团，其中 Rk 为如上文所定义的烷基。

[2176] 如本文使用的术语“（芳基羰基）氨基”，表示式 -NHC(= 0)Rm 基团，其中 Rm 为如上文所定义的芳基。一个（芳基羰基）氨基是苯甲酰氨基。

[2177] 通常，RI 为氢；未取代的或被卤素、羟基、氰基、甲硫基、苯基或 4- 氯苯氧基取代的 C1 lo 烷基；羟基；C3-6 环烷基；卤素；酯；酰氨基；硝基；氰基；氨基；苯基；烷硫基；烷基磺酰基；烷基亚磺酰基；未取代的或被烷基取代的杂环；或胍。

[2178] 在某些实施方案中，RI 为氢；甲基；乙基；异 - 丙基；正 - 丙基；环丙基；正 - 丁基；异 - 丁基；叔 - 丁基；1- 乙基丙基；2,4,4- 三甲基戊基；羟甲基；氯甲基；三氟甲基；2,2,2- 三氟乙基；氰基甲基；2-（甲硫基）乙基；氯；溴；硝基；氰基；氨基；氨基羰基；甲氧羰基；甲硫基；甲基亚磺酰基；甲磺酰基；苯基；2- 呋喃基；3- 呋喃基；1H- 吡咯 -2- 基；1- 甲基 -1H- 吡咯 -2- 基；2- 噻吩基；1H- 吡唑 -3- 基；1,2,3- 噻二唑 -4- 基或 1H- 咪唑 -2- 基。更优选的是，RI 为氢；甲基；乙基；异 - 丙基；正 - 丙基；正 - 丁基；甲硫基；硝基；氰基；氨基；氯或 1H- 吡咯 -2- 基。最优选的是，RI 为氢；甲基；甲硫基；硝基；氰基；氨基或氯。

[2179] 通常，R2 为氢；未取代的或被羟基、烷酰氨基或苯甲酰氨基取代的 C14 烷基；卤素；酯；氰基；烷基氨基甲酸酯；[(N- 甲氧基 -N- 甲基）氨基］羰基。优选的是，R2 为氢；甲基；羟甲基；（乙酰氨基）甲基；（丙酰氨基）甲基；（苯甲酰氨基）甲基；[（苄氧基）羰基］氨基；氯或氰基。在某些实施方案中，R2 为氢；氯或氰基。

[2180] 通常 R3 为氢；未取代的或被羟基取代的 C14 烷基；卤素；酯或氰基。在某些实施

方案中，R3 为氢；羟甲基；氯；氰基。

[2181] 在某些实施方案中，R3 为氢或氰基。在某些实施方案中，R3 为氢。

[2182] 通常，R4 为氢；未取代的或被卤素取代的 C14 烷基；被卤素取代的 C24 烯基或未取代的或被叠氮基或 / 和卤素取代的苯基。优选的是，R4 为氢；正 - 丙基；2,2- 二氟乙烯基；苯基；3- 氯苯基；3- 氟苯基；4- 氯苯基；4- 氟苯基；3,5- 二氟苯基；3,4- 二氟苯基；3- 氯 -4- 氟苯基；2,3,4- 三氟苯基；2,4,5- 三氟苯基；2,3,5- 三氟苯基；3,4,5- 三氟苯基；3- 叠氮基 -2,4- 二氟苯基或 3- 叠氮基 -2,4,6- 三氟苯基。更优选的是，R4 为氢；正 - 丙基；2,2- 二氟乙烯基；苯基；3- 氯苯基；3- 氟苯基；4- 氯苯基；4- 氟苯基；3,5- 二氟苯基；3,4- 二氟苯基；3- 氯 -4- 氟苯基；2,3,4- 三氟苯基；2,4,5- 三氟苯基；2,3,5- 三氟苯基；3,4,5- 三氟苯基或 3- 叠氮基 -2,4- 二氟苯基。最优选的是，R4 为正 - 丙基；2,2- 二氟乙烯基；苯基；3- 氯苯基；3- 氟苯基；3,5- 二氟苯基；2,3,4- 三氟苯基；2,4,5- 三氟苯基；2,3,5- 三氟苯基；3,4,5- 三氟苯基或 3- 叠氮基 -2,4- 二氟苯基。

[2183] 通常，R4a 为氢。

[2184] 通常，R5 为氢。

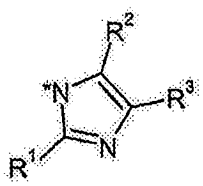
[2185] 通常，R6 为氢或未取代的或被羟基或叠氮基取代的 C1-10 烷基。优选的是，R6 为氢或叠氮基甲基。更优选的是，R6 为氢。

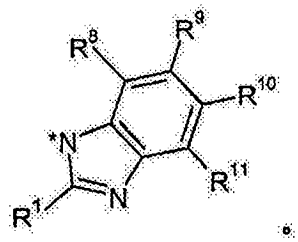
[2186] 通常 R7 为氢。

[2187] 在其它实施方案中，将 R6 和 R7 连接以形成环丙基。

[2188] 在其它实施方案中，R2 和 R3 可连同咪唑环一起形成下列 1H- 苯并咪唑环

[2189]





[2190] 通常，R8 为氢。

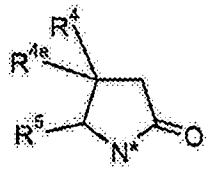
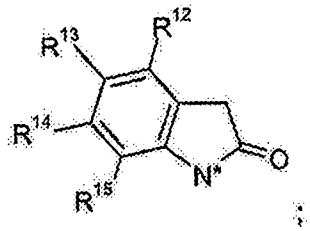
[2191] 通常，R9 为氢；卤素；1-3 烷基或烷氧基。在某些实施方案中，R9 为氢；甲基；氯；甲氧基。在某些实施方案中，R9 为氢。

[2192] 通常，RIO 为氢；卤素；氰基；未取代的或被卤素取代的 C13 烷基；或烷氧基。在某些实施方案中，RIO 为甲基；氢；三氟甲基；氟；氰基或甲氧基。在某些实施方案中，R10 为氢；三氟甲基；氟或氰基。

[2193] 通常，RI1 为氢。

[2194] 在其它实施方案中，R4、R4a 和 R5 可连同 2- 氧代 -1- 吡咯烷环一起形成下列 1,3- 二氢 -2H- 吲哚 -2- 酮环

[2195]

[2196] 通常，R12 为氢或卤素。在某些实施方案中，R12 为氢；氯或氟。在某些实施方案中，R12 为氢。

[2197] 通常，R13 为氢；C13 烷基；卤素或未取代的或被烷基取代的噻唑基，例如甲基噻唑基。在某些实施方案中，R13 为氢；氯；溴；或甲基。在某些实施方案中，R13 为氯；溴或甲基。

[2198] 通常，R14 为氢。

[2199] 通常，R15 为氢。

[2200] 在本发明的一般实施方案中，式 I 化合物，或其药学上可接受的盐，是以下那些，其中

[2201] RI 选自氢；未取代的或被卤素、羟基、氰基、甲硫基、苯基或 4- 氯苯氧基取代的 C1lo 烷基；C36 环烷基；卤素；酯；酰氨基；硝基；氰基；氨基；苯基；烷硫基；烷基磺酰基；烷基亚磺酰基；未取代的或被烷基取代的杂环；或胍；

[2202] R2 选自氢；未取代的或被羟基、烷酰氨基或苯甲酰氨基取代的 C1-4 烷基；卤素；酯；氰基；烷基氨基甲酸酯或［(N- 甲氧基 -N- 甲基）氨基］羰基。

[2203] R3 选自氢；未取代的或被羟基取代的 C14 烷基；卤素；酯或氰基；

[2204] R4 选自氢；未取代的或被卤素取代的 C14 烷基；被卤素取代的 C2-4 烯基或未取代的或被叠氮基或 / 和卤素取代的苯基；

[2205] R4a 为氢；

[2206] R5 为氢；

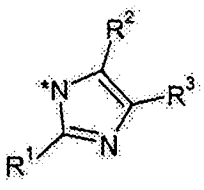
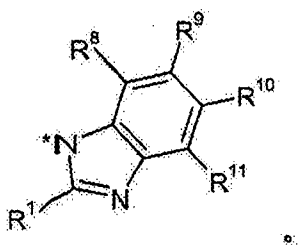
[2207] R6 选自氢或未取代的或被羟基或叠氮基取代的 C1-10 烷基；

[2208] R7 为氢；或

[2209] 可将 R6 和 R7 连接以形成环丙基；或

[2210] R2 和 R3 可连同咪唑环一起形成下列 1H- 苯并咪唑环

[2211]

[2212] R8 为氢；

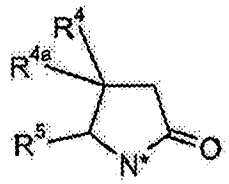
[2213] R9 选自氢；卤素；C1-3 烷基；烷氧基；

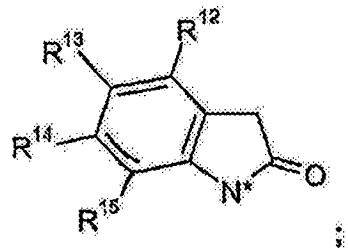
[2214] R10 选自氢；卤素；氰基或未取代的或被卤素取代的 Ci 1 烷基；或烷氧基；

[2215] R1 为氢；或

[2216] R4、R4a和R5可连同2-氧代-1-吡咯烷环一起形成下列1,3-二氢-2H-吲哚-2-酮环

[2217]





;

[2218] R12选自氢或卤素；

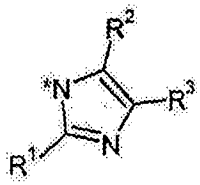
[2219] R13选自氢；CI-3烷基；卤素；未取代的或被烷基取代的噻唑基，例如甲基噻唑基；

[2220] R14为氢；

[2221] R15为氢；

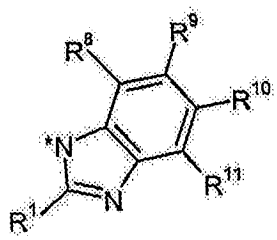
[2222] 条件是当

[2223]



[2224] 表示式

[2225]



[2226] 的基团时，R4不是氢。

[2227] 在本发明的实施方案中，式I化合物，或其药学上可接受的盐，是以下那些，其中

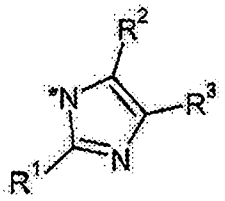
[2228] RI选自氢；甲基；乙基；异-丙基；正-丙基；环丙基；正-丁基；异-丁基；叔-丁基；1-乙基丙基；2,4,4-三甲基戊基；三氟甲基；2,2,2-三氟乙基；羟甲基；氯甲基；氰基甲基；2-(甲硫基)乙基；氯；溴；硝基；氰基；氨基；氨基羰基；甲氧羰基；甲硫基；甲基亚磺酰基；甲磺酰基；苯基；2-呋喃基；3-呋喃基；1H-吡咯-2-基；1-甲基-1H-吡咯-2-基；2-噻吩基；1H-吡唑-3-基；1,2,3-噻二唑-4-基；或1H-咪唑-2-基；

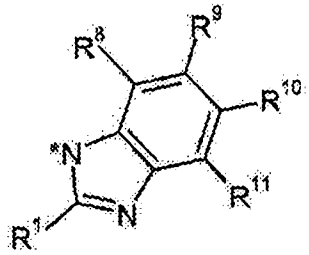
[2229] R2选自氢；甲基；羟甲基；(乙酰氨基)甲基；(丙酰氨基)甲基；(苯甲酰氨基)甲基；(苄氧基羰基)氨基；氯；或氰基；

[2230] R3选自氢；羟甲基；氯；氰基；或

[2231] R2和R3可连同咪唑环一起形成下列1H-苯并咪唑环

[2232]





[2233] R8 为氢；

[2234] R9 选自氢；甲基；氯；甲氧基；

[2235] R10 选自甲基；氢；三氟甲基；氯；氰基；或甲氧基；

[2236] R 为氢；

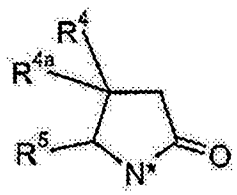
[2237] R4 选自氢；正-丙基；2,2-二氟乙烯基；苯基；3-氯苯基；3-氟苯基；4-氯苯基；4-氟苯基；3,5-二氟苯基；3,4-二氟苯基；3-氯-4-氟苯基；2,3,4-三氟苯基；2,4,5-三氟苯基；2,3,5-三氟苯基；3,4,5-三氟苯基；3-叠氮基-2,4-二氟苯基或 3-叠氮基-2,4,6-三氟苯基。

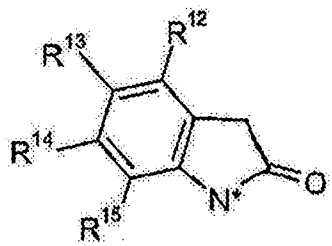
[2238] R4a 为氢；

[2239] R5 为氢；或

[2240] R4、R4a 和 R5 可连同 2-氧代-1-吡咯烷环一起形成下列 1,3-二氢-2H-吲哚-2-酮环

[2241]





[2242] R12 选自氢；氯；氟；

[2243] R13 选自氢；氯；溴；甲基；

[2244] R14 为氢；

[2245] R15 为氢；

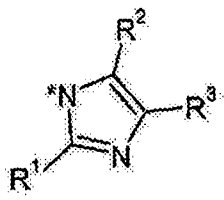
[2246] R6 选自氢；叠氮基甲基；

[2247] R7 为氢；或

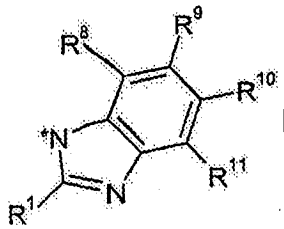
[2248] 将 R6 和 R7 连接以形成环丙基；

[2249] 条件是当

[2250]



[2251] 表示式

[2252]  的基团时，R4 不是氢。

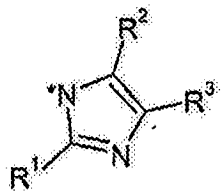
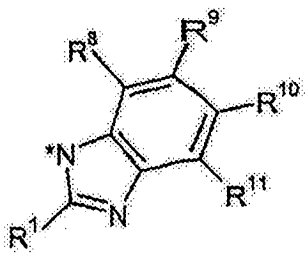
[2253] 在本发明的一个实施方案中，式 I 化合物，或其药学上可接受的盐，是以下那些，其中

[2254] RI 选自氢；甲基；乙基；异-丙基；正-丙基；正-丁基；甲硫基；硝基；氰基；氨基；氯；或 1H-吡咯-2-基；

[2255] R2 选自氢；氯；氰基；

[2256] R3 选自氢；氰基；或

[2257] R2 和 R3 可连同咪唑环一起形成下列 1H-苯并咪唑环

[2258]  

[2259] R8 为氢；

[2260] R9 为氢；

[2261] R10 选自氢；三氟甲基；氟；氰基；

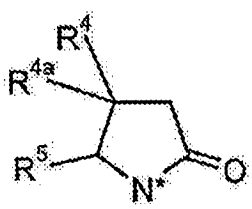
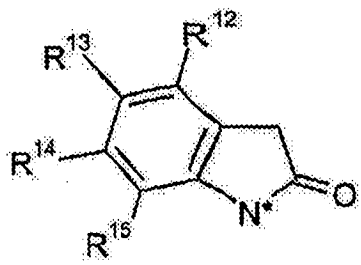
[2262] RI1 为氢；

[2263] R4 选自氢；正-丙基；2,2-二氟乙烯基；苯基；3-氯苯基；3-氟苯基；4-氯苯基；4-氟苯基；3,5-二氟苯基；3,4-二氟苯基；3-氯-4-氟苯基；2,3,4-三氟苯基；2,4,5-三氟苯基；2,3,5-三氟苯基；3,4,5-三氟苯基；或 3-叠氮基-2,4-二氟苯基；

[2264] R4a 为氢；

[2265] R5 为氢；或

[2266] R4、R4a 和 R5 可连同 2-氧代-1-吡咯烷环一起形成下列 1,3-二氢-2H-吲哚-2-酮环

[2267]  

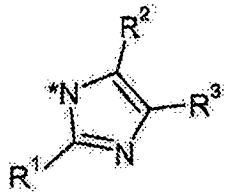
[2268] 其中 R12 为氢；

[2269] R13 选自甲基；氯；溴；

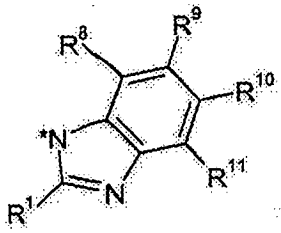
[2270] R14 为氢 ;R15 氢 ;R6 为氢 ;R7 为氢 ;

[2271] 条件是当

[2272]



[2273] R11 表示式

[2274]  的基团时，R4 不是氢。

[2275] 在本发明的一个实施方案中，式 I 化合物，或其药学上可接受的盐，是以下那些，其中

[2276] RI 选自氢 ;甲基 ;甲硫基 ;硝基 ;氰基 ;氨基 ;氯 ;

[2277] R2 选自氢 ;氯 ;氰基 ;

[2278] R3 为氢 ;

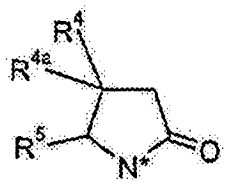
[2279] R4 选自正 - 丙基 ;2, 2- 二氟乙烯基 ;苯基 ;3- 氯苯基 ;3- 氟苯基 ;3, 5- 二氟苯基 ;2, 3, 4- 三氟苯基 ;2, 4, 5- 三氟苯基 ;2, 3, 5- 三氟苯基 ;3, 4, 5- 三氟苯基 ;3- 叠氮基 -2, 4- 二氟苯基 ;

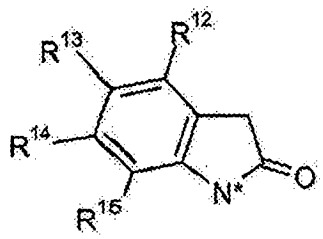
[2280] R4a 为氢 ;

[2281] R5 为氢 ;或

[2282] R4、R4a 和 R5 可连同 2- 氧代 -1- 吡咯烷环一起形成下列 1, 3- 二氢 -2H- 吲哚 -2- 酮环

[2283]





[2284] R12 为氢 ;

[2285] R13 选自氯 ;溴 ;甲基 ;

[2286] R14 为氢 ;

[2287] R15 为氢 ;

[2288] R6 为氢 ;

[2289] R7 为氢。

[2290] 在某些实施方案中，化合物为 :

[2291] 1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2292] 1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2293] 4-(3-叠氮基-2,4,6-三氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2294] 1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[2295] (-)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2296] (+)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2297] 1-[(2-乙基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2298] 1-[(2-异丙基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2299] 1-[(2-甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2300] 1-[(2-苯基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2301] 4-丙基-1-[(2-丙基-1H-咪唑-1-基)甲基]吡咯烷-2-酮；

[2302] (+)-1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[2303] (-)-1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[2304] 4-(2,2-二氟乙烯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2305] 4-(3-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2306] 1-{[2-(甲硫基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2307] 1-{[2-(甲基亚磺酰基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2308] 1-[(2-叔-丁基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2309] 1-[1-(1H-咪唑-1-基)环丙基]吡咯烷-2-酮；

[2310] 1-[(2-甲基-1H-咪唑-1-基)甲基]-4-苯基吡咯烷-2-酮；

[2311] 1-{[2-(甲磺酰基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2312] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-2-羧酰胺；

[2313] 4-(4-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2314] 1-(1H-咪唑-1-基甲基)-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2315] 4-(3-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2316] 4-(3,5-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2317] 4-(3,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2318] 4-(3-氯-4-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2319] 4-(4-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2320] 1-(1H-咪唑-1-基甲基)-4-(2,3,4-三氟苯基)吡咯烷-2-酮；

[2321] 1-(1H-咪唑-1-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[2322] 1-(1H-咪唑-1-基甲基)-4-(2,4,5-三氟苯基)吡咯烷-2-酮；

[2323] 1-{[2-(羟甲基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2324] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-2-羧酸甲基酯；

[2325] 1-[(2-硝基-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2326] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-2-腈；

[2327] 1-[(2-氨基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2328] 1-[(2,4-二氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2329] 1-[(5-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2330] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2331] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2332] (+)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2333] (-)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2334] 1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2335] (-)-1-{[2-氧代-4-(2,3,4-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2336] (+)-1-{[2-氧代-4-(2,3,4-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2337] (-)-1-{[2-氧代-4-(2,3,4-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2338] (+)-1-{[2-氧代-4-(2,3,4-三氟苯基)-1-吡咯烷基]甲基}-1H-咪唑-4-腈；

[2339] (-)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2340] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2341] (+)-1-{[2-氧代-4-(2,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2342] (-)-1-{[2-氧代-4-(2,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2343] (-)-1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基甲基}-1H-咪唑-4-腈；

[2344] (-)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2345] 1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2346] 1-{[2-氧代-4-(2,3,5-三氟苯基)吡咯烷-甲基}-1H-咪唑-5-腈；

[2347] 1-[(5-甲基-2-苯基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2348] 1-[(5-甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2349] 1-[(5-苯基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2350] 1-[(2-乙基-5-甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；1-[(2,5-二甲基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2351] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2352] 1-[2-叠氮基-1-(1H-咪唑-1-基)乙基]-4-丙基吡咯烷-2-酮；

[2353] 1-[(4-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2354] 1-[(2-溴-4,5-二氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2355] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2356] (+)-1-1[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2357] 1-{[5-(羟甲基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2358] 1-{[4-(羟甲基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2359] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-咪唑-5-基氨基甲酸苄基酯；

[2360] N-[(1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-基)甲基]乙酰胺；

[2361] N-[(1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-基)甲基]苯甲酰胺；

[2362] N-1(1-1[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-基)甲基]丙酰胺；

[2363] 1-(1H-苯并咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[2364] 1-[(2-甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2365] 4-丙基-1-[(2-丙基-1H-苯并咪唑-1-基)甲基]吡咯烷-2-酮；

[2366] 1-[(2-异丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2367] 4-丙基-1-{[2-(三氟甲基)-1H-苯并咪唑-1-基]甲基}吡咯烷-2-酮；

[2368] 1-{[2-(甲硫基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2369] 1-[(2-氨基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2370] 1-{[2-(氯甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2371] {1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-2-基}乙腈；

[2372] 1-[(5-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2373] 1-[(5-甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2374] 1-[(5,6-二甲基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2375] 1-{[2-异丙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2376] 1-[(6-氯-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2377] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-丙基-1H-苯并咪唑-5-腈；

[2378] 1-{[2-乙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2379] 4-丙基-1-{[2-(1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}吡咯烷-2-酮；

[2380] 1-[(5-氟-2-丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2381] 1-{[6-甲基-2-(1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2382] 1-[(6-甲氧基-2-丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2383] 2-丁基-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[2384] 1-{[2-[2-(甲硫基)乙基]-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2385] 1-[(5-氟-2-异丁基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2386] 1-{[5-氟-2-(2,4,4-三甲基戊基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2387] 2-环丙基-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[2388] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-(1H-吡唑-3-基)-1H-苯并咪唑-5-腈；

[2389] 1-[(2-环丙基-5-氟-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2390] 1-[(5-氟-2-异丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2391] 1-{[2-(3-呋喃基)-6-甲氧基-1H-苯并咪唑-1-基甲基}-4-丙基吡咯烷-2-酮；

[2392] 1-[(2-环丙基-6-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2393] 1-[(2-异丙基-6-甲氧基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2394] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-(1,2,3-噻二唑-4-基)-1H-苯并咪唑-5-腈；

[2395] 1-{[2-(1H-咪唑-2-基)-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2396] 1-{[5-氟-2-(2,2,2-三氟乙基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯

烷 -2- 酮；

[2397] 1-{[2-(1- 乙基丙基)-6- 甲氧基 -1H- 苯并咪唑 -1- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[2398] 1-{[6- 甲氧基 -2-(1- 甲基 -1H- 吡咯 -2- 基)-1H- 苯并咪唑 -1- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[2399] 1-{[2-(2- 呋喃基)-5-(三氟甲基)-1H- 苯并咪唑 -1- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；4- 丙基 -1-{[2- 噻吩 -2- 基 -5-(三氟甲基)-1H- 苯并咪唑 -1- 基] 甲基 } 吡咯烷 -2- 酮；1-{[2-(3- 呋喃基)-5-(三氟甲基)-1H- 苯并咪唑 -1- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[2400] 1-{[2- 环丙基 -5-(三氟甲基)-1H- 苯并咪唑 -1- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[2401] 4- 丙基 -1-{[2-(1H- 吡咯 -2- 基)-5-(三氟甲基)-1H- 苯并咪唑 -1- 基] 甲基 } 吡咯烷 -2- 酮；

[2402] 1-(1H- 咪唑 -1- 基甲基)-1,3- 二氢 -2H- 吲哚 -2- 酮；

[2403] 5- 溴 -1-(1H- 咪唑 -1- 基甲基)-1,3- 二氢 -2H- 吲哚 -2- 酮；

[2404] 5- 氯 -1-(1H- 咪唑 -1- 基甲基)-1,3- 二氢 -2H- 吲哚 -2- 酮；

[2405] 4- 氟 -1-(1H- 咪唑 -1- 基甲基)-1,3- 二氢 -2H- 吲哚 -2- 酮；

[2406] 4- 氯 -1-(1H- 咪唑 -1- 基甲基)-1,3- 二氢 -2H- 吲哚 -2- 酮；

[2407] 1-(1H- 咪唑 -1- 基甲基)-5- 甲基 -1,3- 二氢 -2H- 吲哚 -2- 酮；

[2408] 1-[(2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基) 甲基]-1H- 咪唑 -5- 腈；和

[2409] 1-[(5- 氯 -2- 氧代 -2,3- 二氢 -1H- 吲哚 -1- 基) 甲基]-1H- 咪唑 -5- 腈。

[2410] 在某些实施方案中，化合物为：

[2411] 1-(1H- 咪唑 -1- 基甲基) 吡咯烷 -2- 酮、

[2412] 1-(1H- 咪唑 -1- 基甲基)-4- 苯基吡咯烷 -2- 酮；1-(1H- 咪唑 -1- 基甲基)-4- 丙基吡咯烷 -2- 酮；

[2413] (-)-4-(3- 叠氮基 -2,4- 二氟苯基)-1-(1H- 咪唑 -1- 基甲基) 吡咯烷 -2- 酮；

[2414] (+)-4-(3- 叠氮基 -2,4- 二氟苯基)-1-(1H- 咪唑 -1- 基甲基) 吡咯烷 -2- 酮；

[2415] 1-[(2- 乙基 -1H- 咪唑 -1- 基) 甲基]-4- 丙基吡咯烷 -2- 酮；

[2416] 1-[(2- 异丙基 -1H- 咪唑 -1- 基) 甲基]-4- 丙基吡咯烷 -2- 酮；

[2417] 1-[(2- 甲基 -1H- 咪唑 -1- 基) 甲基]-4- 丙基吡咯烷 -2- 酮；

[2418] 4- 丙基 -1-[(2- 丙基 -1H- 咪唑 -1- 基) 甲基] 吡咯烷 -2- 酮；

[2419] (+)-1-(1H- 咪唑 -1- 基甲基)-4- 丙基吡咯烷 -2- 酮；

[2420] (-)-1-(1H- 咪唑 -1- 基甲基)-4- 丙基吡咯烷 -2- 酮；

[2421] 4-(2,2- 二氟乙烯基)-1-(1H- 咪唑 -1- 基甲基) 吡咯烷 -2- 酮；

[2422] 4-(3- 氯苯基)-1-(1H- 咪唑 -1- 基甲基) 吡咯烷 -2- 酮；

[2423] 1-{[2-(甲硫基)-1H- 咪唑 -1- 基] 甲基 }-4- 丙基吡咯烷 -2- 酮；

[2424] 1-[(2- 甲基 -1H- 咪唑 -1- 基) 甲基]-4- 苯基吡咯烷 -2- 酮；

[2425] 4-(4- 氟苯基)-1-(1H- 咪唑 -1- 基甲基) 吡咯烷 -2- 酮；

[2426] 1-(1H- 咪唑 -1- 基甲基)-4-(3,4,5- 三氟苯基) 吡咯烷 -2- 酮；

[2427] 4-(3-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2428] 4-(3,5-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2429] 4-(3,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2430] 4-(3-氯-4-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2431] 4-(4-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2432] 1-(1H-咪唑-1-基甲基)-4-(2,3,4-三氟苯基)吡咯烷-2-酮；

[2433] 1-(1H-咪唑-1-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[2434] 1-(1H-咪唑-1-基甲基)-4-(2,4,5-三氟苯基)吡咯烷-2-酮；

[2435] 1-[(2-硝基-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2436] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-2-腈；

[2437] 1-[(2-氨基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2438] 1-[(5-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2439] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2440] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2441] (+)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2442] (-)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2443] (+)-1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-4-腈；

[2444] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2445] 1-[2-叠氮基-1-(1H-咪唑-1-基)乙基]-4-丙基吡咯烷-2-酮；

[2446] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2447] (+)-1-1[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2448] 1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-2-丙基-1H-苯并咪唑-5-腈；

[2449] 1-{[2-乙基-5-(三氟甲基)-1H-苯并咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2450] 4-丙基-1-{[2-(1H-吡咯-2-基)-1H-苯并咪唑-1-基]甲基}吡咯烷-2-酮；

[2451] 1-[(5-氟-2-丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2452] 2-丁基-1-[(2-氧代-4-丙基吡咯烷-1-基)甲基]-1H-苯并咪唑-5-腈；

[2453] 1-[(5-氟-2-异丙基-1H-苯并咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2454] 1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[2455] 5-溴-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[2456] 5-氯-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[2457] 1-(1H-咪唑-1-基甲基)-5-甲基-1,3-二氢-2H-吲哚-2-酮；

[2458] 1-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)甲基]-1H-咪唑-5-腈。

[2459] 在某些实施方案中，化合物为：

[2460] 1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2461] 1-(1H-咪唑-1-基甲基)-4-丙基吡咯烷-2-酮；

[2462] (-)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2463] (+)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2464] 4-(2,2-二氟乙烯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2465] 4-(3-氯苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2466] 1-{[2-(甲硫基)-1H-咪唑-1-基]甲基}-4-丙基吡咯烷-2-酮；

[2467] 1-[(2-甲基-1H-咪唑-1-基)甲基]-4-苯基吡咯烷-2-酮；

[2468] 1-(1H-咪唑-1-基甲基)-4-(3,4,5-三氟苯基)吡咯烷-2-酮；4-(3-氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2469] 4-(3,5-二氟甲基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2470] 1-(1H-咪唑-1-基甲基)-4-(2,3,4-三氟苯基)吡咯烷-2-酮；

[2471] 1-(1H-咪唑-1-基甲基)-4-(2,3,5-三氟苯基)吡咯烷-2-酮；

[2472] 1-H-咪唑-1-基甲基)-4-(2,4,5-三氟苯基)吡咯烷-2-酮；

[2473] 1-[(2-硝基-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2474] 1-{[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-2-腈；

[2475] 1-[(2-氨基-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2476] 1-[(5-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2477] (+)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2478] (-)-1-(1H-咪唑-1-基甲基)-4-苯基吡咯烷-2-酮；

[2479] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-(3,4,5-三氟苯基)吡咯烷-2-酮；

[2480] 1-[(2-氯-1H-咪唑-1-基)甲基]-4-丙基吡咯烷-2-酮；

[2481] (+)-1-1[2-氧代-4-(3,4,5-三氟苯基)吡咯烷-1-基]甲基}-1H-咪唑-5-腈；

[2482] 5-溴-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[2483] 5-氯-1-(1H-咪唑-1-基甲基)-1,3-二氢-2H-吲哚-2-酮；

[2484] 1-(1H-咪唑-1-基甲基)-5-甲基-1,3-二氢-2H-吲哚-2-酮；

[2485] 1-[(5-氯-2-氧代-2,3-二氢-1H-吲哚-1-基)甲基]-1H-咪唑-5-腈。

[2486] 某些化合物为：

[2487] (-)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2488] (+)-4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮；

[2489] 4-(3-叠氮基-2,4-二氟苯基)-1-(1H-咪唑-1-基甲基)吡咯烷-2-酮。

[2490] 以其作为碱的游离形式存在的式I化合物的酸加成盐形式可通过用下列适当的酸处理该游离碱得到：例如无机酸，例如氢卤酸(例如盐酸或氢溴酸)、硫酸、硝酸、磷酸等；或有机酸，例如乙酸、三氟乙酸、羟基乙酸、丙酸、乳酸、丙酮酸、丙二酸、琥珀酸、马来酸、富马酸、苹果酸、酒石酸、柠檬酸、甲苯磺酸、乙苯磺酸、苯磺酸、对-甲苯磺酸、环酸、水杨酸、对-氨基水杨酸、扑酸等。

[2491] 可将含有酸性质子的式I化合物通过用适当的有机和无机碱处理，转化为它们的具有治疗活性、无毒的碱加成盐形式，例如金属或胺盐。适当的碱盐形式包括，例如铵盐，碱金属和碱土金属盐，例如锂、钠、钾、镁、钙盐等，有机碱盐，例如N-甲基-D-葡萄糖胺、海巴明(hydrabamine)盐，以及氨基酸盐例如，精氨酸、赖氨酸等的盐。

[2492] 相反地，可将所述盐形式用适当的碱或酸处理转化为游离形式。

[2493] 式I化合物及它们的盐可为包括在本发明的范围内的溶剂合物的形式。这类溶剂合物包括例如水合物、醇合物等。

[2494] 许多式I化合物和某些它们的中间体在它们的结构中具有至少一个立体异构中心。该立体异构中心可以以R或S构型存在，使用所述R和S符号与在Pure Appl. Chem.，

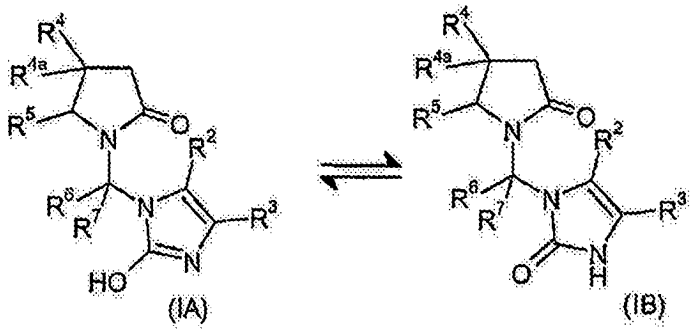
45(1976)11-30 中所述的规则一致。

[2495] 本发明也涉及式 I 化合物的所有的立体异构体形式，例如对映异构和非对映异构形式，或其混合物（包括所有可能的立体异构体的混合物）。

[2496] 某些式 I 化合物还可能存在互变异构形式。这类形式尽管未在上式中明确指明，也旨在将其纳入本发明的范围内。

[2497] 在另一个优选的实施方案中，本发明也涉及式 IA 的化合物和它们的互变异构体形式 IB

[2498]



[2499] 除非特别提及具体的异构体形式，否则就本发明提及的化合物而言旨在包括化合物的每个可能的异构体形式及其混合物。

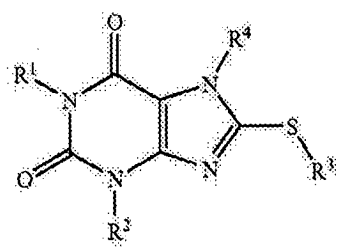
[2500] 根据本发明的化合物可能存在不同的多晶型物。尽管未在上式中明确指明，也旨在将这类形式纳入本发明的范围内。

[2501] 本发明在其范围内还包括式 I 化合物及它的各种亚范围和亚族的前药形式。

[2502] xii) 美国专利申请公开文本第 20090018148 号

[2503] 在一个方面，本发明提供了具有式 I 的化合物、它们的对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体的混合物），或其药学上可接受的盐，

[2504]



(I)

[2505] 其中

[2506] R1 为氢或 C1-6 烷基；

[2507] R2 为氢或 C1-4 烷基；

[2508] R3 为式 -CHR5R6 的基团或苄基；

[2509] R4 为被烷氧羰基、C3-6 环烷基、芳基或杂环任选地取代的 C1-8 烷基；

[2510] R5 为 C2-4 烷基；

[2511] R6 为 C2-4 烷基、酰氨基或 -COOR7；

[2512] R7 为 C1-4 烷基；

[2513] 在一个方面，本发明提供了化合物：

[2514] 当 R1 为氢，R2 为甲基，R3 为 -CHR5R6，R6 为乙氧羰基且 R5 为乙基时，那么 R4 不是甲基、正 - 丙基、异 - 丙基、正 - 戊基、正 - 庚基、3- 溴苄基 4- 氯苄基、4- 甲苄基或 2- 苯乙基；

[2515] 当 R1 为氢，R2 为甲基，R3 为苄基时，那么 R4 不是异 - 丙基、正 - 丁基、3- 甲基丁基、苄基、苯乙基 - 或 3- 苯基丙基；

[2516] 当 R1 和 R2 为甲基，R3 为苄基时，R4 不是甲基、3- 甲基丁基、苄基、3- 苯基丙基或 4- 氯苯基甲基；

[2517] 最终考虑的是 8-(2- 氯 - 苄基硫基)-3- 甲基 -7- 辛基 -3,7- 二氢 - 嘌呤 -2,6- 二酮。

[2518] 通常当 R3 为苄基时，那么 R4 为被烷氧羰基任选地取代的 C1-8 烷基。

[2519] 通常当 R3 为式 -CHR5R6 基团时，那么 R4 为被 C3-6 环烷基、芳基或杂环任选地取代的 C1-8 烷基。

[2520] 如本文使用的术语“烷基”，表示饱和的，单价烃残基，该残基具有直链（无支链）或支链部分，或其组合，并含有 1-8 个碳原子，优选的是 1-6 个碳原子；更优选的是具有 1-4 个碳原子的烷基。烷基部分可被独立选自羟基、烷氧基、氰基、乙炔基、烷氧羰基、酰基、芳基或杂环的 1-5 个取代基任选地取代。烷基部分可经如此后所定义的环烷基任选地取代。根据本发明优选的烷基为甲基、氰基甲基、乙基、2- 乙氧基 -2- 氧代乙基、2- 甲氧基乙基、正 - 丙基、2- 氧代丙基、3- 羟丙基、2- 丙炔基、正 - 丁基、异 - 丁基、正 - 戊基、3- 戊基、正 - 己基、环己基甲基、苄基、2- 溴苄基、3- 溴苄基、4- 溴苄基、3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基、4-（氨基磺酰基）苄基、1- 苯乙基、2- 苯乙基、(3,5- 二甲基异噁唑 -4- 基）甲基或 (5- 硝基 -2- 呋喃基）甲基。更优选的烷基为甲基、乙基、氰基甲基、2- 甲氧乙基、正 - 丙基、3- 羟丙基、2- 丙炔基、正 - 丁基、3- 戊基、正 - 己基、苄基、3- 溴苄基，3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基、(3,5- 二甲基异噁唑 -4- 基）甲基或 (5- 硝基 -2- 呋喃基）甲基。最优选的烷基为甲基、乙基、3- 甲氧苄基、3- 硝基苄基或 (5- 硝基 -2- 呋喃基）甲基。

[2521] 如本文使用的术语“环烷基”，表示衍生自饱和环烃的 3-8 个，优选的是 3-6 个碳原子的单价基团，其可被任何适宜的基团（包括但不限于选自如上所述用于烷基的一个或多个部分）取代。根据本发明优选的环烷基为环己基。

[2522] 将如本文使用的术语“芳基”，定义为被独立地选自卤素、氨基、硝基、烷氧基或氨基磺酰基的 1-4 个取代基任选地取代的苯基。优选的芳基为苯基、2- 溴苯基、3- 溴苯基、4- 溴苯基、3- 甲氧苯基、3- 硝基苯基、3- 氨基苯基或 4-（氨基磺酰基）苯基。

[2523] 如本文使用的术语“苯基”，表示式 -C6H5 的芳族烃基。

[2524] 如本文使用的术语“苄基”，表示式 -CH2- 芳基的基团。优选的苄基为苄基、2- 溴苄基、3- 溴苄基、4- 溴苄基、3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基或 4-（氨基磺酰基）苄基。更优选的苄基为苄基、3- 溴苄基、3- 甲氧苄基、3- 硝基苄基或 3- 氨基苄基。在某些实施方案中，烷基为 3- 甲氧苄基或 3- 硝基苄基。

[2525] 如本文使用的术语“卤素”，表示氯、溴、氟或碘原子。在某些实施方案中，卤素为溴。

[2526] 如本文使用的术语“羟基”，表示式 -OH 的基团。

[2527] 如本文使用的术语“氰基”，表示式 -CN 的基团。

[2528] 如本文使用的术语“氨基”，表示式 -NH2 的基团。

[2529] 如本文使用的术语“乙炔基”，表示式 -C ≡ CH 的基团。

[2530] 如本文使用的术语“烷氧基”，表示式 -ORa 的基团，其中 Ra 为如上文所定义的烷基。在某些实施方案中，烷氧基为甲氧基。

[2531] 如本文使用的术语“硝基”，表示式 -NO2 的基团。

[2532] 如本文使用的术语“酰氨基”，表示式 -C(= O)NH2 的基团。

[2533] 如本文使用的术语“酰基”，表示式 -C(= O)Rb 的基团，其中 Rb 为如上文所定义的烷基。在某些实施方案中，酰基为乙酰基 (-C(= O)Me)。

[2534] 如本文使用的术语“烷氧羰基（或酯）”，表示式 -COORc 的基团，其中 Rc 为烷基；条件是 Rc 不表示被羟基 α - 取代的烷基。在某些实施方案中，烷氧羰基为乙氧羰基。

[2535] 如本文使用的术语“杂环”，表示含有选自 O 或 N 的一个或两个杂原子的 5- 元环。该杂环可经一个或两个 C1-4 烷基或硝基取代。在某些实施方案中，杂环为 (3,5- 二甲基异噁唑 -4- 基）或 (5- 硝基 -2- 呋喃基）。最优选的杂环为 (5- 硝基 -2- 呋喃基）。

[2536] 一般 R1 为氢或 C1-6 烷基；通常 R1 为氢或被羟基、烷氧基、氰基、乙炔基、烷氧羰基或酰基任选地取代的 C1-6 烷基。在某些实施方案中，R1 为氢、甲基、氰基甲基、2- 乙氧基 -2- 氧代乙基、2- 甲氧乙基、正 - 丙基、2- 氧代丙基、3- 羟丙基、2- 丙炔基、正 - 戊基或正 - 己基。在某些实施方案中，R1 为氢、甲基、氰基甲基、2- 甲氧乙基、正 - 丙基、3- 羟丙基或 2- 丙炔基。在某些实施方案中，R1 为氢。

[2537] 一般 R2 为氢或 C1-4 烷基。通常 R2 为氢或未取代的 C1-4 烷基。在某些实施方案中，R2 为氢、甲基、正 - 丁基。在某些实施方案中，R2 为甲基。

[2538] 一般 R3 为式 -CHR5R6 的基团或苄基。在某些实施方案中，R3 为 3- 戊基、1-（氨基羰基）丙基、1-（乙氧羰基）丙基或 3- 溴苄基。在某些实施方案中，R3 为 1-（乙氧羰基）丙基。

[2539] 一般 R4 为被烷氧羰基、C3-6 环烷基、芳基或杂环任选地取代的 C1-8 烷基。通常 R4 为被环己基、苯基、溴苯基、氨基苯基、甲氧苯基、硝基苯基、氨基磺酰基苯基、3,5- 二甲基异噁唑 -4- 基、5- 硝基 -2- 呋喃基或乙氧羰基任选地取代的 C1-8 烷基。在某些实施方案中，R4 为正 - 丁基、异 - 丁基、正 - 戊基、正 - 己基、环己基甲基、苄基、2- 溴苄基、3- 溴苄基、4- 溴苄基、3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基、4-（氨基磺酰基）苄基、1- 苯乙基、2- 苯乙基、(3,5- 二甲基异噁唑 -4- 基）甲基、(5- 硝基 -2- 呋喃基）甲基或 1-（乙氧羰基）丙基。在某些实施方案中，R4 为正 - 丁基、正 - 己基、苄基、3- 溴苄基、3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基、(3,5- 二甲基异噁唑 -4- 基）甲基、(5- 硝基 -2- 呋喃基）甲基或 1-（乙氧羰基）丙基。在某些实施方案中，R4 为 3- 甲氧苄基、3- 硝基苄基或 (5- 硝基 -2- 呋喃基）甲基。

[2540] 一般 R5 为 C2-4 烷基；通常 R5 为未取代的 C2-4 烷基。在某些实施方案中，R5 为乙基。

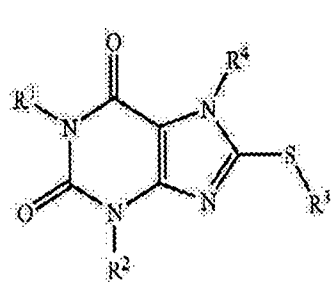
[2541] 一般 R6 为 C2-4 烷基、酰氨基或 -COOR7。通常 R6 为未取代的 C2-4 烷基、酰氨基或 -COOR7。在某些实施方案中，R6 为乙基、酰氨基或乙氧羰基。在某些实施方案中，R6 为乙氧羰基。

[2542] 一般 R7 为 C1-4 烷基。通常 R7 为未取代的 C1-4 烷基。在某些实施方案中，R7 为

乙基。

[2543] 通常，本发明提供了具有式 I 的化合物、它们的对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体的混合物），或其药学上可接受的盐。

[2544]



(I)

[2545] 其中

[2546] R1 为氢或、被羟基、烷氧基、氰基、乙炔基、烷氧羰基或酰基任选地取代的 C1-6 烷基；

[2547] R2 为氢或未取代的 C1-4 烷基；

[2548] R3 为式 -CHR5R6 的基团或苄基；

[2549] R4 为被环己基、苯基、溴苯基、氨基苯基、甲氧苯基、硝基苯基、氨基磺酰基苯基、3,5- 二甲基异噁唑 -4- 基、5- 硝基 -2- 呋喃基或乙氧羰基任选地取代的 C1-8 烷基；

[2550] R5 为未取代的 C2-4 烷基；

[2551] R6 为未取代的 C2-4 烷基、酰氨基或 -COOR7；

[2552] R7 为未取代的 C1-4 烷基；

[2553] 条件是当 R1 为氢，R2 为甲基，R3 为 -CHR5R6，R6 为乙氧羰基且 R5 为乙基时，那么 R4 不是正 - 丙基、异 - 丙基、正 - 戊基、正 - 庚基、3- 溴苄基、4- 氯苄基、4- 甲苄基或 2- 苯乙基。

[2554] 在上述实施方案中，有时，当 R3 为苄基时，那么 R4 为被烷氧羰基任选地取代的 C1-8 烷基。

[2555] 在上述实施方案中，有时，当 R3 为式 -CHR5R6 的基团时，那么 R4 为被 C3-6 环烷基、芳基或杂环任选地取代的 C1-8 烷基。

[2556] 在一个实施方案中，

[2557] R1 为氢、甲基、氰基甲基、2- 乙氧基 -2- 氧代乙基、2- 甲氧乙基、正 - 丙基、2- 氧代丙基、3- 羟丙基、2- 丙炔基、正 - 戊基或正 - 己基。

[2558] R2 为氢、甲基或正 - 丁基；

[2559] R3 为 3- 戊基、1-（氨基羰基）丙基、1-（乙氧羰基）丙基或 3- 溴苄基。

[2560] R4 为正 - 丁基、异 - 丁基、正 - 戊基、正 - 己基、环己基甲基、苄基、2- 溴苄基、3- 溴苄基、4- 溴苄基、3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基、4-（氨基磺酰基）苄基、1- 苯乙基、2- 苯乙基、(3,5- 二甲基异噁唑 -4- 基）甲基、(5- 硝基 -2- 呋喃基）甲基或 1-（乙氧羰基）丙基。

[2561] 条件是当 R1 为氢、R2 为甲基且 R3 为 1-（乙氧羰基）丙基时，那么 R4 不是正 - 戊基、3- 溴苄基或 2- 苯乙基。

[2562] 在上述实施方案中，有时，当 R3 为 3- 溴苄基时，那么 R4 为被烷氧羰基任选地取代

的 C1-8 烷基。

[2563] 在上述实施方案中，有时，当 R3 为 3- 戊基、1-（氨基羰基）丙基或 1-（乙氧羰基）丙基时，那么 R4 不是 1-（乙氧羰基）丙基。

[2564] 在更优选的实施方案中，R1 为氢、甲基、氰基甲基、2- 甲氧乙基、正 - 丙基、3- 羟丙基或 2- 丙炔基。

[2565] R2 为甲基；

[2566] R3 为 3- 戊基、1-（氨基羰基）丙基、1-（乙氧羰基）丙基或 3- 溴苄基。

[2567] R4 为正 - 丁基、正 - 己基、苄基、3- 溴苄基、3- 甲氧苄基、3- 硝基苄基、3- 氨基苄基、(3,5- 二甲基异噁唑 -4- 基）甲基、(5- 硝基 -2- 呋喃基）甲基或 1-（乙氧羰基）丙基；

[2568] 条件是当 R1 为氢，R2 为甲基且 R3 为 1-（乙氧羰基）丙基时，那么 R4 不是 3- 溴苄基。

[2569] 在上述实施方案中，有时，当 R3 为 3- 溴苄基时，那么 R4 为 1-（乙氧羰基）丙基。

[2570] 在上述实施方案中，有时当 R3 为 3- 戊基、1-（氨基羰基）丙基或 1-（乙氧羰基）丙基时，那么 R4 不是 1-（乙氧羰基）丙基。

[2571] 在一个实施方案中，R1 为氢；R2 为甲基；R3 为 1-（乙氧羰基）丙基；且 R4 为 3- 甲氧苯基、3- 硝基苄基或 (5- 硝基 -2- 呋喃基）甲基。

[2572] 另一个实施方案在于化合物，其中 R2 为甲基，R3 为式 -CHR5R6 的基团 (R5 为 C2-4 烷基，R6 为酰氨基）或 -COOR7（且 R7 为甲基或乙基）。

[2573] 在某些实施方案中，化合物为

[2574] 2-[(7- 苄基 -1,3- 二甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基）硫基］丁酸乙酯；

[2575] 2-{[7-(3- 溴苄基）-1-(2- 乙氧基 -2- 氧代乙基）-3- 甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2576] 2-{[7-(3- 溴苄基）-1-(2- 甲氧乙基）-3- 甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2577] 2-{[7-(3- 溴苄基）-2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2578] 2-{[7-(3- 溴苄基）-1,3- 二甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2579] 2-{[7-(2- 溴苄基）-1,3- 二甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2580] 2-{[7-(3- 溴苄基）-1-(氰基甲基）-3- 甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2581] 2-{[7-(3- 溴苄基）-3- 甲基 -2,6- 二氧代 -1- 丙基 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2582] 2-{[7-(3- 溴苄基）-3- 甲基 -2,6- 二氧代 -1-(2- 氧代丙基）-2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2583] 2-{[7-(3- 溴苄基）-1-(3- 羟丙基）-3- 甲基 -2,6- 二氧代 -2,3,6,7- 四氢 -1H- 嘌呤 -8- 基］硫基｝丁酸乙酯；

[2584] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-(2-丙炔基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2585] 2-{[7-(3-甲氧苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2586] 2-{[3-甲基-7-(3-硝基苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2587] 2-{[7-(3-氨基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2588] 2-({7-[4-(氨基磺酰基)苄基]-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫基)丁酸乙酯；

[2589] 2-{[7-(4-溴苄基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2590] 2-{[7-(环己基甲基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2591] 2-{[1,3-二甲基-2,6-二氧代-7-(1-苯乙基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2592] 2-{[1,3-二甲基-2,6-二氧代-7-(2-苯乙基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2593] 2-({7-[(3,5-二甲异噁唑-4-基)甲基]-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫基)丁酸乙酯；

[2594] 2-({3-甲基-7-[(5-硝基-2-呋喃基)甲基]-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫基)丁酸乙酯；

[2595] 2-[(7-丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯；

[2596] 2-{[7-(3-溴苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯；

[2597] 2-[(1,7-二己基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯；

[2598] 2-[(7-己基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯；

[2599] 2-[(3-甲基-2,6-二氧代-1,7-二戊基-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯；

[2600] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酰胺；

[2601] 2-[(7-丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酰胺；

[2602] 7-(3-溴苄基)-8-[(1-乙基丙基)硫基]-3-甲基-3,7-二氢-1H-嘌呤-2,6-二酮；

[2603] 2-{8-[(3-溴苄基)硫基]-1,3-二甲基-2,6-二氧代-1,2,3,6-四氢-7H-嘌

吟-7-基}丁酸乙酯;和

[2604] 2-[(7-异丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯。

[2605] 在某些实施方案中,化合物为:

[2606] 2-[(7-苄基-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯;

[2607] 2-{[7-(3-溴苄基)-1-(2-甲氧乙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2608] 2-{[7-(3-溴苄基)-1,3-二甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2609] 2-{[7-(3-溴苄基)-1-(氰基甲基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2610] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-丙基-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2611] 2-{[7-(3-溴苄基)-1-(3-羟丙基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2612] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-1-(2-丙炔基)-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2613] 2-{[7-(3-甲氧苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2614] 2-{[3-甲基-7-(3-硝基苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2615] 2-{[7-(3-氨基苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2616] 2-({7-[(3,5-二甲基异噁唑-4-基)甲基]-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫基)丁酸乙酯;

[2617] 2-({3-甲基-7-[(5-硝基-2-呋喃基)甲基]-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫基)丁酸乙酯;

[2618] 2-[(7-丁基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯;

[2619] 2-[(7-己基-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基)硫基]丁酸乙酯;

[2620] 2-{[7-(3-溴苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酰胺;

[2621] 7-(3-溴苄基)-8-[(1-乙基丙基)硫基]-3-甲基-3,7-二氢-1H-嘌呤-2,6-二酮;和

[2622] 2-{8-[(3-溴苄基)硫基]-1,3-二甲基-2,6-二氧代-1,2,3,6-四氢-7H-嘌呤-7-基}丁酸乙酯。

[2623] 在某些实施方案中,化合物为:

[2624] 2-{[7-(3-甲氧苄基)-3-甲基-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;

[2625] 2-{[3-甲基-7-(3-硝基苄基)-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基]硫基}丁酸乙酯;和

[2626] 2-({3-甲基-7-[(5-硝基-2-呋喃基)甲基]-2,6-二氧代-2,3,6,7-四氢-1H-嘌呤-8-基}硫基)丁酸乙酯。

[2627] 以其作为碱的游离形式存在的式I化合物的酸加成盐形式可通过用下列适当的酸处理该游离碱得到:例如无机酸,例如氢卤酸(例如盐酸或氢溴酸)、硫酸、硝酸、磷酸等;或有机酸,例如乙酸、三氟乙酸、羟基乙酸、丙酸、乳酸、丙酮酸、丙二酸、琥珀酸、马来酸、富马酸、苹果酸、酒石酸、柠檬酸、甲苯磺酸、乙苯磺酸、苯磺酸、对-甲苯磺酸、环拉酸、水杨酸、对-氨基水杨酸、扑酸等。

[2628] 可将含有酸性质子的式I化合物通过用适当的有机和无机碱处理,转化为它们的具有治疗活性、无毒的碱加成盐形式,例如金属或胺盐。适当的碱盐形式包括,例如铵盐,碱金属和碱土金属盐,例如锂、钠、钾、镁、钙盐等,有机碱盐,例如N-甲基-D-葡萄糖胺、海巴明盐,以及氨基酸盐例如,精氨酸、赖氨酸等的盐。

[2629] 相反地,可将所述盐形式用适当的碱或酸处理转化为游离形式。

[2630] 式I化合物及它们的盐可为纳入本发明的范围内的溶剂合物的形式。这类溶剂合物包括例如水合物、醇合物等。

[2631] 许多式I化合物和某些它们的中间体在它们的结构中具有至少一个立体异构中心。该立体异构中心可以以R或S构型存在,使用所述R和S符号与在Pure Appl. Chem., 45(1976)11-30中所述的规则一致。

[2632] 本发明也涉及所有的立体异构体形式,例如式I化合物的对映异构和非对映异构形式或其混合物(包括所有可能的立体异构体的混合物)。

[2633] 除非特别提及具体的异构体形式,否则就本发明提及的化合物而言旨在包括化合物的每个可能的异构体形式及其混合物。

[2634] 根据本发明的化合物可存在不同的多晶型物。尽管未在上式中明确指明,也旨在将这类形式纳入本发明的范围内。

[2635] xiii) 美国专利7,465,549

[2636] 在某些实施方案中,化合物包括任选地取代的N-烷化的2-氧代-吡咯烷衍生物。在某些实施方案中,那些化合物是在吡咯烷酮环4位和/或5位上取代的烷基酰胺衍生物。任选取代的N-烷化的2-氧代-吡咯烷衍生物的实例包括,但不限于,例如(2S)-2-[(4S)-4-(2,2-二氟乙烯基)-2-氧代吡咯烷基]丁酰胺、(2S)-2-[(4R)-2-氧代-4-丙基吡咯烷基]丁酰胺、(2S)-2-[(4S)-2-氧代-4-丙基吡咯烷基]丁酰胺和(2S)-2-[4-(3-叠氮基苯基)-2-氧代吡咯烷-1-基]丁酰胺的化合物。

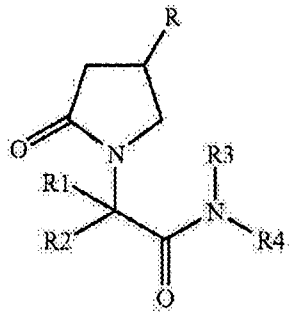
[2637] 在某些实施方案中,化合物进一步包括任选取代的N-烷化的2-氧代-哌啶基衍生物。在某些实施方案中,那些化合物是在2-氧代-哌啶基环4位和/或5和/或6位上取代的烷基酰胺衍生物。任选地取代的N-烷化的2-氧代-吡咯烷衍生物的实例包括,但不限于,例如在国际专利申请PCT/EP02/05503中提及的那些,例如(2S)-2-[5-(碘甲基)-2-氧代-1-哌啶基]丁酰胺、(2S)-2-[5-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰

胺、2-(2- 氧代 -5- 苯基 -1- 哌啶基) 丁酰胺、(2S)-2-[4-(碘甲基)-2- 氧代 -1- 哌啶基] 丁酰胺和 (2S)-2-[4-(2- 氟 -2- 甲基丙基)-2- 氧代 -1- 吡咯烷基] 丁酰胺的化合物。

[2638] 在某些实施方案中，化合物包括外消旋的或异构形式的式 I 的任何环酰胺化合物，或其药学上可接受的盐，

[2639]

(I)



[2640] 其中

[2641] R 表示氢或羟基；

[2642] R1 和 R2 独立地表示氢或 1-4 个碳原子的烷基；且

[2643] R3 和 R4 独立地表示氢、1-4 个碳原子的烷基或 -(CH2)n-NR5R6，其中 n 为 1、2 或 3，且 R5 和 R6 独立地表示氢或 1-4 个碳原子的烷基。

[2644] 这类环酰胺化合物的实例包括，但不限于式 I 化合物，其中 R、R1、R2、R3 和 R4 为氢、2- 氧代 - 吡咯烷乙酰胺，如在英国专利第 1,039,113 和 1,309,692 号中所述的已知通用名为吡拉西坦。

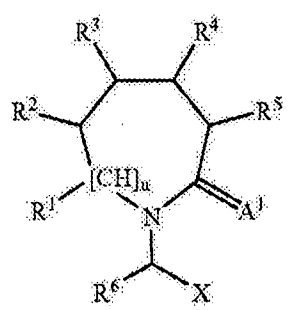
[2645] 在某些实施方案中，化合物也包括任选取代的 N- 烷化的 2- 氧代 - 氮杂环庚烷基衍生物。优选的是，那些化合物为在 2- 氧代 - 氮杂环庚烷基环 4 位和 / 或 5 位和 / 或 6 位和 / 或 7 位上取代的烷基酰胺衍生物。任选取代的 N- 烷化的 2- 氧代 - 氮杂环庚烷基衍生物的实例包括，但不限于，例如在国际专利申请 PCT/EP02/05503 提及的那些化合物，例如 2-[5-(碘甲基)-2- 氧代 -1- 氮杂环庚烷基] 丁酰胺。

[2646] xiv) 美国专利申请公开文本第 2006258704 号

[2647] 本发明提供了式 I 的新化合物

[2648]

(I)



[2649] 其中

[2650] n 表示 0 或 1，由此当 n = 0 时，R<1> 不存在，而当 n = 1 时，R<1> 存在；

[2651] A<1> 表示氧或硫原子；

[2652] X 为 -CONR<7>R<8>、-COOR<9>、-CO-R<10> 或 CN；

[2653] 当 R<1> 存在时，R<2>、R<3>、R<4> 和 R<5> 相同或不同，且各自独立地为氢、卤素、羟基、巯基、氨基、硝基、硝基氧基、氰基、叠氮基、羧基、酰氨基、磺酸、磺酰胺、烷基、烯基、炔基、酯、醚、芳基、杂环或氧基衍生物、硫基衍生物、氨基衍生物、酰基衍生物、磺酰基衍生物或亚磺酰基衍生物，

[2654] 条件是至少一个取代基 R 选自 R<1>（当其存在时），R<2>、R<3>、R<4> 或 R<5> 不是氢；

[2655] R<6> 为氢、烷基、芳基或 -CH2-R<6a>，其中 R<6a> 为芳基、杂环、卤素、羟基、氨基、硝基或氰基；

[2656] R<7>、R<8> 和 R<9> 相同或不同，并各自独立地为氢、羟基、烷基、芳基、杂环或氧基衍生物；且

[2657] R<10> 为氢、羟基、巯基、卤素、烷基、芳基、杂环或硫基衍生物；

[2658] 它们的药学上可接受的盐、几何异构体（包括顺式和反式，Z 和 E 异构体）、对映异构体、非对映异构体及其混合物（包括所有可能的立体异构体的混合物）。

[2659] 在上式中，R<1> 至 R<5> 中的至少一个取代基不是氢。在美国专利第 5,468,733 和 5,516,759 号中提及了某些非取代的化合物。美国专利第 5,468,733 公开了作为癌基因 Ras 蛋白抑制剂的非环取代的 2- 氧代 -1- 吡咯烷基和 2- 氧代 -1- 哌啶基衍生物。具体的是，这些化合物限制了 Ras 将正常细胞转化为癌细胞的能力，并因此可纳入用于治疗癌症的若干化学治疗的组合物中。

[2660] 美国专利第 5,516,759 号公开了存在于具有 LHRH（促黄体生成激素释放激素）拮抗活性的 12 肽的 N- 端的非环取代的 2- 氧代 -1- 吡咯烷基、2- 氧代 -1- 哌啶基和氮杂环庚烷基衍生物。这类 LHRH 拮抗剂用于治疗抑制性甾体在其中起关键作用的各种病症，包括避孕、青春期延迟、治疗良性前列腺增生症 a.o。

[2661] 在下文列出的定义中，除非另外说明，否则 R<11> 和 R<12> 相同或不同，并各自独立地为酰氨基、烷基、烯基、炔基、酰基、酯、醚、芳基、芳烷基、杂环或氧基衍生物、硫基衍生物、酰基衍生物、氨基衍生物、磺酰基衍生物或亚磺酰基衍生物，各自经任何适宜的基团任选地取代，所述适宜的基团包括但不限于，选自低级烷基或如下所述作为烷基的取代基的其它基团的一个或多个部分。

[2662] 将如本文使用的术语“氧基衍生物”，定义为包含 -O-R<11> 基团，其中 R<11> 为除了“氧基衍生物”之外如上所定义的。非限制性实例为烷氧基、烯氧基、炔氧基、酰氧基、氧基酯基、氧基酰氨基、烷基磺酰基氧基、烷基亚磺酰基氧基、芳基磺酰基氧基、芳基亚磺酰基氧基、芳氧基、芳烷氧基或杂环氧基例如戊氧基、烯丙氧基、甲氧基、乙氧基、苯氧基、苄氧基、2- 萘氧基、2- 吡啶基氧基、亚甲二氧基、碳酸酯。

[2663] 将如本文使用的术语“硫基衍生物”，定义为包含 -S-R<11> 基团，其中 R<11> 为除了“硫基衍生物”之外如上所定义的。非限制性实例为烷硫基、烯硫基、炔硫基和芳硫基。

[2664] 将如本文使用的术语“氨基衍生物”，定义为包含 -NHR<11> 或 -NR<11>R<12> 基团，其中 R<11> 和 R<12> 为如上所定义的。非限制实例为单 - 或二 - 烷基 -、烯基 -、炔基 - 和芳基氨基或混合的氨基。

[2665] 如本文使用的术语“酰基衍生物”，表示衍生自羧酸的残基，并因此被定义为包含式 R<11>-CO- 的基团，其中 R<11> 为如上所定义的并也可为氢。优选的是式 -COR<11> 的酰

基衍生物，其中 R<11> 选自氢、C1-12 烷基、C2-12 烯基、C2-12 烯基、杂环和芳基。非限制实例为甲酰基、乙酰基、丙酰基、异丁酰基、戊酰基、月桂酰基、庚二酰基、环己烷羰基、巴豆酰基、富马酰基、丙烯酰基、苯甲酰基、萘甲酰基、糠酰基、烟酰基、4- 羧基丁酰基、草酰基、乙草酰基、半胱氨酰基、草氨酰基。

[2666] 将如本文使用的术语“磺酰基衍生物”，定义为包含式 -SO-R<11> 基团，其中 R<11> 为如前所定义的，除了“磺酰基衍生物”之外。非限制性实例为烷基磺酰基、烯基磺酰基、炔基磺酰基和芳基磺酰基。

[2667] 将如本文使用的术语“亚磺酰基衍生物”，定义为包含式 -SO-R<11> 基团，其中 R<11> 为除了“亚磺酰基衍生物”之外如上所定义的。非限制性实例为烷基亚磺酰基、烯基亚磺酰基、炔基亚磺酰基和芳基亚磺酰基。

[2668] 将如本文使用的术语“烷基”，定义为饱和的，单价烃残基，该残基具有直链、支链或环部分或其组合，并通常含有 1-20 个碳原子，最常为 1-12 个碳原子，对于非环烷基优选的是 1-7 个碳原子，且对于环烷基优选的是 3-7 个碳原子（除非另外限定，否则在这两个优选的情况中都为“低级烷基”），每个经优选的是 1-5 个独立地选自下列基团的取代基任选地取代：卤素、羟基、巯基、氨基、硝基、氰基、氰硫基、酰基、酰氧基、磺酰基衍生物、亚磺酰基衍生物、烷基氨基、羧基、酯、醚、酰氨基、叠氮基、环烷基、磺酸、磺酰胺、硫基衍生物、烷硫基、氧基酯基、氧基酰氨基、杂环、乙烯基、烷氧基（优选的是 C1-5）、芳氧基（优选的是 C6-10）和芳基（优选的是 C6-10）。

[2669] 在某些实施方案中为含有 1-7 个碳原子的烷基，各自被选自下列基团的一个或多个取代基任选地取代：羟基、卤素、氰基、氰硫基、烷氧基、叠氮基、烷硫基、环丙基、酰基和苯基。最优选的是 C1-4 烷基和 C3-7 环烷基，各自被一个或多个羟基、卤素、低级烷基或 / 和叠氮基任选地取代。

[2670] 在某些实施方案中烷基为羟甲基、丙基、丁基、2,2,2- 三氟乙基、2- 溴 -2,2- 二氟乙基、2- 氯 -2,2- 二氟乙基、3,3,3- 三氟丙基、环丙基甲基、碘甲基、叠氮基甲基、2,2- 二氟丙基、2- 碘 -2,2- 二氟乙基。

[2671] 如本文使用的术语“低级烷基”，并且除非另外限定，否则意指 C1-C7 饱和的直链、支链或环烃。非限制性实例为甲基、乙基、丙基、异丙基、丁基、叔丁基、戊基、环丙基、环戊基、异戊基、新戊基、己基、异己基、环己基、3- 甲基戊基、2,2- 二甲基丁基，任选地被任何适宜的基团（包括但不限于一个或多个部分选自如上所述用于烷基的基团）取代。优选的是，低级烷基为甲基。

[2672] 将如本文使用的术语“烯基”，定义为包含支链和无支链、不饱和的、具有至少一个双键的烃残基，并任选地被至少一个选自下列基团的取代基取代：卤素、羟基、巯基、氨基、氰硫基、叠氮基、烷硫基、环烷基、酰基、硝基、氰基、芳基和杂环。

[2673] 在某些实施方案中烯基为 C2-C12 烯基，特别是 C2-6 烯基，例如乙烯基 (ethenyl)（＝乙烯基 (vinyl)）、1- 甲基 -1- 乙烯基、2,2- 二甲基 -1- 乙烯基、1- 丙烯基、2- 丙烯基（＝烯丙基）、1- 丁烯基、2- 丁烯基、3- 丁烯基、4- 戊烯基、1- 甲基 -4- 戊烯基、3- 甲基 -1- 戊烯基、1- 己烯基、2- 己烯基等，其可被选自卤素、氰基、氰硫基、叠氮基、烷硫基、环烷基、苯基和酰基的一个或多个取代基任选地取代。最优选的为被一个或多个卤素或 / 和低级烷基任选地取代的乙烯基，并且特别是 2,2- 二氟乙烯基、2,2- 二溴乙烯基和 2,2- 二氯乙烯基。

[2674] 将如本文使用的术语“炔基”，定义为包含单价支链或无支链、含有至少一个碳 - 碳三键的烃残基，例如乙炔基、2- 丙炔基（＝炔丙基）等，并被至少一个选自卤素、羟基、巯基、氨基、硝基、氰基、芳基、杂环、氰硫基、叠氮基、烷硫基、烷基和酰基的取代基任选地取代。

[2675] 在某些实施方案中炔基为 C2-12 炔基，特别是 C2-6 炔基，该炔基被选自以下的一个或多个取代基任选地取代：卤素、氰基、氰硫基、叠氮基、烷硫基、酰基、例如苯基和烷基的芳基，优选的是环烷基。

[2676] 在某些实施方案中为被低级烷基或 / 和卤素任选地取代的乙炔基、丙炔基和丁炔基，并且特别是 1- 丙炔基、环丙基乙炔基、3- 甲基 -1- 丁炔基和 3,3,3- 三氟 -1- 丙炔基。

[2677] 当作为桥连基存在时，烷基、烯基和炔基表示直链 - 或支链 C1-12，分别优选的是 C1-4- 亚烷基、或 C2-12-，优选的是 C2-4- 亚烯基或 - 亚炔基部分。

[2678] 在支链衍生物通常由例如“正”、“仲”、“异”等前缀限定（例如“正 - 丙基”、“仲 - 丁基”）的情况下，除非另外说明，否则基团都是正 - 形式。

[2679] 将如本文使用的术语“芳基”定义为包含从含有至少一个环、最常为 1-3 个环且通常含有 6-30 个碳原子的芳烃中通过移除一个氢而衍生的有机残基，例如苯基和萘基，各自被选自下列基团的一个或多个取代基任选地取代：卤素、羟基、巯基、氨基、硝基、氰基、酰基、酰氧基、磺酰基、亚磺酰基、烷基氨基、羧基、酯、醚、酰氨基、叠氮基、磺酸、磺酰胺、烷基磺酰基、烷基亚磺酰基、C1-6- 烷硫基、氧基酯基、氧基酰氨基、芳基、C1-6- 烷氧基、C6-10- 芳氧基、C1-6- 烷基、C1-6- 卤代烷基。芳基残基优选地为含有 6-10 个碳原子的单环或双环。优选的芳基为被一个或多个独立选自下列的取代基任选地取代的苯基和萘基：卤素、硝基、氨基、叠氮基、C1-6- 烷氧基、C1-6- 烷基、C1-6- 卤代烷基、磺酰基和苯基。

[2680] 在某些实施方案中，芳基为被一个或多个卤素、低级烷基、叠氮基或硝基任选地取代的苯基，例如 3- 氯苯基和 3- 叠氮基苯基。

[2681] 如本文使用的术语“卤素”，包括 Cl、Br、F、I 的原子。

[2682] 如本文使用的术语“羟基”，表示式 -OH 的基团。

[2683] 如本文使用的术语“巯基”，表示式 -SH 的基团。

[2684] 如本文使用的术语“氰基”，表示式 -CN 的基团。

[2685] 如本文使用的术语“硝基”，表示式 -NO2 的基团。

[2686] 如本文使用的术语“硝基氧基”，表示式 -ONO2 的基团。

[2687] 如本文使用的术语“氨基”，表示式 -NH2 的基团。

[2688] 如本文使用的术语“叠氮基”，表示式 -N3 的基团。

[2689] 如本文使用的术语“羧基”，表示式 -COOH 的基团。

[2690] 如本文使用的术语“磺酸”，表示式 -SO3H 的基团。

[2691] 术如本文使用的语“磺酰胺”，表示式 -SO2NH2 的基团。

[2692] 将如本文使用的术语“酯”，定义为包含式 -COO-R<11> 基团，其中 R<11> 为除了氧基衍生物、硫基衍生物或氨基衍生物之外如上文所定义的。优选的为式 -COOR<11> 的酯，其中 R<11> 选自 C1-12 烷基、C2-12 烯基、C2-12 烯基和芳基。最优选的为其中 R<11> 为低级烷基，特别是甲基的酯。

[2693] 将术语“醚”定义为选自 C1-50- 直链或支链烷基，或 C2-50- 直链或支链烯基或炔

基或其的组合的基团，其被一个或多个氧原子间隔。

[2694] 将术语“酰氨基”定义为包含 -CONH2 或 -CONHR<11> 或 -CONR<11>R<12> 的基团，其中 R<11> 和 R<12> 为如上文所定义的。

[2695] 将如本文使用的术语“杂环”，定义为包含如上文所定义的芳族的或非芳族的环烷基、烯基，或炔基部分，具有间隔碳环结构的至少一个 O、S 和 / 或 N 原子，并任选地，碳环结构的碳之一可经羰基替代，并任选地被任何适宜的基团（包括但不限于选自低级烷基，或如上所述用于烷基的其它基团一个或多个部分）取代。杂环的非限制性实例为被烷基或如上所述用于烷基的基团任选地取代的吡啶基、呋喃基、吡咯基、噻吩基、异噻唑基、三唑基、咪唑基、苯并咪唑基、四唑基、喹唑啉基、喹噁基、萘啶基、哒嗪基、嘧啶基、吡嗪基、喹啉基、异喹啉基、异苯并吡喃基、苯并噻吩基、吡唑基、吲哚基、吲嗪基、嘌呤基、异吲哚基、咔唑基、噻唑基、1, 2, 4- 噻二唑基、硫吗啉基、噻吩并 (2, 3-b) 呋喃基、呋喃并吡喃基、苯并呋喃基、苯并氧杂环庚三烯基、异噁唑基、噁唑基、噻蒽基、苯并噻唑基或苯并噁唑基、噌啉基、酞嗪基、喹喔啉基、1- 氧吡啶基、菲啶基、吖啶基、萘嵌二氮杂苯基、菲咯啉基、吩噻嗪基、呋咱基、苯并间二氧杂环戊烯基、异苯并二氢呋喃基、吲哚啉基、呫吨基、次黄嘌呤基、蝶啶基、5- 氮杂胞苷基、5- 氮杂尿嘧啶基、三唑并吡啶基、咪唑并吡啶基、吡咯并嘧啶基、吡唑并嘧啶基、四氢呋喃基、四氢吡喃基、哌啶基、哌啶基、哌嗪基、咪唑烷基、吗啉代、吗啉基、1- 氧杂螺 (4.5) 癸 -2- 基、吡咯烷基、2- 氧代 - 吡咯烷基、糖部分（即葡萄糖、戊糖、己糖、核糖、果糖，其也可被取代）。术语“杂环”也包括的双环、三环和四环、螺环基团，其中将任何上述杂环与独立地选自以下的一个或两个环稠合：芳环、环己烷环、环己烯环、环戊烷环、环戊烯环或另一个单环杂环，或其中将单环杂环基通过亚烷基桥连，例如奎宁环基、7- 氮杂双环 (2.2.1) 庚烷基、7- 氧杂双环 (2.2.1) 庚烷基、8- 氮杂双环 (3.2.1) 辛烷基。

[2696] 杂环可选自三唑基、四唑基、吡咯烷基、吡啶基、1- 氧吡啶基、硫吗啉基、苯并间二氧杂环戊烯基、呋喃基、噁唑基、嘧啶基、吡咯基、噻二唑基、噻唑基、噻吩基和哌嗪基，各自被选自卤素、烷基、取代的烷基、烷氧基、硝基、氨基、酰基和苯基的一个或多个取代基任选地取代。在某些实施方案中，杂环选自四唑基、吡咯烷基、吡啶基、呋喃基、吡咯基、噻唑基和噻吩基，各自被选自卤素、烷基、被卤素取代的烷基、酰基、烷氧基、硝基、氨基和苯基的一个或多个取代基任选地取代，并且特别选自经一个或多个卤素、例如甲酰基的酰基、氰基和 / 或例如甲基的低级烷基任选地取代的 2- 和 3- 噻吩基。

[2697] 在上文的定义中，应当理解当将例如 R<1>、R<2>、R<3>、R<4>、R<5>、R<7>、R<8>、R<9>、R<10> 的取代基经杂原子或羰基连接至其余分子时，可将直链 - 或支链，C1-12-，优选的是 C1-4- 亚烷基或 C2-12，优选的是 C2-4- 亚烯基或 - 亚炔基桥任选地插入杂原子或羰基和与其余分子的连接点之间。

[2698] 以其作为碱的游离形式存在的式 (I) 化合物的酸加成盐形式可通过用下列适当的酸处理所述游离碱得到：例如无机酸，例如氢卤酸（例如盐酸或氢溴酸）、硫酸、硝酸、磷酸等；或有机酸，例如乙酸、羟基乙酸、丙酸、乳酸、丙酮酸、丙二酸、琥珀酸、马来酸、富马酸、苹果酸、酒石酸、柠檬酸、甲苯磺酸、乙苯磺酸、苯磺酸、对 - 甲苯磺酸、环拉酸、水杨酸、对 - 氨基水杨酸、扑酸等。

[2699] 可将含有酸性质子的式 (I) 化合物通过用适当的有机和无机碱处理，转化为它们的具有治疗活性、无毒的碱加成盐形式，例如金属或胺盐。适当的碱盐形式包括，例如铵盐，

碱金属和碱土金属盐，例如锂、钠、钾、镁、钙盐等，有机碱盐，例如 N- 甲基 -D- 葡萄糖胺、海巴明盐，以及氨基酸盐例如，精氨酸、赖氨酸等的盐。

[2700] 相反地，可将所述盐形式用适当的碱或酸处理转化为游离形式。

[2701] 式 I 化合物及它们的盐可为纳入本发明的范围内的溶剂合物的形式。这类溶剂合物包括例如水合物、醇合物等。

[2702] 许多式 I 化合物和某些它们的中间体在它们的结构中具有至少一个立体异构中心。该立体异构中心可以以 R 或 S 构型存在，使用所述 R 和 S 符号与在 Pure Appl. Chem. (1976), 45, 11-30 中所述的规则一致。

[2703] 本发明也涉及所有的立体异构体形式，例如式 I 化合物的对映异构和非对映异构形式或其混合物（包括所有可能的立体异构体的混合物）。

[2704] 此外，含有烯基的式 I 的某些化合物可作为 Z（顺式）或 E（反式）异构体存在。在每个情况下，本发明包括混合和单独的个体异构体。

[2705] 就哌啶基或氮杂环庚烷基环的平面而言，在哌啶基或氮杂环庚烷基环上的多个取代基也可彼此为顺式或反式关系。

[2706] 某些式 I 化合物也可存在互变异构形式。尽管未在上式中明确指明，也旨在将这类形式纳入本发明的范围内。

[2707] 除非特别提及具体的异构体形式，否则就本发明提及的化合物而言旨在包括化合物的每个可能的异构体形式及其混合物。

[2708] 本发明在其范围内还包括式 I 化合物及它的各种亚范围和亚族的前药形式。

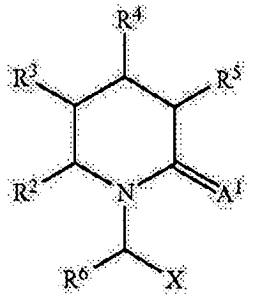
[2709] 如本文使用的术语“前药”包括在体内迅速转化为根据本发明的母体化合物（例如，通过在血液中水解）的化合物形式。前药是在显示它们的药理作用之前具有通过生物转化修饰的基团的化合物。这类基团包含易于氧化、环化或裂解的部分，在生物转化之后的化合物保留了或变得有药理学活性。例如，代谢地可裂解基团形成了本领域技术人员熟知的基团类型。它们包括，但不限于如下基团：如烷酰基（即乙酰基、丙酰基，丁酰基等）、未取代的和取代的碳环芳酰基（例如苯甲酰基、取代的苯甲酰基及 1- 和 2- 萘甲酰基）、烷氧羰基（例如乙氧羰基）、三烷基硅烷基（例如三甲基硅烷基和三乙基硅烷基）、与二羧酸（例如氯琥珀胆碱）、磷酸、硫酸、磺酸、磺酰基、亚磺酰基等形成的单酯。具有可生物转化基团的化合物具有下列优势：由于存在可生物可转化的基团，它们赋予母体化合物提高的溶解度和 / 或吸收速率，因此显示改善的生物利用度。T. Higuchi 和 V. Stella, “Pro-drugs as Novel Delivery System”, Vol. 14, the A. C. S. Symposium Series; “Bioreversible Carriers in Drug Design”, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987。

[2710] 术语“R 取代基”独立地意指 R<1>、R<2>、R<3>、R<4> 或 R<5>。

[2711] 根据一个实施方案，本发明涉及如上文所定义的式 I 化合物，其中 n 表示 0。该化合物为 6 元环结构 (2- 硫代 - 或 2- 氧代 - 哌啶基衍生物)，其中由于 n = 0, R<1> 不存在，并如式 (I-A) 所示

[2712]

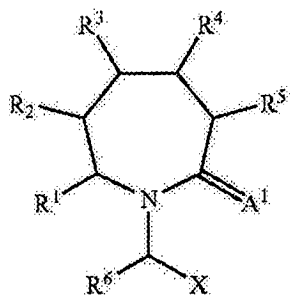
(I-A)



[2713] 根据下列实施方案，本发明涉及根据本发明如上文所定义的式 I 化合物，其中 n 表示 1。该化合物为 7 元环结构 (2- 硫代 - 或 2- 氧代 - 氧杂环庚烷基衍生物)，其中由于 n = 1，R<1> 存在，并如式 (I-B) 所示

[2714]

(I-B)



[2715] 根据一个实施方案，本发明涉及如上文所定义的所述化合物，其中 n = 0，R<3> 和 / 或 R<4> 不是氢，且 R<2> 和 R<5> 表示氢。

[2716] 根据另一个实施方案，本发明涉及如上文所定义的所述化合物，其中 n = 1，R<2>、R<3> 和 / 或 R<4> 不是氢，且其中 R<1> 和 R<5> 表示氢。

[2717] 根据另一个实施方案，本发明涉及如上文所定义的所述化合物，其中当 n = 0 时选自 R<3> 或 R<4>，或当 n = 1 时选自 R<2>、R<3> 或 R<4> 的仅一个 R 取代基不是氢，而剩余的 R 取代基都为氢。我们据此意指单基取代的 2- 硫代 - 或 2- 氧代 - 哌啶基或 2- 硫代 - 或 2- 氧代 - 氮杂环庚烷基衍生物。

[2718] 根据另一个实施方案，本发明涉及根据本发明如上文所定义的式 I 化合物，其中 A<1> 表示氧原子。我们据此意指 2- 氧代 - 哌啶基或 2- 氧代 - 氮杂环庚烷基衍生物。

[2719] 根据另一个实施方案，本发明涉及根据本发明如上文所定义的式 I 化合物，其中 X 为 CONR<7>R<8>，特别是 CONH2。我们据此意指 2- 氧代 (或硫代)- 哌啶基或 2- 氧代 (或硫代)- 氮杂环庚烷基的酰氨基衍生物。

[2720] 根据另一个实施方案，本发明涉及根据本发明如上文所定义的式 I 化合物，其中 R<6> 表示氢、C1-4 烷基或 CH2-R<6a> 基团，其中 R<6a> 表示杂环。最优选的是 R<6> 为 C1-4 烷基，特别是乙基。当 R<6> 为乙基时，我们意指 2-(2- 氧代 (或硫代)-1- 哌啶基) 丁酰胺或 2-(2- 氧代 (或硫代)-1- 氮杂环庚烷基) 丁酰胺衍生物。

[2721] 根据另一个实施方案，本发明涉及根据本发明如上文所定义的式 I 化合物，其中 R<6> 连接的碳原子为 S 构型。在 R<6> 为乙基，A 为氧且 X 为 CONR<7>R<8> 情况下，那么我们意指 (2S)-2-(2- 氧代 -1- 哌啶基) 丁酰胺或 (2S)-2-(2- 氧代 -1- 氮杂环庚烷基) 丁酰胺衍生物。

[2722] 根据一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时 R<2>，R<3> 和 R<4> 相同和或不同，并各自独立地为氢、卤素、硝基、硝基氧基、氰基、羧基、酰氨基、磺酸、磺酰胺、烷基、烯基、炔基、酯、醚、芳基、杂环、酰基衍生物、磺酰基衍生物或亚磺酰基衍生物：

[2723] 当存在时 R<1>，当 n = 0 时 R<2> 和 R<5> 为氢；

[2724] R<6> 为氢、烷基、芳基或 -CH2-R<6a>，其中 R<6a> 为芳基、杂环、卤素、羟基、氨基、硝基或氰基；

[2725] 条件是，当 R<6> 为氢时，X 为 -CONR<7>R<8> 且化合物

[2726] 既不是 (2R)-2-[(6R)-6- 甲基 -2- 氧代氮杂环庚烷基]-3- 苯基丙酸甲酯

[2727] 也不是 (2S)-2-[(4R)-4- 甲基 -2- 氧代氮杂环庚烷基]-3- 苯基丙酸甲酯。

[2728] 根据该实施方案，该化合物通常是这样的，当 R<6> 为苄基时，X 为 -COOCH3 且 n = 1，当 R<3> 和 R<4> 都为氢时 R<2> 不是甲基，且当 R<2> 和 R<3> 都为氢时 R<4> 不是甲基。

[2729] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时 R<2>、R<3> 和 R<4> 相同或不同，且各自独立地为氢；氰基；羧基；酰氨基；

[2730] C1-12 烷基，各自被选自羟基、卤素、氰基、氰硫基、烷氧基、叠氮基、烷硫基、环烷基、酰基、芳基和杂环的一个或多个取代基任选地取代；

[2731] C2-12 烷基，各自被选自卤素、氰基、氰硫基、叠氮基、烷硫基、烷基、芳基和酰基的一个或多个取代基任选地取代；

[2732] C2-12 炔基，各自被选自卤素、氰基、氰硫基、叠氮基、烷硫基、烷基、芳基和酰基的一个或多个取代基任选地取代；式 -CO-R<11> 的酰基衍生物，其中 R<11> 选自 C1-12 烷基、C2-12 烯基、C2-12 炔基、杂环和芳基；

[2733] 式 -CO-O-R<11> 的酯，其中 R<11> 选自 C1-12 烷基、C2-12 烯基、C2-12 烯基和芳基；

[2734] 选自三唑基、四唑基、吡咯烷基、吡啶基、1- 氧吡啶基、硫吗啉基、苯并间二氧杂环戊烯基、呋喃基、噁唑基、嘧啶基、吡咯基、噻二唑基、噻唑基、噻吩基和哌嗪基的杂环，各自被选自卤素、烷基、取代的烷基、烷氧基、硝基、氨基、酰基和苯基的一个或多个取代基任选地取代；

[2735] 芳基，各自被选自 C1-6 烷基、C1-6 卤代烷基、C1-6 烷氧基、C1-6 烷硫基、氨基、叠氮基、磺酰基、芳基和硝基的一个或多个取代基任选地取代。

[2736] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时 R<2>、R<3> 和 R<4> 相同或不同，且各自独立地为氢；

[2737] C1-7 烷基，各自被选自羟基、卤素、氰基、氰硫基、烷氧基、叠氮基、烷硫基、环丙基、酰基和苯基的一个或多个取代基任选地取代；

[2738] C2-6 烷基，各自被选自卤素、氰基、氰硫基、叠氮基、烷硫基、环烷基、烷基、苯基和酰基的一个或多个取代基任选地取代；

[2739] C2-6 烷基，各自被选自卤素、氰基、氰硫基、叠氮基、烷硫基、环烷基、苯基和酰基的一个或多个取代基任选地取代；

[2740] 选自四唑基、吡咯烷基、吡啶基、呋喃基、吡咯基、噻唑基和噻吩基的杂环，各自被选自卤素、烷基、被卤素取代的烷基、酰基、烷氧基、硝基、氨基和苯基的一个或多个取代基

任选地取代；

[2741] 苯基，各自被选自 C1-6 烷基、被卤素取代的烷基、卤素、烷氧基、氨基、叠氮基、磺酰基、苯基和硝基的一个或多个取代基任选地取代。

[2742] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时选自基团 R<2>、R<3> 和 R<4> 或当 n = 0 时选自基团 R<3> 和 <4> 的至少一个 R 取代基，独立地表示经一个或多个卤素、羟基、低级烷基和 / 或叠氮基任选地取代的 C1-4- 烷基或 C3-7- 环烷基。

[2743] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时选自基团 <2>、R<3> 和 R<4> 或当 n = 0 时选自基团 R<3> 和 <4> 的至少一个 R 取代基，独立地表示经一个或多个卤素和 / 或低级烷基任选地取代的乙烯基。

[2744] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时选自基团 <2>、R<3> 和 R<4> 或当 n = 0 时选自基团 R<3> 和 <4> 的至少一个 R 取代基，独立地表示经一个或多个卤素和 / 或低级烷基任选地取代的乙炔基、丙炔基或丁炔基。

[2745] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时选自基团 <2>、R<3> 和 R<4> 或当 n = 0 时选自基团 R<3> 和 <4> 的至少一个 R 取代基，独立地表示经一个或多个卤素、低级烷基、叠氮基和 / 或硝基任选地取代的苯基。

[2746] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时选自基团 <2>、R<3> 和 R<4> 或当 n = 0 时选自基团 R<3> 和 <4> 的至少一个 R 取代基，独立地表示经一个或多个卤素、酰基、氰基和 / 或低级烷基任选地取代的 2- 或 3- 噻吩基。

[2747] 根据具体的实施方案，本发明涉及如上文所定义的化合物，其中当 n = 1 时选自基团 R<3>、R<4> 和 R<2> 或当 n = 0 时选自基团 R<3> 和 R<4> 的至少一个 R 取代基为羟甲基、丙基、丁基、3,3,3- 三氟丙基、2,2,2- 三氟乙基、环丙基甲基、碘甲基、叠氮基甲基、2- 噻吩基、3- 噻吩基、苯基、3- 氯苯基、3- 叠氮基苯基、2,2- 二氟乙烯基、2,2- 二溴乙烯基、2,2- 二氯乙烯基、2- 乙炔基、5- 甲基 -2- 噻吩基、5- 甲酰基 -2- 乙炔基、5- 氰基 -2- 噻吩基、3- 溴 -2- 噻吩基、4- 甲基 -2- 噻吩基、3,3,3- 三氟 -1- 丙炔基、1- 丙炔基、环丙基乙炔基、3- 甲基 -1- 丁炔基、1- 丁炔基、2,2- 二氟丙基、2- 氯 -2,2- 二氟乙基、2- 溴 -2,2- 二氟乙基和 2- 碘 -2,2- 二氟乙基。

[2748] 根据又一个实施方案，本发明涉及如上文所定义的化合物，其中 R<1>、R<2>、R<4> 和 R<5> 都为氢。

[2749] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中 R<1>、R<2>、R<3> 和 R<5> 为氢。

[2750] 根据另一个实施方案，本发明涉及如上文所定义的化合物，其中 n = 1 且 R<1>、R<3>、R<4> 和 R<5> 为氢。

[2751] 在所有上文 - 提及的范围中，当 R<6> 连接的碳原子不对称时，它可为 "S"- 构型。

[2752] 本发明如上文所定义的代表性的化合物选自

[2753] 2-[5-(羟甲基)-2- 氧代 -1- 哌啶基] 丁酰胺、

[2754] 2-(2- 氧代 -5- 丙基 -1- 哌啶基) 丁酰胺、

[2755] 2-[2- 氧代 -5-(3,3,3- 三氟丙基)-1- 哌啶基] 丁酰胺、

[2756] 2-[5-(环丙基甲基)-2- 氧代 -1- 哌啶基] 丁酰胺、

[2757] 2-[5-(碘甲基)-2-氧代-1-哌啶基]丁酰胺、

[2758] 2-[5-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰胺、

[2759] 2-(2-氧代-5-苯基-1-哌啶基)丁酰胺、

[2760] 2-[2-氧代-5-(2-噻吩基)-1-哌啶基]丁酰胺、

[2761] 2-[2-氧代-5-(3-噻吩基)-1-哌啶基]丁酰胺、

[2762] 2-[5-(3-氯苯基)-2-氧代-1-哌啶基]丁酰胺、

[2763] 2-[5-(3-叠氮基苯基)-2-氧代-1-哌啶基]丁酰胺、

[2764] 2-[5-(2,2-二氟乙烯基)-2-氧代-1-哌啶基]丁酰胺、

[2765] 2-[5-(2,2-二溴乙烯基)-2-氧代-1-哌啶基]丁酰胺、

[2766] 2-[5-(2,2-二氯乙烯基)-2-氧代-1-哌啶基]丁酰胺、

[2767] 2-(5-乙炔基-2-氧代-1-哌啶基)丁酰胺、

[2768] 2-[5-(5-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2769] 2-[5-(5-甲酰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2770] 2-[5-(5-氰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2771] 2-[5-(3-溴-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2772] 2-[5-(4-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2773] 2-[2-氧代-5-(3,3,3-三氟-1-丙炔基)-1-哌啶基]丁酰胺、

[2774] 2-[2-氧代-5-(1-丙炔基)-1-哌啶基]丁酰胺、

[2775] 2-[5-(环丙基乙炔基)-2-氧代-1-哌啶基]丁酰胺、

[2776] 2-[5-(3-甲基-1-丁炔基)-2-氧代-1-哌啶基]丁酰胺、

[2777] 2-[5-(1-丁炔基)-2-氧代-1-哌啶基]丁酰胺、

[2778] 2-[5-(2,2-二氟丙基)-2-氧代-1-哌啶基]丁酰胺、

[2779] 2-[5-(2-氯-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺、

[2780] 2-[5-(2-溴-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺、

[2781] 2-[4-(羟甲基)-2-氧代-1-哌啶基]丁酰胺、

[2782] 2-(2-氧代-4-丙基-1-哌啶基)丁酰胺、

[2783] 2-[2-氧代-4-(3,3,3-三氟丙基)-1-哌啶基]丁酰胺、

[2784] 2-[4-(环丙基甲基)-2-氧代-1-哌啶基]丁酰胺、

[2785] 2-[4-(碘甲基)-2-氧代-1-哌啶基]丁酰胺、

[2786] 2-[4-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰胺、

[2787] 2-(2-氧代-4-苯基-1-哌啶基)丁酰胺、

[2788] 2-[2-氧代-4-(2-噻吩基)-1-哌啶基]丁酰胺、

[2789] 2-[2-氧代-4-(3-噻吩基)-1-哌啶基]丁酰胺、

[2790] 2-[4-(3-氯苯基)-2-氧代-1-哌啶基]丁酰胺、

[2791] 2-[4-(3-叠氮基苯基)-2-氧代-1-哌啶基]丁酰胺、

[2792] 2-[4-(2,2-二氟乙烯基)-2-氧代-1-哌啶基]丁酰胺、

[2793] 2-[4-(2,2-二溴乙烯基)-2-氧代-1-哌啶基]丁酰胺、

[2794] 2-[4-(2,2-二氯乙烯基)-2-氧代-1-哌啶基]丁酰胺、

[2795] 2-(4-乙炔基-2-氧代-1-哌啶基)丁酰胺、

[2796] 2-[4-(5-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2797] 2-[4-(5-甲酰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2798] 2-[4-(5-氰基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2799] 2-[4-(3-溴-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2800] 2-[4-(4-甲基-2-噻吩基)-2-氧代-1-哌啶基]丁酰胺、

[2801] 2-[2-氧代-4-(3,3,3-三氟-1-丙炔基)-1-哌啶基]丁酰胺、

[2802] 2-[2-氧代-4-(1-丙炔基)-1-哌啶基]丁酰胺、

[2803] 2-[4-(环丙基乙炔基)-2-氧代-1-哌啶基]丁酰胺、

[2804] 2-[4-(3-甲基-1-丁炔基)-2-氧代-1-哌啶基]丁酰胺、

[2805] 2-[4-(1-丁炔基)-2-氧代-1-哌啶基]丁酰胺、

[2806] 2-[4-(2,2-二氟丙基)-2-氧代-1-哌啶基]丁酰胺、

[2807] 2-[4-(2-氯-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺、

[2808] 2-[4-(2-溴-2,2-二氟乙基)-2-氧代-1-哌啶基]丁酰胺、

[2809] 2-[4-(2,2,2-三氟乙基)-2-氧代-1-哌啶基]丁酰胺、

[2810] 2-[5-(羟甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2811] 2-(2-氧代-5-丙基-1-氮杂环庚烷基)丁酰胺、

[2812] 2-[2-氧代-5-(3,3,3-三氟丙基)-1-氮杂环庚烷基]丁酰胺、

[2813] 2-(5-(环丙基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2814] 2-[5-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2815] 2-[5-(叠氮基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2816] 2-(2-氧代-5-苯基-1-氮杂环庚烷基)丁酰胺、

[2817] 2-[2-氧代-5-(2-噻吩基)-1-氮杂环庚烷基]丁酰胺、

[2818] 2-[2-氧代-5-(3-噻吩基)-1-氮杂环庚烷基]丁酰胺、

[2819] 2-[5-(3-氯苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2820] 2-[5-(3-叠氮基苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2821] 2-[5-(2,2-二氟乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2822] 2-[5-(2,2-二溴乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2823] 2-[5-(2,2-二氯乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2824] 2-(5-乙炔基-2-氧代-1-氮杂环庚烷基)丁酰胺、

[2825] 2-[5-(5-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2826] 2-[5-(5-甲酰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2827] 2-[5-(5-氰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2828] 2-[5-(3-溴-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2829] 2-[5-(4-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2830] 2-[2-氧代-5-(3,3,3-三氟-1-丙炔基)-1-氮杂环庚烷基]丁酰胺、

[2831] 2-[2-氧代-5-(1-丙炔基)-1-氮杂环庚烷基]丁酰胺、

[2832] 2-[5-(环丙基乙炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2833] 2-[5-(3-甲基-1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2834] 2-[5-(1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2835] 2-[5-(2,2-二氟丙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2836] 2-[5-(2-氯-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2837] 2-[5-(2-溴-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2838] 2-[5-(2,2,2-三氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2839] 2-[6-(羟甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2840] 2-(2-氧代-6-丙基-1-氮杂环庚烷基)丁酰胺、

[2841] 2-[2-氧代-6-(3,3,3-三氟丙基)-1-氮杂环庚烷基]丁酰胺、

[2842] 2-[6-(环丙基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2843] 2-[6-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2844] 2-[6-(叠氮基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2845] 2-(2-氧代-6-苯基-1-氮杂环庚烷基)丁酰胺、

[2846] 2-[2-氧代-6-(2-噻吩基)-1-氮杂环庚烷基]丁酰胺、

[2847] 2-[2-氧代-6-(3-噻吩基)-1-氮杂环庚烷基]丁酰胺、

[2848] 2-[6-(3-氯苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2849] 2-[6-(3-叠氮基苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2850] 2-[6-(2,2-二氟乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2851] 2-[6-(2,2-二溴乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2852] 2-[6-(2,2-二氯乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2853] 2-(6-乙炔基-2-氧代-1-氮杂环庚烷基)丁酰胺、

[2854] 2-[6-(5-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2855] 2-[6-(5-甲酰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2856] 2-[6-(5-氰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2857] 2-[6-(3-溴-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2858] 2-[6-(4-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2859] 2-[2-氧代-6-(3,3,3-三氟-1-丙炔基)-1-氮杂环庚烷基]丁酰胺、

[2860] 2-[2-氧代-6-(1-丙炔基)-1-氮杂环庚烷基]丁酰胺、

[2861] 2-[6-(环丙基乙炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2862] 2-[6-(3-甲基-1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2863] 2-[6-(1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2864] 2-[6-(2,2-二氟丙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2865] 2-[6-(2-氯-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2866] 2-[6-(2-溴-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2867] 2-[6-(2,2,2-三氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2868] 2-[4-(羟甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2869] 2-(2-氧代-4-丙基-1-氮杂环庚烷基)丁酰胺、

[2870] 2-[2-氧代-4-(3,3,3-三氟丙基)-1-氮杂环庚烷基]丁酰胺、

[2871] 2-[4-(环丙基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2872] 2-[4-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2873] 2-[4-(叠氮基甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2874] 2-(2-氧代-4-苯基-1-氮杂环庚烷基)丁酰胺、

[2875] 2-[2-氧代-4-(2-噻吩基)-1-氮杂环庚烷基]丁酰胺、

[2876] 2-[2-氧代-4-(3-噻吩基)-1-氮杂环庚烷基]丁酰胺、

[2877] 2-[4-(3-氯苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2878] 2-[4-(3-叠氮基苯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2879] 2-[4-(2,2-二氟乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2880] 2-[4-(2,2-二溴乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2881] 2-[4-(2,2-二氯乙烯基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2882] 2-(4-乙炔基-2-氧代-1-氮杂环庚烷基)丁酰胺、

[2883] 2-[4-(5-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2884] 2-[4-(5-甲酰基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2885] 2-[<4>-(5-氰基-<2>-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2886] 2-[4-(3-溴-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2887] 2-[4-(4-甲基-2-噻吩基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2888] 2-[2-氧代-4-(3,3,3-三氟-1-丙炔基)-1-氮杂环庚烷基]丁酰胺、

[2889] 2-[2-氧代-4-(1-丙炔基)-1-氮杂环庚烷基]丁酰胺、

[2890] 2-[4-(环丙基乙炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2891] 2-[4-(3-甲基-1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2892] 2-[4-(1-丁炔基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2893] 2-[4-(2,2-二氟丙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2894] 2-[4-(2-氯-2,2-二氟乙基]-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2895] 2-[4-(2-溴-2,2-二氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺、

[2896] 2-[4-(2,2,2-三氟乙基)-2-氧代-1-氮杂环庚烷基]丁酰胺。

[2897] 结果得到下列化合物：

[2898] (2S)-2-[5-(碘甲基)-2-氧代-1-哌啶基]丁酰胺，

[2899] (2S)-2-[5-(叠氮基甲基)-2-氧代-1-哌啶基]丁酰胺，

[2900] 2-(2-氧代-5-苯基-1-哌啶基]丁酰胺，

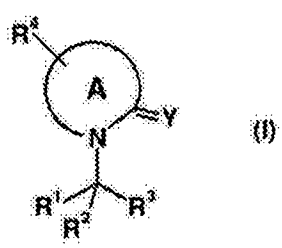
[2901] (2S)-2-[4-(碘甲基)-2-氧代-1-哌啶基]丁酰胺，

[2902] 2-[5-(碘甲基)-2-氧代-1-氮杂环庚烷基]丁酰胺。

[2903] xv) 国际专利申请公开文本第 WO2008/132139 号

[2904] 在某些实施方案中，式 (I) 化合物如下：

[2905]



(I)

[2906] 其中

[2907] Y 为 O 或 S。在某些实施方案中，Y 为 O。R1 为氢或 C-|.g 烷基；

[2908] R2 为氢；

[2909] R3 为 -CONR5R6、-COR7、咪唑基、咪唑并吡啶基、咪唑并哒嗪基；R5、R6 相同或不同，并独立地选自氢和 C-|_6 烷基；

[2910] R7 为 C<；|_6 烷基；

[2911] A 为选自以下的单环或双环的杂环部分：咪唑烷 -1- 基、1,3- 噁唑烷 -3- 基、2,5- 二氢 -1H- 吡咯 -1- 基、1,3- 噻唑 -3(2H)- 基、1,3- 噻唑烷 -3- 基、哌啶 -1- 基、氮杂环庚烷 -1- 基、5,6- 二氢 -4H- 噻吩并 [3,2-b] 吡咯 -4- 基、六氢 -4H- 噻吩并 [3,2-b] 吡咯 -4- 基、2,3- 二氢 -1H- 噻吩并 [3,4-b] 吡咯 -1- 基、1,3- 苯并噻吩 -3(2H)- 基、1,3- 苯并噁唑 -3(2H)- 基、吡唑并 [1,5-a] 吡啶 -1(2H)- 基、3,4- 二氢异喹啉 -2(1H)- 基、3,4- 二氢喹啉 -1(2H)- 基、1,3,4,5- 四氢 -2H-2- 苯并氮杂䓬 -2- 基、1,2,4,5- 四氢 -3H-3- 苯并氮杂䓬 -3- 基；

[2912] R4 为 R^a 或 R^b，取决于 A 是否为单环或双环的杂环：

[2913] 在 A 为单环杂环部分的情况下，R^ 为选自下列基团的 R^a：氢；被选自卤素、C-1.4 烷氧基、C-1.4 烷硫基、叠氮基、硝基氧基或芳基的取代基任选地取代的 C-|.g 烷基；被卤素任选地取代的 C2-6 烯基；被卤素任选地取代的 C2-6 炔基；叠氮基；烷氧基羰基氨基；芳基磺酰基氧基；取代的或未取代的芳基；或 3-8 元的取代的或未取代的杂环；

[2914] 在 A 为双环的杂环部分的情况下，R^ 为选自下列基团的 R^：氢；硝基；氰基；卤素；杂环；氨基；芳基；被至少一个卤素任选地取代的 C-|.g 烷基；或被至少一个卤素任选地取代的 C-|.g 烷氧基；

[2915] 在某些实施方案中，化合物为如下：

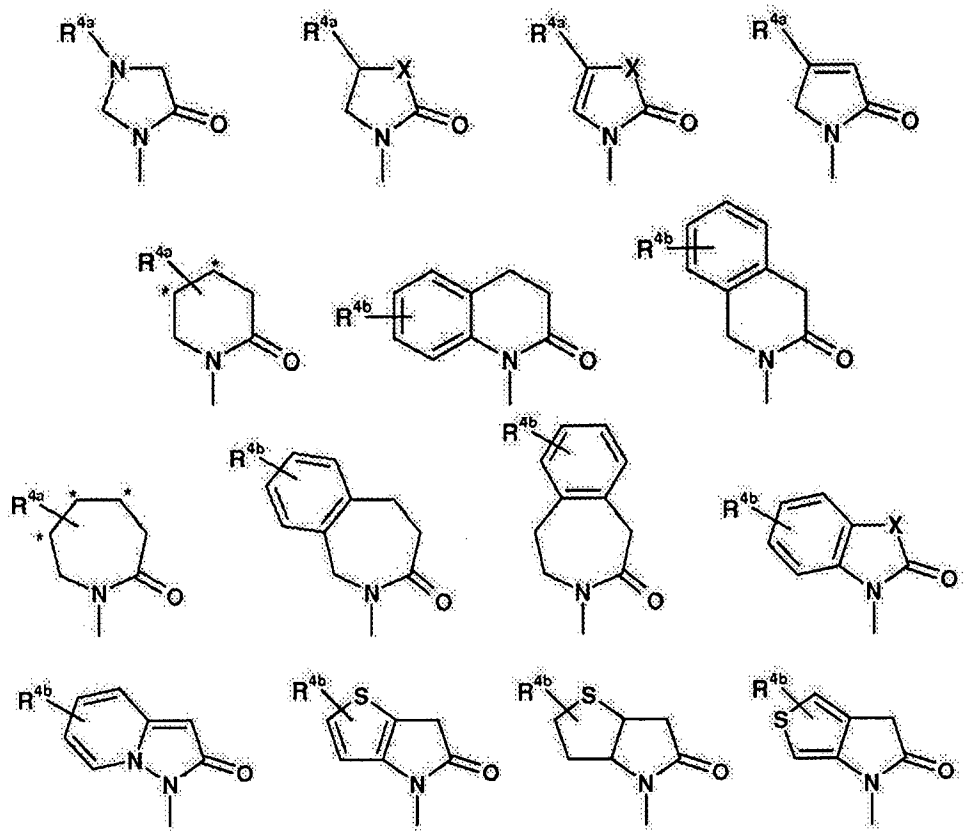
[2916] 对于化合物，在 A = Y 选自 2- 氧代 - 哌啶 -1- 基、2- 氧代 - 氮杂环庚烷 -1- 基、2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基或 2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基的情况下，R3 必须选自咪唑基、咪唑并吡啶基或咪唑并哒嗪基。

[2917] 对于化合物，在 A = Y 为 5- 氧代咪唑烷 -1- 基，R^ 和 R^ 为氢，R3 为 -CONR5R6，R5 和 R6 为如上文所定义的情况下，那么 R^a 不可为烷基、芳烷基或取代的芳烷基。

[2918] 在 A = Y 为 2- 氧代 - 哌啶 -1- 基和 2- 氧代 - 氮杂环庚烷 -1- 基的任一个，R^、R^ 和 R^a 全部为氢的情况下，那么 R^ 不可为 2- 苯基咪唑并 [1,2-a] 吡啶 -3- 基。

[2919] 在具体的实施方案中，A = Y 选自由以下组成的列表：

[2920]



[2921] 其中 X 为 O 或 S，在更具体的实施方案中为 O；在另一个实施方案中，X 为 S。

[2922] 在上文插图中的星号表示取代基 Rˆa 的连接部位。

[2923] 在具体实施方案中，当 Rˆ 为 -CONR5R6 且 Rˆ 为 C-μg 烷基时，R-I 和 Rˆ 连接的碳原子优选地为“S”-构型。

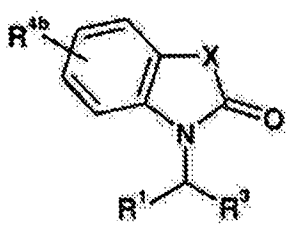
[2924] 在具体的实施方案中，Rˆ 为氢、甲基、乙基且 Rˆ 为氢。在具体的实施方案中，R3 为 -CONH2。

[2925] 在另一个具体的实施方案中，Rˆ 为 1H-咪唑 -1-基、1H-咪唑 -4-基、1H-咪唑 -5-基、咪唑并 [1,2-a] 吡啶 -3-基或咪唑并 [1,2-b] 哒嗪 -3-基。在具体的实施方案中，Rˆa 为可被卤素任选地取代的 C-|.g 烷基；或苯基。

[2926] 在另一个具体的实施方案中，Rˆb 为氢、卤素、硝基、氰基或被卤素任选地取代的 C-μg 烷基。

[2927] 在又一个实施方案中，化合物可用于上文提及病症具体的是癫痫的治疗，该化合物具有式 (I-E)，以及它的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2928]



(I-E)

[2929] 其中

[2930] X 为 O 或 S；

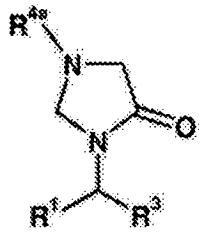
[2931] R-I 为氢或 C-|.g 烷基，在更具体的实施方案中为氢；

[2932] R3 为咪唑基、咪唑并吡啶基、咪唑并哒嗪基；

[2933] Rˆb 为氢；硝基；氰基；卤素；被卤素任选地取代的 C-|.g 烷基；被卤素任选地取代的 C-|.g 烷氧基。

[2934] 本发明的另一个方面在于具有式 (I-A) 的新化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2935]



(I-A)

[2936] 其中

[2937] R1 为氢或 C-|.g 烷基，优选地为氢、甲基或乙基；在更具体的实施方案中，Rˆ 为乙基。

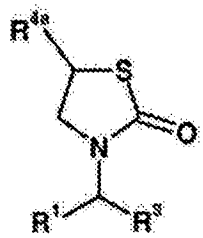
[2938] R3 为 -CONH2、咪唑基、咪唑并吡啶基、咪唑并哒嗪基，优选的是 Rˆ 为 -CONH2。

[2939] Rˆa 为氢或芳基；条件是除 2-(5- 氧代咪唑烷 -1- 基）乙酰胺之外。优选的是 Rˆa 为芳基，例如苯基，其可被卤素、硝基、烷氧基，具体的是被硝基优选地取代。

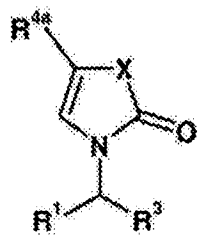
[2940] 在具体的实施方案中，当 Rˆ 为 -CONH2 且 Rˆ 为 C-|.g 烷基时，R1 和 Rˆ 连接的碳原子优选地为“S”- 构型。

[2941] 本发明的另一个方面在于具有式 (I-B1 或 I-B2) 的新化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2942]



(I-B1)



(I-B2)

[2943] 其中在式 (I-B2) 中的 X 为 S 或 O，在更具体的实施方案中为 S。

[2944] R1 为氢或 C-|.g 烷基，优选的为氢、甲基或乙基；在更具体的实施方案中，Rˆ 为乙基。

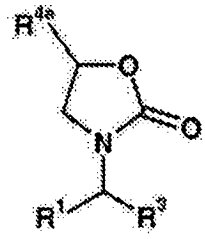
[2945] R3 为 -CONH2、咪唑基、咪唑并吡啶基、咪唑并哒嗪基；优选的是 Rˆ 为 -CONH2。

[2946] Rˆa 为氢；被卤素或 C-1.4 烷氧基任选地取代的 C-|.g 烷基；芳基；或被卤素任选地取代的 C2.g 烯基。优选的是，Rˆa 为被卤素任选地取代的 C-|.g 烷基，或被卤素任选地取代的 C2-6 烯基、或芳基。在更具体的实施方案中，Rˆa 为被卤素任选地取代的 C-|.g 烷基或芳基。

[2947] 在具体的实施方案中，当 R^ 为 -CONH2 且 R^ 为 C-|.g 烷基时，R-I 和 R^ 连接的碳原子优选地为“S”-构型。

[2948] 本发明的另一个方面在于具有式 (I-B3) 的新化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2949]



(I-B3)

[2950] 其中

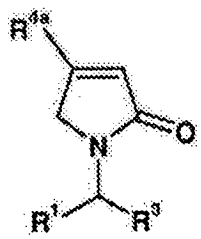
[2951] R1 为氢或 C-μg 烷基，优选的为氢、甲基或乙基；更优选的是 R1 为乙基。

[2952] R3 为 -CONH2、咪唑基、咪唑并吡啶基、咪唑并哒嗪基；优选的是 R^ 为 -CONH2，R^a 为被卤素或 C-1.4 烷氧基任选地取代的 C-|_5 烷基；芳基；或被卤素任选地取代的 C2_g 烯基。优选的是，R^a 为被卤素任选地取代的 C-|.g 烷基，或被卤素任选地取代的 C2_g 烯基。

[2953] 在具体的实施方案中，当 R^ 为 -CONH2 且 R^ 为 C-|.g 烷基时，R-I 和 R^ 连接的碳原子优选地为“S”-构型。

[2954] 本发明的另一个方面在于具有式 (I-C) 的新化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2955]



(I-C)

[2956] 其中

[2957] R1 为氢或 C-|.g 烷基，具体的为氢、甲基或乙基。

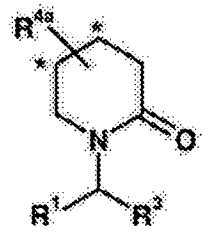
[2958] R3 为 -CONH2、咪唑基、咪唑并吡啶基、咪唑并哒嗪基；具体的是 R^ 为 -CONH2。

[2959] R^a 为被卤素或 C-1.4 烷氧基任选地取代的甲基、乙基、丁基、未取代的苯基或被卤素取代的苯基，被卤素或 C-1.4 烷氧基任选地取代的 C-|.g 烷基；或 R^a 为被卤素任选地取代的 C2-6 烯基。优选的是，R^a 为被卤素任选地取代的甲基、未取代的苯基或被卤素取代的苯基。

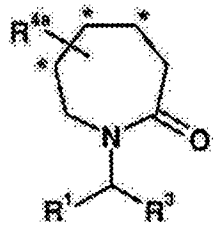
[2960] 在具体的实施方案中，当 R^ 为 -CONH2 且 R^ 为 C-|.g 烷基时，R1 和 Rβ 连接的碳原子优选地为“S”-构型。

[2961] 本发明的另一个方面在于具有式 (I-D1 或 I-D2) 的化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2962]



(I-D1)



(I-D2)

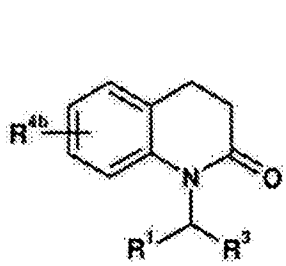
[2963] 其中

[2964] R-I 为氢或 C-|.g 烷基，具体的是氢；R3 为咪唑基、咪唑并吡啶基或咪唑并哒嗪基。在一个实施方案中，R^ 为 1H- 咪唑 -1- 基、1H- 咪唑 -4- 基、1H- 咪唑 -5- 基、咪唑并 [1,2-a] 吡啶 -3- 基或咪唑并 [1,2-b] 哒嗪 -3- 基。在更具体的实施方案中，R^ 为 1H- 咪唑 -1- 基、1H- 咪唑 -4- 基、1H- 咪唑 -5- 基、咪唑并 [1,2-a] 吡啶 -3- 基；R^a 为氢、被卤素或 C-1.4 烷氧基任选地取代的 C-|.g 烷基；芳基；或被卤素任选地取代的 C2-g 烯基。在具体的实施方案中，R^a 为被卤素任选地取代的 C-|.g 烷基；芳基；或被卤素任选地取代的 C2-6 烯基。在更具体的实施方案中，R^a 为被卤素任选地取代的 C-|.g 烷基；或芳基；例如丙基或苯基。

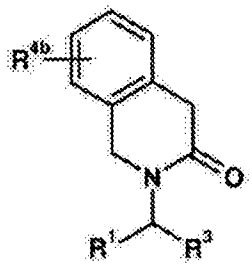
[2965] 条件是当 R^ 和 R^a 为氢时，R^ 不为 2- 苯基咪唑并 [1,2-a] 吡啶 -3- 基。

[2966] 本发明的另一个方面在于具有式 (I-F1、I-F2 或 I-F3) 的化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

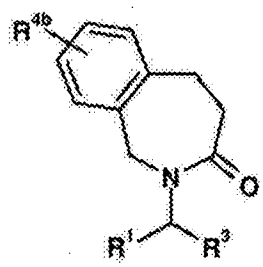
[2967]



(I-F1)



(I-F2)



(I-F3)

[2968] 其中

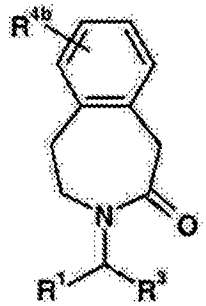
[2969] R-I 为氢或 C-|.g 烷基，优选的为氢、甲基或乙基；更优选的是，R^ 为氢。

[2970] R3 为 -CONH2、咪唑基、咪唑并吡啶基或咪唑并哒嗪基；在更具体的实施方案中，R3 为 -CONH2、1H- 咪唑 -1- 基、1H- 咪唑 -4- 基、1H- 咪唑 -5- 基、咪唑并 [1,2-a] 吡啶 -3- 基或咪唑并 [1,2-b] 哒嗪 -3- 基。R^b 为氢；卤素；硝基；氰基；被卤素任选地取代的 C1-4 烷基；被卤素任选地取代的 C1-4 烷氧基。在更具体的实施方案中，R^ 为氢、卤素或氰基，更具体的是卤素。

[2971] 在具体的实施方案中，当 R^ 为 -CONH2 且 R^ 为 C-|.g 烷基时，R1 和 Rβ 连接的碳原子优选地为“S”- 构型。

[2972] 本发明的另一个方面在于具有式 (I-F4) 的化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

[2973]



(I-F4)

[2974] 其中

[2975] R-I 为氢或 C-|.g 烷基，优选的是氢；

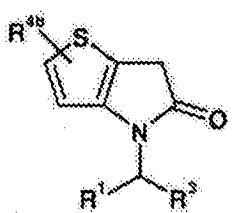
[2976] R3 为咪唑基、咪唑并吡啶基或咪唑并哒嗪基；具体的是，R^ 为 1H- 咪唑 -1- 基、1H- 咪唑 -4- 基、1H- 咪唑 -5- 基、咪唑并 [1,2-a] 吡啶 -3- 基或咪唑并 [1,2-b] 哒嗪 -3- 基。更具体的是，R^ 为 1H- 咪唑 -4- 基或咪唑并 [1,2-a] 吡啶 -3- 基。

[2977] R^b 为氢；卤素；硝基；氰基；被卤素任选地取代的 C-1.4 烷基；被卤素任选地取代的 C-1.4 烷氧基；具体的是，R^ 为氢、卤素或氰基。

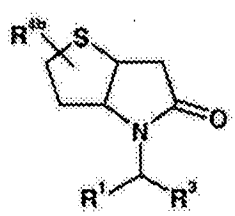
[2978] 在具体的实施方案中，当 R^ 为 -CONH2 且 R^ 为 C-|.g 烷基时，R-I 和 R^ 连接的碳原子优选地为“S”- 构型。

[2979] 本发明的另一个方面在于具有式 (I-G1、I-G2 或 I-G3) 中任一个的化合物、它们的几何异构体、对映异构体、非对映异构体及混合物，或其药学上可接受的盐，

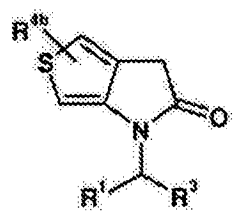
[2980]



(I-G1)



(I-G2)



(I-G3)

[2981] 其中

[2982] R-I 为氢或 C-|.g 烷基；优选的是氢；

[2983] R3 为 -CONH2、咪唑基、咪唑并吡啶基或咪唑并哒嗪基；在更具体的实施方案中，R^ 为 -CONH2、1H- 咪唑 -1- 基、1H- 咪唑 -4- 基、1H- 咪唑 -5- 基、咪唑并 [1,2-a] 吡啶 -3- 基或咪唑并 [1,2-b] 哒嗪 -3- 基。在甚至更具体的实施方案中，R3 为 1H- 咪唑 -4- 基或咪唑并 [1,2-a] 吡啶 -3- 基。

[2984] R4D 为氢；卤素；被卤素任选地取代的 C-1.4 烷基；被卤素任选地取代的 C-1.4 烷氧基。

[2985] 本发明具体的化合物为选自下列的那些：

[2986] (2S)-2-[3-(4- 硝基苯基)-5- 氧代咪唑烷 -1- 基] 丁酰胺；

[2987] (2S)-2-[3-(2,4- 二硝基苯基)-5- 氧代咪唑烷 -1- 基] 丁酰胺；

[2988] (2S)-2-(5- 氧代 -3- 苯基咪唑烷 -1- 基) 丁酰胺；

[2989] 2-[5-(碘甲基)-2- 氧代 -1,3- 噁唑烷 -3- 基] 丁酰胺；

[2990] 2-(2-氧代-2,5-二氢-1H-吡咯-1-基)丁酰胺；

[2991] 2-(2-氧代-4-苯基-2,5-二氢-1H-吡咯-1-基)丁酰胺；

[2992] 2-(4-甲基-2-氧代-2,5-二氢-1H-吡咯-1-基)丁酰胺；

[2993] (2S)-2-(2-氧代-5-丙基-1,3-噻唑-3(2H)-基)丁酰胺；

[2994] 2-(2-氧代-5-丙基-1,3-噻唑-3(2H)-基)丙酰胺；

[2995] 2-(5-丁基-2-氧代-1,3-噻唑烷-3-基)丁酰胺；

[2996] 2-(5-丁基-2-氧代-1,3-噻唑烷-3-基)丙酰胺；

[2997] 2-(2-氧代-5-苯基-1,3-噻唑烷-3-基)丙酰胺；

[2998] 2-(2-氧代-5-丙基-1,3-噻唑烷-3-基)丁酰胺；

[2999] 2-(2-氧代-5-苯基-1,3-噻唑烷-3-基)丁酰胺；

[3000] 2-(2-氧代-5-丙基-1,3-噻唑烷-3-基)丙酰胺；

[3001] (2S)-2-[2-氧代-5-(2,2,2-三氟乙基)-1,3-噻唑烷-3-基]丁酰胺；

[3002] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}哌啶-2-酮；

[3003] 1-(1H-咪唑-4-基甲基)-5-丙基哌啶-2-酮；

[3004] 1-(1H-咪唑-1-基甲基)-5-丙基哌啶-2-酮；

[3005] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-5-丙基哌啶-2-酮；

[3006] 1-(1H-咪唑-1-基甲基)-5-苯基哌啶-2-酮；

[3007] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-5-苯基哌啶-2-酮；

[3008] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-4-苯基哌啶-2-酮；

[3009] 1-(1H-咪唑-1-基甲基)-4-苯基哌啶-2-酮；

[3010] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-4-丙基哌啶-2-酮；

[3011] 1-(1H-咪唑-5-基甲基)-4-丙基哌啶-2-酮；

[3012] 1-(1H-咪唑-1-基甲基)-4-丙基哌啶-2-酮；

[3013] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}氮杂环庚烷-2-酮；

[3014] 1-(1H-咪唑-5-基甲基)-5-丙基氮杂环庚烷-2-酮；

[3015] 5-丙基-1-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}氮杂环庚烷-2-酮；

[3016] 5-苯基-1-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}氮杂环庚烷-2-酮；

[3017] 1-(1H-咪唑-5-基甲基)-6-丙基氮杂环庚烷-2-酮；

[3018] 1-(1H-咪唑-4-基甲基)-4-丙基氮杂环庚烷-2-酮；

[3019] 4-(1H-咪唑-4-基甲基)-4,6-二氢-5H-噻吩并[3,2-b]吡咯-5-酮；

[3020] 2-(5-氧代-5,6-二氢-4H-噻吩并[3,2-b]吡咯-4-基)乙酰胺；

[3021] 4-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}-4,6-二氢-5H-噻吩并[3,2-b]吡咯-5-酮；

[3022] 4-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}六氢-5H-噻吩并[3,2-b]吡咯-5-酮；

[3023] 1-(1H-咪唑-4-基甲基)-1H-噻吩并[3,4-b]吡咯-2(3H)-酮；

[3024] 2-(6-氯-2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺；

[3025] 6- 溴 -3-(1H- 咪唑 -1- 基甲基)-1,3- 苯并噻唑 -2(3H)- 酮 ;

[3026] 2-(6- 溴 -2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 丙酰胺 ;

[3027] 2-(6- 溴 -2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 丙酰胺 ;

[3028] 2-(6- 氟 -2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 乙酰胺 ;

[3029] 2-(6- 甲基 -2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 乙酰胺 ;

[3030] 6- 氟 -3-(1H- 咪唑 -1- 基甲基)-1,3- 苯并噻唑 -2(3H)- 酮 ;

[3031] 1-(1H- 咪唑 -4- 基甲基) 吡唑并 [1,5-a] 吡啶 -2(1H)- 酮 ;

[3032] 2-(6- 氯 -3- 氧代 -3,4- 二氢异喹啉 -2(1H)- 基) 丙酰胺 ;

[3033] 5- 氯 -2-(1H- 咪唑 -4- 基甲基)-1,4- 二氢异喹啉 -3(2H)- 酮 ;

[3034] 2-(6- 氯 -2- 氧代 -3,4- 二氢喹啉 -1(2H)- 基) 乙酰胺 ;

[3035] 2-(6- 溴 -2- 氧代 -3,4- 二氢喹啉 -1(2H)- 基) 乙酰胺 ;

[3036] 1-(1H- 咪唑 -4- 基甲基)-3,4- 二氢喹啉 -2(1H)- 酮 ;

[3037] 2-(6- 碘 -2- 氧代 -3,4- 二氢喹啉 -1(2H)- 基) 乙酰胺 ;

[3038] 2-(6- 氰基 -2- 氧代 -3,4- 二氢喹啉 -1(2H)- 基) 乙酰胺 ;

[3039] 7- 氯 -2-{[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 甲基 }-1,2,4,5- 四氢 -3H-2- 苯并氮杂䓬 -3- 酮 ;

[3040] 7- 氯 -2-(1H- 咪唑 -4- 基甲基)-1,2,4,5- 四氢 -3H-2- 苯并氮杂䓬 -3- 酮 ;

[3041] 7- 氯 -3-(1H- 咪唑 -4- 基甲基)-1,3,4,5- 四氢 -2H-3- 苯并氮杂䓬 -2- 酮 ;和

[3042] 7- 氯 -3-{[2-(三氟甲基) 咪唑并 [1,2-a] 吡啶 -3- 基] 甲基 }-1,3,4,5- 四氢 -2H-3- 苯并氮杂䓬 -2- 酮。

[3043] 在某些实施方案中,本发明具体的化合物为选自下列的那些 :

[3044] 1-(1H- 咪唑 -4- 基甲基)-5- 丙基哌啶 -2- 酮 ;

[3045] 1-(1H- 咪唑 -1- 基甲基)-5- 丙基哌啶 -2- 酮 ;

[3046] 1-(咪唑并 [1,2-a] 吡啶 -3- 基甲基)-5- 丙基哌啶 -2- 酮 ;

[3047] 1-(1H- 咪唑 -1- 基甲基)-5- 苯基哌啶 -2- 酮 ;

[3048] 1-(咪唑并 [1,2-a] 吡啶 -3- 基甲基)-4- 苯基哌啶 -2- 酮 ;

[3049] 1-(1H- 咪唑 -1- 基甲基)-4- 苯基哌啶 -2- 酮 ;

[3050] 1-(咪唑并 [1,2-a] 吡啶 -3- 基甲基)-4- 丙基哌啶 -2- 酮 ;

[3051] 1-(1H- 咪唑 -5- 基甲基)-4- 丙基哌啶 -2- 酮 ;

[3052] 1-(1H- 咪唑 -1- 基甲基)-4- 丙基哌啶 -2- 酮 ;

[3053] 1-(1H- 咪唑 -4- 基甲基)-1H- 噻吩并 [3,4-b] 吡咯 -2(3H)- 酮 ;

[3054] 6- 溴 -3-(1H- 咪唑 -1- 基甲基)-1,3- 苯并噻唑 -2(3H)- 酮 ;

[3055] 2-(6- 溴 -2- 氧代 -1,3- 苯并噻唑 -3(2H)- 基) 丙酰胺 ;和

[3056] 5- 氯 -2-(1H- 咪唑 -4- 基甲基)-1,4- 二氢异喹啉 -3(2H)- 酮。

[3057] 下列段落提供了制备根据本发明化合物的各种化学部分的定义,并且旨在一致地应用于整个说明书和权力要求中,除非另外明确列出的定义提供了更广泛的定义。

[3058] “C-|_β 烷基”意指具有 1-6 个,或 1-4 个碳原子的烷基。将该术语通过下列基团举例说明 :例如甲基、乙基、正 - 丙基、异丙基、正 - 丁基、异丁基、叔 - 丁基、正 - 戊基、正 - 己

基、三氟甲基等。

[3059] “芳基”意指具有单环（例如苯基）或多稠合环（例如萘基）的 6-14 个碳原子的不饱和芳族碳环基团。优选的芳基包括苯基、萘基、菲基等。

[3060] “杂环”意指除了碳原子之外含有至少一个杂原子，例如氮、氧和 / 或硫的饱和的或不饱和的环系统。“杂环”包括“杂芳基”和“杂环烷基”。

[3061] “杂芳基”意指单环杂芳族的，或双环的或三环的稠环杂芳族基团。具体的杂芳族基团的实例包括任选取代的吡啶基、吡咯基、呋喃基、噻吩基、咪唑基、噁唑基、异噁唑基、噻唑基、异噻唑基、吡唑基、1, 2, 3- 三唑基、1, 2, 4- 三唑基、1, 2, 3- 噁二唑基、1, 2, 4- 噁二唑、1, 2, 5- 噁二唑基、1, 3, 4- 噁二唑基、1, 3, 4- 三嗪基、1, 2, 3- 三嗪基、苯并呋喃基、[2, 3- 二氢] 苯并呋喃基、异苯并呋喃基、苯并噻吩基、苯并三唑基、异苯并噻吩基、吲哚基、异吲哚基、3H- 吲哚基、苯并咪唑基、咪唑并吡啶基、苯并噻唑基、苯并噁唑基、喹嗪基、喹唑啉基、酞嗪基、喹喔啉基、噌啉基、萘啶基、吡啶并 [3, 4-b] 吡啶基、吡啶并 [3, 2-b] 吡啶基、吡啶并 [4, 3-b] 吡啶基、喹啉基、异喹啉基、四唑基、5, 6, 7, 8- 四氢喹啉基、5, 6, 7, 8- 四氢异喹啉基、嘌呤基、蝶啶基、咔唑基、呫吨基、苯并喹啉基、咪唑并嘧啶基、咪唑并哒嗪基、咪唑并噻唑基或咪唑并噻二唑基。

[3062] “C2-6 烯基”意指优选地具有 2-6 个碳原子并具有烯基不饱和性质的至少 1 或 2 个部位的烯基。优选的烯基包括乙烯基 (ethenyl)（乙烯基 (vinyl)、-CH = CH2)、正 -2- 丙烯基（烯丙基、-CH2CH = CH2) 等。

[3063] “C2-6 炔基”意指优选地具有 2-6 个碳原子并具有炔基不饱和性质的至少 1-2 个部位的炔基，优选的炔基包括乙炔基 (-C ≡ CH)、炔丙基 (-CH2C ≡ CH) 等。

[3064] “C3-8 环烷基”意指具有单环（例如环己基）或多稠合环（例如降冰片基）的 3-8 个碳原子的饱和碳环基团。优选的环烷基包括环丙基、环丁基、环戊基、环己基、降冰片基等。

[3065] “杂环烷基”意指根据上文定义的 C3-8 环烷基，其中 1-3 碳原子被选自 O、S、NR（将 R 定义为氢或 C-|. g 烷基）的杂原子替代。“烷氧基”意指基团 -O-R，其中 R 包括“C- μ g 烷基”、“C2-6 烯基”、“C2-6 炔基”、“C3-8 环烷基”、“杂环烷基”、“芳基”、“杂芳基”。

[3066] “氨基”意指基团 -NRR'，其中每个 R、R' 独立为氢、“C-|. g 烷基”、“C2-6 烯基”、“C2-6 炔基”、“C3-8 环烷基”、“杂环烷基”、“芳基”、“杂芳基”，并且其中 R 和 R'，连同连接它们的氮原子一起可任选地形成 3-8- 元杂环烷基环。

[3067] “酰氨基”意指基团 -C(= O)NRR'，其中每个 R、R' 独立为氢、“C-|_5 烷基”、“C2-6 烯基”、“C2-6 炔基”、“C3.8 环烷基”、“杂环烷基”、“芳基”。

[3068] “杂芳基”，并且其中 R 和 R'，连同连接它们的氮原子一起可任选地形成 3-8- 元杂环烷基环。

[3069] “酰氨基”意指基团 -NRC(O)R'，其中 R 和 R' 如上文用于氨基的所定义的。

[3070] “脲基”意指基团 -NR”C(O)NRR'，其中 R 和 R' 如上文用于氨基所定义的，且 R”为如上文所定义的。“亚磺酰基”意指基团 -SR，其中 R 包括“C-|. g 烷基”、“C2-6 烯基”、“C2-6 炔基”、“C3.8 环烷基”、“杂环烷基”、“芳基”、“杂芳基”。

[3071] “亚磺酰基”意指基团 -S(= O)R，其中 R 为“C-|. g 烷基”、“C2-6 烯基”、“C2-6 炔基”、“C3.8 环烷基”、“杂环烷基”、“芳基”、“杂芳基”。

[3072] “磺酰基”意指基团 -S(= 0)2R，其中 R 为“C-|.g 烷基”、“C2-6 烯基”、“C2-6 炔基”、“C3.8 环烷基”、“杂环烷基”、“芳基”、“杂芳基”。

[3073] “卤素”意指氟、氯、溴和碘原子。

[3074] “取代的或未取代的”除非被单个取代基的定义另外限制，否则为上文所列的基团，如“烷基”、“烯基”、“炔基”、“芳基”以及

[3075] “杂芳基”等基团可用 1-5 个选自下列的取代基任选地取代：“C-|.g 烷基”、“C2-6 烯基”、“C2-6 炔基”、“环烷基”、“杂环烷基”、“氨基”、“酰氨基”、“酰氨基”、“脲基”、“芳基”、“杂芳基”、“烷氧基”、“卤素”、氰基、羟基、巯基、硝基、“酰氨基”、“硫烷基”、“亚磺酰基”、“磺酰基”等。

[3076] 以其作为碱的游离形式存在的式 (I) 化合物的酸加成盐形式可通过用下列适当的酸处理该游离碱得到：例如无机酸，例如氢卤酸（例如盐酸或氢溴酸）、硫酸、硝酸、磷酸等；或有机酸，例如乙酸、三氟乙酸、羟基乙酸、丙酸、乳酸、丙酮酸、丙二酸、琥珀酸、马来酸、富马酸、苹果酸、酒石酸、柠檬酸、甲苯磺酸、乙苯磺酸、苯磺酸、对 - 甲苯磺酸、环拉酸、水杨酸、对 - 氨基水杨酸、扑酸等。

[3077] 可将含有酸性质子的式 (I) 化合物通过用适当的有机和无机碱处理，转化为它们的具有治疗活性、无毒的碱加成盐形式，例如金属或胺盐。适当的碱盐形式包括，例如铵盐，碱金属和碱土金属盐，例如锂、钠、钾、镁、钙盐等，有机碱盐，例如 N- 甲基 -D- 葡萄糖胺、海巴明盐，以及氨基酸盐例如，精氨酸、赖氨酸等的盐。

[3078] 相反地，可将所述盐形式用适当的碱或酸处理转化为游离形式。

[3079] 式 (I) 化合物及它们的盐可为纳入本发明的范围内的溶剂合物的形式。这类溶剂合物包括例如水合物、醇合物等。

[3080] 许多式 (I) 化合物和某些它们的中间体在它们的结构中具有至少一个立体异构中心。该立体异构中心可以以 R 或 S 构型存在，使用所述 R 和 S 符号与在 Pure Appl. Chem.，45(1976)11-30 中所述的规则一致。

[3081] 本发明也涉及所有的立体异构体形式，例如式 (I) 化合物或其混合物（包括所有可能的立体异构体的混合物）的对映异构和非对映异构形式。除非特别提及具体的异构体形式，否则就本发明提及的化合物而言旨在包括化合物的每个可能的异构体形式及其混合物。

[3082] 根据本发明的化合物可存在不同的多晶型物。尽管未在上式中明确指明，也旨在将这类形式纳入本发明的范围内。

[3083] 某些式 (I) 化合物还可存在互变异构形式。这类形式尽管未在上式中明确指明，也旨在将其纳入本发明的范围内。

[3084] 本发明在其范围内还包括式 (I) 化合物及它的各种亚范围和亚族的前药形式。

[3085] 在具体的实施方案中，本发明涉及选自以下的化合物：

[3086] (2S)-2-[3-(4- 硝基苯基)-5- 氧代咪唑烷 -1- 基] 丁酰胺；

[3087] (2S)-2-[3-(2,4- 二硝基苯基)-5- 氧代咪唑烷 -1- 基] 丁酰胺；

[3088] (2S)-2-(5- 氧代 -3- 苯基咪唑烷 -1- 基) 丁酰胺；

[3089] 2-[5-(碘甲基)-2- 氧代 -1,3- 噁唑烷 -3- 基] 丁酰胺；

[3090] 2-(2- 氧代 -2,5- 二氢 -1H- 吡咯 -1- 基) 丁酰胺；

[3091] 2-(2-氧代-4-苯基-2,5-二氢-1H-吡咯-1-基)丁酰胺；

[3092] 2-(4-甲基-2-氧代-2,5-二氢-1H-吡咯-1-基)丁酰胺；

[3093] (+)-(2S)-2-(2-氧代-4-丙基-2,5-二氢-1H-吡咯-1-基)丁酰胺；

[3094] (2S)-2-(2-氧代-5-丙基-1,3-噻唑-3(2H)-基)丁酰胺；

[3095] 2-(2-氧代-5-丙基-1,3-噻唑-3(2H)-基)丙酰胺；

[3096] 2-(5-丁基-2-氧代-1,3-噻唑烷-3-基)丁酰胺；

[3097] 2-(5-丁基-2-氧代-1,3-噻唑烷-3-基)丙酰胺；

[3098] 2-(2-氧代-5-苯基-1,3-噻唑烷-3-基)丙酰胺；

[3099] 2-(2-氧代-5-丙基-1,3-噻唑烷-3-基)丁酰胺；

[3100] 2-(2-氧代-5-苯基-1,3-噻唑烷-3-基)丁酰胺；

[3101] 2-(2-氧代-5-丙基-1,3-噻唑烷-3-基)丙酰胺；

[3102] (2S)-2-[2-氧代-5-(2,2,2-三氟乙基)-1,3-噻唑烷-3-基]丁酰胺；

[3103] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}哌啶-2-酮；

[3104] 1-(1H-咪唑-4-基甲基)-5-丙基哌啶-2-酮；1-(1H-咪唑-1-基甲基)-5-丙基哌啶-2-酮；

[3105] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-5-丙基哌啶-2-酮；

[3106] 1-(1H-咪唑-1-基甲基)-5-苯基哌啶-2-酮；

[3107] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-5-苯基哌啶-2-酮；

[3108] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-4-苯基哌啶-2-酮；

[3109] 1-(1H-咪唑-1-基甲基)-4-苯基哌啶-2-酮；

[3110] 1-(咪唑并[1,2-a]吡啶-3-基甲基)-4-丙基哌啶-2-酮；

[3111] 1-(1H-咪唑-5-基甲基)-4-丙基哌啶-2-酮；

[3112] 1-(1H-咪唑-1-基甲基)-4-丙基哌啶-2-酮；

[3113] 1-{[6-氯-2-(三氟甲基)咪唑并[1,2-b]哒嗪-3-基]甲基}氮杂环庚烷-2-酮；

[3114] 1-(1H-咪唑-5-基甲基)-5-丙基氮杂环庚烷-2-酮；

[3115] 5-丙基-1-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}氮杂环庚烷-2-酮；

[3116] 1-(1H-咪唑-5-基甲基)-5-苯基氮杂环庚烷-2-酮；

[3117] 5-苯基-1-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}氮杂环庚烷-2-酮；

[3118] 1-(1H-咪唑-5-基甲基)-6-丙基氮杂环庚烷-2-酮；

[3119] 1-(1H-咪唑-4-基甲基)-4-丙基氮杂环庚烷-2-酮；

[3120] 4-(1H-咪唑-4-基甲基)-4,6-二氢-5H-噻吩并[3,2-b]吡咯-5-酮；

[3121] 2-(5-氧代-5,6-二氢-4H-噻吩并[3,2-b]吡咯-4-基)乙酰胺；

[3122] 4-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}-4,6-二氢-5H-噻吩并[3,2-b]吡咯-5-酮；

[3123] 4-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}六氢-5H-噻吩并[3,2-b]吡咯-5-酮；

[3124] 1-(1H-咪唑-4-基甲基)-1H-噻吩并[3,4-b]吡咯-2(3H)-酮；

[3125] 2-(6-溴-2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺;

[3126] 2-(2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺;

[3127] 2-(6-氯-2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺;

[3128] 6-溴-3-(1H-咪唑-1-基甲基)-1,3-苯并噻唑-2(3H)-酮;

[3129] 6-溴-3-(2-氧代丙基)-1,3-苯并噻唑-2(3H)-酮;

[3130] 2-(6-硝基-2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺;

[3131] 2-(6-溴-2-氧代-1,3-苯并噻唑-3(2H)-基)丙酰胺;

[3132] 2-(6-溴-2-氧代-1,3-苯并噻唑-3(2H)-基)丙酰胺;

[3133] 2-(6-氟-2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺;

[3134] 2-(6-甲基-2-氧代-1,3-苯并噻唑-3(2H)-基)乙酰胺;

[3135] 6-氟-3-(1H-咪唑-1-基甲基)-1,3-苯并噻唑-2(3H)-酮;

[3136] 1-(1H-咪唑-4-基甲基)吡唑并[1,5-a]吡啶-2(1H)-酮;

[3137] 2-(6-氯-3-氧代-3,4-二氢异喹啉-2(1H)-基)丙酰胺;

[3138] 5-氯-2-(1H-咪唑-4-基甲基)-1,4-二氢异喹啉-3(2H)-酮;

[3139] 2-(6-氯-2-氧代-3,4-二氢喹啉-1(2H)-基)乙酰胺;

[3140] 2-(6-溴-2-氧代-3,4-二氢喹啉-1(2H)-基)乙酰胺;

[3141] 1-(1H-咪唑-4-基甲基)-3,4-二氢喹啉-2(1H)-酮;

[3142] 2-(6-碘-2-氧代-3,4-二氢喹啉-1(2H)-基)乙酰胺;

[3143] 2-(6-氰基-2-氧代-3,4-二氢喹啉-1(2H)-基)乙酰胺;

[3144] 7-氯-2-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}-1,2,4,5-四氢-3H-2-苯并氮杂䓬-3-酮;

[3145] 7-氯-2-(1H-咪唑-4-基甲基)-1,2,4,5-四氢-3H-2-苯并氮杂䓬-3-酮;

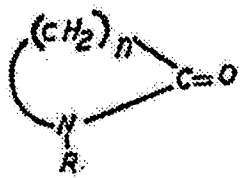
[3146] 7-氯-3-(1H-咪唑-4-基甲基)-1,3,4,5-四氢-2H-3-苯并氮杂䓬-2-酮;和

[3147] 7-氯-3-{[2-(三氟甲基)咪唑并[1,2-a]吡啶-3-基]甲基}-1,3,4,5-四氢-2H-3-苯并氮杂䓬-2-酮。

[3148] xvi)英国专利1,039,113

[3149] 根据本发明的新化合物为以下通式的N-取代的内酰胺:

[3150]



[3151] 其中N为3-5的整数且R表示

[3152]



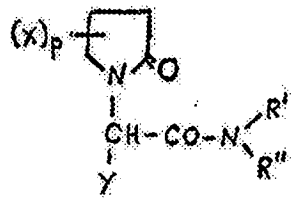
[3153] 的残基,其中m为0、1或2,且R'为氢原子或烷基、环烷基、烯基或炔基残基,该残

基可含有 3 至 6 个碳原子，或芳基残基，且 R"为氢原子或烷基残基，或 R' 和 R"，连同连接它们的氮原子一起形成杂环，例如 5 元吡咯烷环。

[3154] xvii) 英国专利 1,309,692

[3155] 根据本发明，提供了以下通式的新的 N- 取代的内酰胺：

[3156]



[3157] 其中 X 为氢原子或含有 1-6 个碳原子的烷基、烯基或炔基残基，p 为 1 至 6 的整数，Y 为氢原子或含有 1-6 个碳原子的烷基、烯基或炔基残基或环烷基残基，且可为相同或不同的 R' 和 R"，为氢原子或烷基、烯基、炔基、环烷基或芳基残基，或 R' 和 R"，连同连接它们的氮原子一起形成可以含有其它杂原子的杂环残基，条件是符号 X 和 Y 中的至少一个不是氢原子。

[3158] 乙酰胆碱酯酶抑制剂

[3159] 用于本发明方法和组合物的 AChEI 包括下列：

[3160] 扎那哌齐、更斯的明、苯乙基去甲希姆丝氨酸 (phenethylnorcymserine)(PENC)、希姆丝氨酸 (cymserine)、硫代希姆丝氨酸 (thiacymserine)、SPH 1371(加兰他敏加)、ER 127528、RS 1259、F3796、四氢氨基吖啶、DFP(异氟磷或二异丙基氟磷酸)、拉多替吉、Memoquin、SP-004、BGC-20-1259、NP-0361、ZT-1、INM-176、吡啶斯的明、阿伯农、demarcarium、依酚氯铵、解磷定、Amirine、SW-10888、MF-217、Ro 45-5934、HP-290、ENA 713、CP 118.954、ONO 1603、依斯的明、木兰提取物，例如厚朴酚、和厚朴酚、它斯品和巴婆碱、阿拉普利、贝那普利、卡托普利、西罗普利、西拉普利、地拉普利、依那普利、依那普利拉、福辛普利、咪达普利、赖诺普利、莫昔普利、莫维普利、奥马曲拉、培哚普利、喹那普利、雷米普利、山帕曲拉、螺普利 (sprirapril)、替莫普利 (temocaptril)、群多普利、哌啶基 - 烷酰基杂环化合物、N- 苄基 - 哌啶衍生物、4-(1- 苄基哌啶基)- 取代的稠合喹啉衍生物、单胺吖啶类和它们的衍生物、环酰胺衍生物、碳酸衍生物、水杨酸 (盐或酯)(saliclate)、双复磷、双解磷、二乙酰代森二甲胺、癸二胺苯酯、艾考哌齐 (5,7- 二氢 -3-(2-(1-(苯甲基)-4- 哌啶基) 乙基)-6H- 吡咯并 (3,2-f)-1,2- 苯并异噁唑 -6- 酮)、庚基毒扁豆碱、E-2020、胞磷胆碱、马来酸维吖啶、例如甲基磺酰氟 (Moos 和 Hershenson,1989) 和苯甲基磺酰氟 (Ferris,1990 ;Pope 和 Padilla,1990) 的磺酰基氟化物、石杉碱乙、miotine、舒罗吖啶和它的马来酸盐、7- 甲氧基他克林、SM-10888 和它的柠檬酸盐、ENA-713、TAK-147、CP-118954、齐罗硅酮、(SR,9R)-5-(r- 氯 -2- 羟基 -3- 甲氧苯亚甲基 - 氨基)-11- 亚乙基 -7- 甲基 -1,2,5,6,9,10- 六氢 -5,9- 甲撑环辛并 [b] 吡啶 -2- 酮 (ZT1)、司他可茶碱、SPH 1371、SPH 1373 和 SPH 1375、巧丝氨酸 (tolserine)、1-(3- 氟苄基)-4-[(2- 氟 -5,6- 二甲氧基 -1- 茚满酮 -2- 基) 甲基] 哌啶盐酸盐 (ER 127528)、硫代巧丝氨酸 (thiatolserine)、(-)-12- 氨基 -3- 氯 -9- 乙基 -6,7,10,11- 四氢 -7,11- 甲撑环辛并 [b] 喹啉盐酸盐 (huperine X)、N,N- 二甲氨基甲酸 4-[1(S)-(甲氨基)-3-(4- 硝基苯氧基) 丙基] 苯基酯半富马酸盐 (RS 1259)、2-[2-(1- 苄基哌啶 -4- 基) 乙基]-2,3- 二氢 -9- 甲氧基 -1H- 吡

咯并 [3,4-b] 喹啉 -1- 酮半富马酸盐 (T 82)、1,3- 二氯 -6,7,8,9,10,12- 六氢氮杂䓬并 [2,1-b]- 喹唑啉 (CI 1002)、N- 庚基氨基甲酸、2,4a,9- 三甲 -2,3,4,4a,9,9a- 六氢 -1,2- 噁嗪并 [6,5-b] 吲哚 -6- 基酯 -L- 酒石酸盐 (CHF 2060)、3-(2-[1-(1,3- 二氧戊环 -2- 基甲基) 哌啶 -4- 基] 乙基)-3,4- 二氢 -2H-1,3- 苯并噁嗪 -2,4- 二酮盐酸盐 (E 2030)、N-[10-(二乙氨基) 癸基] 氨基甲酸 (3aS,8aR)-1,3a,8- 三甲基 -1,2,3,3a,8,8a- 六氢吡咯并 [2,3-b] 吲哚 -5- 基酯 (MF 247)、5- 氨基 -6- 氯 -4- 羟基 -3,4- 二氢 -1H- 噻喃并 -[3,4-b] 喹啉 (MF 8615)、N-[8-(顺式 2,6- 二甲基吗啉 -4- 基) 辛基] 氨基甲酸 (3aS,aR)-1,3a,8- 三甲基 -1,2,3,3a,8,8a- 六氢吡咯并 [2,3-b] 吲哚 -5- 基酯 L- 酒石酸氢盐水合物 (MF 268)、(-)N-(3- 哌啶子基丙基)-N- 去甲基加兰他敏 (SPH 1286)、N- 炔丙基 -3R 氨基茚满 -5- 基 - 乙基甲氨基甲酸酯 (TV 3326)、隐丹参酮、二氢丹参酮 I 和丹参酮 I。

[3161] 用于本发明方法和组合物的乙酰胆碱酯酶抑制剂包括如下文献中提及的那些化合物或活性剂：

[3162] i) 美国专利申请公开第 20080103105 号

[3163] 在一个实施方案中，AcheI 为美曲膦酯，其也称为美曲膦酯或三氯磷酸酯或它的活性代谢物，2,2- 二甲基二氯乙烯基磷酸酯 (或敌敌畏或 DDVP)。美曲膦酯为下式所示：(CH3O)2-PO-CHOH-OCl 3。

[3164] 依可酯也称为碘依可酯 (ecothiopate)、依可碘酯 (echothiophate iodide)、碘二乙氧磷酰硫胆碱 (phospholine iodide)、(2- 巯乙基) 三甲铵 S- 酯和 O,O'- 二乙基硫代磷酸酯、BRN 1794025、ecothiopatum 或二乙氧磷酰硫胆碱。将依可酯通过 CAS 登记号 6736-03-4 引用。

[3165] 在其它的实施方案中，ACHE 抑制剂为氨吖啶，例如作为非限制性实例的他克林或伊匹达克林。他克林 / COGNEX® (1,2,3,4- 四氢 -9- 氨吖啶盐酸盐) 也称为四氢氨基吖啶或 THA。将他克林通过 CAS 登记号 321-64-2 引用。伊匹达克林也称为阿米利定 (Amiridin)。

[3166] 在另外的实施方案中，AChE 抑制剂为氨基甲酸酯，例如作为非限制性实例的毒扁豆碱、新斯的明或利凡斯的明。

[3167] 将毒扁豆碱 (也称为 1,2,3,3a,8,8a- 六氢 -1,3a,8- 三甲基 - 甲氨基甲酸酯或 (3aS,8aR)- 吡咯并 [2,3-b] 吲哚 -5- 醇) 通过 CAS 号 57-47-6 引用。它是能够通过血脑屏障的叔胺。

[3168] 将新斯的明，或间 - 羟苯基) 三甲基 - 二甲氨基甲酸酯铵通过 CAS 号 59-99-4 引用。

[3169] 利凡斯的明也称为酒石酸利凡斯的明或 (S)-N- 乙基 -N- 甲基 -3-[1-(二甲氨基) 乙基]- 苯基氨基甲酸酯 -(2R,3R)- 酒石酸氢盐或 SDZ ENA 713 或 ENA 713。利凡斯的明的引用为 CAS 登记号 123441-03-2。

[3170] 在另一个实施方案中，AChE 抑制剂为氨基甲酸酯菲衍生物，例如作为非限制性实例的加兰他敏或它的氢溴酸 (hydrogen bromide) 形式。

[3171] 加兰他敏也称为 (4aS,6R,8aS)-4a,5,9,10,11,12- 六氢 -3- 甲氧基 -11- 甲

基 -6H- 苯并呋喃并 (3a, 3, 2-ef) (2) 苯并氮杂䓬 -6- 醇，并经常以它的氢溴酸形式使用。将加兰他敏通过 CAS 号 357-70-0 引用。

[3172] AChE 抑制剂也可为哌啶衍生物，例如作非限制性实例的多奈哌齐。多奈哌齐也称为 2, 3- 二氢 -5, 6- 二甲氧基 -2-((1-(苯甲基)-4- 哌啶基) 甲基)-1H- 茚 -1- 酮，且通过 CAS 号 120014-06-4 引用。

[3173] 伊托必利还可为用于本文公开的实施方案的 AChE 抑制剂。将伊托必利 HCl 通过 CAS 登记号 122898-67-3 引用。在一个实施方案中，伊托必利 HCl 的日总剂量范围为约 25mg 至约 1000mg，或在约 100mg 至约 300mg 之间。在某些实施方案中，AChE 抑制剂，或神经源性活性剂，为伊托必利的 N- 氧化物衍生物，其为伊托必利 HCl 的初级人代谢产物。

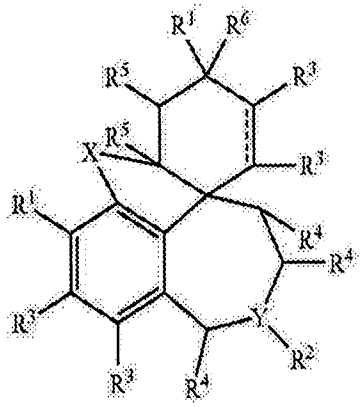
[3174] 用于公开的实施方案的另一个 AChE 抑制剂为 (-)- 石杉碱甲，其还也被称为 HupA 和 1- 氨基 -13- 亚乙基 -11- 甲基 -6- 氮杂 - 三环 [7. 3. 1. 02, 7] 十三碳 -2(7), 3, 10- 三烯 -5- 酮。将它通过 CAS 号 102518-79-6 引用。

[3175] ACHE 抑制剂的另一个实施方案为芬赛林，其结构及合成描述于美国专利第 6, 495, 700 号中。

[3176] 尽管加兰他敏仅为用于本发明的乙酰胆碱酯酶抑制剂的实例，但其它乙酰胆碱酯酶抑制剂也可同样使用。这类化合物的实例包括加兰他敏衍生物，例如式 (I) 的那些化合物：

[3177]

(I)



[3178] 其中：

[3179] 虚线表示单或双碳 - 碳键；

[3180] 两个符号 R1 彼此相同或不同，且各自表示氢原子、羟基、烷基、芳基、芳烷基、羟基烷基、烷硫基、羧基烷基、羧基烷基氨基、烷基氨基、酰基、氰基、氢硫基、C1-C6 烷氧基、烷硫基、芳氧基、芳硫基、脂族的或芳族的氨基甲酰基、芳烷氧基、芳烷基硫基、芳氧基甲基、烷酰氧基、羟基烷酰氧基、苯甲酰氧基、经一个或多个如下文所定义的基团 R3 取代的苯甲酰氧基，或芳氧基羰基；

[3181] R2 表示氢原子、C1-C6 烷基、C2-C6 烯基 (例如烯丙基)、芳烷基、所述烷基、烯基和芳烷基是未取代的或经至少一个选自以下的取代基取代的：卤素原子、环烷基、羟基、烷氧基、硝基、氨基、氨基烷基、酰氨基、芳族的或非芳族的杂环基 (例如 α - 或 β - 呋喃基、α - 或 β - 噻吩基、α - 或 β - 噻吩甲基、吡啶基、吡嗪基或嘧啶基)、经芳族杂环基取代的

烷基、芳基（例如苯基）、芳烷基、氰基、芳酰基或环烷基甲基；

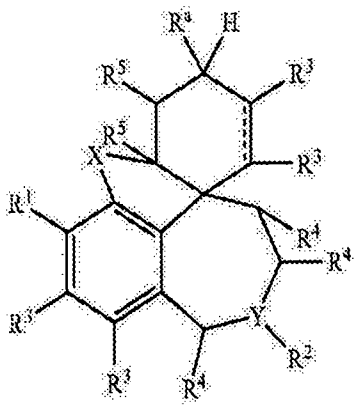
[3182] 符号 R3 彼此相同或不同，且各自表示氢原子、羟基、烷基、芳基、芳烷基、羟基烷基、烷硫基、氢硫基、C1-C6 烷氧基、芳氧基、芳硫基、芳烷氧基、芳烷基硫基、硝基、氨基、烷基氨基、芳氨基、芳烷基氨基、卤素原子或三氟甲基；

[3183] 符号 R4 彼此相同或不同，且各自表示氢原子、卤素原子、三氟甲基或 C1-C4 烷基；

[3184] 两个符号 R5 彼此相同或不同，且各自表示氢原子或羟甲基；

[3185] R6 表示氢原子或 C1-C6 烷基，或当与 R6 连接相同碳原子的符号 R1 表示氢原子时，R6 表示式（Ia）的基团：

[3186]



[3187] 其中 Ra 表示连接键，且 R1、R2、R3、R4、R5、X 和 Y 为如式（I）所定义的；

[3188] 或 R6 和与 R6 连接相同碳原子的 R1 共同表示半卡巴腙；

[3189] X 表示氧原子或式 -NR3 的基团，其中 R3 为如上文所定义的；

[3190] Y 表示氮原子或磷原子；

[3191] 及其药学上可接受的盐。

[3192] 在上式（I）的化合物中，除非另外指明，否则烷基可为直链或支链并优选地具有 1-10 个碳原子，并且这些的实例包括甲基、乙基、丙基、异丙基、丁基、异丁基、仲 - 丁基、叔 - 丁基、戊基、己基、庚基、辛基、壬基和癸基。烷氧基和烷基的其它简单衍生物同样优选地具有 1-10 个，更优选的是 1-6 个碳原子。

[3193] 芳基和杂环基可为未取代的或它们可被选自为 R3 所定义的基团和原子的一个或多个取代基取代，条件是任何 R3 取代基自身不可进一步被取代的芳基或杂环基取代。

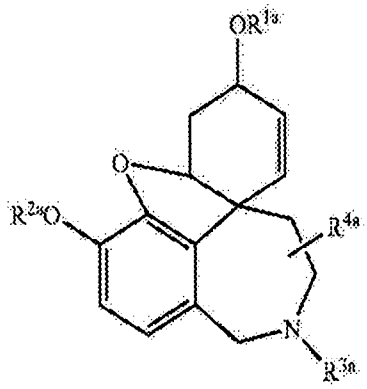
[3194] 优选的卤素原子为氟、氯、溴和碘原子。

[3195] 优选的式（I）化合物为其中烷基含有 1-8 个，更优选的是 1-6 个碳原子，卤素原子为氟、氯或溴原子，芳基为苯基（其可为取代的或未取代的，优选的是未取代的），环烷基含有 3-7 个环碳原子（优选的是环丙基或环丁基），酰基为低级的（例如 C2-C6 烷酰基），且杂环基为芳族的并含有 5-8 个环原子（例如噻吩基、呋喃基、吡啶基、吡咯基或吡嗪基）的那些。

[3196] 用于本发明的具体地优选的化合物为式（II）的那些化合物：

[3197]

(II)



[3198] 其中：

[3199] R1a和R2a彼此相同或不同，且各自表示氢原子、酰基（优选的是低级烷酰基，例如乙酰基）或C1-C6烷基（例如甲基、乙基、丙基或异丙基）；

[3200] R3a表示烷基、烯基或芳烷基，其中任何一个可为未取代的或经一个或多个卤素原子取代的，或它表示环烷基、羟基、烷氧基、硝基、氨基、氨基烷基、酰氨基、芳族的杂环、芳酰基、芳酰基烷基或氰基；且

[3201] R4a表示氢或卤素原子；

[3202] 及其药学上可接受的盐，特别是氢溴酸盐、盐酸盐、甲基磺酸盐或碘甲烷盐(methiodide)。

[3203] 这些化合物中，我们具体地优选加兰他敏及它的盐或多奈哌齐及它的盐，特别是卤化物，例如加兰他敏氢溴酸盐或多奈哌齐盐酸盐。

[3204] 用于本发明的加兰他敏衍生物包括去甲加兰他敏(norgalantamine)、去甲加兰他敏衍生物及表加兰他敏(epigalantamine)。

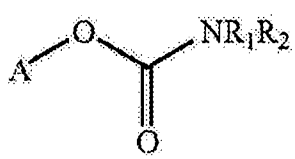
[3205] 可用作乙酰胆碱酯酶抑制剂的其它化合物包括：毒扁豆碱、他克林和他克林类似物、肌束震颤素(fasciculin)、美曲膦酯、庚基-毒扁豆碱、去甲吡啶斯的明(norpyridostigmine)、去甲新斯的明(norneostigmine)、新斯的明、吡啶斯的明、石杉碱或其前药、利凡斯的明或其前药、棉酚或芬赛林，或其前药。

[3206] 另一个具体地优选的乙酰胆碱酯酶抑制剂为多奈哌齐及它的盐，特别是卤化物，例如多奈哌齐盐酸盐。

[3207] i i) 美国专利申请公开文本第20070275959号

[3208] 在一个实施方案中，本发明为具有下列结构的氨基甲酰基酯：

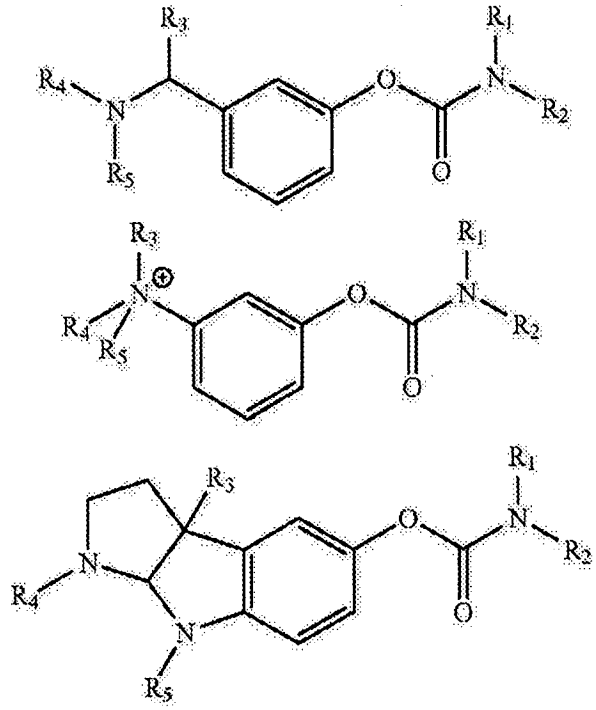
[3209]



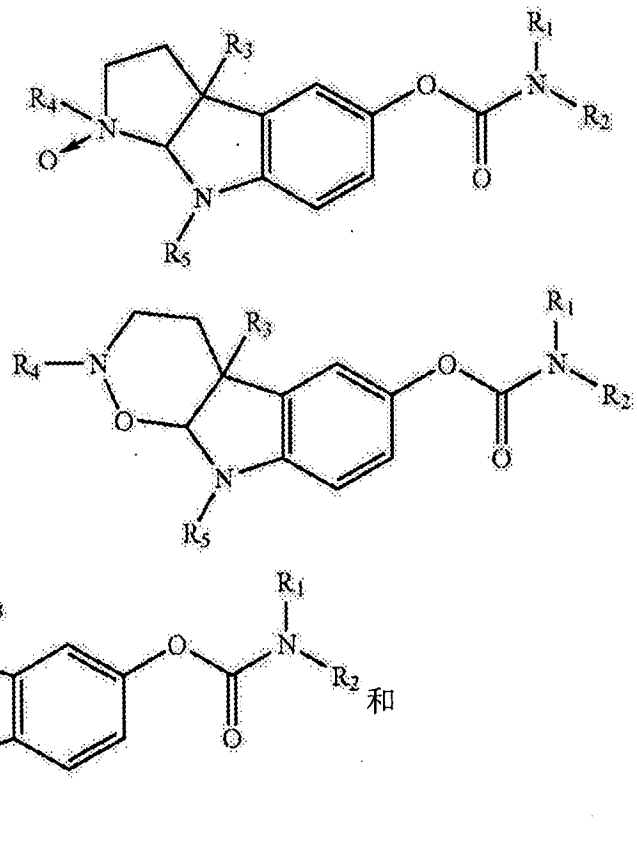
[3210] 其中A选自未取代的芳基、取代的芳基、未取代的杂芳基和取代的杂芳基；且R1和R2各自，独立地或组合地，选自氢、未取代的烷基、取代的烷基、未取代的芳烷基、取代的芳烷基、未取代的杂烷基、取代的杂烷基、未取代的杂芳烷基、取代的杂芳烷基、未取代的芳基、取代的芳基、未取代的杂芳基、取代的杂芳基、未取代的环烷基、取代的环烷基、未取代的杂环烷基和取代的杂环烷基。

[3211] 在另外的实施方案中，本发明为选自下列的氨基甲酰基酯：

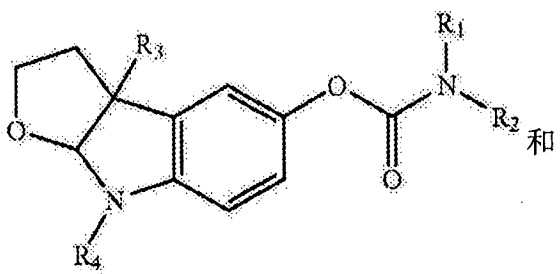
[3212]



[3213]

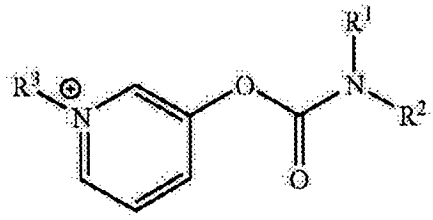


[3214]



和

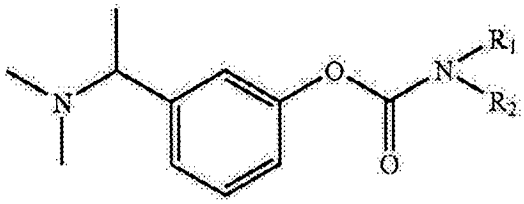
[3215]



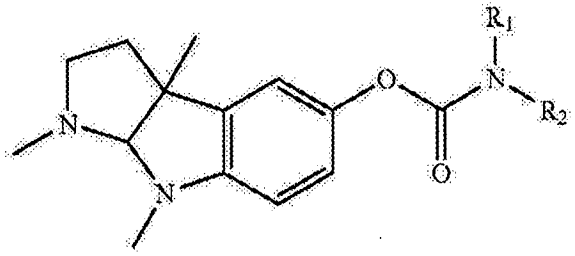
[3216] 其中R3、R4和R5各自，独立地或组合地，选自氢、未取代的烷基、取代的烷基、未取代的芳烷基、取代的芳烷基、未取代的杂烷基、取代的杂烷基、未取代的杂芳烷基、取代的杂芳烷基、未取代的芳基、取代的芳基、未取代的杂芳基、取代的杂芳基、未取代的环烷基、取代的环烷基、未取代的杂环烷基和取代的杂环烷基。

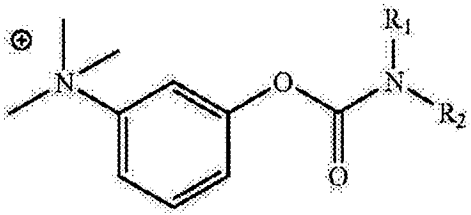
[3217] 在又一个实施方案中，本发明为选自下列的氨基甲酰基酯：

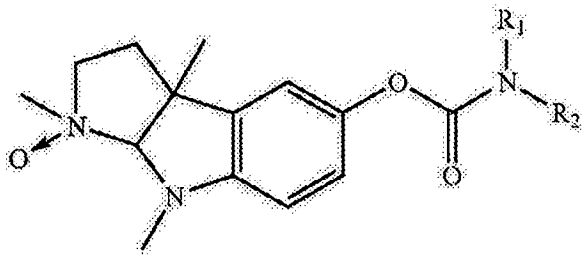
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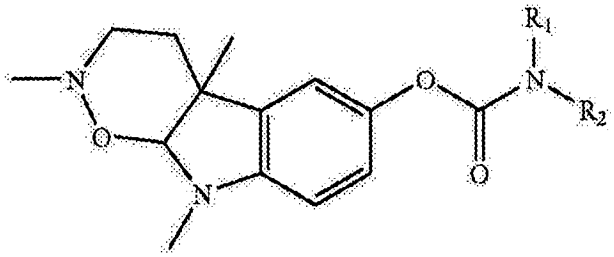


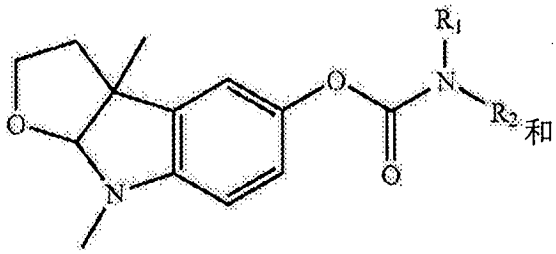
[3219]

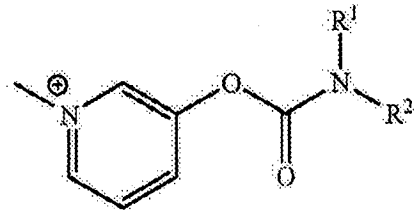






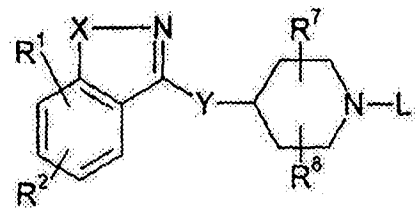


[3220]  和

[3221] 

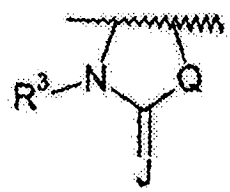
[3222] iii) 欧洲专利申请第 EP1050303 号

[3223] 在本发明的某些实施方案中，乙酰胆碱酯酶抑制剂是式 1 的化合物：

[3224] 

[3225] 其中 R^1和 R^2各自独立地选自氢；(C1-C6) 烷氧基；苄氧基；苯氧基；羟基；苯基；苄基；卤代；硝基；氰基；$-COR^5$；$-COOR^5$；$-CONHR^5$；$-NR^5R^6$；$-NR^5COR^6$；$-OCONR^5R^6$；$-NHCOOR^5$；可被 1-3 个氟原子取代的 (C1-C6) 烷基；SOpCH2- 苯基或 SOp(C1-C6) 烷基，其中 p 为 0、1 或 2；吡啶基甲基氧基或噻吩基甲基氧基；2- 噁唑基；2- 噻唑基；和苯磺酰胺；其中所述苯氧基、苄氧基、苯基、苄基和苯磺酰胺的苯基部分、所述吡啶基甲基氧基或噻吩基甲基氧基的吡啶基和噻吩基部分，以及所述 2- 噁唑基和 2- 噻唑基的噁唑基和噻唑基部分可被 1 或 2 个独立选自卤代、(C1-C4) 烷基、三氟甲基、(C1-C4) 烷氧基、氰基、硝基和羟基的取代基取代。

[3226] 或将 R^1和 R^2连接至邻近碳原子，并连同连接它们的碳原子一起形成式 2 的基团：

[3227] 

[3228] 其中 R^3为氢或 (C1-C6) 烷基；J 为氧、硫或 NR^4；R^4为氢或 (C1-C4) 烷基；且 Q 为氧、硫、NH、CHCH3、C(CH3)2、-CH = CH- 或 $(CH2)_1$，其中 $_1$为 1-3 的整数；

[3229] X 为氧或硫；

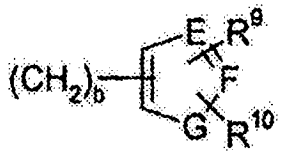
[3230] Y 为 -(CH2)m-、-CH = CH(CH2)n-、-NR<4)<CH2)m- 或 -O(CH2)m-，其中 n 为 0 至 3 的整数，且 m 为 1-3 的整数；

[3231] R^5和 R^6各自独立地选自氢、(C1-C6) 烷基、苯基和苄基，其中所述苯基和苄基的苯

基部分可被 1 或 2 个独立选自氟、氯、溴、碘、(C1-C4) 烷基、三氟甲基、(C1-C4) 烷氧基、氰基、硝基和羟基的取代基取代；或 NR^5R^6 一起形成 4 或 5 元环，其中环的一个原子为氮而其它原子的为碳、氧或氮；或 NR^5COR^6 一起形成 4 或 5 元的内酰胺环；

[3232] L 为苯基、苯基 -(C1-C6) 烷基、肉桂基或哌啶基甲基，其中所述苯基和苯基 -(C1-C6) 烷基的苯基部分可被 1-3 个独立选自 (C1-C6) 烷基、(C1-C6) 烷氧基、(C1-C4) 烷氧羰基、(C1-C6) 烷基羰基、$-OCONR^5R^6$、$-NHCOOR^5$ 和卤代的取代基取代；或 L 为式 3 的基团：

[3233]



[3234] 其中 b 为 1-4 的整数；R^9 和 R^{10} 独立选自氢、(C1-C4) 烷基、卤和苯基；E 和 F 独立地为 -CH- 或氮；且 G 为氧、硫或 NR^4，条件是当 E 和 F 都为氮时，R^9 和 R^{10} 之一不存在；且

[3235] R^7 和 R^8 独立地选自氢、(C1-C6) 烷基、(C1-C6) 烷氧羰基、(C1-C6) 烷基羰基和 (C1-C6) 烷氧基，条件是所述 (C1-C6) 烷氧基未连接至邻近氮的碳；

[3236] 或其药学上可接受的盐或溶剂合物。

[3237] 在本发明某些实施方案中，式 1 的化合物选自：

[3238] 5,7- 二氢 -7- 甲基 -3-[2-[1-(苯甲基)-4- 哌啶基] 乙基]-6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3239] 5,7- 二氢 -7- 乙基 -3-[2[1-(苯甲基)-4- 哌啶基] 乙基]-6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3240] 5,7- 二氢 -3-[2-[1-(2- 氯 -5- 噻吩甲基)-4- 哌啶基] 乙基]6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3241] 5,7- 二氢 -3-[2-[1-(2- 甲基 -4- 噻唑甲基)-4- 哌啶基] 乙基]-6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3242] 3-[2-[1-(3- 溴苯基甲基)-4- 哌啶基] 乙基]-5,7- 二氢 -6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3243] 3-[2-[1-(4- 溴苯基甲基)-4- 哌啶基] 乙基]-5,7- 二氢 -6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3244] 5,7- 二氢 -3-[3-[1-(苯甲基)-4- 哌啶基] 丙基]-6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3245] 6,8- 二氢 -3-[2-[1-(苯甲基)-4- 哌啶基] 乙基]-7H- 吡咯并 [5,4-g]-1,2- 苯并异噁唑 -7- 酮；和

[3246] 5,7- 二氢 -3-[3-[1-(苯甲基)-4- 哌啶基] 乙基]-6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮；

[3247] 在本发明的某些实施方案中，式 1 化合物为 5,7- 二氢 -3-[3-[1-(苯甲基)-4- 哌啶基] 乙基]-6H- 吡咯并 [4,5-f]-1,2- 苯并异噁唑 -6- 酮。

[3248] iv) 国际专利申请公开文本第 WO2000/030446 号

[3249] a) 乙酰胆碱酯酶抑制剂选自加兰他敏、石蒜胺及所述化合物的类似物，其中其甲

氧基被下列基团替代：1-6 个碳原子的另一个烷氧基、羟基、氢、烷酰氧基、苯甲酰氧基或取代的苯甲酰氧基、碳酸酯基或氨基甲酸酯基。

[3250] b) 乙酰胆碱酯酶抑制剂选自加兰他敏和石蒜胺的类似物，其中加兰他敏或石蒜胺的羟基被下列基团替代：1-6 个碳原子的烷氧基、氢、烷酰氧基、苯甲酰氧基或取代的苯甲酰氧基、碳酸酯基或氨基甲酸酯基。

[3251] c) 乙酰胆碱酯酶抑制剂选自加兰他敏和石蒜胺的类似物，其中加兰他敏或石蒜胺的 N- 甲基被下列基团替代：氢、烷基、苄基或环丙基甲基或取代的或未取代的苯甲酰氧基。

[3252] d) 如在 a) 中的乙酰胆碱酯酶抑制剂选自加兰他敏、石蒜胺及其类似物，其中这类化合物的甲氧基被下列基团替代：氢、羟基或 2-6 个碳原子的烷氧基或 1-7 个碳原子的酰氧基。

[3253] e) 如在 a) 中的乙酰胆碱酯酶抑制剂，其中所述乙酰胆碱酯酶抑制剂选自加兰他敏或石蒜胺的类似物，其中其甲氧基被单或二烷基氨基甲酸酯或碳酸酯基替代，其中烷基含有 1-8 个碳原子。

[3254] f) 如在 e) 中的乙酰胆碱酯酶抑制剂，其中所述碳酸酯或氨基甲酸酯基的烷基包含 4-6 个碳原子。

[3255] g) 如在 a) 中的乙酰胆碱酯酶抑制剂，其中所述乙酰胆碱酯酶抑制剂选自加兰他敏或石蒜胺的类似物，其中其羟基被单或二烷基氨基甲酸酯或碳酸酯基替代，其中烷基含有 1-8 个碳原子。

[3256] h) 如在 f) 中的乙酰胆碱酯酶抑制剂，其中所述碳酸酯或氨基甲酸酯基的烷基包含 4-6 个碳原子。

[3257] i) 如在 a) 中的乙酰胆碱酯酶抑制剂，其中所述乙酰胆碱酯酶抑制剂选自加兰他敏或石蒜胺的类似物，其中其甲氧基被芳基氨基甲酸酯或碳酸酯基替代，其中所述芳基选自苯基、萘基、取代的苯基和取代的萘基，其中所述取代基选自 1-6 个碳原子的烷基和烷氧基、三氟甲基和卤代基团。

[3258] i) 如在 b) 中的乙酰胆碱酯酶抑制剂，其中所述乙酰胆碱酯酶抑制剂选自加兰他敏和石蒜胺的类似物，其中其羟基被芳基氨基甲酸酯或碳酸酯基替代，其中所述芳基选自苯基、萘基、取代的苯基和取代的萘基，其中所述取代基选自 1-6 个碳原子的烷基和烷氧基、三氟甲基和卤代基团。

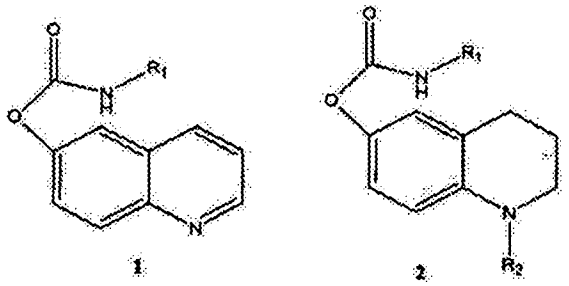
[3259] k) 如在 b) 中的乙酰胆碱酯酶抑制剂，其中所述乙酰胆碱酯酶抑制剂选自加兰他敏、石蒜胺及其类似物，其中这类化合物的羟基被下列基团替代：氢或 1-6 个碳原子的烷氧基或 1-7 个碳原子的酰基。

[3260] l) 如在 a) 中的乙酰胆碱酯酶抑制剂，其中所述乙酰胆碱酯酶抑制剂选自加兰他敏和石蒜胺的类似物，其中加兰他敏或石蒜胺的羟基被下列基团替代：1-6 个碳原子的烷氧基、氢、烷酰氧基、苯甲酰氧基或取代的苯甲酰氧基、碳酸酯基或氨基甲酸酯基。

[3261] v) 国际专利申请公开文本第 WO2006/070394 号

[3262] AChEI 为下式 1 和 2 所示的喹啉衍生物：

[3263]



[3264] 其中 Ri ＝烷基、芳基；R2 ＝ H、烷基、芳烷基。

[3265] 在一个实施方案中，得到的取代的氨基甲酸喹啉基酯选自：

[3266] Ia. 己基－氨基甲酸喹啉 -6- 基酯

[3267] Ib. 庚基－氨基甲酸喹啉 -6- 基酯

[3268] Ic. (2- 氯－苯基)- 氨基甲酸喹啉 -6- 基酯

[3269] Id. (3- 溴－苯基)- 氨基甲酸喹啉 -6- 基酯

[3270] 2a. 己基－氨基甲酸 1,2,3,4- 四氢－喹啉 -6- 基酯

[3271] 2b. 庚基－氨基甲酸 1,2,3,4- 四氢－喹啉 -6- 基酯

[3272] 2c. (3- 溴－苯基)- 氨基甲酸 1,2,3,4- 四氢－喹啉 -6- 基酯

[3273] 2d. (2- 氯－苯基)- 氨基甲酸 1,2,3,4- 四氢－喹啉 -6- 基酯

[3274] 2e. (4- 氯 -3- 三氟甲基－苯基)- 氨基甲酸 1,2,3,4- 四氢－喹啉 -6- 基酯

[3275] 2f. (4- 溴－苯基)- 氨基甲酸 1,2,3,4- 四氢－喹啉 -6- 基酯

[3276] 2g. 庚基－氨基甲酸 1- 苄基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3277] 2h. 己基－氨基甲酸 1- 苄基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3278] 2i. (2- 氯－苯基)- 氨基甲酸 1- 苄基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3279] 2j. (3- 溴－苯基)- 氨基甲酸 1- 苄基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3280] 2k. (4- 氯 -3- 三氟甲基－苯基)- 氨基甲酸 1- 苄基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3281] 2l. (4- 溴－苯基)- 氨基甲酸 1- 苄基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3282] 2m. 己基－氨基甲酸 1- 甲基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3283] 2n. 庚基－氨基甲酸 1- 甲基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3284] 2o. (2- 氯－苯基)- 氨基甲酸 1- 甲基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3285] 2p. (3- 溴－苯基)- 氨基甲酸 1- 甲基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3286] 2q. (4- 氯 -3- 三氟甲基－苯基)- 氨基甲酸 1- 甲基 -1,2,3,4- 四氢－喹啉 -6- 基酯

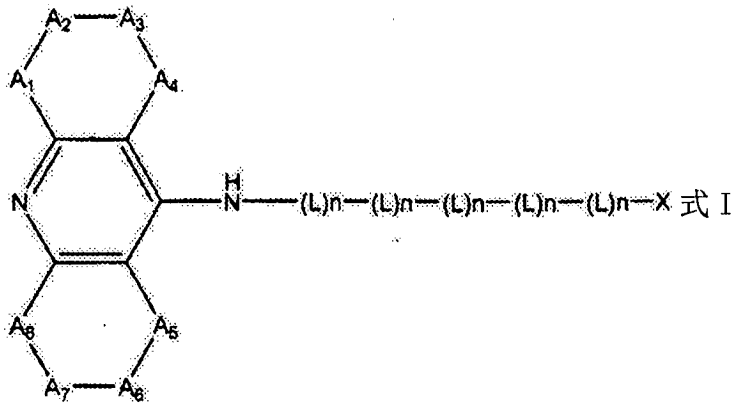
[3287] 2r. (4- 溴－苯基)- 氨基甲酸 1- 甲基 -1,2,3,4- 四氢－喹啉 -6- 基酯

[3288] 在一个本发明的实施方案中，当 R1 为芳基，它选自 2- 氯、3- 溴、4- 溴和 4- 氯 -3- 三氟甲基－苯基。

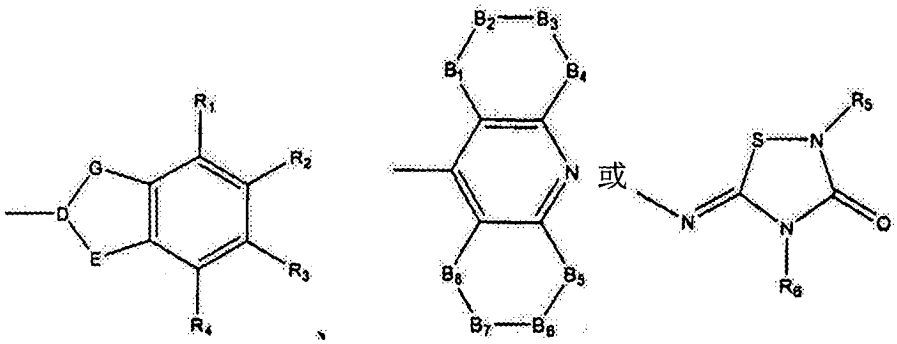
[3289] 在另一个本发明的实施方案中，R2 选自甲基和苄基。

[3290] vi) 国际专利申请公开文本第 WO2004/032929 号

[3291] 一个实施方案涉及式 I 所示的化合物

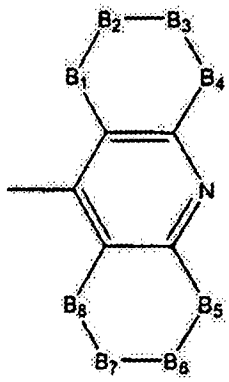
[3292]  式 I

[3293] 其中 :X 为下列残基之一 ;

[3294] 

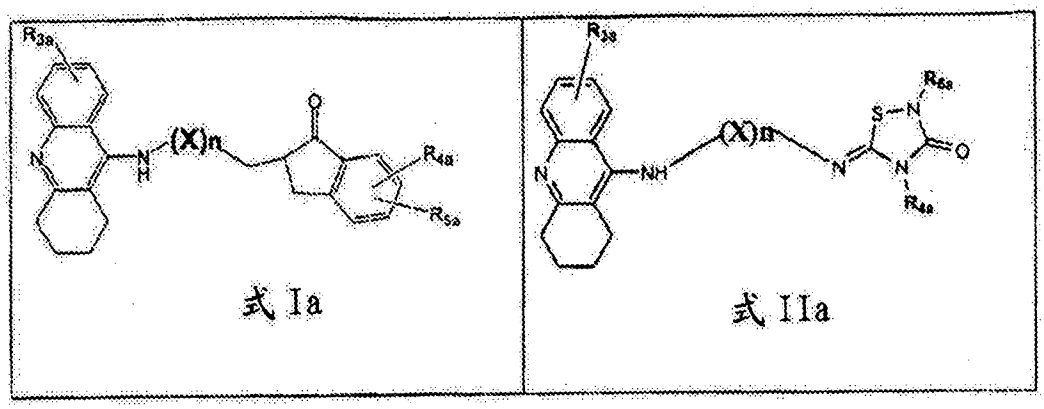
[3295] L 独立地选自 -C(R)(R")-、-CO-、-O- 或 -NR'-,n 为 0、1、2、3、4、5、6、7、8、9 或 10,R 和 R" 独立地选自氢、烷基、芳基、杂芳基、卤代、卤代烷基、烷氧基、羟基、硝基和烷硫基,D 独立地选自 -C(R9)-、= C- 或 -N-Al、A2、As、A4、As、A7、As、Bi、B2、Bs、B4、Bs、B6、B7、Bs、G 和 E 独立地选自 -CO-、-C(Rio)(Rn)-、= C(Rio)-、-N(R12)-、= N-、-O-、-S(0)t-Ri、R2、R3、R4、R9、Rio 和 Ril 独立地选自氢、烷基、烷氧基、羟基、烷硫基、环烷基、卤代烷基、卤代、芳基、-(Z)n-、芳基、杂芳基、-O(R7)、-C(0)R7、-C(0)OR7、-S(0)t、氰基、硝基和巯基、被烷基、烷氧基、羟基、卤代、卤代烷基、硝基或烷硫基取代的芳基 ;及被烷基、烷氧基、羟基、卤代、卤代烷基、硝基或烷硫基取代的杂芳基,R5、R6 和 R12 独立地选自氢、烷基、烷氧基、羟基、环烷基、卤代烷基、芳基、杂芳基、被烷基、烷氧基、羟基、卤代、卤代烷基或烷硫基取代的芳基 ;及被烷基、烷氧基、羟基、卤代、卤代烷基、硝基或烷硫基杂取代的杂芳基,Z 独立地选自 -C(R7)(R8)-、-C(0)-、-O-、-C(=NR7)-、-S(0)t、N(R7)-,R7 和 R8 独立地选自氢、烷基、烷氧基、烷硫基、环烷基、卤代烷基、卤代、芳基、杂芳基、氰基、硝基、巯基、被烷基、烷氧基、羟基、卤代、卤代烷基、硝基或烷硫基取代的芳基 ;及被烷基、烷氧基、羟基、卤代、卤代烷基、硝基或烷硫基取代的杂芳基,t 为 0、1 或 2。

[3296] 通常,我们的条件是当 X 为

[3297]  时，

[3298] a) 在基团 A1-A4、As-As、B1-B4 和 Bs-Bs 中的每个原子决不同时为＝ C(Rio)-，且 b) 在两个基团 Ai-A4 和 As-As 之一中的每个原子，及两个基团 Bi-B4 和 Bs-Bs 之一中的每个原子绝不同时为＝ C(Rio)-。

[3299] 在相关的方面，本发明涉及在式 (I) 之内的化合物并由通式 Ia 和 IIa 所示：

[3300] 

[3301] 其中：X 为 -C(R1a)(R2a)-、-CO-、-O- 或 -NR1a-；n 为 0、1、2、3、4、5、6、7、8、9 或 10；

[3302] R1a 和 R2a 独立地选自氢、烷基、芳基、卤、卤烷基；

[3303] R3a、R4a 和 R5a 独立地选自氢、烷基、环烷基、卤烷基、卤、芳基、-(Z)n- 芳基、杂芳基、OR3a、-C(0)R3a、-C(0)OR3a、-S(0)t-；t 为 0、1 或 2；Z 独立地选自 C(R3a)(R4a)-、-C(0)-、-O-、-C(＝NR3a)-、-S(0)t-、N(R3a)-。

[3304] 定义

[3305] 在 vi) 中，下列术语具有下列含义："烷基"意指直线或支化的烃链，该烃链仅包含碳原子和氢原子并不含有不饱和的键，具有 1-8 个碳原子并通过单键键合至分子的剩余部分，例如，甲基、乙基、正 - 丙基、异 - 丙基、正 - 丁基、叔 - 丁基、正 - 戊基等。烷基残基可被独立选自下列的一个或多个取代基任选地取代：卤素、羟基、烃氧基金属、羧基、氰基、羰基、酰基、烷氧羰基、氨基、硝基、巯基和烷硫基。

[3306] 优选的是，烷基为 C1-C6 烷基。

[3307] "烷氧基"意指式 -ORa 的残基，其中 Ra 为如上所述的烷基残基，例如甲氧基、乙氧基、丙氧基等。

[3308] "烷氧羰基"意指式 -C(0)ORa 的残基，其中 Ra 是如上所述的烷基残基，例如甲氧羰基、乙氧羰基、丙氧基羰基等。"烷硫基"意指式 -SRa 的残基，其中 Ra 为如上所述的烷基残基，例如甲硫基、乙硫基、丙硫基等。

[3309] “氨基”意指式 -NH2 的残基。“芳基”意指苯基或萘基残基。芳基残基可被选自下列中的一个或多个取代基任选地取代：如它们在本文中定义的羟基、巯基、卤素、烷基、苯基、烷氧基、卤烷基、硝基、氰基、二烷基氨基、氨基烷基、酰基和烷氧羰基。

[3310] “酰基”意指式 -C(O)-Ra 和 -C(O)-Rb 的残基，其中

[3311] Ra 为如上文所述的烷基残基且 Rb 为如上文所述的芳基残基，例如乙酰基、丙酰基、苯甲酰基，及类似的。

[3312] “羧基”意指式 -C(O)OH 的残基，“氰基”意指式 -CN 的残基，“环烷基”意指 3-10 个单环或双环成员的稳定的环，该环为饱和的或部分饱和的并且仅仅由碳原子和氢原子组成。该术语也包括环烷基残基，该残基可被独立选自下列的一个或多个取代基任选地取代：烷基、卤素、羟基、氨基、氰基、硝基、烷氧基、羧基和烷氧羰基。“卤素”意指溴、氯、碘或氟。“卤烷基”意指如上文所定义的烷基残基，其被一个或多个卤素取代，也如上文所定义的，例如三氟甲基、三氯甲基、2,2,2-三氟乙基、1-氟甲基 -2-氟乙基，及类似的。

[3313] “杂环”意指杂环残基。杂环意指 3-15 元稳定的环，该环包含碳原子和 1-5 个选自氮、氧和硫的杂原子。为了本发明的目的，杂环可为单环、双环或三环的系统，该系统可包括稠合的环和可任选地被氧化的氮、碳或硫原子，该氮原子可任选地被季铵化，且该杂环可为部分或完全饱和的或芳族的。这些杂环的实例包括，但不限于，氮杂[illegible]、苯并咪唑、苯并噻唑、呋喃、异噻唑、咪唑、吲哚、哌啶、哌嗪、噁唑、喹啉、噻二唑、四氢呋喃。杂环可经如在本发明概述中所定义的 R3 和 R4 任选地取代。

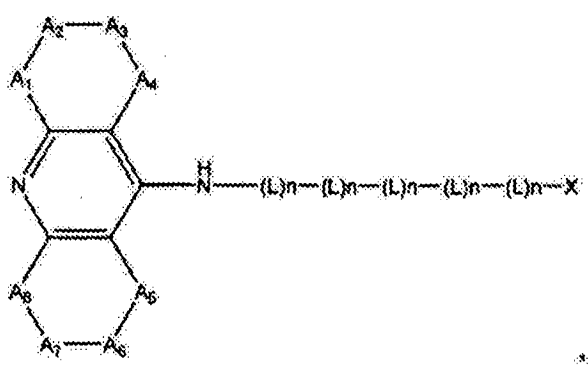
[3314] “巯基”意指式 -SH 的残基。“硝基”意指式 -NO2 的残基。

[3315] 在链 -(L)n-(L)n-(L)n-(L)n-(L)n- 中，所述或每个基团 -(L)n- 优选地为 -(CH2)n-(其中 n 不是 0)、-CO-NH- 或 -NCH3-。

[3316] 优选的是，有至少一个或两个基团 -(L)n-，其中 n 不为 0。适合的链为式 -(CH2)n-、-(CH2)n-NRa-(CH2)n-、-(CH2)n-NRa-CO-、-(CH2)n-NRa-CO-(CH2)n- 或 -(CH2)n-NRa-(CH2)n-NRa-CO-，其中所述或每个 n 不为 0，且所述或每个 Ra 为 -NH- 或 -NCHs-，通常优选的是 -NH-。n 整数的总和优选是 2 至 15。

[3317] 在下式中：

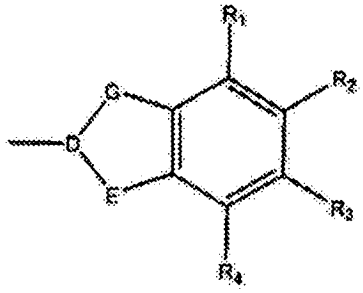
[3318]



[3319] 每个 A 基团（就是，A1 至 As）优选的是＝CH- 或 -CH2-，可是当剩余的 A 基团为＝CH- 时，A2 和 A7 中的一个或两个可为卤代，特别是氯。

[3320] 某些 AChEI 为其中 X 为下式所示的那些：

[3321]



[3322] 优选地 D 为 -CH-、= C- 或 -N-。优选地 E 为 -CO-、-CH2-、= CH-、= N-、-O- 或 -S-。优选地 G 为 -CO-、-CH2-、= CH- 或 = N-。

[3323] 优选的是 R1 至 R4 为氢。

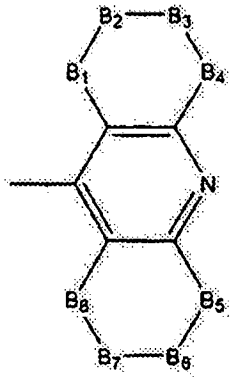
[3324] 在某些实施方案中，在这些化合物之内的为其中 X 为以下的那些化合物：邻苯二甲酰亚胺基 (1,3- 二氧代 -1,3- 二氢 - 异吲哚 -2- 基)、吲哚 -2- 基、茚满酮 -2- 基、苯并咪唑 -2- 基、茚满二酮 -2- 基、吲唑 -2- 基、苯并呋喃 -2- 基、苯并噻吩 -2- 基或苯并三唑 -2- 基。

[3325] 在某些实施方案中为其中 X 为邻苯二甲酰亚胺 (1,3- 二氧代 -1,3- 二氢 - 异吲哚 -2- 基)，且式 I 的环部分表示 9- 吖啶基、1,2,3,4- 四氢 - 吖啶 -9- 基或 6 氯 -1,2,3,4- 四氢 - 吖啶 -9- 基的那些。某些化合物为：2-[6-(吖啶 -9- 基氨基)- 己基]- 异吲哚 -1,3- 二酮 (6)、2-[7-(吖啶 -9- 基氨基)- 庚基]- 异吲哚 -1,3- 二酮 (7)、2-[8-(吖啶 -9- 基氨基)- 辛基]- 异吲哚 -1,3- 二酮 (8)、2-[9-(吖啶 -9- 基氨基)- 壬基]- 异吲哚 -1,3- 二酮 (9)、N-[7-(6- 氯 -1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 庚基]-2-(1,3- 二氧代 -1,3- 二氢 - 异吲哚 -2- 基)- 乙酰胺 (10)、N-(3-{[3-(6- 氯 -1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 丙基]- 甲基 - 氨基}- 丙基)-2-(1,3- 二氧代 -1,3- 二氢 - 异吲哚 -2- 基)- 乙酰胺 (11)、N-[6-(6- 氯 -1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 己基]-2-(1,3- 二氧代 -1,3- 二氢 - 异吲哚 -2- 基)- 乙酰胺 (12)、2-[6-(1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 己氨基]- 茚满 -1,3- 二酮 (3)、2-[7-(1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 庚基]- 异吲哚 -1,3- 二酮 (4) 和 2-[8-(1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 辛基]- 异吲哚 -1,3- 二酮 (5)。

[3326] 某些化合物为其中 X 为 1- 茚满酮 -2- 基，且式 I 的环部分表示 1,2,3,4- 四氢 - 吖啶 -9 基的那些；在这些化合物之内，其中包括下列化合物：5,6- 二甲氧基 -2-{[7-(1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 庚基氨基]- 甲基}- 茚满 -1- 酮 (1) 和 5,6- 二甲氧基 -2-{[6-(1,2,3,4- 四氢 - 吖啶 -9- 基氨基)- 己基氨基]- 甲基}- 茚满 -1- 酮 (2)

[3327] 在上文所述化合物中，包括其中 X 为下式所示的那些化合物：

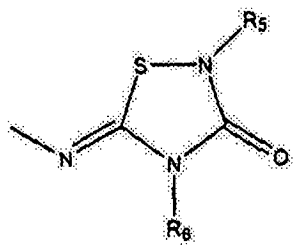
[3328]



[3329] 每个 B 基团（就是，Bi 至 Bs）优选的是＝ CH- 或 -CH2-，可是当剩余的 B 基团为＝ CH- 时，B2 和 B7 中的一个或两个可为卤代，特别的是氯。某些化合物为其中 X 为 9- 吖啶基、6- 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基和 1, 2, 3, 4- 四氢 - 吖啶 -9- 基的那些。在这些化合物之内的为其中式 I 的环部分表示以下的那些：9- 吖啶基、6 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基或 1, 2, 3, 4- 四氢 - 吖啶 -9- 基；在这些化合物之内，其中包括下列化合物：-N-[2-(6- 氯 -1, 2, 3, 4, 4a, 9a- 六氢 - 吖啶 -9- 基氨基）- 乙基]-N' -(6- 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基）-N- 甲基 - 乙烷 -1, 2- 二胺 (19)、-N- 吖啶 -9- 基 -N' -(1, 2, 3, 4- 四氢 - 吖啶 -9- 基）- 壬烷 -1, 9- 二胺 (20)、-N- 吖啶 -9- 基 -N' [2-(1, 2, 3, 4, 4a, 9a- 六氢 - 吖啶 -9- 基氨基）- 乙基]-N' - 甲基 - 乙烷 -1, 2- 二胺 (21)、-N-[2-(吖啶 -9- 基氨基）- 乙基]-N' -(6- 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基）-N- 甲基 - 乙烷 -1, 2- 二胺 (22)、-N- 吖啶 -9- 基 -N' -(6- 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基）- 庚烷 -1, 7- 二胺 (23) 和 -N- 吖啶 -9- 基 -N' -(6- 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基）- 辛烷 -1, 8- 二胺 (24)。

[3330] 在上文所述化合物中，包括其中 X 为下式所示的那些化合物：

[3331]



[3332] 基团 Rs 和 R6 为适合的烷基或取代的烷基，尤其是烷氧羰基烷基。优选的化合物为其中式 I 的环部分表示以下的那些：9- 吖啶基、6- 氯 -1, 2, 3, 4- 四氢 - 吖啶 -9- 基或 1, 2, 3, 4- 四氢 - 吖啶 -9- 基；在本发明这些化合物之内的，包括下列化合物：2- 乙基 -4- 异丙基 -5-[7-(1, 2, 3, 4- 四氢 - 吖啶 -9- 基氨基）- 庚基 - 亚氨基]-[1, 2, 4] 噻二唑烷 -3- 酮 (13)、-2- 乙基 -4- 异丙基 -5-[9-(1, 2, 3, 4- 四氢 - 吖啶 -9- 基氨基）- 壬基 - 亚氨基]-[1, 2, 4] 噻二唑烷 -3- 酮 (14)、4- 异丙基 -3- 氧代 -5-[9-(1, 2, 3, 4- 四氢 - 吖啶 -9- 基氨基）- 壬基 - 亚氨基]-[1, 2, 4] 噻二唑烷 -2- 羧酸乙酯 (15)、4- 乙基 -2- 丙基 -5-[7-(1, 2, 3, 4- 四氢 - 吖啶 -9- 基氨基）- 庚基 - 亚氨基]-[1, 2, 4] 噻二唑烷 -3- 酮 (16)、4- 乙基 -2- 异丙基 -5-[8-(1, 2, 3, 4- 四氢 - 吖啶 -9- 基氨基）- 辛基亚氨基]-[1, 2, 4] 噻二唑烷 -3- 酮 (17) 和 4- 乙基 -2- 异丙基 -5-[6-(1, 2, 3, 4- 四氢 - 吖啶 -9- 基氨基）- 己基 - 亚氨基]-[1, 2, 4] 噻二唑烷 -3- 酮 (18)。

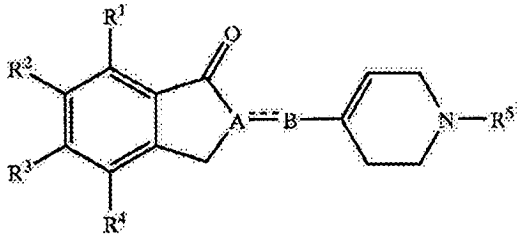
[3333] vii) 美国专利申请公开文本第 20050124642 号

[3334] 在某些实施方案中，AChEI 为：

[3335] 1) 下式所示的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物：

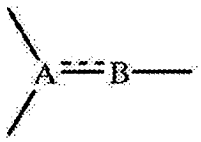
[3336]

(I)



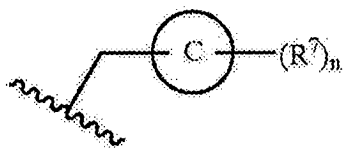
[3337] (在式 (I) 中，R<1>、R<2>、R<3> 和 R<4> 彼此相同或不同，且各自表示选自下列的基团：氢原子、卤素原子、羟基、腈基团、可取代的具有 1-6 个碳原子的烷基、可取代的具有 3-8 个碳原子的环烷基、可取代的具有 1-6 个碳原子的烷氧基、可取代的具有 3-8 个碳原子的环烷氧基、可取代的具有 1-6 个碳原子的酰基、可取代的 C1-C6 烷氧基 - 羰基、可取代的 C1-C6 烷基 - 氨基羰基氧基、可取代的二 -(C1-C6 烷基)- 氨基羰基氧基、硝基、可取代的氨基、可取代的酰胺基、巯基和可取代的具有 1-6 个碳原子的硫代烷氧基，其中 R<1> 和 R<2>，或 R<2> 和 R<3>，或 R<3> 和 R<4> 可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基环；部分结构：

[3338]



[3339] 是下列所示的基团：>C-CH-(CH2)m- 或 >C(R<6>)-CH(R<6>)-(CH2)m-(其中 m 为 0 或 1-5 的整数；且 R<6> 为氢原子、卤素原子、羟基、具有 1-6 个碳原子的烷基、具有 1-6 个碳原子的烷氧基、腈基、具有 1-6 个碳原子的卤烷基、具有 1-6 个碳原子的羟基烷基、氰基 -C1-C6 烷基、具有 1-6 个碳原子的氨基烷基、硝基、叠氮基、可取代的氨基、可取代的氨基甲酰基、可取代的羧基、巯基或具有 1-6 个碳原子的硫代烷氧基)；且 R<5> 为氢原子、可取代的具有 1-6 个碳原子的烷基、可取代的具有 2-6 个碳原子的烯基、可取代的具有 2-6 个碳原子的炔基、可取代的具有 3-8 个碳原子的环烷基、2,2-(亚烷基二氧基) 乙基或下式所示的基团：

[3340]



[3341] (其中环 C 为苯环、脂族的环或杂环的环；R<7> 彼此相同或不同，其各自表示氢原子、卤素原子、羟基、腈基、可取代的具有 1-6 个碳原子的烷基、可取代的具有 2-6 个碳原子的烯基、可取代的具有 2-6 个碳原子的炔基、可取代的具有 3-8 个碳原子的环烷基、取代的具有 1-6 个碳原子的烷氧基、可取代的 C1-C6 烷氧基 - 烷氧基、可取代的芳氧基、可取代的

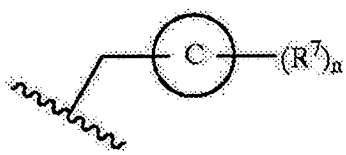
芳烷氧基等，其中 R<7> 中的两个可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基的环；且 n 为 1-5 的整数））,其药理学上可接受的盐或它们的水合物；

[3342] 2) 在 1) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 R<1> 和 R<4> 为氢原子；且 R<2> 和 R<3> 彼此相同或不同，且各自表示氢原子、卤素原子、可取代的具有 1-6 个碳原子的烷基、可取代的具有 3-8 个碳原子的环烷基、可取代的具有 1-6 个碳原子的烷氧基或可取代的具有 3-8 个碳原子的环烷氧基，或 R<2> 和 R<3> 可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基环；

[3343] 3) 在 1) 或 2) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 R<6> 为氢原子、卤素原子或具有 1-6 个碳原子的烷基；

[3344] 4) 在 1) 至 3) 中的任何一个中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐其或它们的水合物，其中 R<5> 为下式所示的基团：

[3345]



[3346] 其中环 C、R<7> 和 n 具有与上文所定义的相同的含义；

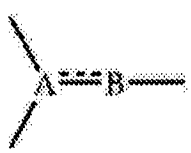
[3347] 5) 在 4) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中环 C 为苯环或具有 3-8 个碳原子的环烷基；

[3348] 6) 在 4) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 R<7> 彼此相同或不同，且各自表示氢原子、卤素原子、可取代的具有 1-6 个碳原子的烷基、可取代的具有 2-6 个碳原子的烯基、可取代的具有 2-6 个碳原子的炔基、可取代的具有 3-8 个碳原子的环烷基，或 R<7> 中的两个可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基环；

[3349] 7) 在 4) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 n 为 1 或 2 的整数；

[3350] 8) 在 1) 至 7) 的任何一个中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐其或它们的水合物，其中部分结构：

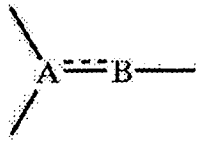
[3351]



[3352] 为 >C(R<6>)-CH(R<6>)-(CH2)m-(其中 m 为 0 或 1-5 的整数；且 R<6> 为氢原子) 所示的基团；

[3353] 9) 在 1) 至 7) 的任何一个中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐其或它们的水合物，其中部分结构：

[3354]



[3355] 为 >C(R<6>)-CH(R<6>)-(CH2)m- 所示的基团（其中 m 为 0 或 1-5 的整数；且 R<6> 为卤素原子、羟基、具有 1-6 个碳原子的烷基、具有 1-6 个碳原子的烷氧基、腈基、具有 1-6 个碳原子的卤烷基、具有 1-6 个碳原子的羟基烷基、氰基 -C1-C6 烷基、具有 1-6 个碳原子氨基烷基、硝基、叠氮基、可取代的氨基、可取代的氨基甲酰基、可取代的羧基、巯基或具有 1-6 个碳原子硫代烷氧基）；

[3356] 10) 在 1) 中所述的 (1- 茚满酮）-(1,2,3,6- 四氢吡啶）化合物、其药理学上可接受的盐或它们的水合物，其中式 (I) 所示的 (1- 茚满酮）-(1,2,3,6- 四氢吡啶）化合物为选自以下的化合物：

[3357] (1)1- 苄基 -4-[(5,6- 二甲氧基 -1- 茚满酮）-2- 基］甲基 -1,2,3,6- 四氢吡啶，

[3358] (2)1- 苄基 -4-[(5,6- 二乙氧基 -1- 茚满酮）-2- 基］甲基 -1,2,3,6- 四氢吡啶，和

[3359] (3)1- 苄基 -4-[(5,6- 二乙氧基 -2- 氟 -1- 茚满酮）-2- 基］甲基 -1,2,3,6- 四氢吡啶；

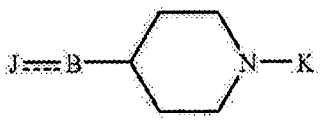
[3360] 也参见，例如，在下列文献中提出的那些 AChE 抑制剂：Brufani 等人，Alzheimer Disease：From Molecular Biology to Therapy，eds. Becker 等人，pp. 171-177(1996)；Schmidt 等人，Alzheimer Disease：From Molecular Biology to Therapy，eds. Becker 等人，pp. 217-221(1996)；Vargas 等人，Alzheimer Disease：From Molecular Biology to Therapy，eds. Becker 等人，pp. 261-255(1996)；Greig 等人，Alzheimer Disease：From Molecular Biology to Therapy，eds. Becker 等人，pp. 231-237(1996)；以及 Giacobini，Alzheimer Disease：From Molecular Biology to Therapy eds. Becker 等人，pp. 187-204(1996)。

[3361] viii) 美国专利 7,378,425

[3362] 在某些实施方案中，下列化合物 ((1) 至 (4)) 为具有乙酰胆碱酯酶抑制作用的化合物。

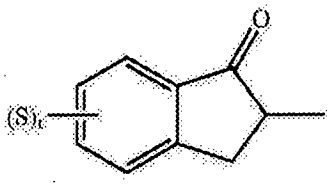
[3363] (1) 下式所示的环胺衍生物、其药理学上可接受的盐其或它们的水合物。

[3364]



[3365] 其中，J 为，例如，式：

[3366]

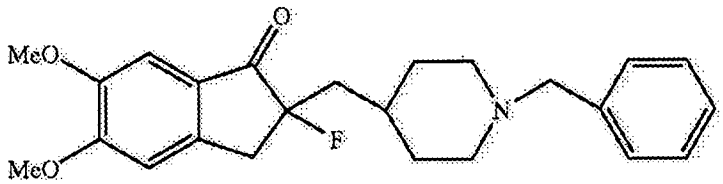


[3367] （其中 S 为，例如，具有 1-6 个碳原子的低级烷氧基；且 t 为 0 或 1-4 的整数）；B

为，例如，亚甲基链；K 为，例如，可取代的苄基；且部分结构：- 为单键或双键，条件是排除其中 J 为 5,6- 二甲氧基 -1- 茚满酮 -2- 基；B 为 -CH2- ；且 K 为未取代的苄基的化合物，其药理学上可接受的盐或它们的水合物 (JP-B2 2733203)。

[3368] (2) 下式所示的化合物：

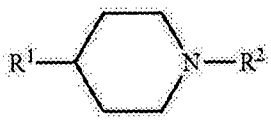
[3369]



[3370] 或其药理学上可接受的盐 (JP-A 2000-319257)。

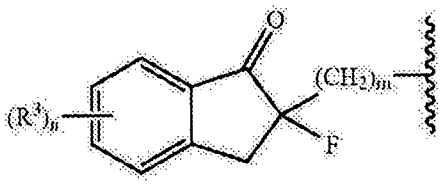
[3371] (3) 下式所示的 4- 取代的哌啶衍生的氟化物：

[3372]



[3373] (其中 R<1> 为，例如，下式所示的取代基：

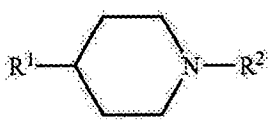
[3374]



[3375] (其中 R<3> 彼此相同或不同，且各自表示，例如，具有 1-6 个碳原子的烷氧基；m 为 0 或 1 至 6 的整数；且 n 为 1-4 的整数)；且 R<2> 为，例如，可取代的苄基，条件是排除 1- 苄基 -4-[(5,6- 二甲氧基 -2- 氟 -1- 茚满酮)-2- 基] 甲基哌啶或其药理学上可接受的盐)，其药理学上可接受的盐或它们的水合物 (JP-A 2000-319258)。

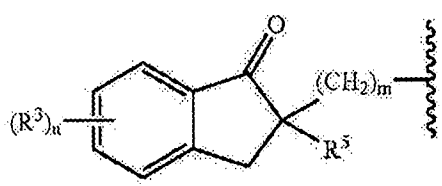
[3376] (4) 下式所示的 4- 取代的哌啶衍生物：

[3377]



[3378] (其中 R<1> 为，例如，下式所示的基团：

[3379]

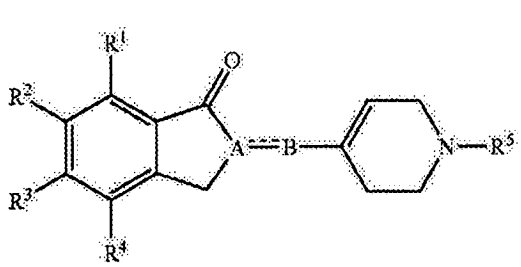


[3380] (其中 R<3> 彼此相同或不同，且各自表示，例如，具有 1-6 个碳原子的烷氧基；R<5> 为，例如，除氟原子之外的卤素原子；m 为 0 或 1 至 6 的整数；且 n 为 1-4 的整数)；且 R<2> 为，例如，可取代的苄基)，药理学上可接受的盐或它们的水合物 (JP-A 2001-139547)。

[3381] 在某些实施方案中，本发明涉及：

[3382] 1）下式所示的（1-茚满酮）-（1,2,3,6-四氢吡啶）化合物：

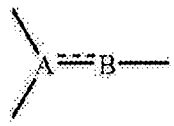
[3383]



(I)

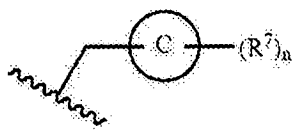
[3384] （在式（I）中，R<1>、R<2>、R<3>和R<4>彼此相同或不同，且各自表示选自下列的基团：氢原子、卤素原子、羟基、腈基、可取代的具有1-6个碳原子的烷基、可取代的具有3-8个碳原子的环烷基、可取代的具有1-6个碳原子的烷氧基、可取代的具有3-8个碳原子的环烷氧基、可取代的具有1-6个碳原子的酰基、可取代的C1-C6烷氧基-羰基、可取代的C1-C6烷基-氨基羰基氧基、可取代的二-(C1-C6烷基)-氨基羰基氧基、硝基、可取代的氨基、可取代的酰胺基、巯基和可取代的具有1-6个碳原子的硫代烷氧基，其中R<1>和R<2>，或R<2>和R<3>，或R<3>和R<4>可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基环；部分结构：

[3385]



[3386] 为>C-CH-(CH2)m-或>C(R<6>)-CH(R<6>)-(CH2)m-所示的基团（其中m为0或1-5的整数；且R<6>为氢原子、卤素原子、羟基、具有1-6个碳原子的烷基、具有1-6个碳原子的烷氧基、腈基、具有1-6个碳原子的卤烷基、具有1-6个碳原子的羟基烷基、氰基-C1-C6烷基、具有1-6个碳原子的氨基烷基、硝基、叠氮基、可取代的氨基、可取代的氨基甲酰基、可取代的羧基、巯基或具有1-6个碳原子的硫代烷氧基）；且R<5>为氢原子、可取代的具有1-6个碳原子的烷基、可取代的具有2-6个碳原子的烯基、可取代的具有2-6个碳原子的炔基、可取代的具有3-8个碳原子的环烷基、2,2-（亚烷基二氧基）乙基或下式所示的基团：

[3387]



[3388] （其中环C为苯环、脂族的环或杂环的环；R<7>彼此相同或不同，且各自表示氢原子、卤素原子、羟基、腈基、可取代的具有1-6个碳原子的烷基、可取代的具有2-6个碳原子的烯基、可取代的具有2-6个碳原子的炔基、可取代的具有3-8个碳原子的环烷基、可取代的具有1-6个碳原子的烷氧基、可取代的C1-C6烷氧基-烷氧基、可取代的芳氧基、可取代的芳烷氧基等，其中R<7>中的两个可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基的环；且n为1-5的整数）），其药理学上可接受的盐或它们的水合物；

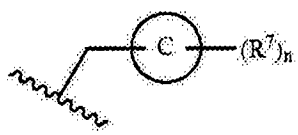
[3389] 2）在1）中所述的（1-茚满酮）-（1,2,3,6-四氢吡啶）化合物、其药理学上可接受

的盐或它们的水合物，其中 R<1> 和 R<4> 为氢原子；且 R<2> 和 R<3> 彼此相同或不同，且各自表示氢原子、卤素原子、可取代的具有 1-6 个碳原子的烷基、可取代的具有 3-8 个碳原子的环烷基、可取代的具有 1-6 个碳原子的烷氧基或可取代的具有 3-8 个碳原子的环烷氧基，或 R<2> 和 R<3> 可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基环；

[3390] 3) 在 1) 或 2) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 R<6> 为氢原子、卤素原子或具有 1-6 个碳原子的烷基；

[3391] 4) 在 1) 至 3) 中的任何一个中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 R<5> 为下式表示的基团：

[3392]



[3393] 其中环 C、R<7> 和 n 具有与上文所定义的相同的含义；

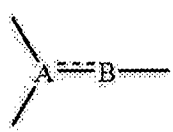
[3394] 5) 在 4) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中环 C 为苯环或具有 3-8 个碳原子的环烷基；

[3395] 6) 在 4) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物、其药理学上可接受的盐或它们的水合物，其中 R<7> 彼此相同或不同，且各自表示氢原子、卤素原子、可取代的具有 1-6 个碳原子的烷基、可取代的具有 2-6 个碳原子的烯基、可取代的具有 2-6 个碳原子的炔基、可取代的具有 3-8 个碳原子的环烷基，或 R<7> 中的两个可一起形成脂族的环、芳族的环、杂环的环或亚烷基二氧基环；

[3396] 7) 在 4) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物，其药理学上可接受的盐或它们的水合物，其中 n 为 1 或 2 的整数；

[3397] 8) 在 1) 至 7) 中的任何一个中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物，其药理学上可接受的盐其或它们的水合物，其中部分结构：

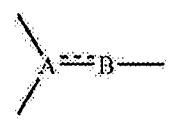
[3398]



[3399] 为 >C(R<6>)-CH(R<6>)-(CH2)m- 所示的基团 (其中 m 为 0 或 1-5 的整数；且 R<6> 为氢原子)；

[3400] 9) 在 1) 至 7) 中的任何一个中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶) 化合物，其药理学上可接受的盐或它们的水合物，其中部分结构：

[3401]



[3402] 为 >C(R<6>)-CH(R<6>)-(CH2)m- 所示的基团 (其中 m 为 0 或 1-5 的整数；且 R<6> 为卤素原子、羟基、具有 1-6 个碳原子的烷基、具有 1-6 个碳原子的烷氧基、腈基、具有 1-6 个碳原子的卤烷基、具有 1-6 个碳原子的羟基烷基、氰基 -C1-C6 烷基、具有 1-6 个碳原子氨

基烷基、硝基、叠氮基、可取代的氨基、可取代的氨基甲酰基、可取代的羧基、巯基或具有 1-6 个碳原子的硫代烷氧基）；

[3403] 10) 在 1) 中所述的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶）化合物，其药理学上可接受的盐或它们的水合物，其中式 (I) 所示的 (1- 茚满酮)-(1,2,3,6- 四氢吡啶）化合物为选自以下的化合物：

[3404] (1)1- 苄基 -4-[(5,6- 二甲氧基 -1- 茚满酮)-2- 基] 甲基 -1,2,3,6- 四氢吡啶，

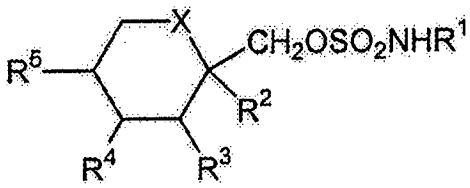
[3405] (2)1- 苄基 -4-[(5,6- 二乙氧基 -1- 茚满酮)-2- 基] 甲基 -1,2,3,6- 四氢吡啶，和

[3406] (3)1- 苄基 -4-[(5,6- 二乙氧基 -2- 氟 -1- 茚满酮)-2- 基] 甲基 -1,2,3,6- 四氢吡啶。

[3407] ix) 国际专利申请公开文本第 WO2003/020289 号

[3408] 本发明的式 I 化合物为下列通式 I 的化合物：

[3409]



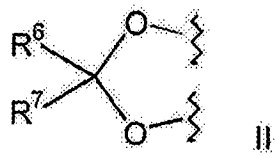
I

[3410] 其中

[3411] X 为 CH2 或氧；

[3412] R1 为氢或烷基；且 R2、R3、R4 和 R5 独立为氢或低级烷基，且当 X 为 CH2 时，R4 和 R5 可为连接以形成苯环的烯基，且当 X 为氧时，R2 和 R3 和 / 或 R4 和 R5 可一起为下式 II 的亚甲二氧基：

[3413]



II

[3414] 其中

[3415] R6 和 R7 相同或不同且为氢、低级烷基或为烷基，且被连接以形成环戊基或环己基环。

[3416] R^1具体为氢或约 1-4 个碳的烷基，例如甲基、乙基和异 - 丙基。整个本说明书的烷基包括直链和支链烷基。用于 R2、R3、R4、R5、R6 和 R7 的烷基具有约 1-3 个碳且包括甲基、乙基、异 - 丙基和正 - 丙基。

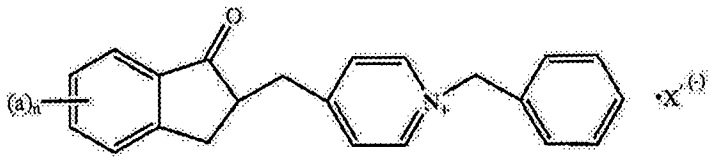
[3417] 当 X 为 CH2 时，R 和 R5 可结合以形成稠合至 6- 元含 X 环的苯环，即 R4 和 R5 由三烯烃基 (alkatrienyl) = C-CH = CH-CH = 定义。

[3418] 具体的一组式 I 化合物为如下化合物，其中 X 为氧，且 R2 和 R3 以及 R4 和 R5 一起为式 I I 的亚甲二氧基，其中 R6 和 R7 都为氢，都为烷基或组合以形成螺环戊基或环己基环，具体的是其中 R6 和 R7 都为例如甲基的烷基。第二组化合物为如下化合物，其中 X 为 CH2，且将 R4 和 R5 连接以形成苯环。第三组式 I 化合物为如下化合物，其中 R2 和 R3 都为氢。

[3419] x) 美国专利申请公开文本第 2003069289 号

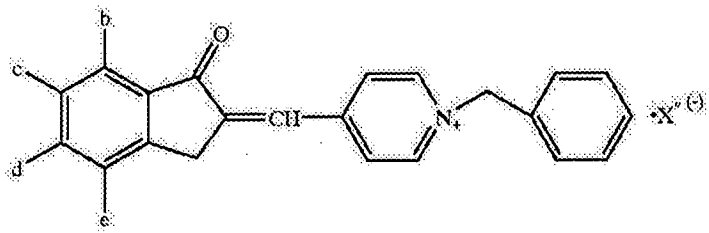
[3420] 鉴于上文所述的情况，本发明的发明人做了广泛的研究，通过该研究他们发现了下式所示的化合物：

[3421]



[3422] （其中“a”部分彼此相同或不同，且各自表示氢原子或 C1-6 烷氧基；n 为 1-4 的整数；且 X<(-)> 表示卤素离子）和下式所示的化合物：

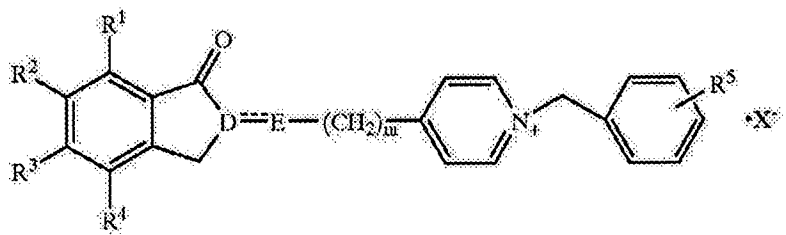
[3423]



[3424] （其中 b、c、d 和 e 彼此相同或不同，且各自表示氢或直链或支链 C1-6 烷基、C1-6 烷氧基、C1-6 烷氧基羰基、C1-6 烷基氨基羰基氧基、二 (C1-6 烷基)- 氨基羰基氧基或卤素；且 X”<(-)> 表示在氯化物、溴化物、碘化物和硫酸盐系列中的阴离子）表现出对乙酰胆碱酯酶优良的抑制作用。而且，基于这些发现，他们又发现了下式所示的 1- 苄基吡啶鎓盐：

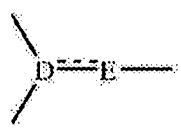
[3425]

(I)



[3426] （其中 R<1>、R<2>、R<3> 和 R<4> 相同或不同，且表示氢原子、卤素原子、羟基、腈基、C1-6 烷基、C1-6 烷氧基、C1-6 烷氧基羰基、C1-6 烷基氨基羰基氧基或二 (C1-6 烷基)- 氨基羰基氧基；R<5> 表示氢原子、卤素原子、C1-6 烷基、C2-6 烯基或 C2-6 炔基；部分结构：

[3427]

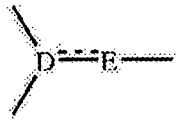


[3428] 为式 >C(R<6>)-CH2-（其中 R<6> 为氢原子或卤素原子）或 >C-CH- 所示的基团；X<-> 表示卤素离子或有机磺酸离子；且 m 为 0 或 1-5 的整数）表现出对乙酰胆碱酯酶优良的抑制作用，并完成了本发明。

[3429] 也就是说，根据本发明的第一方面为 (1) 包括上式 (I) 所示的 1- 苄基吡啶鎓盐的乙酰胆碱酯酶抑制剂。而且，(2) 在上文的条目 (1) 中，R<1>、R<2>、R<3> 和 R<4> 可彼此相

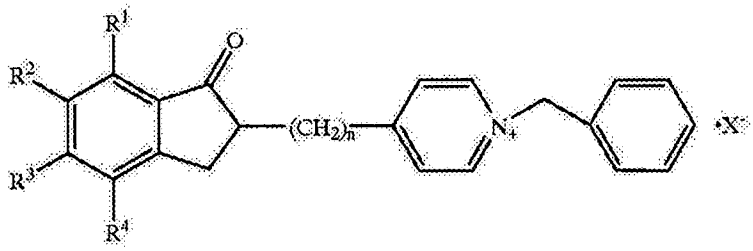
同或不同，且各自表示氢原子或C1-6烷氧基；(3)在上文的条目(1)中，R<1>、R<2>R<3>和R<4>可彼此相同或不同，且各自表示氢原子或甲氧基；(4)在上文的条目(1)中，R<1>和R<4>可表示氢原子；且R<2>和R<3>可表示甲氧基；(5)在上文的条目(1)中，R<5>可为氢原子；(6)在上文的条目(1)中，部分结构：

[3430]



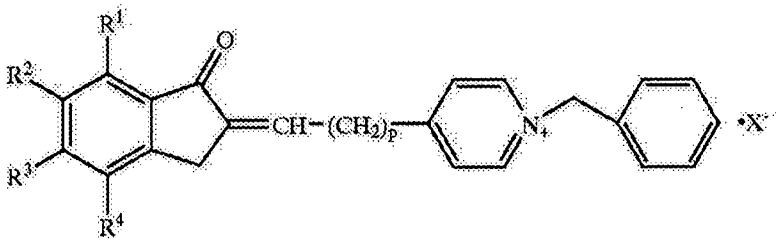
[3431] 可为式>C(R<6>)-CH2-(其中R<6>为氢原子或卤素原子)所示的基团；(7)在上文的条目(1)中，m可为0、2或4；(8)在上文的条目(1)中，X<->所示的卤素离子可为氯离子、溴离子或碘离子，优选的是氯离子或溴离子；(9)在上文的条目(1)中，X<->所示的有机的磺酸离子可为甲磺酸根离子、三氟甲磺酸根离子、乙磺酸根离子、苯磺酸根离子、甲苯磺酸根离子或樟脑磺酸根离子；(10)在上文的条目(1)中，1-苄基吡啶鎓盐可为下式所示的化合物：

[3432]



[3433] 其中R<1>、R<2>、R<3>、R<4>和X<->具有与上文所定义的相同的含义；且n为1至6的整数；(11)在上文的条目(1)中，1-苄基吡啶鎓盐可为下式所示的化合物：

[3434]

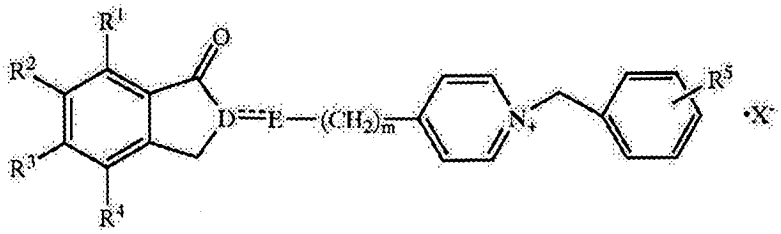


[3435] 其中R<1>、R<2>、R<3>、R<4>和X<->具有与本文所定义的相同的含义；且p为0或1-5的整数；(12)在上文的条目(1)中，制剂可为用于治疗、预防或改善老年性痴呆、脑血管性痴呆或注意力缺陷伴多动障碍的活性剂；且(13)在上文的条目(12)中，老年性痴呆可为阿尔茨海默型老年性痴呆。

[3436] 根据本发明的第二个方面为(14)包含下式所示的1-苄基吡啶鎓盐的药物制剂：

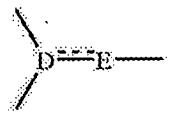
[3437]

(I)



[3438] 其中 R<1>、R<2>、R<3>、R<4>、R<5>，部分结构：

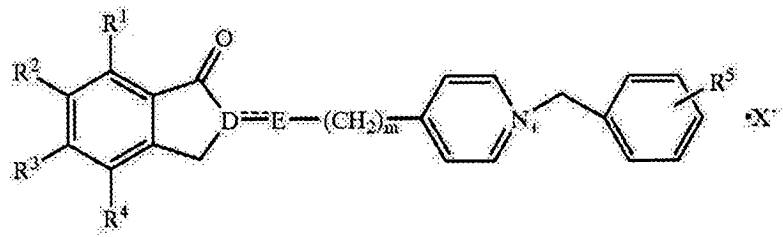
[3439]



[3440] X<->和 m 具有与上文所定义的相同的含义。而且，根据本发明的第三个方面为(15)下式所示的 1-苄基吡啶鎓盐用于制备乙酰胆碱酯酶抑制剂的应用：

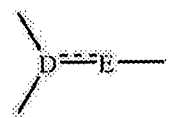
[3441]

(I)



[3442] (其中 R<1>、R<2>、R<3>、R<4>、R<5>、部分结构：

[3443]



[3444] X<->和 m 具有与上文所定义的相同的含义)。

[3445] 通过向患者施用药理学有效剂量的上式(I)所示的 1-苄基吡啶鎓盐，本发明提供了预防、治疗或改善疾病的方法，针对所述疾病对乙酰胆碱酯酶的抑制作用在预防、治疗或改善上是有效的。

[3446] 在本发明中，乙酰胆碱酯酶的抑制作用有效预防、治疗或改善的疾病包括老年性痴呆，例如阿尔茨海默型老年性痴呆和脑血管性痴呆，和注意力缺陷伴多动障碍。

[3447] 在下文中，描述了用于本说明书的符号、术语等的含义，并详细描述了本发明。

[3448] 在本说明书中，为了方便起见，化合物的结构式可表示某一异构体，但本发明包括可出现在化合物结构中的所有可能的异构体，例如几何异构体、基于不对称碳的旋光异构体、立体异构体和互变异构体，及这类异构体的混合物，因此根据本发明的化合物可为任何异构体或其混合物而不限于为了方便起见所示的式子。因此，根据本发明的化合物可具有分子内不对称的碳，因此作为光学活性异构体或外消旋变体存在，且将这类化合物中的任何一者不限制地纳入本发明中。当有晶体的多晶型现象时，根据本发明的化合物可不限制地为单晶形式或混晶形式。化合物(I)或其盐可为酐或水合物，它们中的任何一个都归入

本说明书的实施方案中。而且，化合物（I）在体内分解形成的代谢产物，和化合物（I）的前药或其盐，也归入本说明书的实施方案中。

[3449] 用于本说明书的“卤素原子”意指例如氟原子、氯原子、溴原子或碘原子的原子，优选的是氟原子、氯原子或溴原子。

[3450] 在本说明书中 R<1>、R<2>、R<3> 和 R<4> 所示的“C1-6 烷基”意指具有 1-6 个碳原子的烷基，且其实例包括甲基、乙基、正 - 丙基、异 - 丙基、正 - 丁基、异 - 丁基、仲 - 丁基、叔 - 丁基、正 - 戊基、1,1- 二甲基丙基、1,2- 二甲基丙基、2,2- 二甲基丙基、1- 乙基丙基、2- 乙基丙基、正 - 己基、1- 甲基 -2- 乙基丙基、1- 乙基 -2- 甲基丙基、1,1,2- 三甲基丙基、1- 丙基丙基、1- 甲基丁基、2- 甲基丁基、1,1- 二甲基丁基、1,2- 二甲基丁基、2,2- 二甲基丁基、1,3- 二甲基丁基、2,3- 二甲基丁基、2- 乙基丁基、2- 甲基戊基、3- 甲基戊基等，优选的是甲基、乙基、正 - 丙基、异 - 丙基、正 - 丁基、异 - 丁基和叔 - 丁基。

[3451] 在本说明书中 R<1>、R<2>、R<3> 和 R<4> 所示的“C1-6 烷氧基”意指具有 1-6 个碳原子的烷氧基，且其实例包括甲氧基、乙氧基、正 - 丙氧基、异 - 丙氧基、仲 - 丙氧基、正 - 丁氧基、异 - 丁氧基、仲 - 丁氧基、叔 - 丁氧基、正 - 戊氧基、异 - 戊氧基、仲 - 戊氧基、正 - 己氧基、异 - 己氧基、1,1- 二甲基丙氧基、1,2- 二甲基丙氧基、2,2- 二甲基丙氧基、2- 乙基丙氧基、1- 甲基 -2- 乙基丙氧基、1- 乙基 -2- 甲基丙氧基、1,1,2- 三甲基丙氧基、1,1,2- 三甲基丙氧基、1,1- 二甲基丁氧基、1,2- 二甲基丁氧基、2,2- 二甲基丁氧基、2,3- 二甲基丁氧基、1,3- 二甲基丁氧基、2- 乙基丁氧基、1,3- 二甲基丁氧基、2- 甲基戊氧基、3- 甲基戊氧基、己氧基等，优选的是甲氧基、乙氧基、正 - 丙氧基和异 - 丙氧基。

[3452] 在本说明书中 R<1>、R<2>、R<3> 和 R<4> 所示的“C1-6 烷氧羰基”意指其中具有与上文所定义的相同的含义的 C1-6 烷氧基与羰基结合的基团。例如，甲氧羰基、乙氧羰基、正 - 丙氧羰基、异 - 丙氧羰基、正 - 丁氧羰基、异 - 丁氧羰基、叔 - 丁氧羰基、戊氧羰基、己氧羰基等，优选的是甲氧羰基、乙氧羰基、正 - 丙氧羰基和异 - 丙氧羰基。

[3453] 在本说明书中 R<1>、R<2>、R<3> 和 R<4> 所示的“C1-6 烷基氨基羰基氧基”意指它的氮原子已经被具有与上文所定义的相同的含义的 C1-6 烷基取代的氨基羰基氧基，且其实例包括甲氨基羰基氧基、乙基氨基羰基氧基、正 - 丙基氨基羰基氧基、异 - 丙基氨基羰基氧基、正 - 丁基氨基羰基氧基、异 - 丁基氨基羰基氧基、叔 - 丁基氨基羰基氧基、正 - 戊基氨基羰基氧基、异 - 戊基氨基羰基氧基、新戊基氨基羰基氧基、己基氨基羰基氧基、1- 甲基丙基氨基羰基氧基、1- 甲基丁基氨基羰基氧基、2- 甲基丁基氨基羰基氧基等。

[3454] 在本说明书中 R<1>、R<2>、R<3> 和 R<4> 所示的“二（C1-6 烷基）- 氨基羰基氧基”意指它的氮原子已经被两个 C1-6 烷基取代的氨基羰基氧基，且其实例包括二甲氨基羰基氧基、二乙基氨基羰基氧基、二（正 - 丙基）- 氨基羰基氧基、二 -（异 - 丙基）- 氨基羰基氧基、二（正 - 丁基）- 氨基羰基氧基、二（异 - 丁基）- 氨基羰基氧基、二 -（叔 - 丁基）- 氨基羰基氧基、二（正 - 戊基）- 氨基羰基氧基、二 -（异 - 戊基）- 氨基羰基氧基、二 -（新戊基）- 氨基羰基氧基、二 -（正 - 己基）- 氨基羰基氧基、二 -(1- 甲基丙基）- 氨基羰基氧基、二 -(1- 甲基丁基）- 氨基羰基氧基、二 -(2- 甲基丁基）- 氨基羰基氧基等。

[3455] 如本说明书中 R<1>、R<2>、R<3> 和 R<4> 的优选模式，R<1>、R<2>、R<3> 和 R<4> 彼此相同或不同，且各自表示氢原子、卤素原子、羟基、腈基、C1-6 烷基或 C1-6 烷氧基；更优选的是，它们彼此相同或不同，且各自表示氢原子、卤素原子、羟基、腈基或 C1-6 烷氧基；进一

步优选的是，它们彼此相同或不同，且各自表示氢原子或 C1-6 烷氧基；且最优选的是，R<1> 和 R<4> 表示氢原子，而 R<2> 和 R<3> 彼此相同或不同，且各自表示 C1-6 烷氧基（例如甲氧基、乙氧基等）。

[3456] 在本说明书中 R<5> 所示的“卤素原子”和“C1-6 烷基”意指各自具有与如上文所定义的相同的含义的卤素原子和 C1-6 烷基。

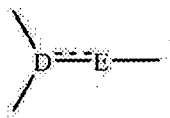
[3457] 在本说明书中 R<5> 所示的“C2-6 烯基”意指具有 2-6 个碳原子的烯基，且其实例包括具直链或支链 C2-6 烯基，例如乙烯基、烯丙基、1- 丙烯基、异丙烯基、1- 丁烯 -1- 基、1- 丁烯 -2- 基、1- 丁烯 -3- 基、2- 丁烯 -1- 基和 2- 丁烯 -2- 基，优选的是乙烯基、烯丙基和异丙烯基。

[3458] 在本说明书中 R<5> 所示的“C2-6 炔基”意指具有 2-6 个碳原子的炔基，且其实例包括直链或支链 C2-6 炔基，例如乙炔基、1- 丙炔基、2- 丙炔基、丁炔基、戊炔基和己炔基。

[3459] 在本说明书中 R<5> 优选的实例包括氢原子和卤素原子（例如氟原子、氯原子、溴原子等）。

[3460] 部分结构：

[3461]

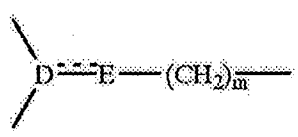


[3462] 可为式 >C(R<6>)-CH2-（其中 R<6> 为氢原子或卤素原子）或 >C-CH- 所示的任一基团，优选的是式 >C(R<6>)-CH2- 所示的基团，其中 R<6> 为氢原子或卤素原子。本文中，R<6> 所示的“卤素原子”指具有与在上文定义的卤素原子含义相同的原子，且 R<6> 优选的是氢原子、氟原子、氯原子或溴原子，更优选的是氢原子或氟原子。就是，可由部分结构所示的基团更优选的是式 >CH-CH2-、>C(F)-CH2-、>C(Cl)-CH2- 或 >C(Br)-CH2-，进一步优选的是式 >CH-CH2- 或 >C(F)-CH2-。

[3463] 本说明书中 X<-> 所示的“卤素离子”意指氟离子、氯离子、溴离子、碘离子等，优选地氯离子、溴离子和碘离子，更优选的是氯离子和溴离子，最优选的是氯离子。X<-> 所示的“有机磺酸离子”意指甲磺酸根离子、三氟甲磺酸根离子、乙磺酸根离子、苯磺酸根离子、甲苯磺酸根离子和樟脑磺酸根离子等。

[3464] 在本说明书中，m 为 0 或 1-5 的整数，其中部分结构：

[3465]



[3466] 分别表示如下 (1) 当 m 为 0 时，所述结构部分表示式 >C(R<6>)-CH2- 或 >C-CH-，(2) 当 m 为 1 时，式 >C(R<6>)-(CH2)2- 或 >C = CH-(CH2)-，(3) 当 m 为 2 时，式 >C(R<6>)-(CH2)3- 或 >C-CH-(CH2)2-，(4) 当 m 为 3 时，式 >C(R<6>)-(CH2)4- 或 >C-CH-(CH2)3-，(5) 当 m 为 4 时，式 >C(R<6>)-(CH2)5- 或 >C-CH-(CH2)4-，和 (6) 当 m 为 5 时，式 >C(R<6>)-(CH2)6- 或 >C-CH-(CH2)5-（在式中，R<6> 具有如与上文所定义的相同的含义）。m 优选的是 0、2 或 4，更优选的是 0 或 2。

[3467] 在本发明中乙酰胆碱酯酶抑制剂的一个实施方案包括，例如包含下列化合物的那些乙酰胆碱酯酶抑制剂。但是，不言而喻，本发明的实施方案并不限于包含下列化合物的那些乙酰胆碱酯酶抑制剂。

[3468] 所述乙酰胆碱酯酶抑制剂包含选自下列的任何一个或两个或多个 1- 苄基吡啶鎓盐：

[3469] 1- 苄基 -4-(1- 茚满酮 -2- 基) 甲基吡啶鎓氯化物；

[3470] 1- 苄基 -4-[(4- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3471] 1- 苄基 -4-[(5- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3472] 1- 苄基 -4-[(6- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3473] 1- 苄基 -4-[(7- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3474] 1- 苄基 -4-[(5,6- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3475] 1- 苄基 -4-[(5,7- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3476] 1- 苄基 -4-[(4,7- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3477] 1- 苄基 -4-[(4,5- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3478] 1- 苄基 -4-[(6,7- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3479] 1- 苄基 -4-[(5,6,7- 三甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3480] 1- 苄基 -4-[(5,6- 二乙氧基 -1- 茚满酮)-2- 基] 甲基吡啶鎓氯化物；

[3481] 1- 苄基 -4-(1- 茚满酮 -2- 基) 甲基吡啶溴化物；

[3482] 1- 苄基 -4-[(4- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3483] 1- 苄基 -4-[(5- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3484] 1- 苄基 -4-[(6- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3485] 1- 苄基 -4-[(7- 甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3486] 1- 苄基 -4-[(5,6- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3487] 1- 苄基 -4-[(5,7- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3488] 1- 苄基 -4-[(4,7- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3489] 1- 苄基 -4-[(4,5- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3490] 1- 苄基 -4-[(6,7- 二甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；

[3491] 1- 苄基 -4-[(5,6,7- 三甲氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物；和

[3492] 1- 苄基 -4-[(5,6- 二乙氧基 -1- 茚满酮)-2- 基] 甲基吡啶溴化物。

[3493] xi) 国际专利申请公开文本第 WO2000/033840 号

[3494] 在某些实施方案中化合物包括多奈哌齐、利凡斯的明、加兰他敏、石蒜胺及加兰他敏和石蒜胺的类似物。适合的化合物为加兰他敏、石蒜胺及它们的类似物，其中加兰他敏或石蒜胺的甲氧基、羟基或甲基中的至少一个被替代如下：

[3495] 甲氧基被 1-6 个碳原子的另一个烷氧基、羟基、氢、烷酰氧基、苯甲酰氧基或取代的苯甲酰氧基、碳酸酯基或氨基甲酸酯基或三烷基甲硅氧基替代；

[3496] 羟基被 1-6 个碳原子的烷氧基、氢、烷酰氧基、苯甲酰氧基或取代的苯甲酰氧基、碳酸酯基或氨基甲酸酯基替代；

[3497] N- 甲基被氢、烷基、苄基、环丙基甲基或取代的或未取代的苯甲酰氧基替代。

[3498] 加兰他敏或石蒜胺的甲氧基、羟基和甲基的一个或多个可被上文注明的基团替

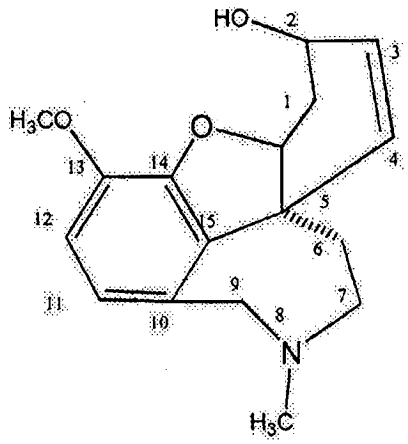
代。

[3499] 当引用取代基时，所述基团可选自 1-6 个碳原子的烷基或烷氧基、卤代基团和例如三氟甲基的卤代烷基。当引用烷基时，在上下文允许的情况下，该术语也包括是或含有环烷基（包括金刚烷基）的基团。芳基典型的为苯基或萘基，但可包括例如吗啉代的杂芳基。

[3500] 加兰他敏和石蒜胺具有下列式：

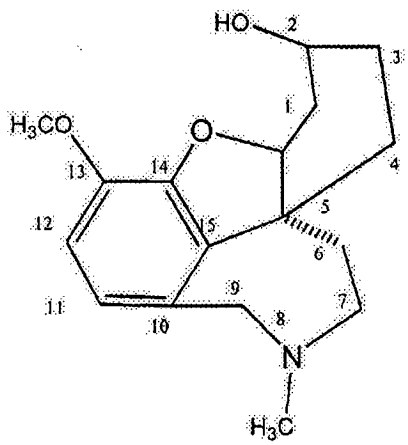
[3501] 加兰他敏

[3502]



[3503] 石蒜胺

[3504]



[3505] 例如在国际专利公开文本 WO88/08708 和 Bores 和 Kosley 在 Drugs of the Future 21 :621-631(1996) 的文章中描述了适合的类似物。

[3506] 用于这类制备的其它有用的药理学活性剂包括利凡斯的明和具有 1-11 小时半衰期的其它药理学活性剂。

[3507] 用于本发明的加兰他敏和石蒜胺的具体有用的类似物包括其类似物，其中这类化合物的甲氧基被氢、羟基或 2-6 个碳原子的烷氧基或酰氧基（例如 1-7 个碳原子的烷酰氧基）或苯甲酰基替代，或其中甲氧基被单或二烷基氨基甲酸酯基或单或二烷基碳酸酯基替代，其中烷基含有 1-8 个碳原子，优选的是 4-8 个碳原子，或其中其甲氧基被芳基氨基甲酸酯或碳酸酯基替代，其中所述芳基选自苯基、萘基、取代的苯基和取代的萘基，其中所述取代基选自 1-6 个碳原子的烷基和烷氧基、三氟甲基和卤代基团。

[3508] 其它有用的类似物包括如下化合物，其中无论是否甲氧基已被替代，羟基被如下

取代基代替：1-6 个碳原子的烷氧基、氢、例如烷酰氧基（典型地具有 1-7 个碳原子）的酰氧基，苯甲酰氧基或取代的苯甲酰氧基、其中所述取代基选自 1-6 个碳原子的烷基和烷氧基、三氟甲基和卤代基团、可为单或二烷基的碳酸酯基或氨基甲酸酯基，或芳基氨基甲酸酯或碳酸酯，其中烷基含有 1-8 个碳原子，优选的是 4-6 个碳原子或所述芳基选自苯基、萘基、取代的苯基和取代的萘基，其中所述取代基选自 1-6 个碳原子的烷基和烷氧基、三氟甲基和卤代基团。

[3509] xii) 国际专利申请公开文本第 WO1999/007359 号

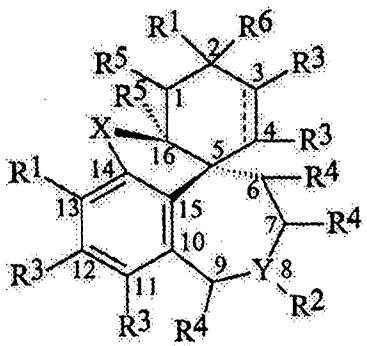
[3510] 在某些实施方案中，胆碱酯酶抑制剂可包括，但不限于，毒扁豆碱、他克林及他克林类似物、肌束震颤素 (fasiculin)、美曲膦酯、庚基 - 毒扁豆碱、去甲吡啶斯的明、去甲新斯的明、石杉碱、多奈哌齐和任何这些的前药，其中抑制剂依照本领域已知的前药构建原理进行修饰。这类修饰的实例包括引入亲水或亲脂性基团以分别增强溶解性或细胞膜穿透。

[3511] 在某些实施方案中，胆碱酯酶抑制剂为乙酰胆碱酯酶抑制剂，具体的是能够通过血脑屏障的那些。

[3512] 用于本发明的具体优选的胆碱酯酶抑制剂包括加兰他敏、表加兰他敏和去甲加兰他敏，及任何这些的类似物、盐和衍生物。加兰他敏以前被称为雪花胺 (galanthamine)。它为叔生物碱，该叔生物碱可从各种雪花莲球茎例如高加索雪花莲雪花莲属雪滴花 (Caucasian snowdrop galanthus woronowii)（石蒜科）及相关物种和水仙花球茎提取或通过化学合成制备。它对乙酰胆碱酯酶而不是丁酰胆碱酯酶具有高选择性。它基本上是选择性作用于烟碱性受体部位，而对毒蕈碱性受体部位基本上没有作用。

[3513] 用于本发明的具体优选的胆碱酯酶抑制剂为式 (I) 的加兰他敏及它的衍生物：

[3514]



[3515] 其中虚线表示在碳原子 3 和 4 之间任选存在的双键，每个 R1 独立地选自氢、羟基、直链或支链烷基、羟基烷基、羧基烷基氨基、烷基氨基、酰基、低级烷酰基、氰基、氢硫基、C16 烷氧基、烷硫基、芳氧基、芳硫基、R3 取代的芳氧基、R3- 取代的芳硫基、芳烷氧基、任选地 R3- 取代的脂族的或芳基氨基甲酰基、芳烷基硫基、R3- 取代的芳烷氧基、R3 取代的芳烷基硫基、芳氧基甲基、R3- 取代的芳氧基甲基、烷酰氧基、羟基 - 取代的烷酰氧基、苯甲酰氧基、R3- 取代的苯甲酰氧基、芳氧基羰基和 R3- 取代的芳氧基羰基。

[3516] R2 选自氢、任选地被卤素原子取代的直链或支链 C16 烷基、烯基或烷芳基或环烷基、羟基、烷氧基、硝基、氨基、氨基烷基、酰氨基、杂芳基、杂芳基 - 烷基、芳基、芳基烷基、氰基、戊基、芳酰基、环烷基甲基、烯丙基、苯基、R3- 取代的苯基、烷基苯基、R3- 取代的烷基苯基、选自 a- 或 ss- 呋喃基、a- 或 ss- 噻吩基、噻吩甲基、吡啶基、吡嗪基和嘧啶基的杂环基、

烷基 - 杂环基或 R'- 取代的杂环基，其中 R'为烷基或烷氧基，

[3517] 每个 R3 独立地选自氢、羟基、氢硫基、烷基、羟基烷基、芳基、芳烷基、烷氧基、巯基烷基、芳氧基、硫代芳氧基、烷芳基氧基、巯基烷芳基、硝基、氨基、N- 烷基氨基、N- 芳氨基，N- 烷芳基氨基、氟、氯、溴、碘和三氟甲基，

[3518] 每个 R4 独立选自氢、卤代、三氟甲基或 C14- 烷基，

[3519] 每个 R5 独立选自氢或羟甲基，

[3520] R6 为氢或 C16 烷基，或当在碳原子 2 处的 R1 为羟基时，R6 可为式 I 的一部分，其中 R6 为氢且 R1 为连接键；或

[3521] 在碳原子 2 处的 R1 和 R6 可连接地形成半卡巴腙，

[3522] X 为氧或 NR3；

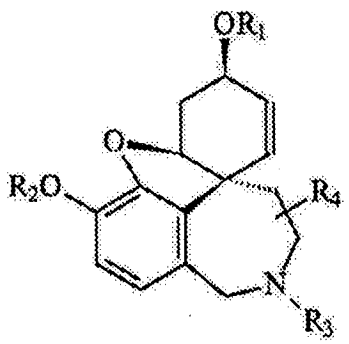
[3523] Y 为氮或磷，

[3524] 和其亚甲二氧基衍生物及其药学上可接受的酸加成盐。

[3525] 可用于本发明方法的式 I 化合物的某些化合物为如下的那些：其中烷基部分含有 1-8 个碳原子，卤素原子优选为氟、溴、氯，芳基部分优选为苯基，环烷基优选为 3- 至 7- 元环，特别是环丙基或环丁基，酰基优选为低级烷酰基且杂芳基部分优选为 5- 至 8- 元环，例如噻吩基、呋喃基、吡啶基、吡咯基、或吡嗪基。

[3526] 在某些实施方案中，式 I 化合物为式 I I 化合物

[3527]



[3528] 其中可为相同或不同的 R1 和 R2 各自表示氢原子或酰基，例如低级烷酰基，例如乙酰基或直链或支链烷基，例如甲基、乙基、丙基或异丙基；

[3529] R3 为被卤素原子或环烷基任选地取代的直链或支链烷基、烯基或烷芳基、羟基、烷氧基、硝基、氨基、氨基烷基、酰氨基、杂芳基、杂芳基烷基、芳酰基、芳酰基烷基或氰基；且

[3530] R4 表示与四环骨架环碳中的至少一个连接的氢或卤素原子，

[3531] 及其药学上可接受的盐，例如氢溴酸盐、盐酸盐、甲基硫酸盐或碘甲烷盐。

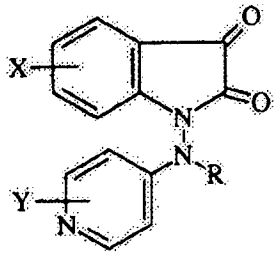
[3532] 式 I I 包括加兰他敏自身。

[3533] 在某些实施方案中，化合物为加兰他敏自身，及其盐例如卤化物，例如加兰他敏氢溴酸盐。

[3534] xiii) 国际专利申请公开文本第 WO1997/038993 号

[3535] 本申请涉及下式化合物

[3536]



(I)

[3537] 其中

[3538] R 为氢、(C1-C6) 烷基或羟基 (C-C6) 烷基；

[3539] X 为氢、羟基、(Ci-C6) 烷氧基、苯基 (C1-C6) 烷氧基或 -O(C = O)NRR ；且

[3540] Y 为氢或卤素；

[3541] 其中 R 为 (C1-C6) 烷基、苯基或苯基 (CI-C6) 烷基，其中苯基被 (C1-C6) 烷基、(C,-C6) 烷氧基、卤素或三氟甲基任选地取代；

[3542] R2 为氢或 (C,-C6) 烷基 ；或

[3543] R 和 R2 连同连接它们的氮一起形成四氢异喹啉基 ；及它的药学上可接受的酸加成盐。

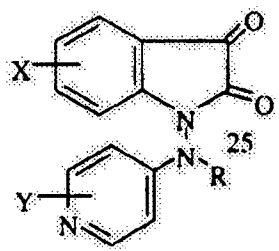
[3544] 术语“烷基”应指规定碳原子数的直链或支链烷基。实例包括，但不限于甲基、乙基、正 - 丙基、异 - 丙基、正 - 丁基、异丁基、仲 - 丁基、叔 - 丁基，及直链和支链戊基和己基。

[3545] 术语“卤代”应指氯、氟、溴或碘。

[3546] 术语“苯基”应指具有独立地选自 (C1-C6) 烷基、(C1-C6) 烷氧基、卤代或三氟甲基的具有 0、1、2 或 3 个取代基的苯基。

[3547] 在本发明的具体实施方案中为如下式 (I) 化合物

[3548]



[3549] 其中

[3550] R 为氢、(C1-C6) 烷基或羟基 (C1-C6) 烷基；

[3551] X 为氢、羟基、(C1-C6) 烷氧基、苄氧基，或 -O(C = O)NR1R2 ；且

[3552] Y 为氢或卤素；

[3553] 其中 R1 为 (C1-C6) 烷基、苯乙基或苄基，其中苯基被 (C,-C6) 烷基、(C1-C6) 烷氧基、卤素或三氟甲基任选取代 ；且

[3554] R2 为氢或 (C,-C6) 烷基 ；及它的药学上可接受的酸加成盐。

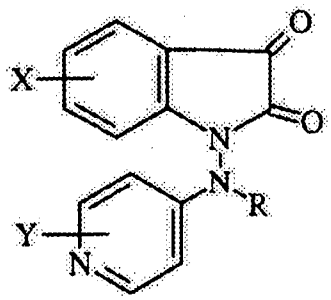
[3555] 在一个实施方案中，当 R1 为 (C-C6) 烷基时，R2 为氢。

[3556] 在一个实施方案中为式 I 化合物，其中 R 为 (C1-C6) 烷基。

[3557] 在一个实施方案中，X 为氢，Y 为氢，且 R 为氢、甲基、乙基或丙基。

[3558] 在另一个实施方案中为如下式 I 化合物

[3559]



(I)

[3560] 其中

[3561] R 为氢、(Cs-C6) 烷基或羟基 (CI-C6) 烷基；

[3562] X 为氢、羟基、(C1-C6) 烷氧基、苄氧基，或 -O(C = O)NRIR2；且

[3563] Y 为氢或卤素；其中

[3564] R 和 R2 连同连接它们的氮一起形成四氢异喹啉基；及它的药学上可接受的酸加成盐。

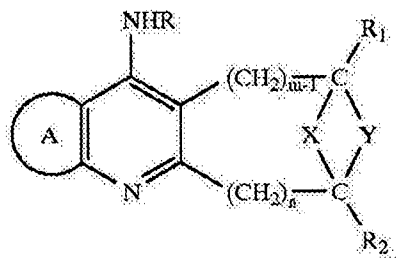
[3565] 在一个实施方案中，X 为 -O(C = O)NR' R2 且 Y 为氢。

[3566] xiv) 美国专利 5,965,569

[3567] 为本发明主题的新氨基吡啶化合物对应于如下通式 (I)：

[3568]

(I)



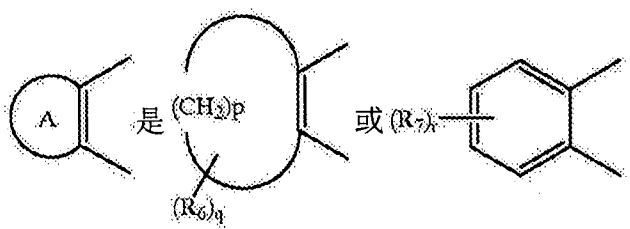
[3569] 其中 R 可为氢、烷基、芳烷基或酰基；

[3570] R1 和 R2 可独立地为氢、烷基、芳烷基、烷氧基、烷氧羰基、氨基或经一个或两个烷基、芳烷基或酰基取代的氨基。

[3571] m 和 n 可采用值 1、2 或 3；

[3572] X 和 Y 可独立地为两个碳之间的键、氧或硫原子、基团 N-R3 或含有 1-5 个碳原子的亚烷基或亚烯基桥且其可含有一个或多个取代基 R4。当 X 为亚烯基时，后者可与饱和的或不饱和的碳环或杂环系统稠合，该环有可能经一个或多个基团 R5 取代；例如 X 可为邻 - 亚苯基；

[3573] 和

[3574] 

[3575] p、q 和 r 具有等于或大于 1 的值，且 R6 和 R7 是可单独为氢、卤素（优选的是氟或

氯）、低级烷氧基或低级烷基的取代基。

[3576] 在上文的定义中：

[3577] 术语“烷基”表示直链的、支链的、取代的环或环烷基链的，具有 1-6 个碳原子的烃残基，例如甲基、乙基、丙基、异丙基、丁基、仲 - 丁基、戊基、环戊基、环戊基甲基、环己基等。

[3578] 术语“芳烷基”指苯基烷基或在苯基上取代的苯基烷基，含有 7 至 12 个碳原子。在“苯基烷基”或“在苯基上取代的苯基烷基”中的术语烷基指具有含有 1-4 个碳原子的直链亚烷基，例如亚甲基、亚乙基、三亚甲基或四亚甲基。在“在苯基上取代的苯基烷基”中所述的取代的苯基为含有选自以下的一个或多个取代基的苯基：卤素，例如氟、氯、溴和碘，包括具有直链或支链、含有 1-4 个碳原子的烷基的低级烷基，例如甲基、乙基、丙基、异丙基、丁基、仲 - 丁基和叔 - 丁基，和包括具有直链或支链、含有 1-4 个碳原子的烷氧基的低级烷氧基，例如甲氧基、乙氧基、丙氧基、异丙氧基、丁氧基和仲 - 丁氧基。

[3579] 这类芳烷基的实例包括苄基、苯乙基、3- 苯基丙基、4- 苯基丁基、2-(4- 甲氧苯基）乙基、2-(2- 甲苯基）乙基、2-(4- 氟苯基）乙基和 4-(4- 氯苯基）丁基。

[3580] 术语“酰基”指烷基羰基或芳烷基羰基，其中烷基和芳烷基残基可采用之前所定义的含义。

[3581] 在上下文的 R1 和 R2 中，术语烷基和芳烷基具有上文给出的用于 R 的含义。烷氧基取代基和烷氧羰基取代基的烷氧基可采用上文给出的用于低级烷氧基的含义。氨基的烷基、芳烷基和酰基取代基也可采用上下文的 R 中给出的含义。

[3582] N-R3 的基团 R3 可采用上文所定义的用于 R 的含义。

[3583] 连接至亚烷基或亚烯基桥的基团 R4 可独立地为氢、直链或支链的具有 1-4 个碳原子的低级烷基、烯基或亚烷基、苯基、经具有 1-4 个碳原子的一个或多个低级烷基取代的苯基、具有 1-4 个碳原子或卤素（氟、氯、溴或碘）的低级烷氧基、在 R 的上下文中如上文所定义的芳烷基、含有 1-4 个碳的低级烷氧基和羟基。

[3584] 基团 R5（其为稠合至 X 或 Y 的环的取代基）可为氢、具有 1-4 个碳原子的低级烷基或低级烷氧基或卤素（氟、氯、溴和碘）。

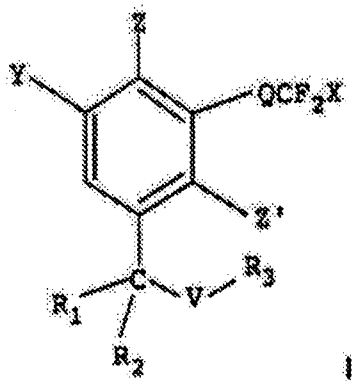
[3585] 由于通式 (I) 的化合物具有至少两个手性中心，就是能产生旋光异构的两个不对称的碳，本发明涉及外消旋的化合物，和涉及这些化合物的所有可能的对映异构体，或涉及不同比例的其混合物。

[3586] 药学上可接受的加成盐可由有机酸或无机酸形成，例如无机酸中的盐酸、氢溴酸、硫酸和硝酸，以及有机酸中的酒石酸、琥珀酸、马来酸、富马酸和柠檬酸。

[3587] xv) 美国专利 5,663,448

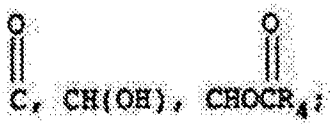
[3588] 本发明的化合物具有下列式 I

[3589]



I

[3590] 立体异构体和其药学上可接受的盐，其中 Z 和 Z' 中的每一个独立地为 H 或 F；

[3591] Q 为 

[3592] X 为 H、Br、Cl、F 或 CF3；Y 为 H、Br、Cl、F、OH、OR5、OC(O)R4、N3、CN、NO2、SO3H、CO2R4、NH2、NHR9、NR9R'9、C(R6)(R7)(V'R8) 或 C(O)R7，条件是当 Z 和 Z' 都为 F 时，那么 Y 为 H 或 F；

[3593] V 和 V' 各自独立地为 CH2 或 O；

[3594] R1 为 H 或 CH3；

[3595] R2、R9 和 R'9 各自独立地为 (C1-6) 烷基，或 R2 和 V-R3 连同连接它们的碳原子一起形成 3-6 元环；

[3596] R3、R6、R7 和 R8 各自独立地为 H、(C1-6) 烷基或 (C3-6) 环烷基；

[3597] R4 为 H、(C1-10) 烷基、(C0-4) 亚烷基芳基或 (C3-8) 环烷基；且

[3598] R5 为 (C1-10) 烷基、苄基、苯乙基或 (C3-6) 环烷基。

[3599] 术语“(C1-6) 烷基”和“(C1-10) 烷基”指分别含有 1-6 个碳原子和 1-10 个碳原子的直链或支链烷基残基，包括，但不限于，甲基、乙基、正 - 丙基、异 - 丙基、正 - 丁基、异 - 丁基、仲 - 丁基、叔 - 丁基、正 - 戊基、1- 甲基丁基、2,2- 二甲基丁基、2- 甲基戊基、2,2- 二甲基丙基、正 - 己基等。同样地，术语“(C0-4) 亚烷基芳基”可指至多 4 个碳原子的直链或支链亚烷基，例如乙基亚乙基、2- 甲基三亚甲基等。C0 当然指没有连接至芳基的亚烷基部分。

[3600] “羟基 (C1-6) 烷基”指在其上具有 1-3 个羟基取代基的 (C1-6) 烷基。优选的是，在 α 位仅有一个羟基取代基（连接至直接连接苯基的碳原子）。

[3601] “Ts”或“甲苯磺酰基”指 ##STR5##，甲苯磺酰基衍生物意指 ##STR6##，其中 R 为 C1-6 烷基。

[3602] “芳基”包括碳环和杂环部分，其中苯基、吡啶基、吲哚基、吲唑基、呋喃基和噻吩基是最感兴趣的；这些部分包括它们的位置异构体例如，2-、3- 或 4- 吡啶基、2- 或 3- 呋喃基和噻吩基、1-、2- 或 3- 吲哚基或 1- 和 3- 吲唑基，以及呋喃基和噻吩基部分的二氢和四氢类似物。也纳入术语“芳基”之内的为下列稠合的碳环部分：例如并环戊二烯基、茚基、萘基、环戊并环庚五烯基、庚搭烯基、苊基、芴基、蒽基、菲基、䓛基、醋菲烯基、醋蒽烯基、三亚苯基、苝基、䓛基和并四苯基。也纳入术语“芳基”之内的为如下的其它杂环残基：2- 或 3- 苯并 [b] 噻吩基、2- 或 3- 萘并 [2,3-b] 噻吩基、2- 或 3- 噻蒽基、2H- 吡喃 -3-(或 4- 或 5-) 基、

1-异苯并呋喃基、2H-色烯基-3-基、2-或3-二苯并氧硫杂环己二烯基(phenoxathiinyl)、2-或3-吡咯基、4-或3-吡唑基、2-吡嗪基、2-嘧啶基、3-哒嗪基、2-吲嗪基、1-异吲哚基、4H-喹嗪-2-基、3-异喹啉基、2-喹啉基、1-酞嗪基、1,8-萘啶基、2-喹喔啉基、2-喹唑啉基、3-噌啉基、2-蝶啶基、4aH-咔唑-2-基、2-咔唑基、β-咔啉-3-基、3-菲啶基、2-吖啶基、2-萘嵌二氮杂苯基、1-吩嗪基、3-异噻唑基、2-吩噻嗪基、3-异噁唑基、2-吩噁嗪基、3-异-色满基、7-色满基、2-吡咯啉-3-基、2-咪唑烷基、2-咪唑啉-4-基、2-吡唑烷基、3-吡唑啉-3-基、2-哌啶基、2-哌嗪基、1-吲哚啉基、1-异吲哚啉基、3-吗啉基、苯并[h]异喹啉基和苯并[b]呋喃基,包括其位置异构体,除了不可将杂环部分通过它们的氮原子直接连接之外。芳基可被独立地选自下列的一个、两个或三个取代基取代或未经取代:C1-6烷基、卤代烷基、烷氧基、硫代烷氧基、氨基烷基氨基、二烷基氨基、羟基、卤代、巯基、硝基、甲醛基(carboxaldehyde)、羧基、烷氧羰酰和羧酰胺。

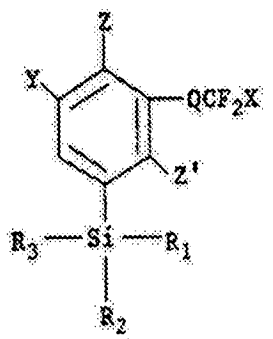
[3603] 当将R2和V-R3连在一起时,它们可形成包括连接R2和V的碳原子的3元环(当R3为H时)。形成的其它环可为4、5和6元环。术语3-6元环意指包含在环结构的碳原子和氧原子数(当V为0时)。

[3604] 式I化合物的"立体异构体"为用于单个分子的所有异构体(仅它们的原子在空间中方向不同)的一般术语。它包括镜像异构体(对映异构体)、几何异构体(顺式/反式)和具有多于一个手性中心(彼此不为镜像)的化合物的异构体(非对映异构体),无论哪个形式都可应用于本发明化合物。

[3605] xvi)欧洲专利申请第EP0611769号

[3606] 本发明的化合物具有下列式I:

[3607]

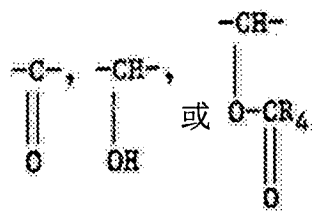


I

[3608] 其立体异构体或其混合物,及其药学上可接受的盐,其中

[3609] Z和Z'中的每个独立地为H或F,条件是Z或Z'中至少一个为F;

[3610]



;

[3611] Q为

[3612] X为H、Br、Cl、F或CF3。

[3613] Y为H、OH、(C1-6)烷基、-(CH2)mOR5、羟基(C1-6)烷基、(CH2)nNR6R6'、叠氮基、CN、CO2R4、COR6、SO3H、Br、Cl、F、NO2或-(CH2)nSiR1'R2'R3',条件是当Z和Z'都为F时,

那么 Y 为 H 或 F ;

[3614] R1、R2、R3、R1'、R2' 和 R3' 各自独立地为 C1-10 烷基或 (CH2)n 芳基 ;

[3615] R4 为 H、(C1-10) 烷基、苯基、苄基或苯乙基 ;

[3616] R5 为 H、(C1-10) 烷基、苄基或苯乙基 ;

[3617] R6 和 R6' 独立地为氢或 C1-10 烷基 ;

[3618] m 为 0、1、2、3 或 4 的整数 ;且

[3619] n 为 0、1 或 2 的整数。

[3620] 术语“(C1-6) 烷基”和“(C1-10) 烷基”指分别含有 1-6 个碳原子和 1-10 个碳原子的直链或支链烷基残基,包括,但不限于,甲基、乙基、正 - 丙基、异 - 丙基、正 - 丁基、异 - 丁基、仲 - 丁基、叔 - 丁基、正 - 戊基、1- 甲基丁基、2,2- 二甲基丁基、2- 甲基戊基、2,2- 二甲基丙基、正 - 己基等。同样地,术语“(CH2)n”或“(CH2)m”可表示可为支链或支链的亚烷基链。

[3621] “羟基 (C1-6) 烷基”指在其上具有 1-3 个羟基取代基的 (C1-6) 烷基。优选的是,在 α 位仅有一个羟基取代基 (连接至直接连接苯基的碳原子)。

[3622] “Ts”或“甲苯磺酰基”指 EMI 3.1,甲苯磺酰基衍生物指 EMI 3.2,其中 R 为 C1-6 亚烷基。

[3623] “芳基”包括碳环和杂环部分,其中的苯基、吡啶基、吲哚基、吲唑基、呋喃基和噻吩基是最感兴趣的 ;这些部分包括它们的位置异构体例如,2-、3- 或 4- 吡啶基、2- 或 3- 呋喃基和噻吩基、1-、2- 或 3- 吲哚基或 1- 和 3- 吲唑基,也包括呋喃基和噻吩基部分的二氢和四氢类似物。也纳入术语“芳基”之内的为下列稠合的碳环部分 :例如并环戊二烯基、茚基、萘基、环戊并环庚五烯基、庚搭烯基、苊基、芴基、蒽基、菲基、䓛基、醋菲烯基、醋蒽烯基、三亚苯基、苝基、䓛基和并四苯基。也纳入术语“芳基”之内的为如下的其它杂环残基 :2- 或 3- 苯并 [b] 噻吩基、2- 或 3- 萘并 [2,3-b] 噻吩基、2- 或 3- 噻蒽基、2H- 吡喃 -3-(或 4- 或 5-) 基、1- 异苯并呋喃基、2H- 色烯基 -3- 基、2- 或 3- 二苯并氧硫杂环己二烯基、2- 或 3- 吡咯基、4- 或 3- 吡唑基、2- 吡嗪基、2- 嘧啶基、3- 哒嗪基、2- 吲嗪基、1- 异吲哚基、4H- 喹嗪 -2- 基、3- 异喹啉基、2- 喹啉基、1- 酞嗪基、1,8- 萘啶基、2- 喹喔啉基、2- 喹唑啉基、3- 噌啉基、2- 蝶啶基、4aH- 咔唑 -2- 基、2- 咔唑基、β - 咔啉 -3- 基、3- 菲啶基、2- 吖啶基、2- 萘嵌二氮杂苯基、1- 吩嗪基、3- 异噻唑基、2- 吩噻嗪基、3- 异噁唑基、2- 吩噁嗪基、3- 异色满基、7- 色满基、2- 吡咯啉 -3- 基、2- 咪唑烷基、2- 咪唑啉 -4- 基、2- 吡唑烷基、3- 吡唑啉 -3- 基、2- 哌啶基、2- 哌嗪基、1- 吲哚啉基、1- 异吲哚啉基、3- 吗啉基、苯并 [h] 异喹啉基和苯并 [b] 呋喃基,包括其位置异构体,除了不可将杂环部分通过它们的氮原子直接连接之外。芳基可被独立地选自下列的一个、两个或三个取代基取代或未经取代 :C1-6 烷基、卤代烷基、烷氧基、硫代烷氧基、氨基烷基氨基、二烷基氨基、羟基、卤代、巯基、硝基、甲醛基、羧基、烷氧羰酰和羧酰胺。

[3624] R1、R2、R3、R1'、R2' 和 R3' 各自独立地选自 C1-10 烷基或 (CH2)n 芳基,其指,例如,R1 可为苄基,而 R2 为甲基。换句话说,R1、R2、R3、R1'、R2' 或 R3' 为不相同的部分,尽管可能情况允许。

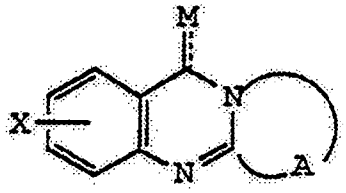
[3625] 式 I 化合物的“立体异构体”为用于单个分子的所有异构体 (仅它们的原子在空间中方向不同) 的一般术语。它包括镜像异构体 (对映异构体)、几何异构体 (顺式 / 反式)

和具有多于一个手性中心（彼此不为镜像）的化合物的异构体（非对映异构体），无论哪个形式都可应用于该化合物。

[3626] xvii）国际专利申请公开文本第 WO1993/03034 号

[3627] 本发明也包括下式的新化合物

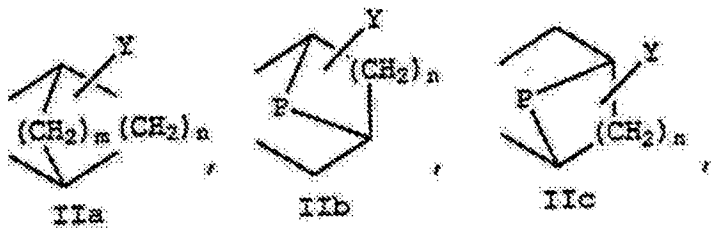
[3628]



I

[3629] 其中 A 表示

[3630]



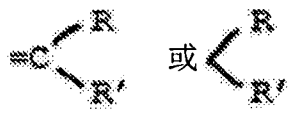
IIa IIb IIc

[3631] 

IId 或 IIe

[3632] 其中 n 为 1-10，P 为键或 (CH2)m，其中 m 为 0-10，其中氮、氧或硫原子可替代在环 A 中的亚甲基，该亚甲基未邻近喹唑啉部分，且连接环 A 中碳原子的为 Y，其中 Y 为氢、羟基、卤素、羧基、低级烷氧基、低级烷基、芳基、杂芳基、酮基、低级烷氧基羰基或低级烷酰基。

[3633] M 为＝ S、＝ NR，

[3634] 

或

[3635] 其中 R 和 R' 独立地为氢、羟基、低级烷基、低级烷氧基、低级烯基、低级炔基、芳基、芳氧基、芳基低级烷基、杂芳基或杂芳基低级烷基，并当连在一起时，可形成任选地含有选自氮、氧和硫的 1-3 个杂原子的 3- 至 6- 元环；且

[3636] X 为不存在或为选自下列的 1-4 个取代基：卤素、直链或支链饱和的烷基 (C1-22) 或烯基或炔基，如果适当尺寸的烷基可形成：饱和的或不饱和的、含有（或不含）一个或多个杂原子，例如 O、S、N、Se、P 等的环，或芳族的或杂芳族的环，其含有（或不含）一个或多个杂原子（例如 O、S、N、Se 等）、伯、仲或叔氨基硝基 - 低级烷硫基、或芳基（或杂芳基）硫基、巯基、羟基、羧基、低级烷氧基或芳基（或杂芳基）氧基、烷基 (C1-22) 或芳基（或杂芳基）亚磺酰基、烷基 (C1-22) 或芳基（或杂芳基）磺酰基、例如三氟甲基的全氟烷基 (C1-22)、

例如三氟甲氧基的全氟烷氧基 (C1-22)r、例如三氟甲基硫基的全氟烷基硫基 (C122)、例如三氟甲基亚磺酰基的全氟烷基亚磺酰基 (C122)、例如三氟甲基磺酰基的全氟烷基磺酰基 (C1-22)r、烷基 (C1-22) 或芳基 (或杂芳基) 氨基甲酰基,或二酰氨基,包括环酰亚胺基 (例如琥珀酰亚胺基)、烷基 (C1-22) 或芳基 (或杂芳基) 亚磺酰基酰氨基、烷基 (C122) 或芳基 (或杂芳基) 磺酰基酰氨基、例如三氟甲基亚磺酰基酰氨基的全氟烷基 (C1-22) 亚磺酰基酰氨基、例如上文三氟甲基磺酰基酰氨基的全氟烷基 (C1-22) 磺酰基酰氨基、例如三甲基硅烷基或三乙基硅烷基的三烷基硅烷基、例如乙酰基、苯甲酰基、苯乙酰基、氢化肉桂酰基等的酰基、例如三氟乙酰基、七氟丁酰基等的全氟酰基、例如乙酰基甲基、苯甲酰基甲基、苯乙酰基甲基、氢化肉桂酰基甲基等的酰基 - 低级烷基、例如三氟乙酰基甲基、七氟丁酰基甲基等的全氟酰基 - 低级烷基、烷基 (C1-22) 或芳基 (或杂芳基) 氨基甲酰氧基、二烷基 (C122) 或二芳基 (或二杂芳基) 氨基甲酰氧基、烷基 (C1-22) 或芳基 (或杂芳基) 氨基甲酰硫基、烷基 (C1-22) 或芳基 (或杂芳基) 氨基甲酰基烷基,或二酰氨基烷基,包括环酰亚胺基烷基,例如乙酰氨基甲基、辛酰氨基甲基或琥珀酰亚胺基甲基,芳基或芳基低级烷基 (包括被例如卤素和上文所述的基团的基团取代的芳基),杂芳基或杂芳基低级烷基,例如呋喃、噻吩、吡咯、吡啶等,包括被例如卤素和上文所述的基团的基团取代的衍生物 ;

[3637] Z 为氢、卤素、直链或支链、饱和的烷基 (C1-12)r 或烯基或炔基,如果适当尺寸的烷基可形成 :饱和的或不饱和的,含有或不含选自 O、S 和 N 的一个或多个杂原子的环,也可形成芳族或杂芳族的环,其含有或不含一个或多个杂原子 (选自 O、S 和 N)、伯、仲或叔氨基低级烷基硫基 -、芳基 -、杂芳硫基、巯基、羟基、羧基、烷氧羰基 (其中烷基为 C1-C22)、低级烷氧基、芳基或杂芳氧基、全氟烷基 (其中烷基为 C1-C22)、全氟烷氧基 (其中烷基部分为 C1-C22)、烷基 (C1-22)、芳基或杂芳基氨基甲酰基、二酰氨基、环酰亚胺基,或酰基,或其药学上可接受的酸加成盐 ;条件是当 A 为

[3638]



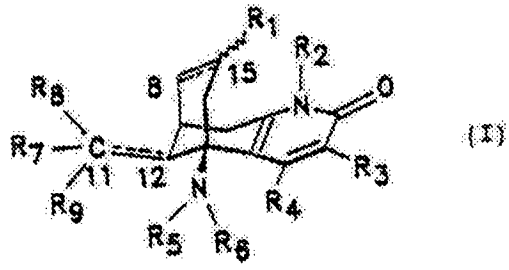
IIa

[3639] 其中 n 为 1-3,m 为 0,Y 为氢,且 M 为 RR',其中 R 和 R' 都为氢,X 不可不存在或不可是单个羟基或甲氧基 ;且当如果 A 为式 I Id 时,X 为 1,3- 二卤代或 2,4- 二卤代。

[3640] xviii) 国际专利申请公开文本第 WO1992/019238 号

[3641] 本发明提供了通式 (I) 的许多化合物,其形式上为石杉碱甲的衍生物 :

[3642]



(I)

[3643] 其中 R1 为 H、(C1-C8) 烷基或卤代；R2 为 H 或 (C1-C8) 烷基；R3 和 R4 独立地为 H、(C1-C8) 烷基、NO2、羟基或卤代；R5 和 R6 独立地为 H、(C1-C8) 烷基、芳基或芳烷基；R7 为 H、卤代或 (C1-C8) 烷基，R8 为卤代或 (C1-C8) 烷基，R9 为不存在或为 H；且 - 所示的键独立地为不存在或连同邻近的键一起，形成单元 C. dbd. C，条件是如果 - 所示的键都存在，那么 R3 和 R4 不可都为 H，除非 R7 或 R8 为卤代；及其药学上可接受的盐。

[3644] 因此，式 I 化合物的种类不包括石杉碱甲自身或其简单的 N- 烷基化的衍生物。优选的是，R1 为 H、卤代 (Cl、Br、I 或 F，最优选的是 F) 或甲基。优选的是 R2 为 H，优选的是 R3 为硝基或卤代，优选的是 R4 为 (C1-C4) 烷基或 OH，且优选的是 R5. dbd. R6. dbd. H。优选的是 R7 和 R9 为 H 且 R8 为 (C1-C4) 烷基。优选的是，- 所示的键中的至少一个为不存在。因此，优选的式 I 化合物为石杉碱甲的二氢或双（二 - 氢）类似物（其也可包含在吡啶酮环上的取代基），或为吡啶酮环 - 取代的石杉碱甲的类似物。

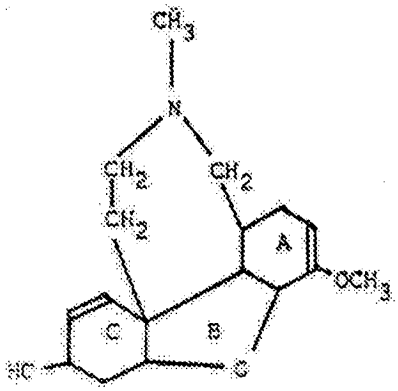
[3645] 通式 I 或 II 的化合物可以以旋光异构体的形式存在，且这些异构体，与外消旋的 (. +-.) 混合物都被纳入本发明之内。本发明也包括本发明化合物的 12R 和 12S 以及 15R 和 15S 的对映异构体，及其未拆分或部分拆分的混合物。术语“烷基”包括直链或支链烷基。术语“芳基”和“芳烷基”完全为上下文所定义的。在某些实施方案中，芳基包括苯基、甲苯基、二甲苯基、甲氧苯基等。在某些实施方案中，芳烷基包括芳氧基 - 和芳基 -(C1-C3) 烷基部分。

[3646] 将 C15-R1 键画成波浪形以表示 R1 取代基，当存在时可为平伏的的或直立的，或其组合。尽管为了方便，使 C11-C12 键处于平伏位置，但它可为平伏的、直立的或其组合。

[3647] xix) 欧洲专利申请第 EP0236684 号

[3648] 通常认为加兰他敏具有以下结构：

[3649]

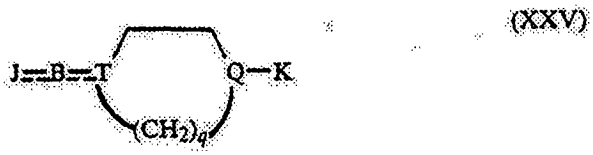


[3650] 类似结构的化合物（其中羟基被甲氧基、乙氧基、例如乙酰氧基的低级烷酰基氧基或氧基替代，甲氧基被氢、甲氧基、乙氧基、或例如乙酰氧基的低级烷酰氧基替代，且取代在氮原子上的甲基被例如下列的其它直链或支链低级烷基替代：乙基、环丙基甲基或环丁基甲基、烯丙基、低级烷基苯基或取代的低级烷基苯基，其中取代基是氟、氯、溴、低级烷氧基、羟基、硝基、氨基低级烷基或 1-5 个碳原子的酰氨基，杂芳基低级烷基，其中杂芳基为噻吩基、呋喃基、吡啶基、吡咯基或吡嗪基，或氰基残基；或未取代的和被卤素取代的苯甲酰基低级烷基，其中取代基在苯基上，和化合物（其中在“核”结构中的氢原子已被氟或氯替代，或在 B 和 C 环共用碳之间的碳 - 碳单键被双键替代）可能具有与加兰他敏相似的性质。

[3651] 和 xx) 美国专利 4,895,841

[3652] 本发明提供了具有下列式 (XXV) 的环胺化合物和其药理学上可接受的盐：

[3653]



(XXV)

[3654] 其中 J 为

[3655] (a) 取代的或未取代的基团，选自 (1) 苯基、(2) 吡啶基、(3) 吡嗪基、(4) 喹啉基、(5) 环己基、(6) 喹喔啉基和 (7) 呋喃基；

[3656] (b) 单价或二价基团，其中苯基可具有取代基，其选自 (1) 茚满基、(2) 茚满酮基、(3) 茚基、(4) 二氢茚酮基、(5) 茚满二酮基、(6) 萘满酮基、(7) 苯并环庚酮基、(8) 茚满醇基 (indanolyl) 和 (9)C6H5-CO-CH(CH3)-；

[3657] (c) 衍生自环酰胺化合物的单价基团；

[3658] (d) 低级烷基或

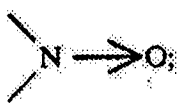
[3659] (e)R21-CH.dbd.CH- 基团，其中 R21 为氢或低级烷氧羰基 (dbd 代表双键)；

[3660] B 为 -(CHR22)r-、-CO-(CHR22)r-、-NR4-(CHR22)r-，R4 为氢、低级烷基、酰基、低级烷基磺酰基、苯基、取代的苯基、苄基或取代的苄基、-CO-NR5-(CHR22)r-，R5 为氢、级烷基或苯基、-CH.dbd.CH-(CHR22)r-、-OCOO-(CHR22)r-、-OOC-NH-(CHR22)r-、-NH-CO-(CHR22)r-、-CH2-CO-NH-(CHR22)r-、-(CH2)2-NH-(CHR22)r-、-CH(OH)-(CHR22)r-，r 为 0 或 1 至 10 的整数，R22 为氢或甲基，以便一个亚烷基可没有甲基支链或具有一个或多个甲基支链，.dbd.(CH-CH.dbd.CH)b-，b 为 1-3 的整数，.dbd.CH-(CH2)c-，c 为 0 或 1 至 9 的整数，.dbd.(CH-CH)d.dbd.，d 为 0 或 1-5 的整数；-CO-CH.dbd.CH-CH2-、-CO-CH2-CH(OH)-CH2-、-CH(CH3)-CO-NH-CH2-、-CH.dbd.CH-CO-NH-(CH2)2-、-NH-、-O-、-S-、二烷基氨基烷基羰基或低级烷氧羰基；

[3661] T 为氮或碳；

[3662] Q 为氮、碳或

[3663]



[3664] 且

[3665] q 为 1-3 的整数；

[3666] K 为氢、苯基、取代的苯基、芳基烷基，其中苯基可具有取代基，肉桂基、低级烷基、吡啶基甲基、环烷基烷基、金刚烷甲基、呋喃基甲基、环烷基、低级烷氧羰基或酰基；且 ═ 表示单键或双键。

[3667] 在具有式 (XXV) 的化合物中，优选的是 J 为 (a) 或 (b)。在定义 (b) 中，(2)、(3) 和 (5) 的单价基团及 (2) 的二价基团为优选的。在 B 的定义中，-(CHR22)r-、.dbd.(CH-CH.dbd.CH)b-、.dbd.CH-(CH2)c- 和 .dbd.(CH-CH)d.dbd. 为优选的。(B) 的这些优选的基团可与 J 的 (b)，具体的是 (b) 的 (2) 连接。

[3668] 在式 (XXV) 中优选的是 Q 为氮，T 为碳和 q 为 1 或 3；且 Q 为碳，T 为氮和 q 为 2。

最优选的是 Q 为氮，T 为碳且 q 为 2。

[3669] 优选的是，K 为苯基烷基或在苯基上具有取代基的苯基烷基。

[3670] 本发明优选的化合物包括：

[3671] 1- 苄基 -4-((5,6- 二甲氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

[3672] 1- 苄基 -4-((5,6- 二甲氧基 -1- 茚满酮)-2- 基茚基) 甲基哌啶、

[3673] 1- 苄基 -4-((5- 甲氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

[3674] 1- 苄基 -4-((5,6- 二乙氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

[3675] 1- 苄基 -4-((5,6- 亚甲二氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

[3676] 1-(间 - 硝基苄基)-4-((5,6- 二甲氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

[3677] 1- 环己基甲基 1-4-((5,6- 二甲氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

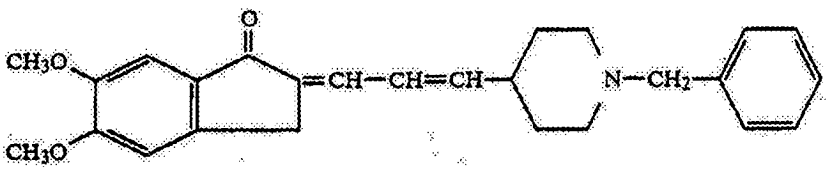
[3678] 1-(间 - 氟苄基)-4-((5,6- 二甲氧基 -1- 茚满酮)-2- 基) 甲基哌啶、

[3679] 1- 苄基 -4-((5,6- 二甲氧基 -1- 茚满酮)-2- 基) 丙基哌啶、

[3680] 1- 苄基 -4-((5- 异丙氧基 -6- 甲氧基 -1- 茚满酮)-2- 基) 甲基哌啶和

[3681] 1- 苄基 -4-((5,6- 二甲氧基 -1- 氧代茚满酮)-2- 基) 丙烯基哌啶，具有下列所示的式的化合物。

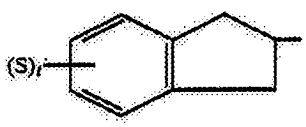
[3682]



[3683] 此外，本发明提供了包含药理学有效量的具有式 (XXV) 的环胺化合物或其药理学上可接受的盐和药理学上可接受的载体的治疗组合物，以及通过向人患者施用具有式 (XXV) 的环胺化合物或其药理学上可接受的盐，用于预防和治疗归因于乙酰胆碱酯酶活性的疾病的方法。

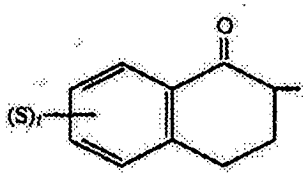
[3684] 优选的化合物具有上文所示的通式，其中 J 为 (b)。基团 (b) 包括分别具有下列所示通式的 10 个基团。S 为氢或例如具有 1-6 个碳原子的低级烷基和具有 1-6 个碳原子的低级烷氧基的取代基。在该取代基之中，甲氧基为最优选的。t 为 1-4 的整数。最优选的苯基是在其上具有 1-3 个甲氧基。(S)t 可在苯基的两个邻近的碳原子上形成亚甲二氧基或亚乙二氧基。

[3685]



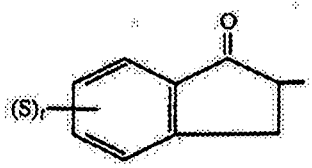
[3686] 茚满基

[3687]



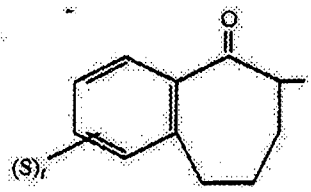
[3688] 四氢萘酮基

[3689]



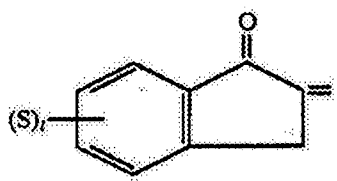
[3690] 茚满酮基

[3691]



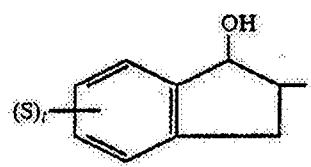
[3692] 苯并环庚酮基

[3693]



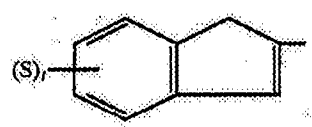
[3694] 亚茚满酮基

[3695]



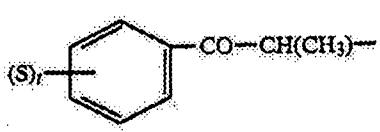
[3696] 茚满醇基

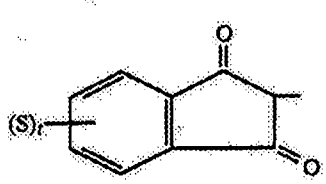
[3697]



[3698] 茚基

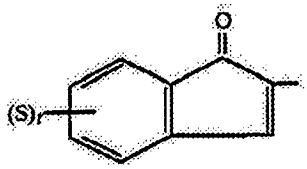
[3699]





[3700] 茚满二酮基

[3701]



[3702] 茚酮基

[3703] B优选的定义包括，-(CHR22)r-、-CO-(CHR22)r-、.dbd.(CH-CH.dbd.CH)b-、.dbd.CH-(CH2)c-和.dbd.(CH-CH)d.dbd.。-(CHR22)r-基团，其中R22为氢且r为1-3的整数，且.dbd.CH-(CH2)c-基团为最优选的。

[3704] 在本发明上文定义的环胺化合物中，优选的是在式中的J为(b)单价或二价基团。在定义(b)中，茚满酮基、茚满二酮基和茚基为最优选的，任选地在苯基上具有取代基。

[3705] 在定义B中，-(CHR22)r-和.dbd.CH-(CH2)c-为优选的。

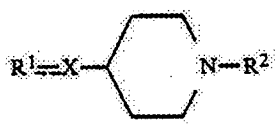
[3706] 在包含T和Q的环中，该环可为5-、6-或7-元环。优选的是Q为氮，T为碳或氮且n为2；Q为氮，T为碳且n为1或3；且Q为碳，T为氮且n为2。

[3707] 在定义K中，苯基、芳基烷基和肉桂基为优选的，任选的是在苯基上具有取代基。

[3708] 将从落入上文所定义的环胺化合物范围内的哌啶化合物的角度对本发明进行详细解释。该解释适用于整个发明的环胺化合物。

[3709] 由式(I)定义哌啶化合物：

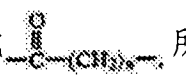
[3710]



(I)

[3711] 其中R1为下列取代的或未取代的基团：.环.1苯基、.环.2吡啶基、.环.3吡嗪基、.环.4喹啉基、.环.5茚满基、.环.6环己基、.环.7喹喔啉基，或11.环.8呋喃基；衍生自茚满酮的具有未取代的或取代的苯环的单价或二价基团；衍生自环酰胺化合物的单价基团；低级烷基或式R3-CH.dbd.C-(其中R3为氢原子或低级烷氧羰基)所示的基团，

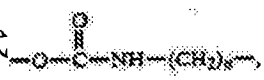
[3712] X为由式-(CH2)n-所示的基团，

[3713] 式  所示的基团，

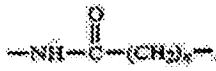
[3714] 式  所示的基团(其中R4为氢原子、低级烷基、酰基、低级烷基磺酰基或取代的或未取代的苯基或苄基)，

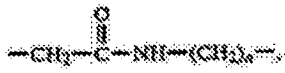
[3715] 式  所示的基团(其中R5为氢原子、低级烷基或苯基)，式-CH.dbd.CH-(CH2)n-所示的基团，

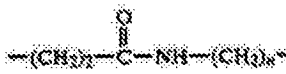
[3716] 式  所示的基团，

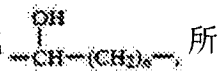
[3717] 式  所示的基团，

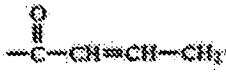
[3718] 式 -CH = CH-CH = CO-，所示的基团，

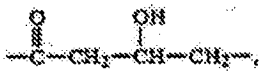
[3719] 式  所示的基团，

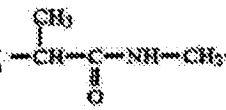
[3720] 式  所示的基团，

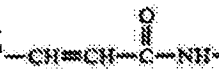
[3721] 式  所示的基团，

[3722] 式  所示的基团，

[3723] 式  所示的基团，

[3724] 式  所示的基团，

[3725] 式  所示的基团，

[3726] 式  所示的基团，

[3727] 二烷基氨基烷基羰基或低级烷氧羰基，

[3728] 条件是在上文 X 的定义中的 n 各自独立地为 0 至 6 的整数，

[3729] R2 为取代的或未取代的苯基、取代的或未取代的芳基烷基、肉桂基、低级烷基、吡啶基甲基、环烷基烷基、金刚烷甲基或糠酰甲基，且在上文通式中的符号 ═══ 指单键或双键。

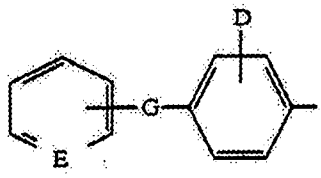
[3730] 用于上文关于本发明的化合物 (I) 的 R1、R2、R4 和 R5 的定义的术语“低级烷基”旨在指具有 1-6 个碳原子的直链或支链的烷基，且其实例包括甲基、乙基、丙基、异丙基、丁基、异丁基、仲 - 丁基、叔 - 丁基、戊基 (pentyl)(戊基 (amyl))、异戊基、新戊基、叔 - 戊基、1- 甲基丁基、2- 甲基丁基、1,2- 二甲基丙基、己基、异己基、1- 甲基戊基、2- 甲基戊基、3- 甲基戊基、1,1- 二甲基丁基、1,2- 二甲基丁基、2,2- 二甲基丁基、1,3- 二甲基丁基、2,3- 二甲基丁基、3,3- 二甲基丁基、1- 乙基丁基、2- 乙基丁基、1,1,2- 三甲基丙基、1,2,2- 三甲基丙基、1- 乙基 -1- 甲基丙基和 1- 乙基 -2- 甲基丙基。在它们之中，甲基、乙基、丙基、异丙基等为优选的。甲基为最优选的。

[3731] 涉及在 R1 的定义中表达“下列取代的或未取代的基团：(1) 苯基、(2) 吡啶基、(3) 吡嗪基、(4) 喹啉基、(5) 茚满基、(6) 环己基、(7) 喹喔啉基或 (8) 呋喃基”的取代基的实例包括，具有 1-6 个碳原子的低级烷基，例如甲基、乙基、正 - 丙基、异丙基、正 - 丁基、异丁基和叔 - 丁基；与上述低级烷基相应的低级烷氧基，例如甲氧基和乙氧基；硝基；例如氯、溴、氟的卤素原子；羧基；与上述低级烷氧基相应的低级烷氧羰基，例如甲氧羰基、乙氧羰基、异丙氧基羰基、正 - 丙氧羰基和正 - 丁氧羰基；氨基；低级单烷基氨基；低级二烷基氨基、氨基甲酰基；衍生自具有 1-6 个碳原子的脂族饱和一元羧酸的酰氨基，例如乙酰氨基、丙酰氨基、丁酰氨基、异丁酰氨基、戊酰氨基和特戊酰氨基；例如环己氧基羰基的环烷氧基羰基；例如甲氨基羰基和乙基氨基羰基的低级烷氨基羰基；与上文所定义的低级烷基相应的低级

烷基羰基氧基，例如甲基羰基氧基、乙基羰基氧基和正－丙基羰基氧基；包括三氟甲基的卤代低级烷基；羟基；甲酰基；和例如乙氧基甲基、甲氧基甲基和甲氧基乙基的低级烷氧基低级烷基。在取代基的上述描述中的“低级烷基”和“低级烷氧基”包括衍生自上文提及的基团的所有基团。该取代基可为它们的 1-3 个，其可相同或不同。

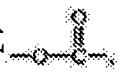
[3732] 而且，当取代基为苯基时，下列基团在取代的苯基的范围内：

[3733]

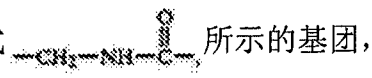


[3734] 其中 G 为

[3735] 式  所示的基团，

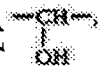
[3736] 式  所示的基团，

[3737] 式 -O- 所示的基团，

[3738] 式  所示的基团，

[3739] 式 -CH2-O- 所示的基团，

[3740] 式 -CH2-SO2- 所示的基团，

[3741] 式  所示的基团，和

[3742] 式  所示的基团，

[3743] 且 E 为碳或氮原子。

[3744] 在它们之中用于苯基的取代基优选的实例包括低级烷基、低级烷氧基、硝基、卤代低级烷基、低级烷氧羰基、甲酰基、羟基和低级烷氧基低级烷基、卤素原子和苯甲酰基和苄基磺酰基。取代基可为它们中的 2 或更多个，其可相同或不同。

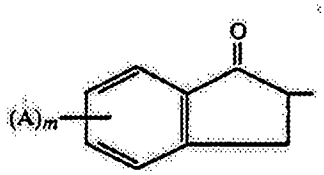
[3745] 用于吡啶基的取代基优选的实例包括低级烷基和氨基及卤素原子。

[3746] 用于吡嗪基的取代基的优选的实例包括低级烷氧羰基、羧基、酰氨基、氨基甲酰基和环烷氧基羰基。

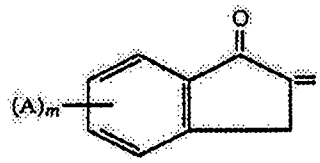
[3747] 关于 R1，吡啶基优选为 2- 吡啶基、3- 吡啶基或 4- 吡啶基；吡嗪基优选为 2- 吡嗪基；喹啉基优选为 2- 喹啉基或 3- 喹啉基；喹喔啉基优选为 2- 喹喔啉基或 3- 喹喔啉基；且呋喃基优选为 2- 呋喃基。

[3748] 具有未取代的或取代的苯基环、衍生自茚满酮的、优选的单价或二价基团的具体的实例包括下列式 (II) 和 (III) 所示的那些：

[3749]



(II)



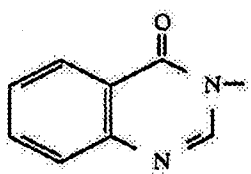
(III)

[3750] 其中 m 各自为 1-4 的整数，且可为相同或不同的 A 为在 R1 定义的上文条目 (1) 至 (8) 中所述的取代基的每一个或氢原子，优选的是氢原子（即未取代的）、低级烷基或低级烷氧基，且最优选的是茚满酮为未取代的或经 1-3 个甲氧基取代。

[3751] 衍生自环酰胺化合物的单价基团的实例包括喹唑啉酮、四氢异喹啉酮、四氢苯并二氮杂䓬酮和六氢苯并氮杂环辛酮。但是，单价基团可为在其结构中具有环酰胺基团的任何一个并不仅限于上述具体实例。环酰胺基团可为衍生自单环或稠合杂环的基团。该稠合的杂环优选地为与苯环稠合形成的环。在这种情况下，苯环可经具有 1-6 个碳原子的低级烷基（优选为甲基）或具有 1-6 个碳原子的低级烷氧基（优选为甲氧基）取代。

[3752] 单价基团的优选实例包括下列基团：

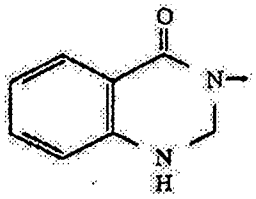
[3753]



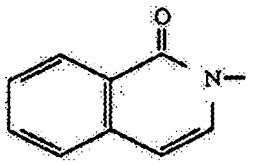
(a)

[3754]

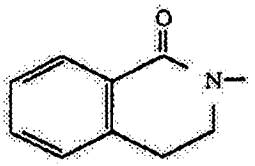
(b)



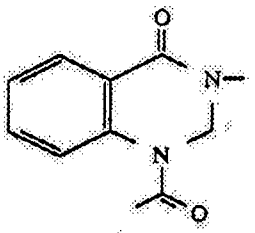
(c)



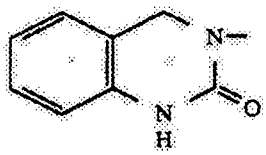
(d)



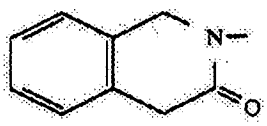
(e)



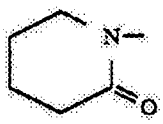
(f)

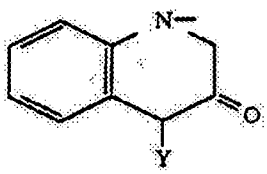


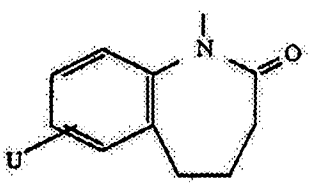
(g)



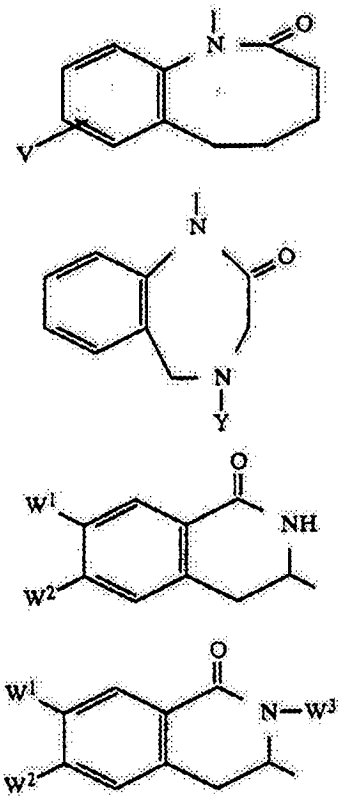
(h)







[3755]



[3756] 在上式中，在式 (i) 和 (l) 中的 Y 各自为氢原子或低级烷基，在式 (k) 中的 V 为氢原子或低级烷氧基，在式 (m) 和 (n) 中的 W1 和 W2 各自为氢原子、低级烷基或低级烷氧基，且 W3 为氢原子或低级烷基。

[3757] 在每个式 (j) 和 (l) 中的右侧环为 7- 元环，然而在式 (k) 中的右侧的环为 8- 元环。

[3758] 上文所定义的 R1 的某些实例包括衍生自具有未取代的或取代的苯基的茚满酮的单价基团和衍生自环酰胺化合物的单价基团。

[3759] 上文所定义的 X 的某些实例包括式 -(CH2)n- 所示的基团，具有酰胺基的基团和通过上式所示的基团，其中 n 为 2。因此，最优选的是式

[3760] R═══X— 所示基团的任何部分，其具有羰基或酰氨基。

[3761] 在上文 R2 的定义中涉及表达“取代的或未取代的苯基”和“取代的或未取代的芳基烷基”的取代基与 R1 的上述定义中的上述条目 (1) 至 (8) 中所述的那些相同。

[3762] 术语“芳基烷基”旨在指未取代的苄基或苯乙基等。

[3763] 吡啶基甲基的具体的实例包括 2- 吡啶基甲基、3- 吡啶基甲基和 4- 吡啶甲基。

[3764] R2 优选的实例包括苄基和苯乙基。符号═══ 指单或双键。该键仅当 R1 为具有未取代的或取代的苯环、衍生自茚满酮的上述二价基团 (III) 时为双键，而在其它情况下为单键。

[3765] 取代基的种类，本发明的化合物可具有不对称的碳原子，并因此具有立体异构体。它们当然在本发明的范围之内。

[3766] 现在描述其一个具体的实施例。当 R1 具有茚满酮骨架时，本发明化合物具有不对称的碳原子，并因此可具有立体异构体、旋光异构体、非对映异构体等。所有这些异构体都在本发明的范围内。

[3767] 用施用 SV2A 抑制剂和 AChEI 或其药学上可接受的盐治疗与 CNS 障碍相关的认知缺损的方法

[3768] 在一个方面，本发明通过在有需要的受试者中组合施用 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物或多晶型物与 AChEI 或其药学上可接受的盐、水合物、溶剂合物或多晶型物，提供了用于在受试者中治疗或改善认知功能的方法和组合物，所述受试者患有与 CNS 障碍相关的认知缺损（例如，与年龄相关的认知缺损、MCI、遗忘性 MCI、痴呆、AD、前驱 AD、PTSD、精神分裂症、双相情感障碍、ALS、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病 (PD)、孤独症、强迫行为和物质成瘾），或处于患有所述障碍风险中。在一些实施方案中，该 SV2A 抑制剂选自左乙拉西坦、塞曲西坦和布立西坦或其衍生物或类似物或药学上可接受的盐、或溶剂合物、或水合物、或多晶型物、或前药。在其它实施方案中，该 SV2A 抑制剂是左乙拉西坦或其衍生物或类似物或药学上可接受的盐、或溶剂合物、或水合物、或多晶型物、或前药。在一些实施方案中，该 AChEI 是多奈哌齐、他克林、利凡斯的明、毒扁豆碱、加兰他敏、或美曲膦酯或其衍生物或类似物或药学上可接受的盐、或溶剂合物、或水合物、或多晶型物、或前药。在其它实施方案中，该 AChEI 是多奈哌齐或其衍生物或类似物或药学上可接受的盐或溶剂合物、或水合物、或多晶型物、或前药。在一些实施方案中，该与 CNS 障碍相关的认知缺损是与年龄相关的认知缺损，例如轻度认知缺损 (MCI)、与年龄相关的记忆缺损 (AAMI)、与年龄相关的认知减退 (ARCD)。在本发明的一个实施方案中，该 MCI 是遗忘性 MCI。在本发明的一些实施方案中，该 CNS 障碍是痴呆、创伤后应激障碍 (PTSD)、精神分裂症、双相情感障碍、肌萎缩性侧索硬化 (ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病 (PD)、孤独症、强迫行为和物质成瘾。在一个实施方案中，患有这类认知缺损的受试者是人患者。该受试者可是人或例如非人灵长类、或啮齿类（例如，大鼠）的其它哺乳动物。在一些实施方案中，该受试者是人患者。

[3769] 当在临床上使用时，多奈哌齐显示出“胆碱能”副作用特征，且施用于患者的剂量受到这类副作用的限制。该 SV2A 抑制剂及其药学上可接受的盐、水合物、溶剂合物和多晶型物与多奈哌齐或其它 AChEI 和它们的药学上可接受的盐、水合物、溶剂合物和多晶型物组合使用减少了治疗涉及认知功能障碍和其它情感障碍的 CNS 障碍（包括 MCI、遗忘性 MCI、AAMI、ARCE、痴呆、AD、PTSD、精神分裂症、双相情感障碍、肌萎缩性侧索硬化 (ALS)、与癌症治疗相关的认知缺损、精神发育迟滞、帕金森病 (PD)、孤独症、强迫行为和物质成瘾）所需的多奈哌齐或其它 AChEI 的量。在一个实施方案中，患有这类认知缺损的受试者是人患者，并因此减少了由多奈哌齐或其它 AChEI 引起的副作用而不降低功效。而且，该 SV2A 抑制剂和多奈哌齐或其它 AChEI 及其药学上可接受的盐、溶剂合物、水合物和多晶型物的组合的功效超过任一药物以其最佳剂量单独施用的功效，并因此是用于与 CNS 障碍相关的认知缺损的改良治疗。

[3770] 可以理解，用于本发明的组合物和方法的化合物和活性剂当在外周施用时优选应易于穿透血脑屏障。但是，不能穿透血脑屏障的化合物，仍然可有效地直接施用于中枢神经系统中，例如，通过心室内或其它神经相容的途径 (neuro-compatible route)。

[3771] 依照本发明，可将该 SV2A 抑制剂和该 AChEI 及其药学上可接受的盐、溶剂合物、水合物、多晶型物经任何适合的途径施用于受试者。在一些实施方案中，将该药物口服施用；但是，也考虑了静脉内、皮下、动脉内、肌内、脊柱内、直肠、胸腔内、腹膜内、脑室内，或经皮、

局部，或通过吸入施用。该活性剂可口服施用，例如，以通过本领域公认的程序制备的片剂、锭剂、胶囊、酏剂、混悬剂、糖浆剂、糯米纸囊剂 (wafers) 等的形式。在一些实施方案中，可将该 SV2A 抑制剂和该 AChEI，及其药学上可接受的盐、溶剂合物、水合物、多晶型物，经不同的途径施用于受试者。例如，将该 SV2A 抑制剂或其盐、溶剂合物、水合物、或多晶型物静脉内施用，而将该 AChEI 或其盐、溶剂合物、水合物、或多晶型物口服施用。

[3772] 在一些实施方案中，所述施用是缓慢释放或缓释。术语“缓释”为药物科学领域公认，并被本文用于意指在延长的时期（自始至终或在该期间），例如大于或等于 1 小时内，活性化合物或活性剂从剂型至环境的控制释放。缓释剂型将以基本上恒定的速率在延长的时期内释放药物，或将基本上恒定量的药物在延长的时期内递增地释放。本文使用的术语“缓释”包括术语“控制释放”、“延长释放”、“持续释放”、“延迟释放”或“缓慢释放”，因为这些术语会用于药物科学。在一些实施方案中，所述缓释剂量以贴剂或泵的形式施用。本文所用的术语“缓释形式”意指包含一种或多种活性成分的剂型，其中在放入水或其它生物流体或溶剂中时，活性成分的至少一种的释放可以在延长期限内出现，例如至少约 1 天、至少约 2 天、至少约 3 天、至少约 4 天、至少约 5 天、至少约 10 天、至少约 20 天、至少约 30 天、至少约 60 天、至少约 90 天或至少约 150 天的期限。

[3773] 本文所用的“立即释放制剂”意指在本领域已知的 USP 溶出方法或由商品制造商中提供的方法中活性药物成分在 1 小时以内释放 80％以上的制剂。典型地，活性成分在立即释放制剂中的释放在小于 30 分钟内大于 80％。

[3774] 在本发明的一些实施方案中，所述 SV2A 抑制剂是缓释形式，且所述 AChEI 不是缓释形式。在一些实施方案中，所述 AChEI 是立即释放形式。

[3775] 当将固体载体用于施用时，该制剂可以是片剂，以粉剂或丸粒的形式置于硬胶囊中，或它可以是锭剂或糖锭的形式。如果使用液体载体，那么该制剂可以是糖浆剂、乳剂、软胶囊、或例如水性或非水性液体悬浮液或溶液的无菌注射液。

[3776] 根据本发明方法的活性剂和组合物的剂量安排将会根据所选的具体化合物或组合物、施用途径、待治疗的病症的本质、患者的年龄和状况、疗程或治疗阶段而变化，并且最终将由主治医师裁定。应当理解，施用的所述 SV2A 抑制剂和所述 AChEI 和它们的药学上可接受的盐、其水合物、溶剂合物及多晶型物的量将是有效产生所需的生物学作用的量，例如有益的结果，包括临床结果（例如，增加 GABA 能活性、减少兴奋性神经传递，以及阻断、抑制或减少乙酰胆碱酯酶活性的量，和 / 或引起认知功能改善的组合量）。应当理解，可将有效量以多于一个剂量并在疗程内施用。

[3777] 施用所述 SV2A 抑制剂和所述 AChEI 和它们的药学上可接受的盐、其水合物、溶剂合物及多晶型物所需的持续时间可通过本领域的技术人员常规试验来确定。例如，可将所述 SV2A 抑制剂和所述 AChEI 和它们的药学上可接受的盐、其水合物、溶剂合物及多晶型物施用持续 1-4 周、1-3 个月、3-6 个月、6-12 个月、1-2 年、或更久，至多患者一生的时期。

[3778] 本领域已知的是，规范化体表面积是用于推断物种间剂量的适当方法。用于该剂量的人等效剂量 (HED) 可使用说明体表面积差异的下列公式来估计（参见 Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers，2002 年 12 月，Center for Biologics Evaluation and Research）：

[3779] HED ＝动物剂量 ×(Km 动物 /Km 人）

[3780] 其中 Km 因子是体重除以体表面积 (Km 大鼠已确定为 6，且 Km 人为 37；参见 Reagan-Saw，Nihal，Ahmad，2007)。因此，大鼠 10mg/kg 的剂量与人 1.6mg/kg 等价 (10mg/kg×(6/37) = 1.6mg/kg)。对于人受试者，为了从以 mg/kg 计的剂量计算出以 mg 计的剂量，将以 mg/kg 计的剂量乘以 70kg 典型的成人体重。

[3781] 在本发明的一些实施方案中，例如，所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以根据美国专利申请 12/580,464、国际专利申请 PCT/US2009/005647、美国专利申请 61/105,847、美国专利申请 61/152,631 和美国专利申请 61/175,536 的剂量施用。在本发明的一些实施方案中，所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物和多晶型物或前药以约 0.001mg/kg-5mg/kg 的每日剂量施用。在一些实施方案中，所述 SV2A 抑制剂或或其药学上可接受的盐、水合物、溶剂合物和多晶型物或前药以约 0.1-5mg/kg 或约 1-2mg/kg 或约 0.1-0.2mg/kg 或约 0.01-2.5mg/kg 或约 0.1-2.5mg/kg 或约 0.4-2.5mg/kg 或约 0.6-1.8mg/kg 或约 0.04-2.5mg/kg 或约 0.06-1.8mg/kg 或约 0.01-1mg/kg 或约 0.001-1mg/kg 或约 0.5-5mg/kg 或约 0.05-0.5mg/kg 的每日剂量施用。对于在若干天或周或更长时间内的重复施用，要根据所针对病症，将该治疗持续直到获得足够水平的认知功能。

[3782] 在本发明的一些实施方案中，例如，所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以根据例如美国专利申请 12/580,464、国际专利申请 PCT/US2009/005647，美国专利申请 61/105,847、美国专利申请 61/152,631、美国专利申请 61/175,536 和美国专利申请 61/441,251 中的剂量施用。在本发明的一些实施方案中，所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以约 0.001-5mg/kg、约 0.001-0.5mg/kg、约 0.01-0.5mg/kg、约 0.1-5mg/kg 或约 1-2mg/kg 或约 2-4mg/kg 或约 2-3mg/kg 或约 3-4mg/kg 或约 0.2-0.4mg/kg 或约 0.2-0.3mg/kg 或约 0.3-0.4mg/kg 或约 0.1-0.2mg/kg 或约 0.01-2.5mg/kg 或约 0.1-2.5mg/kg 或约 0.4-2.5mg/kg 或约 0.6-1.8mg/kg 或约 0.5-2mg/kg 或约 0.8-1.6 或约 0.8-3.6 或约 0.5-4mg/kg 或约 0.04-2.5mg/kg 或约 0.06-1.8mg/kg 或约 0.05-3mg/kg 或约 0.08- 约 1.6mg/kg 或约 0.08-3.6 或约 0.05-2mg/kg 或约 0.01-1mg/kg 或约 0.001-1mg/kg 或约 0.5-5mg/kg 或约 0.05-0.5mg/kg 或约 0.8mg/kg 或约 1.6mg/kg 或约 3.6mg/kg 或约 0.08mg/kg 或约 0.16mg/kg 或约 0.36mg/kg 的每日剂量施用。还可以使用其它高于、中间或小于这些剂量的剂量并且可以由本领域技术人员根据本发明的方法确定。对于在若干天或周或更长时间内的重复施用，要根据所针对病症，将该治疗持续直到获得足够水平的认知功能。

[3783] 在本发明的一些实施方案中，所述 SV2A 抑制剂的剂量为 0.001-5mg/kg/ 天 (给予 70kg 的典型人体受试者约为 0.07-350mg/ 天)。可以使用的剂量包括、但不限于 0.001mg/kg/ 天、0.0015mg/kg/ 天、0.002mg/kg/ 天、0.005mg/kg/ 天、0.0075mg/kg/ 天、0.01mg/kg/ 天、0.015mg/kg/ 天、0.02mg/kg/ 天、0.03mg/kg/ 天、0.04mg/kg/ 天、0.05mg/kg/ 天、0.1mg/kg/ 天、0.2mg/kg/ 天、0.3mg/kg/ 天、0.4mg/kg/ 天、0.5mg/kg/ 天、0.75mg/kg/ 天、1.0mg/kg/ 天、1.5mg/kg/ 天、2.0mg/kg/ 天、2.5mg/kg/ 天、3.0mg/kg/ 天、4.0mg/kg/ 天或 5.0mg/kg/ 天。在一些实施方案中，所述 SV2A 抑制剂的剂量为 0.001-0.5mg/kg/ 天 (给予 70kg 的典型人体受试者约为 0.07-35mg/ 天) 或 0.01-0.5mg/kg/ 天 (其为约 0.7-35mg/ 天)。还可以使用其它高于、中间或小于这些剂量的剂量并且可以由本领域技术人员根据本发明的

方法确定。

[3784] 在本发明的一些实施方案中，所述 SV2A 抑制剂的剂量为 0.1-5mg/kg/ 天（给予 70kg 的典型人体受试者为 7-350mg/ 天）。可以使用的剂量包括、但不限于 0.1mg/kg/ 天、0.5mg/kg/ 天、1mg/kg/ 天、1.5mg/kg/ 天、2mg/kg/ 天、2.5mg/kg/ 天、3mg/kg/ 天、4mg/kg/ 天或 5mg/kg/ 天。在一些实施方案中，所述剂量为 1-2mg/kg/ 天（给予 70kg 的典型人体受试者为 70-140mg/ 天）。在本发明的其它实施方案中，所述 SV2A 抑制剂的剂量为 0.1-0.2mg/kg/ 天。还可以使用其它高于、中间或小于这些剂量的剂量并且可以由本领域技术人员根据本发明的方法确定。

[3785] 在本发明的一些实施方案中，所述 SV2A 抑制剂的剂量为 0.01-2.5mg/kg/ 天（给予 70kg 的典型人体受试者约为 0.7-180mg/ 天）。可以使用的剂量包括、但不限于 0.01mg/kg/ 天、0.02mg/kg/ 天、0.03mg/kg/ 天、0.04mg/kg/ 天、0.06mg/kg/ 天、0.08mg/kg/ 天、0.12mg/kg/ 天、0.14mg/kg/ 天、0.16mg/kg/ 天、0.18mg/kg/ 天、0.2mg/kg/ 天、0.4mg/kg/ 天、0.6mg/kg/ 天、0.8mg/kg/ 天、1.0mg/kg/ 天、1.2mg/kg/ 天、1.4mg/kg/ 天、1.6mg/kg/ 天、1.8mg/kg/ 天、2.0mg/kg/ 天、2.2mg/kg/ 天、2.4mg/kg/ 天或 2.5mg/kg/ 天。在一些实施方案中，所述 SV2A 抑制剂的剂量为 0.1-2.5mg/kg/ 天（给予 70kg 的典型人体受试者约为 7-180mg/ 天）、0.1-0.2mg/kg/ 天（约 7-15mg/ 天）、0.2-0.4mg/kg/ 天（约 14-30mg/ 天）、0.4-2.5mg/kg/ 天（约 25-180mg/ 天）、0.6-1.8mg/kg/ 天（约 40-130mg/ 天）、0.04-2.5mg/kg/ 天（约 2.5-180mg/ 天）或 0.06-1.8mg/kg/ 天（约 4-130mg/ 天）。在本发明的一些实施方案中，所述 SV2A 抑制剂的剂量为 40-130mg、140-300mg、200-300mg 或 140-200mg。还可以使用其它高于、中间或小于这些剂量的剂量并且可以由本领域技术人员根据本发明的方法确定。

[3786] 在本发明的一些实施方案中，所述 SV2A 抑制剂的剂量为 0.0015-7mg/kg/ 天（给予 70kg 的典型人体受试者约 0.1-500mg/ 天）。可以使用的每日剂量包括、但不限于 0.0015mg/kg、0.002mg/kg、0.0025mg/kg、0.005mg/kg、0.01mg/kg、0.02mg/kg、0.03mg/kg、0.04mg/kg、0.05mg/kg、0.06mg/kg、0.07mg/kg、0.08mg/kg、0.09mg/kg、0.1mg/kg、0.2mg/kg、0.3mg/kg、0.4mg/kg、0.5mg/kg、0.6mg/kg、0.7mg/kg、0.8mg/kg、0.9mg/kg、1mg/kg、1.2mg/kg、1.4mg/kg、1.5mg/kg、1.6mg/kg、1.8mg/kg、2.0mg/kg、2.2mg/kg、2.4mg/kg、2.5mg/kg、2.6mg/kg、2.8mg/kg、3.0mg/kg、3.5mg/kg、4.0mg/kg、4.5mg/kg、5.0mg/kg、6.0mg/kg 或 7.0mg/kg；或 0.1mg、0.15mg、0.18mg、0.35mg、0.7mg、1.5mg、2.0mg、2.5mg、2.8mg、3.0mg、3.5mg、4.2mg、5mg、5.5mg、6.0mg、7mg、8mg、9mg、10mg、12mg、15mg、20mg、25mg、28mg、30mg、35mg、40mg、45mg、50mg、55mg、60mg、70mg、75mg、80mg、85mg、90mg、95mg、100mg、110mg、120mg、125mg、140mg、150mg、170mg、175mg、180mg、190mg、200mg、210mg、225mg、250mg、280mg、300mg、350mg、400mg 或 500mg。在一些实施方案中，可以用于本发明方法的 SV2A 抑制剂的每日剂量包括、但不限于 0.0015-5mg/kg（或对于 70kg 的受试者 0.1-350mg）、0.01-0.8mg/kg、0.01-1mg/kg、0.01-1.5mg/kg、0.01-2mg/kg、0.01-2.5mg/kg、0.01-3mg/kg、0.01-3.5mg/kg、0.01-4mg/kg、0.01-5mg/kg、0.025-0.8mg/kg、0.025-1mg/kg、0.025-1.5mg/kg、0.025-2mg/kg、0.025-2.5mg/kg、0.025-3mg/kg、0.025-3.5mg/kg、0.025-4mg/kg、0.05-0.8mg/kg、0.05-1mg/kg、0.05-1.5mg/kg、0.05-2mg/kg、0.05-2.5mg/kg、0.05-3mg/kg、0.05-3.5mg/kg、0.05-4mg/kg、0.075-0.8mg/kg、0.075-1mg/kg、

0.075-1.5mg/kg、0.075-2mg/kg、0.075-2.5mg/kg、0.075-3mg/kg、0.075-3.5mg/kg、0.075-4mg/kg、0.1-0.8mg/kg、0.1-1mg/kg、0.1-1.5mg/kg、0.1-2mg/kg、0.1-2.5mg/kg、0.1-3mg/kg、0.1-3.5mg/kg、0.1-4mg/kg、0.2-0.8mg/kg、0.2-1mg/kg、0.2-1.5mg/kg、0.2-2mg/kg、0.2-2.5mg/kg、0.2-3mg/kg、0.2-3.5mg/kg、0.2-4mg/kg、0.5-0.8mg/kg、0.5-1mg/kg、0.5-1.5mg/kg、0.5-2mg/kg、0.5-2.5mg/kg、0.5-3mg/kg、0.5-3.5mg/kg 或 0.5-4mg/kg ； 或 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg。还可以使用其它高于、中间或小于这些剂量的剂量并且可以由本领域技术人员根据本发明的方法确定。

[3787] 在本发明的一些实施方案中，施用间隔是 24 小时。还可以使用以较低频率间隔施用，例如小于 24 小时 1 次。在一些实施方案中，所述 SV2A 抑制剂以 0.1-5mg/kg 的总每日剂量施用。在一些实施方案中，所述 SV2A 抑制剂每隔 24 小时以 1-2mg/kg 的每日剂量施用。在另一个实施方案中，所述 SV2A 抑制剂每隔 24 小时以 0.1-0.2mg/kg 的每日剂量施用。在一些实施方案中，所述 SV2A 抑制剂以 0.01-2.5mg/kg 的每日剂量施用。在一些实施方案中，所述 SV2A 抑制剂以 0.1-2.5mg/kg 的每日剂量施用。在一些实施方案中，所述 SV2A 抑制剂以 0.4-2.5mg/kg 的每日剂量施用。在一些实施方案中，所述 SV2A 抑制剂以 0.6-1.8mg/kg 的每日剂量施用。在一些实施方案中，SV2A 的选择性抑制剂以 0.04-2.5mg/kg 的每日剂量施用。在一些实施方案中，SV2A 的选择性抑制剂以 0.06-1.8mg/kg 的每日剂量施用。在一些实施方案中，SV2A 的选择性抑制剂以 0.001-5mg/kg 的每日剂量施用。在一些实施方案中，SV2A 的选择性抑制剂以 0.001-0.5mg/kg 的每日剂量施用。在一些实施方案中，SV2A 的选择性抑制剂以 0.01-0.5mg/kg 的每日剂量施用。

[3788] 在本发明的一些实施方案中，所述 SV2A 抑制剂是左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以约 1-2mg/kg 或约 0.1-2.5mg/kg 或约 0.4-2.5mg/kg 或约 0.6-1.8mg/kg 或约 2.0-3.0mg/kg 或约 3.0-4.0mg/kg 或约 2.0-4.0mg/kg 或约 0.1-5mg/kg 或约 70-140mg 或约 7-180mg 或约 25-180mg 或约 40-130mg 或约 140-300mg 或约 200-300mg 或约 140-200mg 或约 7-350mg. 的每日剂量施用。

[3789] 在其它实施方案中，左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药根据如表 1 或表 2 中所列的“+”所示的每日剂量范围之一施用。

[3790] 表 1- 左乙拉西坦的每日剂量

[3791]

下限范围 / 上限范围	0.1mg/kg	0.4mg/kg	0.6mg/kg	1mg/kg	2mg/kg	3mg/kg
1.8mg/kg	+	+	+	+		
2mg/kg	+	+	+	+		
2.5mg/kg	+	+	+	+	+	
3mg/kg	+	+	+	+	+	
4mg/kg	+	+	+	+	+	+
5mg/kg	+	+	+	+	+	+

[3792] 表 2- 左乙拉西在 70KG 人体受试者中的每日剂量

[3793]

下限范围 / 上限范围	7mg	25mg	40mg	70mg	140mg	200mg
130mg	+	+	+	+		
140mg	+	+	+	+		
180mg	+	+	+	+	+	
200mg	+	+	+	+	+	
300mg	+	+	+	+	+	+
350mg	+	+	+	+	+	+

[3794] 在本发明的一些实施方案中，所述 SV2A 抑制剂是左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。左乙拉西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药约 0.1-5mg/kg、约 1-5mg/kg、约 1.5-4mg/kg、约 1.8-3.6mg/kg、约 7-350mg、约 70-350mg、约 100-300mg 或约 125-250mg 的每日剂量施用。

[3795] 在本发明的一些实施方案中，所述 SV2A 抑制剂是布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以约 0.1-0.2mg/kg 或约 0.01-2.5mg/kg 或约 0.04-2.5mg/kg 或约 0.06-1.8mg/kg 或约 0.2-0.4mg/kg 或约 7-15mg 或约 0.7-180mg 或约 2.5-180mg 或约 4.0-130mg 或约 14-30mg 的每日剂量施用。

[3796] 在其它实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以至少 0.1mg、0.5mg、0.75mg、1.0mg、1.5mg 或 2.0mg 的每日剂量、但不超过 2.5mg、5mg、10mg、15mg、20mg、25mg、30mg 或 35mg 的每日剂量施用。在其它实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以至少 0.0015mg/kg、0.0075mg/kg、0.01mg/kg、0.015mg/kg、0.02mg/kg 或 0.03mg/kg 的每日剂量、但不超过 0.5mg/kg、

0.4mg/kg、0.3mg/kg、0.2mg/kg、0.15mg/kg、0.1mg/kg、0.05mg/kg 或 0.04mg/kg 的每日剂量施用。

[3797] 在其它实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以根据如表 3 或表 4 中所列的“+”所示的每日剂量范围之一施用。例如，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以 0.1-35mg、0.5-35mg、0.75-35mg、1.0-35mg、1.5-35mg、2.0-35mg、0.1-30mg、0.1-25mg、0.1-20mg、0.1-15mg、0.1-10mg、0.1-5mg、0.1-2.5mg、0.0015-0.5mg/kg、0.0075-0.5mg/kg、0.01-0.5mg/kg、0.015-0.5mg/kg、0.02-0.5mg/kg、0.03-0.5mg/kg、0.0015-0.4mg/kg、0.0015-0.3mg/kg、0.0015-0.2mg/kg、0.0015-0.15mg/kg、0.0015-0.1mg/kg、0.0015-0.05mg/kg 或 0.0015-0.04mg/kg 的每日剂量施用。

[3798] 表 3- 布立西坦的每日剂量

[3799]

下限范围 / 上限范围	0.0015 mg/kg	0.0075 mg/kg	0.01 mg/kg	0.015 mg/kg	0.02 mg/kg	0.03 mg/kg
0.04mg/kg	+	+	+	+	+	+
0.05mg/kg	+	+	+	+	+	+
0.1mg/kg	+	+	+	+	+	+
0.15mg/kg	+	+	+	+	+	+
0.2mg/kg	+	+	+	+	+	+
0.3mg/kg	+	+	+	+	+	+
0.4mg/kg	+	+	+	+	+	+
0.5mg/kg	+	+	+	+	+	+

[3800] 表 4- 布立西坦 70KG 人体受试者中的每日剂量

[3801]

下限范围 / 上限范围	0.1mg	0.5mg	0.75mg	1.0mg	1.5mg	2.0mg
2.5mg	+	+	+	+	+	+
5mg	+	+	+	+	+	+
10mg	+	+	+	+	+	+
15mg	+	+	+	+	+	+
20mg	+	+	+	+	+	+
25mg	+	+	+	+	+	+
30mg	+	+	+	+	+	+
35mg	+	+	+	+	+	+

[3802] 在其它实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以至少 0.0015mg/kg、0.002mg/kg、0.0025mg/kg、0.005mg/kg、0.01mg/kg、0.02mg/kg、0.03mg/kg、0.04mg/kg、0.05mg/kg、0.06mg/kg、0.07mg/kg、0.08mg/kg、0.09mg/kg、0.1mg/kg、0.2mg/kg、0.3mg/kg、0.4mg/kg、0.5mg/kg 的每日剂量、但不超过 1mg/kg、1.2mg/kg、1.4mg/kg、1.5mg/kg、1.6mg/kg、1.8mg/kg、2.0mg/kg、2.2mg/kg、2.4mg/kg、2.5mg/kg、2.6mg/kg、2.8mg/kg、3.0mg/kg、3.5mg/kg、4.0mg/kg、4.5mg/kg 或 5.0mg/kg 的每日剂量施用。在其它实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以至少 0.1mg、0.15mg、0.18mg、0.35mg、0.7mg、1.5mg、2.0mg、2.5mg、2.8mg、3.0mg、3.5mg、4.2mg、5mg、5.5mg、6.0mg、7mg、10mg、15mg、20mg、25mg、28mg、30mg 或 35mg 的每日剂量、但不超过 70mg、80mg、85mg、100mg、110mg、125mg、140mg、150mg、170mg、175mg、180mg、190mg、200mg、210mg、225mg、250mg、280mg、300mg、或 350mg 的每日剂量施用。在一些实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以 0.0015-5mg/kg、0.1-350mg、0.01-5mg/kg、0.7-350mg、0.05-4mg/kg、3-300mg、0.05-2.0mg/kg、3-150mg、0.05-1.5mg、3-110mg、0.1-1.0mg/kg、7-70mg 的每日剂量施用。

[3803] 在其它实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以根据如表 5 或表 6 中所列的“+”所示的每日剂量范围之一施用。例如，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以 0.01-0.8mg/kg、0.01-1mg/kg、0.01-1.5mg/kg、0.01-2mg/kg、0.01-2.5mg/kg、0.01-3mg/kg、0.01-3.5mg/kg、0.01-4mg/kg、0.01-5mg/kg、0.025-0.8mg/kg、0.025-1mg/kg、0.025-1.5mg/kg、0.025-2mg/kg、0.025-2.5mg/kg、0.025-3mg/kg、0.025-3.5mg/kg、0.025-4mg/kg、0.05-0.8mg/kg、0.05-1mg/kg、0.05-1.5mg/kg、0.05-2mg/kg、0.05-2.5mg/kg、0.05-3mg/kg、0.05-3.5mg/kg、0.05-4mg/kg、0.075-0.8mg/kg、0.075-1mg/kg、0.075-1.5mg/kg、0.075-2mg/kg、0.075-2.5mg/kg、0.075-3mg/kg、0.075-3.5mg/kg、0.075-4mg/kg、0.1-0.8mg/kg、0.1-1mg/kg、0.1-1.5mg/kg、0.1-2mg/kg、0.1-2.5mg/kg、0.1-3mg/kg、0.1-3.5mg/kg、0.1-4mg/kg、0.2-0.8mg/kg、0.2-1mg/kg、0.2-1.5mg/kg、0.2-2mg/kg、

0.2-2.5mg/kg、0.2-3mg/kg、0.2-3.5mg/kg、0.2-4mg/kg、0.5-0.8mg/kg、0.5-1mg/kg、0.5-1.5mg/kg、0.5-2mg/kg、0.5-2.5mg/kg、0.5-3mg/kg、0.5-3.5mg/kg 或 0.5-4mg/kg；或 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg 的每日剂量施用。

[3804] 表 5- 布立西坦的每日剂量 (mg/kg)

[3805]

下限范围 / 上限范围	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	+	+	+	+	+	+	+	+	+

[3806] 表 6- 布立西坦在 70KG(mg) 人体受试者中的每日剂量

[3807]

下限范围 / 上限范围	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	+	+	+	+	+	+	+	+	+

[3808] 在本发明的一些实施方案中，所述 SV2A 抑制剂是塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。在一些实施方案中，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以至少 0.1mg、0.5mg、0.75mg、1.0mg、1.5mg 或 2.0mg 的每日剂量、但不超过 2.5mg、5mg、10mg、15mg、20mg、25mg、30mg 或 35mg 的每日剂量施用。在其它实施方案中，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药以至少 0.0015mg/kg、0.0075mg/kg、0.01mg/kg、0.015mg/kg、0.02mg/kg 或 0.03mg/kg 的每日剂量、但不超过 0.5mg/kg、0.4mg/kg、0.3mg/kg、0.2mg/kg、0.15mg/kg、0.1mg/kg、0.05mg/kg 或 0.04mg/kg 的每日剂量施用。

[3809] 在本发明的一些实施方案中，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以根据如表 7 或表 8 中所列的“+”所示的每日剂量范围之一施用。例如，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物或多晶型物或可以以 0.1-35mg、0.5-35mg、0.75-35mg、1.0-35mg、1.5-35mg、2.0-35mg、0.1-30mg、0.1-25mg、0.1-20mg、0.1-15mg、0.1-10mg、0.1-5mg、0.1-2.5mg、0.0015-0.5mg/kg、0.0075-0.5mg/kg、0.01-0.5mg/kg、0.015-0.5mg/kg、0.02-0.5mg/kg、0.03-0.5mg/kg、0.0015-0.4mg/kg、0.0015-0.3mg/kg、0.0015-0.2mg/kg、0.0015-0.15mg/kg、0.0015-0.1mg/kg、0.0015-0.05mg/kg 或 0.0015-0.04mg/kg 的每日剂量施用。

[3810] 表 7- 塞曲西坦的每日剂量

[3811]

下限范围 / 上限范围	0.0015 mg/kg	0.0075 mg/kg	0.01 mg/kg	0.015 mg/kg	0.02 mg/kg	0.03 mg/kg
0.04mg/kg	+	+	+	+	+	+
0.05mg/kg	+	+	+	+	+	+
0.1mg/kg	+	+	+	+	+	+
0.15mg/kg	+	+	+	+	+	+
0.2mg/kg	+	+	+	+	+	+
0.3mg/kg	+	+	+	+	+	+
0.4mg/kg	+	+	+	+	+	+
0.5mg/kg	+	+	+	+	+	+

[3812] 表 8- 塞曲西坦在 70KG 人体受试者中的每日剂量

[3813]

下限范围 / 上限范围	0.1mg	0.5mg	0.75mg	1.0mg	1.5mg	2.0mg
2.5 mg	+	+	+	+	+	+
5mg	+	+	+	+	+	+
10mg	+	+	+	+	+	+
15mg	+	+	+	+	+	+
20mg	+	+	+	+	+	+
25mg	+	+	+	+	+	+
30mg	+	+	+	+	+	+
35mg	+	+	+	+	+	+

[3814] 在其它实施方案中，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以至少 0.0015mg/kg、0.002mg/kg、0.0025mg/kg、0.005mg/kg、0.01mg/kg、0.02mg/kg、0.03mg/kg、0.04mg/kg、0.05mg/kg、0.06mg/kg、0.07mg/kg、0.08mg/kg、0.09mg/kg、0.1mg/kg、0.2mg/kg、0.3mg/kg、0.4mg/kg、0.5mg/kg 的每日剂量、但不超过 1mg/kg、1.2mg/kg、1.4mg/kg、1.5mg/kg、1.6mg/kg、1.8mg/kg、2.0mg/kg、2.2mg/kg、2.4mg/kg、2.5mg/kg、2.6mg/kg、2.8mg/kg、3.0mg/kg、3.5mg/kg、4.0mg/kg、4.5mg/kg 或 5.0mg/kg 的每日剂量施用。在其它实施方案中，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以至少 0.1mg、0.15mg、0.18mg、0.35mg、0.7mg、1.5mg、2.0mg、2.5mg、2.8mg、3.0mg、3.5mg、4.2mg、5mg、5.5mg、6.0mg、7mg、10mg、15mg、20mg、25mg、28mg、30mg 或 35mg 的每日剂量、但不超过 70mg、80mg、85mg、100mg、110mg、125mg、140mg、150mg、170mg、175mg、180mg、190mg、200mg、210mg、225mg、250mg、280mg、300mg、或 350mg 的每日剂量施用。在一些实施方案中，布立西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以 0.0015-5mg/kg、0.1-350mg、0.01-5mg/kg、0.7-350mg、0.05-4mg/kg、3-300mg、0.05-2.0mg/

kg、3-150mg、0.05-1.5mg、3-110mg、0.1-1.0mg/kg、7-70mg 的每日剂量施用。

[3815] 在其它实施方案中，可以根据如表 9 或表 10 中所列的“+”所示的每日剂量范围之一施用塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药。例如，塞曲西坦或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药可以以 0.01-0.8mg/kg、0.01-1mg/kg、0.01-1.5mg/kg、0.01-2mg/kg、0.01-2.5mg/kg、0.01-3mg/kg、0.01-3.5mg/kg、0.01-4mg/kg、0.01-5mg/kg、0.025-0.8mg/kg、0.025-1mg/kg、0.025-1.5mg/kg、0.025-2mg/kg、0.025-2.5mg/kg、0.025-3mg/kg、0.025-3.5mg/kg、0.025-4mg/kg、0.05-0.8mg/kg、0.05-1mg/kg、0.05-1.5mg/kg、0.05-2mg/kg、0.05-2.5mg/kg、0.05-3mg/kg、0.05-3.5mg/kg、0.05-4mg/kg、0.075-0.8mg/kg、0.075-1mg/kg、0.075-1.5mg/kg、0.075-2mg/kg、0.075-2.5mg/kg、0.075-3mg/kg、0.075-3.5mg/kg、0.075-4mg/kg、0.1-0.8mg/kg、0.1-1mg/kg、0.1-1.5mg/kg、0.1-2mg/kg、0.1-2.5mg/kg、0.1-3mg/kg、0.1-3.5mg/kg、0.1-4mg/kg、0.2-0.8mg/kg、0.2-1mg/kg、0.2-1.5mg/kg、0.2-2mg/kg、0.2-2.5mg/kg、0.2-3mg/kg、0.2-3.5mg/kg、0.2-4mg/kg、0.5-0.8mg/kg、0.5-1mg/kg、0.5-1.5mg/kg、0.5-2mg/kg、0.5-2.5mg/kg、0.5-3mg/kg、0.5-3.5mg/kg 或 0.5-4mg/kg；或 0.7-50mg、0.7-75mg、0.7-100mg、0.7-150mg、0.7-180mg、0.7-225mg、0.7-250mg、0.7-280mg、1.8-50mg、1.8-75mg、1.8-100mg、1.8-150mg、1.8-180mg、1.8-225mg、1.8-250mg、1.8-280mg、3.5-50mg、3.5-75mg、3.5-100mg、3.5-150mg、3.5-180mg、3.5-225mg、3.5-250mg、3.5-280mg、5-50mg、5-75mg、5-100mg、5-150mg、5-180mg、5-225mg、5-250mg、5-280mg、7-50mg、7-75mg、7-100mg、7-150mg、7-180mg、7-225mg、7-250mg、7-280mg、15-50mg、15-75mg、15-100mg、15-150mg、15-180mg、15-225mg、15-250mg、15-280mg、35-50mg、35-75mg、35-100mg、35-150mg、35-180mg、35-225mg、35-250mg 或 35-280mg 的每日剂量施用。

[3816] 表 9- 塞曲西坦的每日剂量 (mg/kg)

[3817]

下限范围 / 上限范围	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	+	+	+	+	+	+	+	+	+

[3818] 表 10- 塞曲西坦在 70KG 人体受试者中的每日剂量 (mg)

[3819]

下限范围 / 上限范围	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	+	+	+	+	+	+	+	+	+

[3820] 当与 AChEI 或它的药学上可接受的盐、水合物、溶剂合物和多晶型物组合提供时，由于 AChEI- 依赖性增加所述 SV2A 抑制剂的治疗指数，可将所述 SV2A 抑制剂或它的药学上可接受的盐、水合物、溶剂合物和多晶型物以亚治疗剂量水平施用。在一些实施方案中，由于与 AChEI 组合，所述 SV2A 抑制剂的治疗指数的增加大于在不存在所述 AChEI 下施用的所述 SV2A 抑制剂的治疗指数的至少约 1.5x 或 2.0x 或 2.5x 或 3.0x 或 3.5x 或 4.0x 或 4.5x 或 5.0x 或 5.5x 或 6.0x 或 6.5x 或 7.0x 或 7.5x 或 8.0x 或 8.5x 或 9.0x 或 9.5x 或 10x、或大于约 10x。在一些实施方案中，SV2A 抑制剂与 AChEI 组合减少了所述 SV2A 抑制剂发挥其治疗作用所需的剂量。在一些实施方案中，与所述 AChEI 组合施用的所述 SV2A 抑制剂的量是亚治疗量。在一些实施方案中，将所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物和多晶型物或前药以小于 5mg/kg、小于 2.5mg/kg、小于 2mg/kg、小于 1.5mg/kg、小于 1mg/kg、小于 0.5mg/kg、小于 0.1mg/kg、小于 0.05mg/kg、小于 0.01mg/kg、小于 0.005mg/kg、或小于 0.001mg/kg 的日剂量施用。

[3821] 所述 AChEI 或它的药学上可接受的盐、水合物、溶剂合物和多晶型物可以以至多为常规剂量水平的剂量水平施用。适合的剂量水平将取决于所选的具体 AChEI。可将所述 AChEI 按至多为每日 2 次、每日 1 次的方案施用，或它可以更少的频率施用。对于 ARICEPT®，当单独施用时典型的每日剂量是约 5 至 10mg。在本发明的一些实施方案中，与 SV2A 抑制剂组合施用的 ARICEPT® 的量是约 0.1 至 10mg。在一些实施方案中，与所述 SV2A 抑制剂组合施用的 ARICEPT® 的量是亚治疗量。在一些实施方案中，与所述 SV2A 抑制剂组合施用的 ARICEPT® 的量小于 10mg 每日、小于 5mg 每日、小于 1mg 每日、小于 0.5mg 每日、或小于 0.1mg 每日。

[3822] 当与 SV2A 抑制剂组合提供时，由于 SV2A 抑制剂 - 依赖性增加所述 AChEI 的治疗指数，可将所述 AChEI 或其盐、水合物、溶剂合物或多晶型物或前药以与常规水平不同的剂量

水平施用。在一些实施方案中，由于与其 SV2A 抑制剂组合，所述 AChEI 的治疗指数的增加大于在不存在 SV2A 抑制剂下施用的所述 AChEI 的治疗指数的至少约 1.5x 或 2.0x 或 2.5x 或 3.0x 或 3.5x 或 4.0x 或 4.5x 或 5.0x 或 5.5x 或 6.0x 或 6.5x 或 7.0x 或 7.5x 或 8.0x 或 8.5x 或 9.0x 或 9.5x 或 10x、或大于约 10x。在一些实施方案中，AChEI 与 SV2A 抑制剂组合减少了所述 AChEI 发挥其治疗作用所需的剂量。在一些实施方案中，与其 SV2A 抑制剂组合施用的所述 AChEI 的量是约 0.1 至 10mg。在一些实施方案中，与所述 SV2A 抑制剂组合施用的所述 AChEI 的量是亚治疗量。在一些实施方案中，与所述 SV2A 抑制剂组合施用的所述 AChEI 的量是小于 10mg 每日、小于 5mg 每日、小于 1mg 每日、小于 0.5mg 每日、或小于 0.1mg 每日。

[3823] 基于施用医师的判断，可将施用本发明组合物的频率在疗程内进行调整。应明确，可将所述 SV2A 抑制剂和所述 AChEI 和它们的盐、水合物、溶剂合物和多晶型物以不同的给药频率或间隔施用。例如，可将 SV2A 抑制剂每日（包括每日多次剂量）或以更低频率施用。可将 AChEI 每日（包括每日多次剂量）或以更低频率施用。在一些实施方案中，SV2A 抑制剂和 AChEI 的持续连续释放制剂可能是所需的。用于获得持续释放的各种制剂和装置是本领域已知的。

[3824] 如上所述，一些 AChEI（例如多奈哌齐）和它们的盐、水合物、溶剂合物和多晶型物可引起胆碱能副作用。使用 SV2A 抑制剂和 AChEI 组合可减少治疗与 CNS 障碍相关的认知缺损所必需的 AChEI 的量，并且可因此减少由所述 AChEI 引起的副作用。具体的是，SV2A 抑制剂与 AChEI 减少量的组合可减少胆碱能副作用，而不会对功效有负面影响。因此，在一些实施方案中，施用亚治疗量的 AChEI。

[3825] 在一些实施方案中，施用适合量的所述 SV2A 抑制剂，以便减少所述 AChEI 的剂量（例如，影响认知功能改善的程度或治疗与年龄相关的认知缺损所需要的剂量），所述减少为单独（即，单独且不与其它治疗活性剂或化合物组合）施用时正常使用的 AChEI 剂量的至少约 20%、至少约 30%、至少约 40%、或至少约 50%、至少约 60%、至少约 70%、至少约 80%、至少约 90%或更多。该减少可反映在给定施用的施用量和 / 或在给定的时期内的施用量（减少的频率）上。

[3826] 在本发明的一些实施方案中，组合施用 SV2A 抑制剂或其盐、水合物、溶剂合物及多晶型物或前药和 AChEI 或其盐、水合物、溶剂合物及多晶型物或前药可在受试者中获得更长或改善的治疗作用，其比通过仅仅施用所述 AChEI 或仅仅所述 SV2A 抑制剂获得的治疗作用长或改善至少约 1.5x、或 2.0x、或 2.5x、或 3.0x、或 3.5x、或 4.0x、或 4.5x、或 5.0x、或 5.5x、或 6.0x、或 6.5x、或 7.0x、或 7.5x、或 8.0x、或 8.5x、或 9.0x、或 9.5x、或 10x、或大于约 10x。

[3827] 本发明的组合物

[3828] 在一个方面，本发明提供组合物，其包含缓释形式的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药和 AChEI 及其盐、水合物、溶剂合物、多晶型物或前药。在一些实施方案中，本发明组合物中存在的所述 AChEI 或其药学上可接受的盐不是缓释形式。在一些实施方案中，本发明组合物中存在的所述 AChEI 或其药学上可接受的盐是立即释放形式。在一些实施方案中，所述 SV2A 抑制剂和所述 AChEI 可以存在于单一剂量单元中（例如共同合并在胶囊、片剂。粉末或液体等中）。在一些实施方案中，组合物

中的所述 AChEI 是多奈哌齐。在一些实施方案中，该组合物包括左乙拉西坦或塞曲西坦或布立西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药作为所述 SV2A 抑制剂，并且包括多奈哌齐或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物或多晶型物或前药作为所述 AChEI。在一些实施方案中，该组合物包括左乙拉西坦或其衍生物或类似物或药学上可接受的盐、水合物、溶剂合物和多晶型物或前药多奈哌齐或其药学上可接受的盐、水合物、溶剂合物和多晶型物或前药。本文所述的组合物可以包含一种以上 SV2A 抑制剂和 / 或一种以上 AChEI。在一些实施方案中，组合物中存在的缓释的 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药不影响同一组合物中存在的所述 AChEI 或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的药代动力学或本申请清除率。例如，多奈哌齐（AChEI 的实例）具有 70 小时的半衰期清除率且左乙拉西坦（SV2A 抑制剂的实例）具有 7±1 小时的半衰期清除率。在一个实施方案中，本发明提供组合物，其包含缓释形式的左乙拉西坦和非缓释形式的多奈哌齐，且这类组合物是每日 1 次的制剂。每日 1 次制剂在患有认知缺损的患者中具有更高的依从性。

[3829] 本文所述的组合物还可含有药学上可接受的赋形剂，且可含有起到增强和 / 或补充所述 SV2A 抑制剂和 / 或所述 AChEI 效应的其它活性剂。该组合物还可含有已知用于治疗认知功能障碍的另外的活性剂。

[3830] 在本发明中所述组合物可以是例如胶囊、片剂、糖衣片 (dragrees)、丸剂、锭剂、粉剂和粒剂的固体剂型。在适当的情况下，可将它们用例如肠溶衣的包衣制备，或可将它们配制以便提供一个或多个活性成分的控制释放，例如根据本领域熟知方法的持续或延长释放。在一些实施方案中，所述组合物为缓慢释放、受控释放或缓释的形式。术语“缓释”为药学领域公认，并被本文用于意指在延长的时期（自始至终或在该期间），例如大于或等于 1 小时内，活性化合物或活性剂从剂型至环境的控制释放。缓释剂型将以基本上恒定速率在延长的时期内释放药物，或将基本上恒定量的药物在延长的时期内递增地释放。本文使用的术语“缓释”包括术语“控制释放”、“延长释放”、“持续释放”或“缓慢释放”，正如这些术语用于药学的情况。在一些实施方案中，所述缓释剂量以贴剂或泵的形式施用。所述组合物还可以是包括溶液、乳剂、混悬剂、糖浆剂和酏剂的液体剂型。

[3831] 可将该组合物通过如本文所述和本领域已知的任何适合途径为施用而具体地配制。用于胃肠外 (parental) 施用的组合物包括无菌水性和非水性可注射溶液、分散剂、混悬剂或乳剂以及临用前在无菌可注射溶液或分散剂中重构的无菌粉剂。用于口内和口服递送的组合物（包括舌下和口腔的施用，例如，Danckwerts 等人，和口服）包括但不限于生物粘附聚合物、片剂、贴剂、液体和半固体（参见例如，Smart 等人）。用于呼吸递送（肺和鼻递送）的组合物包括但不限于各种压力型定量吸入器 (pressurized metered dose inhalers)、干粉吸入器、喷雾器、水雾吸入器 (aqueous mist inhalers)、滴剂、溶液、混悬剂、喷雾剂、粉剂、凝胶剂、乳膏剂，以及例如脂质体和微球的专用系统（参见例如 Owens 等人，“Alternative Routes of Insulin Delivery”和 Martini 等人）。用于透皮递送的组合物包括但不限于胶剂、贴剂和微乳剂。用于上述和其它的其它适合的施用形式包括贮库型可注射制剂、栓剂、喷雾剂、乳膏剂、霜剂、凝胶剂、吸入剂、皮肤贴剂、埋植剂等。

[3832] 所述组合物还可含有助剂，例如防腐剂、润湿剂、乳化剂和分散剂。预防微生物的作用可通过纳入各种抗菌和抗真菌剂，例如，对羟基苯甲酸酯，三氯叔丁醇，苯酚山梨酸，等

来确保。还期望将等渗剂，例如糖、氯化钠等纳入组合物中。此外，延长吸收的可注射药物形式可通过纳入延缓吸收的活性剂，例如单硬脂酸铝和明胶提供。

[3833] 可以通过制药领域众所周知的方法制备治疗制剂，参见，例如 Goodman 等人，2001 ;Ansel 等人，2004 ;Stoklosa 等人，2001 ;和 Bustamante 等人，1993。

[3834] 在本发明的一些实施方案中，包含 SV2A 抑制剂和 AChEI 及其盐、水合物、溶剂合物、多晶型物、前药的组合物包含 0.07-350mg 或 50-200mg 或 3-50mg 的量的所述 SV2A 抑制剂。在一些实施方案中，所述 SV2A 抑制剂的量小于 350mg、小于 250mg、小于 200mg、小于 150mg、小于 100mg、小于 50mg、小于 10mg、小于 5mg、小于 1mg、小于 0.5mg、小于 0.1mg 或小于 0.07mg。在一些实施方案中，组合物中所述 AChEI 的量约为 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg。在一些实施方案中，，组合物中所述 AChEI 的量小于 10mg、小于 9mg、小于 8mg、小于 7mg、小于 6mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg。

[3835] 在一些实施方案中，组合物中存在的所述 SV2A 抑制剂的量为 0.07-60mg、0.07-350mg、25-60mg、25-125mg、50-250mg、5-140mg、0.7-180mg、125-240mg、3-50mg、3-60mg、0.05-35mg、0.07-60mg、0.07-350mg、25-60mg、25-125mg、50-250mg、5-15mg、5-30mg、5-140mg、0.7-180mg、125-240mg、3-50mg 或 0.07-50mg 或 3-60mg。在一些实施方案中，组合物中存在的所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的量小于 350mg、小于 250mg、小于 200mg、小于 150mg、小于 100mg、小于 50mg、小于 35mg、小于 10mg、小于 5mg、小于 1mg、小于 0.5mg、小于 0.1mg、小于 0.07mg 或小于 0.05mg。在一些实施方案中，组合物中存在的所述 SV2A 抑制剂或其药学上可接受的盐、水合物、溶剂合物、多晶型物或前药的量约为 0.1-500mg、0.1-300mg、0.7-300mg、3-300mg、3-150mg、3-110mg、7-70mg、7-300mg、70-300mg、100-300mg、125-250mg、0.5-50mg、0.5-75mg、0.5-100mg、0.5-150mg、0.5-200mg、0.5-225mg、0.5-250mg、0.5-300mg、1.5-50mg、1.5-75mg、1.5-100mg、1.5-150mg、1.5-200mg、1.5-225mg、1.5-250mg、1.5-300mg、3-50mg、3-75mg、3-100mg、3-150mg、3-200mg、3-225mg、3-250mg、3-300mg、5-50mg、5-75mg、5-100mg、5-150mg、5-200mg、5-225mg、5-250mg、5-300mg、7-50mg、7-75mg、7-100mg、7-150mg、7-200mg、7-225mg、7-250mg、7-300mg、15-50mg、15-75mg、15-100mg、15-150mg、15-200mg、15-225mg、15-250mg、15-300mg、30-50mg、30-75mg、30-100mg、30-150mg、30-200mg、30-225mg、30-250mg 或 30-300mg。在上述实施方案的一些中，所述 SV2A 抑制剂是左乙拉西坦，且所述 AChEI 是多奈哌齐。在上述实施方案的一些中，所述 SV2A 抑制剂是布立西坦，且所述 AChEI 是多奈哌齐。在上述实施方案的一些中，所述 SV2A 抑制剂是塞曲西坦，且所述 AChEI 是多奈哌齐。在上述实施方案中，多奈哌齐可以被他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯取代。

[3836] 在本发明的一些实施方案中，包含左乙拉西坦和 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物、前药的组合物包含如表 11 中所示范围之间或小于表 11 中所示的任意上限范围的量的缓释形式的左乙拉西坦或其盐、水合物、溶剂合物、多晶型物、前药或小于和 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 或小于 10mg、小于 9mg、小于 8mg、小于 7mg、小于 6mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的量的 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物或前药。在上述实施方案的一

些中，所述 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物或前药不是缓释形式。

[3837] 在本发明的一些实施方案中，包含布立西坦和 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物、前药的组合物包含表 12 中所示范围之间或小于表 12 中所示任意上限范围的量的缓释形式的布立西坦或其盐、水合物、溶剂合物、多晶型物、前药和 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 或小于 10mg、小于 9mg、小于 8mg、小于 7mg、小于 6mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的量的 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物、前药。在上述实施方案的一些中，所述 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物或前药不是缓释形式。

[3838] 在本发明的一些实施方案中，包含塞曲西坦和 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物、前药的组合物包含表 12 中所示范围之间或小于表 12 中所示任意上述范围的量塞曲西坦或其盐、水合物、溶剂合物、多晶型物、前药和 0.1-10mg、1-10mg、2-10mg、2-8mg 或 2-5mg 或小于 10mg、小于 9mg、小于 8mg、小于 7mg、小于 6mg、小于 5mg、小于 2mg、小于 1mg 或小于 0.5mg 的量的 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物、前药。在上述实施方案的一些中，所述 AChEI（例如多奈哌齐或他克林、利凡斯的明、毒扁豆碱、加兰他敏或美曲膦酯）及其盐、水合物、溶剂合物、多晶型物或前药不是缓释形式。

[3839] 表 11- 组合物中存在的左乙拉西坦的量 (mg)

[3840]

下限范围 / 上限范围	7mg	25mg	40mg	70mg	125mg	140mg	200mg
130mg	+	+	+	+			
140mg	+	+	+	+	+		
180mg	+	+	+	+	+	+	
200mg	+	+	+	+	+	+	
250mg	+	+	+	+	+	+	+
300mg	+	+	+	+	+	+	+
350mg	+	+	+	+	+	+	+

[3841] 表 12- 组合物中存在的塞曲西坦或布立西坦的量 (mg)

[3842]

下限范围 / 上限范围	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	+	+	+	+	+	+	+	+	+

[3843] 本领域的普通技术人员应理解，本文所述的组合物和方法可修改和修饰以适于所针对的适应征，并且本文所述的组合物和方法可用于其它适合的应用，而且这类其它的增加物和修饰并不偏离其范围。

[3844] 从随后的实验细节将会更好地理解本发明。但是，本领域的技术人员将易于理解，讨论的具体的方法和结果仅仅是对如在下文实施方案中更完全描述的本发明进行说明。

实施例

[3845] 认知缺损的介绍和模型

[3846] 表征为认知缺损的各种病症，例如，与年龄相关的记忆缺损 (AAMI)、轻度认知缺损 (MCI) 以及与年龄相关的认知减退 (ARCD) 被认为与衰老有关。其它的有关疾病为，例如，AD。动物模型用作发展和评价这类与年龄相关的认知缺损的治疗的重要资源。在动物模型中表征与年龄相关的认知缺损的特征通常扩展至人中的与年龄相关的认知缺损。因此，在这类动物模型中的功效预测了在人中的功效。

[3847] 可利用的模型中，认知缺损的 Long-Evans 大鼠模型特别适合于区别与疾病相关的认知缺损和与衰老相关的认知缺损间的不同。实际上，大量的行为特征描述已鉴定了在远交系老龄 Long-Evans 大鼠中认知缺损的自然发生形式 (Charles River Laboratories；Gallagher 等人，Behav. Neurosci. 107 :618-626，(1993))。在用莫里斯水迷宫 (MWM) 进行的行为评价中，大鼠学习和记忆由该迷宫周围的空间线索配置引导的逃避平台的位置。表现的认知基础在探查试验中进行测试，所述探查试验使用了动物在搜寻所述逃避平台的位置中的空间偏好的量度。在该研究群体中的老龄大鼠游至可见的平台并无困难，但是当将该平台伪装，需要利用空间信息时，就检测到了年龄依赖性缺损。在远交 Long-Evans 系中的个体老龄大鼠的表现有很大不同。例如，部分那些大鼠与年轻成年大鼠有同样表现。但是，约 40-50％超出了年轻大鼠表现的范围。在老龄大鼠中的这种可变性反映了可靠的个体差异。因此，在老龄群体中一些动物是认知受损的，并称为老龄受损 (AI)，而其它动物是

未受损的，并称为老龄未受损 (AU)。参见，例如，Colombo 等人，Proc. Natl. Acad. Sci. 94 : 14195-14199，(1997) ；Gallagher 和 Burwell，Neurobiol. Aging 10 :691-708，(1989) ；Rapp 和 Gallagher，Proc. Natl. Acad. Sci. 93 :9926-9930，(1996) ；Nicolle 等人，Neuroscience 74 :741-756，(1996) ；和 Nicolle 等人，J. Neurosci. 19 :9604-9610，(1999)。

[3848] 我们使用上述大鼠模型以鉴定个体 AI 和 AU 大鼠。我们随后在施用各种药理学治疗时对 AI 大鼠进行行为评价。

[3849] 实施例 1 ：在放射臂迷宫任务中左乙拉西坦、多奈哌齐和联合治疗的行为评价

[3850] 老龄、雄性 Long-Evans 大鼠在 8 至 9 月龄时从 Charles River 实验室 (Raleigh，NC) 得到，并饲养于动物饲养所直至 24 至 26 月龄。所有大鼠在 25℃下单独饲养，并维持 12 小时光照 / 黑暗循环。除非另外指明，否则随意摄食和饮水。对大鼠在整个实验中的健康和无病原体状态进行检查，并在处死时进行尸检。

[3851] 将所有大鼠以空间认知的标准化评价进行筛选。该背景评价使用了上述充分确立的 MWM 方案。证明在空间认知的标准化评价中记忆表现受损的老龄大鼠，即，AI 大鼠，被选用于药物干预研究。在以下不同的药物 / 对照治疗的条件下，测试所选 AI 大鼠在放射臂迷宫 (RAM) 任务中它们对新空间信息的记忆 ：媒介物对照、仅仅多奈哌齐、仅仅左乙拉西坦，以及多奈哌齐和左乙拉西坦组合。使用食欲动机该 RAM 任务也将行为评价扩展到了空间记忆。我们使用了对不同剂量和组合的药物进行受试者内评价的方案 (Koh 等人，Neuropsychopharmacology，epub. 1-10，(2009))。

[3852] 放射臂迷宫任务

[3853] 该放射迷宫由从八边形的中心平台的每个侧面伸出的八个臂组成，食槽位于每个臂末端。放置树脂玻璃™隔断以阻止进入任何臂中。在迷宫周围的房间中提供迷宫外的线索，并通过顶灯提供照明。如在 Chappell 等人，Neuropharmacology 37 :481-487(1998) 中详细描述的预训练由熟习、标准的得到 - 转移 (win-shift) 训练，以及介于信息和记忆测试阶段间有延迟的得到 - 转移训练组成。在预训练完成后 2 天开始药物治疗。三个臂在每个试验 (信息阶段) 开始时被隔断。隔断臂的特性和配置在每次试验中变化。允许禁食的大鼠从 5 个未隔断臂重新取回食物奖赏 (Kellogg's Froot Loops™ cereal)。随后将大鼠从该迷宫中移除 60 分钟 (保留间隔)，在此期间，将在隔断臂上的屏障移除，允许进入所有的八个臂。随后将大鼠放回中心平台上，并允许重新取回剩下的食物奖赏 (记忆测试阶段)。

[3854] 追踪 AI 大鼠在保留测试阶段形成的“错误”数。错误由回到早已从中得到食物的臂 (所有四只爪都在臂上) 组成。例如，如果大鼠进入已经在试验的延迟部分前从中取回食物的臂或如果它在延迟期后再探访已探访过的臂，错误就在试验中出现。

[3855] 左乙拉西坦治疗

[3856] 独立的 AI 大鼠组 (n = 10) 首先用左乙拉西坦 (Tecoland，Edison，NJ) 测试。在每日试验之前 30-40 分钟，同时用下列六个条件对 AI 大鼠进行预治疗 ：1) 媒介物对照 (0.9% 盐溶液) ；2) 左乙拉西坦 (1.25mg/kg/ 天) ；3) 左乙拉西坦 (2.5mg/kg/ 天) ；4) 左乙拉西坦 (5mg/kg/ 天) ；5) 左乙拉西坦 (10mg/kg/ 天) ；6) 左乙拉西坦 (20mg/kg/ 天) ；通过腹膜内 (i.p.) 注射。每隔一日 (介入清除日) 给予注射。为了等衡任何潜在的偏倚，药物作用使用递升 - 递减剂量系列进行评价，即，该剂量系列首先以递升次序提供，随后以递减次序重复。因此，每个剂量有两项测定。

[3857] 将参数统计（配对 t 检验）用于比较在 RAM 任务的 1 小时延迟期 AI 大鼠在不同剂量的左乙拉西坦和媒介物对照的环境中保留测试表现（参见图 1）。用左乙拉西坦 5mg/kg/ 天（错误的平均数 ± 平均值的标准误 (SEM) = 0.75±0.32）和 10mg/kg/ 天（错误的平均数 ±SEM = 0.80±0.27）治疗在该试验中错误的平均数比使用媒介物对照（错误的平均数 ±SEM = 2.00±0.42）显著更少。相对于媒介物对照治疗，左乙拉西坦在 5mg/kg/ 天 ($t(9) = 2.18, p = 0.057$) 和 10mg/kg/ 天 ($t(9) = 2.37, p = 0.042$) 下显著改善记忆表现。

[3858] 多奈哌齐治疗

[3859] 在左乙拉西坦评价完成之后，将一组新的 AI 大鼠 ($n = 8$) 用多奈哌齐测试。在每日试验之前 30-40 分钟，同时用下列三个条件对 AI 大鼠进行预治疗 :1) 媒介物对照 (0.9% 盐溶液）;2) 多奈哌齐 (1mg/kg/ 天）;3) 多奈哌齐 (2mg/kg/ 天）;通过腹膜内 (i.p.) 注射。每天给予注射。为了等衡任何潜在的偏倚，药物作用使用递升 - 递减剂量系列进行评价，即，该剂量系列首先以递升次序提供，随后以递减次序重复。因此，每个剂量有两项测定。

[3860] 将参数统计（配对 t 检验）用于比较在 RAM 任务的 2 小时延迟期 AI 大鼠在不同剂量的多奈哌齐和媒介物对照的环境中保留测试表现（参见图 2）。使用多奈哌齐 1mg/kg/ 天（错误的平均数 ± 平均值的标准误 (SEM) = 2.88±0.46）和 2mg/kg/ 天（错误的平均数 ±SEM = 2.81±0.43）治疗在该试验中出现错误的平均数与使用媒介物对照（错误的平均数 ±SEM = 2.88±0.67）并无显著差异。相对于媒介物对照治疗，多奈哌齐在 1mg/kg/ 天 ($t(7) = 0, p = 1.00$) 或 2mg/kg/ 天 ($t(7) = 0.91, p = 0.930$) 下并没有显著改善记忆表现。

[3861] 左乙拉西坦和多奈哌齐的组合

[3862] 我们使用相同的 AI 大鼠 ($n = 8$)，测试左乙拉西坦和多奈哌齐组合在亚治疗剂量下施用时的记忆改善效果。在这项实验中，亚治疗剂量是 2.5mg/kg/ 天用于左乙拉西坦和 1mg/kg/ 天用于多奈哌齐。如上所述，当在不存在多奈哌齐的情况下将左乙拉西坦以 2.5mg/kg/ 天的剂量单独施用，它并不会显著地改善 AI 大鼠的记忆表现（参见图 1）。当在不存在左乙拉西坦的情况下将多奈哌齐以 1mg/kg/ 天的剂量单独施用，它并不会显著地改善 AI 大鼠的记忆表现（参见图 2）。

[3863] 在每日试验之前 30-40 分钟，同时用下列两个条件对 AI 大鼠进行预治疗 :1) 媒介物对照 (0.9% 盐溶液）;2) 多奈哌齐 (1mg/kg/ 天）和左乙拉西坦 (2.5mg/kg/ 天）;通过腹膜内 (i.p.) 注射。每天给予注射。为了等衡任何潜在的偏倚，药物作用使用递升 - 递减剂量系列进行评价，即，该剂量系列首先以递升次序提供，随后以递减次序重复。因此，每个剂量有两项测定。

[3864] 将参数统计（配对 t 检验）用于比较在 RAM 任务的 2 小时延迟期 AI 大鼠在左乙拉西坦和多奈哌齐的组合和媒介物对照的环境中保留测试表现（参见图 2）。多奈哌齐 (1mg/kg/ 天）和左乙拉西坦 (2.5mg/kg/ 天）组合施用（错误的平均数 ± 平均值的标准误 (SEM) = 1.69±0.53）在该试验中出现错误的平均数比使用媒介物对照（错误的平均数 ±SEM = 2.88±0.67）显著更少。相对于媒介物对照治疗，多奈哌齐 (1mg/kg/ 天）和左乙拉西坦 (2.5mg/kg/ 天）的组合显著地改善记忆表现 ($t(7) = 2.16, p = 0.034$)。

[3865] 多奈哌齐或左乙拉西坦，当在缺少另一个药物的情况下以如在这项实验中所测试的亚治疗剂量施用时，并不会显著地改善AI大鼠的记忆表现（参见图1和2）。但是，以亚治疗剂量施用的多奈哌齐和左乙拉西坦组合却显著改善了AI大鼠的记忆表现。我们的结果暗示当一起施用时多奈哌齐和左乙拉西坦间的超加（super-additive）或协同相互作用。

[3866] 实施例2：左乙拉西坦在具有aMCI的人体受试者中的治疗

[3867] 进行为期8周的受试者内试验，涉及用左乙拉西坦低剂量治疗的17名、遗忘性MCI(aMCI)受试者和17名年龄匹配对照。在该研究期间，每个aMCI受试者在每个两周的两个周期中都分别接受药物和安慰剂治疗，使治疗次序在不同的aMCI受试者中等衡（参见图3）。用安慰剂治疗的年龄匹配对照受试者用作另一对照。在每个两周周期的药物/安慰剂治疗之后从受试者得到认知测试和fMRI成像数据。

[3868] 参与者和临床表征

[3869] 从在Johns Hopkins医院的阿尔茨海默病研究中心(Alzheimer's Disease Research Center)(ADRC)和其它转诊机构(referrals)招募17名惯用右手的aMCI患者。从ADRC和其它转诊机构的对照参与者库中招募另外17名惯用右手的健康志愿者。对所有参与者实施认知状态的电话会诊，以确定他们是否有可能通过该研究的入围标准（包括用于MRI扫描的标准）。所有参与者还接受使用标准化仪器和方法的神经学、精神病学以及神经心理学检查。精神病学的评价包括实施用于DSM-IV轴I障碍的组织临床会诊(the Structured Clinical Interview for DSM-IV Axis I Disorders)和临床痴呆等级评定(the Clinical Dementia Rating)(CDR)量表。所有aMCI患者的CDR评分为0.5。aMCI的诊断基于由Petersen等人（例如，"Mild cognitive impairment:Aging to Alzheimer's Disease," Oxford University Press, N.Y.(2003)）提议的标准，其包括记忆抱怨（由填报人确证的）、在测试时受损的记忆功能（基准之下1.5个标准偏差）、在其它方面保留的认知功能（基准的1个标准偏差之内）、功能能力没有减退和无痴呆。通过临床共识达到最终的aMCI诊断。淘汰标准包括主要的神经学或精神病学障碍、伴意识丧失的头部损伤、药物滥用或依赖史，以及MRI检查的一般禁忌症（例如心脏起搏器、动脉瘤线圈、幽闭恐怖症）。每个aMCI受试者需要有可提供关于受试者每日功能的信息并确保适当用药的研究搭档（即，填报人）。参见图14A和14B。

[3870] 研究访视：该研究由8周程内的4项访视组成（参见图3）。基线访视是为了进行医学、神经学、精神病学和神经认知的评价。访视1和2与基线访视是相同的，但包括fMRI期。在4周清除期结束时的清除访视，是为了简短的临床评价和开始第二次药物/安慰剂阶段。

[3871] 基线访视：在筛查访视时，从受试者（和MCI受试者的填报人）得到知情同意。该受试者和填报人参与基于临床痴呆等级评定(CDR)量表的用于测定受试者在日常生活中功能性缺损的程度的标准化临床会诊。得到受试者的医学、神经学和精神病学史（包括当前药物的回顾），以及痴呆的家族史。进行简短的医学、神经学和精神病学检查（包括生命体征）。抽血以便进行标准的实验室测试，该测试是确定受试者是否符合入围标准所需的。使用在Kirby成像中心采用的标准形式，对受试者再筛查对MRI扫描的禁忌症。进行简短的认知测试（描述于下面的神经心理学评价部分中）。这些评价用于确定受试者是否符合入围标准。使用标准化形式完成所有前述事项。如果受试者符合该研究的入围标准，那么

给予该受试者该研究的药物（随机选择的药物或安慰剂），和关于如何服用它的说明。对潜在有自杀念头的受试者进行劝导，并且如果发生这样的事，就劝导该受试者停止服用该药物并直接与该研究的医师联系。

[3872] 访视 1：在基线访视之后第一次药物 / 安慰剂期 2 周结束时，重复医学、神经学和精神病学的评价和认知测试。还对受试者的自杀念头进行临床评价。再次抽血以重复标准测试并确定是否有与药物治疗相关的任何变化；还得到了受试者的血液左乙拉西坦水平。收集在基线访视时配制的所有药物（药物或安慰剂），并评价受试者对药物方案的顺应性。在同一天（临床评价的前一刻或后一刻）进行第一个 fMRI 期（具有认知测试）。在该访视时受试者中断第一期治疗。

[3873] 清除访视：在访视 1 之后清除期（4 周）结束时，受试者接受了简短的医学筛查，包括医学和精神病学的评价。抽血以得到血液左乙拉西坦水平（以证实清除）。提供给受试者用于该研究最终阶段的新药物（对先前的治疗期中所指定的药物或安慰剂进行替换的药物或安慰剂）和关于应如何服用它的说明。

[3874] 访视 2：在清除访视之后约 2 周时（即，在开始第二治疗期之后 2 周），重复医学、神经学和精神病学的评价和认知测试。对受试者的自杀念头进行临床评价。再次抽血以重复标准测试并确定是否有与药物治疗相关的任何变化；还得到了受试者的血液左乙拉西坦水平。收集在清除访视时配制的所有药物，并评价受试者对药物方案的顺应性。在同一天（临床评价的前一刻或后一刻）重复第二个 fMRI 期（具有认知测试）。

[3875] 神经心理学的评价

[3876] 所有参与者在对治疗功效评价时（访视 1 和 2）以及在基线访视时接受神经心理学的评价。评价在扫描之后进行，并包括 Buschke 选择联想测试 (Buschke 和 Fuld，1974) 和口头配对相关分测试、逻辑记忆分测试、修订的韦克斯勒记忆量表 (WMS-R) 的视力复现分测试 (Wechsler，1997)，以及 Benton 视觉保留测试，因为这些任务对中颞叶功能和早期记忆问题特别敏感 (Marquis 等人，2002 以及 Masur 等人，1994)。此外，受试者被要求完成更一般的认知功能测试，例如测试以评价一般的精神状态、执行功能、注意力和一般的呼名能力。所有神经心理学的测试通过受训助理研究员在 60- 分钟期间实施。因为该研究中的三项神经心理学的评价在 8 周时期内进行，所以不同版本的神经心理学的测试用于使测试特异性实践效果最小化。按需要向该受试者提供中断。

[3877] 药物施用

[3878] 如上所述，药物治疗期是在访视 1 或 2 之前的两周（在其它访视之前的两周期间是安慰剂阶段）。对于接受药物治疗的受试者，半片刻痕 250mg 的左乙拉西坦片剂用于一日两次获得 125mg/kg 剂量，其约为 3.6mg/kg/ 天（假定平均成人人体重为 70kg）。

[3879] 所有药物和安慰剂制剂都按 1:1 配置。药房按患者登记的最高药物剂量和情况配药随机化，并遵循药物分配表。

[3880] 在口服施用之后左乙拉西坦被快速且几乎完全地吸收，而且它的生物利用度并未受到食物影响。左乙拉西坦的血浆半衰期约为 7±1 小时（考虑在老人中由于降低的肾功能是 9-10 小时）。吸收是快速的，血浆浓度峰值在口服施用后约 1 小时出现。稳态可在每日两次的多次给药 2 天后获得。

[3881] 左乙拉西坦在治疗人癫痫中典型的起始剂量是一日两次 500mg，其约为 14.3mg/

kg/天。随后将该剂量增加直至最佳功效，至多50mg/kg/天。因此，用于该实验的剂量是用于治疗癫痫的最低人剂量的四分之一。

[3882] 基于先前指明低剂量功效的动物研究结果，甚至考虑了更低的剂量，例如，一日两次25-60mg。用于动物模型的左乙拉西坦最高有效剂量是5-10mg/kg(急性给予)。用于治疗人中年龄依赖性认知缺损的剂量的人等效剂量(HED)(如上所述计算的)等于0.8-1.6mg/kg/天(或一天两次28-56mg)。

[3883] MRI数据采集

[3884] 成像数据通过在Stark实验室发展的高分辨率方法得到。在位于Kennedy Krieger研究所(Baltimore，MD)的功能性脑成像F.M.Kirby研究中心(the F.M.Kirby Research Center for Functional Brain Imaging)装配8-通道SENSE(敏感度编码)头部线圈的Phillips 3 Tesla扫描仪上(Eindhoven，The Netherlands)收集数据。高分辨率平面回波图像使用采集矩阵64×64，重复时间1500毫秒，回波时间30毫秒，翻转角70度，SENSE因子2，无间隙的各向同性分辨率1.5mm×1.5mm×1.5mm来收集。平行于海马的主要纵轴并覆盖整个中颞叶区双侧获取19张斜切片(Nineteen oblique slices)。除了功能性运行外，还获取了全脑MPRAGE结构扫描(参数：150张斜切片，1mm各向同性分辨率)。

[3885] 图像分析

[3886] 使用功能性神经成像分析(AFNI，发行于2008_07_18_1710)软件进行数据分析。首先将图像融合(co-registered)以纠正内部-和交叉-扫描头部运动。在其中发生显著的运动事件(相对于先前采集，在任何方向上超过3度的旋转或2mm的平移)的采集，加减一次1.5秒的重复，被排除在该分析之外。将结构的解剖数据融合入标准立体定向空间(Talairach&Tournoux，1988)，并将相同的参数随后应用于功能性数据。行为向量产生出模式不同的试验类型。

[3887] ROI-LDDMM(感兴趣区的大变形微分同胚尺度映射(large deformation diffeomorphic metric mapping))方法，用于穿过受试者校准的技术，通过集中校准功率(具体的是对仅在脑内的ROI(感兴趣区)而非其它)增加了多受试者部位fMRI研究功率。首先，使用AFNI将所有受试者的解剖和功能性扫描标准化至Talairach坐标系。将中颞叶和海马的亚区域(双侧内嗅皮层、鼻周皮层、海马旁皮层、CA3/齿状区、CA1区和下托)在三维MPRAGE扫描上分割。将用于CA3区和齿状回(DG)的标识组合。使用基于测试为靶标的整个样品工具的专门的模版，随后将解剖上定义的ROI用于为每个受试者计算ROI-LDDMM 3D向量场转换。随后将用于每个个体受试者ROI的ROI-LDDMM转换应用于拟合系数图。

[3888] 使用试验类型和组作为固定因素和受试者作为嵌入组内的随机因素的双因素方差分析(ANOVA)来分析组数据。$p<0.05$的宽峰阈(liberal peak threshold)，连同10体素的空间范围阈(spatial extent threshold)用于定义在整个F统计值上的功能性ROI。该方法(而不是使用直接配对对照)减少了体素选择偏倚，因为各种条件中的任何差异都考虑到了待选的体素。随后将该阈与解剖分割组合，以仅仅包含感兴趣区内的体素。这帮助排除不随任何模式因素变化的体素，有效地将该分析限制于显示任何随任务条件或组改变的体素。为进一步分析而将在每个功能性ROI内的体素解体。

[3889] 在访视1和2时fMRI扫描期间的认知测试

[3890] 受试者中颞叶的活动在受试者参与外显3选项强迫选择任务(其中使参与者观察

新的、重复的和类似的（“诱饵”）刺激物）期间通过功能性MRI来测量。将Psychophys ics Toolbox extensions in Matlab7.0(The MathWorks,Natick,MA)用于刺激呈现和行为数据收集。刺激物是常见物体的彩色照片。每个参与者在功能性成像期期间接受一系列测试运行，每个运行由以下三种类型的图像对混合物组成：类似对、相同对和无关衬托（foils)。这些图像对在运行中完全随机化并随一系列的图像单独呈现（参见图6A)。参与者被指示做出关于所看到的每个物体是否是新的、旧的或类似的判断。当类似物体对的第二个（所述“诱饵”;参见图6B)呈现时，极为感兴趣的是参与者的反应。受试者正确识别诱饵刺激物为“类似的”提供了图案分离的行为证据，即将类似的体验分离为不同的无重叠的表示。但是，不正确识别诱饵刺激物为“旧的”或“新的”指明图案分离失败。识别诱饵刺激物为“旧的”指明受试者集中于诱饵刺激物和早期显示的搭档图像之间的类似处。识别诱饵刺激物为“新的”指明受试者未能完全回忆起早期显示的搭档图像。每个运行还包含若干基线试验，该基线试验使用已知的挑战性的知觉辨认任务以提供对中颞叶中基线活动较低和更稳定的估计（Stark&Squire,2001PNAS;Law等人，2005)。

[3891] 如fMRI所测量的在认知测试期间中颞叶中不同亚区的活动水平的调查，显示aMCI受试者在记忆任务的表现期间与年龄匹配对照受试者相比具有活动过强的DG/CA3区和活动减退的内嗅皮层。

[3892] 我们在对照和aMCI受试者中评价了在成功的记忆判断期间DG/CA3中活动的水平。在显示诱饵刺激物被受试者正确地识别为“类似”也就是对基线活动加以校准期间，平均活动从如fMRI所测量的平均活动计算。图4A显示当做出这些判断时aMCI患者显示DG/CA3活动过强（$p = 0.013$)。但是，图4B显示用左乙拉西坦治疗减少了aMCI受试者中DG/CA3过度的活动（$p = 0.037$)。实际上，用药物治疗的aMCI受试者中的活动水平被正常化到了与用安慰剂治疗的对照受试者的活动无统计上差异的程度。参见图4C，其为图4A和4B中所示的平均活动值。

[3893] 在成功的记忆判断期间，与对照相比EC中活动水平在安慰剂治疗的aMCI受试者中显著更低（$p = 0.003$)。参见图5A。但是，左乙拉西坦治疗同样使aMCI受试者EC中的活动正常化。左乙拉西坦治疗在记忆判断期间增加了aMCI受试者的EC活动，以至于与安慰剂治疗的对照受试者无统计上的差异。参见图5C，其为图5A和5B中所示的用于平均活动值。

[3894] 在记忆判断期间通过左乙拉西坦治疗正常化的DG/CA3和EC活动反映在aMCI受试者在认知任务中的表现所见到的变化上。用安慰剂治疗，aMCI患者比对照受试者表现更差，更少正确识别为“类似的”诱饵物品，且更经常不正确识别它们为“旧的”（$p = 0.009$)。参见图7。但是，aMCI受试者的表现在左乙拉西坦治疗下显著改善。参见图8。在药物治疗下更多正确的“类似的”识别与更少不正确“旧的”识别的相互作用导致该记忆任务的表现显著改善（$p = 0.039$)。参见图9，其为图7和8中所示数据的表。

[3895] 还在其它常见的认知测试中将对照-安慰剂受试者和用药物或安慰剂治疗的aMCI受试者的表现进行比较，例如Buschke选择联想测试-延迟回忆（图10A和10B)、Benton视力保持测试（图11A和11B)、口头配对相关测试-识别（图12A和12B)和口头配对相关测试-延迟回忆（图13A和13B)。在所有这些测试中，用安慰剂治疗的aMCI受试者比安慰剂治疗的对照受试者表现更差，并且左乙拉西坦治疗未能改善aMCI受试者的表现。

[3896] 为什么在这些其它认知测试中左乙拉西坦治疗对 aMCI 受试者的表现毫无帮助，存在有许多可能的原因。在 fMRI 研究中所完成的外显 3 选项强迫选择任务是对 DG/CA3 功能特别敏感的任务。照这样，受试者在该任务中的表现可能特别适应由左乙拉西坦治疗产生的DG/CA3活动的变化。而且，aMCI 受试者在实施认知测试之前用左乙拉西坦仅治疗 2 周。预计，比 2 周更长的治疗持续时间（例如，16 周或 8 个月）用于药物治疗将会产生改善的功效。最终，对比的动物研究（参见实施例 1）指明剂量甚至越低越有效。一天两次 125mg 的人剂量等效于 22.3mg/kg/ 天的大鼠剂量。如在实施例 1 和图 1 中所示，在大鼠中 20mg/kg 左乙拉西坦的剂量太高，而它不能改善 AI 大鼠在放射迷宫任务中的表现。用于该动物模型的左乙拉西坦的有效剂量是 5-10mg/kg。最佳大鼠剂量的人等效剂量 (HED) 是 0.8-1.6mg/kg/ 天。这样的剂量会导致一天两次 28-56mg 的施用（其基本上低于用于该研究的一天两次 125mg）。因此，如果他们用等效于大鼠中的有效剂量的较低剂量（例如，左乙拉西坦每天两次 25-60mg）治疗，预计 aMCI 受试者将显示进一步正常化的 DG/CA3 和 EC 活动，以及在认知测试中进一步改善的表现。

[3897] 实施例 3 :左乙拉西坦在具有 aMCI 的受试者中的作用

[3898] 进行为期 8 周的受试者内试验，涉及用左乙拉西坦低剂量治疗的 38 名、遗忘性 MCI(aMCI) 受试者和 17 名年龄匹配对照。在该研究期间，每个 aMCI 受试者在每个两周的两个周期中都分别接受药物和安慰剂治疗，使治疗次序在不同的 aMCI 受试者中等衡（参见图 7）。用安慰剂治疗的年龄匹配对照受试者用作另一对照。在每个两周周期的药物 / 安慰剂治疗之后从受试者得到认知测试和 fMRI 成像数据。

[3899] 参与者和临床表征

[3900] 从在 Johns Hopkins 医院的阿尔茨海默病研究中心 (Alzheimer's Disease Research Center)(ADRC) 和其它转诊机构 (referrals) 招募 38 名惯用右手的 aMCI 患者。从 ADRC 和其它转诊机构的对照参与者库中招募另外 17 名惯用右手的健康志愿者。对所有参与者实施认知状态的电话会诊，以确定他们是否有可能通过该研究的入围标准（包括用于 MRI 扫描的标准）。所有参与者还接受使用标准化仪器和方法的神经学、精神病学以及神经心理学检查。精神病学的评价包括实施用于 DSM-IV 轴 I 障碍的组织临床会诊 (the Structured Clinical Interview for DSM-IV Axis I Disorders) 和临床痴呆等级评定 (the Clinical Dementia Rating)(CDR) 量表。所有 aMCI 患者的 CDR 评分为 0.5。aMCI 的诊断基于由 Petersen 等人（例如，“Mild cognitive impairment :Aging to Alzheimer's Disease,”Oxford University Press, N.Y.(2003)）提议的标准，其包括记忆抱怨（由填报人确证的）、在测试时受损的记忆功能（基准之下 1.5 个标准偏差）、在其它方面保留的认知功能（基准的 1 个标准偏差之内）、功能能力没有减退和无痴呆。通过临床共识达到最终的 aMCI 诊断。淘汰标准包括主要的神经学或精神病学障碍、伴意识丧失的头部损伤、药物滥用或依赖史，以及 MRI 检查的一般禁忌症（例如心脏起搏器、动脉瘤线圈、幽闭恐怖症）。每个 aMCI 受试者需要有可提供关于受试者每日功能的信息并确保适当用药的研究搭档（即，填报人）。

[3901] 研究访视 :该研究由 8 周程内的 4 项访视组成（参见图 7）。基线访视是为了进行医学、神经学、精神病学和神经认知的评价。访视 1 和 2 与基线访视是相同的，但包括 fMRI 期。在 4 周清除期结束时的清除访视，是为了简短的临床评价和开始第二次药物 / 安慰剂

阶段。

[3902] 基线访视：在筛查访视时，从受试者（和 MCI 受试者的填报人）得到知情同意。该受试者和填报人参与基于临床痴呆等级评定 (CDR) 量表的用于测定受试者在日常生活中功能性缺损的程度的标准化临床会诊。得到受试者的医学、神经学和精神病学史（包括当前药物的回顾），以及痴呆的家族史。进行简短的医学、神经学和精神病学检查（包括生命体征）。抽血以便进行标准的实验室测试，该测试是确定受试者是否符合入围标准所需的。使用在 Kirby 成像中心采用的标准形式，对受试者再筛查对 MRI 扫描的禁忌症。进行简短的认知测试（描述于下面的神经心理学评价部分中）。这些评价用于确定受试者是否符合入围标准。使用标准化形式完成所有前述事项。如果受试者符合该研究的入围标准，那么将受试者随机指定入 62.5mg BID 或 250mg BID 研究组并且给予研究药物（随机选择的药物或安慰剂）和关于如何服用它的说明。对潜在有自杀念头的受试者进行劝导，并且如果发生这样的事，就劝导该受试者停止服用该药物并直接与该研究的医师联系。

[3903] 访视 1：在基线访视之后第一次药物 / 安慰剂期 2 周结束时，重复医学、神经学和精神病学的评价和认知测试。还对受试者的自杀念头进行临床评价。再次抽血以重复标准测试并确定是否有与药物治疗相关的任何变化；还得到了受试者的血液左乙拉西坦水平。收集在基线访视时配制的所有药物（药物或安慰剂），并评价受试者对药物方案的顺应性。在同一天（临床评价的前一刻或后一刻）进行第一个 fMRI 期（具有认知测试）。在该访视时受试者中断第一期治疗。

[3904] 清除访视：在访视 1 之后清除期 (4 周）结束时，受试者接受了简短的医学筛查，包括医学和精神病学的评价。抽血以得到血液左乙拉西坦水平（以证实清除）。提供给受试者用于该研究最终阶段的新药物（对先前的治疗期中所指定的药物或安慰剂进行替换的药物或安慰剂）和关于应如何服用它的说明。

[3905] 访视 2：在清除访视之后约 2 周时（即，在开始第二治疗期之后 2 周），重复医学、神经学和精神病学的评价和认知测试。对受试者的自杀念头进行临床评价。再次抽血以重复标准测试并确定是否有与药物治疗相关的任何变化；还得到了受试者的血液左乙拉西坦水平。收集在清除访视时配制的所有药物，并评价受试者对药物方案的顺应性。在同一天（临床评价的前一刻或后一刻）重复第二个 fMRI 期（具有认知测试）。

[3906] 神经心理学的评价

[3907] 所有参与者在对治疗功效评价时（访视 1 和 2) 以及在基线访视时接受神经心理学的评价。评价在扫描之后进行，并包括 Buschke 选择联想测试 (Buschke 和 Fuld，1974) 和口头配对相关分测试、逻辑记忆分测试、修订的韦克斯勒记忆量表 (WMS-R) 的视力复现分测试 (Wechsler，1997)，以及 Benton 视觉保留测试，因为这些任务对中颞叶功能和早期记忆问题特别敏感 (Marquis 等人，2002 以及 Masur 等人，1994)。此外，受试者被要求完成更一般的认知功能测试，例如测试以评价一般的精神状态、执行功能、注意力和一般的呼名能力。所有神经心理学的测试通过受训助理研究员在 60- 分钟期间实施。因为该研究中的三项神经心理学的评价在 8 周时期内进行，所以不同版本的神经心理学的测试用于使测试特异性实践效果最小化。按需要向该受试者提供中断。

[3908] 药物施用

[3909] 如上所述，药物治疗期是在访视 1 或 2 之前的两周（在其它访视之前的两周期间

是安慰剂阶段）。对于接受 250mg BID(BID 表示每日 2 次）药物治疗的受试者，2 片 250mg 的左乙拉西坦片剂用于一日两次获得 250mg 剂量，即 500mg/ 天，其约为 7.1mg/kg/ 天（假定平均成人人体重为 70kg)。对于接受 62.5mg BID 药物治疗的受试者，四分之一片刻痕的 250mg 的左乙拉西坦片剂用于一日两次获得 62.5 剂量，即 125mg/ 天，其约为 1.5mg/kg/ 天。

[3910] 所有药物和安慰剂制剂都按 1:1 配置制备。药房按患者登记的药剂量和情况配药随机化，并遵循药物分配表。

[3911] 在口服施用之后左乙拉西坦被快速且几乎完全地吸收，而且它的生物利用度并未受到食物影响。左乙拉西坦的血浆半衰期约为 7±1 小时（考虑在老人中由于降低的肾功能是 9-10 小时）。吸收是快速的，血浆浓度峰值在口服施用后约 1 小时出现。稳态可在每日两次的多次给药 2 天后获得。

[3912] 左乙拉西坦在治疗人癫痫中典型的起始剂量是一日两次 500mg，其约为 14.3mg/ kg/ 天。随后将该剂量增加直至最佳功效，至多 50mg/kg/ 天。因此，用于该实验的 250mg BID 剂量 (500mg/ 天）是用于治疗癫痫的最低人剂量的一半。62.5mg BID 剂量 (125mg/ 天）是用于治疗癫痫的最低人剂量的八分之一。

[3913] MRI 数据采集

[3914] 成像数据通过在 Stark 实验室发展的高分辨率方法得到。在位于 Kennedy Krieger 研究所 (Baltimore, MD) 的功能性脑成像 F.M.Kirby 研究中心 (the F.M.Kirby Research Center for Functional Brain Imaging) 装配 8- 通道 SENSE（敏感度编码）头部线圈的 Phillips 3 Tesla 扫描仪上 (Eindhoven, The Netherlands) 收集数据。高分辨率平面回波图像使用采集矩阵 64×64，重复时间 1500 毫秒，回波时间 30 毫秒，翻转角 70 度，SENSE 因子 2，无间隙的各向同性分辨率 1.5mm×1.5mm×1.5mm 来收集。平行于海马的主要纵轴并覆盖整个中颞叶区双侧获取 19 张斜切片 (Nineteen oblique slices)。除了功能性运行外，还获取了全脑 MPRAGE 结构扫描（参数 :231 张斜切片，0.65mm 各向同性分辨率）。

[3915] 图像分析

[3916] 使用功能性神经成像分析 (AFNI，发行于 2010_10_19_1028) 软件进行数据分析。首先将图像融合 (co-registered) 以纠正内部 - 和交叉 - 扫描头部运动。在其中发生显著的运动事件（相对于先前采集，在任何方向上超过 3 度的旋转或 2mm 的平移）的采集，加减一次 1.5 秒的重复，被排除在该分析之外。将结构的解剖数据融合入标准立体定向空间 (Talairach&Tournoux, 1988)，并将相同的参数随后应用于功能性数据。行为向量产生出模式不同的试验类型。

[3917] ROI-LDDMM（感兴趣区的大变形微分同胚尺度映射 (large deformation diffeomorphic metric mapping)）方法，用于穿过受试者校准的技术，通过集中校准功率（具体的是对仅在脑内的 ROI（感兴趣区）而非其它）增加了多受试者部位 fMRI 研究功率。首先，使用 AFNI 将所有受试者的解剖和功能性扫描标准化至 Talairach 坐标系。将中颞叶和海马的亚区域（双侧内嗅皮层、鼻周皮层、海马旁皮层、CA3/ 齿状区、CA1 区和下托）在三维 MPRAGE 扫描上分割。将用于 CA3 区和齿状回 (DG) 的标识组合。使用 Advanced Normalization Tools(ANTs) 软件和基于测试为靶标的整个样品工具的专门的模版，随后将解剖上定义的 ROI 用于为每个受试者计算向量场转换。随后将得到的用于每个个体受试者 ROI 向量转换应用于拟合系数图。

[3918] 使用试验类型和组作为固定因素和受试者作为嵌入组内的随机因素的双因素方差分析 (ANOVA) 来分析组数据。p<0.07 的宽峰阈 (liberal peak threshold),连同 40 体素的空间范围阈 (spatial extent threshold) 用于定义在整个 F 统计值上的功能性 ROI。该方法 (而不是使用直接配对对照) 减少了体素选择偏倚,因为各种条件中的任何差异都考虑到了待选的体素。随后将该阈与解剖分割组合,以仅仅包含感兴趣区内的体素。这帮助排除不随任何模式因素变化的体素,有效地将该分析限制于显示任何随任务条件或组改变的体素。为进一步分析而将在每个功能性 ROI 内的体素解体。

[3919] 在访视 1 和 2 时 fMRI 扫描期间的认知测试

[3920] 受试者中颞叶的活动在受试者参与外显 3 选项强迫选择任务 (其中使参与者观察新的、重复的和类似的 ("诱饵") 刺激物) 期间通过功能性 MRI 来测量。将 Psychophysics Toolbox extensions in Matlab7.0(The MathWorks,Natick,MA) 用于刺激呈现和行为数据收集。刺激物是常见物体的彩色照片。每个参与者在功能性成像期期间接受一系列测试运行,每个运行由以下三种类型的图像对混合物组成 :类似对、相同对和无关衬托 (foils)。这些图像对在运行中完全随机化并随一系列的图像单独呈现 (参见图 10A)。参与者被指示做出关于所看到的每个物体是否是新的、旧的或类似的判断。当类似物体对的第二个 (所述"诱饵";参见图 10B) 呈现时,极为感兴趣的是参与者的反应。受试者正确识别诱饵刺激物为"类似的"提供了图案分离的行为证据,即将类似的体验分离为不同的无重叠的表示。但是,不正确识别诱饵刺激物为"旧的"或"新的"指明图案分离失败。识别诱饵刺激物为"旧的"指明受试者集中于诱饵刺激物和早期显示的搭档图像之间的类似处。识别诱饵刺激物为"新的"指明受试者未能完全回忆起早期显示的搭档图像。每个运行还包含若干基线试验,该基线试验使用已知的挑战性的知觉辨认任务以提供对中颞叶中基线活动较低和更稳定的估计 (Stark&Squire,2001PNAS ;Law 等人,2005)。

[3921] 如 fMRI 所测量的在认知测试期间中颞叶中不同亚区的活动水平的调查,显示 aMCI 受试者在记忆任务的表现期间与年龄匹配对照受试者相比具有活动过强的 DG/CA3 区和活动减退的内嗅皮层。

[3922] 我们在对照和 aMCI 受试者中评价了在成功的记忆判断期间 DG/CA3 中活动的水平。在显示诱饵刺激物被受试者正确地识别为"类似"也就是对基线活动加以校准期间,平均活动从如 fMRI 所测量的平均活动计算。图 22A 和 22B 显示当做出这些判断时 62.5mg BID 组 (N = 20) 和 250mg BID 组 (N = 17) 中的 aMCI 患者显示 DG/CA3 活动过强 (分别为 p = 0.0041 和 p = 0.0466)。使用左乙拉西坦治疗均没有显著地减少在 250mg BID 或 62.5mg BID 组中的 aMCI 受试者的 DG/CA3 活动过强。

[3923] 用左乙拉西坦治疗在记忆判断期间的 DG/CA3 活动水平在认知任务中的 aMCI 受试者行为中观察到的改变中反映出来。使用安慰剂治疗,aMCI 患者的行为比对照组受试者差,正确鉴定诱饵物品为"类似"的能力通常较低,且将它们不正确地鉴定为"旧的",通常在 62.5mg BID 组和 250mg BID 组中较多。参见图 19A 和 23B。然而,aMCI 受试者的行为在 62.5mg BID 左乙拉西坦治疗中显著地改善。参见图 20A。在药物治疗中更正确地"类似"鉴定与较不正确地"旧的"鉴定的相互作用导致这种记忆任务的行为显著地改善 (p = 0.041)。aMCI 受试者的行为在 250mg BID 左乙拉西坦治疗中未显著地改善 (p = 0.2396)。参见图 20B。

[3924] 实施例 4 :布立西坦和 Seletractam 在老龄大鼠中的作用

[3925] 受试者

[3926] 8-9 个月龄的老龄的雄性 Long-Evans 大鼠得自 Charles River Laboratories(Raleigh, NC) 并且使其寄居在约翰斯霍普金斯大学的动物饲养所,直到 24-26 个月龄为止。使得自同一来源的年幼大鼠寄居在同一动物饲养所,并且在 6 个月龄时测试。将全部大鼠分别寄居在 25℃并且维持 12hr 光照 / 黑暗周期。除非另有规定,否则随意提供食物和水。在实验的至始至终检查大鼠的健康和无病原体状态并且在处死时进行尸体剖检。根据 National Institutes of Health 的指导,当前研究的全部操作均得到公共动物保护和应用委员会 (Institutional Animal Care and Use Committee) 批准。

[3927] 认知状态的背景表征

[3928] 在属于实验性治疗进行研究之前,在空间认知的标准化评价中筛选全部大鼠。该背景评价使用充分建立的莫里斯水迷宫方案。MWM 方案基本上与实施例 1 中所述的相同。另外参见 Gallagher 等人,Behav. Neurosci. 107 :618-626, (1993)。简言之,训练大鼠 8 天 (每天 3 次试验) 以定位在水迷宫中训练的至始至终保持在同一位置上的伪装逃避平台。每一第六次试验由探头试验 (无逃避平台的自由游泳) 组成,其用于评价对于逃避平台的空间定位寻找的发生。在这些探头试验过程中,根据大鼠对于逃避平台的亲近性生成学习指数并且用于定义老龄中的缺损。学习指数是在探头试验过程中得到的加权亲近性得分总和,其中低得分反映出探查接近逃避平台,而高得分反映出探查远离该平台 (Gallagher 等人,1993)。线索训练 (可见的逃避平台) 在训练的最后 1 天进行以测试感觉运动和激发性因素,与空间学习无关。将具有受损的空间记忆行为 (即具有处于年幼"标准规范"范围之外的学习指数得分的那些)、但成功的线索训练行为的老龄大鼠表征为老龄受损大鼠 (即 AI 大鼠)。AI 大鼠用于如下所述的研究。

[3929] 治疗

[3930] 放射臂迷宫实验在测试期前 30-40min 使用紧急施用通过腹膜内注射给予的塞曲西坦 (0-4mg/kg)、布立西坦 (0-4mg/kg) 或盐水媒介物 (在 1ml/kg 体积中)。在长期治疗实验中,给记忆受损的老龄大鼠经皮下在肩胛区内侧区植入小型渗透泵 (ALZET, Durect Corporation, Cupertino, CA),其中在水迷宫中的评价前 2 周开始使用布立西坦 (2mg/kg/天) 或盐水媒介物。

[3931] 放射臂迷宫中的行为评价

[3932] 放射臂迷宫 (RAM) 任务用于评价使用塞曲西坦和布立西坦紧急药物治疗的作用。该方案允许在受试者评价期间施用不同剂量的药物。放射臂由 8 条从八角形中心平台的每侧投射出,其中食物孔位于每条臂的远端。可以使树脂玻璃块定位以防止进入任何臂。将迷宫外的线索提供在室内迷宫的周围并且用高架光提供照明。

[3933] 如 Chappell 等人 Neuropharmacology 37 :481-487, (1998) 中详细描述的预先训练由习惯、标准 win-shift 训练和 win-shift 训练组成,其中在信息与记忆测试期之间插入延迟。药物治疗从完成预先训练后 2 天开始。在每次试验开始时封闭 3 条臂 (信息期)。在试验过程中改变封闭的臂的身份和结构。允许丧失食物的大鼠从 5 条未封闭的臂中回收食物作为奖赏 (Kellogg's Froot Loops 谷物)。然后从迷宫中取出大鼠 2h(滞留间隔),在此期间,取出封闭的臂上的屏障,允许进入所有 8 条臂。然后将大鼠放回到中心平台上并

且允许回收剩余的食物作为奖赏（记忆测试期）。错误由返回到得到食物的臂组成（臂上的所有4个爪）。首先用一系列药物剂量按照升/降次序测试记忆受损的老龄大鼠（n＝8，塞曲西坦；和n＝9，布立西坦）；由此每个记录测试2次。在每次测定之间有1天清除日。2-hr延迟后的滞留间隔中形成的错误数量用于评价记忆行为。参见图15和图16。测试一系列布立西坦剂量：0.0625mg/kg、0.125mg/kg、0.25mg/kg、0.5mg/kg、1mg/kg、2mg/kg和4mg/kg。测试一系列塞曲西坦剂量：0.0625mg/kg、0.125mg/kg、0.25mg/kg、0.5mg/kg、1mg/kg、2mg/kg和4mg/kg。如图15中所示，布立西坦具有作为测试范围剂量的函数的显著作用（对于受试者对比度内的重复测量ANOVA，$F(1,8) = 6.046$，$p = 0.039$）。如图16中所示，塞曲西坦也具有作为测试范围剂量的函数的显著作用（对于受试者对比度内的重复测量ANOVA，$F(1,7) = 12.577$，$p = 0.009$）。

[3934] 水迷宫中的行为评价

[3935] 在新的水迷宫环境中训练并且测试大鼠以评价药物治疗的作用。本文所用的水迷宫位于不同建筑中并且周围有一组相对于用于起始认知状态评价的迷宫而言新的模式的帘布。训练方案由每日6次试验进行2天组成，以定位浸入水下的逃避平台。在每次试验中，将大鼠从水池周边周围的4个等距离的起始位置放入迷宫中。起始位置因每次试验而不同。如果大鼠在任何试验中无法在60s内确定逃避平台的位置，则实验者将大鼠引导并且放置在该平台上，其中使其停留20s。然后从该平台上取走大鼠并且将其放入停留笼中再经过40s，然后进行下一次试验。在最后训练试验后约24h，在没有逃避平台的存在下给予探头检验，以评价空间记忆。在水迷宫任务中的行为评价结果如图17A和图17B中所示。用2mg/kg/天（$t(2) = 10.000$，$p = 0.010$）布立西坦、但不用媒介物（$t(2) = 1.964$，$p = 0.188$）治疗的大鼠显示对于目标四分圆的空间偏好比对另外的对照四分圆显著。此外，布立西坦-治疗的大鼠（2mg/kg/天）在目标四分圆上花费的时间明显多于媒介物-治疗的大鼠，$t(4) = 3.881$，$p = 0.018$。布立西坦-治疗的大鼠（2mg/kg/天）在目标环形物（逃避平台位置周围的区域）上花费的时间明显多于媒介物-治疗的大鼠，$t(4) = 3.109$，$p = 0.036$。

[3936] 实施例5：使用左乙拉西坦在老龄受损大鼠中的长期治疗

[3937] 受试者

[3938] 8-9个月龄的老龄的雄性Long-Evans大鼠得自Charles River Laboratories(Raleigh，NC)并且使其寄居在约翰斯霍普金斯大学的动物饲养所，直到24-26个月龄为止。使得自同一来源的年幼大鼠寄居在同一动物饲养所，并且在6个月龄时测试。将全部大鼠分别寄居在25℃并且维持12h光照/黑暗周期。除非另有规定，否则随意提供食物和水。在实验的至始至终检查大鼠的健康和无病原体状态并且在处死时进行尸体剖检。根据National Institutes of Health的指导，当前研究的全部操作均得到公共动物保护和应用委员会(Institutional Animal Care and Use Committee)批准。

[3939] 背景行为表征

[3940] 在属于实验性治疗进行研究之前，在空间认知的标准化评价中筛选全部大鼠。该背景评价使用充分建立的如Gallagher等人，1993所述的莫里斯水迷宫方案。简言之，训练大鼠8天（每天3次试验）以定位在水迷宫中训练的至始至终保持在同一位置上的伪装逃避平台。每一第六次试验由探头试验（无逃避平台的自由游泳）组成，其用于评价对于

逃避平台的空间定位寻找的发生。在这些探头试验过程中，根据大鼠对于逃避平台的亲近性生成学习指数并且用于定义老龄中的缺损。学习指数是在探头试验过程中得到的加权亲近性得分总和，其中低得分反映出探查接近逃避平台，而高得分反映出探查远离该平台(Gallagher 等人，1993)。线索训练（可见的逃避平台）在训练的最后 1 天进行以测试感觉运动和激发性因素，与空间学习无关。将具有受损的空间记忆行为（即具有处于年幼“标准规范”范围之外的学习指数得分的那些）、但成功的线索训练行为的老龄大鼠用于如下所述的研究。

[3941] 手术和治疗

[3942] 在异氟烷麻醉下，给记忆受损的老龄大鼠经皮下在肩胛区内植入小型渗透泵(ALZET，Durect Corporation，Cupertino，CA)，其中在灌注前将左乙拉西坦（10mg/kg/ 天）或盐水媒介物施用 4 周。用作对照组的年幼大鼠接受小型泵中的盐水媒介物或不植入。

[3943] 灌注和组织制备

[3944] 在 4- 周治疗期结束时，用异氟烷麻醉大鼠并且跨内侧底段支气管灌注 0.1M 磷酸缓冲盐水，然后灌注 4％在磷酸盐缓冲液中的低聚甲醛。取出脑半球后固定入低聚甲醛过夜。然后将脑转入包含 16％蔗糖的 4％在磷酸盐缓冲液中的低聚甲醛。然后用冷冻切片机的冠状平面上将脑切成 40μm 并且在 4℃储存在 4％低聚甲醛中，用于原位杂交或在 -20℃冷冻保护，用于免疫组织化学。

[3945] 探针分析

[3946] 如 Haberman 等人 (2008) 所述合成探针模板。用于颤蛋白的起始引物序列如下：左，agtactcagacgtgcagtgg，右，ctcatgaagcaaagtccaa；通过限制酶消化验证 PCR 产物。再用通过添加 T7 或 SP6RNA 聚合酶结合位点修饰的相同 PCR 引物进一步扩增起始 PCR 产物。通过 Svgel 和 a PCR 清除试剂盒 (Promega) 纯化包含 T7 和 SP6 延伸物的 PCR 化物。然后使用 Maxiscript 试剂盒 (Ambion) 生成 35S-UTP 标记的 riboprobe。然后用苯酚 / 氯仿提取探针并且在 -80℃用乙醇沉淀。将最终探针重新混悬于无 RNase 的水且用闪烁计数器测定比活性。

[3947] 原位杂交

[3948] 如 Haberman 等人 (2008) 所述进行原位杂交。用 0.75％甘氨酸在 0.1M 磷酸盐缓冲液中的溶液将自由漂浮的组织切片洗涤 2 次，然后用磷酸盐缓冲液单次洗涤。此后，在 37℃将切片在包含 1.0μg/ml 蛋白酶 K 的蛋白酶 K 缓冲液中反应 30 分钟。然后在室温用酸酐溶液 (11.3％三乙醇胺、0.25％乙酐、0.04M 乙酸）将切片处理 10 分钟。此后用 2x 氯化钠 / 柠檬酸哪缓冲液 (SSC 缓冲液；20x 浓度，3M NaCl，0.3M 柠檬酸钠）洗涤 2 次 15- 分钟。接下来将切片转入包含 20％甲酰胺、0.4x Denhardt 溶液、4％硫酸葡聚糖和 1.6x SSC) 的杂交缓冲液，其补充了 0.25mg/ml tRNA、0.33mg/ml 剪切的鲑精 DNA、100mM DTT 和 1x107cpm/ml 35S-UTP- 标记的探针，用于在 60℃的过夜反应。第二天，在 60℃用 4x SSC/0.01M DTT 和 2x SSC/50％甲酰胺洗涤切片。然后将它们与 RNase(20μg/ml) 在 37℃一起温育 30min。用逐步递减浓度的 SSC 洗涤切片，然后固定在载玻片上。将载玻片干燥过夜，暴露于 phosphoimager 屏幕并且通过使用 ImageQuant(GE Healthcare) 定量。从所有动物的内嗅皮质切片中获取数字图像，并且对所关注的亚区分级并且定量。求切片的平均值，得到针对每只动物的单一得分。

[3949] 免疫组织化学

[3950] 用抗-SOM抗血清(Santa Cruz Biotechnology;目录号SC7819-P)、应用建立的免疫过氧化物酶方案标记组织,并且同时处理组织切片以便将复制间变异性降至最低(Haberman等人,2009)。抗-SOM抗血清可以检测生长抑素。简言之,用0.1M磷酸缓冲盐水(PBS)洗涤切片以除去冷冻保护剂,且用0.3% H202的PBS溶液使内源性过氧化物酶猝灭。在进行另外的PBS洗涤后,用含有0.3% Triton的5%正常马血清的PBS溶液封闭切片。然后在4℃在搅拌的同时将切片与初级抗体一起温育72小时,所述初级抗体用包含0.15% Triton和3%正常血清的PBS按照1:1600稀释。在初级抗体温育后,用PBS洗涤切片并且使其与用含有0.15% Triton和5%正常血清的PBS的稀释的马抗-山羊IgG生物素化二次抗体(Vector Laboratories Inc.,Burlingame,CA)反应45分钟。用生物素蛋白-生物素复合物(ABC Elite;Vector Laboratories Inc.,Burlingame,CA)检测二次抗体,并且使用镍-增强的二氨基benzadine(Vector Laboratories Inc.,Burlingame,CA)使抗生物素蛋白-生物素复合物显影。将组织切片固定在包被的载玻片上并且干燥,用递增浓度的乙醇脱水,用二甲苯清洁并且使用DPX固定培养基覆盖盖玻片。

[3951] 使用安装运动平台的Zeiss Axioplan 2显微镜进行中间神经元定量。对有关动物年龄和认知状态进行全部双盲分析。使用Paxinos和Watson大鼠脑寰椎(1998)定义锯齿状门区。使用40x物镜发现背侧门神经元计数双侧来源于每只动物的4个配对的组织切片(冠矢点-3.80mm-4.16mm)。对于每只大鼠,将神经元计数分析为每个海马切片的门中间神经元的总数。

[3952] 结果

[3953] 生长抑素是肽激素,其调节内分泌系统并且通过与G蛋白偶联生长抑素受体的相互作用和抑制大量二次激素释放影响神经传递和细胞增殖。已经证实脑中的生长抑素水平降至与衰老和阿尔茨海默病进展相关的低至10-20%。以10mg/kg/天剂量的左乙拉西坦在老龄受损大鼠中的4-周治疗恢复了DG门中的生长抑素水平。参见图21。施用生理盐水而不是药物的老龄受损大鼠相对于年幼和左乙拉西坦治疗的老龄大鼠具有显著较低数量的SOM-免疫反应性门神经元(N = 18;F2,20 = 15.739,p<0.001;AI-LEV与Y,p = 0.679;AI-LEV与AI-VEH,p<0.01;AI-VEH与Y,p<0.001)。

[3954] 颤蛋白是大量分泌的胞外基质糖蛋白,其有助于调节神经元迁移过程和通过控制细胞间作用定位在发育的脑中。在具有记忆丧失的老龄大鼠、hAPPJ20AD小鼠以及人AD脑中中观察到EC2神经元中减少的颤蛋白表达(Chin等人2007;Stranahan等人2010)。以10mg/kg/天剂量的左乙拉西坦在老龄受损大鼠中的4-周治疗恢复了内嗅皮层(EC2)中的颤蛋白水平。参见图22。一种方式ANOVA显示组间的显著性差异,F(2,20) = 5.035,p = 0.017。另外的分析显示用媒介物对照品治疗的AI大鼠(AI-VEH)的侧面内嗅皮质中的颤蛋白mRNA表达比年幼大鼠显著减少,t(13) = 2.790,p = 0.015。以10mg/kg/天剂量的左乙拉西坦在AI大鼠中治疗28天(AI-LEV)显著地增加了颤蛋白表达,t(13) = 2.386,p = 0.033(与AI-VEH相比)。

[3955] 实施例6:左乙拉西坦血浆水平的评价

[3956] 人:在实施例3和4中所述的人研究中,在每次访视时评价受试者的左乙拉西坦血浆水平。由Johns Hopkins Phlebotomy Service抽取受试者血液并且由Johns Hopkins

Core 实验室或 MedTox Laboratories 在 St. Paul, MN 对 62.5mg BID 组、125mg BID 组和 250mg BID 组进行左乙拉西坦血浆水平分析。在完成左乙拉西坦治疗时,62.5mg BID 组中的受试者显示平均左乙拉西坦血浆水平为 2.88mcg/ml(SEM±0.288),而 125mg BID 中的水平具有 4.4mcg/ml(SEM±0.53),且 250mg BID 组中的受试者显示平均左乙拉西坦血浆水平为 7.9mcg/ml(SEM±0.92)。参见图 23A-23c。

[3957] 大鼠:在 28-天左乙拉西坦治疗期后的灌注过程中通过心脏穿刺从老龄大鼠中抽取血液,并且送去用于由 MedTox Laboratories 在 St. Paul, MN 分析左乙拉西坦血浆水平。用 10mg/kg/ 天左乙拉西坦治疗的老龄老鼠显示平均左乙拉西坦血浆水平为 3.8mcg/ml(SEM±0.255),同时用 60mg/kg/ 天治疗的那些显示平均左乙拉西坦血浆水平为 22.4mcg/ml(SEM±3.371)。

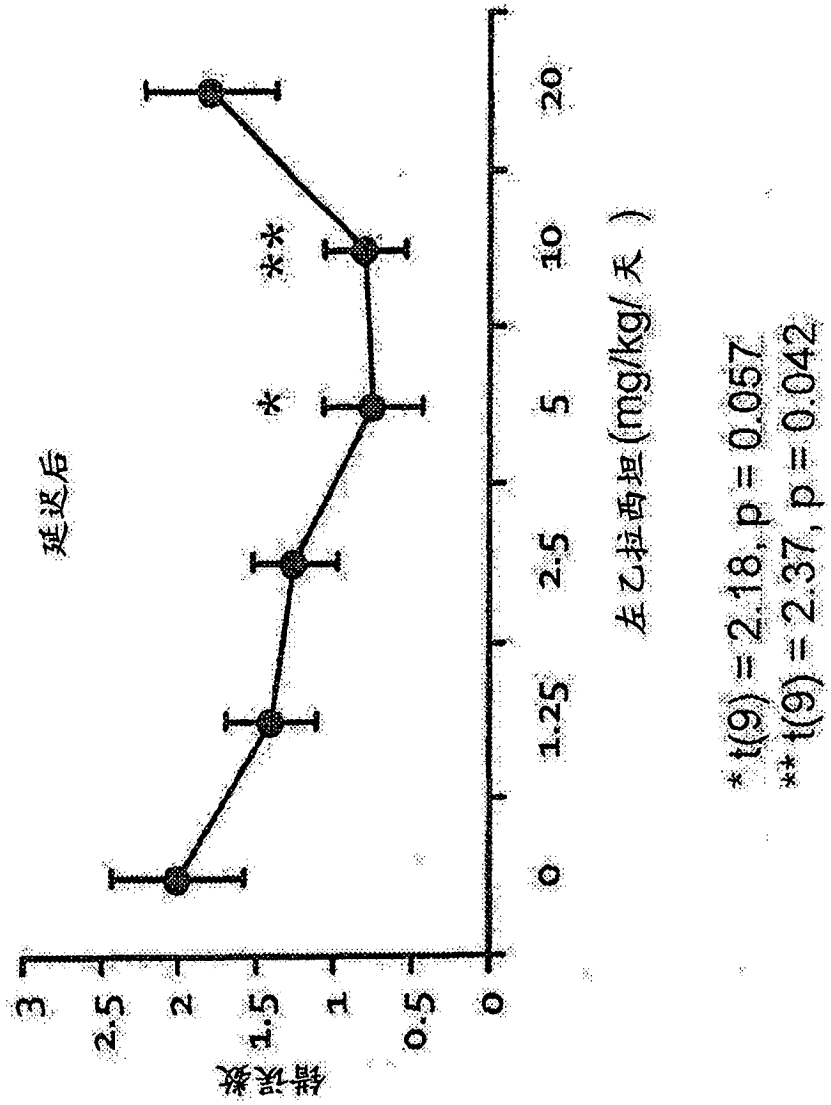

延迟后
错误数
3
2.5
2
1.5
1
0.5
0
0
1.25
2.5
5
10
20
左乙拉西坦(mg/kg/天)
*
**
* t(9) = 2.18, p = 0.057
** t(9) = 2.37, p = 0.042

图 1

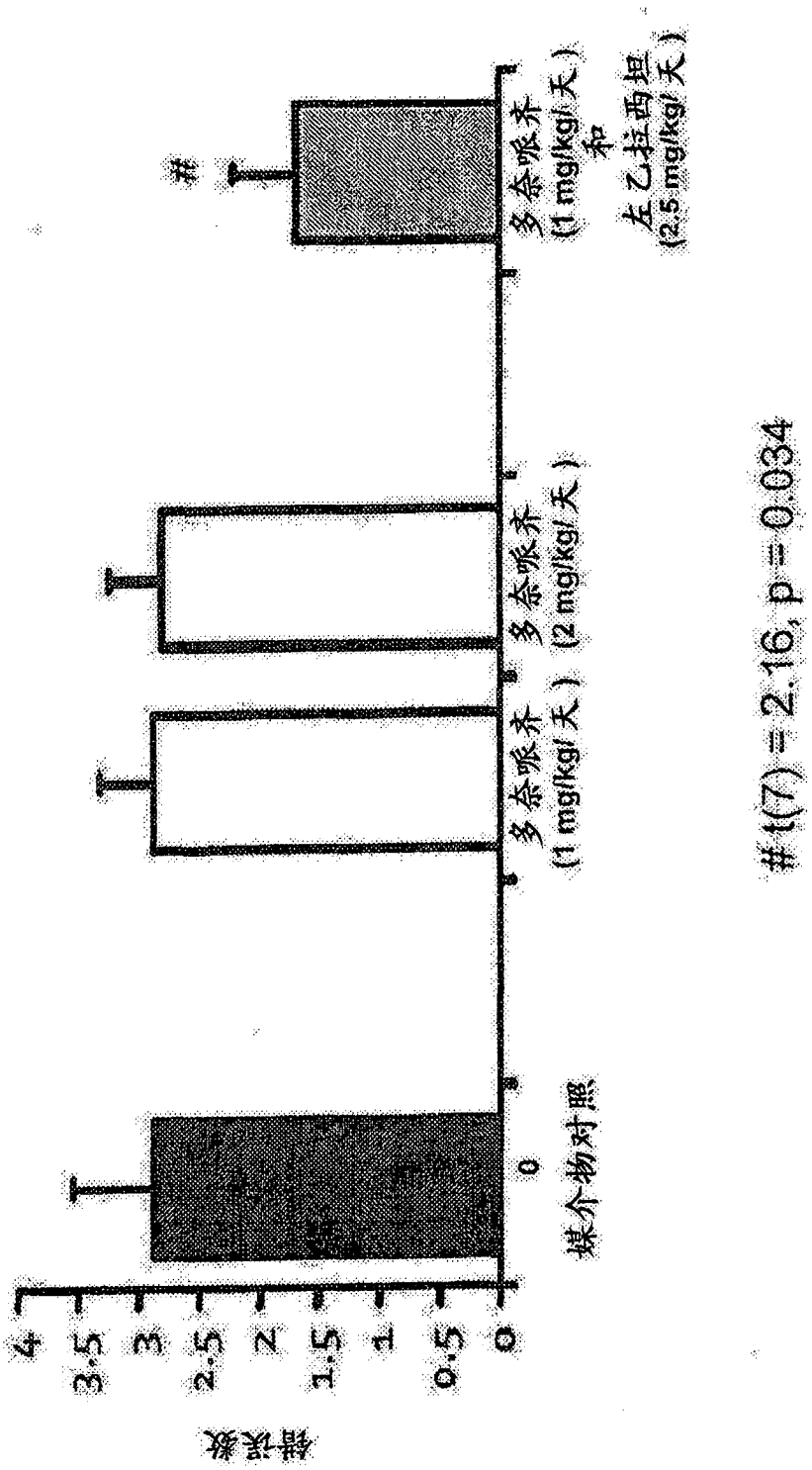

错误数
4
3.5
3
2.5
2
1.5
1
0.5
0
媒介物对照
多奈哌齐 (1 mg/kg/天)
多奈哌齐 (2 mg/kg/天)
多奈哌齐 (1 mg/kg/天) 和 左乙拉西坦 (2.5 mg/kg/天)
#
#t(7) = 2.16, p = 0.034

图 2

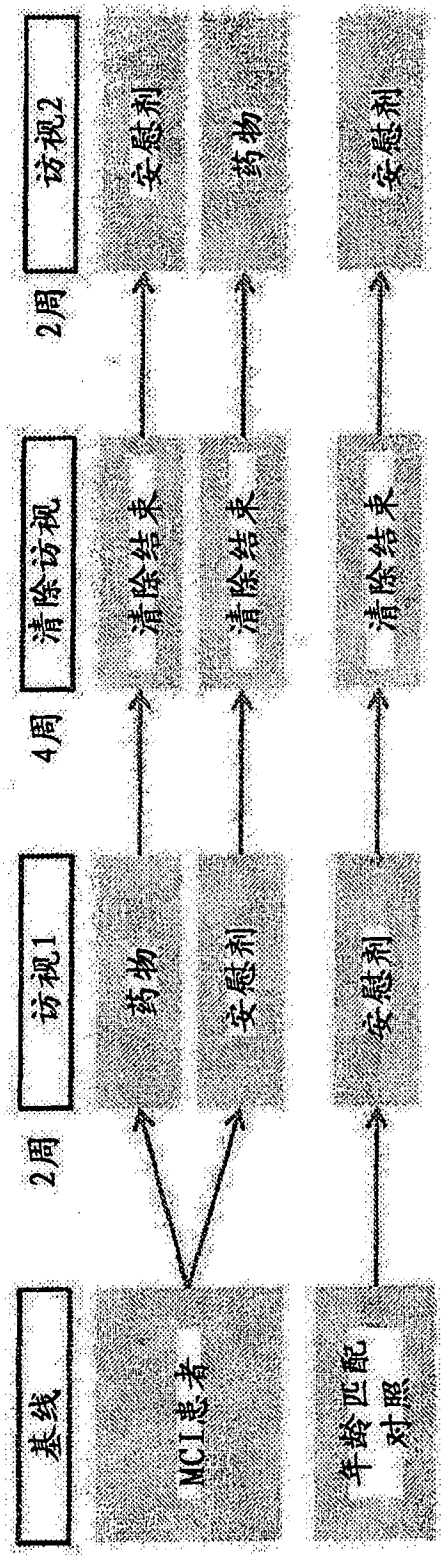

基线
2周
访视1
4周
清除访视
2周
访视2
MCI患者
药物
安慰剂
年龄匹配
对照
安慰剂
清除结束
药物
安慰剂
清除结束
安慰剂
清除结束

图 3

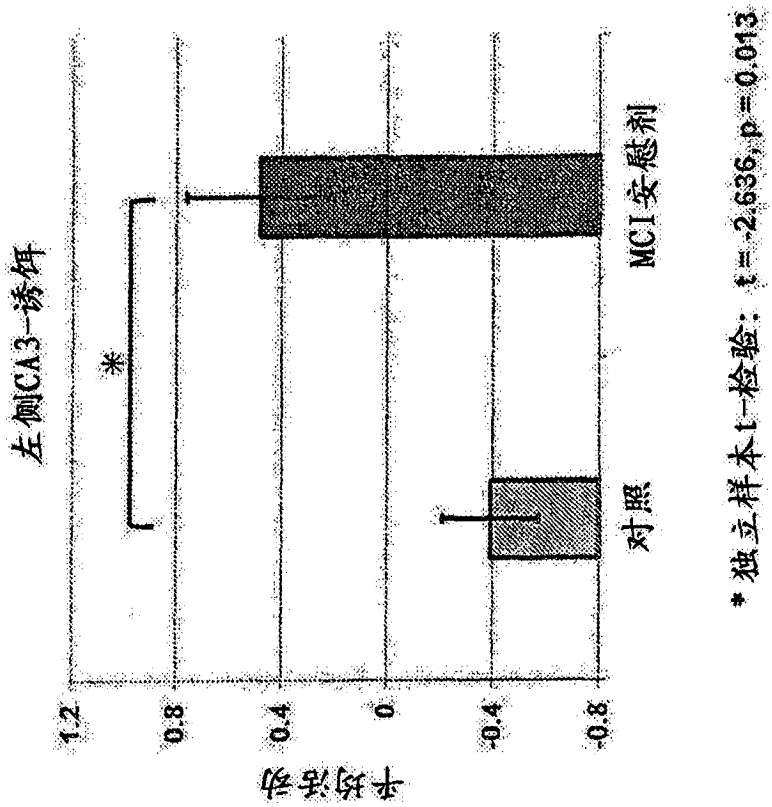


图 4A

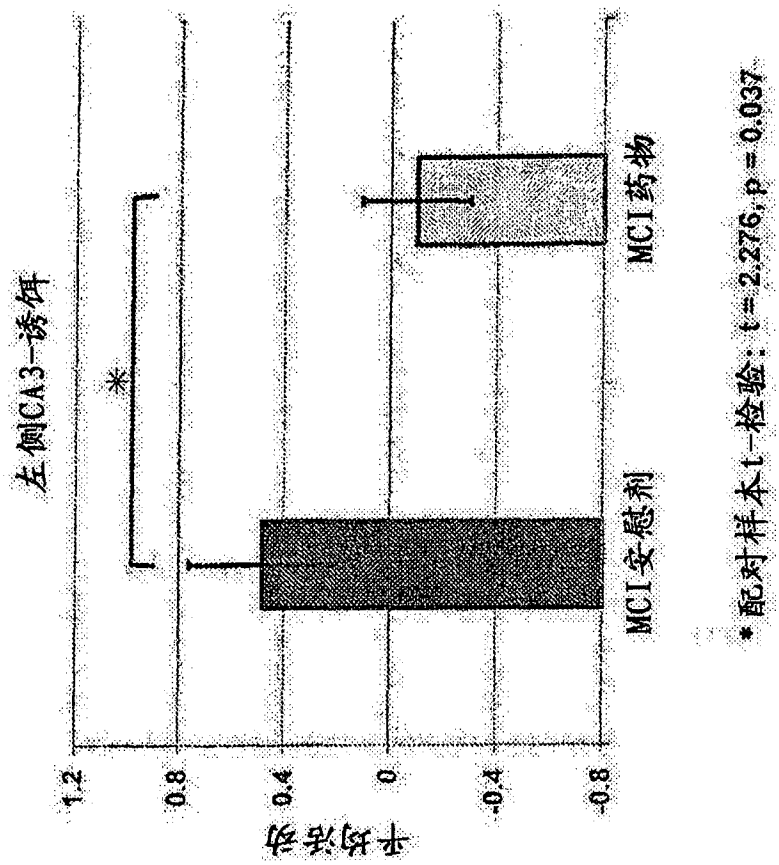

左侧CA3-诱饵
平均活动
1.2
0.8
0.4
0
-0.4
-0.8
MCI药物
MCI安慰剂
*配对样本t-检验：t=2.276,p=0.037

图 4B

左侧CA3诱伴

组别	平均活动	标准误差
对照	-0.39129	0.182628
MCI安慰剂	0.48440	0.277487
MCI药物	-0.09653	0.205892

图 4C

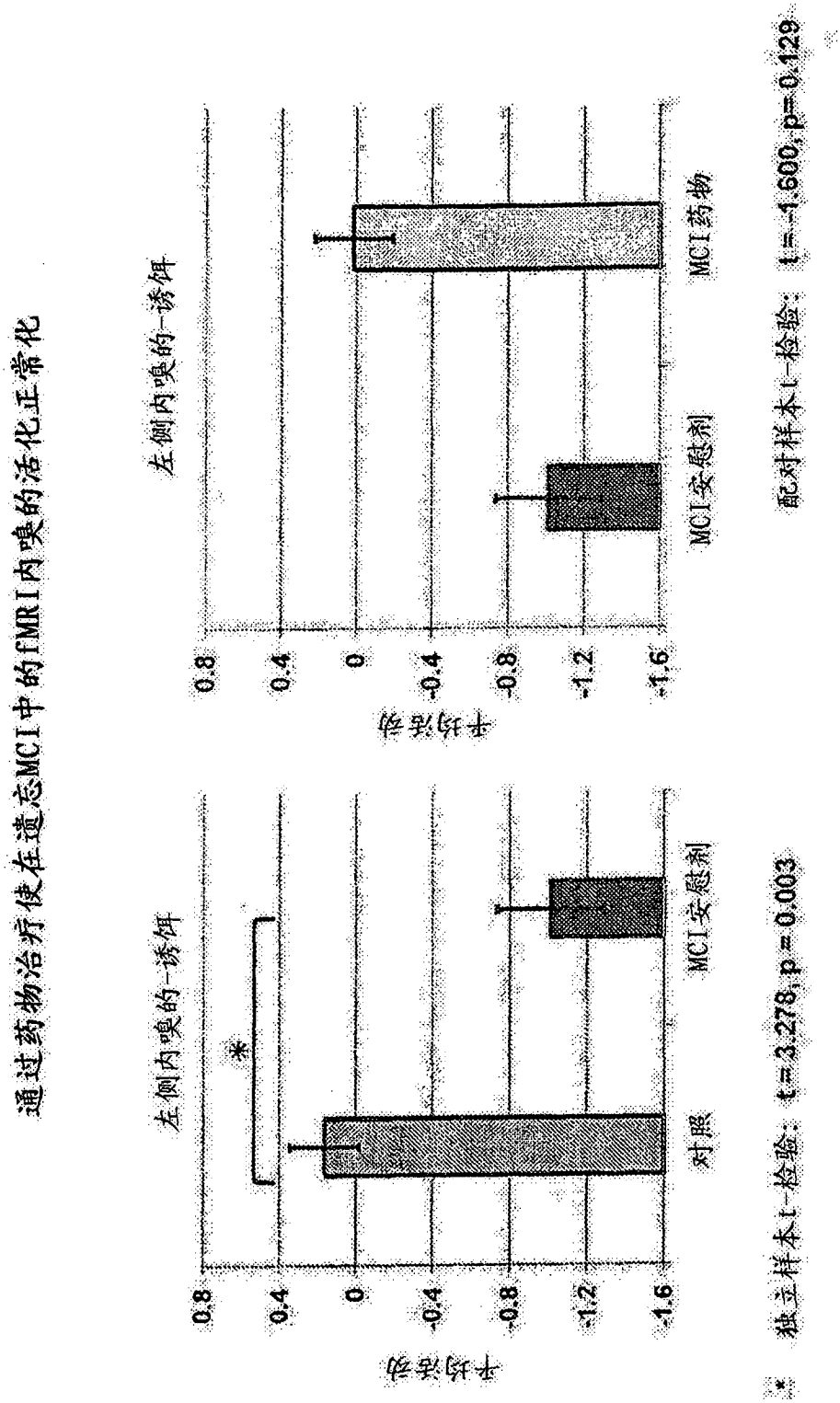

通过药物治疗使在遗忘MCI中的FMRI内嗅的活化正常化
左侧内嗅的-诱饵
平均活动
0.8
0.4
0
-0.4
-0.8
-1.2
-1.6
*
对照
MCI安慰剂
MCI药物
* 独立样本t-检验: t=3.278, p=0.003
配对样本t-检验: t=-1.600, p=0.129

图5A

图5B

左侧内嗅的诱饵

组别	平均活动	标准误差
对照	0.16444	0.143864
MCI安慰剂	-1.01273	0.329062
MCI药物	0.016291	0.411762

图 5C

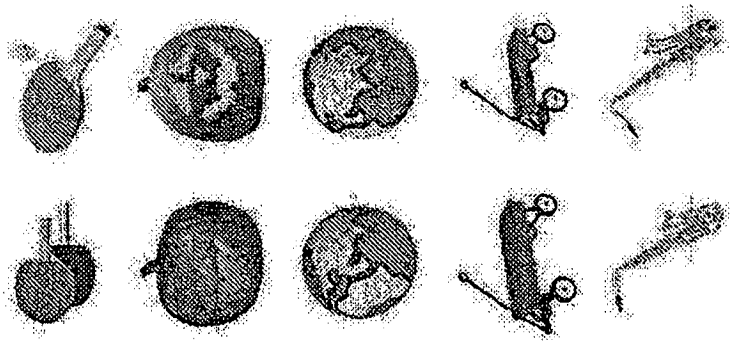


图6B

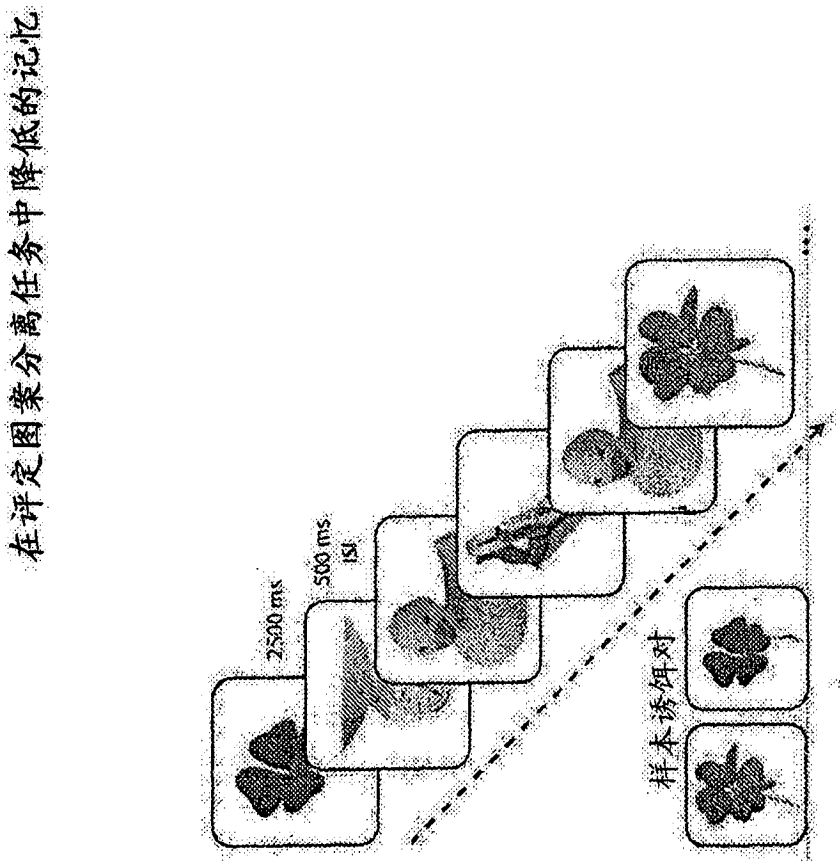


图6A

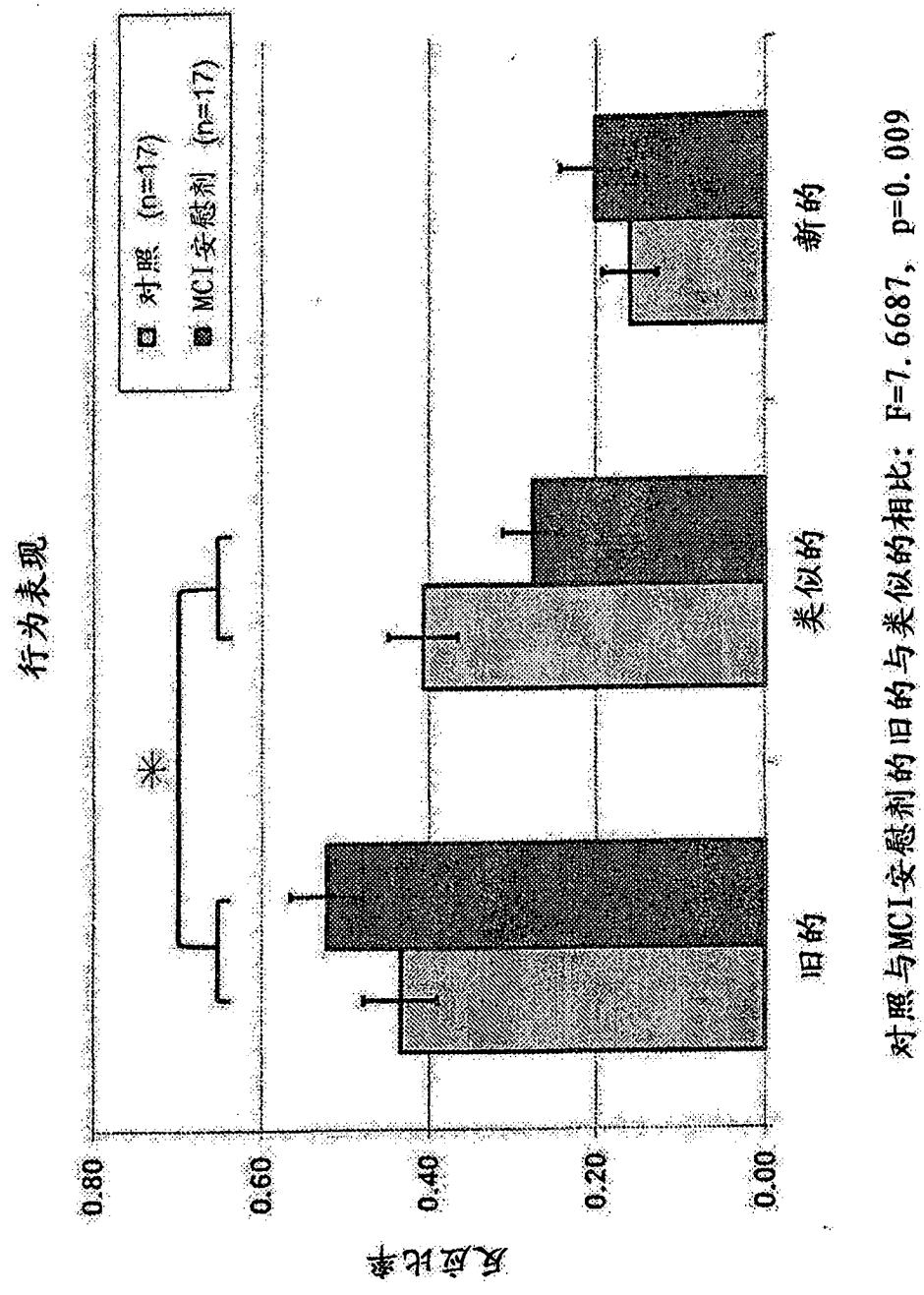

行为表现
对照 (n=17)
MCI安慰剂 (n=17)
*
0.80
0.60
0.40
0.20
0.00
旧的
类似的
新的
对照与MCI安慰剂的旧的与类似的相比：F=7.6687，p=0.009

图 7

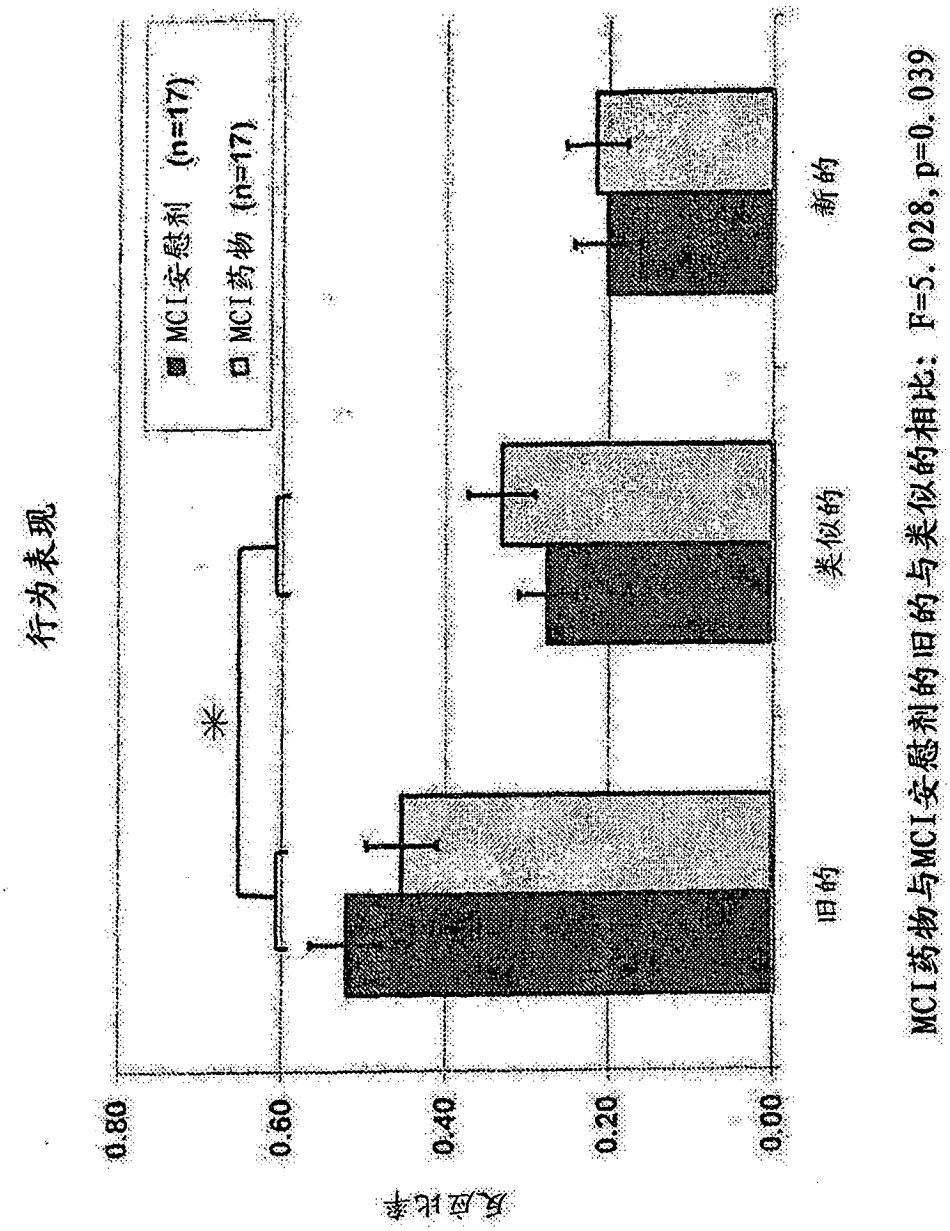

行为表现
MCI安慰剂 (n=17)
MCI药物 (n=17)
*
0.80
0.60
0.40
0.20
0.00
旧的
类似的
新的
MCI药物与MCI安慰剂的旧的与类似的相比: F=5.028, p=0.039

图 8

行为表现

对照受试者	反应比率	标准误差
旧的	0.433676	0.04426
类似的	0.406771	0.04135
新的	0.159553	0.03312
MCI安慰剂受试者	反应比率	标准误差
旧的	0.52262	0.04871
类似的	0.27549	0.03956
新的	0.20188	0.04528
MCI药物受试者	反应比率	标准误差
旧的	0.45361	0.04825
类似的	0.33144	0.04592
新的	0.21494	0.04202

图 9

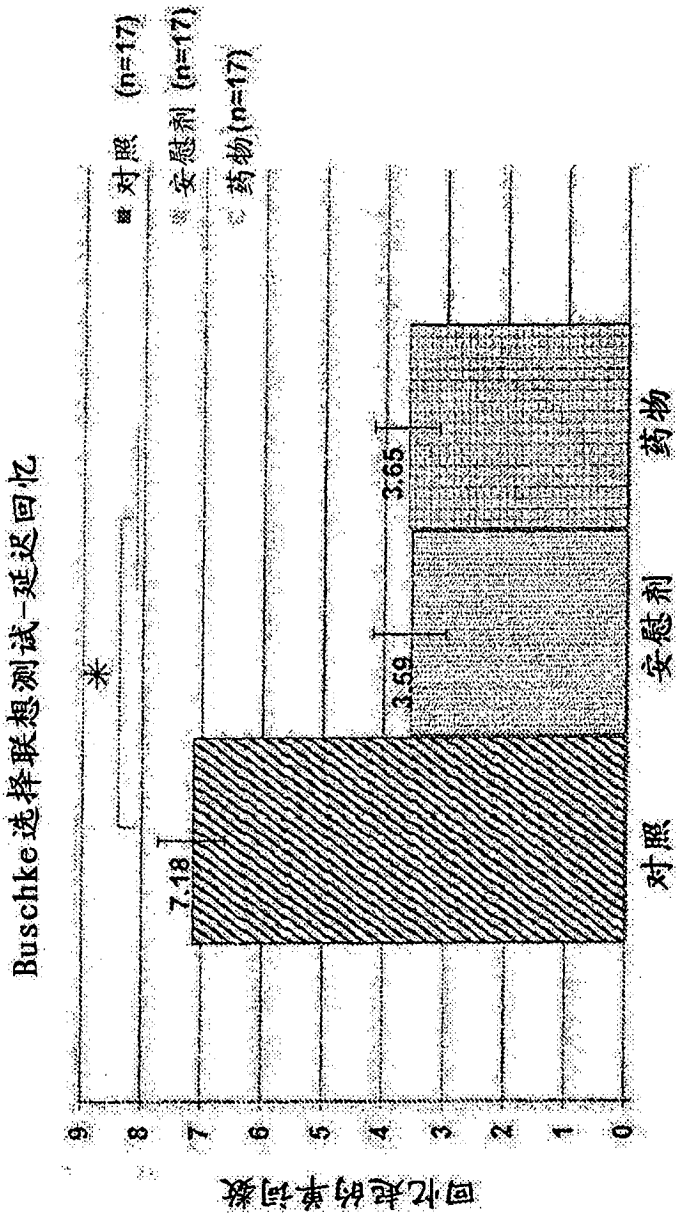


图 10A

组别	平均值	标准误差	延迟的（p-值）
对照	7.18	0.56	对照与安慰剂相比:<0.001
MCI安慰剂	3.59	0.59	对照与药物相比:< 0.001
MCI药物	3.65	0.53	安慰剂与药物相比:0.887

图 10B

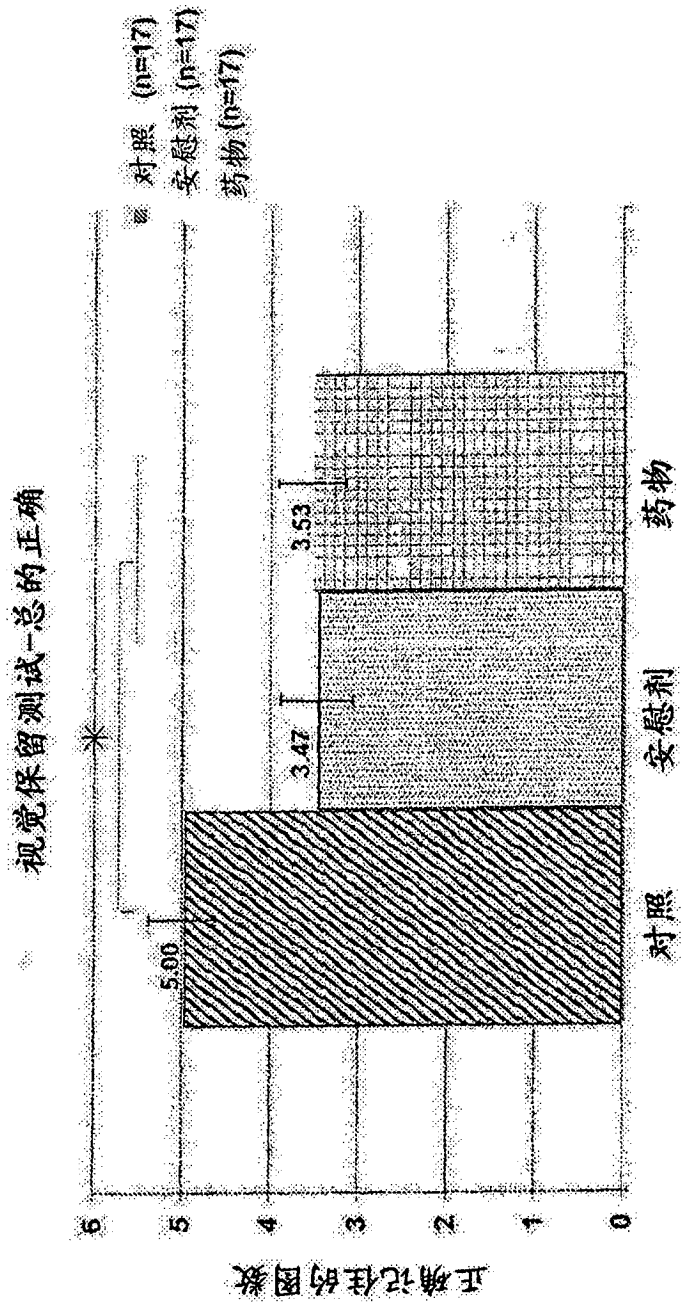


图 11A

组别	平均值	标准误差	总的正确（p-值）
对照	5.00	0.38	对照与安慰剂相比：0.011
MCI安慰剂	3.47	0.41	对照与药物相比：0.011
MCI药物	3.53	0.38	安慰剂与药物相比：0.805

图 11B

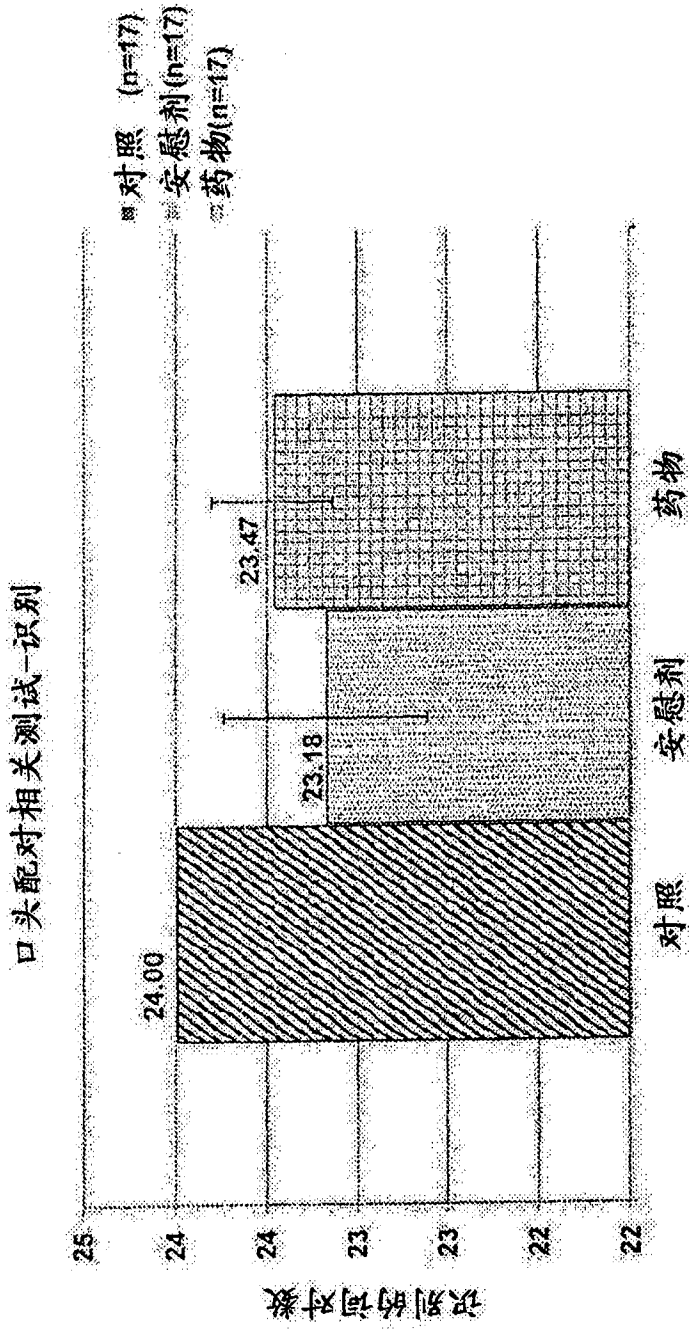


图 12A

组别	平均值	标准误差	识别（p-值）
对照	24.00	0.00	对照与安慰剂相比;0.154
MCI安慰剂	23.18	0.56	对照与药物相比;0.122
MCI药物	23.47	0.33	安慰剂与药物相比;0.428

图 12B

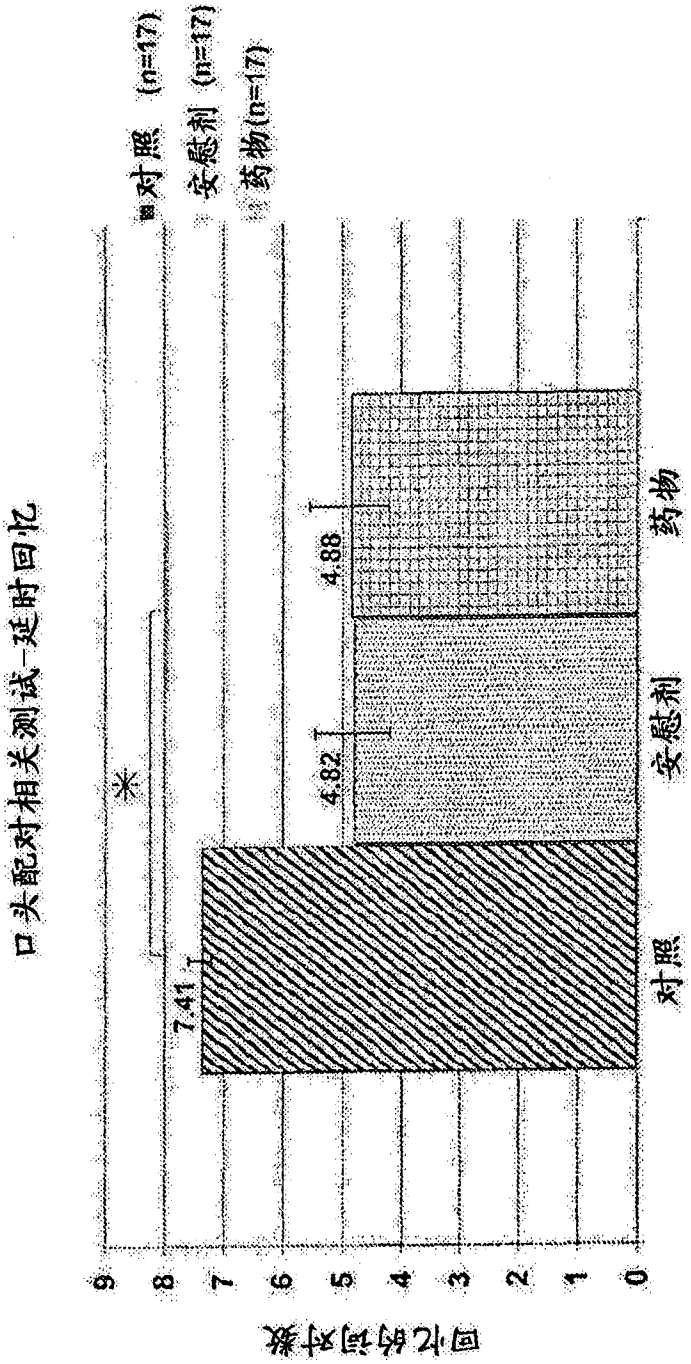


图 13A

组别	平均值	标准误差	延迟回忆(p-值)
对照	7.41	0.19	对照与安慰剂相比:<0.001
MCI安慰剂	4.82	0.63	对照与药物相比:0.001
MCI药物	4.88	0.67	安慰剂与药物相比:0.848

图 13B

研究状况

	对照受试者	MCI受试者	总受试者
参与筛查	26	32	58
筛查失败	4	9	13
登记的	22	23	45
离开或退出研究	5	6	11
用于分析的总的受试者	17	17	34

图 14A

研究样本的特征

	对照受试者	MCI受试者	p
N	17	17	
性别（男/女）	9/8	6/11	0.307
年龄（岁）	69.3 (7.0)	72.9 (8.9)	0.201
教育（年）	15.9 (2.6)	15.8 (2.9)	0.951
人种（高加索人/美国黑人）	17/0	14/3	0.074
西班牙人或拉丁美洲人（是/否）	0/17	1/16	0.317

图 14B

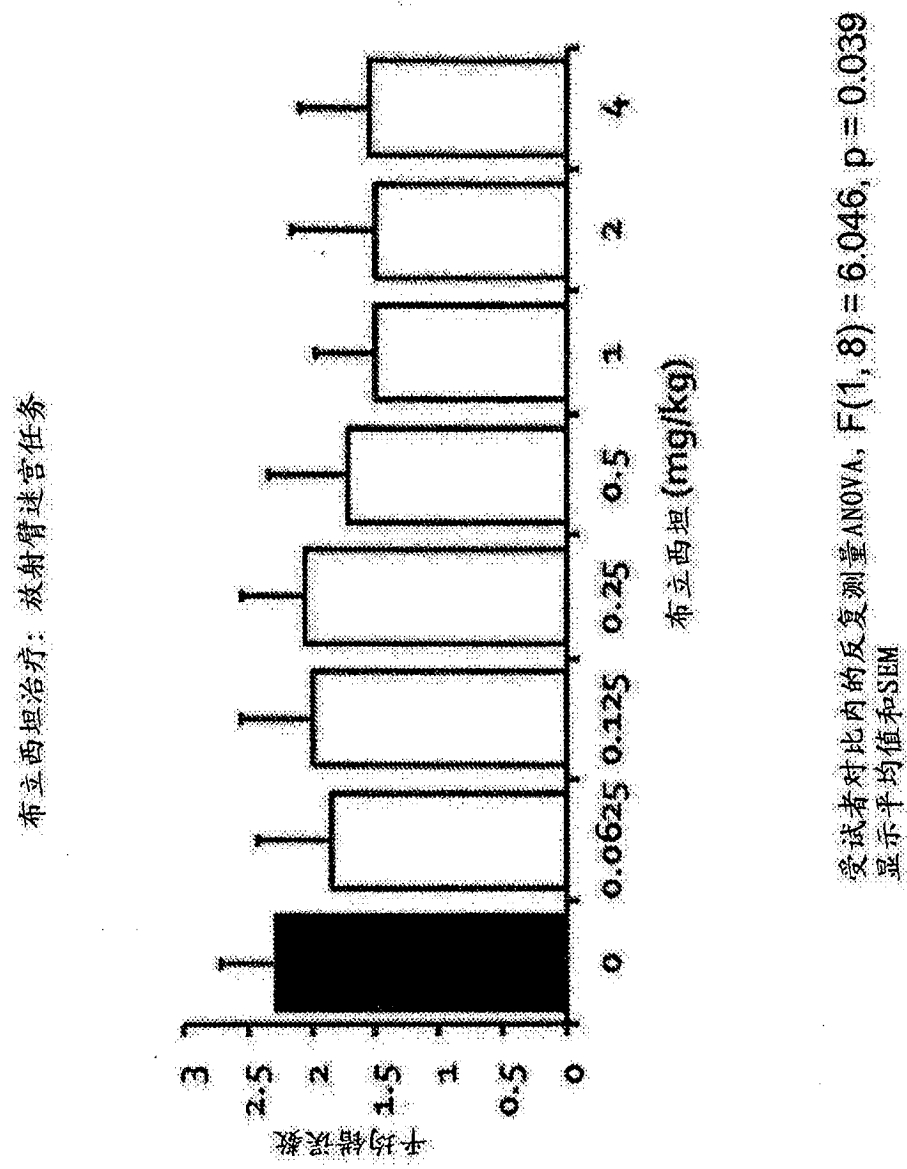

布立西坦治疗：放射臂迷宫任务
平均错误数
3
2.5
2
1.5
1
0.5
0
0
0.0625
0.125
0.25
0.5
1
2
4
布立西坦 (mg/kg)
受试者对比内的反复测量ANOVA, F(1, 8) = 6.046, p = 0.039
显示平均值和SEM

图 15

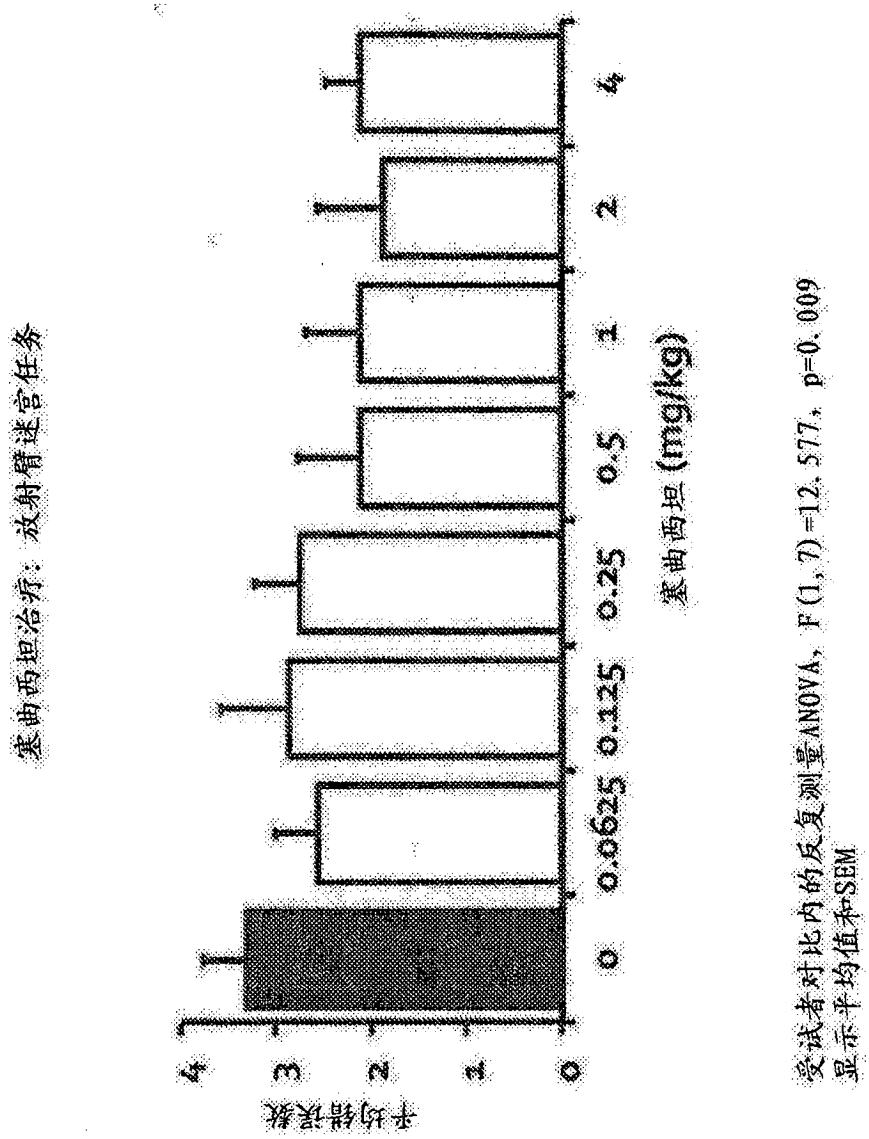

塞曲西坦治疗：放射臂迷宫任务
平均错误数
0
1
2
3
4
0
0.0625
0.125
0.25
0.5
1
2
4
塞曲西坦 (mg/kg)
受试者对比内的反复测量ANOVA，F(1,7)=12.577，p=0.009
显示平均值和SEM

图 16

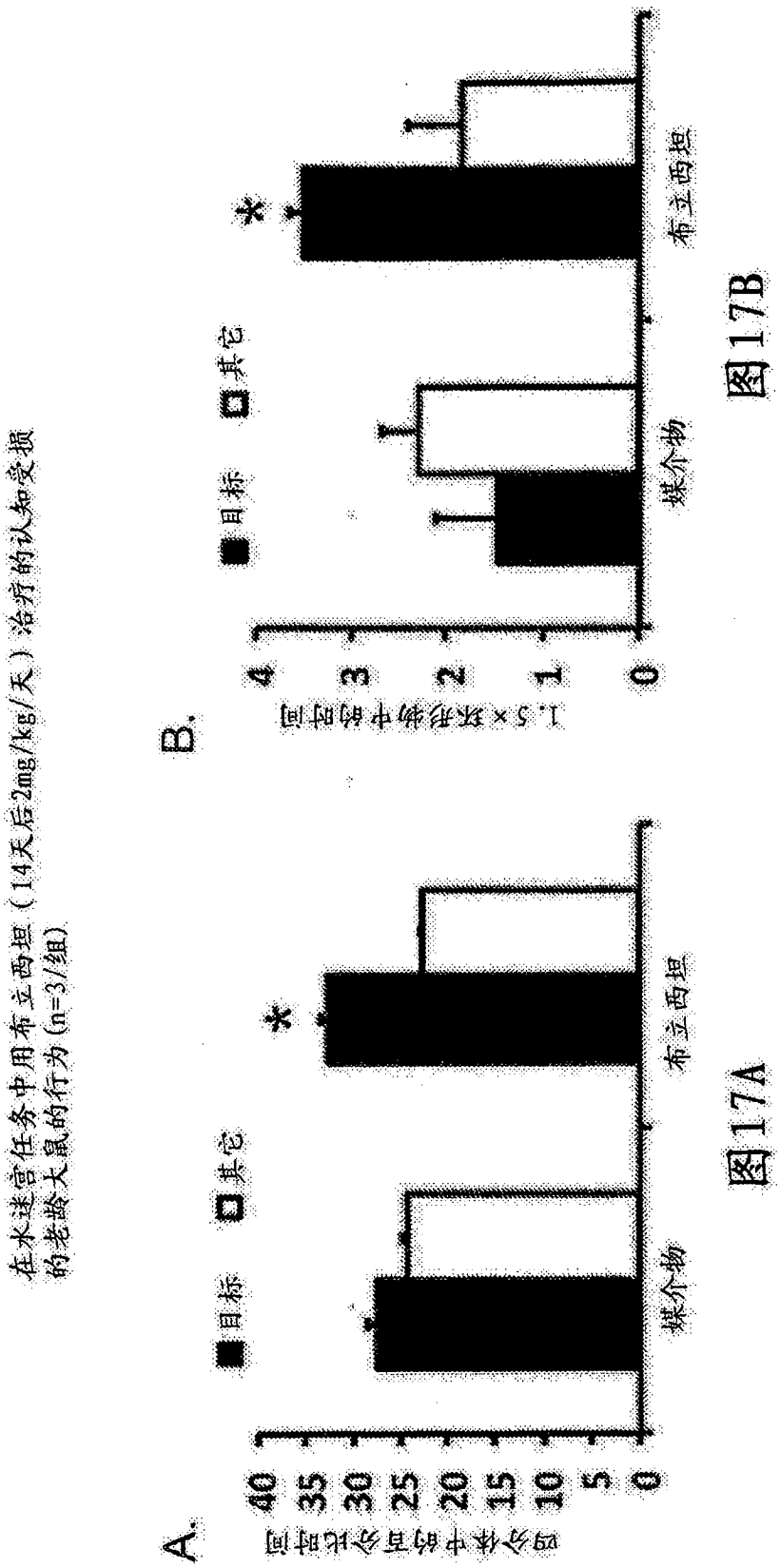

在水迷宫任务中用布立西坦（14天后2mg/kg/天）治疗的认知受损的老龄大鼠的行为(n=3/组)
A.
B.
目标
其它
*
媒介物
布立西坦
四分体中的百分比时间
1.5×环形物中的时间
0
5
10
15
20
25
30
35
40
1
2
3
4

图17A

图17B

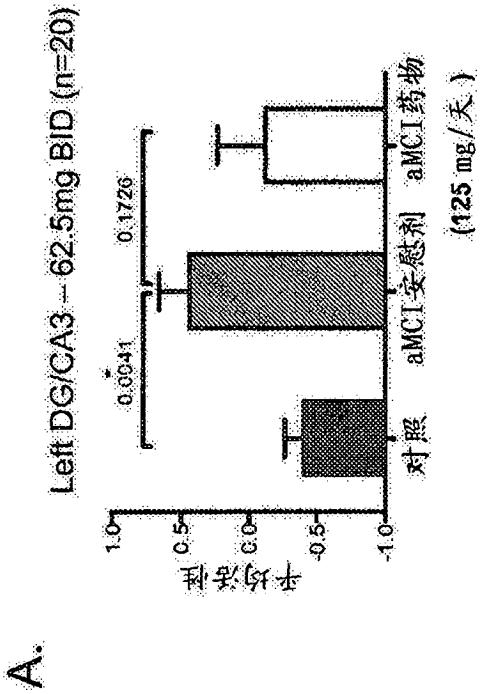


图 18A

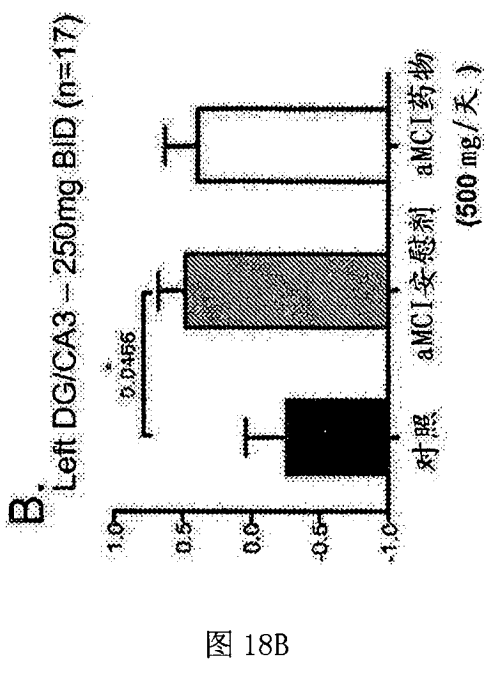


图 18B

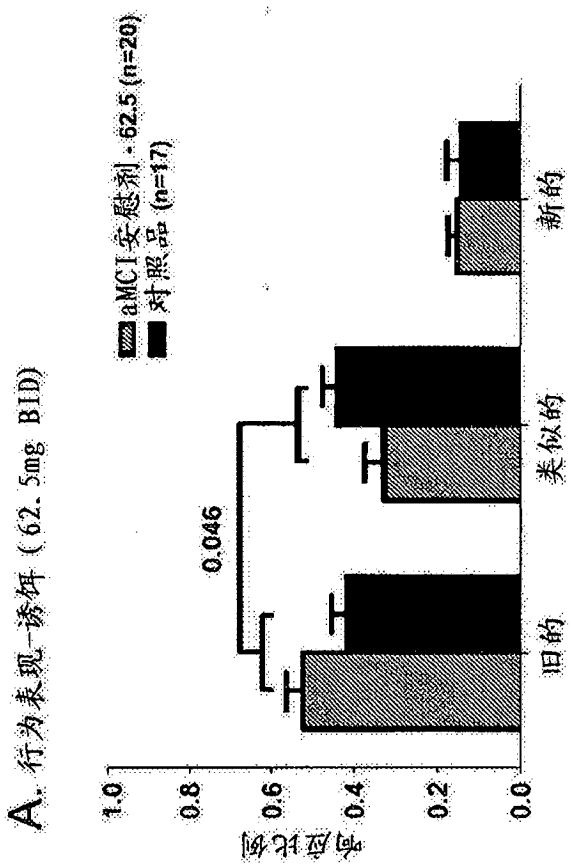


图 19A

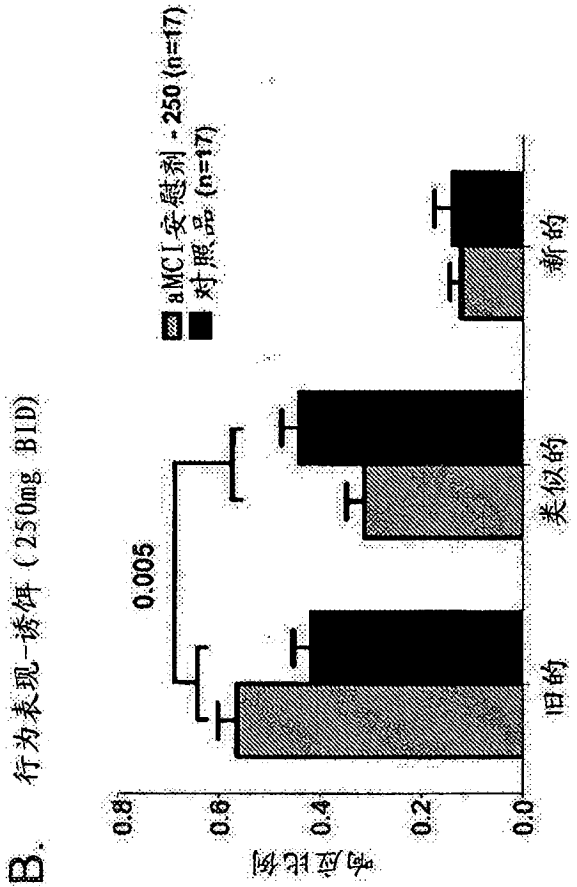

B.
行为表现-诱饵（250mg BID）
aMCI安慰剂 - 250 (n=17)
对照品 (n=17)
0.005
0.8
0.6
0.4
0.2
0.0
旧的
类似的
新的

图 19B

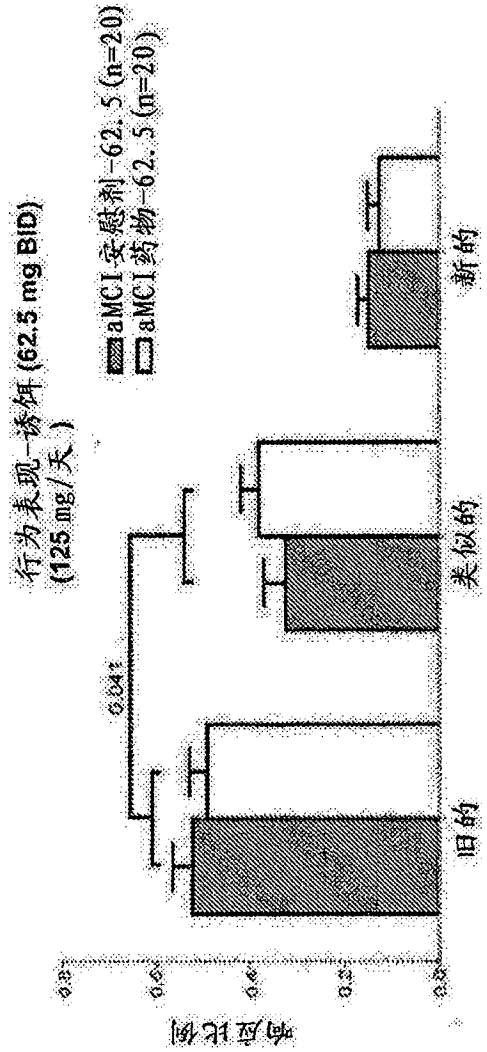

行为表现-诱饵 (62.5 mg BID)
(125 mg/天)
aMCI安慰剂-62.5 (n=20)
aMCI药物-62.5 (n=20)
0.043
旧的
类似的
新的

图 20A

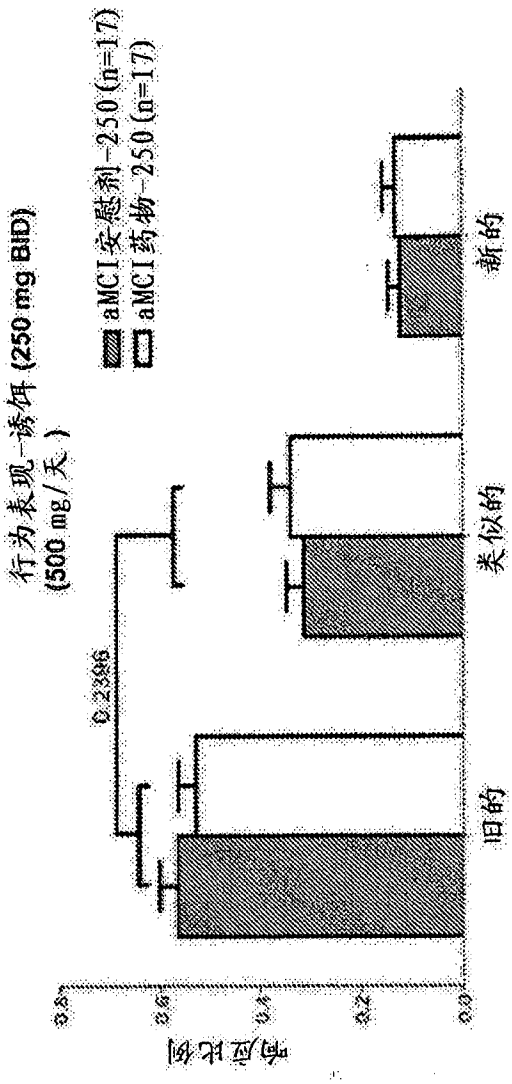

行为表现-诱饵 (250 mg BID)
(500 mg/天)
aMCI安慰剂-250 (n=17)
aMCI药物-250 (n=17)
0.2386
新的
类似的
旧的
响应比例
0.0
0.2
0.4
0.6
0.8

图 20B

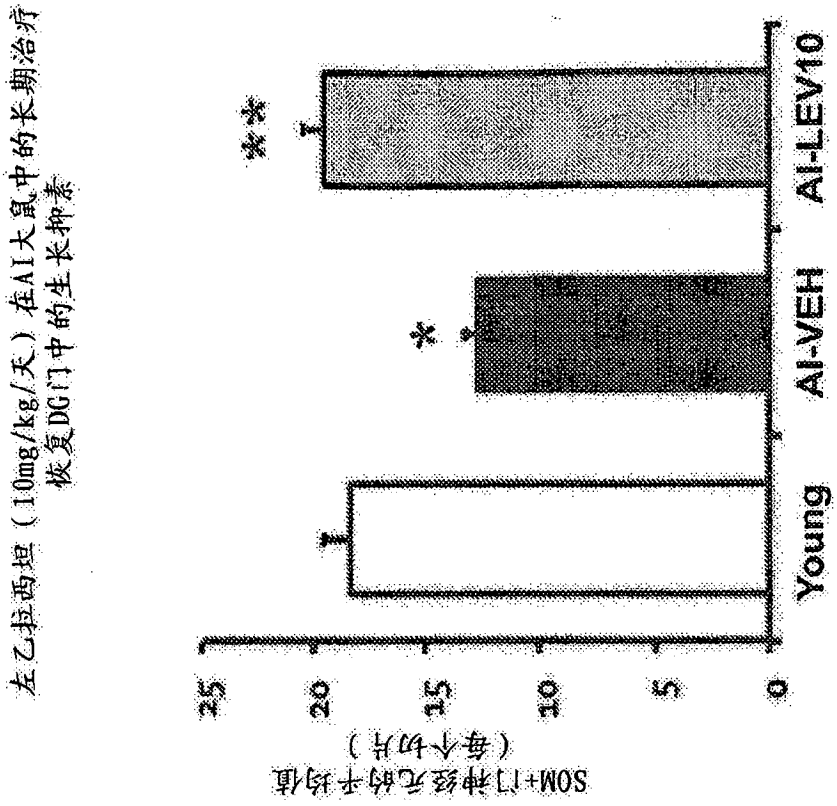

左乙拉西坦（10mg/kg/天）在AI大鼠中的长期治疗
恢复DG门中的生长抑素
SOM+门神经元的平均值
（每个切片）
25
20
15
10
5
0
Young
AI-VEH
AI-LEV10
*
**

图 21

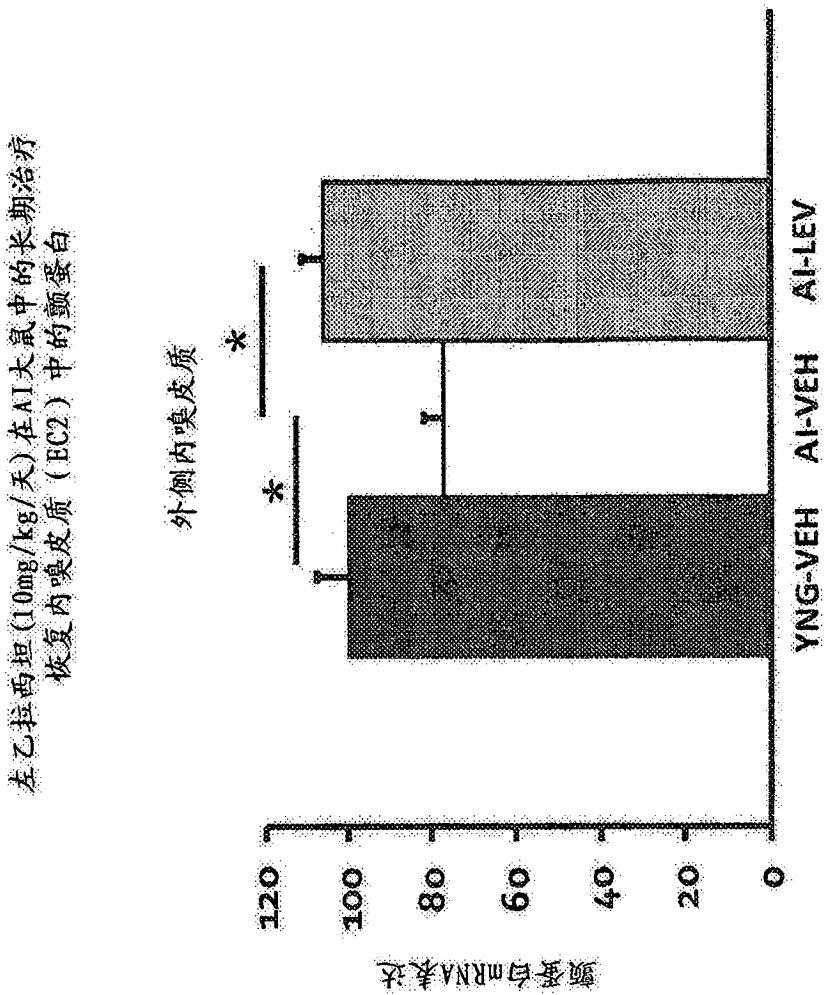

左乙拉西坦(10mg/kg/天)在AI大鼠中的长期治疗
恢复内嗅皮质(EC2)中的颞蛋白
外侧内嗅皮质
颞蛋白mRNA表达
120
100
80
60
40
20
0
YNG-VEH
AI-VEH
AI-LEV

图 22

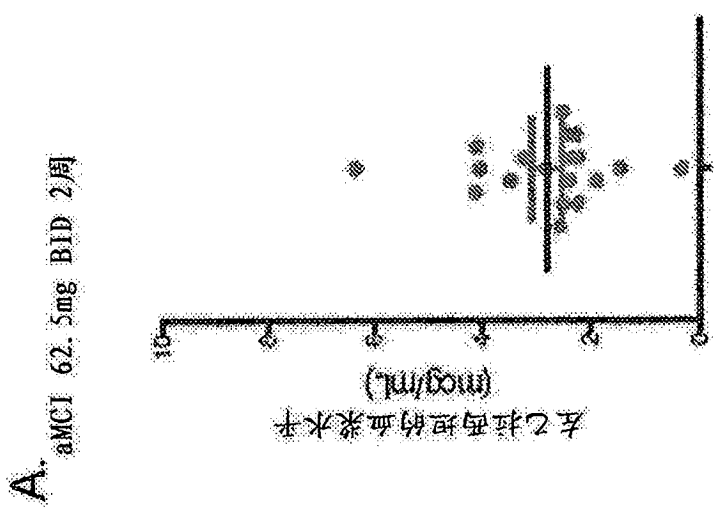

A.
aMCI 62.5mg BID 2周
左乙拉西坦的血浆水平
(mcg/mL)

图 23A

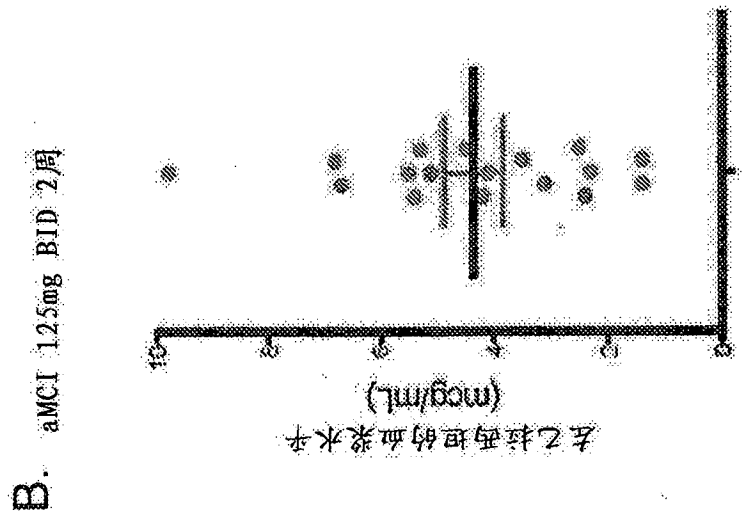

B. aMCI 125mg BID 2周
左乙拉西坦的血浆水平
(mcg/mL)

图 23B

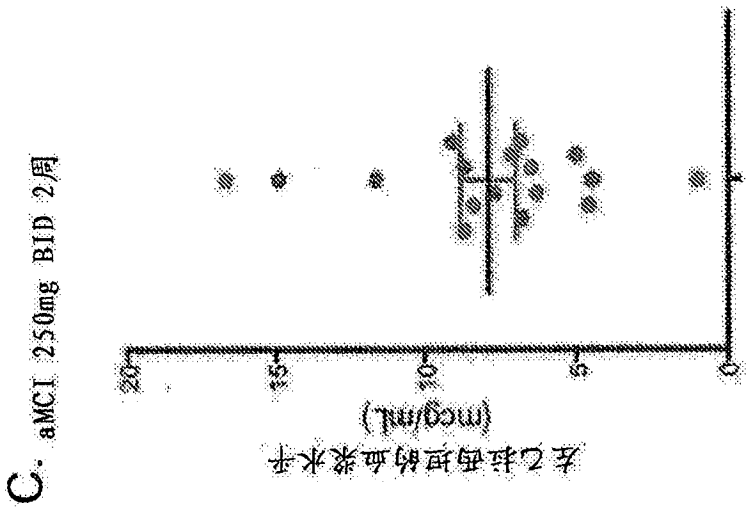

C. aMCI 250mg BID 2周
左乙拉西坦的血浆水平
(mcg/mL)

图 23C